

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 February 2003 (13.02.2003)

PCT

(10) International Publication Number
WO 03/011831 A1

(51) International Patent Classification⁷: **C07D 213/85**,
A61K 31/44, A61P 29/00, 25/00, 19/02

(21) International Application Number: PCT/SE02/01415

(22) International Filing Date: 26 July 2002 (26.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0102639-2 31 July 2001 (31.07.2001) SE

(71) Applicant (for all designated States except US): **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CHEN, Deborah** [US/US]; AstraZeneca Wilmington, P.O. Box 15437, Wilmington, DE 19850-5437 (US). **CHESHIRE, David** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **CONNOLLY, Stephen** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **METE, Antonio** [IT/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report

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

(54) Title: HETEROARYLHETEROALKYLAMINE DERIVATIVES AND THEIR USE AS INHIBITORS OF NITRIC OXIDE SYNTHASE

(57) Abstract: There are provided novel compounds of formula (I) [Chemical formula should be inserted here. Please see paper copy] wherein R¹, R², R³, T, U, X, Y, V and W are as defined in the specification, and pharmaceutically acceptable salts thereof; together with processes for their preparation, compositions containing 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, CNS disorders and pain.



WO 03/011831 A1

HETEROARYLHETEROALKYLAMINE DERIVATIVES AND THEIR USE AS INHIBITORS OF NITRIC OXIDE SYNTHASE

Field of the Invention

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

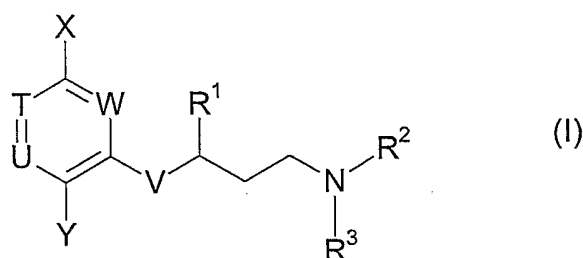
Background of the Invention

- 10 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 (eNOS) is involved with smooth muscle relaxation and the regulation of blood pressure
15 and blood flow, whereas the neuronal enzyme (nNOS) appears to be involved in the regulation of various biological functions. 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).

- 20 Considerable effort has been expended 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.

25 Disclosure of the invention

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



wherein:

X represents H, C1 to 4 alkyl, C1 to 4 alkoxy, halogen, OH, CN, C≡CH, NO₂, CHO, COCH₃,
 5 or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more
 fluorine atoms or by an OH group;

Y represents C1 to 4 alkyl, C1 to 4 alkoxy, halogen, OH, CN, C≡CH, NO₂, CHO, COCH₃ or
 NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more
 10 fluorine atoms;

One of T, U and W represents N and the other two independently represent CR⁴; and each R⁴
 group independently represents H, F or CH₃;

15 V represents O or S(O)_n;

n represents an integer 0, 1 or 2;

R¹ represents C1 to 4 alkyl, C2 to 4 alkenyl, C2 to 4 alkynyl, C3 to 6 cycloalkyl or a 4 to 8
 20 membered saturated heterocyclic ring incorporating one heteroatom selected from O, S and
 N; any of said groups being optionally further substituted by C1 to 4 alkyl, C1 to 4 alkoxy,
 C1 to 4 alkylthio, C3 to 6 cycloalkyl, one or more halogens or phenyl; said phenyl group
 being optionally further substituted by one or more substituents selected independently from
 halogen, C1 to 4 alkyl, C1 to 4 alkoxy, CF₃, OCF₃, CN or NO₂;

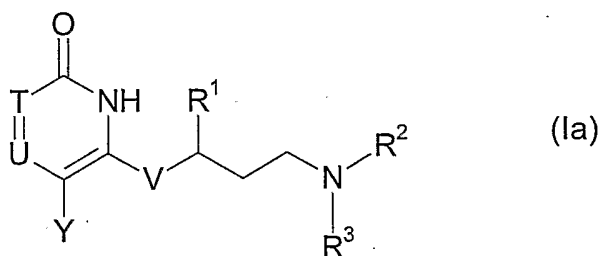
R^2 and R^3 independently represent H, C1 to 4 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally substituted by C1 to 4 alkoxy, halogen, hydroxy, $-Z-NR^7R^8$, phenyl or a five or six membered aromatic or saturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being
5 optionally further substituted by halogen, C1 to 4 alkyl, C1 to 4 alkoxy, CF_3 , OCF_3 , CN or NO_2 ;

Z represents $-CO-$ or a bond;

10 R^7 and R^8 independently represent H or C1 to 4 alkyl;

or a pharmaceutically acceptable salt thereof.

It will be recognised that compounds of formula (I) wherein W represents N and X
15 represents OH may exist in the alternative tautomeric form (Ia):



Analogous tautomeric structures will also exist for compounds of formula (I) wherein T represents N and X represents OH; or wherein U represents N and Y represents OH. All
20 such tautomeric forms and mixtures thereof are included within the scope of the invention.

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.

25 The compounds of formula (I) and their pharmaceutically acceptable salts have the advantage that they are inhibitors of the enzyme nitric oxide synthase (NOS). In general, the compounds

of formula (I) and their pharmaceutically acceptable salts have the advantage that they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase (iNOS). Certain compounds of formula (I) and their pharmaceutically acceptable salts have the advantage that they are additionally or alternatively inhibitors of the neuronal isoform of the enzyme nitric oxide synthase (nNOS). In general, compounds of formula (I) and their pharmaceutically acceptable salts have the advantage that they show good selectivity for the inhibition of iNOS and/or nNOS in comparison to the inhibition of the endothelial isoform, eNOS.

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 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 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.

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

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

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

Another aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of CNS disease.

5

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 thereof.

10

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 thereof.

15

There is also provided a method of treating, or reducing the risk of, CNS 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 thereof.

20

The compounds of the present invention may also be used advantageously in combination with a second pharmaceutically active substance; particularly in combination with a cyclooxygenase inhibitor; more 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 thereof, in combination with a COX-2 inhibitor in the manufacture of a medicament 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

25

30

administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with a COX-2 inhibitor.

In one embodiment, V represents $S(O)_n$ and n represents 0.

5

In another embodiment, V represents O.

In another embodiment, X and Y independently represent Br, Cl, CH_3 , CH_3CH_2 , CH_2F , CHF_2 , CF_3 , NO_2 or CN.

10

In one embodiment, X represents CH_3 , CH_3CH_2 or CF_3 .

In another embodiment Y represents CN.

15

In one embodiment, R^2 represents H or CH_3 .

In one embodiment, R^3 represents H or CH_3 .

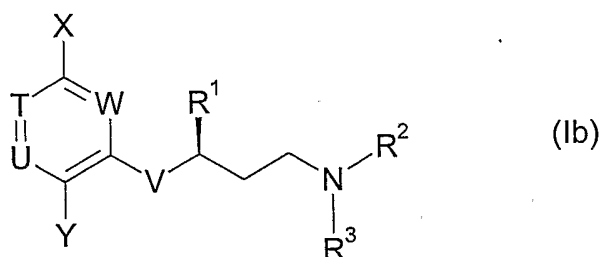
In one embodiment, each R^4 represents H or F.

20

In another embodiment, one of the groups T, U and W represents N, and the other two groups independently represent CH or CF. In a particular embodiment, W represents N, T represents CH or CF and U represents CH.

25

In a particular embodiment, the compounds of formula (I) have the absolute stereochemistry as shown in formula (Ib):



In one particular aspect the invention relates to compounds of formula (I) wherein V represents O or S; X and Y independently represent Br, Cl, CH₃, CH₃CH₂, CH₂F, CHF₂, CF₃, NO₂ or CN; R² and R³ independently represent H or CH₃; R⁴ represents H or F; one of the groups T, U and W represents N, and the other two groups independently represent CH or CF; and pharmaceutically acceptable salts thereof.

Particular compounds of the invention include:

- 6-methyl-2-{3-[1-methylaminohexyl]thio}nicotinonitrile;
 - 6-trifluoromethyl-2-{3-[1-methylaminohexyl]thio}nicotinonitrile;
 - 2-[1-ethyl-3-(methylamino)propoxy]-6-(trifluoromethyl)-3-pyridinecarbonitrile;
 - 2-[[1-ethyl-3-(methylamino)propyl]thio]-6-methyl-3-pyridinecarbonitrile;
 - 2-[1-cyclopentyl-3-(methylamino)thiopropyl]-6-(trifluoromethyl)-3-pyridinecarbonitrile;
 - 2-[1-cyclopentyl-3-(methylamino)thiopropyl]-6-methyl-3-pyridinecarbonitrile;
 - (R)-2-(3-methylamino-1-trifluoromethylpropoxy)-6-trifluoromethyl-nicotinonitrile;
 - (R)-5-fluoro-6-methyl-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile;
 - (R)-6-ethyl-5-fluoro-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile;
 - 6-methyl-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile;
 - 2-(3-amino-1-trifluoromethylpropoxy)-6-trifluoromethyl-nicotinonitrile;
 - 5-fluoro-6-ethyl-2-{3-[1-methylaminopentyl]thio}nicotinonitrile;
 - 6-trifluoromethyl-2-{3-[1-methylaminopentyl]thio}nicotinonitrile;
 - 6-methyl-2-{3-[1-methylaminohex-5-enyl]thio}nicotinonitrile;
 - 2-[1-(2-aminoethyl)-2,2,3,3,3-pentafluoropropoxy]-6-trifluoromethyl-nicotinonitrile;
 - 2-[1-(2-aminoethyl)-2,2,3,3,3-pentafluoropropoxy]-6-methyl-nicotinonitrile;
- and pharmaceutically acceptable salts 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.

5

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.

10

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.

15

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.

20

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.

25

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

30

Examples of a 4 to 8 membered saturated heterocyclic ring incorporating one heteroatom selected from O, S or N include pyrrolidine, piperidine, tetrahydrofuran and perhydroazepine.

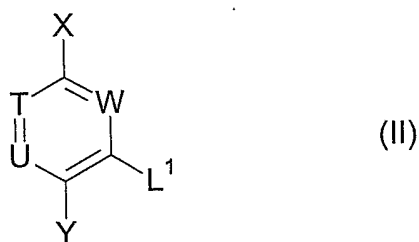
Examples of a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N include furan, thiophene, pyridine, thiazole, imidazole, oxazole, triazole, oxadiazole, thiadiazole and pyrimidine.

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

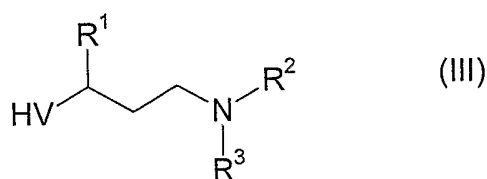
10 Examples of a "C1 to 4 alkyl or C1 to 4 alkoxy optionally further substituted by one or more fluorine atoms" include CH_2F , CHF_2 , CF_3 , CF_3CF_2 , CF_3CH_2 , CH_2FCH_2 , CH_3CF_2 , $\text{CF}_3\text{CH}_2\text{CH}_2$, OCF_3 and OCH_2CF_3 .

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
15 comprises:

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

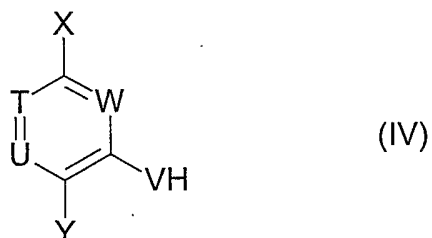


20 wherein T, U, X, Y and W are as defined in formula (I) and L^1 represents a leaving group, with a compound of formula (III)

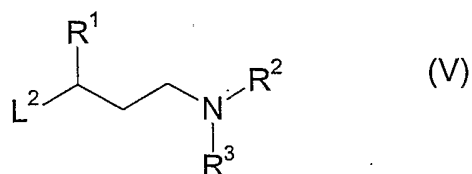


wherein R^1 , R^2 , R^3 and V are as defined in formula (I); or

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

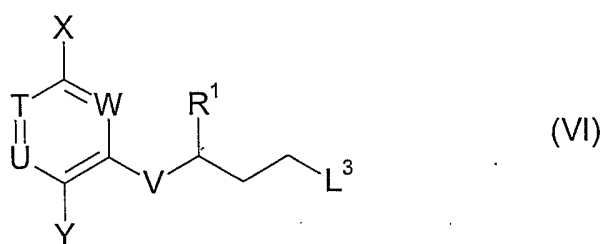


wherein T, U, W, X, Y and V are as defined in formula (I),
with a compound of formula (V)



wherein R^1 , R^2 and R^3 are as defined in formula (I) and L^2 is a leaving group; or

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

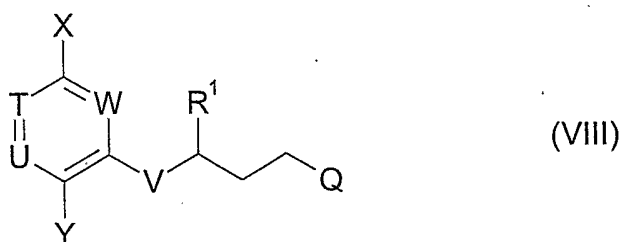


wherein R^1 , T, U, W, X, Y and V are as defined in formula (I) and L^3 is a leaving group,
with a compound of formula (VII)



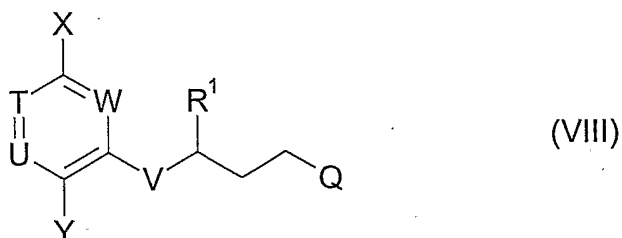
wherein R^2 and R^3 are as defined in formula (I); or

(d) reduction of a compound of formula (VIII)



wherein R^1 , T, U, W, X, Y and V are as defined in formula (I) and Q represents azide (N_3); or

(e) hydrolysis of a compound of formula (VIII)



wherein R^1 , T, U, W, X, Y and V are as defined in formula (I) and Q represents an imide group;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); 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 sulphonates and halides, particularly fluoride or chloride. The reaction is generally performed in the presence of a non-nucleophilic base such as sodium hydride or caesium carbonate. Suitable organic solvents are those such as N,N-dimethylformamide, N-methyl-2-pyrrolidinone, tetrahydrofuran and dimethylsulfoxide. The reaction is generally conducted at a temperature between 0 °C and the boiling point of the solvent.

In process (b), the reactants (IV) and (V) are coupled together in a suitable inert solvent such as tetrahydrofuran using, for example, Mitsunobu conditions. Thus, for example, the reactants are treated with a phosphine derivative and an azo derivative at a suitable temperature, generally between 0 °C and the boiling point of the solvent. Suitable phosphine derivatives include triphenylphosphine and tributylphosphine. Suitable azo derivatives include diethyl azodicarboxylate, diisopropyl azodicarboxylate and 1,1'-(azodicarbonyl)dipiperidine. Suitable leaving groups L^2 include hydroxy.

Alternatively 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 sulphonates and halides, particularly chloride or bromide. The reaction is generally performed in the presence of a non-nucleophilic base such as sodium hydride or caesium carbonate. Suitable organic solvents are those such as N,N-dimethylformamide, N-methyl-2-pyrrolidinone, tetrahydrofuran and dimethylsulfoxide. The reaction is generally conducted at a temperature between 0 °C and the boiling point of the solvent.

In process (c), the compounds of formulae (VI) and (VII) are reacted together in a suitable inert solvent such as dimethylsulphoxide or tetrahydrofuran. The reaction is generally carried out in the presence of a base. The base may be either an added component or an excess of the amine (VII). Suitable leaving groups L^3 include iodide and p-toluenesulphonate.

In processes (d) and (e), the reactions are carried out using standard conditions that will be well known to the man skilled in the art.

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 hydroxyl 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.

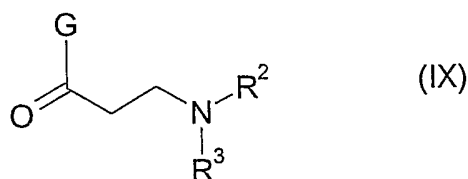
In one preferred embodiment, amine groups are protected as carbamate derivatives, for example, as t-butyloxycarbamates.

Specific examples of the use of protecting groups are given in the Examples section.

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.

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



wherein R^2 and R^3 are as defined in formula (I), and G represents H, Cl or $NCH_3(OCH_3)$,
with an organometallic derivative, R^1-M , wherein R^1 is as defined in formula (I) and M
5 represents a metallic residue such as lithium or magnesium-halide, followed if necessary
by reduction. The resulting compound of formula (III) wherein V represents oxygen may
then be subsequently converted into compounds of formula (III) wherein V represents
sulphur.

10 Compounds of formulae (II), (IV), (V), (VI), (VIII) and (IX) 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
15 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.

20

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.

25

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, 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. Alternatively or additionally, they may have utility as inhibitors of the neuronal isoform of the enzyme nitric oxide synthase and as such are predicted to have utility in the treatment of CNS disorders.

The compounds and their pharmaceutically acceptable salts are indicated for use in the treatment or prophylaxis of diseases or conditions in which synthesis or oversynthesis of nitric oxide forms a contributory part. In one aspect, the compounds are indicated for use in the treatment of inflammatory conditions in mammals including man. In another aspect, the compounds are indicated for use in the treatment of CNS disorders in mammals including man.

As used herein, reference to any of the terms "disease", "condition" and "disorder" is to be taken as a reference to all three terms.

Diseases, conditions and disorders 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 varioliforme, 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.

5 The compounds may also be useful in the treatment of cancer.

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

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

The compounds of formula (I) and their pharmaceutically acceptable salts may also be useful in the treatment or prophylaxis of diseases or conditions in addition to those mentioned above.

15 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
20 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
25 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, muscular dystrophy, Korsakoff's disease, imbecility relating to a cerebral vessel disorder, sleeping disorders, schizophrenia,
30 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 diazepam, treatment of drug addiction, treatment of migraine and other vascular headaches, neurogenic inflammation, in the treatment of gastrointestinal motility disorders and in the induction of labour.

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

10 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.

15 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.

20 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. Thus, another aspect of the invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, 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, inhalation, 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, 30 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 thereof.

There is also provided a process for the preparation of such a pharmaceutical composition
5 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 inhibitor, more particularly in combination with a COX-2 inhibitor. Particularly preferred COX-2 inhibitors are Celecoxib
10 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.

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

Example 1

6-Methyl-2-{3-[1-methylaminohexyl]thio}nicotinonitrile dihydrochloride

20

a) (3-Hydroxyhexyl)methylcarbamic acid, 1,1-dimethylethyl ester

To an ice-cooled stirred solution of methyl-(3-oxopropyl)carbamic acid, 1,1-dimethylethyl ester (11.0 g, 59 mmol) in dry tetrahydrofuran (120 ml) under nitrogen was added a 2M solution of n-propylmagnesium chloride in ether (36 ml). The resulting mixture was stirred
25 at 0 °C for 30 minutes, then allowed to warm to room temperature with stirring over 20 h, and quenched by dropwise addition of saturated aqueous ammonium chloride. The supernatant solution was decanted from the white solids and concentrated to dryness to give the title compound (11.5 g) as an oil.

¹H NMR 300MHz (CDCl₃) 3.70 (1H, bs), 3.47 (1H, bs), 2.83 (3H, s), 1.63 (2H, m), 1.20-
30 1.50 (15H, m), 0.90 (3H, t).

b) [3-(Acetylthio)-hexyl]methylcarbamic acid, 1,1-dimethylethyl ester

To an ice-cooled stirred solution of triphenylphosphine (25.0 g, 95.4 mmol) in tetrahydrofuran (450 ml) under nitrogen was added dropwise diisopropyl azodicarboxylate (19 ml, 93.3 mmol). After 0.5 h, a solution of (3-hydroxyhexyl)methylcarbamic acid, 1,1-dimethylethyl ester (11.5 g, 49.8 mmol) and thiolacetic acid (6.8 ml, 95.2 mmol) in tetrahydrofuran (50 ml) was added slowly. The resulting mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stir overnight. The mixture was concentrated to near dryness, the residue triturated with hexanes, the solids removed by filtration, and the filtrate concentrated and the crude material subjected to flash chromatography using ethyl acetate/hexanes as eluent to give the title compound (12 g) as an oil.

^1H NMR 300MHz (CDCl₃) 3.50 (1H, m), 3.20 (1H, m), 2.83 (3H, s), 2.30 (3H, s), 1.60-1.90 (2H, m), 1.20-1.60 (14H, m), 0.90 (3H, t).

c) 6-Methyl-2-{3-[1-methylaminohexyl]thio}nicotinonitrile dihydrochloride

To a stirred solution of [3-(acetylthio)-hexyl]methylcarbamic acid, 1,1-dimethylethyl ester (0.70 g, 2.4 mmol) in ethanol (20 ml) at room temperature was added in succession 1N sodium hydroxide solution (6 ml) and 2-chloro-6-methylnicotinonitrile (0.5 g, 3.3 mmol). The mixture was stirred overnight, concentrated, and partitioned between ethyl acetate and water. The resulting crude product obtained from the organics was subjected to flash chromatography using ethyl acetate/hexanes as eluent to give the carbamate protected product as an oil. This material was stirred with 4M hydrogen chloride in dioxane (6 ml) for several hours, concentrated to dryness, triturated with isopropanol to give the title compound (160 mg) as a white solid.

MS (APCI+) m/z 264 (M+1)⁺.

^1H NMR 300MHz (d₆-DMSO) 8.58 (2H, brs), 8.10 (1H, d), 7.20 (1H, d), 4.10 (1H, m), 3.30 (3H, s), 3.00 (1H, br m), 2.50 (3H, s), 2.05 (2H, m), 1.70 (2H, m), 1.45 (2H, m), 0.90 (3H, t).

Example 2

6-Trifluoromethyl-2-{3-[1-methylaminohexyl]thio}nicotinonitrile hydrochloride

Prepared by the method of Example 1 using [3-(acetylthio)-hexyl]methylcarbamic acid, 1,1-dimethylethyl ester and 2-chloro-6-(trifluoromethyl)nicotinonitrile to give the title compound which was isolated as the hydrochloride salt.

5 MS (APCI+) m/z 317 (M+1)⁺.

¹H NMR 300MHz (d₆-DMSO) 8.84 (2H, brs), 8.11 (1H, d), 8.00 (1H, s), 7.80 (1H, d), 3.87 (1H, m), 3.30 (3H, s), 3.05 (1H, br m), 2.55 (3H, s), 2.00 (2H, m), 1.60 (2H, m), 1.45 (2H, m), 0.90 (3H, t).

10

Example 3

2-[1-Ethyl-3-(methylamino)propoxy]-6-(trifluoromethyl)-3-pyridinecarbonitrile hydrochloride

15

a) 1,1-Dimethylethyl N-methyl-(3-oxopropyl)carbamate

20

Dimethylsulfoxide (6.22 ml, 87.6 mmol) was dissolved in dry dichloromethane (100 ml) under nitrogen and the solution was cooled to -78 °C with stirring. Oxalyl chloride (3.95 ml, 45.4 mmol) was then added dropwise and the solution was stirred at -78 °C for a further 30 minutes when effervescence had ceased. A solution of 1,1-dimethylethyl (3-hydroxypropyl)methylcarbamate (6.62 g, 35.0 mmol) in dichloromethane (100 ml) was then added dropwise at -78 °C. The resultant solution was stirred at -78 °C for 45 minutes, then a solution of triethylamine (24.4 ml, 175 mmol) in dichloromethane (50 ml) was added. The resultant solution was allowed to warm to room temperature and stirred for a further 18 h. The reaction mixture was then poured into brine and extracted with
25 dichloromethane three times. The combined organic fractions were then washed with brine, dried (MgSO₄) and evaporated. The residue was triturated with diethyl ether and filtered. The solvent was evaporated to give the title compound (6.60 g, 100%) as an orange oil.

30

¹H NMR 300MHz (CDCl₃) 9.81 (1H, s), 3.55 (2H, t), 2.87 (3H, s), 2.68 (2H, t), 1.45 (9H, s).

b) 1,1-Dimethylethyl (3-hydroxypentyl)methylcarbamate

N-Methyl-(3-oxopropyl)carbamic acid, 1,1-dimethylethyl ester (2.00 g, 10.7 mmol) was dissolved in tetrahydrofuran (20 ml) under nitrogen and cooled to 0 °C with stirring. To the resulting solution was added ethylmagnesium bromide and the mixture stirred at 0 °C for a further 30 minutes and then allowed to warm to room temperature with stirring over 20 h. The mixture was then poured into saturated ammonium chloride solution and then extracted with diethyl ether three times. The combined organic fractions were then washed with brine and dried over magnesium sulfate. The solvent was evaporated and the residue eluted down a flash chromatography column using 40% diethyl ether/isohexane as eluent to give 1.70g (65%) of the title compound as an oil.

¹H NMR 300MHz (CDCl₃) 3.90 (1H, m), 2.90-3.50 (2H, m), 2.85 (3H, s), 1.70 (2H, m), 1.50 (11H, m), 0.96 (3H, t).

c) 1,1-Dimethylethyl [3-[[3-cyano-6-(trifluoromethyl)-2-pyridinyl]oxy]pentyl]methylcarbamate

2-Chloro-6-(trifluoromethyl)nicotinonitrile (207 mg) and 1,1-dimethylethyl (3-hydroxypentyl)methylcarbamate (217 mg) were dissolved in dimethylformamide (10 ml) under nitrogen at room temperature. To the resulting solution was added sodium hydride (60% in oil) (80 mg). The solution was then allowed to stir at room temperature under nitrogen for 24 h. The mixture was then poured into water and extracted with diethyl ether three times. The combined organic fractions were washed with brine and then dried (MgSO₄). The solvent was evaporated and the residue was purified by chromatography (silica, 25% ethyl acetate/isohexane as eluent) to give 175 mg (45%) of the subtitle compound as an oil.

¹H NMR 300MHz (CDCl₃) 8.04 (1H, d), 7.31 (1H, d), 5.23 (1H, m), 3.33 (2H, bs), 2.85 (3H, s), 1.77-2.08 (4H, m), 1.40 (9H, s), 0.98 (3H, t).

d) 2-[1-Ethyl-3-(methylamino)propoxy]-6-(trifluoromethyl)-3-pyridinecarbonitrile hydrochloride

1,1-Dimethylethyl [3-[[3-cyano-6-(trifluoromethyl)-2-pyridinyl]oxy]pentyl]methylcarbamate (170 mg) was dissolved in 4M HCl in dioxane (10 ml). The resulting

solution was stirred at room temperature for 2 h, then the solvent was evaporated. The residue was recrystallised from diethyl ether/ethanol to give the title compound (100 mg) as a white solid.

MS APCI +ve m/z 288([M+H]⁺).

5 ¹H NMR 300MHz (d₆-DMSO) 8.69 (2H, bs), 8.61 (1H, d), 7.70 (1H, d), 5.23 (2H, m), 2.99 (2H, m), 2.54 (3H, s), 2.06 (2H, m), 1.76 (2H, m), 0.91 (3H, t).

Example 4

10 2-[[1-Ethyl-3-(methylamino)propyl]thio]-6-methyl-3-pyridinecarbonitrile hydrochloride

a) S-[3-[[[(1,1-Dimethylethoxy)carbonyl]methylamino]-1-ethylpropyl] benzenecarbothioate

To a solution of triphenylphosphine (1.25 g) in tetrahydrofuran (20 ml) under nitrogen at
15 0 °C was added diisopropylazodicarboxylate (0.95 ml) dropwise. The mixture was stirred at 0 °C for 45 minutes and then a solution of thiobenzoic acid (640 mg) and 1,1-dimethylethyl (3-hydroxypentyl)methylcarbamate (500 mg) in tetrahydrofuran (20 ml) added dropwise at 0 °C. After the addition was complete the mixture was stirred at room temperature for 20 h. The mixture was concentrated and the residue was purified by chromatography (silica, 10%
20 diethyl ether/isohexane as eluent) to give the sub-title compound (425 mg) as a yellow oil.
¹H NMR 300MHz (CDCl₃) 7.98 (2H, dd), 7.57 (1H, t), 7.44 (2H, t), 3.68 (1H, m), 3.22-3.49 (2H, m), 2.86 (3H, s), 1.66-2.01 (4H, m), 1.45 (9H, s), 1.02 (3H, t).

b) 1,1-Dimethylethyl [3-[(3-cyano-6-methyl-2-pyridinyl)thio]pentyl]methylcarbamate

25 To a mixture of 2-chloro-6-methyl-3-pyridinecarbonitrile (92 mg) and S-[3-[[[(1,1-dimethylethoxy)carbonyl]methylamino]-1-ethylpropyl] benzenecarbothioate (200 mg) in methanol (5 ml) was added potassium carbonate (90 mg). The mixture was heated to reflux under nitrogen for 20 h. The mixture was then concentrated, water added and extracted with ethyl acetate three times. The organic layers were combined, washed
30 with brine, dried (MgSO₄) and then concentrated. The residue was purified by

chromatography (silica, 10% ethyl acetate/isohehexane as eluent) to give the sub-title compound (110 mg) as an oil.

^1H NMR 300MHz (CDCl_3) 7.65 (1H, d), 6.88 (1H, d), 4.04 (1H, m), 3.37 (2H, t), 2.85 (3H, s), 2.55 (3H, s), 1.69-2.00 (4H, m), 1.44 (9H, s), 1.03 (3H, t).

5

c) 2-[[1-Ethyl-3-(methylamino)propyl]thio]-6-methyl-3-pyridinecarbonitrile hydrochloride

1,1-Dimethylethyl [3-[(3-cyano-6-methyl-2-pyridinyl)thio]pentyl]methylcarbamate (110 mg) was dissolved in 4M HCl in dioxane (10 ml). The resulting solution was stirred at room temperature for 1 h, then the solvent was evaporated off. The residue was recrystallised from diethyl ether/ethanol to give the title compound (90 mg) as a white solid. MS APCI +ve m/z 250 ($[\text{M}+\text{H}]^+$).

10

^1H NMR 300MHz (d_6 -DMSO) 8.70 (2H, bs), 8.10 (1H, d), 7.20 (1H, d), 4.01 (1H, m), 3.32 (3H, s), 3.00 (2H, t), 2.54 (3H, s), 2.05 (2H, m), 1.72 (2H, m), 0.99 (3H, t).

15

Example 5

2-[1-Cyclopentyl-3-(methylamino)thiopropyl]-6-(trifluoromethyl)-3-pyridinecarbonitrile

Prepared by the method of Example 1 using [3-(acetylthio)-3-(cyclopentyl)propyl]methylcarbamic acid, 1,1-dimethylethyl ester and 2-chloro-6-(trifluoromethyl)nicotinonitrile to give the title compound which was isolated as the oxalate salt.

20

MS (APCI+) m/z 344 ($\text{M}+1$) $^+$.

25

^1H NMR 300MHz (d_6 -DMSO) 8.54 (1H, d), 7.82 (1H, d), 4.09 (1H, m), 3.05 (2H, m), 2.50 (3H, s), 2.19 (4H, m), 1.80 (1H, d), 1.58 (4H, m), 1.35 (2H, m).

Example 6

2-[1-Cyclopentyl-3-(methylamino)thiopropyl]-6-methyl-3-pyridinecarbonitrile

30

Prepared by the method of Example 1 using [3-(acetylthio)-3-(cyclopentyl)propyl]methylcarbamic acid, 1,1-dimethylethyl ester and 2-chloro-6-(methyl)nicotinonitrile to give the title compound which was isolated as the oxalate salt.

5 MS (APCI+) m/z 290 (M+1)⁺.

¹H NMR 300MHz (d₆-DMSO) 8.58 (1H, brs), 8.08 (1H, d), 7.19 (1H, d), 4.19 (1H, m), 3.07 (2H, m), 2.59 (3H, s), 2.50 (3H, s), 2.17 (4H, m), 1.85 (1H, d), 1.58 (4H, m), 1.32 (2H, m).

10

Intermediate 1

tert-Butyl (R)-N-Methyl-N-(4,4,4-trifluoro-3-hydroxybutyl)carbamate

a) (R)-4,4,4-Trifluoro-1,3-butanediol

15 A solution of ethyl (R)-(+)-4,4,4-trifluoro-3-hydroxybutyrate (3.12 g, 16.8 mmol) in diethyl ether (8 mL) was added to a 0-5 °C suspension of lithium aluminium hydride (1.01 g, 26.6 mmol) in diethyl ether (17 mL) over 25 minutes. Upon complete addition, the mixture was stirred at ambient temperature for 20h. The mixture was cooled to 0-5 °C and quenched by dropwise addition of 3N HCl (17 mL), followed by stirring at ambient
20 temperature for 3h. The liquid portion was decanted away and the salts were washed with additional diethyl ether. The combined organic portions were washed (brine), dried, and evaporated to give the product as a cloudy, colourless oil (2.34 g, 96%).

¹H NMR (d₆-DMSO) 1.47-1.77 (m, 2H), 3.44-3.61 (m, 2H), 3.92-4.10 (m, 1H), 4.46-4.62 (m, 1H), 6.01 (d, *J* 6.6 Hz, 1H).

25

b) (R)-1,1,1-Trifluoro-4-iodo-2-butanol

Triphenylphosphine (5.09 g, 19.4 mmol) was dissolved in dichloromethane (66 mL) and treated with imidazole (1.33 g, 19.5 mmol) and iodine (4.92 g, 19.4 mmol), respectively, to give an orange suspension. A solution of (R)-4,4,4-trifluoro-1,3-butanediol (2.34 g,

16.2 mmol) in dichloromethane (18 mL) was added to the suspension and stirred for 30 minutes. The reaction mixture was placed on a silica gel flash column and eluted with 100% dichloromethane to give the product as a pale purple oil (3.30 g, 80%).

¹H NMR (d₆-DMSO) 1.89-2.09 (m, 2H), 3.17-3.45 (m, 2H), 3.89-4.06 (m, 1H), 6.38 (d, *J* 6.6 Hz, 1H).

c) (R)-4-Azido-1,1,1-trifluoro-2-butanol

A solution of (R)-1,1,1-trifluoro-4-iodo-2-butanol (3.30 g, 13.0 mmol) in DMSO (22 mL) was treated with sodium azide (0.930 g, 14.3 mmol) at ambient temperature, followed by heating at 50 °C for 20h. The mixture was diluted with cold water (250 mL) and extracted with diethyl ether. The combined organic extracts were washed (brine), dried, and evaporated without heat to give the product as a pale yellow oil (2.20 g, 100%).

¹H NMR (d₆-DMSO) 1.60-1.88 (m, 2H), 3.34-3.61 (m, 2H), 3.92-4.08 (m, 1H), 6.32 (d, *J* 6.6 Hz, 1H).

d) (R)-(4,4,4-Trifluoro-3-hydroxybutyl)carbamic acid *tert*-butyl ester

A solution of (R)-4-azido-1,1,1-trifluoro-2-butanol (2.20 g, 13.0 mmol) in THF (27 mL) was treated with water (6 mL) and triphenylphosphine (3.41 g, 13.0 mmol) at ambient temperature. After 18 h, di-*t*-butyldicarbonate (3.56 g, 16.3 mmol) was added and stirring continued for 3 h. The mixture was concentrated under reduced pressure, and the residue was diluted with water and extracted with diethyl ether. The combined organic extracts were washed (brine), dried, and evaporated to a pale yellow oil. The crude material was purified by silica gel chromatography, eluting with 1:1 hexane/diethyl ether (v/v) and 100% diethyl ether to give the product as a pale yellow oil (3.17 g, 100%).

¹H NMR (d₆-DMSO) 1.38 (s, 9H), 1.46-1.77 (m, 2H), 2.95-3.15 (m, 2H), 3.85-4.00 (m, 1H), 6.05-6.12 (m, 1H), 6.78-6.87 (m, 1H).

e) (R)-1,1,1-Trifluoro-4-methylamino-2-butanol

A solution of (R)-(4,4,4-trifluoro-3-hydroxybutyl)carbamic acid *tert*-butyl ester (3.17 g, 13.0 mmol) in THF (130 mL) was treated with lithium aluminium hydride (1.97 g,

52.0 mmol) at ambient temperature, followed by refluxing for 2 h. Heating was stopped, additional lithium aluminium hydride (0.490 g, 12.9 mmol) was added, and refluxing was continued for 1 h. The mixture was cooled to 0-5 °C and carefully quenched with excess sodium sulfate decahydrate. Additional THF and diethyl ether were added to aid stirring. The mixture was filtered through Celite™ and the filtrate was evaporated to a white wax. The wax was purified by trituration with 9:1 hexane/diethyl ether (v/v) to give the product as a white solid (1.56 g, 76%).

¹H NMR (d₆-DMSO) 1.47-1.74 (m, 2H), 2.20 (s, 3H), 2.56-2.68 (m, 2H), 2.97-3.67 (br m, 2H), 3.96-4.11 (m, 1H).

f) *tert*-Butyl (*R*)-*N*-Methyl-*N*-(4,4,4-trifluoro-3-hydroxybutyl)carbamate

A solution of (*R*)-1,1,1-trifluoro-4-methylamino-2-butanol (1.56 g, 9.93 mmol) in THF (45 mL) was treated with di-*t*-butyldicarbonate (2.73 g, 12.5 mmol) at ambient temperature. After 4 h, the mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:1 hexane/diethyl ether (v/v) and 100% diethyl ether to give the product as a colourless oil (2.55 g, 100%).

¹H NMR (d₆-DMSO) 1.39 (s, 9H), 1.53-1.86 (m, 2H), 2.78 (s, 3H), 3.23-3.37 (m, 2H), 3.82-3.96 (m, 1H), 6.16 (d, *J* 6.6 Hz, 1H).

Example 7

(*R*)-2-(3-Methylamino-1-trifluoromethylpropoxy)-6-trifluoromethyl-nicotinonitrile hydrochloride

a) (*R*)-[3-(3-Cyano-6-trifluoromethyl-pyridin-2-yloxy)-4,4,4-trifluorobutyl]methylcarbamic acid *tert*-butyl ester

A mixture of 2-chloro-6-(trifluoromethyl)nicotinonitrile (0.410 g, 1.98 mmol) and *tert*-butyl (*R*)-*N*-methyl-*N*-(4,4,4-trifluoro-3-hydroxybutyl)carbamate (0.480 g, 1.87 mmol) in DMF (8 mL) was treated with caesium carbonate (1.29 g, 3.96 mmol) at ambient temperature. After stirring for 19 h, the mixture was diluted with water and extracted with diethyl ether. The combined organic extracts were washed (water, brine), dried, and

evaporated to a brown oil that was purified by silica gel chromatography, eluting with 100% dichloromethane and 5% methanol/95% dichloromethane (v/v) to give the product as a pale yellow oil (0.793 g, 99%).

¹H NMR (d₆-DMSO) 1.25 (s, 9H), 2.02-2.28 (m, 2H), 2.76 (s, 3H), 3.20-3.63 (m, 2H),
5 5.71-5.95 (m, 1H), 7.85 (d, *J* 7.6 Hz, 1H), 8.71 (d, *J* 7.7 Hz, 1H).

b) (R)-2-(3-Methylamino-1-trifluoromethylpropoxy)-6-trifluoromethyl-nicotinonitrile hydrochloride

A solution of (R)-[3-(3-cyano-6-trifluoromethyl-pyridin-2-yloxy)-4,4,4-

10 trifluorobutyl]methylcarbamic acid *tert*-butyl ester (0.784 g, 1.83 mmol) in 1,4-dioxane (10 mL) was treated with 4*N* HCl in 1,4-dioxane (4 mL, 16.0 mmol) and stirred at ambient temperature for 14h. The mixture was concentrated under reduced pressure and the residue was vacuum dried. The residue was triturated with diethyl ether and collected by vacuum filtration to give the mono-hydrochloride salt of the product as a white solid (0.622 g,
15 92%).

¹H NMR (d₆-DMSO) 2.20-2.63 (m, 5H), 3.00-3.40 (m, 2H), 6.00-6.17 (m, 1H), 7.89 (d, *J* 7.8 Hz, 1H), 8.67-8.96 (m, 3H).

MS: ^m/_z 328 (M+1)⁺.

Example 8

(R)-5-Fluoro-6-methyl-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile hydrochloride

25 a) (R)-[3-(3-Cyano-5-fluoro-6-methylpyridin-2-yloxy)-4,4,4-trifluorobutyl]-methylcarbamic acid *tert*-butyl ester

A mixture of 2-chloro-5-fluoro-6-methylnicotinonitrile (0.144 g, 0.844 mmol) and *tert*-butyl (R)-*N*-methyl-*N*-(4,4,4-trifluoro-3-hydroxybutyl)carbamate (0.196 g, 0.762 mmol) in DMF (4 mL) was treated with caesium carbonate (0.510 g, 1.56 mmol).

30 After stirring at ambient temperature for 21 h, the mixture was diluted with water and extracted with diethyl ether. The combined organic extracts were washed (water, brine),

dried, and evaporated to an orange oil which was purified by silica gel chromatography, eluting with 1:1 hexane/diethyl ether (v/v), to give the product as an orange oil (0.079 g, 26%).

¹H NMR (d₆-DMSO) 1.30 (s, 9H), 1.95-2.24 (m, 2H), 2.40-2.46 (m, 3H), 2.76 (s, 3H),
5 5.76-5.93 (m, 1H), 8.40 (d, *J* 8.4 Hz, 1H).
MS: ^m/_z 414 (M+23)⁺.

b) (R)-5-Fluoro-6-methyl-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile hydrochloride

10 A solution of (R)-[3-(3-cyano-5-fluoro-6-methylpyridin-2-yloxy)-4,4,4-trifluorobutyl]-methylcarbamic acid *tert*-butyl ester (0.075 g, 0.192 mmol) in 1,4-dioxane (1 mL) was treated with 4*N* HCl in 1,4-dioxane (0.5 mL, 2.0 mmol) and stirred at ambient temperature for 15 h. Additional 4*N* HCl in 1,4-dioxane (0.5 mL, 2.0 mmol) was added and stirring continued for 4 h. The mixture was concentrated under reduced pressure and the residue
15 was vacuum dried. The residue was taken up in diethyl ether and collected by vacuum filtration to give the mono-hydrochloride salt of the product as a white solid (0.053 g, 84%).

¹H NMR (d₆-DMSO) 1.95-2.40 (m, 2H), 2.56 (s, 3H), 2.97-3.12 (m, 2H), 6.00-6.15 (m, 1H), 8.43 (d, *J*=8.4 Hz, 1H), 8.80-8.95 (br s, 2H).
20 MS: ^m/_z 292 (M+1)⁺.

Example 9

25 (R)-6-Ethyl-5-fluoro-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile hydrochloride

a) (R)-[3-(3-Cyano-6-ethyl-5-fluoro-pyridin-2-yloxy)-4,4,4-trifluorobutyl]-methylcarbamic acid *tert*-butyl ester

A solution of *tert*-butyl (R)-*N*-methyl-*N*-(4,4,4-trifluoro-3-hydroxybutyl)carbamate

(0.203 g, 0.789 mmol) in THF (3 mL) was treated with sodium hydride (60% dispersion in mineral oil, 0.050 g, 1.25 mmol) at ambient temperature, followed by treatment with a solution of 2-chloro-6-ethyl-5-fluoronicotinonitrile (0.147 g, 0.796 mol) in THF (2 mL). After heating at 50 °C for 22 h, the mixture was diluted with water and extracted with diethyl ether. The combined organic extracts were washed (1N NaOH, water, brine), dried, and evaporated to a yellow oil which was purified by silica gel chromatography, eluting with 3:1 hexane/diethyl ether (v/v), to give the product as a colourless oil (0.180 g, 56%).
¹H NMR (d₆-DMSO) 1.22 (t, *J*=7.5 Hz, 3H), 1.29 (s, 9H), 1.97-2.26 (m, 2H), 2.68-2.85 (m, 5H), 3.24-3.45 (m, 2H), 5.80-5.96 (m, 1H), 8.40 (d, *J* 8.6 Hz, 1H).

MS: ^m/_z 406 (M+1)⁺.

b) (R)-6-Ethyl-5-fluoro-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile hydrochloride

A solution of (R)-[3-(3-cyano-6-ethyl-5-fluoro-pyridin-2-yloxy)-4,4,4-trifluorobutyl]-methylcarbamic acid *tert*-butyl ester (0.175 g, 0.432 mmol) in 1,4-dioxane (2.3 mL) was treated with 4N HCl in 1,4-dioxane (1.2 mL, 4.8 mmol) and stirred at ambient temperature for 24 h. Additional 4N HCl in 1,4-dioxane (1.0 mL, 4.0 mmol) was added and stirring continued for 2.5 h. The mixture was concentrated under reduced pressure and vacuum dried for 1 h. The residue was triturated with diethyl ether and collected by vacuum filtration to give the mono-hydrochloride salt of the product as a white solid (0.135 g, 91%).

¹H NMR (d₆-DMSO) 1.25 (t, *J*=7.5 Hz, 3H), 2.15-2.42 (m, 2H), 2.55 (s, 3H), 2.75-2.87 (m, 2H), 2.97-3.13 (m, 2H), 6.02-6.15 (m, 1H), 8.42 (d, *J* 8.7 Hz, 1H), 8.90 (br s, 2H).

MS: ^m/_z 306 (M+1)⁺.

Example 10

6-Methyl-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile hydrochloride

a) Toluene-4-sulfonic acid 4,4,4-trifluoro-3-hydroxybutyl ester

A 0-5 °C solution of 4,4,4-trifluoro-1,3-butanediol¹ (2.00 g, 13.4 mmol) in pyridine (4.8 mL) was treated with *p*-toluenesulfonyl chloride (3.18 g, 16.7 mmol). The mixture was stirred cold for 4 h, followed by stirring at ambient temperature for 19 h. The mixture was poured into ice containing 2*N* HCl (20 mL). The aqueous material was extracted with dichloromethane. The combined organic extracts were washed (2*N* HCl, water, brine), dried, and evaporated to a brown oil. The oil was purified by silica gel chromatography, eluting with 100% dichloromethane and 5% methanol/ 95% dichloromethane (v/v), to give the product as an amber oil (1.30 g, 32%).

¹H NMR (d₆-DMSO) 1.67-1.98 (m, 2H), 2.43 (s, 3H), 3.90-4.24 (m, 3H), 6.33 (d, *J* 6.6 Hz, 1H), 7.49 (d, *J* 8.1 Hz, 1H), 7.80 (d, *J* 8.1 Hz, 1H).

b) 4-Azido-1,1,1-trifluoro-2-butanol

A solution of 4-toluenesulfonic acid 4,4,4-trifluoro-3-hydroxybutyl ester (1.30 g, 4.36 mmol) in DMSO (7 mL) was treated with sodium azide (0.306 g, 4.71 mmol) at ambient temperature and then heated at 50 °C for 23 h. The mixture was diluted with cold water and extracted with diethyl ether. The combined organic extracts were washed (brine), dried, and evaporated without heat to give the product as a yellow oil (0.737 g, 100%).

¹H NMR (d₆-DMSO) 1.60-1.90 (m, 2H), 3.26-3.63 (m, 2H), 3.94-4.10 (m, 1H), 6.32 (d, *J* = 6.7 Hz, 1H).

c) (4,4,4-Trifluoro-3-hydroxybutyl)carbamic acid *tert*-butyl ester

A solution of 4-azido-1,1,1-trifluoro-2-butanol (0.737 g, 4.36 mmol) in THF (9 mL) was treated with water (2 mL) and triphenylphosphine (1.15 g, 4.38 mmol) at ambient temperature. After stirring for 16 h, di-*t*-butyldicarbonate (1.11 g, 5.08 mmol) was added and stirring continued for 4 h. The mixture was concentrated under reduced pressure, diluted with water, and extracted with diethyl ether. The combined organic extracts were washed (brine), dried, and evaporated to a tan oil. The crude oil was purified by silica gel chromatography, eluting with 1:1 hexane/diethyl ether (v/v), to give the product as an oil (1.06 g, 100%).

¹ Janzen, E.G.; Zhang, Y.K.; Arimura, M., *J. Org. Chem.* **1995**, *60*, 5434-5440

¹H NMR (d₆-DMSO) 1.38 (s, 9H), 1.45-1.80 (m, 2H), 2.96-3.18 (m, 2H), 3.87-4.03 (m, 1H), 6.07-6.13 (m, 1H), 6.78-6.88 (m, 1H).

d) 1,1,1-Trifluoro-4-methylamino-2-butanol

5 A solution of (4,4,4-trifluoro-3-hydroxybutyl)carbamic acid *tert*-butyl ester (0.55 g, 2.26 mmol) in THF (21 mL) was treated with lithium aluminium hydride (0.321 g, 8.46 mmol) at ambient temperature, followed by refluxing for 3 h. The mixture was cooled to ambient temperature and carefully quenched with excess sodium sulphate decahydrate. Additional THF and diethyl ether were added to aid stirring. The mixture
10 was filtered through a bed of Celite™ and the filtrate was evaporated to a white solid. The solid was purified by silica gel chromatography, eluting with 10% 2M ammonia in methanol/90% dichloromethane and 20% 2M ammonia in methanol/ 80% dichloromethane (v/v), to give the product as a white solid (0.218 g, 61%).

¹H NMR (d₆-DMSO) 1.48-1.76 (m, 2H), 2.28 (s, 3H), 2.53-2.70 (m, 2H), 3.00-3.66 (br m, 2H), 3.94-4.13 (m, 1H).
15

e) *tert*-Butyl *N*-methyl-*N*-(4,4,4-trifluoro-3-hydroxybutyl)carbamate

A solution of 1,1,1-trifluoro-4-methylamino-2-butanol (0.211 g, 1.34 mmol) in THF (6 mL) was treated with di-*t*-butyldicarbonate (0.367 g, 1.68 mmol) and stirred at ambient
20 temperature for 4 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:1 hexane/diethyl ether (v/v) to provide the product as a yellow oil (0.345 g, 100%).

¹H NMR (d₆-DMSO) 1.39 (s, 9H), 1.50-1.88 (m, 2H), 2.78 (s, 3H), 3.80-3.98 (m, 1H), 6.13-6.20 (m, 1H).
25

f) [3-(3-Cyano-6-methyl-pyridin-2-yloxy)-4,4,4-trifluorobutyl]-methylcarbamic acid *tert*-butyl ester

A mixture of 2-chloro-6-methylnicotinonitrile (0.215 g, 1.41 mmol) and *tert*-butyl *N*-methyl-*N*-(4,4,4-trifluoro-3-hydroxybutyl)carbamate (0.345 g, 1.34 mmol) in DMF (6 mL)
30 was treated with caesium carbonate (0.875 g, 2.69 mmol) at ambient temperature. After stirring for 4 days, the mixture was diluted with water and extracted with diethyl ether.

The combined organic extracts were washed (water, brine), dried, and evaporated to an orange oil/solid mixture. The crude material was purified by silica gel chromatography, eluting with 100% dichloromethane and 5% methanol/95% dichloromethane (v/v) to give the product as a yellow oil (0.156 g, 31%).

5 ^1H NMR ($\text{d}_6\text{-DMSO}$) 1.29 (s, 9H), 1.95-2.25 (m, 2H), 2.43-2.54 (m, 3H), 2.76 (s, 3H), 5.87-6.03 (m, 1H), 7.18 (d, J 7.8 Hz, 1H), 8.23 (d, J 7.5 Hz, 1H).

MS: m/z 274 ($\text{M}-100$) $^+$.

g) 6-Methyl-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile hydrochloride

10 A solution of [3-(3-cyano-6-methyl-pyridin-2-yloxy)-4,4,4-trifluorobutyl]-methylcarbamic acid *tert*-butyl ester (0.150 g, 0.402 mmol) in 1,4-dioxane (3 mL) was treated with 4*N* HCl in 1,4-dioxane (1.0 mL, 4.0 mmol) at ambient temperature and stirred for 17 h. The mixture was concentrated and the residue was vacuum dried. The residue was triturated with diethyl ether and collected by vacuum filtration to give the mono-hydrochloride salt of the product as a white solid (0.100 g, 90%).

15 ^1H NMR ($\text{d}_6\text{-DMSO}$) 2.16-2.70 (m, 5H), 2.94-3.14 (m, 2H), 3.18-4.42 (m, 3H), 6.07-6.24 (m, 1H), 7.22 (d, J 7.7 Hz, 1H), 8.26 (d, J 7.8 Hz, 1H), 8.93 (br s, 2H).

MS: m/z 274 ($\text{M}+1$) $^+$.

20

Example 11

2-(3-Amino-1-trifluoromethylpropoxy)-6-trifluoromethylnicotinonitrile hydrochloride

a) 1,1,1-Trifluoro-4-iodo-2-butanol

25 A solution of triphenylphosphine (1.09 g, 4.16 mmol) in dichloromethane (14 mL) was treated with imidazole (0.283 g, 4.16 mmol) and iodine (1.06 g, 4.16 mmol), respectively, to give an orange suspension. A solution of 4,4,4-trifluoro-1,3-butanediol (0.500 g, 3.47 mmol) in dichloromethane (4 mL) was added to the suspension and stirred for 20 minutes. The solid was removed by filtration and the filtrate was concentrated under reduced pressure without heat to yield a black oil. The crude oil was purified by silica gel chromatography, eluting with 100% dichloromethane, to give the product as an oil

30

(0.640 g, 72%).

^1H NMR (d_6 -DMSO) 1.87-2.10 (m, 2H), 3.17-3.47 (m, 2H), 3.88-4.07 (m, 1H), 6.39 (d, J 6.3 Hz, 1H).

5 b) 4-Azido-1,1,1-trifluoro-2-butanol

A solution of 1,1,1-trifluoro-4-iodo-2-butanol (0.604 g, 2.38 mmol) in DMSO (4 mL) was treated with sodium azide (0.178 g, 2.74 mmol) at ambient temperature, followed by heating at 50 °C for 21 h. The mixture was diluted with cold water and extracted with ethyl acetate. The combined organic extracts were washed (brine), dried, and evaporated to give
10 the product as a pale yellow oil (0.372 g, 92%).

^1H NMR (d_6 -DMSO) 1.60-1.89 (m, 2H), 3.37-3.63 (m, 2H), 3.93-4.11 (m, 1H), 6.31 (d, J 6.6 Hz, 1H).

c) 2-(3-Azido-1-trifluoromethylpropoxy)-6-trifluoromethylnicotinonitrile

15 A mixture of 2-chloro-6-(trifluoromethyl)nicotinonitrile (0.675 g, 3.27 mmol) and 4-azido-1,1,1-trifluoro-2-butanol (0.552 g, 3.26 mmol) in DMF (8.5 mL) was treated with caesium carbonate (2.18 g, 6.69 mmol) at ambient temperature. After 20 h, the mixture was diluted with water and extracted with diethyl ether. The combined organic extracts were washed (water, brine), dried, and evaporated to give the product as a brown oil (1.01 g, 90%).

20 ^1H NMR (d_6 -DMSO) 2.07-2.30 (m, 2H), 3.46-3.66 (m, 2H), 5.98-6.13 (m, 1H), 7.87 (d, J 7.8 Hz, 1H), 8.72 (d, J 7.5 Hz, 1H).

d) [3-(3-Cyano-6-trifluoromethylpyridin-2-yloxy)-4,4,4-trifluorobutyl]carbamic acid *tert*-butyl ester

25 A solution of 2-(3-azido-1-trifluoromethylpropoxy)-6-trifluoromethylnicotinonitrile (1.00 g, 2.95 mmol) in THF (6 mL) was treated with water (1.3 mL) and triphenylphosphine (0.774 g, 2.95 mmol) at ambient temperature and was stirred for 18 h. Di-*t*-butyldicarbonate (0.710 g, 3.25 mmol) was added. After 3 h, the mixture was concentrated under reduced pressure. The residue was diluted with water and extracted
30 with diethyl ether. The combined organic extracts were washed (water, brine), dried, and evaporated to a brown oil. The crude material was purified by silica gel chromatography,

eluting with 100% dichloromethane and 5% methanol/95% dichloromethane (v/v) to give the product as a solid (0.212 g, 17%).

^1H NMR ($\text{d}_6\text{-DMSO}$) 1.25 (s, 9H), 2.00-2.13 (m, 2H), 3.00-3.36 (m, 2H), 5.85-5.96 (m, 1H), 6.78-6.87 (m, 1H), 7.84 (d, J 7.8 Hz, 1H), 8.70 (d, J 7.5 Hz, 1H).

5 e) 2-(3-Amino-1-trifluoromethylpropoxy)-6-trifluoromethylnicotinonitrile hydrochloride

A solution of [3-(3-cyano-6-trifluoromethylpyridin-2-yloxy)-4,4,4-trifluorobutyl]carbamic acid *tert*-butyl ester (0.212 g, 0.513 mmol) in 1,4-dioxane (3 mL) was treated with 4*N* HCl in 1,4-dioxane (0.5 mL, 2.0 mL) at ambient temperature and stirred for 24 h. Additional
10 4*N* HCl in 1,4-dioxane (0.5 mL, 2.0 mmol) was added and stirring continued for 6 h. The mixture was concentrated under reduced pressure and vacuum dried for 30 minutes. The residue was triturated with diethyl ether and collected by vacuum filtration to give the mono-hydrochloride salt of the product as a white solid (0.081 g, 45%).

^1H NMR ($\text{d}_6\text{-DMSO}$) 2.11-2.47 (m, 2H), 2.86-3.14 (m, 2H), 6.00-6.18 (m, 1H), 7.80-8.25
15 (m, 4H), 8.65-8.78 (m, 1H).

MS: m/z 314 ($\text{M}+1$) $^+$.

Example 12

20 5-Fluoro-6-ethyl-2-{3-[1-methylaminopentyl]thio}nicotinonitrile dihydrochloride

a) 2-Chloro-5-fluoro-6-ethyl-3-pyridinecarbonitrile

To a vigorously stirred mixture of 2,6-dichloro-5-fluoro-3-pyridinecarbonitrile (15.0 g, 78.5 mmol), potassium phosphate (17.0 g, 74.0 mmol), and

25 [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.5 g, 1.8 mmol) in dry THF (300 mL) at room temperature was added in a stream triethylborane (85 mL of a 1M solution in THF). The resulting mixture was heated at reflux temperature for 16 h, cooled, concentrated, and partitioned between ethyl acetate and water. The resulting crude product obtained from the organics was subjected to flash chromatography using ethyl

30 acetate/hexanes as eluent to give the title compound (8 g) as a solid.

^1H NMR 300MHz (CDCl_3) 7.62 (1H, d), 2.90 (2H, m), 1.30 (3H, t).

b) 5-Fluoro-6-ethyl-2-{3-[1-methylaminopentyl]thio}nicotinonitrile dihydrochloride

Prepared by the method of Example 1 (c) using [3-(acetylthio)-pentyl]methylcarbamic acid, 1,1-dimethylethyl ester and 2-chloro-5-fluoro-6-ethyl-3-pyridinecarbonitrile to give the title compound which was isolated as the hydrochloride salt.

^1H NMR 300MHz (D_2O) 7.75 (1H, d), 3.90 (1H, m), 3.21 (2H, t), 2.85 (2H, m), 2.71 (3H, s), 2.17 (1H, m), 2.09 (1H, m), 1.74 (2H, m), 1.25 (3H, t), 0.98 (3H, t).

MS (APCI+) m/z 282 (M+1) $^+$.

Example 13

6-Trifluoromethyl-2-{3-[1-methylaminopentyl]thio}nicotinonitrile hydrochloride

Prepared by the method of Example 1 but using ethylmagnesium chloride in place of n-propylmagnesium chloride and 2-chloro-6-(trifluoromethyl)nicotinonitrile in place of 2-chloro-6-(methyl)nicotinonitrile to give the title compound which was isolated as the hydrochloride salt.

MS (APCI+) m/z 304 (M+1) $^+$.

^1H NMR 300MHz (D_2O) 8.14 (1H, d), 7.55 (1H, d), 3.98 (1H, m), 3.08 (2H, m), 2.57 (3H, s), 2.04 (2H, m), 1.69 (2H, m), 0.90 (3H, t).

Example 14

6-Methyl-2-{3-[1-methylaminohex-5-enyl]thio}nicotinonitrile oxalate

Prepared by the method of Example 1 but using 1-propenylmagnesium chloride in place of ethylmagnesium chloride to give the title compound which was isolated as the oxalate salt.

MS (APCI+) m/z 262 (M+1) $^+$.

^1H NMR 300MHz (d_6 -DMSO) 8.06 (1H, d), 7.19 (1H, d), 5.86 (1H, m), 5.15 (2H, m), 4.16 (1H, m), 3.07 (2H, m), 2.50 (3H, s), 2.50 (2H, m), 2.07 (2H, m).

Example 15

2-[1-(2-Aminoethyl)-2,2,3,3,3-pentafluoropropoxy]-6-trifluoromethyl-nicotinonitrile
5 fumarate

a) 1,1,1,2,2-Pentafluoro-5-iodo-3-pentanol

To a solution of triphenylphosphine (2.38 g, 9.08 mmol) in dichloromethane (30 ml) was added imidazole (630 mg, 9.25 mmol) followed by iodine (2.30 g, 9.08 mmol). A dark
10 brown suspension was obtained. To this was added a solution of 4,4,5,5,5-pentafluoropentan-1,3-diol¹ (1.47 g, 7.57 mmol) in dichloromethane (8 ml) and diethyl ether (3 ml). Additional dichloromethane (5 ml) and diethyl ether (1 ml) were used to ensure complete transfer. The reaction was complete after 15 minutes. The suspension was filtered to remove a white solid and the filtrate was evaporated to yield a dark brown
15 liquid. Purification by silica gel chromatography using dichloromethane yielded the title compound as a dark brown liquid (1.99 g, 99%).

¹H NMR 300MHz (CDCl₃) 4.28 (m, 1H), 3.28-3.49 (m, 2H), 2.06-2.23 (m, 3H).

b) 5-Azido-1,1,1,2,2-pentafluoro-3-pentanol

20 A solution of 1,1,1,2,2-pentafluoro-5-iodo-3-pentanol (1.99 g, 7.48 mmol) in dimethylsulfoxide (20 ml) was treated with sodium azide (585 mg, 8.98 mmol) and the reaction was heated to 50 °C. After stirring overnight, the reaction was cooled to room temperature. It was then added to water (30 ml) and extracted with diethyl ether (3 x 30 ml). The combined organics were washed with brine (40 ml) and dried over anhydrous
25 sodium sulphate. Removal of the solvents yielded an orange liquid. Purification by silica gel chromatography using 1:1 hexanes/ethyl acetate gave the title compound as an orange liquid (1.7 g, 100%).

¹H NMR 300MHz (CDCl₃) 4.26 (m, 1H), 3.60 (dd, 2H), 3.30 (d, 1H), 1.82-2.05 (m, 2H).

¹ Kitazume, T.; Ohnogi, T.; Lin, J. T.; Yamazaki, T.; Ito, K. *J. Fluorine Chem.* **1989**, 42, 17-29.

c) 2-[1-(2-Azidoethyl)-2,2,3,3,3-pentafluoropropoxy]-6-trifluoromethyl-nicotinonitrile

To a solution of 5-azido-1,1,1,2,2-pentafluoro-3-pentanol (500 mg, 2.28 mmol) in dimethylformamide (10 ml) was added 2-chloro-6-(trifluoromethyl)nicotinonitrile (565 mg, 2.74 mmol) followed by caesium carbonate (2.20 g, 6.75 mmol). The reaction mixture
5 turned brown. After 2 h, the reaction mixture was added to water (10 ml) and extracted with diethyl ether (2 x 15 ml). The combined organics were washed with brine (20 ml) and dried over anhydrous sodium sulfate. Removal of the solvents yielded a brown liquid. Purification by silica gel chromatography using hexanes/ethyl acetate (10:1 then 1:1) gave the title compound as a yellow liquid (780 mg, 88%).

10 ^1H NMR 300MHz (CDCl_3) 8.18 (d, 1H), 7.51 (d, 1H), 6.19 (m, 1H), 3.39-3.62 (m, 2H), 2.25 (m, 2H).

d) 2-[1-(2-Aminoethyl)-2,2,3,3,3-pentafluoropropoxy]-6-trifluoromethyl-nicotinonitrile fumarate

15 To a solution of 2-[1-(2-azidoethyl)-2,2,3,3,3-pentafluoropropoxy]-6-trifluoromethyl-nicotinonitrile (350 mg, 0.899 mmol) in tetrahydrofuran (3.5 ml) and water (3 drops) was added triphenylphosphine (360 mg, 1.35 mmol). After 3 h, the solvents were removed and the residue was loaded directly onto a silica gel column and eluted with dichloromethane followed by 10:1 dichloromethane/2M ammonia in methanol. A yellow liquid (63 mg)
20 was obtained. This was taken up in diethyl ether (3 ml) and added to a stirring solution of fumaric acid (22 mg) in diethyl ether (5 ml) containing a few drops of methanol. The resulting suspension was stirred for 30 minutes and the solid was collected by vacuum filtration and dried overnight under vacuum at 40 °C. The title compound was obtained as a white solid (46 mg).

25 ^1H NMR 300MHz ($\text{d}_6\text{-DMSO}$) 8.75 (d, 1H), 7.89 (d, 1H), 6.55 (s, 2H), 6.24 (m, 1H), 2.99 (m, 2H), 2.29 (m, 2H).

MS: m/z 364 ($\text{M}+1$)⁺.

Example 16

30

2-[1-(2-Aminoethyl)-2,2,3,3,3-pentafluoropropoxy]-6-methyl-nicotinonitrile fumarate

The title compound was prepared by the method of Example 15 but using 5-azido-1,1,1,2,2-pentafluoro-3-pentanol and 2-chloro-6-methyl-3-pyridinecarbonitrile to give the title compound which was isolated as the fumarate salt as a white solid in 37% yield.

5 ^1H NMR 300MHz ($\text{d}_6\text{-DMSO}$) 8.25 (d, 1H), 7.21 (d, 1H), 6.44 (s, 2H), 6.29 (m, 1H), 2.85 (m, 2H), 2.50 (s, 3H), 2.14 (m, 2H).

MS: m/z 310 ($\text{M}+1$) $^+$.

10

Screens

The pharmacological activity of compounds according to the invention may be assessed using the following screens.

15

Screen 1

The activity of compounds of formula (I), or a pharmaceutically acceptable salt thereof, may be screened for nitric oxide synthase inhibiting activity by a procedure based on that of
20 Förstermann *et al.*, Eur. J. Pharm., 1992, **225**, 161-165. Nitric oxide synthase converts ^3H -L-arginine into ^3H -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
25 (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 $^\circ\text{C}$ and in a humidified atmosphere containing 5% CO_2 .

30

Nitric oxide synthase is produced by cells in response to interferon- γ (IFN γ) 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 IFN γ . 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 phenylmethanesulphonyl fluoride (50 mg/ml).

For the assay, 25 μ l of substrate cocktail (50 mM Tris-HCl (pH 7.5 at 20 °C), 400 μ M NADPH, 20 μ M flavin adenine dinucleotide, 20 μ M flavin mononucleotide, 4 μ M tetrahydrobiopterin, 12 μ M L-arginine and 0.025 mCi L-[3 H] arginine) is added to wells of a 96 well filter plate (0.45 μ m pore size) containing 25 μ l of a solution of test compound in 50 mM Tris-HCl. The reaction is started by adding 50 μ l of cell lysate (prepared as above) and after incubation for 1 hour at room temperature is terminated by addition of 50 μ l 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 μ l 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 μ l 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 μ l 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 μ M, 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 μ M are classed as being active and are subjected to at least one retest.

Screen 2

5

Recombinant human NO synthases (iNOS, eNOS & nNOS) were expressed in *E. coli* and lysates were prepared in Hepes buffer (pH 7.4) containing co-factors (FAD, FMN, H_4B), protease inhibitors, lysozyme and the detergent, CHAPS. These preparations were used, at suitable dilution, to assess inhibition of the various isoforms. Inhibition of NOS was
10 determined by measuring the formation of L-[3H]citrulline from L-[3H]arginine using an adaptation of the method of Förstermann *et al.*⁹ Enzyme assays were performed in the presence of 3 μ M [3H]arginine, 1 mM NADPH and other co-factors required to support NOS activity (FAD, FMN, H_4B , calmodulin, Ca^{2+}). Since various NOS inhibitors have been reported to exhibit slow binding kinetics, or to inactivate the enzyme in a time
15 dependent manner, enzyme and inhibitor were pre-incubated for 60 min in the presence of NADPH before addition of arginine to initiate the reaction. Incubations continued for a further 60 min before the assays were quenched and [3H]citrulline separated from unreacted substrate by chromatography on Dowex-50W resin in a 96-well format.

20 In the above screen, the compounds of Examples 1 to 16 were tested and gave IC_{50} values of less than 10 μ M against the iNOS and nNOS enzymes, and showed good selectivity with respect to the inhibition of eNOS, indicating that they are expected to show useful therapeutic activity.

25 Screen 3

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

30 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

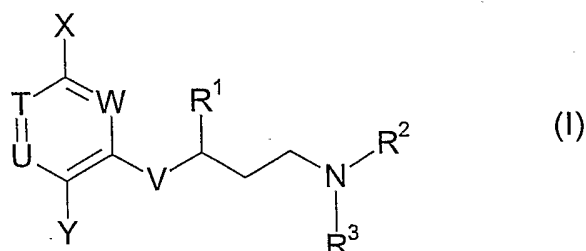
5% CO₂.

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 °C / 5% CO₂ in RPMI 1640 containing 100µM L-arginine and 100µM verapamil-HCl in the presence and absence of test compounds.

- 10 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. IC₅₀ values were estimated from a semi-log plot of % inhibition versus concentration of compound.

CLAIMS:

1. A compound of formula (I)



wherein:

X represents H, C1 to 4 alkyl, C1 to 4 alkoxy, halogen, OH, CN, C≡CH, NO₂, CHO, COCH₃ or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more
 10 fluorine atoms or by an OH group;

Y represents C1 to 4 alkyl, C1 to 4 alkoxy, halogen, OH, CN, C≡CH, NO₂, CHO, COCH₃ or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more
 15 fluorine atoms;

One of T, U and W represents N and the other two independently represent CR⁴; and each R⁴
 group independently represents H, F or CH₃;

V represents O or S(O)_n;

n represents an integer 0, 1 or 2;

R¹ represents C1 to 4 alkyl, C2 to 4 alkenyl, C2 to 4 alkynyl, C3 to 6 cycloalkyl or a 4 to 8
 membered saturated heterocyclic ring incorporating one heteroatom selected from O, S and
 25 N; any of said groups being optionally further substituted by C1 to 4 alkyl, C1 to 4 alkoxy,

C1 to 4 alkylthio, C3 to 6 cycloalkyl, one or more halogens or phenyl; said phenyl group being optionally further substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, CF₃, OCF₃, CN or NO₂;

5 R² and R³ independently represent H, C1 to 4 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally substituted by C1 to 4 alkoxy, halogen, hydroxy, -Z-NR⁷R⁸, 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, CF₃, OCF₃, CN or
10 NO₂;

Z represents -CO- or a bond;

R⁷ and R⁸ independently represent H or C1 to 4 alkyl;

15 or a pharmaceutically acceptable salt thereof; or a tautomer thereof.

2. A compound of formula (I), according to Claim 1, wherein V represents O.

20 3. A compound of formula (I), according to Claim 1, wherein V represents S(O)_n and n represents 0.

4. A compound of formula (I), according to any one of Claims 1 to 3, wherein X represents CH₃, CH₃CH₂ or CF₃.

25 5. A compound according to Claim 4 wherein Y represents CN.

6. A compound of formula (I), according to Claim 1, which is:

6-methyl-2-{3-[1-methylaminoethyl]thio}nicotinonitrile;

- 6-trifluoromethyl-2-{3-[1-methylaminohexyl]thio}nicotinonitrile;
2-[1-ethyl-3-(methylamino)propoxy]-6-(trifluoromethyl)-3-pyridinecarbonitrile;
2-[[1-ethyl-3-(methylamino)propyl]thio]-6-methyl-3-pyridinecarbonitrile;
2-[1-cyclopentyl-3-(methylamino)thiopropyl]-6-(trifluoromethyl)-3-pyridinecarbonitrile;
5 2-[1-cyclopentyl-3-(methylamino)thiopropyl]-6-methyl-3-pyridinecarbonitrile;
(R)-2-(3-methylamino-1-trifluoromethylpropoxy)-6-trifluoromethyl-nicotinonitrile;
(R)-5-fluoro-6-methyl-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile;
(R)-6-ethyl-5-fluoro-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile;
6-methyl-2-(3-methylamino-1-trifluoromethylpropoxy)nicotinonitrile;
10 2-(3-amino-1-trifluoromethylpropoxy)-6-trifluoromethylnicotinonitrile;
5-fluoro-6-ethyl-2-{3-[1-methylaminopentyl]thio}nicotinonitrile;
6-trifluoromethyl-2-{3-[1-methylaminopentyl]thio}nicotinonitrile;
6-methyl-2-{3-[1-methylaminohex-5-enyl]thio}nicotinonitrile;
2-[1-(2-aminoethyl)-2,2,3,3,3-pentafluoropropoxy]-6-trifluoromethyl-nicotinonitrile;
15 2-[1-(2-aminoethyl)-2,2,3,3,3-pentafluoropropoxy]-6-methyl-nicotinonitrile;
or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I), according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt 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 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 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 of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.
- 5 11. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of CNS diseases.
12. The use as claimed in Claim 10 wherein the disease is rheumatoid arthritis or
10 osteoarthritis.
13. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of pain.
- 15 14. The use as claimed in Claim 11 wherein the disease is migraine.
15. 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
20 therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, to a person suffering from, or at risk of, such diseases or conditions.
16. A method of treating, or reducing the risk of, inflammatory disease in a person suffering
25 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 thereof.
17. A method of treating, or reducing the risk of, CNS disease in a person suffering from, or
30 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 thereof.

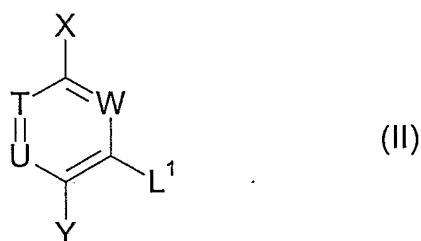
18. A method of treating, or reducing the risk of, pain in a person suffering from, or at risk of, said condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable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

19. A method of treatment as claimed in Claim 17 wherein the disease is migraine.

10

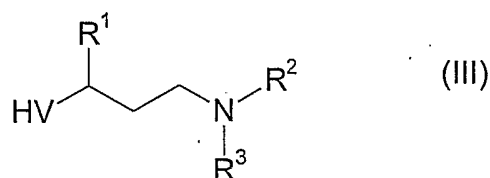
20. A process for the preparation of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, or a tautomer thereof, wherein the process comprises:

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



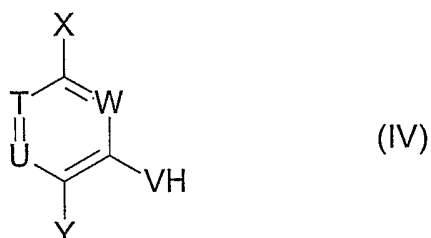
wherein T, U, X, Y and W are as defined in Claim 1 and L^1 represents a leaving group, with a compound of formula (III)

20



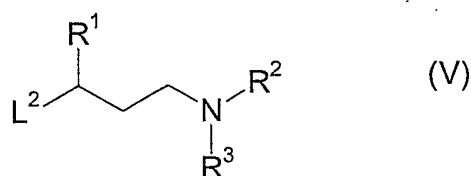
wherein R^1 , R^2 , R^3 and V are as defined in Claim 1; or

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



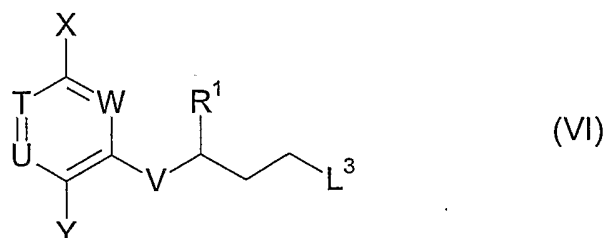
wherein T, U, W, X, Y and V are as defined in Claim 1,

5 with a compound of formula (V)



wherein R¹, R² and R³ are as defined in Claim 1 and L² is a leaving group; or

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



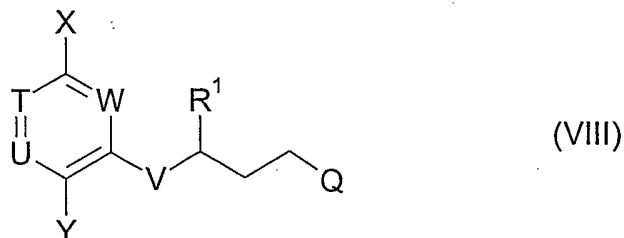
wherein R¹, T, U, W, X, Y and V are as defined in Claim 1 and L³ is a leaving group,

15 with a compound of formula (VII)



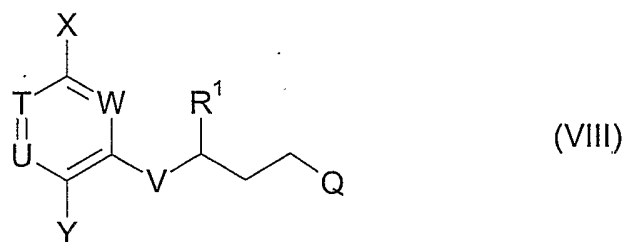
wherein R² and R³ are as defined in Claim 1; or

(d) reduction of a compound of formula (VIII)



5 wherein R^1 , T, U, W, X, Y and V are as defined in Claim 1 and Q represents azide (N_3); or

(e) hydrolysis of a compound of formula (VIII)



10

wherein R^1 , T, U, W, X, Y and V are as defined in Claim 1 and Q represents an imide group;

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

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01415

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 213/85, A61K 31/44, A61P 29/00, A61P 25/00, A61P 19/02
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

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)

CHEM. ABSS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2060622 A (JOHN WYETH & BROTHER LIMITED), 7 May 1981 (07.05.81) --	1-20
X	EP 0399504 A2 (A/S FERROSAN), 28 November 1990 (28.11.90) --	1-20
X	EP 0571685 A1 (NOVO NORDISK A/S), 1 December 1993 (01.12.93) --	1-20
X	US 4666910 A (SCHNEIDER ET AL), 19 May 1987 (19.05.87) --	1-20

☒ 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

7 November 2002

Date of mailing of the international search report

11-11-2002

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

Nebil Gecer/EÖ

Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01415

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, file CAPLUS, CAPLUS accession no. 1977:189458, document no. 86:189458, Rohto Pharmaceuticals Co., Ltd.: "Aromatic amino ether quaternary ammonium salts"; JP,B4,51044934, 19761201 --	1-20
X	EP 0707007 A1 (MERCK PATENT GMBH), 17 April 1996 (17.04.96) -- -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE 02/01415

Patent document cited in search report				Publication date		Patent family member(s)		Publication date	
GB	2060622	A	07/05/81	GB	2059953 A,B	29/04/81			
				GB	2060618 A	07/05/81			
				GB	2060619 A,B	07/05/81			
				GB	2060620 A,B	07/05/81			
				GB	2060621 A	07/05/81			
				US	4325953 A	20/04/82			
				US	4330546 A	18/05/82			

EP	0399504	A2	28/11/90	SE	0399504 T3				
				AT	122031 T	15/05/95			
				AU	641653 B	30/09/93			
				AU	5582190 A	29/11/90			
				CA	2017468 A	26/11/90			
				DE	69019060 D,T	31/08/95			
				DK	258389 D	00/00/00			
				DK	399504 T	04/09/95			
				ES	2071699 T	01/07/95			
				FI	902629 D	00/00/00			
				IE	70070 B,L	30/10/96			
				IE	901790 L	26/11/90			
				IL	94452 A	27/11/95			
				JP	3017046 A	25/01/91			
				NO	174342 B,C	10/01/94			
				NO	902338 A	27/11/90			
				NZ	233809 A	28/04/93			
				PT	94167 A,B	08/01/91			
				US	5145870 A	08/09/92			
				US	5310756 A	10/05/94			
				ZA	9004072 A	27/03/91			

EP	0571685	A1	01/12/93	NONE					

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE 02/01415

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
US	4666910	A	19/05/87	AR 231534 A	28/12/84
				AT 18551 T	15/03/86
				AU 550614 B	27/03/86
				AU 8873882 A	14/04/83
				CA 1171086 A	17/07/84
				DE 3138550 A	07/04/83
				DE 3269839 D	00/00/00
				DK 156718 B,C	25/09/89
				DK 428582 A	29/03/83
				EP 0075752 A,B	06/04/83
				SE 0075752 T3	
				ES 515972 A	16/09/83
				ES 8308543 A	01/12/83
				FI 78074 B,C	28/02/89
				FI 823246 A	29/03/83
				GB 2106902 A,B	20/04/83
				GR 77657 A	25/09/84
				IE 53959 B	26/04/89
				IE 822330 L	28/03/83
				IL 66870 A	28/02/86
				JP 1657178 C	13/04/92
				JP 3016952 B	06/03/91
				JP 58069865 A	26/04/83
				KR 8802705 B	26/12/88
				NO 159999 B,C	21/11/88
				NO 823253 A	29/03/83
				NZ 202015 A	08/11/85
				PH 23219 A	06/06/89
				PT 75611 A,B	01/10/82
				ZA 8207055 A	30/05/84

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE 02/01415

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
EP	0707007	A1	17/04/96	SE 0707007 T3	
				EP 1123933 A	16/08/01
				SI 707007 T	00/00/00
				AT 210657 T	15/12/01
				AU 703637 B	25/03/99
				AU 3421895 A	26/04/96
				BR 9504379 A	27/05/97
				CA 2160447 A	15/04/96
				CN 1130180 A	04/09/96
				CZ 9502661 A	17/04/96
				DE 69524528 D,T	01/08/02
				DK 707007 T	18/03/02
				ES 2169102 T	01/07/02
				FI 954874 A	15/04/96
				HU 75644 A	28/05/97
				HU 9502976 D	00/00/00
				JP 8225501 A	03/09/96
				NO 308848 B	06/11/00
				NO 954080 A	15/04/96
				PL 181165 B	29/06/01
				PL 310932 A	15/04/96
				PT 707007 T	28/06/02
				RU 2155753 C	10/09/00
				SK 126695 A	05/06/96
				TR 960308 A	00/00/00
				TW 420664 B	00/00/00
				US 5767132 A	16/06/98
				ZA 9508673 A	22/05/96