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(54) **Titre :** DERIVES DE TETRAHYDROIMIDAZOPYRIDINE COMME MODULATEURS DE L'ACTIVITE DU TNF
(54) **Title:** TETRAHYDROIMIDAZOPYRIDINE DERIVATIVES AS MODULATORS OF TNF ACTIVITY

(57) **Abrégé/Abstract:**

A series of substituted 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine derivatives, being potent treatment and/or prevention of various human ailments, including autoimmune and inflammatory disorders; neurological and neurodegenerative disorders; pain and nociceptive disorders; cardiovascular disorders; metabolic disorders; ocular disorders; and oncological disorders.



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(54) Title: TETRAHYDROIMIDAZOPYRIDINE DERIVATIVES AS MODULATORS OF TNF ACTIVITY

(57) Abstract: A series of substituted 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine derivatives, being potent treatment and/or prevention of various human ailments, including autoimmune and inflammatory disorders; neurological and neurodegenerative disorders; pain and nociceptive disorders; cardiovascular disorders; metabolic disorders; ocular disorders; and oncological disorders.

TETRAHYDROIMIDAZOPYRIDINE DERIVATIVES AS **MODULATORS OF TNF ACTIVITY**

The present invention relates to a class of fused imidazole derivatives, and to their
5 use in therapy. More particularly, this invention is concerned with pharmacologically
active substituted 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine derivatives. These
compounds are modulators of the signalling of TNF α , and are accordingly of benefit as
pharmaceutical agents, especially in the treatment of adverse inflammatory and
autoimmune disorders, neurological and neurodegenerative disorders, pain and nociceptive
10 disorders, cardiovascular disorders, metabolic disorders, ocular disorders, and oncological
disorders.

TNF α is the prototypical member of the Tumour Necrosis Factor (TNF)
superfamily of proteins that share a primary function of regulating cell survival and cell
death. One structural feature common to all known members of the TNF superfamily is
15 the formation of trimeric complexes that bind to, and activate, specific TNF superfamily
receptors. By way of example, TNF α exists in soluble and transmembrane forms and
signals through two receptors, known as TNFR1 and TNFR2, with distinct functional
endpoints.

Various products capable of modulating TNF α activity are already commercially
20 available. All are approved for the treatment of inflammatory and autoimmune disorders
such as rheumatoid arthritis and Crohn's disease. All currently approved products are
macromolecular and act by inhibiting the binding of human TNF α to its receptor. Typical
macromolecular TNF α inhibitors include anti-TNF α antibodies; and soluble TNF α
receptor fusion proteins. Examples of commercially available anti-TNF α antibodies
25 include fully human antibodies such as adalimumab (Humira®) and golimumab
(Simponi®), chimeric antibodies such as infliximab (Remicade®), and pegylated Fab'
fragments such as certolizumab pegol (Cimzia®). An example of a commercially
available soluble TNF α receptor fusion protein is etanercept (Enbrel®).

TNF superfamily members, including TNF α itself, are implicated in a variety of
30 physiological and pathological functions that are believed to play a part in a range of
conditions of significant medical importance (see, for example, M.G. Tansey & D.E.
Szymkowski, *Drug Discovery Today*, 2009, **14**, 1082-1088; and F.S. Carneiro *et al.*, *J.*
Sexual Medicine, 2010, **7**, 3823-3834).

The compounds in accordance with the present invention, being potent modulators of human TNF α activity, are therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders; neurological and neurodegenerative disorders; pain and nociceptive disorders;

5 cardiovascular disorders; metabolic disorders; ocular disorders; and oncological disorders.

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, in one embodiment, the compounds of this invention may be useful as radioligands in assays for detecting

10 pharmacologically active compounds. In an alternative embodiment, certain compounds of this invention may be useful for coupling to a fluorophore to provide fluorescent conjugates that can be utilised in assays (e.g. a fluorescence polarisation assay) for detecting pharmacologically active compounds.

Co-pending international patent applications WO 2013/186229 (published 19

15 December 2013), WO 2014/009295 (published 16 January 2014) and WO 2014/009296 (also published 16 January 2014) describe fused imidazole derivatives which are modulators of human TNF α activity.

None of the prior art available to date, however, discloses or suggests the precise structural class of 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine derivatives as provided

20 by the present invention.

The compounds in accordance with the present invention potently inhibit the binding of a fluorescence conjugate to TNF α when tested in the fluorescence polarisation assay described herein. Indeed, when tested in that assay, the compounds of the present invention exhibit an IC₅₀ value of 50 μ M or less, generally of 20 μ M or less, usually of 5

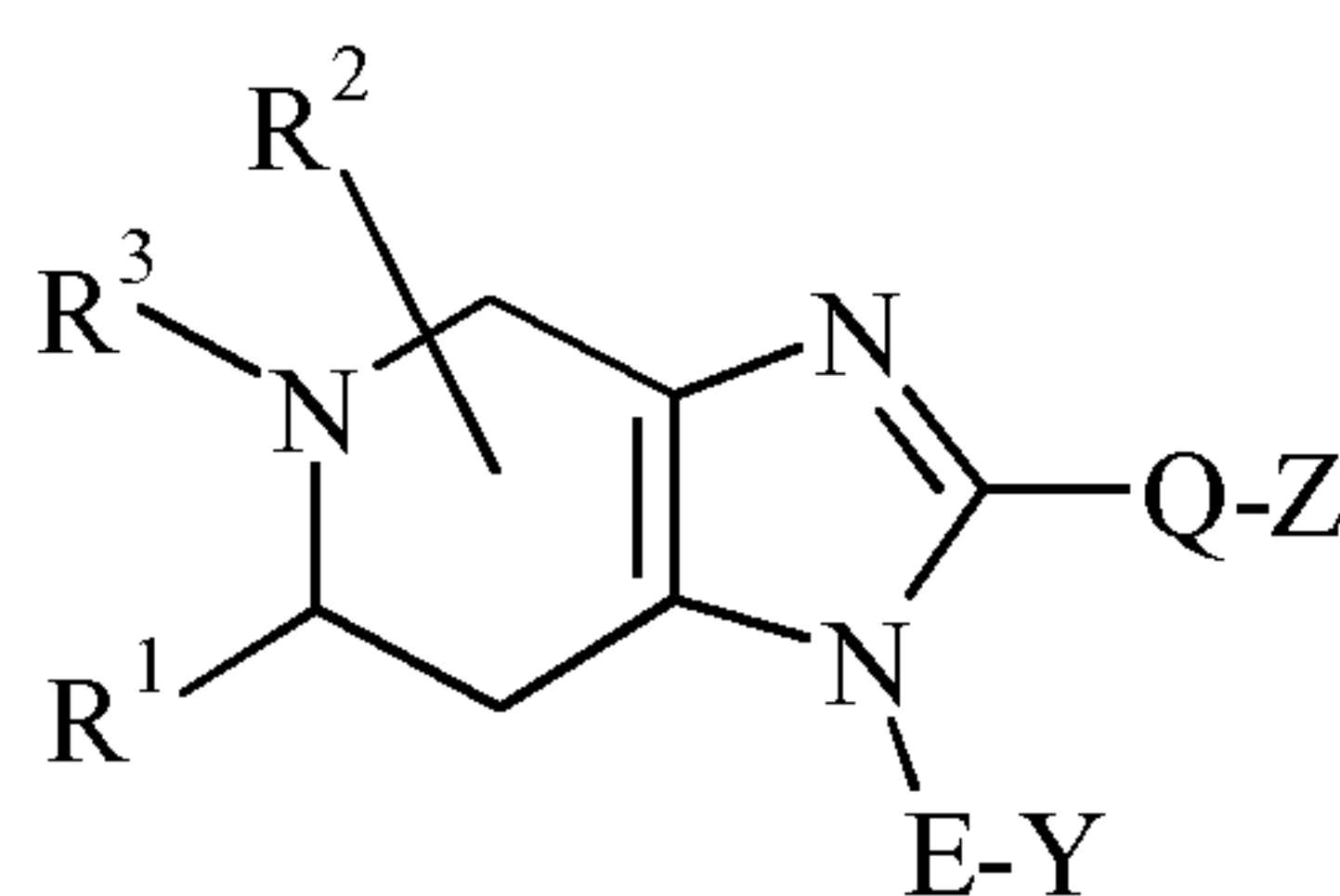
25 μ M or less, typically of 1 μ M or less, suitably of 500 nM or less, ideally of 100 nM or less, and preferably of 20 nM or less (the skilled person will appreciate that a *lower* IC₅₀ figure denotes a *more active* compound).

Certain compounds in accordance with the present invention potently neutralise the activity of TNF α in a commercially available HEK-293 derived reporter cell line known as

30 HEK-Blue™ CD40L. This is a stable HEK-293 transfected cell line expressing SEAP (secreted embryonic alkaline phosphatase) under the control of the IFN β minimal promoter fused to five NF- κ B binding sites. Secretion of SEAP by these cells is stimulated in a concentration-dependent manner by TNF α . When tested in the HEK-293

bioassay, also referred to herein as the reporter gene assay, certain compounds of the present invention exhibit an IC_{50} value of 50 μM or less, generally of 20 μM or less, usually of 5 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 (as before, 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, or a glucuronide derivative thereof, or a co-crystal thereof:



(I)

wherein

E represents a covalent bond; or E represents $-S(O)_2-$ or $-N(R^4)-$; or E represents an optionally substituted straight or branched C_{1-4} alkylene chain;

Q represents a covalent bond; or Q represents $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)(NR^5)-$, $-N(R^5)-$, $-C(O)N(R^5)-$, $-N(R^5)C(O)-$, $-S(O)_2N(R^5)-$ or $-N(R^5)S(O)_2-$; or Q represents an optionally substituted straight or branched C_{1-6} alkylene chain optionally comprising one, two or three heteroatom-containing linkages independently selected from $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)(NR^5)-$, $-N(R^5)-$, $-C(O)N(R^5)-$, $-N(R^5)C(O)-$, $-S(O)_2N(R^5)-$ and $-N(R^5)S(O)_2-$;

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

Z represents hydrogen, halogen or trifluoromethyl; or Z represents C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; or Z represents $-Z^1-Z^2$ or $-Z^1-C(O)-Z^2$, either of which moieties may be optionally substituted by one or more substituents;

Z^1 represents a divalent radical derived from an aryl, C_{3-7} heterocycloalkyl or heteroaryl group;

Z^2 represents aryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl or heteroaryl;

R^1 and R^2 independently represent hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SF_5$, $-NR^bR^c$, $-NR^cCOR^d$, $-NR^cCO_2R^d$, $-NHCONR^bR^c$, $-NR^cSO_2R^e$, $-N(SO_2R^e)_2$, $-NHSO_2NR^bR^c$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$, $-SO_2NR^bR^c$ or $-SO(NR^b)R^d$; or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, 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, C_{3-7} heterocycloalkenyl, C_{4-9} heterobicycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-aryl-, heteroaryl(C_{3-7})heterocycloalkyl-, (C_{3-7})cycloalkyl-heteroaryl-, (C_{3-7})cycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{4-7})cycloalkenyl-heteroaryl-, (C_{4-9})bicycloalkyl-heteroaryl-, (C_{3-7})heterocycloalkyl-heteroaryl-, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{3-7})heterocycloalkenyl-heteroaryl-, (C_{4-9})heterobicycloalkyl-heteroaryl- or (C_{4-9})spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents;

R^3 represents hydrogen, trifluoromethyl, $-SO_2R^a$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$, $-SO_2NR^bR^c$ or $-SO(NR^a)R^e$; or R^3 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_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-aryl-, (C_{3-7})cycloalkyl-heteroaryl-, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-heteroaryl-, (C_{4-7})cycloalkenyl-heteroaryl-, (C_{4-9})bicycloalkyl-heteroaryl-, (C_{3-7})heterocycloalkyl-heteroaryl-, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{3-7})heterocycloalkenyl-heteroaryl-, (C_{4-9})heterobicycloalkyl-heteroaryl- or (C_{4-9})spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents;

R^4 and R^5 independently represent hydrogen or C_{1-6} alkyl;

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.

The present invention also provides a compound of formula (I) as defined above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, for use in therapy.

The present invention also provides a compound of formula (I) as defined above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, for use in the treatment and/or prevention of disorders for which the administration of a modulator of $TNF\alpha$ function is indicated.

In another aspect, the present invention provides a compound of formula (I) as defined above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, for use in the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.

The present invention also provides a method for the treatment and/or prevention of disorders for which the administration of a modulator of $TNF\alpha$ function is indicated which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof.

In another aspect, the present invention provides a method for the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a

metabolic disorder, an ocular disorder, or an oncological disorder, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof.

5 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
10 pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of use in the invention or of their pharmaceutically acceptable salts. Standard principles underlying the selection and preparation of pharmaceutically acceptable salts are described, for example, in *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, ed. P.H. Stahl & C.G. Wermuth, Wiley-VCH, 2002.
15 Suitable pharmaceutically acceptable salts of the compounds of use in this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of use in 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.
20 Furthermore, where the compounds of use in 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; ammonium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts, and meglumine salts.

25 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.
30 Alternatively, the solvates of the compounds of formula (I) may be formed with water, in which case they will be hydrates.

 The present invention also includes co-crystals within its scope. The technical term “co-crystal” is used to describe the situation where neutral molecular components are

present within a crystalline compound in a definite stoichiometric ratio. The preparation of pharmaceutical co-crystals enables modifications to be made to the crystalline form of an active pharmaceutical ingredient, which in turn can alter its physicochemical properties without compromising its intended biological activity (see *Pharmaceutical Salts and Co-*
5 *crystals*, ed. J. Wouters & L. Quere, RSC Publishing, 2012). Typical examples of co-crystal formers, which may be present in the co-crystal alongside the active pharmaceutical ingredient, include *L*-ascorbic acid, citric acid, glutaric acid, urea and nicotinamide.

The present invention includes within its scope prodrugs of the compounds of
10 formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

15 Suitable alkyl groups which may be present on the compounds of use in the invention include straight-chained and branched C₁₋₆ alkyl groups, for example C₁₋₄ alkyl groups. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, 2,2-dimethylpropyl and 3-
20 methylbutyl. Derived expressions such as “C₁₋₆ alkoxy”, “C₁₋₆ alkylthio”, “C₁₋₆ alkylsulphonyl” and “C₁₋₆ alkylamino” are to be construed accordingly.

The expression “C₁₋₄ alkylene chain” refers to a divalent straight or branched alkylene chain containing 1 to 4 carbon atoms. Typical examples include methylene, ethylene, methylenemethylene, ethylenemethylene and dimethylenemethylene.

25 Suitable C₂₋₆ alkenyl groups include vinyl and allyl.

Suitable C₂₋₆ alkynyl groups include ethynyl, propargyl and butynyl.

The term “C₃₋₇ cycloalkyl” as used herein refers to monovalent groups of 3 to 7 carbon atoms derived from a saturated monocyclic hydrocarbon, and may comprise benzo-fused analogues thereof. Suitable C₃₋₇ cycloalkyl groups include cyclopropyl, cyclobutyl,
30 benzocyclobutenyl, cyclopentyl, indanyl, cyclohexyl and cycloheptyl.

The term “C₄₋₇ cycloalkenyl” as used herein refers to monovalent groups of 4 to 7 carbon atoms derived from a partially unsaturated monocyclic hydrocarbon. Suitable C₄₋₇ cycloalkenyl groups include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl.

The term “C₄₋₉ bicycloalkyl” as used herein refers to monovalent groups of 4 to 9 carbon atoms derived from a saturated bicyclic hydrocarbon. Typical bicycloalkyl groups include bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl and bicyclo[2.2.2]octanyl.

The term “aryl” as used herein refers to monovalent carbocyclic aromatic groups derived from a single aromatic ring or multiple condensed aromatic rings. Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C₁₋₆)alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

The term “C₃₋₇ heterocycloalkyl” as used herein refers to saturated monocyclic rings containing 3 to 7 carbon atoms and at least one heteroatom selected from oxygen, sulphur and nitrogen, and may comprise benzo-fused analogues thereof. Suitable heterocycloalkyl groups include oxetanyl, azetidiny, tetrahydrofuranyl, dihydrobenzofuranyl, dihydrobenzothienyl, pyrrolidiny, indoliny, isoindoliny, oxazolidiny, thiazolidiny, isothiazolidiny, imidazolidiny, tetrahydropyranyl, chromanyl, tetrahydrothiopyranyl, piperidiny, 1,2,3,4-tetrahydroquinoliny, 1,2,3,4-tetrahydroisoquinoliny, piperaziny, 1,2,3,4-tetrahydroquinoxaliny, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyraziny, homopiperaziny, morpholiny, benzoxaziny, thiomorpholiny, azepanyl, oxazepanyl, diazepanyl, thiadiazepanyl and azocanyl.

The term “C₃₋₇ heterocycloalkenyl” as used herein refers to monounsaturated or polyunsaturated monocyclic rings containing 3 to 7 carbon atoms and at least one heteroatom selected from oxygen, sulphur and nitrogen, and may comprise benzo-fused analogues thereof. Suitable heterocycloalkenyl groups include thiazoliny, isothiazoliny, imidazoliny, dihydropyranyl, dihydrothiopyranyl and 1,2,3,6-tetrahydropyridiny.

The term “C₄₋₉ heterobicycloalkyl” as used herein corresponds to C₄₋₉ bicycloalkyl wherein one or more of the carbon atoms have been replaced by one or more heteroatoms selected from oxygen, sulphur and nitrogen. Typical heterobicycloalkyl groups include 3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 6-azabicyclo[3.2.0]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, 2-oxabicyclo[2.2.2]octanyl, quinuclidiny, 2-oxa-5-azabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 3,6-diazabicyclo[3.2.2]nonanyl, 3-oxa-7-azabicyclo[3.3.1]nonanyl and 3,9-diazabicyclo[4.2.1]nonanyl.

The term “C₄₋₉ spiroheterocycloalkyl” as used herein refers to saturated bicyclic ring systems containing 4 to 9 carbon atoms and at least one heteroatom selected from oxygen, sulphur and nitrogen, in which the two rings are linked by a common atom.

Suitable spiroheterocycloalkyl groups include 5-azaspiro[2.3]hexanyl, 5-azaspiro[2.4]-
 5 heptanyl, 2-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.4]-
 octanyl, 2-oxa-6-azaspiro[3.5]nonanyl, 7-oxa-2-azaspiro[3.5]nonanyl, 2-oxa-7-azaspiro-
 [3.5]nonanyl and 2,4,8-triazaspiro[4.5]decanyl.

The term “heteroaryl” as used herein refers to monovalent aromatic groups containing at least 5 atoms derived from a single ring or multiple condensed rings, wherein
 10 one or more carbon atoms have been replaced by one or more heteroatoms selected from oxygen, sulphur and nitrogen. Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, thieno[2,3-*c*]pyrazolyl, thieno[3,4-*b*][1,4]dioxinyl, dibenzothienyl, pyrrolyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[3,2-*c*]pyridinyl, pyrrolo[3,4-*b*]pyridinyl, pyrazolyl, pyrazolo[1,5-*a*]pyridinyl, pyrazolo[3,4-*d*]pyrimidinyl,
 15 indazolyl, 4,5,6,7-tetrahydroindazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, imidazo[2,1-*b*]thiazolyl, imidazo[1,2-*a*]pyridinyl, imidazo[4,5-*b*]pyridinyl, purinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*a*]pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, [1,2,4]triazolo[1,5-*a*]-
 pyrimidinyl, benzotriazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, naphthyridinyl,
 20 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
 25 may accordingly exist as enantiomers. Where the compounds of use in the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to the use of 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
 30 and all possible mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (I) may exist as tautomers, for example keto ($\text{CH}_2\text{C}=\text{O}$) $\leftrightarrow$ enol ($\text{CH}=\text{CHOH}$) tautomers or amide ($\text{NHC}=\text{O}$) $\leftrightarrow$ hydroxyimine ($\text{N}=\text{COH}$) 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 ^1H , ^2H (deuterium) or ^3H (tritium) atom, preferably ^1H . 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 one aspect, the present invention provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, wherein

Q represents -O-, -S-, -S(O)-, -S(O)₂-, -S(O)(NR⁵)-, -N(R⁵)-, -C(O)N(R⁵)-, -N(R⁵)C(O)-, -S(O)₂N(R⁵)- or -N(R⁵)S(O)₂-; or Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain optionally comprising one, two or three heteroatom-containing linkages independently selected from -O-, -S-, -S(O)-, -S(O)₂-, -S(O)(NR⁵)-, -N(R⁵)-, -C(O)N(R⁵)-, -N(R⁵)C(O)-, -S(O)₂N(R⁵)- and -N(R⁵)S(O)₂-;

Z represents C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; or Z represents -Z¹-Z² or -Z¹-C(O)-Z², either of which moieties may be optionally substituted by one or more substituents; and

E, Y, R¹, R², R³, R⁵, Z¹ and Z² are as defined above.

In another aspect, the present invention provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, wherein

R¹ represents halogen or cyano; or C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkenyl, C₄₋₉ heterobicycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₃₋₇)cycloalkyl-heteroaryl-, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₄₋₉)bicycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or

(C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents; and

E, Q, Y, Z, R² and R³ are as defined above.

Where the compounds in accordance with the invention comprise an optionally substituted straight or branched alkylene chain, typical values thereof include methylene (-CH₂-), (methyl)methylene, ethylene (-CH₂CH₂-), (ethyl)methylene, (dimethyl)methylene, (methyl)ethylene, propylene (-CH₂CH₂CH₂-), (propyl)methylene and (dimethyl)ethylene, any of which chains may be optionally substituted by one or more substituents. Suitably, such chains are unsubstituted, monosubstituted or disubstituted. Typically, such chains are unsubstituted or monosubstituted. In one embodiment, such chains are unsubstituted. In another embodiment, such chains are monosubstituted. In a further embodiment, such chains are disubstituted.

Examples of typical substituents on the alkylene chain which may be present in a compound in accordance with the invention include halogen, cyano, trifluoromethyl, oxo, hydroxy, C₁₋₆ alkoxy, carboxy(C₁₋₆)alkoxy, trifluoromethoxy, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, carboxy, benzyloxycarbonyl, tetrazolyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl and di(C₁₋₆)alkylaminocarbonyl.

Specific examples of suitable substituents on the alkylene chain which may be present in a compound in accordance with the invention include fluoro, cyano, trifluoromethyl, hydroxy, methoxy, carboxymethoxy, amino, acetylamino, carboxy, benzyloxycarbonyl and tetrazolyl.

In a first embodiment, E represents a covalent bond, whereby the integer Y is attached directly to the imidazole ring.

In a second embodiment, E represents -S(O)₂- or -N(R⁴)-. In a first aspect of that embodiment, E represents -S(O)₂-. In a second aspect of that embodiment, E represents -N(R⁴)-.

In a third embodiment, E represents an optionally substituted straight or branched C₁₋₄ alkylene chain. In a first aspect of that embodiment, E represents an optionally substituted methylene (-CH₂-) linkage. In a second aspect of that embodiment, E represents an optionally substituted (methyl)methylene linkage. In a third aspect of that embodiment, E represents an optionally substituted (ethyl)methylene linkage.

Generally, E represents a covalent bond; or E represents -N(R⁴)-; or E represents an optionally substituted straight or branched C₁₋₄ alkylene chain.

Typically, E represents $-N(R^4)-$; or E represents an optionally substituted straight or branched C_{1-4} alkylene chain.

Suitably, E represents a covalent bond; or E represents $-N(R^4)-$; or E represents methylene ($-CH_2-$), (methyl)methylene or (ethyl)methylene, any of which groups may be optionally substituted by one or more substituents.

Generally, E represents $-N(R^4)-$; or E represents methylene ($-CH_2-$) or (ethyl)methylene, either of which groups may be optionally substituted by one or more substituents.

Appositely, E represents $-N(R^4)-$, or optionally substituted methylene.

Selected examples of typical substituents on the linkage represented by E include halogen, trifluoromethyl, oxo, hydroxy, C_{1-6} alkoxy, carboxy(C_{1-6})alkoxy, trifluoromethoxy, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, carboxy, benzyloxycarbonyl and tetrazolyl.

Specific examples of typical substituents on the linkage represented by E include fluoro, trifluoromethyl, oxo, hydroxy, methoxy, carboxymethoxy, trifluoromethoxy, amino, methylamino, dimethylamino, acetylamino, carboxy, benzyloxycarbonyl and tetrazolyl.

Typical values of E include $-N(R^4)-$, $-CH_2-$, $-C(O)-$, $-CH(OCH_3)-$, $-CH(OCH_2CO_2H)-$, $-CH(NHCOCH_3)-$, $-CH(CO_2benzyl)-$, $-CH(CH_3)-$ and $-CH(CH_2CH_3)-$; or E may represent a covalent bond.

Illustrative values of E include $-CH_2-$ and $-CH(CH_3)-$.

Suitable values of E include $-N(R^4)-$ and $-CH_2-$. In one embodiment, E represents $-N(R^4)-$. In another embodiment, E represents $-CH_2-$.

In another embodiment, E represents $-C(O)-$.

In another embodiment, E represents $-CH(OCH_3)-$.

In an additional embodiment, E represents $-CH(CH_3)-$. In a particular aspect of that embodiment, the $-CH(CH_3)-$ linkage represented by E is in the (*R*) stereochemical configuration.

In a further embodiment, E represents $-CH(CH_2CH_3)-$.

In a first embodiment, Q represents a covalent bond, whereby the integer Z is attached directly to the imidazole ring.

In a second embodiment, Q represents $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)(NR^5)-$, $-N(R^5)-$, $-C(O)N(R^5)-$, $-N(R^5)C(O)-$, $-S(O)_2N(R^5)-$ or $-N(R^5)S(O)_2-$. In a first aspect of

that embodiment, Q represents -O-. In a second aspect of that embodiment, Q represents -S-. In a third aspect of that embodiment, Q represents -S(O)-. In a fourth aspect of that embodiment, Q represents -S(O)₂-. In a fifth aspect of that embodiment, Q represents -S(O)(NR⁵)-. In a sixth aspect of that embodiment, Q represents -N(R⁵)-. In a seventh aspect of that embodiment, Q represents -C(O)N(R⁵)-. In an eighth aspect of that embodiment, Q represents -N(R⁵)C(O)-. In a ninth aspect of that embodiment, Q represents -S(O)₂N(R⁵)-. In a tenth aspect of that embodiment, Q represents -N(R⁵)S(O)₂-.

In a third embodiment, Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain optionally comprising one, two or three heteroatom-containing linkages independently selected from -O-, -S-, -S(O)-, -S(O)₂-, -S(O)(NR⁵)-, -N(R⁵)-, -C(O)N(R⁵)-, -N(R⁵)C(O)-, -S(O)₂N(R⁵)- and -N(R⁵)S(O)₂-. In a first aspect of that embodiment, Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain. In a second aspect of that embodiment, Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain comprising one heteroatom-containing linkage independently selected from -O-, -S-, -S(O)-, -S(O)₂-, -S(O)(NR⁵)-, -N(R⁵)-, -C(O)N(R⁵)-, -N(R⁵)C(O)-, -S(O)₂N(R⁵)- and -N(R⁵)S(O)₂-. In a third aspect of that embodiment, Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain comprising two heteroatom-containing linkages independently selected from -O-, -S-, -S(O)-, -S(O)₂-, -S(O)(NR⁵)-, -N(R⁵)-, -C(O)N(R⁵)-, -N(R⁵)C(O)-, -S(O)₂N(R⁵)- and -N(R⁵)S(O)₂-. In a fourth aspect of that embodiment, Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain comprising three heteroatom-containing linkages independently selected from -O-, -S-, -S(O)-, -S(O)₂-, -S(O)(NR⁵)-, -N(R⁵)-, -C(O)N(R⁵)-, -N(R⁵)C(O)-, -S(O)₂N(R⁵)- and -N(R⁵)S(O)₂-. In a fifth aspect of that embodiment, Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain comprising one, two or three heteroatom-containing linkages independently selected from -O-, -S-, -N(R⁵)-, -C(O)N(R⁵)- and -N(R⁵)C(O)-.

Typically, Q represents a covalent bond; or Q represents -S(O)- or -S(O)₂-; or Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain optionally comprising one or two heteroatom-containing linkages selected from -O-, -S-, -N(R⁵)-, -C(O)N(R⁵)-, and -N(R⁵)C(O)-.

Selected examples of typical substituents on the linkage represented by Q include halogen, cyano, trifluoromethyl, hydroxy, C₁₋₆ alkoxy and amino.

Specific examples of typical substituents on the linkage represented by Q include fluoro, cyano, trifluoromethyl, hydroxy, methoxy and amino.

Suitably, Q represents a covalent bond; or Q represents -S(O)-, -S(O)₂- or -N(R⁵)-; or Q represents -CH₂-, -CH(F)-, -CF₂-, -CH(CN)-, -CH(CH₃)-, -CH(OH)-, -CH(CH₂OH)-, -CH(OCH₃)-, -CH(NH₂)-, -CH₂CH₂-, -CH(OH)CH₂-, -CH(OH)CF₂-, -CH(OCH₃)CH₂-,
 5 -CH₂O-, -CH(CH₃)O-, -C(CH₃)₂O-, -CH(CH₂CH₃)O-, -CH(CF₃)O-, -CH₂S-, -CH₂S(O)-, -CH₂S(O)₂-, -CH₂N(R⁵)-, -CH₂CH₂CH₂-, -CH(OH)CH₂CH₂-, -CH(OCH₃)CH₂CH₂-, -CH₂CH₂O-, -CH₂OCH₂-, -CH₂OCH(F)-, -CH₂OCF₂-, -CH₂OCH(CH₃)-, -CH(CH₃)OCH₂-, -CH₂OC(CH₃)₂-, -C(CH₃)₂OCH₂-, -CH₂SCH₂-, -CH₂S(O)CH₂-,
 10 -CH₂S(O)₂CH₂-, -CH₂CH₂N(R⁵)-, -CH₂N(R⁵)CH₂-, -CH₂N(R⁵)C(O)-, -CH₂CH₂OCH₂-, -CH₂CH₂N(R⁵)C(O)-, -CH₂OCH₂CH₂-, -CH₂OCH₂CF₂-, -CH₂OCH₂CH(CH₃)-, -CH₂OCH(CH₃)CH₂-, -CH₂OC(CH₃)₂CH₂-, -CH₂OCH₂CH(CH₃)CH₂-, -CH₂OCH₂CH₂O-, -CH₂OCH₂C(O)N(R⁵)- or -CH₂OCH₂CH₂OCH₂-.

Appositely, Q represents a covalent bond; or Q represents -CH₂-, -CH(CN)-, -CH(OH)-, -CH(OCH₃)-, -CH₂O-, -CH₂N(R⁵)- or -CH₂OCH₂-.
 15

Appropriately, Q represents a covalent bond; or Q represents -CH₂- or -CH₂O-.

Particular values of Q include -CH₂-, -CH(OH)-, -CH₂O-, -CH₂S- and -CH₂OCH₂-. In a first embodiment, Q represents -CH₂-. In a second embodiment, Q represents -CH(OH)-. In a third embodiment, Q represents -CH₂O-. In a fourth
 20 embodiment, Q represents -CH₂S-. In a fifth embodiment, Q represents -CH₂OCH₂-.

Generally, Y represents C₃₋₇ cycloalkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Typically, Y represents aryl or heteroaryl, either of which groups may be optionally substituted by one or more substituents.

25 In a first embodiment, Y represents optionally substituted C₃₋₇ cycloalkyl. In one aspect of that embodiment, Y represents unsubstituted C₃₋₇ cycloalkyl. In another aspect of that embodiment, Y represents monosubstituted C₃₋₇ cycloalkyl. In a further aspect of that embodiment, Y represents disubstituted C₃₋₇ cycloalkyl.

In a second embodiment, Y represents optionally substituted aryl. In one aspect of
 30 that embodiment, Y represents unsubstituted aryl. In another aspect of that embodiment, Y represents monosubstituted aryl. In a further aspect of that embodiment, Y represents disubstituted aryl.

In a third embodiment, Y represents optionally substituted C₃₋₇ heterocycloalkyl. In one aspect of that embodiment, Y represents unsubstituted C₃₋₇ heterocycloalkyl. In another aspect of that embodiment, Y represents monosubstituted C₃₋₇ heterocycloalkyl. In a further aspect of that embodiment, Y represents disubstituted C₃₋₇ heterocycloalkyl.

5 In a fourth embodiment, Y represents optionally substituted heteroaryl. In one aspect of that embodiment, Y represents unsubstituted heteroaryl. In another aspect of that embodiment, Y represents monosubstituted heteroaryl. In a further aspect of that embodiment, Y represents disubstituted heteroaryl.

Suitably, Y represents benzocyclobutenyl, phenyl, thienyl, thiazolyl or pyridinyl,
10 any of which groups may be optionally substituted by one or more substituents.

Appropriately, Y represents phenyl, thienyl or thiazolyl, any of which groups may be optionally substituted by one or more substituents.

Appositely, Y represents phenyl, which may be optionally substituted by one or more substituents.

15 Examples of optional substituents which may be present on the moiety Y include one, two or three substituents independently selected from halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, (C₁₋₆)alkylsulfonyloxy, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, arylamino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino,
20 formyl, C₂₋₆ alkylcarbonyl, C₃₋₆ cycloalkylcarbonyl, C₃₋₆ heterocycloalkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆)alkylaminosulfonyl.

Typical examples of optional substituents on the moiety Y include halogen, cyano and difluoromethoxy.

25 Suitable examples of optional substituents on the moiety Y include halogen and difluoromethoxy, especially halogen.

Examples of particular substituents on the moiety Y include fluoro, chloro, bromo, cyano, nitro, methyl, isopropyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, methylsulfonyloxy, amino,
30 methylamino, *tert*-butylamino, dimethylamino, phenylamino, acetylamino, methylsulfonylamino, formyl, acetyl, cyclopropylcarbonyl, azetidiny carbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, piperazinylcarbonyl, morpholinylcarbonyl, carboxy,

methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl and dimethylaminosulfonyl.

Typical examples of particular substituents on the moiety Y include fluoro, chloro, cyano and difluoromethoxy, especially chloro.

5 Suitable examples of particular substituents on the moiety Y include chloro and difluoromethoxy, especially chloro.

Typical values of Y include benzocyclobutenyl, phenyl, fluorophenyl (including 2-fluorophenyl, 3-fluorophenyl and 4-fluorophenyl), chlorophenyl (including 2-chlorophenyl, 3-chlorophenyl and 4-chlorophenyl), difluorophenyl (including 2,6-difluorophenyl), (chloro)(fluoro)phenyl (including 5-chloro-2-fluorophenyl and 2-chloro-5-fluorophenyl), dichlorophenyl (including 2,5-dichlorophenyl and 2,6-dichlorophenyl), methylphenyl (including 4-methylphenyl), dimethylphenyl (including 2,5-dimethylphenyl and 2,6-dimethylphenyl), (trifluoromethyl)phenyl [including 2-(trifluoromethyl)phenyl], (chloro)(trifluoromethyl)phenyl [including 5-chloro-2-(trifluoromethyl)phenyl], (methyl)-
 10 (trifluoromethyl)phenyl [including 2-methyl-5-(trifluoromethyl)phenyl], bis(trifluoromethyl)phenyl [including 2,5-bis(trifluoromethyl)phenyl], methoxyphenyl (including 2-methoxyphenyl), (difluoromethoxy)phenyl [including 2-(difluoromethoxy)phenyl and 3-(difluoromethoxy)phenyl], (difluoromethoxy)(fluoro)phenyl [including 2-(difluoromethoxy)-5-fluorophenyl and 2-(difluoromethoxy)-6-fluorophenyl], (chloro)(difluoro-
 15 methoxy)phenyl [including 5-chloro-2-(difluoromethoxy)phenyl and 6-chloro-2-(difluoromethoxy)phenyl], (cyano)(difluoromethoxy)phenyl [including 6-cyano-2-(difluoromethoxy)phenyl], (trifluoromethoxy)phenyl [including 2-(trifluoromethoxy)-phenyl], methylsulfonyloxyphenyl, (amino)(chloro)phenyl (including 5-amino-2-chlorophenyl), methylthienyl (including 3-methylthien-2-yl), methylthiazolyl (including 2-methyl-1,3-thiazol-4-yl), (chloro)(methyl)thiazolyl (including 5-chloro-2-methyl-1,3-thiazol-4-yl), dimethylthiazolyl (including 2,4-dimethyl-1,3-thiazol-5-yl) and pyridinyl (including pyridin-3-yl and pyridin-4-yl).
 20

Selected values of Y include phenyl, dichlorophenyl, dimethylphenyl, (difluoromethoxy)phenyl, (difluoromethoxy)(fluoro)phenyl, methylsulfonyloxyphenyl, methylthienyl and dimethylthiazolyl.
 30

Suitable values of Y include dichlorophenyl and (difluoromethoxy)phenyl.

In one embodiment, Y represents phenyl.

In another embodiment, Y represents 2,5-dichlorophenyl.

In another embodiment, Y represents 2,5-dimethylphenyl.

In a particular embodiment, Y represents 2-(difluoromethoxy)phenyl.

In another embodiment, Y represents (difluoromethoxy)(fluoro)phenyl.

In another embodiment, Y represents 3-methylthien-2-yl.

5 In another embodiment, Y represents 2,4-dimethyl-1,3-thiazol-5-yl.

In one embodiment, Z represents hydrogen.

In another embodiment, Z is other than hydrogen.

In a selected embodiment, Z represents hydrogen; or Z represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl or heteroaryl, any of
10 which groups may be optionally substituted by one or more substituents; or Z represents -Z¹-Z² or -Z¹-C(O)-Z², either of which moieties may be optionally substituted by one or more substituents.

In a further embodiment, Z represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl or heteroaryl, any of which groups may be
15 optionally substituted by one or more substituents; or Z represents -Z¹-Z² or -Z¹-C(O)-Z², either of which moieties may be optionally substituted by one or more substituents.

Suitably, Z represents hydrogen; or Z represents C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; or Z
20 represents -Z¹-Z², which moiety may be optionally substituted by one or more substituents.

Appropriately, Z represents hydrogen; or Z represents C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Generally, Z represents hydrogen; or Z represents C₁₋₆ alkyl or heteroaryl, either
25 of which groups may be optionally substituted by one or more substituents.

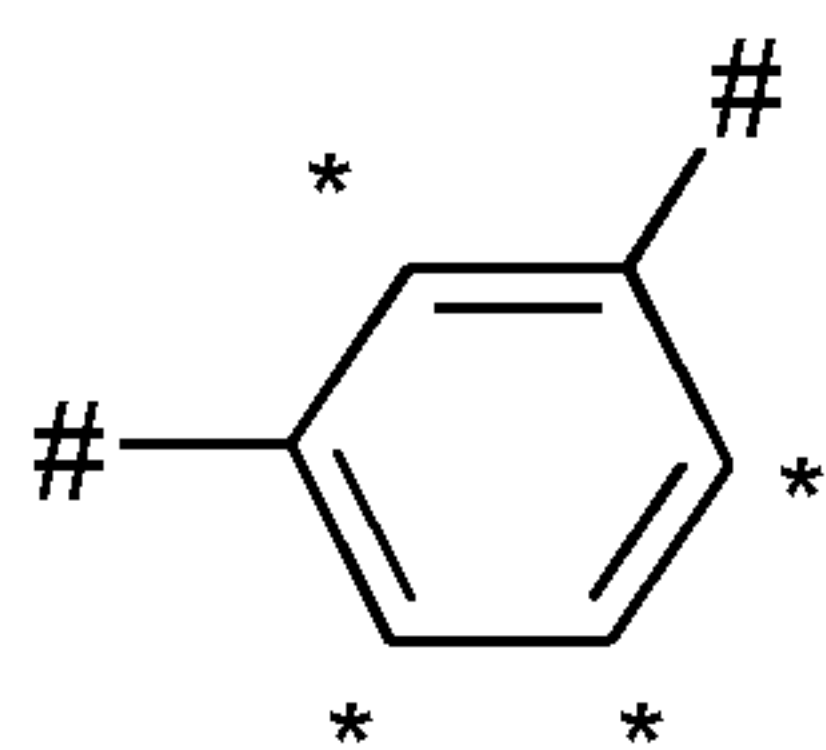
Typically, Z represents hydrogen, fluoro or trifluoromethyl; or Z represents methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, tetrahydrofuranyl, pyrrolidinyl, indolinyl, tetrahydropyranyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, morpholinyl, azocanyl,
30 thiazolinyl, furyl, thienyl, pyrazolyl, 4,5,6,7-tetrahydroindazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, imidazolyl, benzimidazolyl, [1,2,4]triazolo[1,5-*a*]-pyrimidinyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, phthalazinyl, pyrimidinyl or pyrazinyl, any of which groups may be optionally substituted by one or more substituents;

or Z represents $-Z^1-Z^2$ or $-Z^1-C(O)-Z^2$, either of which moieties may be optionally substituted by one or more substituents.

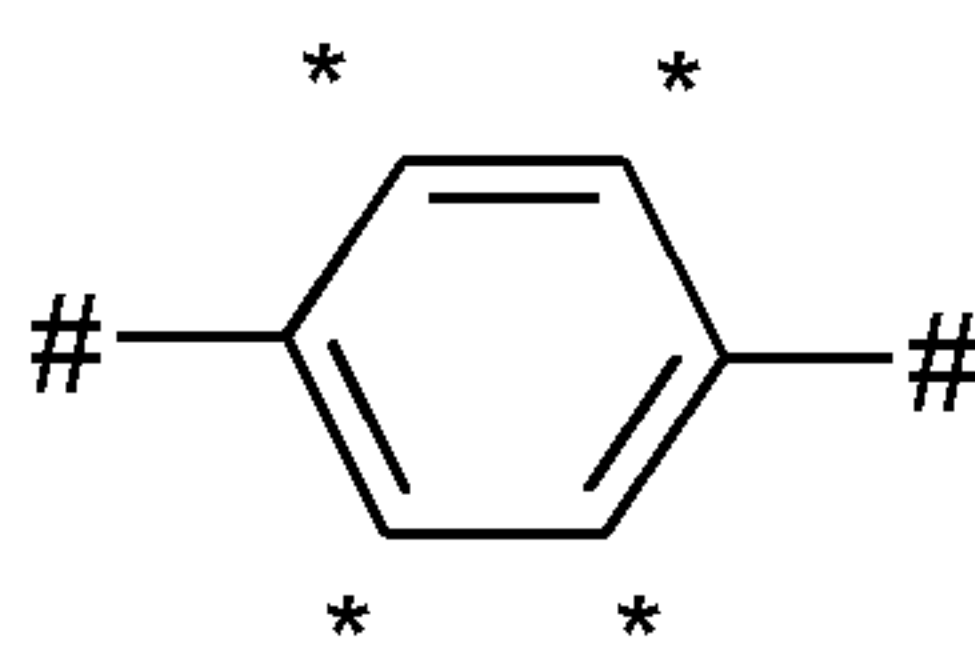
Appositely, Z represents hydrogen; or Z represents methyl, phenyl or pyridinyl, any of which groups may be optionally substituted by one or more substituents.

5 More generally, Z represents hydrogen; or Z represents methyl or pyridinyl, either of which groups may be optionally substituted by one or more substituents.

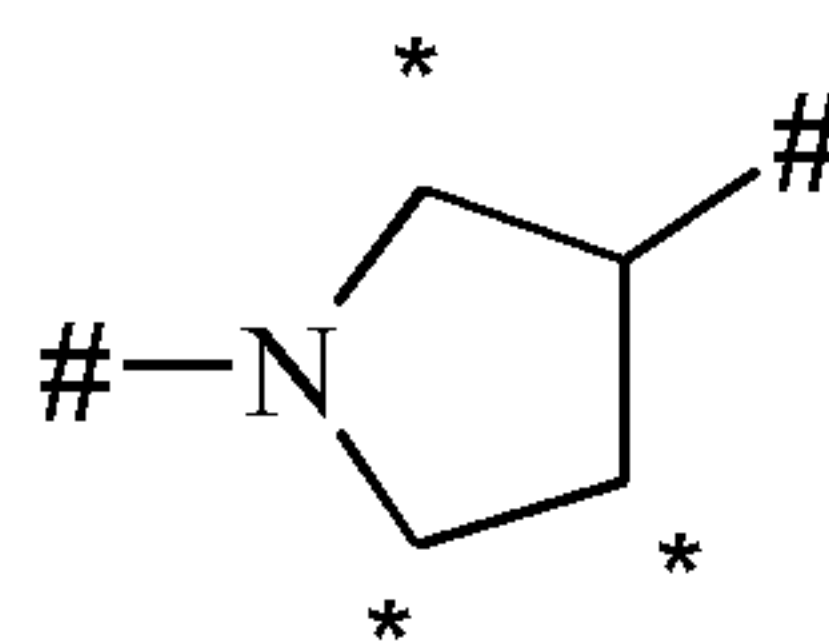
The moiety Z^1 represents a divalent radical derived from an aryl, C_{3-7} heterocycloalkyl or heteroaryl group, any of which groups may be optionally substituted by one or more substituents. Typically, the moiety Z^1 represents a divalent radical derived from a
 10 phenyl, pyrrolidinyl, piperazinyl, pyrazolyl, thiazolyl, triazolyl, tetrazolyl or pyridinyl group, any of which groups may be optionally substituted by one or more substituents. Typical values of the moiety Z^1 include the groups of formula (Za), (Zb), (Zc), (Zd), (Ze), (Zf), (Zg), (Zh), (Zj) and (Zk):



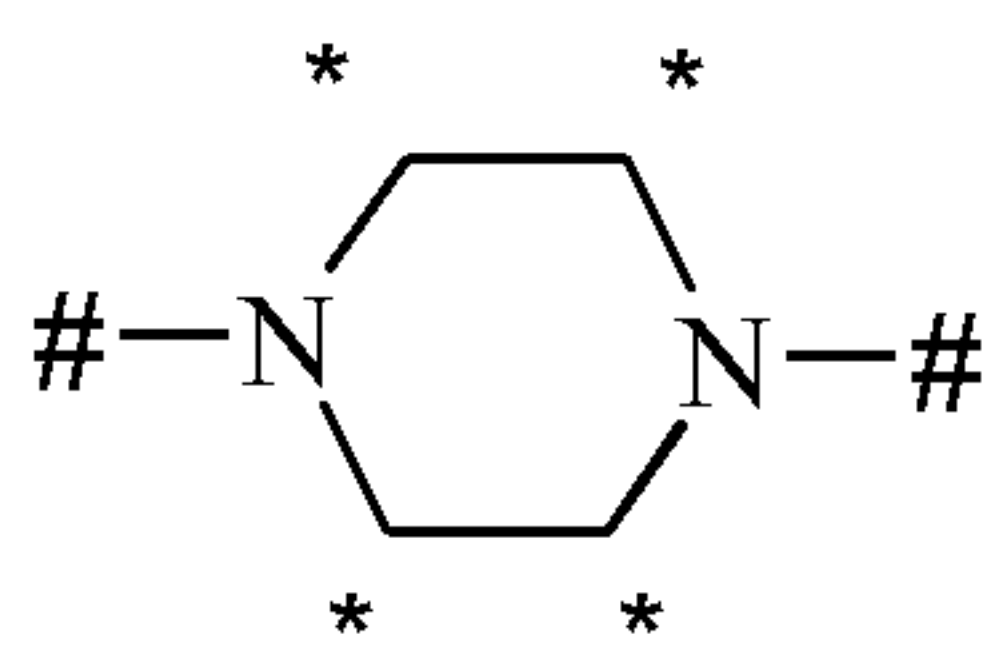
(Za)



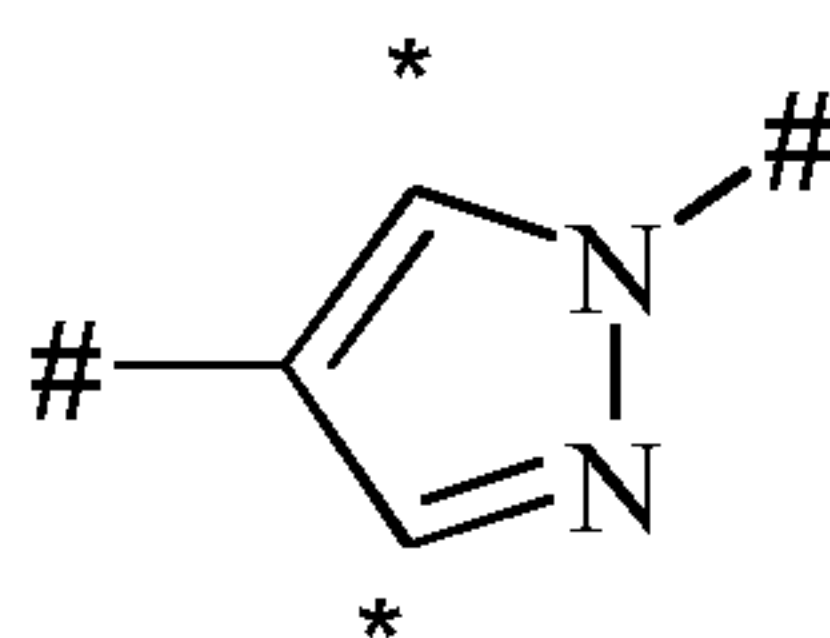
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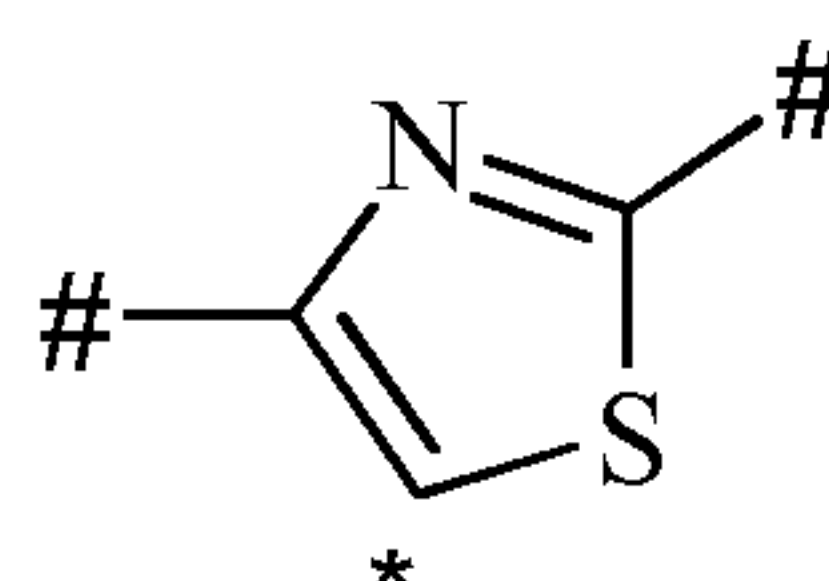
(Zc)



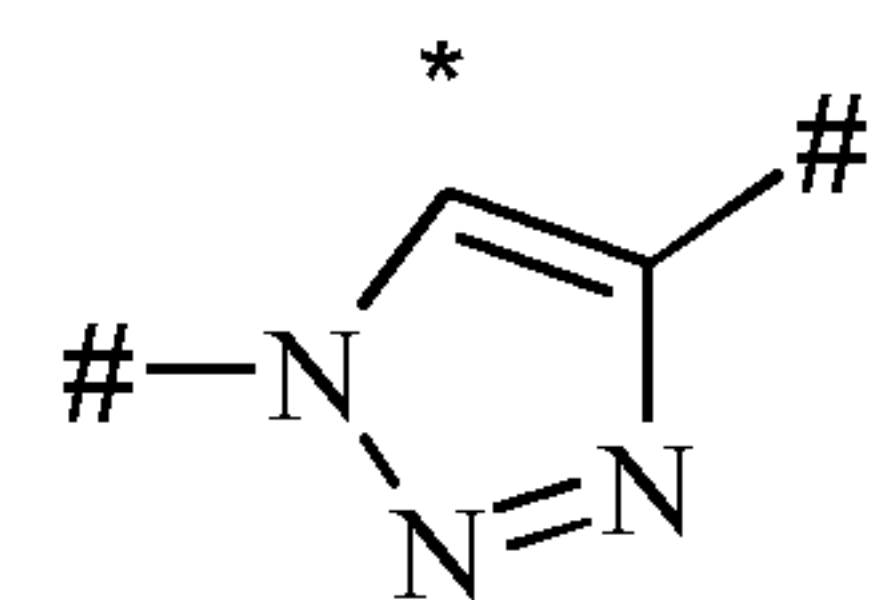
(Zd)



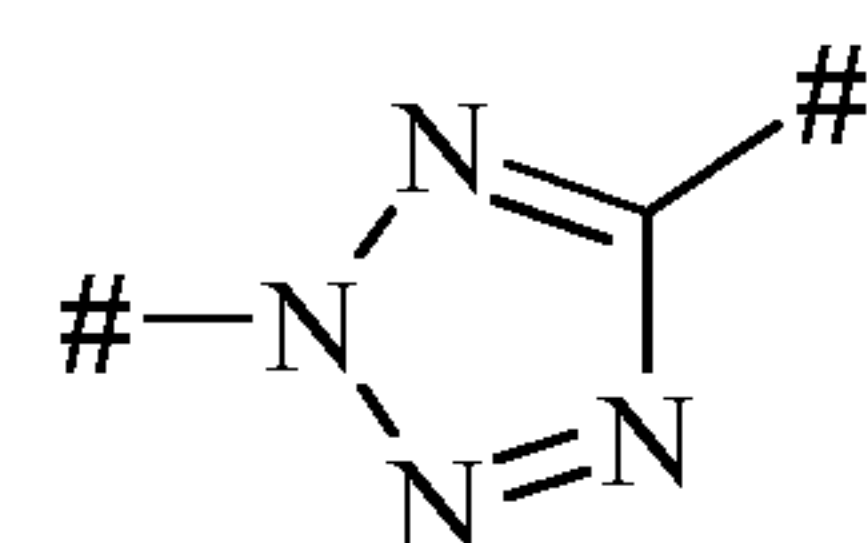
(Ze)



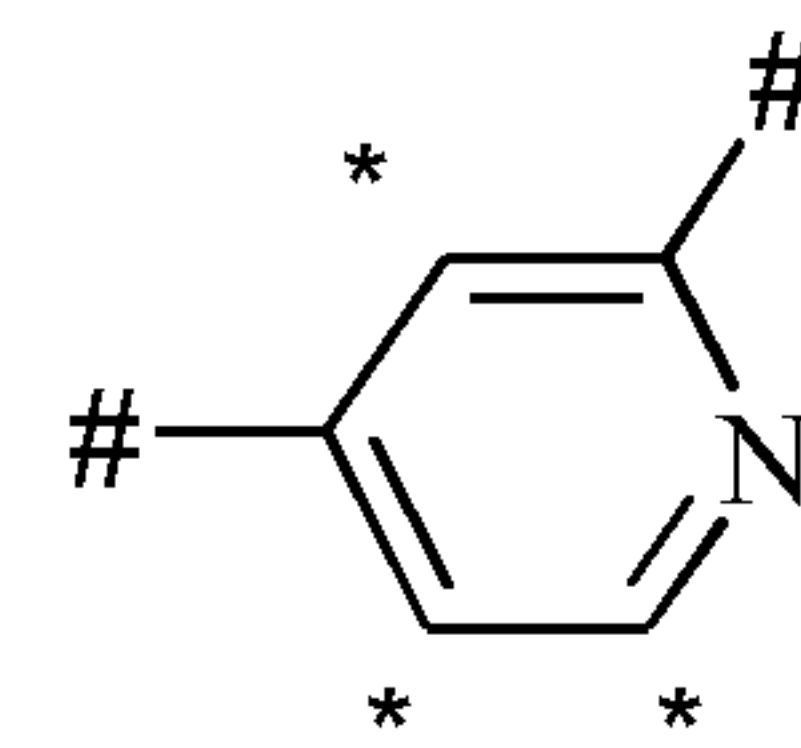
(Zf)



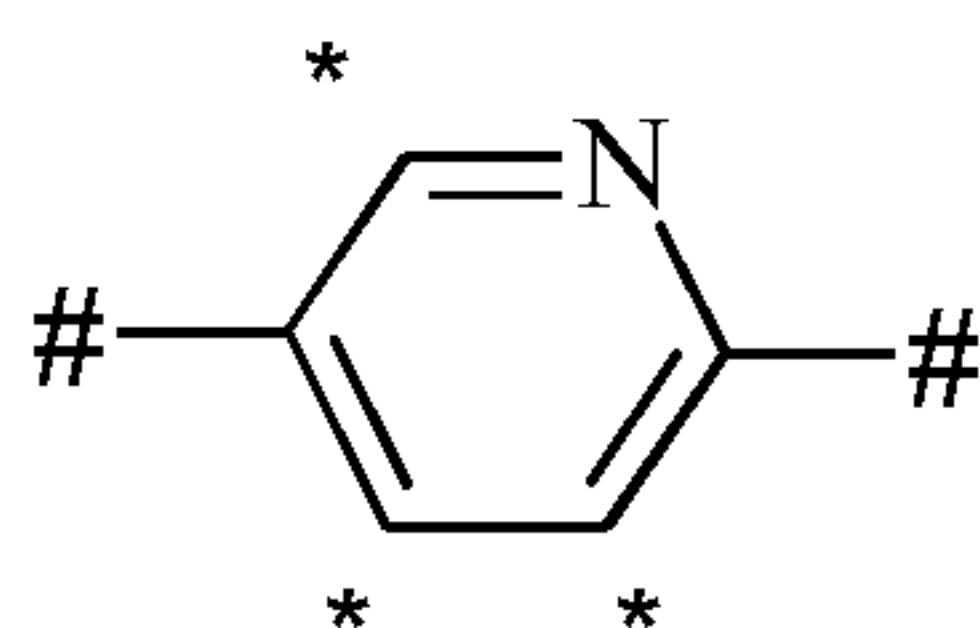
(Zg)



(Zh)



(Zj)



(Zk)

15

wherein

the symbols # represent the points of attachment of the moiety Z^1 to the remainder of the molecule; and

5 the asterisks (*) represent the site of attachment of optional substituents.

Particular values of the moiety Z^1 include the groups of formula (Za), (Zc), (Ze), (Zf), (Zg), (Zh) and (Zj) as depicted above.

The moiety Z^2 represents aryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl or heteroaryl, any of which groups may be optionally substituted by one or more
10 substituents. Typically, Z^2 represents phenyl, pyrrolidinyl, oxazolidinyl, imidazolidinyl, morpholinyl, imidazolinyl, thiazolyl, imidazolyl, tetrazolyl or pyridinyl, any of which groups may be optionally substituted by one or more substituents.

Examples of optional substituents which may be present on the moiety Z, Z^1 or Z^2 include one, two or three substituents independently selected from halogen, cyano, nitro,
15 C_{1-6} alkyl, trifluoromethyl, oxo, hydroxy, hydroxy(C_{1-6})alkyl, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-3} alkylenedioxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, di(C_{1-6})alkylamino(C_{1-6})alkyl, C_{2-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxy carbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylamino-
20 carbonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6})alkylaminosulfonyl, aminocarbonylamino and hydrazinocarbonyl.

Examples of particular substituents on the moiety Z, Z^1 or Z^2 include fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, isopropyl, trifluoromethyl, oxo, hydroxy, hydroxymethyl, methoxy, difluoromethoxy, trifluoromethoxy, methylenedioxy,
25 methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, *tert*-butylamino, dimethylamino, dimethylaminomethyl, dimethylaminoethyl, acetylamino, methylsulfonylamino, formyl, acetyl, carboxy, methoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl, dimethylaminosulfonyl, aminocarbonylamino and hydrazinocarbonyl.

30 Typical values of Z^2 include phenyl, hydroxyphenyl, oxopyrrolidinyl, dioxopyrrolidinyl, (hydroxy)(oxo)pyrrolidinyl, (amino)(oxo)pyrrolidinyl, (oxo)oxazolidinyl, oxoimidazolidinyl, morpholinyl, imidazolinyl, methylthiazolyl, formylthiazolyl, imidazolyl, tetrazolyl and pyridinyl.

Selected values of Z^2 include oxopyrrolidinyl and (oxo)oxazolidinyl. In one embodiment, Z^2 represents oxopyrrolidinyl. In another embodiment, Z^2 represents (oxo)oxazolidinyl.

Typical values of Z include hydrogen, fluoro, trifluoromethyl, methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl, cyclopropyl, cyclopentyl, cyclohexyl, oxo-cyclohexyl, phenyl, bromophenyl, cyanophenyl, nitrophenyl, methoxyphenyl, difluoromethoxyphenyl, trifluoromethoxyphenyl, methylenedioxyphenyl, methylsulfonylphenyl, dimethylaminophenyl, acetaminophenyl, methylsulfonylaminophenyl, carboxyphenyl, aminocarbonylphenyl, methylaminocarbonylphenyl, dimethylaminocarbonylphenyl, aminocarbonylaminophenyl, tetrahydrofuranyl, oxopyrrolidinyl, dimethylaminopyrrolidinyl, *tert*-butoxycarbonylpyrrolidinyl, indolinyl, tetrahydropyranyl, piperidinyl, ethylpiperidinyl, *tert*-butoxycarbonylpiperidinyl, aminocarbonylpiperidinyl, 2-oxo-3,4-dihydroquinolinyl, morpholinyl, azocanyl, oxothiazolinyl, furyl, hydroxymethylfuryl, thienyl, methylpyrazolyl, dimethylpyrazolyl, 4,5,6,7-tetrahydroindazolyl, benzoxazolyl, methylisoxazolyl, dimethylisoxazolyl, methylthiazolyl, aminothiazolyl, benzothiazolyl, methylbenzothiazolyl, aminobenzothiazolyl, imidazolyl, methylimidazolyl, methylbenzimidazolyl, dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidinyl, dimethylaminoethyltetrazolyl, pyridinyl, fluoropyridinyl, chloropyridinyl, cyanopyridinyl, methylpyridinyl, (cyano)-(methyl)pyridinyl, trifluoromethylpyridinyl, oxopyridinyl, methoxypyridinyl, methylsulfonylpyridinyl, dimethylaminomethylpyridinyl, acetaminopyridinyl, carboxypyridinyl, methoxycarbonylpyridinyl, aminocarbonylpyridinyl, (aminocarbonyl)(fluoro)pyridinyl, methylaminocarbonylpyridinyl, dimethylaminocarbonylpyridinyl, hydrazinocarbonylpyridinyl, quinolinyl, isoquinolinyl, (methyl)(oxo)phthalazinyl, pyrimidinyl, pyrazinyl, oxopyrrolidinylphenyl, dioxopyrrolidinylphenyl, (hydroxy)(oxo)pyrrolidinylphenyl, (amino)(oxo)pyrrolidinylphenyl, (oxo)oxazolidinylphenyl, oxoimidazolidinylphenyl, imidazolinylphenyl, methylthiazolylphenyl, formylthiazolylphenyl, imidazolylphenyl, tetrazolylphenyl, phenylpyrrolidinyl, hydroxyphenylpiperazinyl, (methyl)-(phenyl)pyrazolyl, oxoimidazolidinylthiazolyl, hydroxyphenyltriazolyl, morpholinyltetrazolyl, oxopyrrolidinylpyridinyl, (oxo)oxazolidinylpyridinyl, oxoimidazolidinylpyridinyl, pyridinylthiazolyl, pyridinyltetrazolyl and morpholinylcarbonylphenyl.

Particular values of Z include hydrogen, methyl, phenyl, methylsulfonylphenyl, aminocarbonylphenyl, pyridinyl, methylsulfonylpyridinyl, aminocarbonylpyridinyl, oxopyrrolidinylphenyl, (hydroxy)(oxo)pyrrolidinylphenyl and (oxo)oxazolidinylphenyl.

Suitable values of Z include hydrogen, methyl and pyridinyl.

In a first embodiment, Z represents hydrogen. In a second embodiment, Z represents methyl. In a third embodiment, Z represents phenyl. In a fourth embodiment, Z represents methylsulfonylphenyl. In one aspect of that embodiment, Z represents 3-(methylsulfonyl)phenyl. In another aspect of that embodiment, Z represents 4-(methylsulfonyl)phenyl. In a fifth embodiment, Z represents aminocarbonylphenyl. In one aspect of that embodiment, Z represents 4-(aminocarbonyl)phenyl. In a sixth embodiment, Z represents pyridinyl. In one aspect of that embodiment, Z represents pyridin-4-yl. In a seventh embodiment, Z represents aminocarbonylpyridinyl. In one aspect of that embodiment, Z represents 6-(aminocarbonyl)pyridin-3-yl. In an eighth embodiment, Z represents oxopyrrolidinylphenyl. In one aspect of that embodiment, Z represents 3-(2-oxopyrrolidin-1-yl)phenyl. In a ninth embodiment, Z represents (hydroxy)(oxo)pyrrolidinylphenyl. In one aspect of that embodiment, Z represents 3-(3-hydroxy-2-oxopyrrolidin-1-yl)phenyl. In another aspect of that embodiment, Z represents 3-(4-hydroxy-2-oxopyrrolidin-1-yl)phenyl. In a tenth embodiment, Z represents (oxo)oxazolidinylphenyl. In one aspect of that embodiment, Z represents 3-(2-oxo-oxazolidinyl-3-yl)phenyl. In an eleventh embodiment, Z represents methylsulfonylpyridinyl.

Suitably, R^1 and R^2 independently represent hydrogen, halogen, cyano, trifluoromethyl, $-OR^a$ or $-CO_2R^d$; or C_{1-6} alkyl, C_{2-6} alkynyl, aryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl, heteroaryl, (C_{3-7}) heterocycloalkyl(C_{1-6})alkyl-aryl-, heteroaryl- (C_{3-7}) heterocycloalkyl-, (C_{3-7}) cycloalkyl-heteroaryl-, (C_{3-7}) cycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{4-7}) cycloalkenyl-heteroaryl-, (C_{4-9}) bicycloalkyl-heteroaryl-, (C_{3-7}) heterocycloalkyl-heteroaryl-, (C_{3-7}) heterocycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{3-7}) heterocycloalkenyl-heteroaryl-, (C_{4-9}) heterobicycloalkyl-heteroaryl- or (C_{4-9}) spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents.

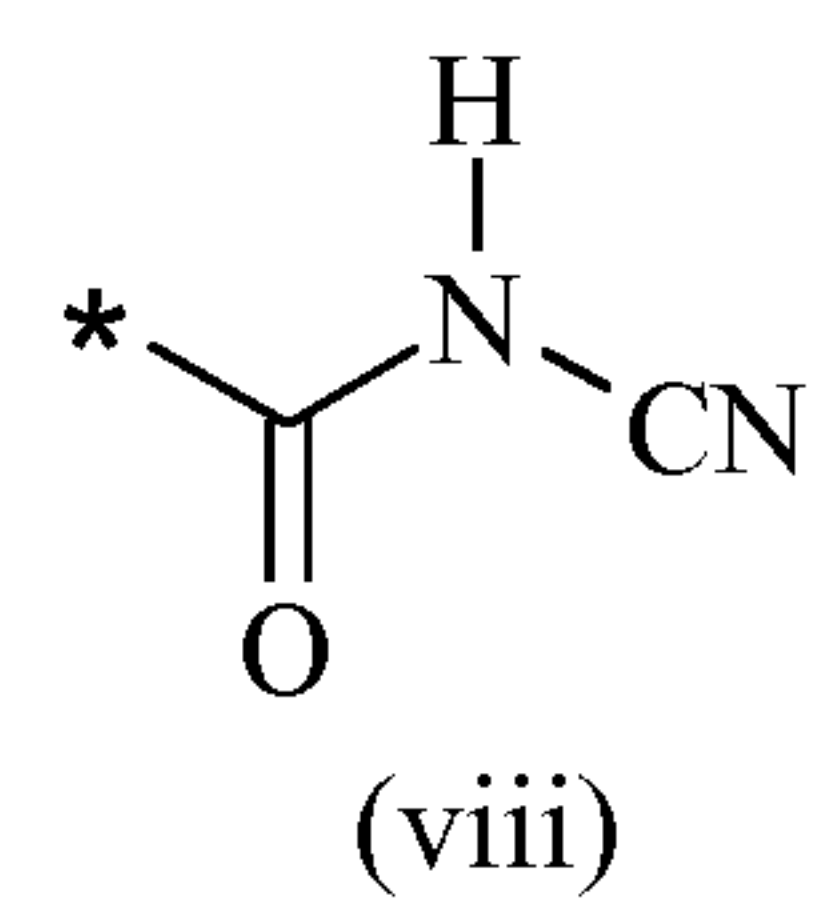
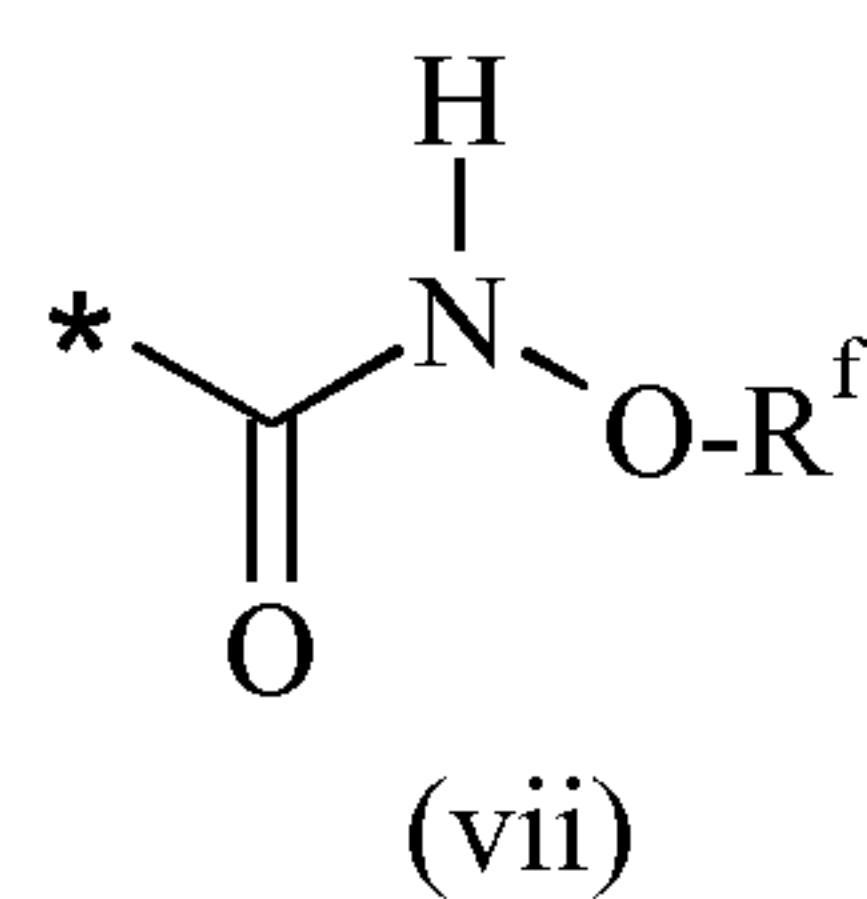
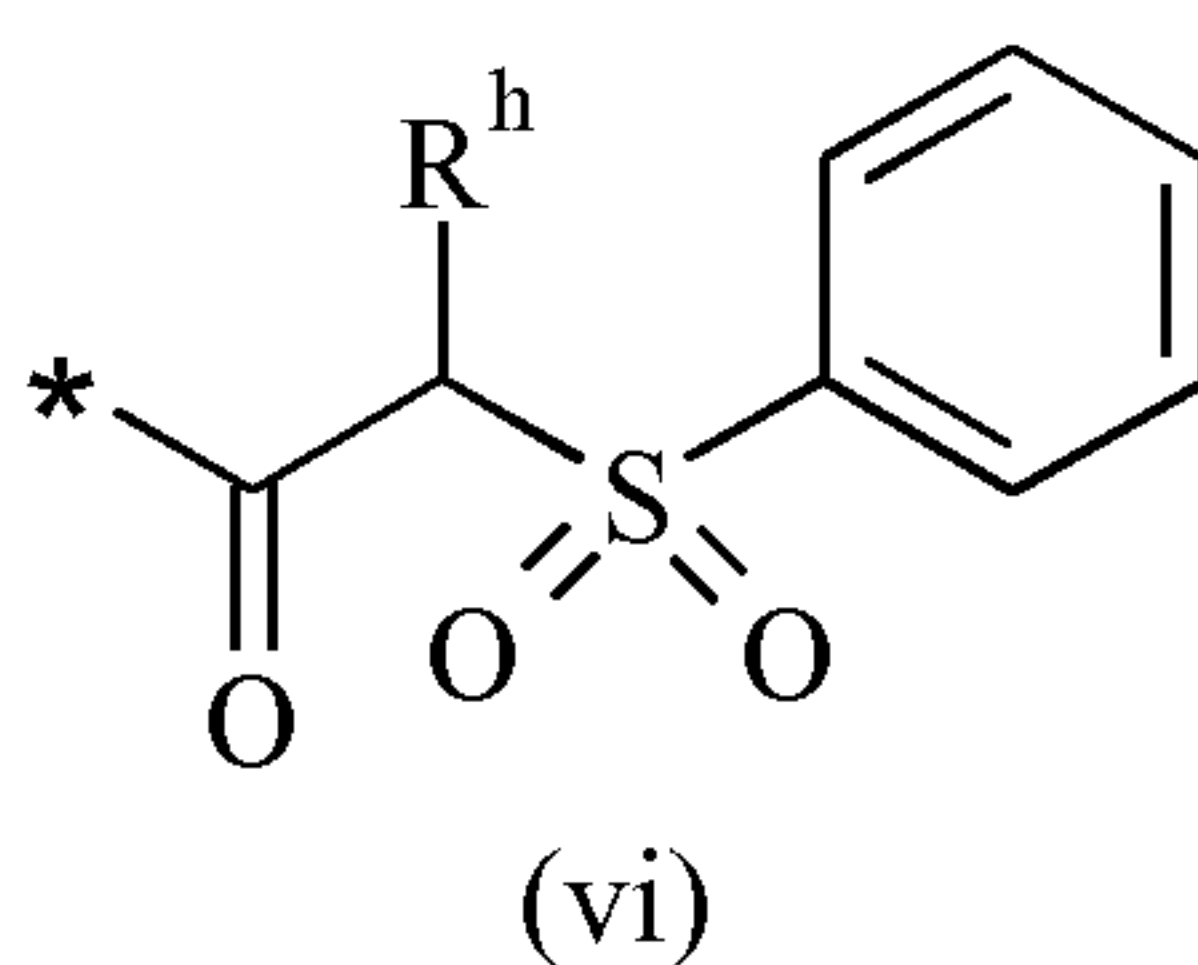
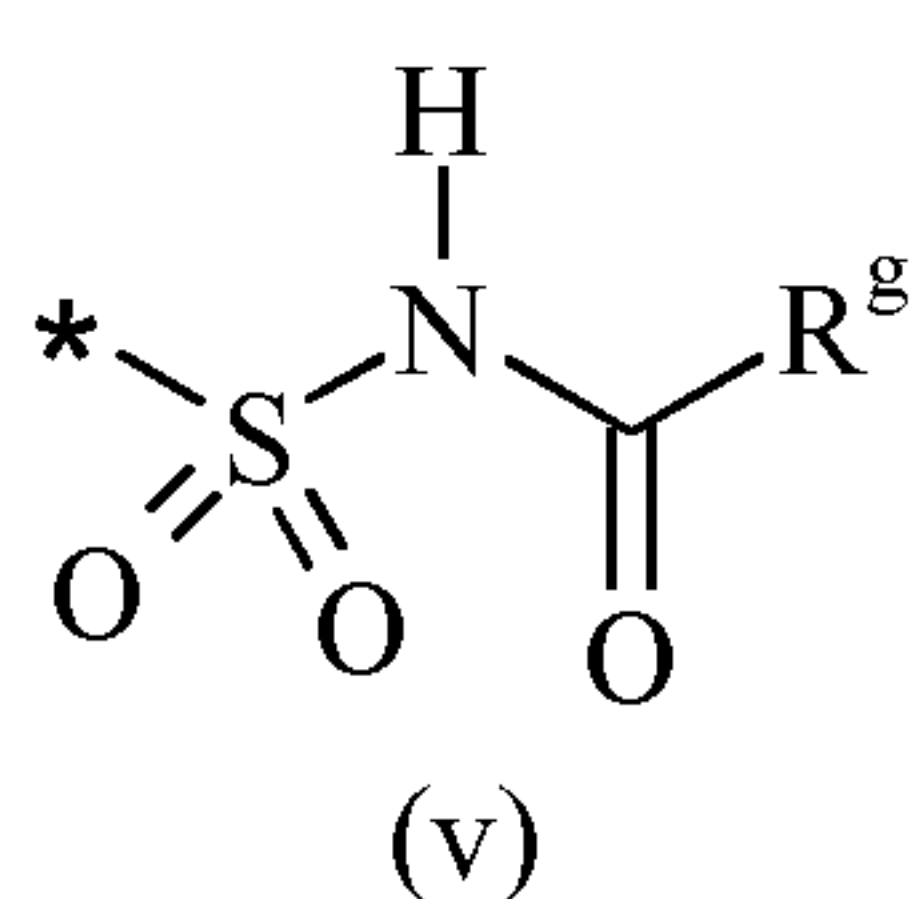
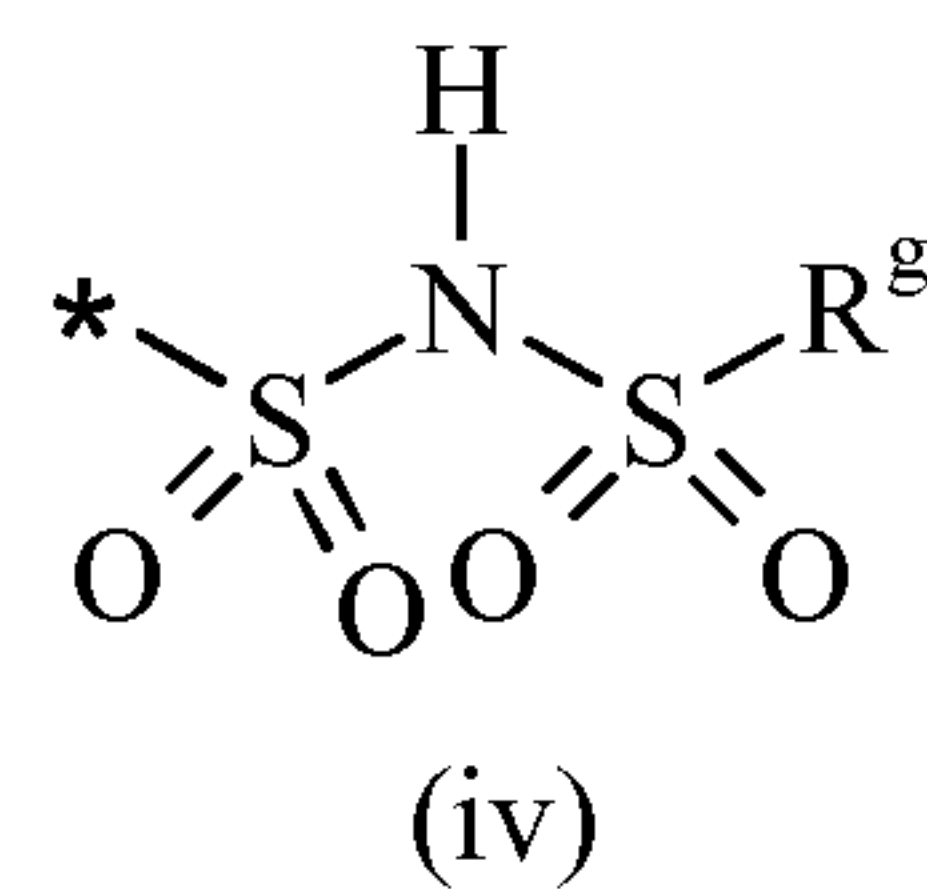
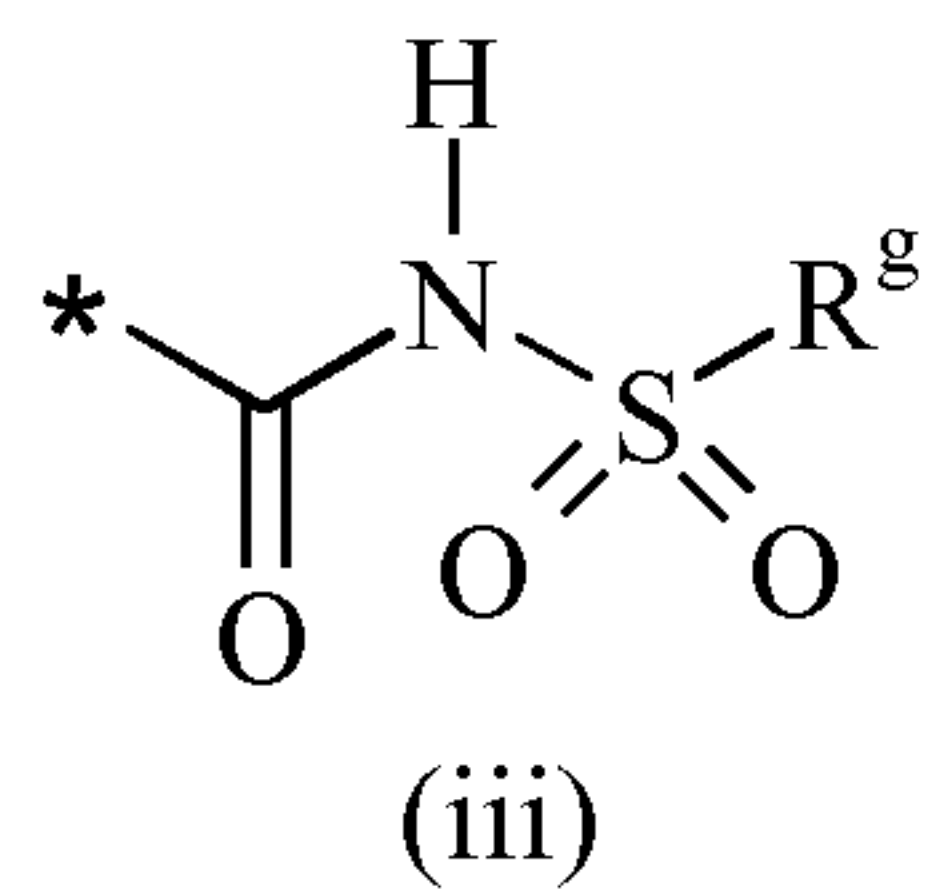
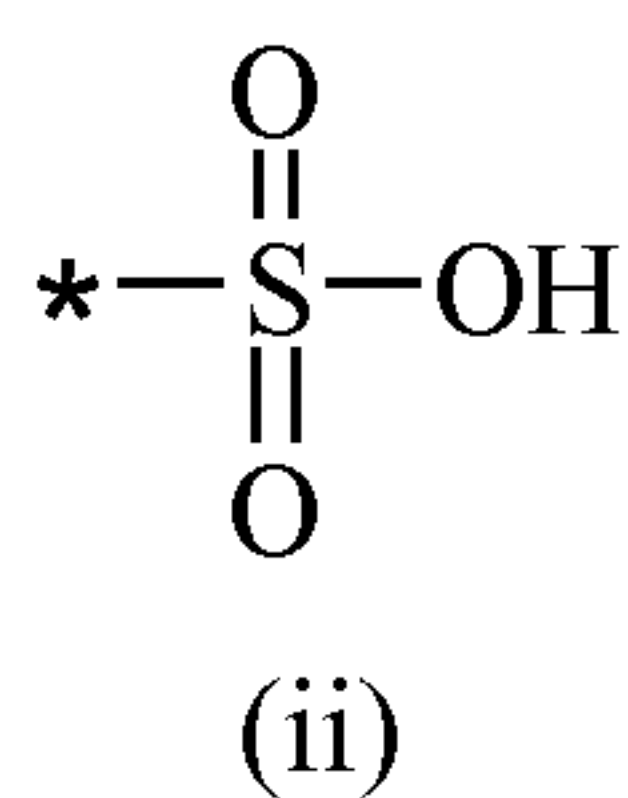
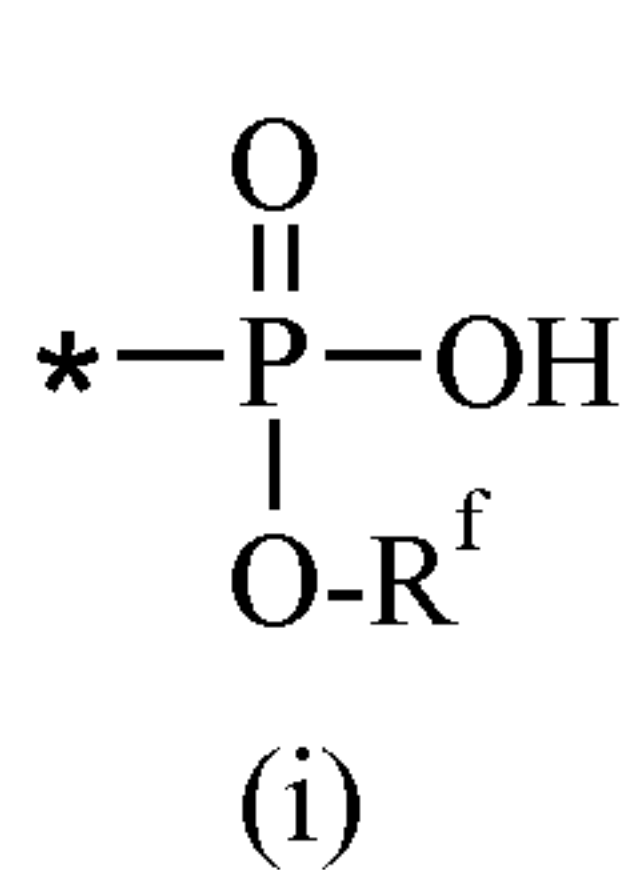
Suitably, R^3 represents hydrogen, $-SO_2R^a$, $-COR^d$, $-CO_2R^d$ or $-CONR^bR^c$; or R^3 represents C_{1-6} alkyl or heteroaryl, either of which groups may be optionally substituted by one or more substituents.

Examples of optional substituents which may be present on R^1 , R^2 or R^3 include one, two or three substituents independently selected from halogen, halo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, nitro, nitro(C_{1-6})alkyl, C_{1-6} alkyl, difluoromethyl, trifluoromethyl,

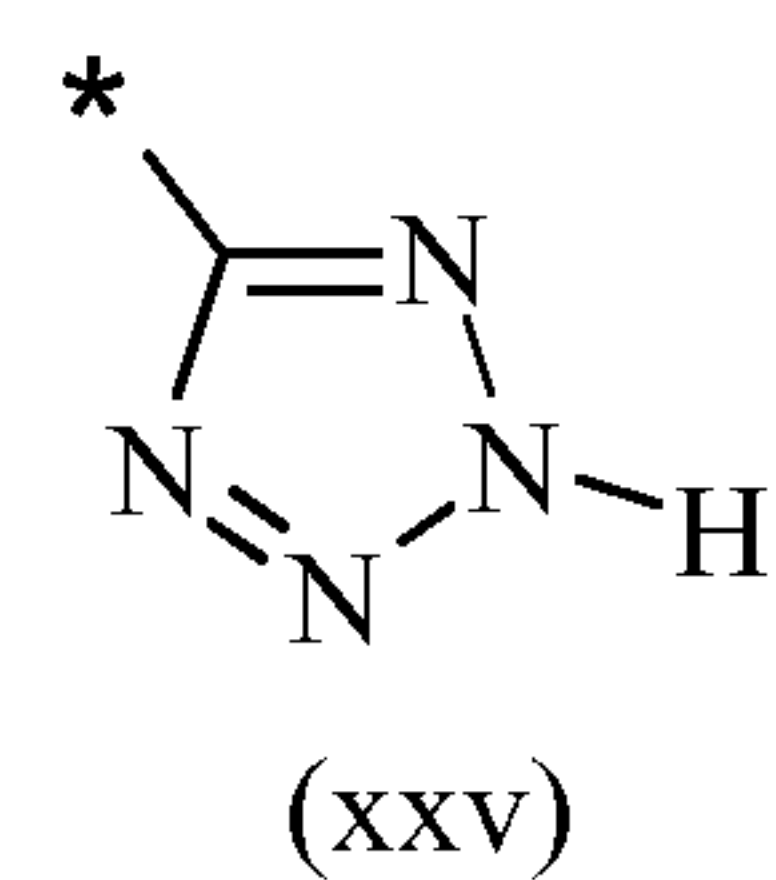
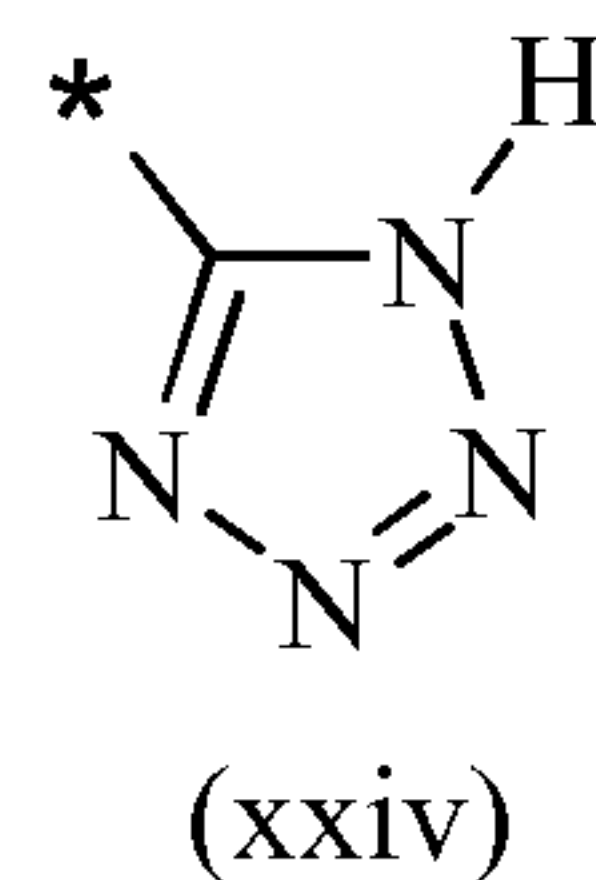
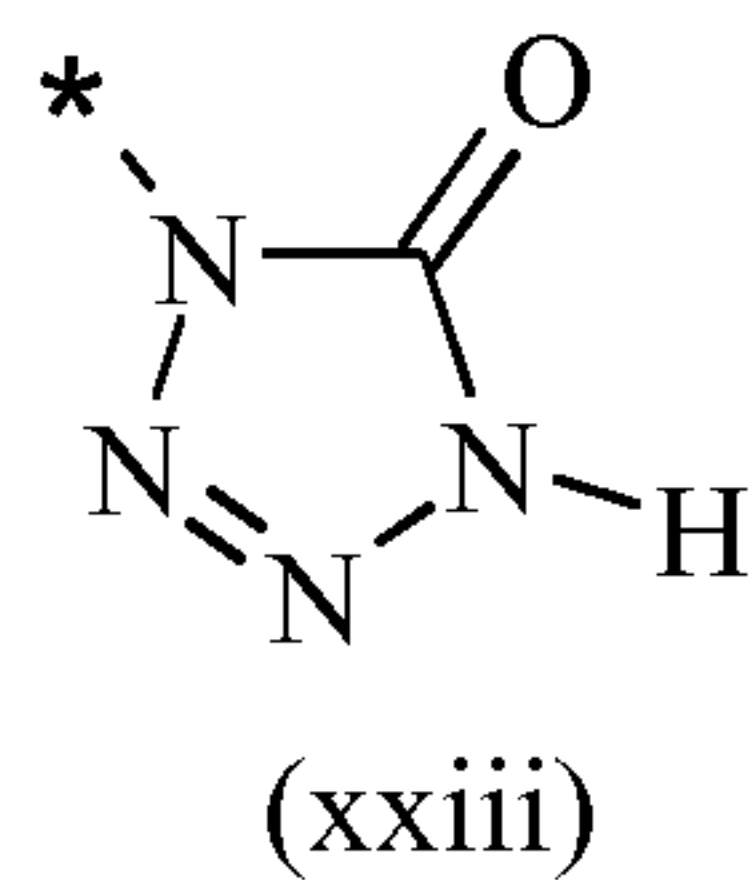
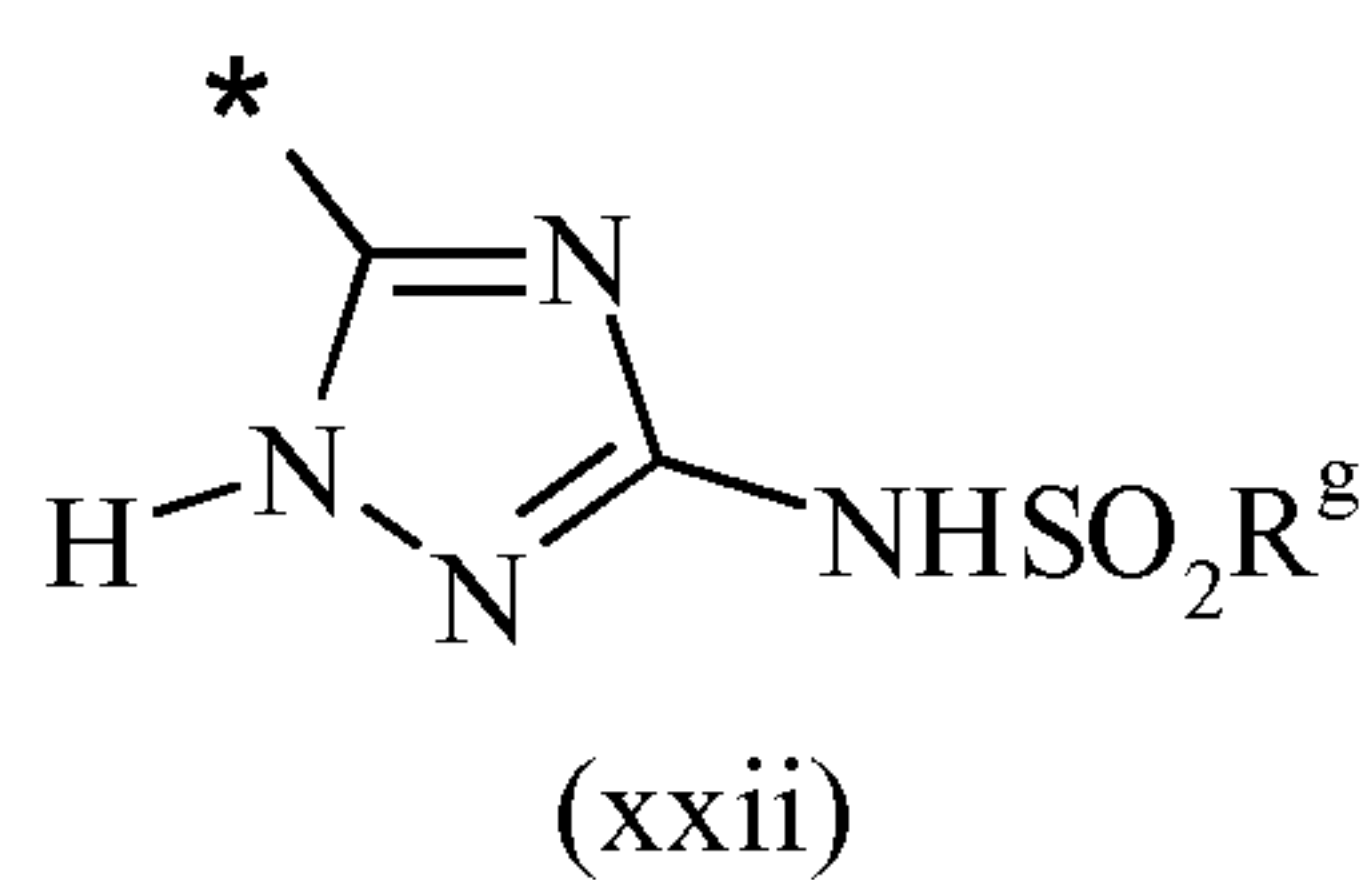
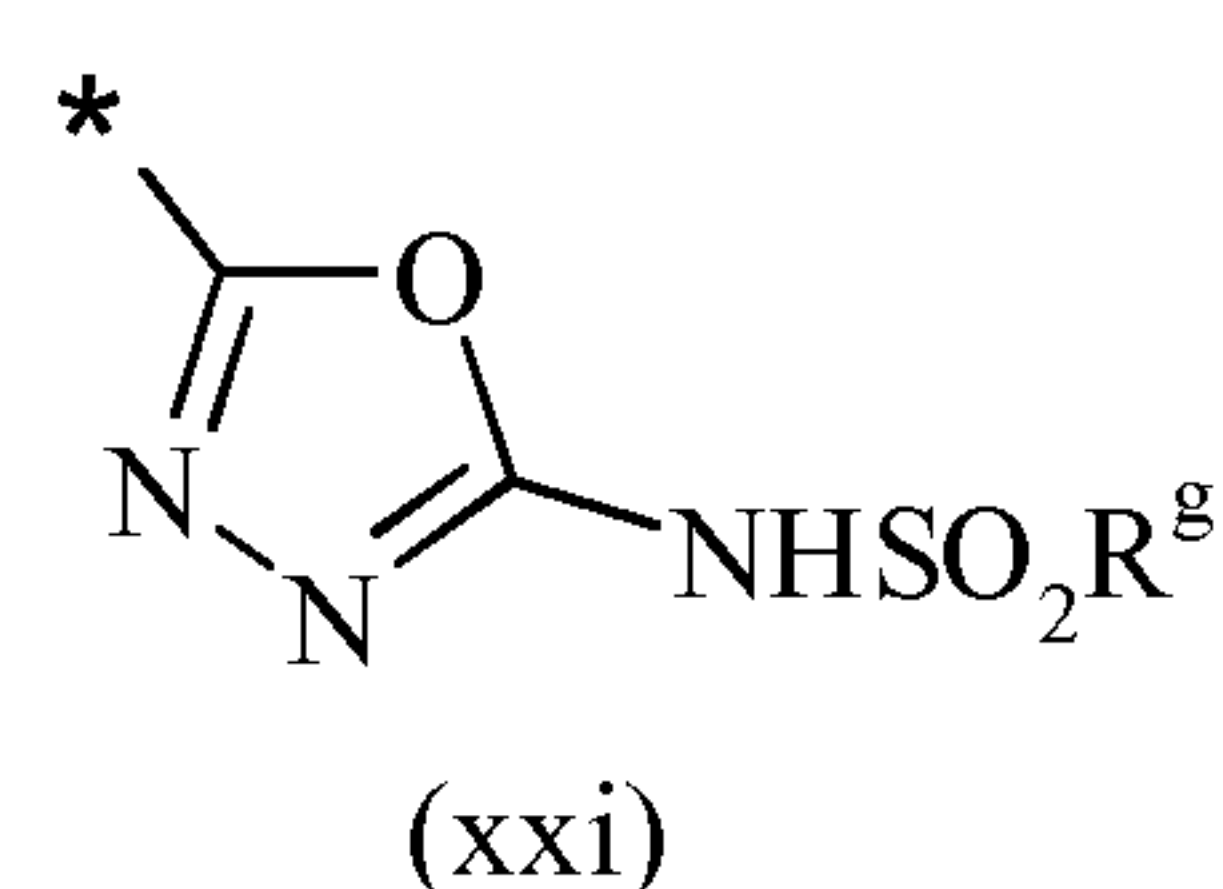
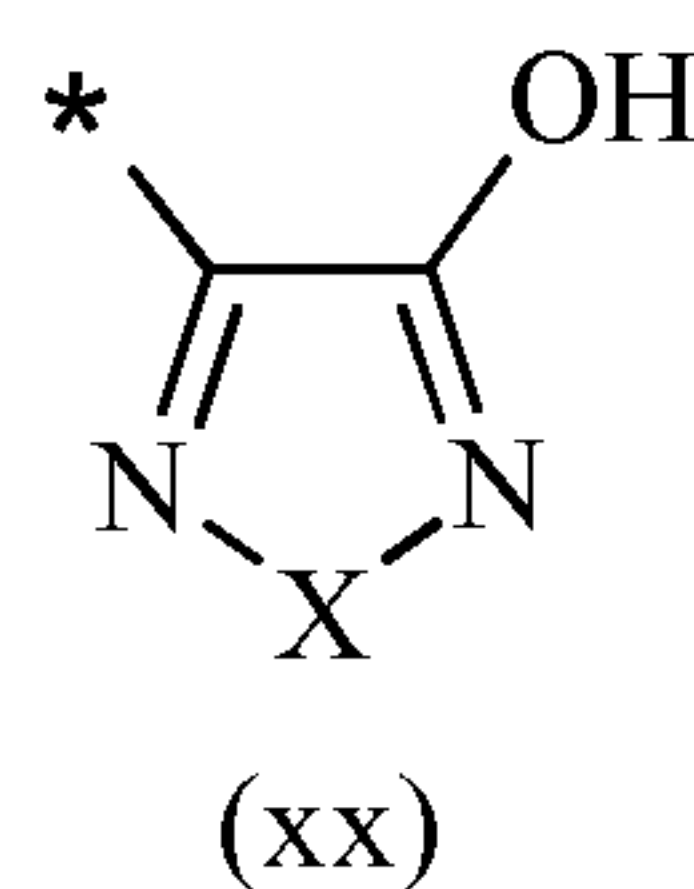
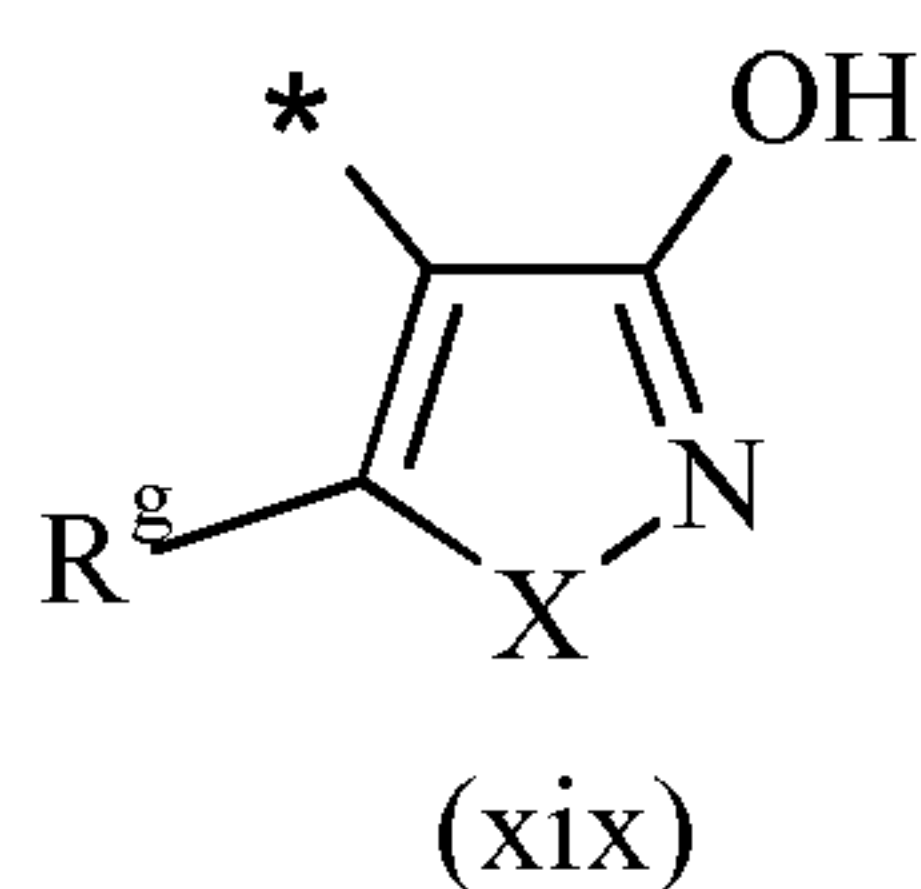
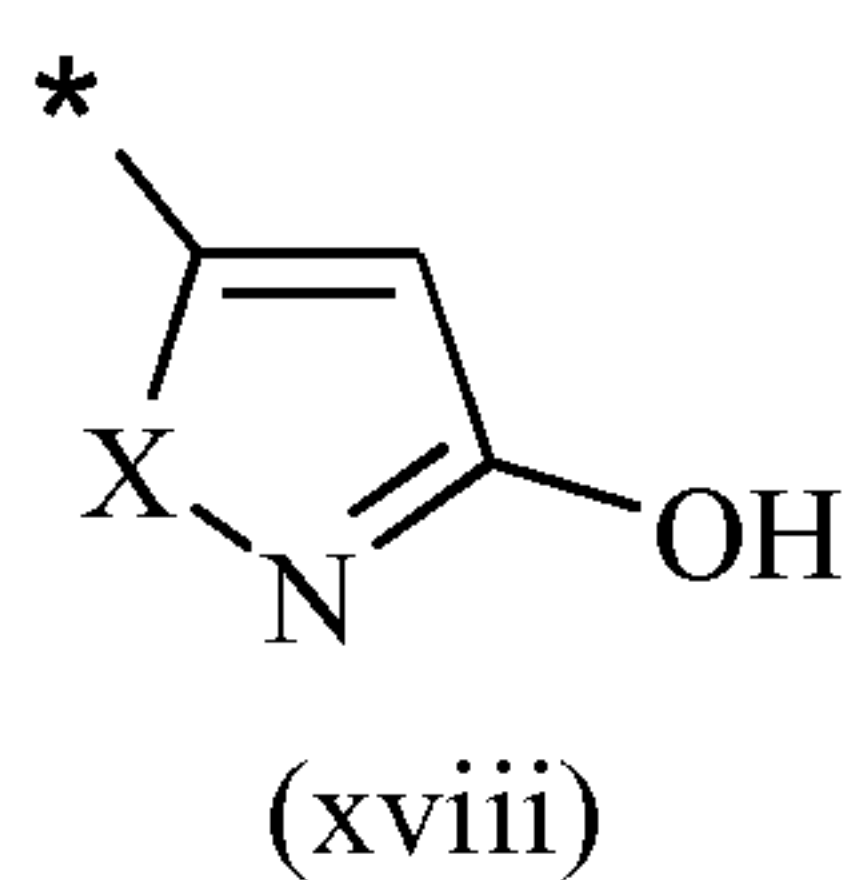
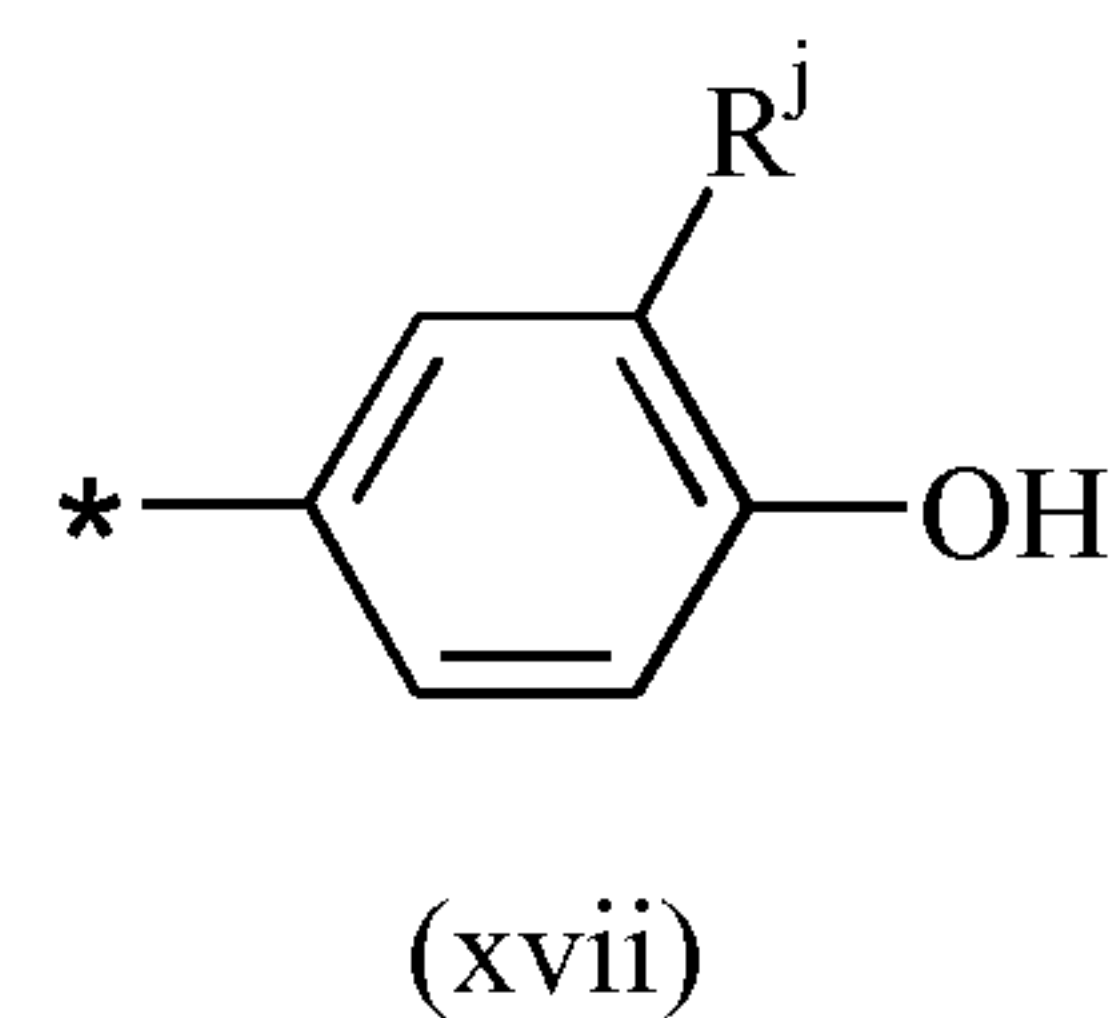
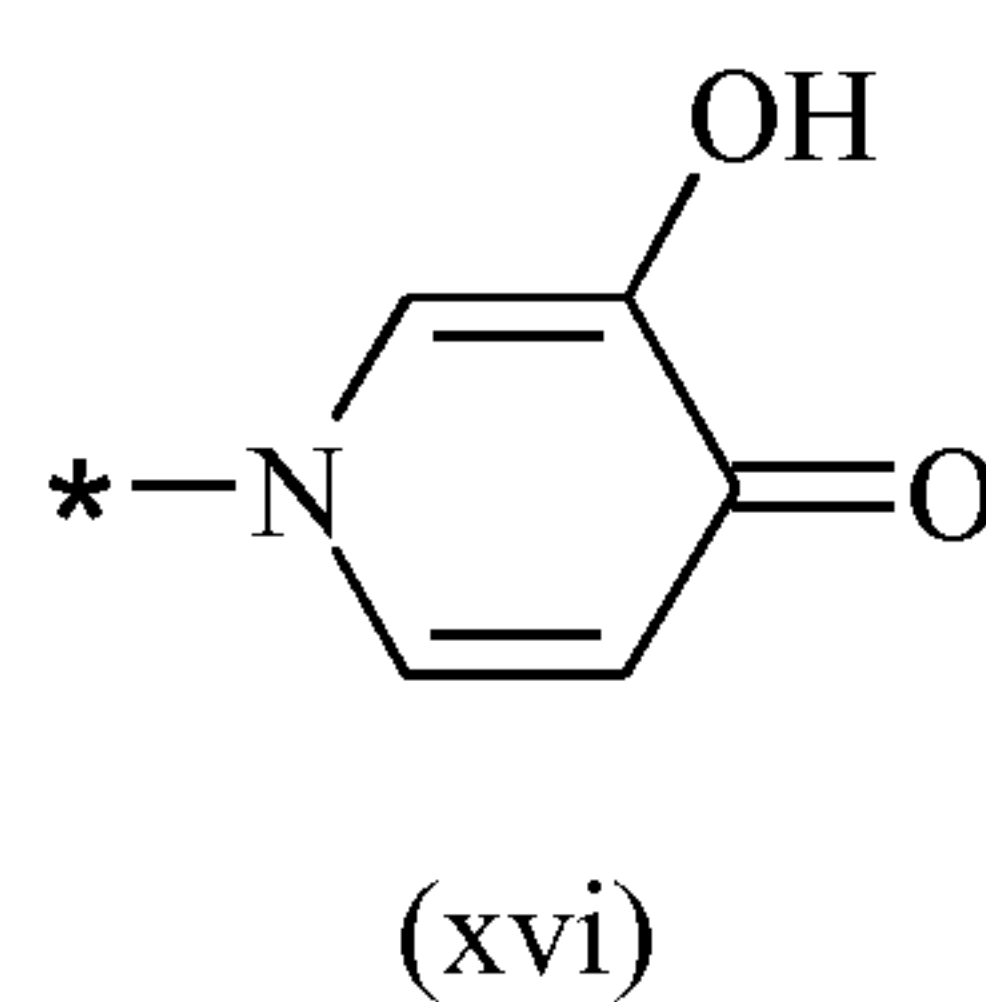
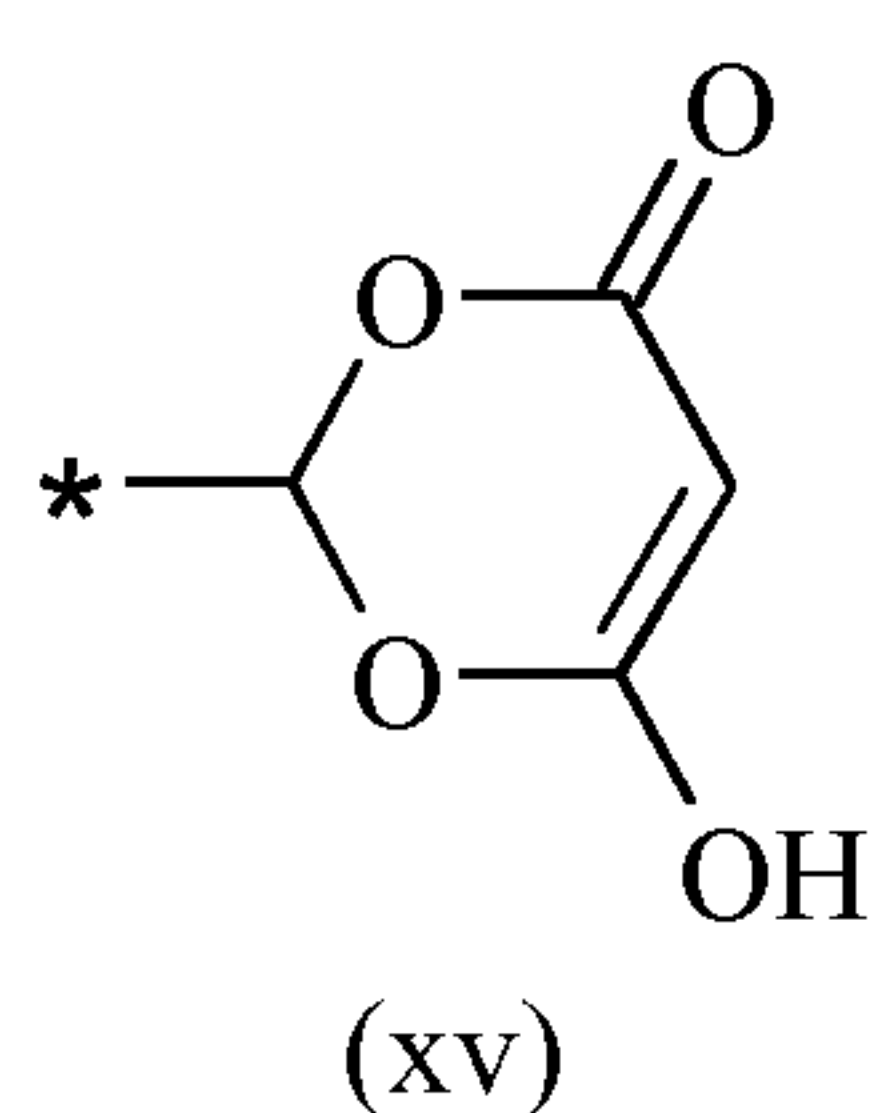
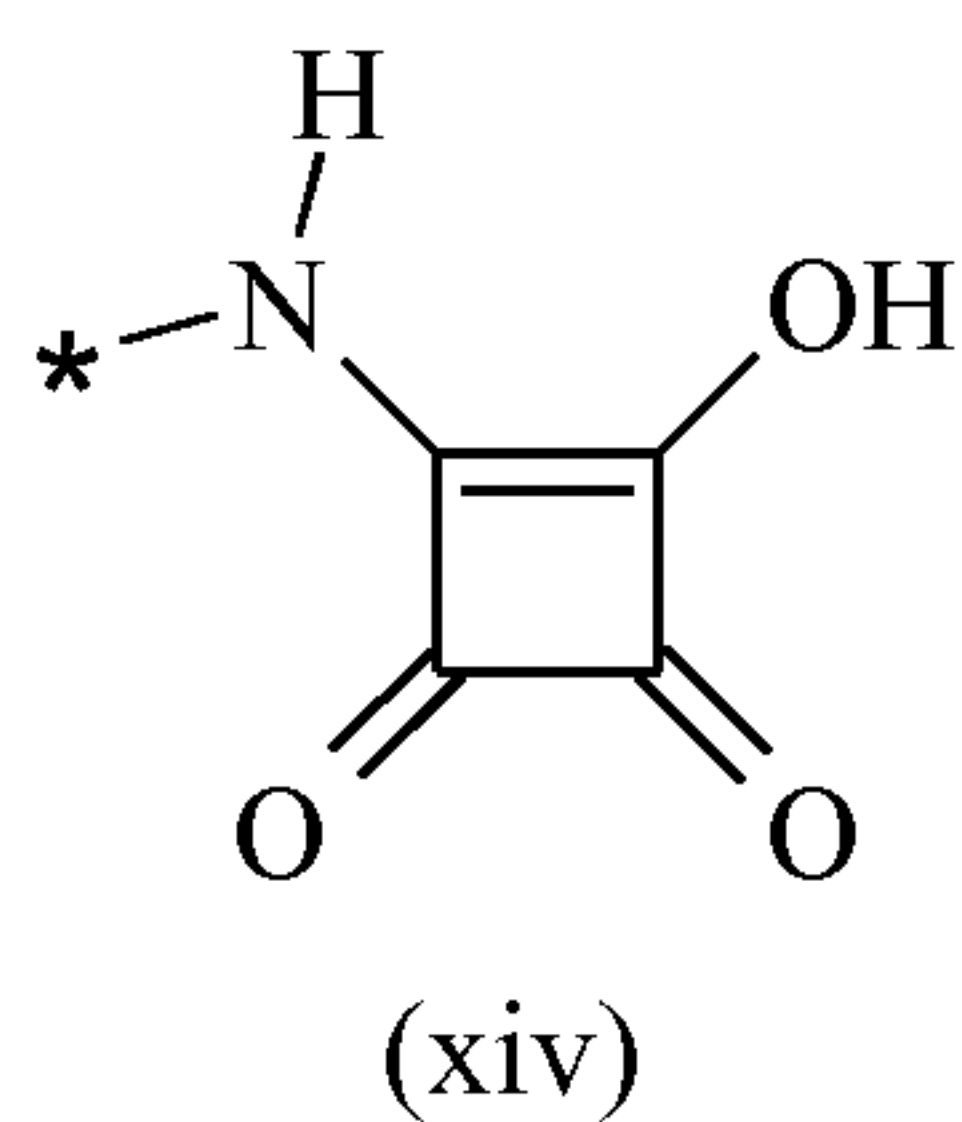
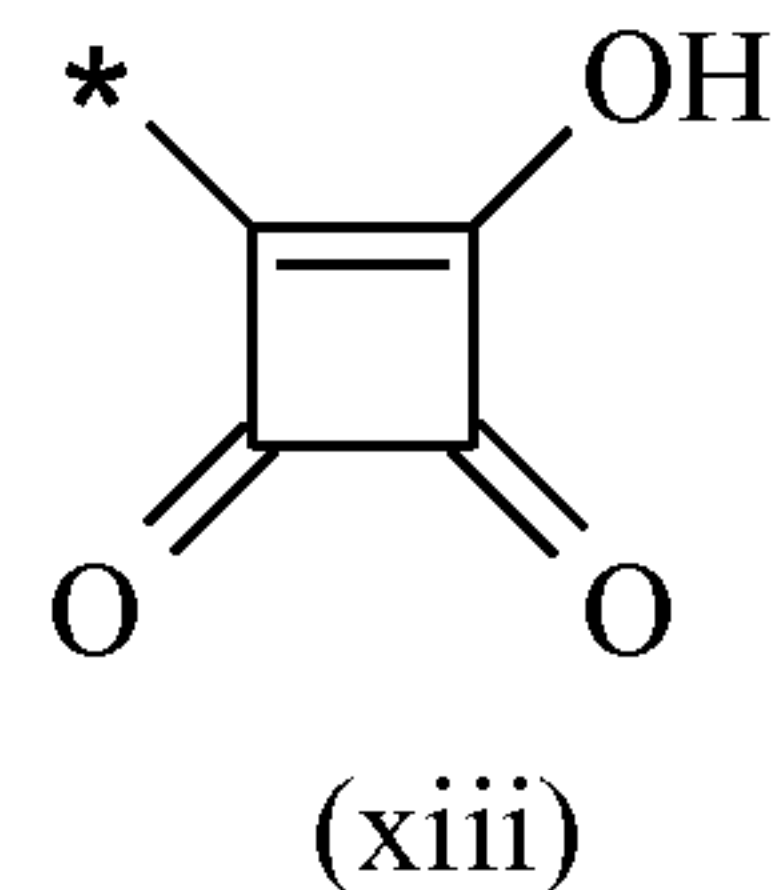
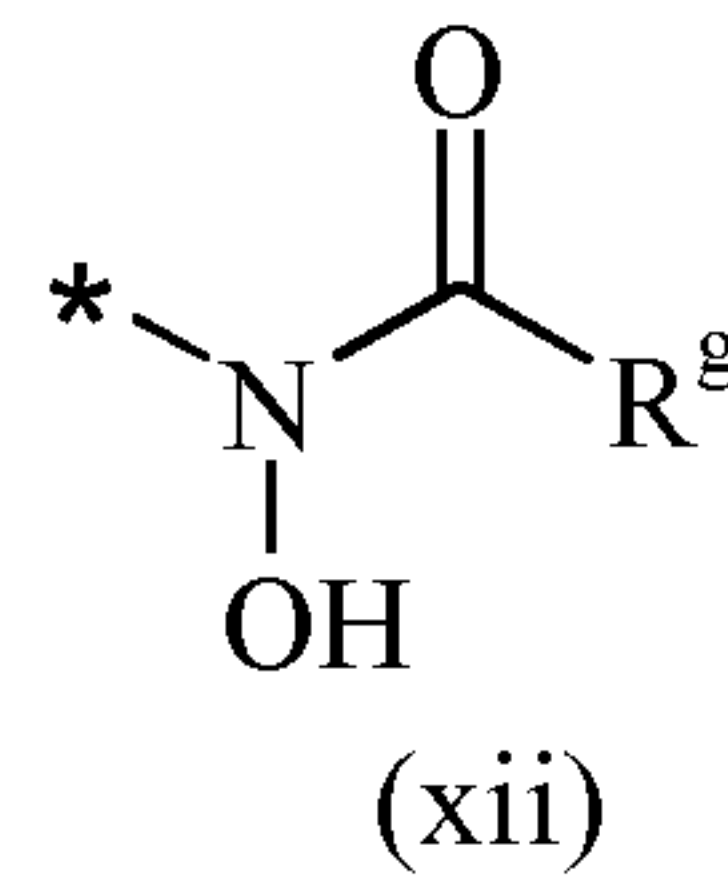
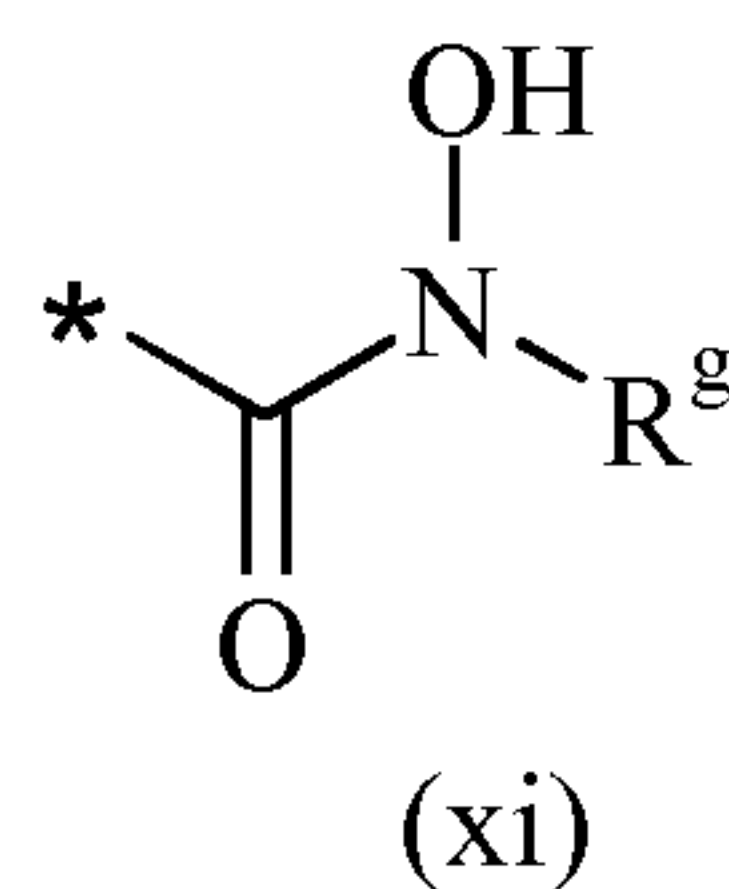
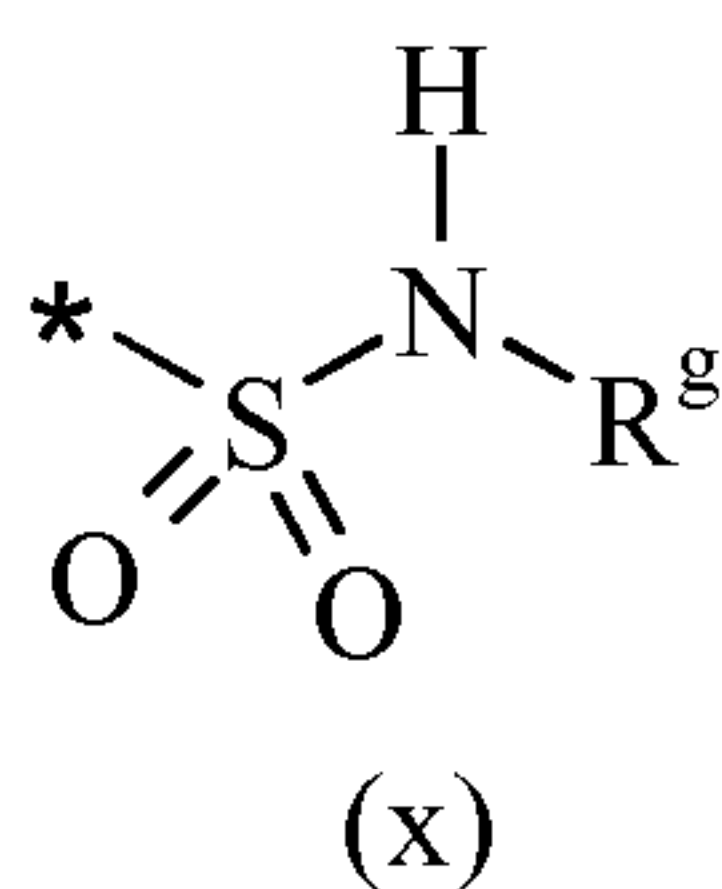
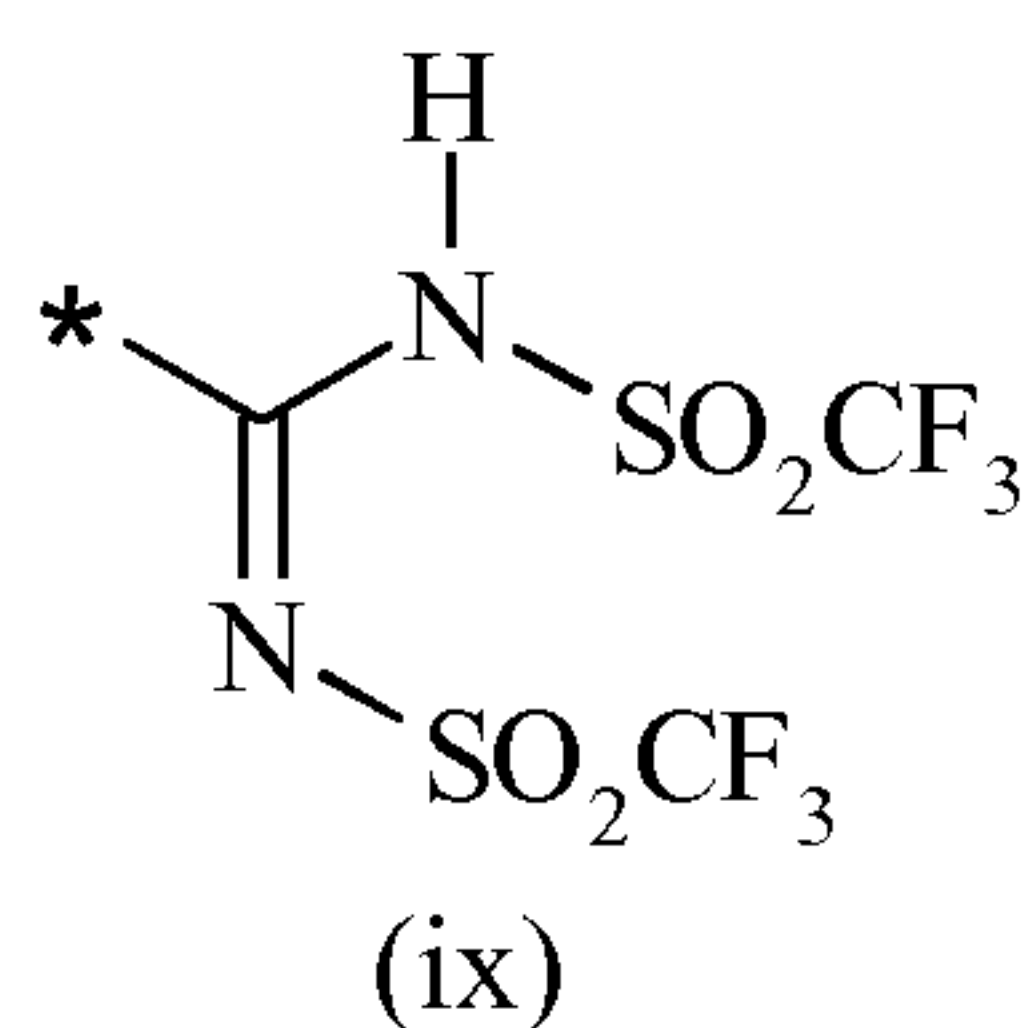
difluoroethyl, trifluoroethyl, C₂₋₆ alkenyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy,
 difluoromethoxy, trifluoromethoxy, trifluoroethoxy, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₃
 alkylendioxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkyl-
 sulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, amino, amino(C₁₋₆)alkyl, C₁₋₆ alkylamino,
 5 di(C₁₋₆)alkylamino, hydroxy(C₁₋₆)alkylamino, C₁₋₆ alkoxyamino, (C₁₋₆)alkoxy(C₁₋₆)alkyl-
 amino, [(C₁₋₆)alkoxy](hydroxy)(C₁₋₆)alkylamino, [(C₁₋₆)alkylthio](hydroxy)(C₁₋₆)alkyl-
 amino, N-[(C₁₋₆)alkyl]-N-[hydroxy(C₁₋₆)alkyl]amino, di(C₁₋₆)alkylamino(C₁₋₆)alkylamino,
 N-[di(C₁₋₆)alkylamino(C₁₋₆)alkyl]-N-[hydroxy(C₁₋₆)alkyl]amino, hydroxy(C₁₋₆)alkyl-
 (C₃₋₇)cycloalkylamino, (hydroxy)[(C₃₋₇)cycloalkyl(C₁₋₆)alkyl]amino,
 10 (C₃₋₇)heterocycloalkyl(C₁₋₆)alkylamino, oxo(C₃₋₇)heterocycloalkyl(C₁₋₆)alkylamino,
 (C₁₋₆)alkylheteroaryl amino, heteroaryl(C₁₋₆)alkylamino, (C₁₋₆)alkylheteroaryl(C₁₋₆)alkyl-
 amino, C₂₋₆ alkylcarbonylamino, N-[(C₁₋₆)alkyl]-N-[(C₂₋₆)alkylcarbonyl]amino, (C₂₋₆)alkyl-
 carbonylamino(C₁₋₆)alkyl, C₃₋₆ alkenylcarbonylamino, bis[(C₃₋₆)alkenylcarbonyl]amino, N-
 [(C₁₋₆)alkyl]-N-[(C₃₋₇)cycloalkylcarbonyl]amino, C₂₋₆ alkoxycarbonylamino, C₂₋₆
 15 alkoxycarbonyl(C₁₋₆)alkylamino, C₁₋₆ alkylaminocarbonylamino, C₁₋₆ alkylsulphonyl-
 amino, N-[(C₁₋₆)alkyl]-N-[(C₁₋₆)alkylsulphonyl]amino, bis[(C₁₋₆)alkylsulphonyl]amino, N-
 [(C₁₋₆)alkyl]-N-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino, carboxy-
 (C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, formyl, C₂₋₆ alkylcarbonyl, (C₃₋₇)cycloalkylcarbonyl,
 phenylcarbonyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆
 20 alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆
 alkoxycarbonylmethylidenyl, a carboxylic acid isostere or prodrug moiety Ω ,
 -(C₁₋₆)alkyl- Ω , aminocarbonyl, C₁₋₆ alkylaminocarbonyl, hydroxy(C₁₋₆)alkylamino-
 carbonyl, di(C₁₋₆)alkylaminocarbonyl, aminocarbonyl(C₁₋₆)alkyl, aminosulphonyl,
 di(C₁₋₆)alkylaminosulphonyl, (C₁₋₆)alkylsulphoximinyl and [(C₁₋₆)alkyl][N-(C₁₋₆)alkyl]-
 25 sulphoximinyl.

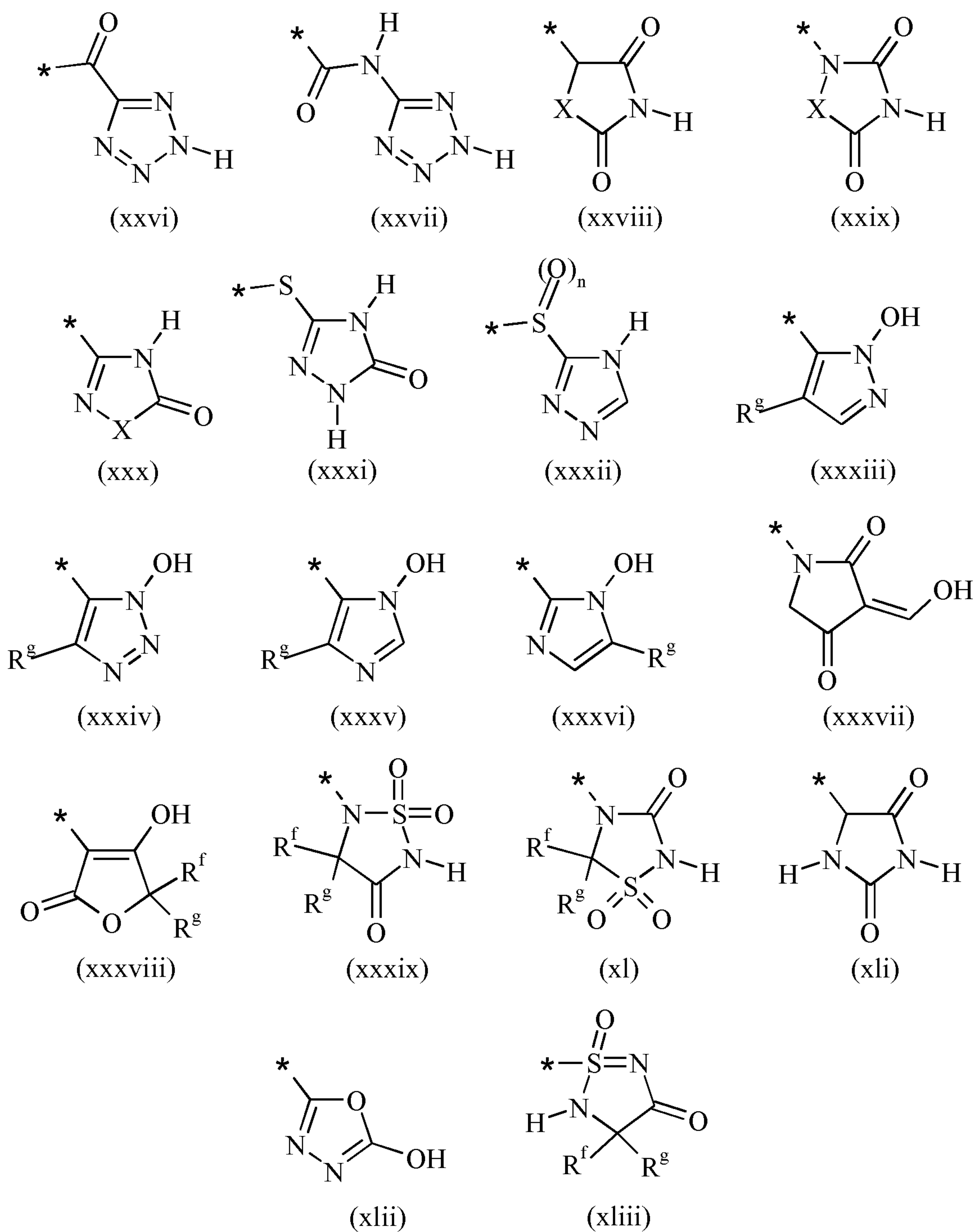
By the expression "carboxylic acid isostere or prodrug moiety" is meant any
 functional group, structurally distinct from a carboxylic acid moiety, that will be
 recognised by a biological system as being similar to, and thus capable of mimicking, a
 carboxylic acid moiety, or will be readily convertible by a biological system *in vivo* into a
 30 carboxylic acid moiety. A synopsis of some common carboxylic acid isosteres is
 presented by N.A. Meanwell in *J. Med. Chem.*, 2011, **54**, 2529-2591 (cf. in particular
 Figures 25 and 26). An alternative carboxylic acid isostere is described by N Pemberton *et al.*
 in *ACS Med. Chem. Lett.*, 2012, **3**, 574-578. Typical examples of suitable carboxylic

acid isostere or prodrug moieties represented by Ω include the functional groups of formula (i) to (xliii):



5





5

wherein

the asterisk (*) represents the site of attachment to the remainder of the molecule;

n is zero, 1 or 2;

10

X represents oxygen or sulphur;

 R^f represents hydrogen, C_{1-6} alkyl or $-CH_2CH(OH)CH_2OH$; R^g represents C_{1-6} alkyl, trifluoromethyl, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$ or $-CF_2CF_3$;

R^h represents hydrogen, cyano or $-CO_2R^d$, in which R^d is as defined above; and R^j represents hydrogen or halogen.

In one embodiment, n is zero. In another embodiment, n is 1. In a further embodiment, n is 2.

5 In one embodiment, X represents oxygen. In another embodiment, X represents sulphur.

In one embodiment, R^f represents hydrogen. In another embodiment, R^f represents C_{1-6} alkyl, especially methyl. In a further embodiment, R^f is $-CH_2CH(OH)CH_2OH$.

10 In one embodiment, R^g represents C_{1-6} alkyl, especially methyl. In another embodiment, R^g represents trifluoromethyl, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$ or $-CF_2CF_3$. In a first aspect of that embodiment, R^g represents trifluoromethyl. In a second aspect of that embodiment, R^g represents $-CH_2CH_2F$. In a third aspect of that embodiment, R^g represents $-CH_2CHF_2$. In a fourth aspect of that embodiment, R^g represents $-CH_2CF_3$. In a fifth aspect of that embodiment, R^g represents $-CF_2CF_3$.

15 In one embodiment, R^h is hydrogen. In another embodiment, R^h represents cyano. In a further embodiment, R^h represents $-CO_2R^d$, especially methoxycarbonyl.

In one embodiment, R^j represents hydrogen. In another embodiment, R^j represents halogen, especially chloro.

20 In a selected embodiment, Ω represents tetrazolyl, especially a C -linked tetrazolyl moiety of formula (xxiv) or (xxv) as depicted above, in particular a group of formula (xxiv) as depicted above.

In another embodiment, Ω represents C_{1-6} alkylsulphonylaminocarbonyl, i.e. a moiety of formula (iii) as depicted above wherein R^g represents C_{1-6} alkyl.

25 In another embodiment, Ω represents C_{1-6} alkylaminosulphonyl, i.e. a moiety of formula (x) as depicted above wherein R^g represents C_{1-6} alkyl.

In a further embodiment, Ω represents (C_{1-6}) alkylcarbonylaminosulphonyl, i.e. a moiety of formula (v) as depicted above wherein R^g represents C_{1-6} alkyl.

Typical examples of optional substituents which may be present on R^1 , R^2 or R^3 include $di(C_{1-6})$ alkylamino.

30 Examples of particular substituents on R^1 , R^2 or R^3 include fluoro, chloro, bromo, fluoromethyl, fluoroisopropyl, cyano, cyanoethyl, nitro, nitromethyl, methyl, ethyl, isopropyl, isobutyl, *tert*-butyl, difluoromethyl, trifluoromethyl, difluoroethyl, trifluoroethyl, ethenyl, hydroxy, hydroxymethyl, hydroxyisopropyl, methoxy, isopropoxy,

difluoromethoxy, trifluoromethoxy, trifluoroethoxy, carboxycyclobutyloxy, methylene-
 dioxy, ethylenedioxy, methoxymethyl, methoxyethyl, methylthio, methylsulphinyl,
 methylsulphonyl, methylsulphonyl-ethyl, oxo, amino, aminomethyl, aminoisopropyl,
 methylamino, ethylamino, dimethylamino, hydroxyethylamino, hydroxypropylamino,
 5 (hydroxy)(methyl)propylamino, methoxyamino, methoxyethylamino, (hydroxy)-
 (methoxy)(methyl)propylamino, (hydroxy)(methylthio)butylamino, *N*-(hydroxyethyl)-*N*-
 (methyl)amino, dimethylaminoethylamino, (dimethylamino)(methyl)propylamino, *N*-
 (dimethylaminoethyl)-*N*-(hydroxyethyl)amino, hydroxymethylcyclopentylamino,
 hydroxycyclobutylmethylamino, (cyclopropyl)(hydroxy)propylamino, morpholinylethyl-
 10 amino, oxopyrrolidinylmethylamino, ethyloxadiazolylamino, methylthiadiazolylamino,
 thiazolylmethylamino, thiazolyethylamino, pyrimidinylmethylamino, methylpyrazolyl-
 methylamino, acetylamino, *N*-acetyl-*N*-methylamino, *N*-isopropylcarbonyl-*N*-methyl-
 amino, acetylaminomethyl, ethenylcarbonylamino, bis(ethenylcarbonyl)amino, *N*-
 cyclopropylcarbonyl-*N*-methylamino, methoxycarbonylamino, ethoxycarbonylamino, *tert*-
 15 butoxycarbonylamino, methoxycarbonyl-ethylamino, ethylaminocarbonylamino,
 butylaminocarbonylamino, methylsulphonylamino, *N*-methyl-*N*-(methylsulphonyl)amino,
 bis(methylsulphonyl)amino, *N*-(carboxymethyl)-*N*-methylamino, *N*-(carboxyethyl)-*N*-
 methylamino, carboxycyclopentylamino, carboxycyclopropylmethylamino, formyl, acetyl,
 isopropylcarbonyl, cyclobutylcarbonyl, phenylcarbonyl, acetoxymethyl, carboxy,
 20 carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *n*-butoxycarbonyl, *tert*-
 butoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonyl-ethyl,
 morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, methylsulphonylamino-
 carbonyl, acetylaminosulphonyl, methoxyaminocarbonyl, tetrazolyl, tetrazolylmethyl,
 hydroxyoxadiazolyl, aminocarbonyl, methylaminocarbonyl, hydroxyethylaminocarbonyl,
 25 dimethylaminocarbonyl, aminocarbonylmethyl, aminosulphonyl, methylaminosulphonyl,
 dimethylaminosulphonyl, methylsulphoximinyl and (methyl)(*N*-methyl)sulphoximinyl.

Typical examples of particular substituents on R¹, R² or R³ include dimethylamino.

Typically, R¹ represents hydrogen, halogen, cyano, -OR^a or -CO₂R^d; or C₁₋₆ alkyl,
 C₂₋₆ alkynyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl,
 30 (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-,
 (C₃₋₇)cycloalkyl-heteroaryl-, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-
 heteroaryl-, (C₄₋₉)bicycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-,
 (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-,

(C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents.

Suitably, R¹ represents halogen, cyano, -OR^a or -CO₂R^d; or C₁₋₆ alkyl, C₂₋₆ alkynyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl,
 5 (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-,
 (C₃₋₇)cycloalkyl-heteroaryl-, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-
 heteroaryl-, (C₄₋₉)bicycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-,
 (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-,
 (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of
 10 which groups may be optionally substituted by one or more substituents.

Generally, R¹ represents halogen, cyano or -OR^a; or C₁₋₆ alkyl, C₂₋₆ alkynyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl-
 (C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₃₋₇)cycloalkyl-heteroaryl-,
 (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₄₋₉)bicycloalkyl-
 15 heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-
 heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or
 (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally
 substituted by one or more substituents.

In a first embodiment, R¹ represents hydrogen.

20 In a second embodiment, R¹ represents halogen. In one aspect of that
 embodiment, R¹ represents bromo. In another aspect of that embodiment, R¹ represents
 chloro.

In a third embodiment, R¹ represents -OR^a.

In a fourth embodiment, R¹ represents -CO₂R^d.

25 In a fifth embodiment, R¹ represents optionally substituted C₁₋₆ alkyl. In one
 aspect of that embodiment, R¹ represents optionally substituted ethyl.

In a sixth embodiment, R¹ represents optionally substituted C₂₋₆ alkynyl. In one
 aspect of that embodiment, R¹ represents optionally substituted butynyl.

In a seventh embodiment, R¹ represents optionally substituted aryl. In one aspect
 30 of that embodiment, R¹ represents optionally substituted phenyl.

In an eighth embodiment, R¹ represents optionally substituted C₃₋₇
 heterocycloalkyl.

In a ninth embodiment, R¹ represents optionally substituted C₃₋₇ heterocycloalkenyl.

In a tenth embodiment, R¹ represents optionally substituted heteroaryl. In selected aspects of that embodiment, R¹ represents benzofuryl, thienyl, indolyl, pyrazolyl, indazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, quinolinyl, pyridazinyl, pyrimidinyl or pyrazinyl, any of which groups may be optionally substituted by one or more substituents.

In an eleventh embodiment, R¹ represents optionally substituted (C₃₋₇)-heterocycloalkyl(C₁₋₆)alkyl-aryl-. In a first aspect of that embodiment, R¹ represents optionally substituted pyrrolidinylmethylphenyl-. In a second aspect of that embodiment, R¹ represents optionally substituted piperazinylmethylphenyl-.

In a twelfth embodiment, R¹ represents optionally substituted heteroaryl(C₃₋₇)-heterocycloalkyl-. In one aspect of that embodiment, R¹ represents optionally substituted pyridinylpiperazinyl-.

In a thirteenth embodiment, R¹ represents optionally substituted (C₃₋₇)cycloalkyl-heteroaryl-. In a first aspect of that embodiment, R¹ represents optionally substituted cyclohexylpyrazolyl-. In a second aspect of that embodiment, R¹ represents optionally substituted cyclohexylpyridinyl-. In a third aspect of that embodiment, R¹ represents optionally substituted cyclopropylpyrimidinyl-. In a fourth aspect of that embodiment, R¹ represents optionally substituted cyclobutylpyrimidinyl-. In a fifth aspect of that embodiment, R¹ represents optionally substituted cyclopentylpyrimidinyl-. In a sixth aspect of that embodiment, R¹ represents optionally substituted cyclohexylpyrimidinyl-. In a seventh aspect of that embodiment, R¹ represents optionally substituted cyclohexylpyrazinyl-.

In a fourteenth embodiment, R¹ represents optionally substituted (C₄₋₇)-cycloalkenyl-heteroaryl-.

In a fifteenth embodiment, R¹ represents optionally substituted (C₃₋₇)-heterocycloalkyl-heteroaryl-. In a first aspect of that embodiment, R¹ represents optionally substituted pyrrolidinylpyridinyl-. In a second aspect of that embodiment, R¹ represents optionally substituted tetrahydropyranylpyridinyl-. In a third aspect of that embodiment, R¹ represents optionally substituted piperidinylpyridinyl-. In a fourth aspect of that embodiment, R¹ represents optionally substituted piperazinylpyridinyl-. In a fifth aspect of that embodiment, R¹ represents optionally substituted morpholinylpyridinyl-. In

a sixth aspect of that embodiment, R¹ represents optionally substituted thiomorpholinyl-pyridinyl-. In a seventh aspect of that embodiment, R¹ represents optionally substituted diazepanylpyridinyl-. In an eighth aspect of that embodiment, R¹ represents optionally substituted oxetanylpurimidinyl-. In a ninth aspect of that embodiment, R¹ represents optionally substituted azetidinylpurimidinyl-. In a tenth aspect of that embodiment, R¹ represents optionally substituted tetrahydrofuranylpurimidinyl-. In an eleventh aspect of that embodiment, R¹ represents optionally substituted pyrrolidinylpurimidinyl-. In a twelfth aspect of that embodiment, R¹ represents optionally substituted tetrahydropyranylpurimidinyl-. In a thirteenth aspect of that embodiment, R¹ represents optionally substituted piperidinylpurimidinyl-. In a fourteenth aspect of that embodiment, R¹ represents optionally substituted piperazinylpurimidinyl-. In a fifteenth aspect of that embodiment, R¹ represents optionally substituted morpholinylpurimidinyl-. In a sixteenth aspect of that embodiment, R¹ represents optionally substituted thiomorpholinyl-purimidinyl-. In a seventeenth aspect of that embodiment, R¹ represents optionally substituted azepanylpurimidinyl-. In an eighteenth aspect of that embodiment, R¹ represents optionally substituted oxazepanylpurimidinyl-. In a nineteenth aspect of that embodiment, R¹ represents optionally substituted diazepanylpurimidinyl-. In a twentieth aspect of that embodiment, R¹ represents optionally substituted thiadiazepanylpurimidinyl-. In a twenty-first aspect of that embodiment, R¹ represents optionally substituted oxetanylpurazinyl-. In a twenty-second aspect of that embodiment, R¹ represents optionally substituted piperidinylpurazinyl-.

In a sixteenth embodiment, R¹ represents optionally substituted (C₃₋₇)-heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-. In a first aspect of that embodiment, R¹ represents optionally substituted morpholinylmethylthienyl-. In a second aspect of that embodiment, R¹ represents optionally substituted morpholinylethylpyrazolyl-.

In a seventeenth embodiment, R¹ represents optionally substituted (C₃₋₇)-heterocycloalkenyl-heteroaryl-.

In an eighteenth embodiment, R¹ represents optionally substituted (C₄₋₉)-heterobicycloalkyl-heteroaryl-.

In a nineteenth embodiment, R¹ represents optionally substituted (C₄₋₉)-spiroheterocycloalkyl-heteroaryl-.

In a twentieth embodiment, R¹ represents optionally substituted (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl-heteroaryl-. In one aspect of that embodiment, R¹ represents optionally substituted cyclohexylmethylpyrimidinyl-.

In a twenty-first embodiment, R¹ represents optionally substituted (C₄₋₉)-
5 bicycloalkyl-heteroaryl-.

In a twenty-second embodiment, R¹ represents optionally substituted C₃₋₇ cycloalkyl. In one aspect of that embodiment, R¹ represents optionally substituted cyclopropyl.

Appositely, R¹ represents hydrogen, chloro, bromo, cyano, -OR^a or -CO₂R^d; or
10 ethyl, butynyl, cyclopropyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,2,3,6-tetrahydropyridinyl, benzofuryl, thienyl, indolyl, pyrazolyl, indazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, quinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethylphenyl, piperazinylmethylphenyl, pyridinylpiperazinyl, cyclohexylpyrazolyl, cyclohexylpyridinyl, cyclopropylpyrimidinyl, cyclobutylpyrimidinyl,
15 cyclopentylpyrimidinyl, cyclohexylpyrimidinyl, cyclohexylpyrazinyl, cyclohexylmethylpyrimidinyl, cyclohexenylpyridinyl, cyclohexenylpyrimidinyl, bicyclo[3.1.0]hexanylpyridinyl, bicyclo[3.1.0]hexanylpyrimidinyl, bicyclo[4.1.0]heptanylpyrimidinyl, bicyclo[2.2.2]octanylpyrimidinyl, pyrrolidinylpyridinyl, tetrahydropyranylpyridinyl, piperidinylpyridinyl, piperazinylpyridinyl, morpholinylpyridinyl, thiomorpholinylpyridinyl,
20 pyridinyl, diazepanylpyridinyl, oxetanylpyrimidinyl, azetidylpyrimidinyl, tetrahydrofuranylpyrimidinyl, pyrrolidinylpyrimidinyl, tetrahydropyranylpyrimidinyl, piperidinylpyrimidinyl, piperazinylpyrimidinyl, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]-pyrazinylpyrimidinyl, morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, azepanylpyrimidinyl, oxazepanylpyrimidinyl, diazepanylpyrimidinyl, thiadiazepanylpyrimidinyl,
25 oxetanylpyrazinyl, piperidinylpyrazinyl, morpholinylmethylthienyl, morpholinylethylpyrazolyl, 3-azabicyclo[3.1.0]hexanylpyridinyl, 3-azabicyclo[3.1.0]hexanylpyridazinyl, 3-azabicyclo[3.1.0]hexanylpyrimidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl, 3-azabicyclo[3.1.1]heptanylpyrimidinyl, 3-azabicyclo[4.1.0]heptanylpyridinyl, 3-azabicyclo[4.1.0]heptanylpyrimidinyl, 2-oxabicyclo[2.2.2]octanylpyrimidinyl, 3-azabicyclo[3.2.1]octanylpyrimidinyl, 8-azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-azabicyclo[3.2.1]octanylpyrimidinyl, 3,6-diazabicyclo[3.2.2]nonanylpyrimidinyl, 3-oxa-7-azabicyclo[3.3.1]nonanylpyrimidinyl, 5-azaspiro[2.3]hexanylpyrimidinyl, 5-azaspiro[2.4]heptanylpyrimidinyl, 2-azaspiro[3.3]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.3]-

heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.4]octanylpyrimidinyl, 2-oxa-6-azaspiro[3.5]-nonanylpyrimidinyl, 2-oxa-7-azaspiro[3.5]nonanylpyrimidinyl or 2,4,8-triazaspiro[4.5]-decanylpyrimidinyl, any of which groups may be optionally substituted by one or more substituents.

5 Typical examples of optional substituents on R¹ include one, two or three substituents independently selected from halogen, halo(C₁₋₆)alkyl, cyano, cyano(C₁₋₆)alkyl, nitro(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₂₋₆ alkenyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, trifluoroethoxy, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, amino, amino-
 10 (C₁₋₆)alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, C₁₋₆ alkylsulphonylamino, *N*-[(C₁₋₆)alkyl]-*N*-[(C₁₋₆)alkylsulphonyl]amino, bis[(C₁₋₆)alkylsulphonyl]amino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, formyl, C₂₋₆ alkylcarbonyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆ alkoxycarbonylmethylenyl, a carboxylic acid isostere or prodrug moiety Ω as defined herein, -(C₁₋₆)alkyl- Ω , aminocarbonyl, aminosulphonyl, (C₁₋₆)alkylsulphoximinyl and [(C₁₋₆)alkyl][*N*-(C₁₋₆)alkyl]sulphoximinyl.

20 Typical examples of particular substituents on R¹ include one, two or three substituents independently selected from fluoro, chloro, fluoromethyl, fluoroisopropyl, cyano, cyanoethyl, nitromethyl, methyl, ethyl, isopropyl, trifluoromethyl, trifluoroethyl, ethenyl, hydroxy, hydroxymethyl, hydroxyisopropyl, methoxy, isopropoxy, trifluoroethoxy, carboxycyclobutyloxy, methylthio, methylsulphonyl, methylsulphonyl ethyl, oxo, amino, aminomethyl, aminoisopropyl, methylamino, dimethylamino, methoxyethylamino, *N*-(hydroxyethyl)-*N*-(methyl)amino, acetaminomethyl, methylsulphonylamino, *N*-methyl-*N*-(methylsulphonyl)amino, bis(methylsulphonyl)amino, *N*-(carboxyethyl)-*N*-(methyl)amino, carboxycyclopentylamino, carboxycyclopropylmethylamino, formyl, acetyl, acetoxymethyl, carboxy, carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *n*-butoxycarbonyl, *tert*-butoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonyl ethyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylenyl, methylsulphonylaminocarbonyl, acetaminosulphonyl, methoxyamino-

carbonyl, tetrazolyl, tetrazolylmethyl, hydroxyoxadiazolyl, aminocarbonyl, amino-sulphonyl, methylsulphoximinyl and (methyl)(*N*-methyl)sulphoximinyl.

In a particular embodiment, R¹ is substituted by hydroxy(C₁₋₆)alkyl. In one aspect of that embodiment, R¹ is substituted by hydroxyisopropyl, especially 2-hydroxyprop-2-yl.

5 Selected values of R¹ include hydrogen, chloro, bromo, cyano, -OR^a, -CO₂R^d, methoxycarbonylethyl, ethoxycarbonylethyl, hydroxybutynyl, cyclopropyl, chlorophenyl, hydroxyphenyl, methylsulphonylphenyl, aminomethylphenyl, aminoisopropylphenyl, acetylaminomethylphenyl, acetylphenyl, methoxycarbonylphenyl, aminocarbonylphenyl, aminosulphonylphenyl, acetylaminosulphonylphenyl, (methoxycarbonyl)(methyl)-
 10 pyrrolidinyl, oxopiperidinyl, ethoxycarbonylpiperidinyl, methylsulphonylpiperazinyl, morpholinyl, methylsulphonyl-1,2,3,6-tetrahydropyridinyl, acetyl-1,2,3,6-tetrahydro-pyridinyl, *tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridinyl, methoxycarbonylmethyl-1,2,3,6-tetrahydropyridinyl, benzofuryl, thienyl, indolyl, pyrazolyl, methylpyrazolyl, dimethylpyrazolyl, (methyl)[*N*-methyl-*N*-(methylsulfonyl)amino]pyrazolyl,
 15 methylindazolyl, dimethylisoxazolyl, hydroxyisopropylthiazolyl, methylimidazolyl, dimethylimidazolyl, pyridinyl, fluoropyridinyl, cyanopyridinyl, methylpyridinyl, (cyano)(methyl)pyridinyl, dimethylpyridinyl, trifluoromethylpyridinyl, ethenylpyridinyl, hydroxyisopropylpyridinyl, methoxypyridinyl, (methoxy)(methyl)pyridinyl, isopropoxy-pyridinyl, trifluoroethoxypyridinyl, (methyl)(trifluoroethoxy)pyridinyl, methylsulphonyl-
 20 pyridinyl, oxopyridinyl, (methyl)(oxo)pyridinyl, (dimethyl)(oxo)pyridinyl, amino-pyridinyl, methylaminopyridinyl, dimethylaminopyridinyl, methoxyethylaminopyridinyl, *N*-(hydroxyethyl)-*N*-(methyl)aminopyridinyl, methylsulphonylaminopyridinyl, [bis(methylsulphonyl)amino]pyridinyl, carboxypyridinyl, quinolinyl, hydroxypyridazinyl, pyrimidinyl, fluoroisopropylpyrimidinyl, hydroxyisopropylpyrimidinyl, methoxy-
 25 pyrimidinyl, carboxycyclobutyloxy-pyrimidinyl, methylthiopyrimidinyl, methylsulphonyl-pyrimidinyl, oxopyrimidinyl, aminopyrimidinyl, dimethylaminopyrimidinyl, methoxyethylaminopyrimidinyl, *N*-(carboxyethyl)-*N*-(methyl)aminopyrimidinyl, carboxycyclopentylaminopyrimidinyl, carboxycyclopropylmethylaminopyrimidinyl, acetoxisopropylpyrimidinyl, ethoxycarbonylethylpyrimidinyl, hydroxypyrazinyl,
 30 hydroxyisopropylpyrazinyl, pyrrolidinylmethylphenyl, piperazinylmethylphenyl, pyridinylpiperazinyl, carboxycyclohexylpyrazolyl, carboxycyclohexylpyridinyl, fluoromethylcyclopropylpyrimidinyl, acetylaminomethylcyclopropylpyrimidinyl, hydroxycyclobutylpyrimidinyl, carboxycyclopentylpyrimidinyl, carboxycyclohexyl-

pyrimidinyl, (carboxy)(methyl)cyclohexylpyrimidinyl, (carboxy)(hydroxy)cyclohexyl-
 pyrimidinyl, carboxymethylcyclohexylpyrimidinyl, ethoxycarbonylcyclohexyl-
 pyrimidinyl, (methoxycarbonyl)(methyl)cyclohexylpyrimidinyl, (ethoxycarbonyl)-
 (methyl)cyclohexylpyrimidinyl, carboxycyclohexylpyrazinyl, carboxycyclohexylmethyl-
 5 pyrimidinyl, carboxycyclohexenylpyridinyl, carboxycyclohexenylpyrimidinyl,
 ethoxycarbonylcyclohexenylpyrimidinyl, carboxybicyclo[3.1.0]hexanylpyridinyl,
 carboxybicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonylbicyclo[3.1.0]hexanyl-
 pyrimidinyl, carboxybicyclo[4.1.0]heptanylpyrimidinyl, carboxybicyclo[2.2.2]octanyl-
 pyrimidinyl, pyrrolidinylpyridinyl, hydroxypyrrolidinylpyridinyl,
 10 hydroxytetrahydropyranylpyridinyl, piperidinylpyridinyl, acetyl piperidinylpyridinyl,
 (carboxy)(methyl)piperidinylpyridinyl, [(carboxy)(methyl)piperidinyl](fluoro)pyridinyl,
 [(carboxy)(methyl)piperidinyl](chloro)pyridinyl, piperazinylpyridinyl, (methyl)-
 (piperazinyl)pyridinyl, cyanoethylpiperazinylpyridinyl, trifluoroethylpiperazinylpyridinyl,
 methylsulphonylpiperazinylpyridinyl, methylsulphonylethylpiperazinylpyridinyl,
 15 oxopiperazinylpyridinyl, acetyl piperazinylpyridinyl, (*tert*-butoxycarbonylpiperazinyl)-
 (methyl)pyridinyl, carboxymethylpiperazinylpyridinyl, carboxyethylpiperazinylpyridinyl,
 ethoxycarbonylmethylpiperazinylpyridinyl, ethoxycarbonylethylpiperazinylpyridinyl,
 morpholinylpyridinyl, thiomorpholinylpyridinyl, oxothiomorpholinylpyridinyl,
 dioxothiomorpholinylpyridinyl, oxodiazepanylpyridinyl, fluoro oxetanylpyrimidinyl,
 20 hydroxyoxetanylpyrimidinyl, hydroxyazetidiny pyrimidinyl, (hydroxy)(methyl)-
 azetidiny pyrimidinyl, carboxyazetidiny pyrimidinyl, (*tert*-butoxycarbonyl)(hydroxy)-
 azetidiny pyrimidinyl, tetrazolylazetidiny pyrimidinyl, hydroxytetrahydrofuranyl-
 pyrimidinyl, hydroxypyrrolidinylpyrimidinyl, carboxypyrrolidinylpyrimidinyl,
 (carboxy)(methyl)pyrrolidinylpyrimidinyl, carboxymethylpyrrolidinylpyrimidinyl,
 25 ethoxycarbonylpyrrolidinylpyrimidinyl, fluorotetrahydropyranylpyrimidinyl,
 hydroxytetrahydropyranylpyrimidinyl, difluoropiperidinylpyrimidinyl, (cyano)(methyl)-
 piperidinylpyrimidinyl, (hydroxy)(nitromethyl)piperidinylpyrimidinyl, (hydroxy)-
 (methyl)piperidinylpyrimidinyl, (hydroxy)(trifluoromethyl)piperidinylpyrimidinyl,
 (hydroxymethyl)(methyl)piperidinylpyrimidinyl, methylsulphonylpiperidinylpyrimidinyl,
 30 oxopiperidinylpyrimidinyl, (formyl)(methyl)piperidinylpyrimidinyl, carboxypiperidinyl-
 pyrimidinyl, (carboxy)(fluoro)piperidinylpyrimidinyl, (carboxy)(methyl)piperidinyl-
 pyrimidinyl, (carboxy)(ethyl)piperidinylpyrimidinyl, (carboxy)(trifluoromethyl)-
 piperidinylpyrimidinyl, (carboxy)(hydroxy)piperidinylpyrimidinyl, (carboxy)-

(hydroxymethyl)piperidinympyrimidinyl, (carboxy)(methoxy)piperidinympyrimidinyl,
 (amino)(carboxy)piperidinympyrimidinyl, carboxymethylpiperidinympyrimidinyl,
 methoxycarbonylpiperidinympyrimidinyl, ethoxycarbonylpiperidinympyrimidinyl,
 (ethoxycarbonyl)(fluoro)piperidinympyrimidinyl, (methoxycarbonyl)(methyl)piperidinyl-
 5 pyrimidinyl, (ethyl)(methoxycarbonyl)piperidinympyrimidinyl, (isopropyl)-
 (methoxycarbonyl)piperidinympyrimidinyl, (ethoxycarbonyl)(methyl)piperidinyl-
 pyrimidinyl, (*n*-butoxycarbonyl)(methyl)piperidinympyrimidinyl, (ethoxycarbonyl)-
 (trifluoromethyl)piperidinympyrimidinyl, (ethoxycarbonyl)(hydroxymethyl)piperidinyl-
 pyrimidinyl, (methoxy)(methoxycarbonyl)piperidinympyrimidinyl, (carboxy)-
 10 (methoxycarbonyl)piperidinympyrimidinyl, (methyl)(morpholinylethoxycarbonyl)-
 piperidinympyrimidinyl, ethoxycarbonylmethylpiperidinympyrimidinyl, methylsulphonyl-
 aminocarbonylpiperidinympyrimidinyl, acetaminosulphonylpiperidinympyrimidinyl,
 methoxyaminocarbonylpiperidinympyrimidinyl, tetrazolylpiperidinympyrimidinyl,
 hydroxyoxadiazolylpiperidinympyrimidinyl, aminosulphonylpiperidinympyrimidinyl,
 15 piperazinympyrimidinyl, methylsulphonylpiperazinympyrimidinyl, oxopiperazinyl-
 pyrimidinyl, carboxypiperazinympyrimidinyl, carboxyethylpiperazinympyrimidinyl, *tert*-
 butoxycarbonylpiperazinympyrimidinyl, tetrazolylmethylpiperazinympyrimidinyl,
 trioxohexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinympyrimidinyl, morpholinylpyrimidinyl,
 dimethylmorpholinylpyrimidinyl, hydroxymethylmorpholinylpyrimidinyl, carboxy-
 20 morpholinylpyrimidinyl, (carboxy)(methyl)morpholinylpyrimidinyl, carboxymethyl-
 morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl,
 carboxyazepanylpypyrimidinyl, carboxyoxazepanylpypyrimidinyl, oxodiazepanylpypyrimidinyl,
 (oxodiazepanyl)(trifluoromethyl)pyrimidinyl, (oxodiazepanyl)(methoxy)pyrimidinyl,
 (methyl)(oxo)diazepanylpypyrimidinyl, dioxothiadiazepanylpypyrimidinyl, hydroxyoxetanyl-
 25 pyrazinyl, (carboxy)(methyl)piperidinympyrazinyl, (ethoxycarbonyl)(methyl)piperidinyl-
 pyrazinyl, morpholinylmethylthienyl, morpholinylethylpyrazolyl, carboxy-3-azabicyclo-
 [3.1.0]hexanylpyridinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyridazinyl, carboxy-3-
 azabicyclo[3.1.0]hexanylpyrimidinyl, (carboxy)(methyl)-3-azabicyclo[3.1.0]hexanyl-
 pyrimidinyl, methoxycarbonyl-3-azabicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonyl-3-
 30 azabicyclo[3.1.0]hexanylpyrimidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl,
 carboxy-2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl, carboxy-3-azabicyclo[3.1.1]-
 heptanylpyrimidinyl, carboxy-3-azabicyclo[4.1.0]heptanylpyridinyl, carboxy-3-
 azabicyclo[4.1.0]heptanylpyrimidinyl, methoxycarbonyl-3-azabicyclo[4.1.0]heptanyl-

pyrimidinyl, ethoxycarbonyl-3-azabicyclo[4.1.0]heptanylpyrimidinyl, (hydroxy)(methyl)-(oxo)-2-oxabicyclo[2.2.2]octanylpyrimidinyl, carboxy-3-azabicyclo[3.2.1]octanylpyrimidinyl, methoxycarbonyl-3-azabicyclo[3.2.1]octanylpyrimidinyl, oxo-8-azabicyclo[3.2.1]octanylpyrimidinyl, ethoxycarbonylmethylidenyl-8-azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-azabicyclo[3.2.1]octanylpyrimidinyl, oxo-3,6-diazabicyclo[3.2.2]-nonanylpyrimidinyl, carboxy-3-oxa-7-azabicyclo[3.3.1]nonanylpyrimidinyl, carboxy-5-azaspiro[2.3]hexanylpyrimidinyl, (carboxy)(methyl)-5-azaspiro[2.3]hexanylpyrimidinyl, carboxy-5-azaspiro[2.4]heptanylpyrimidinyl, carboxy-2-azaspiro[3.3]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.3]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.4]octanylpyrimidinyl, 2-oxa-6-azaspiro[3.5]nonanylpyrimidinyl, 2-oxa-7-azaspiro[3.5]nonanylpyrimidinyl and (dioxo)(methyl)-2,4,8-triazaspiro[4.5]decanylpyrimidinyl.

Illustrative values of R^1 include hydrogen.

Typically, R^2 represents hydrogen, halogen or C_{1-6} alkyl.

In a first embodiment, R^2 represents hydrogen. In a second embodiment, R^2 represents halogen. In one aspect of that embodiment, R^2 represents fluoro. In a third embodiment, R^2 represents C_{1-6} alkyl. In one aspect of that embodiment, R^2 represents methyl. In another aspect of that embodiment, R^2 represents ethyl.

Typically, R^3 represents $-\text{CONR}^b\text{R}^c$; or R^3 represents heteroaryl, which group may be optionally substituted by one or more substituents.

Appositely, R^3 represents $-\text{CONR}^b\text{R}^c$; or R^3 represents pyridinyl, which group may be optionally substituted by one or more substituents.

Typical examples of optional substituents on R^3 include $\text{di}(C_{1-6})\text{alkylamino}$.

Typical examples of particular substituents on R^3 include dimethylamino.

Typical values of R^3 include $-\text{CONR}^b\text{R}^c$ and dimethylaminopyridinyl.

Suitably, R^4 represents hydrogen or methyl.

In a first embodiment, R^4 represents hydrogen. In a second embodiment, R^4 represents C_{1-6} alkyl, especially methyl.

Suitably, R^5 represents hydrogen, methyl or ethyl.

In a first embodiment, R^5 represents hydrogen. In a second embodiment, R^5 represents C_{1-6} alkyl, especially methyl or ethyl. In one aspect of that embodiment, R^5 represents methyl. In another aspect of that embodiment, R^5 represents ethyl.

Typical examples of suitable substituents on R^a , R^b , R^c , R^d or R^e , or on the heterocyclic moiety $-\text{NR}^b\text{R}^c$, include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, difluoromethoxy,

trifluoromethoxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, hydroxy, hydroxy(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, cyano, trifluoromethyl, oxo, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkylcarbonyloxy, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, phenylamino, pyridinylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkylcarbonylamino(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulphonylamino, aminocarbonyl, C₁₋₆ alkylaminocarbonyl and di(C₁₋₆)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, acetoxyl, amino, methylamino, ethylamino, dimethylamino, phenylamino, pyridinylamino, acetyl amino, *tert*-butoxycarbonylamino, acetylaminomethyl, methylsulphonylamino, aminocarbonyl, methylaminocarbonyl and dimethylaminocarbonyl.

Suitably, R^a represents C₁₋₆ alkyl, aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl, 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 C₁₋₆ alkoxy and oxo.

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

In one embodiment, R^a represents optionally substituted C₁₋₆ alkyl. In one aspect of that embodiment, R^a ideally represents unsubstituted C₁₋₆ alkyl, especially methyl. In another aspect of that embodiment, R^a ideally represents substituted C₁₋₆ 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(C₁₋₆)alkyl, ideally unsubstituted aryl(C₁₋₆)alkyl, especially benzyl. In a further embodiment, R^a represents optionally substituted heteroaryl. In a further embodiment, R^a represents optionally substituted heteroaryl(C₁₋₆)alkyl, e.g. dioxoisindolylpropyl.

Specific values of R^a include methyl, methoxyethyl, benzyl and dioxoisindolylpropyl.

In a particular aspect, R^b represents hydrogen or trifluoromethyl; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

5 Selected values of R^b include hydrogen; or C₁₋₆ alkyl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl or C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

Typical values of R^b include hydrogen and C₁₋₆ alkyl.

10 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, azetidiny, tetrahydrofuryl, tetrahydrothienyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, azetidinylmethyl, tetrahydrofurylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, 15 pyrrolidinylpropyl, thiazolidinylmethyl, imidazolidinylethyl, piperidinylmethyl, piperidinylethyl, tetrahydroquinolinylmethyl, piperazinylpropyl, morpholinylmethyl, morpholinylethyl, morpholinylpropyl, pyridinyl, indolylmethyl, pyrazolylmethyl, pyrazolyethylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, triazolylmethyl, pyridinylmethyl or pyridinylethyl, any of which groups may be optionally substituted by 20 one or more substituents.

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

25 Selected examples of suitable substituents on R^b include C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, hydroxy, cyano, C₂₋₆ alkoxy carbonyl, di-(C₁₋₆)alkylamino and C₂₋₆ alkoxy carbonylamino.

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

30 Specific values of R^b include hydrogen, methyl, methoxyethyl, methylthioethyl, methylsulphinylethyl, methylsulphonylethyl, hydroxyethyl, cyanoethyl, dimethylaminoethyl, *tert*-butoxycarbonylaminoethyl, dihydroxypropyl, 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.

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

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

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

Specific values of R^c include hydrogen, methyl, cyclobutyl, cyclopentyl,
15 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.

20 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.

25 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} alkoxy carbonyl, amino, C_{2-6} alkylcarbonyl-amino, C_{2-6} alkylcarbonylamino(C_{1-6})alkyl, C_{2-6} alkoxy carbonylamino, C_{1-6} alkyl-sulphonylamino and aminocarbonyl.

30 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, aminomethylazetidin-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.

In a particular embodiment, $-NR^bR^c$ represents morpholin-4-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. 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.

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

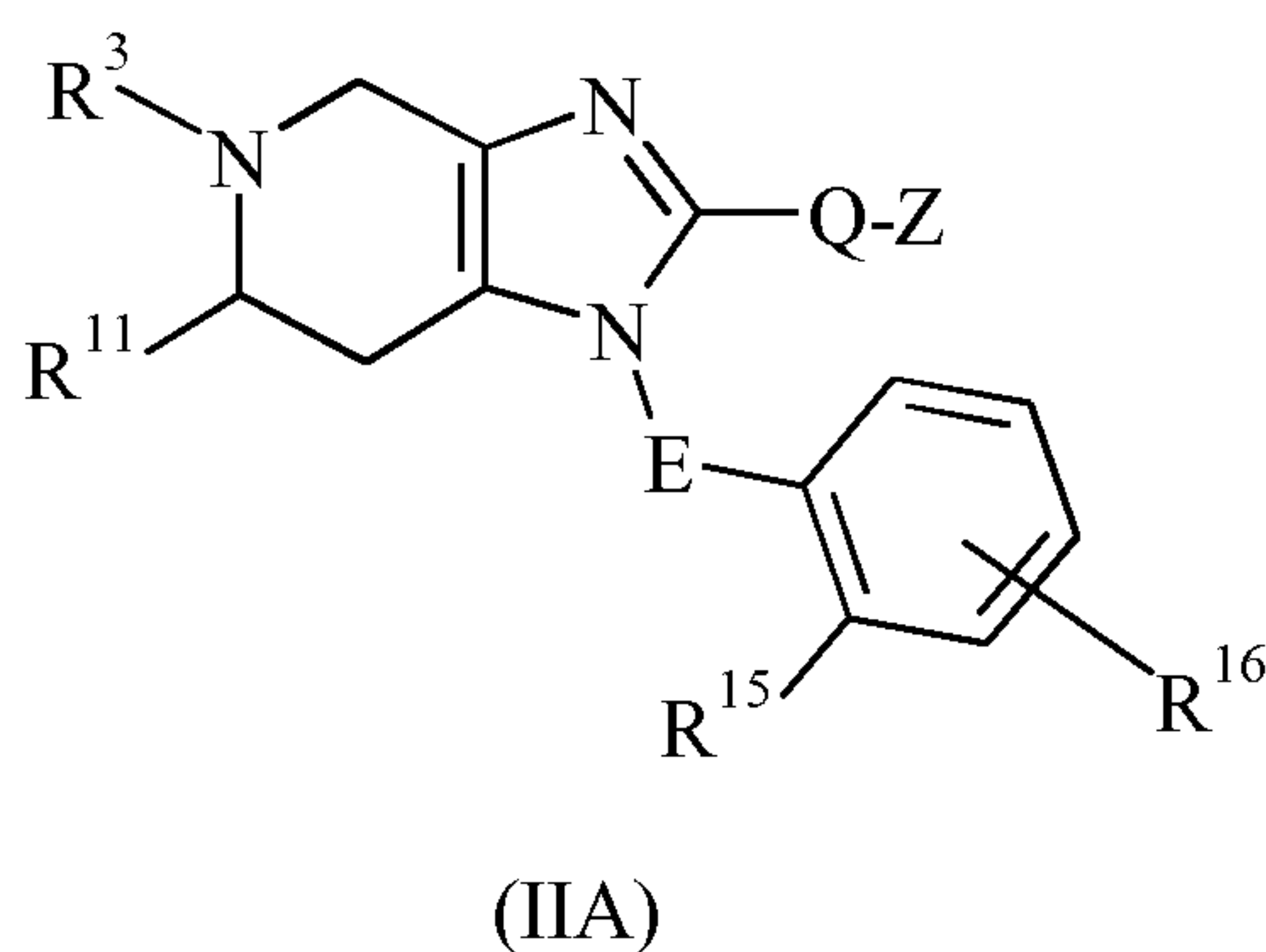
Suitably, R^e represents C_{1-6} alkyl or aryl, either of which groups may be optionally substituted by one or more substituents.

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, 15 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.

20 One sub-class of compounds according to the invention is represented by the compounds of formula (IIA) and *N*-oxides thereof, and pharmaceutically acceptable salts and solvates thereof, and glucuronide derivatives thereof, and co-crystals thereof:



25

wherein

R^{11} represents hydrogen, halogen or $-OR^a$; or R^{11} represents C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl, heteroaryl,

(C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-,
 (C₃₋₇)cycloalkyl-heteroaryl-, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-
 heteroaryl-, (C₄₋₉)bicycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-,
 (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-,
 5 (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of
 which groups may be optionally substituted by one or more substituents;

R¹⁵ and R¹⁶ independently represent hydrogen, halogen, cyano, nitro, C₁₋₆ alkyl,
 trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio,
 C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino,
 10 arylamino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl,
 C₃₋₆ cycloalkylcarbonyl, C₃₋₆ heterocycloalkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl,
 aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆
 alkylaminosulfonyl or di(C₁₋₆)alkylaminosulfonyl; and

E, Q, Z, R³ and R^a are as defined above.

15 Examples of optional substituents which may be present on R¹¹ include one,
 two or three substituents independently selected from halogen, halo(C₁₋₆)alkyl, cyano,
 cyano(C₁₋₆)alkyl, nitro, nitro(C₁₋₆)alkyl, C₁₋₆ alkyl, difluoromethyl, trifluoromethyl,
 difluoroethyl, trifluoroethyl, C₂₋₆ alkenyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy,
 difluoromethoxy, trifluoromethoxy, trifluoroethoxy, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₃
 20 alkylenedioxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkyl-
 sulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, amino, amino(C₁₋₆)alkyl, C₁₋₆ alkylamino,
 di(C₁₋₆)alkylamino, hydroxy(C₁₋₆)alkylamino, C₁₋₆ alkoxyamino, (C₁₋₆)alkoxy(C₁₋₆)alkyl-
 amino, [(C₁₋₆)alkoxy](hydroxy)(C₁₋₆)alkylamino, [(C₁₋₆)alkylthio](hydroxy)(C₁₋₆)alkyl-
 amino, N-[(C₁₋₆)alkyl]-N-[hydroxy(C₁₋₆)alkyl]amino, di(C₁₋₆)alkylamino(C₁₋₆)alkylamino,
 25 N-[di(C₁₋₆)alkylamino(C₁₋₆)alkyl]-N-[hydroxy(C₁₋₆)alkyl]amino, hydroxy(C₁₋₆)alkyl-
 (C₃₋₇)cycloalkylamino, (hydroxy)[(C₃₋₇)cycloalkyl(C₁₋₆)alkyl]amino,
 (C₃₋₇)heterocycloalkyl(C₁₋₆)alkylamino, oxo(C₃₋₇)heterocycloalkyl(C₁₋₆)alkylamino,
 (C₁₋₆)alkylheteroarylamino, heteroaryl(C₁₋₆)alkylamino, (C₁₋₆)alkylheteroaryl(C₁₋₆)alkyl-
 amino, C₂₋₆ alkylcarbonylamino, N-[(C₁₋₆)alkyl]-N-[(C₂₋₆)alkylcarbonyl]amino, (C₂₋₆)alkyl-
 30 carbonylamino(C₁₋₆)alkyl, C₃₋₆ alkenylcarbonylamino, bis[(C₃₋₆)alkenylcarbonyl]amino, N-
 [(C₁₋₆)alkyl]-N-[(C₃₋₇)cycloalkylcarbonyl]amino, C₂₋₆ alkoxycarbonylamino, C₂₋₆
 alkoxycarbonyl(C₁₋₆)alkylamino, C₁₋₆ alkylaminocarbonylamino, C₁₋₆ alkylsulphonyl-
 amino, N-[(C₁₋₆)alkyl]-N-[(C₁₋₆)alkylsulphonyl]amino, bis[(C₁₋₆)alkylsulphonyl]amino, N-

- [(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino, carboxy-
 (C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, formyl, C₂₋₆ alkylcarbonyl, (C₃₋₇)cycloalkylcarbonyl,
 phenylcarbonyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆
 alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆
 5 alkoxycarbonylmethylidenyl, a carboxylic acid isostere or prodrug moiety Ω as defined
 herein, -(C₁₋₆)alkyl- Ω , aminocarbonyl, C₁₋₆ alkylaminocarbonyl, hydroxy(C₁₋₆)alkylamino-
 carbonyl, di(C₁₋₆)alkylaminocarbonyl, aminocarbonyl(C₁₋₆)alkyl, aminosulphonyl,
 di(C₁₋₆)alkylaminosulphonyl, (C₁₋₆)alkylsulphoximinyl and [(C₁₋₆)alkyl][*N*-(C₁₋₆)alkyl]-
 sulphoximinyl.
- 10 Examples of particular substituents on R¹¹ include fluoro, chloro, bromo,
 fluoromethyl, fluoroisopropyl, cyano, cyanoethyl, nitro, nitromethyl, methyl, ethyl,
 isopropyl, isobutyl, *tert*-butyl, difluoromethyl, trifluoromethyl, difluoroethyl, trifluoro-
 ethyl, ethenyl, hydroxy, hydroxymethyl, hydroxyisopropyl, methoxy, isopropoxy,
 difluoromethoxy, trifluoromethoxy, trifluoroethoxy, carboxycyclobutyloxy, methylene-
 15 dioxy, ethylenedioxy, methoxymethyl, methoxyethyl, methylthio, methylsulphinyl,
 methylsulphonyl, methylsulphonylethyl, oxo, amino, aminomethyl, aminoisopropyl,
 methylamino, ethylamino, dimethylamino, hydroxyethylamino, hydroxypropylamino,
 (hydroxy)(methyl)propylamino, methoxyamino, methoxyethylamino, (hydroxy)-
 (methoxy)(methyl)propylamino, (hydroxy)(methylthio)butylamino, *N*-(hydroxyethyl)-*N*-
 20 (methyl)amino, dimethylaminoethylamino, (dimethylamino)(methyl)propylamino, *N*-
 (dimethylaminoethyl)-*N*-(hydroxyethyl)amino, hydroxymethylcyclopentylamino,
 hydroxycyclobutylmethylamino, (cyclopropyl)(hydroxy)propylamino, morpholinylethyl-
 amino, oxopyrrolidinylmethylamino, ethyloxadiazolylamino, methylthiadiazolylamino,
 thiazolylmethylamino, thiazolylethylamino, pyrimidinylmethylamino, methylpyrazolyl-
 25 methylamino, acetylamino, *N*-acetyl-*N*-methylamino, *N*-isopropylcarbonyl-*N*-methyl-
 amino, acetylaminomethyl, ethenylcarbonylamino, bis(ethenylcarbonyl)amino, *N*-
 cyclopropylcarbonyl-*N*-methylamino, methoxycarbonylamino, ethoxycarbonylamino, *tert*-
 butoxycarbonylamino, methoxycarbonylethylamino, ethylaminocarbonylamino,
 butylaminocarbonylamino, methylsulphonylamino, *N*-methyl-*N*-(methylsulphonyl)amino,
 30 bis(methylsulphonyl)amino, *N*-(carboxymethyl)-*N*-methylamino, *N*-(carboxyethyl)-*N*-
 methylamino, carboxycyclopentylamino, carboxycyclopropylmethylamino, formyl, acetyl,
 isopropylcarbonyl, cyclobutylcarbonyl, phenylcarbonyl, acetoxymethyl, carboxy,
 carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *n*-butoxycarbonyl, *tert*-

butoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, methylsulphonylamino-carbonyl, acetylaminosulphonyl, methoxyaminocarbonyl, tetrazolyl, tetrazolylmethyl, hydroxyoxadiazolyl, aminocarbonyl, methylaminocarbonyl, hydroxyethylaminocarbonyl, 5 dimethylaminocarbonyl, aminocarbonylmethyl, aminosulphonyl, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphoximinyl and (methyl)(*N*-methyl)sulphoximinyl.

Generally, R¹¹ represents C₁₋₆ alkyl, C₂₋₆ alkynyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl-(C₃₋₇)heterocycloalkyl-, (C₃₋₇)cycloalkyl-heteroaryl-, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl- 10 heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₄₋₉) bicycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents.

15 In a first embodiment, R¹¹ represents hydrogen.

In a second embodiment, R¹¹ represents halogen. In one aspect of that embodiment, R¹¹ represents bromo. In another aspect of that embodiment, R¹¹ represents chloro.

In a third embodiment, R¹¹ represents -OR^a.

20 In a fourth embodiment, R¹¹ represents optionally substituted C₁₋₆ alkyl. In one aspect of that embodiment, R¹¹ represents optionally substituted ethyl.

In a fifth embodiment, R¹¹ represents optionally substituted C₂₋₆ alkynyl. In one aspect of that embodiment, R¹¹ represents optionally substituted butynyl.

In a sixth embodiment, R¹¹ represents optionally substituted aryl. In one aspect of 25 that embodiment, R¹¹ represents optionally substituted phenyl.

In a seventh embodiment, R¹¹ represents optionally substituted C₃₋₇ heterocycloalkyl.

In an eighth embodiment, R¹¹ represents optionally substituted C₃₋₇ heterocycloalkenyl.

30 In a ninth embodiment, R¹¹ represents optionally substituted heteroaryl. In selected aspects of that embodiment, R¹¹ represents benzofuryl, thienyl, indolyl, pyrazolyl, indazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, quinoliny, pyridazinyl,

pyrimidinyl or pyrazinyl, any of which groups may be optionally substituted by one or more substituents.

In a tenth embodiment, R¹¹ represents optionally substituted (C₃₋₇)-heterocycloalkyl(C₁₋₆)alkyl-aryl-. In a first aspect of that embodiment, R¹¹ represents optionally substituted pyrrolidinylmethylphenyl-. In a second aspect of that embodiment, R¹¹ represents optionally substituted piperazinylmethylphenyl-.

In an eleventh embodiment, R¹¹ represents optionally substituted heteroaryl(C₃₋₇)-heterocycloalkyl-. In one aspect of that embodiment, R¹¹ represents optionally substituted pyridinylpiperazinyl-.

In a twelfth embodiment, R¹¹ represents optionally substituted (C₃₋₇)cycloalkyl-heteroaryl-. In a first aspect of that embodiment, R¹¹ represents optionally substituted cyclohexylpyrazolyl-. In a second aspect of that embodiment, R¹¹ represents optionally substituted cyclohexylpyridinyl-. In a third aspect of that embodiment, R¹¹ represents optionally substituted cyclopropylpyrimidinyl-. In a fourth aspect of that embodiment, R¹¹ represents optionally substituted cyclobutylpyrimidinyl-. In a fifth aspect of that embodiment, R¹¹ represents optionally substituted cyclopentylpyrimidinyl-. In a sixth aspect of that embodiment, R¹¹ represents optionally substituted cyclohexylpyrimidinyl-. In a seventh aspect of that embodiment, R¹¹ represents optionally substituted cyclohexylpyrazinyl-.

In a thirteenth embodiment, R¹¹ represents optionally substituted (C₄₋₇)cycloalkenyl-heteroaryl-.

In a fourteenth embodiment, R¹¹ represents optionally substituted (C₃₋₇)-heterocycloalkyl-heteroaryl-. In a first aspect of that embodiment, R¹¹ represents optionally substituted pyrrolidinylpyridinyl-. In a second aspect of that embodiment, R¹¹ represents optionally substituted tetrahydropyranylpyridinyl-. In a third aspect of that embodiment, R¹¹ represents optionally substituted piperidinylpyridinyl-. In a fourth aspect of that embodiment, R¹¹ represents optionally substituted piperazinylpyridinyl-. In a fifth aspect of that embodiment, R¹¹ represents optionally substituted morpholinylpyridinyl-. In a sixth aspect of that embodiment, R¹¹ represents optionally substituted thiomorpholinylpyridinyl-. In a seventh aspect of that embodiment, R¹¹ represents optionally substituted diazepanylpyridinyl-. In an eighth aspect of that embodiment, R¹¹ represents optionally substituted oxetanylpyrimidinyl-. In a ninth aspect of that embodiment, R¹¹ represents optionally substituted azetidinympyrimidinyl-. In a tenth

aspect of that embodiment, R^{11} represents optionally substituted tetrahydrofuranyl-
 pyrimidinyl-. In an eleventh aspect of that embodiment, R^{11} represents optionally
 substituted pyrrolidinylpyrimidinyl-. In a twelfth aspect of that embodiment, R^{11}
 represents optionally substituted tetrahydropyranylpyrimidinyl-. In a thirteenth aspect of
 5 that embodiment, R^{11} represents optionally substituted piperidinylpyrimidinyl-. In a
 fourteenth aspect of that embodiment, R^{11} represents optionally substituted piperazinyl-
 pyrimidinyl-. In a fifteenth aspect of that embodiment, R^{11} represents optionally
 substituted morpholinylpyrimidinyl-. In a sixteenth aspect of that embodiment, R^{11}
 represents optionally substituted thiomorpholinylpyrimidinyl-. In a seventeenth aspect of
 10 that embodiment, R^{11} represents optionally substituted azepanylpyrimidinyl-. In an
 eighteenth aspect of that embodiment, R^{11} represents optionally substituted oxazepanyl-
 pyrimidinyl-. In a nineteenth aspect of that embodiment, R^{11} represents optionally
 substituted diazepanylpyrimidinyl-. In a twentieth aspect of that embodiment, R^{11}
 represents optionally substituted thiadiazepanylpyrimidinyl-. In a twenty-first aspect of
 15 that embodiment, R^{11} represents optionally substituted oxetanylpyrazinyl-. In a twenty-
 second aspect of that embodiment, R^{11} represents optionally substituted piperidinyl-
 pyrazinyl-.

In a fifteenth embodiment, R^{11} represents optionally substituted (C_{3-7})-
 heterocycloalkyl(C_{1-6})alkyl-heteroaryl-. In a first aspect of that embodiment, R^{11}
 20 represents optionally substituted morpholinylmethylthienyl-. In a second aspect of that
 embodiment, R^{11} represents optionally substituted morpholinylethylpyrazolyl-.

In a sixteenth embodiment, R^{11} represents optionally substituted (C_{3-7})-
 heterocycloalkenyl-heteroaryl-.

In a seventeenth embodiment, R^{11} represents optionally substituted (C_{4-9})-
 25 heterobicycloalkyl-heteroaryl-.

In an eighteenth embodiment, R^{11} represents optionally substituted (C_{4-9})-
 spiroheterocycloalkyl-heteroaryl-.

In a nineteenth embodiment, R^{11} represents optionally substituted (C_{3-7})-
 cycloalkyl(C_{1-6})alkyl-heteroaryl-. In one aspect of that embodiment, R^{11} represents
 30 optionally substituted cyclohexylmethylpyrimidinyl-.

In a twentieth embodiment, R^{11} represents optionally substituted (C_{4-9})-
 bicycloalkyl-heteroaryl-.

In a twenty-first embodiment, R¹¹ represents optionally substituted C₃₋₇ cycloalkyl. In one aspect of that embodiment, R¹¹ represents optionally substituted cyclopropyl.

Appositely, R¹¹ represents hydrogen, chloro, bromo or -OR^a; or R¹¹ represents
 5 ethyl, butynyl, cyclopropyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,
 1,2,3,6-tetrahydropyridinyl, benzofuryl, thienyl, indolyl, pyrazolyl, indazolyl, isoxazolyl,
 thiazolyl, imidazolyl, pyridinyl, quinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl,
 pyrrolidinylmethylphenyl, piperazinylmethylphenyl, pyridinylpiperazinyl, cyclohexyl-
 pyrazolyl, cyclohexylpyridinyl, cyclopropylpyrimidinyl, cyclobutylpyrimidinyl,
 10 cyclopentylpyrimidinyl, cyclohexylpyrimidinyl, cyclohexylpyrazinyl, cyclohexylmethyl-
 pyrimidinyl, cyclohexenylpyridinyl, cyclohexenylpyrimidinyl, bicyclo[3.1.0]hexanyl-
 pyridinyl, bicyclo[3.1.0]hexanylpyrimidinyl, bicyclo[4.1.0]heptanylpyrimidinyl,
 bicyclo[2.2.2]octanylpyrimidinyl, pyrrolidinylpyridinyl, tetrahydropyranylpyridinyl,
 piperidinylpyridinyl, piperazinylpyridinyl, morpholinylpyridinyl, thiomorpholinyl-
 15 pyridinyl, diazepanylpyridinyl, oxetanylpyrimidinyl, azetidanylpyrimidinyl,
 tetrahydrofuranylpyrimidinyl, pyrrolidinylpyrimidinyl, tetrahydropyranylpyrimidinyl,
 piperidinylpyrimidinyl, piperazinylpyrimidinyl, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]-
 pyrazinylpyrimidinyl, morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, azepanyl-
 pyrimidinyl, oxazepanylpyrimidinyl, diazepanylpyrimidinyl, thiadiazepanylpyrimidinyl,
 20 oxetanylpyrazinyl, piperidinylpyrazinyl, morpholinylmethylthienyl, morpholinylethyl-
 pyrazolyl, 3-azabicyclo[3.1.0]hexanylpyridinyl, 3-azabicyclo[3.1.0]hexanylpyridazinyl,
 3-azabicyclo[3.1.0]hexanylpyrimidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl, 3-
 azabicyclo[3.1.1]heptanylpyrimidinyl, 3-azabicyclo[4.1.0]heptanylpyridinyl, 3-
 azabicyclo[4.1.0]heptanylpyrimidinyl, 2-oxabicyclo[2.2.2]octanylpyrimidinyl, 3-
 25 azabicyclo[3.2.1]octanylpyrimidinyl, 8-azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-
 azabicyclo[3.2.1]octanylpyrimidinyl, 3,6-diazabicyclo[3.2.2]nonanylpyrimidinyl, 3-oxa-
 7-azabicyclo[3.3.1]nonanylpyrimidinyl, 5-azaspiro[2.3]hexanylpyrimidinyl, 5-azaspiro-
 [2.4]heptanylpyrimidinyl, 2-azaspiro[3.3]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.3]-
 heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.4]octanylpyrimidinyl, 2-oxa-6-azaspiro[3.5]-
 30 nonanylpyrimidinyl, 2-oxa-7-azaspiro[3.5]nonanylpyrimidinyl or 2,4,8-triazaspiro[4.5]-
 decanylpyrimidinyl, any of which groups may be optionally substituted by one or more
 substituents.

Typical examples of optional substituents on R¹¹ include one, two or three substituents independently selected from halogen, halo(C₁₋₆)alkyl, cyano, cyano(C₁₋₆)alkyl, nitro(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₂₋₆ alkenyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, trifluoroethoxy, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, amino, amino-(C₁₋₆)alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, C₁₋₆ alkylsulphonylamino, *N*-[(C₁₋₆)alkyl]-*N*-[(C₁₋₆)alkylsulphonyl]amino, bis[(C₁₋₆)alkylsulphonyl]amino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, formyl, C₂₋₆ alkylcarbonyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆ alkoxycarbonylmethylidenyl, a carboxylic acid isostere or prodrug moiety Ω as defined herein, -(C₁₋₆)alkyl- Ω , aminocarbonyl, aminosulphonyl, (C₁₋₆)alkylsulphoximinyl and [(C₁₋₆)alkyl][*N*-(C₁₋₆)alkyl]sulphoximinyl.

Typical examples of particular substituents on R¹¹ include one, two or three substituents independently selected from fluoro, chloro, fluoromethyl, fluoroisopropyl, cyano, cyanoethyl, nitromethyl, methyl, ethyl, isopropyl, trifluoromethyl, trifluoroethyl, ethenyl, hydroxy, hydroxymethyl, hydroxyisopropyl, methoxy, isopropoxy, trifluoroethoxy, carboxycyclobutyloxy, methylthio, methylsulphonyl, methylsulphonyl ethyl, oxo, amino, aminomethyl, aminoisopropyl, methylamino, dimethylamino, methoxyethylamino, *N*-(hydroxyethyl)-*N*-(methyl)amino, acetaminomethyl, methylsulphonylamino, *N*-methyl-*N*-(methylsulphonyl)amino, bis(methylsulphonyl)amino, *N*-(carboxyethyl)-*N*-(methyl)amino, carboxycyclopentylamino, carboxycyclopropylmethylamino, formyl, acetyl, acetoxymethyl, carboxy, carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *n*-butoxycarbonyl, *tert*-butoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonyl ethyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, methylsulphonylaminocarbonyl, acetaminosulphonyl, methoxyaminocarbonyl, tetrazolyl, tetrazolylmethyl, hydroxyoxadiazolyl, aminocarbonyl, aminosulphonyl, methylsulphoximinyl and (methyl)(*N*-methyl)sulphoximinyl.

In a particular embodiment, R¹¹ is substituted by hydroxy(C₁₋₆)alkyl. In one aspect of that embodiment, R¹¹ is substituted by hydroxyisopropyl, especially 2-hydroxyprop-2-yl.

Selected values of R¹¹ include hydrogen, chloro, bromo, -OR^a, methoxycarbonyl-ethyl, ethoxycarbonyl-ethyl, hydroxybutynyl, cyclopropyl, chlorophenyl, hydroxyphenyl, methylsulphonylphenyl, aminomethylphenyl, aminoisopropylphenyl, acetaminomethylphenyl, acetylphenyl, methoxycarbonylphenyl, aminocarbonylphenyl, aminosulphonylphenyl, acetylaminosulphonylphenyl, (methoxycarbonyl)(methyl)pyrrolidinyl, oxopiperidinyl, ethoxycarbonylpiperidinyl, methylsulphonylpiperazinyl, morpholinyl, methylsulphonyl-1,2,3,6-tetrahydropyridinyl, acetyl-1,2,3,6-tetrahydropyridinyl, *tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridinyl, methoxycarbonylmethyl-1,2,3,6-tetrahydropyridinyl, benzofuryl, thienyl, indolyl, pyrazolyl, methylpyrazolyl, dimethylpyrazolyl, (methyl)[*N*-methyl-*N*-(methylsulfonyl)amino]pyrazolyl, methylindazolyl, dimethylisoxazolyl, hydroxyisopropylthiazolyl, methylimidazolyl, dimethylimidazolyl, pyridinyl, fluoropyridinyl, cyanopyridinyl, methylpyridinyl, (cyano)(methyl)pyridinyl, dimethylpyridinyl, trifluoromethylpyridinyl, ethenylpyridinyl, hydroxyisopropylpyridinyl, methoxypyridinyl, (methoxy)(methyl)pyridinyl, isopropoxypyridinyl, trifluoroethoxypyridinyl, (methyl)(trifluoroethoxy)pyridinyl, methylsulphonylpyridinyl, oxopyridinyl, (methyl)(oxo)pyridinyl, (dimethyl)(oxo)pyridinyl, aminopyridinyl, methylaminopyridinyl, dimethylaminopyridinyl, methoxyethylaminopyridinyl, *N*-(hydroxyethyl)-*N*-(methyl)aminopyridinyl, methylsulphonylaminopyridinyl, [bis(methylsulphonyl)amino]pyridinyl, carboxypyridinyl, quinolinyl, hydroxypyridazinyl, pyrimidinyl, fluoroisopropylpyrimidinyl, hydroxyisopropylpyrimidinyl, methoxypyrimidinyl, carboxycyclobutylloxypyrimidinyl, methylthiopyrimidinyl, methylsulphonylpyrimidinyl, oxopyrimidinyl, aminopyrimidinyl, dimethylaminopyrimidinyl, methoxyethylaminopyrimidinyl, *N*-(carboxyethyl)-*N*-(methyl)aminopyrimidinyl, carboxycyclopentylaminopyrimidinyl, carboxycyclopropylmethylaminopyrimidinyl, acetoxisopropylpyrimidinyl, ethoxycarbonyl-ethylpyrimidinyl, hydroxypyrazinyl, hydroxyisopropylpyrazinyl, pyrrolidinylmethylphenyl, piperazinylmethylphenyl, pyridinylpiperazinyl, carboxycyclohexylpyrazolyl, carboxycyclohexylpyridinyl, fluoromethylcyclopropylpyrimidinyl, acetaminomethylcyclopropylpyrimidinyl, hydroxycyclobutylpyrimidinyl, carboxycyclopentylpyrimidinyl, carboxycyclohexylpyrimidinyl, (carboxy)(methyl)cyclohexylpyrimidinyl, (carboxy)(hydroxy)cyclohexylpyrimidinyl, carboxymethylcyclohexylpyrimidinyl, ethoxycarbonylcyclohexylpyrimidinyl, (methoxycarbonyl)(methyl)cyclohexylpyrimidinyl, (ethoxycarbonyl)(methyl)cyclohexylpyrimidinyl, carboxycyclohexylpyrazinyl, carboxycyclohexylmethylpyrimidinyl, carboxycyclohexenyl-

pyridinyl, carboxycyclohexenylpyrimidinyl, ethoxycarbonylcyclohexenylpyrimidinyl, carboxybicyclo[3.1.0]hexanylpyridinyl, carboxybicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonylbicyclo[3.1.0]hexanylpyrimidinyl, carboxybicyclo[4.1.0]heptanylpyrimidinyl, carboxybicyclo[2.2.2]octanylpyrimidinyl, pyrrolidinylpyridinyl,

5 hydroxypyrrolidinylpyridinyl, hydroxytetrahydropyranylpyridinyl, piperidinylpyridinyl, acetylpiperidinylpyridinyl, (carboxy)(methyl)piperidinylpyridinyl, [(carboxy)(methyl)piperidinyl](fluoro)pyridinyl, [(carboxy)(methyl)piperidinyl](chloro)pyridinyl, piperazinylpyridinyl, (methyl)(piperazinyl)pyridinyl, cyanoethylpiperazinylpyridinyl, trifluoroethylpiperazinylpyridinyl, methylsulphonylpiperazinylpyridinyl, methylsulphonylethylpiperazinylpyridinyl, oxopiperazinylpyridinyl, acetylpiperazinylpyridinyl,

10 (tert-butoxycarbonylpiperazinyl)(methyl)pyridinyl, carboxymethylpiperazinylpyridinyl, carboxyethylpiperazinylpyridinyl, ethoxycarbonylmethylpiperazinylpyridinyl, ethoxycarbonylethylpiperazinylpyridinyl, morpholinylpyridinyl, thiomorpholinylpyridinyl, oxothiomorpholinylpyridinyl, dioxothiomorpholinylpyridinyl, oxodiazepanylpyridinyl, fluoroxyetanylpyrimidinyl, hydroxyoxyetanylpyrimidinyl, hydroxyazetidinylpyrimidinyl, (hydroxy)(methyl)azetidinylpyrimidinyl, carboxyazetidinylpyrimidinyl, (tert-butoxycarbonyl)(hydroxy)azetidinylpyrimidinyl, tetrazolylazetidinylpyrimidinyl, hydroxytetrahydrofuranylpyrimidinyl, hydroxypyrrolidinylpyrimidinyl, carboxypyrrolidinylpyrimidinyl, (carboxy)(methyl)pyrrolidinylpyrimidinyl, carboxymethylpyrrolidinylpyrimidinyl, ethoxycarbonylpyrrolidinylpyrimidinyl, fluoro-

20 tetrahydropyranylpyrimidinyl, hydroxytetrahydropyranylpyrimidinyl, difluoropiperidinylpyrimidinyl, (cyano)(methyl)piperidinylpyrimidinyl, (hydroxy)(nitromethyl)piperidinylpyrimidinyl, (hydroxy)(methyl)piperidinylpyrimidinyl, (hydroxy)(trifluoromethyl)piperidinylpyrimidinyl, (hydroxymethyl)(methyl)piperidinylpyrimidinyl, methylsulphonylpiperidinylpyrimidinyl, oxopiperidinylpyrimidinyl, (formyl)(methyl)piperidinylpyrimidinyl, carboxypiperidinylpyrimidinyl, (carboxy)(fluoro)piperidinylpyrimidinyl, (carboxy)(methyl)piperidinylpyrimidinyl, (carboxy)(ethyl)piperidinylpyrimidinyl, (carboxy)(trifluoromethyl)piperidinylpyrimidinyl, (carboxy)(hydroxy)piperidinylpyrimidinyl, (carboxy)(hydroxymethyl)piperidinylpyrimidinyl, (carboxy)(methoxy)piperidinylpyrimidinyl, (amino)(carboxy)piperidinylpyrimidinyl, carboxymethylpiperidinylpyrimidinyl, methoxycarbonylpiperidinylpyrimidinyl, ethoxycarbonylpiperidinylpyrimidinyl, (ethoxycarbonyl)(fluoro)piperidinylpyrimidinyl, (methoxycarbonyl)(methyl)piperidinylpyrimidinyl, (ethyl)(methoxycarbonyl)piperidinyl-

25
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pyrimidinyl, (isopropyl)(methoxycarbonyl)piperidinylpyrimidinyl, (ethoxycarbonyl)-
 (methyl)piperidinylpyrimidinyl, (*n*-butoxycarbonyl)(methyl)piperidinylpyrimidinyl,
 (ethoxycarbonyl)(trifluoromethyl)piperidinylpyrimidinyl, (ethoxycarbonyl)-
 (hydroxymethyl)piperidinylpyrimidinyl, (methoxy)(methoxycarbonyl)piperidinyl-
 5 pyrimidinyl, (carboxy)(methoxycarbonyl)piperidinylpyrimidinyl, (methyl)-
 (morpholinylethoxycarbonyl)piperidinylpyrimidinyl, ethoxycarbonylmethylpiperidinyl-
 pyrimidinyl, methylsulphonylaminocarbonylpiperidinylpyrimidinyl, acetyl-amino-
 sulphonylpiperidinylpyrimidinyl, methoxyaminocarbonylpiperidinylpyrimidinyl,
 tetrazolylpiperidinylpyrimidinyl, hydroxyoxadiazolylpiperidinylpyrimidinyl, amino-
 10 sulphonylpiperidinylpyrimidinyl, piperazinylpyrimidinyl, methylsulphonylpiperazinyl-
 pyrimidinyl, oxopiperazinylpyrimidinyl, carboxypiperazinylpyrimidinyl, carboxyethyl-
 piperazinylpyrimidinyl, *tert*-butoxycarbonylpiperazinylpyrimidinyl, tetrazolylmethyl-
 piperazinylpyrimidinyl, trioxohexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinylpyrimidinyl,
 morpholinylpyrimidinyl, dimethylmorpholinylpyrimidinyl, hydroxymethylmorpholinyl-
 15 pyrimidinyl, carboxymorpholinylpyrimidinyl, (carboxy)(methyl)morpholinylpyrimidinyl,
 carboxymethylmorpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, dioxo-
 thiomorpholinylpyrimidinyl, carboxyazepanylpyrimidinyl, carboxyoxazepanyl-
 pyrimidinyl, oxodiazepanylpyrimidinyl, (oxodiazepanyl)(trifluoromethyl)pyrimidinyl,
 (oxodiazepanyl)(methoxy)pyrimidinyl, (methyl)(oxo)diazepanylpyrimidinyl, dioxo-
 20 thiadiazepanylpyrimidinyl, hydroxyoxetanylpyrazinyl, (carboxy)(methyl)piperidinyl-
 pyrazinyl, (ethoxycarbonyl)(methyl)piperidinylpyrazinyl, morpholinylmethylthienyl,
 morpholinylethylpyrazolyl, carboxy-3-azabicyclo[3.1.0]hexanylpyridinyl, carboxy-3-
 azabicyclo[3.1.0]hexanylpyridazinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyrimidinyl,
 (carboxy)(methyl)-3-azabicyclo[3.1.0]hexanylpyrimidinyl, methoxycarbonyl-3-
 25 azabicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonyl-3-azabicyclo[3.1.0]hexanyl-
 pyrimidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl, carboxy-2-oxa-5-azabicyclo-
 [2.2.1]heptanylpyrimidinyl, carboxy-3-azabicyclo[3.1.1]heptanylpyrimidinyl, carboxy-3-
 azabicyclo[4.1.0]heptanylpyridinyl, carboxy-3-azabicyclo[4.1.0]heptanylpyrimidinyl,
 methoxycarbonyl-3-azabicyclo[4.1.0]heptanylpyrimidinyl, ethoxycarbonyl-3-azabicyclo-
 30 [4.1.0]heptanylpyrimidinyl, (hydroxy)(methyl)(oxo)-2-oxabicyclo[2.2.2]octanyl-
 pyrimidinyl, carboxy-3-azabicyclo[3.2.1]octanylpyrimidinyl, methoxycarbonyl-3-
 azabicyclo[3.2.1]octanylpyrimidinyl, oxo-8-azabicyclo[3.2.1]octanylpyrimidinyl,
 ethoxycarbonylmethylidenyl-8-azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-azabicyclo-

[3.2.1]octanylpyrimidinyl, oxo-3,6-diazabicyclo[3.2.2]nonanylpyrimidinyl, carboxy-3-oxa-7-azabicyclo[3.3.1]nonanylpyrimidinyl, carboxy-5-azaspiro[2.3]hexanylpyrimidinyl, (carboxy)(methyl)-5-azaspiro[2.3]hexanylpyrimidinyl, carboxy-5-azaspiro[2.4]heptanylpyrimidinyl, carboxy-2-azaspiro[3.3]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.3]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.4]octanylpyrimidinyl, 2-oxa-6-azaspiro[3.5]nonanylpyrimidinyl, 2-oxa-7-azaspiro[3.5]nonanylpyrimidinyl and (dioxo)(methyl)-2,4,8-triazaspiro[4.5]decanylpyrimidinyl.

Illustrative values of R^{11} include hydrogen.

Typically, R^{15} and R^{16} may independently represent hydrogen, fluoro, chloro, bromo, cyano, nitro, methyl, isopropyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, *tert*-butylamino, dimethylamino, phenylamino, acetylamino, methylsulfonylamino, formyl, acetyl, cyclopropylcarbonyl, azetidiny carbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, piperazinylcarbonyl, morpholinylcarbonyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl and dimethylaminosulfonyl.

Typical values of R^{15} include hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, difluoromethoxy and trifluoromethoxy.

Illustrative values of R^{15} include halogen and difluoromethoxy.

In a first embodiment, R^{15} represents hydrogen. In a second embodiment, R^{15} represents halogen. In a first aspect of that embodiment, R^{15} represents fluoro. In a second aspect of that embodiment, R^{15} represents chloro. In a third embodiment, R^{15} represents C_{1-6} alkyl. In one aspect of that embodiment, R^{15} represents methyl. In a fourth embodiment, R^{15} represents trifluoromethyl. In a fifth embodiment, R^{15} represents C_{1-6} alkoxy. In one aspect of that embodiment, R^{15} represents methoxy. In a sixth embodiment, R^{15} represents difluoromethoxy. In a seventh embodiment, R^{15} represents trifluoromethoxy.

Selected values of R^{15} include hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy.

Particular values of R^{15} include chloro and difluoromethoxy.

Typical values of R^{16} include hydrogen, halogen, cyano, C_{1-6} alkyl, trifluoromethyl, difluoromethoxy and amino.

Illustrative values of R^{16} include hydrogen and halogen.

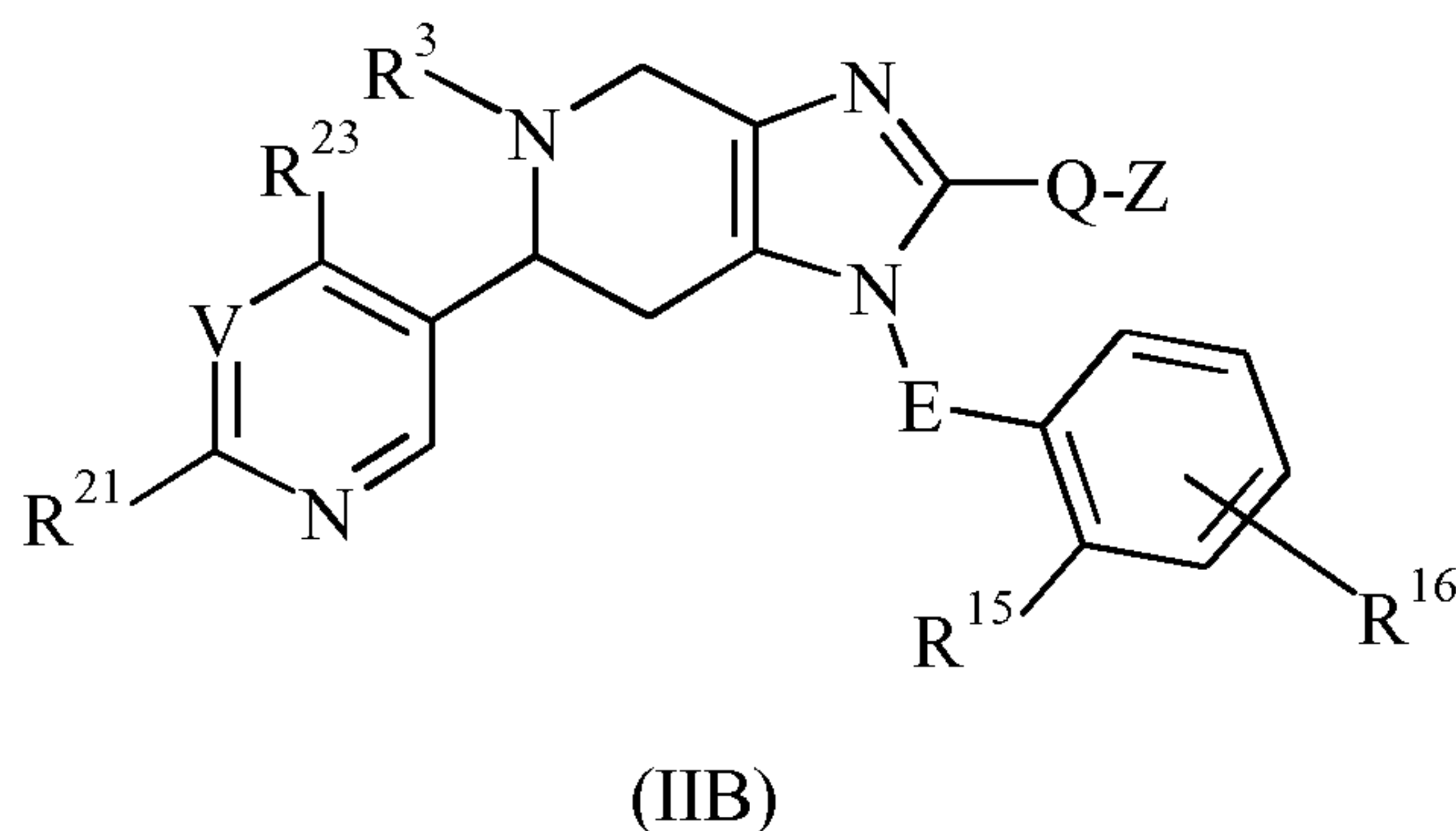
In a first embodiment, R^{16} represents hydrogen. In a second embodiment, R^{16} represents halogen. In a first aspect of that embodiment, R^{16} represents fluoro. In a second aspect of that embodiment, R^{16} represents chloro. In a third embodiment, R^{16} represents cyano. In a fourth embodiment, R^{16} represents C_{1-6} alkyl. In one aspect of that
 5 embodiment, R^{16} represents methyl. In a fifth embodiment, R^{16} represents trifluoromethyl. In a sixth embodiment, R^{16} represents difluoromethoxy. In a seventh embodiment, R^{16} represents amino.

Selected values of R^{16} include hydrogen, fluoro, chloro, cyano, methyl, trifluoromethyl, difluoromethoxy and amino.

10 Particular values of R^{16} include hydrogen and chloro.

In a particular embodiment, R^{16} is attached at the *para*-position of the phenyl ring relative to the integer R^{15} .

A particular sub-group of the compounds of formula (IIA) above is represented by the compounds of formula (IIB) and *N*-oxides thereof, and pharmaceutically acceptable
 15 salts and solvates thereof, and glucuronide derivatives thereof, and co-crystals thereof:



wherein

20 V represents $C-R^{22}$ or N;

R^{21} represents hydrogen, halogen, halo(C_{1-6})alkyl, cyano, C_{1-6} alkyl, trifluoromethyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, hydroxy(C_{1-6})alkyl, C_{1-6} alkoxy, (C_{1-6})alkoxy-
 25 (C_{1-6})alkyl, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, carboxy(C_{3-7})cycloalkyloxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, (C_{1-6})alkylsulphonyl(C_{1-6})alkyl, amino, amino-
 (C_{1-6})alkyl, C_{1-6} alkylamino, di(C_{1-6})alkylamino, (C_{1-6})alkoxy(C_{1-6})alkylamino, *N*-[(C_{1-6})-alkyl]-*N*-[hydroxy(C_{1-6})alkyl]amino, C_{2-6} alkylcarbonylamino, (C_{2-6})alkylcarbonylamino-
 (C_{1-6})alkyl, C_{2-6} alkoxycarbonylamino, *N*-[(C_{1-6})alkyl]-*N*-[carboxy(C_{1-6})alkyl]amino, carboxy(C_{3-7})cycloalkylamino, carboxy(C_{3-7})cycloalkyl(C_{1-6})alkylamino, C_{1-6} alkyl-

5 sulphonylamino, C₁₋₆ alkylsulphonylamino(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, morpholinyl(C₁₋₆)alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonylmethylidenyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl,
 10 aminosulphonyl, C₁₋₆ alkylaminosulphonyl, di(C₁₋₆)alkylaminosulphonyl, (C₁₋₆)alkylsulphoximinyl or [(C₁₋₆)alkyl][N-(C₁₋₆)alkyl]sulphoximinyl; or R²¹ represents (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl, (C₄₋₇)cycloalkenyl, (C₄₋₉)bicycloalkyl, (C₃₋₇)heterocycloalkyl, (C₃₋₇)heterocycloalkenyl, (C₄₋₉)heterobicycloalkyl or (C₄₋₉)spiroheterocycloalkyl, any of which groups may be optionally substituted by one or
 15 more substituents;

R²² represents hydrogen, halogen or C₁₋₆ alkyl;

R²³ represents hydrogen, C₁₋₆ alkyl, trifluoromethyl or C₁₋₆ alkoxy; and

E, Q, Z, R³, R¹⁵ and R¹⁶ are as defined above.

In one embodiment, V represents C-R²². In another embodiment, V represents N.

15 Typically, R²¹ represents hydrogen, halogen, halo(C₁₋₆)alkyl, cyano, C₁₋₆ alkyl, trifluoromethyl, C₂₋₆ alkenyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, trifluoroethoxy, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, N-[(C₁₋₆)alkyl]-N-[hydroxy(C₁₋₆)alkyl]-amino, N-[(C₁₋₆)alkyl]-N-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino,
 20 carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, C₁₋₆ alkylsulphonylamino, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, carboxy, morpholinyl(C₁₋₆)alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl or C₂₋₆ alkoxy carbonylmethylidenyl; or R²¹ represents (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl, (C₄₋₇)cycloalkenyl, (C₄₋₉)bicycloalkyl, (C₃₋₇)heterocycloalkyl, (C₄₋₉)heterobicycloalkyl or (C₄₋₉)spiroheterocycloalkyl, any of which groups may be
 25 optionally substituted by one or more substituents.

Where R²¹ represents an optionally substituted (C₃₋₇)cycloalkyl group, typical values include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, any of which groups may be optionally substituted by one or more substituents.

30 Where R²¹ represents an optionally substituted (C₃₋₇)cycloalkyl(C₁₋₆)alkyl group, a typical value is cyclohexylmethyl, which group may be optionally substituted by one or more substituents.

Where R^{21} represents an optionally substituted (C_{4-7})cycloalkenyl group, typical values include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl, any of which groups may be optionally substituted by one or more substituents.

Where R^{21} represents an optionally substituted (C_{4-9})bicycloalkyl group, typical values include bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl and bicyclo[2.2.2]octanyl, any of which groups may be optionally substituted by one or more substituents.

Where R^{21} represents an optionally substituted (C_{3-7})heterocycloalkyl group, typical values include oxetanyl, azetidiny, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinyl, morpholinyl, thiomorpholinyl, azepanyl, oxazepanyl, diazepanyl and thiadiazepanyl, any of which groups may be optionally substituted by one or more substituents.

Where R^{21} represents an optionally substituted (C_{3-7})heterocycloalkenyl group, a typical value is optionally substituted 1,2,3,6-tetrahydropyridinyl.

Where R^{21} represents an optionally substituted (C_{4-9})heterobicycloalkyl group, typical values include 3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, 2-oxabicyclo[2.2.2]octanyl, quinuclidinyl, 2-oxa-5-azabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 3,6-diazabicyclo[3.2.2]nonanyl, 3-oxa-7-azabicyclo[3.3.1]nonanyl and 3,9-diazabicyclo[4.2.1]nonanyl, any of which groups may be optionally substituted by one or more substituents.

Where R^{21} represents an optionally substituted (C_{4-9})spiroheterocycloalkyl group, typical values include 5-azaspiro[2.3]hexanyl, 5-azaspiro[2.4]heptanyl, 2-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-6-azaspiro[3.5]nonanyl, 2-oxa-7-azaspiro[3.5]nonanyl and 2,4,8-triazaspiro[4.5]-decanyl, any of which groups may be optionally substituted by one or more substituents.

Illustratively, R^{21} represents hydroxy, hydroxy(C_{1-6})alkyl, methoxy, carboxycyclobutyloxy, methylthio, methylsulphonyl, methylamino, *N*-[carboxyethyl]-*N*-methylamino, carboxycyclopentylamino, carboxycyclopropylmethylamino or ethoxycarbonyl-ethyl; or R^{21} represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, cyclohexenyl, bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl, bicyclo[2.2.2]octanyl, oxetanyl, azetidiny, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinyl, morpholinyl,

thiomorpholinyl, azepanyl, oxazepanyl, diazepanyl, thiadiazepanyl, 3-azabicyclo[3.1.0]-hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, 2-oxabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 3,6-diazabicyclo[3.2.2]nonanyl, 3-oxa-7-azabicyclo[3.3.1]nonanyl, 5-azaspiro[2.3]hexanyl, 5-azaspiro[2.4]heptanyl or 2-azaspiro[3.3]heptanyl, any of which groups may be optionally substituted by one or more substituents.

Examples of optional substituents which may be present on R²¹ include one, two or three substituents independently selected from halogen, halo(C₁₋₆)alkyl, cyano, cyano-
 10 (C₁₋₆)alkyl, nitro, nitro(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₂₋₆ alkenyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, (C₂₋₆)alkylcarbonylamino-
 15 (C₁₋₆)alkyl, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, morpholinyl-
 (C₁₋₆)alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonylmethylidenyl, a carboxylic acid isostere or prodrug moiety Ω as defined herein, -(C₁₋₆)alkyl- Ω , amino-carbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, di(C₁₋₆)alkylaminosulphonyl, (C₁₋₆)alkylsulphoximinyl and [(C₁₋₆)alkyl][N-(C₁₋₆)alkyl]-
 20 sulphoximinyl.

Suitable examples of optional substituents on R²¹ include one, two or three substituents independently selected from fluoro, fluoromethyl, chloro, bromo, cyano, cyanomethyl, cyanoethyl, nitro, nitromethyl, methyl, ethyl, isopropyl, trifluoromethyl, trifluoroethyl, ethenyl, hydroxy, hydroxymethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, methylthio, methylsulphonyl, methylsulphonylmethyl, methylsulphonylethyl, oxo, amino, methylamino, dimethylamino, acetylamino, acetylaminomethyl, methoxycarbonylamino, ethoxycarbonylamino, *tert*-butoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *n*-butoxycarbonyl, *tert*-butoxycarbonyl, morpholinyl-
 25 ethoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, ethoxycarbonylmethylidenyl, acetaminosulphonyl, methoxyaminocarbonyl, tetrazolyl, tetrazolylmethyl, hydroxyoxadiazolyl, aminocarbonyl, methylaminocarbonyl, dimethyl-

aminocarbonyl, methylsulphonylaminocarbonyl, aminosulphonyl, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphoximinyl and (methyl)(*N*-methyl)sulphoximinyl.

Typically, R²¹ represents hydrogen, fluoro, fluoroisopropyl, cyano, methyl, trifluoromethyl, ethenyl, hydroxy, hydroxyisopropyl, methoxy, isopropoxy, trifluoro-
 5 ethoxy, carboxycyclobutyloxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, methoxyethylamino, *N*-(hydroxyethyl)-*N*-(methyl)amino, *N*-[carboxyethyl]-*N*-methylamino, carboxycyclopentylamino, carboxycyclopropylmethylamino, methylsulphonylamino, acetoxisopropyl, carboxy, ethoxycarbonyl-ethyl, fluoromethyl-
 10 cyclopropyl, acetylaminomethylcyclopropyl, hydroxycyclobutyl, carboxycyclopentyl, carboxycyclohexyl, (carboxy)(methyl)cyclohexyl, (carboxy)(hydroxy)cyclohexyl, carboxymethylcyclohexyl, ethoxycarbonylcyclohexyl, (methoxycarbonyl)(methyl)-
 cyclohexyl, (ethoxycarbonyl)(methyl)cyclohexyl, carboxycyclohexylmethyl, carboxy-
 cyclohexenyl, ethoxycarbonylcyclohexenyl, carboxybicyclo[3.1.0]hexanyl, ethoxycarbonylbicyclo[3.1.0]hexanyl, carboxybicyclo[4.1.0]heptanyl, carboxybicyclo-
 15 [2.2.2]octanyl, fluoroxyetanyl, hydroxyoxyetanyl, hydroxyazetidiny, (hydroxy)(methyl)-
 azetidiny, carboxyazetidiny, (*tert*-butoxycarbonyl)(hydroxy)azetidiny, tetrazolyl-
 azetidiny, hydroxytetrahydrofuranyl, pyrrolidiny, hydroxypyrrolidiny, carboxy-
 pyrrolidiny, (carboxy)(methyl)pyrrolidiny, carboxymethylpyrrolidiny, ethoxycarbonyl-
 pyrrolidiny, fluorotetrahydropyranyl, hydroxytetrahydropyranyl, piperidiny, difluoro-
 20 piperidiny, (cyano)(methyl)piperidiny, (hydroxy)(nitromethyl)piperidiny, (hydroxy)-
 (methyl)piperidiny, (hydroxy)(trifluoromethyl)piperidiny, (hydroxymethyl)(methyl)-
 piperidiny, methylsulphonylpiperidiny, oxopiperidiny, (formyl)(methyl)piperidiny, acetyl-
 piperidiny, carboxypiperidiny, (carboxy)(fluoro)piperidiny, (carboxy)(methyl)-
 piperidiny, (carboxy)(ethyl)piperidiny, (carboxy)(trifluoromethyl)piperidiny, (carboxy)-
 25 (hydroxy)piperidiny, (carboxy)(hydroxymethyl)piperidiny, (carboxy)(methoxy)-
 piperidiny, (amino)(carboxy)piperidiny, carboxymethylpiperidiny, methoxycarbonyl-
 piperidiny, (methoxycarbonyl)(methyl)piperidiny, (ethyl)(methoxycarbonyl)piperidiny, (isopropyl)(methoxycarbonyl)piperidiny, (methoxy)(methoxycarbonyl)piperidiny,
 (carboxy)(methoxycarbonyl)piperidiny, ethoxycarbonylpiperidiny, (ethoxycarbonyl)-
 30 (fluoro)piperidiny, (ethoxycarbonyl)(methyl)piperidiny, (ethoxycarbonyl)(trifluoro-
 methyl)piperidiny, (ethoxycarbonyl)(hydroxymethyl)piperidiny, (*n*-butoxycarbonyl)-
 (methyl)piperidiny, (methyl)(morpholinylethoxycarbonyl)piperidiny, ethoxycarbonyl-
 methylpiperidiny, methylsulphonylaminocarbonylpiperidiny, acetylaminosulphonyl-

piperidinyl, methoxyaminocarbonylpiperidinyl, tetrazolylpiperidinyl, hydroxyoxadiazolyl-
 piperidinyl, aminosulphonylpiperidinyl, piperazinyl, cyanoethylpiperazinyl, trifluoroethyl-
 piperazinyl, methylsulphonylpiperazinyl, methylsulphonylethylpiperazinyl,
 oxopiperazinyl, acetyl piperazinyl, carboxypiperazinyl, *tert*-butoxycarbonylpiperazinyl,
 5 carboxymethylpiperazinyl, carboxyethylpiperazinyl, ethoxycarbonylmethylpiperazinyl,
 ethoxycarbonylethylpiperazinyl, tetrazolylmethylpiperazinyl, trioxohexahydro-
 [1,2,5]thiadiazolo[2,3-*a*]pyrazinyl, morpholinyl, dimethylmorpholinyl, hydroxymethyl-
 morpholinyl, carboxymorpholinyl, (carboxy)(methyl)morpholinyl, carboxymethyl-
 morpholinyl, thiomorpholinyl, oxothiomorpholinyl, dioxothiomorpholinyl, carboxy-
 10 azepanyl, carboxyoxazepanyl, oxodiazepanyl, (methyl)(oxo)diazepanyl, dioxo-
 thiadiazepanyl, carboxy-3-azabicyclo[3.1.0]hexanyl, (carboxy)(methyl)-3-azabicyclo-
 [3.1.0]hexanyl, methoxycarbonyl-3-azabicyclo[3.1.0]hexanyl, ethoxycarbonyl-3-
 azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, carboxy-2-oxa-5-
 azabicyclo[2.2.1]heptanyl, carboxy-3-azabicyclo[3.1.1]heptanyl, carboxy-3-azabicyclo-
 15 [4.1.0]heptanyl, methoxycarbonyl-3-azabicyclo[4.1.0]heptanyl, ethoxycarbonyl-3-
 azabicyclo[4.1.0]heptanyl, (hydroxy)(methyl)(oxo)-2-oxabicyclo[2.2.2]octanyl, carboxy-
 3-azabicyclo[3.2.1]octanyl, methoxycarbonyl-3-azabicyclo[3.2.1]octanyl, oxo-8-
 azabicyclo[3.2.1]octanyl, ethoxycarbonylmethylidenyl-8-azabicyclo[3.2.1]octanyl, 3-oxa-
 8-azabicyclo[3.2.1]octanyl, oxo-3,6-diazabicyclo[3.2.2]nonanyl, carboxy-3-oxa-7-
 20 azabicyclo[3.3.1]nonanyl, carboxy-5-azaspiro[2.3]hexanyl, (carboxy)(methyl)-5-azaspiro-
 [2.3]hexanyl, carboxy-5-azaspiro[2.4]heptanyl, carboxy-2-azaspiro[3.3]heptanyl, 2-oxa-6-
 azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-6-azaspiro[3.5]nonanyl, 2-oxa-
 7-azaspiro[3.5]nonanyl or (dioxo)(methyl)-2,4,8-triazaspiro[4.5]decanyl.

In a particular embodiment, R²¹ represents hydroxy(C₁₋₆)alkyl. In one aspect of
 25 that embodiment, R²¹ represents hydroxyisopropyl, especially 2-hydroxyprop-2-yl.

Generally, R²² represents hydrogen or C₁₋₆ alkyl.

Suitably, R²² represents hydrogen, chloro or methyl.

Typically, R²² represents hydrogen or methyl.

In one embodiment, R²² represents hydrogen. In another embodiment, R²²
 30 represents C₁₋₆ alkyl, especially methyl. In a further embodiment, R²² represents halogen.
 In one aspect of that embodiment, R²² represents fluoro. In another aspect of that
 embodiment, R²² represents chloro.

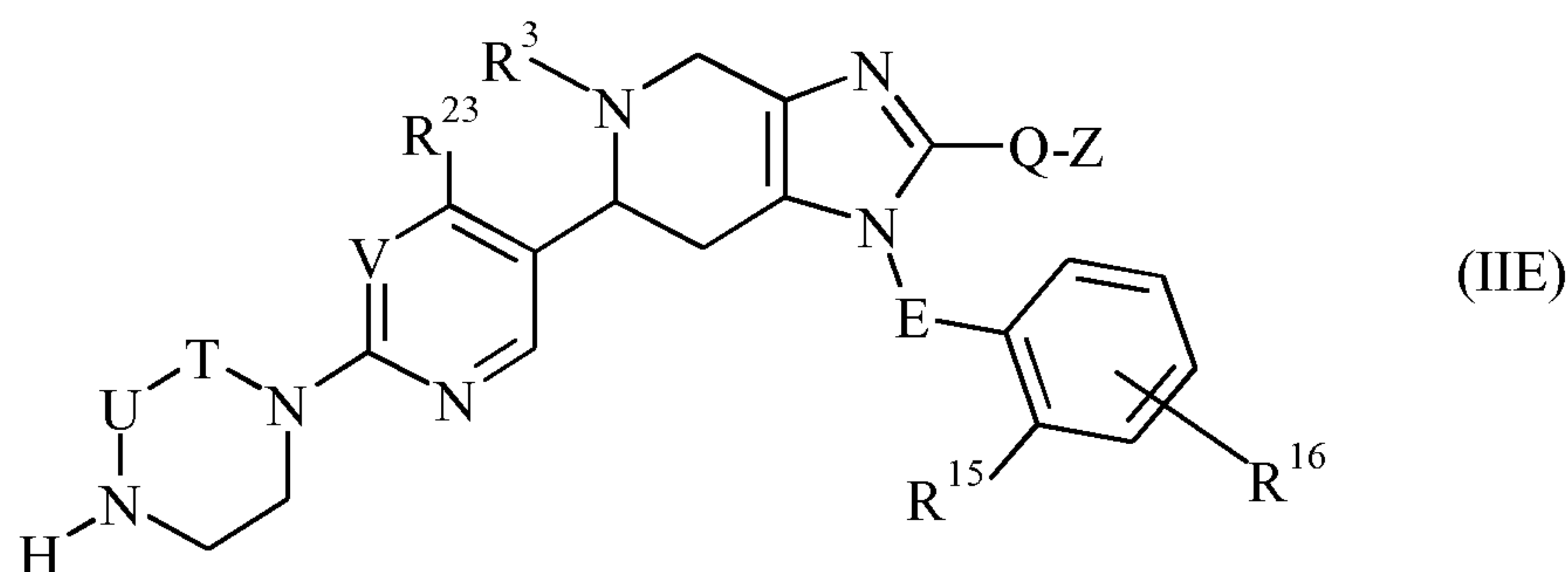
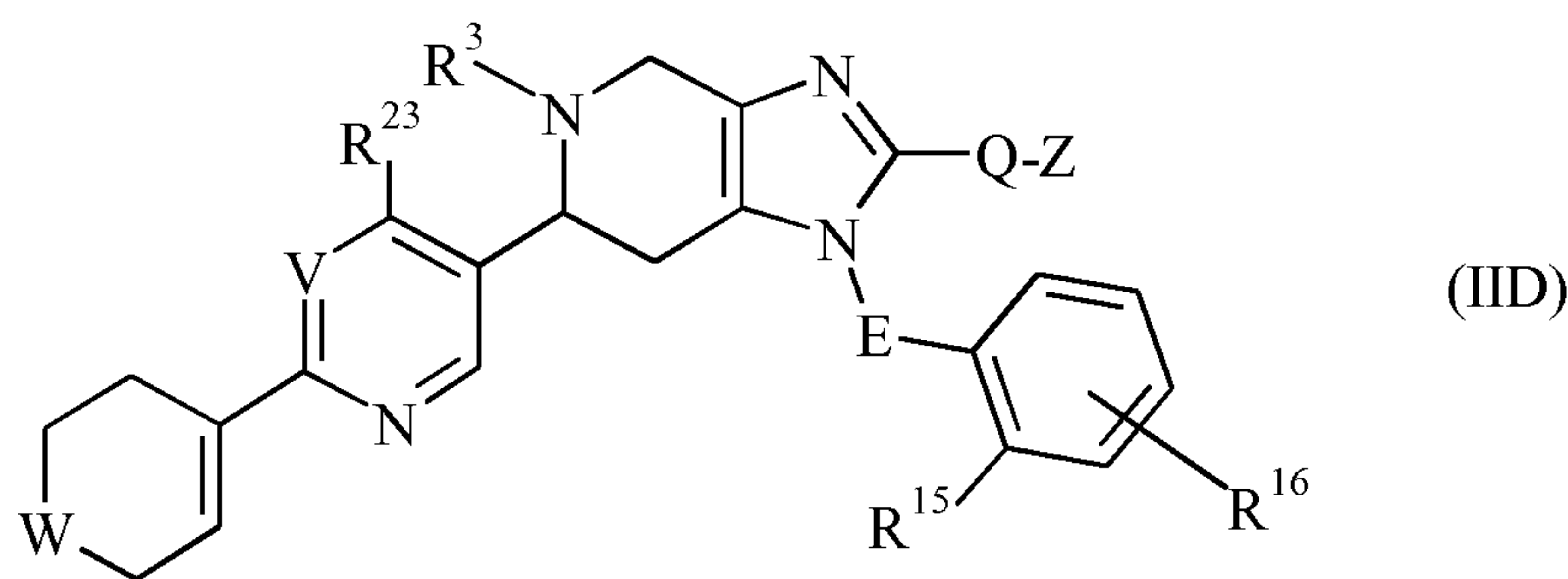
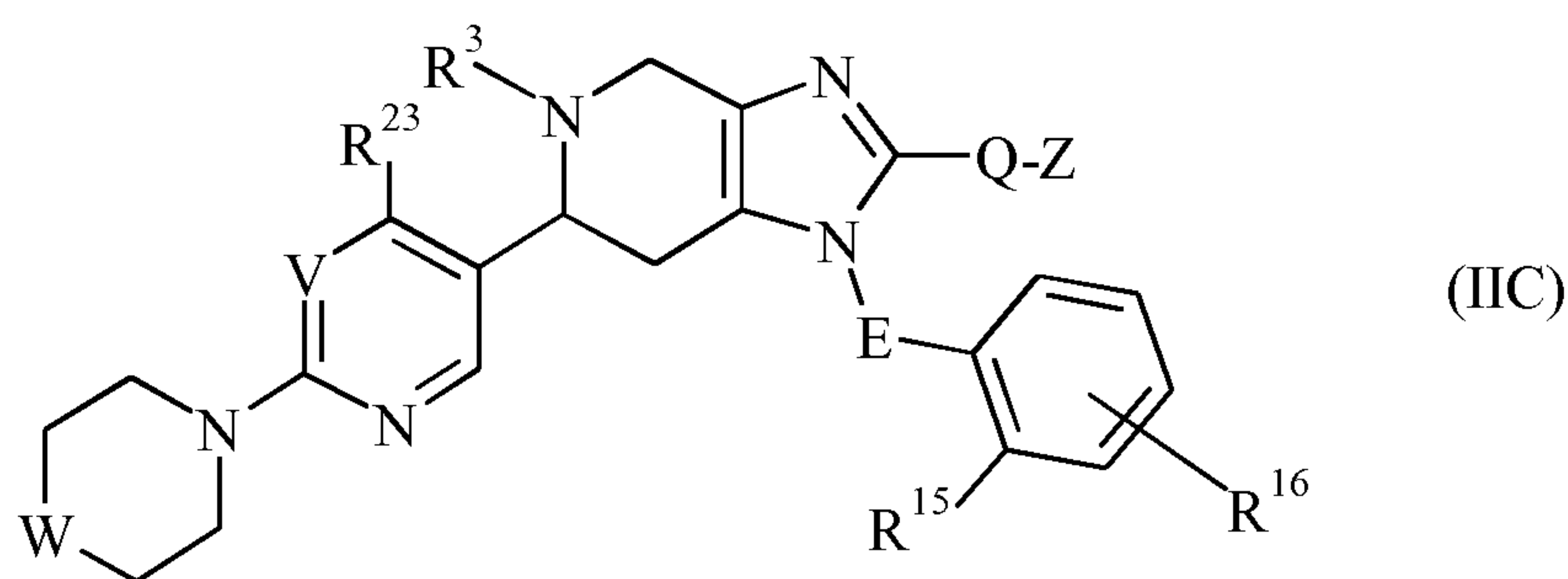
Generally, R²³ represents hydrogen or C₁₋₆ alkyl.

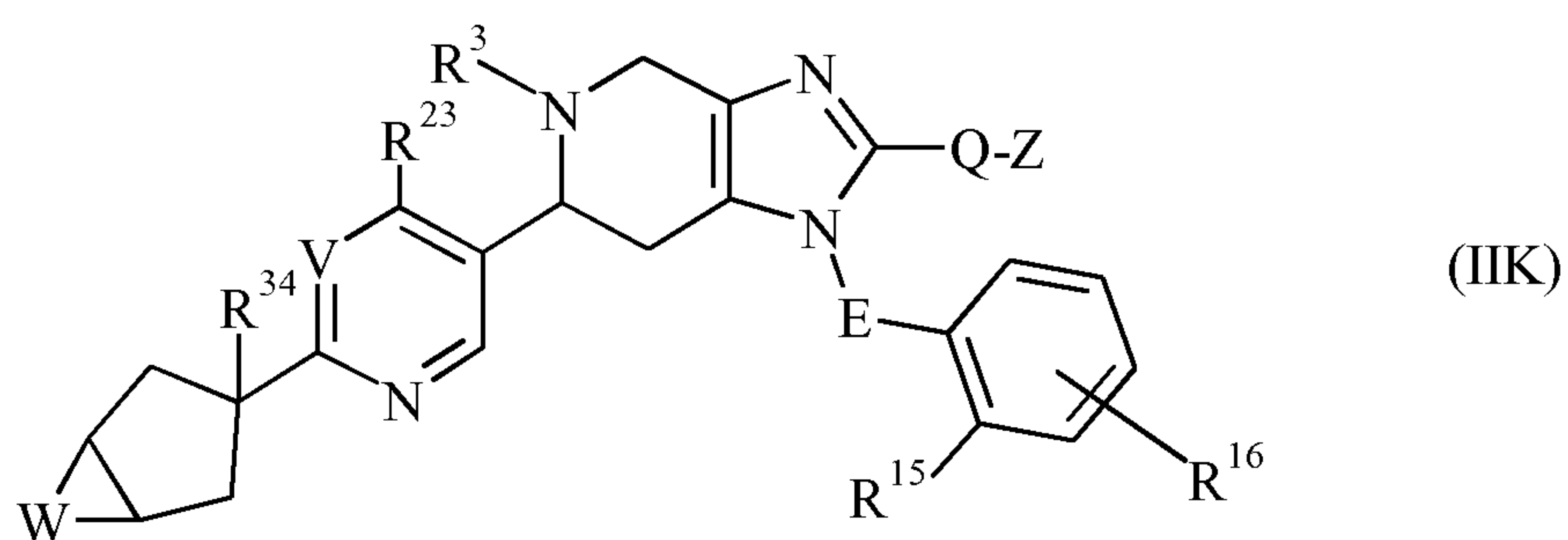
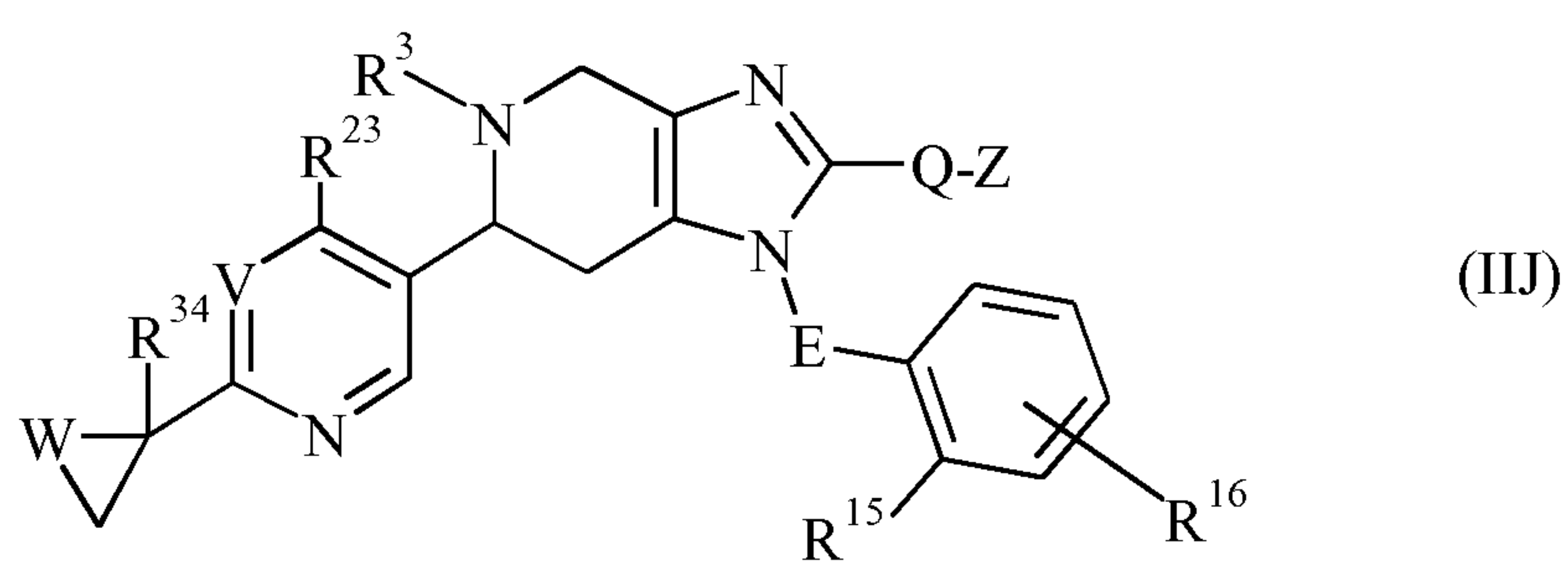
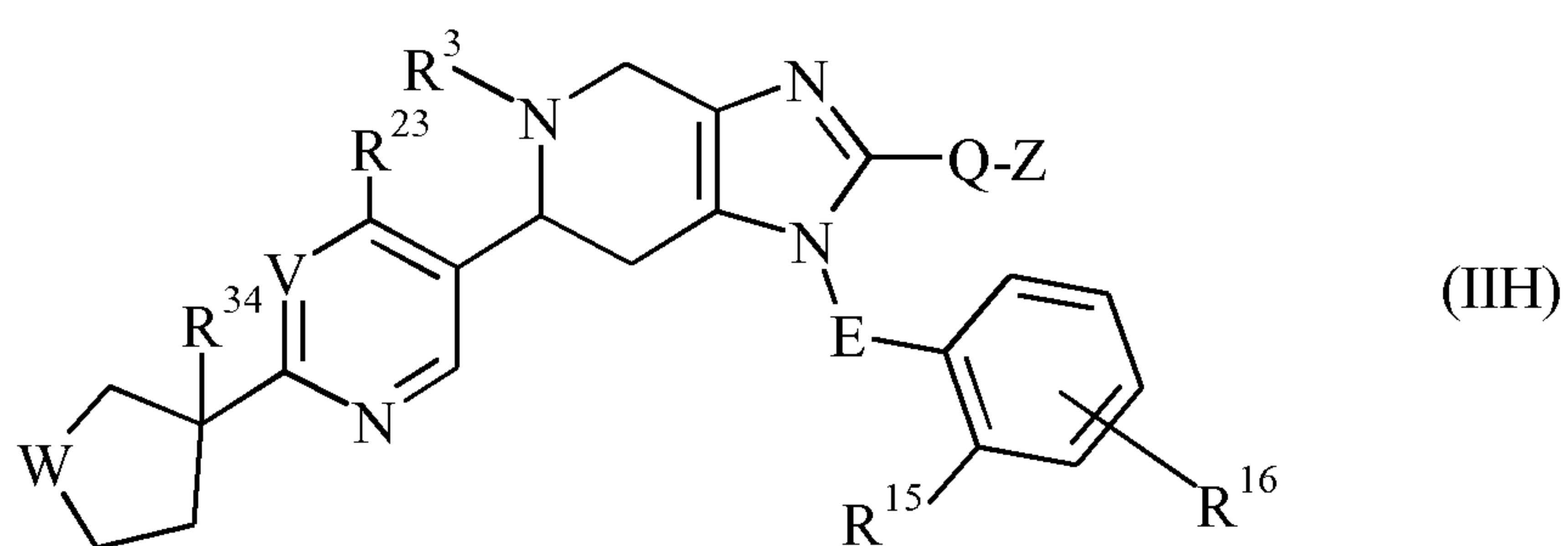
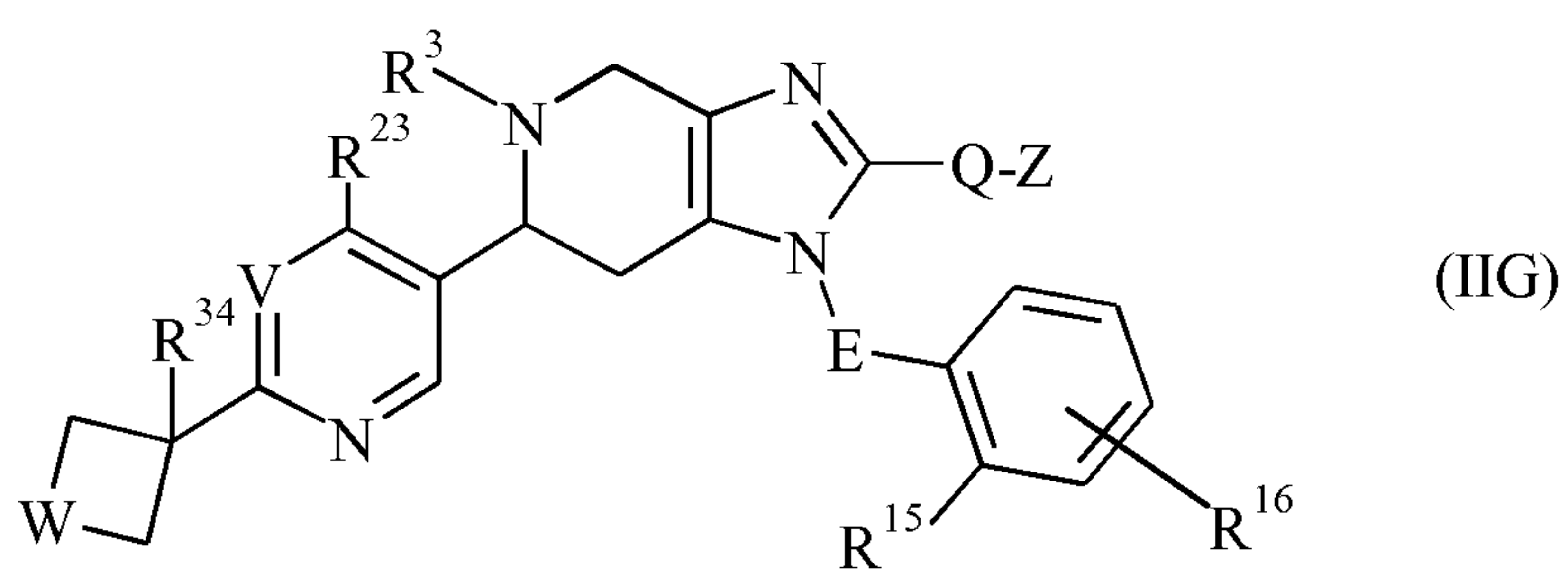
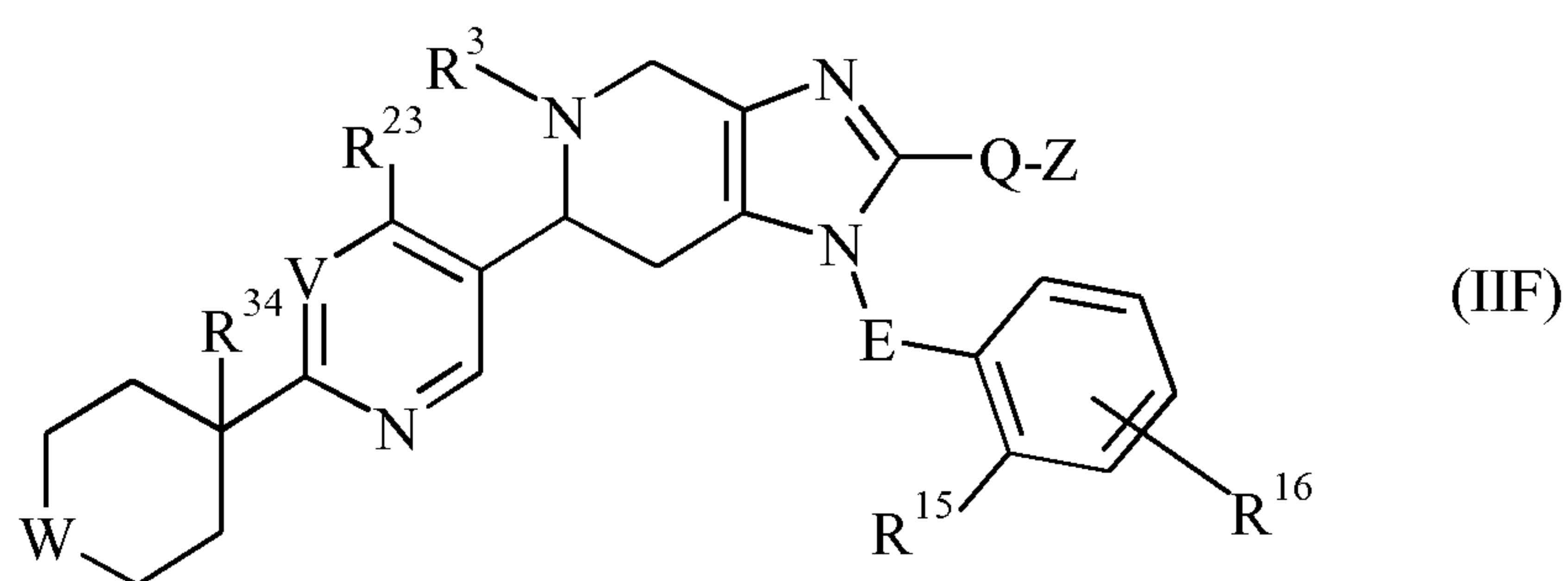
Suitably, R^{23} represents hydrogen, methyl, trifluoromethyl or methoxy.

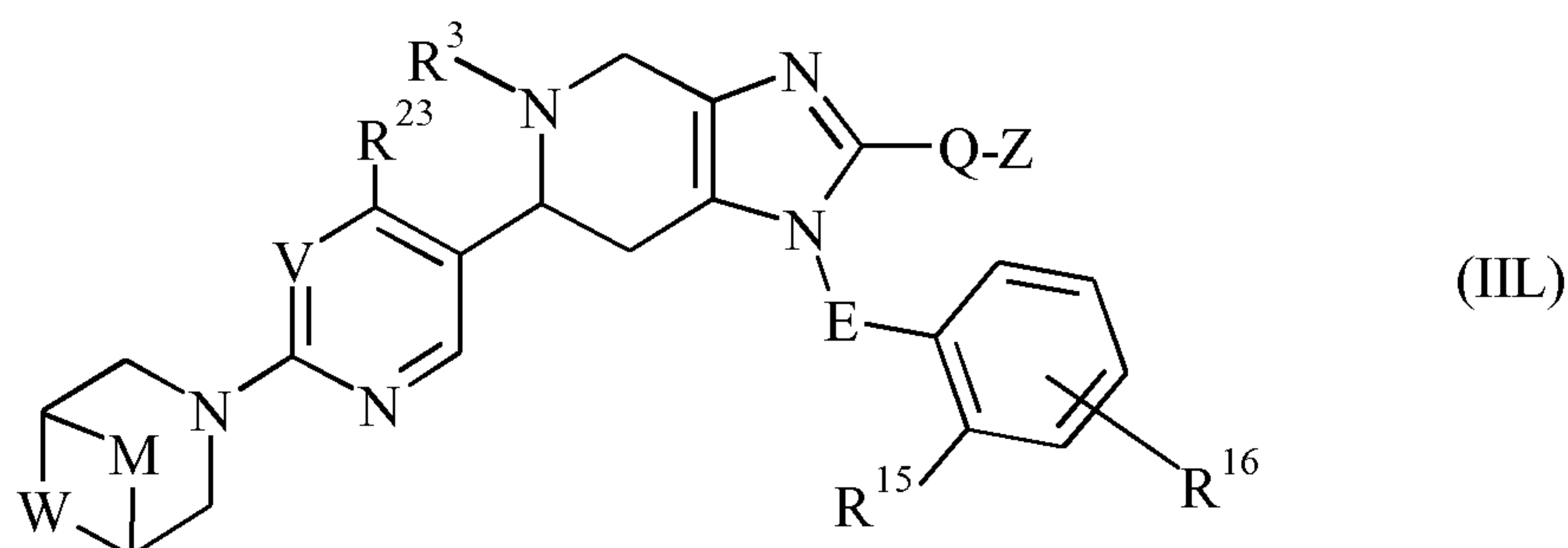
Typically, R^{23} represents hydrogen or methyl.

In one embodiment, R^{23} represents hydrogen. In another embodiment, R^{23} represents C_{1-6} alkyl, especially methyl. In a further embodiment, R^{23} represents trifluoromethyl. In an additional embodiment, R^{23} represents C_{1-6} alkoxy, especially methoxy.

Particular sub-groups of the compounds of formula (IIB) above are represented by the compounds of formula (IIC), (IID), (IIE), (IIF), (IIG), (IIH), (IIJ), (IIK) and (IIL), and *N*-oxides thereof, and pharmaceutically acceptable salts and solvates thereof, and glucuronide derivatives thereof, and co-crystals thereof:







wherein

T represents -CH₂- or -CH₂CH₂-;

5 U represents C(O) or S(O)₂;

W represents O, S, S(O), S(O)₂, S(O)(NR⁵), N(R³¹) or C(R³²)(R³³);

-M- represents -CH₂- or -CH₂CH₂-;

R³¹ represents hydrogen, cyano(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, a
 10 carboxylic acid isostere or prodrug moiety Ω, -(C₁₋₆)alkyl-Ω, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl or di(C₁₋₆)alkylaminosulphonyl;

R³² represents hydrogen, halogen, cyano, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkylsulphonyl, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, aminosulphonyl, (C₁₋₆)alkylsulphoximinyl, [(C₁₋₆)alkyl][N-(C₁₋₆)alkyl]sulphoximinyl, a carboxylic acid isostere or
 15 prodrug moiety Ω, or -(C₁₋₆)alkyl-Ω;

R³³ represents hydrogen, halogen, C₁₋₆ alkyl, trifluoromethyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, amino or carboxy;
 20 (C₁₋₆)alkyl, C₁₋₆ alkoxy, amino or carboxy;

R³⁴ represents hydrogen, halogen, halo(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₂₋₆)alkylcarbonylamino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, (C₁₋₆)alkylsulphonylamino or (C₁₋₆)alkylsulphonylamino(C₁₋₆)alkyl; and

25 V, E, Q, Z, R³, R⁵, R¹⁵, R¹⁶, R²³ and Ω are as defined above.

In a first embodiment, T represents -CH₂-. In a second embodiment, T represents -CH₂CH₂-.

In a first embodiment, U represents C(O). In a second embodiment, U represents S(O)₂.

Generally, W represents O, S(O)₂, N(R³¹) or C(R³²)(R³³).

Typically, W represents O, N(R³¹) or C(R³²)(R³³).

5 Appositely, W represents O or N(R³¹).

In a first embodiment, W represents O. In a second embodiment, W represents S. In a third embodiment, W represents S(O). In a fourth embodiment, W represents S(O)₂. In a fifth embodiment, W represents S(O)(NR⁵). In a sixth embodiment, W represents N(R³¹). In a seventh embodiment, W represents C(R³²)(R³³).

10 In one embodiment, -M- represents -CH₂-. In another embodiment, -M- represents -CH₂CH₂-.

Typically, R³¹ represents hydrogen, cyano(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl-
15 (C₁₋₆)alkyl, tetrazolyl(C₁₋₆)alkyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl or di(C₁₋₆)alkylaminosulphonyl.

Typical values of R³¹ include hydrogen, cyanoethyl, methyl, ethyl, isopropyl, trifluoromethyl, trifluoroethyl, methylsulphonyl, methylsulphonylethyl, formyl, acetyl,
20 carboxy, carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, tetrazolylmethyl, aminocarbonyl, methylamino-carbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl.

In a particular embodiment, R³¹ represents hydrogen.

25 Generally, R³² represents halogen, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω, or -(C₁₋₆)alkyl-Ω.

Typically, R³² represents hydrogen, halogen, cyano, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkylsulphonyl, formyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, aminosulphonyl, (C₁₋₆)alkylsulphoximinyl, [(C₁₋₆)alkyl][N-(C₁₋₆)alkyl]sulphoximinyl, (C₁₋₆)alkylsulphonylaminocarbonyl, (C₂₋₆)alkylcarbonylamino-
30 sulphonyl, (C₁₋₆)alkoxyaminocarbonyl, tetrazolyl or hydroxyoxadiazolyl.

Typical values of R^{32} include hydrogen, fluoro, cyano, hydroxy, hydroxymethyl, methylsulphonyl, formyl, carboxy, carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, methoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, aminosulphonyl, methylsulphoximinyl, (methyl)(*N*-methyl)sulphoximinyl, methylsulphonylaminocarbonyl, acetylaminosulphonyl, methoxyaminocarbonyl, tetrazolyl and hydroxyoxadiazolyl.

In a selected embodiment, R^{32} represents carboxy.

Generally, R^{33} represents hydrogen, halogen or C_{1-6} alkyl.

Suitably, R^{33} represents hydrogen or C_{1-6} alkyl.

Selected values of R^{33} include hydrogen, fluoro, methyl, ethyl, isopropyl, trifluoromethyl, hydroxy, hydroxymethyl, methoxy, amino and carboxy.

Selected values of R^{33} include hydrogen and methyl.

In a first embodiment, R^{33} represents hydrogen. In a second embodiment, R^{33} represents halogen. In one aspect of that embodiment, R^{33} represents fluoro. In a third embodiment, R^{33} represents C_{1-6} alkyl. In a first aspect of that embodiment, R^{33} represents methyl. In a second aspect of that embodiment, R^{33} represents ethyl. In a third aspect of that embodiment, R^{33} represents isopropyl. In a fourth embodiment, R^{33} represents trifluoromethyl. In a fifth embodiment, R^{33} represents hydroxy. In a sixth embodiment, R^{33} represents hydroxy(C_{1-6})alkyl. In one aspect of that embodiment, R^{33} represents hydroxymethyl. In a seventh embodiment, R^{33} represents C_{1-6} alkoxy. In one aspect of that embodiment, R^{33} represents methoxy. In an eighth embodiment, R^{33} represents amino. In a ninth embodiment, R^{33} represents carboxy.

In a first embodiment, R^{34} represents hydrogen. In a second embodiment, R^{34} represents halogen. In one aspect of that embodiment, R^{34} represents fluoro. In a third embodiment, R^{34} represents halo(C_{1-6})alkyl. In one aspect of that embodiment, R^{34} represents fluoromethyl. In a fourth embodiment, R^{34} represents hydroxy. In a fifth embodiment, R^{34} represents C_{1-6} alkoxy, especially methoxy. In a sixth embodiment, R^{34} represents C_{1-6} alkylthio, especially methylthio. In a seventh embodiment, R^{34} represents C_{1-6} alkylsulphinyl, especially methylsulphinyl. In an eighth embodiment, R^{34} represents C_{1-6} alkylsulphonyl, especially methylsulphonyl. In a ninth embodiment, R^{34} represents amino. In a tenth embodiment, R^{34} represents C_{1-6} alkylamino, especially methylamino. In an eleventh embodiment, R^{34} represents di(C_{1-6})alkylamino, especially dimethylamino. In a twelfth embodiment, R^{34} represents (C_{2-6})alkylcarbonylamino, especially acetylamino.

In a thirteenth embodiment, R^{34} represents (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, especially acetylaminomethyl. In a fourteenth embodiment, R^{34} represents (C₁₋₆)alkylsulphonylamino, especially methylsulphonylamino. In a fifteenth embodiment, R^{34} represents (C₁₋₆)alkylsulphonylamino(C₁₋₆)alkyl, especially methylsulphonylaminomethyl.

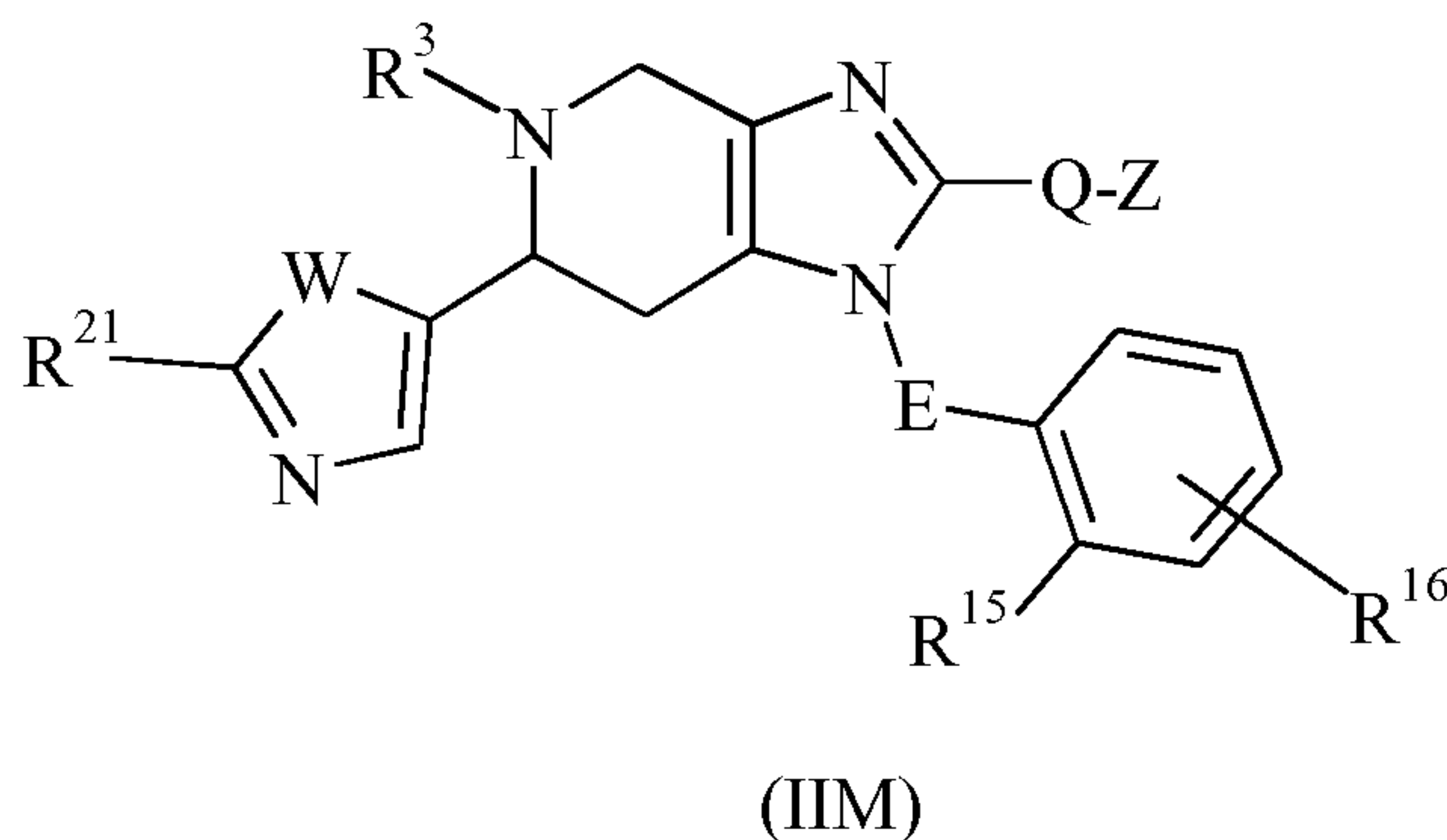
5 Typically, R^{34} represents hydrogen, halogen, halo(C₁₋₆)alkyl, hydroxy or (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl.

Selected values of R^{34} include hydrogen, fluoro, fluoromethyl, hydroxy, methoxy, methylthio, methylsulphinyl, methylsulphonyl, amino, methylamino, dimethylamino and acetylaminomethyl.

10 Particular values of R^{34} include hydrogen, fluoro, fluoromethyl, hydroxy and acetylaminomethyl.

Suitably, R^{34} represents hydrogen or hydroxy.

An alternative sub-class of compounds according to the invention is represented by the compounds of formula (IIM) and *N*-oxides thereof, and pharmaceutically acceptable
15 salts and solvates thereof, and glucuronide derivatives thereof, and co-crystals thereof:



wherein

20 E, Q, Z, W, R^3 , R^{15} , R^{16} and R^{21} are as defined above.

With specific reference to formula (IIM), the integer W is suitably O, S or N- R^{31} , especially S or N- R^{31} .

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

The compounds in accordance with the present invention are beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders; neurological and neurodegenerative disorders; pain and

nociceptive disorders; cardiovascular disorders; metabolic disorders; ocular disorders; and oncological disorders.

Inflammatory and autoimmune disorders include systemic autoimmune disorders, autoimmune endocrine disorders and organ-specific autoimmune disorders. Systemic
 5 autoimmune disorders include systemic lupus erythematosus (SLE), psoriasis, psoriatic arthropathy, vasculitis, polymyositis, scleroderma, multiple sclerosis, systemic sclerosis, ankylosing spondylitis, rheumatoid arthritis, non-specific inflammatory arthritis, juvenile inflammatory arthritis, juvenile idiopathic arthritis (including oligoarticular and polyarticular forms thereof), anaemia of chronic disease (ACD), Still's disease (juvenile
 10 and/or adult onset), Behçet's disease and Sjögren's syndrome. Autoimmune endocrine disorders include thyroiditis. Organ-specific autoimmune disorders include Addison's disease, haemolytic or pernicious anaemia, acute kidney injury (AKI; including cisplatin-induced AKI), diabetic nephropathy (DN), obstructive uropathy (including cisplatin-induced obstructive uropathy), glomerulonephritis (including Goodpasture's syndrome,
 15 immune complex-mediated glomerulonephritis and antineutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis), lupus nephritis (LN), minimal change disease, Graves' disease, idiopathic thrombocytopenic purpura, inflammatory bowel disease (including Crohn's disease, ulcerative colitis, indeterminate colitis and pouchitis), pemphigus, atopic dermatitis, autoimmune hepatitis, primary biliary cirrhosis, autoimmune
 20 pneumonitis, autoimmune carditis, myasthenia gravis, spontaneous infertility, osteoporosis, osteopenia, erosive bone disease, chondritis, cartilage degeneration and/or destruction, fibrosing disorders (including various forms of hepatic and pulmonary fibrosis), asthma, rhinitis, chronic obstructive pulmonary disease (COPD), respiratory distress syndrome, sepsis, fever, muscular dystrophy (including Duchenne muscular
 25 dystrophy) and organ transplant rejection (including kidney allograft rejection).

Neurological and neurodegenerative disorders include Alzheimer's disease, Parkinson's disease, Huntington's disease, ischaemia, stroke, amyotrophic lateral sclerosis, spinal cord injury, head trauma, seizures and epilepsy.

Cardiovascular disorders include thrombosis, cardiac hypertrophy, hypertension,
 30 irregular contractility of the heart (e.g. during heart failure), and sexual disorders (including erectile dysfunction and female sexual dysfunction). Modulators of TNF α function may also be of use in the treatment and/or prevention of myocardial infarction (see J.J. Wu *et al.*, *JAMA*, 2013, **309**, 2043-2044).

Metabolic disorders include diabetes (including insulin-dependent diabetes mellitus and juvenile diabetes), dyslipidemia and metabolic syndrome.

Ocular disorders include retinopathy (including diabetic retinopathy, proliferative retinopathy, non-proliferative retinopathy and retinopathy of prematurity), macular
5 oedema (including diabetic macular oedema), age-related macular degeneration (ARMD),
vascularisation (including corneal vascularisation and neovascularisation), retinal vein
occlusion, and various forms of uveitis and keratitis.

Oncological disorders, which may be acute or chronic, include proliferative disorders, especially cancer, and cancer-associated complications (including skeletal
10 complications, cachexia and anaemia). 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
15 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
20 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,
25 rectum, colon, lymph node, bladder, kidney, pancreas, liver, ovary, uterus, cervix, brain,
skin, bone, stomach and muscle. Modulators of TNF α function may also be used to
increase the safety of the potent anticancer effect of TNF (see F.V. Hauwermeiren *et al.*, *J. Clin. Invest.*, 2013, **123**, 2590-2603).

The present invention also provides a pharmaceutical composition which
30 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
5 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
10 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
15 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
20 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.

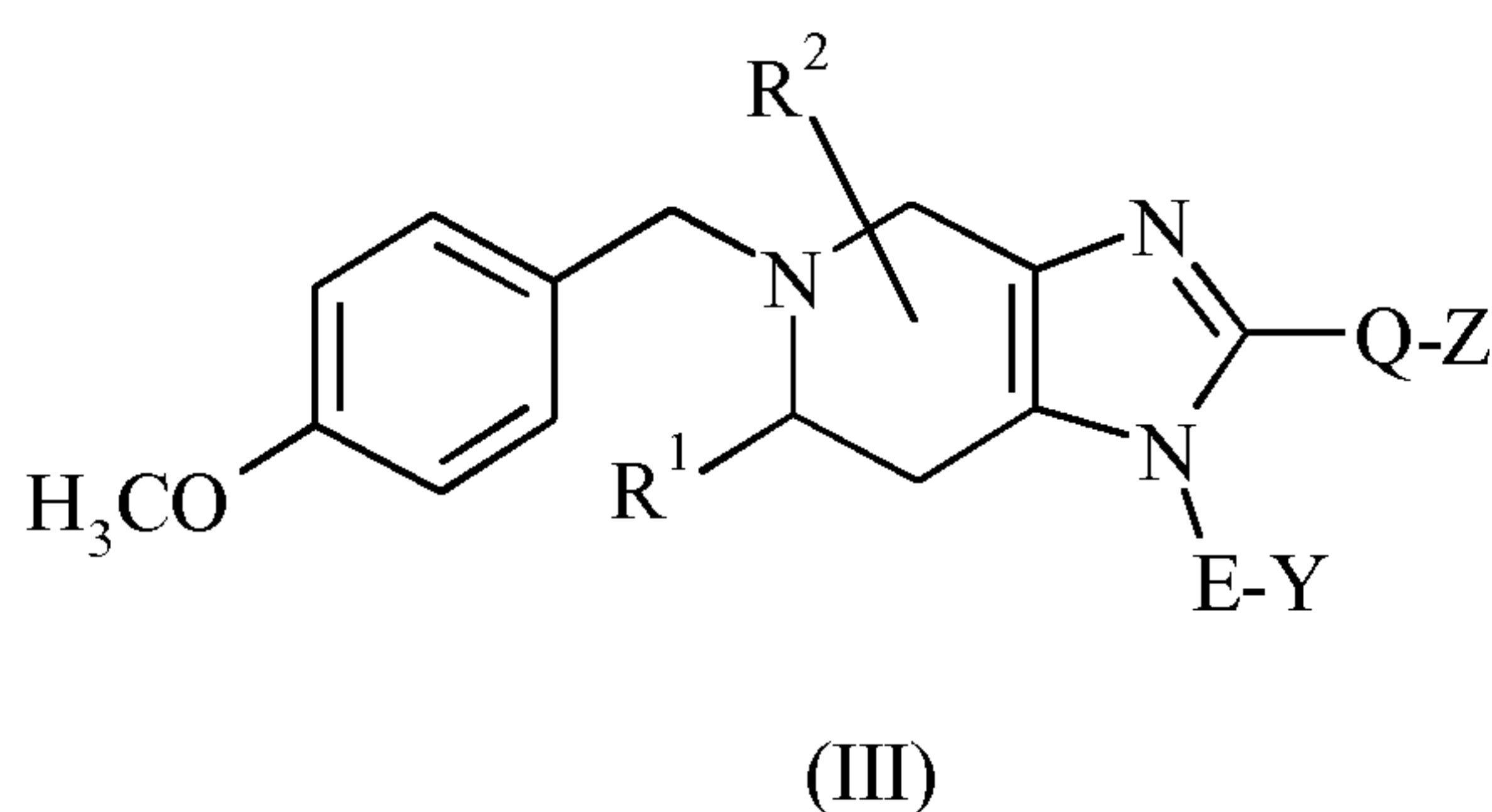
For rectal administration the compounds of use in the present invention may be
25 conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt 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
30 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.

If desired, a compound in accordance with the present invention may be co-administered with another pharmaceutically active agent, e.g. an anti-inflammatory molecule such as methotrexate or prednisolone.

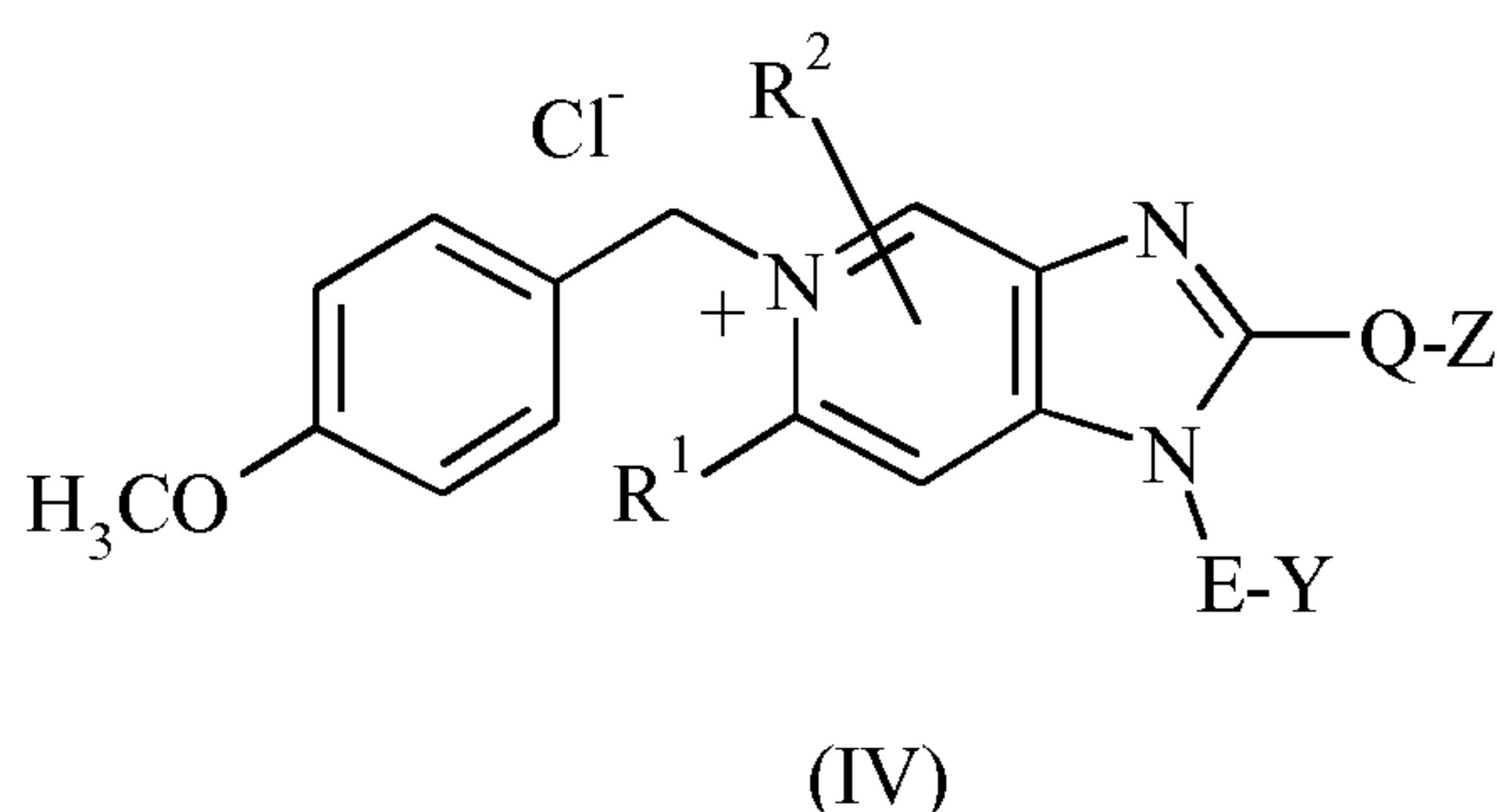
The compounds of formula (I) above wherein R^3 represents hydrogen may be prepared by a process which comprises reacting a compound of formula (III):



wherein E, Q, Y, Z, R^1 and R^2 are as defined above; with trifluoroacetic acid.

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

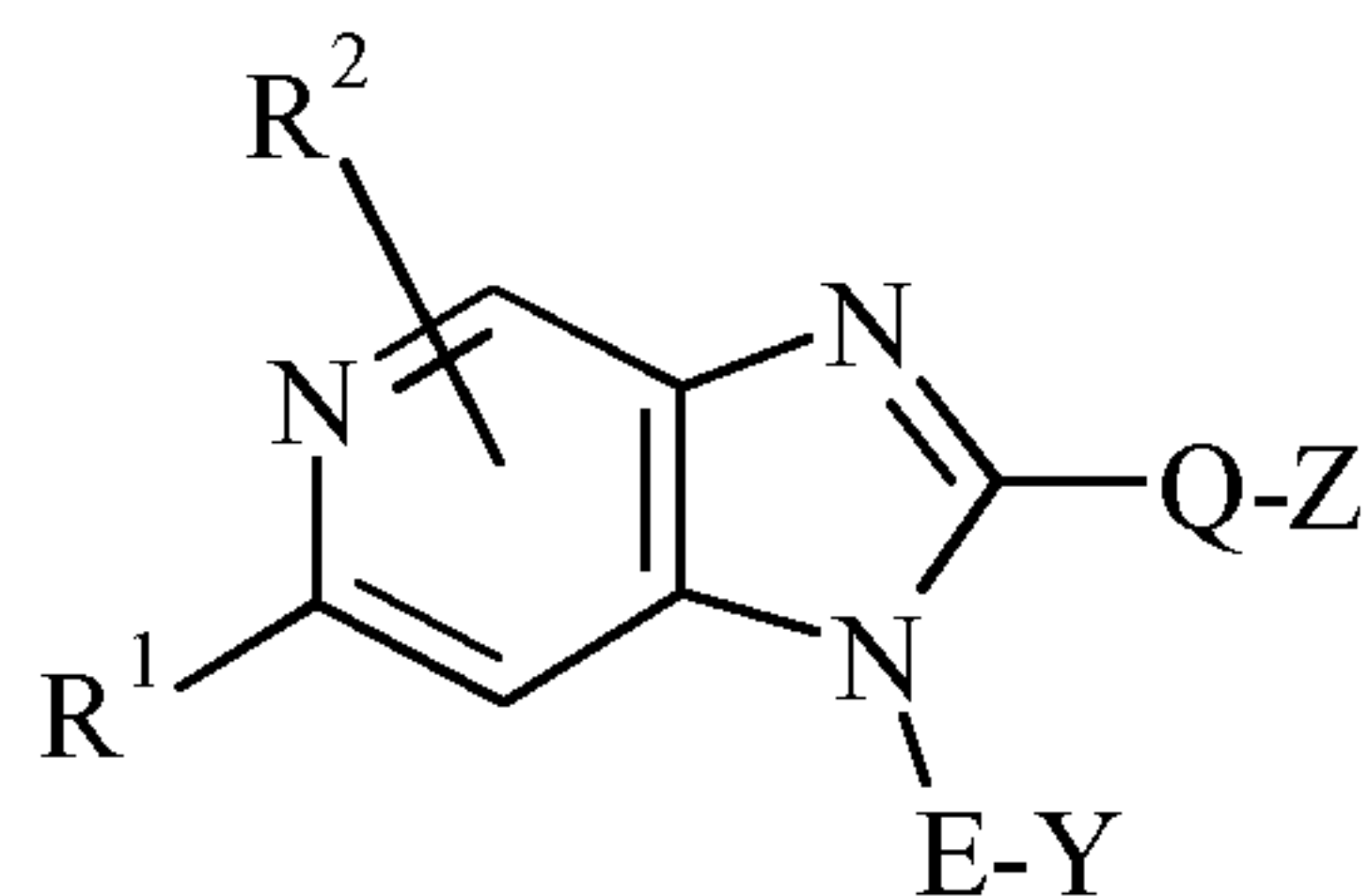
The intermediates of formula (III) above may be prepared by reducing a compound of formula (IV):



wherein E, Q, Y, Z, R^1 and R^2 are as defined above.

The reaction may be performed by treating compound (IV) with a reducing agent. A suitable reducing agent is sodium borohydride. The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. a C_{1-4} alkanol such as methanol.

The intermediates of formula (IV) above may be prepared by reacting a compound of formula (V):



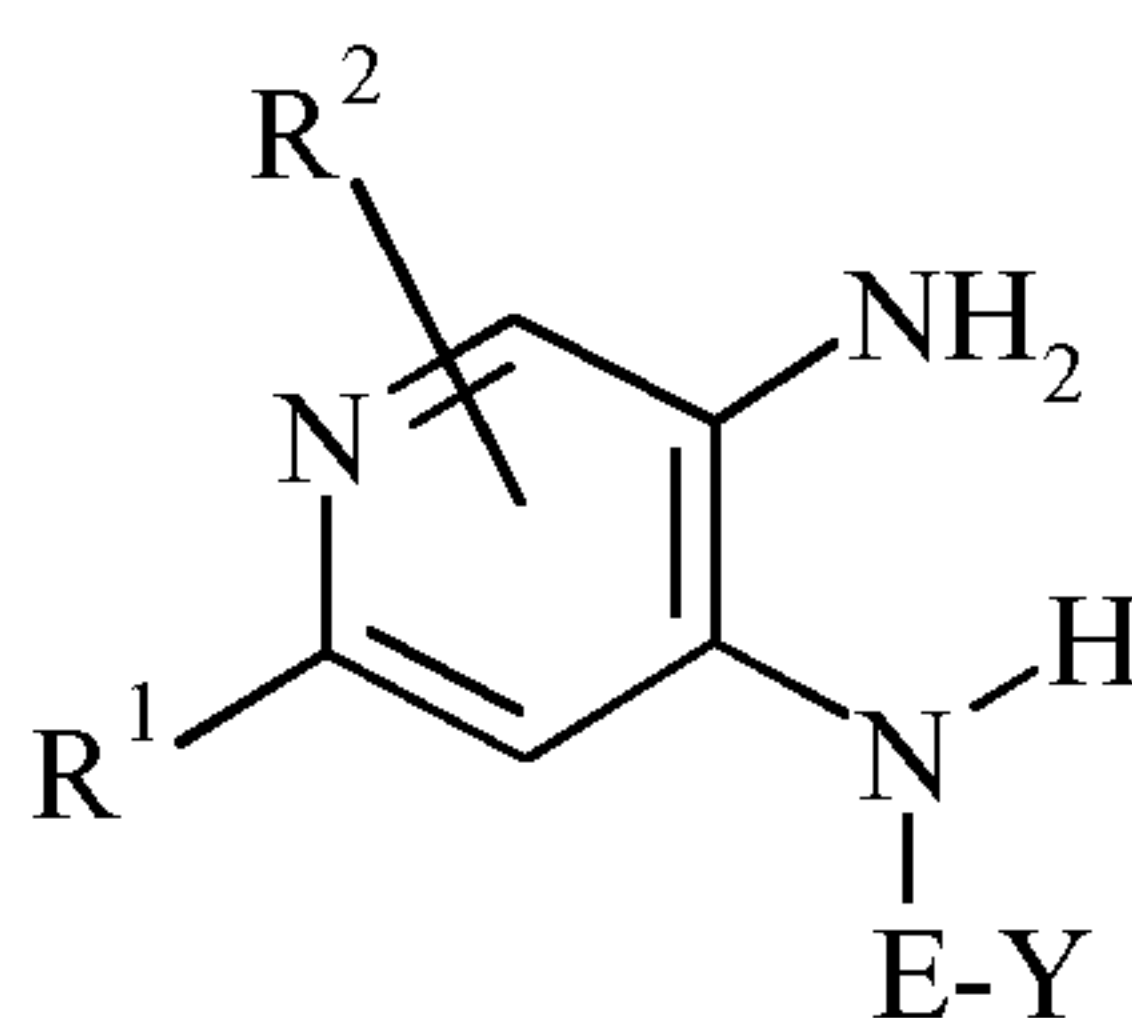
(V)

5

wherein E, Q, Y, Z, R¹ and R² are as defined above; with 4-methoxybenzyl chloride.

The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. acetone.

The compounds of formula (V) above may be prepared by reacting a compound of formula Z-Q-CO₂H or a carboxylate salt thereof (e.g. a carboxylate salt with an alkali metal such as lithium, sodium or potassium) with a compound of formula (VI):



(VI)

15 wherein E, Q, Y, Z, R¹ and R² are as defined above.

The reaction may possibly be performed in the presence of a peptide coupling reagent such as 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU), optionally in the presence of a suitable base, e.g. an organic base such as *N,N*-diisopropylethylamine or triethylamine. The reaction is
20 conveniently effected at ambient or elevated temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide, and/or a chlorinated solvent such as dichloromethane.

Alternatively, the reaction may be accomplished in the presence of a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), typically in the presence of a reagent such as 1-hydroxybenzotriazole (HOBT) and a suitable base, e.g. an organic base such as *N,N*-diisopropylethylamine or triethylamine.

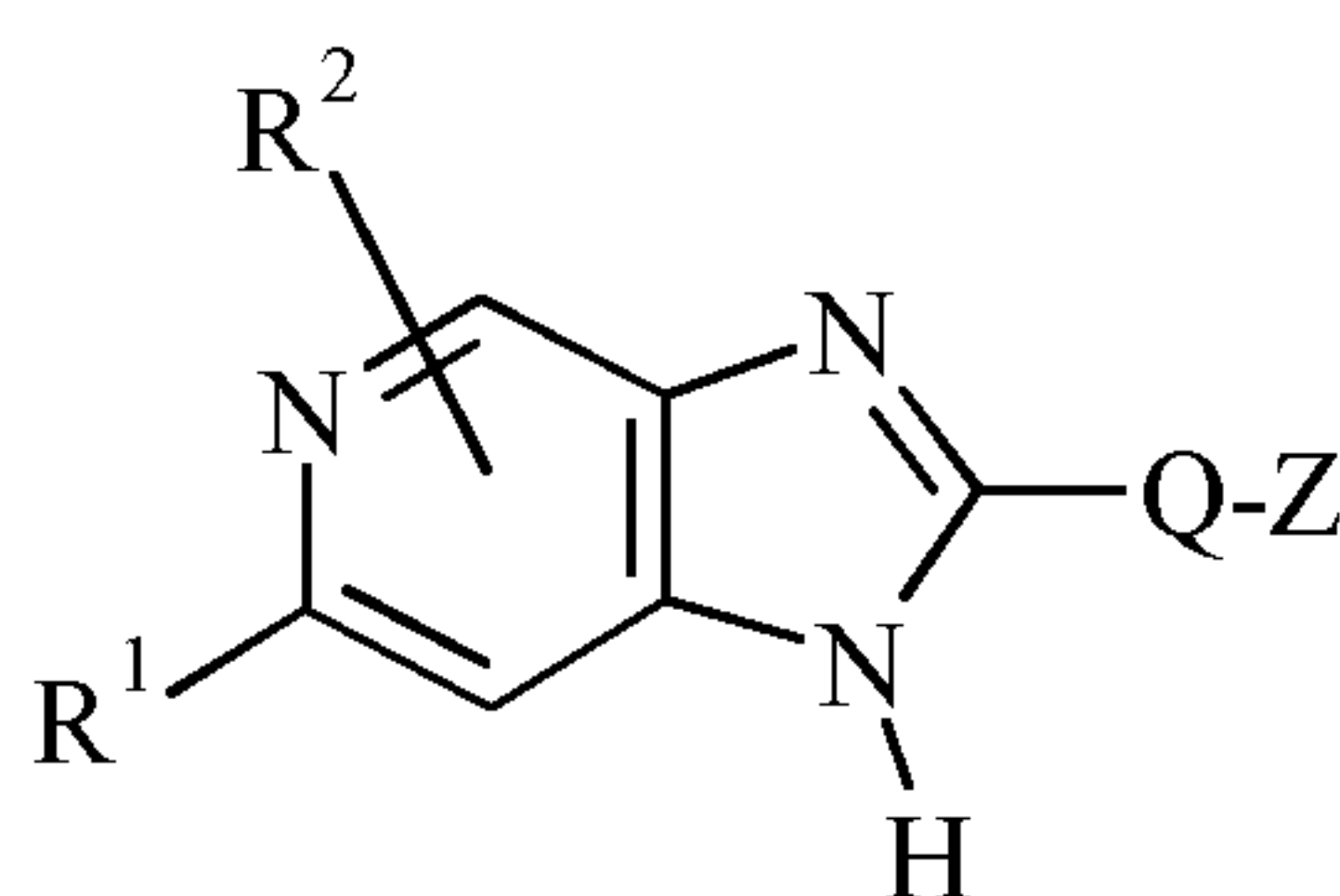
- 5 The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide, or a chlorinated solvent such as dichloromethane.

The product thereby obtained is suitably treated with an acid, ideally an organic acid such as acetic acid, or *p*-toluenesulphonic acid, or a mineral acid such as hydrochloric
10 acid, typically at an elevated temperature.

Alternatively, the reaction may conveniently be effected at an elevated temperature in the presence of a mineral acid, e.g. hydrochloric acid.

Alternatively, the reaction may conveniently be effected at an elevated temperature in the presence of a lower alkanol, e.g. a C₁₋₄ alkanol such as methanol.

- 15 In an alternative procedure, the compounds of formula (V) above wherein E represents a covalent bond or an optionally substituted straight or branched C₁₋₄ alkylene chain may be prepared by reacting a compound of formula L¹-E¹-Y with a compound of formula (VII):



(VII)

20

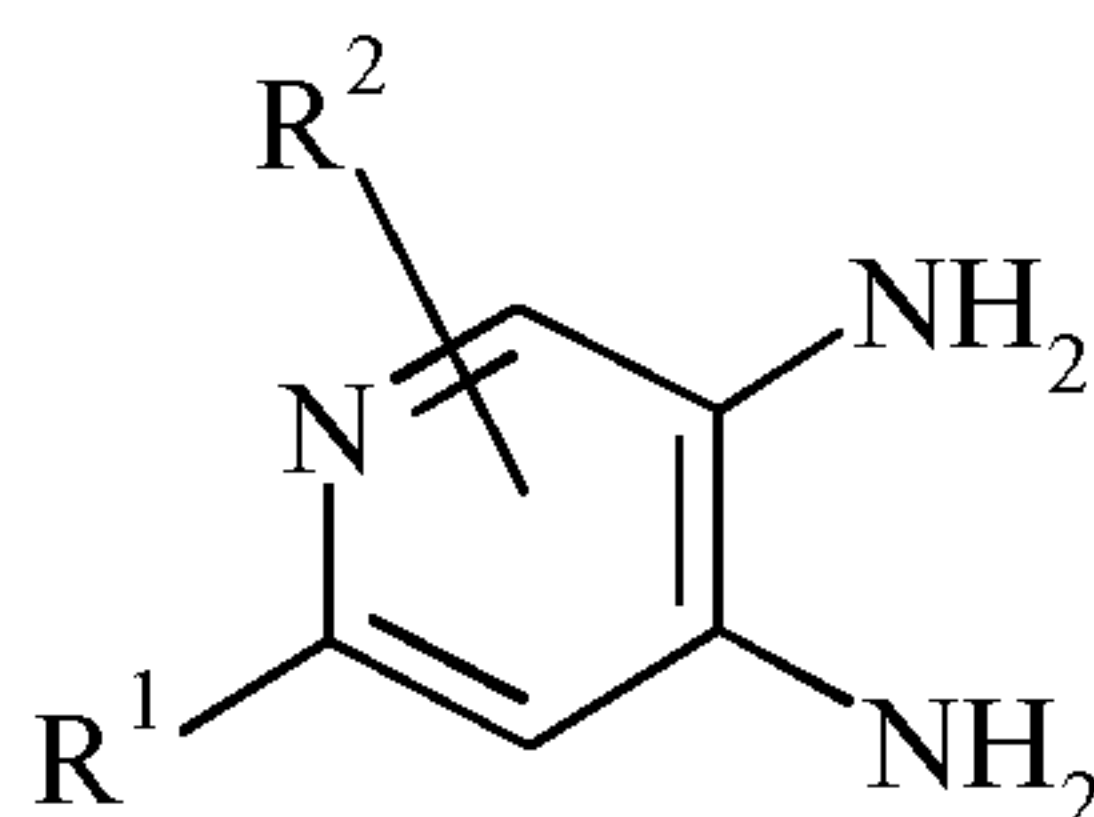
wherein Q, Y, Z, R¹ and R² are as defined above, E¹ represents a covalent bond or an optionally substituted straight or branched C₁₋₄ alkylene chain, and L¹ represents a suitable leaving group.

- 25 The leaving group L¹ is typically a halogen atom, e.g. chloro or bromo.

The reaction is conveniently effected at ambient or elevated temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide, or a chlorinated solvent such as dichloromethane, or a cyclic ether such as tetrahydrofuran.

The reaction may be performed in the presence of a suitable base, e.g. an inorganic base such as potassium carbonate, cesium carbonate or sodium hydride.

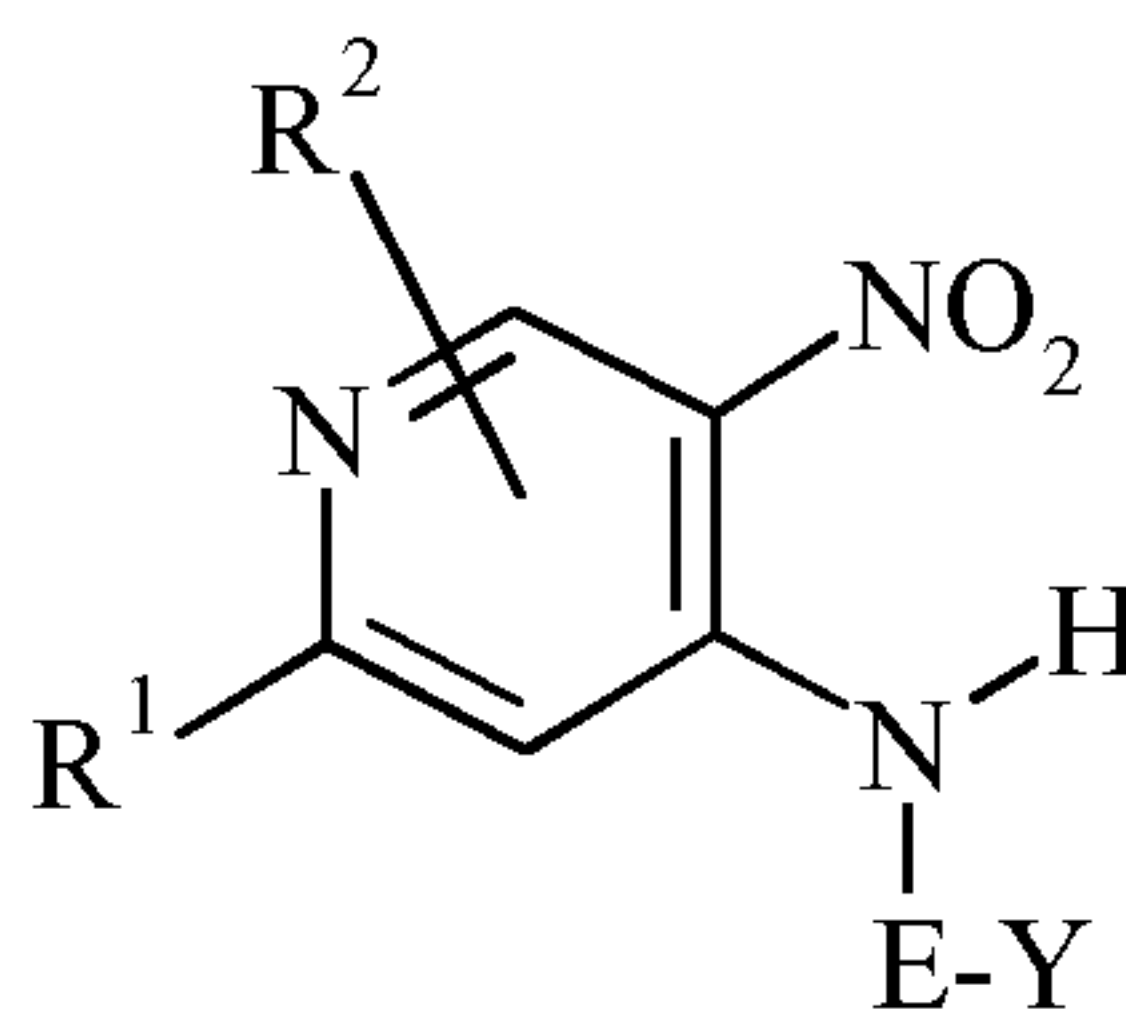
The intermediates of formula (VII) above may be prepared by reacting a compound of formula Z-Q-CO₂H or a carboxylate salt thereof (e.g. a carboxylate salt with an alkali metal such as lithium, sodium or potassium) with a compound of formula (VIII):



(VIII)

wherein Q, Z, R¹ and R² are as defined above; under conditions analogous to those described above for the reaction between compound (VI) and a compound of formula Z-Q-CO₂H or a carboxylate salt thereof.

The intermediates of formula (VI) above may be prepared by reducing a compound of formula (IX):



(IX)

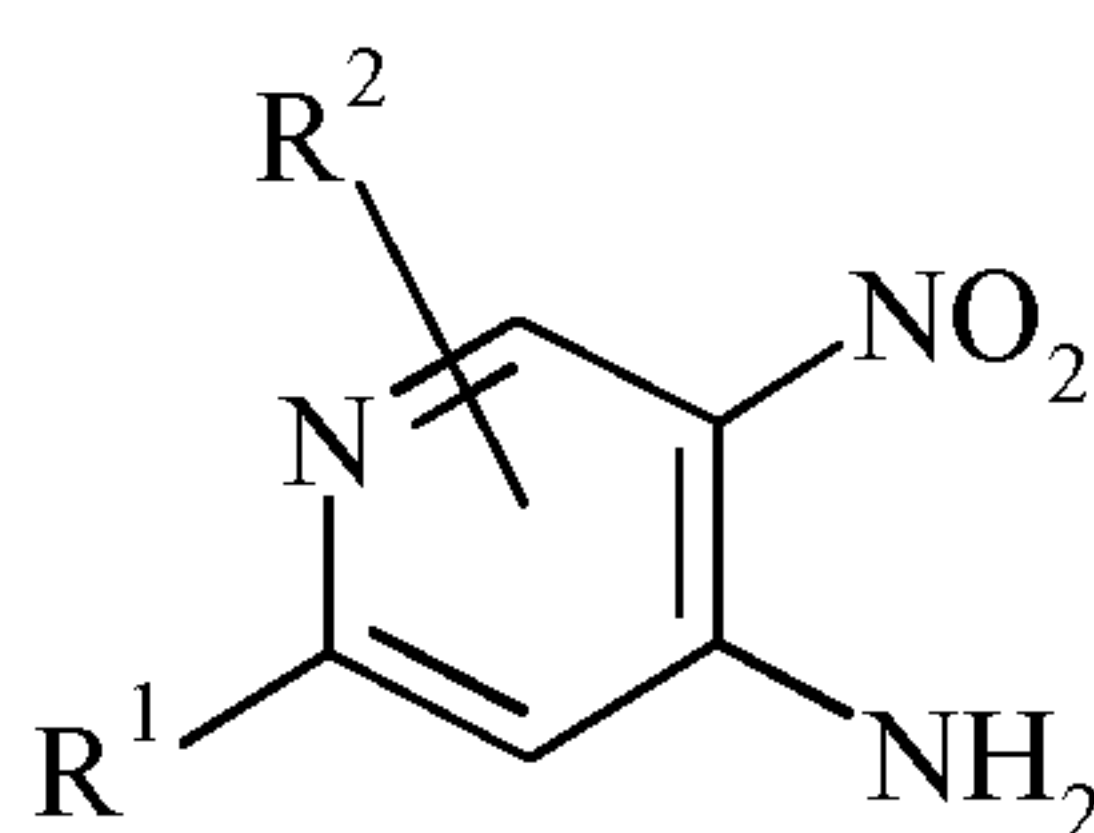
wherein E, Y, R¹ and R² are as defined above.

The transformation is conveniently effected by catalytic hydrogenation of compound (IX), which typically comprises treating compound (IX) with gaseous hydrogen in the presence of a hydrogenation catalyst such as palladium on carbon.

Alternatively, the reduction of compound (IX) may be effected by treatment with elemental iron or zinc, typically at an elevated temperature in the presence of ammonium formate or ammonium chloride.

Alternatively, the reduction of compound (IX) may be effected by treatment with tin(II) chloride, typically at an elevated temperature in the presence of a mineral acid such as hydrochloric acid.

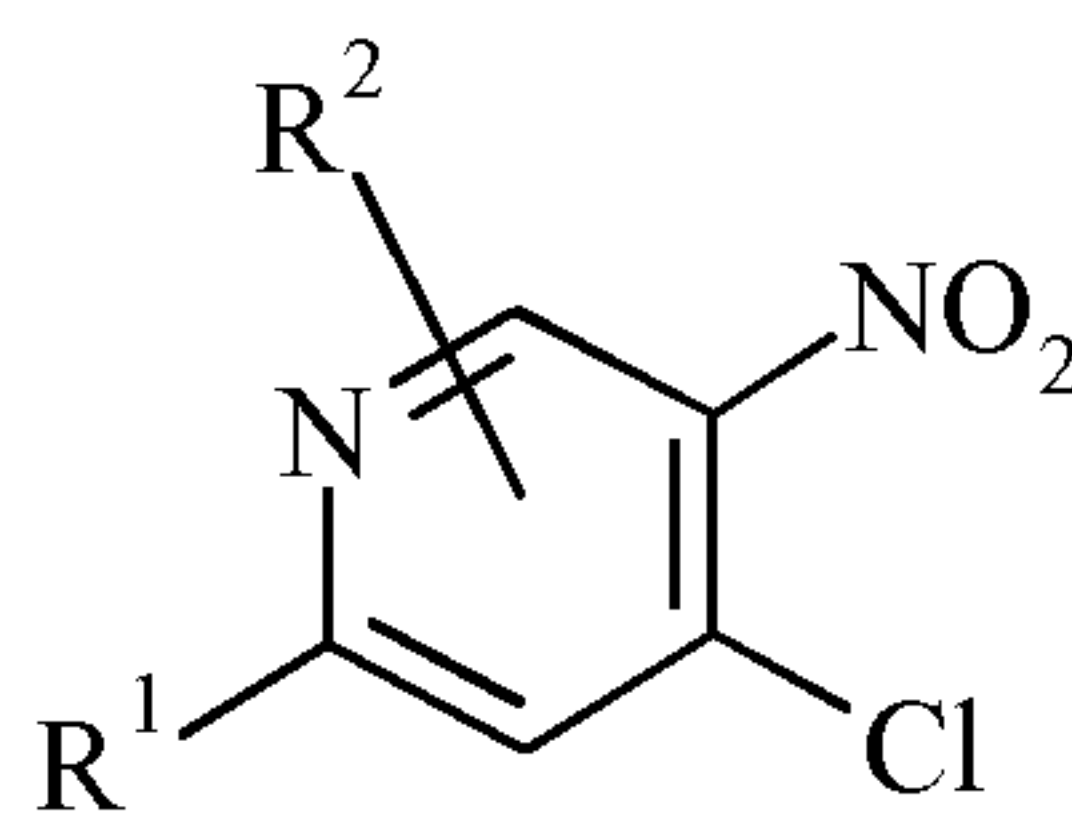
- 5 The intermediates of formula (IX) wherein E represents a covalent bond or an optionally substituted straight or branched C₁₋₄ alkylene chain may be prepared by reacting a compound of formula L¹-E¹-Y with a compound of formula (X):



(X)

- 10 wherein E¹, Y, R¹, R² and L¹ are as defined above; under conditions analogous to those described above for the reaction between compound (VII) and a compound of formula L¹-E¹-Y.

- 15 Alternatively, the intermediates of formula (IX) wherein E represents a covalent bond or an optionally substituted straight or branched C₁₋₄ alkylene chain may be prepared by reacting a compound of formula Y-E¹-NH₂ with a compound of formula (XI):



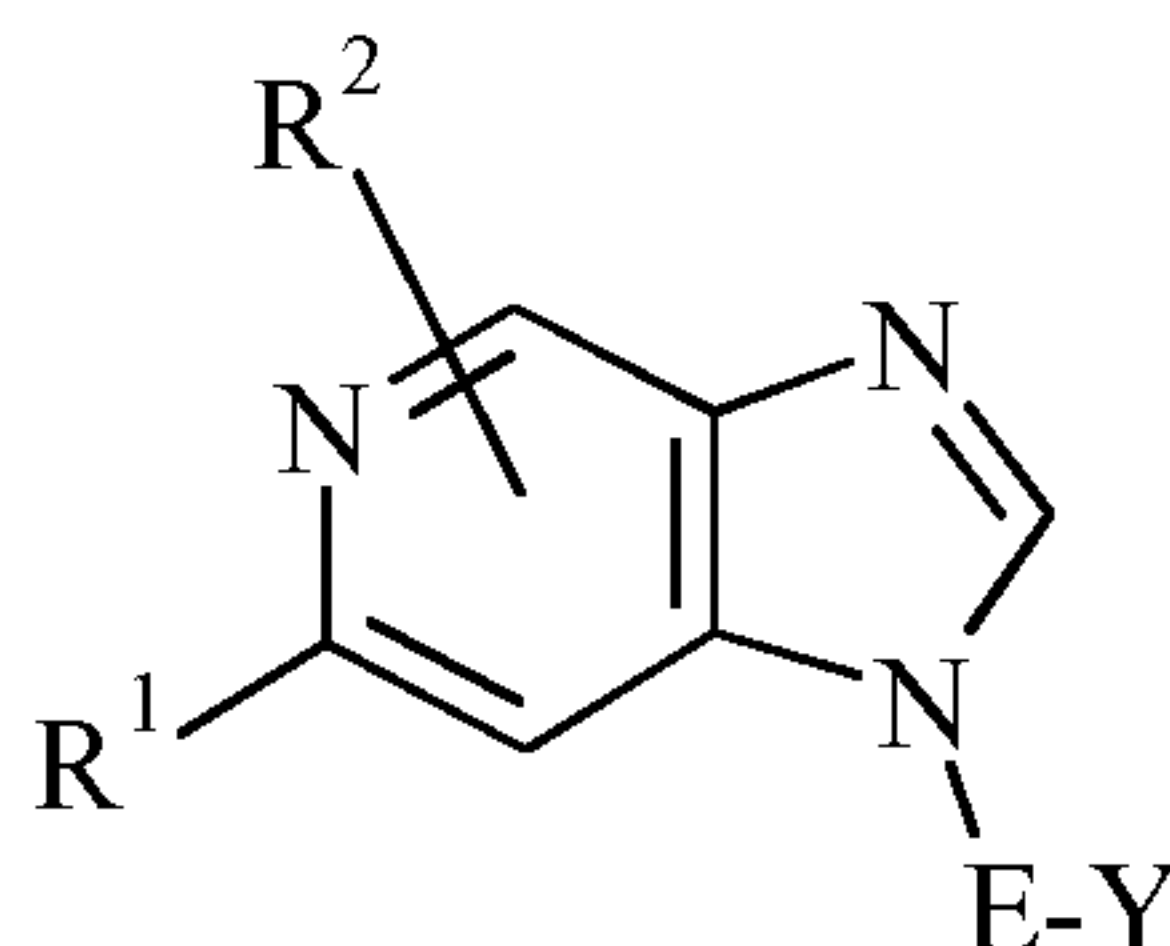
(XI)

wherein E¹, Y, R¹ and R² are as defined above.

- 20 The reaction is conveniently effected at ambient or elevated temperature in a suitable solvent, e.g. 1-methyl-2-pyrrolidinone (NMP), a C₁₋₄ alkanol such as ethanol, a hydrocarbon solvent such as toluene, a cyclic ether such as tetrahydrofuran, or a dipolar aprotic solvent such as *N,N*-dimethylformamide. The reaction may be performed in the

presence of a suitable base, e.g. an organic base such as triethylamine, or an inorganic base such as sodium hydride or potassium carbonate.

In another procedure, the compounds of formula (V) above, wherein Q corresponds to a group of formula $-\text{CH}(\text{OH})-\text{Q}^1-$, may be prepared by reacting an aldehyde of formula
 5 $\text{OHC}-\text{Q}^1-\text{Z}$ with a compound of formula (XII):

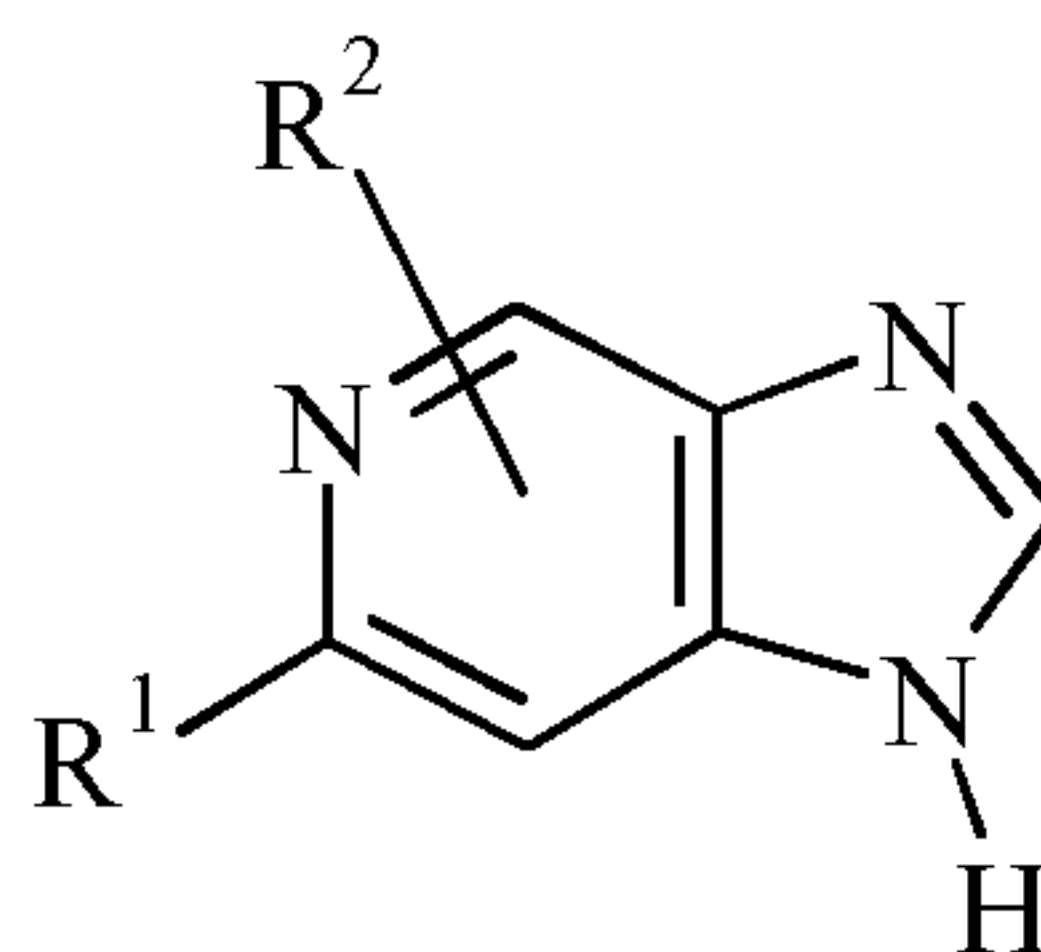


(XII)

wherein E, Y, Z, R^1 and R^2 are as defined above.

10 The reaction is conveniently effected in the presence of a strong base, e.g. *n*-butyllithium or lithium diisopropylamide (LDA). The reaction is carried out in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran.

The intermediates of formula (XII) above wherein E represents a covalent bond or an optionally substituted straight or branched C_{1-4} alkylene chain may be prepared by
 15 reacting a compound of formula $\text{L}^1-\text{E}^1-\text{Y}$ with a compound of formula (XIII):

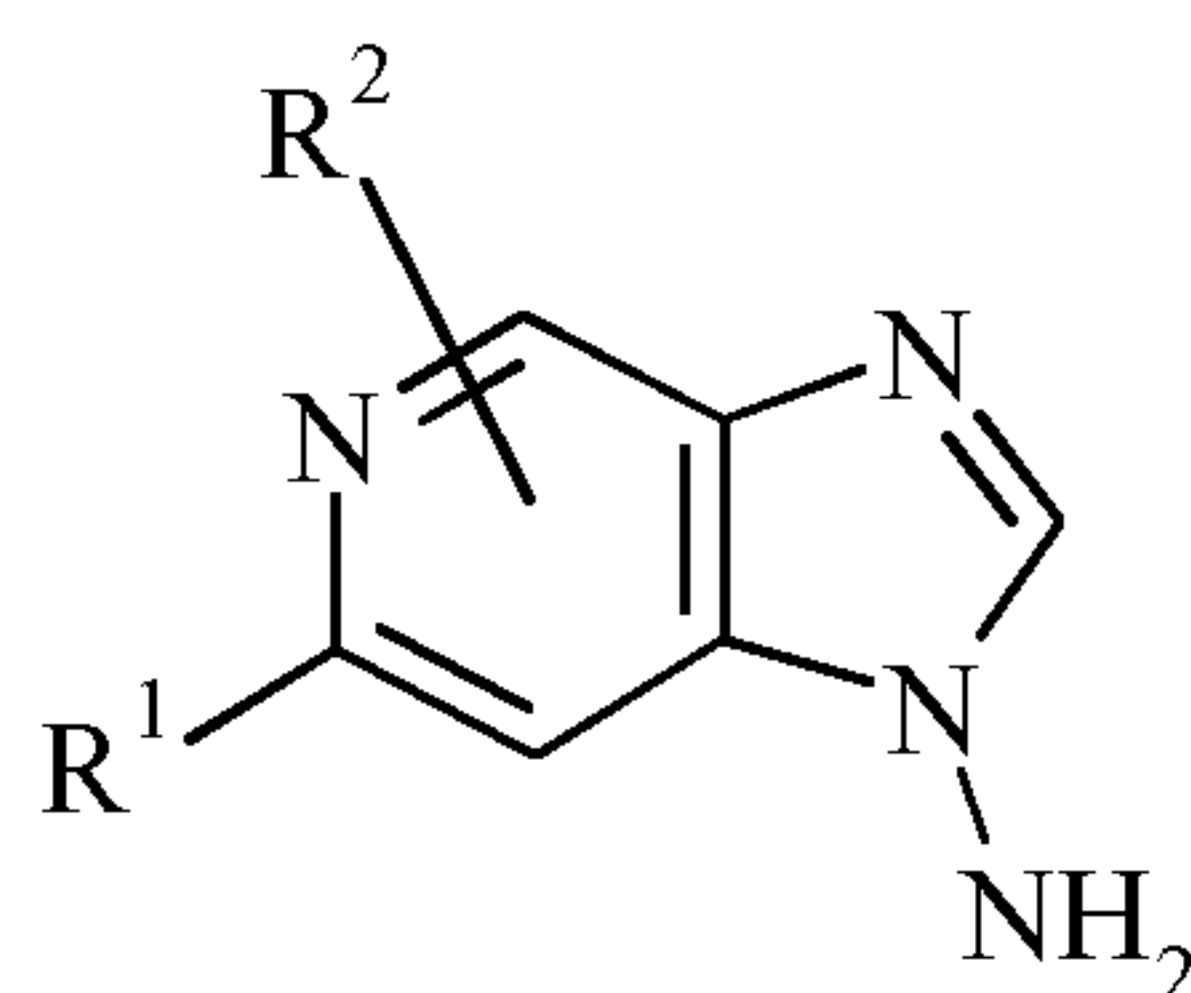


(XIII)

wherein E^1 , Y, R^1 , R^2 and L^1 are as defined above; under conditions analogous to those
 20 described above for the reaction between compound (VII) and a compound of formula $\text{L}^1-\text{E}^1-\text{Y}$.

Alternatively, the intermediates of formula (XII) above may be prepared by reacting a compound of formula (VI) as defined above with formic acid, ideally at ambient temperature.

The intermediates of formula (XII) above wherein E represents -N(H)- may be prepared by reacting a compound of formula L^2 -Y with a compound of formula (XIV):



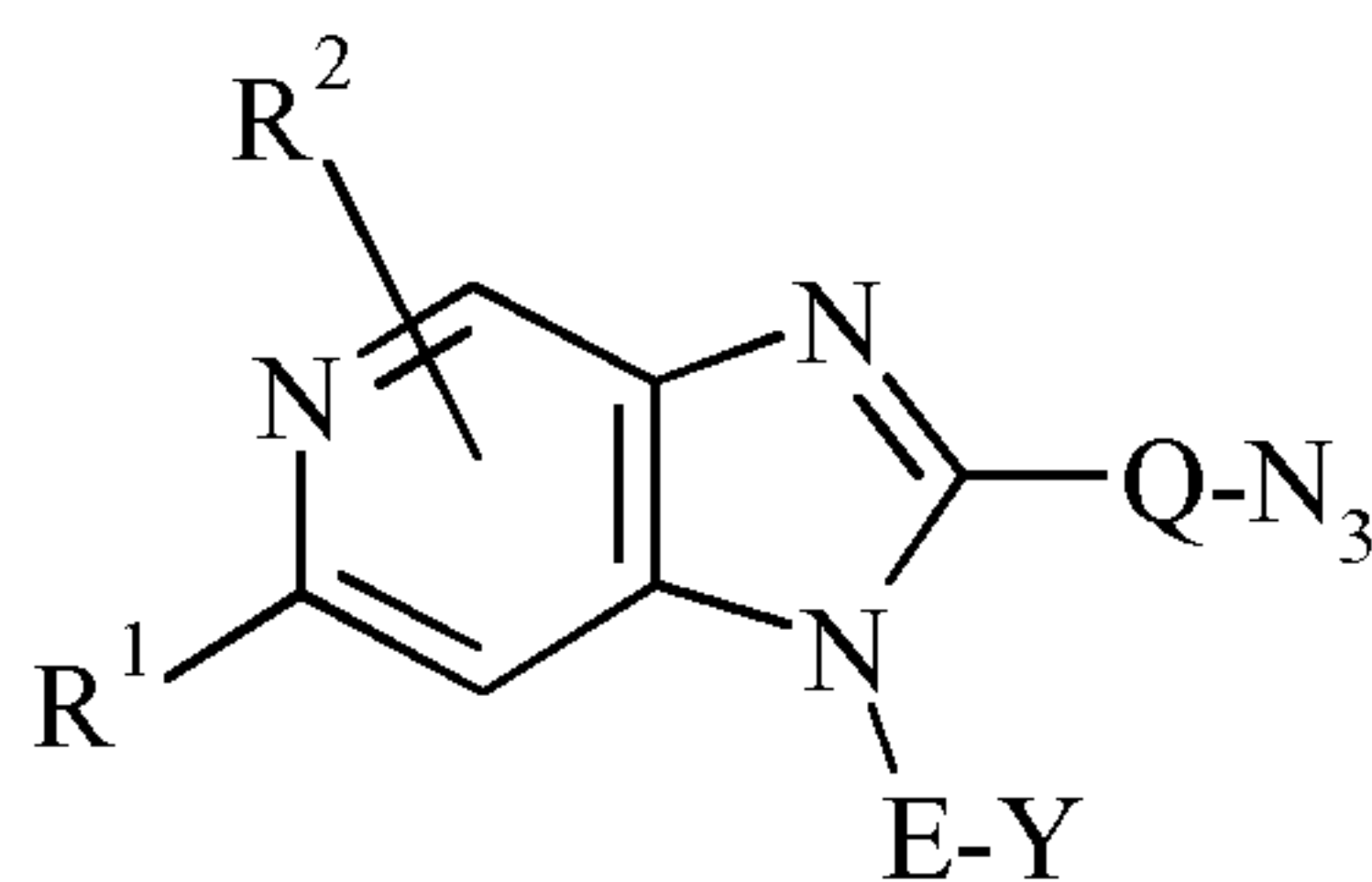
(XIV)

wherein Y, R^1 and R^2 are as defined above, and L^2 represents a suitable leaving group; in the presence of a transition metal catalyst.

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

A suitable transition metal catalyst for use in the above reaction is tris(dibenzylideneacetone)dipalladium(0), in which case the reaction is conveniently performed in the presence of 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl. The reaction is suitably carried out at an elevated temperature in a suitable solvent, e.g. *N,N*-dimethylformamide, typically in the presence of a base, e.g. an inorganic base such as cesium carbonate.

In a further procedure, the compounds of formula (V) above wherein Z represents a 1*H*-[1,2,3]triazol-1-yl moiety, optionally substituted in the 4-position, may be prepared by reacting a compound of formula $H-C\equiv C-R^Z$ with a compound of formula (XV):



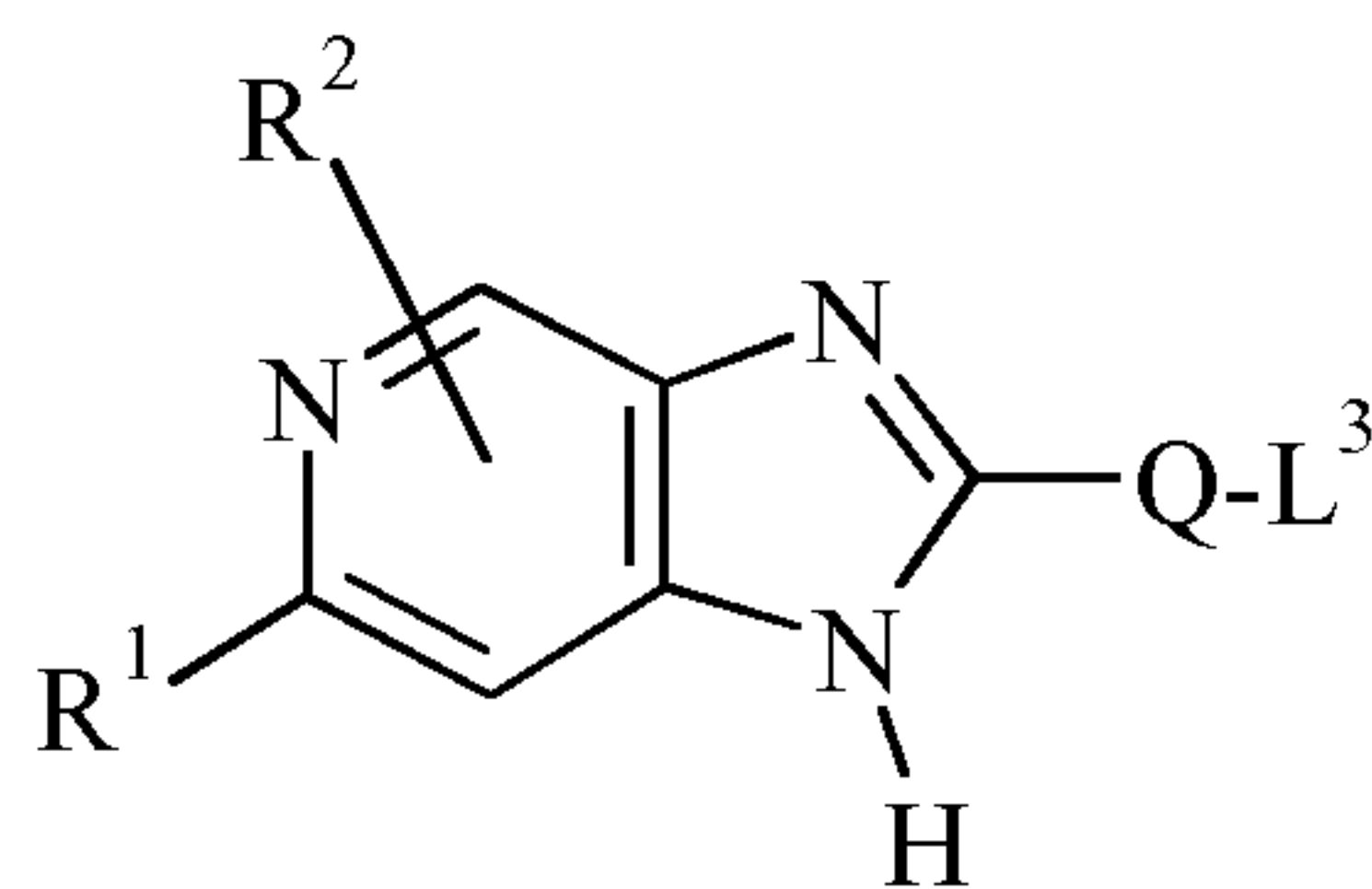
(XV)

wherein E, Q, Y, R¹ and R² are as defined above, and R^z represents an optional substituent on Z.

The reaction is conveniently performed in the presence of copper sulfate pentahydrate and sodium ascorbate. Suitably, the reaction is carried out at ambient
5 temperature in a suitable solvent, e.g. a cyclic ether solvent such as tetrahydrofuran, typically in admixture with water.

The intermediates of formula (XV) above wherein E represents a covalent bond or an optionally substituted straight or branched C₁₋₄ alkylene chain may be prepared by reacting a compound of formula (XVI):

10



(XVI)

wherein Q, R¹ and R² are as defined above, and L³ represents a suitable leaving group; with sodium azide; followed by reaction of the resulting compound with a compound of
15 formula L¹-E¹-Y under conditions analogous to those described above for the reaction between compound (VII) and a compound of formula L¹-E¹-Y.

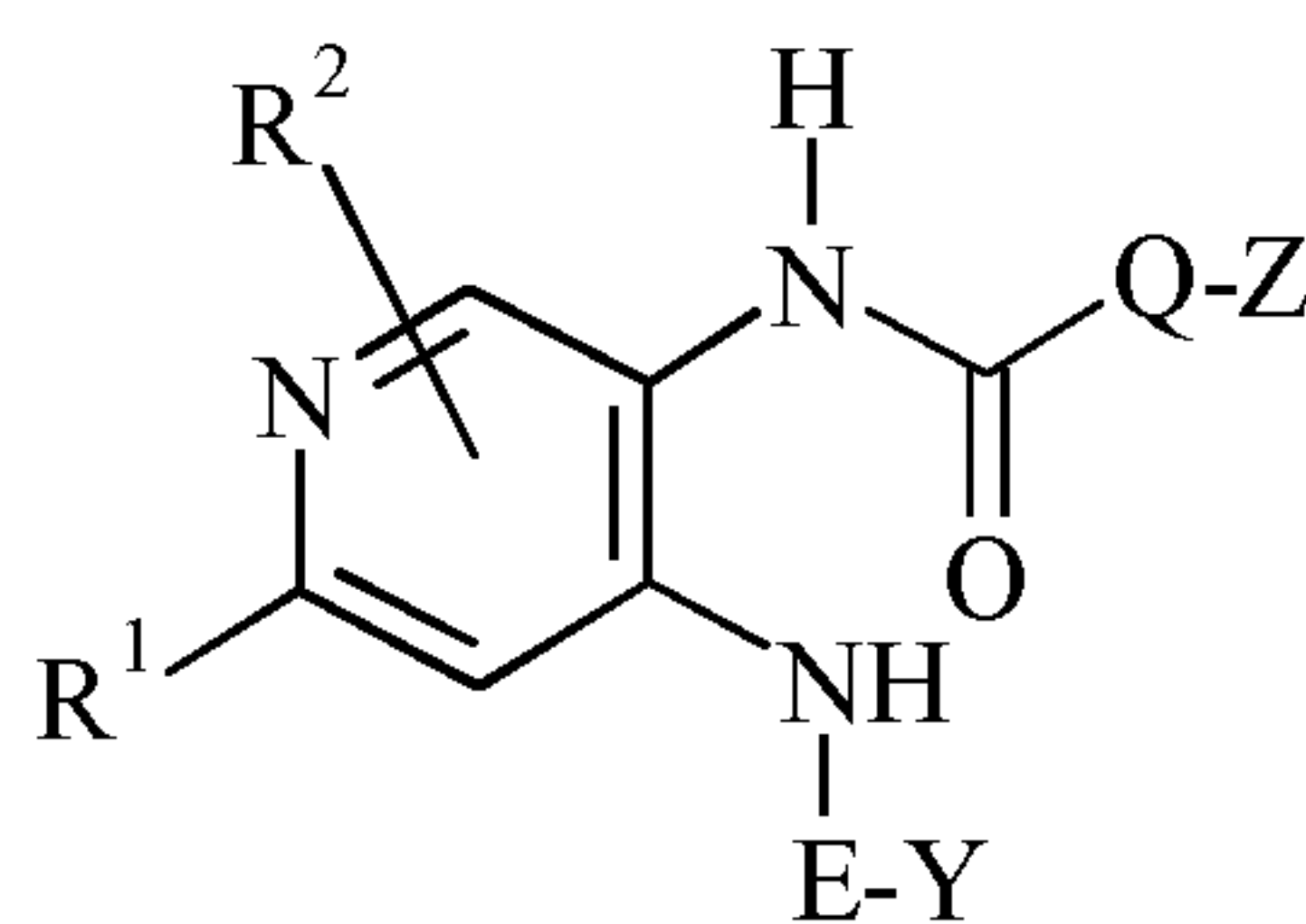
The leaving group L³ is typically a halogen atom, e.g. chloro.

The reaction between compound (XVI) and sodium azide is conveniently effected at ambient temperature in a suitable solvent, e.g. *N,N*-dimethylformamide.

20 The compounds of formula (V) above wherein Q represents -S- may be prepared by reacting a compound of formula Z-S-Z with a compound of formula (XII) as defined above.

The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. *N,N*-dimethylformamide. The reaction may be performed in the presence of a suitable
25 base, e.g. an inorganic base such as potassium carbonate.

In a further procedure, the compounds of formula (V) above may be prepared by a process which comprises cyclising a compound of formula (XVII):

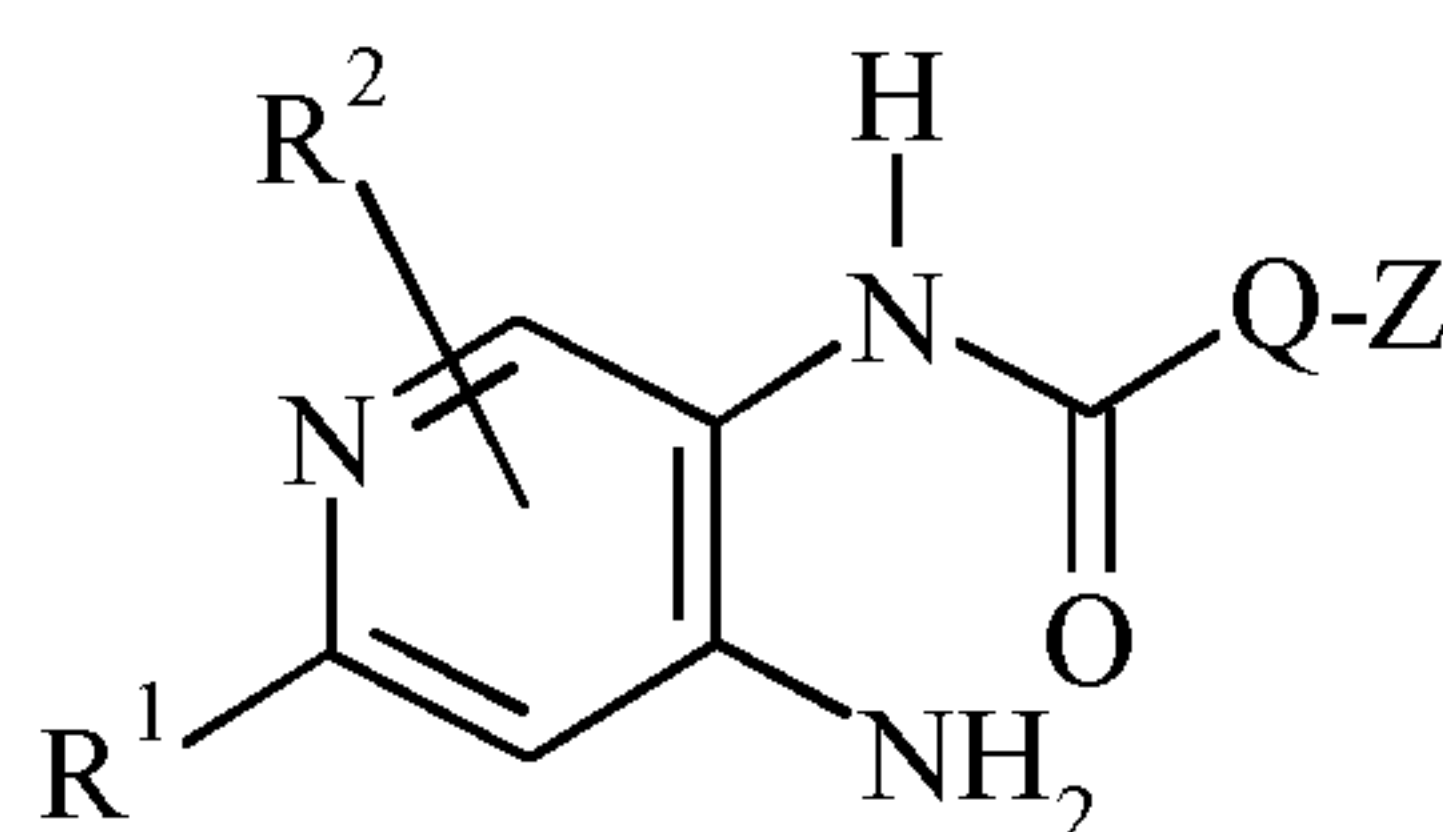


(XVII)

wherein E, Q, Y, Z, R¹ and R² are as defined above.

The cyclization reaction is conveniently effected by heating compound (XVII) in
5 acetic acid.

The intermediates of formula (XVII) above may be prepared by a process which comprises reacting an aldehyde derivative of formula Y-E²-CHO with a compound of formula (XVIII):



(XVIII)

10

wherein Q, Y, Z, R¹ and R² are as defined above, and -E²-CH₂- corresponds to a group E as defined above; in the presence of a reducing agent.

The reducing agent for use in the above reaction is suitably sodium triacetoxy-
15 borohydride or sodium borohydride.

In a further procedure, the compounds of formula (V) above wherein -Q-Z represents dimethylamino may be prepared by reacting a compound of formula (VI) as defined above with (dichloromethylene)dimethylammonium chloride.

The reaction is conveniently effected in a suitable solvent, e.g. a chlorinated
20 solvent such as dichloromethane, typically in the presence of a base, e.g. an organic base such as *N,N*-diisopropylethylamine.

As will be appreciated, the compounds of formula (XII) above correspond to compounds of formula (V) wherein Q represents a covalent bond and Z is hydrogen.

Where they are not commercially available, the starting materials of formula (VIII), (X), (XI), (XIII), (XIV), (XVI) and (XVIII) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

5 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. By way of example, a compound of formula (I) wherein E represents $-\text{CH}_2-$ may be converted into the corresponding compound wherein E represents $-\text{CH}(\text{CH}_3)-$ by treatment with a methyl
10 halide, e.g. methyl iodide, in the presence of a base such as lithium hexamethyldisilazide.

A compound of formula (I) which contains a hydroxy group may be alkylated by treatment with the appropriate alkyl halide in the presence of a base, e.g. sodium hydride, or silver oxide. A compound of formula (I) wherein $-\text{Q}-\text{Z}$ represents $-\text{CH}_2\text{OH}$ may be arylated in a two-step procedure which comprises: (i) treatment with thionyl chloride; and
15 (ii) treatment of the chloro derivative thereby obtained with the appropriate aryl or heteroaryl hydroxide. Alternatively, a compound of formula (I) wherein $-\text{Q}-\text{Z}$ represents $-\text{CH}_2\text{OH}$ may be arylated by treatment with the appropriate aryl or heteroaryl hydroxide in the presence of triphenylphosphine and an azodicarbonyl reagent such as 1,1'-(azodicarbonyl)dipiperidine (ADDP). A compound of formula (I) wherein $-\text{Q}-\text{Z}$
20 represents $-\text{CH}_2\text{OH}$ may be converted into the corresponding compound of formula (I) wherein $-\text{Q}-\text{Z}$ represents $-\text{CH}_2\text{S}-\text{Z}$ via a two-step procedure which comprises: (i) treatment with thionyl chloride; and (ii) treatment of the chloro derivative thereby obtained with a compound of formula $\text{Z}-\text{SH}$, typically in the presence of a base, e.g. an inorganic base such as potassium carbonate. A compound of formula (I) wherein $-\text{Q}-\text{Z}$ represents
25 $-\text{CH}_2\text{OH}$ may be converted into the corresponding compound of formula (I) wherein $-\text{Q}-\text{Z}$ represents $-\text{CH}_2\text{CN}$ via a two-step procedure which comprises: (i) treatment with thionyl chloride; and (ii) treatment of the chloro derivative thereby obtained with a cyanide salt such as sodium cyanide. A compound of formula (I) which contains hydroxy may be converted into the corresponding fluoro-substituted compound by treatment with
30 diethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (BAST). A compound of formula (I) which contains hydroxy may be converted into the corresponding difluoro-substituted compound via a two-step procedure which comprises:

(i) treatment with an oxidising agent, e.g. manganese dioxide; and (ii) treatment of the carbonyl-containing compound thereby obtained with DAST.

A compound of formula (I) wherein -Q-Z represents -CH₂OH may be converted into the corresponding compound wherein -Q-Z represents -CH(OH)Z in a two-step
5 procedure which comprises: (i) oxidation with a suitable oxidising agent, e.g. Dess-Martin periodinane or manganese(IV) oxide; and (ii) treatment of the aldehyde derivative thereby obtained with a Grignard reagent, e.g. a compound of formula Z-MgBr or Z-MgCl.

A compound of formula (I) wherein -Q-Z represents -CH₂OH may be converted into the corresponding compound wherein -Q-Z represents -CH(OH)CF₃ in a two-step
10 procedure which comprises: (i) oxidation with a suitable oxidising agent, e.g. Dess-Martin periodinane or manganese(IV) oxide; and (ii) treatment of the aldehyde derivative thereby obtained with (trifluoromethyl)trimethylsilane and cesium fluoride.

A compound of formula (I) which contains an N-H moiety, e.g. a compound of formula (I) wherein R³ is hydrogen, may be alkylated by treatment with the appropriate
15 alkyl halide, typically at an elevated temperature in an organic solvent such as acetonitrile; or at ambient temperature in the presence of a base, e.g. an alkali metal hydride such as sodium hydride, or an alkali metal carbonate such as potassium carbonate or cesium carbonate, in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran, or a dipolar aprotic solvent such as *N,N*-dimethylformamide. Alternatively, a compound of formula (I)
20 which contains an N-H moiety, e.g. a compound of formula (I) wherein R³ is hydrogen, may be alkylated by treatment with the appropriate alkyl tosylate in the presence of a base, e.g. an inorganic base such as sodium hydride, or an organic base such as 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU).

A compound of formula (I) which contains an N-H moiety, e.g. a compound of
25 formula (I) wherein R³ is hydrogen, may be methylated by treatment with formaldehyde in the presence of a reducing agent, e.g. sodium triacetoxyborohydride.

A compound of formula (I) which contains an N-H moiety, e.g. a compound of formula (I) wherein R³ is hydrogen, may be arylated by treatment with the appropriate aryl or heteroaryl halide, e.g. a bromopyridinyl derivative. The reaction may be effected with
30 the assistance of palladium diacetate, in the presence of a reagent such as 2,2'-bis-(diphenylphosphino)-1,1'-binaphthalene (BINAP) and a base, e.g. an inorganic base such as cesium carbonate.

A compound of formula (I) which contains an N-H moiety, e.g. a compound of formula (I) wherein R³ is hydrogen, may be acylated by treatment with the appropriate acid chloride, e.g. acetyl chloride or 4-morpholinecarbonyl chloride, or with the appropriate carboxylic acid anhydride, e.g. acetic anhydride, typically at ambient temperature in the presence of a base, e.g. an organic base such as triethylamine.

A compound of formula (I) which contains an N-H moiety, e.g. a compound of formula (I) wherein R³ is hydrogen, may be converted into the corresponding compound wherein the nitrogen atom is substituted by C₁₋₆ alkylsulphonyl, e.g. methylsulphonyl, by treatment with the appropriate C₁₋₆ alkylsulphonyl chloride, e.g. methanesulphonyl chloride, or with the appropriate C₁₋₆ alkylsulphonic acid anhydride, e.g. methanesulphonic anhydride, typically at ambient temperature in the presence of a base, e.g. an organic base such as triethylamine or *N,N*-diisopropylethylamine.

A compound of formula (I) substituted by amino (-NH₂) may be converted into the corresponding compound substituted by C₁₋₆ alkylsulphonylamino, e.g. methylsulphonylamino, or bis[(C₁₋₆)alkylsulphonyl]amino, e.g. bis(methylsulphonyl)amino, by treatment with the appropriate C₁₋₆ alkylsulphonyl halide, e.g. a C₁₋₆ alkylsulphonyl chloride such as methanesulphonyl chloride. Similarly, a compound of formula (I) substituted by hydroxy (-OH) may be converted into the corresponding compound substituted by C₁₋₆ alkylsulphonyloxy, e.g. methylsulphonyloxy, by treatment with the appropriate C₁₋₆ alkylsulphonyl halide, e.g. a C₁₋₆ alkylsulphonyl chloride such as methanesulphonyl chloride.

A compound of formula (I) containing the moiety -S- may be converted into the corresponding compound containing the moiety -S(O)- by treatment with 3-chloroperoxybenzoic acid. Likewise, a compound of formula (I) containing the moiety -S(O)- may be converted into the corresponding compound containing the moiety -S(O)₂- by treatment with 3-chloroperoxybenzoic acid. Alternatively, a compound of formula (I) containing the moiety -S- may be converted into the corresponding compound containing the moiety -S(O)₂- by treatment with Oxone® (potassium peroxymonosulfate).

A compound of formula (I) containing an aromatic nitrogen atom may be converted into the corresponding *N*-oxide derivative by treatment with 3-chloroperoxybenzoic acid.

A bromophenyl derivative of formula (I) may be converted into the corresponding optionally substituted 2-oxopyrrolidin-1-ylphenyl or 2-oxooxazolidin-3-ylphenyl derivative by treatment with pyrrolidin-2-one or oxazolidin-2-one, or an appropriately

substituted analogue thereof. The reaction is conveniently effected at an elevated temperature in the presence of copper(I) iodide, *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine and an inorganic base such as potassium carbonate.

A compound of formula (I) substituted by halogen, e.g. chloro or bromo, may be converted into the corresponding compound substituted by an optionally substituted aryl or heteroaryl moiety by treatment with the appropriately substituted aryl or heteroaryl boronic acid or a cyclic ester thereof formed with an organic diol, e.g. pinacol, 1,3-propanediol or neopentyl glycol. The reaction is typically effected in the presence of a transition metal catalyst, e.g. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II), tetrakis(triphenylphosphine)palladium(0), or bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex, and a base, e.g. an inorganic base such as sodium carbonate or potassium carbonate, or potassium phosphate.

A compound of formula (I) substituted by halogen, e.g. bromo, may be converted into the corresponding compound substituted by an optionally substituted aryl, heteroaryl or heterocycloalkenyl moiety via a two-step procedure which comprises: (i) reaction with bis(pinacolato)diboron or bis(neopentyl glycolato)diboron; and (ii) reaction of the compound thereby obtained with an appropriately functionalised halo- or tosyloxy-substituted aryl, heteroaryl or heterocycloalkenyl derivative. Step (i) is conveniently effected in the presence of a transition metal catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), or bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex. Step (ii) is conveniently effected in the presence of a transition metal catalyst such as tetrakis(triphenylphosphine)palladium(0), or bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex, and a base, e.g. an inorganic base such as sodium carbonate or potassium carbonate.

A compound of formula (I) substituted by halogen, e.g. bromo, may be converted into the corresponding compound substituted by an optionally substituted C₂₋₆ alkynyl moiety by treatment with an appropriately substituted alkyne derivative, e.g. 2-hydroxybut-3-yne. The reaction is conveniently accomplished with the assistance of a transition metal catalyst, e.g. tetrakis(triphenylphosphine)palladium(0), typically in the presence of copper(I) iodide and a base, e.g. an organic base such as triethylamine.

A compound of formula (I) substituted by halogen, e.g. bromo, may be converted into the corresponding compound substituted by an optionally substituted imidazol-1-yl moiety by treatment with the appropriately substituted imidazole derivative, typically in the presence of copper(II) acetate and an organic base such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA).

A compound of formula (I) substituted by halogen, e.g. bromo, may be converted into the corresponding compound substituted by 2-(methoxycarbonyl)ethyl via a two-step procedure which comprises: (i) reaction with methyl acrylate; and (ii) catalytic hydrogenation of the alkenyl derivative thereby obtained, typically by treatment with a hydrogenation catalyst, e.g. palladium on charcoal, under an atmosphere of hydrogen gas. Step (i) is typically effected in the presence of a transition metal catalyst, e.g. palladium(II) acetate or bis(dibenzylideneacetone)palladium(0), and a reagent such as tri(*ortho*-tolyl)-phosphine.

In general, a compound of formula (I) containing a -C=C- functionality may be converted into the corresponding compound containing a -CH-CH- functionality by catalytic hydrogenation, typically by treatment with a hydrogenation catalyst, e.g. palladium on charcoal, under an atmosphere of hydrogen gas, optionally in the presence of a base, e.g. an alkali metal hydroxide such as sodium hydroxide.

A compound of formula (I) substituted by 6-methoxypyridin-3-yl may be converted into the corresponding compound substituted by 2-oxo-1,2-dihydropyridin-5-yl by treatment with pyridine hydrochloride; or by heating with a mineral acid such as hydrochloric acid. By utilising similar methodology, a compound of formula (I) substituted by 6-methoxy-4-methylpyridin-3-yl may be converted into the corresponding compound substituted by 4-methyl-2-oxo-1,2-dihydropyridin-5-yl; and a compound of formula (I) substituted by 6-methoxy-5-methylpyridin-3-yl may be converted into the corresponding compound substituted by 3-methyl-2-oxo-1,2-dihydropyridin-5-yl.

A compound of formula (I) substituted by 2-oxo-1,2-dihydropyridin-5-yl may be converted into the corresponding compound substituted by 2-oxopiperidin-5-yl by catalytic hydrogenation, typically by treatment with gaseous hydrogen in the presence of a hydrogenation catalyst such as platinum(IV) oxide.

A compound of formula (I) containing an ester moiety, e.g. a C₂₋₆ alkoxycarbonyl group such as methoxycarbonyl or ethoxycarbonyl, may be converted into the

corresponding compound containing a carboxy ($-\text{CO}_2\text{H}$) moiety by treatment with an acid, e.g. a mineral acid such as hydrochloric acid.

A compound of formula (I) containing an *N*-(*tert*-butoxycarbonyl) moiety may be converted into the corresponding compound containing an N-H moiety by treatment with
5 an acid, e.g. a mineral acid such as hydrochloric acid, or an organic acid such as trifluoroacetic acid.

A compound of formula (I) containing an ester moiety, e.g. a C_{2-6} alkoxycarbonyl group such as methoxycarbonyl or ethoxycarbonyl, may alternatively be converted into the corresponding compound containing a carboxy ($-\text{CO}_2\text{H}$) moiety by treatment with a base,
10 e.g. an alkali metal hydroxide selected from lithium hydroxide, sodium hydroxide and potassium hydroxide; or an organic base such as sodium methoxide or sodium ethoxide.

A compound of formula (I) containing a carboxy ($-\text{CO}_2\text{H}$) moiety may be converted into the corresponding compound containing an amide moiety by treatment with the appropriate amine in the presence of a condensing agent such as 1-ethyl-3-(3-dimethyl-
15 aminopropyl)carbodiimide.

A compound of formula (I) containing a carbonyl ($\text{C}=\text{O}$) moiety may be converted into the corresponding compound containing a $-\text{C}(\text{CH}_3)(\text{OH})-$ moiety by treatment with methylmagnesium bromide. Similarly, a compound of formula (I) containing a carbonyl ($\text{C}=\text{O}$) moiety may be converted into the corresponding compound containing a
20 $-\text{C}(\text{CF}_3)(\text{OH})-$ moiety by treatment with (trifluoromethyl)trimethylsilane and cesium fluoride. A compound of formula (I) containing a carbonyl ($\text{C}=\text{O}$) moiety may be converted into the corresponding compound containing a $-\text{C}(\text{CH}_2\text{NO}_2)(\text{OH})-$ moiety by treatment with nitromethane.

A compound of formula (I) containing a hydroxymethyl moiety may be converted
25 into the corresponding compound containing a formyl ($-\text{CHO}$) moiety by treatment with an oxidising agent such as Dess-Martin periodinane. A compound of formula (I) containing a hydroxymethyl moiety may be converted into the corresponding compound containing a carboxy moiety by treatment with an oxidising agent such as tetrapropylammonium perruthenate.

30 A compound of formula (I) containing an oxo moiety can be converted into the corresponding compound containing an ethoxycarbonylmethylidene moiety by treatment with triethyl phosphonoacetate in the presence of a base such as sodium hydride.

A compound of formula (IIB) wherein R^{21} represents ethenyl may be prepared by reacting a compound of formula (IIB) wherein R^{21} represents halogen, e.g. chloro, with potassium vinyl trifluoroborate. The reaction is typically effected in the presence of a transition metal catalyst, e.g. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II),
 5 and a base, e.g. an organic base such as triethylamine.

A compound of formula (IIB) wherein R^{21} represents halogen, e.g. chloro, may be converted into the corresponding compound wherein R^{21} represents an optionally substituted C_{4-7} cycloalkenyl moiety by treatment with the appropriately substituted cycloalkenyl boronic acid or a cyclic ester thereof formed with an organic diol, e.g.
 10 pinacol, 1,3-propanediol or neopentyl glycol. The reaction is typically effected in the presence of a transition metal catalyst, e.g. bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex, and a base, e.g. an inorganic base such as potassium carbonate.

A compound of formula (IIB) wherein R^{21} represents a substituent containing at
 15 least one nitrogen atom, which substituent is linked to the remainder of the molecule via a nitrogen atom, may be prepared by reacting a compound of formula (IIB) wherein R^{21} represents halogen, e.g. chloro, with the appropriate compound of formula $R^{21}-H$ [e.g. 2-methoxyethylamine, *N*-methyl-*L*-alanine, 2-aminocyclopentanecarboxylic acid, 3-aminocyclopentanecarboxylic acid, 1-(aminomethyl)cyclopropanecarboxylic acid, methyl
 20 azetidine-3-carboxylate, pyrrolidin-3-ol, pyrrolidine-3-carboxylic acid, piperidine-2-carboxylic acid, piperidine-3-carboxylic acid, 4-(1*H*-tetrazol-5-yl)piperidine, piperazine, 1-(methylsulfonyl)piperazine, piperazin-2-one, 2-(piperazin-1-yl)propanoic acid, morpholine, morpholine-2-carboxylic acid, thiomorpholine, thiomorpholine 1,1-dioxide, 1,4-diazepan-5-one, 2-oxa-5-azabicyclo[2.2.1]heptane or an appropriately substituted
 25 azaspiroalkane], optionally in the presence of a base, e.g. an organic base such as triethylamine or *N,N*-diisopropylethylamine and/or 1-methyl-2-pyrrolidinone, or pyridine, or an inorganic base such as potassium carbonate.

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
 30 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
5 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
10 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
15 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.

20 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 &
25 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.

30 The compounds in accordance with this invention potently inhibit the binding of a fluorescence conjugate to TNF α when tested in the fluorescence polarisation assay described below. Moreover, certain compounds in accordance with this invention potently inhibit TNF α -induced NF- κ B activation in the reporter gene assay described below.

Fluorescence Polarisation Assay

Preparation of Compound (A)

1-(2,5-Dimethylbenzyl)-6-[4-(piperazin-1-ylmethyl)phenyl]-2-(pyridin-4-yl-methyl)-1*H*-benzimidazole – hereinafter referred to as “*Compound (A)*” – can be prepared by the procedure described in Example 499 of WO 2013/186229 (published 19 December 2013); or by a procedure analogous thereto.

Preparation of fluorescence conjugate

Compound (A) (27.02 mg, 0.0538 mmol) was dissolved in DMSO (2 mL). 5 (-6) Carboxy-fluorescein succinimyl ester (24.16 mg, 0.0510 mmol) (Invitrogen catalogue number: C1311) was dissolved in DMSO (1 mL) to give a bright yellow solution. The two solutions were mixed at room temperature, the mixture turning red in colour. The mixture was stirred at room temperature. Shortly after mixing a 20 µL aliquot was removed and diluted in a 80:20 mixture of AcOH:H₂O for LC-MS analysis on the 1200RR-6140 LC-MS system. The chromatogram showed two closely eluting peaks at retention times of 1.42 and 1.50 minutes, both with mass (M+H)⁺ = 860.8 amu, corresponding to the two products formed with the 5- and 6-substituted carboxyfluorescein group. A further peak at retention time 2.21 minutes had a mass of (M+H)⁺ = 502.8 amu, corresponding to *Compound (A)*. No peak was observed for unreacted 5(-6) carboxyfluorescein succinimyl ester. The peak areas were 22.0%, 39.6% and 31.4% for the three signals, indicating a 61.6% conversion to the two isomers of the desired fluorescence conjugate at that time-point. Further 20 µL aliquots were extracted after several hours and then after overnight stirring, diluted as before and subjected to LC-MS analysis. The percentage conversion was determined as 79.8% and 88.6% respectively at these time-points. The mixture was purified on a UV-directed preparative HPLC system. The pooled purified fractions were freeze-dried to remove excess solvent. After freeze-drying, an orange solid (23.3 mg) was recovered, equivalent to 0.027 mmol of fluorescence conjugate, corresponding to an overall yield of 53% for the reaction and preparative HPLC purification.

Inhibition of binding of fluorescence conjugate to TNF α

Compounds were tested at 10 concentrations starting from 25 μ M in a final assay concentration of 5% DMSO, by pre-incubation with TNF α for 60 minutes at ambient temperature in 20 mM Tris, 150 mM NaCl, 0.05% Tween 20, before addition of the fluorescence conjugate and a further incubation for 20 hours at ambient temperature. The final concentrations of TNF α and the fluorescence conjugate were 10 nM and 10 nM respectively in a total assay volume of 25 μ L. Plates were read on a plate reader capable of detecting fluorescence polarisation (e.g. an Analyst HT plate reader; or an Envision plate reader). An IC₅₀ value was calculated using XLfit™ (4 parameter logistic model) in ActivityBase.

When tested in the fluorescence polarisation assay, the compounds of the accompanying Examples were all found to exhibit IC₅₀ values of 50 μ M or better.

Reporter Gene Assay*Inhibition of TNF α -induced NF- κ B activation*

Stimulation of HEK-293 cells by TNF α leads to activation of the NF- κ B pathway. The reporter cell line used to determine TNF α activity was purchased from InvivoGen. HEK-Blue™ CD40L is a stable HEK-293 transfected cell line expressing SEAP (secreted embryonic alkaline phosphatase) under the control of the IFN β minimal promoter fused to five NF- κ B binding sites. Secretion of SEAP by these cells is stimulated in a dose-dependent manner by TNF α , with an EC₅₀ of 0.5 ng/mL for human TNF α . Compounds were diluted from 10 mM DMSO stocks (final assay concentration 0.3% DMSO) to generate a 10-point 3-fold serial dilution curve (e.g. 30,000 nM to 2 nM final concentration). Diluted compound was preincubated with TNF α for 60 minutes prior to addition to a 384-well microtitre plate and incubated for 18 h. The final TNF α concentration in the assay plate was 0.5 ng/mL. SEAP activity was determined in the supernatant using a colorimetric substrate, e.g. QUANTI-Blue™ or HEK-Blue™ Detection media (InvivoGen). Percentage inhibitions for compound dilutions were calculated between a DMSO control and maximum inhibition (by excess control compound) and an IC₅₀ value calculated using XLfit™ (4 parameter logistic model) in ActivityBase.

When tested in the reporter gene assay, certain compounds of the accompanying Examples were found to exhibit IC₅₀ values of 50 μ M or better.

EXAMPLES**Abbreviations**

- 5 DCM: dichloromethane THF: tetrahydrofuran
 MeOH: methanol DMSO: dimethylsulfoxide
 TFA: trifluoroacetic acid TBAF: tetrabutylammonium fluoride
 ADDP: 1,1'-(azodicarbonyl)dipiperidine
 BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
 10 h: hour M: mass
 HPLC: High Performance Liquid Chromatography
 LCMS: Liquid Chromatography Mass Spectrometry
 ES+: Electrospray Positive Ionisation RT: retention time

15 **Nomenclature**

Compounds were named with the aid of ACD/Name Batch (Network) version 11.01, and/or Accelrys Draw 4.0.

Analytical Conditions20 ***Analytical HPLC***

- Column: Waters X-Bridge, 20 x 2.1 mm, 2.5µm
 Solvent A: 10 mM ammonium formate in water + 0.1% ammonia
 Solvent B: acetonitrile + 5% Solvent A+0.1% ammonia
 Injection volume: 5.0 µL
 25 Flow rate: 1.00 mL/minute
 Gradient program: 5% B to 95% B in 4 minutes; hold till 5.00 minutes; at 5.10 minutes
 B concentration is 5% up to 6.5 minutes

INTERMEDIATE 1

30

N-[(2,5-Dichlorophenyl)methyl]-3-nitropyridin-4-amine

To a solution of 4-chloro-3-nitropyridine (3.2 g, 20 mmol) in ethanol (40 mL) were added triethylamine (8.35 mL, 60 mmol) and (2,5-dichlorophenyl)methanamine

hydrochloride (8.5 g, 40 mmol) at 0°C. The reaction mixture was heated at 80°C for 1 h, then concentrated by evaporation *in vacuo* and diluted with ethyl acetate (~30 mL). The organic layer was washed with brine (2 x 20 mL), dried over Na₂SO₄ and concentrated by evaporation *in vacuo*. The residue was purified by column chromatography, using 100-
5 200 mesh size silica and 1% MeOH in DCM as eluent, to afford the *title compound* (1.7 g, 80%). δ_{H} (400 MHz, CDCl₃) 9.27 (s, 2H), 8.57 (br s, 1H), 8.32 (d, *J* 6.0 Hz, 1H), 7.38 (d, *J* 8.4 Hz, 1H), 7.30-7.26 (m, 1H), 6.60 (d, *J* 6.0 Hz, 1H), 4.64 (d, *J* 6.0 Hz, 2H). LCMS (ES⁺) 297.9 (M+H)⁺, RT 2.39 minutes.

10

INTERMEDIATE 2

N⁴-(2,5-Dichlorophenyl)methyl]pyridine-3,4-diamine

To a stirred solution of *Intermediate 1* (4.8 g, 16 mmol) in methanol (30 mL) was added Zn powder (5.28 g, 80 mmol) at 0°C. The mixture was stirred for 5 minutes, then
15 ammonium formate (4.07 g, 64 mmol) was added at 0°C. The reaction mixture was stirred for 3 h, then filtered using celite. The filtrate was concentrated by evaporation *in vacuo*. The residue was purified by column chromatography, using 100-200 mesh size silica and 8% MeOH in DCM + 0.1% NH₃ as eluent, to afford the *title compound* (0.6 g, 65%). δ_{H} (400 MHz, CD₃OD) 7.77 (s, 1H), 7.63 (d, *J* 5.2 Hz, 1H), 7.41 (d, *J* 8.4 Hz, 1H),
20 7.33 (d, *J* 2.0 Hz, 1H), 7.27 (dd, *J* 6.0, 2.4 Hz, 1H), 6.26 (d, *J* 5.6 Hz, 1H), 4.52 (s, 2H). LCMS (ES⁺) 268.0 (M+H)⁺, RT 2.29 minutes.

INTERMEDIATE 3

1-[(2,5-Dichlorophenyl)methyl]-2-methylimidazo[4,5-*c*]pyridine

A solution of *Intermediate 2* (2.8 g, 10 mmol) in glacial acetic acid (30 mL) was stirred at 120°C for 20 h, then the acetic acid was removed by evaporation *in vacuo*. The residue was neutralized with NaOH solution, extracted with ethyl acetate (2 x 20 mL) and dried over Na₂SO₄, then concentrated by evaporation *in vacuo* and purified by column
30 chromatography, using 100-200 mesh silica and 5% methanol in DCM as eluent, to afford the *title compound* (0.4 g, 70%) as a brown solid. δ_{H} (400 MHz, CD₃OD) 9.24 (s, 1H), 8.53 (d, *J* 6.4 Hz, 1H), 8.03 (d, *J* 6.8 Hz, 1H), 7.54 (d, *J* 8.4 Hz, 1H), 7.43 (dd, *J* 6.4, 2.0

Hz, 1H), 6.97 (d, *J* 2.0 Hz, 1H), 5.78 (s, 2H), 2.72 (s, 3H). LCMS (ES⁺) 291.9 (M+H)⁺, RT 1.90 minutes.

INTERMEDIATE 4

5

1-[(2,5-Dichlorophenyl)methyl]-5-[(4-methoxyphenyl)methyl]-2-methylimidazo[4,5-*c*]-pyridin-5-ium chloride

To a solution of *Intermediate 3* (1 g, 3.4 mmol) in acetone (5 mL) was added 4-methoxybenzyl chloride (0.717 mL, 6.8 mmol). The mixture was heated in a sealed tube at 80°C overnight, then the acetone was removed by evaporation *in vacuo*. The residue was washed with diethyl ether to afford the *title compound* (0.2 g, 71%) as a brown solid. δ_{H} (400 MHz, CD₃OD) 9.41 (s, 1H), 8.65 (d, *J* 6.8 Hz, 1H), 7.98 (d, *J* 6.8 Hz, 1H), 7.53-7.41 (m, 5H), 7.00-6.99 (m, 2H), 5.78 (s, 2H), 5.74 (s, 2H), 3.80 (s, 3H), 2.69 (s, 3H). LCMS (ES⁺) 412.1 (M)⁺, RT 0.08 minutes.

15

INTERMEDIATE 5

1-[(2,5-Dichlorophenyl)methyl]-5-[(4-methoxyphenyl)methyl]-2-methyl-6,7-dihydro-4*H*-imidazo[4,5-*c*]pyridine

To a solution of *Intermediate 4* (1 g, 2.4 mmol) in methanol (15 mL) was added NaBH₄ (0.181 g, 4.8 mmol) at 0°C. The reaction mixture was stirred at 25-28°C for 2 h, quenched by the addition of dilute HCl and methanol, then concentrated by evaporation *in vacuo*. The residue was basified with 1N aqueous NaOH solution and extracted with DCM (2 x 20 mL), then dried over Na₂SO₄ and concentrated by evaporation *in vacuo*. The resulting material was purified by column chromatography, using 100-200 mesh silica and 10% methanol in DCM (+ 0.1% NH₃) as eluent, to afford the *title compound* (0.15 g, 75%) as a brown solid. δ_{H} (400 MHz, CDCl₃) 7.34-7.20 (m, 5H), 6.85 (d, *J* 8.4 Hz, 1H), 6.53 (s, 1H), 4.97 (s, 2H), 3.79 (s, 3H), 3.67 (s, 2H), 3.56 (s, 2H), 2.75 (t, *J* 5.2 Hz, 2H), 2.41 (br s, 2H), 2.28 (s, 3H). LCMS (ES⁺) 416.1 (M+H)⁺, RT 2.92 minutes.

30

INTERMEDIATE 61-[(2,5-Dichlorophenyl)methyl]-2-methyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine

A solution of *Intermediate 5* (0.760 g, 1.8 mmol) in TFA (3 mL) was heated under microwave irradiation at 130°C for 15 minutes, then the TFA was removed by evaporation *in vacuo*. The residue was neutralized with saturated aqueous NaHCO₃ solution and extracted with DCM (3 x 20 mL), then dried over Na₂SO₄ and concentrated by evaporation *in vacuo*. The resulting material was purified by column chromatography, using 100-200 mesh silica and 10% methanol in DCM (+ 0.1% NH₃) as eluent, to afford the *title compound* (0.49 g, 92%) as a brown gum. δ_{H} (400 MHz, CD₃OD) 7.47 (d, *J* 8.4 Hz, 1H), 7.34 (dd, *J* 6.0, 2.0 Hz, 1H), 6.52 (s, 1H), 5.18 (s, 2H), 3.76 (s, 2H), 3.05 (t, *J* 5.6 Hz, 2H), 2.45 (br s, 2H), 2.28 (s, 3H). LCMS (ES⁺) 296.0 (M+H)⁺, RT 2.69 minutes.

INTERMEDIATE 7{1-[(2,5-Dichlorophenyl)methyl]imidazo[4,5-c]pyridin-2-yl}methanol

To a solution of *Intermediate 2* (2.4 g, 9 mmol) in methanol (5 mL) was added glycolic acid (1.36 g, 17 mmol). The reaction mixture was heated at 120°C for 20 h, then the methanol was removed by evaporation *in vacuo*. The residue was neutralized with saturated aqueous NaHCO₃ solution and extracted with DCM (3 x 20 mL), then dried over Na₂SO₄ and concentrated by evaporation *in vacuo*. The resulting material was purified by column chromatography, using 100-200 mesh silica and 5% methanol in DCM as eluent, to afford the *title compound* (2.1 g, 74%) as a brown solid. δ_{H} (400 MHz, CDCl₃) 9.08 (s, 1H), 8.40 (d, *J* 5.6 Hz, 1H), 7.40 (d, *J* 8.4 Hz, 1H), 7.24-7.10 (m, 1H), 7.13 (d, *J* 5.6 Hz, 1H), 6.59 (s, 1H), 5.53 (s, 2H), 4.92 (s, 2H). LCMS (ES⁺) 307.9 (M+H)⁺, RT 1.56 minutes.

INTERMEDIATE 8*tert*-Butyl({1-[(2,5-dichlorophenyl)methyl]imidazo[4,5-c]pyridin-2-yl}methoxy)-dimethylsilane

To solution of *Intermediate 7* (2.09 g, 6.8 mmol) in dichloromethane (10 mL) was added imidazole (0.92 g, 13.6 mmol) and the reaction mixture was stirred for 5 minutes.

tert-Butyldimethylsilyl chloride (2.05 g, 13.6 mmol) was added, followed by stirring at 25-28°C overnight. The reaction mixture was neutralized with saturated aqueous NaHCO₃ solution and extracted with DCM (3 x 30 mL), then dried over Na₂SO₄ and concentrated by evaporation *in vacuo*. The residue was purified by column chromatography, using 100-200 mesh silica and 2% methanol in dichloromethane as eluent, to afford the *title compound* (2.2 g, 77%) as a brown solid. δ_{H} (400 MHz, CDCl₃) 9.12 (s, 1H), 8.41 (d, *J* 5.6 Hz, 1H), 7.38 (d, *J* 8.4 Hz, 1H), 7.25 (dd, *J* 8.0, 2.0 Hz, 1H), 7.12 (d, *J* 5.6 Hz, 1H), 6.53 (d, *J* 1.6 Hz, 1H), 5.58 (s, 2H), 4.99 (s, 2H), 0.81 (s, 9H), 0.04 (s, 6H). LCMS (ES⁺) 422.1 (M+H)⁺, RT 3.43 minutes.

INTERMEDIATE 9

tert-Butyl-({1-[(2,5-dichlorophenyl)methyl]-5-[(4-methoxyphenyl)methyl]imidazo[4,5-*c*]pyridin-5-ium-2-yl}methoxy)dimethylsilane chloride

To a solution of *Intermediate 8* (2.19 g, 5.2 mmol) in acetone (5 mL) was added 4-methoxybenzyl chloride (1.48 mL, 10.4 mmol). The mixture was heated in a sealed tube at 80°C for 16 h, then the acetone was removed by evaporation *in vacuo*. The residue was washed with diethyl ether (2 x 20 mL) to afford the *title compound* (2.12 g, 75%) as an off white solid, that was utilised in the next step without further purification. δ_{H} (400 MHz, CD₃OD) 9.55 (s, 1H), 8.69 (d, *J* 6.8 Hz, 1H), 8.02 (d, *J* 6.8 Hz, 1H), 7.53-7.47 (m, 4H), 7.38 (dd, *J* 6.0, 2.0 Hz, 1H), 7.00 (d, *J* 8.4 Hz, 1H), 6.72 (d, *J* 2.0 Hz, 1H), 5.84 (s, 2H), 5.80 (s, 2H), 5.09 (s, 2H), 3.80 (s, 3H), 0.80 (s, 9H), 0.05 (s, 6H).

INTERMEDIATE 10

tert-Butyl({1-[(2,5-dichlorophenyl)methyl]-5-[(4-methoxyphenyl)methyl]-6,7-dihydro-4*H*-imidazo[4,5-*c*]pyridin-2-yl}methoxy)dimethylsilane

To a solution of *Intermediate 9* (2.1 g, 3.8 mmol) in methanol (30 mL) was added NaBH₄ (0.296 g, 7.7 mmol) at 0°C. The reaction mixture was allowed to warm to 25°C and stirred for 2 h, then quenched with dilute HCl (~10 mL). The methanol was removed by evaporation *in vacuo*. The residue was basified with 1N NaOH solution, extracted with DCM (3 x 20 mL) and dried over Na₂SO₄, then the solvent was removed by evaporation *in vacuo*. The resulting material was purified by column chromatography,

using 100-200 mesh silica and 8% methanol in DCM as eluent, to afford the *title compound* (1.8 g, 85%) as an off-white solid. δ_{H} (400 MHz, CD_3OD) 7.43 (d, J 8.8 Hz, 2H), 7.31-7.27 (m, 2H), 6.89 (d, J 8.4 Hz, 2H), 6.57 (d, J 1.6 Hz, 1H), 5.29 (s, 2H), 4.83 (s, 2H), 4.70 (s, 2H), 3.78 (s, 3H), 3.68 (br s, 1H), 3.50 (br s, 1H), 2.81 (t, J 6.0 Hz, 2H),
 5 2.47 (t, J 5.6 Hz, 2H), 0.75 (s, 9H), 0.01 (s, 6H). LCMS (ES^+) 546.15 ($\text{M}+\text{H}^+$), RT 4.08 minutes.

INTERMEDIATE 11

10 {1-[(2,5-Dichlorophenyl)methyl]-5-[(4-methoxyphenyl)methyl]-6,7-dihydro-4*H*-imidazo-[4,5-*c*]pyridin-2-yl}methanol

To a solution of *Intermediate 10* (1.8 g, 3.2 mmol) in THF (10 mL) was added 1M TBAF in THF (9.89 mL, 9.8 mmol) at 0°C. The reaction mixture was stirred at 25-28°C for 2 h, then quenched with ice and extracted with DCM (3 x 30 mL). The solvent was
 15 removed by evaporation *in vacuo*. The residue was purified by column chromatography, using 100-200 mesh silica and 5% methanol in dichloromethane as eluent, to afford the *title compound* (1.2 g, 86%) as a yellow gum. δ_{H} (400 MHz, CD_3OD) 7.44 (d, J 8.4 Hz, 2H), 7.33-7.27 (m, 2H), 6.89 (d, J 8.4 Hz, 2H), 6.68 (d, J 2.0 Hz, 1H), 5.33 (s, 2H), 4.83 (s, 2H), 4.56 (s, 2H), 3.78 (s, 3H), 3.68 (br s, 1H), 3.49 (br s, 1H), 2.81 (t, J 6.0 Hz, 2H),
 20 2.45 (t, J 5.6 Hz, 2H). LCMS (ES^+) 432.0 ($\text{M}+\text{H}^+$), RT 2.39 minutes.

INTERMEDIATE 12

25 1-[(2,5-Dichlorophenyl)methyl]-5-[(4-methoxyphenyl)methyl]-2-(pyridin-3-yloxy-methyl)-6,7-dihydro-4*H*-imidazo[4,5-*c*]pyridine

To a solution of *Intermediate 11* (0.99 g, 2.3 mmol) in toluene (5 mL) were added triphenylphosphine (1.20 g, 4.6 mmol), ADDP (1.16 g, 4.6 mmol) and 3-hydroxypyridine (0.323 g, 3.4 mmol) at 25-28°C. The reaction mixture was stirred at the same temperature overnight, then concentrated by evaporation *in vacuo*. The residue was purified by
 30 column chromatography, using 100-200 mesh silica and 10% methanol in DCM as eluent, to afford the *title compound* (0.514 g, 44%) as a yellow gum. δ_{H} (400 MHz, CD_3OD) 8.08 (d, J 4.4 Hz, 1H), 7.91 (s, 1H), 7.42 (d, J 8.8 Hz, 1H), 7.33-7.26 (m, 5H), 6.90 (d, J

8.0 Hz, 2H), 6.47 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H), 3.78 (s, 3H), 3.70 (s, 2H), 3.52 (s, 2H), 2.80 (br s, 2H), 2.53 (br s, 2H). LCMS (ES⁺) 509.1 (M+H)⁺, RT 2.75 minutes.

INTERMEDIATE 13

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1-[(2,5-Dichlorophenyl)methyl]-2-(pyridin-3-yloxymethyl)-4,5,6,7-tetrahydroimidazo-[4,5-*c*]pyridine

A solution of *Intermediate 12* (0.500 g, 0.9 mmol) in TFA (2 mL) was heated under microwave irradiation at 130°C for 1 h. The TFA was evaporated under vacuum, then the residue was neutralized with saturated aqueous NaHCO₃ solution, extracted with DCM and dried over Na₂SO₄. The solvent was removed by evaporation *in vacuo*. The resulting material was purified by column chromatography, using 100-200 mesh silica and 10% methanol in DCM (+ 0.1% NH₃) as eluent, to afford the *title compound* (0.303 g, 80%) as a brown gum. δ_{H} (400 MHz, d₆-DMSO) 8.09 (d, *J* 4.4 Hz, 1H), 7.93 (d, *J* 2.8 Hz, 1H), 7.43 (d, *J* 8.8 Hz, 1H), 7.36-7.27 (m, 3H), 6.47 (s, 1H), 5.35 (s, 2H), 5.24 (s, 2H), 3.84 (s, 2H), 3.08 (t, *J* 6.0 Hz, 2H), 2.51 (d, *J* 5.2 Hz, 2H). LCMS (ES⁺) 389.0 (M+H)⁺, RT 2.30 minutes.

15

EXAMPLE 1

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4-{1-[(2,5-Dichlorophenyl)methyl]-2-methyl-6,7-dihydro-4*H*-imidazo[4,5-*c*]pyridin-5-yl}-*N,N*-dimethylpyridin-2-amine

To a solution of *Intermediate 6* (200 mg, 0.676 mmol) in toluene (5 mL) were added 4-bromo-*N,N*-dimethylpyridine-2-amine (162.7 mg, 0.813 mmol), BINAP (84.3 mg, 0.135 mmol) and Cs₂CO₃ (441.13 mg, 1.35 mmol) at 25-28°C. The reaction mixture was degassed for 1 h, followed by the addition of palladium acetate (7.59 mg, 0.033 mmol). The reaction mixture was heated at 100°C for 16 h, then quenched with water (~5 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated by evaporation *in vacuo*. The crude residue was purified by preparative HPLC to give the *title compound* (23 mg, 8%). δ_{H} (400 MHz, CD₃OD) 7.61 (d, *J* 8.0 Hz, 1H), 7.53 (d, *J* 8.4 Hz, 1H), 7.45 (dd, *J* 6.4, 2.0 Hz, 1H), 7.14 (d, *J* 2.0 Hz, 1H), 6.70 (dd, *J* 5.6, 2.0 Hz, 1H), 6.07 (d, *J* 1.6 Hz, 1H), 5.48 (s, 2H), 4.72 (s, 2H), 3.96

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(t, *J* 5.6 Hz, 2H), 3.19 (s, 6H), 2.68 (m, 5H). LCMS (ES⁺) 416.2 (M+H)⁺, RT 2.36 minutes.

EXAMPLE 2

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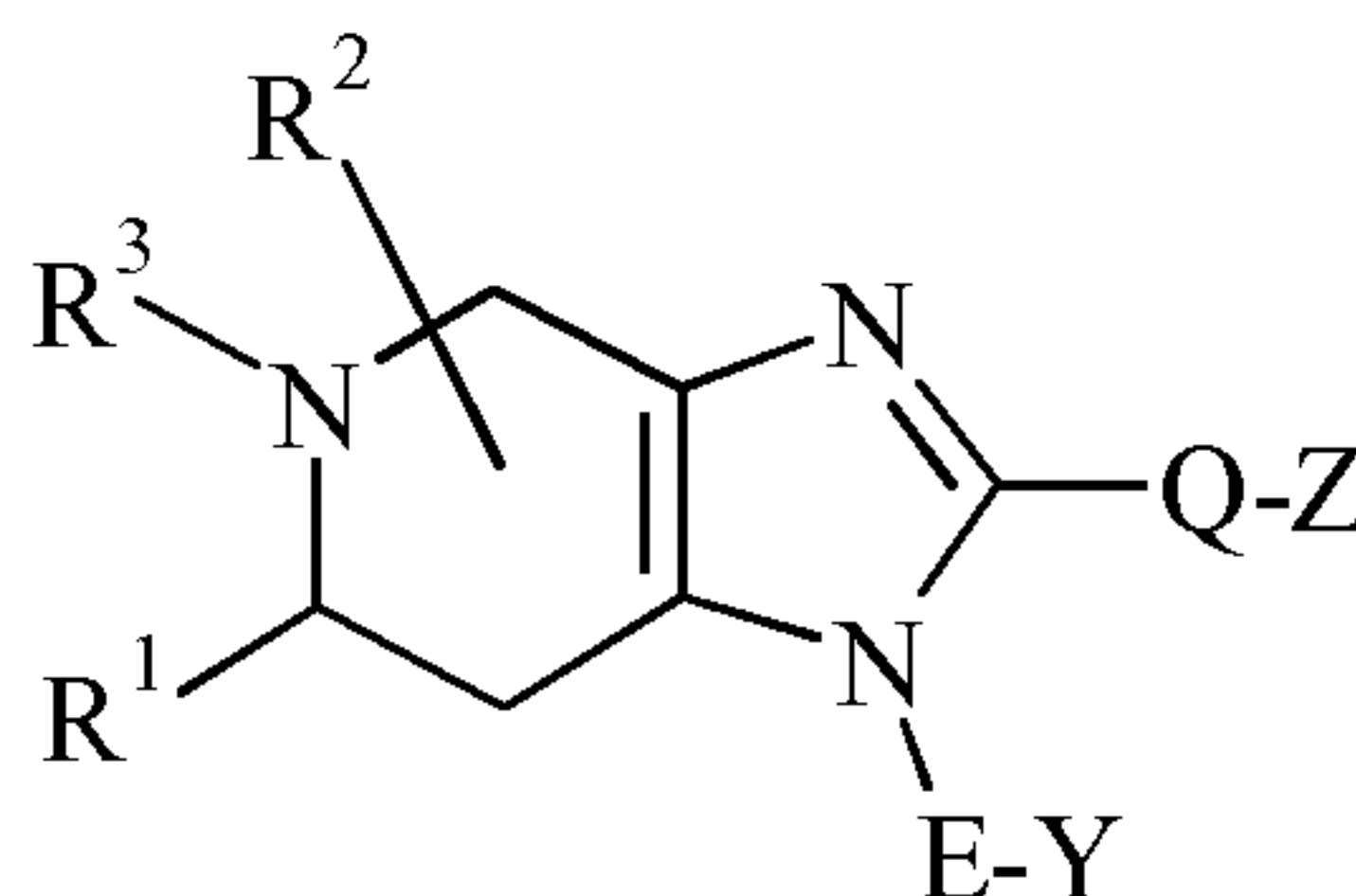
{1-[(2,5-Dichlorophenyl)methyl]-2-(pyridin-3-yloxymethyl)-6,7-dihydro-4*H*-imidazo-[4,5-*c*]pyridin-5-yl}(morpholin-4-yl)methanone

To a solution of *Intermediate 13* (200 mg, 0.51 mmol) in DCM (5 mL) was added triethylamine (213 μ L, 1.02 mmol) at 0°C, and the reaction mixture was stirred for 5
10 minutes. 4-Morpholinecarbonyl chloride (153.21 mg, 1.02 mmol) was added at 0°C. The reaction mixture was allowed to warm to 25-28°C and stirred for 2 h, then quenched with ice and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated by evaporation *in vacuo*. The crude residue was purified by preparative HPLC, giving the *title compound* (40 mg, 16%). δ_{H} (400 MHz, CD₃OD) 8.10
15 (d, *J* 4.0 Hz, 1H), 7.95 (d, *J* 2.4 Hz, 1H), 7.42 (d, *J* 8.8 Hz, 1H), 7.36-7.26 (m, 3H), 6.44 (d, *J* 1.6 Hz, 1H) 5.35 (s, 2H), 5.23 (s, 2H), 4.37 (s, 2H), 3.68 (t, *J* 4.4 Hz, 4H), 3.58 (t, *J* 5.4 Hz, 4H), 3.31 (br s, 2H), 2.60 (br s, 2H). LCMS (ES⁺) 502.2 (M+H)⁺, RT 1.99 minutes.

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Claims:

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



(I)

wherein

- 10 E represents a covalent bond; or E represents -S(O)₂- or -N(R⁴)-; or E represents an optionally substituted straight or branched C₁₋₄ alkylene chain;

- Q represents a covalent bond; or Q represents -O-, -S-, -S(O)-, -S(O)₂-, -S(O)(NR⁵)-, -N(R⁵)-, -C(O)N(R⁵)-, -N(R⁵)C(O)-, -S(O)₂N(R⁵)- or -N(R⁵)S(O)₂-; or Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain optionally comprising one, two or three heteroatom-containing linkages independently selected from -O-, -S-, -S(O)-, -S(O)₂-, -S(O)(NR⁵)-, -N(R⁵)-, -C(O)N(R⁵)-, -N(R⁵)C(O)-, -S(O)₂N(R⁵)- and -N(R⁵)S(O)₂-;

Y represents C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents;

- 20 Z represents hydrogen, halogen or trifluoromethyl; or Z represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; or Z represents -Z¹-Z² or -Z¹-C(O)-Z², either of which moieties may be optionally substituted by one or more substituents;

- 25 Z¹ represents a divalent radical derived from an aryl, C₃₋₇ heterocycloalkyl or heteroaryl group;

Z² represents aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl or heteroaryl;

R^1 and R^2 independently represent hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SF_5$, $-NR^bR^c$, $-NR^cCOR^d$, $-NR^cCO_2R^d$, $-NHCONR^bR^c$, $-NR^cSO_2R^e$, $-N(SO_2R^e)_2$, $-NHSO_2NR^bR^c$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$, $-SO_2NR^bR^c$ or $-SO(NR^b)R^d$; or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, 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, C_{3-7} heterocycloalkenyl, C_{4-9} heterobicycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-aryl-, heteroaryl(C_{3-7})heterocycloalkyl-, (C_{3-7})cycloalkyl-heteroaryl-, (C_{3-7})cycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{4-7})cycloalkenyl-heteroaryl-, (C_{4-9})bicycloalkyl-heteroaryl-, (C_{3-7})heterocycloalkyl-heteroaryl-, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{3-7})heterocycloalkenyl-heteroaryl-, (C_{4-9})heterobicycloalkyl-heteroaryl- or (C_{4-9})spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents;

R^3 represents hydrogen, trifluoromethyl, $-SO_2R^a$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$, $-SO_2NR^bR^c$ or $-SO(NR^a)R^e$; or R^3 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_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-aryl-, (C_{3-7})cycloalkyl-heteroaryl-, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-heteroaryl-, (C_{4-7})cycloalkenyl-heteroaryl-, (C_{4-9})bicycloalkyl-heteroaryl-, (C_{3-7})heterocycloalkyl-heteroaryl-, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{3-7})heterocycloalkenyl-heteroaryl-, (C_{4-9})heterobicycloalkyl-heteroaryl- or (C_{4-9})spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents;

R^4 and R^5 independently represent hydrogen or C_{1-6} alkyl;

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,

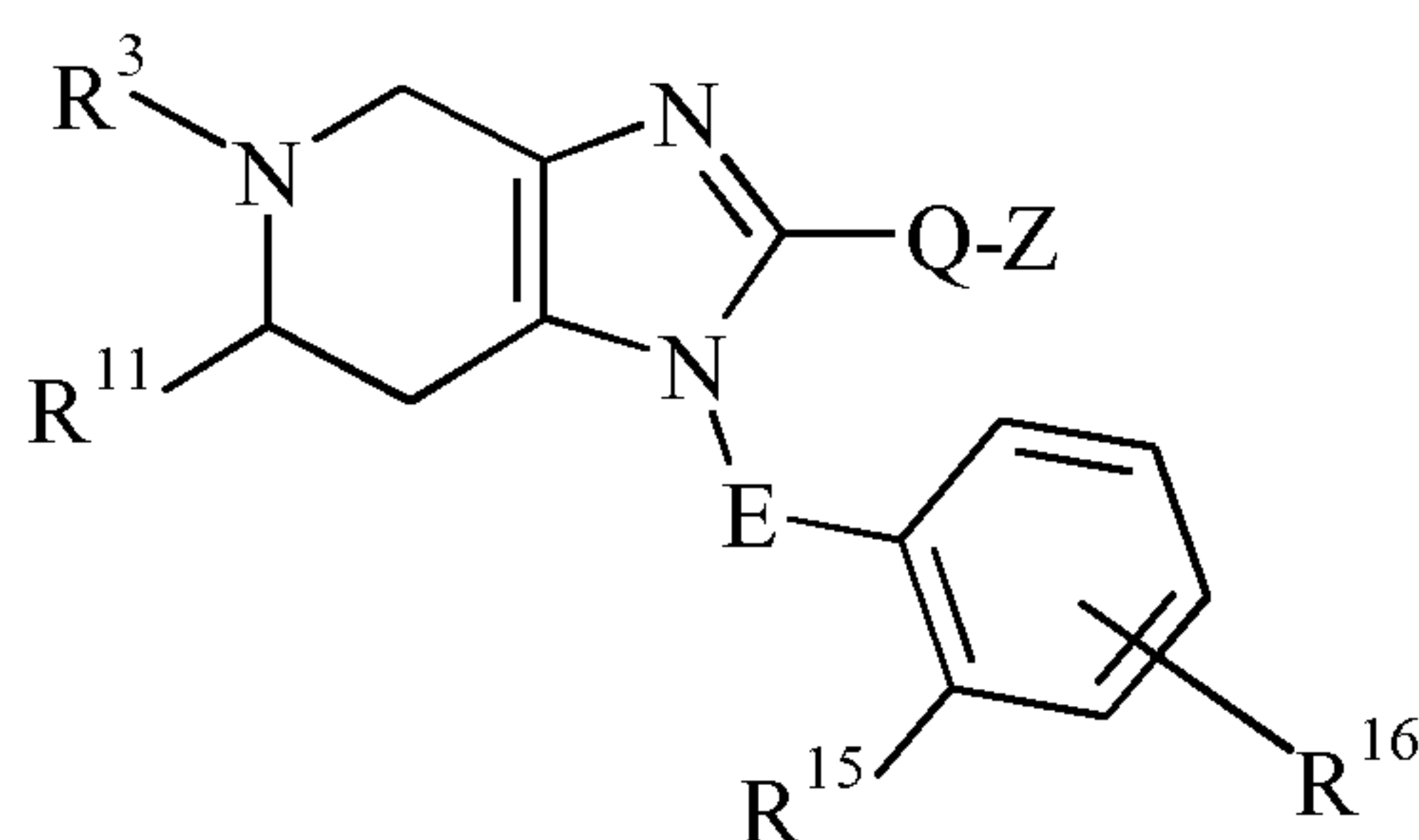
piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents;

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 wherein Y represents phenyl, which group may be optionally substituted by one or more substituents.

3. A compound as claimed in claim 1 represented by formula (IIA) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof:



(IIA)

wherein

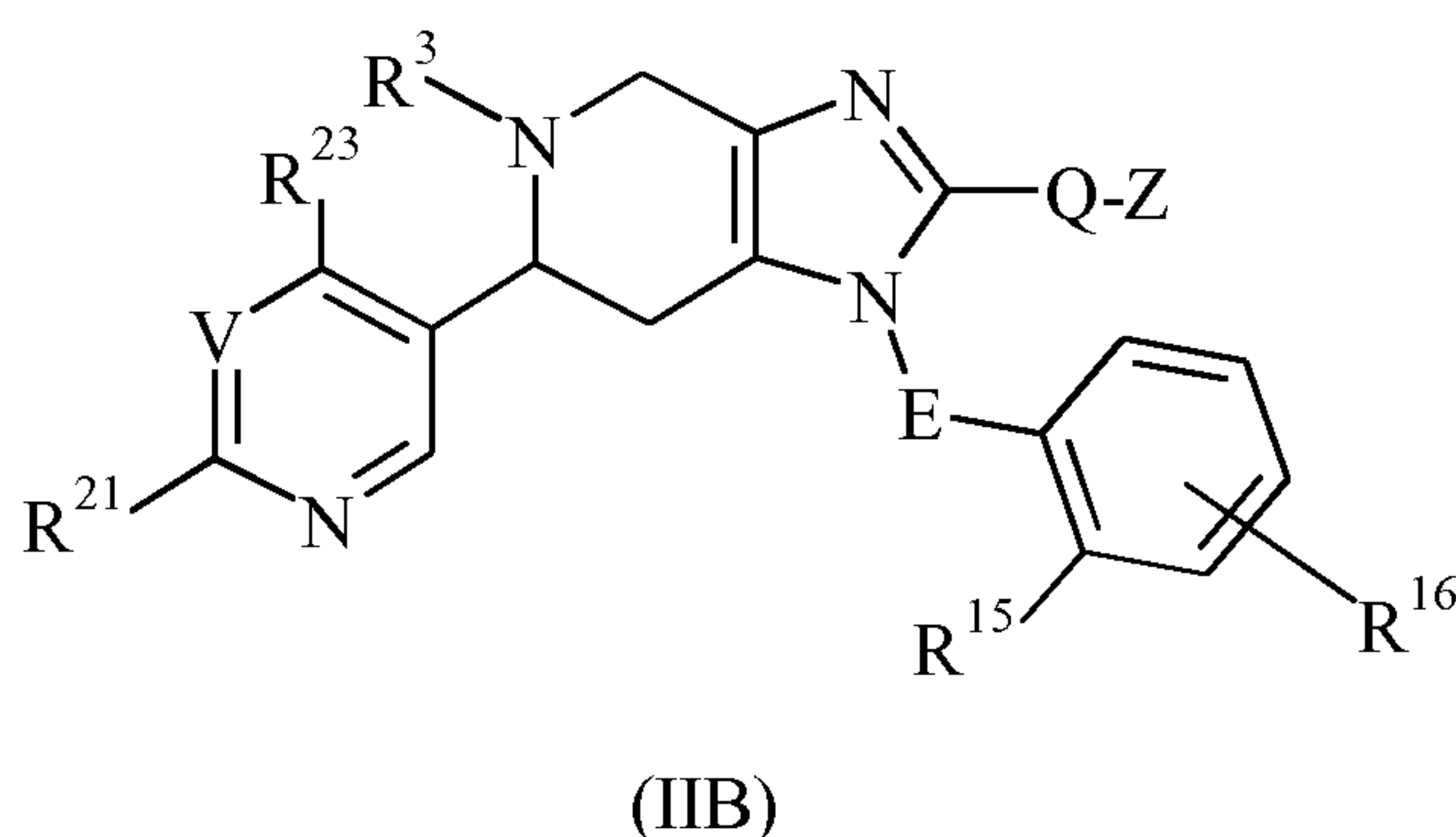
R^{11} represents hydrogen, halogen or $-OR^a$; or R^{11} represents C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl, heteroaryl, (C_{3-7}) heterocycloalkyl(C_{1-6})alkyl-aryl-, heteroaryl(C_{3-7})heterocycloalkyl-, (C_{3-7}) cycloalkyl-heteroaryl-, (C_{3-7}) cycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{4-7}) cycloalkenyl-heteroaryl-, (C_{4-9}) bicycloalkyl-heteroaryl-, (C_{3-7}) heterocycloalkyl-heteroaryl-, (C_{3-7}) heterocycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{3-7}) heterocycloalkenyl-heteroaryl-, (C_{4-9}) heterobicycloalkyl-heteroaryl- or (C_{4-9}) spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents;

R^{15} and R^{16} independently represent hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylthio,

C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, arylamino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, C₃₋₆ cycloalkylcarbonyl, C₃₋₆ heterocycloalkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl or di(C₁₋₆)alkylaminosulfonyl; and

E, Q, Z, R³ and R^a are as defined in claim 1.

4. A compound as claimed in claim 3 represented by formula (IIB) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof:



wherein

V represents C-R²² or N;

R²¹ represents hydrogen, halogen, halo(C₁₋₆)alkyl, cyano, C₁₋₆ alkyl, trifluoromethyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, (C₁₋₆)alkoxy, (C₁₋₆)alkyl, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, amino, amino-(C₁₋₆)alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, C₂₋₆ alkylcarbonylamino, (C₂₋₆)alkylcarbonylamino-(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonylamino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, C₁₋₆ alkylsulphonylamino, C₁₋₆ alkylsulphonylamino(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, morpholinyl(C₁₋₆)alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonylmethylenyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl, di(C₁₋₆)alkylaminosulphonyl, (C₁₋₆)alkyl-

sulphoximinyl or [(C₁₋₆)alkyl][N-(C₁₋₆)alkyl]sulphoximinyl; or R²¹ represents (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl, (C₄₋₇)cycloalkenyl, (C₄₋₉)bicycloalkyl, (C₃₋₇)heterocycloalkyl, (C₃₋₇)heterocycloalkenyl, (C₄₋₉)heterobicycloalkyl or (C₄₋₉)spiroheterocycloalkyl, any of which groups may be optionally substituted by one or
 5 more substituents;

R²² represents hydrogen, halogen or C₁₋₆ alkyl;

R²³ represents hydrogen, C₁₋₆ alkyl, trifluoromethyl or C₁₋₆ alkoxy;

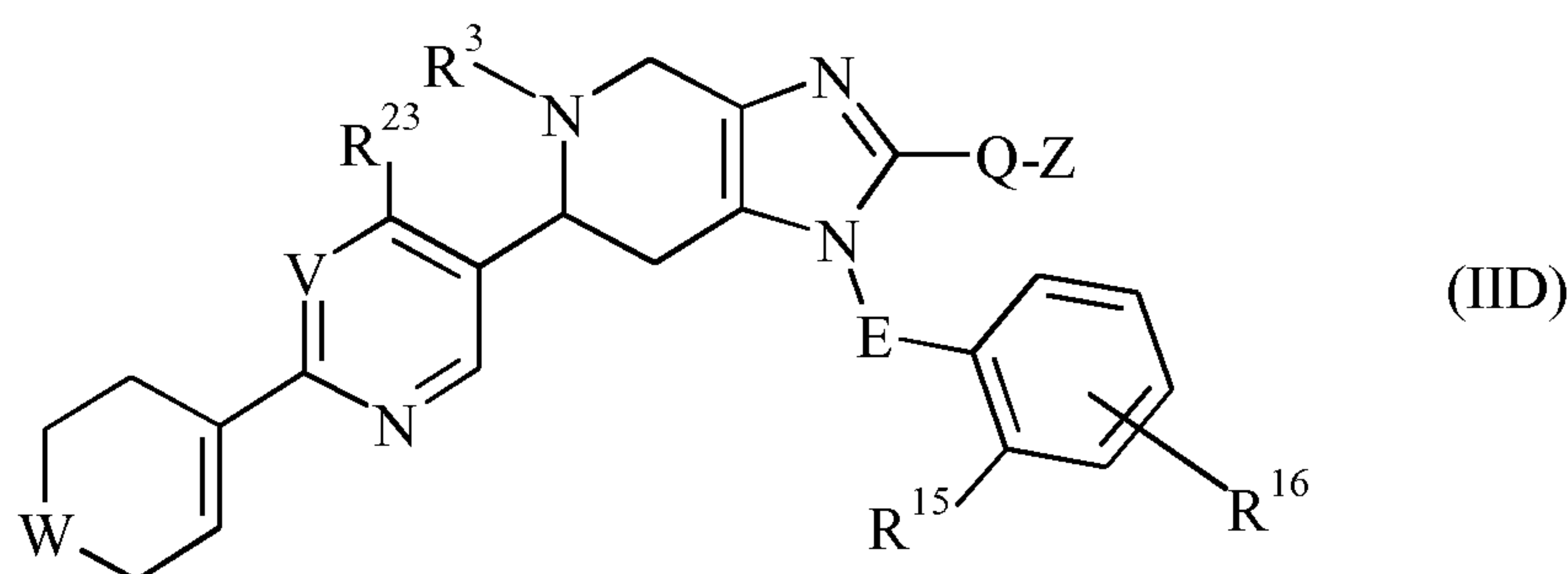
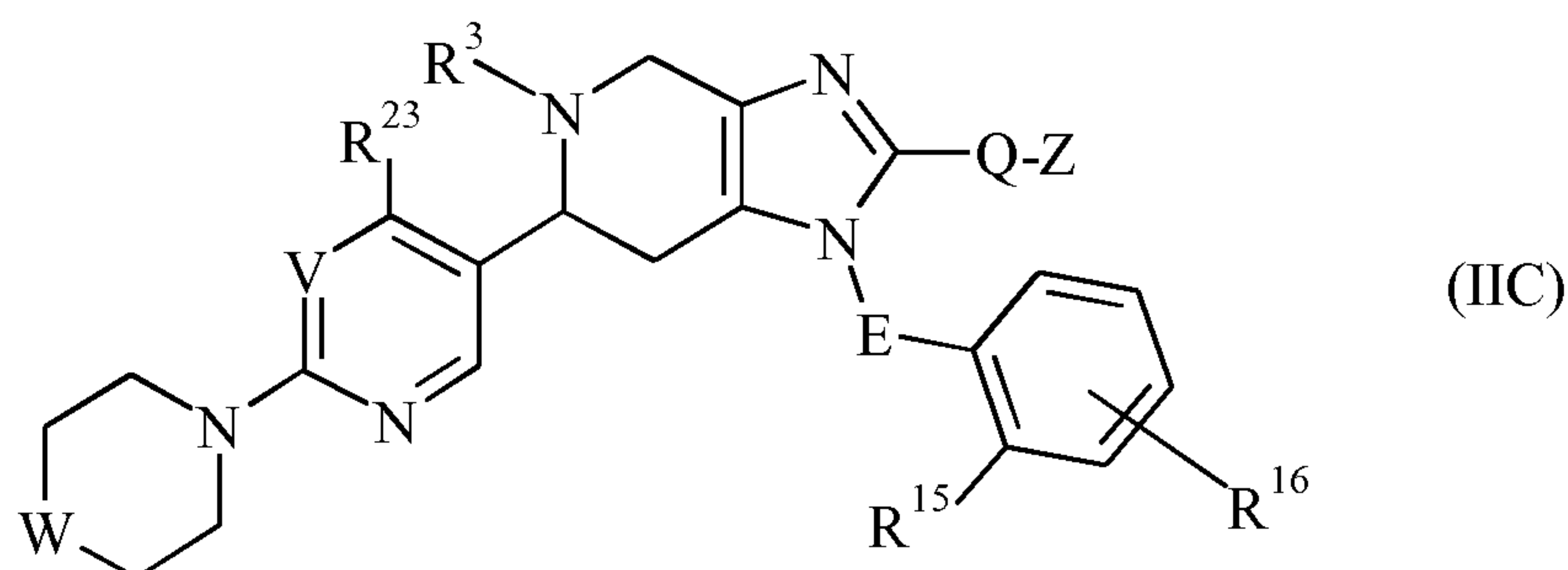
E, Q, Z and R³ are as defined in claim 1; and

R¹⁵ and R¹⁶ are as defined in claim 3.

10

5. A compound as claimed in claim 4 represented by formula (IIC), (IID), (IIE), (IIF), (IIG), (IIH), (IIJ), (IIK) or (IIL) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof:

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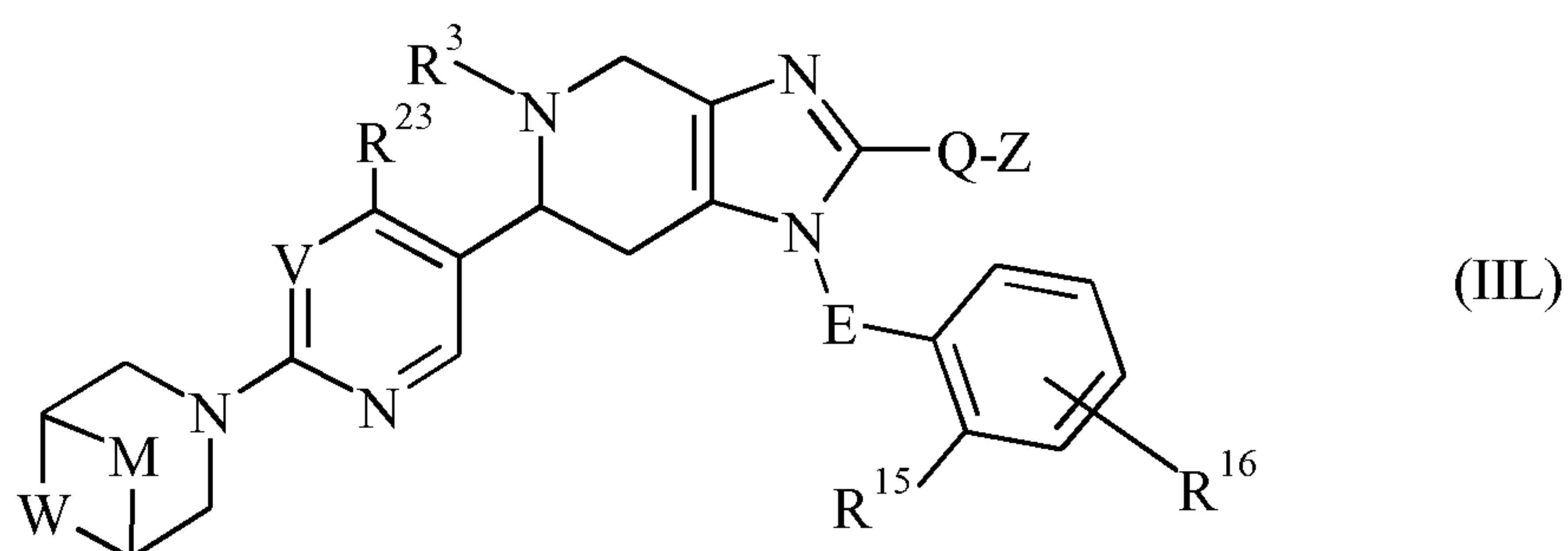
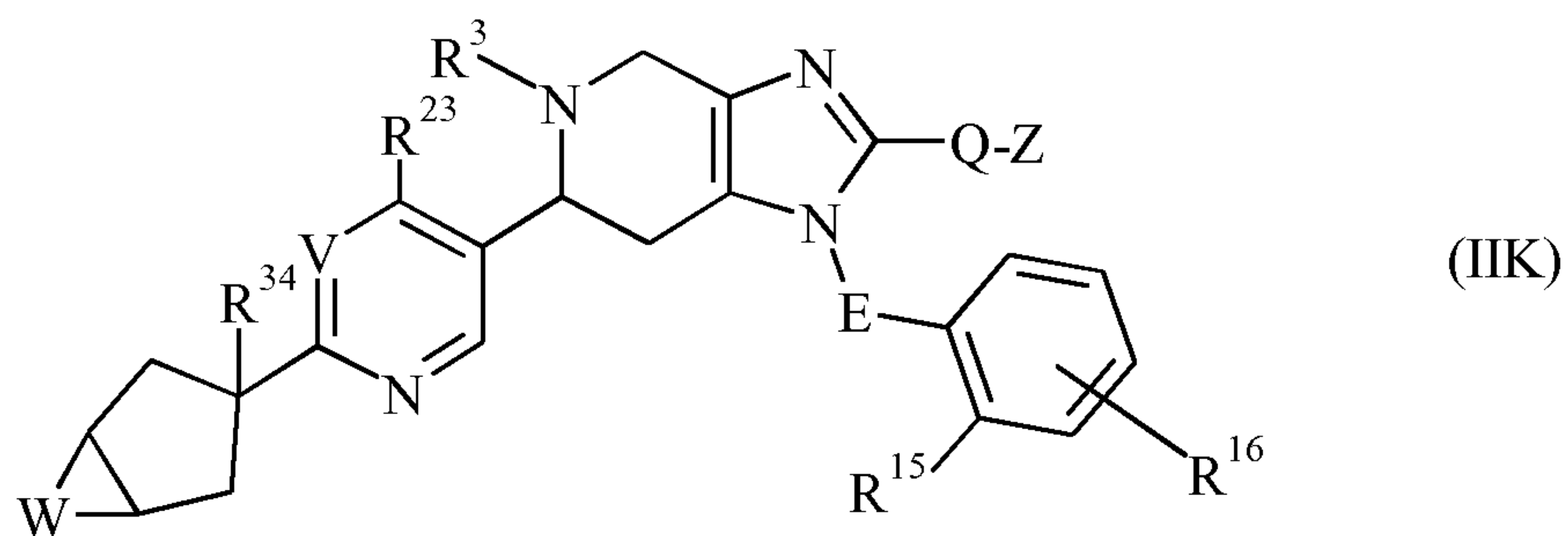
(III)

(IIF)

(IIG)

(IIIH)

(IIJ)



5

wherein

T represents $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$;

U represents C(O) or S(O)₂;

W represents O, S, S(O), S(O)₂, S(O)(NR⁵), N(R³¹) or C(R³²)(R³³);

10 -M- represents -CH₂- or -CH₂CH₂-;

R³¹ represents hydrogen, cyano(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω , -(C₁₋₆)alkyl- Ω , aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl or di(C₁₋₆)alkylaminosulphonyl;

R³² represents hydrogen, halogen, cyano, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkylsulphonyl, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, aminosulphonyl, (C₁₋₆)alkylsulphoximinyl, [(C₁₋₆)alkyl][N-(C₁₋₆)alkyl]sulphoximinyl, a carboxylic acid isostere or prodrug moiety Ω, or -(C₁₋₆)alkyl-Ω;

R³³ represents hydrogen, halogen, C₁₋₆ alkyl, trifluoromethyl, hydroxy, hydroxy-(C₁₋₆)alkyl, C₁₋₆ alkoxy, amino or carboxy;

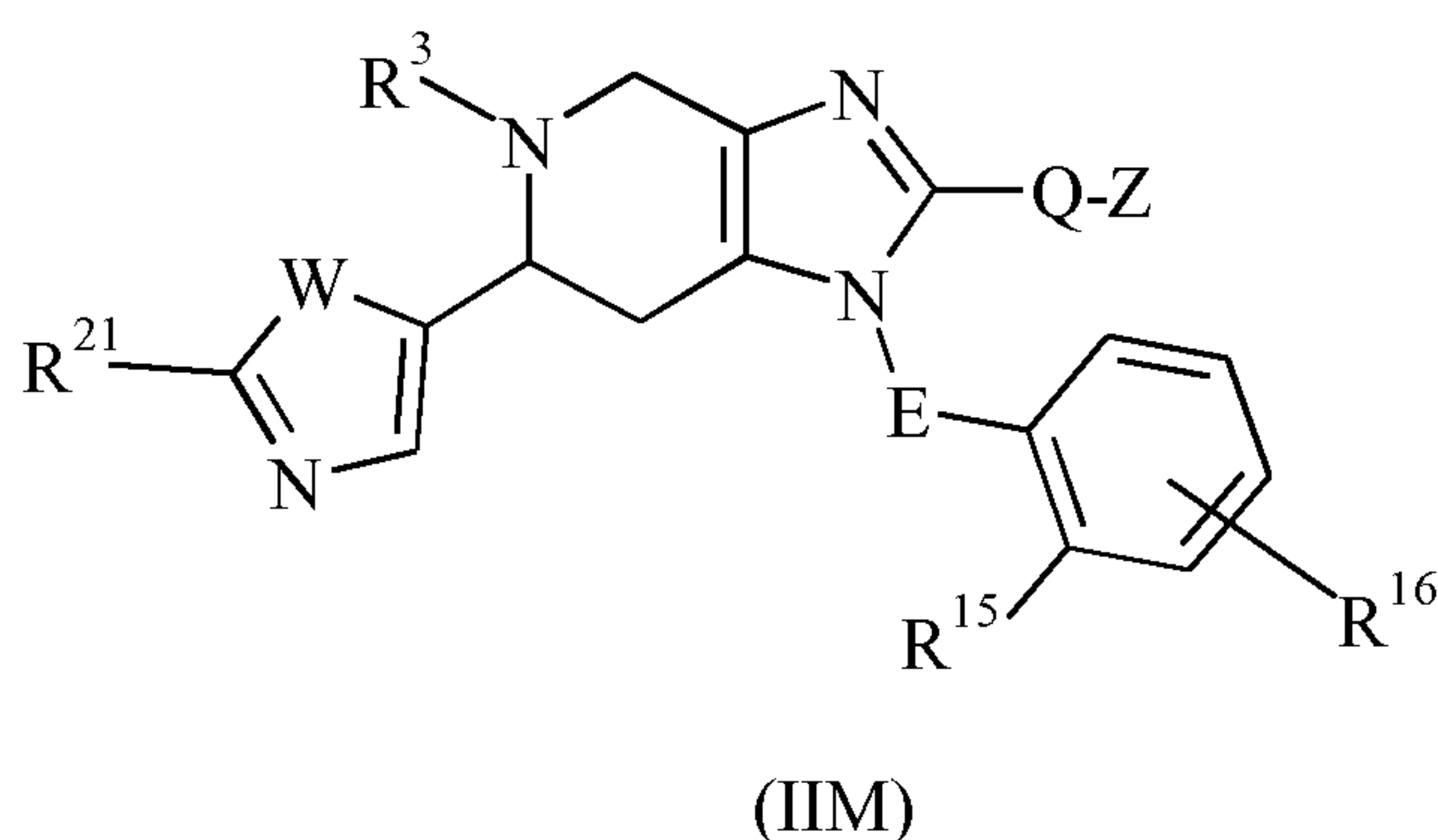
R^{34} represents hydrogen, halogen, halo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, (C_{2-6})alkylcarbonylamino, (C_{2-6})alkylcarbonylamino(C_{1-6})alkyl, (C_{1-6})alkylsulphonylamino or (C_{1-6})alkylsulphonylamino(C_{1-6})alkyl;

5 E, Q, Z, R^3 and R^5 are as defined in claim 1;

R^{15} and R^{16} are as defined in claim 3; and

V and R^{23} are as defined in claim 4.

6. A compound as claimed in claim 3 represented by formula (IIM) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof:



15 wherein

E, Q, Z and R^3 are as defined in claim 1;

R^{15} and R^{16} are as defined in claim 3;

R^{21} is as defined in claim 4; and

W is as defined in claim 5.

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7. A compound as claimed in any one of the preceding claims wherein E represents $-CH_2-$.

8. A compound as claimed in any one of the preceding claims wherein R^3 represents $-CONR^bR^c$, in which R^b and R^c are as defined in claim 1; or R^3 represents heteroaryl, which group may be optionally substituted by one or more substituents.

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9. A compound as claimed in any one of claims 3 to 8 wherein R¹⁵ represents difluoromethoxy.

10. A compound as herein specifically disclosed in any one of the Examples.

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

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12. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, for use in the treatment and/or prevention of disorders for which the administration of a modulator of TNF α function is indicated.

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13. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, for use in the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an
20 oncological disorder.

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14. 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, or a glucuronide derivative thereof, or a co-crystal thereof, in association with a pharmaceutically acceptable carrier.

15. A pharmaceutical composition as claimed in claim 14 further comprising an additional pharmaceutically active ingredient.

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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, or a glucuronide derivative thereof, or a co-crystal thereof, for the manufacture of a medicament for the

treatment and/or prevention of disorders for which the administration of a modulator of TNF α function is indicated.

17. 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, or a glucuronide derivative thereof, or a co-crystal thereof, for the manufacture of a medicament for the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.

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18. A method for the treatment and/or prevention of disorders for which the administration of a modulator of TNF α function is indicated 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, or a glucuronide derivative thereof, or a co-crystal thereof.

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19. A method for the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder, 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, or a glucuronide derivative thereof, or a co-crystal thereof.

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