



(86) **Date de dépôt PCT/PCT Filing Date:** 2006/04/25
(87) **Date publication PCT/PCT Publication Date:** 2006/11/02
(45) **Date de délivrance/Issue Date:** 2014/02/04
(85) **Entrée phase nationale/National Entry:** 2007/10/22
(86) **N° demande PCT/PCT Application No.:** GB 2006/001505
(87) **N° publication PCT/PCT Publication No.:** 2006/114606
(30) **Priorité/Priority:** 2005/04/26 (GB0508471.0)

(51) **Cl.Int./Int.Cl. C07D 277/82** (2006.01),
A61K 31/425 (2006.01), **A61K 31/5377** (2006.01),
A61K 31/55 (2006.01), **C07D 513/04** (2006.01)

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(54) **Titre : DERIVES DE THIAZOLE FUSIONNE EN TANT QU'INHIBITEURS DE LA KINASE**
(54) **Title: FUSED THIAZOLE DERIVATIVES AS KINASE INHIBITORS**

(57) **Abrégé/Abstract:**

A series of 5,6-dihydro-1,3-benzothiazol-7(4H)-one derivatives, and analogues thereof, which are substituted in the 2-position by an optionally substituted morpholin-4-yl moiety, being selective inhibitors of PD kinase enzymes, are accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive or ophthalmic conditions.



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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 November 2006 (02.11.2006)

PCT

(10) International Publication Number
WO 2006/114606 A1

(51) International Patent Classification:

A61K 31/4188 (2006.01) C07D 277/82 (2006.01)
A61K 31/4184 (2006.01) C07D 491/04 (2006.01)
A61K 31/55 (2006.01)

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(21) International Application Number:

PCT/GB2006/001505

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(22) International Filing Date: 25 April 2006 (25.04.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0508471.0 26 April 2005 (26.04.2005) GB

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

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(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FUSED THIAZOLE DERIVATIVES AS KINASE INHIBITORS

(57) Abstract: A series of 5,6-dihydro-1,3-benzothiazol-7(4H)-one derivatives, and analogues thereof, which are substituted in the 2-position by an optionally substituted morpholin-4-yl moiety, being selective inhibitors of PD kinase enzymes, are accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive or ophthalmic conditions.

WO 2006/114606 A1

FUSED THIAZOLE DERIVATIVES AS KINASE INHIBITORS

The present invention relates to the use of a class of fused thiazole derivatives in therapy. More particularly, the invention provides a therapeutic use for a family of 5,6-dihydro-1,3-benzothiazol-7(4*H*)-one derivatives, and analogues thereof, which are substituted in the 2-position by an optionally substituted morpholin-4-yl moiety. These compounds are selective inhibitors of phosphoinositide 3-kinase (PI3K) enzymes, and are accordingly of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive and ophthalmic conditions.

The PI3K pathway is implicated in a variety of physiological and pathological functions that are believed to be operative in a range of human diseases. Thus, PI3Ks provide a critical signal for cell proliferation, cell survival, membrane trafficking, glucose transport, neurite outgrowth, membrane ruffling, superoxide production, actin reorganization and chemotaxis (cf. S. Ward *et al.*, *Chemistry & Biology*, 2003, **10**, 207-213; and S.G. Ward & P. Finan, *Current Opinion in Pharmacology*, 2003, **3**, 426-434); and are known to be involved in the pathology of cancer, and metabolic, inflammatory and cardiovascular diseases (cf. M.P. Wymann *et al.*, *Trends in Pharmacol. Sci.*, 2003, **24**, 366-376). Aberrant upregulation of the PI3K pathway is implicated in a wide variety of human cancers (cf. S. Brader & S.A. Eccles, *Tumori*, 2004, **90**, 2-8).

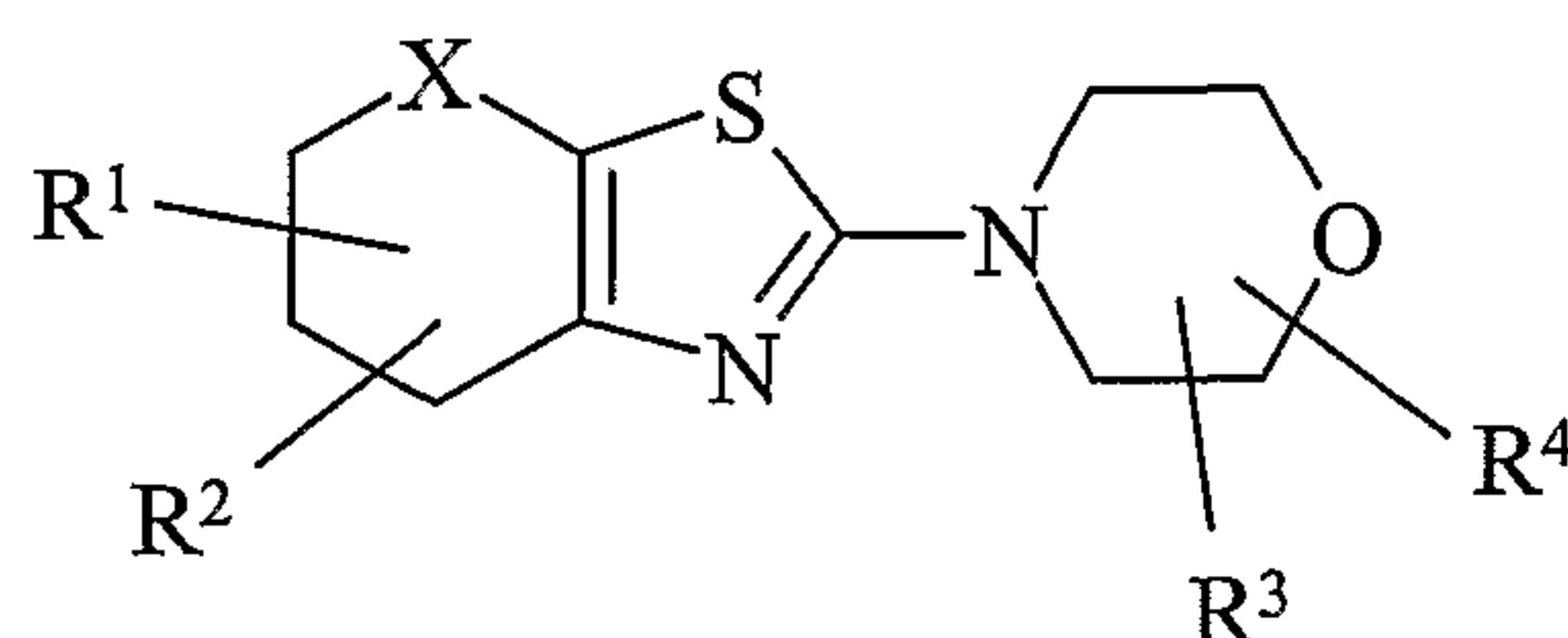
The compounds of use in the present invention, being potent and selective PI3K inhibitors, are therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, asthma, inflammatory bowel disease, psoriasis and transplant rejection; cardiovascular disorders including thrombosis, cardiac hypertrophy, hypertension, and irregular contractility of the heart (e.g. during heart failure); neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke, amyotrophic lateral sclerosis, spinal cord injury, head trauma and seizures; metabolic disorders such as obesity and type 2 diabetes; oncological conditions including leukaemia, glioblastoma, lymphoma, melanoma, and human cancers of the liver, bone, skin, brain, pancreas, lung, breast, stomach, colon, rectum, prostate, ovary and cervix; pain and nociceptive disorders; and ophthalmic disorders including age-related macular degeneration (ARMD).

In addition, the compounds of use in the present invention may be beneficial as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds of use in this invention may be useful as radioligands in assays for detecting compounds capable of binding to human
 5 PI3K enzymes.

The specific compounds 2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one, 5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one, 2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one and 7,7-dimethyl-2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one are
 10 disclosed in *Russian Journal of General Chemistry* (translation of *Zhurnal Obshchei Khimii*), 2000, 70[5], 784-787; but no therapeutic utility is ascribed therein to those compounds.

The compounds of use in the present invention are potent and selective PI3K inhibitors having a binding affinity (IC_{50}) for the human PI3K α and/or PI3K β and/or
 15 PI3K γ and/or PI3K δ isoform of 50 μ M or less, generally of 20 μ M or less, usually of 5 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* IC_{50} figure denotes a *more active* compound). The compounds of the invention may possess at least a
 20 10-fold selective affinity, typically at least a 20-fold selective affinity, suitably at least a 50-fold selective affinity, and ideally at least a 100-fold selective affinity, for the human PI3K α and/or PI3K β and/or PI3K γ and/or PI3K δ isoform relative to other human kinases.

The present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:

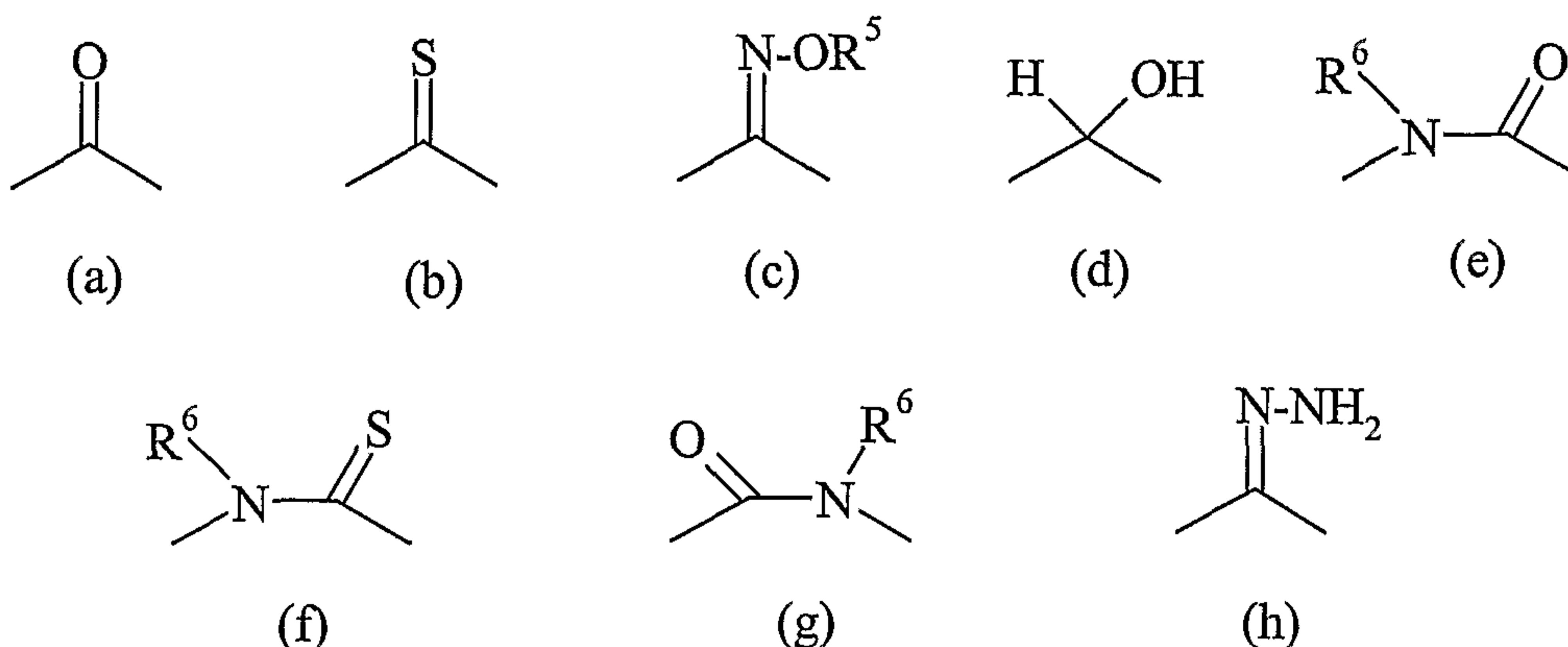


(I)

wherein

-X- represents a group of formula (a), (b), (c), (d), (e), (f), (g) or (h):

- 3 -



R¹ and R² independently represent hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl-
 5 (C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; or

R¹ and R², when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C₃₋₇ cycloalkyl or C₃₋₇ heterocycloalkyl, either of which groups may be optionally substituted by one or more
 10 substituents; or

R¹ and R², when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C₅₋₇ cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

R³ and R⁴ independently represent hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, aryl(C₂₋₆)alkenyl, aryl(C₂₋₆)alkynyl, biaryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkylcarbonyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, heteroaryl-aryl(C₁₋₆)alkyl or aryl-heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or
 15 more substituents; or
 20

R³ and R⁴, when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C₃₋₇ cycloalkyl or C₃₋₇ heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

R³ and R⁴, when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C₅₋₇ cycloalkyl, phenyl or heteroaryl,

any of which groups may be optionally benzo-fused and/or substituted by one or more substituents; and

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

for the manufacture of a medicament for the treatment and/or prevention of disorders for which the administration of a selective PI3K inhibitor is indicated.

More particularly, the present invention provides the use of a compound of formula (I) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein

-X- represents a group of formula (a), (b), (c), (d) or (e) as defined above;

R^1 and R^2 are as defined above; and

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

R^3 and R^4 , when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

for the manufacture of a medicament for the treatment and/or prevention of disorders for which the administration of a selective PI3K inhibitor is indicated.

The present invention also provides a method for the treatment and/or prevention of disorders for which the administration of a selective PI3K inhibitor 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 a pharmaceutically acceptable salt or solvate thereof.

Where R^1 and/or R^2 and/or R^3 and/or R^4 in the compounds of formula (I) above is other than hydrogen, this group may be unsubstituted, or substituted by one or more substituents. Typically, R^1 and/or R^2 and/or R^3 and/or R^4 will be unsubstituted, or substituted by one or two substituents. Suitably, R^1 and/or R^2 and/or R^3 and/or R^4 will be unsubstituted or monosubstituted.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of use in the invention or of their pharmaceutically acceptable salts. 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. 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; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

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

Suitable alkyl groups which may be present on the compounds of 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 and 2,2-dimethylpropyl. Derived expressions such as "C₁₋₆ alkoxy", "C₁₋₆ alkylthio", "C₁₋₆ alkylsulphonyl" and "C₁₋₆ alkylamino" are to be construed accordingly.

Specific C₃₋₇ cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

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

Specific aryl(C₂₋₆)alkenyl groups include 2-phenylethenyl and 3-phenylprop-2-en-1-yl.

A specific aryl(C₂₋₆)alkynyl group is 3-phenylprop-2-yn-1-yl.

Particular biaryl(C₁₋₆)alkyl groups include biphenyl and naphthylphenyl.

Suitable heterocycloalkyl groups include azetidiny, tetrahydrofuranyl, pyrrolidinyl, imidazolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl.

Typical C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl groups, which may comprise benzo-fused analogues thereof, include indolinylmethyl, 1,2,3,4-tetrahydroquinolinylmethyl and 1,2,3,4-tetrahydroisoquinolinylmethyl.

Typical C₃₋₇ heterocycloalkylcarbonyl groups, which may comprise benzo-fused analogues thereof, include piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolinylcarbonyl, 1,2,3,4-tetrahydroisoquinolinylmethyl and 1,2,3,4-tetrahydroquinoxalinylcarbonyl.

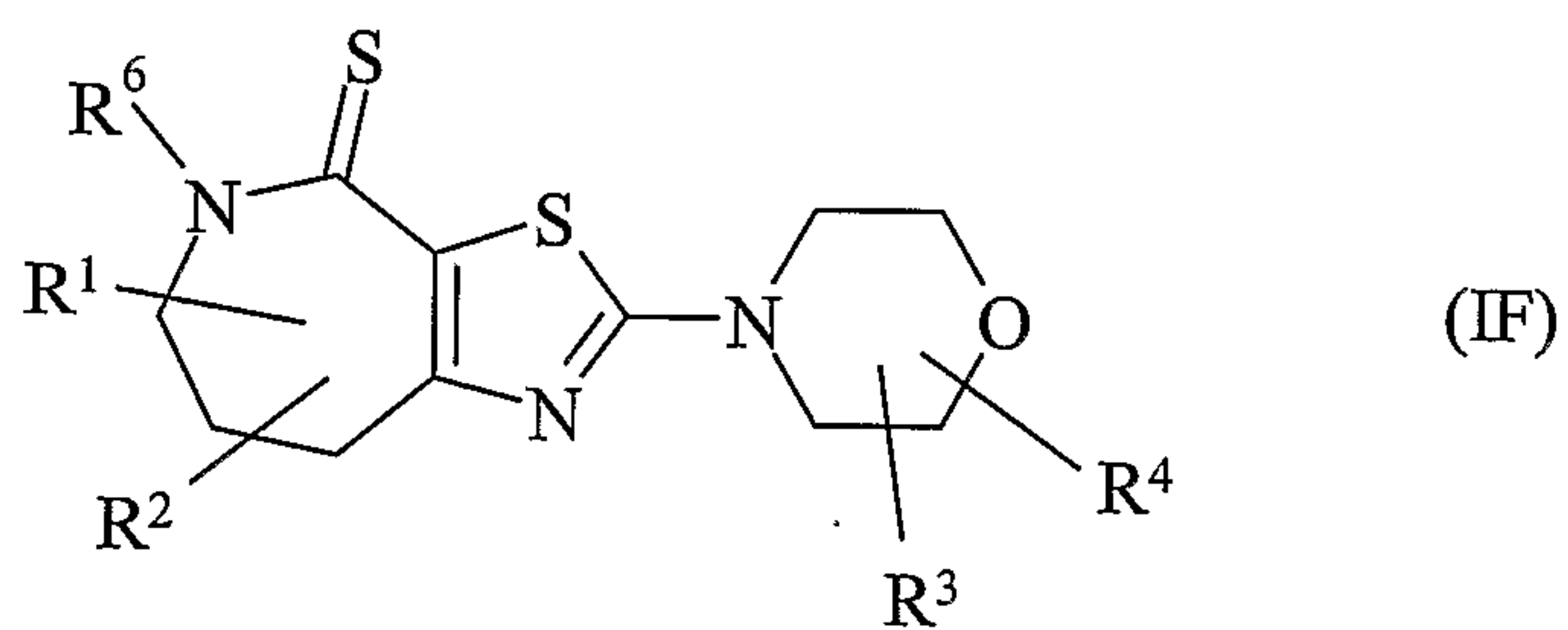
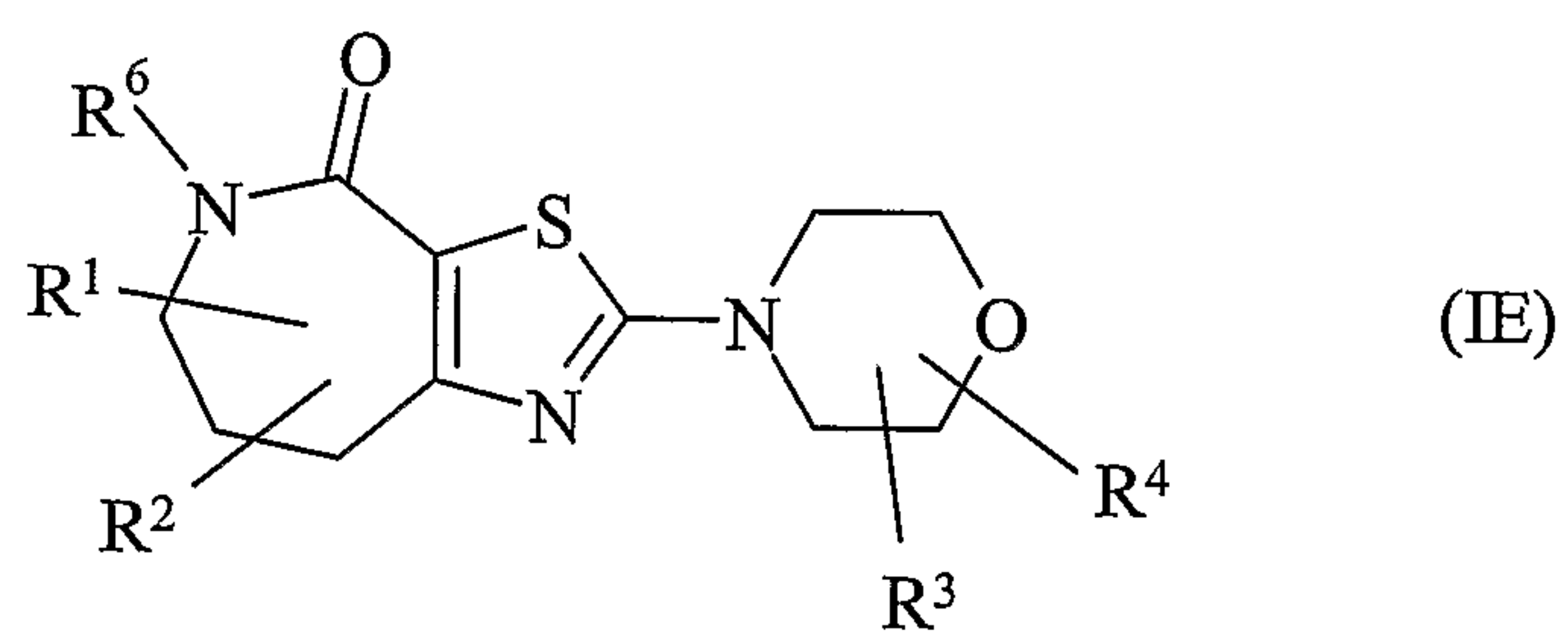
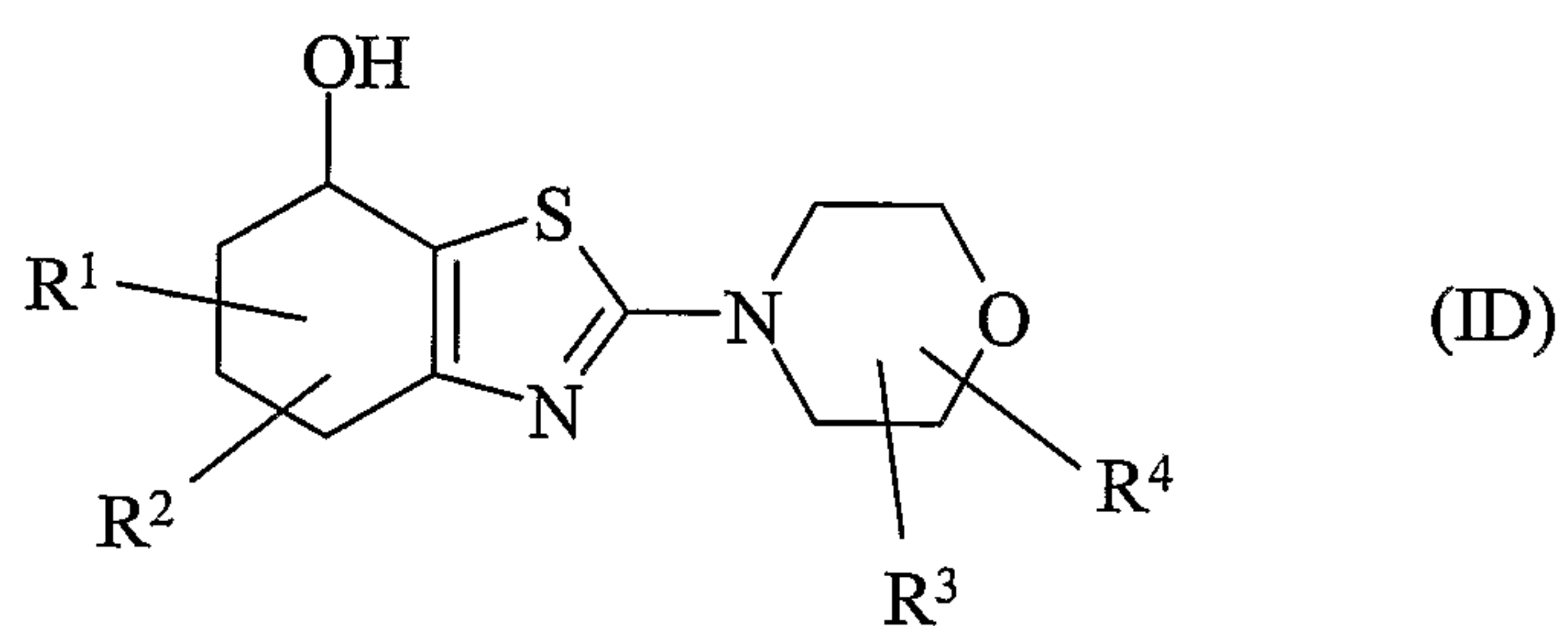
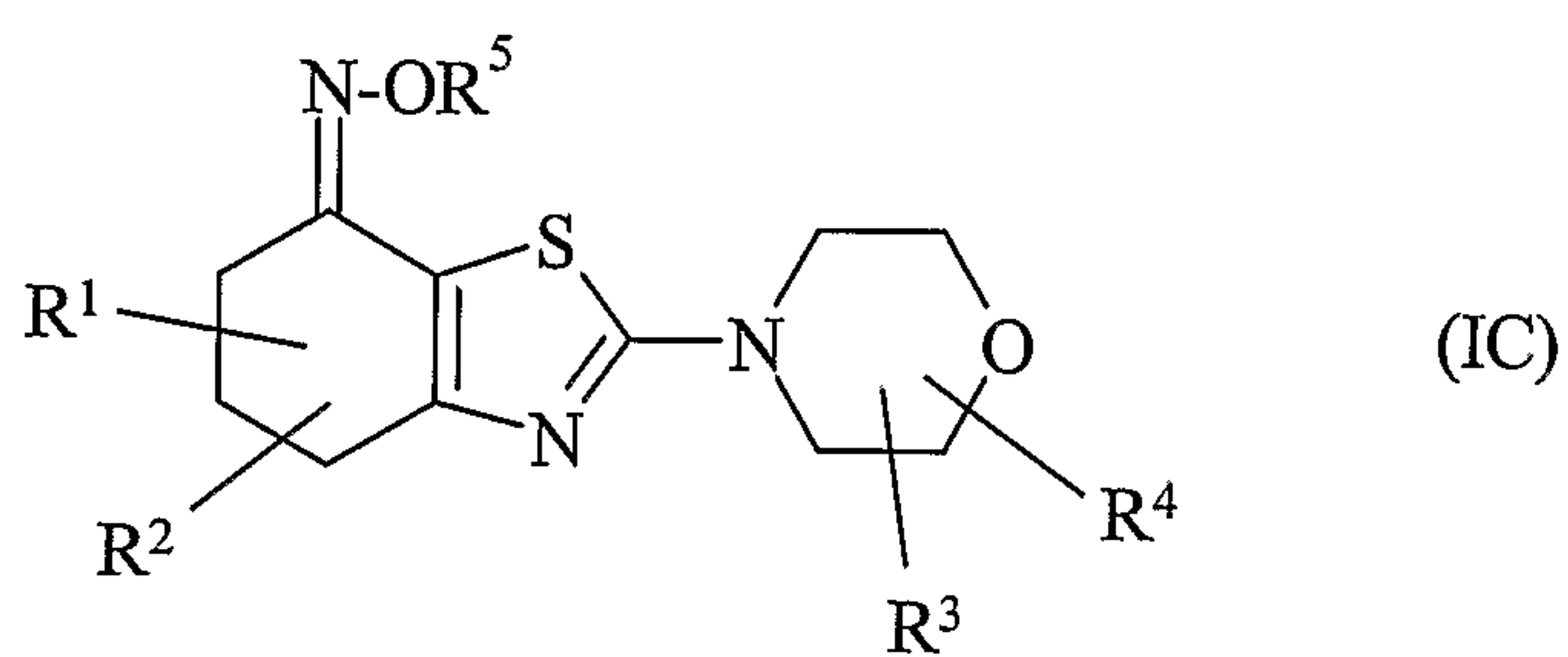
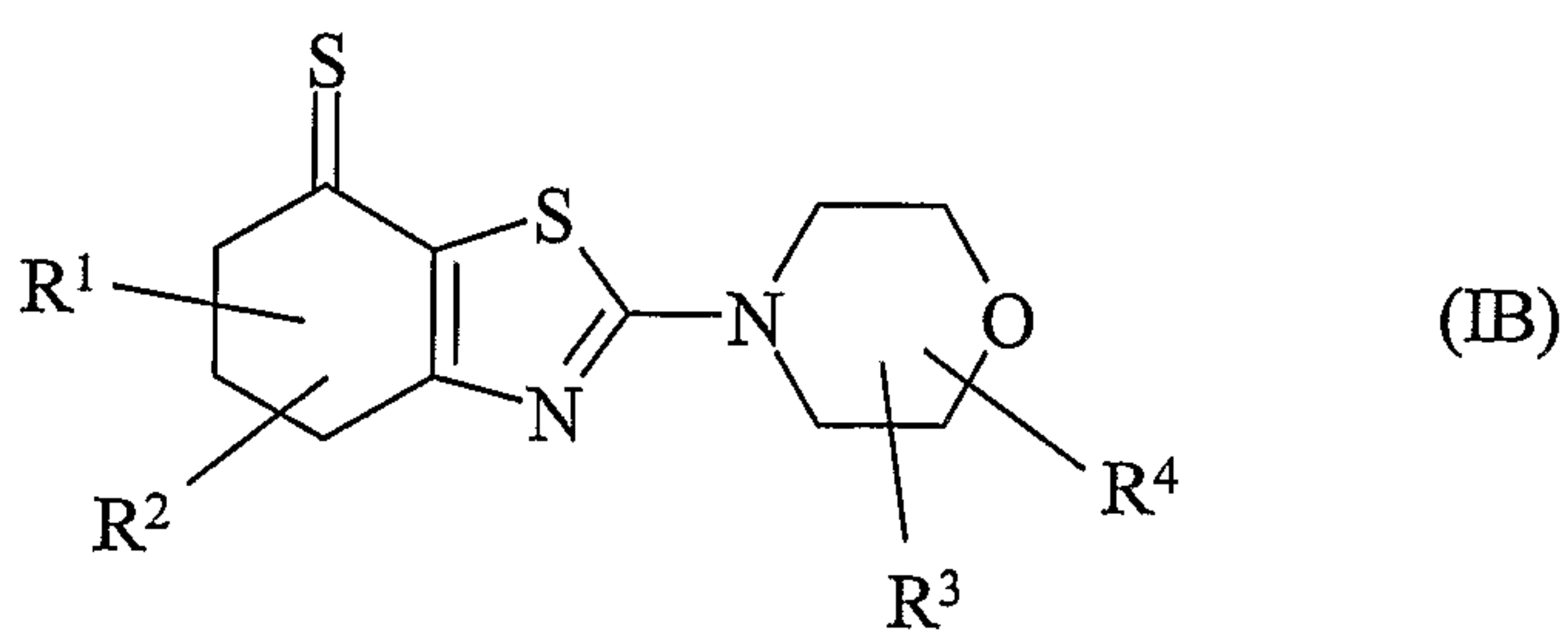
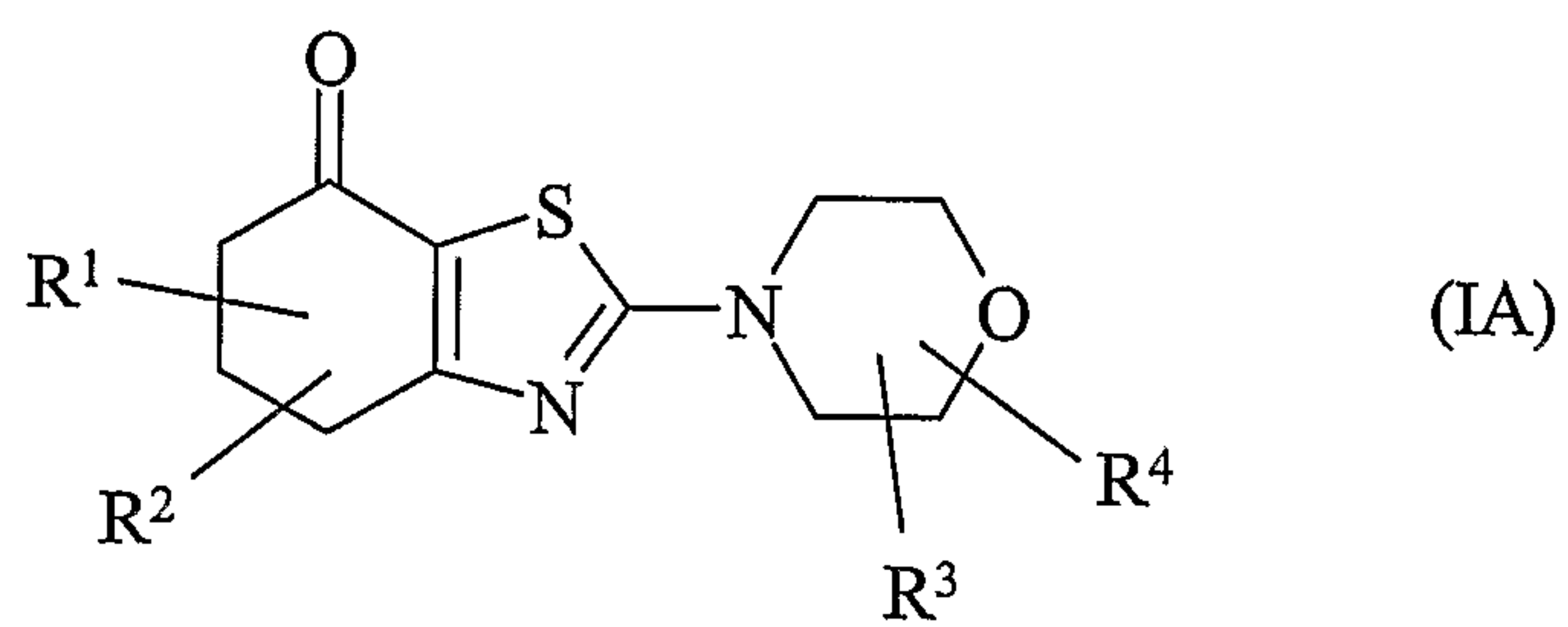
Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, pyrrolyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl and pyrazinyl groups.

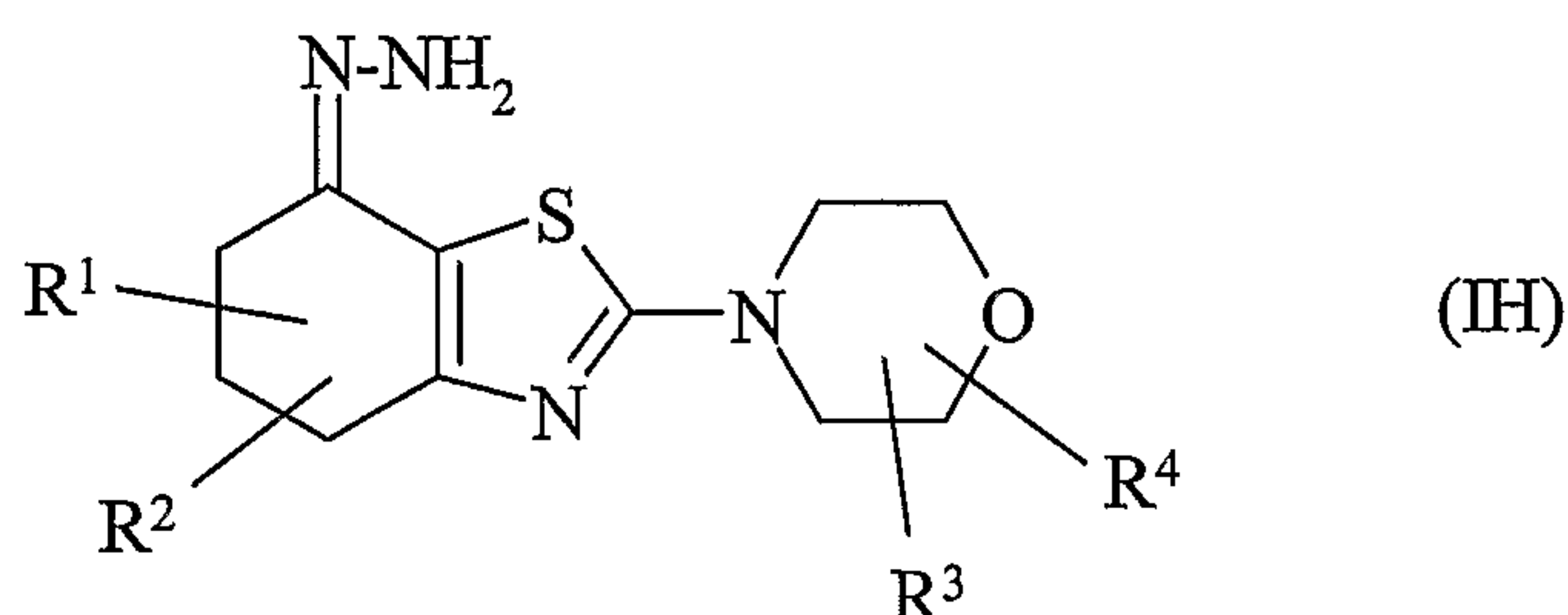
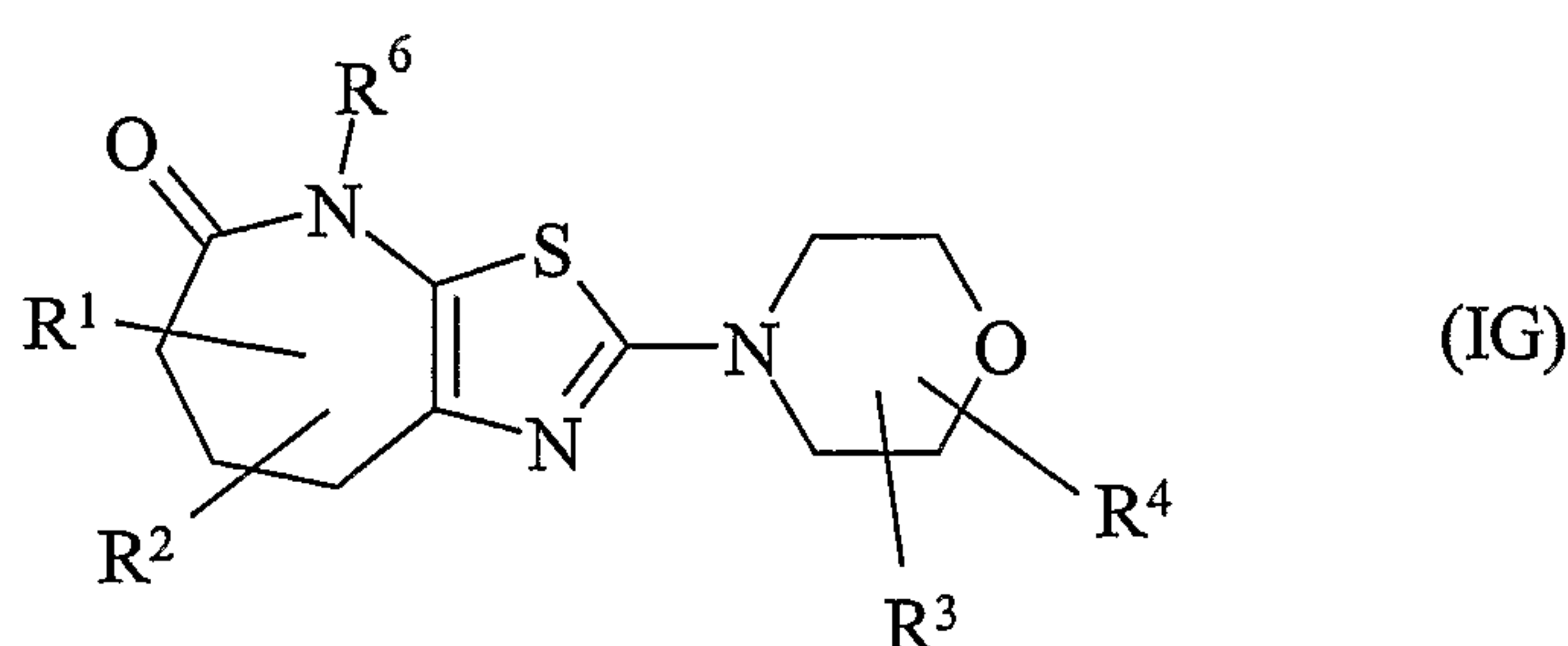
The term "halogen" as used herein is intended to include fluorine, chlorine, bromine and iodine atoms, especially fluoro or chloro.

Where the compounds of formula (I) have one or more asymmetric centres, they 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 and all possible mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (I) may exist as tautomers, for example keto (CH₂C=O)-enol (CH=CHOH) 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.

Specific sub-classes of compounds of use in the present invention are represented by the compounds of formula (IA), (IB), (IC), (ID), (IE), (IF), (IG) and (IH):

- 7 -





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

5 In a specific embodiment, the present invention provides the use, for the manufacture of a medicament for the treatment and/or prevention of disorders for which the administration of a selective PI3K inhibitor is indicated, of a compound selected from the following:

- 2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one;
- 10 5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one;
- 2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one;
- 7,7-dimethyl-2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one;
- and pharmaceutically acceptable salts and solvates thereof.

15 Likewise, the present invention provides a method for the treatment and/or prevention of disorders for which the administration of a selective PI3K inhibitor is indicated which comprises administering to a patient in need of such treatment an effective amount of a compound selected from the following:

- 2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one;
- 5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one;
- 20 2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one;
- 7,7-dimethyl-2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one;
- and pharmaceutically acceptable salts and solvates thereof.

Certain compounds falling within the definition of formula (I) above are novel. Accordingly, in one aspect, the present invention provides a compound of formula (IB) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 , R^2 ,

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R³ and R⁴ are as defined above. In another aspect, the present invention provides a compound of formula (IC) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹, R², R³, R⁴ and R⁵ are as defined above. In an additional aspect, the present invention provides a compound of formula (ID) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹, R², R³ and R⁴ are as defined above. In a further aspect, the present invention provides a compound of formula (IF) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹, R², R³, R⁴ and R⁶ are as defined above. In a still further aspect, the present invention provides a compound of formula (IG) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹, R², R³, R⁴ and R⁶ are as defined above. In yet further aspect, the present invention provides a compound of formula (IH) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹, R², R³ and R⁴ are as defined above.

In a further aspect, the present invention provides a compound of formula (IA) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹, R², R³ and R⁴ are as defined above, with the exception of the following compounds:

2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one; and
5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one.

In a still further aspect, the present invention provides a compound of formula (IE) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹, R², R³, R⁴ and R⁶ are as defined above, with the exception of the following compounds:

2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one; and
7,7-dimethyl-2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one.

In one embodiment, the present invention provides a compound of formula (IA) or (IE) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein

R¹ represents hydrogen; or C₂₋₆ 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; and

R² represents 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; or

R^1 and R^2 , when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

5 R^1 and R^2 , when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

R^3 and R^4 independently represent hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, 10 biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

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

R^3 and R^4 , when attached to adjacent carbon atoms, represent, when taken together 20 with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents; and

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

In a particular aspect of this embodiment, the present invention provides a 25 compound of formula (IA) or (IE) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 represents hydrogen; or C_{2-6} 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 30 substituents; and

R^2 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or

heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; or

R¹ and R², when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C₃₋₇ cycloalkyl or C₃₋₇ heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

R¹ and R², when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C₅₋₇ cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

R³ and R⁴ independently represent hydrogen; 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; or

R³ and R⁴, when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C₃₋₇ cycloalkyl or C₃₋₇ heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

R³ and R⁴, when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C₅₋₇ cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents; and

R⁶ represents hydrogen or C₁₋₆ alkyl.

In another embodiment, the present invention provides a compound of formula (IA) or (IE) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein

R¹ and R² independently represent hydrogen; 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; or

R¹ and R², when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C₃₋₇ cycloalkyl or C₃₋₇

heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

R^1 and R^2 , when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

R^3 represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^4 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl, heteroaryl- (C_{1-6}) alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

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

R^3 and R^4 , when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents; and

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

In a particular aspect of this embodiment, the present invention provides a compound of formula (IA) or (IE) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 and R^2 independently represent hydrogen; 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^1 and R^2 , when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

5 R^1 and R^2 , when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

10 R^3 represents hydrogen; 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; and

15 R^4 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

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

R^3 and R^4 , when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents; and

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

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

Suitably, R^2 represents hydrogen or optionally substituted C_{1-6} alkyl.

30 Examples of typical substituents on R^1 and/or R^2 include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxy carbonylamino, C_{1-6} alkylsulphonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxy carbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl,

di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl; especially halogen, C₁₋₆ alkoxy or C₁₋₆ alkylthio.

Examples of particular substituents on R¹ and/or R² include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, methoxy or methylthio.

10 Typical values of R¹ include hydrogen, methyl, *n*-propyl, isopropyl, phenyl, chlorophenyl, methoxyphenyl, methylthiophenyl and furyl. A particular value of R¹ is methyl.

Typical values of R² include hydrogen and methyl. In one embodiment, R² is hydrogen. In another embodiment, R² is C₁₋₆ alkyl, especially methyl.

15 Alternatively, R¹ and R², when both are attached to the same carbon atom, may together form an optionally substituted spiro linkage. Thus, R¹ and R², when both are attached to the same carbon atom, may represent, when taken together with the carbon atom to which they are both attached, C₃₋₇ cycloalkyl or C₃₋₇ heterocycloalkyl, either of which groups may be unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, R¹ and R², when taken together with the carbon atom to which they are both attached, may suitably represent an optionally substituted cyclopentyl, cyclohexyl, pyrrolidine or piperidine ring, especially cyclopentyl or cyclohexyl.

25 Alternatively, R¹ and R², when attached to adjacent carbon atoms, may together form an optionally benzo-fused and/or substituted cycloalkyl, phenyl or heteroaryl (e.g. pyridinyl) ring fused to the ring containing the variable X. Thus, R¹ and R², when attached to adjacent carbon atoms, may represent, when taken together with the carbon atoms to which they are attached, C₅₋₇ cycloalkyl, phenyl or heteroaryl (e.g. pyridinyl), any of which groups may be benzo-fused and/or unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, in one embodiment, R¹ and R², when taken together with the adjacent carbon atoms to which they are attached, suitably represent a phenyl ring fused to the ring containing the variable X. Also in this context, in another embodiment, R¹ and R², when taken together with the adjacent carbon atoms to

30

which they are attached, suitably represent a benzo-fused cyclopentyl ring, i.e. an indanyl moiety fused to the ring containing the variable X.

Typically, R^3 represents hydrogen; or C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, aryl-
(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl-
5 carbonyl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any
of which groups may be optionally substituted by one or more substituents.

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

10 In a representative embodiment, R^3 represents C_{1-6} alkyl, aryl(C_{1-6})alkyl, biaryl-
(C_{1-6})alkyl, heteroaryl(C_{1-6})alkyl or heteroaryl-aryl(C_{1-6})alkyl, any of which groups may be
optionally substituted by one or more substituents. Preferably, R^3 represents methyl,
arylmethyl, biarylmethyl, heteroarylmethyl or heteroaryl-arylmethyl, any of which groups
may be optionally substituted by one or more substituents.

15 In a particular embodiment, R^3 represents substituted or unsubstituted indolyl-
(C_{1-6})alkyl. Advantageously, R^3 represents substituted or unsubstituted indolylmethyl.

Illustratively, R^3 represents hydrogen; or methyl, phenyl, benzyl, phenylethyl,
naphthylmethyl, phenylpropynyl, biphenylmethyl, naphthylphenylmethyl,
indolylmethyl, 1,2,3,4-tetrahydroquinolylmethyl, 1,2,3,4-tetrahydroisoquinolyl-
20 methyl, piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolylcarbonyl, 1,2,3,4-
tetrahydroisoquinolylcarbonyl, 1,2,3,4-tetrahydroquinoxalylcarbonyl,
benzothienylmethyl, indolylmethyl, pyrrolo[2,3-*b*]pyridylmethyl, benzimidazolylmethyl,
benzotriazolylmethyl, pyridylmethyl, quinolylmethyl, isoquinolylmethyl,
benzofurylbenzyl, thienylbenzyl, benzothienylbenzyl, indolylbenzyl, isoxazolylbenzyl,
25 pyrazolylbenzyl, pyridylbenzyl, pyrimidinylbenzyl or phenylpyridylmethyl, any of
which groups may be optionally substituted by one or more substituents.

Suitably, R^4 represents hydrogen or optionally substituted C_{1-6} alkyl.

Examples of suitable substituents on R^3 and/or R^4 include halogen, cyano, nitro,
 C_{1-6} alkyl, hydroxy(C_{1-6})alkyl, trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy,
30 difluoromethoxy, trifluoromethoxy, aryloxy, aryl(C_{1-6})alkoxy, methylenedioxy, C_{1-6}
alkylthio, arylthio, C_{1-6} alkylsulphonyl, arylsulphonyl, C_{1-6} alkylsulphonyloxy, amino, C_{1-6}
alkylamino, di(C_{1-6})alkylamino, phenylamino, [(C_{1-6})alkyl](phenyl)amino, pyridinylamino,
pyrrolidinyl, morpholinyl, C_{2-6} alkylcarbonylamino, benzofurylcarbonylamino, C_{2-6}

alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl.

- 5 Selected examples of suitable substituents on R³ and/or R⁴ include halogen, cyano, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, trifluoromethoxy, aryloxy, aryl(C₁₋₆)alkoxy, methylenedioxy, C₁₋₆ alkylthio, arylthio, arylsulphonyl, C₁₋₆ alkylsulphonyloxy, amino, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, pyridinylamino, pyrrolidinyl, morpholinyl, C₂₋₆ alkylcarbonylamino,
- 10 benzofurylcarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, C₂₋₆ alkylcarbonyl, aminocarbonyl and benzothienylmethylaminocarbonyl.

- Examples of typical substituents on R³ and/or R⁴ include halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino,
- 15 phenylamino, [(C₁₋₆)alkyl](phenyl)amino, morpholinyl, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl; especially halogen, C₁₋₆ alkyl, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, morpholinyl or C₂₋₆
- 20 alkylcarbonyl.

- Examples of representative substituents on R³ and/or R⁴ include fluoro, chloro, bromo, cyano, nitro, methyl, hydroxymethyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, phenoxy, benzyloxy, methylenedioxy, methylthio, phenylthio, methylsulphonyl, phenylsulphonyl, methylsulphonyloxy, amino,
- 25 methylamino, dimethylamino, phenylamino, *N*-methyl-*N*-phenylamino, pyridinylamino, pyrrolidinyl, morpholinyl, acetylamino, benzofurylcarbonylamino, methoxycarbonylamino, methylsulphonylamino, phenylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and
- 30 dimethylaminosulphonyl.

Selected examples of representative substituents on R³ and/or R⁴ include fluoro, chloro, bromo, cyano, methyl, hydroxymethyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, trifluoromethoxy, phenoxy, benzyloxy, methylenedioxy, methylthio, phenylthio,

phenylsulphonyl, methylsulphonyloxy, amino, phenylamino, *N*-methyl-*N*-phenylamino, pyridinylamino, pyrrolidinyl, morpholinyl, acetylamino, benzofurylcarbonylamino, methylsulphonylamino, phenylsulphonylamino, acetyl, aminocarbonyl and benzothienylmethylaminocarbonyl.

- 5 Examples of particular substituents on R³ and/or R⁴ include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, phenylamino, *N*-methyl-*N*-phenylamino, morpholinyl, acetylamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, 10 methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, bromo, methyl, phenylamino, *N*-methyl-*N*-phenylamino, morpholinyl or acetyl.

- Specific values of R³ include hydrogen, methyl, phenoxymethyl, phenylthiomethyl, aminomethyl, phenylaminomethyl, *N*-methyl-*N*-phenylaminomethyl, pyridinylamino- 15 methyl, benzofurylcarbonylamino, phenylsulphonylamino, benzothienylmethylaminocarbonylmethyl, phenyl, benzyl, chlorobenzyl, bromobenzyl, pyrrolidinylbenzyl, morpholinylbenzyl, phenylethyl, naphthylmethyl, phenylpropynyl, biphenylmethyl, fluorobiphenylmethyl, difluorobiphenylmethyl, chlorobiphenylmethyl, dichlorobiphenylmethyl, bromobiphenylmethyl, cyanobiphenylmethyl, methylbiphenyl- 20 methyl, (fluoro)(methyl)biphenylmethyl, dimethylbiphenylmethyl, hydroxymethylbiphenylmethyl, trifluoromethylbiphenylmethyl, bis(trifluoromethyl)biphenylmethyl, methoxybiphenylmethyl, dimethoxybiphenylmethyl, ethoxybiphenylmethyl, methylenedioxybiphenylmethyl, trifluoromethoxybiphenylmethyl, phenoxybiphenylmethyl, methylthiobiphenylmethyl, aminobiphenylmethyl, acetylamino- 25 biphenylmethyl, methylsulphonylamino, acetylbiphenylmethyl, aminocarbonylbiphenylmethyl, naphthylphenylmethyl, indolylmethyl, 1,2,3,4-tetrahydroquinolylmethyl, 1,2,3,4-tetrahydroisoquinolylmethyl, piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolylcarbonyl, methyl-1,2,3,4-tetrahydroquinolylcarbonyl, methoxy-1,2,3,4-tetrahydroquinolylcarbonyl, 1,2,3,4-tetrahydroisoquinolylcarbonyl, 1,2,3,4-tetrahydroquinoxalylcarbonyl, benzothienylmethyl, indolylmethyl, methyl- 30 indolylmethyl, hydroxyindolylmethyl, benzyloxyindolylmethyl, acetylindolylmethyl, methylsulphonyloxyindolylmethyl, pyrrolo[2,3-*b*]pyridinylmethyl, benzimidazolylmethyl, benzotriazolylmethyl, bromopyridinylmethyl, quinolylmethyl, isoquinolylmethyl,

benzofurylbenzyl, thienylbenzyl, methylthienylbenzyl, acetylthienylbenzyl, benzothienylbenzyl, phenylsulphonylindolylbenzyl, dimethylisoxazolylbenzyl, methylpyrazolylbenzyl, benzylpyrazolylbenzyl, pyridinylbenzyl, fluoropyridinylbenzyl, chloropyridinylbenzyl, methoxypyridinylbenzyl, pyrimidinylbenzyl and
5 phenylpyridinylmethyl.

Typical values of R^3 include hydrogen, methyl, phenylaminomethyl, *N*-methyl-*N*-phenylaminomethyl, phenyl, benzyl, chlorobenzyl, bromobenzyl, morpholinyl-benzyl, phenylethyl, naphthylmethyl, indolinylmethyl, 1,2,3,4-tetrahydroquinolinylmethyl, 1,2,3,4-tetrahydroisoquinolinylmethyl, indolylmethyl, methylindolyl-methyl and
10 acetylintolyl-methyl.

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

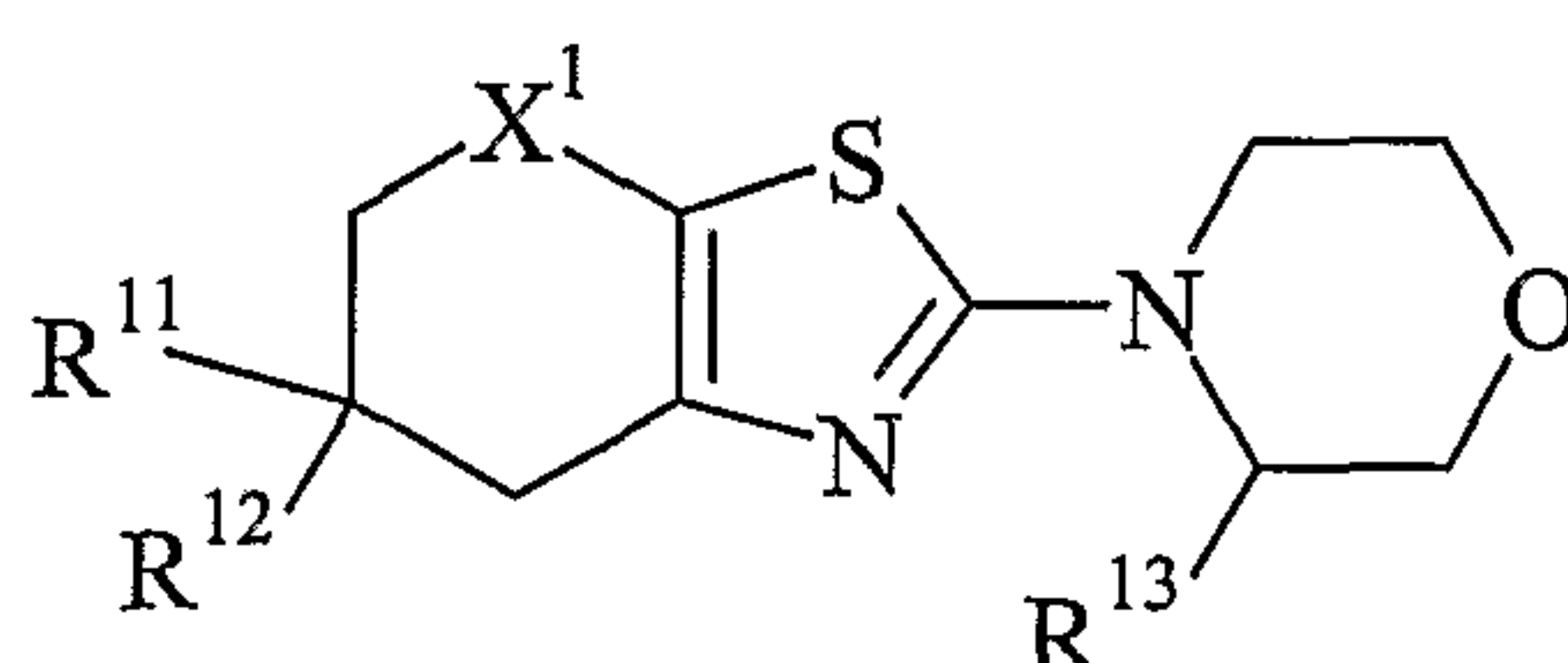
Alternatively, R^3 and R^4 , when both are attached to the same carbon atom, may together form an optionally substituted spiro linkage. Thus, R^3 and R^4 , when both are
15 attached to the same carbon atom, may represent, when taken together with the carbon atom to which they are both attached, C_{3-7}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

Alternatively, R^3 and R^4 , when attached to adjacent carbon atoms, may together form an optionally benzo-fused and/or substituted cycloalkyl, phenyl or heteroaryl (e.g. pyridinyl) ring fused to the morpholine ring. Thus, R^3 and R^4 , when attached to adjacent carbon atoms, may represent, when taken together with the carbon atoms to which they are
25 attached, C_{5-7} cycloalkyl, phenyl or heteroaryl (e.g. pyridinyl), any of which groups may be benzo-fused and/or unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, in one embodiment, R^3 and R^4 , when taken together with the adjacent carbon atoms to which they are attached, suitably represent a phenyl ring fused to the morpholine ring. Also in this context, in another embodiment, R^3 and R^4 ,
30 when taken together with the adjacent carbon atoms to which they are attached, suitably represent a benzo-fused cyclopentyl ring, i.e. an indanyl moiety fused to the morpholine ring.

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

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

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



(IIA)

10 wherein

- X^1 - represents a group of formula (a) or (e) as defined above;

R^{11} represents hydrogen or optionally substituted C_{2-6} alkyl; and

R^{12} represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or
15 heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^{11} and R^{12} , when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; and

20 R^{13} represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

25 The present invention also provides a compound of formula (IIA) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein

R^{13} represents hydrogen; 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(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; and

-X¹-, R¹¹ and R¹² are as defined above.

In one embodiment, -X¹- represents a group of formula (a). In another
5 embodiment, -X¹- represents a group of formula (e).

Where R¹¹ and/or R¹² and/or R¹³ in the compounds of formula (IIA) above is stated
to be optionally substituted, this group may be unsubstituted, or substituted by one or more
substituents. Typically, R¹¹ and/or R¹² and/or R¹³ will be unsubstituted, or substituted by
one or two substituents. Suitably, R¹¹ and/or R¹² and/or R¹³ will be unsubstituted or
10 monosubstituted.

Suitably, R¹¹ represents hydrogen or unsubstituted C₂₋₆ alkyl, especially hydrogen.

Suitably, R¹² represents C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be
optionally substituted by one or more substituents.

Examples of typical substituents on R¹¹ and/or R¹² include halogen, cyano, nitro,
15 C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy,
aryloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino,
C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulphonylamino, formyl,
C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylamino-
carbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and
20 di(C₁₋₆)alkylaminosulphonyl; especially halogen, C₁₋₆ alkoxy or C₁₋₆ alkylthio.

Examples of particular substituents on R¹¹ and/or R¹² include fluoro, chloro,
bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy,
trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino,
dimethylamino, acetylamino, methoxycarbonylamino, methylsulphonylamino, formyl,
25 acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl,
dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and
dimethylaminosulphonyl; especially chloro, methoxy or methylthio.

Typical values of R¹² include methyl, *n*-propyl, isopropyl, phenyl, chlorophenyl,
methoxyphenyl, methylthiophenyl and furyl.

30 Alternatively, R¹¹ and R¹² may together form an optionally substituted spiro
linkage. Thus, R¹¹ and R¹², when taken together with the carbon atom to which they are
both attached, may represent C₃₋₇ cycloalkyl or C₃₋₇ heterocycloalkyl, either of which
groups may be unsubstituted, or substituted by one or more, typically by one or two,

substituents. In this context, R^{11} and R^{12} , when taken together with the carbon atom to which they are both attached, may suitably represent an optionally substituted cyclopentyl, cyclohexyl, pyrrolidine or piperidine ring, especially cyclopentyl or cyclohexyl.

Typically, R^{13} represents hydrogen; or C_{1-6} alkyl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R^{13} represents hydrogen; or C_{1-6} alkyl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

In a representative embodiment, R^{13} represents C_{1-6} alkyl, aryl(C_{1-6})alkyl, biaryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkyl or heteroaryl-aryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents. Preferably, R^{13} represents methyl, arylmethyl, biaryl-methyl, heteroaryl-methyl or heteroaryl-aryl-methyl, any of which groups may be optionally substituted by one or more substituents.

In a particular embodiment, R^{13} represents substituted or unsubstituted indolyl- (C_{1-6})alkyl. Advantageously, R^{13} represents substituted or unsubstituted indolylmethyl.

Illustratively, R^{13} represents hydrogen; or methyl, benzyl, phenylethyl, naphthylmethyl, phenylpropynyl, biphenylmethyl, naphthylphenylmethyl, indolylmethyl, 1,2,3,4-tetrahydroquinolylmethyl, 1,2,3,4-tetrahydroisoquinolylmethyl, piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolylcarbonyl, 1,2,3,4-tetrahydroisoquinolylcarbonyl, 1,2,3,4-tetrahydroquinoxalylcarbonyl, benzothienylmethyl, indolylmethyl, pyrrolo[2,3-*b*]pyridylmethyl, benzimidazolylmethyl, benzotriazolylmethyl, pyridylmethyl, quinolylmethyl, isoquinolylmethyl, benzofurylbenzyl, thienylbenzyl, benzothienylbenzyl, indolylbenzyl, isoxazolylbenzyl, pyrazolylbenzyl, pyridylbenzyl, pyrimidinylbenzyl or phenylpyridylmethyl, any of which groups may be optionally substituted by one or more substituents.

Examples of suitable substituents on R^{13} include halogen, cyano, nitro, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl, trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, aryl(C_{1-6})alkoxy, methylenedioxy, C_{1-6} alkylthio, arylthio, C_{1-6} alkylsulphonyl, arylsulphonyl, C_{1-6} alkylsulphonyloxy, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, phenylamino, [(C_{1-6})alkyl](phenyl)amino, pyridylamino, pyrrolidinyl, morpholinyl, C_{2-6} alkylcarbonylamino, benzofurylcarbonylamino, C_{2-6}

alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl.

- 5 Selected examples of suitable substituents on R¹³ include halogen, cyano, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, trifluoromethoxy, aryloxy, aryl(C₁₋₆)alkoxy, methylenedioxy, C₁₋₆ alkylthio, arylthio, arylsulphonyl, C₁₋₆ alkylsulphonyloxy, amino, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, pyridinylamino, pyrrolidinyl, morpholinyl, C₂₋₆ alkylcarbonylamino,
- 10 benzofurylcarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, C₂₋₆ alkylcarbonyl, aminocarbonyl and benzothienylmethylaminocarbonyl.

- Examples of typical substituents on R¹³ include halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, phenylamino,
- 15 [(C₁₋₆)alkyl](phenyl)amino, morpholinyl, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl; especially halogen, C₁₋₆ alkyl, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, morpholinyl or C₂₋₆
- 20 alkylcarbonyl.

- Examples of representative substituents on R¹³ include fluoro, chloro, bromo, cyano, nitro, methyl, hydroxymethyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, phenoxy, benzyloxy, methylenedioxy, methylthio, phenylthio, methylsulphonyl, phenylsulphonyl, methylsulphonyloxy, amino, methylamino,
- 25 dimethylamino, phenylamino, *N*-methyl-*N*-phenylamino, pyridinylamino, pyrrolidinyl, morpholinyl, acetylamino, benzofurylcarbonylamino, methoxycarbonylamino, methylsulphonylamino, phenylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl.

- 30 Selected examples of representative substituents on R¹³ include fluoro, chloro, bromo, cyano, methyl, hydroxymethyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, trifluoromethoxy, phenoxy, benzyloxy, methylenedioxy, methylthio, phenylthio, phenylsulphonyl, methylsulphonyloxy, amino, phenylamino, *N*-methyl-*N*-phenylamino,

pyridinylamino, pyrrolidinyl, morpholinyl, acetylamino, benzofurylcarbonylamino, methylsulphonylamino, phenylsulphonylamino, acetyl, aminocarbonyl and benzothienylmethylaminocarbonyl.

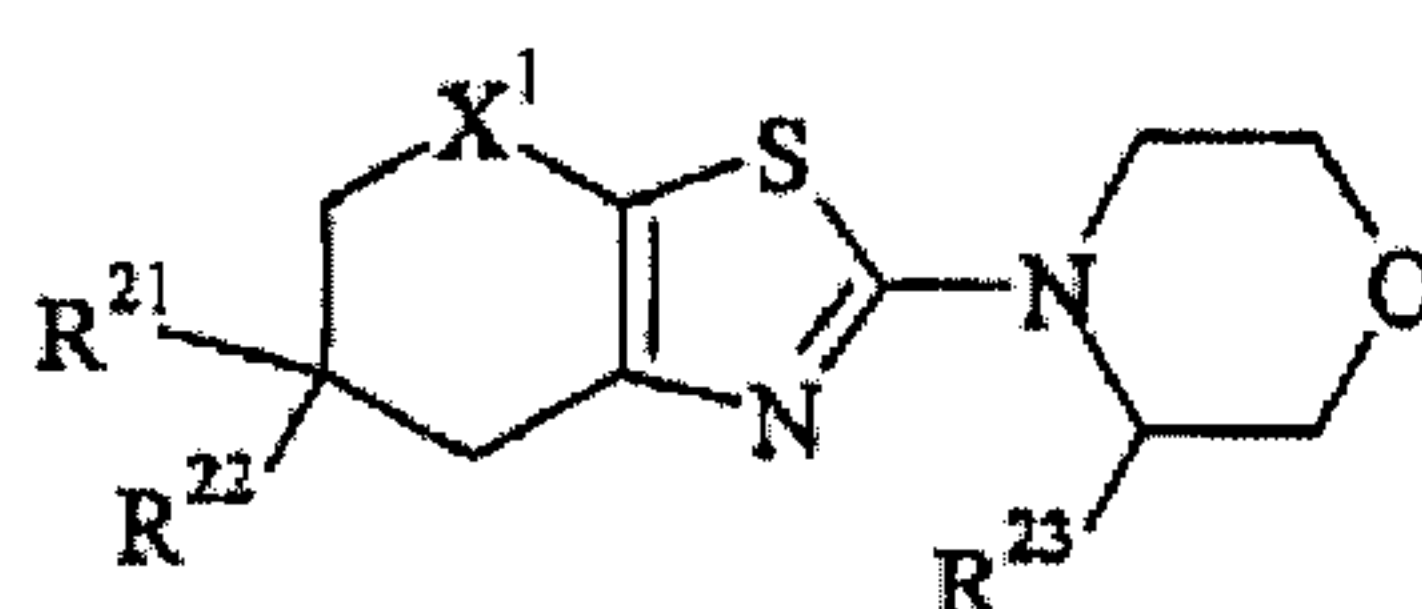
Examples of particular substituents on R¹³ include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, phenylamino, *N*-methyl-*N*-phenylamino, morpholinyl, acetylamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, bromo, methyl, phenylamino, *N*-methyl-*N*-phenylamino, morpholinyl or acetyl.

Specific values of R¹³ include hydrogen, phenoxymethyl, phenylthiomethyl, aminomethyl, phenylaminomethyl, *N*-methyl-*N*-phenylaminomethyl, pyridinylaminomethyl, benzofurylcarbonylamino, phenylsulphonylamino, benzothienylmethylaminocarbonylmethyl, benzyl, chlorobenzyl, bromobenzyl, pyrrolidinylbenzyl, morpholinyl-benzyl, phenylethyl, naphthylmethyl, phenylpropynyl, biphenylmethyl, fluorobiphenylmethyl, difluorobiphenylmethyl, chlorobiphenylmethyl, dichlorobiphenylmethyl, bromobiphenylmethyl, cyanobiphenylmethyl, methylbiphenylmethyl, (fluoro)(methyl)biphenylmethyl, dimethylbiphenylmethyl, hydroxymethylbiphenylmethyl, trifluoromethylbiphenylmethyl, bis(trifluoromethyl)biphenylmethyl, methoxybiphenylmethyl, dimethoxybiphenylmethyl, ethoxybiphenylmethyl, methylenedioxybiphenylmethyl, trifluoromethoxybiphenylmethyl, phenoxybiphenylmethyl, methylthiobiphenylmethyl, aminobiphenylmethyl, acetylaminobiphenylmethyl, methylsulphonylaminobiphenylmethyl, acetylaminobiphenylmethyl, aminocarbonylbiphenylmethyl, naphthylphenylmethyl, indolylmethyl, 1,2,3,4-tetrahydroquinolylmethyl, 1,2,3,4-tetrahydroisoquinolylmethyl, piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolylcarbonyl, methyl-1,2,3,4-tetrahydroquinolylcarbonyl, methoxy-1,2,3,4-tetrahydroquinolylcarbonyl, 1,2,3,4-tetrahydroisoquinolylcarbonyl, 1,2,3,4-tetrahydroquinoxalylcarbonyl, benzothienylmethyl, indolylmethyl, methylindolylmethyl, hydroxyindolylmethyl, benzyloxyindolylmethyl, acetylindolylmethyl, methylsulphonyloxyindolylmethyl, pyrrolo[2,3-*b*]pyridinylmethyl, benzimidazolylmethyl, benzotriazolylmethyl, bromopyridinylmethyl, quinolylmethyl, isoquinolylmethyl, benzofurylbenzyl, thienylbenzyl, methylthienylbenzyl, acetylthienylbenzyl,

benzothienylbenzyl, phenylsulphonylindolylbenzyl, dimethylisoxazolybenzyl,
methylpyrazolybenzyl, benzylpyrazolybenzyl, pyridinylbenzyl, fluoropyridinylbenzyl,
chloropyridinylbenzyl, methoxypyridinylbenzyl, pyrimidinylbenzyl and
5 phenylpyridinylmethyl.

Typical values of R^{13} include hydrogen, phenylaminomethyl, iV-methyl-iV-
phenylaminomethyl, benzyl, chlorobenzyl, bromobenzyl, morpholinyl-benzyl,
phenylethyl, naphthylmethyl, indolinylmethyl, 1,2,3,4-tetrahydroquinolinylmethyl,
1,2,3,4-tetrahydroisoquinolinylmethyl, indolylmethyl, methylindolyl-methyl and
10 acetylindolyl-methyl.

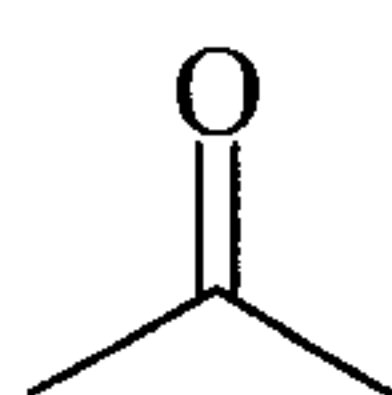
Another sub-class of novel compounds according to the invention which is the one
specifically claimed hereinafter, is represented by the compounds of formula (HB), and
pharmaceutically acceptable salts and solvates thereof:



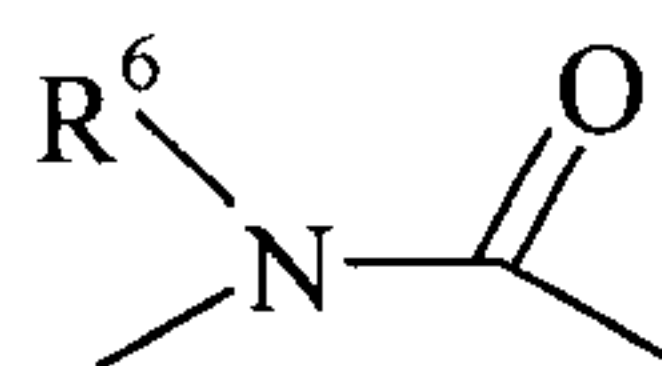
(IIB)

wherein

$-X^1-$ represents a group of formula (a) or (e):



(a)



(e)

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

R^{21} represents hydrogen or C_{1-6} alkyl; and

25 R^{22} represents hydrogen; or C_{1-6} alkyl, aryl or heteroaryl, any of which groups may
be optionally substituted by one or more substituents independently selected from halogen,
 C_{1-6} alkoxy or C_{1-6} alkylthio; or

R^{21} and R^{22} , when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl; and

R^{23} represents C_{1-6} alkyl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents independently selected from halogen, cyano, nitro, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl, trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, aryl(C_{1-6})alkoxy, methylenedioxy, C_{1-6} alkylthio, arylthio, C_{1-6} alkylsulphonyl, arylsulphonyl, C_{1-6} alkylsulphonyloxy, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, phenylamino, [(C_{1-6})alkyl](phenyl)amino, pyridinylamino, pyrrolidinyl, morpholinyl, C_{2-6} alkylcarbonylamino, benzofurylcarbonylamino, C_{2-6} alkoxy carbonylamino, C_{1-6} alkylsulphonylamino, arylsulphonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxy carbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl and di(C_{1-6})alkylaminosulphonyl.

The present invention also provides a compound of formula (IBB) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein

R^{23} represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

$-X^1-$, R^{21} and R^{22} are as defined above.

Where R^{21} and/or R^{22} and/or R^{23} in the compounds of formula (HB) above is stated to be optionally substituted, this group may be unsubstituted, or substituted by one or more substituents. Typically, R^{21} and/or R^{22} and/or R^{23} will be unsubstituted, or substituted by one or two substituents. Suitably, R^{21} and/or R^{22} and/or R^{23} will be unsubstituted or monosubstituted.

Suitably, R^{21} represents hydrogen or unsubstituted C_{1-6} alkyl.

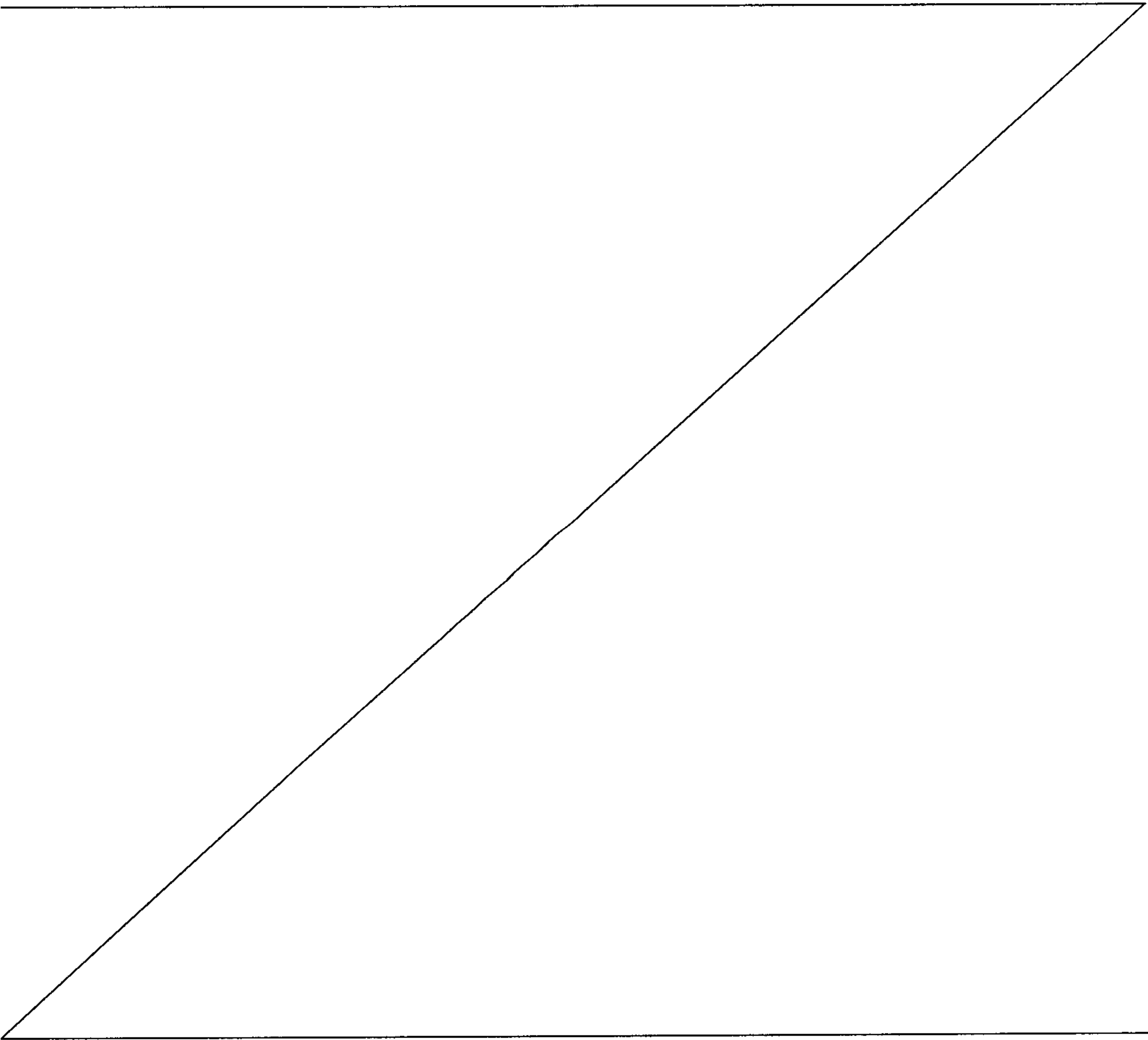
Suitably, R^{22} represents hydrogen; or C_{1-6} alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Examples of typical substituents on R and/or R include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6}

alkylcarbonylamino, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylamino-carbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl; especially halogen, C₁₋₆ alkoxy or C₁₋₆ alkylthio.

- 5 Examples of particular substituents on R²¹ and/or R²² include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl,
- 10 dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, methoxy or methylthio.

Typical values of R²¹ include hydrogen and methyl. In one embodiment, R²¹ is hydrogen. In another embodiment, R²¹ is methyl.



Typical values of R^{22} include hydrogen, methyl, *n*-propyl, isopropyl, phenyl, chlorophenyl, methoxyphenyl, methylthiophenyl and furyl. A particular value of R^{22} is methyl.

Alternatively, R^{21} and R^{22} may together form an optionally substituted spiro linkage. Thus, R^{21} and R^{22} , when taken together with the carbon atom to which they are both attached, may represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, R^{21} and R^{22} , when taken together with the carbon atom to which they are both attached, may suitably represent an optionally substituted cyclopentyl, cyclohexyl, pyrrolidine or piperidine ring, especially cyclopentyl or cyclohexyl.

Typically, R^{23} represents C_{1-6} alkyl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkynyl, biaryl- (C_{1-6}) alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl- (C_{1-6}) alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R^{23} represents C_{1-6} alkyl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

In a representative embodiment, R^{23} represents C_{1-6} alkyl, aryl(C_{1-6})alkyl, biaryl- (C_{1-6}) alkyl, heteroaryl(C_{1-6})alkyl or heteroaryl-aryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents. Preferably, R^{23} represents methyl, arylmethyl, biarylmethyl, heteroarylmethyl or heteroaryl-arylmethyl, any of which groups may be optionally substituted by one or more substituents.

In a particular embodiment, R^{23} represents substituted or unsubstituted indolyl- (C_{1-6}) alkyl. Advantageously, R^{23} represents substituted or unsubstituted indolylmethyl.

Illustratively, R^{23} represents methyl, benzyl, phenylethyl, naphthylmethyl, phenylpropynyl, biphenylmethyl, naphthylphenylmethyl, indolylmethyl, 1,2,3,4-tetrahydroquinolylmethyl, 1,2,3,4-tetrahydroisoquinolylmethyl, piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolylcarbonyl, 1,2,3,4-tetrahydroisoquinolylcarbonyl, 1,2,3,4-tetrahydroquinoxalylcarbonyl, benzothienylmethyl, indolylmethyl, pyrrolo[2,3-*b*]-pyridylmethyl, benzimidazolylmethyl, benzotriazolylmethyl, pyridylmethyl, quinolylmethyl, isoquinolylmethyl, benzofurylbenzyl, thienylbenzyl, benzothienylbenzyl, indolylbenzyl, isoxazolylbenzyl, pyrazolylbenzyl, pyridylbenzyl,

pyrimidinylbenzyl or phenylpyridinylmethyl, any of which groups may be optionally substituted by one or more substituents.

Examples of suitable substituents on R²³ include halogen, cyano, nitro, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, aryl(C₁₋₆)alkoxy, methylenedioxy, C₁₋₆ alkylthio, arylthio, C₁₋₆ alkylsulphonyl, arylsulphonyl, C₁₋₆ alkylsulphonyloxy, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, pyridinylamino, pyrrolidinyl, morpholinyl, C₂₋₆ alkylcarbonylamino, benzofurylcarbonylamino, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl.

Selected examples of suitable substituents on R²³ include halogen, cyano, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, trifluoromethoxy, aryloxy, aryl(C₁₋₆)alkoxy, methylenedioxy, C₁₋₆ alkylthio, arylthio, arylsulphonyl, C₁₋₆ alkylsulphonyloxy, amino, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, pyridinylamino, pyrrolidinyl, morpholinyl, C₂₋₆ alkylcarbonylamino, benzofurylcarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, C₂₋₆ alkylcarbonyl, aminocarbonyl and benzothienylmethylaminocarbonyl.

Examples of typical substituents on R²³ include halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, morpholinyl, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl; especially halogen, C₁₋₆ alkyl, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, morpholinyl or C₂₋₆ alkylcarbonyl.

Examples of representative substituents on R²³ include fluoro, chloro, bromo, cyano, nitro, methyl, hydroxymethyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, phenoxy, benzyloxy, methylenedioxy, methylthio, phenylthio, methylsulphonyl, phenylsulphonyl, methylsulphonyloxy, amino, methylamino, dimethylamino, phenylamino, *N*-methyl-*N*-phenylamino, pyridinylamino, pyrrolidinyl,

morpholinyl, acetamino, benzofurylcarbonylamino, methoxycarbonylamino, methylsulphonylamino, phenylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl.

5 Selected examples of representative substituents on R^{23} include fluoro, chloro, bromo, cyano, methyl, hydroxymethyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, trifluoromethoxy, phenoxy, benzyloxy, methylenedioxy, methylthio, phenylthio, phenylsulphonyl, methylsulphonyloxy, amino, phenylamino, *N*-methyl-*N*-phenylamino, pyridinylamino, pyrrolidinyl, morpholinyl, acetamino, benzofurylcarbonylamino, methylsulphonylamino, phenylsulphonylamino, acetyl, aminocarbonyl and
10 benzothienylmethylaminocarbonyl.

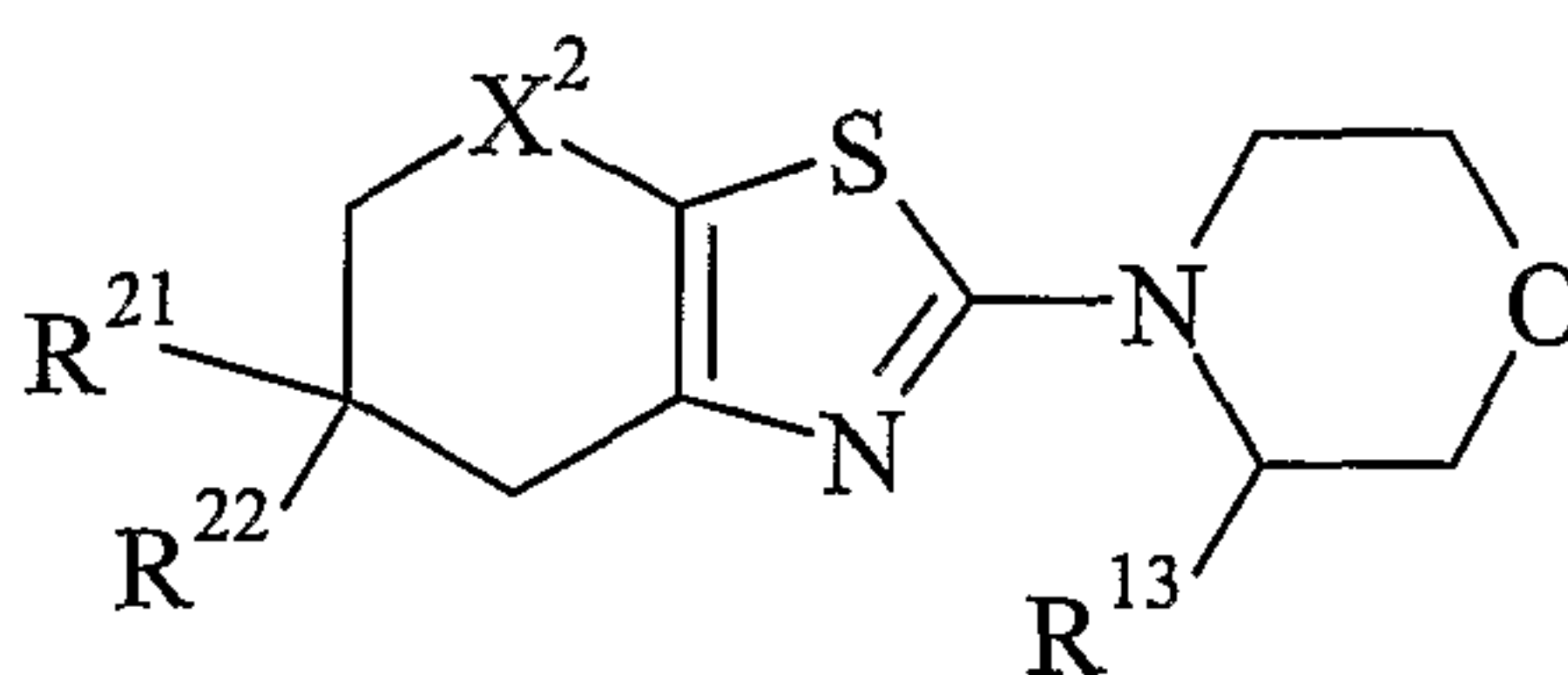
Examples of particular substituents on R^{23} include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino,
15 phenylamino, *N*-methyl-*N*-phenylamino, morpholinyl, acetamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, bromo, methyl, phenylamino, *N*-methyl-*N*-phenylamino, morpholinyl or acetyl.

20 Specific values of R^{23} include phenoxymethyl, phenylthiomethyl, aminomethyl, phenylaminomethyl, *N*-methyl-*N*-phenylaminomethyl, pyridinylaminomethyl, benzofurylcarbonylamino, phenylsulphonylamino, benzothienylmethylaminocarbonylmethyl, benzyl, chlorobenzyl, bromobenzyl, pyrrolidinylbenzyl, morpholinyl-benzyl, phenylethyl, naphthylmethyl, phenylpropynyl,
25 biphenylmethyl, fluorobiphenylmethyl, difluorobiphenylmethyl, chlorobiphenylmethyl, dichlorobiphenylmethyl, bromobiphenylmethyl, cyanobiphenylmethyl, methylbiphenylmethyl, (fluoro)(methyl)biphenylmethyl, dimethylbiphenylmethyl, hydroxymethylbiphenylmethyl, trifluoromethylbiphenylmethyl, bis(trifluoromethyl)biphenylmethyl, methoxybiphenylmethyl, dimethoxybiphenylmethyl, ethoxybiphenylmethyl,
30 methylenedioxybiphenylmethyl, trifluoromethoxybiphenylmethyl, phenoxybiphenylmethyl, methylthiobiphenylmethyl, aminobiphenylmethyl, acetamino-biphenylmethyl, methylsulphonylaminobiphenylmethyl, acetylaminobiphenylmethyl, aminocarbonylbiphenylmethyl, naphthylphenylmethyl, indolylmethyl, 1,2,3,4-

tetrahydroquinolinylmethyl, 1,2,3,4-tetrahydroisoquinolinylmethyl, piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolinylcarbonyl, methyl-1,2,3,4-tetrahydroquinolinylcarbonyl, methoxy-1,2,3,4-tetrahydroquinolinylcarbonyl, 1,2,3,4-tetrahydroisoquinolinylcarbonyl, 1,2,3,4-tetrahydroquinoxalinylcarbonyl, benzothienylmethyl, indolylmethyl, methyl-
 5 indolylmethyl, hydroxyindolylmethyl, benzyloxyindolylmethyl, acetylindolylmethyl, methylsulphonyloxyindolylmethyl, pyrrolo[2,3-*b*]pyridinylmethyl, benzimidazolylmethyl, benzotriazolylmethyl, bromopyridinylmethyl, quinolinylmethyl, isoquinolinylmethyl, benzofurylbenzyl, thienylbenzyl, methylthienylbenzyl, acetylthienylbenzyl, benzothienylbenzyl, phenylsulphonylindolylbenzyl, dimethylisoxazolylbenzyl,
 10 methylpyrazolylbenzyl, benzylpyrazolylbenzyl, pyridinylbenzyl, fluoropyridinylbenzyl, chloropyridinylbenzyl, methoxypyridinylbenzyl, pyrimidinylbenzyl and phenylpyridinylmethyl.

Typical values of R^{23} include phenylaminomethyl, *N*-methyl-*N*-phenylaminomethyl, benzyl, chlorobenzyl, bromobenzyl, morpholinyl-benzyl,
 15 phenylethyl, naphthylmethyl, indolinylmethyl, 1,2,3,4-tetrahydroquinolinylmethyl, 1,2,3,4-tetrahydroisoquinolinylmethyl, indolylmethyl, methylindolyl-methyl and acetylindolyl-methyl.

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



(IIC)

wherein

25 $-X^2-$ represents a group of formula (b), (c), (d), (f), (g) or (h) as defined above;

R^{13} is as defined above in relation to formula (IIA); and

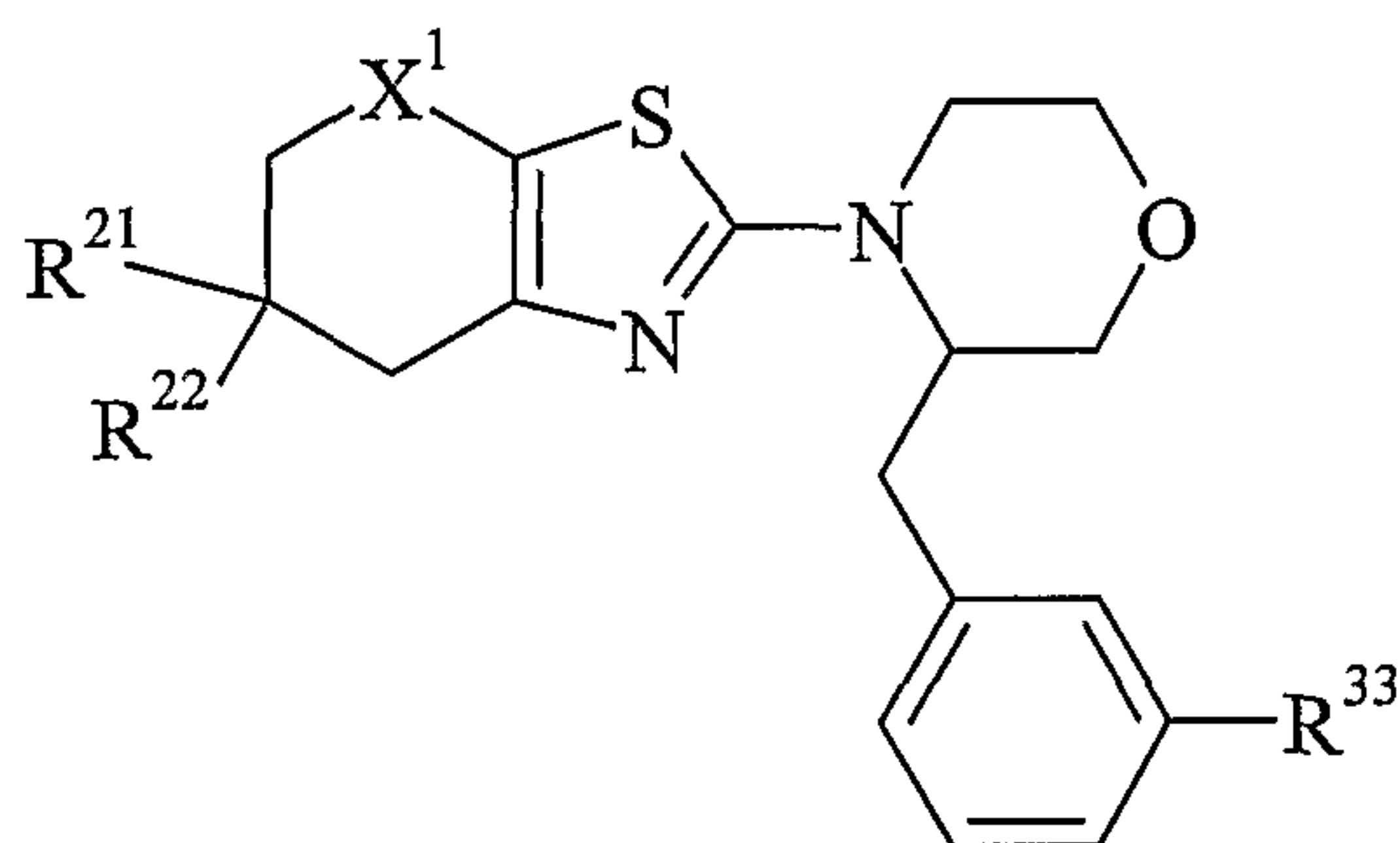
R^{21} and R^{22} are as defined above in relation to formula (IIB).

Suitably, $-X^2-$ represents a group of formula (b), (c) or (d) as defined above.

- 30 -

In one embodiment, $-X^2-$ represents a group of formula (b). In another embodiment, $-X^2-$ represents a group of formula (c). In a further embodiment, $-X^2-$ represents a group of formula (d). In a still further embodiment, $-X^2-$ represents a group of formula (f). In a yet further embodiment, $-X^2-$ represents a group of formula (g). In an additional embodiment, $-X^2-$ represents a group of formula (h).

One particular sub-group of the compounds of formula (IIB) is represented by the compounds of formula (IID), and pharmaceutically acceptable salts and solvates thereof:



(IID)

10

wherein

$-X^1-$, R^{21} and R^{22} are as defined above; and

R^{33} represents aryl or heteroaryl, either of which groups may be optionally substituted by one or more substituents.

15

In one embodiment, R^{33} represents unsubstituted or substituted aryl. In another embodiment, R^{33} represents unsubstituted or substituted heteroaryl.

Illustratively, R^{33} represents phenyl, naphthyl, benzofuryl, thienyl, benzothienyl, indolyl, isoxazolyl, pyrazolyl, pyridinyl or pyrimidinyl, any of which groups may be optionally substituted by one or more substituents.

20

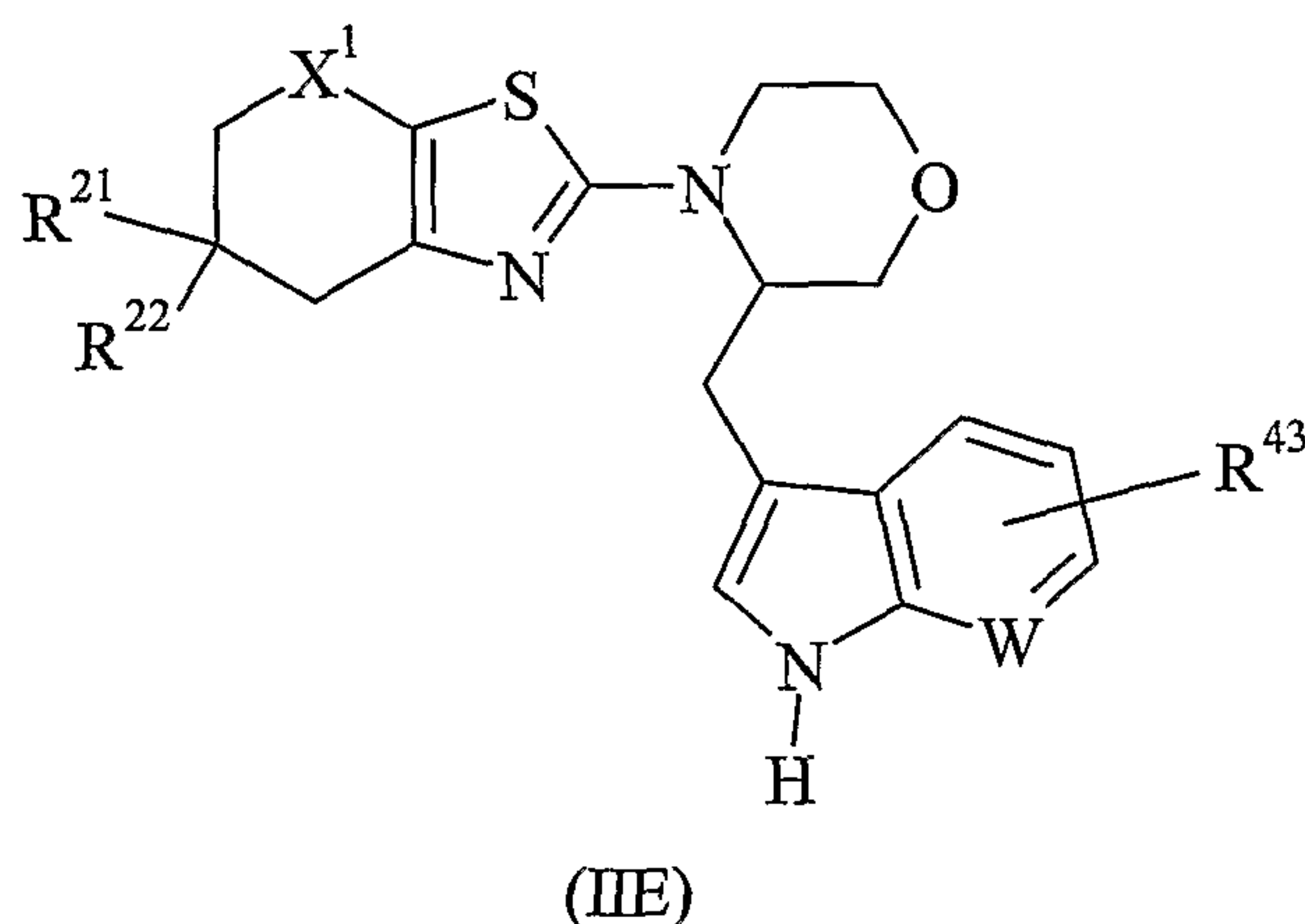
Selected examples of suitable substituents on R^{33} include halogen, cyano, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl, trifluoromethyl, C_{1-6} alkoxy, trifluoromethoxy, aryloxy, methylenedioxy, C_{1-6} alkylthio, arylsulphonyl, amino, C_{2-6} alkylcarbonylamino, C_{1-6} alkylsulphonylamino, C_{2-6} alkylcarbonyl and aminocarbonyl.

Selected examples of representative substituents on R^{33} include fluoro, chloro, bromo, cyano, methyl, hydroxymethyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, phenoxy, methylenedioxy, methylthio, phenylsulphonyl, amino, acetylamino, methylsulphonylamino, acetyl and aminocarbonyl.

25

Specific values of R^{33} include phenyl, fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, bromophenyl, cyanophenyl, methylphenyl, (fluoro)(methyl)phenyl, dimethylphenyl, hydroxymethylphenyl, trifluoromethylphenyl, bis(trifluoromethyl)-phenyl, methoxyphenyl, dimethoxyphenyl, ethoxyphenyl, methylenedioxyphenyl, trifluoromethoxyphenyl, phenoxyphenyl, methylthiophenyl, aminophenyl, acetaminophenyl, methylsulphonylaminophenyl, acetylphenyl, aminocarbonylphenyl, naphthyl, benzofuryl, thienyl, methylthienyl, acetylthienyl, benzothienyl, phenylsulphonylindolyl, dimethylisoxazolyl, methylpyrazolyl, benzylpyrazolyl, pyridinyl, fluoropyridinyl, chloropyridinyl, methoxypyridinyl and pyrimidinylbenzyl.

Another particular sub-group of the compounds of formula (IIB) is represented by the compounds of formula (IIE), and pharmaceutically acceptable salts and solvates thereof:



wherein

$-X^1$ -, R^{21} and R^{22} are as defined above;

W represents CH or N; and

R^{43} represents hydrogen, halogen, cyano, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl, trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, trifluoromethoxy, aryloxy, aryl(C_{1-6})alkoxy, C_{1-6} alkylthio, arylsulphonyl, C_{1-6} alkylsulphonyloxy, amino, C_{2-6} alkylcarbonylamino, C_{1-6} alkylsulphonylamino, C_{2-6} alkylcarbonyl or aminocarbonyl.

In a preferred embodiment, W is CH. In another embodiment, W is N.

Suitable values of R^{43} include hydrogen, C_{1-6} alkyl, hydroxy, aryl(C_{1-6})alkoxy and C_{1-6} alkylsulphonyloxy.

Specific values of R^{43} include hydrogen, fluoro, chloro, bromo, cyano, methyl, hydroxymethyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, trifluoromethoxy, phenoxy, benzyloxy, methylthio, phenylsulphonyl, methylsulphonyloxy, amino, acetylamino, methylsulphonylamino, acetyl and aminocarbonyl; especially hydrogen, methyl, hydroxy, benzyloxy or methylsulphonyloxy.

A particular value of R^{43} is hydrogen.

Specific novel compounds in accordance with the present invention include each of the compounds whose preparation is described in accompanying Examples 1-5, 7-42, 45-47, 49, 50, and 51-158, and pharmaceutically acceptable salts and solvates thereof.

The present invention also provides a pharmaceutical composition which comprises a novel 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
5 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,
10 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
15 to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which
20 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 according to the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular
25 carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds according to the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan
30 monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

For ophthalmic administration the compounds according to the present invention may be conveniently formulated as microionized suspensions in isotonic, pH-adjusted

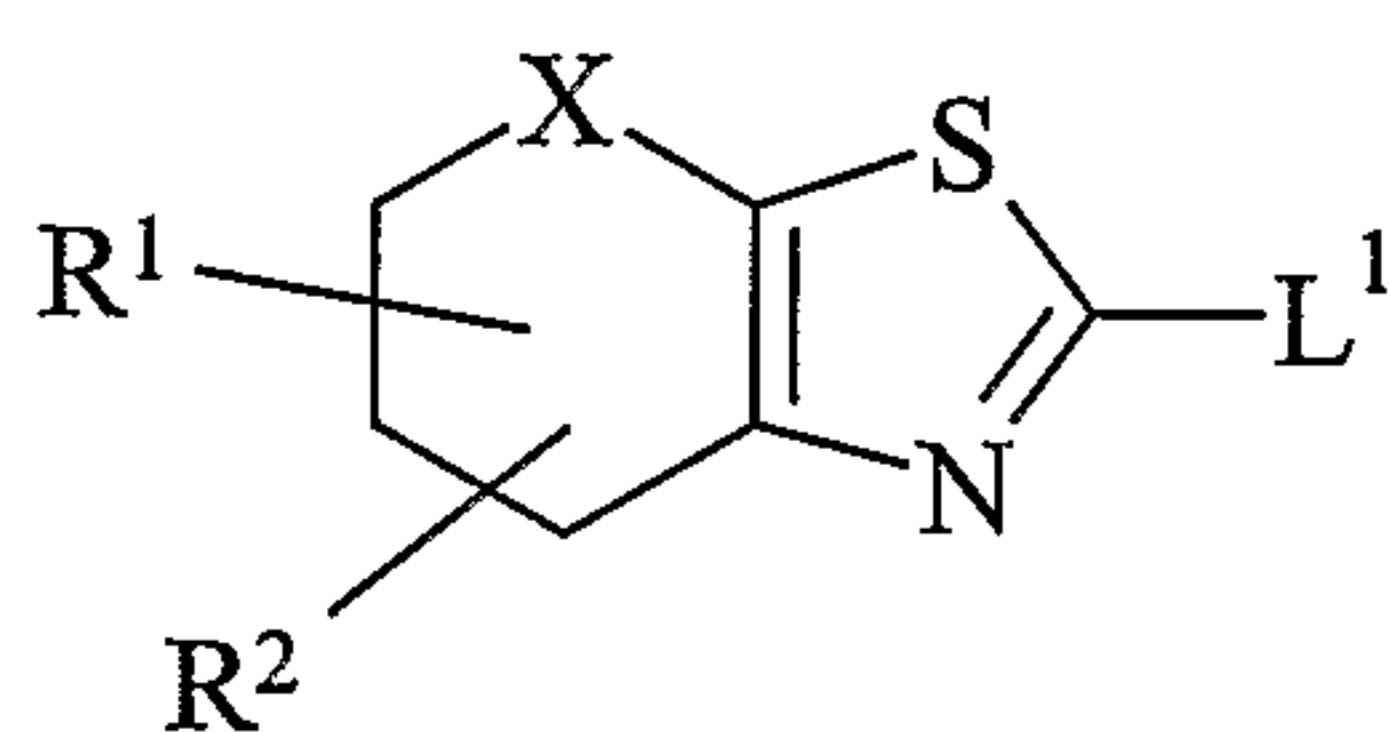
sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

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

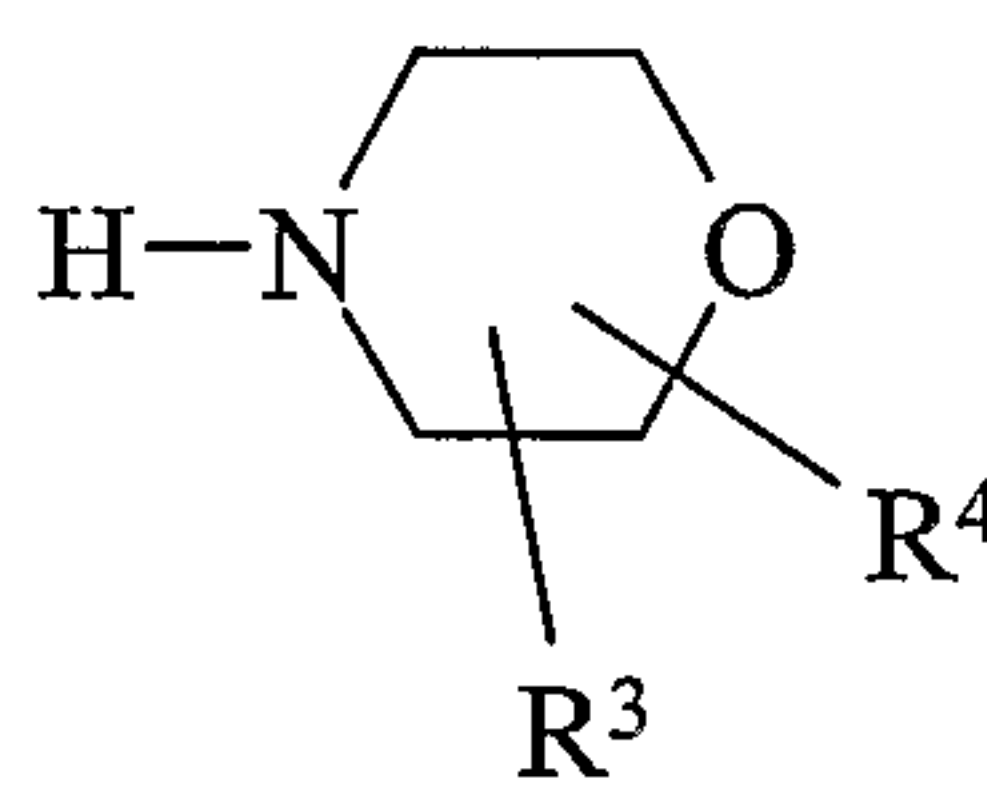
10 The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from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

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

20



(III)



(IV)

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

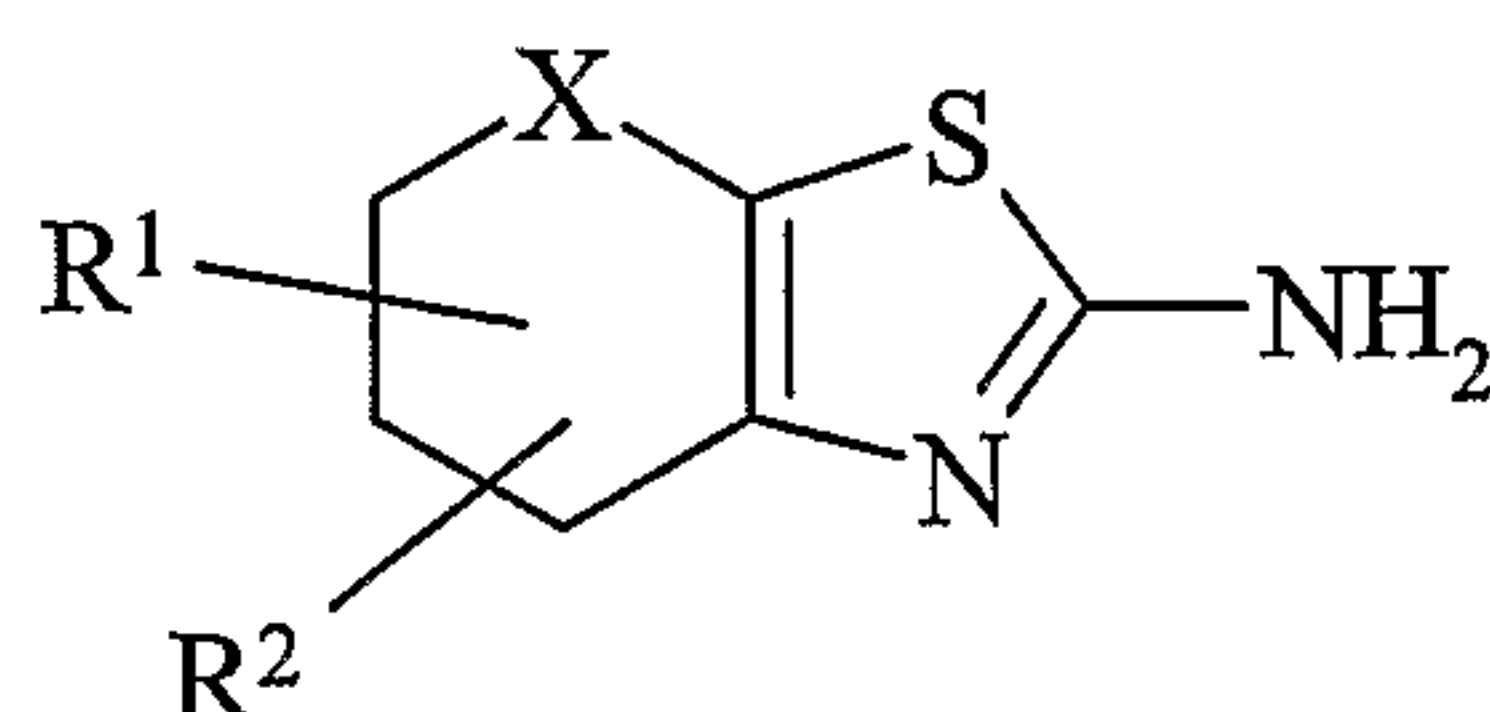
25 The leaving group L^1 is typically a halogen atom, e.g. bromo.

The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a lower alkanol such as isopropanol or a cyclic ether such as tetrahydrofuran, typically under basic conditions, e.g. in the presence of an organic base such as *N,N*-diisopropylethylamine.

- 35 -

Alternatively, the reaction may be effected at an elevated temperature in a solvent such as 2-ethoxyethanol in the presence of a catalytic quantity of a mineral acid, e.g. concentrated hydrochloric acid.

5 The intermediates of formula (III) above wherein L¹ is bromo may be prepared from a compound of formula (V):

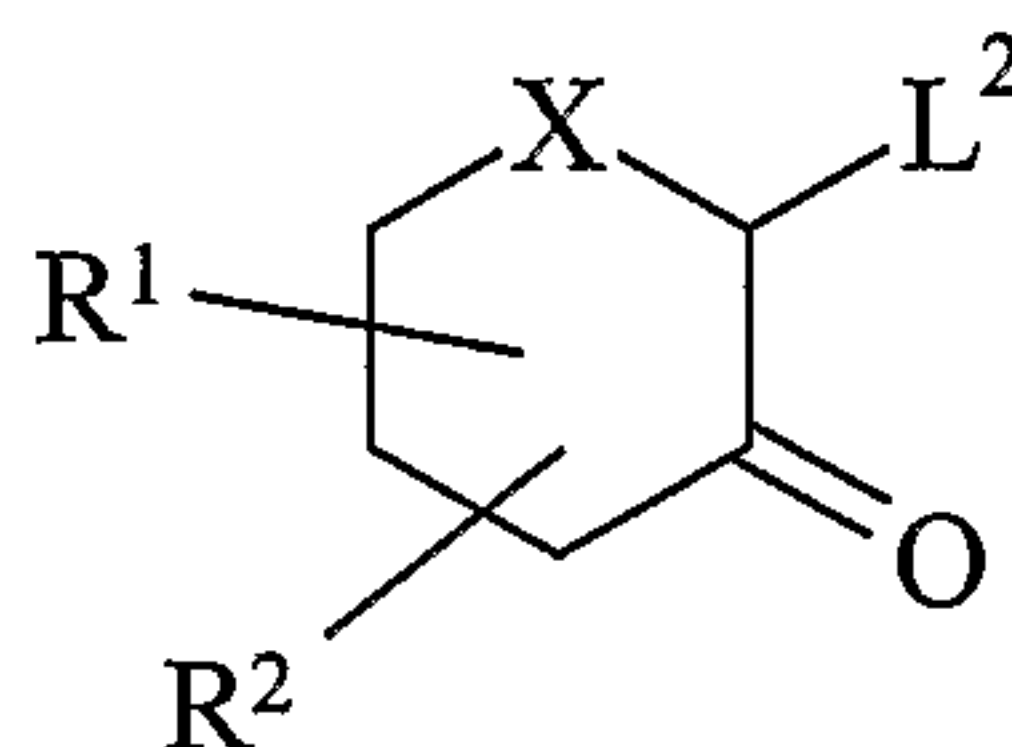


(V)

wherein R¹, R² and X are as defined above; by diazotization/bromination.

10 The reaction is conveniently effected by stirring compound (V) with *tert*-butyl nitrite and copper(II) bromide in a suitable solvent, e.g. acetonitrile.

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



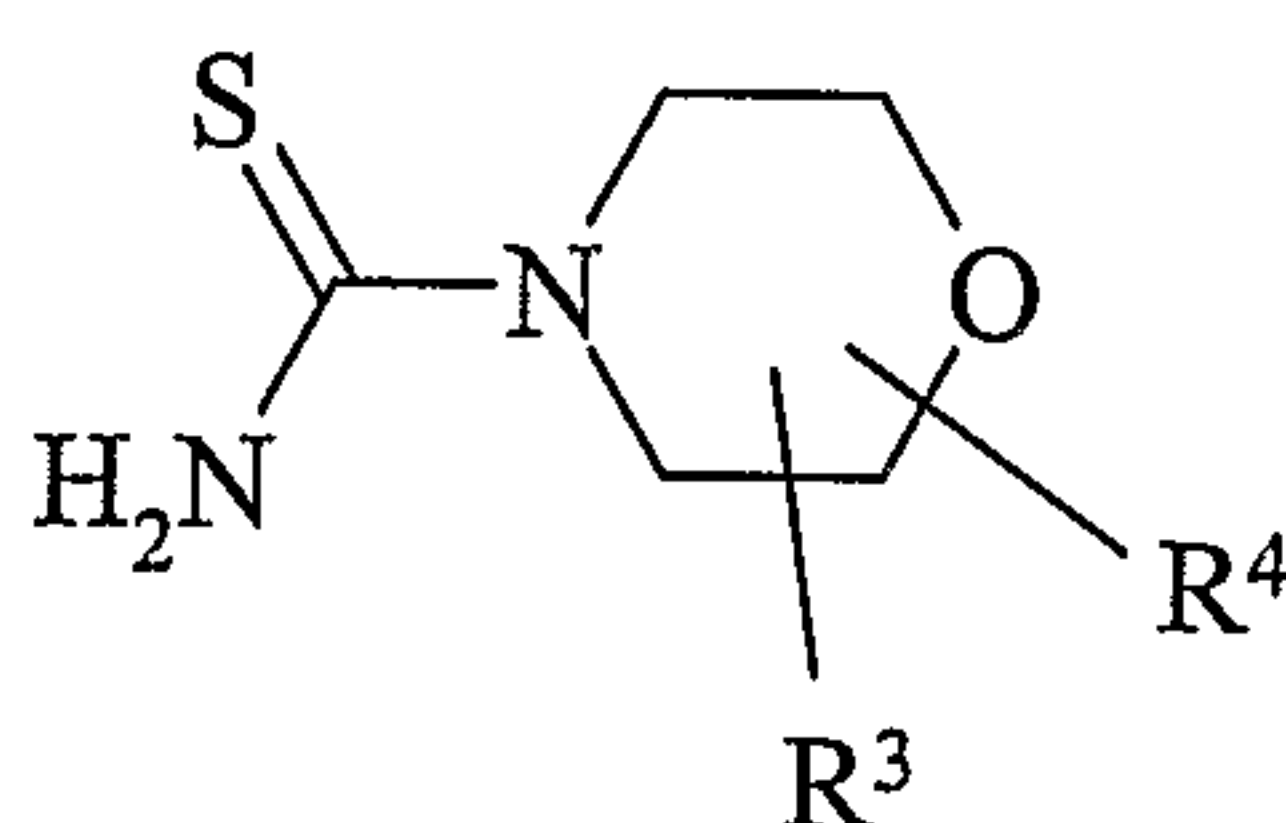
(VI)

wherein R¹, R² and X are as defined above, and L² represents a suitable leaving group.

The leaving group L² is typically a halogen atom, e.g. bromo.

20 The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran, typically under basic conditions, e.g. in the presence of an organic base such as *N,N*-diisopropylethylamine.

In another procedure, the compounds of formula (I) may be prepared by a process which comprises reacting a compound of formula (VI) as defined above with a compound of formula (VII):



(VII)

wherein R^3 and R^4 are as defined above; under conditions analogous to those described above for the reaction between thiourea and compound (VI).

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

It will be understood that any compound of formula (I) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula (I) by techniques known from the art. By way of example, a
 10 compound of formula (IA) may be converted into the corresponding compound of formula (IB) by treatment with Lawesson's Reagent (i.e. 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide). Similarly, a compound of formula (IE) may be converted into the corresponding compound of formula (IF) by treatment with Lawesson's Reagent.
 15 A compound of formula (IA) may be converted into the corresponding compound of formula (IC) by treatment with a hydroxylamine derivative of formula H_2N-OR^5 . A compound of formula (IA) may be converted into the corresponding compound of formula (ID) by treatment with a reducing agent such as lithium aluminium hydride. A compound of formula (IA) may be converted into the corresponding compound of formula (IG) by
 20 treatment with hydroxylamine-*O*-sulfonic acid, typically in the presence of formic acid at an elevated temperature. A compound of formula (IA) may be converted into the corresponding compound of formula (IH) by treatment with hydrazine hydrate. A compound of formula (IC) may be converted into the corresponding compound of formula (IE) by treatment with *p*-toluenesulphonyl chloride, typically in the presence of pyridine at
 25 an elevated temperature. A compound of formula (IA) wherein R^1 is hydrogen may be converted into the corresponding compound wherein R^1 is methyl by treatment with a methyl halide, e.g. iodomethane, in the presence of a strong base, e.g. lithium diisopropylamide.

A compound of formula (I) wherein R³ represents aryl(C₁₋₆)alkyl, substituted on the aryl moiety by a halogen atom such as bromo, may be converted into the corresponding compound wherein R³ represents biaryl(C₁₋₆)alkyl or heteroaryl-aryl(C₁₋₆)alkyl by treatment with, respectively, an aryl or heteroaryl boronic acid, in the presence of a catalyst. Similarly, a compound of formula (I) wherein R³ represents heteroaryl(C₁₋₆)alkyl, substituted on the heteroaryl moiety by a halogen atom such as bromo, may be converted into the corresponding compound wherein R³ represents aryl-heteroaryl(C₁₋₆)alkyl by treatment with an aryl boronic acid, in the presence of a catalyst. The catalyst may typically be a transition metal catalyst. A suitable catalyst is tetrakis(triphenylphosphine)palladium(0), in which case the transformation may conveniently be effected at an elevated temperature in the presence of a base such as sodium carbonate or potassium carbonate, in an inert solvent such as 1,2-dimethoxyethane or 1,4-dioxane. Alternatively, the catalyst may be palladium(II) acetate, in which case the transformation may conveniently be effected at an elevated temperature in the presence of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl and potassium phosphate.

A compound of formula (I) wherein R³ represents hydroxymethyl may be converted into the corresponding compound wherein R³ represents a substituted aminomethyl moiety, e.g. phenylaminomethyl, *N*-methyl-*N*-phenylaminomethyl, pyridin-3-ylaminomethyl, indolin-1-ylmethyl, 1,2,3,4-tetrahydroquinolin-1-ylmethyl or 1,2,3,4-tetrahydroisoquinolin-2-ylmethyl, by a two-stage procedure which comprises (i) Swern oxidation of the hydroxymethyl derivative by treatment with oxalyl chloride and dimethyl sulphoxide in the presence of triethylamine; and (ii) reductive amination of the formyl derivative thereby obtained by treatment with the appropriate amine, e.g. aniline, *N*-methylaniline, 3-aminopyridine, indoline, 1,2,3,4-tetrahydroquinoline or 1,2,3,4-tetrahydroisoquinoline, in the presence of a reducing agent such as sodium cyanoborohydride.

A compound of formula (I) wherein R³ represents hydroxymethyl may be converted into the corresponding compound wherein R³ represents an optionally substituted C₃₋₇ heterocycloalkylcarbonyl moiety, e.g. piperidin-1-ylcarbonyl, 1,2,3,4-tetrahydroquinolin-1-ylcarbonyl, 6-methyl-1,2,3,4-tetrahydroquinolin-1-ylcarbonyl, 6-methoxy-1,2,3,4-tetrahydroquinolin-1-ylcarbonyl, 1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl or 1,2,3,4-tetrahydroquinoxalin-1-ylcarbonyl, by a two-stage procedure which comprises (i) oxidation of the hydroxymethyl moiety by treatment with potassium

permanganate; and (ii) reaction of the carboxy derivative thereby obtained with the appropriate amine, e.g. piperidine, 1,2,3,4-tetrahydroquinoline, 6-methyl-1,2,3,4-tetrahydroquinoline, 6-methoxy-1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydro-isoquinoline or 1,2,3,4-tetrahydroquinoxaline, in the presence of a condensing agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU).

A compound of formula (I) wherein R^3 contains a phenyl moiety substituted by chloro may be converted into the corresponding compound wherein the phenyl ring is substituted by morpholin-4-yl by treatment with morpholine in the presence of tris(dibenzylideneacetone)dipalladium(0), 2-(di-*tert*-butylphosphino)biphenyl and sodium *tert*-butoxide. A compound of formula (I) wherein R^3 contains a phenyl moiety substituted by bromo may be converted into the corresponding compound wherein the phenyl ring is substituted by pyrrolidin-1-yl by treatment with pyrrolidine in the presence of tris(dibenzylideneacetone)dipalladium(0), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl and a base such as potassium carbonate. A compound of formula (I) wherein R^3 contains an indole moiety may be methylated on the indole ring by treatment with a methyl halide, e.g. iodomethane, in the presence of a strong base such as sodium hydride. A compound of formula (I) wherein R^3 contains an indole moiety may be acetylated on the indole ring by treatment with acetic anhydride and 4-dimethylaminopyridine, typically in the presence of an organic base such as triethylamine. A compound of formula (I) wherein R^3 contains an indoline moiety may be converted into the corresponding compound wherein R^3 contains an indole moiety by treatment with an oxidising agent such as manganese dioxide. A compound of formula (I) wherein R^3 contains a hydroxy substituent may be converted into the corresponding compound wherein R^3 contains a C_{1-6} alkylsulphonyloxy substituent, e.g. methylsulphonyloxy, by treatment with a C_{1-6} alkylsulphonyl halide, e.g. methanesulphonyl chloride. A compound of formula (I) wherein R^3 contains an amino ($-NH_2$) or carboxy ($-CO_2H$) moiety may be converted into the corresponding compound wherein R^3 contains an amido moiety ($-NHCO-$ or $-CONH-$ respectively) by treatment with, respectively, a compound containing a carboxy or amino group, in the presence of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), typically in a dipolar aprotic solvent such as *N,N*-dimethylformamide. A compound of formula (I) wherein R^3 contains an amino substituent may be converted into the corresponding compound wherein R^3 contains

an arylsulphonylamino substituent, e.g. phenylsulphonylamino, by treatment with an arylsulphonyl halide, e.g. benzenesulphonyl chloride.

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

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

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

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

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

The compounds in accordance with this invention potentially inhibit the activity of human PI3K α and/or PI3K β and/or PI3K γ and/or PI3K δ .

5

Enzyme Inhibition Assays

Measurement of the ability of compounds to inhibit the lipid kinase activity of the four class 1 PI3 kinase isoforms (α , β , γ and δ) was performed using a commercially available homogeneous time-resolved fluorescence assay as described by Gray *et al.*,
 10 *Anal. Biochem.*, 2003, **313**, 234-245, according to the manufacturer's instructions (Upstate). All assays were performed at 2 μ M ATP and a concentration of purified class 1 PI3 kinase known to generate product within the linear range of the assay. Dilutions of inhibitor in DMSO were added to the assay and compared with assays run in the presence of 2% (v/v) DMSO alone (100% activity). The concentration of inhibitor required to
 15 inhibit the enzyme activity by 50% is quoted as the IC₅₀.

When tested in the above assay, the compounds of the accompanying Examples were all found to possess IC₅₀ values for inhibition of activity of human PI3K α and/or PI3K β and/or PI3K γ and/or PI3K δ of 50 μ M or better.

20

EXAMPLES

Abbreviations

AcOH - acetic acid	EtOAc - ethyl acetate
25 Et ₂ O - diethyl ether	Me - methyl
MeCN - acetonitrile	MeOH - methanol
DCM - dichloromethane	DMSO - dimethylsulphoxide
IPA - isopropanol	THF - tetrahydrofuran
DMAP - 4-dimethylaminopyridine	PhMe - toluene
30 Pd ₂ dba ₃ - tris(dibenzylideneacetone)dipalladium(0)	
Ac - acetyl	dba - dibenzylideneacetone
NMM - <i>N</i> -methylmorpholine	BOC - <i>tert</i> -butoxycarbonyl
DMF - <i>N,N</i> -dimethylformamide	EtOH - ethanol

- 41 -

ⁱPr - isopropyl^tBu - *tert*-butyl

BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

DIPEA - *N,N*-diisopropylethylamine SiO₂ - silicaTMEDA - *N,N,N',N'*-tetramethylethylenediamine5 HBTU - *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate

r.t. - room temperature

RT - retention time

conc. - concentrated

sat. - saturated

h - hour

br - broad

HPLC - High Performance Liquid Chromatography

10 LCMS - Liquid Chromatography Mass Spectrometry

ES⁺ - Electrospray Positive Ionisation**Analytical Conditions**

All NMRs were obtained either at 300 MHz or 400 MHz.

15 Compounds were named with the aid of ACD Labs Name (v. 7.0) supplied by Advanced Chemical Development, Toronto, Canada.

Chiral purity was determined by HPLC using a CHIRALPAK AD 250*4.6 mm 10 µm column; mobile phase 40% IPA, 60% heptane; flow rate 1.0 ml/min; column temperature 40°C.

20 Examples 85–141 were prepared as a library and final purities were determined by LCMS using a Luna C18, 4.6 mm, 5 µm column: mobile phase A: 99.9% water, 0.1% formic acid; mobile phase B; 99.9% MeCN, 0.1% formic acid.

Gradient program (flow rate 6.5 mL/min, column temperature 35°C):

	Time	A%	B%
25	0.00	95.0	5.0
	4.40	5.0	95.0
	5.30	5.0	95.0
	5.32	95.0	5.0
	6.50	95.0	5.0

30

Preparative LC was performed at pH 3.2 using a Luna C18, 21.2 mm, 5 µm column: mobile phase A: 90% water, 10 % MeCN, 0.1% formic acid; mobile phase B: 90% MeCN, 10% water, 0.1% formic acid.

Gradient program for pH 3.2 method (flow rate 20 mL/min, column temperature 35°C):

Time	A%	B%
0.00	95.0	5.0
11.00	5.0	95.0
11.50	95.0	5.0
12.00	95.0	5.0

All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen atmosphere using dried solvents and glassware.

INTERMEDIATE 1 (METHOD A)

2-Bromocyclohexane-1,3-dione

To a stirred solution of cyclohexane-1,3-dione (1.12 g, 10 mmol) in AcOH (20 mL) at r.t. was added bromine (1.6 g, 0.51 mL, 10 mmol) dropwise. The reaction mixture was stirred for 2 h and then the product was isolated by filtration. The precipitate was washed twice with Et₂O (100 mL) and then dried *in vacuo* to give the *title compound* in quantitative yield as a buff solid, which was used without further purification. LCMS (ES+) 190.9 (M+H)⁺.

INTERMEDIATE 2

2-Bromo-5,5-dimethylcyclohexane-1,3-dione

To a stirred solution of 5,5-dimethylcyclohexane-1,3-dione (1.4 g, 10 mmol) in AcOH (20 mL) at r.t. was added bromine (1.6 g, 0.51 mL, 10 mmol) dropwise. The reaction was carried out according to Method A to give the *title compound* in quantitative yield as a light brown solid, which was used without further purification. LCMS (ES+) 218.9 (M+H)⁺.

INTERMEDIATE 3

2-Bromo-5-isopropylcyclohexane-1,3-dione

- 43 -

To a stirred solution of 5-isopropylcyclohexane-1,3-dione (2 g, 12.9 mmol) in AcOH (20 mL) at r.t. was added bromine (2.06 g, 0.66 mL, 12.9 mmol) dropwise. The reaction was then carried out according to Method A to give the *title compound* (2.91 g, 96%) as a white solid. δ_{H} (DMSO- d_6) 2.55-2.48 (4H, m), 2.38-2.32 (1H, m), 1.91-1.82 (1H, m), 1.79-1.54 (1H, m), 0.87 (6H, d, J 6.7 Hz). LCMS (ES+) 234.9 (M+H)⁺.

INTERMEDIATE 4

2-Bromo-5-propylcyclohexane-1,3-dione

To a stirred solution of 5-propylcyclohexane-1,3-dione (1.54 g, 10 mmol) in AcOH (20 mL) at r.t. was added bromine (1.6 g, 0.51 mL, 1 mmol) dropwise. The reaction was carried out according to Method A to give the *title compound* in quantitative yield as a light brown solid, which was used without further purification. LCMS (ES+) 232.9 (M+H)⁺.

INTERMEDIATE 5

2-Bromo-5-phenylcyclohexane-1,3-dione

To a stirred solution of 5-phenylcyclohexane-1,3-dione (1.88 g, 10 mmol) in AcOH (20 mL) at r.t. was added bromine (1.6 g, 0.51 mL, 10 mmol) dropwise. The reaction was carried out according to Method A to give the *title compound* in quantitative yield as a light brown solid, which was used without further purification. LCMS (ES+) 266.8 (M+H)⁺.

INTERMEDIATE 6

2-Bromo-5-(4-chlorophenyl)cyclohexane-1,3-dione

To a stirred solution of 5-(4-chlorophenyl)cyclohexane-1,3-dione (5 g, 22.6 mmol) in AcOH (40 mL) at r.t. was added bromine (3.61 g, 1.15 mL, 22.6 mmol) dropwise. The reaction was then carried out according to Method A to give the *title compound* (2.0 g, 66%) as a white solid. δ_{H} (DMSO- d_6) 7.38 (4H, m), 3.41-3.38 (1H, m), 2.97-2.85 (2H, m), 2.67 (2H, dd, J 16.4 and 4.2 Hz), 2.50 (1H, bs).

INTERMEDIATE 7**2-Bromo-4,4-dimethylcyclohexane-1,3-dione**

To a stirred solution of 4,4-dimethylcyclohexane-1,3-dione (1.4 g, 10 mmol) in
5 AcOH (20 mL) at r.t. was added bromine (1.6 g, 0.51 mL, 10 mmol) dropwise. The
reaction was carried out according to Method A to give the *title compound* in quantitative
yield as a light brown solid which was used without further purification. LCMS (ES+)
218.9 (M+H)⁺.

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INTERMEDIATE 8**2-Bromo-5-methylcyclohexane-1,3-dione**

To a stirred solution of 5-methylcyclohexane-1,3-dione (1.26 g, 10 mmol) in
AcOH (20 mL) at r.t. was added bromine (1.6 g, 0.51 mL, 10 mmol) dropwise. The
15 reaction was carried out according to Method A to give the *title compound* in quantitative
yield as a light brown solid which was used without further purification. LCMS (ES+)
204.9 (M+H)⁺.

INTERMEDIATE 9

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2-Bromo-5-(4-methoxyphenyl)cyclohexane-1,3-dione

To a stirred solution of 5-(4-methoxyphenyl)cyclohexane-1,3-dione (5 g, 22.6
mmol) in AcOH (40 mL) at r.t. was added bromine (3.61 g, 1.18 mL, 22.6 mmol)
dropwise. The reaction was then carried out according to Method A to give the *title*
25 *compound* in quantitative yield as a white solid. δ_{H} (DMSO-d₆) 7.24 (2H, d, *J* 8.6 Hz),
6.87 (2H, d, *J* 8.6 Hz), 3.72 (3H, s), 3.31-3.21 (1H, m), 2.88-2.82 (2H, m), 2.77-2.62 (3H,
m). LCMS (ES+) 296.9 (M+H)⁺.

INTERMEDIATE 10

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2-Bromo-5-[4-(methylthio)phenyl]cyclohexane-1,3-dione

To a stirred solution of 5-[4-(methylthio)phenyl]cyclohexane-1,3-dione (1.08 g,
4.6 mmol) in AcOH (10 mL) at r.t. was added bromine (0.74 g, 0.23 mL, 4.6 mmol)

dropwise. The reaction was then carried out according to Method A to give the *title compound* (1.03 g, 70%) as a white solid. LCMS (ES+) 314.9 (M+H)⁺.

INTERMEDIATE 11

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2-Bromo-5-(2-furyl)cyclohexane-1,3-dione

To a stirred solution of 5-(2-furyl)cyclohexane-1,3-dione (1 g, 5.6 mmol) in THF (50 mL) was added *N*-bromosuccinimide (1 g, 5.6 mmol). The reaction mixture was heated to 85°C for 12 h and on completion was filtered. The filtrate was concentrated *in vacuo* to give the *title compound* (1.0 g, 69%) as a white solid. LCMS (ES+) 256.8 (M+H)⁺.

10

INTERMEDIATE 12

3-Bromospiro[5,5]undecane-2,4-dione

To a stirred solution of spiro[5,5]undecane-2,4-dione (1.29 g, 5 mmol) in AcOH (10 mL) at r.t. was added bromine (0.8 g, 0.25 ml, 5 mmol) dropwise. The reaction was carried out according to Method A to give the *title compound* in quantitative yield as a light brown solid which was used without further purification. LCMS (ES+) 258.9 (M+H)⁺.

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INTERMEDIATE 13

Morpholine-4-carbothioamide

To a stirred solution of 1,1'-thiocarbonyldiimidazole (10.0 g, 56.1 mmol) in THF (150 mL) was added morpholine (4.24 g, 4.2 mL, 48.7 mmol). The reaction was stirred for 72 h at r.t. and then concentrated *in vacuo* to 30 mL. Ammonia (60 mL, 2.0M in MeOH) was added to the reaction mixture, which was then stirred at r.t. in a sealed flask overnight. The reaction mixture was filtered and the solid washed with Et₂O to give the *title compound* (2.0 g, 28%) as a white solid. δ_{H} (DMSO-d₆) 7.46 (2H, bs), 3.80-3.60 (4H, m), 3.60-3.50 (4H, m).

30

INTERMEDIATE 14**2-Amino-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one**

To a stirred solution of Intermediate 2 (12 g, 60 mmol) in THF (200 mL) was added thiourea (4.2 g, 60 mmol) and *N,N*-diisopropylethylamine (7.76 g, 10.45 mL, 60 mmol). The reaction was carried out according to Method B to yield the *title compound* (8.6 g, 73%) as a yellow solid. δ_{H} (DMSO- d_6) 8.07 (2H, s), 2.59 (2H, s), 2.27 (2H, s), 1.05 (6H, s). LCMS (ES+) 197.0 (M+H)⁺.

INTERMEDIATE 15 (METHOD C)**2-Bromo-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one**

To a stirred solution of Intermediate 14 (7 g, 36 mmol) in MeCN (150 mL) was added copper(II) bromide (8.7 g, 39 mmol) and *tert*-butyl nitrite (5.1 g, 49 mmol). After stirring at r.t. for 2 h, the reaction mixture was poured into 10% HCl (100 mL) and extracted with DCM (2 x 150 mL). The organic fraction was dried over MgSO₄ and concentrated *in vacuo* to give the *title compound* (7.0 g, 74%) as an orange solid. δ_{H} (CDCl₃) 2.84 (2H, s), 2.41 (2H, s), 1.07 (6H, s). LCMS (ES+) 260.0 (M+H)⁺.

INTERMEDIATE 16 (METHOD D)**(2R)-2-Amino-3-(1H-indol-3-yl)propan-1-ol**

To a solution of (*R*)-tryptophan (4.0 g, 20 mmol) in THF (100 mL) at 0°C was slowly added borane-dimethylsulphide complex (5.9 mL, 10M solution in THF, 59 mmol). The reaction mixture was heated to 70°C for 16 h and the excess borane was quenched by the addition of methanol (10 mL) at 0°C. The reaction mixture was concentrated, and the residue dissolved in EtOAc (120 mL) and washed with 20% NaOH solution (2 x 70 mL). The organic layer was then extracted into aqueous 2M HCl (2 x 100 mL). The combined acidic aqueous layers were then basified to pH 14 (addition of solid NaOH) and were re-extracted with EtOAc (2 x 150 mL). The combined organic fractions were washed with brine (70 mL), dried over MgSO₄ and concentrated *in vacuo* to give the *title compound* (3.5 g, 92%) as a white solid. δ_{H} (MeOD- d_3) 7.46 (1H, d, *J* 7.9 Hz), 7.21 (1H, d, *J* 8.0 Hz), 6.96 (3H, m), 3.79 (1H, dd, *J* 11.3 and 3.6 Hz), 3.54 (1H, dd,

J 11.2 and 6.2 Hz), 3.05 (1H, m), 2.80 (1H, m), 2.61 (1H, m). Note: exchangeable protons not evident in MeOD.

INTERMEDIATE 17 (METHOD E)

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2-Chloro-*N*-[(1*R*)-2-hydroxy-1-(1*H*-indol-3-ylmethyl)ethyl]acetamide

To a stirred solution of Intermediate 16 (2 g, 10 mmol) and triethylamine (1.32 g, 1.8 mL, 13 mmol) in THF (120 mL) at 0°C was added chloroacetyl chloride (1.36 g, 0.92 mL, 12 mmol) dropwise. The reaction mixture was then stirred at r.t. for 1.5 h before
10 being quenched by the addition of water (5 mL). The reaction mixture was diluted with EtOAc (120 mL) and partitioned with water (100 mL). The organic fraction was washed with brine (100 mL), dried over MgSO₄ and concentrated *in vacuo* to give the *title compound* (2.4 g, 90%) as a solid. δ_{H} (CDCl₃) 8.15 (1H, s), 7.59 (1H, d, *J* 7.9 Hz), 7.28 (1H, d, *J* 8.0 Hz), 7.11 (3H, m), 6.97 (1H, d, *J* 2.3 Hz), 4.19 (1H, m), 3.92 (2H, d, *J* 2.9
15 Hz), 3.59 (2H, m), 2.98 (2H, d, *J* 6.0 Hz), 2.52 (1H, br. s).

INTERMEDIATE 18 (METHOD F)

(5*R*)-5-(1*H*-Indol-3-ylmethyl)morpholin-3-one

To a stirred solution of Intermediate 17 (2.4 g, 9.5 mmol) in THF (100 mL) at 0°C was added sodium hydride (0.8 g, 60% dispersion in oil, 19 mmol) portionwise. The reaction mixture was then stirred at r.t. for 1.5 h before quenching by the addition of ice. The reaction mixture was then partitioned between EtOAc (100 mL) and water (100 mL) and the organic fraction was dried over MgSO₄ and concentrated *in vacuo* to give the *title compound* (1.8 g, 82%) as a solid. δ_{H} (MeOD-*d*₃) 7.46 (1H, d, *J* 7.8 Hz), 7.25 (1H, d, *J* 7.8 Hz), 6.95 (3H, m), 3.99 (2H, s), 3.65 (2H, m), 3.52 (1H, m), 2.91 (2H, d, *J* 6.3 Hz). Exchangeable protons were not observed. LCMS (ES+) 231.0 (M+H)⁺.
25

INTERMEDIATE 19 (METHOD G)

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3-[(3*R*)-Morpholin-3-ylmethyl]-1*H*-indole

To a stirred solution of Intermediate 18 (1.8 g, 7.8 mmol) in THF (100 mL) was added, at 0°C, LiAlH₄ (1 g, 27 mmol). After stirring overnight at r.t. the reaction mixture

- 48 -

was quenched by dropwise addition of Na₂CO₃ solution (20 mL). The resulting mixture was filtered through Celite® and the filtrate was concentrated *in vacuo*. The resulting solid was dissolved in PhMe and the solvent removed by evaporation *in vacuo*. Column chromatography (SiO₂, EtOAc-hexane) yielded the *title compound* (1.5 g, 89%) as a solid. δ_{H} (CDCl₃) 8.11 (1H, s), 7.55 (1H, d, *J* 7.8 Hz), 7.28 (1H, d, *J* 8.0 Hz), 7.11 (4H, m), 3.83 (1H, dd, *J* 10.9 and 2.8 Hz), 3.71 (1H, dt, *J* 11.1 and 2.2 Hz), 3.47 (1H, m), 3.24 (1H, t, *J* 9.8 Hz), 3.06 (1H, m), 2.78 (3H, m), 2.56 (1H, m), 1.92 (1H, br. s). LCMS (ES+) 217.0 (M+H)⁺.

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INTERMEDIATE 20**2-Amino-3-(2-naphthyl)propan-1-ol**

The *title compound* was prepared from 3-(2-naphthyl)alanine according to Method D and was isolated as a solid in 89% yield. δ_{H} (CDCl₃) 7.68 (3H, d, *J* 8.9 Hz), 7.49 (1H, m), 7.31 (2H, m), 7.18 (1H, dd, *J* 8.5 and 1.5 Hz), 3.50 (2H, m), 3.32 (1H, m), 3.05 (1H, m), 2.79 (3H, m), 2.52 (1H, m).

20

2-Chloro-N-[2-hydroxy-1-(2-naphthylmethyl)ethyl]acetamide

The *title compound* was prepared from Intermediate 20 according to Method E and was isolated as an oil in 72% yield. δ_{H} (CDCl₃) 7.75 (3H, m), 7.61 (1H, s), 7.35 (2H, m), 7.29 (1H, m), 6.82 (1H, bs), 4.21 (1H, m), 3.93 (2H, d, *J* 5.1 Hz), 3.61 (2H, m), 2.99 (2H, dd, *J* 7.3 and 1.7 Hz), 2.34 (1H, bs). LCMS (ES+) 277.9 (M+H)⁺.

25

INTERMEDIATE 22**5-(2-Naphthylmethyl)morpholin-3-one**

The *title compound* was prepared from Intermediate 21 according to Method F and was isolated as an oil in 53% yield. δ_{H} (CDCl₃) 7.72 (3H, m), 7.56 (1H, s), 7.36 (2H, m), 7.17 (1H, m), 6.83 (1H, bs), 4.07 (2H, s), 3.75 (1H, m), 3.54 (1H, m), 2.98 (1H, m), 2.81 (2H, m). LCMS (ES+) 242.0 (M+H)⁺.

INTERMEDIATE 23**3-(2-Naphthylmethyl)morpholine**

The *title compound* was prepared from Intermediate 22 according to Method G and was isolated as a solid in 74% yield after purification by column chromatography (SiO₂, EtOAc). δ_{H} (CDCl₃) 7.71 (3H, m), 7.57 (1H, s), 7.36 (2H, m), 7.25 (1H, dd, J 8.4 and 1.7 Hz), 3.79 (1H, dd, J 10.9 and 2.9 Hz), 3.70 (1H, dt, J 11.3 and 2.4 Hz), 3.47 (1H, m), 3.25 (1H, m), 3.04 (1H, m), 2.75 (3H, m), 2.56 (1H, m), 1.82 (1H, bs).

INTERMEDIATE 24**2-Amino-3-(1-naphthyl)propan-1-ol**

The *title compound* was prepared from 3-(1-naphthyl)alanine according to Method D and was isolated as a solid in 89% yield. δ_{H} (CDCl₃) 7.94 (1H, d, J 7.1 Hz), 7.75 (1H, dd, J 7.0 and 2.5 Hz), 7.65 (1H, d, J 8.0 Hz), 7.42 (2H, m), 7.31 (2H, m), 3.55 (2H, m), 3.37 (1H, m), 3.23 (1H, m), 2.83 (1H, m), 2.65 (3H, bs).

INTERMEDIATE 25**2-Chloro-N-[2-hydroxy-1-(1-naphthylmethyl)ethyl]acetamide**

The *title compound* was prepared from Intermediate 24 according to Method E and was isolated as an oil in 92% yield. δ_{H} (CDCl₃) 8.16 (1H, d, J 8.5 Hz), 7.79 (1H, dd, J 8.0 and 1.7 Hz), 7.69 (1H, d, J 7.8 Hz), 7.45 (2H, m), 7.30 (2H, m), 6.88 (1H, bs), 4.27 (1H, m), 3.94 (2H, d, J 4.2 Hz), 3.61 (2H, m), 3.30 (2H, m), 2.10 (1H, bs). LCMS (ES+) 278.0 (M+H)⁺.

INTERMEDIATE 26**5-(1-Naphthylmethyl)morpholin-3-one**

The *title compound* was prepared from Intermediate 25 according to Method F and was isolated as a yellow oil in 44% yield. δ_{H} (CDCl₃) 7.82 (1H, d, J 7.7 Hz), 7.72 (1H, d, J 7.3 Hz), 7.62 (1H, d, J 8.1 Hz), 7.12-7.42 (4H, m), 6.73 (1H, bs), 3.97 (2H, d, J 5.0 Hz), 3.63 (2H, m), 3.41 (1H, m), 3.11 (2H, m).

INTERMEDIATE 27**3-(1-Naphthylmethyl)morpholine**

5 The *title compound* was prepared from Intermediate 26 according to Method G and was isolated as a yellow oil in 64% yield after purification by column chromatography (SiO₂, 9.5:1 EtOAc/MeOH). δ_{H} (CDCl₃) 8.04 (1H, d, *J* 8.0 Hz), 7.84 (1H, dd, *J* 7.6 and 2.3 Hz), 7.73 (1H, d, *J* 7.9 Hz), 7.32-7.54 (4H, m), 3.87 (1H, dd, *J* 10.5 and 2.2 Hz), 3.74 (1H, dt, *J* 11.0 and 2.4 Hz), 3.54 (1H, m), 3.35 (1H, m), 3.14 (2H, m),
10 2.88 (1H, m), 2.71 (2H, m), 2.00 (1H, bs).

INTERMEDIATE 28**2-Amino-4-phenylbutan-1-ol**

15 The *title compound* was prepared from 2-amino-4-phenylbutanoic acid according to Method D and was isolated as a solid in 94% yield. δ_{H} (CDCl₃) 7.21 (2H, m), 7.10 (3H, m), 3.53 (1H, dd, *J* 10.5 and 3.9 Hz), 3.24 (1H, m), 2.81 (1H, bs), 2.65 (2H, m), 2.17 (3H, bs), 1.49-1.76 (2H, m).

20

INTERMEDIATE 29**2-Chloro-N-[1-(hydroxymethyl)-3-phenylpropyl]acetamide**

 The *title compound* was prepared from Intermediate 28 according to Method E and was isolated as a solid in 87% yield. δ_{H} (CDCl₃) 7.24 (2H, m), 7.17 (3H, m), 6.59
25 (1H, bs), 3.97 (2H, d, *J* 0.8 Hz), 3.63 (2H, dq, *J* 11.1 and 3.8 Hz), 2.63 (2H, m), 1.86 (4H, m). LCMS 242.1 (M+H)⁺.

INTERMEDIATE 30

30 **5-(2-Phenethyl)morpholin-3-one**

 The *title compound* was prepared from Intermediate 29 according to Method F and was isolated as an oil in 51% yield. δ_{H} (CDCl₃) 6.95-7.09 (5H, m), 5.97 (1H, bs),

3.98 (3H, m), 3.65 (1H, m), 3.30 (1H, m), 2.44 (2H, m), 1.71 (2H, m). LCMS 206.0 (M+H)⁺.

INTERMEDIATE 31

5

3-(2-Phenethyl)morpholine

The *title compound* was prepared from Intermediate 30 according to Method G and was isolated as an oil in 71% yield. δ_{H} (CDCl₃) 7.21-7.32 (5H, m), 3.84 (2H, m), 3.52 (1H, dt, *J* 10.6 and 3.3 Hz), 3.20 (1H, t, *J* 9.9 Hz), 2.94 (3H, m), 2.66 (2H, m), 1.76 (3H, m).

INTERMEDIATE 32

N-[(1S)-1-Benzyl-2-hydroxyethyl]-2-chloroacetamide

15 The *title compound* was prepared from (2S)-2-amino-3-phenylpropan-1-ol according to Method E and was isolated as an oil in 86% yield. δ_{H} (CDCl₃) 7.13 (5H, m), 6.92 (1H, bd, *J* 8.2 Hz), 4.13 (1H, m), 3.85 (2H, d, *J* 4.3 Hz), 3.51 (3H, m), 2.80 (2H, m).

INTERMEDIATE 33

20

(5S)-5-Benzylmorpholin-3-one

The *title compound* was prepared from Intermediate 32 according to Method F and was isolated as an oil in 69% yield. δ_{H} (CDCl₃) 7.27 (4H, m), 7.13 (1H, d, *J* 6.5 Hz), 5.86 (1H, bs), 4.10 (2H, d, *J* 2.2 Hz), 3.84 (1H, m), 3.72 (1H, m), 3.48 (1H, m), 2.82 (1H, dd, *J* 13.5 and 5.6 Hz), 2.64 (1H, m).

INTERMEDIATE 34

(3S)-3-Benzylmorpholine

30 The *title compound* was prepared from Intermediate 33 according to Method G and was isolated as a colourless oil in 81% yield after purification by column chromatography (SiO₂, EtOAc). δ_{H} (CDCl₃) 7.13 (5H, m), 3.72 (2H, t, *J* 11.1 Hz), 3.47

(1H, m), 3.19 (1H, t, J 9.8 Hz), 2.94 (1H, m), 2.74 (2H, m), 2.57 (1H, m), 2.41 (1H, dd, J 13.3 and 9.0 Hz), 1.67 (1H, bs).

INTERMEDIATE 35

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2-Chloro-*N*-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetamide

The *title compound* was prepared from (1*S*,2*R*)-1-aminoindan-2-ol according to Method E and was isolated as an oil in 79% yield. δ_{H} (DMSO- d_6) 8.20 (1H, d, J 8.4 Hz), 7.24 (4H, m), 5.16 (2H, m), 4.45 (1H, m), 4.24 (2H, m), 3.07 (1H, dd, J 16.2 and 5.0 Hz),
10 2.82 (1H, dd, J 16.2 and 1.5 Hz).

INTERMEDIATE 36

(4*aS*,9*aR*)-4,4*a*,9,9*a*-Tetrahydroindeno[2,1-*b*][1,4]oxazin-3(2*H*)-one

15 The *title compound* was prepared from Intermediate 35 according to Method F and was isolated as an oil in 49% yield. δ_{H} (CDCl₃) 8.42 (1H, bs), 7.36 (1H, m), 7.28 (3H, m), 4.77 (1H, m), 4.53 (1H, m), 4.17 (2H, m), 3.20 (1H, dd, J 4.7 and 16.8 Hz), 3.09 (1H, d, J 16.8 Hz).

20

INTERMEDIATE 37

(4*aS*,9*aR*)-2,3,4,4*a*,9,9*a*-Hexahydroindeno[2,1-*b*][1,4]oxazine

The *title compound* was prepared from Intermediate 36 according to Method G and was isolated as a colourless oil in 84% yield after purification by column
25 chromatography (SiO₂, EtOAc). δ_{H} (CDCl₃) 7.39 (1H, m), 7.26 (3H, m), 4.34 (1H, m), 4.26 (1H, m), 3.68 (2H, m), 2.94 (3H, m), 2.70 (1H, m), 2.05 (1H, bs).

INTERMEDIATE 38

2-Chloro-*N*-[1-(4-chlorobenzyl)-2-hydroxyethyl]acetamide

30 The *title compound* was prepared from 2-amino-3-(4-chlorophenyl)propan-1-ol according to Method E and was isolated as an oil in 82% yield. δ_{H} (CDCl₃) 7.20 (2H, d, J

8.4 Hz), 7.08 (2H, d, J 8.4 Hz), 6.76 (1H, bd, J 7.3 Hz), 4.13 (1H, m), 3.93 (2H, d, J 3.0 Hz), 3.53 (2H, m), 2.81 (2H, m), 2.45 (1H, bs).

INTERMEDIATE 39

5

5-(4-Chlorobenzyl)morpholin-3-one

The *title compound* was prepared from Intermediate 38 according to Method F and was isolated as an oil in 53% yield. δ_{H} (CDCl_3) 6.85-7.17 (5H, m), 3.95 (2H, m), 3.21-3.62 (4H, m), 2.52 (1H, m).

10

INTERMEDIATE 40

3-(4-Chlorobenzyl)morpholine

The *title compound* was prepared from Intermediate 39 according to Method G and was isolated as a colourless solid in 62% yield after purification by column chromatography (SiO_2 , EtOAc). δ_{H} (CDCl_3) 7.04-7.33 (2H, m), 7.05 (2H, m), 3.73 (2H, m), 3.49 (1H, m), 3.17 (1H, t, J 5.0 Hz), 2.91 (1H, m), 2.82 (2H, m), 2.55 (1H, m), 2.41 (1H, m), 1.75 (1H, bs).

20

INTERMEDIATE 41

2-Amino-3-(5-methyl-1H-indol-3-yl)propan-1-ol

The *title compound* was prepared from 5-methyltryptophan according to Method D and was isolated as an oil in 97% yield. δ_{H} (CDCl_3) 7.89 (1H, bs), 7.40 (1H, d, J 8.1 Hz), 7.08 (1H, s), 6.89 (2H, m), 3.60 (1H, dd, J 10.5 and 3.9 Hz), 3.33 (1H, dd, J 10.5 and 7.1 Hz), 3.18 (1H, m), 2.83 (1H, dd, J 14.3 and 8.4 Hz), 2.39 (3H, s), 1.81 (3H, bs).

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INTERMEDIATE 42

2-Chloro-N-{2-hydroxy-1-[(5-methyl-1H-indol-3-yl)methyl]ethyl}acetamide

30

The *title compound* was prepared from Intermediate 41 according to Method E and was isolated as a solid in 77% yield. δ_{H} (CDCl_3) 7.86 (1H, bs), 7.47 (1H, d, J 8.0

Hz), 7.09 (1H, s), 6.93 (2H, m), 6.80 (1H, bs), 4.22 (1H, m), 3.94 (2H, d, *J* 2.6 Hz), 3.64 (2H, m), 2.98 (2H, d, *J* 6.8 Hz), 2.39 (3H, s), 1.67 (1H, bs).

INTERMEDIATE 43

5

5-[(5-Methyl-1*H*-indol-3-yl)methyl]morpholin-3-one

The *title compound* was prepared from Intermediate 42 according to Method F and was isolated as an oil in 57% yield. δ_{H} (DMSO- d_6) 10.60 (1H, bs), 8.02 (1H, bs), 7.51 (1H, m), 7.05 (2H, m), 6.79 (1H, m), 3.98 (2H, m), 3.61 (2H, m), 3.41 (1H, m), 2.72 (2H, m), 2.31 (3H, s).

10

INTERMEDIATE 44

5-Methyl-3-(morpholin-3-ylmethyl)-1*H*-indole

The *title compound* was prepared from Intermediate 43 according to Method G and was isolated as a colourless solid in 52% yield after purification by column chromatography (SiO₂, EtOAc). δ_{H} (CDCl₃) 7.97 (1H, bs), 7.53 (1H, d, *J* 8.1 Hz), 7.18 (1H, s), 6.99 (2H, m), 3.96 (1H, dd, *J* 11.4 and 2.9 Hz), 3.82 (1H, m), 3.71 (1H, m), 3.50 (1H, m), 3.26 (1H, m), 2.94 (4H, m), 2.48 (3H, s), 1.99 (1H, bs).

20

INTERMEDIATE 45

2-Amino-3-(1*H*-indol-3-yl)propan-1-ol

The *title compound* was prepared from tryptophan according to Method D and was isolated as a solid in 92% yield. δ_{H} (MeOD- d_3) 7.46 (1H, d, *J* 7.9 Hz), 7.21 (1H, d, *J* 8.0 Hz), 6.96 (3H, m), 3.79 (1H, dd, *J* 11.3 and 3.6 Hz), 3.54 (1H, dd, *J* 11.2 and 6.2 Hz), 3.05 (1H, m), 2.80 (1H, m), 2.61 (1H, m). Note: exchangeable protons not evident in MeOD.

30

INTERMEDIATE 46

2-Chloro-*N*-[2-hydroxy-1-(1*H*-indol-3-ylmethyl)ethyl]acetamide

- 55 -

The *title compound* was prepared from Intermediate 45 according to Method E and was isolated as a solid in 82% yield. δ_{H} (CDCl_3) 8.15 (1H, s), 7.59 (1H, d, J 7.9 Hz), 7.28 (1H, d, J 8.0 Hz), 7.11 (3H, m), 6.97 (1H, d, J 2.3 Hz), 4.19 (1H, m), 3.92 (2H, d, J 2.3 Hz), 3.59 (2H, m), 2.98 (2H, d, J 6.0 Hz), 2.52 (1H, br. s).

5

INTERMEDIATE 47

5-(1H-Indol-3-ylmethyl)morpholin-3-one

The *title compound* was prepared from Intermediate 46 according to Method F and was isolated as a solid in 72% yield. δ_{H} (MeOD-d_3) 7.46 (1H, d, J 7.8 Hz), 7.25 (1H, d, J 8.0 Hz), 6.95 (3H, m), 3.99 (2H, s), 3.65 (2H, m), 3.52 (1H, m), 2.91 (2H, d, J 6.3 Hz). Exchangeable protons were not observed. LCMS (ES+) 231.0 ($\text{M}+\text{H}$)⁺.

15

INTERMEDIATE 48

3-(Morpholin-3-ylmethyl)-1H-indole

The *title compound* was prepared from Intermediate 47 according to Method G and was isolated as a colourless solid in 69% yield after purification by column chromatography (SiO_2 , EtOAc). δ_{H} (CDCl_3) 8.11 (1H, s), 7.55 (1H, d, J 7.8 Hz), 7.28 (1H, d, J 8.0 Hz), 7.11 (4H, m), 3.83 (1H, dd, J 10.9 and 2.8 Hz), 3.71 (1H, d, J 11.1 and 2.2 Hz), 3.47 (1H, m), 3.24 (1H, t, J 9.8 Hz), 3.06 (1H, m), 2.78 (2H, m), 2.56 (1H, m), 1.92 (1H, br. s). LCMS (ES+) 217.0 ($\text{M}+\text{H}$)⁺.

25

INTERMEDIATE 49

(2S)-2-Amino-3-(1H-indol-3-yl)propan-1-ol

The *title compound* was prepared from (*S*)-tryptophan according to Method D and was isolated as a solid in 92% yield. δ_{H} (MeOD-d_3) 7.46 (1H, d, J 7.9 Hz), 7.21 (1H, d, J 8.0 Hz), 6.96 (3H, m), 3.79 (1H, dd, J 11.3 and 3.6 Hz), 3.54 (1H, dd, J 11.3 and 6.2 Hz), 3.05 (1H, m), 2.80 (1H, m), 2.61 (1H, m). Note: exchangeable protons not evident in MeOD.

30

INTERMEDIATE 50**2-Chloro-N-[(1S)-2-hydroxy-1-(1H-indol-3-ylmethyl)ethyl]acetamide**

The *title compound* was prepared from Intermediate 49 according to Method E
5 and was isolated as a solid in 84% yield. δ_{H} (CDCl_3) 8.15 (1H, s), 7.59 (1H, d, J 7.9 Hz),
7.28 (1H, d, J 8.0 Hz), 7.11 (3H, m), 6.97 (1H, d, J 2.3 Hz), 4.19 (1H, m), 3.92 (2H, d, J
2.9 Hz), 3.59 (2H, m), 2.98 (2H, d, J 6.0 Hz), 2.52 (1H, br. s).

INTERMEDIATE 51

10

(5S)-5-(1H-Indol-3-ylmethyl)morpholin-3-one

The *title compound* was prepared from Intermediate 50 according to Method F
and was isolated as a solid in 70% yield. δ_{H} (MeOD-d_3) 7.46 (1H, d, J 7.8 Hz), 7.25 (1H,
d, J 8.0 Hz), 6.95 (3H, m), 3.99 (2H, s), 3.65 (2H, m), 3.52 (1H, m), 2.91 (2H, d, J 6.3
15 Hz). Exchangeable protons were not observed. LCMS (ES+) 231.0 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 52**3-[(3S)-Morpholin-3-ylmethyl]-1H-indole**

20

The *title compound* was prepared from Intermediate 51 according to Method G
and was isolated as a colourless solid in 67% yield after purification by column
chromatography (SiO_2 , EtOAc). δ_{H} (CDCl_3) 8.11 (1H, s), 7.55 (1H, d, J 7.8 Hz), 7.28
(1H, d, J 8.0 Hz), 7.11 (4H, m), 3.83 (1H, dd, J 10.9 and 2.8 Hz), 3.71 (1H, dt, J 11.1 and
2.2 Hz), 3.47 (1H, m), 3.24 (1H, t, J 9.8 Hz), 3.06 (1H, m), 2.78 (2H, m), 2.56 (1H, m),
25 1.92 (1H, br. s). LCMS (ES+) 217.0 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 53**2-Amino-3-(4-bromophenyl)propan-1-ol**

30

The *title compound* was prepared from 4-bromophenylalanine according to
Method D and was isolated as a solid in 90% yield. δ_{H} (CDCl_3) 7.36 (2H, d, J 8.4 Hz),
7.00 (2H, d, J 8.4 Hz), 3.54 (1H, dd, J 10.7 and 4.1 Hz), 3.30 (1H, dd, J 10.7 and 6.9 Hz),

3.03 (1H, m), 2.67 (1H, dd, J 13.6 and 5.4 Hz), 2.43 (1H, dd, J 13.5 and 8.5 Hz).

Exchangeable protons were not observed.

INTERMEDIATE 54

5

N-[1-(4-Bromobenzyl)-2-hydroxyethyl]-2-chloroacetamide

The *title compound* was prepared from Intermediate 53 according to Method E and was isolated as an oil in 79% yield. δ_{H} (CDCl₃) 7.36 (2H, d, J 8.4 Hz), 7.03 (2H, d, J 8.4 Hz), 6.73 (1H, bd, J 7.3 Hz), 4.10 (1H, m), 3.94 (2H, d, J 3.0 Hz), 3.56 (2H, dq, J 11.0 and 3.9 Hz), 2.81 (2H, m), 2.45 (1H, bs).

INTERMEDIATE 55

5-(4-Bromobenzyl)morpholin-3-one

The *title compound* was prepared from Intermediate 54 according to Method F and was isolated as an oil in 61% yield. δ_{H} (CDCl₃) 7.47 (2H, d, J 8.3 Hz), 7.07 (2H, d, J 8.3 Hz), 6.26 (1H, bs), 4.39 (1H, m), 4.09 (1H, m), 3.87 (1H, dd, J 11.7 and 3.6 Hz), 3.75 (1H, m), 3.56 (1H, dd, J 11.7 and 5.9 Hz), 2.84 (2H, m).

20

INTERMEDIATE 56

3-(4-Bromobenzyl)morpholine

The *title compound* was prepared from Intermediate 55 according to Method G and was isolated as a colourless solid in 63% yield after purification by column chromatography (SiO₂, EtOAc). δ_{H} (CDCl₃) 7.35 (2H, d, J 8.4 Hz), 7.00 (2H, d, J 8.4 Hz), 3.68 (2H, m), 3.44 (1H, m), 3.15 (1H, t, J 5.0 Hz), 2.94 (1H, m), 2.75 (2H, m), 2.54 (1H, m), 2.35 (1H, m), 1.95 (1H, bs).

30

INTERMEDIATE 57 (METHOD W)

N-Benzylserine

Racemic serine (14.7 g, 140 mmol) was dissolved in 2M NaOH (70 mL) and benzaldehyde (14.64 g, 14.0 mL, 138 mmol) added with stirring. The mixture was stirred

at r.t. for 1 h before cooling to 5°C. Sodium borohydride (1.5 g, 40 mmol) was added portionwise such that an internal temperature of between 6 and 10°C was maintained. After addition the reaction mixture was allowed to stir at 5°C for 30 minutes and then at r.t. for 1 h. The reaction mixture was cooled to 5°C and a further portion of sodium
5 borohydride (1.5 g, 40 mmol) added portionwise such that an internal temperature <10°C was maintained. The ice bath was removed on completion of addition and the reaction stirred at r.t. for 16 h. The reaction mixture was extracted with Et₂O (3 x 100 mL) and the aqueous phase acidified to pH 5 with concentrated hydrochloric acid. The resultant white precipitate was filtered and washed with water. The product was dried *in vacuo* to give
10 the *title compound* (24.0 g, 88%). δ_{H} (DMSO-d₆) 7.45-7.30 (5H, m), 4.04-3.91 (2H, m), 3.70-3.61 (3H, m), 3.17 (1H, t, *J* 5.8 Hz). Some exchangeable protons were not observed.

INTERMEDIATE 58 (METHOD X)

15 4-Benzyl-5-oxomorpholine-3-carboxylic acid

To a solution of Intermediate 57 (35.0 g, 179 mmol) in NaOH solution (9.3 g in 200 mL) at 0°C was slowly added chloroacetyl chloride (24.17 g, 17.0 mL, 214 mmol). The reaction mixture was allowed to warm to r.t. and stirred for 30 minutes. NaOH solution (30 wt %; 45 mL) was added and the reaction mixture heated to 38°C for 4 h.
20 The reaction mixture was cooled to 10°C and acidified to pH 1 with concentrated HCl. On standing at 4°C the product crystallised from the mixture and was collected by filtration, washed with cold water and then dried *in vacuo* to give the *title compound* (18.0 g, 43%). δ_{H} (DMSO-d₆) 13.50-12.50 (1H, bs), 7.38-7.25 (5H, m), 5.27 (1H, d, *J* 15.3 Hz), 4.24-4.10 (3H, m), 3.94-3.88 (2H, m), 3.83 (1H, d, *J* 15.3 Hz). LCMS (ES+) 236.0
25 (M+H)⁺.

INTERMEDIATE 59 (METHOD Y)

(4-Benzylmorpholin-3-yl)methanol

30 To a solution of Intermediate 58 (17.7 g, 75.3 mmol) in THF (300 mL) was added triethylamine (7.29 g, 10.0 mL, 72 mmol). The solution was cooled to 0°C and borane dimethylsulphide complex (~10M in THF, 45 mL, 450 mmol) added slowly. The reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled to 0°C

and the excess borane destroyed by slow addition of water. Excess THF was removed *in vacuo* and the residue made strongly alkaline with 2M NaOH solution (250 mL) and extracted with EtOAc (3 x 150 mL). The aqueous phase was acidified with concentrated HCl until pH 1, then extracted with EtOAc (3 x 200 mL). The combined organic
5 fractions were washed with brine (150 mL), dried (MgSO₄) and concentrated *in vacuo* to give the *title compound* (13.5 g, 87%) as a clear oil. δ_{H} (CDCl₃) 7.29-7.16 (5H, m), 4.05 (1H, d, *J* 12.8 Hz), 3.88 (1H, dd, *J* 11.5 and 4.5 Hz), 3.78 (1H, m), 3.70-3.53 (2H, m), 3.51-3.40 (2H, m), 3.20 (1H, d, *J* 13.2 Hz), 2.68 (1H, dt, *J* 12.1 and 2.8 Hz), 2.48 (1H, m), 2.27 (1H, m), 2.20-2.15 (1H, bs).

10

INTERMEDIATE 60

Morpholin-3-ylmethanol

To a nitrogen-flushed solution of Intermediate 59 (10.0 g, 48.3 mmol) in MeOH
15 (300 mL) was added palladium on carbon (10 wt %; 2 g) and the reaction mixture placed in a Parr[®] apparatus under 50 psi of hydrogen for 18 h. The resulting mixture was filtered through Celite[®] and concentrated *in vacuo* to give the *title compound* (5.2 g, 92%) as a clear oil. δ_{H} (CDCl₃) 3.81-3.76 (2H, m), 3.58-3.43 (3H, m), 3.35-3.28 (1H, m), 2.99-2.91 (5H, bm). LCMS (MS⁺) 118.0 (M+H)⁺.

20

INTERMEDIATE 61

2-[3-(Hydroxymethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

To a solution of Intermediate 15 (5.0 g, 19.3 mmol) in IPA (15 mL) was added
25 *N,N*-diisopropylethylamine (6.67 g, 8.99 mL, 51.6 mmol) and Intermediate 60 (5.0 g, 42.7 mmol). The reaction mixture was heated at reflux for 18 h. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (300 mL) and brine (500 mL). The aqueous fraction was extracted with two further portions of EtOAc (200 mL) and the
30 organic fractions combined, dried (MgSO₄), filtered and the solvents removed *in vacuo*. The crude residue was subjected to column chromatography (SiO₂, 1:1 to 1:0 EtOAc/hexanes) to give the *title compound* (4.28 g, 75%) as an orange foam. δ_{H} (DMSO-

d₆) 5.02 (1H, t, *J* 5.8 Hz), 3.97 (1H, d, *J* 10.7 Hz), 3.90-3.70 (4H, m), 3.58-3.35 (4H, m), 2.64 (2H, s), 2.31 (2H, s), 1.05 (3H, s), 1.04 (3H, s). LCMS (MS+) 297.0 (M+H)⁺.

INTERMEDIATE 62

5

4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholine-3-carbaldehyde

To a solution of oxalyl chloride (1.79 g, 1.23 mL, 14.125 mmol) in DCM (50 mL) at -78°C was added DMSO (2.34 g, 2.13 mL, 30 mmol) and the resultant solution allowed to stir at -78°C for 15 minutes. A solution of Intermediate 61 (3.7 g, 12.5 mmol) in DCM (150 mL) was added *via* cannula and the reaction mixture stirred at -78°C for a further 2 h. Triethylamine (6.32 g, 8.71 mL, 62.5 mmol) was added and the mixture stirred at -78°C for 30 minutes, warmed to r.t. and stirred for a further 1 h. The reaction mixture was concentrated by evaporation *in vacuo* and the residue partitioned between water (200 mL) and EtOAc (200 mL). The aqueous fraction was extracted with EtOAc (2 x 200 mL) and the combined organic fractions washed with brine (300 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo* to give a crude yellow solid. The crude product was purified by column chromatography (SiO₂, 1:1 EtOAc/hexanes) to give the *title compound* (3.1 g, 84%) as a pale yellow solid. δ_H (CDCl₃) 9.71 (1H, s), 4.90 (1H, bs), 4.54 (1H, d, *J* 12.3 Hz), 4.00 (1H, d, *J* 10.8 Hz), 3.86 (1H, dd, *J* 12.1 and 4.1 Hz), 3.75-3.55 (3H, m), 2.68 (2H, s), 2.41 (2H, s), 1.14 (3H, s), 1.13 (3H, s). LCMS (MS+) 313.0 (M+H)⁺ for the hemi-acetal (aldehyde plus H₂O); 295.0 (M+H)⁺ for the aldehyde.

INTERMEDIATE 63 (METHOD J)

25

(7*E,Z*)-2-Bromo-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one oxime

To a stirred solution of Intermediate 15 (0.50 g, 1.92 mmol) in pyridine (5 mL) was added 4Å molecular sieves (3 pellets) and hydroxylamine hydrochloride (0.66 g, 9.54 mmol). The reaction mixture was stirred for 16 h then filtered. The filtrate was concentrated *in vacuo* and water (10 mL) was added to the residue. The solid obtained was filtered, washed with water (5 x 10 mL) and dried *in vacuo* to give the *title compound* (0.33 g, 62%) as a white solid consisting of a mixture of two regioisomers in ratio 1:15. δ_H (DMSO-d₆) 11.85 (1H, s, minor regioisomer), 11.82 (1H, s, major regioisomer), 2.76

(2H, s, major regioisomer), 2.74 (2H, s, minor regioisomer), 2.41 (2H, s), 1.01 (6H, s).
LCMS (ES+) 275.0 (M+H)⁺.

INTERMEDIATE 64

5

4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-morpholine-3-carboxylic acid

To a stirred solution of Intermediate 62 (0.60 g, 2.04 mmol) in 1,4-dioxane (15 mL) was added a sat. aqueous solution of KMnO₄ in aqueous 2M NaOH (15 mL) and the
10 resultant mixture allowed to stir at r.t. for 16 h. The reaction mixture was then filtered through Celite[®] to remove MnO₂ and concentrated by evaporation *in vacuo*. The crude residue was dissolved in aqueous 10% NaOH solution (200 mL) and washed with EtOAc (3 x 100 mL). The aqueous fraction was acidified to pH 3 with concentrated HCl and
15 extracted with EtOAc (3 x 150 mL). The combined organic fractions were washed with brine (200 mL), dried (MgSO₄) and filtered. The solvents were removed *in vacuo* to give the *title compound* as a gum (0.55 g, 87%). δ_{H} (DMSO-d₆) 13.00-12.00 (1H, br. s), 4.73 (1H, br. s), 4.26 (1H, d, *J* 11.9 Hz), 3.94 (1H, d, *J* 11.5 Hz), 3.77 (1H, dd, *J* 11.8 and 3.8 Hz), 3.65-3.47 (3H, m), 2.66 (2H, d, *J* 2.0 Hz), 2.33 (2H, d, *J* 4.1 Hz), 1.05 (3H, s), 1.03 (3H, s). LCMS (ES+) 311.0 (M+H)⁺

20

INTERMEDIATE 65

3-Bromo-L-phenylalanine

(2*S*)-3-(3-Bromophenyl)-2-(*tert*-butoxycarbonylamino)propionic acid (5.0 g, 14.5
25 mmol) was suspended in 4M HCl in 1,4-dioxane (75 mL) and stirred for 16 h at r.t.. The white precipitate was filtered and washed with Et₂O to give the *title compound* as a white solid (3.2 g, 89%) that required no further purification. δ_{H} (CDCl₃) 8.32 (2H, s), 7.50-7.48 (2H, m), 7.34-7.29 (2H, m), 4.22 (1H, t, *J* 6.2 Hz), 3.13-3.11 (2H, m). An exchangeable proton was not observed.

30

INTERMEDIATE 66

(2*S*)-2-Amino-3-(3-bromophenyl)propan-1-ol

- 62 -

The *title compound* was prepared from Intermediate 65 according to Method D and was isolated as a colourless oil (56%) that required no further purification. δ_{H} (CDCl_3) 7.42-7.35 (2H, m), 7.29-7.19 (2H, m), 3.59 (1H, m), 3.39 (1H, m), 3.10 (1H, m), 2.78 (1H, dd, J 13.5 and 5.3 Hz), 2.51 (1H, dd, J 13.5 and 8.5 Hz). Exchangeable protons were not observed.

INTERMEDIATE 67

N-[*(1S)*-1-(3-Bromobenzyl)-2-hydroxyethyl]-2-chloroacetamide

The *title compound* was prepared from Intermediate 66 according to Method E and was isolated as a yellow oil (77%) after purification by column chromatography (SiO_2 , 1:1 EtOAc/DCM). δ_{H} ($\text{DMSO}-d_6$) 8.06 (1H, d, J 8.4 Hz), 7.42 (1H, s), 7.39-7.35 (1H, m), 7.26-7.19 (2H, m), 4.85 (1H, t, J 5.6 Hz), 3.98 (2H, s), 3.87 (1H, m), 3.39-3.15 (2H, m), 2.84 (1H, dd, J 13.7 and 5.4 Hz), 2.65 (1H, dd, J 13.7 and 8.6 Hz).

INTERMEDIATE 68

(5S)-5-(3-Bromobenzyl)morpholin-3-one

The *title compound* was prepared from Intermediate 67 according to Method F and was isolated as a white solid (50%) after purification by column chromatography (SiO_2 , 1:1 EtOAc/DCM). δ_{H} (CDCl_3) 7.36-7.32 (1H, m), 7.28 (1H, s), 7.19-7.11 (1H, m), 7.06-7.03 (1H, m), 6.26 (1H, br. s), 4.09 (2H, s), 3.81 (1H, dd, J 11.7 and 3.6 Hz), 3.71-3.62 (1H, m), 3.50 (1H, dd, J 11.6 and 6.0 Hz), 2.79 (1H, dd, J 13.6 and 6.1 Hz), 2.67 (1H, dd, J 13.6 and 8.2 Hz). LCMS (ES+) 270.0 and 272.0 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 69

(3S)-3-(3-Bromobenzyl)morpholine

To a stirred solution of Intermediate 68 (0.8 g, 3.0 mmol) in THF (100 mL) at 0°C was added, under nitrogen, $\text{BH}_3\cdot\text{Me}_2\text{S}$ complex (1.7 mL, 10M solution in THF, 17.7 mmol) dropwise. The reaction was then carried out according to Method D to give the *title compound* as a clear oil (0.7 g, 83%). LCMS (ES+) 256.0 and 258.0 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 70**2-Amino-7,7-dimethyl-5,6,7,8-tetrahydro-4H-[1,3]thiazolo[5,4-c]azepin-4-one**

5 To a stirred solution of Intermediate 14 (26.7 g, 100.0 mmol) in CHCl₃ (900 mL) was added concentrated H₂SO₄ (86 mL). NaN₃ (9.8 g, 200.0 mmol) was added portionwise over 2 h and the apparatus was fitted with a bubbler to monitor gas formation. The reaction mixture was then stirred for 48 h at r.t., after which time the solvent was decanted off and ice was added to the resulting oil. A solution of sat.
10 aqueous Na₂CO₃ was added slowly until a pH of 9 was reached. The resulting brown solid was filtered and washed several times with water and Et₂O to give the *title compound* as a light brown solid (18.5 g, 63%) that was used crude. δ_{H} (DMSO-d₆) 7.55 (1H, t, *J* 4.9 Hz), 7.34 (2H, s), 2.91 (2H, d, *J* 5.1 Hz), 0.96 (6H, s). Some exchangeable protons were not observed. LCMS (ES+) 211.0 (M+H)⁺.

15

INTERMEDIATE 71**2-Bromo-7,7-dimethyl-5,6,7,8-tetrahydro-4H-[1,3]thiazolo[5,4-c]azepin-4-one**

The *title compound* was prepared from Intermediate 70 according to Method C
20 and was isolated as a yellow solid (84%) that required no further purification. δ_{H} (DMSO-d₆) 8.29 (1H, br. s), 2.98 (2H, d, *J* 5.2 Hz), 2.89 (s, 2H), 0.99 (s, 6H). LCMS (ES+) 277.0 and 275.0 (M+H)⁺.

INTERMEDIATE 72

25

4-Benzyl-3-(iodomethyl)morpholine

A solution of Intermediate 59 (0.10 g, 0.49 mmol), PPh₃ (0.10 g, 0.49 mmol) and imidazole (0.03 g, 0.49 mmol) in DCM (5 mL) was stirred at 0°C for 5 minutes. I₂ (0.12 g, 0.47 mmol) was added portionwise and stirring was continued at 0°C for 2.5 h. The
30 reaction mixture was then concentrated *in vacuo* and purified by column chromatography (SiO₂, 7:3 hexanes/EtOAc) to give the *title compound* as a white solid (0.12 g, 77%). δ_{H} (CDCl₃) 7.53-7.17 (5H, m), 3.85 (1H, d, *J* 13.1 Hz), 3.72 (2H, m), 3.61 (2H, m), 3.35

(1H, m), 3.24 (2H, m), 2.59 (1H, m), 2.34 (1H, m), 2.21 (1H, m). LCMS (ES+) 317.9 (M+H)⁺.

INTERMEDIATE 73

5

N-(4-Methoxybenzyl)-D-serine

The *title compound* was prepared from D-serine (29.6 g, 0.3 mmol) and *p*-methoxybenzaldehyde (68.0 mL, 0.6 mmol) according to Method W and was obtained as a white solid (36.2 g, 57%) that required no further purification. δ_{H} (DMSO- d_6) 7.37 (2H, dd, *J* 8.7 and 1.9 Hz), 6.93 (2H, dd, *J* 8.7 and 1.9 Hz), 3.99 (2H, s), 3.55 (3H, s), 3.73 (3H, m), 3.15 (1H, t, *J* 4.7 Hz). Some exchangeable protons were not observed. LCMS (ES+) 225.8 (M+H)⁺.

10

INTERMEDIATE 74

15

(3R)-4-(4-Methoxybenzyl)-5-oxomorpholine-3-carboxylic acid

The *title compound* was prepared from Intermediate 73 (35.0 g, 159.0 mmol) according to Method X and was isolated as a white solid (17.0 g, 41%) that required no further purification. δ_{H} (DMSO- d_6) 7.20 (2H, d, *J* 8.6 Hz), 6.89 (2H, d, *J* 8.6 Hz), 5.19 (1H, d, *J* 15.5 Hz), 4.14-4.04 (3H, m), 3.88 (1H, m), 3.85 (1H, m), 3.83 (3H, s), 3.73 (1H, d, *J* 15.3 Hz). Exchangeable proton was not observed. LCMS (ES+) 266.2 (M+H)⁺.

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INTERMEDIATE 75

[(3S)-4-(4-Methoxybenzyl)morpholin-3-yl]methanol

The *title compound* was prepared from Intermediate 74 (17.7 g, 67.0 mmol) according to Method Y and was isolated as a white solid (14.0 g, 88%) that required no further purification. δ_{H} (CDCl₃) 7.25 (2H, d, *J* 8.6 Hz), 6.88 (2H, d, *J* 8.6 Hz), 4.12 (1H, d, *J* 13.1 Hz), 3.98 (1H, dd, *J* 11.5 and 4.4 Hz), 3.84 (1H, dd, *J* 11.6 and 3.9 Hz), 3.82 (3H, s), 3.75 (2H, m), 3.58 (2H, m), 3.26 (1H, d, *J* 13.1 Hz), 2.75 (1H, m), 2.57 (1H, br. m), 2.35 (1H, m). Exchangeable proton was not observed.

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INTERMEDIATE 76**2-Amino-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)propan-1-ol**

5 To a stirred solution of 3-(1H-pyrrolo[2,3-b]pyridin-3-yl)alanine monohydrate (10.0 g, 50.0 mmol) in THF (140 mL) at 0°C was slowly added BF₃.Et₂O complex (7.0 mL, 60.0 mmol) followed by BH₃.Me₂S complex (10M in THF, 14.5 mL, 145.0 mmol). The reaction mixture was stirred at r.t. for 16 h and on completion the excess borane was quenched by the addition of MeOH (5 mL) at 0°C. The reaction mixture was
10 concentrated, dissolved in EtOAc (120 mL) and washed with aqueous 20% NaOH solution (2 x 60 mL). The organic layer was then extracted into aqueous 2M HCl (2 x 150 mL). The combined acidic aqueous layers were then basified to pH 14 (addition of solid NaOH) and re-extracted with EtOAc (2 x 100 mL). The combined organic fractions were then dried over MgSO₄, filtered and concentrated *in vacuo* to give the *title*
15 *compound* as a white solid (4.9 g, 52%). δ_H (MeOD-d₃) 12.13 (1H, br. s), 8.97 (1H, dd, *J* 4.7 and 1.5 Hz), 8.06 (1H, s), 7.82 (1H, m), 4.12 (1H, dd, *J* 10.3 and 4.9 Hz), 4.01 (1H, dd, *J* 10.3 and 6.5 Hz), 3.75 (1H, m), 3.59 (1H, dd, *J* 14.0 and 5.5 Hz), 3.37 (1H, dd, *J* 14.0 and 7.3 Hz). Exchangeable protons were not observed.

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INTERMEDIATE 77**2-Chloro-N-[2-hydroxy-1-(1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]ethyl]acetamide**

To a stirred solution of Intermediate 76 (0.5 g, 2.6 mmol) in MeCN (9 mL) and MeOH (2 mL) at -10°C was added NEt₃ (0.4 mL, 3.1 mmol) followed by chloroacetyl
25 chloride (0.2 mL, 2.9 mmol) dropwise. The reaction mixture was allowed to warm to r.t. and stirred for 40 minutes. On completion, the reaction mixture was concentrated *in vacuo* and the resulting pink solid was triturated with water, filtered and dried to give the *title compound* as a white solid (0.5 g, 72%). δ_H (MeOD-d₃) 12.13 (1H, br. s), 8.97 (1H, dd, *J* 4.7 and 1.5 Hz), 8.93 (1H, d, *J* 8.2 Hz), 8.80 (1H, dd, *J* 7.8 and 1.3 Hz), 8.04 (1H, d, *J* 2.2 Hz), 7.83 (1H, dd, *J* 7.8 and 4.7 Hz), 5.65 (1H, t, *J* 5.6 Hz), 4.84 (2H, s), 4.76 (1H, m), 4.21 (2H, m), 3.73 (1H, dd, *J* 14.6 and 6.3 Hz), 3.59 (1H, dd, *J* 14.5 and 7.0 Hz).
30 LCMS (ES+) 268.1 (M+H)⁺.

INTERMEDIATE 78**5-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-ylmethyl)morpholin-3-one**

To a solution of potassium *tert*-butoxide (0.7 g, 2.2 mmol) in *tert*-amyl alcohol (4 mL) was added dropwise, at r.t., Intermediate 77 (0.4 g, 1.4 mmol) as a solution in *tert*-amyl alcohol (3 mL). The reaction mixture was stirred at r.t. for 16 h and was then concentrated *in vacuo* to give a white solid. To this was added Et₂O (2 mL) and water (2 mL) and the resultant solid was isolated by filtration and dried *in vacuo* to give the *title compound* as a white solid (0.3 g, 75%). δ_{H} (MeOD-*d*₃) 8.20 (1H, dd, *J* 4.8 and 1.5 Hz), 8.05 (1H, dd, *J* 7.8 and 1.5 Hz), 7.30 (1H, s), 7.11 (1H, dd, *J* 7.8 and 4.8 Hz), 4.10 (2H, s), 3.78 (2H, m), 3.64 (1H, m), 3.05 (2H, m). Exchangeable protons were not observed. LCMS (ES⁺) 232.1 (M+H)⁺.

INTERMEDIATE 79**3-(Morpholin-3-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridine**

Sodium bis(2-methoxyethoxy)aluminium dihydride (3.2 mL, 10.4 mmol, 65% wt solution in toluene) was added dropwise to a solution of Intermediate 78 (0.5 g, 2.1 mmol) in THF (10 mL) at 0°C. The reaction mixture was allowed to warm to r.t. and stirred for a further 5 h before it was quenched by the addition of aqueous sat. NaHCO₃ solution at 0°C. The precipitate formed on quenching was removed by filtration through Celite[®] and the filtrate was concentrated *in vacuo*. The resulting dark oil was purified by column chromatography (SiO₂, 1:9 MeOH/EtOAc) to give the *title compound* as a white solid (0.2 g, 42%). δ_{H} (CDCl₃) 9.59 (1H, br. s), 8.24 (1H, dd, *J* 4.8 and 1.4 Hz), 7.94 (1H, dd, *J* 7.9 and 1.4 Hz), 7.21 (1H, s), 7.07 (1H, dd, *J* 7.9 and 4.8 Hz), 3.92 (1H, dd, *J* 11.1 and 2.9 Hz), 3.82 (1H, m), 3.61 (1H, m), 3.38 (1H, dd, *J* 9.8 and 1.2 Hz), 3.15 (1H, m), 2.95 (2H, m), 2.85 (1H, dd, *J* 14.4 and 4.9 Hz), 2.72 (1H, dd, *J* 14.4 and 8.9 Hz), 2.55 (1H, br. s). LCMS (ES⁺) 218.0 (M+H)⁺.

INTERMEDIATE 80**(3*R*)-3-(Iodomethyl)-4-(4-methoxybenzyl)morpholine**

- 67 -

A solution of Intermediate 75 (0.20 g, 0.97 mmol), PPh₃ (0.25 g, 0.97 mmol) and imidazole (0.07 g, 0.97 mmol) in DCM (9 mL) was stirred at 0°C for 5 minutes. I₂ (0.25 g, 0.97 mmol) was added portionwise and stirring was continued at 0°C for 2.5 h. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography (SiO₂, 3:1 hexanes/EtOAc) to give the *title compound* as a white solid (0.22 g, 65%). δ_{H} (CDCl₃) 7.29 (2H, d, *J* 8.3 Hz), 6.89 (2H, d, *J* 8.3 Hz), 3.85 (1H, d, *J* 13.1 Hz), 3.82 (3H, s), 3.70 (2H, m), 3.59 (2H, m), 3.35 (1H, m), 3.24 (2H, m), 2.57 (1H, m), 2.35 (1H, m), 2.25 (1H, m).

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INTERMEDIATE 81**(3R)-4-(4-Methoxybenzyl)-3-[(phenylthio)methyl]morpholine**

To a stirred solution of thiophenol (0.07 mL, 0.71 mmol) in DMF (5 mL) was slowly added, at 0°C, NaH (0.03 g, 0.71 mmol, 60% dispersion in oil). The reaction mixture was allowed to stir at r.t. for 30 minutes before the temperature was lowered to 0°C again and Intermediate 80 (0.24 g, 0.71 mmol) was added slowly. The reaction mixture was then stirred at r.t. for 1.5 h before it was quenched by the addition of ice. EtOAc (20 mL) was added and this was then washed with water (30 mL) and brine (25 mL), dried (MgSO₄), filtered and concentrated to give the *title compound* as a yellow oil (0.17 g, 52%) that was used crude. LCMS (ES⁺) 330.3 (M+H)⁺.

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INTERMEDIATE 82**(3R)-3-[(Phenylthio)methyl]morpholine**

To a stirred solution of Intermediate 81 (0.17 g, 0.50 mmol) in MeCN (5 mL) and water (5 mL) was added Ce(NH₃)₄NO₂ (0.82 g, 1.50 mmol) and the reaction mixture was stirred at r.t. for 16 h. On completion, aqueous 10% HCl (10 mL) was added and this was then washed with Et₂O (2 x 10 mL). The aqueous layer was then basified to pH 9 with solid NaHCO₃ and extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried (MgSO₄), filtered and concentrated *in vacuo* to give the *title compound* as a yellow solid (0.09 g, 86%) that was used crude. LCMS (ES⁺) 209.8 (M+H)⁺.

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INTERMEDIATE 83**4-Benzyl-3-(phenoxymethyl)morpholine**

To a stirred solution of Intermediate 72 (1.27 g, 4.00 mmol) and Ag₂CO₃ (1.32 g, 4.80 mmol) in MeCN (50 mL) was added phenol (0.51 g, 4.80 mmol). The reaction mixture was then stirred at 60°C for 16 h in the absence of light. On completion the reaction mixture was partitioned between DCM (100 mL) and aqueous sat. NaHCO₃ solution (20 mL). The organic phase was then dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, DCM/hexanes) gave the *title compound* as an orange oil (0.77 g, 68%) which also contained 4-benzyl-6-phenoxy-1,4-oxazepane. LCMS (ES+) 284.2 (M+H)⁺.

INTERMEDIATE 84**2-Amino-3-(1-benzothien-3-yl)propan-1-ol**

The *title compound* was prepared from 3-(1-benzothien-3-yl)alanine according to Method D and was isolated as a white solid (89%) that required no further purification. δ_H (MeOD-d₃) 7.89 (2H, m), 7.35 (3H, m), 3.58 (1H, dd, *J* 10.7 and 4.6 Hz), 3.44 (1H, dd, *J* 10.7 and 6.5 Hz), 3.19 (1H, m), 3.05 (1H, m), 2.85 (1H, m). Exchangeable protons were not observed.

INTERMEDIATE 85**N-[2-(1-Benzothien-3-yl)-1-(hydroxymethyl)ethyl]-2-chloroacetamide**

The *title compound* was prepared from Intermediate 84 according to Method E and was isolated as a pink solid (91%) that was used crude. δ_H (CDCl₃) 7.92 (2H, m), 7.35 (2H, m), 7.24 (1H, s), 6.96 (1H, br. s), 4.36 (1H, m), 4.04 (1H, d, *J* 2.4 Hz), 3.71 (2H, m), 3.18 (2H, m). Exchangeable protons were not observed.

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INTERMEDIATE 86**5-(1-Benzothien-3-ylmethyl)morpholin-3-one**

The *title compound* was prepared from Intermediate 85 according to Method F and was isolated as a white solid (61%) that was used crude. δ_{H} (CDCl_3) 7.73 (1H, m), 7.61 (1H, m), 7.26 (2H, m), 7.05 (1H, s), 4.03 (2H, s), 3.65 (2H, m), 3.43 (1H, m), 2.95 (2H, m). Exchangeable proton was not observed.

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INTERMEDIATE 87

3-(1-Benzothien-3-ylmethyl)morpholine

The *title compound* was prepared from Intermediate 86 according to Method G and was isolated as a white solid (84%) after purification by column chromatography (SiO_2 , EtOAc). LCMS (ES+) 234.0 ($\text{M}+\text{H}$)⁺.

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INTERMEDIATE 88

N-{[4-(4-Methoxybenzyl)morpholin-3-yl]methyl}benzenesulfonamide

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To a stirred solution of benzenesulfonamide (0.14 g, 0.84 mmol) in DMF (5 mL) was added, at 0°C, NaH (0.04 g, 0.86 mmol, 60 % dispersion in mineral oil). The reaction mixture was then stirred for 30 minutes before the addition of Intermediate 113 (0.30 g, 0.86 mmol) in one portion. After stirring at r.t. for 45 minutes, the reaction was quenched by the addition of ice and partitioned between water (10 mL) and EtOAc (12 mL). The organic layer was washed with brine (10 mL), dried (MgSO_4), filtered and concentrated *in vacuo* to give a yellow oil. The *title compound* was obtained as a white solid (0.11 g, 34%) after purification by column chromatography (SiO_2 , 1:1 EtOAc/hexanes). LCMS (ES+) 376.9 ($\text{M}+\text{H}$)⁺.

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INTERMEDIATE 89

N-(Morpholin-3-ylmethyl)benzenesulfonamide

To a stirred solution of Intermediate 88 (0.30 g, 0.80 mmol) in a mixture of MeCN (6 mL) and water (6 mL) at r.t. was added $\text{Ce}(\text{NH}_3)_4\text{NO}_2$ (1.30 g, 2.39 mmol). After stirring for 16 h, 10% aqueous HCl (10 mL) was added and the solution was washed with Et_2O (2 x 20 mL). The aqueous layer was then basified to pH 9 with aqueous sat. NaHCO_3 solution and extracted with EtOAc (3 x 25 mL). The combined organic

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fractions were dried over MgSO_4 , filtered and concentrated *in vacuo* to give the *title compound* as a yellow oil (0.10 g, 49%) that was used crude. LCMS (ES+) 256.8 $(\text{M}+\text{H})^+$.

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INTERMEDIATE 90***tert*-Butyl 3-(hydroxymethyl)morpholine-4-carboxylate**

To a stirred solution of Intermediate 60 (4.50 g, 40.00 mmol) in DCM (100 mL) was added NEt_3 (5.50 mL, 0.04 mol) and di-*tert*-butyl dicarbonate (8.20 g, 40.00 mmol).
10 The reaction mixture was stirred at r.t. for 16 h and was then transferred to a separating funnel and washed with aqueous sat. NaHCO_3 (60 mL) and brine (50 mL). The organics were dried over MgSO_4 , filtered and concentrated *in vacuo* to give the *title compound* (6.50 g, 75%) as a colourless oil that required no further purification. δ_{H} (CDCl_3) 4.00 (1H, br. m), 3.94 (1H, d, J 11.9 Hz), 3.87-3.81 (3H, m), 3.74 (1H, br. d, J 13.3 Hz), 3.55
15 (1H, dd, J 11.9 and 3.5 Hz), 3.46 (1H, dt, J 12.1 and 3.1 Hz), 3.21 (1H, br. m), 2.05 (1H, br. s), 1.48 (9H, s).

INTERMEDIATE 91***tert*-Butyl 3-formylmorpholine-4-carboxylate**

To a stirred solution of oxalyl chloride (3.73 g, 2.56 mL, 29.00 mmol) in DCM (80 mL) at -78°C was added DMSO (4.93 g, 4.47 mL, 63.00 mmol) and, after 15 minutes, a solution of Intermediate 90 (5.70 g, 26.26 mmol) in DCM (50 mL) was added. The reaction mixture was then stirred at -78°C for a further 2 h. NEt_3 (13.12 g, 18.71 mL,
25 129.70 mmol) was added and the reaction mixture was stirred at -78°C for 30 minutes, warmed to r.t. and stirred for a further 1 h. The reaction mixture was then concentrated *in vacuo* and the residue partitioned between water (200 mL) and EtOAc (200 mL). The aqueous fraction was extracted with EtOAc (2 x 200 mL) and the combined organic fractions were washed with brine (300 mL), dried (MgSO_4), filtered and the solvents
30 removed *in vacuo* to give the *title compound* (4.80 g, 84%) as a pale yellow solid that was used crude. δ_{H} (CDCl_3) 9.58 (1H, s), 4.31 (2H, m), 3.62 (2H, br. m), 3.41 (1H, br. m), 3.11 (1H, br. s), 2.93 (1H, br. m), 1.40 (9H, s).

INTERMEDIATE 92 (METHOD Q)tert-Butyl 3-[1-benzothien-2-yl(hydroxy)methyl]morpholine-4-carboxylate

A stirred solution of benzothiophene (0.50 g, 2.32 mmol) in THF (15 mL) was cooled to -78°C and ⁿBuLi (1.6M in hexanes, 0.97 mL, 2.22 mmol) was added dropwise. After stirring at this temperature for 40 minutes, Intermediate 94 was added and the reaction mixture was allowed to warm to r.t.. After stirring for 1.5 h, the reaction was quenched with ice and partitioned between EtOAc (30 mL) and aqueous NH₄Cl (20 mL). The organic layer was washed with brine (15 mL), dried over MgSO₄, filtered and concentrated *in vacuo* into a yellow oil. The crude material was purified by column chromatography (SiO₂, 1.5:1 EtOAc/hexanes) to give the *title compound* (0.53 g, 65%) as a white solid. LCMS (ES+) 276.2 (M-*tert*-butoxide)⁺.

INTERMEDIATE 93 (METHOD R)tert-Butyl 3-(1-benzothien-2-yl{[(methylthio)carbonothioyl]oxy}methyl)morpholine-4-carboxylate

To a stirred solution of Intermediate 92 (0.40 g, 1.20 mmol) in THF (25 mL) at 0°C was added CS₂ (6.30 g, 5.00 mL, 83.00 mmol) followed by MeI (11.00 g, 5.00 mL, 81.00 mmol). After stirring for 15 minutes, NaH (0.10 g, 2.50 mmol, 60% dispersion in mineral oil) was added slowly and the reaction mixture was stirred at 0°C for 20 minutes. The reaction mixture was then quenched with ice and partitioned between EtOAc (30 mL) and water (25 mL). The organic layer was washed with brine (20 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to give a dark oil. The crude product was purified by column chromatography (SiO₂, 6:1 hexanes/EtOAc) to give the *title compound* (0.31 g, 62%) as a white solid. LCMS (ES+) 350.3 (M- *tert*-butyl)⁺.

INTERMEDIATE 94 (METHOD S)tert-Butyl 3-(1-benzothien-2-ylmethyl)morpholine-4-carboxylate

To a stirred solution of Intermediate 93 (0.16 g, 0.40 mmol) in toluene (12 mL) was added Bu₃SnH (0.58 g, 0.54 mL, 2.00 mmol) and 2,2'-azobis(2-methylpropionitrile) (0.01 g, 0.02 mmol). The reaction mixture was heated to reflux for 1 h and on completion

- 72 -

was cooled and concentrated *in vacuo* to a yellow oil. The tin by-products were removed by column chromatography (SiO₂, hexanes) followed by purification of the crude material (SiO₂, 4:1 hexanes/EtOAc) to give the *title compound* (0.07 g, 51%) as a white solid. δ_{H} (CDCl₃) 7.68 (1H, dd, *J* 8.0 and 1.1 Hz), 7.58 (1H, dd, *J* 6.8 and 1.4 Hz), 7.22 (2H, m),
5 7.01 (1H, s), 4.13 (1H, br. s), 3.82 (2H, m), 3.73 (1H, d, *J* 11.6 Hz), 3.42 (2H, dd, *J* 11.9 and 2.9 Hz), 3.27 (1H, dd, *J* 14.2 and 8.7 Hz), 3.18 (1H, dd, *J* 13.1 and 3.7 Hz), 3.07 (1H, dd, *J* 14.2 and 6.4 Hz), 1.29 (9H, s).

INTERMEDIATE 95 (METHOD T)

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3-(1-Benzothien-2-ylmethyl)morpholine hydrochloride

To Intermediate 94 (0.07 g, 0.20 mmol) was added a solution of 4M HCl in 1,4-dioxane (5.00 mL, 0.60 mmol) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then concentrated *in vacuo* to give the *title compound*
15 (0.05 g, 97%) as a white solid. LCMS (ES+) 234.2 (M+H)⁺.

INTERMEDIATE 96

tert-Butyl 3-[hydroxy(isoquinolin-4-yl)methyl]morpholine-4-carboxylate

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The *title compound* was prepared from Intermediate 91 and 4-bromoisoquinoline according to Method Q and was isolated as a white solid (54%) after purification by column chromatography (SiO₂, 1:1 DCM/EtOAc). LCMS (ES+) 345.5 (M+H)⁺.

INTERMEDIATE 97

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tert-Butyl 3-(isoquinolin-4-yl{[(methylthio)carbonothioyl]oxy}methyl)morpholine-4-carboxylate

The *title compound* was prepared from Intermediate 96 according to Method R and was isolated as a white solid (51%) after purification by column chromatography
30 (SiO₂, 1:1 DCM/EtOAc). LCMS (ES+) 435.5 (M+H)⁺.

INTERMEDIATE 98

tert-Butyl 3-(isoquinolin-4-ylmethyl)morpholine-4-carboxylate

The *title compound* was prepared from Intermediate 97 according to Method S and was isolated as a white solid (76%) after purification by column chromatography (SiO₂, hexanes followed by 2:1 DCM/EtOAc). LCMS (ES+) 329.5 (M+H)⁺.

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INTERMEDIATE 99

4-(Morpholin-3-ylmethyl)isoquinoline dihydrochloride

The *title compound* was prepared from Intermediate 98 according to Method T and was isolated as a white solid (96%) that required no further purification. LCMS (ES+) 229.0 (M+H)⁺.

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INTERMEDIATE 100

tert-Butyl 3-[hydroxy(quinolin-5-yl)methyl]morpholine-4-carboxylate

The *title compound* was prepared from Intermediate 91 and 5-bromoquinoline according to Method Q and was isolated as a white solid (34%) after purification by column chromatography (SiO₂, 1:2 hexanes/EtOAc). LCMS (ES+) 345.2 (M+H)⁺.

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INTERMEDIATE 101

tert-Butyl 3-[[[(methylthio)carbonothioyl]oxy}(quinolin-5-yl)methyl]morpholine-4-carboxylate

The *title compound* was prepared from Intermediate 100 according to Method R and was isolated as a white solid (70%) after purification by column chromatography (SiO₂, DCM). LCMS (ES+) 435.4 (M+H)⁺.

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INTERMEDIATE 102

tert-Butyl 3-(quinolin-5-ylmethyl)morpholine-4-carboxylate

The *title compound* was prepared from Intermediate 101 according to Method S and was isolated as a white solid (98%) after purification by column chromatography (SiO₂, hexanes followed by DCM). LCMS (ES+) 329.2 (M+H)⁺.

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INTERMEDIATE 1035-(Morpholin-3-ylmethyl)quinoline dihydrochloride

5 The *title compound* was prepared from Intermediate 102 according to Method T and was isolated as a white solid (98%) that required no further purification. LCMS (ES+) 229.2 (M+H)⁺.

INTERMEDIATE 104

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tert-Butyl 3-[hydroxy(quinolin-8-yl)methyl]morpholine-4-carboxylate

 The *title compound* was prepared from Intermediate 91 and 8-bromoquinoline according to Method Q and was isolated as a white solid (41%) after purification by column chromatography (SiO₂, 1:1 DCM/EtOAc). LCMS (ES+) 345.4 (M+H)⁺.

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INTERMEDIATE 105tert-Butyl 3-[[[(methylthio)carbonothioyl]oxy}(quinolin-8-yl)methyl]morpholine-4-carboxylate

20 The *title compound* was prepared from Intermediate 104 according to Method R and was isolated as a white solid (86%) after purification by column chromatography (SiO₂, 4:1 DCM/EtOAc). LCMS (ES+) 435.4 (M+H)⁺.

INTERMEDIATE 106

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tert-Butyl 3-(quinolin-8-ylmethyl)morpholine-4-carboxylate

 The *title compound* was prepared from Intermediate 105 according to Method S and was isolated as a white solid (76%) after purification by column chromatography (SiO₂, hexanes followed by 2:1 DCM/EtOAc). LCMS (ES+) 329.2 (M+H)⁺.

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INTERMEDIATE 1078-(Morpholin-3-ylmethyl)quinoline dihydrochloride

The *title compound* was prepared from Intermediate 106 according to Method T and was isolated as a white solid (96%) that required no further purification. LCMS (ES+) 229.2 (M+H)⁺.

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INTERMEDIATE 108

Tetrahydro-3H-[1,2,3]oxathiazolo[4,3-c][1,4]oxazine 1,1-dioxide

To a stirred solution of Intermediate 60 (0.50 g, 4.27 mmol) in DCM (5 mL) was added pyridine (0.68 g, 0.98 mL, 8.54 mmol) and the solution was cooled to -70°C. At this temperature was added sulphuryl chloride (0.58 g, 0.34 mL, 4.27 mmol) dissolved in DCM (5 mL) dropwise. The reaction mixture was stirred at this temperature for 1 h and at -10°C for a further hour before being quenched by the addition of water (12 mL) and hexanes (30 mL). After extraction with DCM (2 x 20 mL), the combined organic fractions were washed with brine (2 x 15 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to give the *title compound* as a colourless solid (0.52 g, 69%). δ_{H} (CDCl₃) 4.51 (1H, dd, *J* 8.1 and 6.4 Hz), 4.23 (1H, dd, *J* 9.1 and 8.1 Hz), 3.95 (1H, dd, *J* 11.6 and 3.4 Hz), 3.84-3.64 (3H, m), 3.54 (1H, dd, *J* 11.6 and 7.7 Hz), 3.29 (1H, dt, *J* 12.0 and 3.4 Hz), 3.06 (1H, m).

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INTERMEDIATE 109

3-[(6-Bromopyridin-2-yl)methyl]morpholine

To a stirred solution of 2,6-dibromopyridine (0.40 g, 1.68 mmol) in THF (3.5 mL) at -78°C was added ⁿBuLi (1.05 mL, 1.68 mmol, 1.60 M in hexanes) dropwise. After stirring at this temperature for 1 h, a solution of Intermediate 108 (0.25 g, 1.40 mmol) dissolved in THF (3 mL) was added slowly and the reaction mixture was allowed to warm to r.t.. After stirring at r.t. for 16 h, the reaction mixture was quenched by the addition of water (a few drops) and the solvent was removed *in vacuo*. To the resultant dark oil were added aqueous HCl (2M, 3 mL) and EtOH (3 mL) and the reaction mixture was heated to reflux overnight. After cooling, the solvent was removed by evaporation *in vacuo* and DCM (20 mL) and aqueous sat. NaHCO₃ solution (10 mL) were added. After extraction with DCM (3 x 20 mL), the combined organics were concentrated *in vacuo* to give a dark oil. The crude material was purified by column chromatography (SiO₂, Chromabond[®]

Flash FM 70/20 NH₂ column, DCM) to give the *title compound* as a white solid (0.14 g, 38%). LCMS (ES+) 257.1 and 259.1 (M+H)⁺.

INTERMEDIATE 110

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N-(4-Methoxybenzyl)serine

The *title compound* was prepared from serine (29.6 g, 0.3 mmol) and *p*-methoxybenzaldehyde (68.0 mL, 0.6 mmol) according to Method W and was obtained as a white solid (36.2 g, 59%) that was used crude. δ_{H} (DMSO-d₆) 7.37 (2H, dd, *J* 8.7 and 1.9 Hz), 6.93 (2H, dd, *J* 8.7 and 1.9 Hz), 3.99 (2H, s), 3.55 (3H, s), 3.73 (3H, m), 3.15 (1H, t, *J* 4.7 Hz). Not all exchangeable protons were observed.

10

INTERMEDIATE 111

15 4-(4-Methoxybenzyl)-5-oxomorpholine-3-carboxylic acid

The *title compound* was prepared from Intermediate 110 (35.0 g, 159.0 mmol) according to Method X and was isolated as a white solid (17.0 g, 42%) that was used crude. δ_{H} (DMSO-d₆) 7.20 (2H, d, *J* 8.6 Hz), 6.89 (2H, d, *J* 8.6 Hz), 5.19 (1H, d, *J* 15.5 Hz), 4.04-4.14 (3H, m), 3.85 (1H, m), 3.88 (1H, m), 3.73 (3H, s), 3.83 (1H, d, *J* 15.3 Hz). Exchangeable proton was not observed. LCMS (ES+) 266.2 (M+H)⁺.

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INTERMEDIATE 112

[4-(4-Methoxybenzyl)morpholin-3-yl]methanol

The *title compound* was prepared from Intermediate 111 (17.7 g, 67.0 mmol) according to Method Y and was isolated as a white solid (14.0 g, 88%) that required no further purification. δ_{H} (CDCl₃) 7.25 (2H, d, *J* 8.6 Hz), 6.88 (2H, d, *J* 8.6 Hz), 4.12 (1H, d, *J* 13.1 Hz), 3.98 (1H, dd, *J* 11.5 and 4.4 Hz), 3.84 (1H, dd, *J* 11.6 and 3.9 Hz), 3.82 (3H, s), 3.75 (2H, m), 3.58 (2H, m), 3.26 (1H, d, *J* 13.1 Hz), 2.75 (1H, m), 2.57 (1H, br. m), 2.35 (1H, m). The exchangeable proton was not observed.

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INTERMEDIATE 113

3-(Iodomethyl)-4-(4-methoxybenzyl)morpholine

A solution of Intermediate 112 (0.20 g, 0.97 mmol), PPh₃ (0.25 g, 0.97 mmol) and imidazole (0.07 g, 0.97 mmol) in DCM (9 mL) was stirred at 0°C for 5 minutes. I₂ (0.25 g, 0.97 mmol) was added portionwise and stirring was continued at 0°C for 2.5 h. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography (SiO₂, 3:1 hexanes/EtOAc) to give the *title compound* as a white solid (0.22 g, 71%). δ_{H} (CDCl₃) 7.29 (2H, d, *J* 8.3 Hz), 6.89 (2H, d, *J* 8.3 Hz), 3.85 (1H, d, *J* 13.1 Hz), 3.82 (3H, s), 3.70 (2H, m), 3.59 (2H, m), 3.35 (1H, m), 3.24 (2H, m), 2.57 (1H, m), 2.35 (1H, m), 2.25 (1H, m).

INTERMEDIATE 114N-Benzyl-D-serine

The *title compound* was prepared from D-serine and benzaldehyde according to Method W and was obtained as a white solid (88%) that was used crude. δ_{H} (DMSO-d₆) 7.45-7.30 (5H, m), 4.04-3.91 (2H, m), 3.70-3.61 (3H, m), 3.17 (1H, t, *J* 5.8 Hz). Not all exchangeable protons were observed.

INTERMEDIATE 115(3R)-4-Benzyl-5-oxomorpholine-3-carboxylic acid

The *title compound* was prepared from Intermediate 114 according to Method X and was isolated as a white solid (43%) that was used crude. δ_{H} (DMSO-d₆) 13.51-12.53 (1H, br. s), 7.38-7.25 (5H, m), 5.27 (1H, d, *J* 15.3 Hz), 4.24-4.10 (3H, m), 3.94-3.88 (2H, m), 3.83 (1H, d, *J* 15.3 Hz). LCMS (ES⁺) 236.0 (M+H)⁺.

INTERMEDIATE 116[(3S)-(4-Benzylmorpholin-3-yl)]methanol

The *title compound* was prepared from Intermediate 115 according to Method Y and was isolated as a colourless oil (87%) that required no further purification. δ_{H} (CDCl₃) 7.29-7.16 (5H, m), 4.05 (1H, d, *J* 12.8 Hz), 3.88 (1H, dd, *J* 11.5 and 4.5 Hz),

3.78 (1H, m), 3.70-3.53 (2H, m), 3.51-3.40 (2H, m), 3.20 (1H, d, J 13.2 Hz), 2.68 (1H, dt, J 12.1 and 2.8 Hz), 2.48 (1H, m), 2.27 (1H, m), 2.20-2.15 (1H, br. s).

INTERMEDIATE 117

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(3S)-Morpholin-3-ylmethanol

To a nitrogen flushed solution of Intermediate 116 (10.0 g, 48.3 mmol) in MeOH (300 mL) was added 10 wt % palladium on carbon (2.0 g) and the reaction mixture placed in a Parr[®] apparatus under 50 psi of hydrogen for 18 h. The resulting mixture was then
10 filtered through Celite[®] and concentrated *in vacuo* to give the *title compound* as a clear oil (5.2 g, 92%). δ_{H} (CDCl₃) 3.81-3.76 (2H, m), 3.58-3.43 (3H, m), 3.35-3.28 (1H, m), 2.99-2.91 (5H, br. m). LCMS (ES+) 118.0 (M+H)⁺.

INTERMEDIATE 118

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Ethyl N-(tert-butoxycarbonyl)-5-hydroxy-L-tryptophanate

To a stirred solution of ethyl 5-hydroxy-L-tryptophanate hydrochloride (23.5 g, 82.6 mmol) in DCM (500 mL) was added NEt₃ (25.4 g, 35.0 mL, 247.8 mmol) and di-*tert*-butyl dicarbonate (18.0 g, 82.6 mmol). The reaction mixture was stirred for 3 h at r.t.
20 and then partitioned with water (250 mL). The organic layer was washed with brine (200 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give the *title compound* as a cream solid (28.1 g, 98%) that required no further purification. δ_{H} (DMSO-d₆) 10.50 (1H, br. s), 8.58 (s, 1H), 7.14-7.05 (3H, m), 6.79 (1H, d, J 2.2 Hz), 6.59 (1H, dd, J 8.6 and 2.3 Hz), 5.75-3.99 (3H, s), 3.03-2.86 (2H, m), 1.35 (9H, s), 1.11 (3H, t, J 6.1 Hz). LCMS
25 (ES+) 349.0 (M+H)⁺.

INTERMEDIATE 119

Ethyl 5-(benzyloxy)-N-(tert-butoxycarbonyl)-L-tryptophanate

30 To a stirred solution of Intermediate 118 (5.4 g, 15.6 mmol) in MeCN (200 mL) was added Cs₂CO₃ (5.6 g, 17.1 mmol) and benzyl bromide (2.2 g, 2.0 mL, 17.1 mmol). The reaction mixture was stirred at 90°C for 2.5 h, cooled and then stirred at r.t. for 48 h. After removal of the solvent *in vacuo*, the reaction mixture was partitioned between DCM

- 79 -

(200 mL) and water (150 mL). The organic fraction was dried (MgSO₄), filtered and concentrated *in vacuo* to give a brown oil. To this crude material was added Et₂O (50 mL) and a solid precipitated out to give the *title compound* as a white solid (4.2 g, 59%). δ_{H} (DMSO-d₆) 10.68 (1H, br. s), 7.50-7.30 (7H, m), 7.23 (1H, d, *J* 8.7 Hz), 7.12 (1H, br. s), 6.79 (1H, dd, *J* 8.7 and 2.4 Hz), 5.09 (2H, s), 4.20-4.11 (1H, m), 4.09-4.00 (2H, m), 3.09-2.92 (2H, m), 1.33 (9H, s), 1.12 (3H, t, *J* 7.1 Hz). LCMS (ES+) 461.0 (M+H)⁺.

INTERMEDIATE 120

10 Ethyl 5-(benzyloxy)-L-tryptophanate hydrochloride

The *title compound* was prepared from Intermediate 119 according to Method T and was isolated as a white solid (96%) that required no further purification. δ_{H} (DMSO-d₆) 10.90 (1H, br. s), 8.47 (3H, br. s), 7.49-7.26 (6H, m), 7.19 (2H, d, *J* 2.0 Hz), 6.83 (1H, dd, *J* 8.7 and 2.3 Hz), 5.10 (2H, s), 4.20 (1H, t, *J* 6.2 Hz), 4.10 (2H, dd, *J* 14.3 and 7.1 Hz), 3.26-3.22 (2H, m), 1.12 (3H, t, *J* 7.1 Hz). LCMS (ES+) 339.0 (M+H)⁺.

INTERMEDIATE 121

(2S)-2-Amino-3-[5-(benzyloxy)-1H-indol-3-yl]propan-1-ol

20 To a stirred solution of Intermediate 120 (3.30 g, 8.90 mmol) in THF (30 mL), at -10°C, was slowly added LiAlH₄ (1.00 g, 26.70 mmol). The reaction mixture was allowed to warm to r.t. and stirred for 2 h before being quenched, at 0°C, by the dropwise addition of aqueous sat. NaHCO₃. After filtration through Celite[®], the filtrate was partitioned between EtOAc (50 mL) and water (35 mL). The organic layer was washed
25 with brine (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give the *title compound* (2.31 g, 88%) as an orange oil that required no further purification. δ_{H} (DMSO-d₆) 10.63 (1H, br. s), 7.50-7.29 (7H, m), 7.23 (1H, d, *J* 8.7 Hz), 7.11 (1H, dd, *J* 13.3 and 2.2 Hz), 6.79 (1H, dd, *J* 8.7 and 2.4 Hz), 5.08 (2H, s), 4.50 (1H, br. s), 3.37-3.18 (2H, m), 2.99-2.91 (1H, m), 2.74 (1H, dd, *J* 14.1 and 5.7 Hz), 2.54 (1H, d, *J* 7.2 Hz), 1.77
30 (1H, br. s). LCMS (ES+) 297.0 (M+H)⁺.

INTERMEDIATE 122

N-[(1S)-2-[5-(Benzyloxy)-1H-indol-3-yl]-1-(hydroxymethyl)ethyl]-2-chloroacetamide

The *title compound* was prepared from Intermediate 121 according to Method E and was isolated as an orange oil (99%) that was used crude. LCMS (ES+) 373.0 (M+H)⁺.

5

INTERMEDIATE 123(5S)-5-{[5-(Benzyloxy)-1H-indol-3-yl]methyl}morpholin-3-one

The *title compound* was prepared from Intermediate 122 according to Method F and was isolated as a brown foam (93%) that was used crude. LCMS (ES+) 337.0 (M+H)⁺.

10

INTERMEDIATE 1245-(Benzyloxy)-3-[(3S)-morpholin-3-ylmethyl]-1H-indole

The *title compound* was prepared from Intermediate 123 according to Method G and was isolated as a brown foam (84%) that was used crude. LCMS (ES+) 323.0 (M+H)⁺.

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20

INTERMEDIATE 1253-[(3S)-Morpholin-3-ylmethyl]-1H-indol-5-ol

To a nitrogen purged stirred solution of Intermediate 124 (2.00 g, 6.20 mmol) in AcOH (120 mL) was added a slurry of 10 wt % palladium on carbon (0.50 g suspended in IPA). The reaction mixture was stirred at 100°C under 100 bar of hydrogen for 16 h. The reaction mixture was then filtered through Celite[®] and the solvents removed *in vacuo* to give the *title compound* (0.70 g, 50%) as a white solid. LCMS (ES+) 233.0 (M+H)⁺.

25

INTERMEDIATE 126

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(3aR)-Tetrahydro-3H-[1,2,3]oxathiazolo[4,3-c][1,4]oxazine 1,1-dioxide

To a stirred solution of Intermediate 117 (0.50 g, 4.27 mmol) in DCM (5 mL) was added pyridine (0.68 g, 0.98 mL, 8.54 mmol) and the solution was cooled to -70°C. At

- 81 -

this temperature was added a solution of sulphuryl chloride (0.58 g, 0.34 mL, 4.27 mmol) in DCM (5 mL) dropwise. The reaction mixture was stirred at this temperature for 1 h, and then at -10°C for a further hour, before it was quenched by the addition of water (12 mL) and hexanes (30 mL). After extraction with DCM (2 x 20 mL), the combined
5 organic fractions were washed with brine (2 x 15 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give the *title compound* as a colourless solid (0.52 g, 69%). δ_{H} (CDCl₃) 4.51 (1H, dd, *J* 8.1 and 6.4 Hz), 4.23 (1H, dd, *J* 9.1 and 8.1 Hz), 3.95 (1H, dd, *J* 11.6 and 3.4 Hz), 3.84-3.64 (3H, m), 3.54 (1H, dd, *J* 11.6 and 7.7 Hz), 3.29 (1H, dt, *J* 12.0 and 3.4 Hz), 3.06 (1H, m).

10

INTERMEDIATE 127

(3S)-3-(3-Phenylprop-2-yn-1-yl)morpholine

To a stirred solution of Intermediate 126 (0.11 g, 0.60 mmol) and TMEDA (0.30
15 mL) in THF (3 mL) was added, at -78°C, lithium phenylacetylide (0.72 mL, 0.72 mmol) dropwise. After stirring for 3 h at r.t. the reaction mixture was quenched by the dropwise addition of water (a few drops) and then concentrated *in vacuo*. The resultant crude material was dissolved in MeOH (3 mL) and aqueous 10% HCl (1 mL) and the reaction mixture was stirred for 16 h at r.t. and for 2 h at 80°C. The solvent was then removed by
20 evaporation *in vacuo*. To the resultant crude material was added DCM (20 mL) and the solution was basified by addition of aqueous sat. NaHCO₃ solution (10 mL). After extraction with DCM (3 x 20 mL), the combined organic fractions were dried (MgSO₄), filtered and concentrated *in vacuo* to give the *title compound* as a dark oil (0.05 g, 42%) which was used crude. LCMS (ES+) 202.0 (M+H)⁺.

25

INTERMEDIATE 128 (METHOD AA)

1-[(3S)-Morpholin-3-ylmethyl]-1H-benzotriazole

To a stirred solution of Intermediate 126 (0.25 g, 1.40 mmol) in MeCN (5 mL)
30 was added benzotriazole (0.36 g, 3.00 mmol). The reaction mixture was stirred at 60°C for 6 h, cooled and then concentrated *in vacuo*. The resulting residue was dissolved in a mixture of EtOH (3 mL) and 10% aqueous HCl (3 mL). The reaction mixture was then stirred at 80°C for 2 h and after cooling the solvent was removed by evaporation *in vacuo*.

To the resultant crude material was added DCM (20 mL) and the solution was basified by addition of aqueous sat. NaHCO₃ solution (10 mL). After extraction with DCM (3 x 20 mL), the combined organics were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, Chromabond[®] Flash FM 70/20 NH₂ column, 0-5% MeOH/DCM) yielded the *title compound* (0.12 g, 37%) as a pale yellow solid. LCMS (ES+) 219.1 (M+H)⁺.

INTERMEDIATE 129

10 1-[(3*S*)-Morpholin-3-ylmethyl]-1*H*-benzimidazole

The *title compound* was prepared from Intermediate 126 and benzimidazole according to Method AA, to give a pale yellow gum (0.06 g, 19%) that was used crude. LCMS (ES+) 218.1 (M+H)⁺.

15 INTERMEDIATE 130 (METHOD AC)

[4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-2-yl]acetic acid

To a stirred solution of 2-morpholineacetic acid (0.10 g, 0.69 mmol) and Intermediate 15 (0.18 g, 0.69 mmol) in THF (4 mL) was added DIPEA (0.18 g, 1.38 mmol) and the mixture was heated under microwave irradiation in a sealed tube to 120°C for 1 h. The reaction mixture was then concentrated *in vacuo*. Purification by preparative HPLC gave the *title compound* (0.07 g, 33%) as a white solid. δ_H (CDCl₃) 4.10 (3H, m), 3.80 (2H, m), 3.30 (1H, m), 3.10 (1H, m), 2.70-2.60 (4H, m), 2.40 (2H, s), 1.10 (6H, s). Exchangeable proton was not observed. LCMS (ES+) 325.0 (M+H)⁺.

INTERMEDIATE 131

30 2-{[4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione

The *title compound* was prepared from 2-(1,4-oxazinan-2-ylmethyl)-1*H*-isoindole-1,3-(2*H*)-dione and Intermediate 15 according to Method AC and was isolated as a white solid (81%) after purification by preparative HPLC. δ_H (CDCl₃) 7.90 (2H, m), 7.71 (2H,

m), 4.15-3.90 (4H, m), 3.80-3.60 (3H, m), 3.35 (1H, m), 3.10 (1H, m), 2.70 (2H, s), 2.40 (2H, s), 1.10 (6H, s). LCMS (ES+) 426.0 (M+H)⁺.

EXAMPLE 1

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2-(Morpholin-4-yl)-4H-spiro[1,3-benzothiazole-5,1'-cyclopentan]-7(6H)-one

To a stirred solution of spiro[4,5]decane-7,9-dione (1.03 g, 6.2 mmol) in AcOH (10 mL) was added bromine (0.99 g, 0.32 mL, 6.2 mmol) dropwise. The reaction mixture was stirred for 2 h and then the product was isolated by filtration. The precipitate was
10 washed twice with Et₂O (100 mL) and then dried *in vacuo*. The crude product (0.44 g) was dissolved in THF (50 mL). Intermediate 13 (0.262 g, 1.8 mmol) and *N,N*-diisopropylethylamine (0.23 g, 0.31 mL, 1.8 mmol) were added. The reaction mixture was heated to 85°C for 2 h and then poured into NaHCO₃ solution (150 mL) and extracted with EtOAc (150 mL). The organic fraction was dried over MgSO₄ and
15 concentrated *in vacuo*. The crude product was subjected to column chromatography (SiO₂, EtOAc) to yield the *title compound* (0.03 g, 2%, 2 steps) as a white solid. δ_H (DMSO-d₆) 3.73-3.68 (4H, m), 3.59-3.48 (4H, m), 2.74 (2H, s), 2.42 (2H, s), 1.68-1.57 (4H, m), 1.57-1.38 (4H, m). LCMS (ES+) 293.0 (M+H)⁺.

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EXAMPLE 2 (METHOD B)

5-Isopropyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one

To a stirred solution of Intermediate 3 (1 g, 4.2 mmol) in THF (50 mL) was added Intermediate 13 (0.62 g, 4.2 mmol) and *N,N*-diisopropylethylamine (0.54 g, 0.73 mL, 4.2
25 mmol). The reaction mixture was heated to 85°C overnight and then poured onto NaHCO₃ solution (150 mL) and extracted with EtOAc (150 mL) twice. The organic fraction was dried over MgSO₄ and concentrated *in vacuo*. The solid was chromatographed (SiO₂, hexane-DCM) and then triturated with MeCN to yield the *title compound* (0.22 g, 19%) as a white solid. δ_H (DMSO-d₆) 3.69 (4H, d, *J* 5.2 Hz), 3.55
30 (4H, d, *J* 5.2 Hz), 2.80 (1H, dd, *J* 16.0 and 3.8 Hz), 2.55-2.23 (3H, m), 2.08-1.90 (1H, m), 1.69-1.58 (1H, m), 0.91 (6H, d, *J* 6.7 Hz). LCMS (ES+) 281.0 (M+H)⁺.

EXAMPLE 3**5-(4-Chlorophenyl)-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one**

To a stirred solution of Intermediate 6 (1 g, 3.3 mmol) in THF (50 mL) was added Intermediate 13 (0.48 g, 3.3 mmol) and *N,N*-diisopropylethylamine (0.54 g, 0.73 mL, 4.2 mmol). The reaction was carried out according to Method B to yield the *title compound* (1.1 g, 96%) as a white solid. δ_{H} (DMSO- d_6) 7.46-7.45 (4H, m), 3.75 (4H, d, *J* 5.3 Hz), 3.63 (4H, d, *J* 5.3 Hz), 3.06-3.04 (2H, m), 2.87 (1H, dd, *J* 6.2 and 1.9 Hz), 2.64-2.62 (1H, m), 2.56 (1H, bs). LCMS (ES+) 349.0 (M+H)⁺.

EXAMPLE 4**2-(Morpholin-4-yl)-5-phenyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one**

To a stirred solution of Intermediate 5 (0.27 g, 1 mmol) in THF (10 mL) was added Intermediate 13 (0.15 g, 1 mmol) and *N,N*-diisopropylethylamine (0.13 g, 0.17 mL, 1 mmol). The reaction was carried out according to Method B to yield the *title compound* (0.189 g, 60%) as a white solid. δ_{H} (DMSO- d_6) 7.40-7.16 (5H, m), 3.78-3.63 (4H, m), 3.62-3.43 (5H, m), 3.01 (2H, d, *J* 7.8 Hz), 2.82 (1H, dd, *J* 12.0 and 12.0 Hz), 2.57 (1H, dd, *J* 4.0 and 6.0 Hz). LCMS (ES+) 315.0 (M+H)⁺.

EXAMPLE 5**2-(Morpholin-4-yl)-4H-spiro[1,3-benzothiazole-5,1'-cyclohexan]-7(6H)-one**

To a stirred solution of Intermediate 12 (0.26 g, 1 mmol) in THF (10 mL) was added Intermediate 13 (0.15 g, 1 mmol) and *N,N*-diisopropylethylamine (0.13 g, 0.17 mL, 1 mmol). The reaction was carried out according to Method B to yield the *title compound* (0.09 g, 34%) as a white solid. δ_{H} (DMSO- d_6) 3.76-3.65 (4H, m), 3.60-3.50 (4H, m), 2.72 (2H, s), 2.38 (2H, s), 1.52-1.28 (10H, m). LCMS (ES+) 307.0 (M+H)⁺.

PREPARATIVE EXAMPLE 6**2-(Morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one**

To a stirred solution of Intermediate 1 (0.19 g, 1 mmol) in THF (10 mL) was added Intermediate 13 (0.15 g, 1 mmol) and *N,N*-diisopropylethylamine (0.13 g, 0.17 mL, 1 mmol). The reaction was carried out as for Method B to yield, after recrystallisation from Et₂O, the *title compound* (0.07 g, 28%) as a white solid. δ_{H} (DMSO-*d*₆) 3.78-3.68 (4H, m), 3.60-3.50 (4H, m), 2.74 (2H, d, *J* 6.1 Hz), 2.41 (2H, d, *J* 5.9 Hz), 2.02 (2H, quin, *J* 6.4 Hz). LCMS (ES+) 238.9 (M+H)⁺.

EXAMPLE 7

10 5-(4-Methoxyphenyl)-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a stirred solution of Intermediate 9 (1.0 g, 3.5 mmol) in THF (50 mL) was added Intermediate 13 (0.51 g, 3.5 mmol) and *N,N*-diisopropylethylamine (0.45 g, 0.61 mL, 3.5 mmol). The reaction was carried out according to Method B to yield the *title compound* (0.13 g, 10%) as a white solid. δ_{H} (DMSO-*d*₆) 7.29-7.27 (2H, m), 6.90-6.87 (2H, m), 3.73-3.69 (5H, m), 3.58-3.51 (4H, m), 3.49-3.40 (1H, m), 3.29 (3H, s), 2.98-2.95 (2H, m), 2.77 (1H, dd, *J* 16.3 and 11.9 Hz). LCMS (ES+) 345.0 (M+H)⁺.

EXAMPLE 8

20 2-(Morpholin-4-yl)-5-propyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a stirred solution of Intermediate 4 (0.23 g, 1 mmol) in THF (10 mL) was added Intermediate 13 (0.15 g, 1 mmol) and *N,N*-diisopropylethylamine (0.23 g, 0.17 mL, 1 mmol). The reaction was carried out according to Method B to yield, after recrystallisation from Et₂O, the *title compound* (0.06 g, 20%) as a white solid. δ_{H} (DMSO-*d*₆) 3.78-3.62 (4H, m), 3.60-3.50 (4H, m), 2.85 (1H, dd, *J* 1.3 and 5.7 Hz), 2.50-2.30 (2H, m), 2.32-2.10 (2H, m), 1.47-1.26 (4H, m), 0.99-0.80 (3H, m). LCMS (ES+) 281.0 (M+H)⁺.

EXAMPLE 9

30

5-Methyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a stirred solution of Intermediate 8 (0.21 g, 1 mmol) in THF (10 mL) was added Intermediate 13 (0.15 g, 1 mmol) and *N,N*-diisopropylethylamine (0.13 g, 0.17 mL,

1 mmol). The reaction was carried out according to Method B to yield, after recrystallisation from Et₂O, the *title compound* (0.05 g, 19%) as a white solid. δ_{H} (DMSO-d₆) 3.75-3.65 (4H, m), 3.59-3.50 (4H, m), 2.84 (1H, dd, *J* 4.3 and 16.8 Hz), 2.56-2.22 (4H, m), 1.06 (3H, d, *J* 6.0 Hz). LCMS (ES+) 253.0 (M+H)⁺.

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EXAMPLE 10

6,6-Dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one

To a stirred solution of Intermediate 7 (0.22 g, 1 mmol) in THF (10 mL) was added Intermediate 13 (0.15 g, 1 mmol) and *N,N*-diisopropylethylamine (0.23 g, 0.17 mL, 1 mmol). The reaction was carried out according to Method B to yield, after recrystallisation from Et₂O, the *title compound* (0.08 g, 29%) as a white solid. δ_{H} (DMSO-d₆) 3.75-3.65 (4H, m), 3.58-3.50 (4H, m), 2.78 (2H, t, *J* 6.2 Hz), 1.90 (2H, t, *J* 6.2 Hz), 1.08 (6H, s). LCMS (ES+) 267.0 (M+H)⁺.

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EXAMPLE 11

5-[4-(Methylthio)phenyl]-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one

To a stirred solution of Intermediate 10 (1.0 g, 3.1 mmol) in THF (30 mL) was added Intermediate 13 (0.46 g, 3.1 mmol) and *N,N*-diisopropylethylamine (0.40 g, 0.54 mL, 3.1 mmol). The reaction was carried out according to Method B to yield the *title compound* (0.65 g, 52%) as a white solid. δ_{H} (CDCl₃) 7.18-7.14 (4H, m), 3.76-3.72 (4H, m), 3.57-3.54 (4H, m), 3.47-3.33 (1H, m), 3.07 (1H, dd, *J* 17.0 and 4.5 Hz), 2.91-2.81 (1H, m), 2.79-2.66 (2H, m), 2.41 (3H, s). LCMS (ES+) 361.0 (M+H)⁺.

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EXAMPLE 12

5-(2-Furyl)-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one

To a stirred solution of Intermediate 11 (0.71 g, 2.7 mmol) in THF (30 mL) was added Intermediate 13 (0.40 g, 2.7 mmol) and *N,N*-diisopropylethylamine (0.35 g, 0.47 mL, 2.7 mmol). The reaction was carried out according to Method B to yield the *title compound* (0.19 g, 22%) as a white solid. δ_{H} (CDCl₃) 7.61 (1H, m), 6.43 (1H, d, *J* 4.9

30

Hz), 6.22 (1H, d, J 4.9 Hz), 3.77-3.70 (4H, m), 3.69-3.60 (5H, m), 3.21 (1H, dd, J 16.9 and 4.9 Hz), 3.06-3.01 (1H, m), 2.98-2.71 (2H, m). LCMS (ES+) 305.0 (M+H)⁺.

EXAMPLE 13

5

6-Methyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one

A solution of *N,N*-diisopropylamine (0.60 g, 0.83 mL, 5.9 mmol) in dry THF (5 mL) was cooled to -78°C and *n*-butyllithium (2.36 mL, 2.5M in hexane, 5.9 mmol) was added dropwise. The reaction mixture was allowed to warm to 0°C, stirred for 15
10 minutes and cooled to -78°C. A suspension of Example 6 (1.4 g, 5.9 mmol) in THF (5 mL) was added slowly. The reaction mixture was warmed to 0°C and stirred for 10 min at 0°C before dropwise addition of methyl iodide (0.84 g, 0.37 mL, 5.9 mmol). A solid formed immediately. The reaction mixture was allowed to warm slowly to r.t. The solid was filtered, washed with THF and then purified by column chromatography (SiO₂, 1:3
15 EtOAc/hexane) to give the *title compound* (0.20 g, 13%) as a white solid. δ_{H} (DMSO-*d*₆) 3.70 (4H, t, J 4.9 Hz), 3.54 (4H, t, J 4.9 Hz), 2.80-2.72 (2H, m), 2.55-2.45 (1H, m), 2.15-2.09 (1H, m), 1.82-1.72 (1H, m), 1.10 (3H, d, J 6.9 Hz). LCMS (ES+) 253.0 (M+H)⁺.

EXAMPLE 14 (METHOD H)

20

2-[(3R)-3-(1H-Indol-3-ylmethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

To a stirred solution of Intermediate 19 (1.4 g, 6.5 mmol) and Intermediate 15 (1.5 g, 5.9 mmol) in IPA (60 mL) was added *N,N*-diisopropylethylamine (0.76 g, 1.03 mL, 5.9
25 mmol) and the mixture was heated to 85°C for 16 h. The reaction mixture was concentrated *in vacuo*. Column chromatography (SiO₂, EtOAc) gave the *title compound* (1.1 g, 47%) as a solid. δ_{H} (CDCl₃) 8.22 (1H, s), 7.81 (1H, d, J 6.8 Hz), 7.28 (1H, m), 7.11 (2H, m), 7.02 (1H, d, J 2.3 Hz), 4.05 (2H, m), 3.82 (2H, m), 3.62 (2H, m), 3.44 (2H, m), 2.99 (1H, dd, J 13.7 and 4.0 Hz), 2.65 (2H, s), 2.34 (2H, s), 1.07 (6H, s). LCMS
30 (ES+) 396.0 (M+H)⁺. Chiral purity: 93.6% ee, RT 5.10 minutes.

EXAMPLE 15

5,5-Dimethyl-2-[3-(2-naphthylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Intermediate 23 and Intermediate 15 according to Method H and was isolated as a solid in 83% yield after purification by column chromatography (SiO₂, 1.5:1 hexane/EtOAc). δ_{H} (CDCl₃) 7.75 (3H, m), 7.66 (1H, s), 7.41 (3H, m), 4.04 (2H, m), 3.82 (1H, bs), 3.75 (1H, d, *J* 11.9 Hz), 3.60 (2H, m), 3.47 (1H, dd, *J* 10.8 and 2.0 Hz), 3.30 (1H, m), 3.05 (1H, dd, *J* 12.9 and 4.5 Hz), 2.61 (2H, d, *J* 3.1 Hz), 2.31 (2H, s), 1.04 (6H, s). LCMS (ES+) 407.0 (M+H)⁺.

EXAMPLE 16

5,5-Dimethyl-2-[3-(1-naphthylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Intermediate 27 and Intermediate 15 according to Method H and was isolated as a solid in 76% yield after purification by column chromatography (SiO₂, 1:1 hexane/EtOAc). δ_{H} (CDCl₃) 8.53 (1H, d, *J* 8.4 Hz), 7.88 (1H, d, *J* 8.0 Hz), 7.77 (1H, d, *J* 7.6 Hz), 7.22-7.68 (4H, m), 4.48 (1H, bs), 4.15 (1H, d, *J* 8.6 Hz), 3.75 (5H, m), 3.48 (2H, m), 2.75 (2H, d, *J* 3.1 Hz), 2.44 (2H, s), 1.18 (6H, s). LCMS (ES+) 407.0 (M+H)⁺.

EXAMPLE 17

5,5-Dimethyl-2-[3-(2-phenethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Intermediate 31 and Intermediate 15 according to Method H and was isolated as a solid in 74% yield. δ_{H} (CDCl₃) 7.20 (2H, m), 7.09 (3H, m), 3.85 (4H, m), 3.30-3.62 (3H, m), 2.63-2.45 (2H, m), 2.58 (2H, s), 2.30 (2H, s), 2.13 (2H, m), 1.05 (6H, s). LCMS (ES+) 371.0 (M+H)⁺.

EXAMPLE 18

2-[(3S)-3-Benzylmorpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Intermediate 34 and Intermediate 15 according to Method H and was isolated as a solid in 84% yield after purification by

column chromatography (SiO₂, 1:1 hexane/EtOAc). δ_{H} (CDCl₃) 7.29 (5H, m), 4.03 (1H, m), 3.95 (2H, bm), 3.81 (1H, d, *J* 11.9 Hz), 3.62 (3H, m), 3.21 (1H, dd, *J* 12.9 and 10.5 Hz), 2.95 (1H, dd, *J* 12.9 and 4.5 Hz), 2.70 (2H, s), 2.40 (2H, s), 1.13 (6H, s). LCMS (ES+) 357.0 (M+H)⁺.

5

EXAMPLE 19

5,5-Dimethyl-2-[(4a*S*,9a*R*)-2,3,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazin-4(4a*H*)-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

10 The *title compound* was prepared from Intermediate 37 and Intermediate 15 according to Method H and was isolated as a solid in 79% yield after purification by column chromatography (SiO₂, 1:1 hexane/EtOAc). δ_{H} (CDCl₃) 7.24 (2H, m), 7.14 (1H, t, *J* 7.6 Hz), 7.02 (1H, d, *J* 7.5 Hz), 5.33 (1H, bs), 4.41 (1H, t, *J* 3.9 Hz), 3.77 (1H, dd, *J* 11.0 and 2.5 Hz), 3.68 (1H, bs), 3.63 (1H, dt, *J* 11.6 and 2.4 Hz), 3.28 (1H, m), 3.06 (1H, 15 dd, *J* 16.6 and 4.0 Hz), 2.93 (1H, d, *J* 16.5 Hz), 2.65 (2H, s), 2.35 (2H, s), 1.09 (6H, s). LCMS (ES+) 355.0 (M+H)⁺.

EXAMPLE 20

20 2-[3-(4-Chlorobenzyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Intermediate 40 and Intermediate 15 according to Method H and was isolated as a solid in 87% yield after purification by column chromatography (SiO₂, 1:1 hexane/EtOAc). δ_{H} (CDCl₃) 7.24 (4H, m), 4.06 (2H, 25 m), 3.77 (2H, m), 3.61 (3H, m), 3.16 (1H, m), 2.93 (1H, dd, *J* 13.1 and 4.7 Hz), 2.68 (2H, s), 2.38 (2H, s), 1.12 (6H, s). LCMS (ES+) 391.0 (M+H)⁺.

EXAMPLE 21

30 5,5-Dimethyl-2-[3-(5-methyl-1*H*-indol-3-ylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Intermediate 44 and Intermediate 15 according to Method H and was isolated as a solid in 82% yield after purification by

column chromatography (SiO₂, 1:1 hexane/EtOAc). δ_{H} (CDCl₃) 10.71 (1H, s), 7.63 (1H, d, *J* 8.1 Hz), 7.10 (2H, m), 6.86 (1H, d, *J* 8.1 Hz), 4.16 (1H, bs), 3.98 (1H, d, *J* 8.0 Hz), 3.73 (2H, m), 3.57 (3H, m), 3.31 (1H, m), 2.90 (1H, m), 2.51 (2H, s), 2.49 (3H, s), 2.38 (2H, s), 1.05 (6H, s). LCMS (ES+) 410.0 (M+H)⁺.

5

EXAMPLE 22

5,5-Dimethyl-2-{3-[4-(morpholin-4-yl)benzyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4H)-one

10 To a mixture of Pd₂(dba)₃ (0.06 g, 0.06 mmol), 2-(di-*tert*-butylphosphino)biphenyl (0.08 g, 0.26 mmol), Example 20 (0.50 g, 1.28 mmol) and ^tBuONa (0.17 g, 1.79 mmol) was added toluene (3 mL) and morpholine (0.17 g, 1.92 mmol). The reaction mixture was stirred at 110°C for 16 h. EtOAc (50 mL) was added and the organic phase washed with brine (40 mL), dried over MgSO₄ and concentrated to give an oil. Purification by
15 column chromatography (SiO₂, 1:1 EtOAc/hexanes) gave the *title compound* (0.18 g, 31%) as a solid. δ_{H} (CDCl₃) 7.13 (2H, d, *J* 8.6 Hz), 6.81 (2H, d, *J* 8.6 Hz), 3.91 (2H, m), 3.78 (5H, m), 3.69 (1H, s), 3.50 (3H, m), 3.08 (5H, m), 2.78 (1H, dd, *J* 13.2 and 4.1 Hz), 2.63 (2H, s), 2.33 (2H, s), 1.06 (6H, s). LCMS (ES+) 442.2 (M+H)⁺.

20

EXAMPLE 23

2-(2,3-Dihydro-4H-1,4-benzoxazin-4-yl)-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

To a solution of 3,4-dihydro-2H-1,4-benzoxazine (0.19 g, 1.27 mmol) in
25 ethoxyethanol (5 mL) with one drop of conc. HCl was added Intermediate 15 (0.30 g, 1.15 mmol) and the reaction mixture was heated under microwave irradiation in a sealed tube to 160°C for 20 minutes. The reaction mixture was then poured into EtOAc (25 mL) and washed with brine (25 mL). The organic fraction was dried over MgSO₄ and concentrated *in vacuo* to give the *title compound* (0.26 g, 64%) as a colourless solid. δ_{H}
30 (CDCl₃) 7.83 (1H, dd, *J* 8.8 and 1.8 Hz), 7.01 (1H, m), 6.89 (2H, m), 4.27 (2H, m), 4.13 (2H, m), 2.69 (2H, s), 2.35 (2H, m), 1.07 (6H, s). LCMS (ES+) 315.0 (M+H)⁺.

EXAMPLE 24**5,5-Dimethyl-2-[3-(1*H*-indol-3-ylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one**

5 The *title compound* was prepared from Intermediate 48 and Intermediate 15 according to Method H and was isolated as a solid in 85% yield after purification by column chromatography (SiO₂, 1:1 hexane/EtOAc). δ_{H} (CDCl₃) 8.22 (1H, s), 7.81 (1H, d, *J* 6.8 Hz), 7.28 (1H, m), 7.11 (2H, m), 7.02 (1H, d, *J* 2.3 Hz), 4.05 (2H, m), 3.82 (2H, m), 3.62 (2H, m), 3.44 (2H, m), 2.99 (1H, dd, *J* 13.7 and 4.0 Hz), 2.65 (2H, s), 2.34 (2H, s), 1.07 (6H, s). LCMS (ES⁺) 396 (M+H)⁺.

10

EXAMPLE 25**15 5,5-Dimethyl-2-[(3*S*)-3-(1*H*-indol-3-ylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one**

 The *title compound* was prepared from Intermediate 52 and Intermediate 15 according to Method H and was isolated as a solid in 88% yield after purification by column chromatography (SiO₂, 1:1 hexane/EtOAc). δ_{H} (CDCl₃) 8.22 (1H, s), 7.81 (1H, d, *J* 6.8 Hz), 7.28 (1H, m), 7.11 (2H, m), 7.02 (1H, d, *J* 2.3 Hz), 4.05 (2H, m), 3.82 (2H, m), 3.62 (2H, m), 3.44 (2H, m), 2.99 (1H, dd, *J* 13.7 and 4.0 Hz), 2.65 (2H, s), 2.34 (2H, s), 1.07 (6H, s). LCMS (ES⁺) 396.0 (M+H)⁺. Chiral purity: 97.6% ee, RT 5.60 minutes.

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EXAMPLE 26**25 5,5-Dimethyl-2-{3-[(1-methyl-1*H*-indol-3-yl)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one**

 To a stirred solution of Example 24 (0.10 g, 0.25 mmol) in DMF (5 mL) at 0°C was added sodium hydride (0.01 g, 40% dispersion in oil, 0.28 mmol). After stirring at this temperature for 10 minutes, methyl iodide (0.02 mL, 0.28 mmol) was added. The reaction was stirred at r.t. for 1 h and then quenched by the addition of ice. The reaction mixture was then partitioned between EtOAc (15 mL) and water (10 mL) and the organic phase was dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 1:1 EtOAc/hexanes) gave the *title compound* (0.08 g, 79%) as a

30

white solid. δ_{H} (CDCl_3) 7.79 (1H, d, J 7.7 Hz), 7.09-7.24 (3H, m), 6.90 (1H, s), 4.05 (2H, m), 3.82 (1H, d, J 12.0 Hz), 3.79 (1H, bs), 3.68 (3H, s), 3.57 (2H, m), 3.41 (2H, m), 2.95 (1H, m), 2.67 (2H, s), 2.34 (2H, s), 1.11 (6H, s). LCMS (ES+) 410.0 ($\text{M}+\text{H}$)⁺.

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EXAMPLE 27

2-[(3*S*)-3-[(1-Acetyl-1*H*-indol-3-yl)methyl]morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a stirred solution of Example 25 (0.10 g, 0.25 mmol) in DCM (10 mL) was
10 added triethylamine (0.03 g, 0.04 mL, 0.28 mmol), acetic anhydride (0.03 g, 0.03 mL, 0.30 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at r.t. for 16 h before being diluted with DCM (50 mL) and washed with sat. NaHCO_3 solution (2 x 25 mL) and sat. brine (25 mL). The organic fraction was dried over MgSO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , 45:55 EtOAc/
15 hexanes) gave the *title compound* (0.05 g, 49%) as a white solid. δ_{H} (CDCl_3) 8.37 (1H, d, J 7.1 Hz), 7.82 (1H, dd, J 6.7 and 2.5 Hz), 7.32 (3H, m), 4.35 (1H, bs), 4.02 (1H, m), 3.82 (1H, d, J 11.9 Hz), 3.48-3.69 (4H, m), 3.31 (1H, m), 3.00 (1H, m), 2.66 (2H, d, J 3.3 Hz), 2.55 (3H, s), 2.34 (2H, s), 1.08 (6H, s). LCMS (ES+) 438.0 ($\text{M}+\text{H}$)⁺.

20

EXAMPLE 28

5,5-Dimethyl-2-(2-phenylmorpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Intermediate 15 and 2-phenylmorpholine according to Method H and was isolated as a solid in 81% yield after purification by
25 column chromatography (SiO_2 , 1:1 hexane/EtOAc). δ_{H} (CDCl_3) 7.41 (5H, m), 4.62 (1H, dd, J 10.7 and 2.8 Hz), 4.16 (1H, dd, J 11.0 and 2.8 Hz), 4.13 (1H, d, J 16.3 Hz), 3.95 (1H, d, J 16.0 Hz), 3.87 (1H, dd, J 12.0 and 2.9 Hz), 3.45 (1H, m), 3.21 (1H, m), 2.72 (2H, s), 2.41 (2H, s), 1.15 (6H, s). LCMS (ES+) 343.0 ($\text{M}+\text{H}$)⁺.

30

EXAMPLE 29

2-[3-(4-Bromobenzyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Intermediate 56 and Intermediate 15 according to Method H and was isolated as a solid in 82% yield after purification by column chromatography (SiO₂, 1:1 hexane/EtOAc). δ_{H} (CDCl₃) 7.35 (2H, d, *J* 8.3 Hz), 7.09 (2H, d, *J* 8.3 Hz), 3.95 (2H, m), 3.70 (2H, m), 3.61-3.45 (3H, m), 3.09 (1H, dd, *J* 13.2 and 10.2 Hz), 2.83 (1H, dd, *J* 13.2 and 4.7 Hz), 2.62 (2H, s), 2.33 (2H, s), 1.06 (6H, s). LCMS (ES⁺) 436.9 (M+H)⁺.

EXAMPLE 30

10 2-[3-(2,3-Dihydro-1*H*-indol-1-ylmethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a solution of Intermediate 62 (0.22 g, 0.76 mmol) in MeOH (5 mL) was added indoline (0.11 g, 0.912 mmol) and the mixture was allowed to stir for 15 minutes at r.t. NaBH₃CN (0.06 g, 0.91 mmol) was added and the reaction mixture allowed to stir at r.t. 15 for 24 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (50 mL) and brine (50 mL). The aqueous fraction was extracted with two further portions of EtOAc (50 mL) and the combined organic fractions washed with brine (100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂, 1:4 EtOAc/hexanes) and subsequent 20 crystallisation from Et₂O and hexanes gave the *title compound* (0.07 g, 25%) as pale yellow crystals. δ_{H} (CDCl₃) 7.10-7.03 (2H, m), 6.75-6.67 (2H, m), 4.24 (1H, bs), 4.13-4.05 (2H, m), 3.83-3.78 (1H, m), 3.77-3.60 (3H, m), 3.59-3.43 (3H, m), 3.21 (1H, dd, *J* 13.6 and 4.4 Hz), 3.02-2.94 (2H, m), 2.79-2.67 (2H, m), 2.42 (2H, s), 1.16 (3H, s), 1.15 (3H, s). LCMS (MS⁺) 398.0 (M+H)⁺.

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EXAMPLE 31

5,5-Dimethyl-2-[3-(1*H*-indol-1-ylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

30 To a solution of Example 30 (0.08 g, 0.2 mmol) in DCM (10 mL) was added manganese dioxide (0.15 g, 1.7 mmol) and the reaction mixture stirred at r.t. for 24 h. The reaction mixture was filtered through Celite[®] and the solvents removed *in vacuo*. Purification by column chromatography (SiO₂, 1:19 to 1:4 EtOAc/hexanes) gave the title

compound (0.04 g, 44%) as a pale yellow solid. δ_{H} (CDCl_3) 7.60 (1H, d, J 8.2 Hz), 7.53 (1H, d, J 7.9 Hz), 7.23-7.20 (1H, m), 7.09-7.02 (2H, m), 6.43 (1H, m), 4.54-4.47 (2H, m), 4.31-4.24 (1H, m), 4.06-4.01 (1H, m), 3.69-3.49 (5H, m), 2.65 (2H, d, J 5.3 Hz), 2.33 (2H, s), 1.08 (3H, s), 1.07 (3H, s). LCMS (MS^+) 396.0 ($\text{M}+\text{H}$)⁺.

5

EXAMPLE 32

5,5-Dimethyl-2-(trans-2,6-dimethylmorpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one

10 The *title compound* was prepared from Intermediate 15 (0.26 g, 1 mmol) and 2,6-dimethylmorpholine (mixture of *cis* and *trans* isomers, 0.17 g, 1.49 mmol) according to Method H and was isolated by column chromatography (SiO_2 , 15:85 EtOAc/hexanes) to give the *title product* (0.04 g, 12%) as a white solid. δ_{H} (CDCl_3) 4.11-4.02 (2H, m), 3.65 (2H, dd, J 12.8 and 3.4 Hz), 3.20 (2H, dd, J 12.9 and 6.4 Hz), 2.61 (2H, s), 2.31 (2H, s),
15 1.19 (6H, d, J 6.4 Hz), 1.05 (6H, s). LCMS (MS^+) 295.0 ($\text{M}+\text{H}$)⁺.

EXAMPLE 33 (METHOD I)

2-[3-(Anilinomethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

20

To a stirred solution of Intermediate 62 (0.10 g, 0.34 mmol) and aniline (0.16 g, 0.15 mL, 1.7 mmol) in MeOH (5 mL) with 4Å molecular sieves was added NaBH_3CN (0.03 g, 0.40 mmol) and a catalytic amount of AcOH. After stirring for 16 h at r.t., the reaction mixture was filtered, concentrated *in vacuo* and partitioned between EtOAc (20 mL) and sat. NaHCO_3 solution (20 mL). The organic fraction was dried over MgSO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , EtOAc/hexane) gave the *title compound* (3 mg, 2%) as a solid. δ_{H} (CDCl_3) 7.13-7.09 (2H, m), 6.67-6.64 (3H, m), 4.34 (1H, bs), 4.03-3.94 (2H, m), 3.63-3.44 (7H, m), 2.64 (2H, s), 2.33 (2H, s), 1.08 (3H, s), 1.07 (3H, s). LCMS (ES^+) 372.0 ($\text{M}+\text{H}$)⁺.

30

EXAMPLE 34

5,5-Dimethyl-2-{3-[(*N*-methyl-*N*-phenylamino)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a stirred solution of Intermediate 62 (0.25 g, 0.85 mmol) and *N*-methylaniline (0.46 g, 0.46 mL, 4.25 mmol) in MeOH (20 mL) with 4Å molecular sieves was added
 5 NaBH₃CN (0.06 g, 1.02 mmol) and a catalytic amount of AcOH. The reaction was then carried out according to Method I to give the *title compound* (0.108 g, 32%) as a solid. δ_H (CDCl₃) 7.20-7.16 (2H, m), 6.83-6.81 (2H, m), 6.66 (1H, t, *J* 7.3 Hz), 4.22 (1H, bs), 3.98 (1H, dd, *J* 11.0 and 3.4 Hz), 3.93-3.90 (1H, m), 3.77-3.62 (1H, m), 3.60-3.56 (3H, m), 3.48-3.36 (2H, m), 2.94 (3H, s), 2.62 (2H, s), 2.32 (2H, s), 1.07 (3H, s), 1.06 (3H, s).
 10 LCMS (ES⁺) 386.0 (M+H)⁺.

EXAMPLE 35

2-[3-(3,4-Dihydroquinolin-1(2*H*)-ylmethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a stirred solution of Intermediate 62 (0.25 g, 0.85 mmol) and 1,2,3,4-tetrahydroquinoline (0.57 g, 0.53 mL, 4.25 mmol) in MeOH (20 mL) with 4Å molecular sieves was added NaBH₃CN (0.06 g, 1.02 mmol) and a catalytic amount of AcOH. The reaction was then carried out according to Method I to give the *title compound* (0.08 g, 22%) as a solid. δ_H (CDCl₃) 7.03 (1H, t, *J* 7.2 Hz), 6.94 (1H, d, *J* 8.1 Hz), 6.87 (1H, d, *J* 7.2 Hz), 6.54 (1H, t, *J* 7.2 Hz), 4.00 (1H, bs), 3.99-3.92 (2H, m), 3.69-3.57 (4H, m), 3.49-3.45 (1H, m), 3.33-3.27 (3H, m), 2.66 (2H, t, *J* 6.2 Hz), 2.61 (2H, s), 2.32 (2H, s), 1.89-1.79 (2H, m), 1.06 (6H, s). LCMS (ES⁺) 412.0 (M+H)⁺.

EXAMPLE 36

2-[3-(3,4-Dihydroisoquinolin-2(1*H*)-ylmethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a stirred solution of Intermediate 62 (0.25 g, 0.85 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.57 g, 0.53 mL, 4.25 mmol) in MeOH (20 mL) with 4Å molecular sieves was added NaBH₃CN (0.06 g, 1.02 mmol) and a catalytic amount of AcOH. The reaction was then carried out according to Method I to give the *title compound* (0.09 g, 25%) as a solid. δ_H (CDCl₃) 7.15-7.03 (4H, m), 4.19 (1H, d, *J* 11.8

Hz), 4.02 (2H, m), 3.99-3.79 (3H, m), 3.69-3.60 (2H, m), 3.49-3.39 (1H, m), 3.11-3.04 (1H, m), 2.94-2.86 (4H, m), 2.68-2.62 (3H, m), 2.39 (2H, s), 1.14 (3H, s), 1.12 (3H, s). LCMS (ES+) 412.0 (M+H)⁺.

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EXAMPLE 37

(7E,Z)-5,5-Dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one oxime

The *title compound* (mixture of two regioisomers, ratio 1:5.5) was prepared by Method J by reaction of Example 48 (2.5 g, 9.39 mmol), hydroxylamine (6.5 g, 93.98 mmol) and pyridine (50 mL) in quantitative yield. δ_{H} (DMSO-d₆) 10.81 (1H, s, major regioisomer), 10.57 (1H, s, minor regioisomer), 3.69 (4H, t, *J* 4.8 Hz), 3.43 (4H, t, *J* 4.9 Hz), 2.54 (2H, s), 2.26 (2H, s), 0.99 (6H, s). LCMS (ES+) 282 (M+H)⁺.

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EXAMPLE 38

(7Z)-5,5-Dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one oxime

To a stirred solution of Intermediate 63 (1:15 ratio of two regioisomers, 0.35 g, 1.27 mmol) in IPA (5 mL) was added morpholine (0.22 g, 0.22 mL, 2.55 mmol) and *N,N*-diisopropylethylamine (0.33 g, 0.44 mL, 2.55 mmol). The reaction mixture was stirred at 80°C for 2 days, then cooled to r.t. Water (10 mL) was added. The solid formed was filtered and washed with water (3 x 10 mL), EtOAc (3 x 10 mL), MeOH (3 x 10 mL) then Et₂O (10 mL), to give the *title compound* (0.03 g, 7.5%) (contaminated with 3% of the other regioisomer) as a grey solid. δ_{H} (DMSO-d₆) 10.81 (1H, s), 3.69 (4H, t, *J* 4.8 Hz), 3.43 (4H, t, *J* 4.9 Hz), 2.53 (2H, s), 2.26 (2H, s), 0.99 (6H, s). LCMS (ES+) 282.0 (M+H)⁺.

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EXAMPLE 39

(7E,Z)-2-(Morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one oxime

The *title compound* (mixture of two regioisomers, ratio 1:7.7) was prepared by Method J by reaction of Example 6 (1.0 g, 4.2 mmol), hydroxylamine (2.9 g, 42 mmol) and pyridine (20 mL). δ_{H} (DMSO-d₆) 10.80 (1H, s, major regioisomer), 10.56 (1H, s, minor regioisomer), 3.69 (4H, t, *J* 4.8 Hz), 3.43 (4H, t, *J* 4.9 Hz), 2.68 (2H, t, *J* 6.1 Hz),

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2.53-2.60 (2H, m, minor regioisomer), 2.44 (2H, t, J 6.2 Hz), 1.81-1.89 (2H, m). LCMS (ES+) 254.0 (M+H)⁺.

EXAMPLE 40

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(7E,Z)-5,5-Dimethyl-2-[(3S)-3-(1H-indol-3-ylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one oxime

The *title compound* (mixture of two regioisomers, ratio 1:5) was prepared by Method J by reaction of Example 25 (1.0 g, 2.53 mmol), hydroxylamine (1.8 g, 25.32 mmol) and pyridine (15 mL). δ_{H} (DMSO- d_6) 10.89 (1H, s, major regioisomer), 10.80 (1H, s), 10.57 (1H, s, minor regioisomer), 7.84 (1H, d, J 7.8 Hz), 7.35 (1H, d, J 8.1 Hz), 7.18 (1H, s), 7.09 (1H, t, J 7.1 Hz), 7.00 (1H, d, J 7.4 Hz), 4.13 (1H, d, J 9.7 Hz), 3.96 (1H, d, J 9.8 Hz), 3.71 (1H, d, J 11.5 Hz), 3.64 (1H, d, J 10.8 Hz), 3.46-3.59 (3H, m), 3.28 (1H, d, J 10.9 Hz), 2.86 (1H, dd, J 3.5 and 13.6 Hz), 2.60 (2H, s), 2.28 (2H, s), 1.01 (6H, s). LCMS (ES+) 411.0 (M+H)⁺.

EXAMPLE 41

(7E,Z)-6-Methyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one oxime

The *title compound* (mixture of two regioisomers, ratio 1:11) was prepared by Method J by reaction of Example 13 (0.19 g, 0.74 mmol), hydroxylamine (0.51 g, 7.38 mmol) and pyridine (5 mL). The reaction was complete after 4 days. δ_{H} (DMSO- d_6) 10.92 (1H, s, major regioisomer), 10.54 (1H, s, minor regioisomer), 3.69 (4H, t, J 4.8 Hz), 3.42 (4H, t, J 4.8 Hz), 2.60-2.76 (3H, m), 1.89-1.97 (1H, m), 1.64-1.72 (1H, m), 1.15 (6H, d, J 6.8 Hz, major regioisomer), 1.15 (6H, d, J 7.1 Hz, minor regioisomer). LCMS (ES+) 268.0 (M+H)⁺.

EXAMPLE 42

(7E,Z)-6,6-Dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one oxime

The *title compound* (mixture of two regioisomers) was prepared by Method J by reaction of Example 10 (0.36 g, 1.36 mmol), hydroxylamine (0.95 g, 13.65 mmol) and pyridine (5 mL). The reaction was complete after 4 days. δ_{H} (DMSO- d_6) 11.00 (1H, s),

3.69 (4H, t, J 4.8 Hz), 3.42 (4H, t, J 4.9 Hz), 2.68 (2H, t, J 6.2 Hz), 1.72 (2H, t, J 6.2 Hz), 1.16 (6H, s). LCMS (ES+) 282.0 (M+H)⁺.

PREPARATIVE EXAMPLE 43 (METHOD K)

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7,7-Dimethyl-2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4H-[1,3]thiazolo[5,4-c]azepin-4-one

To a stirred solution of Example 37 (4.10 g, 14.59 mmol) in pyridine (70 mL) was added *p*-toluenesulphonyl chloride (3.10 g, 16.05 mmol). The reaction mixture was stirred at 65°C for 16 h. The solvent was evaporated *in vacuo* and DCM (30 mL) and
10 water (20 mL) were added. The aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were washed with water (3 x 30 mL), dried (MgSO₄), filtered and the solvent evaporated *in vacuo*. The oily residue was purified by column chromatography (SiO₂, loading with CH₂Cl₂ and eluting with 1:1 EtOAc/hexane, then EtOAc) to give the *title compound* (0.78 g, 19%) as a white solid. δ_{H} (DMSO-d₆) 7.69-
15 7.71 (1H, t, J 4.7 Hz), 3.68 (4H, t, J 4.9 Hz), 3.40 (4H, t, J 4.9 Hz), 2.94 (2H, d, J 5.0 Hz), 2.67 (2H, s), 0.97 (6H, s). LCMS (ES+) 282.0 (M+H)⁺. CHN analysis: Found (%C 55.19, %H 6.77, %N 14.79), Calculated for C₁₃H₁₉N₃SO₂ (%C 55.49, %H 6.81, %N 14.93).

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PREPARATIVE EXAMPLE 44

2-(Morpholin-4-yl)-5,6,7,8-tetrahydro-4H-[1,3]thiazolo[5,4-c]azepin-4-one

The *title compound* was prepared by Method K by reaction of Example 39 (1.4 g, 5.53 mmol), *p*-toluenesulphonyl chloride (1.2 g, 6.09 mmol) and pyridine (30 mL). δ_{H}
25 (DMSO-d₆) 7.77 (1H, s), 3.68 (4H, t, J 4.9 Hz), 3.40 (4H, t, J 4.9 Hz), 3.18-3.21 (2H, m), 2.84 (2H, t, J 6.4 Hz), 1.87-1.92 (2H, m). LCMS (ES+) 254.0 (M+H)⁺.

EXAMPLE 45

7,7-Dimethyl-2-[(3*S*)-3-(1*H*-indol-3-ylmethyl)morpholin-4-yl]-5,6,7,8-tetrahydro-4H-[1,3]thiazolo[5,4-c]azepin-4-one

The *title compound* was prepared by Method K by reaction of Example 40 (1.0 g, 2.53 mmol), *p*-toluenesulphonyl chloride (0.53 g, 2.78 mmol) and pyridine (20 mL). δ_{H}

(DMSO-d₆) 10.89 (1H, s), 7.80 (1H, d, *J* 7.8 Hz), 7.70 (1H, d, *J* 4.7 Hz), 7.34 (1H, d, *J* 7.8 Hz), 7.19 (1H, s), 7.08 (1H, t, *J* 7.4 Hz), 7.01 (1H, d, *J* 7.2 Hz), 4.07 (1H, s), 3.96 (1H, d, *J* 7.5 Hz), 3.70 (1H, d, *J* 11.5 Hz), 3.60 (1H, d, *J* 8.9 Hz), 3.38-3.56 (3H, m), 3.25-3.31 (1H, m), 2.95 (2H, d, *J* 4.4 Hz), 2.88 (1H, dd, *J* 3.7 and 13.7 Hz), 2.73 (2H, s), 0.99 (6H, s). LCMS (ES+) 411.0 (M+H)⁺.

EXAMPLE 46

6-Methyl-2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one

10 The *title compound* was prepared by Method K by reaction of Example 41 (0.16 g, 0.61 mmol), *p*-toluenesulphonyl chloride (0.14 g, 0.73 mmol) and pyridine (5 mL). δ_H (DMSO-d₆) 7.61 (1H, d, *J* 2.5 Hz), 3.69 (4H, t, *J* 4.9 Hz), 3.46-3.50 (1H, m), 3.40 (4H, t, *J* 4.9 Hz), 2.84 (2H, t, *J* 6.6 Hz), 1.80-1.94 (1H, m), 1.73-1.79 (1H, m), 1.16 (3H, d, *J* 6.7 Hz). LCMS (ES+) 268.0 (M+H)⁺.

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EXAMPLE 47

6,6-Dimethyl-2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one

20 The *title compound* was prepared by Method K by reaction of Example 42 (0.36 g, 1.28 mmol), *p*-toluenesulphonyl chloride (0.29 g, 1.54 mmol) and pyridine (8 mL). δ_H (DMSO-d₆) 7.51 (1H, s), 3.68 (4H, t, *J* 4.9 Hz), 3.40 (4H, t, *J* 4.9 Hz), 2.83 (2H, t, *J* 6.3 Hz), 1.84 (2H, t, *J* 6.3 Hz), 1.20 (6H, s). LCMS (ES+) 282.0 (M+H)⁺.

PREPARATIVE EXAMPLE 48

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5,5-Dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from morpholine and Intermediate 15 according to Method H and was isolated as white crystals in 60% yield after purification by recrystallisation from EtOAc. δ_H (DMSO-d₆) 3.77-3.60 (4H, m), 3.59-3.50 (4H, m), 2.65 (2H, s), 2.31 (2H, s), 1.04 (6H, s). LCMS (ES+) 267.1 (M+H)⁺.

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EXAMPLE 49

5,5-Dimethyl-2-(morpholin-4-yl)-4,5,6,7-tetrahydro-1,3-benzothiazol-7-ol

- 100 -

To a stirred solution of Example 48 (0.13 g, 0.5 mmol) in THF (10 mL) at r.t. was added LiAlH₄ (0.5 mL, 1M solution in THF, 0.5 mmol) dropwise. The reaction mixture was stirred at r.t. for 2 h and then poured into 10% NaOH solution (20 mL) and extracted with DCM (2 x 20 mL). The combined organic fractions were dried over MgSO₄, filtered and the solvent removed by evaporation *in vacuo*. Purification by column chromatography gave the *title compound* (0.07 g, 52%) as a solid. δ_{H} (DMSO-d₆) 5.23 (1H, d, *J* 6.5 Hz), 4.65 (1H, dt, *J* 8.1 and 6.7 Hz), 3.77-3.70 (4H, m), 3.39 (4H, m), 2.40-2.24 (2H, m), 1.84 (1H, dd, *J* 5.9 and 11.3 Hz), 1.48 (1H, dd, *J* 8.8 and 12.6 Hz), 1.09 (3H, s), 0.94 (3H, s). LCMS (ES+) 269.0 (M+H)⁺.

EXAMPLE 50

5,5-Dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazole-7(4H)-thione

To a stirred solution of Example 48 (0.266 g, 1 mmol) in THF (10 mL) at r.t. was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide (0.808 g, 2 mmol). The reaction mixture was stirred for 2 h and then poured into saturated NaHCO₃ solution (50 mL) and extracted with DCM (2 x 50 mL). The combined organic fractions were dried over MgSO₄, filtered and the solvent removed by evaporation *in vacuo* to give the *title compound* (0.14 g, 50%) as a solid. δ_{H} (DMSO-d₆) 3.72-3.60 (8H, m), 2.74 (2H, s), 2.61 (2H, s), 1.02 (6H, s). LCMS (ES+) 283.0 (M+H)⁺.

EXAMPLE 51

2-[(3S)-3-(3-Bromobenzyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Intermediate 69 and Intermediate 15 according to Method H and was isolated as a pale yellow solid (22%) after purification by column chromatography (SiO₂, 1:1 hexanes/EtOAc). δ_{H} (DMSO-d₆) 7.46 (1H, s), 7.39-7.36 (1H, m), 7.26-7.16 (2H, m), 4.15-4.04 (2H, m), 3.81-3.77 (2H, m), 3.71-3.53 (2H, m), 3.16 (1H, dd, *J* 13.0 and 10.0 Hz), 2.97 (1H, dd, *J* 13.0 and 4.9 Hz), 2.72 (2H, s), 2.41 (2H, s), 1.15 (6H, s). LCMS (ES+) 437.2 (M+H)⁺.

EXAMPLE 52 (METHOD L)

2-[(3S)-3-(Biphenyl-3-ylmethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

Pd(PPh₃)₄ (0.03 g, 0.02 mmol) was added to a mixture of Example 51 (0.10 g, 0.22 mmol), phenylboronic acid (0.40 g, 0.34 mmol) and 2M Na₂CO₃ solution (0.22 mL, 0.45 mmol) in DME (5 mL), and the mixture was heated at 80°C for 16 h. On completion, the reaction mixture was concentrated *in vacuo* and partitioned between EtOAc (100 mL) and brine (100 mL). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 1:1 hexanes/EtOAc) gave the *title compound* as a white solid (0.07 g, 68%). δ_H (DMSO-d₆) 7.52-7.49 (2H, m), 7.48-7.22 (7H, m), 4.06-4.00 (2H, m), 3.98 (2H, d, *J* 7.8 Hz), 3.59-3.47 (4H, m), 3.19 (1H, dd, *J* 13.1 and 10.2 Hz), 2.60 (2H, br. s), 2.31 (2H, br. s), 1.04 (6H, s). LCMS (ES+) 432.0 (M+H)⁺.

EXAMPLE 53

5,5-Dimethyl-2-[(3S)-3-(3-(pyridin-3-yl)benzyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and 3-pyridineboronic acid according to Method L and was isolated as a white solid (55%). δ_H (DMSO-d₆) 8.83-8.82 (1H, m), 8.56 (1H, dd, *J* 4.7 and 1.5 Hz), 7.99 (1H, dd, *J* 6.7 and 2.2 Hz), 7.65-7.31 (5H, m), 4.26 (1H, br. s), 3.99-3.96 (1H, m), 3.80-3.51 (5H, m), 3.15 (2H, t, *J* 6.8 Hz), 2.50 (2H, s), 2.22 (2H, s), 0.95 (3H, s), 0.93 (3H, s). LCMS (ES+) 434.2 (M+H)⁺.

EXAMPLE 54 (METHOD M)

5,5-Dimethyl-2-{(3S)-3-[3-(3-thienyl)benzyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4H)-one

Pd(OAc)₂ (0.002 g, 0.006 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.006 g, 0.010 mmol) were added to Example 51 (0.150 g, 0.330 mmol), 3-thiopheneboronic acid (0.065 g, 0.510 mmol) and K₃PO₄ (0.140 g, 0.660 mmol)

in BuOH/water (2.5 mL/1.0 mL), and the mixture heated at 80°C for 16 h. On completion, the reaction mixture was concentrated *in vacuo* and partitioned between EtOAc (100 mL) and brine (100 mL). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 1:1 hexanes/EtOAc) gave the *title compound* as a white solid (0.047 g, 31%). δ_{H} (DMSO-d₆) 7.79-7.77 (1H, m), 7.64-7.61 (1H, m), 7.57 (1H, s), 7.51-7.48 (2H, m), 7.30 (1H, t, *J* 7.6 Hz), 7.20-7.18 (1H, m), 4.23 (1H, br. s), 3.99-3.96 (1H, m), 3.77-3.51 (5H, m), 3.11-3.09 (2H, m), 2.54-2.50 (2H, m), 2.24 (2H, s), 0.96 (6H, s). LCMS (ES⁺) 439.2 (M+H)⁺.

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EXAMPLE 55

5,5-Dimethyl-2-[(3*S*)-3-(3-(pyridin-4-yl)benzyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and 4-pyridineboronic acid according to Method M and was isolated as a white solid (22%). δ_{H} (DMSO-d₆) 8.62 (2H, dd, *J* 4.5 and 1.6 Hz), 7.82-7.57 (4H, m), 7.44-7.36 (2H, m), 4.27 (1H, br. s), 3.99-3.96 (1H, m), 3.80-3.51 (5H, m), 3.27-3.09 (2H, m), 2.51-2.49 (2H, m), 2.22 (2H, s), 0.94 (3H, s), 0.93 (3H, s). LCMS (ES⁺) 434.5 (M+H)⁺.

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EXAMPLE 56

5,5-Dimethyl-2-[(3*S*)-3-(3-(pyrimidin-5-yl)benzyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and 3,5-pyrimidineboronic acid according to Method M and was isolated as a yellow solid (27%). δ_{H} (DMSO-d₆) 9.18 (1H, s), 9.06 (2H, s), 7.65-7.61 (2H, m), 7.46-7.40 (2H, m), 4.28 (1H, br. s), 3.99-3.96 (1H, m), 3.81-3.55 (6H, m), 3.27-3.13 (3H, m), 2.22 (2H, s), 0.95 (3H, s), 0.92 (3H, s). LCMS (ES⁺) 435.3 (M+H)⁺.

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EXAMPLE 57 (METHOD U)

2-[(3*S*)-3-(3-Bromobenzyl)morpholin-4-yl]-7,7-dimethyl-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one

To a stirred solution of Intermediate 69 (0.70 g, 2.75 mmol) and Intermediate 71 (0.65 g, 2.50 mmol) in THF (3 mL) was added DIPEA (0.90 mL, 5.20 mmol) and the reaction mixture was heated under microwave irradiation in a sealed tube to 180°C for 3 h. On completion, the reaction mixture was concentrated *in vacuo* and partitioned between EtOAc (100 mL) and brine (100 mL). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 1:1 hexanes/EtOAc) gave the *title compound* as a white solid (0.35 g, 33%).

δ_{H} (DMSO-*d*₆) 7.64 (1H, t, *J* 4.8 Hz), 7.45 (1H, s), 7.39-7.35 (1H, m), 7.25-7.21 (2H, m), 4.08 (1H, br. s), 3.94-3.88 (1H, m), 3.66-3.44 (5H, m), 3.07-3.00 (2H, m), 2.98-2.90 (2H, m), 2.63 (2H, s), 0.96 (6H, s). LCMS (ES⁺) 452.2 (M+H)⁺.

EXAMPLE 58

2-[(3*S*)-3-(Biphenyl-3-ylmethyl)morpholin-4-yl]-7,7-dimethyl-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one

The *title compound* was prepared from Example 57 and phenylboronic acid according to Method M and was isolated as a yellow solid (15%). δ_{H} (DMSO-*d*₆) 7.64-7.63 (3H, m), 7.61-7.39 (6H, m), 7.26-7.24 (1H, m), 4.09 (1H, br. s), 3.96-3.90 (1H, m), 3.72-3.62 (2H, m), 3.56-3.51 (2H, m), 3.16-2.98 (3H, m), 2.90-2.88 (2H, m), 2.62 (2H, s), 0.93 (6H, s). LCMS (ES⁺) 448.2 (M+H)⁺.

EXAMPLE 59

7,7-Dimethyl-2-[(3*S*)-3-(3-(pyridin-3-yl)benzyl)morpholin-4-yl]-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one

The *title compound* was prepared from Example 57 and 3-pyridineboronic acid according to Method M and was isolated as a yellow solid (14%). δ_{H} (DMSO-*d*₆) 8.84 (1H, d, *J* 2.3 Hz), 8.56 (1H, dd, *J* 4.7 and 1.6 Hz), 8.04-8.01 (1H, m), 7.63-7.40 (5H, m), 7.33-7.30 (1H, m), 4.12 (1H, t, *J* 6.8 Hz), 3.96-3.90 (1H, m), 3.74-3.51 (5H, m), 3.12-3.09 (2H, m), 2.88-2.87 (2H, m), 2.60-2.59 (2H, m), 0.92 (6H, s). LCMS (ES⁺) 449.5 (M+H)⁺.

EXAMPLE 60**5,5-Dimethyl-2-[3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one**

5 The *title compound* was prepared from Intermediate 15 and Intermediate 79 according to Method H and was isolated as a white solid (71%) after purification by column chromatography (SiO₂, 7:3 hexanes/EtOAc). δ_{H} (CDCl₃) 9.88 (1H, br. s), 8.39 (1H, d, *J* 5.8 Hz), 8.33 (1H, d, *J* 3.4 Hz), 7.32 (1H, s), 7.24 (1H, dd, *J* 5.8 and 3.8 Hz), 4.25 (1H, br. s), 4.09 (1H, d, *J* 6.7 Hz), 3.85 (1H, d, *J* 8.9 Hz), 3.71 (2H, m), 3.56 (1H, d, 10 *J* 7.8 Hz), 3.44 (1H, dd, *J* 10.1 and 8.5 Hz), 3.07 (1H, br. dd, *J* 10.3 and 2.5 Hz), 2.75 (2H, d, *J* 2.0 Hz), 2.44 (2H, s), 1.17 (6H, s). Exchangeable proton not observed. LCMS (ES+) 397.3 (M+H)⁺.

EXAMPLE 61

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7,7-Dimethyl-2-[(3*R*)-3-(1*H*-indol-3-ylmethyl)morpholin-4-yl]-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one

 The *title compound* was prepared from Intermediate 71 and Intermediate 19 according to Method U and was isolated as a white solid (37%) after purification by 20 column chromatography (SiO₂, 1:1 hexanes/EtOAc). δ_{H} (DMSO-*d*₆) 10.89 (1H, s), 7.80 (1H, d, *J* 7.8 Hz), 7.70 (1H, d, *J* 4.7 Hz), 7.34 (1H, d, *J* 7.8 Hz), 7.19 (1H, s), 7.08 (1H, t, *J* 7.4 Hz), 7.01 (1H, d, *J* 7.2 Hz), 4.07 (1H, s), 3.96 (1H, d, *J* 7.5 Hz), 3.70 (1H, d, *J* 11.5 Hz), 3.60 (1H, d, *J* 8.9 Hz), 3.58-3.36 (3H, m), 3.35-3.21 (1H, m), 2.95 (2H, d, *J* 4.4 Hz), 2.88 (1H, dd, *J* 13.7 and 3.7 Hz), 2.73 (2H, s), 0.99 (6H, s). LCMS (ES+) 411.0 (M+H)⁺.

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EXAMPLE 62**7,7-Dimethyl-2-[3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)morpholin-4-yl]-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one**

30 The *title compound* was prepared from Intermediate 71 and Intermediate 79 according to Method U and was isolated as a white solid (51%) after purification by column chromatography (SiO₂, 4:6 hexanes/EtOAc). δ_{H} (CDCl₃) 11.39 (1H, br. s), 8.18 (2H, m), 7.68 (1H, br. t, *J* 4.9 Hz), 7.30 (1H, d, *J* 2.3 Hz), 7.06 (1H, dd, *J* 7.8 and 4.7 Hz),

4.13 (1H, m), 3.97 (1H, m), 3.70 (1H, d, *J* 11.6 Hz), 3.53 (3H, m), 3.22 (2H, m), 2.97 (1H, m), 2.93 (2H, d, *J* 5.1 Hz), 2.66 (2H, d, *J* 5.5 Hz), 0.98 (6H, s). LCMS (ES+) 412.0 (M+H)⁺.

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EXAMPLE 63

5,5-Dimethyl-2-[(3*R*)-3-[(phenylthio)methyl]morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Intermediate 15 and Intermediate 82 according to Method H and was isolated after purification by column chromatography (SiO₂, 1:1 hexanes/EtOAc) as a yellow solid (34%). δ_H (CDCl₃) 7.40 (2H, d, *J* 1.5 Hz), 7.24 (3H, m), 4.23 (1H, d, *J* 11.9 Hz), 4.04 (1H, m), 3.91 (1H, m), 3.54 (3H, m), 3.40 (1H, m), 3.29 (1H, dd, *J* 13.6 and 10.3 Hz), 3.14 (1H, dd, *J* 13.6 and 4.6 Hz), 2.59 (2H, s), 2.31 (2H, s), 1.35 (3H, s), 1.05 (3H, s). LCMS (ES+) 389.5 (M+H)⁺.

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EXAMPLE 64

5,5-Dimethyl-2-[3-(phenoxy)methyl]morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

A mixture of Intermediate 83 (0.47 g, 1.66 mmol), and HCOONH₄ (1.00 g, 16.60 mmol) was stirred in EtOH (30 mL). Palladium on carbon (10 wt %) (0.06 g) was added carefully and the reaction mixture was heated to 60°C for 16 h. The reaction mixture was then filtered through Celite[®] and concentrated *in vacuo*. The *title compound* was prepared from the reaction product and Intermediate 15 according to Method H and was isolated by column chromatography (SiO₂, 1:1 EtOAc/hexanes) as a white solid (0.03 g, 5 %). δ_H (DMSO-d₆ @ 80°C) 7.37-7.25 (2H, m), 6.97-6.92 (3H, m), 4.36-4.32 (2H, m), 4.26-4.18 (1H, m), 4.03-4.01 (1H, m), 3.94-3.92 (1H, m), 3.88-3.58 (2H, m), 3.57-3.48 (2H, m), 2.64 (2H, br. s), 2.32 (2H, s), 1.04 (6H, s). LCMS (ES+) 373.0 (M+H)⁺.

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EXAMPLE 65 (METHOD N)

7,7-Dimethyl-2-(morpholin-4-yl)-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepine-4-thione

- 106 -

To a stirred solution of Example 43 (0.10 g, 0.36 mmol) in THF (10 mL) was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulphide (1.40 g, 0.36 mmol). The suspension was stirred for 7 days and then DCM (10 mL) and water (10 mL) were added, and the aqueous layer was extracted with DCM (3 x 15 mL). The
5 combined organic layers were washed with water (3 x 20 mL), dried (MgSO₄), filtered and the solvent evaporated *in vacuo*. The oily residue was purified by column chromatography (SiO₂, 1:1 EtOAc/hexanes) and the resulting solid washed with Et₂O to give the *title compound* as a yellow solid (0.03 g, 31%). δ_{H} (DMSO-d₆) 9.38 (1H, br. s), 3.69 (4H, t, *J* 4.8 Hz), 3.51 (4H, t, *J* 4.8 Hz), 3.07 (2H, d, *J* 5.3 Hz), 2.67 (2H, s), 0.96
10 (6H, s). LCMS (ES+) 256.0 (M+H)⁺.

EXAMPLE 66

7,7-Dimethyl-2-[(3*S*)-3-(1*H*-indol-3-ylmethyl)morpholin-4-yl]-5,6,7,8-tetrahydro-4*H*-
15 [1,3]thiazolo[5,4-*c*]azepine-4-thione

The *title compound* was prepared as a yellow solid (17%) from Example 45 according to Method N. δ_{H} (DMSO-d₆) 10.88 (1H, s), 9.71 (1H, br. s), 7.81 (1H, d, *J* 7.8 Hz), 7.34 (1H, d, *J* 8.0 Hz), 7.18 (1H, d, *J* 2.0 Hz), 7.10-7.06 (1H, m), 7.02-6.97 (1H, m), 4.17 (1H, br. s), 3.96 (1H, d, *J* 7.0 Hz), 3.71 (1H, d, *J* 11.6 Hz), 3.68-3.40 (4H, m), 3.30-
20 3.25 (1H, m), 3.08 (2H, d, *J* 5.0 Hz), 2.91 (1H, dd, *J* 10.1 and 3.9 Hz), 2.70 (2H, d, *J* 2.7 Hz), 0.98 (6H, s). LCMS (ES+) 427.0 (M+H)⁺.

EXAMPLE 67

25 5,5-Dimethyl-2-{3-[(pyridin-3-ylamino)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a stirred solution of Intermediate 62 (0.50 g, 1.60 mmol) and 3-aminopyridine (0.80 g, 8.50 mmol) in MeOH (30 mL) with 4Å molecular sieves was added NaBH₃CN (0.13 g, 2.04 mmol) and a catalytic amount of AcOH. The reaction was then carried out
30 according to Method I to give the *title compound* (0.05 g, 8%) as a white solid. δ_{H} (DMSO-d₆) 8.04 (1H, t, *J* 1.5 Hz), 7.77 (1H, t, *J* 2.9 Hz), 7.08 (2H, m), 6.16 (1H, t, *J* 6.3 Hz), 4.18 (1H, br. s), 3.89 (2H, m), 3.53 (5H, m), 3.29 (1H, m), 2.61 (2H, d, *J* 2.9 Hz), 2.30 (2H, s), 1.04 (6H, s). LCMS (ES+) 373.0 (M+H)⁺.

EXAMPLE 68 (METHOD O)

5,5-Dimethyl-2-[3-(piperidin-1-ylcarbonyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

To a stirred solution of Intermediate 64 (0.10 g, 0.32 mmol) in DCM (5 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.07 g, 0.38 mmol) and the reaction mixture was stirred at r.t. for 15 minutes. To this was added piperidine (0.03 g, 0.38 mmol) and the reaction mixture was stirred for 72 h at r.t.. The solution was then concentrated *in vacuo* and purified by column chromatography (SiO₂, 1:1 EtOAc/hexanes) to give the *title compound* (0.04 g, 24%) as a white solid. δ_{H} (DMSO-d₆) 5.08 (1H, br. s), 4.00 (1H, d, *J* 11.3 Hz), 3.95 (1H, dd, *J* 11.3 and 4.2 Hz), 3.82 (2H, m), 3.73-3.52 (4H, m), 3.39 (1H, br. m), 3.13 (1H, br. m), 2.69 (2H, s), 2.34 (2H, d, *J* 8.4 Hz), 1.75-1.32 (6H, br. m), 1.05 (3H, s), 1.03 (3H, s). LCMS (ES+) 378.1 (M+H)⁺.

EXAMPLE 69

2-[3-(3,4-Dihydroquinolin-1(2H)-ylcarbonyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Intermediate 64 and 3,4-dihydroquinoline according to Method O and was isolated as a white solid (50%) after purification by column chromatography (SiO₂, 2:3 EtOAc/hexanes). δ_{H} (CDCl₃) 7.58 (1H, d, *J* 7.7 Hz), 7.15 (3H, m), 5.57 (1H, br. s), 4.26 (1H, m), 4.11-3.96 (2H, m), 3.69 (1H, br. m), 3.61-3.45 (2H, m), 3.39-3.18 (2H, m), 2.83 (1H, m), 2.68 (3H, m), 2.32 (2H, q, *J* 16.0 Hz), 2.13 (1H, m), 1.75 (1H, m), 1.09 (3H, s), 1.06 (3H, s). LCMS (ES+) 426.1 (M+H)⁺.

EXAMPLE 70

2-[3-(1-Benzothien-3-ylmethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Intermediate 87 and Intermediate 15 according to Method H and was isolated as a white solid (81%) after purification by column chromatography (SiO₂, 2:3 EtOAc/hexanes). δ_{H} (CDCl₃) 8.18 (1H, d, *J* 7.9 Hz),

7.87 (1H, d, *J* 7.8 Hz), 7.47 (2H, m), 7.29 (1H, s), 4.42 (2H, br. m), 4.09 (1H, br. d, *J* 5.5 Hz), 3.84 (1H, d, *J* 11.9 Hz), 3.69 (2H, m), 3.55 (2H, m), 3.18 (1H, dd, *J* 13.6 and 4.5 Hz), 2.72 (2H, d, *J* 4.1 Hz), 2.42 (2H, s), 1.16 (6H, s). LCMS (ES+) 412.8 (M+H)⁺.

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EXAMPLE 71**2-[3-(Biphenyl-4-ylmethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one**

The *title compound* was prepared from Example 29 and benzeneboronic acid according to Method L and was isolated as a white solid (68%) after purification by column chromatography (SiO₂, 4:1 EtOAc/hexanes). δ_H (CDCl₃) 7.51 (3H, m), 7.38-7.21 (6H, m), 4.00-3.71 (4H, m), 3.64-3.51 (3H, m), 3.19 (1H, dd, *J* 12.6 and 10.5 Hz), 2.90 (1H, dd, *J* 12.6 and 4.5 Hz), 2.63 (2H, s), 2.32 (2H, s), 1.05 (6H, s). LCMS (ES+) 433.0 (M+H)⁺.

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EXAMPLE 72**5,5-Dimethyl-2-[3-(4-(pyridin-3-yl)benzyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one**

The *title compound* was prepared from Example 29 and 3-pyridineboronic acid according to Method L and was isolated as a white solid (75%) after purification by column chromatography (SiO₂, 3:1 EtOAc/hexanes). δ_H (CDCl₃) 8.79 (1H, br. s), 8.55 (1H, br. s), 7.87 (1H, d, *J* 7.9 Hz), 7.48 (2H, d, *J* 8.2 Hz), 7.36 (3H, d, *J* 8.1 Hz), 4.09-3.97 (2H, m), 3.84-3.74 (2H, m), 3.64-3.48 (3H, m), 3.20 (1H, dd, *J* 13.0 and 10.4 Hz), 2.93 (1H, dd, *J* 13.0 and 4.5 Hz), 2.63 (2H, s), 2.32 (2H, s), 1.05 (6H, s). LCMS (ES+) 434.0 (M+H)⁺.

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EXAMPLE 73 (METHOD P)**5,5-Dimethyl-2-{3-[(5-methyl-1*H*-indol-3-yl)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazole-7(4H)-thione**

To a stirred solution of Example 21 (0.06 g, 0.15 mmol) in THF (10 mL) at r.t. was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulphide (0.06 g,

30

0.15 mmol). The reaction mixture was stirred for 2 h and then poured into aqueous sat. NaHCO₃ solution (50 mL) and extracted with DCM (2 x 50 mL). The combined organic fractions were dried over MgSO₄, filtered and the solvent removed *in vacuo* to give the *title compound* (0.02 g, 35%) as an orange solid. δ_{H} (DMSO-d₆) 10.33 (1H, br. s), 7.63 (1H, d, *J* 8.0 Hz), 7.10 (2H, m), 6.86 (1H, d, *J* 8.0 Hz), 4.16 (1H, br. s), 3.98 (1H, d, *J* 8.0 Hz), 3.73 (2H, m), 3.57 (3H, m), 3.31 (1H, m), 3.01 (1H, m), 2.74 (2H, s), 2.57 (2H, d, *J* 5.6 Hz), 2.40 (3H, s), 1.04 (6H, s). LCMS (ES+) 426.9 (M+H)⁺.

EXAMPLE 74

5,5-Dimethyl-2-[3-(1-naphthylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazole-7(4H)-thione

The *title compound* was prepared from Example 16 according to Method P and was isolated as an orange solid (77%) that required no further purification. δ_{H} (CDCl₃) 8.41 (1H, d, *J* 8.3 Hz), 7.78 (1H, d, *J* 8.7 Hz), 7.70 (1H, dd, *J* 7.0 and 2.3 Hz), 7.57-7.42 (2H, m), 7.36 (2H, m), 4.46 (1H, br. m), 4.05 (1H, d, *J* 10.8 Hz), 3.73-3.55 (5H, m), 3.42-3.31 (2H, m), 2.77 (2H, s), 2.55 (2H, d, *J* 5.4 Hz), 1.05 (6H, s). LCMS (ES+) 423.8 (M+H)⁺.

EXAMPLE 75

2-[3-(1-Benzothien-3-ylmethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazole-7(4H)-thione

The *title compound* was prepared from Example 70 according to Method P and was isolated as an orange solid (72%) that required no further purification. δ_{H} (CDCl₃) 8.11 (1H, br. d, *J* 7.6 Hz), 7.93 (1H, d, *J* 7.6 Hz), 7.51-7.32 (3H, m), 4.07 (1H, m), 3.81 (2H, m), 3.64 (2H, m), 3.47-3.25 (4H, m), 2.66 (2H, s), 2.51 (2H, m), 0.96 (3H, s), 0.94 (3H, s). LCMS (ES+) 428.8 (M+H)⁺.

EXAMPLE 76

N-{[4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-3-yl]methyl}benzenesulfonamide

- 110 -

The *title compound* was prepared from Intermediate 89 and Intermediate 15 according to Method H and was isolated as a white solid (52%) after purification by column chromatography (SiO₂, 2:3 EtOAc/hexanes). δ_{H} (CDCl₃) 7.83 (2H, m), 7.74-7.48 (3H, m), 5.41 (1H, br. s), 4.39 (1H, br. m), 3.95 (2H, d, *J* 12.1 Hz), 3.70-3.31 (6H, m), 2.71 (2H, d, *J* 4.9 Hz), 2.43 (2H, s), 1.19 (3H, s), 1.11 (3H, s). LCMS (ES+) 435.8 (M+H)⁺.

EXAMPLE 77

10 2-[3-(1-Benzothien-2-ylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Intermediate 95 and Intermediate 15 according to Method H and was isolated as a white solid (71%) after purification by column chromatography (SiO₂, 2:3 EtOAc/hexanes). δ_{H} (CDCl₃) 7.69 (1H, d, *J* 7.1 Hz), 7.61 (1H, dd, *J* 7.1 and 1.9 Hz), 7.25 (2H, m), 7.07 (1H, s), 4.14 (1H, br. m), 3.96 (1H, 15 m), 3.87 (1H, d, *J* 11.9 Hz), 3.76 (1H, d, *J* 11.4 Hz), 3.65-3.42 (4H, m), 3.13 (1H, dd, *J* 14.1 and 4.7 Hz), 2.59 (2H, d, *J* 3.3 Hz), 2.30 (2H, s), 1.04 (3H, s), 1.01 (3H, s). LCMS (ES+) 413.2 (M+H)⁺.

EXAMPLE 78

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7,7-Dimethyl-2-[3-(isoquinolin-4-ylmethyl)morpholin-4-yl]-7,7-dimethyl-5,6,7,8-tetrahydro-4*H*-[1,3]thiazolo[5,4-*c*]azepin-4-one

The title compound was prepared from Intermediate 99 and Intermediate 71 according to Method U and was isolated as a white solid (23%) after purification by column chromatography (SiO₂, 1:4 hexanes/EtOAc). δ_{H} (CDCl₃) 9.16 (1H, s), 8.64 (1H, 25 d, *J* 8.6 Hz), 8.50 (1H, s), 8.00 (1H, d, *J* 8.0 Hz), 7.78 (1H, dt, *J* 6.9 and 1.3 Hz), 7.63 (1H, dt, *J* 8.0 and 0.9 Hz), 5.79 (1H, br. s), 4.44 (1H, br. d, *J* 11.0 Hz), 4.10 (1H, m), 3.75-3.43 (6H, m), 3.35 (1H, dd, *J* 13.1 and 3.9 Hz), 3.12 (2H, d, *J* 5.2 Hz), 2.88 (2H, d, *J* 2.0 Hz), 1.14 (6H, s). LCMS (ES+) 423.3 (M+H)⁺.

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EXAMPLE 79

7,7-Dimethyl-2-[3-(quinolin-5-ylmethyl)morpholin-4-yl]-5,6,7,8-tetrahydro-4H-[1,3]thiazolo[5,4-c]azepin-4-one

The *title compound* was prepared from Intermediate 103 and Intermediate 71 according to Method U and was isolated as a white solid (42%) after purification by column chromatography (SiO₂, EtOAc). δ_{H} (CDCl₃) 8.96 (1H, d, *J* 8.4 Hz), 8.86 (1H, dd, *J* 4.1 and 1.5 Hz), 7.95 (1H, d, *J* 8.4 Hz), 7.59 (1H, t, *J* 8.4 Hz), 7.45-7.35 (2H, m), 5.91 (1H, br. t, *J* 4.9 Hz), 4.26 (1H, br. d, *J* 10.9 Hz), 4.06 (1H, m), 3.65-3.30 (7H, m), 3.06 (2H, d, *J* 5.0 Hz), 2.78 (2H, d, *J* 5.4 Hz), 1.07 (3H, s), 1.06 (3H, s). LCMS (ES⁺) 423.3 (M+H)⁺.

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EXAMPLE 80

7,7-Dimethyl-2-[3-(quinolin-8-ylmethyl)morpholin-4-yl]-5,6,7,8-tetrahydro-4H-[1,3]thiazolo[5,4-c]azepin-4-one

15 The *title compound* was prepared from Intermediate 107 and Intermediate 71 according to Method U and was isolated as a white solid (39%) after purification by column chromatography (SiO₂, 4:1 EtOAc/DCM). δ_{H} (CDCl₃) 9.01 (1H, dd, *J* 4.1 and 1.8 Hz), 8.12 (1H, dd, *J* 8.2 and 1.8 Hz), 7.65 (2H, m), 7.41 (2H, m), 5.83 (1H, br. m), 4.44 (1H, br. m), 4.08 (1H, m), 3.95-3.54 (7H, m), 3.03 (2H, m), 2.60 (2H, ABq, *J* 17.7 Hz),
20 1.04 (6H, s). LCMS (ES⁺) 423.3 (M+H)⁺.

EXAMPLE 81

25 5,5-Dimethyl-2-[3-(quinolin-8-ylmethyl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Intermediate 107 and Intermediate 15 according to Method H and was isolated as a white solid (71%) after purification by column chromatography (SiO₂, 1:1 EtOAc/DCM). δ_{H} (CDCl₃) 9.00 (1H, dd, *J* 4.2 and 1.8 Hz), 8.09 (1H, dd, *J* 8.3 and 1.7 Hz), 7.64 (2H, m), 7.42 (2H, m), 4.49 (1H, br. m), 4.05
30 (2H, m), 3.94-3.79 (4H, m), 3.64 (2H, dt, *J* 11.5 and 3.3 Hz), 2.43 (2H, ABq, *J* 16.9 Hz), 2.29 (2H, s), 1.06 (3H, s), 1.04 (3H, s). LCMS (ES⁺) 408.0 (M+H)⁺.

EXAMPLE 82

5,5-Dimethyl-2-[(3*S*)-3-(3-(pyrrolidin-1-yl)benzyl)morpholin-4-yl]-5,6-dihydro-1,3-
5 benzothiazol-7(4*H*)-one

To a schlenk tube was added Example 51 (0.08 g, 0.18 mmol), K₂CO₃ (0.06 g, 0.45 mmol), Pd₂(dba)₃ (0.01 g, 0.01 mmol) and 2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl (0.02 g, 0.05 mmol). To this was added ^tBuOH (1.5 mL) and pyrrolidine (0.02 g, 0.02 mL, 0.27 mmol). The schlenk tube was sealed and the reaction
10 mixture was heated to 110°C for 16 h. The dark solution was then dissolved in EtOAc (15 mL) and washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo* into a dark oil. The crude material was purified by column chromatography (SiO₂, 1:1 hexanes/EtOAc) to give the *title compound* as a white solid (0.07 g, 92%). δ_H (CDCl₃) 7.18 (1H, t, *J* 7.7 Hz), 6.62 (1H, d, *J* 7.4 Hz), 6.49 (2H, br. m),
15 4.04 (1H, m), 3.95 (2H, br. m), 3.89 (1H, d, *J* 11.9 Hz), 3.71-3.52 (3H, m), 3.31 (3H, m), 3.18 (1H, m), 2.88 (1H, dd, *J* 12.8 and 3.8 Hz), 2.72 (2H, s), 2.42 (2H, s), 2.02 (3H, br. m), 1.68 (2H, br. s), 1.16 (6H, s). LCMS (ES⁺) 426.3 (M+H)⁺.

EXAMPLE 83

20 2-{3-[(6-Bromopyridin-2-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-
benzothiazol-7(4*H*)-one

The *title compound* was prepared from Intermediate 109 and Intermediate 15 according to Method H and was isolated as a white solid (85%) after purification by
25 column chromatography (SiO₂, 1:1 EtOAc/DCM). δ_H (CDCl₃) 7.34 (1H, t, *J* 7.5 Hz), 7.22 (1H, d, *J* 7.5 Hz), 7.07 (1H, d, *J* 7.4 Hz), 4.40 (1H, br. m), 3.97 (1H, d, *J* 7.1 Hz), 3.82 (1H, d, *J* 11.8 Hz), 3.61 (4H, m), 3.20 (2H, d, *J* 7.4 Hz), 2.54 (2H, d, *J* 3.2 Hz), 2.28 (2H, s), 1.03 (3H, s), 1.02 (3H, s). LCMS (ES⁺) 436.2 and 438.2 (M+H)⁺.

EXAMPLE 84

30 5,5-Dimethyl-2-{3-[(6-phenylpyridin-2-yl)methyl]morpholin-4-yl}-5,6-dihydro-1,3-
benzothiazol-7(4*H*)-one

- 113 -

Pd(OAc)₂ (0.002 g, 0.006 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.007 g, 0.016 mmol) were added to a stirred solution of Example 83 (0.140 g, 0.320 mmol), phenylboronic acid (0.059 g, 0.480 mmol) and K₃PO₄ (0.136 g, 0.640 mmol) in toluene (1.5 mL), and the reaction mixture was heated at 100°C for 2 h.

5 On completion, the reaction mixture was concentrated *in vacuo* and partitioned between EtOAc (100 mL) and brine (100 mL). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 1:1 DCM/EtOAc) gave the *title compound* as a white solid (0.058 g, 42%). δ_H (CDCl₃) 8.03 (2H, m), 7.66 (1H, t, *J* 7.4 Hz), 7.57 (1H, m), 7.44 (3H, m), 7.18 (1H, d, *J* 7.4 Hz), 4.47 (1H, br. m), 4.10-3.99 (3H, m), 3.78-3.65 (3H, m), 3.45 (1H, dd, *J* 13.5 and 8.9 Hz), 3.29 (1H, dd, *J* 13.5 and 5.9 Hz), 2.62 (2H, s), 2.35 (2H, s), 1.09 (3H, s), 1.08 (3H, s). LCMS (ES+) 434.0 (M+H)⁺.

EXAMPLE 85 (METHOD V)

15

5,5-Dimethyl-2-[(3*S*)-3-[(2'-methylbiphenyl-3-yl)methyl]morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a mixture of polystyrene Pd(PPh₃)₄ (0.008 g, 0.001 mmol) and (2-methylphenyl)boronic acid (0.003 g, 0.023 mmol) was added a solution of Example 51 (0.007 g, 0.015 mmol) in 1,4-dioxane (0.400 mL) and aqueous K₂CO₃ (2M, 0.100 mL). The reaction mixture was heated under microwave irradiation in a sealed tube to 125°C for 10 minutes and was then filtered and washed with 1,4-dioxane. The filtrate was concentrated *in vacuo* and the *title compound* was obtained in 95% purity after purification by preparative LC. LCMS (ES+) 447.0 (M+H)⁺, RT 4.60 minutes.

25

EXAMPLE 86

5,5-Dimethyl-2-[(3*S*)-3-[(3'-methoxybiphenyl-3-yl)methyl]morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

30

The *title compound* was prepared from Example 51 and (3-methoxyphenyl)-boronic acid according to Method V and was isolated in 98% purity after purification by preparative LC. LCMS (ES+) 463.0 (M+H)⁺, RT 4.34 minutes.

EXAMPLE 87

5,5-Dimethyl-2-[(3*S*)-3-{[2'-(trifluoromethyl)biphenyl-3-yl]methyl}morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

5 The *title compound* was prepared from Example 51 and (2-trifluoromethyl-phenyl)boronic acid according to Method V and was isolated in 98% purity after purification by preparative LC. LCMS (ES+) 501.0 (M+H)⁺, RT 4.59 minutes.

EXAMPLE 88

10

2{(3*S*)-3-[(2'-Chlorobiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

15 The *title compound* was prepared from Example 51 and (2-chlorophenyl)boronic acid according to Method V and was isolated in 96% purity after purification by preparative LC. LCMS (ES+) 467.0 (M+H)⁺, RT 4.54 minutes.

EXAMPLE 89

20 5,5-Dimethyl-2-{(3*S*)-3-[3-(1-naphthyl)benzyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

 The *title compound* was prepared from Example 51 and 1-naphthylboronic acid according to Method V and was isolated in 98% purity after purification by preparative LC. LCMS (ES+) 483.0 (M+H)⁺, RT 4.77 minutes.

25

EXAMPLE 90

5,5-Dimethyl-2-{(3*S*)-3-[3-(2-naphthyl)benzyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

30 The *title compound* was prepared from Example 51 and 2-naphthylboronic acid according to Method V and was isolated in 96% purity after purification by preparative LC. LCMS (ES+) 483.0 (M+H)⁺, RT 4.78 minutes.

EXAMPLE 91

2-{(3S)-3-[(3'-Chlorobiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (3-chlorophenyl)boronic acid according to Method V and was isolated in 100% purity after purification by preparative LC. LCMS (ES+) 467.0 (M+H)⁺, RT 4.68 minutes.

EXAMPLE 92

10 5,5-Dimethyl-2-{(3S)-3-[(3'-fluorobiphenyl-3-yl)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (3-fluorophenyl)boronic acid according to Method V and was isolated in 95% purity after purification by preparative LC. LCMS (ES+) 451.0 (M+H)⁺, RT 4.43 minutes.

15

EXAMPLE 93

5,5-Dimethyl-2-{(3S)-3-[(2'-fluorobiphenyl-3-yl)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4H)-one

20 The *title compound* was prepared from Example 51 and (2-fluorophenyl)boronic acid according to Method V and was isolated in 98% purity after purification by preparative LC. LCMS (ES+) 451.0 (M+H)⁺, RT 4.39 minutes.

EXAMPLE 94

25

2-{(3S)-3-[(2',6'-Difluorobiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (2,6-difluorophenyl)-boronic acid according to Method V and was isolated in 97% purity after purification by preparative LC. LCMS (ES+) 469.0 (M+H)⁺, RT 4.34 minutes.

30

EXAMPLE 95

2-((3S)-3-[(3',4'-Dichlorobiphenyl-3-yl)methyl]morpholin-4-yl)-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from example 51 and (3,4-dichlorophenyl)-boronic acid according to Method V and was isolated in 98% purity after purification by preparative LC. LCMS (ES+) 501.0 and 503.0 (M+H)⁺, RT 4.92 minutes.

EXAMPLE 96

5,5-Dimethyl-2-[(3S)-3-{[4'-(methylthio)biphenyl-3-yl]methyl}morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and [4-(methylthio)-phenyl]boronic acid according to Method V and was isolated in 97% purity after purification by preparative LC. LCMS (ES+) 479.0 (M+H)⁺, RT 4.58 minutes.

EXAMPLE 97

2-((3S)-3-[3-(1-Benzofuran-2-yl)benzyl]morpholin-4-yl)-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and 1-benzofuran-2-ylboronic acid according to Method V and was isolated in 93% purity after purification by preparative LC. LCMS (ES+) 473.0 (M+H)⁺, RT 4.66 minutes.

EXAMPLE 98

2-((3S)-3-[3-(1-Benzothien-2-yl)benzyl]morpholin-4-yl)-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and 1-benzothien-2-ylboronic acid according to Method V and was isolated in 96% purity after purification by preparative LC. LCMS (ES+) 489.0 (M+H)⁺, RT 4.77 minutes.

EXAMPLE 99

5,5-Dimethyl-2-[(3*S*)-3-[(3'-methylbiphenyl-3-yl)methyl]morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (3-methylphenyl)boronic acid according to Method V and was isolated in 99% purity after purification by preparative LC. LCMS (ES+) 447.0 (M+H)⁺, RT 4.63 minutes.

EXAMPLE 100

5,5-Dimethyl-2-[(3*S*)-3-[(2'-methoxybiphenyl-3-yl)methyl]morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (2-methoxyphenyl)boronic acid according to Method V and was isolated in 100% purity after purification by preparative LC. LCMS (ES+) 463.0 (M+H)⁺, RT 4.38 minutes.

EXAMPLE 101

5,5-Dimethyl-2-[(3*S*)-3-[3-(thien-2-yl)benzyl]morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and 2-thienylboronic acid according to Method V and was isolated in 99% purity after purification by preparative LC. LCMS (ES+) 439.0 (M+H)⁺, RT 4.31 minutes.

EXAMPLE 102

5,5-Dimethyl-2-[(3*S*)-3-[(3'-ethoxybiphenyl-3-yl)methyl]morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (3-ethoxyphenyl)boronic acid according to Method V and was isolated in 97% purity after purification by preparative LC. LCMS (ES+) 477.0 (M+H)⁺, RT 4.56 minutes.

EXAMPLE 103

5,5-Dimethyl-2-{(3*S*)-3-[3-(4-methylthien-2-yl)benzyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (4-methyl-2-thienyl)-boronic acid according to Method V and was isolated in 95% purity after purification by preparative LC. LCMS (ES+) 453.2 (M+H)⁺, RT 4.56 minutes.

EXAMPLE 104

2-{(3*S*)-3-[3-(5-Acetylthien-2-yl)benzyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (5-acetyl-2-thienyl)-boronic acid according to Method V and was isolated in 75% purity after purification by preparative LC. LCMS (ES+) 481.0 (M+H)⁺, RT 3.32 minutes.

EXAMPLE 105

2-{(3*S*)-3-[3-(1-Benzothien-3-yl)benzyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and 1-benzothien-3-ylboronic acid according to Method V and was isolated in 97% purity after purification by preparative LC. LCMS (ES+) 489.0 (M+H)⁺, RT 4.73 minutes.

EXAMPLE 106

5,5-Dimethyl-2-{(3*S*)-3-[(4'-methylbiphenyl-3-yl)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (4-methylphenyl)boronic acid according to Method V and was isolated in 99% purity after purification by preparative LC. LCMS (ES+) 447.0 (M+H)⁺, RT 4.64 minutes.

EXAMPLE 107

2-{(3*S*)-3-[(3'-Acetylbiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (3-acetylphenyl)boronic acid according to Method V and was isolated in 92% purity after purification by preparative LC. LCMS (ES+) 475.0 (M+H)⁺, RT 4.05 minutes.

EXAMPLE 108

10 2-{(3*S*)-3-[(4'-Acetylbiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (4-acetylphenyl)boronic acid according to Method V and was isolated in 91% purity after purification by preparative LC. LCMS (ES+) 475.0 (M+H)⁺, RT 4.01 minutes.

15 **EXAMPLE 109**

2-{(3*S*)-3-[(2'-Bromobiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

20 The *title compound* was prepared from Example 51 and (2-bromophenyl)boronic acid according to Method V and was isolated in 83% purity after purification by preparative LC. LCMS (ES+) 511.0 and 513.0 (M+H)⁺, RT 4.60 minutes.

EXAMPLE 110

25 2-{(3*S*)-3-[(3'-Bromobiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (3-bromophenyl)boronic acid according to Method V and was isolated in 79% purity after purification by preparative LC. LCMS (ES+) 511.0 and 513.0 (M+H)⁺, RT 4.74 minutes.

30

EXAMPLE 111

2-[(3S)-3-[(4'-Bromobiphenyl-3-yl)methyl]morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (4-bromophenyl)boronic acid according to Method V and was isolated in 88% purity after purification by preparative LC. LCMS (ES+) 511.0 and 513.0 (M+H)⁺, RT 4.74 minutes.

EXAMPLE 112

2-[(3S)-3-[[3',5'-Bis(trifluoromethyl)biphenyl-3-yl]methyl]morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and [3,5-bis(trifluoromethyl)phenyl]boronic acid according to Method V and was isolated in 100% purity after purification by preparative LC. LCMS (ES+) 569.0 (M+H)⁺, RT 4.95 minutes.

EXAMPLE 113

2-[(3S)-3-[(4'-Chlorobiphenyl-3-yl)methyl]morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (4-chlorophenyl)boronic acid according to Method V and was isolated in 100% purity after purification by preparative LC. LCMS (ES+) 467.0 (M+H)⁺, RT 4.68 minutes.

EXAMPLE 114

2-[(3S)-3-[(2',5'-Dichlorobiphenyl-3-yl)methyl]morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (2,5-dichlorophenyl)boronic acid according to Method V and was isolated in 94% purity after purification by preparative LC. LCMS (ES+) 501.0 and 503.0 (M+H)⁺, RT 4.84 minutes.

EXAMPLE 115

2-{(3S)-3-[(3',5'-Difluorobiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (3,5-difluorophenyl)-boronic acid according to Method V and was isolated in 92% purity after purification by preparative LC. LCMS (ES+) 469.0 (M+H)⁺, RT 4.52 minutes.

EXAMPLE 116

2-{(3S)-3-[(3',4'-Dimethoxybiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (3,4-dimethoxyphenyl)-boronic acid according to Method V and was isolated in 99% purity after purification by preparative LC. LCMS (ES+) 493.0 (M+H)⁺, RT 4.02 minutes.

EXAMPLE 117

2-{(3S)-3-[(2',3'-Dimethylbiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (2,3-dimethylphenyl)-boronic acid according to Method V and was isolated in 100% purity after purification by preparative LC. LCMS (ES+) 461.0 (M+H)⁺, RT 4.77 minutes.

EXAMPLE 118

2-{(3S)-3-[(3',5'-Dimethylbiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (3,5-dimethylphenyl)-boronic acid according to Method V and was isolated in 99% purity after purification by preparative LC. LCMS (ES+) 461.0 (M+H)⁺, RT 4.85 minutes.

EXAMPLE 119

2-{(3*S*)-3-[(2',5'-Dimethylbiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (2,5-dimethylphenyl)-boronic acid according to Method V and was isolated in 98% purity after purification by preparative LC. LCMS (ES+) 461.0 (M+H)⁺, RT 4.81 minutes.

EXAMPLE 120

5,5-Dimethyl-2-{(3*S*)-3-[(4'-fluoro-3'-methylbiphenyl-3-yl)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (4-fluoro-3-methylphenyl)boronic acid according to Method V and was isolated in 100% purity after purification by preparative LC. LCMS (ES+) 465.0 (M+H)⁺, RT 4.65 minutes.

EXAMPLE 121

5,5-Dimethyl-2-{(3*S*)-3-[(4'-fluorobiphenyl-3-yl)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (4-fluorophenyl)boronic acid according to Method V and was isolated in 100% purity after purification by preparative LC. LCMS (ES+) 451.0 (M+H)⁺, RT 4.41 minutes.

EXAMPLE 122

5,5-Dimethyl-2-{(3*S*)-3-[(4'-methoxybiphenyl-3-yl)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (4-methoxyphenyl)-boronic acid according to Method V and was isolated in 99% purity after purification by preparative LC. LCMS (ES+) 463.0 (M+H)⁺, RT 4.32 minutes.

EXAMPLE 123

2-{(3*S*)-3-[3-(1,3-benzodioxol-5-yl)benzyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and 1,3-benzodioxol-5-ylboronic acid according to Method V and was isolated in 98% purity after purification
5 by preparative LC. LCMS (ES+) 477.0 (M+H)⁺, RT 4.24 minutes.

EXAMPLE 124

5,5-Dimethyl-2-{(3*S*)-3-[(4'-phenoxybiphenyl-3-yl)methyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (4-phenoxyphenyl)-boronic acid according to Method V and was isolated in 97% purity after purification by preparative LC. LCMS (ES+) 525.0 (M+H)⁺, RT 4.30 minutes.

EXAMPLE 125

5,5-Dimethyl-2-[(3*S*)-3-{[3'-(trifluoromethyl)biphenyl-3-yl]methyl}morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (3-trifluoromethyl-phenyl)boronic acid according to Method V and was isolated in 99% purity after purification by preparative LC. LCMS (ES+) 501.0 (M+H)⁺, RT 4.68 minutes.

EXAMPLE 126

2-{(3*S*)-3-[(3',4'-Difluorobiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (3,4-difluorophenyl)-boronic acid according to Method V and was isolated in 94% purity after purification by preparative LC. LCMS (ES+) 469.0 (M+H)⁺, RT 4.45 minutes.

EXAMPLE 127

N-(3'-{[(3S)-4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-3-yl]methyl}biphenyl-3-yl)acetamide

The *title compound* was prepared from Example 51 and (3-acetamidophenyl)-boronic acid according to Method V and was isolated in 94% purity after purification by preparative LC. LCMS (ES+) 490.0 (M+H)⁺, RT 3.52 minutes.

EXAMPLE 128

2-{(3S)-3-[(3'-Aminobiphenyl-3-yl)methyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (3-aminophenyl)boronic acid according to Method V and was isolated in 86% purity after purification by preparative LC. LCMS (ES+) 448.0 (M+H)⁺, RT 3.20 minutes.

EXAMPLE 129

3'-{[(3S)-4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-3-yl]methyl}biphenyl-4-carbonitrile

The *title compound* was prepared from Example 51 and (4-cyanophenyl)boronic acid according to Method V and was isolated in 98% purity after purification by preparative LC. LCMS (ES+) 458.0 (M+H)⁺, RT 4.08 minutes.

EXAMPLE 130

5,5-Dimethyl-2-[(3S)-3-{[3'-(hydroxymethyl)biphenyl-3-yl]methyl}morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and [3-(hydroxymethyl)-phenyl]boronic acid according to Method V and was isolated in 80% purity after purification by preparative LC. LCMS (ES+) 463.0 (M+H)⁺, RT 3.59 minutes.

EXAMPLE 131

5,5-Dimethyl-2-[(3S)-3-{[2'-(hydroxymethyl)biphenyl-3-yl]methyl}morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and [2-(hydroxymethyl)-phenyl]boronic acid according to Method V and was isolated in 74% purity after
5 purification by preparative LC. LCMS (ES+) 463.0 (M+H)⁺, RT 3.68 minutes.

EXAMPLE 132

10 5,5-Dimethyl-2-[(3S)-3-{[3'-(trifluoromethoxy)biphenyl-3-yl]methyl}morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and [3-(trifluoromethoxy)-phenyl]boronic acid according to Method V and was isolated in 99% purity after purification by preparative LC. LCMS (ES+) 517.0 (M+H)⁺, RT 4.77 minutes.

15 **EXAMPLE 133**

5,5-Dimethyl-2-{(3S)-3-[3-(6-methoxypyridin-3-yl)benzyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (6-methoxypyridin-3-yl)boronic acid according to Method V and was isolated in 93% purity after purification
20 by preparative LC. LCMS (ES+) 464.0 (M+H)⁺, RT 4.04 minutes.

EXAMPLE 134

25 N-(3'-{[(3S)-4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-3-yl]methyl}biphenyl-3-yl)methanesulfonamide

The *title compound* was prepared from Example 51 and {3-[(methylsulfonyl)-amino]phenyl}boronic acid according to Method V and was isolated in 99% purity after purification by preparative LC. LCMS (ES+) 526.0 (M+H)⁺, RT 3.64 minutes.

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EXAMPLE 135

2-((3S)-3-[3-(3,5-Dimethylisoxazol-4-yl)benzyl]morpholin-4-yl)-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (3,5-dimethylisoxazol-4-yl)boronic acid according to Method V and was isolated in 93% purity after purification
5 by preparative LC. LCMS (ES+) 452.0 (M+H)⁺, RT 3.82 minutes.

EXAMPLE 136

5,5-Dimethyl-2-((3S)-3-{3-[1-(phenylsulfonyl)-1H-indol-3-yl]benzyl}morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and [1-(phenylsulfonyl)-1H-indol-3-yl]boronic acid according to Method V and was isolated in 94% purity after purification by preparative LC. LCMS (ES+) 612.0 (M+H)⁺, RT 4.71 minutes.

EXAMPLE 137

2-((3S)-3-[3-(6-Chloropyridin-3-yl)benzyl]morpholin-4-yl)-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Example 51 and (6-chloropyridin-3-yl)boronic acid according to Method V and was isolated in 94% purity after purification
20 by preparative LC. LCMS (ES+) 468.0 (M+H)⁺, RT 4.03 minutes.

EXAMPLE 138

3'-{[(3S)-4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-3-yl]methyl}biphenyl-4-carboxamide

The *title compound* was prepared from Example 51 and (4-carbamoylphenyl)boronic acid according to Method V and was isolated in 98% purity after purification by preparative LC. LCMS (ES+) 476.0 (M+H)⁺, RT 3.14 minutes.

30

EXAMPLE 139

5,5-dimethyl-2-{(3*S*)-3-[3-(3-fluoropyridin-4-yl)benzyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (3-fluoropyridin-4-yl)boronic acid according to Method V and was isolated in 90% purity after purification
5 by preparative LC. LCMS (ES+) 452.0 (M+H)⁺, RT 3.57 minutes.

EXAMPLE 140

10 2-{(3*S*)-3-[3-(1-Benzyl-1*H*-pyrazol-4-yl)benzyl]morpholin-4-yl}-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (1-benzyl-1*H*-pyrazol-4-yl)boronic acid according to Method V and was isolated in 92% purity after purification by preparative LC. LCMS (ES+) 513.0 (M+H)⁺, RT 4.02 minutes.

15 **EXAMPLE 141**

5,5-Dimethyl-2-{(3*S*)-3-[3-(1-methyl-1*H*-pyrazol-4-yl)benzyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Example 51 and (1-methyl-1*H*-pyrazol-4-yl)boronic acid according to Method V and was isolated in 94% purity after purification
20 by preparative LC. LCMS (ES+) 437.0 (M+H)⁺, RT 3.32 minutes.

EXAMPLE 142

25 7,7-Dimethyl-2-(morpholin-4-yl)-4,6,7,8-tetrahydro-5*H*-[1,3]thiazolo[5,4-*b*]azepin-5-one

To a stirred solution of Example 48 (1.00 g, 3.77 mmol) in formic acid (40 mL) was added, dropwise, hydroxylamine-*O*-sulfonic acid (0.64 g, 5.66 mmol). After refluxing overnight the reaction mixture was quenched with ice/water and neutralised with aqueous 5% NaOH and then extracted with DCM (2 x 40 mL). The organics were
30 combined, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 3:1 DCM/EtOAc) gave the *title compound* (0.24 g, 22%) as an off-white solid. δ_H (DMSO-*d*₆) 10.77 (1H, s), 3.69 (4H, m), 3.42 (4H, m), 2.52 (2H, s), 2.25 (2H, s), 0.98 (6H, s). LCMS (ES+) 282.0 (M+H)⁺.

EXAMPLE 143

5 2-[(3S)-3-{[5-(Benzyloxy)-1H-indol-3-yl]methyl}morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Intermediate 124 and Intermediate 15 according to Method H and was isolated as a white solid (52%) after purification by trituration (Et₂O). δ_{H} (CDCl₃) 7.98 (1H, br. s), 7.62-7.21 (7H, m), 7.14 (1H, d, *J* 2.2 Hz), 6.98 (1H, dd, *J* 8.8 and 2.4 Hz), 5.20 (2H, s), 4.35 (1H, s), 4.09 (1H, d, *J* 7.3 Hz), 3.92
10 (1H, d, *J* 11.8 Hz), 3.78-3.63 (3H, m), 3.55 (1H, dd, *J* 11.8 and 1.9 Hz), 3.41 (1H, dd, *J* 13.7 and 10.9 Hz), 3.06 (1H, dd, *J* 13.9 and 4.1 Hz), 2.75 (2H, s), 2.40 (2H, s), 1.09 (3H, s), 1.08 (3H, s). LCMS (ES+) 502.0 (M+H)⁺.

EXAMPLE 144

15 5,5-Dimethyl-2-[(3S)-3-{[5-(hydroxy)-1H-indol-3-yl]methyl}morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4H)-one

The *title compound* was prepared from Intermediate 125 and Intermediate 15 according to Method H and was isolated as a white solid (62%) after purification by
20 trituration (Et₂O). δ_{H} (CDCl₃) 10.57 (1H, br. s), 8.58 (1H, s), 7.12-7.08 (2H, m), 7.03 (1H, d, *J* 2.0 Hz), 6.61 (1H, dd, *J* 8.6 and 2.2 Hz), 4.20-4.00 (1H, br. m), 3.98 (1H, d, *J* 7.2 Hz), 3.74-3.70 (2H, m), 3.64-3.48 (3H, m), 3.27-3.19 (1H, m), 2.84 (1H, dd, *J* 13.9 and 4.9 Hz), 2.69 (2H, s), 2.32 (2H, s), 1.05 (6H, s). LCMS (ES+) 412.0 (M+H)⁺.

25 **EXAMPLE 145**

7,7-Dimethyl-2-{(3S)-3-[(5-hydroxy-1H-indol-3-yl)methyl]morpholin-4-yl}-5,6,7,8-tetrahydro-4H-[1,3]thiazolo[5,4-c]azepin-4-one

The *title compound* was prepared from Intermediate 125 and Intermediate 71
30 according to Method U and was isolated as a white solid (13%) after purification by preparative LC. δ_{H} (CDCl₃) 10.52 (1H, br. s), 8.51 (1H, br. s), 7.63 (1H, t, *J* 4.9 Hz), 7.09 (1H, d, *J* 8.6 Hz), 7.03 (2H, s), 6.58 (1H, dd, *J* 8.6 and 2.3 Hz), 3.94-3.91 (2H, m), 3.66

(1H, d, *J* 11.4 Hz), 3.60-3.40 (4H, m), 3.26-3.12 (1H, m), 2.91 (1H, d, *J* 4.9 Hz), 2.78-2.76 (1H, m), 2.71 (2H, d, *J* 3.1 Hz), 0.96 (6H, s). LCMS (ES+) 427.0(M+H)⁺.

EXAMPLE 146

5

3-{[(3*S*)-4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-3-yl]methyl}-1*H*-indol-5-yl methanesulfonate

To a stirred solution of Example 144 (0.11 g, 0.25 mmol) in THF (5 mL) was added, at 0°C, methanesulphonyl chloride (0.20 mL, 2.68 mmol). After stirring for 96 h at
10 r.t., the reaction mixture was evaporated *in vacuo* and DCM (10 mL) and water (5 mL) were added. The aqueous layer was extracted with DCM (2 x 10 mL) and the combined organic layers were washed with water (3 x 10 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography (SiO₂, DCM, followed by 1:1 DCM/EtOAc, followed by EtOAc) to give the *title compound* (0.06
15 g, 47%) as a pale yellow solid. δ_{H} (DMSO-*d*₆) 11.12 (1H, s), 7.83 (1H, s), 7.39 (1H, d, *J* 8.7 Hz), 7.33 (1H, d, *J* 2.2 Hz), 7.07 (1H, dd, *J* 8.8 and 2.3 Hz), 4.40-4.20 (1H, m), 3.98 (1H, d, *J* 9.6 Hz), 3.75 (1H, d, *J* 11.7 Hz), 3.59-3.49 (4H, m), 3.33 (3H, s), 3.31-3.09 (1H, m), 2.95 (1H, dd, *J* 13.7 and 4.7 Hz), 2.69 (2H, s), 2.30 (2H, s), 1.04 (3H, s), 1.03 (3H, s). LCMS (ES+) 490.3 (M+H)⁺.

20

EXAMPLE 147 (METHOD Z)

2-[3-(3,4-Dihydroisoquinolin-2(1*H*)-ylcarbonyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a stirred solution of 1,2,3,4-tetrahydroisoquinoline (0.08 mL, 0.64 mmol) in DMF (2 mL) was added Intermediate 64 (0.20 g, 0.64 mmol), HBTU (0.25 g, 0.64 mmol) and DIPEA (0.33 mL, 1.92 mmol) dropwise. The reaction mixture was stirred for 2 h at ambient temperature and then concentrated *in vacuo*. Purification by column chromatography (SiO₂, 0-10% MeOH in DCM) followed by trituration with MeOH/Et₂O
30 gave the *title compound* (0.19 g, 69%) as a pink solid. δ_{H} (DMSO-*d*₆, 130°C) 7.20 (4H, br. s), 5.18-5.15 (1H, m), 4.78 (1H, d, *J* 6.5 Hz), 4.61 (1H, d, *J* 6.5 Hz), 4.10 (1H, d, *J* 12.0 Hz), 4.02-3.91 (3H, m), 3.80-3.76 (2H, m), 3.72-3.64 (1H, m), 3.60-2.54 (1H, m), 3.00-2.79 (4H, m), 2.30 (2H, s), 1.05 (3H, s), 1.02 (3H, s). LCMS (ES+) 426.0 (M+H)⁺.

EXAMPLE 148

2-[3-(3,4-Dihydroquinoxalin-1(2*H*)-ylcarbonyl)morpholin-4-yl]-5,5-dimethyl-5,6-
5 dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Intermediate 64 and 1,2,3,4-tetrahydroquinoxaline according to Method Z and was isolated as an off-white solid (45%) after purification by preparative LC. δ_{H} (DMSO- d_6) 7.30-7.23 (1H, br. m), 6.99-6.88 (1H, br. m), 6.69-6.62 (1H, br. m), 6.56-6.46 (1H, br. m), 6.34-6.22 (1H, br. m),
10 5.48-5.35 (1H, br. m), 4.20-4.11 (1H, br. m), 4.04-3.95 (1H, br. m), 3.90-3.36 (6H, br. m), 3.28-3.08 (2H, br. m), 2.76-2.62 (2H, br. m), 2.39-2.26 (2H, br. m), 1.08-1.00 (6H, br. m). LCMS (ES+) 426.5 (M+H)⁺.

EXAMPLE 149

15 5,5-Dimethyl-2-{3-[(6-methyl-3,4-dihydroquinolin-1(2*H*)-yl)carbonyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Intermediate 64 and 6-methyltetrahydroquinoline according to Method O and was isolated as an off-white solid (7%) after
20 purification by column chromatography (SiO₂, from 100% heptane to 60% EtOAc). δ_{H} (DMSO- d_6) 7.42 (1H, d, *J* 8.0 Hz), 7.10-7.00 (2H, m), 5.40 (1H, br. s), 4.10-3.95 (2H, m), 3.90-3.40 (6H, m), 2.80-2.60 (4H, m), 2.35 (2H, m), 2.25 (3H, s), 2.00-1.75 (2H, m), 1.05 (3H, s), 1.04 (3H, s). LCMS (ES+) 440.0 (M+H)⁺.

EXAMPLE 150

25 5,5-Dimethyl-2-{3-[(6-methoxy-3,4-dihydroquinolin-1(2*H*)-yl)carbonyl]morpholin-4-yl}-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

The *title compound* was prepared from Intermediate 64 and 6-methoxytetrahydroquinoline according to Method O and was isolated as a white solid (3%) after purification
30 by column chromatography (SiO₂, from 100% heptane to 100% EtOAc). δ_{H} (CDCl₃) 7.55 (1H, d, *J* 9.5 Hz), 6.82-6.75 (2H, m), 5.50 (1H, br. s), 4.35-4.22 (1H, m), 4.20-4.00

(2H, m), 3.80 (3H, s), 3.70-3.20 (5H, m), 2.80-2.60 (4H, m), 2.45-2.33 (2H, m), 2.20-2.10 (1H, m), 1.85-1.70 (1H, m), 1.15 (3H, s), 1.14 (3H, s). LCMS (ES+) 456.0 (M+H)⁺.

EXAMPLE 151 (METHOD AB)

5

5,5-Dimethyl-2-[(3*S*)-3-(3-phenylprop-2-yn-1-yl)morpholin-4-yl]-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

To a stirred solution of Intermediate 127 (0.05 g, 0.25 mmol) in IPA (2 mL) was added Intermediate 15 (0.07 g, 0.28 mmol) and DIPEA (0.05 mL, 0.31 mmol). The reaction mixture was then heated under microwave irradiation in a sealed tube to 160°C for 1.5 h. After cooling to r.t. the solvent was removed *in vacuo* and the crude material was purified by column chromatography (SiO₂, 1.5:1 EtOAc/hexanes) to give the *title compound* (0.02 g, 20%) as a yellow oil. δ_{H} (DMSO-d₆) 7.32-7.22 (5H, m), 4.33 (1H, m), 3.96-3.92 (2H, m), 3.71-3.66 (2H, m), 3.60-3.48 (2H, m), 2.95 (2H, d, *J* 7.7 Hz), 2.63 (2H, s), 2.29-2.27 (2H, m), 1.01 (6H, s). LCMS (ES+) 381.0 (M+H)⁺.

10
15

EXAMPLE 152

2-[(3*S*)-3-(1*H*-Benzotriazol-1-ylmethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

20

The *title compound* was prepared from Intermediate 128 and Intermediate 15 according to Method AB and was isolated as a pale yellow solid (47%) after purification by column chromatography (SiO₂, 1:1 EtOAc/hexanes). δ_{H} (DMSO-d₆) 7.95 (2H, dd, *J* 17.6 and 8.4 Hz), 7.57 (1H, m), 7.36 (1H, m), 5.15 (2H, m), 4.77 (1H, m), 4.06-3.84 (3H, m), 3.83-3.57 (3H, m), 2.33-1.91 (4H, m), 0.92 (3H, s), 0.87 (3H, s). LCMS (ES+) 398.3 (M+H)⁺.

25

EXAMPLE 153

2-[(3*S*)-3-(1*H*-Benzimidazol-1-ylmethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one

30

The *title compound* was prepared from Intermediate 129 and Intermediate 15 according to Method AB and was isolated as a white solid (13%) after purification by

column chromatography (SiO₂, 1:1 EtOAc/hexanes). δ_{H} (DMSO-d₆) 8.11 (1H, s), 7.76 (1H, d, *J* 7.9 Hz), 7.54 (1H, d, *J* 7.9 Hz), 7.27 (1H, m), 7.17 (1H, m), 4.65 (3H, m), 4.03-3.83 (3H, m), 3.70-3.55 (3H, m), 2.36 (1H, d, *J* 17.0 Hz), 2.15 (3H, m), 0.94 (3H, s), 0.91 (3H, s). LCMS (ES+) 397.3 (M+H)⁺.

5

EXAMPLE 154

2-[2-(Aminomethyl)morpholin-4-yl]-5,5-dimethyl-5,6-dihydro-1,3-benzothiazol-7(4H)-one

10 To a stirred solution of Intermediate 131 (0.46 g, 1.07 mmol) in EtOH (20 mL) was added hydrazine hydrate (1.00 mL, 19.00 mmol) and the reaction mixture was heated to 80°C for 2 h. After cooling, the reaction mixture was concentrated *in vacuo* and purification by preparative HPLC gave the *title compound* (0.30 g, 94%) as a white solid. δ_{H} (CDCl₃) 4.10-3.90 (2H, m), 3.80-3.60 (5H, m), 3.30 (1H, m), 3.00 (1H, m), 2.85 (2H, 15 m), 2.70 (2H, s), 2.40 (2H, s), 1.10 (6H, s). LCMS (ES+) 296.0 (M+H)⁺.

EXAMPLE 155 (METHOD AD)

20 *N*-(1-Benzothien-3-ylmethyl)-2-[4-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-2-yl]acetamide

To a stirred solution of 1-(1-benzothien-3-yl)methanamine (0.03 g, 0.15 mmol) and Intermediate 130 (0.18 g, 0.15 mmol) in DMF (2 mL) was added HBTU (0.07 g, 0.18 mmol) and the reaction mixture was stirred at room temperature for 4 h. The solvent was then removed *in vacuo* and purification by preparative HPLC gave the *title compound* 25 (0.05 g, 57%) as a white solid. δ_{H} (CDCl₃) 7.90 (1H, m), 7.80 (1H, m), 7.40 (3H, m), 6.30 (1H, m), 4.70 (2H, d, *J* 5.6 Hz), 4.00 (3H, m), 3.70 (2H, m), 3.18 (1H, dt, *J* 12.6 and 4.0 Hz), 2.99 (1H, dd, *J* 11.0 and 2.2 Hz), 2.70 (2H, s), 2.46 (2H, m), 2.40 (2H, s) 1.10 (6H, s). LCMS (ES+) 470.0 (M+H)⁺.

30

EXAMPLE 156

N-{[4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-2-yl]methyl}-1-benzofuran-2-carboxamide

The *title compound* was prepared from 2-benzofuran carboxylic acid and Example 154 according to Method AD and was isolated as a white solid (39%) after purification by preparative HPLC. δ_{H} (CDCl_3) 7.68 (1H, d, J 7.8 Hz), 7.60-7.40 (3H, m), 7.30 (1H, t, J 7.8 Hz), 7.00 (1H, m), 4.10 (2H, m), 3.90-3.70 (3H, m), 3.50 (1H, m), 3.35 (1H, m), 3.30 (1H, m), 3.10 (1H, m), 2.70 (2H, s), 2.40 (2H, s), 1.10 (6H, s). LCMS (ES+) 440.0 (M+H)⁺.

EXAMPLE 157

10 *N*-{[4-(5,5-Dimethyl-7-oxo-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)morpholin-2-yl]methyl}benzenesulfonamide

To a stirred solution of Example 154 (0.10 g, 0.34 mmol) and pyridine (0.04 g, 0.51 mmol) in DCM (10 mL) was added benzenesulphonyl chloride (0.06 g, 0.34 mmol) and the reaction mixture was stirred at room temperature for 4 h. The solvent was then removed *in vacuo* and purification by preparative HPLC gave the *title compound* (0.03 g, 20%) as a white solid. δ_{H} (CDCl_3) 7.90 (2H, dd, J 6.9 and 1.5 Hz), 7.60 (3H, m), 4.87 (1H, t, J 6.0 Hz), 4.00 (2H, m), 3.75 (1H, m), 3.60 (2H, m), 3.20 (2H, m), 3.00 (2H, m), 2.70 (2H, s), 2.40 (2H, s), 1.10 (6H, s). LCMS (ES+) 436.0 (M+H)⁺.

20 EXAMPLE 158

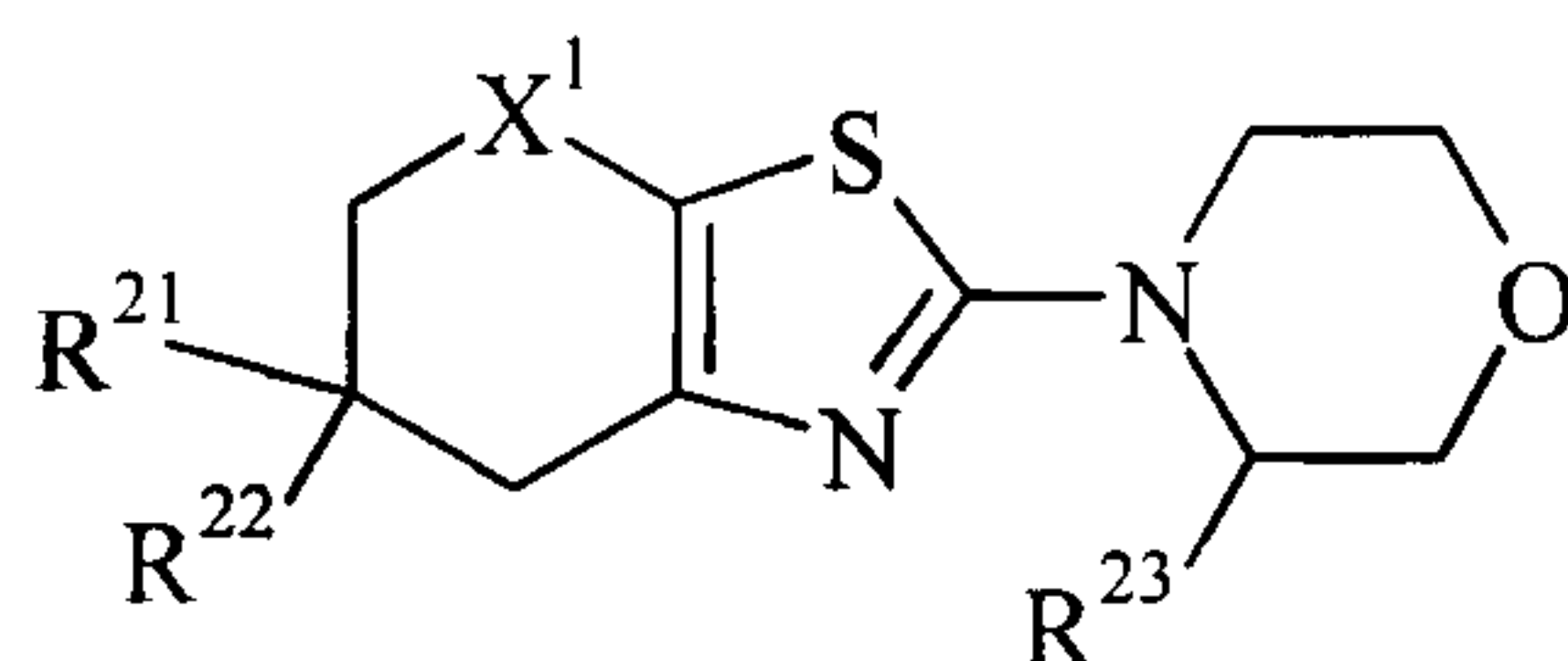
(7*E*)-5,5-Dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1,3-benzothiazol-7(4*H*)-one hydrazone

To a stirred solution of Example 48 (0.27 g, 1.00 mmol) in EtOH (10 mL) was added hydrazine monohydrate (0.05 g, 0.05 mL, 1.00 mmol) and a catalytic amount of AcOH. The reaction mixture was then heated to reflux for 8 h. Upon cooling, the reaction mixture was poured into aqueous sat. NaHCO_3 (50 mL) and extracted with DCM (2 x 50 mL). The combined organic fractions were dried over MgSO_4 , filtered and concentrated *in vacuo* to give the *title compound* as a white solid (0.10 g, 35%). δ_{H} (DMSO- d_6) 5.93 (2H, br. s), 3.68 (4H, t, J 4.9 Hz), 3.36 (4H, t, J 4.9 Hz), 2.42 (2H, s), 2.22 (2H, s), 1.00 (6H, s). LCMS (ES+) 281.2 (M+H)⁺.

Claims:

1. A compound of formula (IIB), or a pharmaceutically acceptable salt or solvate thereof:

5

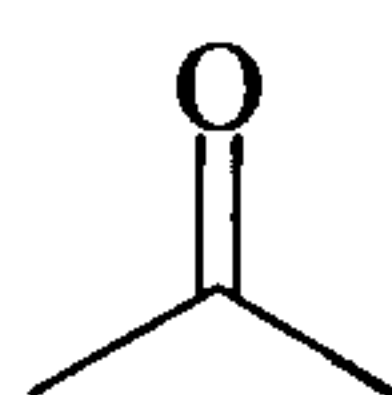


(IIB)

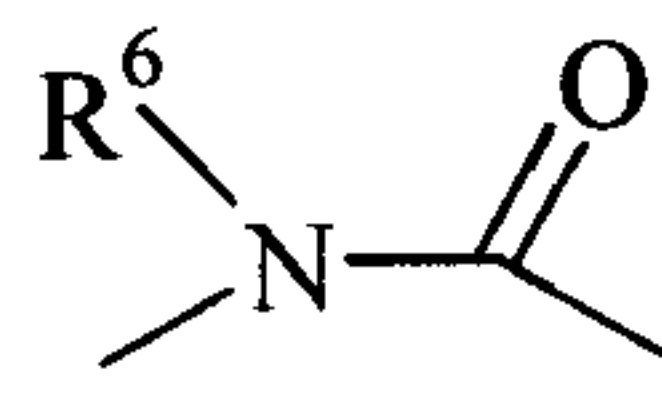
wherein

-X¹- represents a group of formula (a) or (e):

10



(a)



(e)

R⁶ represents hydrogen or C₁₋₆ alkyl;

R²¹ represents hydrogen or C₁₋₆ alkyl; and

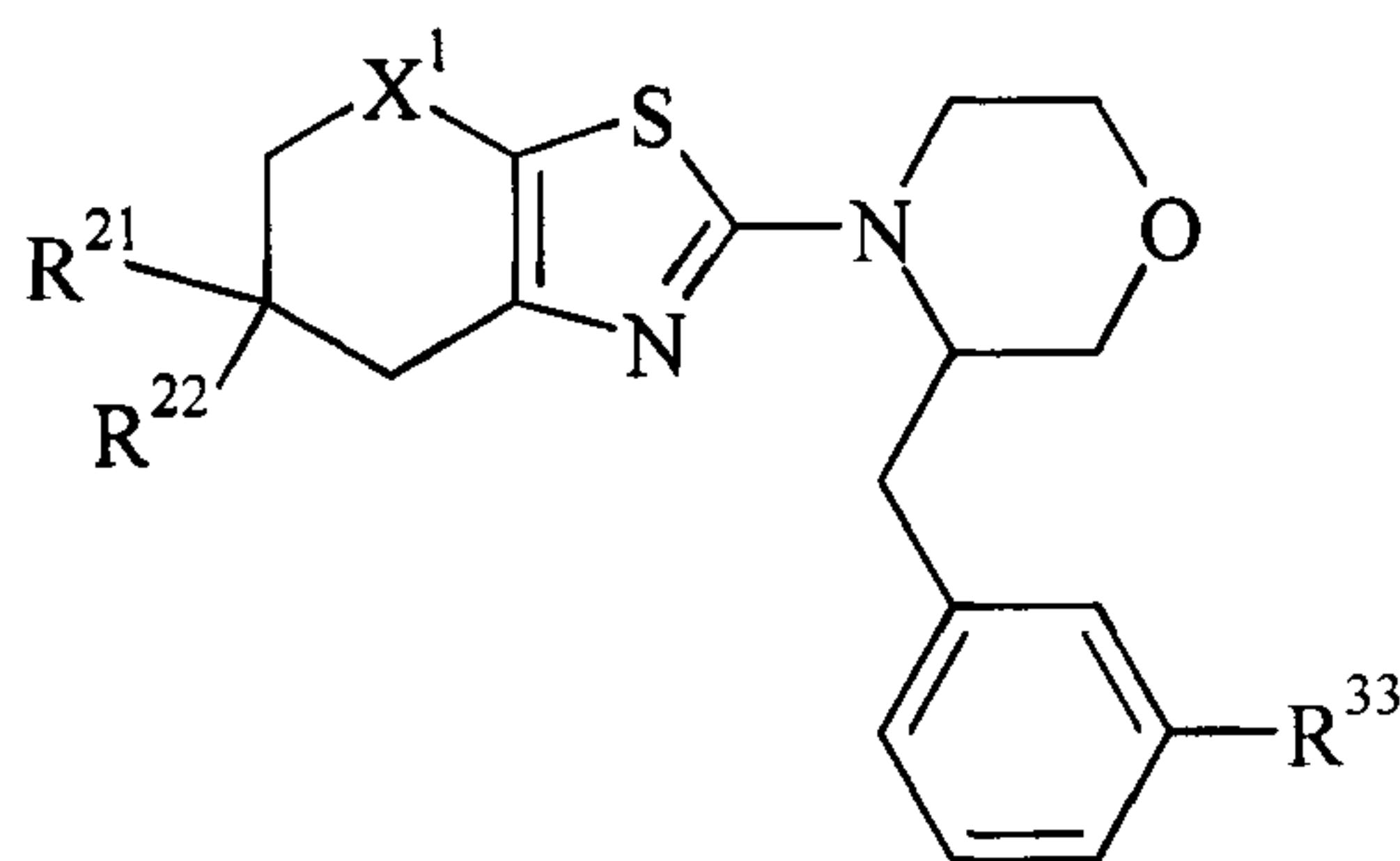
15 R²² represents hydrogen; or C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents independently selected from halogen, C₁₋₆ alkoxy or C₁₋₆ alkylthio; or

R²¹ and R²², when taken together with the carbon atom to which they are both attached, represent C₃₋₇ cycloalkyl; and

20 R²³ represents C₁₋₆ alkyl, aryl(C₁₋₆)alkyl, aryl(C₂₋₆)alkynyl, biaryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkylcarbonyl, heteroaryl(C₁₋₆)alkyl, heteroaryl-aryl(C₁₋₆)alkyl or aryl-heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents independently selected from halogen, cyano, nitro, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, aryl(C₁₋₆)alkoxy, methylenedioxy, 25 C₁₋₆ alkylthio, arylthio, C₁₋₆ alkylsulphonyl, arylsulphonyl, C₁₋₆ alkylsulphonyloxy,

amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, pyridinylamino, pyrrolidinyl, morpholinyl, C₂₋₆ alkylcarbonylamino, benzofurylcarbonylamino, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl.

2. A compound as claimed in claim 1 wherein R⁶ represents hydrogen.
3. A compound as claimed in claim 1 or claim 2 wherein R²¹ represents methyl.
4. A compound as claimed in claim 1, 2 or 3 wherein R²² represents methyl.
5. A compound as claimed in claim 1, 2, 3 or 4 wherein R²³ represents C₁₋₆ alkyl, aryl(C₁₋₆)alkyl, biaryl(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkyl or heteroaryl-aryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents as defined in claim 1.
6. A compound as claimed in claim 5 wherein R²³ represents indolylmethyl, which group may be unsubstituted, or substituted by one or more substituents as defined in claim 1.
7. A compound as claimed in claim 1 represented by formula (IID), or a pharmaceutically acceptable salt or solvate thereof:



(IID)

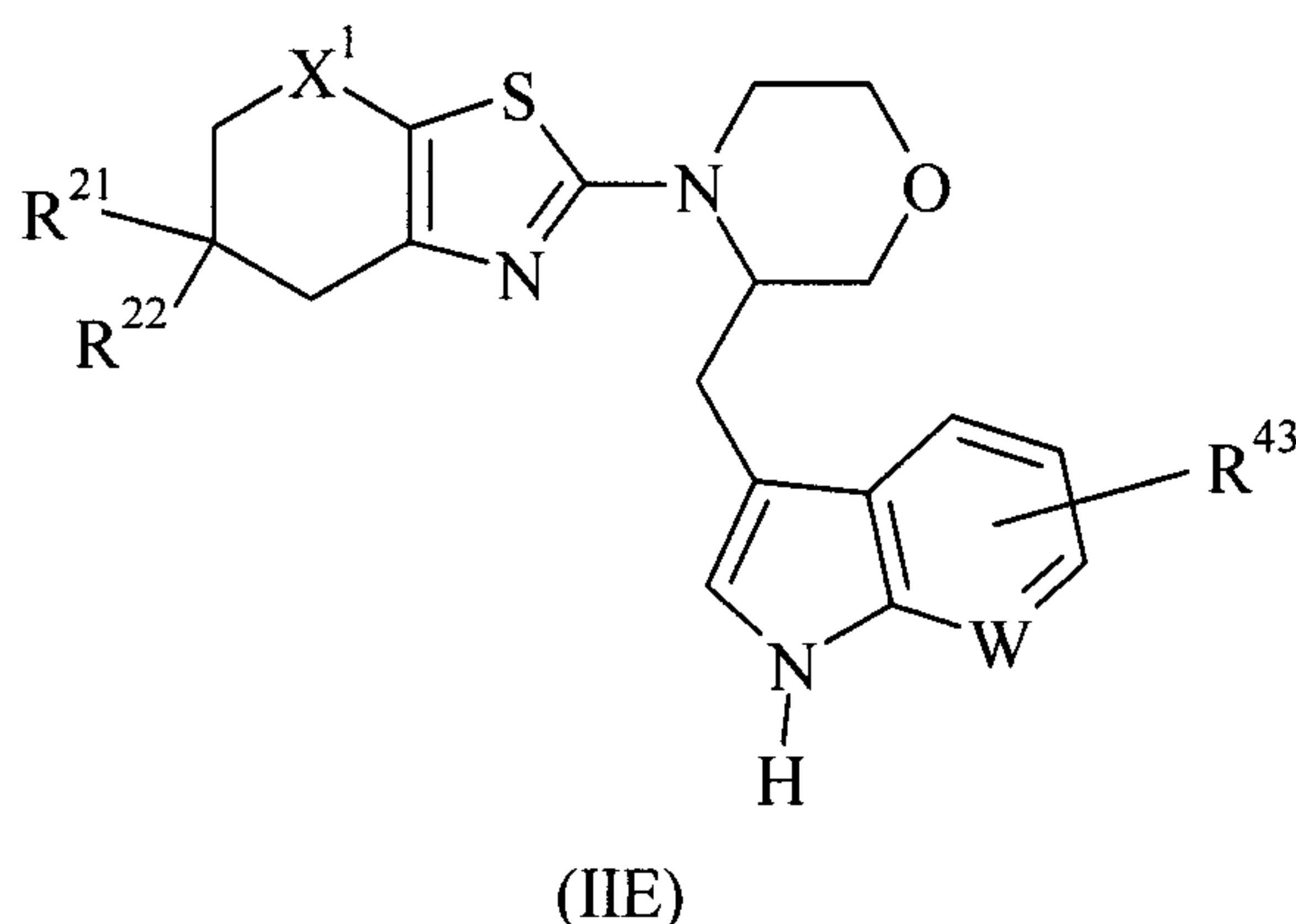
wherein

$-X^1$ -, R^{21} and R^{22} are as defined in claim 1; and

R^{33} represents phenyl, naphthyl, benzofuryl, thienyl, benzothienyl, indolyl,
 5 isoxazolyl, pyrazolyl, pyridinyl or pyrimidinyl, any of which groups may be optionally
 substituted by one or more substituents independently selected from halogen, cyano, C_{1-6}
 alkyl, hydroxy(C_{1-6})alkyl, trifluoromethyl, C_{1-6} alkoxy, trifluoromethoxy, aryloxy,
 methylenedioxy, C_{1-6} alkylthio, arylsulphonyl, amino, C_{2-6} alkylcarbonylamino, C_{1-6}
 alkylsulphonylamino, C_{2-6} alkylcarbonyl and aminocarbonyl.

10

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



15

wherein

$-X^1$ -, R^{21} and R^{22} are as defined in claim 1;

W represents CH or N; and

R^{43} represents hydrogen, halogen, cyano, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl,
 20 trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, trifluoromethoxy, aryloxy,
 aryl(C_{1-6})alkoxy, C_{1-6} alkylthio, arylsulphonyl, C_{1-6} alkylsulphonyloxy, amino, C_{2-6}
 alkylcarbonylamino, C_{1-6} alkylsulphonylamino, C_{2-6} alkylcarbonyl or aminocarbonyl.

9. A compound as claimed in claim 8 wherein W represents CH.

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10. A compound as claimed in claim 8 or claim 9 wherein R⁴³ represents hydrogen.

11. A pharmaceutical composition comprising a compound of formula (IIB)
5 according to claim 1 in association with a pharmaceutically acceptable carrier.

12. A compound of formula (IIB) according to claim 1 for use in therapy.

13. A compound of formula (IIB) according to claim 1 for use in the treatment
10 and/or prevention of disorders for which the administration of a selective PI3K inhibitor is indicated.

14. The use of a compound of formula (IIB) according to claim 1 for the
manufacture of a medicament for the treatment and/or prevention of disorders for which
15 the administration of a selective PI3K inhibitor is indicated.