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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 July 2008 (31.07.2008)

PCT

(10) International Publication Number
WO 2008/090382 A1

(51) International Patent Classification:
C07D 263/34 (2006.01) *C07D 413/14* (2006.01)
C07D 263/48 (2006.01) *C07D 417/04* (2006.01)
C07D 277/40 (2006.01) *C07D 417/14* (2006.01)
C07D 277/42 (2006.01) *A61K 31/4164* (2006.01)
C07D 277/46 (2006.01) *A61K 31/4178* (2006.01)
C07D 277/48 (2006.01) *A61K 31/421* (2006.01)
C07D 277/56 (2006.01) *A61K 31/422* (2006.01)
C07D 413/04 (2006.01)

(21) International Application Number:
PCT/GB2008/050052

(22) International Filing Date: 25 January 2008 (25.01.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0701426.9 25 January 2007 (25.01.2007) GB

(71) Applicant *(for all designated States except US)*: **THE UNIVERSITY OF SHEFFIELD** [GB/GB]; Firth Court, Western Bank, Sheffield South Yorkshire S10 2TN (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **CHEN, Beining** [CN/GB]; Department of Chemistry, University of Sheffield, Brook Hill, Sheffield South Yorkshire S3 7HF (GB).

(74) Agent: **Harrison, Goddard, Foote**; Belgrave Hall, Belgrave Street, Leeds Yorkshire LS2 8DD (GB).

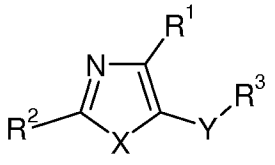
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, 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*

WO 2008/090382 A1

(54) Title: THIAZOLE AND OXAZOLE DERIVATIVES FOR USE IN THE TREATMENT OF PRION DISEASES, CANCER AND CONDITIONS OF THE CENTRAL NERVOUS SYSTEM AS WELL AS IN THE REGULATION OF STEM CELLS



(I)

(57) Abstract: Compounds of the formula (I) are provided: Fomula (I) wherein X, Y, R1, R2 and R3 are as defined in the specification. The compounds may be useful in the treatment of various diseases and conditions, in particular prion diseases.

THIAZOLE AND OXAZOLE DERIVATIVES FOR THE USE IN THE TREATMENT OF PRION DISEASES, CANCER AND CONDITIONS OF THE CENTRAL NERVOUS SYSTEM AS WELL AS IN THE REGULATION OF STEM CELLS

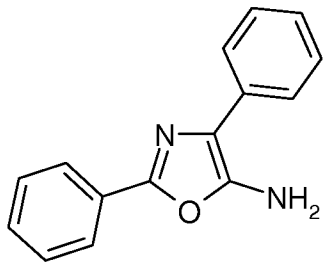
Field of the Invention

This invention relates to compounds and their use in therapy, especially in the treatment of prion diseases and the regulation of stem cells.

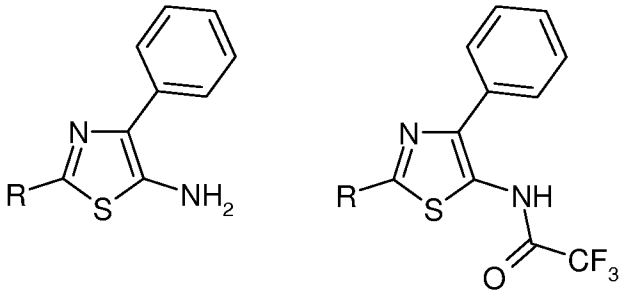
Background to the Invention

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are invariably fatal neurodegenerative disorders affecting humans and animals. As yet, no effective curative or prophylactic therapy exists. Prominent examples of prion diseases include bovine spongiform encephalopathy (BSE, cattle), scrapie (sheep), chronic wasting disorder (CWD, deer and elk) and transmissible mink encephalopathy (TME). Since a new variant of the human TSE Creutzfeldt-Jacob disease (vCJD) was discovered, thought to have been triggered by the consumption of contaminated beef products, prion diseases have been the focus of much research effort. They represent a highly significant risk to public health due to transmission both to and between humans. TSEs are associated with a post-translational conversion of the cell-surface glycosylphosphatidylinositol (GPI)-anchored protein PrP^{C} (or PrP^{sen}) to a partially protease resistant isoform denoted PrP^{Sc} (or PrP^{res}).

Lichtenberger *et al* (*Bull. Soc. Chim. Fr.* 1956, 1184-1192) report the compound 2,4-diphenyloxazol-5-ylamine, i.e.:



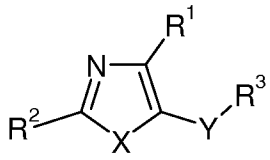
Thompson *et al* (*Tetrahedron Lett.* 2006, *47*, 2361-2364) report the synthesis of the following 5-aminothiazole compounds:



wherein, in each case, R is selected from phenyl, 4-methoxyphenyl, thiophen-2-yl, cyclohexyl and isopropyl.

Summary of the Invention

According to the present invention, there is provided a compound of the formula (I):



(I)

wherein

X is oxygen or sulphur;

Y is a bond or a linker having 1 to 10 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^5)- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^7;

one of R^1 and R^2 is selected from carbocyclyl and heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7; and the other is -Z-R^4;

R^3 is selected from hydrogen; R^7; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -$(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7;

Z is a bond or a linker having 1 to 10 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -$S(O)_l$-, -$N(R^5)$- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^7;

R^4 is selected from hydrogen; R^7; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -$(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7;

R^5 is selected from R^6, -OR^6, -$C(O)R^6$, -$C(O)OR^6$ and -$S(O)_lR^6$;

R^6 is selected from hydrogen; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -$(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7;

each R^7 is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, -OR^8, -$C(O)R^8$, -$C(O)OR^8$, -$OC(O)R^8$, -$S(O)_lR^8$, -$N(R^8)R^9$, -$C(O)N(R^8)R^9$, -$S(O)_lN(R^8)R^9$ and R^{10};

R^8 and R^9 are each independently hydrogen or R^{10};

R^{10} is selected from hydrocarbyl and -$(CH_2)_k$-heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy, C_{1-6} alkyl and C_{1-6} alkoxy;

k is 0, 1, 2, 3, 4, 5 or 6; and

l is 0, 1 or 2;

or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides a pharmaceutical formulation comprising a compound of formula (I) and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the invention relates to the use of a compound of formula (I), for the manufacture of a medicament for the treatment, prevention or delay of progression of a prion disease. A method of treating, preventing or delaying progression of a prion disease is also provided, which involves administering a therapeutically effective amount of a compound of the invention to a subject.

Compounds of the invention may also be useful in the regulation of stem cells. Accordingly, in another aspect there is provided a method of regulating stem cell activity, which comprises contacting one or more stem cells with a compound of the invention. The compounds may also be useful in the treatment, prevention or delay of progression of cancer and diseases or conditions of the central nervous system, or in regenerative medicine.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

Description of Various Embodiments

Hydrocarbyl

The term "hydrocarbyl" as used herein includes reference to moieties consisting exclusively of hydrogen and carbon atoms; such a moiety may comprise an aliphatic and/or an aromatic moiety. The moiety may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. Examples of hydrocarbyl groups include C_{1-6} alkyl (e.g. C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl); C_{1-6} alkyl substituted by aryl (e.g. benzyl) or by cycloalkyl (e.g cyclopropylmethyl); cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl); alkenyl (e.g. 2-butenyl); alkynyl (e.g. 2-butynyl); aryl (e.g. phenyl, naphthyl or fluorenyl) and the like.

Alkyl

The terms "alkyl" and "C_{1-6} alkyl" as used herein include reference to a straight or branched chain alkyl moiety having 1, 2, 3, 4, 5 or 6 carbon atoms. This term includes reference to groups such as methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, sec-butyl or tert-butyl), pentyl, hexyl and the like. In particular, alkyl may have 1, 2, 3 or 4 carbon atoms.

Alkenyl

The terms "alkenyl" and "C_{2-6} alkenyl" as used herein include reference to a straight or branched chain alkyl moiety having 2, 3, 4, 5 or 6 carbon atoms and having, in addition, at least one double bond, of either E or Z stereochemistry where applicable. This term includes reference to groups such as ethenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, 2-hexenyl and 3-hexenyl and the like.

Alkynyl

The terms "alkynyl" and "C_{2-6} alkynyl" as used herein include reference to a straight or branched chain alkyl moiety having 2, 3, 4, 5 or 6 carbon atoms and having, in addition, at least one triple bond. This term includes reference to groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl and 3-hexynyl and the like.

Alkoxy

The terms “alkoxy” and "C_{1-6} alkoxy" as used herein include reference to -O-alkyl, wherein alkyl is straight or branched chain and comprises 1, 2, 3, 4, 5 or 6 carbon atoms. In one class of embodiments, alkoxy has 1, 2, 3 or 4 carbon atoms. This term includes reference to groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, hexoxy and the like.

Cycloalkyl

The term “cycloalkyl” as used herein includes reference to an alicyclic moiety having 3, 4, 5, 6, 7 or 8 carbon atoms. The group may be a bridged or polycyclic ring system. More often cycloalkyl groups are monocyclic. This term includes reference to groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]octyl and the like.

Cycloalkenyl

The term “cycloalkenyl” as used herein includes reference to a non-aromatic cycloalkyl group having a double bond between one or more pairs of ring carbon atoms. The group

may be a bridged or polycyclic ring system. More often cycloalkenyl groups are monocyclic. This term includes reference to groups such as cyclopentadienyl and the like.

Aryl

The term "aryl" as used herein includes reference to an aromatic ring system comprising 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring carbon atoms. Aryl is often phenyl but may be a polycyclic ring system, having two or more rings, at least one of which is aromatic. This term includes reference to groups such as phenyl, naphthyl, fluorenyl, azulenyl, indenyl, anthryl and the like.

Carbocyclyl

The term "carbocyclyl" as used herein includes reference to a saturated (e.g. cycloalkyl) or unsaturated (e.g. cycloalkenyl or aryl) ring moiety having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 carbon ring atoms. In particular, carbocyclyl includes a 3- to 10-membered ring or ring system and, in particular, a 5- or 6-membered ring, which may be saturated or unsaturated. A carbocyclic moiety is, for example, selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]octyl, phenyl, naphthyl, fluorenyl, azulenyl, indenyl, anthryl and the like.

Heterocyclyl

The term "heterocyclyl" as used herein includes reference to a saturated (e.g. heterocycloalkyl) or unsaturated (e.g. heteroaryl) heterocyclic ring moiety having from 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, at least one of which is selected from nitrogen, oxygen, phosphorus, silicon and sulphur. In particular, heterocyclyl includes a 3- to 10-membered ring or ring system and more particularly a 5- or 6-membered ring, which may be saturated or unsaturated.

A heterocyclic moiety is, for example, selected from oxiranyl, azirinyl, 1,2-oxathiolanyl, imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2*H*-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl,

pyridazinyl, morpholinyl, thiomorpholinyl, especially thiomorpholino, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl, chromanyl and the like.

Heterocycloalkyl

The term "heterocycloalkyl" as used herein includes reference to a saturated heterocyclic moiety having 3, 4, 5, 6 or 7 ring carbon atoms and 1, 2, 3, 4 or 5 ring heteroatoms selected from nitrogen, oxygen, phosphorus and sulphur. The group may be a polycyclic ring system but more often is monocyclic. This term includes reference to groups such as azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, oxiranyl, pyrazolidinyl, imidazolyl, indolizidinyl, piperazinyl, thiazolidinyl, morpholinyl, thiomorpholinyl, quinolizidinyl and the like.

Heteroaryl

The term "heteroaryl" as used herein includes reference to an aromatic heterocyclic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, at least one of which is selected from nitrogen, oxygen and sulphur. The group may be a polycyclic ring system, having two or more rings, at least one of which is aromatic, but is more often monocyclic. This term includes reference to groups such as pyrimidinyl, furanyl, benzo[b]thiophenyl, thiophenyl, pyrrolyl, imidazolyl, pyrrolidinyl, pyridinyl, benzo[b]furanyl, pyrazinyl, purinyl, indolyl, benzimidazolyl, quinolinyl, phenothiazinyl, triazinyl, phthalazinyl, 2H-chromenyl, oxazolyl, isoxazolyl, thiazolyl, isoindolyl, indazolyl, purinyl, isoquinolinyl, quinazolinyl, pteridinyl and the like.

Halogen

The term "halogen" as used herein includes reference to F, Cl, Br or I. In a particular, halogen may be F or Cl, of which F is more common.

Substituted

The term "substituted" as used herein in reference to a moiety means that one or more, especially up to 5, more especially 1, 2 or 3, of the hydrogen atoms in said moiety are replaced independently of each other by the corresponding number of the described substituents. The term "optionally substituted" as used herein means substituted or unsubstituted.

It will, of course, be understood that substituents are only at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort whether a particular substitution is possible. For example, amino or hydroxy groups with free hydrogen may be unstable if bound to carbon atoms with unsaturated (e.g. olefinic) bonds. Additionally, it will of course be understood that the substituents described herein may themselves be substituted by any substituent, subject to the aforementioned restriction to appropriate substitutions as recognised by the skilled man.

Pharmaceutically acceptable

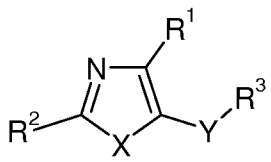
The term "pharmaceutically acceptable" as used herein includes reference to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. This term includes acceptability for both human and veterinary purposes.

Independently

Where two or more moieties are described as being "each independently" selected from a list of atoms or groups, this means that the moieties may be the same or different. The identity of each moiety is therefore independent of the identities of the one or more other moieties.

Compounds

Compounds of the invention are of the formula (I):



(I)

wherein

X is oxygen or sulphur;

Y is a bond or a linker having 1 to 10 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^5)- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^7;

one of R^1 and R^2 is selected from carbocyclyl and heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7; and the other is -Z-R^4;

R^3 is selected from hydrogen; R^7; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -$(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7;

Z is a bond or a linker having 1 to 10 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^5)- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^7;

R^4 is selected from hydrogen; R^7; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -$(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7;

R^5 is selected from R^6, -OR^6, -C(O)R^6, -C(O)OR^6 and -S(O)$_l R^6$;

R^6 is selected from hydrogen; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -$(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7;

each R^7 is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, =NR^8, -OR^8, -C(O)R^8, -C(O)OR^8, -OC(O)R^8, -S(O)$_l R^8$, -N(R^8)R^9, -C(O)N(R^8)R^9, -S(O)$_l$N(R^8)R^9 and R^{10};

R^8 and R^9 are each independently hydrogen or R^{10};

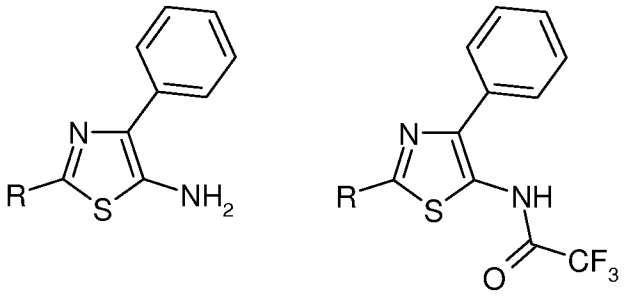
R^{10} is selected from hydrocarbyl and -$(CH_2)_k$-heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy, C_{1-6} alkyl and C_{1-6} alkoxy;

k is 0, 1, 2, 3, 4, 5 or 6; and

l is 0, 1 or 2;

or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound is not 2,4-diphenyloxazol-5-ylamine or a compound of the following formulae:



wherein, in each case, R is selected from phenyl, 4-methoxyphenyl, thiophen-2-yl, cyclohexyl and isopropyl.

Further embodiments of the invention are described below. It will be appreciated that the features specified in each embodiment may be combined with other specified features, to provide yet further embodiments.

X

In one class of compounds, X is oxygen. In another class of compounds, X is sulphur.

R^1 & R^2

According to formula (I), one of R^1 and R^2 is selected from carbocyclyl and heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7; and the other is -Z-R^4,

wherein Z is a bond or a linker having 1 to 10 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^5)- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^7; and R^4 is selected from hydrogen; R^7; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -(CH_2)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

In one embodiment, R^1 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7; and R^2 is -Z-R^4.

In another embodiment, R^2 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7; and R^1 is -Z-R^4.

Of mention are compounds in which Z is a bond or one of the following linkers:

-Z^1-;
-Z^1-Z^2-;
-Z^1-Z^2-Z^3-;
-Z^1-Z^2-Z^3-Z^4-; and
-Z^1-Z^2-Z^3-Z^4-Z^5-;

wherein Z^1, Z^2, Z^3, Z^4 and Z^5 are each independently selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^4)- and hydrocarbylene (e.g. C_{1-5} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R^7.

Of particular mention are compounds in which Z is a bond.

R^4 may be, for example, hydrocarbyl (e.g. C_{1-6} alkyl, C_{2-6} alkenyl or carbocyclyl) or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. In embodiments, Z is a bond and R^4 is selected from C_{1-6} alkyl (e.g. C_1, C_2, C_3 or C_4 alkyl), carbocyclyl and heterocyclyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

Where R^4 is carbocyclyl, it may be, for example, cycloalkyl or aryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. For example, R^4 may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl or naphthyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. In a particular embodiment, R^4 is aryl, in particular phenyl or naphthyl, and is optionally substituted with 1, 2, 3, 4 or 5 R^7. In embodiments, R^4 is phenyl, cyclopropyl or cyclohexyl, either of which is optionally substituted with 1, 2,

3, 4 or 5 R^7. In this case, the or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In a particular embodiment, R^4 is phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms. Of mention are compounds in which R^1 is phenyl.

Where R^4 is heterocyclyl, it may be, for example, heterocycloalkyl or heteroaryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. The heterocyclyl group may be monocyclic or bicyclic, usually monocyclic. In particular, R^4 may be selected from oxiranyl, azirinyl, 1,2-oxathiolanyl, imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2*H*-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl and chromanyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

In a further embodiment, R^4 is heteroaryl (often monocyclic) optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-

butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In a particular embodiment, R^4 is cyclohexyl, cyclopropyl, phenyl, furanyl, benzofuranyl, thiophenyl or isoxazolyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. Of particular mention are compounds in which Z is a bond and R^4 is phenyl, furanyl, benzofuranyl, thiophenyl or isoxazolyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

In a particular embodiment, Z is a bond and R^4 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. Thus, the invention includes compounds in which R^1 and R^2 are each independently carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. For example, R^1 and R^2 may be each independently cycloalkyl (e.g. cyclopropyl or cyclohexyl), aryl (e.g. phenyl) or heteroaryl (e.g. thiophenyl), any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

In a further embodiment, R^2 is carbocyclyl (e.g. phenyl) or heterocyclyl, and is substituted with at least one R^7, wherein said R^7 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy, C_{1-6} alkyl and C_{1-6} alkoxy.

In a further embodiment, R^2 is selected from cycloalkyl (e.g. cyclopropyl or cyclohexyl), cycloalkenyl (e.g. cyclopentadienyl), phenyl, furanyl, benzofuranyl, thiophenyl, isoxazolyl, quinolinyl, isoquinolinyl, quinoxazolinyl, benzothiazolyl and benzothiophenyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7;

In particular compounds, R^1 and R^2 are each independently phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7. Of particular mention are compounds in which R^1 and R^2 are each phenyl.

-Y-R^3

In formula (I), Y is a bond or a linker having 1 to 10 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^5)- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^7; and R^3 is selected from hydrogen; R^7; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -(CH_2)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

In one embodiment, Y is a bond. In another embodiment, Y is a linker having 1 to 10 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^5)- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^7. In certain compounds, Y comprises at least one -N(R^5)- linkage. Of mention are compounds in which Y comprises an amide linkage, e.g. an -N(R^5)C(O)- or -C(O)N(R^5)- linkage.

In a further embodiment, Y is a bond or is selected from the following linkers:

-Y^1-;

-Y^1-Y^2-;

-Y^1-Y^2-Y^3-;

-Y^1-Y^2-Y^3-Y^4-; and

-Y^1-Y^2-Y^3-Y^4-Y^5-;

wherein Y^1, Y^2, Y^3, Y^4 and Y^5 are each independently selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^4)- and hydrocarbylene (e.g. C_{1-5} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R^7.

In a further embodiment, Y is -Y^1- or -Y^1-Y^2-. In particular compounds, -Y^1-Y^2- is -N(R^5)C(O)- or -C(O)N(R^5)-. R^5 may be, for example, selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -(CH_2)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7. Of mention are compounds in which R^5 is hydrogen or C_{1-6} alkyl (e.g. C_1, C_2, C_3 or C_4 alkyl).

In a further embodiment, Y is -Y^1-Y^2-Y^3-. In particular compounds, Y is -N(R^5)C(O)-Y^3- or -C(O)N(R^5)-Y^3-. R^5 may be, for example, selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -(CH_2)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7. Of mention are compounds in which R^5 is hydrogen or C_{1-6} alkyl (e.g. C_1, C_2, C_3 or C_4 alkyl).

R^3 may be, for example, selected from hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -$(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

In one embodiment, R^3 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^7. Of mention are compounds in which R^3 is C_1, C_2, C_3 or C_4 alkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms. Of particular mention are compounds in which R^3 is trifluoromethyl.

In another embodiment, R^3 is carbocyclyl (e.g. cycloalkyl or aryl) or heterocyclyl (e.g. heterocycloalkyl or heteroaryl), either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

Where R^3 is carbocyclyl, it may be, for example, cycloalkyl or aryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. For example, R^3 may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl or naphthyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. In a particular embodiment, R^3 is aryl, in particular phenyl or naphthyl, and is optionally substituted with 1, 2, 3, 4 or 5 R^7. In embodiments, R^3 is phenyl or cyclohexyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. In this case, the or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In a particular embodiment, R^3 is phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms. Of mention are compounds in which R^3 is phenyl.

Where R^3 is heterocyclyl, it may be, for example, heterocycloalkyl or heteroaryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. The heterocyclyl group may be monocyclic or bicyclic, usually monocyclic. In particular, R^3 may be selected from oxiranyl, azirinyl, 1,2-oxathiolanyl, imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2*H*-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl and chromanyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

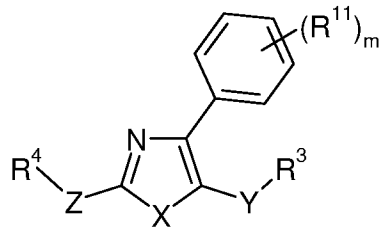
In a further embodiment, R^3 is heteroaryl (often monocyclic) optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In a further embodiment, R^3 is selected from C_{1-6} alkyl, aryl and heteroaryl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. Of mention are compounds in which R^3 is methyl, phenyl, furanyl, benzofuranyl, thiophenyl or isoxazolyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. Of particular mention are compounds in which R^3 is selected from methyl, trifluoromethyl and phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

In a further embodiment, Y is $-N(R^5)C(O)-$ or $-C(O)N(R^5)-$; and R^3 is selected from hydrogen, trifluoromethyl, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, amino, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$, $-N(R^8)S(O)_lR^8$, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and $-(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

Also of mention are compounds in which $-Y-R^3$ is $-N(R^8)R^9$, for example amino.

In a particular embodiment, there is provided a compound of the formula (II):



(II)

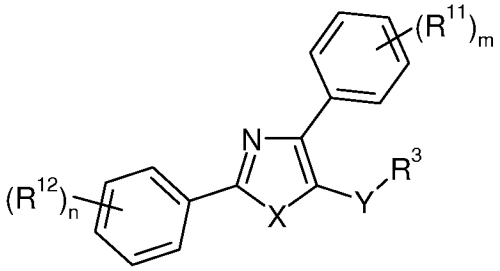
wherein

each R^{11} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

m is 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment, there is provided a compound of the formula (III):



(III)

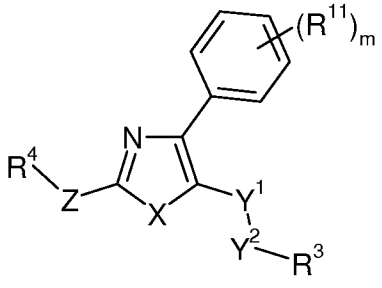
wherein

R^{11} and R^{12} are each independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

m and n are each independently 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment, there is provided a compound of the formula (IV):



(IV)

wherein

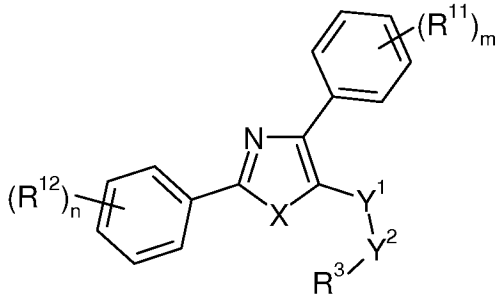
Y^1 and Y^2 are each independently selected from -O-, -C(O)-, $-S(O)_l$-, $-N(R^5)$- and hydrocarbylene (e.g. C_{1-5} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R^7.

each R^{11} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

m is 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

In a particular embodiment, there is provided a compound of the formula (V):



(V)

wherein

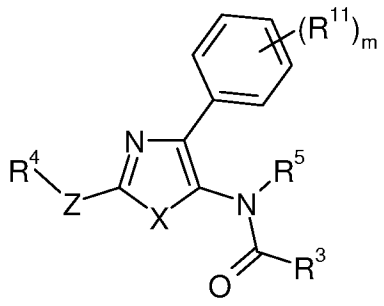
Y^1 and Y^2 are each independently selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^5)- and hydrocarbylene (e.g. C_{1-5} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R^7;

R^{11} and R^{12} are each independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, =NR^8, -OR^8, -C(O)R^8, -C(O)OR^8, -OC(O)R^8, -S(O)$_l R^8$, -N(R^8)R^9, -C(O)N(R^8)R^9, -S(O)$_l$N(R^8)R^9 and R^{10}; and

m and n are each independently 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment, there is provided a compound of the formula (VI):



(VI)

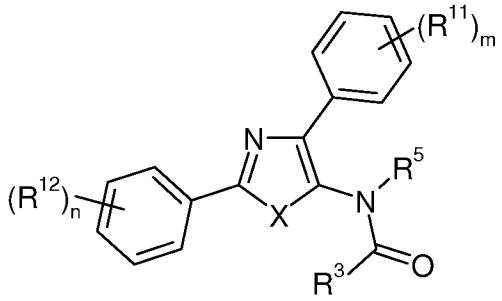
wherein

each R^{11} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

m is 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment, there is provided a compound of the formula (VII):



(VII)

R^{11} and R^{12} are each independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

m and n are each independently 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

In embodiments of formulae (II) to (VII), X is oxygen. In other embodiments, X is sulphur.

In compounds of the formulae (II) to (VII), the or each R^{11} may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally

substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms. In embodiments, m is 0, 1 or 2. In a particular embodiment, m is 0.

With regard to formulae (II), (IV) and (VI), Z may be, for example, a bond. R^4 may be, for example, hydrocarbyl (e.g. C_{1-6} alkyl, C_{2-6} alkenyl or carbocyclyl) or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. In embodiments, Z is a bond and R^4 is selected from carbocyclyl or heterocyclyl.

Where R^4 is carbocyclyl, it may be, for example, cycloalkyl or aryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. For example, R^4 may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl or naphthyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. In a particular embodiment, R^4 is aryl, in particular phenyl or naphthyl, and is optionally substituted with 1, 2, 3, 4 or 5 R^7. In embodiments, R^4 is phenyl or cyclohexyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. In this case, the or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In a particular embodiment, R^4 is phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms. Of mention are compounds in which R^1 is phenyl.

Where R^4 is heterocyclyl, it may be, for example, heterocycloalkyl or heteroaryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. The heterocyclyl group may be

monocyclic or bicyclic, usually monocyclic. In particular, R^4 may be selected from oxiranyl, azirinyl, 1,2-oxathiolanyl, imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2*H*-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl and chromanyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

In a further embodiment, R^4 is heteroaryl (often monocyclic) optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In a particular embodiment, R^4 is cyclohexyl, cyclopropyl, phenyl, furanyl, benzofuranyl, thiophenyl or isoxazolyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

With regard to formulae (III), (V) and (VII), R^{12} may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms. In embodiments, n is 0, 1 or 2. In a particular embodiment, n is 0.

With regard to formulae (V) and (VII), $-Y^1-Y^2-$ may be, for example, $-N(R^5)C(O)-$ or $-C(O)N(R^5)-$. R^5 may be, for example, selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and $-(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7. Of mention are compounds in which R^5 is hydrogen or C_{1-6} alkyl (e.g. C_1, C_2, C_3 or C_4 alkyl).

With regard to formulae (VI) and (VII), R^5 may be, for example, selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and $-(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7. Of mention are compounds in which R^5 is hydrogen or C_{1-6} alkyl (e.g. C_1, C_2, C_3 or C_4 alkyl).

With regard to each of formulae (II) to (VII), R^3 may be, for example, selected from hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and $-(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

In one embodiment, R^3 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^7. Of mention are compounds in which R^3 is C_1, C_2, C_3 or C_4 alkyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms. Of particular mention are compounds in which R^3 is trifluoromethyl.

In another embodiment, R^3 is carbocyclyl (e.g. cycloalkyl or aryl) or heterocyclyl (e.g. heterocycloalkyl or heteroaryl), either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

Where R^3 is carbocyclyl, it may be, for example, cycloalkyl or aryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. For example, R^3 may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl or naphthyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. In a particular embodiment, R^3 is aryl, in particular phenyl or naphthyl, and is optionally substituted with 1, 2, 3, 4 or 5 R^7. In embodiments, R^3 is phenyl or cyclohexyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. In this case, the or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In a particular embodiment, R^3 is phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms. Of mention are compounds in which R^3 is phenyl.

Where R^3 is heterocyclyl, it may be, for example, heterocycloalkyl or heteroaryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. The heterocyclyl group may be monocyclic or bicyclic, usually monocyclic. In particular, R^3 may be selected from oxiranyl, azirinyl, 1,2-oxathiolanyl, imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2*H*-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl,

phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl and chromanyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

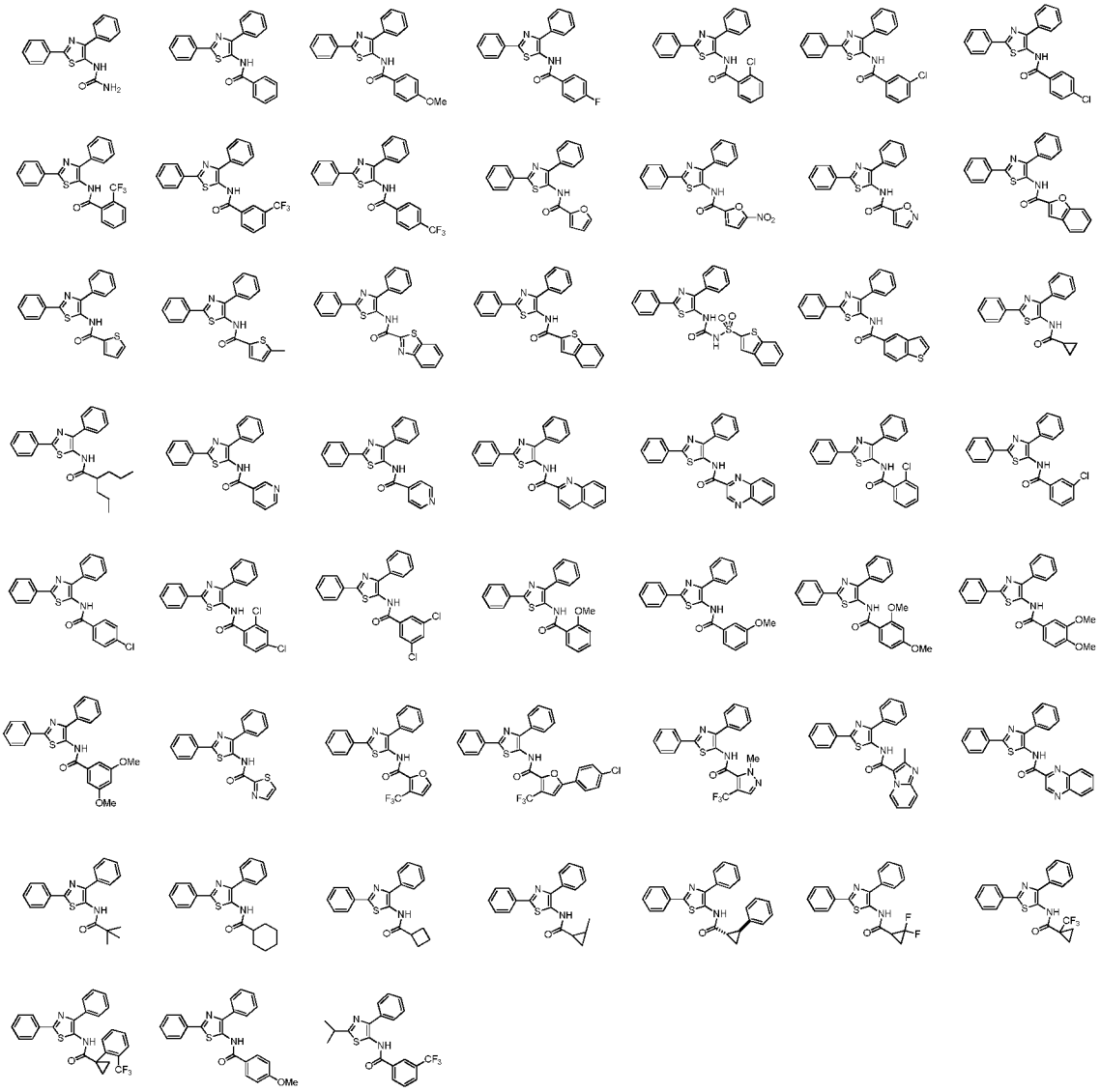
In a further embodiment, R^3 is heteroaryl (often monocyclic) optionally substituted with 1, 2, 3, 4 or 5 R^7. The or each R^7 may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

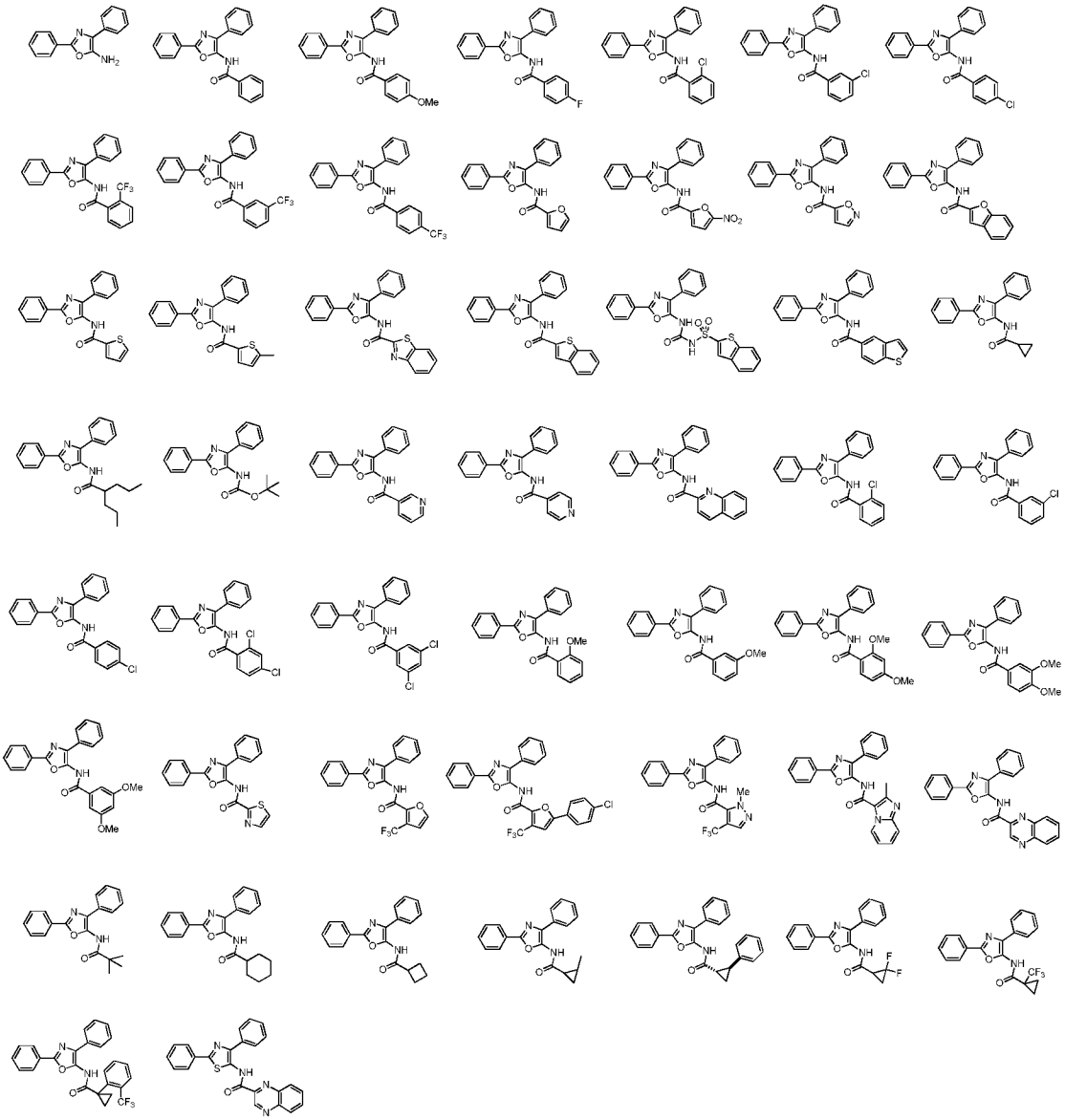
In a further embodiment, R^3 is selected from C_{1-6} alkyl, aryl and heteroaryl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. Of mention are compounds in which R^3 is methyl, phenyl, furanyl, benzofuranyl, thiophenyl or isoxazolyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

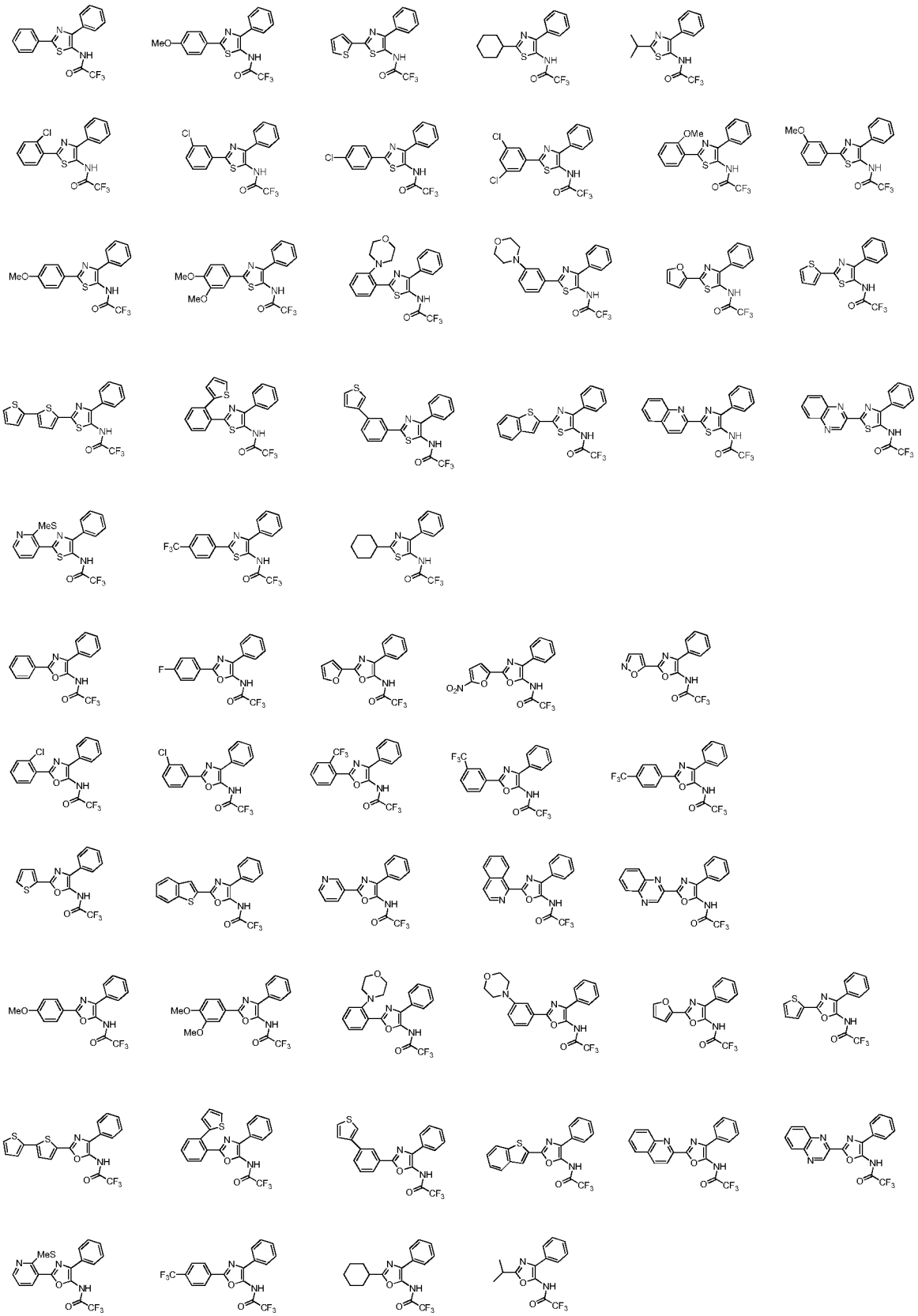
Of mention are compounds, especially those of formula (VII) in which R^3 is selected from C_{1-6} alkyl (e.g. methyl) or phenyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7. Of particular mention are compounds of formula (VII) in which R^3 is trifluoromethyl or phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

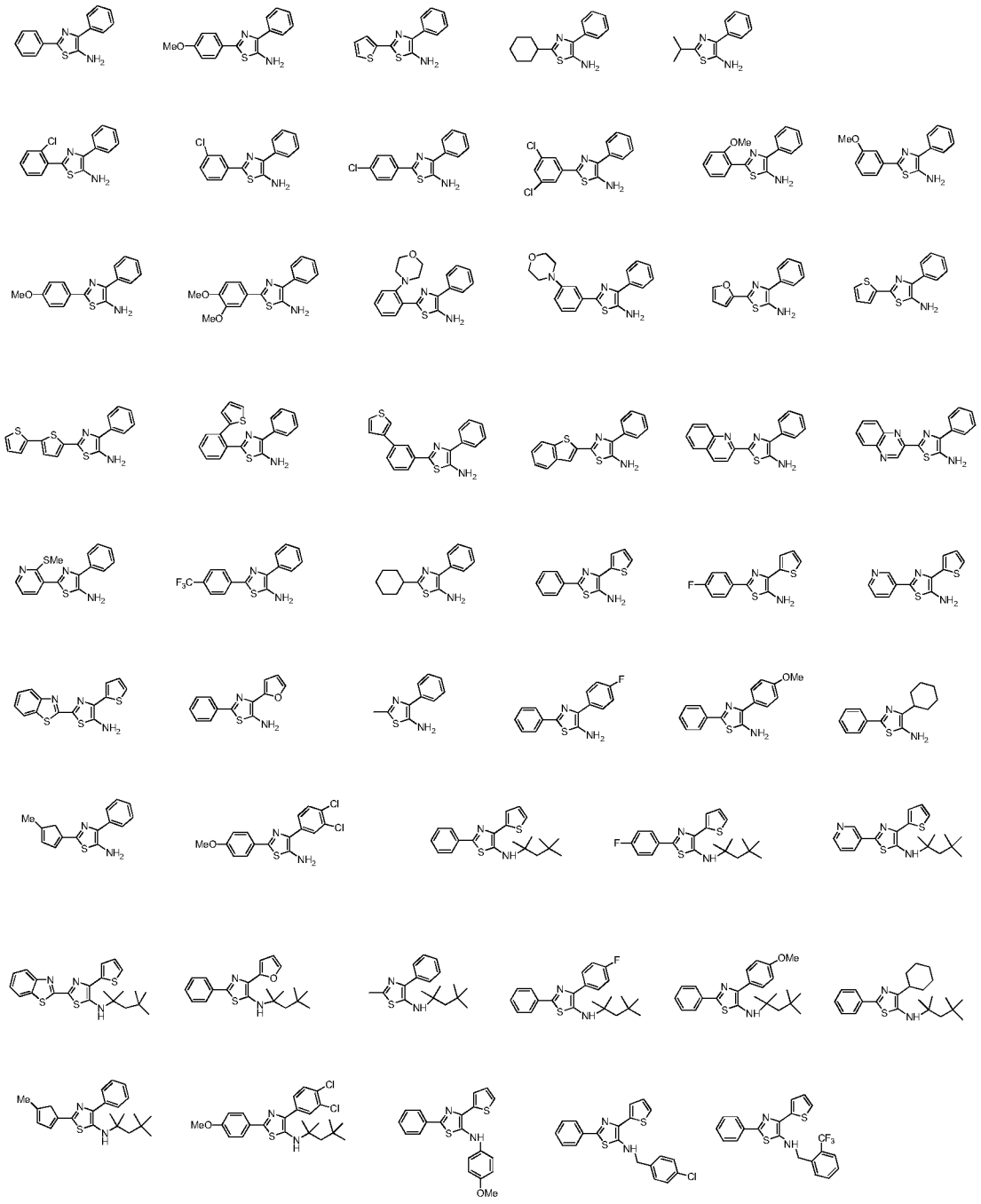
Also of mention are compounds in which -Y-R^3 is -N(R^8)R^9, for example amino.

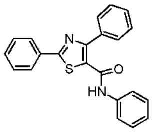
Examples of compounds of the invention include those shown below. It will of course be appreciated that, where appropriate, each compound may be in the form of the free compound, an acid or base addition salt, or a prodrug.

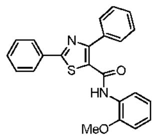


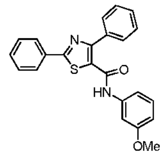


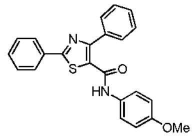


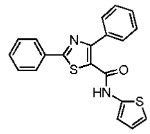


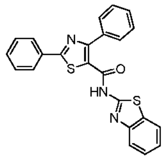

N
S
O
HN

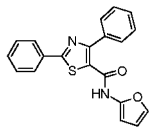

N
S
O
HN
MeO

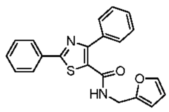

N
S
O
HN
OMe

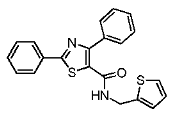

N
S
O
HN
OMe

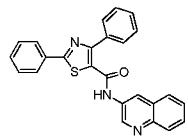

N
S
O
HN
S

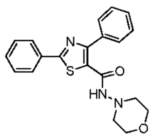

N
S
O
HN
S
N

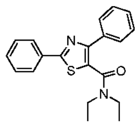

N
S
O
HN
O

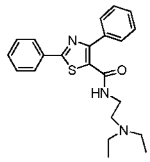

N
S
O
HN
O

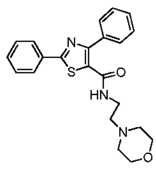

N
S
O
HN
S

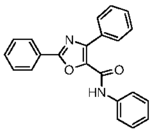

N
S
O
HN
N

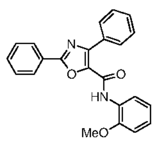

N
S
O
HN
N
O

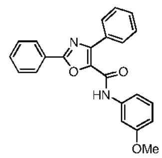

N
S
O
N

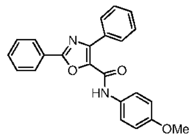

N
S
O
HN
N

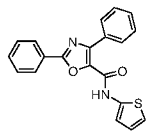

N
S
O
HN
N
O

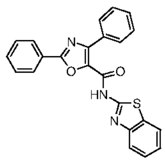

N
O
O
HN

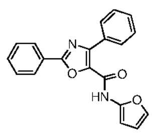

N
O
O
HN
MeO

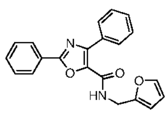

N
O
O
HN
OMe

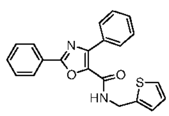

N
O
O
HN
OMe

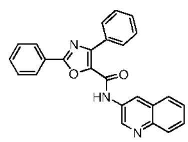

N
O
O
HN
S

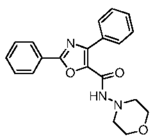

N
O
O
HN
S
N

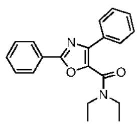

N
O
O
HN
O

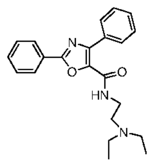

N
O
O
HN
O

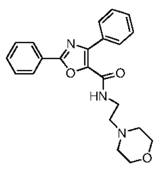

N
O
O
HN
S


N
O
O
HN
N


N
O
O
HN
N
O


N
O
O
N


N
O
O
HN
N


N
O
O
HN
N
O

Compounds of the invention may be in the form of pharmaceutically acceptable salts. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts may be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., US, 1985, p. 1418, the disclosure of which is hereby incorporated by reference; see also Stahl et al, Eds, *"Handbook of Pharmaceutical Salts Properties Selection and Use"*, Verlag Helvetica Chimica Acta and Wiley-VCH, 2002.

The invention thus includes pharmaceutically-acceptable salts of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof, for example the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g. from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

The invention includes prodrugs for the active pharmaceutical species of the invention, for example in which one or more functional groups are protected or derivatised but can be converted *in vivo* to the functional group, as in the case of esters of carboxylic acids

convertible *in vivo* to the free acid, or in the case of protected amines, to the free amino group. The term "prodrug," as used herein, represents in particular compounds which are rapidly transformed *in vivo* to the parent compound, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; H Bundgaard, ed, Design of Prodrugs, Elsevier, 1985; and Judkins, et al. Synthetic Communications, 26(23), 4351-4367 (1996), each of which is incorporated herein by reference.

Prodrugs therefore include drugs having a functional group which has been transformed into a reversible derivative thereof. Typically, such prodrugs are transformed to the active drug by hydrolysis. Examples of such groups include carboxylic groups (reversible derivatives including esters, e.g. acyloxyalkyl esters and amides), alcohol groups (reversible derivatives including sulfates, phosphates and carboxylic acid esters), amine groups (reversible derivatives including amides, carbamates, imines and enamines) and carbonyl groups, e.g. aldehyde and ketone groups (reversible derivatives including imines, oximes, acetals/ketals, enol esters, oxazolidines and thiazoxolidines).

Prodrugs also include compounds convertible to the active drug by an oxidative or reductive reaction. As examples of oxidative activation may be mentioned N- and O-dealkylation, oxidative deamination, N-oxidation and epoxidation. As examples of reductive activation may be mentioned azo reduction, sulfoxide reduction, disulfide reduction, bioreductive alkylation and nitro reduction.

Also to be mentioned as metabolic activations of prodrugs are nucleotide activation, phosphorylation activation and decarboxylation activation. For additional information, see "The Organic Chemistry of Drug Design and Drug Action", R B Silverman (particularly Chapter 8, pages 497 to 546), incorporated herein by reference.

The use of protecting groups is fully described in `Protective Groups in Organic Chemistry`, edited by J W F McOmie, Plenum Press (1973), and `Protective Groups in Organic Synthesis`, 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

Thus, it will be appreciated by those skilled in the art that, although protected derivatives of compounds of the disclosure may not possess pharmacological activity as such, they

may be administered, for example parenterally or orally, and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives are therefore examples of "prodrugs". All prodrugs of the described compounds are included within the scope of the disclosure.

Some groups mentioned herein (especially those containing heteroatoms and conjugated bonds) may exist in tautomeric forms and all these tautomers are included in the scope of the disclosure. More generally, many species may exist in equilibrium, as for example in the case of organic acids and their counterpart anions; a reference herein to a species accordingly includes reference to all equilibrium forms thereof.

The compounds of the disclosure may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. All diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the disclosure. Where a single enantiomer or diasteromer is disclosed, the disclosure also covers the other enantiomers or diastereomers, and also racemates; in this regard, particular reference is made to the specific compounds listed herein.

Geometric isomers may also exist in the compounds of the present disclosure. The present disclosure contemplates the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond and designates such isomers as of the Z or E configuration, wherein the term "Z" represents substituents on the same side of the carbon-carbon double bond and the term "E" represents substituents on opposite sides of the carbon-carbon double bond.

The disclosure therefore includes all variant forms of the defined compounds, for example any tautomer or any pharmaceutically acceptable salt, ester, acid or other variant of the defined compounds and their tautomers as well as substances which, upon administration, are capable of providing directly or indirectly a compound as

defined above or providing a species which is capable of existing in equilibrium with such a compound.

Synthesis

A compound of the invention may be prepared according to the processes described herein. It will be understood that these processes are solely for the purpose of illustrating the invention and should not be construed as limiting. A process utilising similar or analogous reagents and/or conditions known to one skilled in the art may also be used to obtain a compound of the invention.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in a known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallisation, or by the formation of a salt if appropriate or possible under the circumstances.

Administration & Pharmaceutical Formulations

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route, as an oral or nasal spray or via inhalation, The compounds may be administered in the form of pharmaceutical preparations comprising prodrug or active compound either as a free compound or, for example, a pharmaceutically acceptable non-toxic organic or inorganic acid or base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Typically, therefore, the pharmaceutical compounds of the invention may be administered orally or parenterally ("parenterally" as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion) to a host. In the case of larger animals, such as humans, the compounds may be administered alone or as compositions in combination with pharmaceutically acceptable diluents, excipients or carriers.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

In certain embodiments, an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. In a particular embodiment, the dosage level is about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0 and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, e.g. once or twice per day. The dosage regimen may be adjusted to provide the optimal therapeutic response.

According to a further aspect of the invention there is thus provided a pharmaceutical composition including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Pharmaceutical compositions of this invention for parenteral injection suitably comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials

such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol or phenol sorbic acid. It may also be desirable to include isotonic agents such as sugars or sodium chloride, for example. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents (for example aluminum monostearate and gelatin) which delay absorption.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are suitably made by forming microencapsule matrices of the drug in biodegradable polymers, for example polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations may also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is typically mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or one or more: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c)

humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycol, for example.

Suitably, oral formulations contain a dissolution aid. The dissolution aid is not limited as to its identity so long as it is pharmaceutically acceptable. Examples include nonionic surface active agents, such as sucrose fatty acid esters, glycerol fatty acid esters, sorbitan fatty acid esters (e.g. sorbitan trioleate), polyethylene glycol, polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, methoxypolyoxyethylene alkyl ethers, polyoxyethylene alkylphenyl ethers, polyethylene glycol fatty acid esters, polyoxyethylene alkylamines, polyoxyethylene alkyl thioethers, polyoxyethylene polyoxypropylene copolymers, polyoxyethylene glycerol fatty acid esters, pentaerythritol fatty acid esters, propylene glycol monofatty acid esters, polyoxyethylene propylene glycol monofatty acid esters, polyoxyethylene sorbitol fatty acid esters, fatty acid alkylolamides, and alkylamine oxides; bile acid and salts thereof (e.g. chenodeoxycholic acid, cholic acid, deoxycholic acid, dehydrocholic acid and salts thereof, and glycine or taurine conjugate thereof); ionic surface active agents, such as sodium laurylsulfate, fatty acid soaps, alkylsulfonates, alkylphosphates, ether phosphates, fatty acid salts of basic amino acids; triethanolamine soap, and alkyl quaternary ammonium salts; and amphoteric surface active agents, such as betaines and aminocarboxylic acid salts.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, and/or in delayed fashion. Examples of embedding compositions include polymeric substances and waxes.

The active compounds may also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

The active compounds may be in finely divided form, for example they may be micronised.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof. Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents. Suspensions, in addition to the active compounds, may contain suspending agents such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolisable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilisers, preservatives, excipients and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p 33 et seq.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Use

Compounds of the invention may be useful in the therapy of a variety of diseases and conditions. The subject of said therapy may be a human or an animal. In particular, compounds of the invention may be useful in the treatment or prevention of prion diseases. Prion diseases are often characterized by symptoms of dementia or cognitive impairment. The prion disease may be inherited, infectious or sporadic. Examples of prion disease include Creutzfeldt-Jakob disease, kuru, Gerstmann-Straussler-Sheinker disease, fatal familial insomnia and transmissible spongiform encephalopathies (TSEs). Examples of TSEs include bovine spongiform encephalopathy (BSE), scrapie, chronic wasting disease (e.g. in deer or elk) and transmissible mink encephalopathy (TME).

The compounds may also be useful in the regulation of stem cells. Thus, the invention also provides a method of regulating stem cell activity, comprising contacting one or more types of stem cells with a compound of the invention. Said contacting generally takes place under conditions such that activity is regulated. In one embodiment, said contacting takes place *in vitro*.

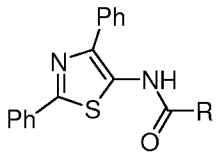
The following Examples illustrate the invention.

In the Examples, melting points were measured using a Bibby-Sterilin SMP10 melting point apparatus and are uncorrected. Accurate mass and nominal mass measurements were measured using a Waters-Micromass LCT electrospray mass spectrometer. Flash column chromatography was carried out using Fluorochem silica gel 60 Å. All compounds were isolated in >95% purity unless otherwise stated (as determined by HPLC under two sets of conditions-HPLC 1; Luna 5 μ C18, 150 × 4.6 mm, 5–95% acetonitrile (0.1% TFA) in water (0.1% TFA) over 4 min, 1 mL min^{-1}, 20 μL injection,

detection at 256 nm, run time 10 min. HPLC 2; Altima HP 3 μ C18 EPS, 150 × 4.6 mm, 35–98% acetonitrile (0.1% TFA) in water (0.1% TFA) over 4 min, 1.0 mL min^{-1}, 20 μL injection, detection at 256 nm, run time 11 min). All reagents were purchased directly from commercial sources and used as supplied.

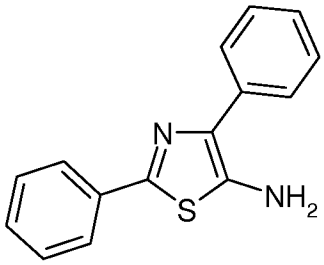
Example 1: Thiazoles

Thiazole compounds **1c** to **1x** were prepared. The structures of compounds **1c** and **1e** to **1x** are shown below:



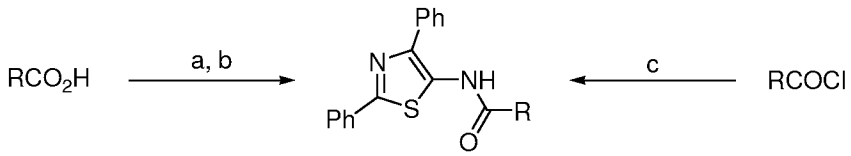
Compound	R
1c	CF_3
1e	Ph
1f	4-F-Ph
1g	4-OMe-Ph
1h	2-CF_3-Ph
1i	3-CF_3-Ph
1j	4-CF_3-Ph
1k	3-Pyridyl
1l	4-Pyridyl
1m	2-Quinoyl
1n	2-Furyl
1o	5-NO_2-2-furyl
1p	5-Isoxazoyl
1q	2-Thiophenyl
1r	5-Me-2-thiophenyl
1s	2-Benzothiophenyl
1t	2-Benzofuranyl
1u	2-Benzothiazoyl
1v	6-Benzothiophenyl
1w	Cyclopropyl
1x	CH(*n*-propyl)$_2$

Compound **1d** has the following structure:



Compounds **1c** and **1d** were obtained as described in Thompson, M. J.; Heal, W.; Chen, B. *Tetrahedron Lett.* 2006, *47*, 2361–2364. Full ^{1}H NMR. ^{13}C NMR and IR spectral data for these compounds are given in the supplementary information section of that paper.

Compounds **1e** to **1x** were prepared from compound **1d**, as shown in Scheme 1:



1e–1x

Scheme 1. Reagents and conditions: (a) $(COCl)_2$, DCM, room temp., 80 min; (b) **1d**, pyridine, room temp., 18 h; (c) pyridine, DMAP, **1d**, room temp., 18 h.

Acid chloride (0.33 mmol) was added to a solution of **1d** (76 mg, 0.30 mmol) and DMAP (10 mg) in pyridine (3 mL). The reaction mixture was stirred at ambient temperature for 18 hours. All volatiles were removed under reduced pressure and the residue taken up in DCM (30 mL). This solution was washed thoroughly with 1 M HCl (4 × 30 mL) then sat. $NaHCO_3$ (2 × 30 mL), dried over $MgSO_4$, filtered and evaporated to dryness to provide the product. Where necessary, further purification was carried out by flash column chromatography on silica gel. In the case of **1g**, **1r**, the relevant acid chloride was not available commercially. These amide derivatives were prepared from the carboxylic acids, through *in situ* formation of the acid chloride followed by reaction with amine **1d** in pyridine.

***N*-(2,4-Diphenylthiazol-5-yl)-benzamide (1e).**

Yield 74%; mp 181–183° C; *m/z* (ES); HRMS, 357 ($[M+H]^+$); HRMS, found 357.1047 ($C_{22}H_{17}N_2OS$, $[M+H]^+$, requires 357.1062).

***N*-(2,4-Diphenylthiazol-5-yl)-4-fluorobenzamide (1f).**

Yield 86%; mp 201–203° C; *m/z* (ES), 375 ($[M+H]^+$); HRMS, found 375.0961 ($C_{22}H_{16}FN_2OS$, $[M+H]^+$, requires 375.0967).

***N*-(2,4-Diphenylthiazol-5-yl)-4-methoxybenzamide (1g).**

A stirred suspension of *p*-anisic acid (44 mg, 0.29 mmol) in DCM (3.0 mL) was treated with oxalyl chloride (26.2 μL, 0.30 mmol) and DMF (40 μL), at which point effervescence was observed. A homogeneous solution was gradually obtained as the reaction took place. After 80 min the reaction mixture was concentrated under reduced pressure and dried further under high vacuum (with periodical warming) to yield the crystalline, crude acid chloride. 2,4-Diphenyl-5-aminothiazole (70 mg, 0.28 mmol), pyridine (3.0 mL) and DMAP (10 mg) were added, and the resultant orange solution stirred at ambient temperature for 18 hours. The pyridine was removed under vacuum and the residue taken up in DCM (40 mL) then washed with 1 M HCl (4 × 50 mL) followed by sat. $NaHCO_3$ (2 × 40 mL). The organic layer was evaporated and the residue purified by flash column chromatography on silica gel, eluted with 60–75–90% DCM–hexane, to provide **1e** as a yellowish solid (13 mg, 12%). *m/z* (ES), 409 ($[M+Na]^+$); HRMS, found 409.1006 ($C_{23}H_{18}N_2NaO_2S$, $[M+Na]^+$, requires 409.0987).

***N*-(2,4-Diphenylthiazol-5-yl)-2-trifluoromethylbenzamide (1h).**

Yield 83%; mp 230–231° C (dec.); *m/z* (ES), 425 ($[M+H]^+$); HRMS, found 425.0938 ($C_{23}H_{16}F_3N_2OS$, $[M+H]^+$, requires 425.0935).

***N*-(2,4-Diphenylthiazol-5-yl)-3-trifluoromethylbenzamide (1i).**

Yield 83%; mp 154–157° C (dec.); *m/z* (ES), 425 ($[M+H]^+$); HRMS, found 425.0926 ($C_{23}H_{16}F_3N_2OS$, $[M+H]^+$, requires 425.0935).

***N*-(2,4-Diphenylthiazol-5-yl)-4-trifluoromethylbenzamide (1j).**

Yield 79%; mp 201–203° C (dec.); *m/z* (ES), 425 ($[M+H]^+$); HRMS, found 425.0949 ($C_{23}H_{16}F_3N_2OS$, $[M+H]^+$, requires 425.0935).

***N*-(2,4-Diphenylthiazol-5-yl)nicotinamide (1k).**

Yield 69%; mp 184–185° C (dec.); *m/z* (ES), 358 ($[M+H]^+$); HRMS, found 358.1000 ($C_{21}H_{16}N_3OS$, $[M+H]^+$, requires 358.1014).

***N*-(2,4-Diphenylthiazol-5-yl)isonicotinamide (1l).**

Yield 75%; mp 214–215° C (dec.); *m/z* (EI), 357 (M^+); HRMS, found 357.0922 ($C_{21}H_{15}N_3OS$, M^+, requires 357.0936).

Quinoline-2-carboxylic acid (2,4-diphenylthiazol-5-yl)amide (1m).

Yield 65%; mp 229–230° C; *m/z* (ES), 408 ($[M+H]^+$); HRMS, found 408.1155 ($C_{25}H_{18}N_3OS$, $[M+H]^+$, requires 408.1171).

Furan-2-carboxylic acid (2,4-diphenylthiazol-5-yl)amide (1n).

Yield 51%; *m/z* (ES), 346 ($[M+H]^+$); HRMS, found 347.0868 ($C_{20}H_{15}N_2O_2S$, $[M+H]^+$, requires 347.0854).

5-Nitrofuran-2-carboxylic acid (2,4-diphenylthiazol-5-yl)amide (1o).

Yield 9%; *m/z* (ES), 392 ($[M+H]^+$); HRMS, found 392.0710 ($C_{20}H_{14}N_3O_4S$, $[M+H]^+$, requires 392.0705).

Isoxazole-5-carboxylic acid (2,4-diphenylthiazol-5-yl)amide (1p).

Yield 74%; mp 191° C (dec.); *m/z* (ES), 348 ($[M+H]^+$); HRMS, found 348.0790 ($C_{19}H_{14}N_3O_2S$, $[M+H]^+$, requires 348.0807).

Thiophene-2-carboxylic acid (2,4-diphenylthiazol-5-yl)amide (1q).

Yield 82%; mp 161° C (dec.); *m/z* (ES), 363 ($[M+H]^+$); HRMS, found 363.0615 ($C_{20}H_{15}N_2OS_2$, $[M+H]^+$, requires 363.0626).

5-Methylthiophene-2-carboxylic acid (2,4-diphenylthiazol-5-yl)amide (1r).

5-Methylthiophene-2-carboxylic acid (213 mg, 1.50 mmol) was suspended in DCM (5.0 mL) then oxalyl chloride (131 μL, 1.50 mmol) and DMF–DCM (1:9, 20 μL) was added. After stirring at ambient temperature for 1 h, a solution of 2,4-diphenyl-5-aminothiazole (252 mg, 1.00 mmol) in pyridine (5.0 mL) was added and stirring of the resultant mixture continued at ambient temperature for 18 hours. The reaction mixture was diluted with DCM (60 mL) and washed successively with 1 M HCl (4 × 40 mL) and sat. $NaHCO_3$ (2 × 40 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated giving crude material, which was purified by flash column chromatography on silica gel, eluted with 60–75% DCM–hexane, yielding **1r** as an off-white solid (252 mg, 67%). mp 190° C; *m/z* (EI), 376 (M^+); HRMS, found 376.0695 ($C_{21}H_{16}N_2OS_2$, M^+, requires 376.0704).

Benzo[β]thiophene-2-carboxylic acid (2,4-diphenylthiazol-5-yl)amide (1s).

Yield 83%; mp 209–210° C (dec.); *m/z* (ES), 413 ($[M+H]^+$); HRMS, found 413.0780 ($C_{24}H_{17}N_2OS_2$, $[M+H]^+$, requires 413.0782).

Benzofuran-2-carboxylic acid (2,4-diphenylthiazol-5-yl)amide (1t).

Yield 86%; mp 196–197° C; *m/z* (ES), 397 ($[M+H]^+$); HRMS, found 397.1005 ($C_{24}H_{17}N_2O_2S$, $[M+H]^+$, requires 397.1011).

Benzothiazole-2-carboxylic acid (2,4-diphenylthiazol-5-yl)amide (1u).

Yield 27%; mp 227° C; *m/z* (ES), 414 ($[M+H]^+$); HRMS, found 414.0748 ($C_{23}H_{16}N_3OS_2$, $[M+H]^+$, requires 414.0735).

Benzo[β]thiophene-5-carboxylic acid (2,4-diphenylthiazol-5-yl)amide (1v).

Yield 59%; mp 205–206° C (dec.); *m/z* (ES), 413 ($[M+H]^+$); HRMS, found 413.0788 ($C_{24}H_{17}N_2OS_2$, $[M+H]^+$, requires 413.0782).

Cyclopropanecarboxylic acid (2,4-diphenylthiazol-5-yl)amide (1w).

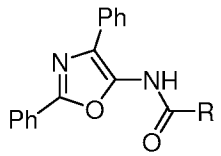
Yield 61%; mp 215–216° C; *m/z* (ES), 343 ([M+Na]$^+$); HRMS, found 343.0893 ($C_{19}H_{16}NaN_2OS$, [M+Na]$^+$, requires 343.0881).

2-Propylpentanoic acid (2,4-diphenylthiazol-5-yl)amide (1x).

A stirred solution of 2-propylpentanoic acid (218 μL, 200 mg, 1.39 mmol) in DCM (3 mL) was treated with oxalyl chloride (122 μL, 177 mg, 1.39 mmol) and DMF–DCM (1:4, 20 μL). After stirring for 1 h, the reaction mixture was evaporated to dryness and further dried under high vacuum to yield the crude acid chloride. **1d** (70 mg, 0.28 mmol) in pyridine (3 mL) was added, followed by DMAP (10 mg), and the solution stirred at ambient temperature for 18 h. All volatiles were removed under reduced pressure and the residue taken up in DCM (40 mL). This solution was washed thoroughly with 1 M HCl (3 × 40 mL) then sat. $NaHCO_3$ (3 × 40 mL) and evaporated. Purification by flash column chromatography on silica gel, eluted with 40–50% DCM–hexane, afforded the bis-amide product, 2,4-Diphenyl-5-[*N,N*-bis(2-propylpentanoyl)amino]thiazole (57 mg, 41%), which crystallised as a pale orange solid on scratching. A portion of this material (47 mg) was suspended in 2-propanol (2.0 mL), then tetraethylammonium hydroxide, 20% w/v aqueous solution (146 μL, 2.0 mmol) was added. Dissolution of the starting material was observed as hydrolysis took place. After 2.5 hours the mixture was diluted with 1 M HCl (50 mL) and DCM (50 mL). The organic layer was separated, dried over $MgSO_4$, filtered and evaporated. Purification by flash column chromatography on silica gel, eluted with 50–65% DCM–hexane, yielded **1x** as a white, crystalline solid (26 mg, 74%). *m/z* (ES), 379 ([M+H]$^+$); HRMS, found 379.1841 ($C_{23}H_{27}N_2OS$, [M+H]$^+$, requires 379.1844).

Example 2: Oxazoles

The following oxazole compounds were prepared:

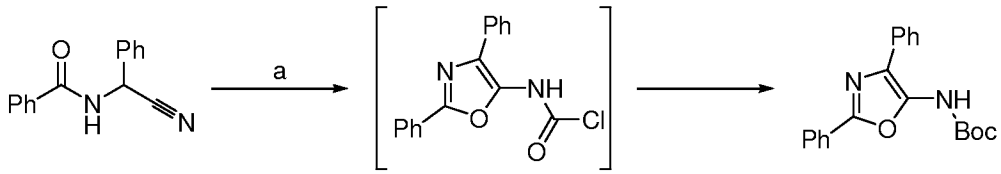


Compound	R
2a	CF_3
2c	*O*-*t*-Butyl

2d	Ph
2e	4-F-Ph
2f	4-OMe-Ph
2g	2-CF_3-Ph
2h	3-CF_3-Ph
2i	4-CF_3-Ph
2j	3-Pyridyl
2k	4-Pyridyl
2l	2-Quinoyl
2m	2-Furyl
2n	5-NO_2-2-furyl
2o	5-Isoxazoyl
2p	2-Thiophenyl
2q	5-Me-2-thiophenyl
2r	2-Benzothiophenyl
2s	2-Benzofuranyl
2t	2-Benzothiazoyl
2u	6-Benzothiophenyl
2v	Cyclopropyl
2w	CH(*n*-Propyl)$_2$

Compound **2a** was obtained as described in Thompson, M. J.; Heal, W.; Chen, B. *Tetrahedron Lett.* 2006, *47*, 2361-2364. Full ^{1}H NMR. ^{13}C NMR and IR spectral data for this compound are given in the supplementary information section of that paper.

Compound **2c** was prepared according to Scheme 2:



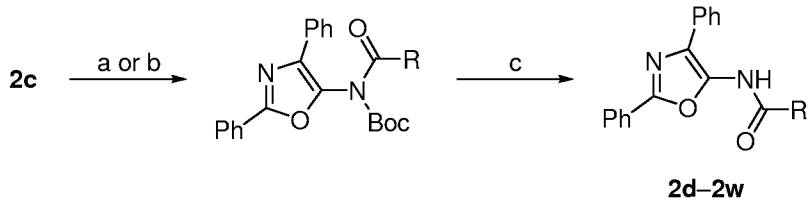
3 **4** **2c**

Scheme 2

2-(Benzoylamino)-2-phenylglycinonitrile hydrochloride (3.89 g, 14.3 mmol) was partitioned between DCM (70 mL) and water (50 mL) and sodium carbonate added portionwise, with thorough mixing, until the aqueous layer was basic to universal indicator paper (pH 10). The organic layer was separated, dried over $MgSO_4$ and filtered. The filtrate (~100 mL) was added slowly to a solution of triphosgene (4.23 g, 14.3 mmol) in DCM (30 mL). A precipitate began to appear during this addition. After stirring for 15 minutes, *tert*-butanol (30 mL) was added cautiously. A homogeneous solution resulted after 2-3 minutes, at which point stirring was continued for an additional 5 minutes. The reaction was quenched by addition of 0.1 M K_2CO_3 (200 mL) and the organic layer

separated, washed with further 0.1 M K_2CO_3 (2 × 150 mL), dried over $MgSO_4$. The crude material was purified by flash column chromatography on silica gel, eluted with 60-90-100% DCM-hexane, giving **2c** as an off-white foam (1.07 g, 22%). mp 150° C (dec.); *m/z* (EI^-), 335 (M^-); HRMS, found 335.1396 ($C_{20}H_{20}N_2O_3$, M^-, requires 335.1396).

Compounds **2d** to **2w** were synthesised according to Scheme 3:



2d–2w

Scheme 3. Reagents and conditions: (a) NaH, THF, room temp., 5 min, then RCOCl, THF, room temp., 10 min; (b) RCOCl, DMAP, DIPEA, room temp., 2 h; (c) TFAA (20%) in DCM, room temp., 18 h.

To a suspension of sodium hydride (60% dispersion in mineral oil, 0.65 mmol) in dry THF (3.0 mL) was added a solution of **2c** (0.59 mmol) in dry THF (4.0 mL). The after 5 minutes the reaction mixture was clear and a solution of acid chloride (0.65 mmol) was added. The reaction was deemed complete by TLC after 10 minutes. The reaction was quenched by the cautious addition of water followed by the removal of all volatiles under reduced pressure. The aqueous mixture remaining was extracted thoroughly with DCM. The combined organic phases were combined, dried over $MgSO_4$ and concentrated to a volume of 50 mL under reduced pressure. TFA was added to a concentration of 20% and the mixture stirred at ambient temperature for 18 hours. Removal of all volatiles under reduced pressure gave the crude product, which was recrystallised from hot n-hexane-ethyl acetate.

***N*-(2,4-Diphenyloxazol-5-yl)benzamide (2d).**

Yield 72%; mp 196–197° C; *m/z* (ES), 341 ($[M+H]^+$); HRMS, found 341.1289 ($C_{22}H_{17}N_2O_2$, $[M+H]^+$, requires 341.1290).

***N*-(2,4-Diphenyloxazol-5-yl)-4-fluorobenzamide (2e).**

Yield 81%; mp 245–247° C; *m/z* (ES), 359 ($[M+H]^+$); HRMS, found 359.1188 ($C_{22}H_{16}N_2O_2F$, $[M+H]^+$, requires 359.1196).

***N*-(2,4-Diphenyloxazol-5-yl)-4-methoxybenzamide (2f) (DMAP procedure).**

2,4-Diphenyl-5-*N*-Boc-aminooxazole **2c** (100 mg, 0.30 mmol) was dissolved in dry DCM (3.0 mL) then *N*,*N*-diisopropylethylamine (58 μL, 0.33 mmol) and DMAP (~7 mg, 20 mol %) were added followed by 2-furoyl chloride (33 μL, 0.33 mmol). The reaction was deemed complete by TLC after 150 minutes' stirring at ambient temperature. TFA (0.75 mL) was then added and stirring continued at ambient temperature for 18 h. DCM (40 mL) was added and the solution washed with water (2 × 40 mL) then dried over $MgSO_4$. Further purification was achieved by flash column chromatography on silica gel, eluted with 0–1% MeOH–DCM, to provide **2f** as an off-white foam (76 mg, 77%). mp 224–225° C; *m/z* (ES), 371 ($[M+H]^+$); HRMS, found 371.1383 ($C_{23}H_{19}N_2O_3$, $[M+H]^+$, requires 371.1396).

***N*-(2,4-Diphenyloxazol-5-yl)-2-trifluoromethylbenzamide (2g).**

Yield 71%; mp 201–202° C; *m/z* (ES), 409 ($[M+H]^+$); HRMS, found 409.1151 ($C_{23}H_{16}F_3N_2O_2$, $[M+H]^+$, requires 409.1164).

***N*-(2,4-Diphenyloxazol-5-yl)-3-trifluoromethylbenzamide (2h).**

Yield 54%; mp 213–215° C; *m/z* (ES), 409 ($[M+H]^+$); HRMS, found 409.1180 ($C_{23}H_{16}F_3N_2O_2$, $[M+H]^+$, requires 409.1164).

***N*-(2,4-Diphenyloxazol-5-yl)-4-trifluoromethylbenzamide (2i).**

Yield 31%; mp 220–221° C; *m/z* (ES), 409 ($[M+H]^+$); HRMS, found 409.1149 ($C_{23}H_{16}F_3N_2O_2$, $[M+H]^+$, requires 409.1164).

***N*-(2,4-Diphenyloxazol-5-yl)nicotinamide (2j).**

Yield 14%; mp 146–149° C; *m/z* (ES), 342 ($[M+H]^+$); HRMS, found 342.1235 ($C_{21}H_{16}N_3O_2$, $[M+H]^+$, requires 342.1234).

***N*-(2,4-Diphenyloxazol-5-yl)isonicotinamide (2k).**

Yield 59%; mp 201–204° C (dec.); *m/z* (ES), 342 ($[M+H]^+$); HRMS, found 342.1245 ($C_{21}H_{16}N_3O_2$, $[M+H]^+$, requires 342.1243).

Quinoline-2-carboxylic acid (2,4-diphenyloxazol-5-yl)amide (2l).

Yield 27%; mp 180° C (dec.); *m/z* (ES), 392 ($[M+H]^+$); HRMS, found 392.1384 ($C_{25}H_{18}N_3O_2$, $[M+H]^+$, requires 392.1399).

Furan-2-carboxylic acid (2,4-diphenyloxazol-5-yl)amide (2m).

Yield 39%; mp 84–86° C; *m/z* (ES), 331 ($[M+H]^+$); HRMS, found 331.1093 ($C_{20}H_{15}N_2O_3$, $[M+H]^+$, requires 331.1083).

5-Nitrofuran-2-carboxylic acid (2,4-diphenyloxazol-5-yl)amide (2n).

Yield 19%; mp 184–186° C; *m/z* (ES), 376 ($[M+H]^+$); HRMS, found 376.0934 ($C_{20}H_{14}N_3O_5$, $[M+H]^+$, requires 376.0933).

Isoxazole-5-carboxylic acid (2,4-diphenyloxazol-5-yl)amide (2o).

Purification by flash column chromatography (n-hexane–ethyl acetate, 4:1) gave **2o** (58.2 mg, 23%) mp 151–153° C; *m/z* (ES), 332 ($[M+H]^+$); HRMS, found 332.1023 ($C_{19}H_{14}N_3O_3$, $[M+H]^+$, requires 332.1035).

Thiophene-2-carboxylic acid (2,4-diphenyloxazol-5-yl)amide (2p).

Yield 79%; mp 194–196° C; *m/z* (ES), 347 ($[M+H]^+$); HRMS, found 347.0851 ($C_{20}H_{15}N_2O_2S$, $[M+H]^+$, requires 347.0854).

5-Methylthiophene-2-carboxylic acid (2,4-diphenyloxazol-5-yl)amide (2q).

Yield 56%; mp 194° C; *m/z* (ES), 361 ($[M+H]^+$); HRMS, found 361.1007 ($C_{21}H_{17}N_2O_2S$, $[M+H]^+$, requires 361.1011).

Benzo[*β*]thiophene-2-carboxylic acid (2,4-diphenyloxazol-5-yl)amide (2r).

Yield 18%; mp 218–220° C; *m/z* (ES), 397 ($[M+H]^+$); HRMS, found 397.1001 ($C_{24}H_{17}N_2O_2S$, $[M+H]^+$, requires 397.1011).

Benzofuran-2-carboxylic acid (2,4-diphenyloxazol-5-yl)amide (2s).

Yield 55%; mp 198–199° C; *m/z* (ES), 381 ($[M+H]^+$); HRMS, found 381.1250 ($C_{24}H_{17}N_2O_3$, $[M+H]^+$, requires 381.1239).

Benzothiazole-2-carboxylic acid (2,4-diphenyloxazol-5-yl)amide (2t).

Yield 47%; mp 195–196° C; *m/z* (ES), 398 ($[M+H]^+$); HRMS, found 398.0977 ($C_{23}H_{16}N_3O_2S$, $[M+H]^+$, requires 398.0963).

Benzo[*β*]thiophene-5-carboxylic acid (2,4-diphenyloxazol-5-yl)amide (2u).

Yield 65%; mp 195–200° C; *m/z* (ES), 397 ($[M+H]^+$); HRMS, found 397.1029 ($C_{24}H_{17}N_2O_2S$, $[M+H]^+$, requires 397.1011).

Cyclopropanecarboxylic acid (2,4-diphenyloxazol-5-yl)amide (2v).

Yield 54%; mp 183–185° C; *m/z* (ES), 305 ($[M+H]^+$); HRMS, found 305.1278 ($C_{19}H_{17}N_2O_2$, $[M+H]^+$, requires 305.1290).

2-Propylpentanoic acid (2,4-diphenyloxazol-5-yl)amide (2w).

Yield 38%; mp 138° C; *m/z* (ES), 363 ($[M+H]^+$); HRMS, found 363.2066 ($C_{23}H_{27}N_2O_2$, $[M+H]^+$, requires 363.2073).

Example 3: Activity assay

The activity of various compounds of the invention towards prion proteins was assessed using surface plasmon resonance (SPR) and shed mediastinal blood (SMB) cells.

SPR screening methodology

Surface plasmon resonance (SPR) was carried out using a BIAcore 3000 (BIAcore, Uppsala, Sweden) equipped with a CM5 sensor chip (carboxymethylated dextran). The methodology was as reported previously (Touil, F.; Pratt, S.; Mutter, R.; Chen, B., *J. Pharm. Biomed. Anal.* 2006, *40*, 822-832). Interactions were measured with two forms of prion protein, full length human ($huPrP^C$) and full length murine ($moPrP^C$). Compounds were screened at 40 μM in running buffer (10 mM sodium phosphate, pH 7.4, 150 mM NaCl, 3.4 mM EDTA, 0.005% (v/v) surfactant P20) containing 6.5% DMSO. DMSO calibration using buffer samples containing 5.5-7.5% DMSO was carried out to correct for solvent effects. Compounds producing a response of more than 2.5 response units (RU) were considered to be binders.

SMB cell screening methodology

Compounds were screened for inhibition of PrP^{Sc} formation in SMB cells of mesodermal origin, the procedure used being based upon that reported by Rudyk, H.; Vasiljevic, S.; Hennion, R. M.; Birkett, C. R.; Hope, J.; Gilbert, I. H., *J. Gen. Virol.* 2000, *81*, 1155-1164. A persistently infected mouse cell line (SMB), cloned originally from scrapie infected mouse brain but of non-neuronal origin (Clarke, M. C.; Haig, D. A.., *Nature* 1970, *225*, 100–101) was used. Cells were grown in tissue culture treated plastic dishes in Medium 199 (phenol red free), supplemented with 10% newborn calf serum (heat inactivated), 5% foetal calf serum (heat inactivated) and penicillin–streptomycin at 10 mg L^{-1} at 37 °C in an atmosphere of 5% CO_2 in air at 95% relative humidity. Medium was changed every 3rd or 4th day, and every 7 days confluent cells were passaged using 0.05% trypsin and 0.002% EDTA at a split ratio of 4. To assess the effects of compounds cells were distributed into 96-well cluster plates at 3×10^4 cells per well and incubated for 24 h to allow for cell attachment. The compounds were diluted to 400 times the required concentration in DMSO as stock solutions then transferred, at a 20-fold dilution, into Hank's balanced salt solution. This solution was then transferred at a further 20-fold dilution into the cell medium. The cells were incubated with the compound-containing medium for 5 days.

After 5 days cell viability was assessed by the MTT assay following the standard protocol supplied with the reagent (Sigma). For dot blot analyses cells were extracted using lysis buffer (10 mM Tris-HCl [pH 7.6], 100 mM NaCl, 10mM EDTA, 0.5% v/v NP40 and 0.5% w/v sodium deoxycholate), and the content of the well loaded onto a nitrocellulose membrane (0.45 μm) under gentle vacuum at a total cellular protein concentration of

approximately 30-40 μg/well (determined by the Bradford assay following the protocol supplied with the reagent - Sigma). The membrane was air dried and subjected to 75 μg mL^{-1} proteinase K digestion for 1 h at 37 °C. The reaction was stopped with 1 mM phenylmethylsulfonyl fluoride (PMSF) in 20 mM Tris–HCl-buffered saline (TBS), the membrane washed extensively with TBS, and immersed in 1.8 M guanidine thiocyanate in TBS for 10 min at room temperature. After further washing with TBS the membrane was blocked using 5% fat-free milk powder in phosphate buffered saline (PBS), processed with 0.2 μg mL^{-1} mouse monoclonal anti-PrP 6H4 (Prionics) and developed using an ECL kit (Amersham Pharmacia Biotech).

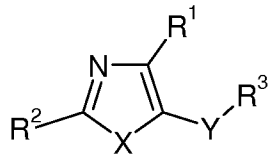
Each experiment was carried out in triplicate and an average value for PrP^{Sc} concentration calculated, relative to an untreated control, together with a standard deviation. Compounds were initially screened at 1 and 10 μM and were considered to be active if PrP^{Sc} levels were reduced to less than 70% of that of the untreated control after 5 days' exposure. Where an acceptable dose-response curve was observed, EC_{50} values were determined.

Results

Compounds of the invention were found to bind to PrP^{C} and showed potent inhibition of PrP^{Sc} formation. In the case of exemplary compounds, their IC_{50}s were found to range from 1.5 to 20 μM.

Claims

1. A compound of formula (I):



(I)

wherein

X is oxygen or sulphur;

Y is a bond or a linker having 1 to 10 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^5)- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^7;

one of R^1 and R^2 is selected from carbocyclyl and heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7; and the other is -Z-R^4;

R^3 is selected from hydrogen; R^7; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -$(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7;

Z is a bond or a linker having 1 to 10 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_l$-, -N(R^5)- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^7;

R^4 is selected from hydrogen; R^7; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -$(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7;

R^5 is selected from R^6, -OR^6, -C(O)R^6, -C(O)OR^6 and -S(O)$_l R^6$;

R^6 is selected from hydrogen; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and -$(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7;

each R^7 is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10};

R^8 and R^9 are each independently hydrogen or R^{10};

R^{10} is selected from hydrocarbyl and $-(CH_2)_k$-heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy, C_{1-6} alkyl and C_{1-6} alkoxy;

k is 0, 1, 2, 3, 4, 5 or 6; and

l is 0, 1 or 2;

or a pharmaceutically acceptable salt or prodrug thereof;

for use in the treatment, prevention or delay of progression of a prion disease.

2. A compound according to claim 1, wherein R^1 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7; and R^2 is $-Z-R^4$.

3. A compound according to claim 2, wherein R^1 is carbocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

4. A compound according to claim 3, wherein R^1 is phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

5. A compound according to claim 4, wherein R^1 is phenyl.

6. A compound according to any preceding claim, wherein Z is a bond.

7. A compound according to any preceding claim, wherein R^4 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

8. A compound according to any of claims 2 to 5, wherein R^2 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

9. A compound according to claim 8, wherein R^2 is phenyl, furanyl, benzofuranyl, thiophenyl or isoxazole, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

10. A compound according to any preceding claim, wherein Y is a linker having 1 to 10 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, $-S(O)_l-$, $-N(R^5)-$ and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R^7.

11. A compound according to claim 10, wherein Y comprises an amide linkage.

12. A compound according to claim 10 or claim 11, wherein Y is selected from the following linkers:

$-Y^1-$;

$-Y^1-Y^2-$;

$-Y^1-Y^2-Y^3-$;

$-Y^1-Y^2-Y^3-Y^4-$; and

$-Y^1-Y^2-Y^3-Y^4-Y^5-$;

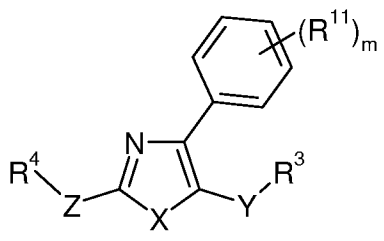
wherein Y^1, Y^2, Y^3, Y^4 and Y^5 are each independently selected from -O-, -C(O)-, $-S(O)_l-$, $-N(R^5)-$ and hydrocarbylene (e.g. C_{1-5} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R^7.

13. A compound according to claim 12, wherein Y is $-Y^1-$ or $-Y^1-Y^2-$.

14. A compound according to claim 13, wherein Y is $-N(R^5)C(O)-$ or $-C(O)N(R^5)-$.

15. A compound according to claim 14, wherein R^5 is hydrogen or C_{1-6} alkyl.

16. A compound according to claim 1, which is of the formula (II):



(II)

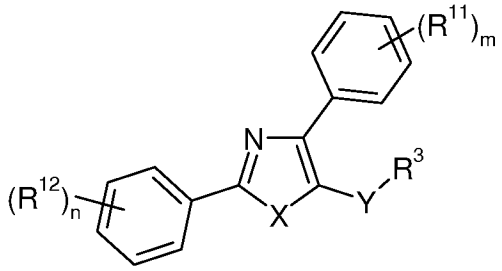
wherein

each R^{11} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

m is 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

17. A compound according to claim 16, which is of the formula (III):



(III)

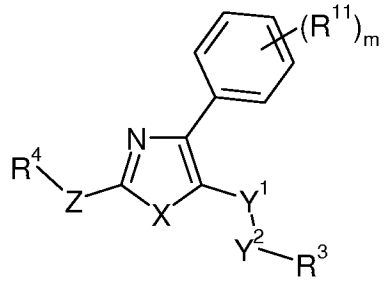
wherein

each R^{12} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

n is 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

18. A compound according to claim 1, which is of the formula (IV):



(IV)

wherein

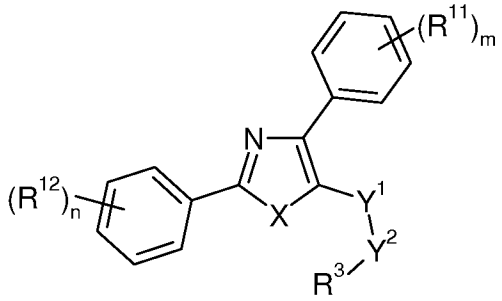
Y^1 and Y^2 are each independently selected from -O-, -C(O)-, $-S(O)_l-$, $-N(R^5)-$ and hydrocarbylene (e.g. C_{1-5} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R^7.

each R^{11} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

m is 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

19. A compound according to claim 18, which is of the formula (V):



(V)

wherein

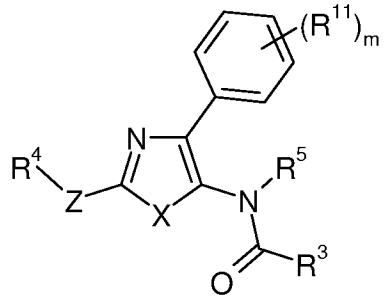
Y^1 and Y^2 are each independently selected from -O-, -C(O)-, $-S(O)_l-$, $-N(R^5)-$ and hydrocarbylene (e.g. C_{1-5} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R^7;

R^{11} and R^{12} are each independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

m and n are each independently 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

20. A compound according to claim 1, which is of the formula (VI):



(VI)

wherein

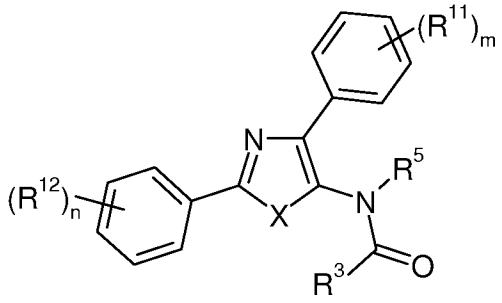
Y^1 and Y^2 are each independently selected from -O-, -C(O)-, $-S(O)_l$-, $-N(R^5)$- and hydrocarbylene (e.g. C_{1-5} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R^7.

each R^{11} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

m is 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

21. A compound according to claim 20, which is of the formula (VII):



(VII)

each R^{12} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $=NR^8$, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, $-N(R^8)R^9$, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$ and R^{10}; and

n is 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

22. A compound according to claim 20 or claim 21, wherein R^5 is hydrogen.

23. A compound according to any preceding claim, wherein R^3 is selected from hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and $-(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

24. A compound according to claim 23, wherein R^3 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

25. A compound according to claim 23, wherein R^3 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

26. A compound according to claim 25, wherein R^3 is carbocyclyl (e.g. aryl or cycloalkyl) optionally substituted with 1, 2, 3, 4 or 5 R^7.

27. A compound according to claim 26, wherein R^3 is phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

28. A compound according to claim 25, wherein R^3 is heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

29. A compound according to claim 28, wherein R^3 is furanyl, benzofuranyl, thiophenyl or isoxazolyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7.

30. A compound according to any preceding claim, wherein X is oxygen.

31. A compound according to any of claims 1 to 29, wherein X is sulphur.

32. A compound according to any preceding claim, wherein the disease is selected from Creutzfeldt-Jakob disease, kuru, Gerstmann-Straussler-Sheinker disease, fatal familial insomnia and transmissible spongiform encephalopathies (TSEs).

33. A compound according to claim 32, wherein the disease is selected from bovine spongiform encephalopathy (BSE), scrapie, chronic wasting disease and transmissible mink encephalopathy (TME).

34. A compound of claim 1, independent of use, wherein:

R^1 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^7;

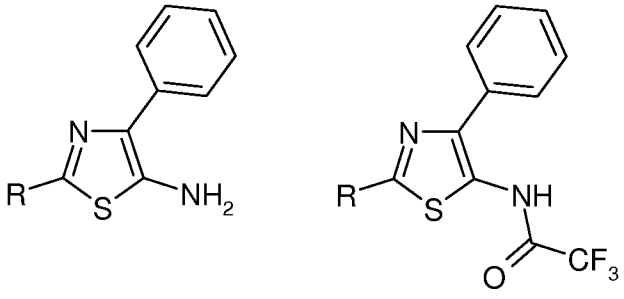
R^2 is selected from cycloalkyl, cycloalkenyl, phenyl, furanyl, benzofuranyl, thiophenyl, isoxazolyl, quinolinyl, isoquinolinyl, quinoxazolinyl, benzothiazolyl and benzothiophenyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^7;

Y is $-N(R^5)C(O)-$ or $-C(O)N(R^5)-$; and R^3 is selected from hydrogen, trifluoromethyl, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-S(O)_lR^8$, amino, $-C(O)N(R^8)R^9$, $-S(O)_lN(R^8)R^9$, $-N(R^8)S(O)_lR^8$, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^7; and $-(CH_2)_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^7;

or $-Y-R^3$ is $-N(R^8)R^9$; and

R^{10} is selected from hydrocarbyl and $-(CH_2)_k$-heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy and C_{1-6} alkyl;

with the proviso that the compound is not 2,4-diphenyloxazol-5-ylamine or a compound of one of the following formulae:



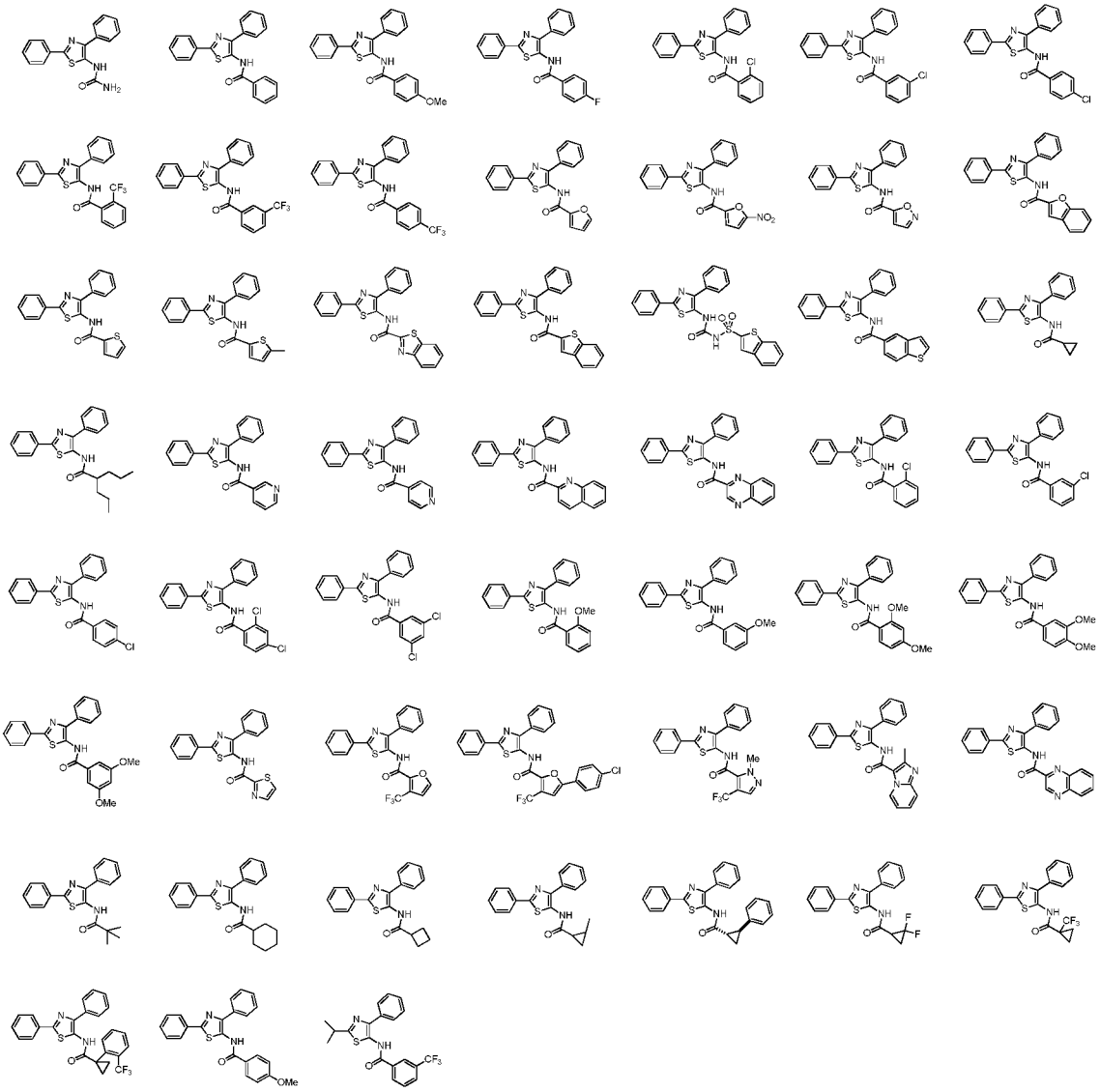
wherein, in each case, R is selected from phenyl, 4-methoxyphenyl, thiophen-2-yl, cyclohexyl.

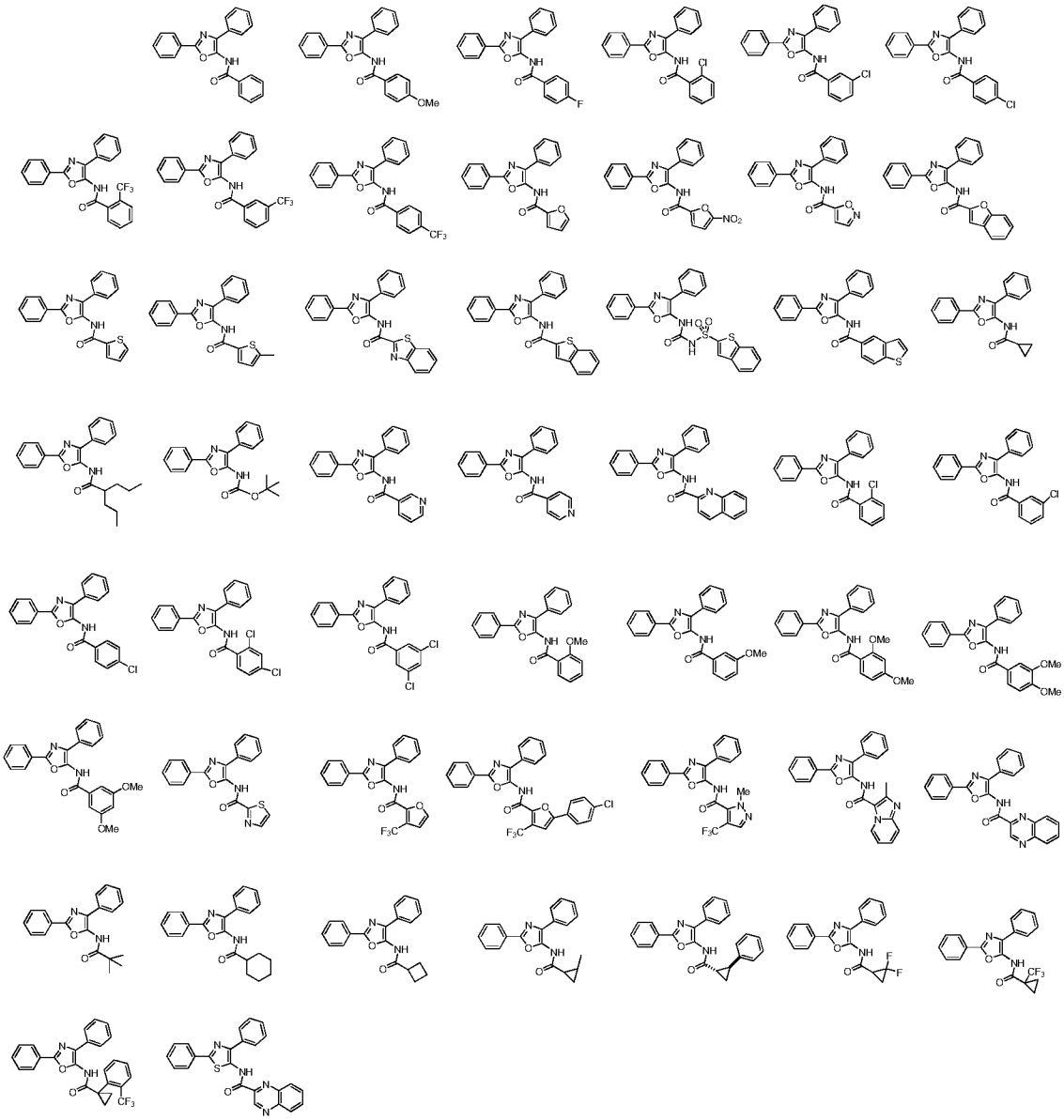
35. A compound according to claim 34, wherein R^1 is as defined in any of claims 2 to 5.

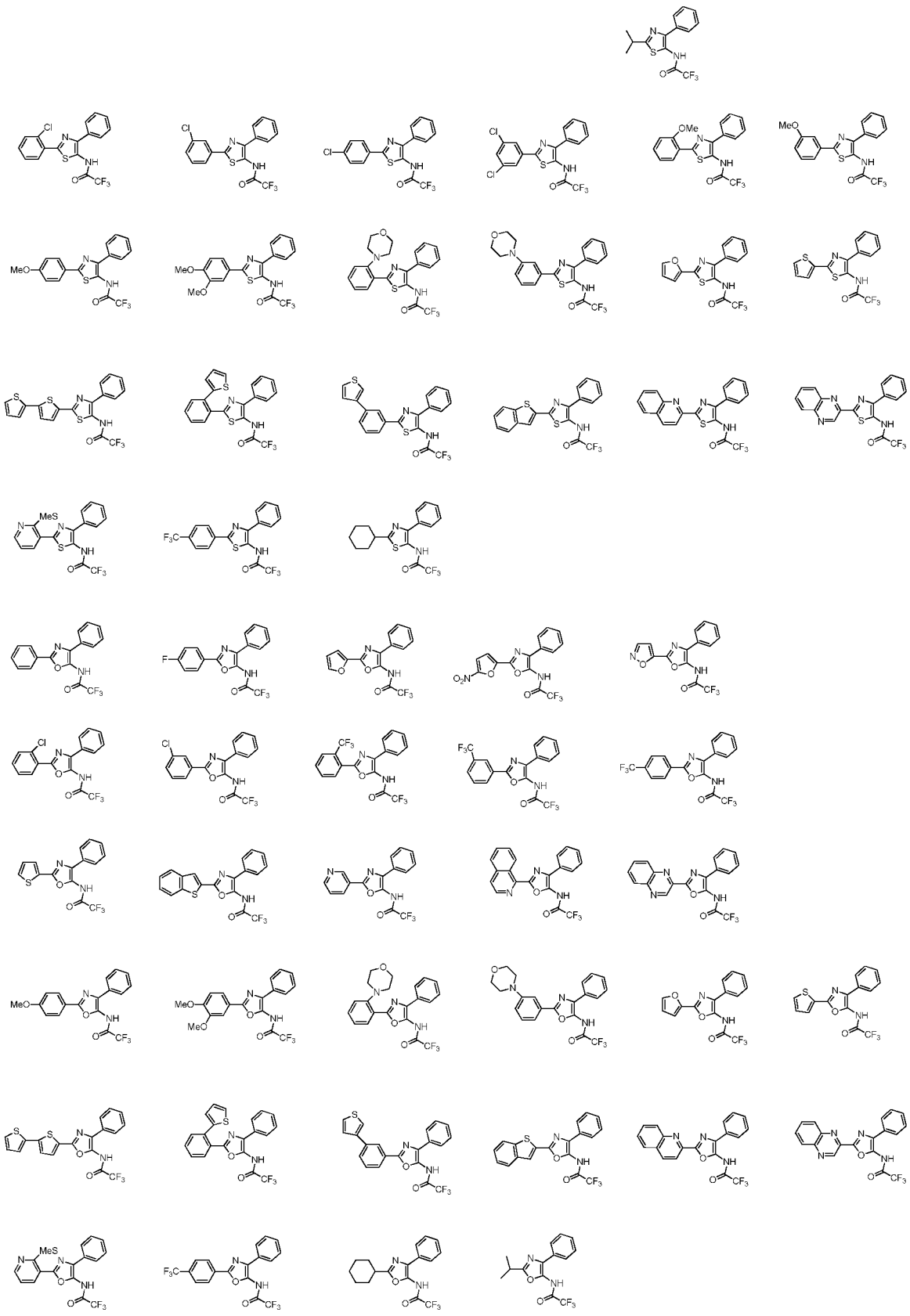
36. A compound according to claim 35, wherein R^1 is phenyl optionally substituted with 1, 2, 3, 4 or 5 R^7.

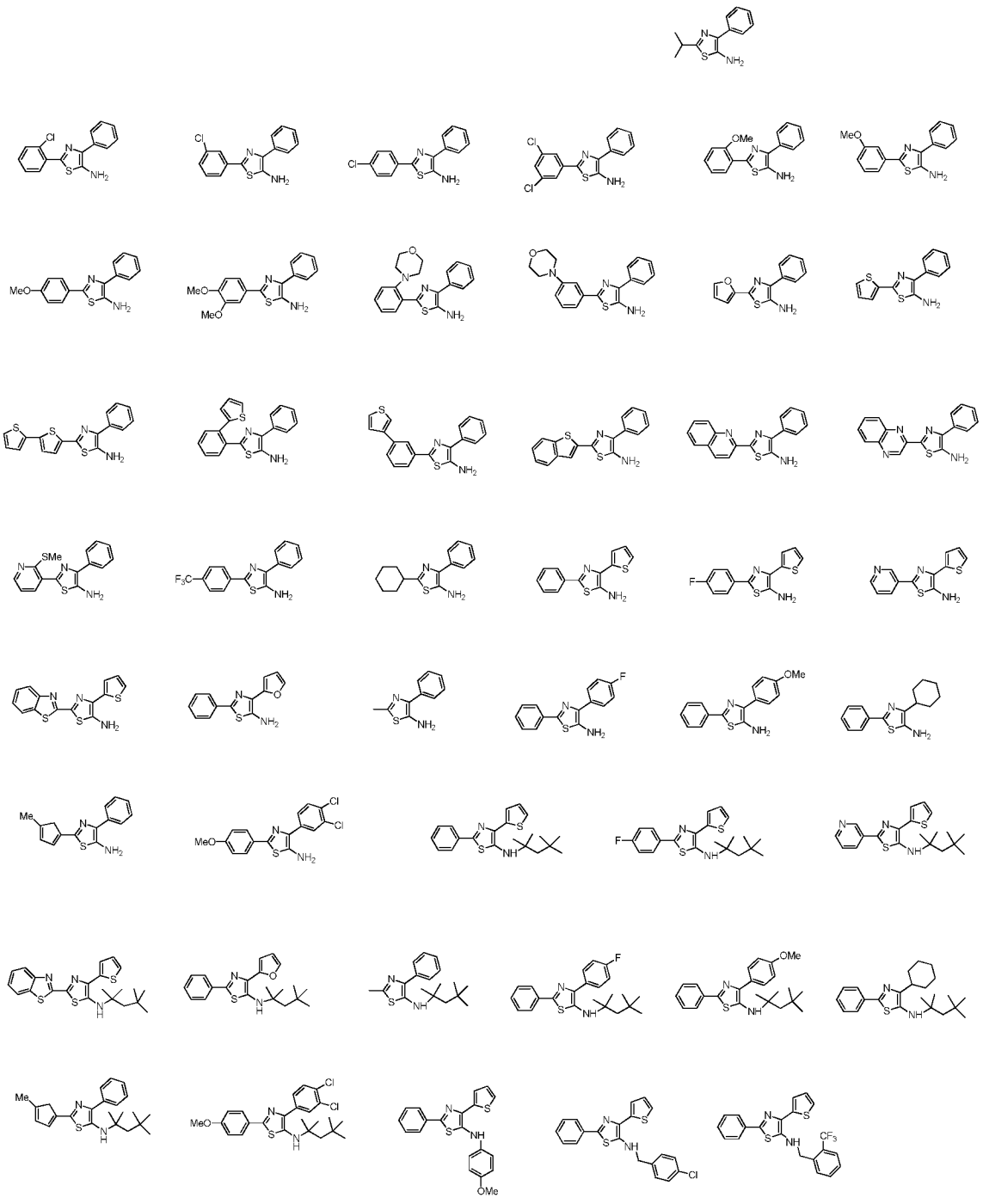
37. A compound according to any of claims 34 to 36, wherein R^3 is as defined in any of claims 23 to 29.

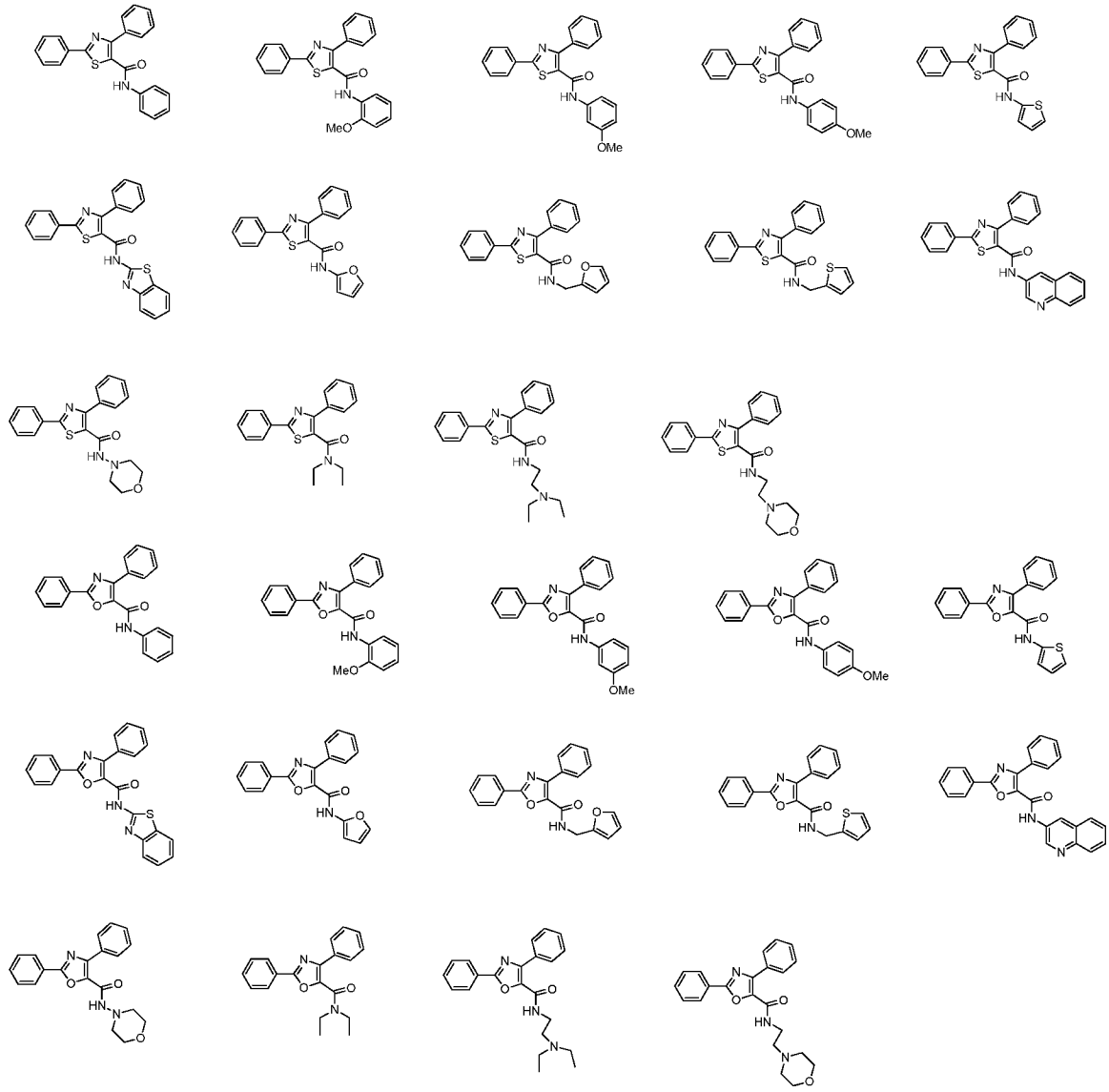
38. A compound selected from:











and pharmaceutically acceptable salts or prodrugs thereof:

39. A compound of any of claims 34 to 38, for therapeutic use.

40. A pharmaceutical formulation comprising a compound of any of claims 34 to 38.

41. A formulation according to claim 40, which comprises a pharmaceutically acceptable carrier or excipient.

42. Use of a compound of formula (I) as defined in any of claims 1 to 31, for the manufacture of a medicament for the treatment, prevention or delay of progression of a prion disease.

43. A method of treating, preventing or delaying the progression of a prion disease in a subject, comprising administering a therapeutically effective amount of a compound of any of claims 1 to 31.

44. A method according to claim 39, wherein the disease is as defined in claim 32 or claim 33.

45. A method of regulating stem cell activity, which comprises contacting one or more stem cells with a compound of formula (I) as defined in any of claims 1 to 31.

46. A method according to claim 45, wherein said contacting takes place *in vitro*.

47. Use of a compound of formula (I) as defined in any of claims 1 to 31, for regulating stem cell activity.

48. Use according to claim 47, for regulating stem cell activity *in vitro*.

49. Use of a compound of formula (I) as defined in any of claims 1 to 31, for the manufacture of a medicament for the treatment, prevention or delay of progression of cancer or a disease or condition of the central nervous system.

50. Use of a compound of formula (I) as defined in any of claims 1 to 31, for the manufacture of a medicament for use in regenerative medicine.

51. Use according to claim 49 or claim 50, wherein the compound is a compound of any of claims 34 to 38.

52. A compound of formula (I) as defined in any of claims 1 to 31, for use in the treatment, prevention or delay of progression of cancer or a disease or condition of the central nervous system.

53. A compound of formula (I) as defined in any of claims 1 to 31, for use in regenerative medicine.

54. A compound according to claim 52 or claim 53, wherein the compound is a compound of any of claims 34 to 38.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/050052

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D263/34 C07D263/48 C07D277/40 C07D277/42 C07D277/46
C07D277/48 C07D277/56 C07D413/04 C07D413/14 C07D417/04
C07D417/14 A61K31/4164 A61K31/4178 A61K31/421 A61K31/422

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/026137 A (VERTEX PHARMA [US]) 24 March 2005 (2005-03-24) page 7, paragraph 14 compounds 2-7,9,18,20,21,35,39,43-53,55,58-62,67-88, 104-116,159-178,196-199,226-233 claims 1,12,185,194,220 page 224, paragraph 295	1-54
X	WO 2006/137658 A (DONGBU HANNONG CHEMICALS CO LT [KR]) 28 December 2006 (2006-12-28) examples claims 1,17	1-54

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2008	06/05/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cortés, José

3

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/114274 A (GLAXO GROUP LTD [GB]) 2 November 2006 (2006-11-02) page 20, line 10 examples 131-160,162-183 claim 1	1-54
X	EP 1 700 856 A (KYOWA HAKKO KOGYO KK [JP]) 13 September 2006 (2006-09-13) page 18, paragraph 28 page 99, paragraph 131 compounds 23,86-90,93,94 claims 1,24,29,50	1-54
X	WO 2005/097114 A (PFIZER PROD INC [US]) 20 October 2005 (2005-10-20) page 11 - page 14 example 20 claims 1,13,14,16,18	1-54
X	WO 2005/073225 A (SCIENCE AB [FR]) 11 August 2005 (2005-08-11) page 62, line 11 examples claims 1,3,7,14	1-54
X	WO 2005/049018 A (VERTEX PHARMA [US]) 2 June 2005 (2005-06-02) page 8, paragraph 29 compounds 1,2,4,45,46,47-50 claims 1,5	1-54
X	WO 2005/040139 A (SCIENCE AB [FR]) 6 May 2005 (2005-05-06) page 50, line 17 claims 1,18	1-54
X	WO 2004/033439 A (PFIZER PROD INC [US]) 22 April 2004 (2004-04-22) page 50, line 16 - page 51, line 8 examples 6,29 claims 1,14	1-54
X	EP 1 256 578 A (PFIZER PROD INC [US]) 13 November 2002 (2002-11-13) paragraphs [0039], [0072], [0073], [0117] examples claim 1	1-54
X	WO 01/74811 A (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 11 October 2001 (2001-10-11) the whole document	1-54

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/04116 A (ORTHO MCNEIL PHARM INC [US]) 18 January 2001 (2001-01-18) page 21, lines 7,15,16 compounds 11-23,40-43 claim 1	1-54
X	EP 1 205 478 A (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 15 May 2002 (2002-05-15) the whole document	1-54
X	US 2003/191167 A1 (WARNER LAMBERT CO [US]) 9 October 2003 (2003-10-09) page 1, paragraph 1 page 2, paragraph 24 - paragraph 34; compounds page 2, paragraph 37 - paragraph 45; compounds	34-41, 51,54
X	WO 00/02871 A (MERCK & CO INC [US]) 20 January 2000 (2000-01-20) claims; examples	34-41, 51,54
X	KATRIZKY ET AL: "Convenient Synthesis of Novel N-Substituted-5-aminothiazole Derivatives" JOURNAL OF ORGANIC CHEMISTRY (EN), vol. 65, no. 23, 2000, pages 8077-8079, XP002477265 page 1, paragraph 1 page 8078, compounds 15a-m	34-41, 51,54
X	FRALEY ET AL: BIOORGANIC MEDICINAL CHEMISTRY LETTERS (EN), vol. 13, no. 18, 2003, pages 2973-2976, XP002477266 page 2974, compounds 2a-f	34-41, 51,54
X	EP 0 761 658 A (NIHON NOHYAKU CO LTD [JP]) 12 March 1997 (1997-03-12) claims; examples	34-37
X	US 4 113 731 A (WINTERS GIORGIO ET AL) 12 September 1978 (1978-09-12) example 5: 5-amino-2-(p-tolyl)-4-phenylthiazole (intermediate)	34-37

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/050052

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2006, BALYA, A. G. ET AL: "Convenient method for addition of azolyl fragments to the 5 position of the thiazole ring" XP002477298 retrieved from STN Database accession no. 2007:165324 abstract & ZHURNAL ORGANICHNOI TA FARMATSEVTICHNOI KHIMII , 4(4), 49-53 CODEN: ZOFKAM, 2006, -----	34-38
X	THOMPSON ET AL: "Synthesis of 5-aminothiazoles as building blocks for library synthesis" TETRAHEDRON LETTERS, vol. 47, 17 February 2006 (2006-02-17), pages 2361-2364, XP002477306 cited in the application page 2362, table 1, compound 8b -----	38
P,X	HEAL ET AL: JOURNAL OF MEDICINAL CHEMISTRY, vol. 50, 17 February 2007 (2007-02-17), pages 1347-1353, XP002477267 the whole document -----	1-54
P,X	EP 1 845 081 A (TAKEDA PHARMACEUTICAL [JP]) 17 October 2007 (2007-10-17) page 23, paragraph 152 examples 16,66 -----	34-41, 51,54

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 43-46, 47 and 48 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

international application No.
PCT/GB2008/050052

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

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

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

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

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

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

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

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

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

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

Remark on Protest

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

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

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2008/050052

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005026137 A	24-03-2005	AU 2004272599 A1	24-03-2005
		CA 2537841 A1	24-03-2005
		CN 1898221 A	17-01-2007
		EP 1664006 A2	07-06-2006
		JP 2007504255 T	01-03-2007
		KR 20060088537 A	04-08-2006
		MX PA06002567 A	04-09-2006
		US 2005176789 A1	11-08-2005
WO 2006137658 A	28-12-2006	KR 20060133464 A	26-12-2006
WO 2006114274 A	02-11-2006	EP 1874776 A1	09-01-2008
EP 1700856 A	13-09-2006	AU 2004309279 A1	14-07-2005
		BR PI0418082 A	17-04-2007
		CA 2551611 A1	14-07-2005
		CN 1902196 A	24-01-2007
		WO 2005063743 A1	14-07-2005
		KR 20060126519 A	07-12-2006
		US 2007105919 A1	10-05-2007
WO 2005097114 A	20-10-2005	BR PI0509464 A	11-09-2007
		CA 2561928 A1	20-10-2005
		EP 1734957 A2	27-12-2006
		JP 2007530699 T	01-11-2007
WO 2005073225 A	11-08-2005	AU 2005209485 A1	11-08-2005
		BR PI0507271 A	26-06-2007
		CA 2554925 A1	11-08-2005
		CN 1934107 A	21-03-2007
		EP 1711497 A1	18-10-2006
		JP 2007519711 T	19-07-2007
		KR 20060129413 A	15-12-2006
WO 2005049018 A	02-06-2005	AU 2004290581 A1	02-06-2005
		CA 2545719 A1	02-06-2005
		CN 1925854 A	07-03-2007
		EP 1682127 A1	26-07-2006
		JP 2007511538 T	10-05-2007
		KR 20060121185 A	28-11-2006
		MX PA06005343 A	10-07-2006
WO 2005040139 A	06-05-2005	AU 2004283162 A1	06-05-2005
		BR PI0415467 A	19-12-2006
		CA 2542909 A1	06-05-2005
		CN 1950347 A	18-04-2007
		EP 1684750 A2	02-08-2006
		JP 2007509130 T	12-04-2007
		KR 20060118500 A	23-11-2006
WO 2004033439 A	22-04-2004	AU 2003265068 A1	04-05-2004
		CA 2501803 A1	22-04-2004
		EP 1551815 A1	13-07-2005
		JP 2006504796 T	09-02-2006
		KR 20050070046 A	05-07-2005
		MA 27451 A1	01-07-2005
		NL 1024499 C2	13-10-2004
		NL 1024499 A1	13-04-2004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004033439 A		UY 28011 A1	30-04-2004
EP 1256578 A	13-11-2002	AT 315555 T	15-02-2006
		BR 0201691 A	11-03-2003
		CA 2385692 A1	11-11-2002
		DE 60208630 T2	17-08-2006
		ES 2254611 T3	16-06-2006
		JP 2002338556 A	27-11-2002
		MX PA02004790 A	11-02-2003
WO 0174811 A	11-10-2001	AU 4461801 A	15-10-2001
		CA 2404384 A1	11-10-2001
		EP 1268474 A2	02-01-2003
		US 2004053973 A1	18-03-2004
WO 0104116 A	18-01-2001	AU 781235 B2	12-05-2005
		AU 5485500 A	30-01-2001
		BR 0012327 A	02-07-2002
		CA 2379149 A1	18-01-2001
		CN 1382140 A	27-11-2002
		CZ 20020065 A3	17-07-2002
		EP 1202990 A2	08-05-2002
		HU 0202249 A2	28-12-2002
		JP 2003504367 T	04-02-2003
		MX PA02000330 A	21-05-2004
		PL 352432 A1	25-08-2003
		RU 2241709 C2	10-12-2004
		TW 589311 B	01-06-2004
		US 6809107 B1	26-10-2004
EP 1205478 A	15-05-2002	AU 6471300 A	05-03-2001
		CA 2381215 A1	15-02-2001
		WO 0110865 A1	15-02-2001
		US 6962933 B1	08-11-2005
US 2003191167 A1	09-10-2003	AU 2003212310 A1	13-10-2003
		BR 0308765 A	11-01-2005
		CA 2480679 A1	09-10-2003
		WO 03082839 A1	09-10-2003
		EP 1348701 A1	01-10-2003
		JP 2005531526 T	20-10-2005
		MX PA04009476 A	25-01-2005
WO 0002871 A	20-01-2000	AU 747427 B2	16-05-2002
		AU 5208299 A	01-02-2000
		CA 2336848 A1	20-01-2000
		EP 1097147 A1	09-05-2001
		JP 2002520324 T	09-07-2002
EP 0761658 A	12-03-1997	AU 679887 B2	10-07-1997
		AU 6428596 A	13-03-1997
		CA 2185082 A1	12-03-1997
		NZ 299242 A	19-12-1997
US 4113731 A	12-09-1978	IT 1054655 B	30-11-1981
EP 1845081 A	17-10-2007	WO 2006082952 A1	10-08-2006

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2008/050052

Patent document cited in search report	Publication date	Patent family member(s)	Publication date