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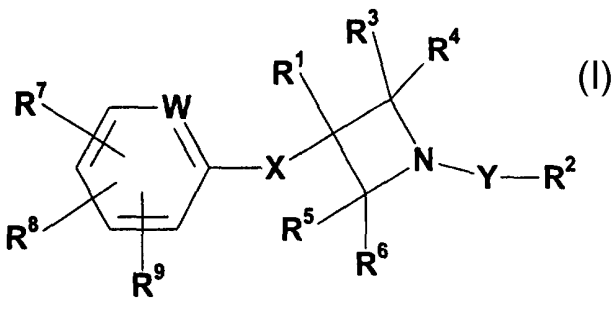
(54) Title: NOVEL PHENYLHETEROAZETIDINES, USEFUL AS NITRIC OXIDE SYNTHASE INHIBITORS



(I)

(57) Abstract: There are provided novel compounds of formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, W, X and Y are as defined in the specification, and pharmaceutically acceptable salts thereof, and enantiomers and racemates thereof; together with processes for their preparation, compositions bontaining them and their use in therapy. The compounds are inhibitors of nitric oxide synthase and are thereby particularly useful in the treatment or prophylaxis of inflammatory disease and pain.

NOVEL PHENYLHETEROAZETIDINES, USEFUL AS NITRIC OXIDE SYNTHASE INHIBITORS

Field of the Invention

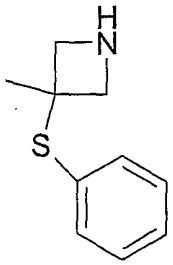
The present invention relates to novel phenylheteroazetidine derivatives, processes for their preparation, compositions containing them and their use in therapy.

Background of the Invention

Nitric oxide is produced in mammalian cells from L-arginine by the action of specific nitric oxide synthases (NOSs). These enzymes fall into two distinct classes - constitutive NOS (cNOS) and inducible NOS (iNOS). At the present time, two constitutive NOSs and one inducible NOS have been identified. Of the constitutive NOSs, an endothelial enzyme (ecNOS) is involved with smooth muscle relaxation and the regulation of blood pressure and blood flow, whereas the neuronal enzyme (ncNOS) serves as a neurotransmitter and appears to be involved in the regulation of various biological functions such as cerebral ischaemia. Inducible NOS has been particularly implicated in the pathogenesis of inflammatory diseases. Regulation of these enzymes should therefore offer considerable potential in the treatment of a wide variety of disease states (J. E. Macdonald, *Ann. Rep. Med. Chem.*, 1996, **31**, 221 - 230).

Considerable effort has been expended in efforts to identify compounds that act as specific inhibitors of one or more isoforms of the enzyme nitric oxide synthase. The use of such compounds in therapy has also been widely claimed.

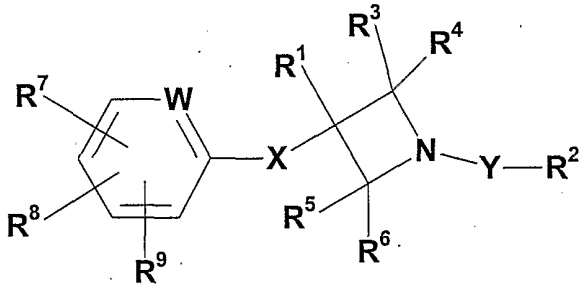
W. Funke (Chem. Ber., 1969, 102, 3148-3158) discloses 3-methyl-3-phenylthio-azetidine,



No pharmacological activity is ascribed to this compound.

Disclosure of the invention

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



(I)

wherein

R^1 represents C1 to 5 alkyl, C2 to 4 alkenyl, C2 to 4 alkynyl, C3 to 6 cycloalkyl or a 4 to 8 membered saturated heterocyclic ring incorporating one or two heteroatoms independently selected from O, S and N; any of said groups being optionally further substituted by one or more substituents selected independently from C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkylthio, C3 to 6 cycloalkyl, halogen and phenyl; said phenyl group being optionally further substituted by one or more substituents selected independently from halogen, C1 to 4 alkoxy, CF_3, OCF_3, CN, NO_2, $NR^{10}R^{11}$, $COOR^{12}$, $CONR^{13}R^{14}$ and C1 to 4 alkyl; said alkyl group being optionally substituted by OH or $NR^{15}R^{16}$;

or R^1 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, OH, CN, NO_2 or $NR^{10}R^{11}$; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

R^2 represents H, C1 to 4 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally substituted by C1 to 4 alkoxy, halogen, hydroxy, $NR^{17}R^{18}$, phenyl or a five or six membered aromatic or saturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally further substituted by halogen, C1 to 4 alkyl, C1 to 4 alkoxy, CF_3, OCF_3, CN or NO_2;

R^3, R^4, R^5 and R^6 independently represent H or C1 to 4 alkyl; said alkyl group being optionally substituted by OH, SR^{19}, $NR^{20}R^{21}$ or C2 to 4 alkenyl;

R^7, R^8 and R^9 independently represent H, C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CF_3, OCF_3, CN, C≡CH, $S(O)_mCH_3$, or NO_2;

m represents an integer 0, 1 or 2;

W represents N or CH;

X represents O, $S(O)_n$ or NR^{22};

n represents an integer 0, 1 or 2;

Y represents –CO– or a bond;

R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} independently represent H or C1 to 4 alkyl;

or a pharmaceutically acceptable salt, enantiomer or racemate thereof;
with the proviso that 3-methyl-3-phenylthio-azetidine is excluded.

The compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers and racemates have the advantage that they are inhibitors of the enzyme nitric oxide synthase (NOS). In particular, the compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers and racemates have the advantage that they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase (iNOS).

The invention further provides a process for the preparation of compounds of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

According to the invention there is also provided a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer or racemate thereof, for use as a medicament.

Another aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in the manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

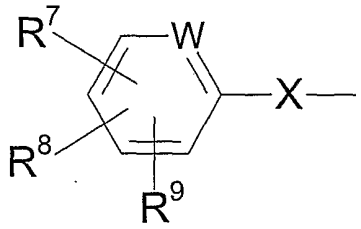
A more particular aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory disease.

According to the invention, there is also provided a method of treating, or reducing the risk of, diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

More particularly, there is also provided a method of treating, or reducing the risk of, inflammatory disease in a person suffering from or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

The compounds of the present invention may also be used advantageously in combination with a second pharmaceutically active substance, particularly in combination with a selective inhibitor of the inducible isoform of cyclooxygenase (COX-2). Thus, in a further aspect of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in combination with a COX-2 inhibitor for the treatment of inflammation, inflammatory disease and inflammatory related disorders. And there is also provided a method of treating, or reducing the risk of, inflammation, inflammatory disease and inflammatory related disorders in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof in combination with a COX-2 inhibitor.

In one preferred embodiment, the group



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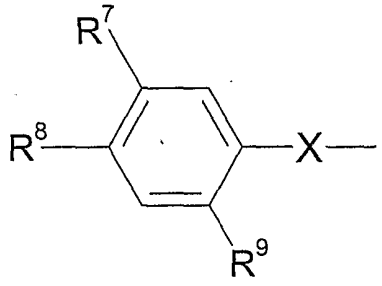
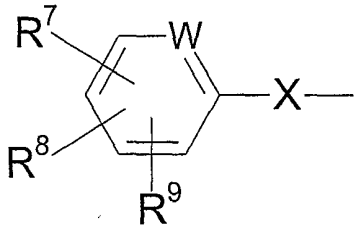


In another preferred embodiment, the group



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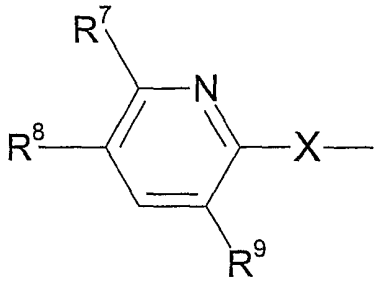


In another preferred embodiment, X represents O or S.

In yet another preferred embodiment, R^3, R^4, R^5 and R^6 each represent H.

It is preferred that R^7 does not represent H.

It is preferred that R^9 does not represent H.

It is particularly preferred that R^8 represents H or fluoro.

It is particularly preferred that R^7 and R^9 are independently selected from halogen, CN or CF_3; more especially from Cl, CN or CF_3.

When R^1 represents a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N, it is preferred that R^1 represents furyl, thienyl, thiazolyl, isothiazolyl or pyridyl.

Particular compounds of the invention include:

4-chloro-2-(3-phenyl-azetidin-3-yloxy)-benzonitrile;

4-chloro-2-(3-ethyl-azetidin-3-yloxy)-benzonitrile;
4-chloro-2-(3-thiophen-2-yl-azetidin-3-yloxy)-benzonitrile;
4-chloro-5-fluoro-2-(3-pyridin-3-yl-azetidin-3-yloxy)-benzonitrile;
4-chloro-5-fluoro-2-(3-furan-3-yl-azetidin-3-yloxy)-benzonitrile;
3-(2-chloro-5-trifluoromethyl-phenoxy)-3-furan-3-yl-azetidine;
4-chloro-5-fluoro-2-(3-propyl-azetidin-3-yloxy)-benzonitrile;
4-chloro-5-fluoro-2-(3-furan-2-yl-azetidin-3-yloxy)-benzonitrile;
3-(2,5-dichloro-phenylsulfanyl)-3-ethyl-azetidine;
4-chloro-5-fluoro-2-(3-thiazol-2-yl-azetidin-3-yloxy)-benzonitrile;
4-chloro-5-fluoro-2-(3-trifluoromethyl-azetidin-3-yloxy)-benzonitrile;
2-(3-thiazol-2-yl-azetidin-3-yloxy)-4-trifluoromethyl-benzonitrile;
2-[[3-(5-isothiazolyl)-3-azetidinyl]oxy]-6-methyl-3-pyridinecarbonitrile;
4-chloro-5-fluoro-2-[3-(4-methyl-thiazol-2-yl)-azetidin-3-yloxy]-benzonitrile;
2-[3-(2,5-dichloro-phenoxy)-azetidin-3-yl]-thiazole;
4-chloro-5-fluoro-2-(3-vinyl-azetidin-3-yloxy)-benzonitrile;
2-[3-(2,5-dichloro-phenylsulfanyl)-azetidin-3-yl]-thiazole;
3-(2,5-dichloro-phenylsulfanyl)-3-propyl-azetidine;
2-[1-(2-amino-ethyl)-3-phenyl-azetidin-3-yloxy]-4-chloro-benzonitrile;
2-[3-(2-amino-thiazol-4-yl)-azetidin-3-yloxy]-4-chloro-5-fluoro-benzonitrile;
4-chloro-5-fluoro-2-[3-(2-methyl-thiazol-4-yl)-azetidin-3-yloxy]-benzonitrile;
3-[(2,5-dichlorophenyl)thio]-β-oxo-3-propyl-1-azetidineethanamine;
3-[(2,5-dichlorophenyl)thio]-3-propyl-1-azetidineethanol;
4-chloro-2-[(3-propyl-3-azetidinyl)thio] benzonitrile;
4-chloro-5-fluoro-2-[[(2*S*,3*S*)-3-(3-furanyl)-2-methyl-3-azetidinyl]oxy]benzonitrile;
2-[(3-propyl-3-azetidinyl)thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile;
and pharmaceutically acceptable salts, enantiomers or racemates thereof.

Unless otherwise indicated, the term "C1 to 4 alkyl" referred to herein denotes a straight or branched chain alkyl group having from 1 to 4 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl.

The term "C1 to 5 alkyl" is to be interpreted analogously.

Unless otherwise indicated, the term "C3 to 6 cycloalkyl" referred to herein denotes a cycloalkyl group having from 3 to 6 carbon atoms. Examples of such groups include cyclopropyl, cyclopentyl and cyclohexyl.

Unless otherwise indicated, the term "C2 to 4 alkenyl" referred to herein denotes a straight or branched chain alkyl group having from 2 to 4 carbon atoms incorporating at least one carbon-carbon double bond. Examples of such groups include ethenyl, propenyl and butenyl.

Unless otherwise indicated, the term "C2 to 4 alkynyl" referred to herein denotes a straight or branched chain alkyl group having from 2 to 4 carbon atoms incorporating at least one carbon-carbon triple bond. Examples of such groups include ethynyl, propynyl, and butynyl.

Unless otherwise indicated, the term "C1 to 4 alkoxy" referred to herein denotes a straight or branched chain alkoxy group having from 1 to 4 carbon atoms. Examples of such groups include methoxy, ethoxy, n-propoxy, i-propoxy and t-butoxy.

The term "C1 to 4 alkylthio" is to be interpreted analogously.

Unless otherwise indicated, the term "halogen" referred to herein denotes fluoro, chloro, bromo and iodo.

Examples of a 4 to 8 membered saturated azacyclic ring optionally incorporating one further heteroatom selected from O, S or N include pyrrolidine, piperidine, piperazine, morpholine and perhydroazepine.

Examples of a 4 to 8 membered saturated heterocyclic ring incorporating one or two heteroatoms independently selected from O, S or N include azetidine, pyrrolidine, piperidine, tetrahydrofuran, morpholine, piperazine, thiomorpholine and perhydroazepine.

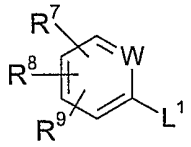
Examples of a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N include furan, thiophene, pyridine, thiazole, imidazole, oxazole, triazole, oxadiazole, thiadiazole and pyrimidine.

Examples of a five or six membered saturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N include pyrrolidine, tetrahydrofuran, piperidine, morpholine and piperazine.

Examples of a "C1 to 4 alkyl or C1 to 4 alkoxy optionally further substituted by one or more fluorine atoms" include CF_3, CF_3CF_2, CF_3CH_2, CH_2FCH_2, CH_3CF_2, $CF_3CH_2CH_2$, OCF_3 and OCH_2CF_3.

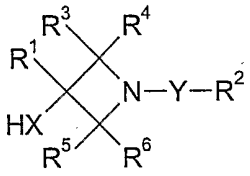
According to the invention, we further provide a process for the preparation of compounds of formula (I), or a pharmaceutically acceptable salt, enantiomer or racemate thereof which comprises:

(a) reaction of a compound of formula (II)



(II)

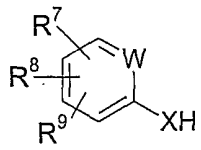
wherein R^7, R^8, R^9 and W are as defined in formula (I) and L^1 represents a leaving group, with a compound of formula (III)



(III)

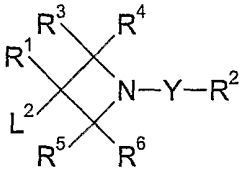
wherein R^1, R^2, R^3, R^4, R^5, R^6, X and Y are as defined in formula (I);

(b) reaction of a compound of formula (IV)



(IV)

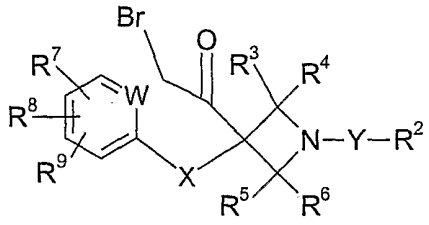
wherein R^7, R^8, R^9, W and X are as defined in formula (I),
with a compound of formula (V)



(V)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and Y are as defined in formula (I), and L^2 represents a leaving group; or

(c) reaction of a compound of formula (VI)



(VI)

wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, W, X and Y are as defined in formula (I), with an amide, thioamide, urea, thiourea or guanidine;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof, or *vice versa*, and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

In process (a), the reaction is performed by treating a nucleophile of formula (III) with an electrophile of formula (II) in an inert solvent. Suitable leaving groups L^1 include trifluorosulfonate and halides, particularly fluoride. The reaction is generally performed in the presence of a non-nucleophilic base such as sodium hydride. Suitable organic solvents are those such as N-methyl-2-pyrrolidinone, tetrahydrofuran, N,N-dimethylformamide and dimethylsulfoxide. The reaction is generally conducted at a temperature between 0 °C and the boiling point of the solvent.

Alternatively, in process (a), the reaction will take place using an appropriate palladium source such as palladium(II) acetate in the presence of a suitable phosphine ligand such as BINAP.

In process (b), the reaction is performed by treating a nucleophile of formula (IV) with an electrophile of formula (V) in an inert solvent. Suitable leaving groups L^2 include sulfonate, trifluorosulfonate, tosylate and halides selected from the group chloride, bromide or iodide. The reaction is generally performed in the presence of a non-nucleophilic base such as sodium hydride or a metal carbonate, especially an alkali metal carbonate, a metal oxide or hydroxide, or a tertiary amine. Suitable organic solvents are those such as acetonitrile, dioxane, N,N-dimethylformamide, N-methyl-2-pyrrolidinone, tetrahydrofuran, dimethylsulfoxide, sulfolane and C1 to 4 alcohols. The reaction is generally conducted at a temperature between 0 °C and the boiling point of the solvent.

In process (c), the reaction is performed by treating an electrophile of formula (VI) with a nucleophile in an inert solvent, if necessary followed by a second dehydration step. Suitable nucleophiles include particularly amides, thioamides, ureas, thioureas or guanidines. Suitable organic solvents are those such as acetonitrile, toluene, water, dioxane, N,N-dimethylformamide, N-methyl-2-pyrrolidinone, tetrahydrofuran, dimethylsulfoxide, sulfolane and C1 to 4 alcohols. The reaction is generally conducted at a temperature between 0 °C and the boiling point of the solvent. Suitable dehydration agents include organic or mineral acid, thionyl chloride and aryl or alkyl sulfonyl halides; particularly thionyl chloride.

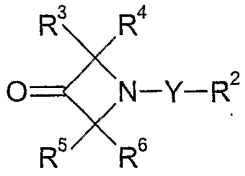
It will be apparent to a person skilled in the art that in the above processes it may be desirable or necessary to protect an amine or other potentially reactive group. Suitable protecting groups and details of processes for adding and removing such groups may be found by reference to the standard text "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts. In one preferred embodiment, amine groups are protected as diphenylmethyl (benzhydryl) derivatives or as carbamate derivatives, for example, as t-butyloxycarbamates.

The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, methanesulphonic and benzenesulphonic acids.

Salts of compounds of formula (I) may be formed by reacting the free base, or a salt, enantiomer or racemate thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, for example, water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed *in vacuo* or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin.

Certain novel intermediates of formulae (III), (V) and (VI) form another aspect of the invention.

Compounds of formula (III) may be prepared by reaction of a compound of formula (VII)



(VII)

wherein R^2, R^3, R^4, R^5, R^6 and Y are as defined in formula (I),

with an organometallic derivative, R^1— M, wherein R^1 is as defined in formula (I) and M represents a metallic residue such as lithium or magnesium-halide.

Compounds of formulae (II), (IV) and (VII) are either known or may be prepared by conventional methods that will be readily apparent to the man skilled in the art.

Intermediate compounds may be used as such or in protected form. Protecting groups and details of processes for their removal may be found by reference to the standard text "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

The compounds of the invention and intermediates thereto may be isolated from their reaction mixtures and, if necessary further purified, by using standard techniques.

The compounds of formula (I) may exist in enantiomeric forms. Therefore, all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation, or HPLC.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified enantiomers, diastereomers, racemates or mixtures.

The compounds of formula (I), and their pharmaceutically acceptable salts, enantiomers and racemates, are useful because they possess pharmacological activity in animals. In particular, the compounds are active as inhibitors of the enzyme nitric oxide synthase. More particularly, they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase and as such

are predicted to be useful in therapy, for example, as anti-inflammatory agents. They may also have utility as inhibitors of the neuronal isoform of the enzyme nitric oxide synthase.

The compounds and their pharmaceutically acceptable salts, enantiomers and racemates are indicated for use in the treatment or prophylaxis of diseases or conditions in which synthesis or oversynthesis of nitric oxide synthase forms a contributory part. In particular, the compounds are indicated for use in the treatment of inflammatory conditions in mammals including man.

Conditions that may be specifically mentioned are:
osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis and other arthritic conditions, inflamed joints;
eczema, psoriasis, dermatitis or other inflammatory skin conditions such as sunburn;
inflammatory eye conditions including uveitis, glaucoma and conjunctivitis;
lung disorders in which inflammation is involved, for example, asthma, bronchitis, chronic obstructive pulmonary disease, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome;
bacteraemia, endotoxaemia (septic shock), aphthous ulcers, gingivitis, pyresis, pain, meningitis and pancreatitis;
conditions of the gastrointestinal tract including inflammatory bowel disease, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, irritable bowel syndrome, reflux oesophagitis, damage to the gastrointestinal tract resulting from infections by, for example, *Helicobacter pylori*, or from treatments with non-steroidal anti-inflammatory drugs;
and other conditions associated with inflammation.

The compounds will also be useful in the treatment and alleviation of acute pain or persistent inflammatory pain or neuropathic pain or pain of a central origin.

We are particularly interested in the conditions inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease and pain.

The compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers and racemates may also be useful in the treatment or prophylaxis of diseases or conditions in addition to those mentioned above. For example, the compounds may be useful in the treatment of atherosclerosis, cystic fibrosis, hypotension associated with septic and/or toxic shock, in the treatment of dysfunction of the immune system, as an adjuvant to short-term immunosuppression in organ transplant therapy, in the control of onset of diabetes, in the maintenance of pancreatic function in diabetes, in the treatment of vascular complications associated with diabetes and in co-therapy with cytokines, for example TNF or interleukins.

The compounds of formula (I) may also be useful in the treatment of hypoxia, for example in cases of cardiac arrest and stroke, neurodegenerative disorders including nerve degeneration and/or nerve necrosis in disorders such as ischaemia, hypoxia, hypoglycaemia, epilepsy, and in external wounds (such as spinal cord and head injury), hyperbaric oxygen convulsions and toxicity, dementia, for example pre-senile dementia, Alzheimer's disease and AIDS-related dementia, Sydenham's chorea, Parkinson's disease, Tourette's Syndrome, Huntington's disease, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Korsakoff's disease, imbecility relating to a cerebral vessel disorder, sleeping disorders, schizophrenia, depression, pain, autism, seasonal affective disorder, jet-lag, depression or other symptoms associated with Premenstrual Syndrome (PMS), anxiety and septic shock. Compounds of formula (I) may also be expected to show activity in the prevention and reversal of drug addiction or tolerance such as tolerance to opiates and diazepines, treatment of drug addiction, treatment of migraine and other vascular headaches, neurogenic inflammation, in the treatment of gastrointestinal motility disorders, cancer and in the induction of labour.

We are particularly interested in the conditions stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis, schizophrenia, migraine, cancer, septic shock and pain.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or

those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

For the above mentioned therapeutic indications, the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of the solid form of between 1 mg and 2000 mg per day.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may be used on their own, or in the form of appropriate pharmaceutical compositions in which the compound or derivative is in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Administration may be by, but is not limited to, enteral (including oral, sublingual or rectal), intranasal, intravenous, topical or other parenteral routes. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988. The pharmaceutical composition preferably comprises less than 80% and more preferably less than 50% of a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may also be advantageously used in combination with a COX-2 inhibitor. Particularly preferred COX-2 inhibitors are Celecoxib and MK-966. The NOS inhibitor and the COX-2 inhibitor may either be formulated together within the same pharmaceutical composition for administration in a single dosage unit, or each component may be individually formulated such that separate dosages may be administered either simultaneously or sequentially.

The invention is illustrated, but in no way limited, by the following examples:

Example 1

4-Chloro-2-(3-phenyl-azetidin-3-yloxy)-benzonitrile hydrochloride

a) 3-Hydroxy-3-phenyl-azetidine-1-carboxylic acid *tert*-butyl ester

To a solution of 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester (0.5 g) in tetrahydrofuran (10 ml) at 0 °C was added phenylmagnesium bromide (10 ml of a 1M solution in tetrahydrofuran) dropwise. After 1 h the reaction was poured into 0.5M aqueous ammonium chloride / diethyl ether and the organic layer separated. The aqueous layer was extracted with further diethyl ether and the combined organic layers were dried (sodium sulfate) and the solvent removed *in vacuo*. Column chromatography (10-25% ethyl acetate in *iso*-hexane on silica gel) gave the sub-title product (0.25 g) as a colourless oil.

^{1}H NMR 300MHz ($CDCl_3$) 7.56-7.30 (5H, m), 4.29 (2H, d), 4.17 (2H, d), 2.43 (1H, bd), 1.47 (9H, s).

b) 3-(5-Chloro-2-cyano-phenoxy)-3-phenyl-azetidine-1-carboxylic acid *tert*-butyl ester

To a solution of the product from step (a) (0.25 g) in methyl sulfoxide (4 ml) was added sodium hydride (0.12 g of a 60% dispersion in mineral oil) and the reaction stirred for 1 h. 4-Chloro-2-fluorobenzonitrile (0.19 g) was added and the reaction stirred for 16 h. The reaction was poured into water / diethyl ether and the organic layer separated. The aqueous layer was extracted with further diethyl ether. The combined organic layers were washed with 1 M aqueous sodium hydroxide and brine and then dried (sodium sulfate) and the solvent removed *in vacuo*. Column chromatography (silica , 10-20% ethyl acetate in *iso*-hexane) gave the sub-title product (0.24 g) as a colourless oil.

^{1}H NMR 400MHz ($CDCl_3$) 7.53 (1H, d), 7.45-7.34 (5H, m), 6.98 (1H, dd), 6.17 (1H, d), 4.45-4.38 (4H, m), 1.48 (9H, s).

c) 4-Chloro-2-(3-phenyl-azetidin-3-yloxy)-benzonitrile hydrochloride

The product from Example 1b (0.24 g) was dissolved in 4M hydrogen chloride in dioxane and stood for 2 h. The crystals were filtered off and the liquor stood for a further 16 h. The solvent was removed *in vacuo* and the residue was washed with diethyl ether to afford a

further crop of crystals. The combined crops of crystals were dried to give the title compound (0.17 g) as a white solid. M.p. 217 – 219 °C.

^{1}H NMR 300MHz (CD_3OD) 7.69 (1H, d), 7.60 (2H, m), 7.51 (3H, m), 7.14 (1H, d), 6.51 (1H, s), 4.80 (2H, m), 4.64 (2H, bs).

$C_{16}H_{14}Cl_2N_2O$	requires:	C 59.8, H 4.4, N 8.7%
	Found:	C 59.7, H 4.4, N 8.7 %

Example 2

4-Chloro-2-(3-ethyl-azetidin-3-yloxy)-benzonitrile hydrochloride

a) 3-Ethyl-3-hydroxy-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and ethylmagnesium chloride (2M solution in diethyl ether) according to the procedure described in Example 1a. Yellow oil.

^{1}H NMR 400MHz ($CDCl_3$) 3.84 (2H, d), 3.79 (2H, d), 1.92 (1H, bs), 1.76 (2H, q), 1.44 (9H, s), 0.97 (3H, t).

b) 3-(5-Chloro-2-cyano-phenoxy)-3-ethyl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 2a and 4-chloro-2-fluoro-benzonitrile according to the procedure described in Example 1b. White solid.

^{1}H NMR 400MHz ($CDCl_3$) 7.53 (1H, dd), 7.04 (1H, dt), 6.56 (1H, s), 4.21 (2H, d), 4.04 (2H, d), 2.09 (2H, q), 1.46 (9H, s), 0.96 (3H, t).

c) 4-Chloro-2-(3-ethyl-azetidin-3-yloxy)-benzonitrile hydrochloride

Prepared from the product from Example 2b according to the procedure described in Example 1c. White solid. M.p. 211 – 213 °C.

^{1}H NMR 300MHz (CD_3OD) 7.74 (1H, d), 7.26 (1H, dd), 6.99 (1H, d), 4.43 (4H, s), 2.26 (2H, q), 0.94 (3H, t).

MS APCI +ve $^m/_z$ 237.0794 ($[M+H-HCl]^+$).

Example 3

4-Chloro-2-(3-thiophen-2-yl-azetidin-3-yloxy)-benzonitrile hydrochloride

a) 3-Hydroxy-3-thiophen-2-yl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and 2-thienyllithium (generated from thiophene and n-BuLi) at 0 °C according to the procedure described in Example 1a. Yellow oil.

^{1}H NMR 400MHz ($CDCl_3$) 7.30 (1H, dd), 7.10 (1H, dd), 7.01 (1H, dd), 4.28 (2H, d), 4.20 (2H, dd), 1.46 (9H, s).

b) 3-(5-Chloro-2-cyano-4-fluoro-phenoxy)-3-thiophen-2-yl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 3a and 4-chloro-2,5-difluoro-benzonitrile according to the procedure described in Example 1b. Red foam.

^{1}H NMR 400MHz ($CDCl_3$) 7.36 (2H, m), 7.15 (1H, dd), 7.03 (1H, dd), 6.47 (1H, d), 4.48 (2H, d), 4.40 (2H, d), 1.46 (9H, s).

c) 4-Chloro-5-fluoro-2-(3-thiophen-2-yl-azetidin-3-yloxy)-benzonitrile hydrochloride

Prepared from the product from Example 3b according to the procedure described in Example 1c. White solid. M.p. 185 – 189 °C.

^{1}H NMR 300MHz (CD_3OD) 7.74 (1H, d), 7.63 (1H, dd), 7.53 (1H, dd), 7.14 (1H, dd), 6.86 (1H, d), 4.84 (2H, d), 4.78 (2H, d).

MS APCI +ve $^m/_z$ 309.0264 ($[M+H-HCl]^+$).

$C_{14}H_{11}Cl_2FN_2OS$	requires:	C 48.7, H 3.2, N 8.1%
	found:	C 48.8, H 3.0, N 7.9%

Example 4

4-Chloro-5-fluoro-2-(3-pyridin-3-yl-azetidin-3-yloxy)-benzonitrile hydrochloride

a) 3-Hydroxy-3-pyridin-3-yl-azetidine-1-carboxylic acid *tert*-butyl ester

To a solution of (3-tri-n-butylstannyl)pyridine (2.6 g) in tetrahydrofuran (10 ml) at –78 °C was added n-BuLi (3.1 ml of a 2.3M solution in hexanes) dropwise. After 30 minutes, extra tetrahydrofuran (15 ml) was added followed by a solution of 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester (0.4 g) in tetrahydrofuran (10 ml) and the reaction warmed to -50 °C over 1 h. The reaction was poured into saturated aqueous sodium hydrogen carbonate / dichloromethane and the organic layer separated. The aqueous layer was extracted with further dichloromethane and the combined organic layers were dried (sodium sulfate) and the solvent removed *in vacuo*. Column chromatography (10% methanol in dichloromethane on silica gel) gave the sub-title product (0.38 g) as a brown oil.

^{1}H NMR 300MHz ($CDCl_3$) 8.79 (1H, d), 8.55 (1H, dd), 7.86 (1H, m), 7.34 (1H, ddd), 4.22 (4H, m), 1.47 (9H, s).

b) 3-(5-Chloro-2-cyano-4-fluoro-phenoxy)-3-pyridin-3-yl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 4a and 4-chloro-2,5-difluoro-benzonitrile according to the procedure described in Example 1b. Yellow solid.

^{1}H NMR 400MHz ($CDCl_3$) 8.76 (1H, s), 8.66 (1H, d), 7.76 (1H, dd), 7.42 (1H, dd), 7.38 (1H, m), 6.18 (1H, dd), 4.48 (2H, d), 4.37 (2H, d), 1.49 (9H, s).

c) 4-Chloro-5-fluoro-2-(3-pyridin-3-yl-azetidin-3-yloxy)-benzonitrile hydrochloride

The product from Example 4b (0.11 g) was dissolved in 4M hydrogen chloride in dioxane and stood for 16 h. The solution was diluted with diethyl ether and the resulting crystals were filtered off and dried to give the title product (0.10 g) as a white solid. M.p. 210 (dec.) °C.

^{1}H NMR 400MHz (CD_3OD) 9.21 (1H, bs), 8.91 (1H, bd), 8.73 (1H, bs), 8.10 (1H, bs), 7.83 (1H, d), 6.82 (1H, d), 5.01 (2H, d), 4.73 (2H, d).

$C_{15}H_{12}Cl_2FN_3O$	requires:	C 59.8, H 4.4, N 8.7%
	found:	C 59.7, H 4.4, N 8.7 %

Example 5

4-Chloro-5-fluoro-2-(3-furan-3-yl-azetidin-3-yloxy)-benzonitrile hydrochloride

a) 3-Furan-3-yl-3-hydroxy-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and 3-furyllithium (generated from 3-bromofuran and n-BuLi at -78°C) at -78 °C according to the procedure described in Example 1a. Yellow solid.

^{1}H NMR 400MHz ($CDCl_3$) 7.48 (1H, dd), 7.43 (1H, dd), 6.46 (1H, dd), 4.12 (4H, s), 2.31 (1H, s), 1.46 (9H, s).

b) 3-(5-Chloro-2-cyano-4-fluoro-phenoxy)-3-furan-3-yl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 5a and 4-chloro-2,5-difluoro-benzonitrile according to the procedure described in Example 1b.

^{1}H NMR 400MHz ($CDCl_3$) 7.49 (1H, bs), 7.46 (1H, t), 7.37 (1H, d), 6.48 (1H, d), 6.40 (1H, bs), 4.42 (2H, d), 4.26 (2H, d), 1.47 (9H, s).

c) 4-Chloro-5-fluoro-2-(3-furan-3-yl-azetidin-3-yloxy)-benzonitrile hydrochloride

Prepared from the product from Example 5b according to the procedure described in Example 4c. White solid. M.p. 197 (dec.) °C.

^{1}H NMR 400MHz (CD_3OD) 7.94 (1H, t), 7.72 (1H, d), 7.61 (1H, t), 6.90 (1H, d), 6.51 (1H, m), 4.68 (4H, q).

MS APCI +ve $^m/_z$ 293.0496 ($[M+H-HCl]^+$).

Example 6

3-(2-Chloro-5-trifluoromethyl-phenoxy)-3-furan-3-yl-azetidine hydrochloride

Prepared from the product from Example 5a and 1-chloro-2-fluoro-4-trifluoromethyl-benzene followed by treatment with hydrogen chloride according to the procedures described in Examples 1b and 1c (crystals washed with *iso*-hexane). Brown solid. M.p. 58 (dec.) °C.

^{1}H NMR 400MHz (CD_3OD) 7.91 (1H, t), 7.63 (1H, dd), 7.57 (1H, m), 7.31 (1H, d), 6.83 (1H, s), 6.47 (1H, m), 4.71 (4H, q).

MS APCI +ve ^{m}/z 318.0518 ($[M+H-HCl]^+$).

Example 7

4-Chloro-5-fluoro-2-(3-propyl-azetidin-3-yloxy)-benzonitrile hydrochloride

a) 3-Hydroxy-3-propyl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and propylmagnesium chloride (2M solution in diethyl ether) according to the procedure described in Example 1a. Yellow oil.

^{1}H NMR 400MHz ($CDCl_3$) 3.81 (4H, q), 1.93 (1H, bs), 1.72 (2H, m), 1.44 (9H, s), 1.44 (2H, m), 0.97 (3H, t).

b) 4-Chloro-5-fluoro-2-(3-propyl-azetidin-3-yloxy)-benzonitrile hydrochloride

Prepared from the product from Example 7a and 4-chloro-2-fluoro-benzonitrile followed by treatment with hydrogen chloride according to the procedures described in Examples 1b and 1c. White solid. M.p. 198 – 200 °C.

^{1}H NMR 400MHz (CD_3OD) 7.76 (1H, d), 7.13 (1H, d), 4.40 (4H, s), 2.17 (2H, m), 1.36 (2H, m), 0.94 (3H, t).

MS APCI +ve ^{m}/z 269.0845 ($[M+H-HCl]^+$).

Example 8

4-Chloro-5-fluoro-2-(3-furan-2-yl-azetidin-3-yloxy)-benzonitrile hydrochloride

a) 3-Furan-2-yl-3-hydroxy-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and 2-furyllithium (generated from furan and n-BuLi at –78 °C) at -78 °C according to the procedure described in Example 1a. Yellow oil.

^{1}H NMR 400MHz ($CDCl_3$) 7.42 (1H, s), 6.36 (2H, m), 4.29 (2H, d), 4.11 (2H, d), 2.58 (1H, bd), 1.45 (9H, s).

b) 3-(5-Chloro-2-cyano-4-fluoro-phenoxy)-3-furan-2-yl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 8a and 4-chloro-2,5-difluoro-benzonitrile according to the procedure described in Example 1b.

^{1}H NMR 400MHz ($CDCl_3$) 7.45 (1H, m), 7.36 (1H, dd), 6.55 (1H, dd), 6.42 (2H, m), 4.45 (4H, q), 1.47 (9H, s).

c) 4-Chloro-5-fluoro-2-(3-furan-2-yl-azetidin-3-yloxy)-benzonitrile hydrochloride

Prepared from the product from Example 8b according to the procedure described in Example 1c. Beige solid. M.p. 133 (dec.) °C.

^{1}H NMR 400MHz (CD_3OD) 7.68 (2H, m), 6.92 (1H, m), 6.83 (1H, m), 6.51 (1H, m), 4.75 (4H, m).

MS APCI +ve ^{m}/z 293.0502 ([M+H-HCl]).

Example 9

3-(2,5-Dichloro-phenylsulfanyl)-3-ethyl-azetidine oxalate

To a solution of 1,1-bis-bromomethyl-propylamine hydrobromide (3 g) (J. Org. Chem. 1994, 59, 1608-1612) in diethyleneglycol (10 ml) was added potassium hydroxide (5.6 g) and the solution heated at 180 °C. A clear liquid distilled out which was collected, dissolved in diethyl ether (20 ml) and 2,5-dichloro-benzenethiol (0.5 ml) added dropwise. After 3 h the organic layer was washed with 1M aqueous sodium hydroxide solution, dried (sodium sulfate) and the solvents were removed *in vacuo*. The residue was purified by column chromatography (0 to 7M ammonia in methanol on SCX resin) followed by RPHPLC to give a colourless oil. This was taken up in diethyl ether and a solution of oxalic acid (10 mg) in diethyl ether (2 ml) added. The resulting white solid was filtered off and dried. M.p. 166 – 170 °C.

^{1}H NMR 300MHz (CD_3OD) 7.74 (1H, d), 7.26 (1H, dd), 6.99 (1H, d), 4.43 (4H, s), 2.26 (2H, q), 0.94 (3H, t).

MS APCI +ve $^m/_z$ 237.0794 ($[M+H-HCl]^+$).

Example10

4-Chloro-5-fluoro-2-(3-thiazol-2-yl-azetidin-3-yloxy)-benzonitrile hydrochloride

a) 3-Hydroxy-3-thiazol-2-yl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and 2-thiazolyllithium (generated from 2-bromothiazole and n-BuLi) at -40 °C according to the procedure described in Example 1a. Colourless oil.

^{1}H NMR 400MHz ($CDCl_3$) 7.76 (1H, d), 7.39 (1H, d), 4.35 (2H, d), 4.24 (2H, dd), 1.47(9H, s).

b) 3-(5-Chloro-2-cyano-4-fluoro-phenoxy)-3-thiazol-2-yl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 10a and 4-chloro-2,5-difluoro-benzonitrile according to the procedure described in Example 1b. Brown solid.

MS APCI +ve ^{m}/z 310 ([M+H-(t-butoxycarbonyl)])$^{+}$.

c) 4-Chloro-5-fluoro-2-(3-thiazol-2-yl-azetidin-3-yloxy)-benzonitrile hydrochloride

Prepared from the product from Example 10b according to the procedure described in Example 1c. Yellow solid. M.p. 205 – 207 °C.

^{1}H NMR 300MHz (DMSO-d_6) 9.76 (2H, br s), 8.19 (1H, d), 8.01 (2H, d), 6.83 (1H, d), 4.84 (2H, d), 4.64 (2H, d).

MS APCI +ve ^{m}/z 310 ([M+H-HCl]$^{+}$).

Example 11

4-Chloro-5-fluoro-2-(3-trifluoromethyl-azetidin-3-yloxy)-benzonitrile hydrochloride

a) 3-Hydroxy-3-trifluoromethyl-azetidine-1-carboxylic acid *tert*-butyl ester

To a solution of 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester (439 mg) and trifluoromethyl trimethylsilane (465 µl) in tetrahydrofuran (15 ml) at 0 °C was added a solution of tetrabutylammonium fluoride (1.5 ml of a 1M solution in tetrahydrofuran). The reaction mixture was allowed to warm to room temperature. After 2 h the reaction was poured into 0.5 M aqueous ammonium chloride and diethyl ether and the organic layer separated. The aqueous layer was further extracted with diethyl ether and the combined organic layers were dried (magnesium sulfate) and the solvent removed *in vacuo*. Column chromatography (33% ethyl acetate in *iso*-hexane on silica gel) gave the sub-title product (0.55 g) as a colourless oil.

^{1}H NMR 300MHz ($CDCl_3$) 4.20 (2H, d), 3.93 (2H, d), 3.20 (1H, s), 1.45 (9H, s).

b) 3-(5-Chloro-2-cyano-4-fluoro-phenoxy)-3-trifluoromethyl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 11a and 4-chloro-2,5-difluoro-benzonitrile according to the procedure described in Example 1b using N,N-dimethylformamide as solvent. Cream solid.

MS APCI +ve ^{m}/z 295 ([M+H-(t-butoxycarbonyl)]).

c) 4-Chloro-5-fluoro-2-(3-trifluoromethyl-azetidin-3-yloxy)-benzonitrile hydrochloride

Prepared from the product from Example 11b according to the procedure described in Example 1c. Cream solid. M.p. 201 – 202 °C.

^{1}H NMR 300MHz (DMSO-d_6) 9.84 (2H, bs), 8.26 (1H, d), 7.66 (1H, d), 4.66 (2H, d), 4.49 (2H, d).

MS APCI +ve ^{m}/z 295 ([M+H-HCl]$^{+}$).

Example 12

2-(3-Thiazol-2-yl-azetidin-3-yloxy)-4-trifluoromethyl-benzonitrile hydrochloride

a) 3-Hydroxy-3-(5-trimethylsilanyl-thiazol-2-yl)-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and 2-trimethylsilylthiazolyllithium (generated from 2-trimethylsilylthiazole and n-BuLi) at -40 °C according to the procedure described in Example 1a. Cream solid.

^{1}H NMR 400MHz ($CDCl_3$) 7.72 (1H, s), 4.32 (2H, d), 4.25 (2H, d), 1.47 (9H, s), 0.35 (9H, s).

The reaction also afforded as a minor product the des-trimethylsilyl analogue of the sub-title compound – 3-hydroxy-3-thiazol-5-yl-azetidine-1-carboxylic acid *tert*-butyl ester. Yellow oil.

^{1}H NMR 400MHz ($CDCl_3$) 7.76 (1H, s), 7.39 (1H, s), 4.34 (2H, d), 4.24 (2H, d), 1.49(9H, s).

b) 3-(2-Cyano-2-trifluoromethyl-phenoxy)-3-thiazol-5-yl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the minor product from Example 12a and 2-fluoro-4-(trifluoromethyl)benzonitrile according to the procedure described in Example 1b. Colourless oil.

MS APCI +ve ^{m}/z 326.1 ([M+H-^{t}butoxycarbonyl]).

c) 2-(3-Thiazol-2-yl-azetidin-3-yloxy)-4-trifluoromethyl-benzonitrile hydrochloride

Prepared from the product from Example 12b according to the procedure described in Example 1c. White solid. M.p. 207 – 208 °C.

^{1}H NMR 300MHz (DMSO-d_6) 8.16 (1H, d), 8.00 (2H, dd), 7.59 (1H, d), 6.73 (1H, s), 4.87 (2H, m), 4.70 (2H, m).

MS APCI +ve ^{m}/z 326 ([M+H-HCl]$^{+}$).

Example 13

2-[[3-(5-Isothiazolyl)-3-azetidinyl]oxy]-6-methyl-3-pyridinecarbonitrile oxalate

a) 1,1-Dimethylethyl ester 3-hydroxy-3-(5-isothiazolyl)-1-azetidinecarboxylic acid

The sub-title compound was prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and 5-isothiazolyllithium (generated from isothiazole and n-BuLi) at 0 °C according to the procedure described in Example 1a. Yellow oil, (1.63 g, 42%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (1H, d), 7.25 (1H, d), 4.24 (4H, q), 3.69 (1H, s), 1.46 (9H, s).

b) 1,1-Dimethylethyl ester 3-[(3-cyano-6-methyl-2-pyridinyl)oxy]-3-(5-isothiazolyl)-1-azetidinecarboxylic acid

The product from Example 13a (900 mg) and 2-chloro-6-methyl-3-pyridinecarbonitrile (536 mg) were dissolved in dimethylformamide (60 ml) and caesium carbonate (2.29 g) added. The reaction was heated to 60 °C and stirred for 24 h. The reaction was cooled to room temperature and water added. The mixture was extracted with ethyl acetate

(3 x 80 ml) and the combined extracts were washed with water (3 x 25 ml), dried (magnesium sulphate) and evaporated *in vacuo*. The residue was purified by chromatography (silica, 25% ethyl acetate in hexane as eluent) to give the sub-title compound. Yellow oil, (581 mg, 44%)

MS APCI +ve ^{m}/z 273 ($[M+H-Boc]^{+}$).

c) 2-[[3-(5-Isothiazolyl)-3-azetidinyl]oxy]-6-methyl-3-pyridinecarbonitrile oxalate

The product from step b) was dissolved in 4M hydrogen chloride in dioxan (20 ml) and the solution stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue purified by chromatography (silica, 2% 7M ammonia in methanol/dichloromethane as eluent). The product was converted into an oxalate salt to give the title compound. White solid (342 mg, 63%).

^{1}H NMR (300 MHz, d_6-DMSO) δ 8.57 (1H, d), 8.25 (1H, d), 7.82 (1H, d), 7.16 (1H, dd), 4.66 (4H, q), 2.46 (3H, s).

MS APCI +ve ^{m}/z 273 ($[M+H]^{+}$).

Example 14

4-Chloro-5-fluoro-2-[3-(4-methyl-thiazol-2-yl)-azetidin-3-yloxy]-benzonitrile hydrochloride

a) 3-Hydroxy-3-(4-methyl-thiazol-2-yl)-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and 4-methylthiazolyllithium (generated from 4-methylthiazole and n-BuLi) at -40 °C according to the procedure described in Example 1a. White solid.

^{1}H NMR 400MHz ($CDCl_3$) 6.91 (1H, s), 4.30 (2H, d), 4.22 (2H, d), 3.99 (1H, s), 2.44(3H, s), 1.47 (9H, s).

b) 3-(5-Chloro-2-cyano-4-fluoro-phenoxy)-3-(4-methyl-thiazol-2-yl)-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 14a and 4-chloro-2,5-difluoro-benzonitrile according to the procedure described in Example 1b. Yellow oil.

MS APCI +ve ^{m}/z 324.1 ([M+H-(t-butoxycarbonyl)]).

c) 4-Chloro-5-fluoro-2-[3-(4-methyl-thiazol-2-yl)-azetidin-3-yloxy]-benzonitrile hydrochloride

Prepared from the product from Example 14b according to the procedure described in Example 1c. Yellow solid. M.p. 178 – 179 °C.

^{1}H NMR 300MHz (DMSO-d_6) 9.8-10.0 (2H, 2 bs), 8.20 (1H, d), 7.52 (1H, s), 6.85 (1H, s), 4.81 (2H, d), 4.60 (2H, d), 2.45 (3H, s).

MS APCI +ve ^{m}/z 324.1 ([M+H-HCl]$^{+}$).

Example 15

2-[3-(2,5-Dichloro-phenoxy)-azetidin-3-yl]-thiazole hydrochloride

a) 3-(2,5-Dichloro-phenoxy)-3-thiazol-2-yl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 10a and 2,5-dichloro-fluorobenzene according to the procedure described in Example 1b. Brown oil.

MS APCI +ve ^{m}/z 301.1/303.1 ([M+H-(t-butoxycarbonyl)]).

b) 2-[3-(2,5-Dichloro-phenoxy)-azetidin-3-yl]-thiazole hydrochloride

Prepared from the product from Example 15a according to the procedure described in Example 1c. Cream solid. M.p. 193 – 194 °C.

^{1}H NMR 300MHz (DMSO-d_6) 9.77 (2H, bs), 8.01 (1H, d), 7.95 (1H, d), 7.59 (1H, d), 7.14 (1H, dd), 6.54 (1H, d), 4.81 (2H, d), 4.62 (2H, d).

MS APCI +ve ^{m}/z 301.1/303.1 ([M+H-HCl]$^{+}$).

Example 16

4-Chloro-5-fluoro-2-(3-vinyl-azetidin-3-yloxy)-benzonitrile hydrochloride

a) 3-Hydroxy-3-vinyl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and vinylmagnesium chloride (1M solution in tetrahydrofuran) according to the procedure described in Example 1a. Colourless oil.

^{1}H NMR 400MHz ($CDCl_3$) 6.15 (1H, dd), 5.37 (1H, d), 5.24 (1H, d), 4.00 (2H, d), 3.93 (2H, d), 2.19 (1H, bs), 1.45 (9H, s).

b) 3-(5-Chloro-2-cyano-4-fluoro-phenoxy)-3-vinyl-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 16a and 4-chloro-2-fluoro-benzonitrile according to the procedure described in Example 1b. White solid.

^{1}H NMR 300MHz ($CDCl_3$) 7.39 (1H, d), 6.53 (1H, d), 6.12 (1H, dd), 5.46 (2H, m), 4.24 (2H, d), 4.16 (2H, d), 1.46 (9H, s).

c) 4-Chloro-5-fluoro-2-(3-vinyl-azetidin-3-yloxy)-benzonitrile hydrochloride

Prepared from the product from Example 16b according to the procedure described in Example 1c. White solid. M.p. 203 – 205 °C.

^{1}H NMR 400MHz (CD_3OD) 7.76 (1H, d), 6.92 (1H, d), 6.21 (1H, dd), 5.61 (2H, m), 4.57 (2H, d), 4.45 (2H, d).

$C_{12}H_{11}Cl_2FN_2O$	requires:	C 49.9, H 3.8, N 9.7%
	Found:	C 50.2, H 3.6, N 9.4 %

Example 17

2-[3-(2,5-Dichloro-phenylsulfanyl)-azetidin-3-yl]-thiazole oxalate

a) 1-Benzhydryl-3-thiazol-2-yl-azetidin-3-ol

Prepared from 1-benzhydryl-azetidin-3-one and 2-thiazolyllithium (generated from 2-bromothiazole and n-BuLi) at -78 °C according to the procedure described in Example 1a. Brown solid.

^{1}H NMR 400MHz ($CDCl_3$) 7.70 (1H, d), 7.50-7.48 (4H, m), 7.38 (1H, m), 7.30-7.17 (6H, m), 4.52 (1H, s), 4.45 (1H, s), 3.54 (2H, dd), 3.37 (2H, dd).

b) 2-[3-(2,5-Dichloro-phenylsulfanyl)-azetidin-3-yl]-thiazole oxalate

The product from Example 17a (0.50 g) and triethylamine (0.65 ml) were dissolved in dichloromethane (5 ml) and cooled to 0 °C. Methanesulfonyl chloride (0.36 ml) was added dropwise and the solution stirred for 2 h. The reaction was poured into saturated aqueous sodium bicarbonate and the organic layer separated. The organic layer was washed with water, dried (sodium sulfate) and the solvent removed *in vacuo*. The crude mesylate was dissolved in acetonitrile (10 ml). Potassium carbonate (0.43 g) and 2,5-dichloro-benzenethiol (0.43 ml) were added and the reaction heated at 70 °C for 3 h. After cooling to room temperature the reaction was poured into ethyl acetate / water and the organic layer separated. The organic layer was washed with 1M aqueous sodium hydroxide solution, dried (magnesium sulfate) and the solvents were removed *in vacuo*. The residue (the N-benzhydryl derivative of the title product) was dissolved in dichloroethane (10 ml), cooled to 0 °C and ACE-chloride (0.84 ml) added dropwise. The reaction was heated at 80 °C (extra ACE-chloride (1 ml) was added after 2 h and 5 h) for 16 h. The solvents were removed *in vacuo*, methanol (20 ml) added, and the reaction heated at 60 °C for 1 h. The solvents were removed *in vacuo* and the residue purified by column chromatography (0 to 7M ammonia in methanol on SCX resin) followed by RPHPLC to give a colourless oil. This was taken up in ethyl acetate and a solution of oxalic acid (22 mg) in diethyl ether (2 ml) added. The resulting white solid was filtered off and dried. M.p. 190 – 203 °C.

^{1}H NMR 400MHz (CD_3OD) 7.81 (1H, d), 7.71 (1H, d), 7.47 (1H, d), 7.30 (1H, dd), 6.92 (1H, d), 4.94 (2H, d), 4.54 (2H, d).

$C_{14}H_{12}Cl_2N_2O_4S_2$	requires:	C 41.3, H 3.0, N 6.9%
	found:	C 41.1, H 2.8, N 7.0 %

Example 18

3-(2,5-Dichloro-phenylsulfanyl)-3-propyl-azetidine oxalate

a) 1-Benzhydryl-3-propyl-azetidin-3-ol

Prepared from 1-benzhydryl-azetidin-3-one and propylmagnesium chloride (2M solution in diethyl ether) according to the procedure described in Example 1a. Colourless oil.

^{1}H NMR 300MHz ($CDCl_3$) 7.42-7.14 (10H, m), 4.35 (1H, s), 3.20 (2H, d), 2.96 (2H, d), 1.86 (1H, s), 1.76 (2H, m), 1.44 (2H, m), 0.96 (3H, t).

b) 3-(2,5-Dichloro-phenylsulfanyl)-3-propyl-azetidine oxalate

Prepared from the product from Example 18a and 2,5-dichloro-benzenethiol according to the procedure described in Example 17b. Brown solid. M.p. 165 – 170 °C.

^{1}H NMR 400MHz (CD_3OD) 7.59 (2H, m), 7.46 (1H, dd), 4.17 (2H, d), 4.13 (2H, d), 1.95 (2H, m), 1.52 (2H, m), 0.95 (3H, t).

Example 19

2-[1-(2-Amino-ethyl)-3-phenyl-azetidin-3-yloxy]-4-chloro-benzonitrile oxalate

The product from Example 1c (40 mg), potassium carbonate (102 mg) and 2-bromoethylamine hydrobromide (153 mg) were dissolved in ethanol (1 ml) and the reaction heated at 50 °C for 12 h. After cooling to room temperature, the reaction was poured into 1M aqueous potassium hydroxide / dichloromethane and the organic layer separated. The organic layer was dried (sodium sulfate) and the solvent removed *in vacuo*. The residue was dissolved in ethanol and a solution of oxalic acid (10 mg) in ethanol

added. The solution was diluted with ethyl acetate and the resulting white solid was filtered off and dried. M.p. 185 – 188 °C.

^{1}H NMR 300MHz (CD_3OD) 7.67 (1H, d), 7.63 (1H, m), 7.61 (1H, m), 7.45 (2H, m), 7.38 (1H, m), 7.08 (1H, dd), 6.37 (1H, d), 4.07 (2H, m), 3.77 (2H, d), 3.00 (2H, m), 2.93 (2H, m).

MS APCI +ve ^{m}/z 328.1210 ($[M+H-(COOH)_2]^+$).

Example 20

2-[3-(2-Amino-thiazol-4-yl)-azetidin-3-yloxy]-4-chloro-5-fluoro-benzonitrile dihydrochloride

a) 3-(1-Ethoxy-vinyl)-3-hydroxy-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from 3-oxo-azetidine-1-carboxylic acid *tert*-butyl ester and 1-ethoxyvinyl-1-lithium (generated from ethyl vinyl ether and t-BuLi) at -78 °C according to the procedure described in Example 1a. Yellow oil.

^{1}H NMR 400MHz ($CDCl_3$) 4.33 (1H, d), 4.15 (2H, d), 4.12 (1H, d), 3.89 (2H, dd), 3.81 (2H, q), 2.70 (1H, s), 1.45 (9H, s), 1.33 (3H, t).

b) 3-(5-Chloro-2-cyano-4-fluoro-phenoxy)-3-(1-ethoxy-vinyl)-azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from the product from Example 20a and 4-chloro-2,5-difluoro-benzonitrile according to the procedure described in Example 1b. Yellow oil.

^{1}H NMR 300MHz ($CDCl_3$) 7.37 (1H, d), 6.61 (1H, d), 4.37 (2H, d), 4.24 (1H, d), 4.20 (1H, d), 4.14 (2H, d), 3.83 (2H, q), 1.46 (9H, s), 1.36 (3H, t).

c) 3-(2-Bromo-acetyl)-3-(5-chloro-2-cyano-4-fluoro-phenoxy)-azetidine-1-carboxylic acid *tert*-butyl ester

To a solution of the product from Example 20b (0.67 g) in acetonitrile / water (10 ml, 1:1) at 0 °C was added N-bromosuccinimide (0.33 g) and the reaction stirred for 30 minutes.

The reaction was poured into water / diethyl ether and the organic layer separated. The aqueous layer was extracted with further diethyl ether. The combined organic layers were washed with water and then dried (sodium sulfate) and the solvent removed *in vacuo*. Column chromatography (10-20% ethyl acetate in *iso*-hexane on silica gel) gave the sub-title product (0.39 g) as a white solid.

^{1}H NMR 300MHz ($CDCl_3$) 7.48 (1H, d), 6.38 (1H, d), 4.52 (2H, d), 4.21 (2H, d), 4.04 (2H, s), 1.47 (9H, s).

d) 3-(2-Amino-thiazol-4-yl)-3-(5-chloro-2-cyano-4-fluoro-phenoxy)-azetidine-1-carboxylic acid *tert*-butyl ester

To a solution of the product from Example 20c (0.10 g) in ethanol (3 ml) was added thiourea (0.05 g) and the reaction heated at 50 °C for 1 h followed by 80 °C for 5 h. The reaction was cooled to room temperature and then poured into 1M sodium hydroxide solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried (sodium sulfate) and the solvent removed *in vacuo*. Column chromatography (20-30% ethyl acetate in *iso*-hexane on silica gel) gave the sub-title product (0.05 g) as a white solid.

^{1}H NMR 300MHz ($CDCl_3$) 7.38 (1H, d), 6.53 (1H, d), 6.37 (1H, s), 5.12 (2H, bs), 4.49 (2H, d), 4.31 (2H, d), 1.47 (9H, s).

e) 2-[3-(2-Amino-thiazol-4-yl)-azetidin-3-yloxy]-4-chloro-5-fluoro-benzonitrile dihydrochloride

Prepared from the product from Example 20d according to the procedure described in Example 1c. White solid. M.p. 188 (dec.) °C.

^{1}H NMR 300MHz (CD_3OD) 7.79 (1H, d), 7.06 (1H, s), 6.95 (1H, d), 4.82 (2H, d), 4.63 (2H, d).

Example 21

4-Chloro-5-fluoro-2-[3-(2-methyl-thiazol-4-yl)-azetidin-3-yloxy]-benzonitrile oxalate

a) 3-(5-Chloro-2-cyano-4-fluoro-phenoxy)-3-(4-hydroxy-2-methyl-4,5-dihydro-thiazol-4-yl)-azetidine-1-carboxylic acid *tert*-butyl ester

A solution of the product from Example 20c (50 mg) and thioacetamide (20 mg) in toluene (5 ml) was heated at 90 °C for 5 h. The reaction was cooled to room temperature and then poured into ethyl acetate / water. The organic layer was separated, dried (sodium sulfate) and the solvent was removed *in vacuo*. Column chromatography (10-40% ethyl acetate in *iso*-hexane on silica gel) gave the sub-title product (80 mg) as a white solid.

^{1}H NMR 400MHz ($CDCl_3$) 7.43 (1H, d), 7.36 (1H, d), 4.40 (1H, d), 4.26 (1H, d), 4.15 (2H, *t*), 3.73 (1H, *t*), 3.42 (1H, *d*), 3.00 (1H, s), 2.25 (3H, s), 1.45 (9H, s).

b) 4-Chloro-5-fluoro-2-[3-(2-methyl-thiazol-4-yl)-azetidin-3-yloxy]-benzonitrile oxalate

A solution the product from Example 21a (0.05 g) in thionyl chloride (5 ml) was heated at 90 °C for 1 h. The solvent was removed *in vacuo* and the residue azeotroped with toluene. Column chromatography (0 to 7M ammonia in methanol on SCX resin) gave an oil. This was taken up in ethyl acetate and a solution of oxalic acid (12 mg) in ethyl acetate (2 ml) added. The resulting beige solid was filtered off and dried. M.p. 177 °C (dec.).

^{1}H NMR 300MHz (CD_3OD) 7.76 (1H, d), 7.54 (1H, s), 6.76 (1H, d), 4.85 (2H, d), 4.68 (2H, d), 2.76 (3H, s).

Example 22

3-[(2,5-Dichlorophenyl)thio]-*β*-oxo-3-propyl-1-azetidineethanamine hydrochloride

a) Carbamic acid , [2-[3-[(2,5-dichlorophenyl)thio]-3-propyl-1-azetidinyl]-2-oxoethyl]-, 1,1-dimethyl ester

N, *N*-Dimethylaminopyridine (42 mg), the product from Example 18b (107 mg),

N-methylpyrrolidine (35 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (66 mg) were added in rapid succession to a stirred solution of N-(tert-butoxycarbonyl)glycine (69 mg) in dry dichloromethane (3 ml). The reaction mixture was then stirred at room temperature for 16 h then diluted with dichloromethane (10 ml). The resulting solution was washed with 2M aqueous hydrochloric acid, 10% aqueous sodium bicarbonate solution and brine, dried (magnesium sulfate) and the solvents were removed *in vacuo*. The resulting colourless oil was used without further purification.

b) 3-[(2,5-Dichlorophenyl)thio]-β-oxo-3-propyl-1-azetidineethanamine hydrochloride

Prepared from the product from step a) according to the procedure described in Example 4c. Formation of the hydrochloride salt afforded the title product as a white solid after trituration with dry diethyl ether. M.p. 197 – 199 °C.

^{1}H NMR 400MHz (d_6-DMSO) 8.15 (3H, br s), 7.62 (1H, d), 7.44 (1H, d), 7.31 (1H, s), 4.42 (1H, d), 4.35 (1H, d), 4.18 (1H, d), 4.04 (1H, d), 3.64 (2H, m), 1.88 (2H, t), 1.40 (2H, m), 0.87 (3H, t).

$C_{14}H_{19}Cl_3N_2OS$	Requires:	C 45.5, H 5.2, N 7.6, S 8.7%
	Found:	C 45.3, H 5.1, N 7.8, S 8.9%

Example 23

3-[(2,5-Dichlorophenyl)thio]-3-propyl-1-azetidineethanol

The product from Example 18 (216 mg), 2-bromoethanol (515 mg) and potassium carbonate (570 mg) were dissolved in ethanol and heated under reflux for 36 h. A further portion of 2-bromoethanol (515 mg) was then added and the reaction mixture heated under reflux for a further 48 h. The reaction mixture was then evaporated to dryness and the residue partitioned between ethyl acetate and water. The organic layer was separated, dried (magnesium sulfate) and evaporated to dryness to give a pale yellow gum. Purification by column chromatography (2.5% 7M ammonia in ethanol / dichloromethane) followed by RPHPLC gave the title product as a colourless solid (30 mg).

^{1}H NMR 400MHz (d_6-DMSO) 7.63 (1H, d), 7.46 (2H, m), 4.11 (2H, d), 3.97 (2H, d), 3.52 (2H), 3.01 (2H, s), 1.89 (2H, m), 1.37 (2H, m), 0.84 (3H, t).

Example 24

4-Chloro-2-[(3-propyl-3-azetidinyl)thio] benzonitrile oxalate

a) 2-[(1-Benzhydryl-3-propyl-3-azetidinyl)thio]-benzoxazole

The product from Example 18a (1.43 g) and triethylamine (3.54 ml) were dissolved in dichloromethane (10 ml) and cooled to -20 °C. Methanesulfonyl chloride (1.18 ml) was added dropwise and the solution stirred for 2 h. The reaction was poured into saturated aqueous sodium bicarbonate and the organic layer separated. The organic layer was washed with water, dried (sodium sulfate) and the solvent removed *in vacuo* to give a crude mesylate (1.92 g). This mesylate (1.28 g) was dissolved in dimethylformamide (20 ml). Potassium carbonate (0.98 g) and 2-benzoxazolethiol (1.08 g) were added and the reaction heated at 70 °C for 10 h. After cooling to room temperature the reaction was poured into ethyl acetate and water and the organic layer separated. The organic layer was washed with 1M aqueous sodium hydroxide solution, brine, dried (sodium sulfate) and the solvents were removed *in vacuo*. The resulting yellow solid was used without further purification.

^{1}H NMR 300MHz ($CDCl_3$) 7.61-7.15 (14H, m), 4.52 (1H, s), 3.55 (2H, d), 3.41 (2H, d), 2.19 (2H, m), 1.48 (2H, m), 0.86 (3H, t).

b) 4-Chloro-2-[(3-propyl-3-azetidinyl)thio] benzonitrile-oxalate

The product from Example 24a was dissolved in ethanol (8 ml). Concentrated hydrochloric acid (0.5 ml) was added and the solution heated at 80 °C for 2 h. After cooling to room temperature, the volatiles were removed *in vacuo*. Potassium carbonate (0.44 g) and 2,4-dichloro-benzonitrile (0.23 g) were added and the reaction heated at 80 °C for 48 h. After cooling to room temperature the reaction was poured into ethyl acetate and water and

the organic layer separated. The organic layer was washed with 1M aqueous sodium hydroxide solution, dried (magnesium sulfate) and the solvents were removed *in vacuo*. The residue (the N-benzhydryl derivative of the title product) was dissolved in dichloroethane (5 ml), cooled to 0 °C and ACE-chloride (0.25 ml) added dropwise. The reaction was heated at 70 °C (extra ACE-chloride (0.25 ml) was added after 2 h) for 3 h. The solvents were removed *in vacuo*, methanol (10 ml) added, and the reaction heated at 70 °C for 1 h. The solvents were removed *in vacuo* and the residue purified by column chromatography (0 to 7M ammonia in methanol on SCX resin) followed by RPHPLC to give a colourless oil. This was taken up in methanol and a solution of oxalic acid (20 mg) in diethyl ether (2 ml) added. The resulting white solid was filtered off and dried to give the title product (20 mg) as a white solid. M.p. 178 – 182 °C.

^{1}H NMR 400MHz (CD_3OD) 7.89 (1H, d), 7.78 (1H, d), 7.68 (1H, dd), 4.21 (2H, d), 4.16 (2H, d), 1.94 (2H, m), 1.55 (2H, m), 0.97 (3H, t).

Example 25

4-Chloro-5-fluoro-2-[[(2*S*,3*S*)-3-(3-furanyl)-2-methyl-3-azetidinyl]oxy]benzonitrile hydrochloride

a) (2*S*,3*S*)-3-(3-Furanyl)-3-hydroxy-2-methyl-1-azetidinecarboxylic acid, 1,1-dimethylethyl ester

Prepared from (2*S*)-2-methyl-3-oxo-1-azetidinecarboxylic acid, 1,1-dimethylethyl ester and 3-furyllithium (generated from 3-bromofuran and n-BuLi at –78 °C) at -78 °C according to the procedure described in Example 1a. Pale yellow oil.

^{1}H NMR 400MHz ($CDCl_3$) 7.44-7.42 (2H, m), 6.42 (1H, dd), 4.35 (1H, q), 4.09 (1H, q), 3.97 (1H, dd), 1.46 (9H, s), 1.42 (3H, d).

b) (2*S*,3*S*)-3-(5-Chloro-2-cyano-4-fluorophenoxy)-3-(3-furanyl)-2-methyl-1-azetidinecarboxylic acid,, 1,1-dimethylethyl ester

Prepared from the product from Example 25a and 4-chloro-2,5-difluoro-benzonitrile according to the procedure described in Example 1b. Yellow solid.

^{1}H NMR 400MHz ($CDCl_3$) 7.46 (2H, m), 7.37 (1H, d), 6.50 (1H, d), 6.36 (1H, m), 4.37 (1H, m), 4.36 (1H, d), 4.22 (1H, d), 1.64 (3H, d), 1.46 (9H, s).

c) 4-Chloro-5-fluoro-2-[[(2*S*,3*S*)-3-(3-furanyl)-2-methyl-3-azetidinyl]oxy]-benzonitrile hydrochloride

Prepared from the product from Example 25b according to the procedure described in Example 4c. Purification by RPHPLC and formation of the hydrochloride salt afforded the title product as a white solid. M.p. 219 – 220 °C.

^{1}H NMR 400MHz (d_6-DMSO) 9.63 (2H, bd), 8.12 (1H, d), 8.08 (1H, s), 7.74 (1H, s), 6.94 (1H, d), 6.59 (1H, s), 4.76 (1H, d), 4.66 (1H, q), 4.37 (1H, d), 1.66 (3H, d).

Example 26

2-[(3-Propyl-3-azetidinyl)thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile trifluoroacetate

Prepared from the product from Example 24a and 2-chloro-6-(trifluoromethyl)-3-pyridinecarbonitrile according to the procedure described in Example 24b. The final compound was purified by column chromatography (0 to 7M ammonia in methanol on SCX resin) followed by RPHPLC to give the title compound as a white solid.

M.p. 163 – 165 °C.

^{1}H NMR 400MHz (CD_3OD) 8.37 (1H, d), 7.74 (1H, d), 4.36 (2H, d), 4.32 (2H, d), 2.25 (2H, m), 1.49 (2H, m), 0.96 (3H, t).

$C_{15}H_{15}F_6N_3O_2S$	Requires:	C 43.4, H 3.6, N 10.1, S 7.7%
	Found:	C 43.9, H 4.0, N 10.1, S 7.9%

Screens

The pharmacological activity of compounds according to the invention was tested in the following screens.

Screen 1

The activity of compounds of formula (I), or a pharmaceutically acceptable salt, enantiomer or racemate thereof, may be screened for nitric oxide synthase inhibiting activity by a procedure based on that of Förstermann *et al.*, Eur. J. Pharm., 1992, **225**, 161-165. Nitric oxide synthase converts ^{3}H-L-arginine into ^{3}H-L-citrulline which can be separated by cation exchange chromatography and quantified by liquid scintillation counting.

Enzyme is prepared, after induction, from the cultured murine macrophage cell line J774A-1 (obtained from the laboratories of the Imperial Cancer Research Fund). J774A-1 cells are cultured in Dulbeccos Modified Eagles Medium (DMEM) supplemented with 10% foetal bovine serum, 4 mM L-glutamine and antibiotics (100 units/ml penicillin G, 100 mg/ml streptomycin & 0.25 mg/ml amphotericin B). Cells are routinely grown in 225 cm^3 flasks containing 35 ml medium kept at 37 °C and in a humidified atmosphere containing 5% CO_2.

Nitric oxide synthase is produced by cells in response to interferon-g (IFNg) and lipopolysaccharide (LPS). The medium from confluent culture flasks is removed and replaced with 25 ml (per flask) of fresh medium containing 1 mg/ml LPS and 10 units/ml IFNg. After a period of 17-20 hours in culture, harvesting of cells is accomplished by scraping the cell sheet from the flask surface into the culture medium. Cells are collected by centrifugation (1000 g for 10 minutes) and lysate prepared by adding to the cell pellet a solution containing 50 mM Tris-HCl (pH 7.5 at 20 °C), 10% (v/v) glycerol, 0.1% (v/v) Triton-X-100, 0.1 mM dithiothreitol and a cocktail of protease inhibitors comprising leupeptin (2 mg/ml), soya bean trypsin inhibitor (10 mg/ml), aprotinin (5 mg/ml) and phenylmethylsulphonyl fluoride (50 mg/ml).

For the assay, 25 µl of substrate cocktail (50 mM Tris-HCl (pH 7.5 at 20 °C), 400 µM NADPH, 20 µM flavin adenine dinucleotide, 20 µM flavin mononucleotide, 4 µM

tetrahydrobiopterin, 12 μM L-arginine and 0.025 mCi L-[^{3}H] arginine) is added to wells of a 96 well filter plate (0.45μM pore size) containing 25 μl of a solution of test compound in 50 mM Tris-HCl. The reaction is started by adding 50 μl of cell lysate (prepared as above) and after incubation for 1 hour at room temperature is terminated by addition of 50 μl of an aqueous solution of 3 mM nitroarginine and 21 mM EDTA.

Labelled L-citrulline is separated from labelled L-arginine using Dowex AG-50W. 150 μl of a 25% aqueous slurry of Dowex 50W (Na^+ form) is added to the assay after which the whole is filtered into 96 well plates. 75 μl of filtrate is sampled and added to wells of 96 well plates containing solid scintillant. After allowing the samples to dry the L-citrulline is quantified by scintillation counting.

In a typical experiment basal activity is 300 dpm per 75 μl sample which is increased to 1900 dpm in the reagent controls. Compound activity is expressed as IC_{50} (the concentration of drug substance which gives 50% enzyme inhibition in the assay) and aminoguanidine, which gives an IC_{50} (50% inhibitory concentration) of 10 μM, is tested as a standard to verify the procedure. Compounds are tested at a range of concentrations and from the inhibitions obtained IC_{50} values are calculated. Compounds that inhibit the enzyme by at least 25% at 100 μM are classed as being active and are subjected to at least one retest.

In the above screen, the compounds of Examples 1 to 26 were tested and gave IC_{50} values of less than 25 μM indicating that they are expected to show useful therapeutic activity.

Screen 2

Compounds also show activity against the human form of induced nitric oxide synthase as can be demonstrated in the following assay.

The human colorectal carcinoma cell line, DLD-1 (obtained from the European Collection of Animal Cell Culture - cell line number 90102540) was routinely grown in RPMI 1640 supplemented with 10%(v/v) foetal bovine serum, and 2mM L-glutamine, at 37 °C in

5% CO_2.

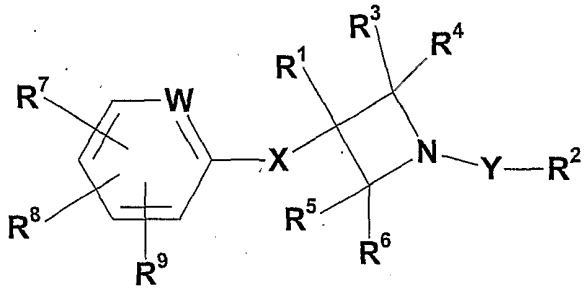
Nitric oxide synthase was induced in cells by addition of medium containing human recombinant gamma-IFN (1000 units/ml), TNF-alpha (200 U/ml), IL-6 (200 U/ml) and IL-1-beta (250 U/ml). After incubation for 18 hours at 37 °C, the medium was removed and the cells washed with warm phosphate buffered saline. Cells were incubated for a further
5 hours at 37 ^{0}C / 5% CO_2 in RPMI 1640 containing 100μM L-arginine and 100μM verapamil-HCl in the presence and absence of test compounds.

Nitrite accumulation was determined by mixing an equal volume of culture media with Griess reagent (10 mg/ml sulphanilamide, 1 mg *N*-(1-naphthyl)ethylenediamine in 1 ml 2.5% (v/v) phosphoric acid). Inhibition in the presence of compounds was calculated relative to the nitrite levels produced by untreated cells. IC_{50} values were estimated from a semi-log plot of % inhibition versus concentration of compound.

In this screen the compounds of Examples 1 to 26 gave IC_{50} values of less than 25 μM, indicating that they are predicted to show useful therapeutic activity.

CLAIMS:

1. A compound of formula (I)



(I)

wherein

R^1 represents C1 to 5 alkyl, C2 to 4 alkenyl, C2 to 4 alkynyl, C3 to 6 cycloalkyl or a 4 to 8 membered saturated heterocyclic ring incorporating one or two heteroatoms independently selected from O, S and N; any of said groups being optionally further substituted by one or more substituents selected independently from C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkylthio, C3 to 6 cycloalkyl, halogen and phenyl; said phenyl group being optionally further substituted by one or more substituents selected independently from halogen, C1 to 4 alkoxy, CF_3, OCF_3, CN, NO_2, $NR^{10}R^{11}$, $COOR^{12}$, $CONR^{13}R^{14}$ and C1 to 4 alkyl; said alkyl group being optionally substituted by OH or $NR^{15}R^{16}$;

or R^1 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, OH, CN, NO_2 or $NR^{10}R^{11}$; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

R^2 represents H, C1 to 4 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally substituted by C1 to 4 alkoxy, halogen, hydroxy, $NR^{17}R^{18}$, phenyl or a five or six

membered aromatic or saturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally further substituted by halogen, C1 to 4 alkyl, C1 to 4 alkoxy, CF_3, OCF_3, CN or NO_2;

R^3, R^4, R^5 and R^6 independently represent H or C1 to 4 alkyl; said alkyl group being optionally substituted by OH, SR^{19}, $NR^{20}R^{21}$ or C2 to 4 alkenyl;

R^7, R^8 and R^9 independently represent H, C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CF_3, OCF_3, CN, C≡CH, $S(O)_mCH_3$, or NO_2;

m represents an integer 0, 1 or 2;

W represents N or CH;

X represents O, $S(O)_n$ or NR^{22};

n represents an integer 0, 1 or 2;

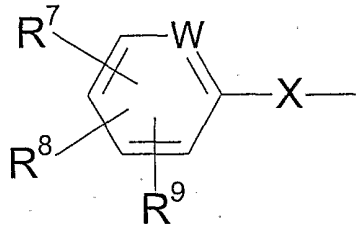
Y represents –CO– or a bond;

R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} independently represent H or C1 to 4 alkyl;

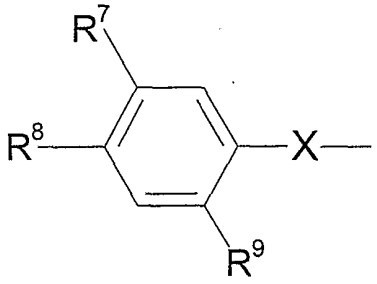
or a pharmaceutically acceptable salt, enantiomer or racemate thereof;

with the proviso that 3-methyl-3-phenylthio-azetidine is excluded.

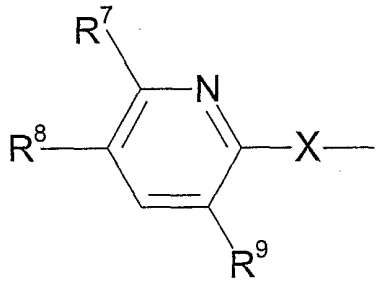
2. A compound of formula (I), according to Claim 1, wherein the group



represents



or



3. A compound of formula (I), according to Claim 1 or Claim 2, wherein X represents O or S.

4. A compound of formula (I), according to any preceding claim, wherein R^8 represents H or F.

5. A compound of formula (I), according to any preceding claim, wherein R^7 and R^9 do not represent H.

6. A compound of formula (I), according to Claim 1, which is:
4-chloro-2-(3-phenyl-azetidin-3-yloxy)-benzonitrile;
4-chloro-2-(3-ethyl-azetidin-3-yloxy)-benzonitrile;
4-chloro-2-(3-thiophen-2-yl-azetidin-3-yloxy)-benzonitrile;
4-chloro-5-fluoro-2-(3-pyridin-3-yl-azetidin-3-yloxy)-benzonitrile;
4-chloro-5-fluoro-2-(3-furan-3-yl-azetidin-3-yloxy)-benzonitrile;
3-(2-chloro-5-trifluoromethyl-phenoxy)-3-furan-3-yl-azetidine;
4-chloro-5-fluoro-2-(3-propyl-azetidin-3-yloxy)-benzonitrile;

4-chloro-5-fluoro-2-(3-furan-2-yl-azetidin-3-yloxy)-benzonitrile;
3-(2,5-dichloro-phenylsulfanyl)-3-ethyl-azetidine;
4-chloro-5-fluoro-2-(3-thiazol-2-yl-azetidin-3-yloxy)-benzonitrile;
4-chloro-5-fluoro-2-(3-trifluoromethyl-azetidin-3-yloxy)-benzonitrile;
2-(3-thiazol-2-yl-azetidin-3-yloxy)-4-trifluoromethyl-benzonitrile;
2-[[3-(5-isothiazolyl)-3-azetidinyl]oxy]-6-methyl-3-pyridinecarbonitrile;
4-chloro-5-fluoro-2-[3-(4-methyl-thiazol-2-yl)-azetidin-3-yloxy]-benzonitrile;
2-[3-(2,5-dichloro-phenoxy)-azetidin-3-yl]-thiazole;
4-chloro-5-fluoro-2-(3-vinyl-azetidin-3-yloxy)-benzonitrile;
2-[3-(2,5-dichloro-phenylsulfanyl)-azetidin-3-yl]-thiazole;
3-(2,5-dichloro-phenylsulfanyl)-3-propyl-azetidine;
2-[1-(2-amino-ethyl)-3-phenyl-azetidin-3-yloxy]-4-chloro-benzonitrile;
2-[3-(2-amino-thiazol-4-yl)-azetidin-3-yloxy]-4-chloro-5-fluoro-benzonitrile;
4-chloro-5-fluoro-2-[3-(2-methyl-thiazol-4-yl)-azetidin-3-yloxy]-benzonitrile;
3-[(2,5-dichlorophenyl)thio]-*β*-oxo-3-propyl-1-azetidineethanamine;
3-[(2,5-dichlorophenyl)thio]-3-propyl-1-azetidineethanol;
4-chloro-2-[(3-propyl-3-azetidinyl)thio] benzonitrile;
4-chloro-5-fluoro-2-[[(2*S*,3*S*)-3-(3-furanyl)-2-methyl-3-azetidinyl]oxy]benzonitrile;
2-[(3-propyl-3-azetidinyl)thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile;
or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

7. A compound of formula (I), according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, for use as a medicament.

8. A pharmaceutical composition comprising a compound of formula (I) according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. The use of a compound of formula (I) according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

10. The use as claimed in Claim 9 wherein it is predominantly inducible nitric oxide synthase that is inhibited.

11. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.

12. The use as claimed in Claim 11 wherein the disease is inflammatory bowel disease.

13. The use as claimed in Claim 11 wherein the disease is rheumatoid arthritis.

14. The use as claimed in Claim 11 wherein the disease is osteoarthritis.

15. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in the manufacture of a medicament, for the treatment or prophylaxis of pain.

16. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in combination with a COX-2 inhibitor, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.

17. A method of treating, or reducing the risk of, human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, to a person suffering from, or at increased risk of, such diseases or conditions.

18. A method of treatment according to Claim 17 in which it is predominantly inducible nitric oxide synthase that is inhibited.

19. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

20. The method of treatment as claimed in Claim 19 wherein the disease is inflammatory bowel disease.

21. The method of treatment as claimed in Claim 19 wherein the disease is rheumatoid arthritis.

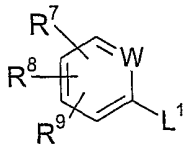
22. The method of treatment as claimed in Claim 19 wherein the disease is osteoarthritis.

23. A method of treating, or reducing the risk of, pain in a person suffering from, or at risk of, said condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

24. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a combination of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, with a COX-2 inhibitor.

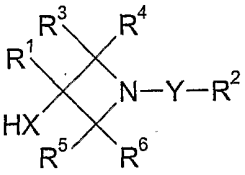
25. A process for the preparation of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, wherein the process comprises:

(a) reaction of a compound of formula (II)



(II)

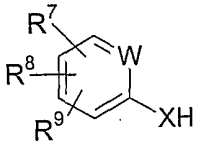
wherein R^7, R^8, R^9 and W are as defined in Claim 1 and L^1 represents a leaving group, with a compound of formula (III)



(III)

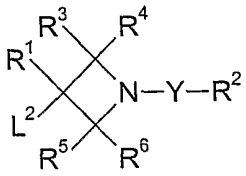
wherein R^1, R^2, R^3, R^4, R^5, R^6, X and Y are as defined in Claim 1; or

(b) reaction of a compound of formula (IV)



(IV)

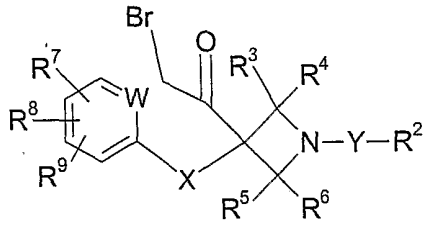
wherein R^7, R^8, R^9, W and X are as defined in Claim 1,
with a compound of formula (V)



(V)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and Y are as defined in Claim 1, and L^2 represents a leaving group; or

(c) reaction of a compound of formula (VI)



(VI)

wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, X, W and Y are as defined in Claim 1,

with an amide, thioamide, urea, thiourea or guanidine;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof, or *vice versa*, and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01688

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 205/04, C07D 401/12, C07D 405/04, C07D 417/04, A61K 31/397, A61K 31/34, A61K 31/425, A61K 31/4427

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)

IPC7: C07D, A61K, A61P

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPI DATA, CHEM.ABS.DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9834919 A1 (PFIZER PRODUCTS INC.), 13 August 1998 (13.08.98), see ex 38, 83-85 --	1-25
P,X	WO 0071107 A2 (PFIZER PRODUCTS INC.), 30 November 2000 (30.11.00), page 109, line 24 --	1-25
A	WO 9858934 A1 (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)), 30 December 1998 (30.12.98) --	1-25
A	Chem. Ber., Volume 102, 1969, Wolfgang Funke: "Über Synthesen und Reaktionen von 1-Aza-bicyclo[1.1.0]butanen", pages 3148-3158 --	1-25

☐ Further documents are listed in the continuation of Box C. ☒ 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 application or patent 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
13 December 2001	02 -01- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer ANNA SJÖLUND/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01688

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. ☒ Claims Nos.: 17-24
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

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 II Observations where unity of invention is lacking (Continuation of item 2 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 all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers 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.

☐ No protest accompanied the payment of additional search fees.

Claims 17-24 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/11/01

International application No.
PCT/SE 01/01688

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9834919 A1	13/08/98	AP 833 A	10/05/00
		AU 5572798 A	26/08/98
		BG 103633 A	30/11/00
		BR 9811093 A	18/07/00
		CN 1246848 T	08/03/00
		EP 0958282 A	24/11/99
		HR 980069 A	31/12/98
		HU 0000762 A	28/09/00
		IL 130898 D	00/00/00
		JP 2000509408 T	25/07/00
		NO 993823 A	09/08/99
		PL 335161 A	10/04/00
		SK 101199 A	09/10/00
		TR 9901917 T	00/00/00
		US 2001007873 A	12/07/01
WO 0071107 A2	30/11/00	AU 2935300 A	12/12/00
WO 9858934 A1	30/12/98	AU 737964 B	06/09/01
		AU 8218998 A	04/01/99
		BR 9810197 A	08/08/00
		CN 1264385 T	23/08/00
		EP 0991654 A	12/04/00
		FR 2764889 A,B	24/12/98
		IL 133223 D	00/00/00
		NO 996208 A	15/02/00
		PL 337499 A	28/08/00
		SK 179699 A	16/05/00
		TR 9903175 T	00/00/00
		TW 422842 B	00/00/00
		ZA 9805392 A	20/01/99