Pyrrolopyrrolone derivatives as inhibitors of neutrophil elastase

The present invention relates to therapeutically active bicyclic compounds, processes for their manufacture, pharmaceutical formulations containing them and their use in chemotherapy. In particular, we have found a group of novel bicyclic compounds which are effective in treating inflammatory diseases.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by circulating leukocytes binding to and extravasation through vascular endothelium. Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes.

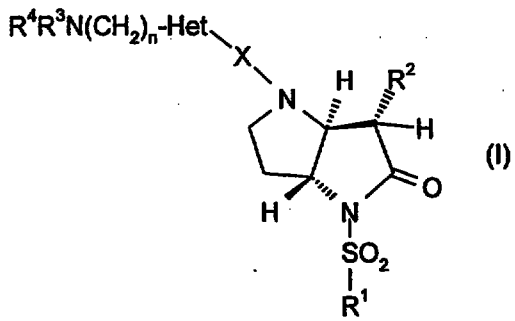
The inflammatory process can be triggered in a number of ways, including by infection, tissue damage and autoimmune reactions. As part of the inflammatory process, neutrophils move from the bloodstream into the tissue at the site of tissue lesion. The neutrophils contain large numbers of different intracellular granules and when activated at the site of inflammation the contents of these granules are secreted into the tissue. The different granules contain a variety of enzymes and other proteins, many of which have antibacterial properties.

One of the enzymes found in the azurophilic granules is neutrophil elastase. Neutrophil elastase has a wide spectrum of activities in the body. For example, within the lung the enzyme increases mucus production and changes the cellular composition of the epithelium The enzyme also causes vascular permeability changes within the microcirculation of many tissues and it is a potent destructive agent against a number of connective tissue components.

Although there are within the body endogenous inhibitors of elastase, including the anti-trypsin and the leukocyte protease inhibitor, elastase activity has been implicated in the pathogenesis of a number of disease states including inflammatory diseases of the airways, the joints and the skin. The enzyme is also responsible for some or most of the symptoms of acute respiratory distress syndrome (ARDS) and other acute inflammatory states brought about by trauma and/or sepsis.

We have now found a group of novel compounds which inhibit neutrophil elastase. These compounds are therefore of potential therapeutic benefit in the treatment and amelioration of symptoms of diseases where elastase activity is implicated.

Thus, according to one aspect of this invention, we provide a compound of the formula (I)



(I)

(relative stereochemistry indicated)

wherein:

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

R^2 represents C_{2-4}alkyl or C_{2-4}alkenyl;

X represents CO or SO_2;

Het represents an optionally substituted 5 to 10 membered monocylic or bicyclic aromatic ring system containing 1 to 4 heteroatoms selected from O, N and S;

n represents an integer 0 to 4;

R^3 and R^4 independently represent hydrogen, C_{1-8}alkyl, $-(CH_2)_{1-4}CONR^5R^6$, COC_{1-4}alkyl or $(CH_2)_{0-2}$Ph where Ph represents phenyl optionally substituted by one or more C_{1-4}alkyl or halogen groups or NR^3R^4 together represents azetidinyl, pyrrolidinyl, piperidinyl, azepinyl, morpholinyl, piperazinyl optionally N-substituted by C_{1-6}alkyl, phenyl (optionally substituted by halogen or C_{1-4}alkyl) or benzyl (optionally substituted on the benzene ring by halogen or C_{1-4}alkyl) or NR^3R^4 together represents a ring as just described save that it is substituted on carbon by one or more C_{1-4}alkyl, $CONR^5R^6$ or $COOR^6$ groups;

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

and salts and solvates thereof (hereinafter "compounds of the invention").

Formula (I) shows the relative stereochemistry of the chiral centres.

The invention embraces compounds of the invention in racemic form as well as in a form in which one enantiomer predominates or is present exclusively. Generally, we prefer to provide a compound of formula (I) in enantiomerically pure form, most particularly the enantiomer having the absolute stereochemistry illustrated in formula (I).

The present invention also covers the physiologically acceptable salts of the compounds of formula (I). Suitable physiologically acceptable salts of the compounds of formula (I) include inorganic and organic acid salts such as hydrochloride and tartrate.

When used herein "alkyl" includes branched as well as straight chain alkyl and may also include cycloalkyl when 3 or more carbon atoms are present.

Suitable R_1 alkyl groups include methyl, ethyl and propyl.

Examples of Het groups include furanyl, imidazolyl, thiophenyl, pyrrolyl, thiazolyl, isoxazolyl, pyrazolyl, pyridinyl and pyrazinyl.

Het may be connected to the pyrrolidine ring via X in any position. Examples of connectivities include furan-2-yl, furan-3-yl, imidazol-2-yl, imidazol-4-yl, thiophen-2-yl, pyrrol-2-yl, thiazol-4-yl, isoxazol-3-yl, pyrazol-3-yl, pyrazol-5-yl, pyridin-3-yl, 1-methyl-pyrrol-2-yl, 1-methyl-pyrazol-3-yl, 1-methyl-pyrazol-5-yl and pyrazin-2-yl.

Examples of substituents for Het include C_{1-6}alkyl (e.g. methyl, ethyl), C_{1-6}alkoxy (e.g. methoxy), nitro and halogen (e.g. chlorine, bromine, fluorine, iodine). The substituent(s) may be on carbon or nitrogen.

Examples of substituted Het include 1-methyl pyrrolyl, 1-methyl pyrazolyl.

Examples of positions for the sidechain shown in formula (I) include for furan-2-yl the 5 position, for furan-3-yl the 2 position, for thiophen-2-yl the 5 position, for pyrrol-2-yl the 4 or 5 position, for 1-methyl pyrrol-2-yl the 5 position, for thiazol-4-yl the 2 position, for isoxazol-3-yl the 5 position, for 1-methyl-pyrazol-3-yl the 5 position, for 1-methyl-pyrazol-5-yl the 3 position, for pyridin-3-yl the 6 position and for pyrazin-2-yl the 5 position.

When R^3 and R^4 independently represent C_{1-8}alkyl, examples include methyl, ethyl, cyclopropyl, n-propyl, isopropyl, n-butyl, $CH(iPr)_2$ and cyclohexyl.

When R^3 and R^4 independently represent $(CH_2)_{0-2}Ph$, examples include phenyl, benzyl and (4-F-phenyl)methyl.

When NR^3R^4 together represents N-substituted piperazinyl, examples include N-phenyl-piperazinyl and N-methyl-piperazinyl.

When NR^3R^4 together represents a ring substituted on carbon, examples of substituents include methyl, $CONH_2$ and COOMe. Examples of such NR^3R^4 include 4-methyl piperidin-1-yl.

We prefer R^1 to represent methyl or ethyl, especially methyl.

We prefer R^2 to represent isopropyl or propyl, especially isopropyl.

We prefer X to represent CO.

We prefer Het to represent a 5 or 6 membered monocyclic aromatic ring containing 1 or 2 heteroatoms selected from O, N and S which is more preferably thiazolyl, isoxazolyl, pyrazolyl or pyrazinyl, especially thiazolyl (particularly thiazol-4-yl) or pyrazinyl.

We also prefer Het to represent pyridinyl, especially 3-pyridinyl.

We most especially prefer Het to represent pyrazinyl. Ideally Het represents pyrazin-2-yl in which the sidechain is in the 5-position.

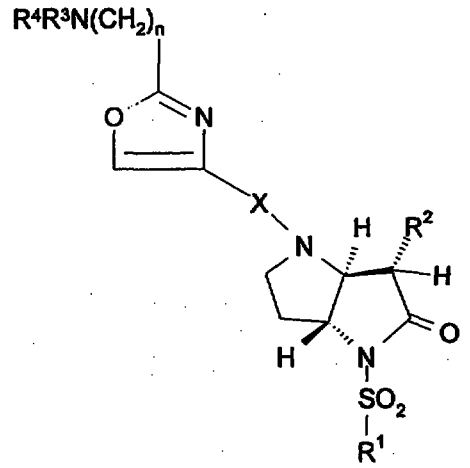
We also prefer Het to represent oxazolyl, particularly oxazol-4-yl.

We prefer n to represent 1 to 3, particularly 1 or 2, especially 1.

We prefer R^3 and R^4 independently to represent hydrogen or C_{1-8}alkyl or for NR^3R^4 to represent pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl optionally

N-substituted by C_{1-8}alkyl or phenyl (optionally substituted by halogen or C_{1-4}alkyl). When R^3 and R^4 independently represent hydrogen or C_{1-8}alkyl, preferred NR^3R^4 groups are NMe_2, N(n-butyl)$_2$, NHMe, NH(cyclopropyl), NHCH(iPr)$_2$ and N(cyclohexyl)$_2$.

A set of compounds of formula (I) of particular interest are compounds of formula (IA) in which Het represents oxazol-4-yl with the sidechain in the 2-position:



(IA)

(relative stereochemistry indicated)

wherein R^4, R^3, n, X, R^2 and R^1 are as defined above.

We prefer X to represent CO. We prefer R^2 to represent isopropyl or propyl, especially isopropyl. We prefer R^1 to represent methyl or ethyl, especially methyl. We prefer n to represent 1 to 3, particularly 1 or 2, especially 1. We prefer R^3 and R^4 independently to represent hydrogen or C_{1-8}alkyl or for NR^3R^4 to represent pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl optionally N-substituted by C_{1-8}alkyl or phenyl (optionally substituted by halogen or C_{1-4}alkyl). We particularly prefer -NR^3R^4 to represent pyrrolidinyl, piperidinyl, N-phenylpiperazinyl, N(butyl)$_2$, NMe(cyclopropyl) or N(cyclohexyl)$_2$, most particularly pyrrolidinyl.

The potential for compounds of the invention to inhibit neutrophil elastase activity may be demonstrated, for example, using the following *in vitro* and *in vivo* assays:

In vitro assays of human neutrophil elastase

Assay contents:

50mM Tris/HCl (pH 8.6)
150mM NaCl
11.8nM purified human neutrophil elastase
Suitable concentrations of compound under test diluted with water from a 10mM stock solution in dimethylsulphoxide. Values above are final concentrations after the addition of substrate solution (see below).

The mixture above is incubated for fifteen minutes at 30°C at which time the remaining elastase activity is measured for 10 minutes in a BioTek 340i plate-reader, after the addition of 0.6mM MeO-succinyl-alanyl-alanyl-prolyl-valyl-p-nitroanilide. The rate of increase in absorbance at 405nm is proportional to elastase activity. Enzyme activity is plotted against concentration of inhibitor and an IC_{50} determined using curve fitting software.

In vivo activity of inhibitors of human neutrophil elastase:
An oral in vivo model using IL-8 induced lung infiltrates for the assessment of intracellular elastase inhibition

Adult hamsters (100-150g) are randomised into groups (n=4) and fasted overnight. Under gaseous anaesthetic (3% isofluorane) animals are dosed orally with 1mL/100g water as vehicle or containing predissolved compounds. Either

at the same time, or subsequently under anaesthetic, animals are dosed intratracheally with 1ug recombinant human IL-8 in 100uL sterile saline. Six hours after IL-8 dosing animals are sacrificed using intraperitoneal pentobarbitone. The lungs are lavaged with 2 x 2.5 mL sterile saline and femurs are removed by dissection.

Intracellular elastase is prepared from neutrophils collected by lavage and from femoral bone marrow . This is achieved by sonication of the neutrophils and centrifugation to yield intracellular granules. These are disrupted by freeze/thawing and sonication. Elastase and myeloperoxidase assays are then performed on these samples to assess the efficacy of the compounds and to normalise for neutrophil recovery.

Human whole blood elastase inhibition assay

Triplicate aliquots of fresh, heparinised human whole blood (200µl) are added to appropriately diluted samples (10µl) of compounds under test. Control samples (6 replicates) contain water in place of compound. Samples are mixed thoroughly by pipette, and are then incubated for 30 minutes at 37°C. Cold red cell lysis buffer (750µl of 155mM ammonium chloride, 0.12mM EDTA, 10mM potassium bicarbonate, pH 7.4) is then added. Tubes are capped, inverted several times, and maintained at 4°C for 15 minutes, inverting every 5 minutes. After centrifugation at 250g for 10 minutes, at 4°C, the resulting pelleted cells are washed. The wash is with saline (300µl), followed by centrifugation at 100g for 10 minutes at 4°C. Pellets are washed twice more, before resuspension of the final cell pellet in buffer (200µl of 100mM Tris, 300mM NaCl, 1% (w/v) HTAB, pH 8.6). Samples are stored at -20 °C. After freeze-thawing of the samples four times, elastase activity is determined by a colorimetric assay in 50mM Tris,

150mM NaCl, 0.6mM MeO-Succ-Ala-Ala-Ala-Pro-Val-pNA at pH 8.6, measuring the rate of increase in absorbance at 405nm.

Accordingly, the compounds of the invention are of potential therapeutic benefit in the treatment and amelioration of symptoms of diseases where elastase activity is implicated. Such diseases particularly include bronchitis, including chronic bronchitis. Also any chronic obstructive pulmonary disease (COPD).

Examples of disease states in which the compounds of the invention have potentially beneficial effects include inflammatory diseases of the respiratory tract such as bronchitis (including chronic bronchitis), bronchiectasis, asthma and hyper-reactivity states of the lung, acute respiratory distress syndrome and septic shock, inflammatory or destructive conditions of the lung such as emphysema and cystic fibrosis and inflammatory or destructive conditions of external tissue such as skin diseases (e.g. lupus and psoriasis) and periodontal disease including gingivitis.

Further examples of disease states and conditions in which compounds of the invention have potentially beneficial effects include wound healing and treatment of burns, cardiovascular diseases such as myocardial infarction and stroke, peripheral vascular disease including intermittent claudication, atherosclerosis, reperfusion injury, cardiovascular changes occurring during cardiopulmonary bypass surgery and septicemia.

Compounds of the invention may also be useful in the treatment of connective tissue disorders such as rheumatoid arthritis, osteoarthritis and spondylitis and inflammatory conditions of the kidney such as glomerulonephritis.

They may also be useful in the treatment of certain leukemias including acute myelogenous leukemia, acute myelomonocytic leukemia and the chronic monocytic leukemias and in prevention or inhibition of metastasis of solid tumours e.g. lung, breast, prostate and stomach cancers and melanomas.

A particular aspect of the present invention is the use of compounds of formula (I) in the treatment of chronic bronchitis. Chronic bronchitis is a condition which results from the exposure of the airway surface to noxious chemicals or agents or is secondary to another disease. The symptoms of the condition are caused by the excessive secretion of mucus onto the surface of the airways. This excess mucus cannot be cleared effectively and the result is reduced gas exchange within the lungs resulting in laboured breathing and hypoxemia, recurrent microbial infections and persistent cough associated with the expectoration of mucoid material. The proposed mechanism for the excessive secretion of mucus involves the recruitment of neutrophils into the airways following the exposure of the epithelium to irritant materials; the neutrophils secrete elastase onto the surface of the airways and the enzyme brings about both an increase in the amount of mucus secreted onto the airway surfaces and a dramatic change in the cellular composition of the airway epithelium. Inhibition of elastase activity by the administration of compounds of this invention is therefore an approach to the treatment of chronic bronchitis. Reduced lung function in COPD (eg in chronic bronchitics with airflow obstruction) is also due to elastase mediated lung damage leading to airway narrowing and inflammation. Thus an elastase inhibitor will improve lung function.

As indicated above, compounds of the invention are useful in human or veterinary medicine, in particular as inhibitors of the enzyme neutrophil elastase.

Thus, there is provided as a further aspect of the present invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use in human or veterinary medicine, particularly in the treatment of conditions where elastase activity is implicated such as chronic bronchitis.

It will be appreciated that references herein to treatment extend to prophylaxis as well as the treatment of established conditions.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of conditions where elastase activity is implicated, particularly in chronic bronchitis.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with a condition caused or mediated by elastase activity which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof in admixture with one or more physiologically acceptable diluents or carriers.

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

The compounds according to the invention may, for example, be formulated for oral, buccal, parenteral, topical or rectal administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or toxicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluorethane, carbon dioxide or other suitable gas.

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatin, may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents such as corticosteroids or NSAIDs, bronchodilators such as beta-2 adrenergic agonists and xanthines (e.g. theophylline), mucolytic agents, anti-muscarinics, anti-leukotrienes, inhibitors of cell adhesion (e.g. ICAM antagonists), anti-oxidants (eg N-acetylcysteine), lung surfactants and/or antimicrobial and anti-viral agents. The compositions according to the invention may also be used in combination with gene replacement therapy.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent.

The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

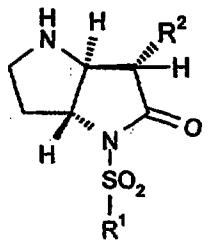
The compound of the invention may conveniently be administered in amounts of, for example, 0.01 to 50mg/kg body weight, suitably 0.05 to 25mg/kg body weight orally, one or more times a day. The precise dose will of course depend on the age and condition of the patient, the particular route of administration chosen, and the disease being treated. The compound is preferably administered orally for the treatment of bronchitis. Other routes of administration may be needed for other indications, for instance i.v. for ARDS.

The compounds of the invention have useful duration of action.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

A process according to the invention for preparing a compound of formula (I) comprises:

(i) condensation of a compound of formula (II):

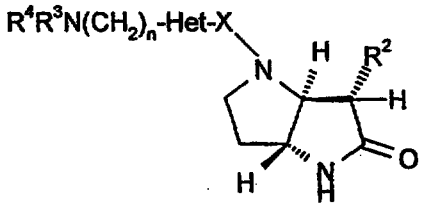


(II)

(relative stereochemistry indicated)

with a compound $R^4R^3N(CH_2)_nHetCOOH$ or an acid derivative thereof such as an acid chloride, activated ester, acid anhydride, or a mixed anhydride or with a compound $R^4R^3N(CH_2)_nHetXY$, where Y is a reactive group such as halogen, e.g. chlorine, or a protected derivative thereof; or

(ii) sulphonylation of a compound of formula (III):



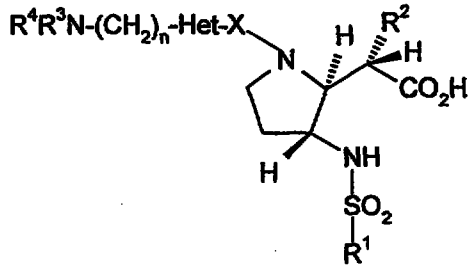
(III)

(relative stereochemistry indicated)

or a protected derivative thereof

with a compound YO_2SR^1 wherein Y is a reactive group such as halogen, e.g. chlorine; or

(iii) cyclising a compound of formula (IV):

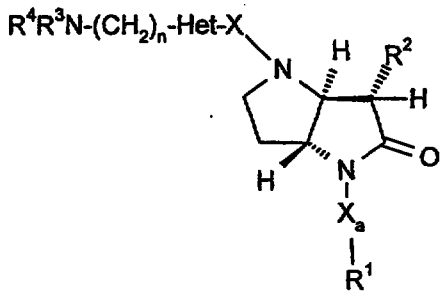


(IV)

(relative stereochemistry indicated)

or a carboxylic acid ester thereof; or

(iv) oxidation of a corresponding compound of formula (V)

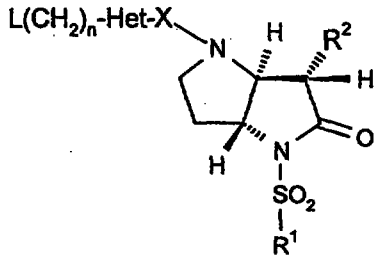


(V)

(relative stereochemistry indicated)

wherein X_a is sulphur or SO; or

(v) reaction of a corresponding compound of formula (VI)



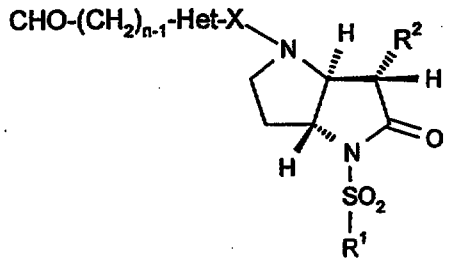
(VI)

(relative stereochemistry indicated)

wherein L is a leaving group

with a compound of formula R^4R^3NH; or

(vi) preparation of a compound of formula I in which n represents an integer 1 to 4 by reduction of the product of reaction of a corresponding compound of formula (VII)

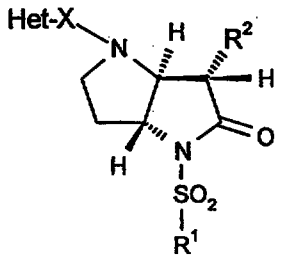


(VII)

(relative stereochemistry indicated)

with a compound of formula R^4R^3NH; or

(vii) preparation of a compound of formula I in which n represents 1 by reaction of a corresponding compound of formula (VIII)



(VIII)

(relative stereochemistry indicated)

with formaldehyde or paraformaldehyde together with a compound of formula R^4R^3NH under acidic conditions; or

(viii) deprotecting a compound of formula (I) which is protected; or

(ix) purifying one enantiomer of the compound of formula (I) from a mixture of enantiomers;

and where desired or necessary converting a resultant free base compound of formula I into a physiologically acceptable salt form or vice versa or converting one salt form into another physiologically acceptable salt form.

Process (i)

The condensation reaction with $R^4R^3N(CH_2)_nHetCOOH$ is suitably carried out in the presence of a coupling agent such as 1-(3-N,N-dimethylaminopropyl)-3-ethylcarbodiimide, preferably also in the presence of HOBT, and a solvent such as dichloromethane, DMF, MeCN or tetrahydrofuran at a temperature of suitably

between O°C and ambient. When an acid derivative such as the acid chloride, activated ester, acid anhydride, or a mixed anhydride is used, reaction conditions will be modified accordingly, for instance by inclusion of a base. If one or both of R^3, R^4 represents hydrogen, it will generally be preferred to protect the nitrogen, e.g. with BOC.

With $R^4R^3N(CH_2)_nHetSO_2Y$, the reaction is suitably carried out in the presence of a base such as triethylamine and a solvent such as DCM, suitably at 0°C-ambient.

Process (ii)

The sulphonylation reaction is suitably carried out in the presence of LHMDS or NaH, in a solvent such as tetrahydrofuran at a temperature of suitably between -78°C to O°C.

When one or both of R^3 and R^4 represents hydrogen, it may be necessary to protect the nitrogen, e.g. with BOC.

Process (iii)

The cyclisation reaction is suitably carried out in the presence of 2-chloro-1-methylpyridinium iodide, or EDC, in a solvent such as dichloromethane, at a temperature of suitably 0°C - reflux. This reaction may also be performed using a carboxylic acid thioester derivative of the compound of formula (IV). Alternatively, another acid derivative such as an acid halide (e.g. acid chloride) may be used.

Process (iv)

This oxidation reaction may be carried out in conventional manner such as by peracid oxidation.

Process (v)

Preferred leaving groups include halogen (such as chlorine, bromine or iodine), mesylate and tosylate. The reaction may be performed by combining the reactants optionally in the presence of a base such as triethylamine or potassium carbonate in an inert solvent such as DMF or MeCN.

Process (vi)

This reaction will take place on combining the reagents in an inert solvent, e.g. DCM at ambient or elevated temperature.

Reduction can be performed *in situ* using a conventional mild reducing agent such as $NaBH_3CN$ or $NaBH(OAc)_3$.

Process (vii)

Reaction of the heterocyclic compound of formula (VIII) with formaldehyde or paraformaldehyde and the amine will take place under standard Mannich conditions, e.g. reflux under acid conditions, typically in acetic acid/ethanol. If the amine is used as an acid salt (e.g. the hydrochloride) the acetic acid may be omitted.

Process (viii)

Protecting groups, especially nitrogen protecting groups, and means for deprotection are described in T W Greene "Protective Groups in Organic Synthesis", 2nd Ed (1991) J Wiley & Sons.

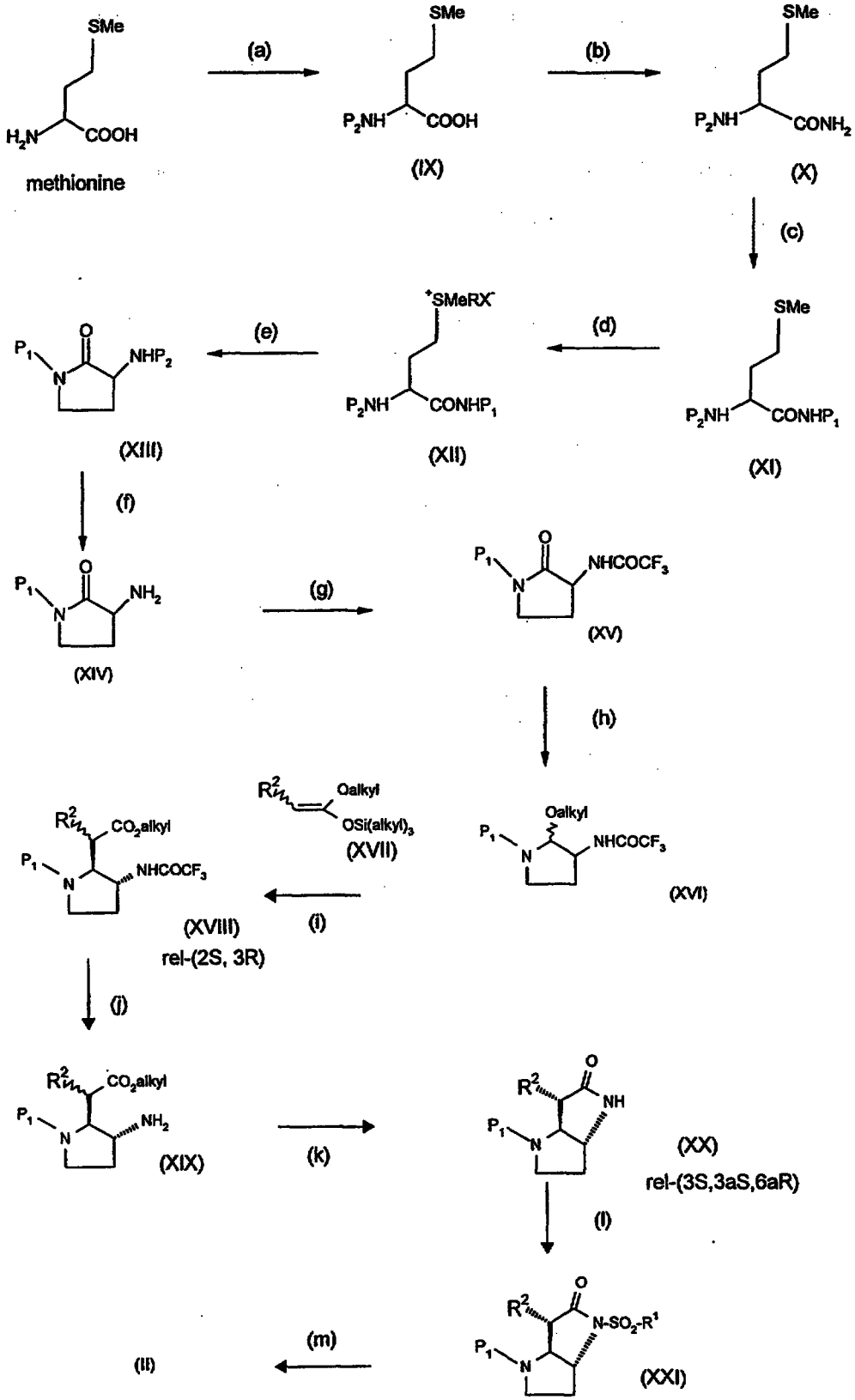
Process (ix)

Purification of a single enantiomer may be achieved by conventional methods such as chiral chromatography (e.g. chiral HPLC) and crystallisation with a homochiral acid (e.g. tartaric acid).

Physiologically acceptable acid salts of the compound of formula (I) such as the hydrochloride or tartrate may be prepared by treating a basic compound of formula (I) with the desired acid.

Intermediate compounds of formula (II) may conveniently be prepared according to the methodology in Scheme I below:

Scheme 1


SMe
H2N
COOH
methionine
(a)
SMe
P2NH
COOH
(IX)
(b)
SMe
P2NH
CONH2
(X)
(c)
SMe
P2NH
CONHP1
(XI)
(d)
+SMeRX-
P2NH
CONHP1
(XII)
(e)
P1
N
O
NHP2
(XIII)
(f)
P1
N
O
NH2
(XIV)
(g)
P1
N
O
NHCOCF3
(XV)
(h)
Oalkyl
P1
N
NHCOCF3
(XVI)
R2
Oalkyl
OSi(alkyl)3
(XVII)
(i)
R2
CO2alkyl
P1
N
NHCOCF3
(XVIII)
rel-(2S, 3R)
(j)
R2
CO2alkyl
P1
N
NH2
(XIX)
(k)
R2
O
NH
P1
N
(XX)
rel-(3S,3aS,6aR)
(l)
R2
O
N-SO2-R1
P1
N
(XXI)
(m)
(II)

Step (a)

This is a conventional protection reaction which, in the case when P_2 represents BOC, may be performed by reacting with $(BOC)_2O$ in the presence of base (e.g. NaOH) in a polar solvent system such as dioxan/water.

Step (b)

This conversion may be performed on treatment with ammonium bicarbonate in the presence of a suitable solvent such as pyridine/DMF and in the presence of $(BOC)_2O$ or suitable equivalent.

Step (c)

This is a conventional protection reaction which, in the case when P_1 represents CBZ, may be performed by reaction with nBuLi followed by CBZ-Cl in the presence of an inert solvent such as THF below -50 °C.

Step (d)

This reaction may be performed by treatment with RX where RX is a compound (e.g. MeI, benzyl iodide or Me_2SO_4) capable of converting sulphur in the SMe moiety to sulphonium in a suitable solvent, e.g. propanone or acetonitrile. Generally R will represent alkyl or aralkyl and X will represent halide, especially iodide, or sulphate. Protection of the amide is convenient, although not essential, for this reaction.

Step (e)

This ring closure reaction may be performed by treatment with Dowex 2 x 8 400 mesh OH^- resin in a suitable solvent, e.g. MeCN. Alternatively, the ring closure may be performed by treatment with potassium carbonate in a suitable solvent, e.g. MeCN.

Step (f)

Deprotection may be performed in a conventional manner, for example, a BOC protecting group may be removed by treatment with HCl, e.g. in dioxan.

Step (g)

This reaction may be performed by treatment with a trifluoroacetic acid alkyl ester (e.g. the methyl ester) or trifluoroacetic anhydride in the presence of a suitable base e.g. N-methylmorpholine.

Step (h)

This conversion will take place on treating the compound of formula (XV) with a reducing agent e.g. lithium borohydride, followed by treatment with concentrated sulphuric acid in the presence of an alkyl alcohol e.g. ethanol solvent.

Step (i)

The reaction of compounds of formula (XVI) and (XVII) takes place in the presence of a Lewis acid e.g. boron trifluoride dietherate and an inert solvent e.g. dichloromethane or MeCN. The group "alkyl" in Oalkyl and $OSi(alkyl)_3$ generally represents C_{1-6}alkyl. In the compound of formula (XVII), suitable alkyl groups in the silyl alkyl moiety include methyl, isopropyl and t-butyl. Preferred Oalkyl is OEt and preferred $OSi(alkyl)_3$ is $OSi(i\text{-}Pr)_3$ or $OSi(Me)_2(t\text{-}Bu)$. The use of variants of compounds of formula (XVII) in which Oalkyl is replaced by $OSi(alkyl)_3$ is also envisaged.

Compounds of formula (XVII) may be prepared by treatment of the corresponding carboxylic acid ester (R^2CH_2COOEt or another alkyl ester, which compounds are either known or may be prepared by known methods) with a strong base (eg LHMDS) followed by a trialkylsilylchloride (such as trimethylsilylchloride) or a trialkylsilyltriflate. Typically the reaction will be

performed at low temperature (less than 0 °C) in an inert solvent (such as THF) in the presence of DMPU.

Step (j)

This deprotection reaction will take place on treatment with base, such as potassium carbonate.

Step (k)

This ring closure reaction may be performed on treatment with an alkyl Grignard reagent (e.g. t-butylmagnesium choride) in an inert solvent such as THF in the presence of tetramethylethylenediamine at a temperature of -20°C to 25°C.

Step (l)

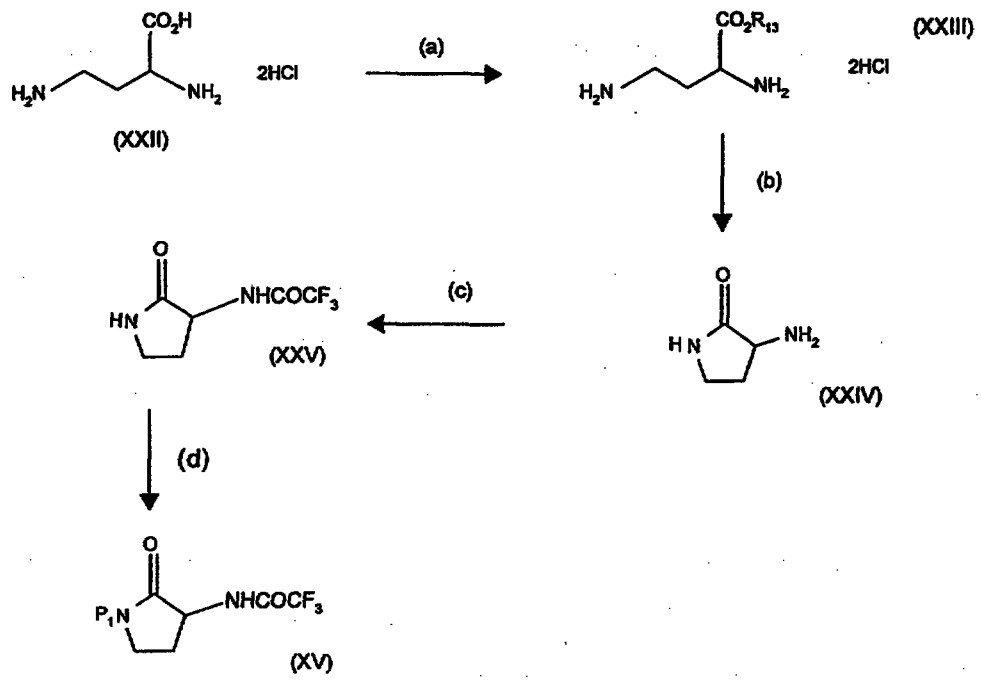
This is a lactam sulphonylation reaction. It is suitably carried out by reaction with R^1SO_2-Y, wherein Y is a reactive group, preferably chloro, in the presence of LHMDS, NaH or KH, in a solvent such as THF, at a temperature of suitably -78° to 0°C.

Step (m)

This is a N-deprotection reaction, which can suitably be carried out in conventional manner. Thus when P_1 is CBZ, it is suitably carried out by hydrogenation over Pd $(OH)_2$ catalyst in solvents such as ethyl acetate or THF.

Compounds of formula (XV) may also be prepared by following a route described in Scheme 2:

Scheme 2



Step (a)

The reaction will proceed under standard conditions for forming alkyl esters, for example by treatment with an alcohol eg methanol in the presence of $SOCl_2$. R_{13} is suitably a C_{1-6}alkyl group, preferably methyl.

Step (b)

The cyclisation reaction will take place on stirring in water with Dowex 2X8 (preferably 400 mesh).

Step (c)

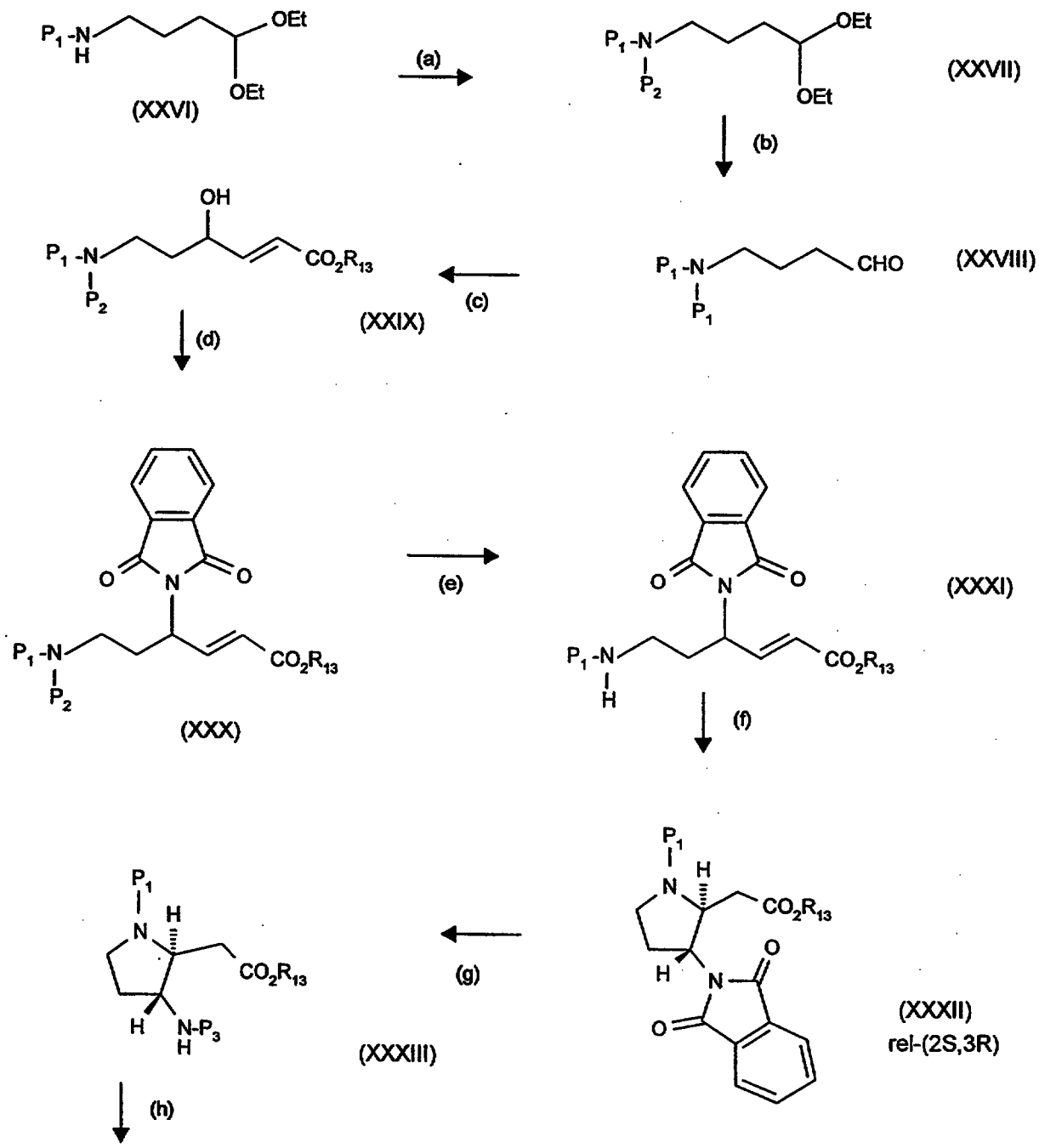
The TFA protected amine is formed by treating the compound of formula (XXIV) with methyl trifluoroacetate in a polar protic solvent, eg MeOH.

Step (d)

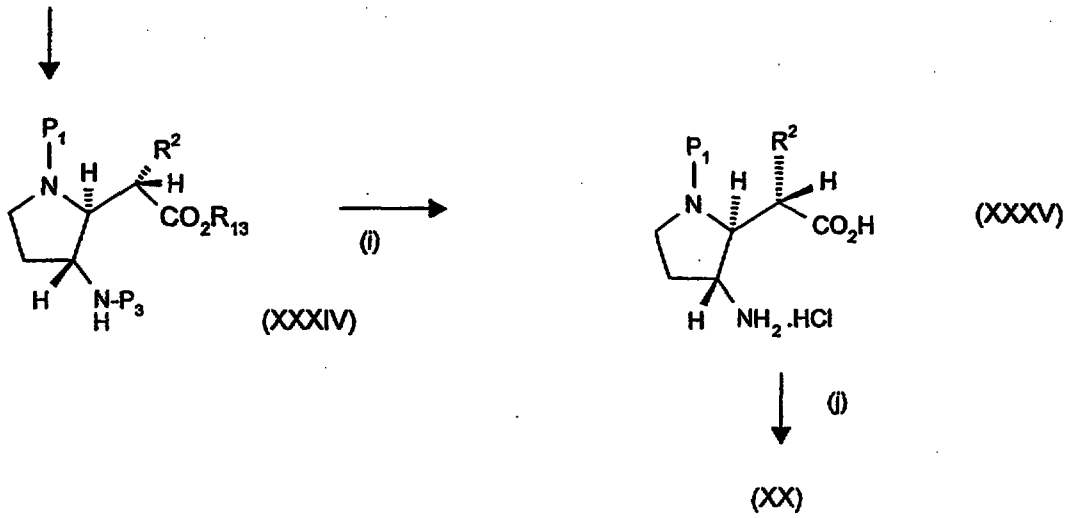
Suitable protecting groups P_1 include CBZ. In this case, the compound of formula (XXV) may be treated with a strong base such as LHMDS or nBuLi in an inert solvent such as THF, followed by treatment with CBZ-Cl.

An alternative route for preparation of compounds of formula (XX) from Scheme 1 is given in Scheme 3:

Scheme 3



Scheme 3 continued



Step (a)

The compounds of formula (XXVI) are either known compounds or may be made in analogous manner to known compounds. P_1 is a N-protecting group, preferably CBZ. Step (a) is a further N-protection reaction. P_2 in formula (XXVII) is a different N-protecting group, preferably BOC. When P_2 is BOC, the reaction is suitably carried out using BOC_2O.

Suitably the reaction is carried out in the presence of a base such as triethylamine or 4-dimethylaminopyridine in a solvent such as ethyl acetate, at temperature of suitably 0°-25° C.

Step (b)

This conversion is suitably carried out with pyridinium p-toluenesulfonate, in a solvent such as acetone/water, at a temperature suitably between 25°-75° C.

Step (c)

This is a condensation rearrangement reaction suitably carried out using a 2-phenylsulfinyl acetic acid ester ($PhSOCH_2CO_2R_{13}$) and piperidine, in a solvent such as acetonitrile, suitably at ambient temperature.

R_{13} is suitably a C_{1-6}alkyl group, preferably methyl.

Step (d)

This is a Mitsunobu substitution reaction, using phthalimide, PPh_3 and a dialkylazodicarboxylate such as DEAD, in the presence of a solvent such as THF, at a temperature of suitably 0°-40° C.

Step (e)

This is a deprotection reaction, preferably using a strong acid such as TFA in a solvent such as DCM, at a temperature of suitably 0°-40° C.

R_{13} is suitably C_{1-6}alkyl, preferably ethyl.

Step (f)

This is a cyclisation reaction, suitably carried out as an intramolecular Michael reaction. Suitably NaH is used, in a solvent such as THF, at a temperature such as 0° - 25° C.

Step (g)

In this step two reactions occur: N-deprotection and re-protection. The phthalimido group is removed suitably with hydrazine hydrate in a solvent such as ethanol at a temperature between 0°C and reflux. Protecting group P_3 is incorporated in a conventional manner. When P_3 is BOC, this is suitably achieved with BOC_2O.

Step (h)

The R^2 side chain may be introduced by alkylation, using as reactant R^2-Y, wherein Y is a reactive group such as bromo or iodo. Thus the reaction is carried out using a base, preferably a strong base such as LHMDS. With LHMDS suitably a cosolvent DMPU in THF is used. Suitable reaction temperatures are -78° to 50°C. Under these conditions the reaction generally takes place with good stereochemical control.

Step (i)

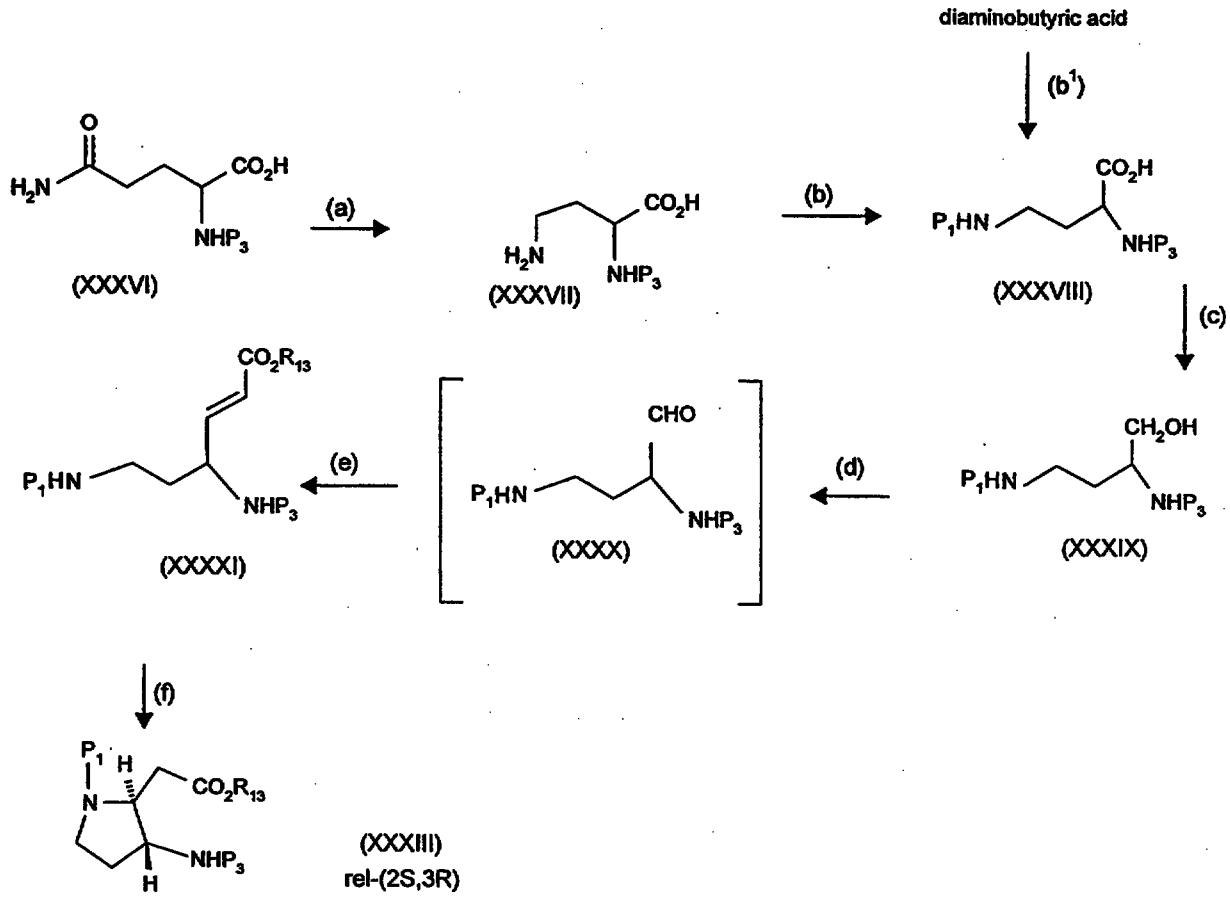
This is an ester hydrolysis reaction, followed by a N-deprotection reaction. The former is carried out in a conventional manner, for example by using KOH in aqueous ethanol, at a temperature of suitably 25°-80°C . The latter is carried out in a conventional manner, for example by using HCl in dioxan, at a temperature of suitably 0°-50°C or, if the protecting group is trifluoroacetate, by treatment with base.

Step (j)

This is a cyclocondensation reaction, suitably carried out in the presence of 2-chloro-1-methylpyridinium iodide and a suitable base such as N, N-diisopropyl ethylamine in a solvent such as dichloromethane, at a temperature of suitably 0°C-reflux. We have also found that it is possible to use the compound of formula (XXXV) as a carboxylic acid ester in which case the ester hydrolysis of step (i) is not necessary. In this case the preferred conditions for the cyclocondensation reaction involve the use of an alkyl Grignard reagent eg t-BuMgCl in THF at a temperature between -20°C and 25°C.

An alternative process for preparation of compounds of formula (XXXIII) is shown in Scheme 4:

Scheme 4



Step (a)

The compounds of formula (XXXVI) are either known compounds or may be prepared in analogous manner to known compounds. P_3 is a protecting group as discussed above, and is suitably BOC. The reaction is suitably carried out using PIFA (phenyl iodosylbis(trifluoroacetate)) and a base such as pyridine in an aqueous solvent, such as aqueous THF, dioxan or acetonitrile. This is the method of Stansfield, C.F. Organic Preparations and Procedures Int., 1990, 22(5), 593-603.

Step (b)

P_1 is a protecting group eg CBZ. This protection reaction may be carried out in a conventional manner. For instance it is suitably carried out in a water miscible

solvent such as THF, DMF or dioxan using N-(benzyloxycarbonyloxy)succinamide, benzyloxycarbonyl chloride, or any suitable source of the benzyloxycarbonyl group, with pH adjustment to alkaline with sodium carbonate.

As an alternative step (b^1), the compound of formula (XXXVIII) can be prepared in conventional manner from diaminobutyric acid.

Step (c)

This reaction is suitably carried out in two stages. The first stage involves reacting the compound of formula (XXXVIII) at reduced temperature with N-methylmorpholine and then an alkyl chloroformate such as ethyl chloroformate, in an organic solvent such as DCM, dioxan or THF. In the second stage the product is reduced, suitably with sodium borohydride at reduced temperature, such as -20° to 10°C, in a solvent such as THF.

Step (d)

This oxidation reaction may be carried out in any suitable manner, for instance using oxalyl chloride in DMSO and methylene dichloride under nitrogen at reduced temperature, such as -30° to -70°C, followed by triethylamine. The intermediate (XXXX) suitably is not isolated.

Step (e)

This reaction is suitably carried out using a Wittig reagent such as a triphenylphosphorane $R_{13}O_2CCH=PPh_3$, or may also be carried out using a phosphonate in a Wadsworth-Emmons reaction.

Step (f)

This Michael addition reaction is suitably carried out using LHMDS or other strong base in an organic solvent such as THF, ether or toluene, and preferably a complexing agent such as TMEDA is also present.

The intermediate compounds of formula (III) may be prepared by reacting a deprotected compound of formula (XX) from Scheme 1 with $R^4R^3N(CH_2)_nHetCOOH$ or $R^4R^3N(CH_2)_nHetXY$ in the manner described above in relation to main process (i) above.

(The initial N- deprotection may be carried out as described above under Scheme 1 Step (m).

The intermediate compounds of formula (IV) may be prepared from a compound of formula (XIX) (with the primary amine suitably protected) in an analogous manner to that described above for preparing a compound of formula (III) from a compound of formula (XX) together with main process (ii) above.

Compounds of formula (V) wherein X_a represents S may be prepared by reaction of a corresponding compound of formula (III) with a compound of formula R^1SSR^1 under standard conditions for nucleophilic displacement. Compounds of formula (V) wherein X_a represents SO may be prepared by peracid oxidation of a corresponding compound wherein X_a represents S.

Compounds of formula (VI), (VII) and (VIII) may be prepared from compounds of formula (II) following conventional methods known *per se*. Mesylate and tosylate derivatives may be prepared from the corresponding alcohol following treatment with $MeSO_2Cl$ or paramethylbenzenesulphonylchloride.

Compounds of formula $R^4R^3N(CH_2)_nHetCOOH$ or an acid derivative thereof, and $R^4R^3N(CH_2)_nHetXY$ are either known or may be prepared by conventional methods known *per se*.

It will be apparent that Schemes 1, 2, 3 and 4 may be modified to produce homochiral products by using homochiral starting materials (e.g. S-methionine in Scheme 1 or S-diaminobutyric acid in Scheme 4) or by performing an additional chiral resolution step.

If compounds of formula (XIV) in racemic form are prepared following Scheme 1 from racemic methionine, we have found that the isomers of the compounds of formula (XIV) may be resolved by a dynamic resolution procedure. Thus a racemic compound of formula (XIV) may be treated with homochiral di-p-toluoyl tartaric acid in the presence of 3,5-dichloro-2-hydroxybenzaldehyde as catalyst in an inert solvent, e.g. THF. A homochiral salt of the compound of formula (XIV) results. A compound of formula (XV) may then be produced by subsequent treatment with trifluoroacetic acid methyl ester in the presence of N-methylmorpholine.

Both enantiomers of the compound of formula (XIV) may also be produced from a synthesis based on S-methionine or R-methionine following similar procedures.

It will be apparent to a person skilled in the art that the above synthetic processes for the preparation of compounds of formula (I) may be modified so as to include or omit protecting groups or so as to use alternative protecting groups (for example those described in T W Greene "Protective Groups in Organic Synthesis", 2nd Ed (1991) J Wiley & Sons) in the course of routine optimisation of experimental conditions.

Novel chiral intermediates in the above described chiral and resolution sections also form an important aspect of this invention.

Processes for preparation of intermediates are also provided as an aspect of this invention.

The compounds of the invention have the advantage that they may be more efficacious, show greater selectivity, have fewer side effects, have a longer duration of action, be more bioavailable by the preferred route have more attractive pharmacodynamic or pharmacokinetic properties or have other more desirable properties than similar known compounds.

The following non-limiting Examples illustrate the present invention.

ABBREVIATIONS

BOC	t-butyloxycarbonyl
CBZ	Benzyloxycarbonyl
$(BOC)_20$	Di-tert-butyldicarbonate
THF	Tetrahydrofuran
LHMDS	Lithium bis (trimethylsilyl)amide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro 2 (1H)-pyrimidinone
DMAP	4-dimethylaminopyridine
DMF	Dimethylformamide
EDC	1-(3-N,N-dimethylaminopropyl)-3-ethylcarbodiimide
DEAD	diethylazodicarboxylate
DCM	dichloromethane

TMEDA	tetramethylethylenediamine
DMSO	dimethylsulphoxide
HOBT	1-hydroxybenzotriazole
$NaBH(OAc)_3$	sodium triacetoxyborohydride

In the foregoing Intermediates and Examples, all T.l.c. experiments were performed on silica plates.

Intermediates

Intermediate 1

2,4-Diamino-butyric acid methyl ester dihydrochloride

To D,L-diaminobutyric acid dihydrochloride (350g) in methanol (1.6l) at 0°C was added thionyl chloride (200ml) over ½h. After reflux for 3h, the solvent was removed in vacuo and the residue tritrurated with toluene (650ml) to give the title compound as a white solid (385g).

Mass spec. of free base MH^+ (found) 133 MH^+ (calculated) 133

Intermediate 2

3-Amino-pyrrolidin-2-one

Intermediate 1 (1g), water (70ml) and Dowex 2x8-400 mesh (16.4ml) were stirred for 1h. The resin was then filtered and the filtrate concentrated in vacuo to give the title compound as a white solid (0.40g), T.l.c (6:1 ethyl acetate: methanol) Rf 0.07.

Intermediate 3

2,2,2-Trifluoro-N-(2-oxo-pyrrolidin-3-yl)-acetamide

A suspension of Intermediate 2 (181g), methyl trifluoroacetate (218ml) and methanol (2.6l) was suspended for 2h. The solvent was then removed in vacuo to afford the title compound as a cream solid (355g).

Mass spec. MNH_4^+ (found) 214 MNH_4^+ (calculated) 214

Intermediate 4

2-Oxo-3-(2,2,2-trifluoro-acetylamino)-pyrrolidine-1-carboxylic acid benzyl ester

To intermediate 3 (3.5g) and tetrahydrofuran (100ml) at -70°C was added LHMDS (20ml). After ¼h, benzyl chloroformate (2.8ml) was added. The mixture was warmed to room temperature for 1h and 1M hydrochloric acid (25ml) added. After extraction with ethyl acetate (3x25ml), the combined extracts were washed with 2% ammonia solution, 2M hydrochloric acid and brine then dried ($MgSO_4$). After solvent removal, the white solid was recrystallised from ethyl acetate: hexane 5:1 to give the title compound as white crystals (4.2g), T.l.c. (9:1 ethyl acetate: methanol) Rf 0.7.

Intermediate 5

2-Ethoxy-3-(2,2,2-trifluoro-acetylamino)-pyrrolidine-1-carboxylic acid benzyl ester

To Intermediate 4 (34g) in ethanol (1070ml) at -5°C was added sodium borohydride (9.86g). A solution of 4M hydrogen chloride in 1,4-dioxan (20ml) was then added dropwise. Periodically further portions of 4M hydrogen chloride in 1,4-dioxan (2x5ml, 1x10ml) and sodium borohydride (2g) were added. After 3h, concentrated sulphuric acid (11ml) was added and the mixture warmed to room temperature for 2h. Saturated aqueous sodium bicarbonate (300ml) was then added and the ethanol and dioxan removed in vacuo. The residue was diluted with water (500ml) and extracted with ethyl acetate (3x500ml). The combined extracts were washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel 9385 eluting with ether, to give the title compound as a solid (21g). Mass spec. MNH_4^+ (found) 378 MNH_4^+ (calculated) 378

Intermediate 6

trans-2-(1-Ethoxycarbonyl-2-methyl-propyl)-3-(2,2,2-trifluoro-acetylamino)-pyrrolidine-1-carboxylic acid benzyl ester

Intermediate 5 (10g), ethyl trimethylsilyl isopropylketene acetal (11ml) and dichloromethane (250ml) were cooled to 5°C and boron trifluoride dietherate (17ml) added over ¼h. After 1h, further boron trifluoride dietherate (3.4ml) and ketene acetal (11ml) were added. After a further 1h, 1M hydrochloric acid (200ml) was added and the organic layer separated and washed with brine and dried ($MgSO_4$). Solvent removal in vacuo gave the title compound as an oil (16.7g), T.l.c.(2:1 ether: cyclohexane) Rf 0.18 and 0.27.

Intermediate 7

trans-3-Amino-2-(1-ethoxycarbonyl-2-methyl-propyl)-pyrrolidine-1-carboxylic acid benzyl ester

Intermediate 6 (31g), potassium carbonate (71g), water (930ml) and ethanol (930ml) were warmed at 60°C for 3h. The ethanol was removed in vacuo and the aqueous residue extracted with ethyl acetate (3x300ml). The combined extracts were washed with brine and dried ($MgSO_4$) and concentrated in vacuo to give the title compound as a brown oil (17.5g).

Mass spec. MH^+ (found)) 349 MH^+ (calculated) 349

Intermediate 8

rel-(3R,3aR,6aS)-6-Isopropyl-5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carboxylic acid benzyl ester

Intermediate 7 (17.5g) in tetrahydrofuran (1,800ml) was cooled to -5°C and 1M t-butylmagnesium chloride in tetrahydrofuran(204ml) was added over ½h. After 2h, 1M hydrochloric acid (250ml) and brine (300ml) were added and the mixture was extracted with ethyl acetate (250ml). After concentrating the extracts to half the volume in vacuo, the extracts were washed with brine and dried ($MgSO_4$).

Solvent removal in vacuo followed by trituration with diethyl ether (60ml) gave a white solid. This was recrystallised from ethyl acetate to give the title compound (3.4g). Mass spec. MH^+ (found) 303 MH^+ (calculated) 303

Intermediate 9

rel-(3R,3aR,6aS)-6-Isopropyl-4-methanesulfonyl-5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carboxylic acid benzyl ester

To a stirred solution of Intermediate 8 (15.01g) in anhydrous tetrahydrofuran (950ml) at -74°C under nitrogen, was added 1.0M LHMDS in tetrahydrofuran (69.5ml) dropwise. After stirring at -74°C for 10 min, the mixture was allowed to warm up to 0°C over 45 min, then left at this temperature for 20 min. It was then cooled to -76°C, treated dropwise with methanesulfonyl chloride (9.61ml) and left to stir at this temperature for 1.5h. It was then warmed to -50°C, quenched with saturated ammonium chloride solution (480ml) and allowed to warm up to room temperature. The mixture was partitioned between water (300ml) and ethyl acetate (750ml), the aqueous layer extracted with further ethyl acetate (750ml), then the combined organic extracts washed with brine (450ml), dried (Na_2SO_4) and concentrated in vacuo to a cream solid. Purification by flash column chromatography on silica (Merck 9385) eluting with ethyl acetate: cyclohexane (1:3, 1:2, 1:1 then 3:1) gave the title compound as a white crystalline solid (13.65g). T.l.c. (dichloromethane) Rf 0.22 Mass spec MNH_4^+ (found) = 398 MNH_4^+ (calculated) = 398

Intermediate 10

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one

A suspension of Intermediate 9 (13.63g) in ethyl acetate (900ml) was added to 20% palladium hydroxide (moist) on carbon (3.16g) and the resulting black suspension stirred vigorously under hydrogen at room temperature for 90 min.

The mixture was then filtered through Harborlite J2 and concentrated in vacuo to give the title compound as a fine white powder (8.63g). Tlc (Methanol:dichloromethane 1:9) Rf 0.50 Mass spec MH^+ (found) = 247 MH^+ (calculated) = 247

Intermediate 11

rel-5-(6R-Isopropyl-4-methanesulfonyl-5-oxo-hexahydro-(3aS,6aR)-pyrrolo[3,2-b]pyrrole-1-carbonyl)-furan-2-carbaldehyde

To a stirred solution of Intermediate 10 (100mg) in acetonitrile (5ml) was added 5-formyl-2-furoic acid (74mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (156mg). The reaction mixture was stirred for 3 days. The acetonitrile was removed *in vacuo* and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by flash column chromatography (Merck 9385 silica; eluent dichloromethane:acetonitrile 9:1) to give the title compound (80mg) as a white solid. Mass spec. MH^+ (found) 369 MH^+ (calculated) 369.

Intermediate 12

rel-(3R,3aR,6aS)-3-(6-Isopropyl-4-methanesulfonyl-5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl)-furan-2-carbaldehyde

To a stirred solution of Intermediate 10 (540mg) in acetonitrile (40ml) was added 2-formyl-3-furoic acid (400mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (841mg). The reaction mixture was stirred for 16h. The acetonitrile was removed *in vacuo* and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane. The combined organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by flash column chromatography (Merck 9385 silica; eluent

dichloromethane:acetonitrile 9:1) to give the title compound (626mg) as a cream solid. Mass spec. MH^+ (found) 369 MH^+ (calculated) 369.

Intermediate 13

rel-(3R,3aR,6aS)-5-(6-Isopropyl-4-methanesulfonyl-5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl)-thiophene-2-carbaldehyde

To a stirred solution of Intermediate 10 (250mg) in acetonitrile (10ml) was added 5-formylthiophene-2-carboxylic acid (206mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (389mg). The reaction mixture was stirred for 3h. The acetonitrile was removed *in vacuo* and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane. The combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to leave a foam. The foam was purified by flash column chromatography (Merck 9385 silica; eluent dichloromethane:acetonitrile 9:1) to give the title compound (280mg) as a cream solid. Mass spec. MH^+ (found) 385 MH^+ (calculated) 385.

Intermediate 14

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one

A solution of pyrrole-2-carboxylic acid (60mg), 1-hydroxybenzotriazole (81mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (115mg) and triethylamine (101mg) in dimethylformamide (3ml) was stirred for 5 min. then treated with Intermediate 10 (100mg). The reaction mixture was stirred for 6h. then partitioned between 8% sodium bicarbonate solution (25ml) and ethyl acetate (50ml). The organic phase was separated, washed with water (2x50ml) and the solvent removed *in vacuo* to leave a solid. A suspension of the solid in diethyl ether (25ml) was stirred for 10 min. then filtered under suction. The residue was dried to give the title compound (123mg) as a white powder.

Melting point 200-203^{0}C Mass spec. MH^+ (found) 340 MH^+ (calculated) 340.

Intermediate 15

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one

A solution of 1-methylpyrrole-2-carboxylic acid (150mg), 1-hydroxybenzotriazole (180mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (250mg) and triethylamine (240mg) in dimethylformamide (5ml) was stirred for 15 min. then treated with Intermediate 10 (246mg). The reaction mixture was stirred for 18h. then partitioned between 2% sodium bicarbonate solution (135ml) and ethyl acetate (150ml). The organic phase was separated, washed with water (2x120ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to leave a semi-solid. The semi-solid was suspended in diethyl ether (20ml) and the suspension was stirred for 10 min. The ether was decanted and replaced by more ether (10ml). The resultant suspension was stirred for 10 min. The ether was again decanted and the residue dried to give the title compound (227mg) as a pale brown solid. Melting point 176-178^{0}C Mass spec. MH^+ (found) 354 MH^+ (calculated) 354.

Intermediate 16

2-(2,2-Dimethyl-propionyloxymethyl)-thiazole-4-carboxylic acid

A mixture of α-bromopyruvic acid (1.85g), 1-(tert-butylcarbonyloxy) thioacetamide (1.75g) and activated 4 Angstrom molecular sieves (10g) in ethanol (100ml) was stirred for 24h. The solvent was removed *in vacuo* and replaced by dichloromethane (100ml). The resultant suspension was stirred for 5 min. then filtered through Harborlite J2. The filtrate was evaporated to leave a solid, which was dissolved in ethyl acetate, dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound (1.83g) as a pale yellow, waxy solid.

Melting point 155-158^{0}C Mass spec. MH^+ (found) 244 MH^+ (calculated) 244.

Intermediate 17

2-Hydroxymethyl-thiazole-4-carboxylic acid

A solution of Intermediate 16 (1.78g) and potassium carbonate (1.80g) in methanol (90ml) and water (30ml) was stirred and heated at reflux for 4.5h., cooled, concentrated to 30ml, acidified with 2M hydrochloric acid and extracted with dichloromethane (5x60ml), then concentrated *in vacuo* to leave a solid which was extracted with a hot (2:1) mixture of industrial methylated spirits and ethyl acetate (2x150ml). These extracts were combined with the dichloromethane extracts and the solvents were removed *in vacuo*. The residual gum was crystallised from diethyl ether to give the title compound (834mg) as a brown powder. Melting point 121-127^{0}C Mass spec. MH^+ (found) 160 MH^+ (calculated) 160.

Intermediate 18

rel-(3S,3aS,6aR)-4-(2-Hydroxymethyl-thiazole-4-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one

A solution of Intermediate 17 (787mg), Intermediate 10 (1.00g), triethylamine (655mg), 1-hydroxybenzotriazole (718mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (997mg) in dimethylformamide (5ml) was stirred for 17h. then partitioned between 8% sodium bicarbonate solution (250ml) and ethyl acetate (250ml). The aqueous phase was separated and extracted with ethyl acetate (250ml). The combined organics were washed with 0.5M hydrochloric acid (2x200ml) and water (2x200ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a foam. The foam was suspended in diethyl ether (100ml), with stirring, for 5 min. The resultant solid suspension was filtered under suction. The residue was dried to leave the title compound (1.23g) as a

brown powder. Melting point 197-201^{0}C Mass spec. MH^+ (found) 388 MH^+ (calculated) 388.

Intermediate 19

2-Dimethylaminomethyl-thiazole-4-carboxylic acid

A mixture of α-bromopyruvic acid (370mg), 1-(dimethylamino)thioacetamide hydrochloride (300mg) and sodium bicarbonate (200mg) in ethanol (25ml) was stirred and heated at reflux for 1.5h. Potassium carbonate (213mg) was added and refluxing was maintained for 0.75h. The reaction mixture was cooled and the solvent was removed *in vacuo*. The residue was stirred in ethyl acetate (30ml) for 0.5 h. The solvent was decanted. The residual solid was partitioned between 0.5M hydrochloric acid (16ml) and ethyl acetate (20ml). The aqueous phase was separated and concentrated *in vacuo* to leave a gum. The gum was treated with methanol (20ml) and filtered. The filtrate was concentrated *in vacuo* and the residue dried to leave the title compound (430mg) as a dark brown powder. Mass spec. MH^+ (found) 187 MH^+ (calculated) 187.

Intermediate 20

5-Formyl-isoxazole-3-carboxylic acid

A solution of ethyl-5-formylisoxazole-3-carboxylate (25mg) in 1,4-dioxan (3ml) and 2M hydrochloric acid (1ml) was stirred and heated at reflux for 5h.; cooled and the solvents removed *in vacuo*. The residue was triturated in diethyl ether. The solvent was removed and the residue dried to leave the title compound (18mg) as an orange/brown solid. T.l.c. (dichloromethane:methanol 9:1) Rf = 0.32.

Intermediate 21

rel-(3R,3aR,6aS)-3-(6-Isopropyl-4-methanesulfonyl-5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl)-isoxazole-5-carbaldehyde

To a stirred solution of Intermediate 10 (670mg) in acetonitrile (50ml) was added Intermediate 20 (500mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.04g). The reaction mixture was stirred for 4h. The acetonitrile was removed *in vacuo* and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic phase was separated and passed through a Varian SPE bond elution silica cartridge, eluting sequentially with dichloromethane, chloroform, diethyl ether, ethyl acetate, acetonitrile and methanol. Fractions containing the required product were combined and evaporated to give the title compound (660mg) as a white solid. T.l.c. (dichloromethane:acetonitrile 9:1) Rf = 0.33.

Intermediate 22

1-Methyl-5-styryl-1H-pyrazole-3-carboxylic acid ethyl ester

A solution of (E)-ethyl-2,4-dioxo-6-phenylhex-5-enoate (40g) and methylhydrazine (9g) in ethanol (250ml) was heated at reflux for 2h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica, using a (1:1) mixture of diethyl ether and cyclohexane as the eluent. Fractions containing the more polar of the two major new components were combined and the solvent evaporated to leave the title compound (25.4g) as yellow crystals. T.l.c. (diethyl ether:cyclohexane 1:1) Rf = 0.14.

Also isolated from this reaction was Intermediate 23:

Intermediate 23

2-Methyl-5-styryl-2H-pyrazole-3-carboxylic acid ethyl ester

Fractions containing the less polar of the two major new components obtained from the chromatographic purification of Intermediate 22 were combined and the solvent evaporated to leave the title compound (11.4g) as a yellow oil.

T.l.c. (diethyl ether:cyclohexane 1:1) Rf = 0.62.

Intermediate 24

5-Formyl-1-methyl-1H-pyrazole-3-carboxylic acid ethyl ester

Ozone was bubbbled through a stirred solution of Intermediate 22 (156mg) in ethyl acetate (10ml) at -78°C for 2h. Nitrogen was then bubbled through the solution, triphenylphosphine (500mg) was added, the solution was warmed to room temperature and the solvent was removed *in vacuo*. The product was passed through a Varian SPE bond elution silica cartridge, eluting sequentially with dichloromethane, chloroform and diethyl ether. Fractions containing the required product were combined and evaporated to give the title compound (127mg) as white crystals. T.l.c. (diethyl ether:cyclohexane 1:1) Rf = 0.58.

Intermediate 25

5-Formyl-1-methyl-1H-pyrazole-3-carboxylic acid

A solution of Intermediate 24 (1.02g) in 1,4-dioxan (10ml) and 2M hydrochloric acid (10ml) was stirred and heated at reflux for 24h. The reaction mixture was cooled and the solvent was removed *in vacuo* to leave the title compound as a pale yellow solid (0.85g). T.l.c. (dichloromethane:methanol 9:1) Rf = 0.19 (streaking).

Intermediate 26

rel-(3R,3aR,6aS)-5-(6-Isopropyl-4-methanesulfonyl-5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl)-2-methyl-2H-pyrazole-3-carbaldehyde

To a stirred solution of Intermediate 10 (783mg) in acetonitrile (60ml) were added Intermediate 25 (645mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.22g). The reaction mixture was stirred overnight. The acetonitrile was removed *in vacuo* and the residue was partitioned between dichloromethane and saturated sodium bicarbonate

solution. The organic phase was separated and passed through a Varian SPE bond elution silica cartridge, eluting sequentially with dichloromethane, chloroform, diethyl ether and ethyl acetate. Fractions containing the required product were combined and evaporated to give the title compound (315mg) as a white solid. T.l.c. (dichloromethane:acetonitrile 9:1) Rf = 0.24.

Intermediate 27

rel-(3R,3aR,6aS)-5-(6-Isopropyl-4-methanesulfonyl-5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl)-2-methyl-2H-pyrazole-3-carbaldehyde

Ozone was bubbbled through a stirred solution of Intermediate 23 (124mg) in ethyl acetate (15ml) at -78^{0}C for 3h. Nitrogen was then bubbled through the solution, triphenylphosphine (500mg) was added, the solution was warmed to room temperature and the solvent was removed *in vacuo*. The product was passed through a Varian SPE bond elution silica cartridge, eluting sequentially with dichloromethane, chloroform and diethyl ether. Fractions containing the required product were combined and evaporated to give the title compound (62mg) as white crystals. T.l.c. (diethyl ether:cyclohexane 1:1) Rf = 0.70.

Intermediate 28

5-Formyl-2-methyl-2H-pyrazole-3-carboxylic acid

A solution of Intermediate 27 (1.0g) in 1,4-dioxan (10ml) and 2M hydrochloric acid (10ml) was stirred and heated at reflux overnight. The reaction mixture was cooled and the solvent was removed *in vacuo* to leave the title compound as a pale yellow solid (0.8g). T.l.c. (dichloromethane:methanol 9:1) Rf = 0.54 (streaking).

Intermediate 29

rel-(3R,3aR,6aS)-5-(6-Isopropyl-4-methanesulfonyl-5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl)-1-methyl-1H-pyrazole-3-carbaldehyde

To a stirred solution of Intermediate 10 (812mg) in acetonitrile (45ml) was added Intermediate 28 (660mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.26g). The reaction mixture was stirred for 22h. The acetonitrile was removed *in vacuo* and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic phase was separated and passed through a Varian SPE bond elution silica cartridge, eluting sequentially with dichloromethane, chloroform, diethyl ether and ethyl acetate. Fractions containing the required product were combined and evaporated to give the title compound (955mg) as a white solid.
T.l.c. (dichloromethane:acetonitrile 9:1) Rf = 0.22.

Intermediate 30

6-Bromomethyl-nicotinic acid

A mixture of methyl 2-(bromomethyl)pyridine-5-carboxylate (3.8g) and bis(tri-^{n}butyltin)oxide (16.5ml) in toluene (80ml) was stirred and heated at 80^{0}C for 24h. The reaction mixture was cooled and extracted with 2M hydrochloric acid (2x50ml). The combined aqueous extracts were washed with toluene (40ml) and concentrated *in vacuo* to leave the title compound (3.0g) as a yellow/brown solid. Mass spec. MH^+ (found) 216,218 MH^+ (calculated) 216,218.

Intermediate 31

rel-(3R,3aR,6aS)-4-(6-Chloromethyl-pyridine-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one

To a stirred suspension of Intermediate 30 (177mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (236mg) in acetonitrile (5ml) was added Intermediate 10 (100mg). The reaction mixture was stirred for 2h. The acetonitrile was removed *in vacuo* and the residue was partitioned between dichloromethane (40ml) and 2M sodium carbonate solution (40ml). The organic phase was separated, washed with 2M sodium carbonate solution

(20ml) and water (20ml), dried ($MgSO_4$) and concentrated to leave an oil. The oil was purified using flash column chromatography on silica, with dichloromethane:acetonitrile (7:3) as the eluent, to give the title compound (76mg) as a white foam. T.l.c. (dichloromethane:acetonitrile 7:3) Rf = 0.45.

Intermediate 32

5-Bromomethyl-pyrazine-2-carboxylic acid methyl ester

A mixture of Methyl(5-methyl)pyrazine-2-carboxylate (5.3g), N-bromosuccinimide (6.3g) and dibenzoylperoxide (0.33g) in carbon tetrachloride (125ml) was stirred and heated at reflux, with irradiation using a 200W tungsten lamp, for 5h. The reaction mixture was cooled, washed with 10% sodium sulphite solution (2x20ml), water (20ml) and saturated brine (15ml), dried ($MgSO_4$) and concentrated to leave an oil. The oil was purified using flash column chromatography on silica, with cyclohexane:ethyl acetate (3:2) as the eluent, to give the title compound (3.8 g) as a brown solid. T.l.c. (cyclohexane:ethyl acetate 3:2) Rf = 0.28.

Intermediate 33

5-Bromomethyl-pyrazine-2-carboxylic acid hydrochloride

A mixture of Intermediate 32 (3.48g) and sodium hydroxide (6.00g) in water (40ml) was stirred for 2h.;acidified with 2M hydrochloric acid and extracted with ethyl acetate (4x30ml). The combined extracts were washed with saturated brine (15ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to leave the title compound (2.58g) as a pale yellow solid. Mass spec. MH^+ (found) 217,219 MH^+ (calculated) 217,219.

Intermediate 34

rel-(3R,3aR,6aS)-4-(5-Chloromethyl-pyrazine-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one

To a stirred solution of Intermediate 10 (800mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (934mg) in acetonitrile (10ml) was added Intermediate 33 (1.23g). The reaction mixture was stirred for 18h. The acetonitrile was removed *in vacuo* and the residue was partitioned between dichloromethane (20ml) and 2M sodium carbonate solution (25ml). The aqueous phase was separated and extracted with dichloromethane (2x20ml). The combined organics were washed with water (15ml) and saturated brine (15ml), dried ($MgSO_4$) and concentrated to leave an oil. The oil was purified using flash column chromatography on silica, with dichloromethane:acetonitrile (7:3) as the eluent, to give the title compound (562mg) as a white foam. T.l.c. (dichloromethane:acetonitrile 7:3) Rf = 0.42.

Intermediate 35

2R-(2,2,2-Trifluoro-acetylamino)-succinamic acid

To a stirring suspension of D-Asparagine (37.9g, powdered and dried at 110°C for 48hrs) in methanol (144ml, dried over 3A sieves for 5 hours) under an atmosphere of nitrogen was added triethylamine (40.2ml) followed by methyl trifluoroacetate (36ml). The resulting mixture was left to stir for 48hrs. To the reaction mixture was added dry methanol (145ml) then Dowex 50 resin H^+ form (115g, dried at 56°C for 24 hours). The resultant mixture was stirred for 10 minutes, filtered and the solvent removed in vacuo to give a crude white solid containing the title compound. This crude product was combined with crude product from a similar experiment and recrystallised from hot water to afford the title compound as a white crystalline solid (106g). Mass spec MNH_4^+ (found) 246 MNH_4^+ (calculated) 246

Intermediate 36

2R-(2,2,2-Trifluoro-acetylamino)-succinamic acid methyl ester

A stirring solution of Intermediate 35 (95.14g) in Methanol (1150ml, dried over 3A molecular sieves) was cooled to -70°C. Acetyl chloride (162ml) was slowly added whilst maintaining the reaction temperature below -60°C. The reaction mixture was allowed to warm to -20°C and was left for 48 hours at this temperature. The solvent was removed in vacuo to give a clear and colourless oil containing the title compound. This was triturated with diethyl ether and the resultant white solid was recrystallised from boiling water to afford the title compound as a white crystalline solid (42g). Mass spec MH^+ (found) 243 MH^+ (calculated) 243

Intermediate 37

3-Cyano-2R-(2,2,2-trifluoro-acetylamino)-propionic acid methyl ester

To a stirring suspension of Intermediate 36 (3.0g) in dichloromethane (20ml) was added pyridine (4.92ml) and p-toluene sulfonyl chloride (4.92g). More dichloromethane (15ml) was added and the brown solution left to stir at room temperature for 48 hours. The reaction mixture was diluted with dichloromethane (25ml), washed with 1M aqueous H_3PO_4 (74ml), dried (Na_2SO_4) filtered and the solvent removed in vacuo to give a crude brown solid (3.57g) containing the title compound. The crude mixture was purified by flash chromatography (SiO_2, Merck, 9385) eluting with 1:3 then 1:2½ ethyl acetate:cyclohexane. The eluent was evaporated in vacuo to give the title compound as a white crystalline solid (1.62g). T.L.C (1:1 Ethyl acetate: cyclohexane) Rf 0.5 Mass spec MNH_4^+ (found) 242 MNH_4^+ (calculated) 242

Intermediate 38

2,2,2-Trifluoro-N-(2-oxo-pyrrolidin-3R-yl)-acetamide

A solution of Intermediate 37 (200mg) in ethanol (10ml) was stirred under an atmosphere of hydrogen gas with 5% Rhodium on alumina (1.00g) for 3 hours.

The catalyst was removed by filtration and the filtrate concentrated in vacuo to afford a crude gum containing the title compound. The mixture was purified by flash chromatography (SiO_2, Merck, 9385) eluting with acetonitrile. The eluent was evaporated in vacuo to afford the title compound as a white solid (40mg). T.L.C (Acetonitrile) Rf 0.63 Mass spec MNH_4^+ (found) 214 MNH_4^+ (calculated) 214

Intermediate 39

2-Oxo-3R-(2,2,2-trifluoro-acetylamino)-pyrrolidine-1-carboxylic acid benzyl ester

To a stirring solution of Intermediate 38 (1.04g) in tetrahydrofuran cooled to -70°C, was added n-butyl lithium (1.6M in hexanes, 3.31ml). After 5 minutes benzylchloroformate (833µl) was added and the reaction mixture was allowed to warm to room temperature. After 2½ hours the reaction mixture was diluted with ethyl acetate (100ml) and washed with 1M hydrochloric acid (2x150ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give a crude orange/white solid which was purified by trituration with diethyl ether to afford the title compound as a white solid (1.25g). Mass spec MNH_4^+ (found) 348 MNH_4^+ (calculated) 348 Chiral HPLC (Chiracel AD, eluent system ethanol:heptane 15:85, flow rate = 1ml/min). Retention time of R enantiomer = 10.08 min (71.8%). Retention time of S enantiomer = 12.50 min (28.2%)

Intermediate 40

2-Ethoxy-3R-(2,2,2-trifluoro-acetylamino)-pyrrolidine-1-carboxylic acid benzyl ester

Intermediate 39 (100mg) was dissolved in dry tetrahydrofuran (1ml), cooled to -20°C and lithium borohydride (2.0M in THF, 0.15ml) added. After ½ hour ethanol (1ml) was added followed by concentrated H_2SO_4 (33µl) and the resultant stirring solution was left at room temperature for 3½ hours. The

reaction mixture was adjusted to pH8-9 by addition of saturated aqueous sodium bicarbonate and the organic solvents were removed in vacuo. The resultant residue was partitioned between ethyl acetate (20ml) and water (10ml) and the acqueous phase extracted with further ethyl acetate (10ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo to afford the title compound as a clear oil (101mg) which was used without further purification. Mass Spec. MNH_4^+ (found) 378 MNH_4^+(calculated) 378

Intermediate 40 (Alternative Synthesis)

2-Ethoxy-3R-(2,2,2-trifluoro-acetylamino)-pyrrolidine-1-carboxylic acid benzyl ester

A solution of Intermediate 39 (214.8g) in dry THF (1200ml) was stirred and cooled to -30°C. Lithium borohydride (2.0M in THF, 336ml) was added (after an initial temperature rise to -12°C, the temperature was maintained below -17°C throughout the addition). The mixture was stirred at -20°C for 90 minutes before ethanol (760ml) was added to the mixture whilst maintaining the temperature below -19°C. A cooled mixture of concentrated sulphuric acid (75ml) in ethanol (215ml) was slowly added to the mixture whilst maintaining the internal temperature below -18°C. The cooling bath was removed and the reaction left to stir for 90 minutes, whereupon the internal temperature had risen to +15°C. A saturated solution of sodium bicarbonate (1600ml) was carefully added to the mixture over 35 min before removal of the volatiles in vacuo. The residual aqueous phase was extracted with ethyl acetate (1000ml + 2x800ml) the combined extracts washed with brine (800ml), dried (Na_2SO_4) overnight and the solvent removed in vacuo to give the title compound (211.6g) as an orange oil. Tlc (4:1; CH_2C1_2:Et_20) Rf = 0.64 and 0.43

Intermediate 41

(2S,3R)-2-(rel-1S-Ethoxycarbonyl-2-methyl-propyl)-3-(2,2,2-trifluoro-acetylamino)-pyrrolidine-1-carboxylic acid benzyl ester

Intermediate 40 (90mg), (1-Ethoxy-3-methyl-but-1-enyloxy)-triisopropyl-silane (Intermediate 95 from International Patent Application No WO97/36903) (0.22g) and dichloromethane (1.1ml) were cooled to 5°C and boron trifluoride diethyrate (0.15ml) added. After 55 min the reaction was quenched with 2M aqueous sodium bicarbonate (15ml) and diluted with dichloromethane (10ml). The aqueous layer was separated and the organic layer was washed with a saturated aqueous solution of sodium chloride (10ml). The organic extract was dried ($MgSO_4$), filtered and concentrated in vacuo to afford the title compound as a colourless oil (106mg). Mass spec MH^+ (found) 445 MH^+ (calculated) 445

Intermediate 41 (Alternative Synthesis)

(2S,3R)-2-(rel-1S-Ethoxycarbonyl-2-methyl-propyl)-3-(2,2,2-trifluoro-acetylamino)-pyrrolidine-1-carboxylic acid benzyl ester

Intermediate 40 (97.9g), (Z)-(1-ethoxy-3-methyl-but-l-enyloxyl-triisopropyl-silane) (233g) and dichloromethane (600ml) were cooled to 5°C under nitrogen and boron trifluoride diethyl etherate (200ml) added over 15 minutes. After a further 15 minutes, 2M sodium carbonate (750ml) was added, keeping the temperature below 20°C. The reaction mixture was filtered through Hyflo and the solid material washed with dichloromethane (2x200ml). After adding the washes to the 2-phase mixture the aqueous layer was separated and extracted with dichloromethane (2x400ml). The combined extracts were washed with brine (2x250ml), dried ($MgSO_4$) and concentrated in vacuo to give the title compound. (154g). Tlc SiO_2 (1:3 ; ethyl acetate:cylcohexane) Rf = 0.49 (β-anomer), 0.42 (α-anomer). Mass spec. (found) MH^+ = 445 (calc) MH^+ = 445

Intermediate 42

(2S,3R)-3-Amino-2-(1-ethoxycarbonyl-2-methyl-propyl)-pyrrolidine-1-carboxylic acid benzyl ester

Intermediate 41 (97mg), potassium carbonate (300mg), ethanol (2ml) and water (2ml) were warmed at reflux for 2¼ hours. The ethanol and water were evaporated in vacuo and the residue was partitioned between ethyl acetate (10ml) and water (10ml). The aqueous extract was taken to pH9-10 by addition of 2M aqueous sodium hydroxide solution and extracted with diethyl ether (3x20ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to afford the title compound as a clear oil (56mg).

Intermediate 42 (Alternative Synthesis)
(2S,3R)-3-Amino-2-(1-ethoxycarbonyl-2-methyl-propyl)-pyrrolidine-1-carboxylic acid benzyl ester

Intermediate 41 (153g), potassium carbonate (183.3g), ethanol (1000ml) and water (1000ml) were refluxed together for 5h. The organic layer was then separated and concentrated in vacuo. The residue, the aqueous layer and brine (200ml) were extracted with ether (2x500ml, + 250ml) and the combined extracts extracted with 1M hydrochloric acid (3x500ml). The combined acidic extracts were then taken to pH8 with solid sodium hydrogen carbonate (150g) and extracted with dichloromethane (600ml, + 3x300ml). The combined dichloromethane extracts were dried ($MgSO_4$) and concentrated in vacuo to afford the title compound (87.9g). Tlc SiO_2 (100:8:1 dichloromethane:ethanol:ammonia) Rf = 0.55 Mass spec (found) MH^+ = 349 (calc) MH^+ = 349

Intermediate 43
(3aR,6S,6aS)-6-Isopropyl-5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carboxylic acid benzyl ester

Intermediate 42 (50mg) was dissolved in tetrahydrofuran (1ml) and tetramethylethylenediamine (1ml) then 1M t-butylmagnesium chloride in tetrahydrofuran (0.4ml) added. After stirring for 3 hours the reaction was quenched with saturated ammonium chloride solution (1ml). The aqueous layer was separated and extracted with ethylacetate (4ml). The combined organic extracts were evaporated in vacuo. The residue was partitioned between dichloromethane (10ml) and 2M hydrochloric acid (10ml). The aqueous phase was separated and extracted with dichloromethane (3x5ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give a crude white solid containing the title compound. Purification by flash chromatography (SiO_2, Merck, 9385) eluting with 1:1 ethyl acetate:cyclohexane afforded the title compound as a white solid (16mg). T.L.C (2:1 ethyl acetate:cyclohexane) Rf 0.38 Chiral HPLC (chiracel AD Column, eluent system ethanol:heptane 10:90, flow rate 1ml/min). Retention time of RRS lactam = 9.92min (73.6%). Retention time of SSR lactam = 13.12min (26.4%)

Intermediate 44

(3aR,6S,6aS)-6-Isopropyl-4-methanesulfonyl-5-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carboxylic acid benzyl ester

To Intermediate 43 (0.46g) in dry tetrahydrofuran (30ml) at -70°C under nitrogen was added 1M lithium hexamethyldisilazide in tetrahydrofuran (2.0ml). The solution was warmed to 0°C for 15 minutes and then recooled to -70°C when methane sulphonyl chloride (0.30ml) was added. After 1.5 hours, saturated aqueous ammonium chloride was added (30ml) and the mixture extracted with ethyl acetate (3x5ml). The combined extracts were washed with brine (2x25ml), dried ($MgSO_4$) and the solvent removed in vacuo. Flash chromatography of the residue on silica with 1:1 ethyl acetate:cyclohexane gave the title compound as a white solid (0.34g). T.l.c SiO_2 (1:1 ethyl acetate:cyclohexane) Rf 0.4 Mass spec MNH_4^+ (found) = 398 MNH_4^+ (calculated) = 398

Intermediate 45

(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one

Intermediate 44 (0.31g), 10% palladium hydroxide on carbon (0.24g) 1,4-dioxan (25ml) and ethyl acetate (25ml) were mixed under hydrogen for 3 hours. The catalyst was then removed by filtration through hyflo and the filtrate concentrated in vacuo to afford the title compound as a pale yellow solid (0.20g). T.l.c SiO_2(9:1 chloroform: methanol) Rf = 0.36 Mass spec MH^+ (found) = 247 MH^+ (calculated) = 247

Intermediate 46

(3S,3aS,6aR)-4-(5-Chloromethyl-pyrazine-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one

To a stirred solution of Intermediate 45 (900mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.25g) in acetonitrile (25ml) was added Intermediate 1 (1.16g). The reaction mixture was stirred for 1h and further acetonitrile (25ml) was added. The mixture was stirred for 19 hours before the acetonitrile was removed *in vacuo* and the residue was partitioned between dichloromethane (30ml) and 2M sodium carbonate solution (30ml). The aqueous phase was separated and extracted with dichloromethane (2x30ml). The combined organics were dried ($MgSO_4$), filtered and concentrated to leave a brown foam. The foam was purified using flash column chromatography on silica (Merck 9385), with 20% acetonitrile/dichloromethane as the eluent. The required fractions were evaporated to dryness *in vacuo* to give the title compound (1.095g) as a white foam.

T.l.c. (20% acetonitrile/dichloromethane) Rf = 0.52.

Mass spec. MH^+ (found) 401,403, MH^+ (calc) 401,403

Intermediate 47

5-[(tert-Butoxycarbonyl-cyclopropyl-amino)-methyl]-pyrazine-2-carboxylic acid

Bromine was added to a stirred suspension of 2-methylpyrazin-5-carboxylic acid (60g) in acetic acid (300ml). The reaction mixtire was then heated to 80°C for one hour. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate (250ml) and 2M aqueous HCl (250ml). The aqueous phase was extracted with further ethyl acetate (5x250ml), the combined organics were washed with 2M HCl (100ml) and saturated brine solution (100ml), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave a brown solid. The solid was stirred in acetonitrile (900ml) and triethylamine (60ml) and cyclopropylamine (30ml) were added. After stirring for 20 hours at room temperature, further cyclopropylamine (30ml) was added and the mixture stirred for a further 15 minutes. The volatiles were evaporated in vacuo, and the residue partitioned between ethyl acetate (200ml) and 2M aqueous HCl (300ml). The organic phase was extracted with further 2M HCl (4x200ml), the combined aqueous extracts were washed with ethyl acetate (50ml), cooled in an ice bath and basified with 10M aqueous sodium hydroxide (120ml). The solution was washed with ethyl acetate (3x200ml) and diethyl ether (200ml), and remaining organic volatiles were removed *in vacuo* to give a brown aqueous solution. To the solution was added 1,4-dioxane (500ml) and di-tert-butyldicarbonate (71g) and the mixture was stirred at room temperature for 20 hours. Further di-tert-butyldicarbonate (10g) was added and stirring continued for a further 24 hours. Citric acid (85g) was added to the stirred mixture before extracting it with ethyl acetate (2x200ml+3x150ml+2x100ml). The combined extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil which was purified by flash column chromatography on silica (Merck 9385), with 100:8:1 dichloromethane/methanol/acetic acid as the eluent. The required fractions were evaporated to dryness *in vacuo* to give a tan coloured solid which

was stirred vigorously in 5:1 cyclohexane/diethyl ether until finely divided. The solid was filtered off and dried *in vacuo* to give the title compound as a orange/brown solid (16.65g).

T.l.c. (100:8:1 dichloromethane/methanol/acetic acid) Rf = 0.31.

Mass spec. MH^+ (found) 294, MH^+ (calc) 294

Intermediate 48

Cyclopropyl-[5-(6S-isopropyl-4-methanesulfonyl-5-oxo-hexahydro-(3aR,6aS)-pyrrolo[3,2-b]pyrrole-1-carbonyl)-pyrazin-2-ylmethyl]-carbamic acid tert-butyl ester

Intermediate 45 (11.36g), Intermediate 47 (13.53g) and O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (19.3g) were stirred in acetonitrile (260ml) at room temperature and N,N-diisopropylethylamine (16ml) added. After stirring for two hours, the solvent was removed *in vacuo*, the residue diluted with dichloromethane (250ml) and washed with 1M sodium carbonate solution (250ml). The aqueous phase was extracted with dichloromethane (3x150ml). The combined organics were washed with 1M sodium carbonate solution (50ml), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave a yellow-brown solid. The solid was purified by flash column chromatography (Merck 9385 silica) and eluted with 50% ethyl acetate/cyclohexane, and the required fractions evaporated to dryness *in vacuo* to give the title compound as a white foam (21.55g)

Mass spec. MH^+ (found) 522, MH^+ (calc) 522.

$[\alpha]_D^{20}$ +69.5 (c = 0.8, MeCN)

Intermediate 49:

2-Pyrrolidin-1-ylmethyl-oxazole-4-carboxylic acid ethyl ester

To a stirred solution of 2-(bromomethyl)oxazole-4-carboxylic acid ethyl ester (43.9g) in acetonitrile (300ml) was added pyrrolidine (15.7ml). After stirring for

10 minutes more pyrrolidine (7.8ml) was added. After a further 30 minutes the solvent was removed *in vacuo* to leave an orange oil. The oil was partitioned between 1M sodium carbonate (400ml) and dichloromethane (500ml) and the phases were separated. The organic phase was washed with water (100ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the title compound as an orange oil (24.0g).

Mass spec MH^+ (found) = 225. MH^+ (calculated) = 225.

Intermediate 50

2-Pyrrolidin-1-ylmethyl-oxazole-4-carboxylic acid methyl ester

Pyrrolidine (14mg) was added to a suspension of potassium carbonate (25mg) and 2-(bromomethyl)oxazole-4-carboxylic acid methyl ester (27.5mg) in acetonitrile (2.5ml). The reaction mixture was stirred for 6h. The solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (15ml) and water (5ml). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound (23mg) as a pale brown oil.

Mass spec MH^+ (found) = 211. MH^+ (calculated) = 211.

The following Intermediates 51-55 were prepared in a similar manner to Intermediate 2 from 2-(bromomethyl)oxazole-4-carboxylic acid methyl ester:

Intermediate 51:

2-[(Cyclopropyl-methyl-amino)-methyl]-oxazole-4-carboxylic acid methyl ester hydrochloride

Isolated as the hydrochloride: a pale brown gum.

Mass spec MH^+ (found) = 211. MH^+ (calculated) = 211.

Intermediate 52:

2-[(Dicyclohexylamino)-methyl]-oxazole-4-carboxylic acid methyl ester

Pale yellow, waxy solid. Mass spec MH^+ (found) = 321. MH^+ (calculated) = 321.

Intermediate 53:

2-Piperidin-1-ylmethyl-oxazole-4-carboxylic acid methyl ester

Pale brown, waxy solid. Mass spec MH^+ (found) = 225. MH^+ (calculated) = 225.

Intermediate 54:

2-(4-Phenyl-piperazin-1-ylmethyl)-oxazole-4-carboxylic acid methyl ester

Pale yellow, waxy solid. Mass spec MH^+ (found) = 302. MH^+ (calculated) = 302.

Intermediate 55:

2-Dibutylaminomethyl-oxazole-4-carboxylic acid methyl ester

Viscous, pale yellow oil. Mass spec MH^+ (found) = 269. MH^+ (calculated) = 269.

Intermediate 56:

2-Pyrrolidin-1-ylmethyl-oxazole-4-carboxylic acid/2-Pyrrolidin-1-ylmethyl-oxazole-4-carboxylic acid potassium salt

First Preparation:

Potassium carbonate (14.8g) was added to a solution of Intermediate 49 (24.0g) in ethanol (150ml) and water (150ml). The reaction mixture was refluxed with stirring for 4h. The solvent was removed *in vacuo*. The orange/brown residue was azeotroped with toluene (x3) and then dried *in vacuo*. The solid obtained was stirred vigorously with ether (100ml) and filtered off before drying *in vacuo* to give a mixture of the title compound and potassium bicarbonate as a brown solid (34.5g). This material was used without further purification.

Second Preparation:

A solution of Intermediate 50 (22mg) in dioxan (1.5ml) and 1.0M. sodium hydroxide (0.3ml) was stirred for 5.0h. The solution was neutralised (pH *ca* 7) by the dropwise addition of 2.0M. hydrochloric acid. The solvents were removed *in vacuo* and the solid residue was dried further *in vacuo* to give a mixture of the title compound and sodium chloride as a pale yellow solid (40mg).
Mass spec MH^+ (found) = 197. MH^+ (calculated) = 197.

The following Intermediates 57-59 were prepared in a similar manner to Intermediate 56 (second preparation) from Intermediates 53-55 respectively.

Intermediate 57:

2-Piperidin-1-ylmethyl-oxazole-4-carboxylic acid

Cream solid. Mass spec MH^+ (found) = 211. MH^+ (calculated) = 211.

Intermediate 58:

2-(4-Phenyl-piperazin-1-ylmethyl)-oxazole-4-carboxylic acid

White solid. Mass spec MH^+ (found) = 288. MH^+ (calculated) = 288.

Intermediate 59:

2-Dibutylaminomethyl-oxazole-4-carboxylic acid

Pale yellow semi-solid. Mass spec MH^+ (found) = 255. MH^+ (calculated) = 255.

Examples

In the foregoing, dihydrochloride salts are indicated by the qualification "(2:1)" after the chemical name.

Example 1

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-pyrrolidin-1-ylmethyl-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A mixture of Intermediate 11 (80mg) and pyrrolidine (17mg) in dichloromethane (6ml) was stirred for 2h. Sodium triacetoxyborohydride (69mg) was added and stirring was continued overnight. The reaction mixture was washed with 8% aqueous sodium bicarbonate solution and water. The organic phase was passed through a Varian SPE bond elution silica cartridge (which had been pre-conditioned by eluting a column volume of dichloromethane), eluting sequentially with dichloromethane, chloroform, diethyl ether, a (1:1) mixture of diethyl ether and ethyl acetate, ethyl acetate, acetonitrile and methanol. Fractions containing the required product were combined and evaporated to give a gum which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a yellow solid (80mg). Mass Spec MH^+ (found) = 424 MH^+ (calculated) = 424 T.l.c. (dichloromethane: methanol 9:1): Rf = 0.27.

The following Examples 2-4 were prepared in a similar manner to Example 1 from Intermediate 11:

Example 2

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-morpholin-4-ylmethyl-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 440 MH^+ (calculated) = 440

T.l.c. (dichloromethane:methanol 9:1): Rf = 0.60.

Example 3

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-phenyl-piperazin-1-ylmethyl)-furan-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Red solid. Mass Spec MH^+ (found) = 515 MH^+ (calculated) = 515

T.l.c. (dichloromethane:methanol 9:1): Rf = 0.65.

Example 4

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-methyl-piperazin-1-ylmethyl)-furan-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

White solid. Mass Spec MH^+ (found) = 453 MH^+ (calculated) = 453

T.l.c. (dichloromethane:methanol 9:1): Rf = 0.16.

Example 5

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-morpholin-4-ylmethyl-furan-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A mixture of Intermediate 12 (50mg) and morpholine (13mg) in dichloromethane (3.5ml) was stirred for 1.5h. Sodium triacetoxyborohydride (43mg) was added and stirring was continued overnight. The reaction mixture was diluted with dichloromethane and extracted with 2M hydrochloric acid. The aqueous extracts were made basic with 8% aqueous sodium bicarbonate solution and extracted with dichloromethane. The dichloromethane extracts were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo* to leave a solid, which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a cream solid (32mg). Mass Spec MH^+ (found) = 440 MH^+ (calculated) = 440 T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.68.

The following Examples 6-10 were prepared in a similar manner to Example 5 from Intermediate 12:

Example 6

rel-(3R,3aR,6aS)-4-(2-Dimethylaminomethyl-furan-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 398 MH^+ (calculated) = 398

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.70.

Example 7

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-piperidin-1-ylmethyl-furan-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Beige solid. Mass Spec MH^+ (found) = 438 MH^+ (calculated) = 438

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.68.

Example 8

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-pyrrolidin-1-ylmethyl-furan-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Yellow solid. Mass Spec MH^+ (found) = 424 MH^+ (calculated) = 424

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.67.

Example 9

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[2-(4-phenyl-piperazin-1-ylmethyl)-furan-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Yellow solid. Mass Spec MH^+ (found) = 515 MH^+ (calculated) = 515

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.86.

Example 10

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[2-(4-methyl-piperazin-1-ylmethyl)-furan-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 453 MH^+ (calculated) = 453

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.50.

Example 11

rel-(3R,3aR,6aS)-4-(5-Dimethylaminomethyl-thiophene-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A mixture of Intermediate 13 (60mg), dimethylammonium chloride (36mg) and sodium triacetoxyborohydride (66mg) in dichloromethane (6ml) was stirred overnight. The reaction mixture was diluted with dichloromethane and extracted with 2M hydrochloric acid. The aqueous extracts were washed with dichloromethane then made basic with 2M sodium carbonate solution and extracted with dichloromethane. These dichloromethane extracts were washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a gum, which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a yellow solid (15mg). Mass Spec MH^+ (found) = 414 MH^+ (calculated) = 414 T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.44.

The following Example 12 was prepared in a similar manner to Example 11 from Intermediate 13:

Example 12

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-piperidin-1-ylmethyl-thiophene-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Yellow solid. Mass Spec MH^+ (found) = 454 MH^+ (calculated) = 454 T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.52.

Example 13

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(5-morpholin-4-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A mixture of Intermediate 14 (80mg), paraformaldehyde (28mg) and morpholine (40mg) in ethanol (4ml) and glacial acetic acid (1.5ml) was stirred and heated at reflux for 18h. The mixture was cooled to room temperature and partitioned between 8% aqueous sodium bicarbonate solution (25ml) and ethyl acetate (25ml). The aqueous phase was further extracted with ethyl acetate (30ml). The

combined organic phases were dried (Na_2SO_4) and the solvent evaporated *in vacuo* to leave a gum. The gum was purified by flash column chromatography (Merck 9385 silica; eluent dichloromethane:ethanol:ammonia 200:8:1) to give a white powder (21mg) which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a white powder (22mg) Melting Point 184-188° Mass Spec MH^+ (found) = 439 MH^+ (calculated) = 439

The following Examples 14-20 were prepared in a similar manner to Example 13 from Intermediate 14:

Example 14

rel-(3S,3aS,6aR)-4-(5-Dimethylaminomethyl-1H-pyrrole-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

White powder, Melting Point 233-236°C

Mass Spec MH^+ (found) = 397 MH^+ (calculated) = 397

T.l.c. (Dichloromethane:ethanol:ammonia 100:8:1) Rf = 0.45

Example 15

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(5-piperidin-1-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

White powder, Melting Point 160-164°C

Mass Spec MH^+ (found) = 437 MH^+ (calculated) = 437

Example 16

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(5-pyrrolidin-1-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

White powder, Melting Point 175-178°C

Mass Spec MH^+ (found) = 423 MH^+ (calculated) = 423

Example 17

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-phenyl-piperazin-1-ylmethyl)-1H-pyrrole-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Cream powder, Melting Point 156-160°C

Mass Spec MH^+ (found) = 514 MH^+ (calculated) = 514

Example 18

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-methyl-piperazin-1-ylmethyl)-1H-pyrrole-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Cream powder, Melting Point 177-181°C

Mass Spec MH^+ (found) = 452 MH^+ (calculated) = 452

Example 19

rel-(3S,3aS,6aR)-4-(5-Dibutylaminomethyl-1H-pyrrole-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Pale yellow powder, Melting Point 116-120°C

Mass Spec MH^+ (found) = 481 MH^+ (calculated) = 481

Example 20

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(5-methylaminomethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream powder, Melting Point 210-215°C

Mass Spec MH^+ (found) = 383 MH^+ (calculated) = 383

Example 21

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-piperidin-1-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A mixture of Intermediate 15 (40mg), paraformaldehyde (15mg) and piperidine (23mg) in ethanol (3ml) and glacial acetic acid (1.5ml) was stirred and heated at reflux for 22h. The mixture was cooled to room temperature and partitioned between 8% aqueous sodium bicarbonate solution (30ml) and ethyl acetate (20ml). The organic phase was dried (Na_2SO_4) and the solvent evaporated *in vacuo* to leave a gum. The gum was purified by flash column chromatography (Merck 9385 silica; eluent dichloromethane:ethanol:ammonia 100:8:1) to give a white solid (26mg) which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a white powder (28mg). Melting Point 149-153°C Mass Spec MH^+ (found) = 451 MH^+ (calculated) = 451

The following Examples 22-25 were prepared in a similar manner to Example 21 from Intermediate 15:

Example 22

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-morpholin-4-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Pale yellow powder, Melting Point 150-154°C

Mass Spec MH^+ (found) = 453 MH^+ (calculated) = 453

Example 23

rel-(3S,3aS,6aR)-4-(5-Dimethylaminomethyl-1-methyl-1H-pyrrole-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

White powder, Melting Point 137-141°C

Mass Spec MH^+ (found) = 411 MH^+ (calculated) = 411

Example 24

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-pyrrolidin-1-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Yellow powder, Melting Point 135-139°C

Mass Spec MH^+ (found) = 437 MH^+ (calculated) = 437

Example 25

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-methylaminomethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

White powder, Melting Point 216-218°C

Mass Spec MH^+ (found) = 397 MH^+ (calculated) = 397

Example 26

rel-(3S,3aS,6aR)-4-(4-Dimethylaminomethyl-1H-pyrrole-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A mixture of Intermediate 14 (80mg), paraformaldehyde (25mg), dimethylammonium chloride (38mg) and activated 4 Angstrom molecular sieves (200mg) in ethanol (10ml) was stirred and heated at reflux for 24h. The mixture was cooled to room temperature and the solvent was evaporated *in vacuo* to leave a gum. The gum was purified by flash column chromatography, using two columns (Merck 9385 silica; eluent dichloromethane:ethanol:ammonia; 80:8:1 for the first column, 100:8:1 for the second column) to isolate a white powder (16mg) which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a white powder (16mg). Melting Point 160-165°C

Mass Spec MH^+ (found) = 397 MH^+ (calculated) = 397

T.l.c (dichloromethane:ethanol:ammonia 100:8:1) Rf = 0.20

Example 27

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-pyrrolidin-1-ylmethyl-thiazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A solution of Intermediate 18 (387mg) and triethylamine (202mg) in dichloromethane (42ml) was stirred and treated with methanesulphonyl chloride (172mg). The reaction mixture was stirred for 1.5h. An aliquot (7ml) was removed and added to a stirred solution of pyrrolidine (30mg) in dichloromethane (2ml). The solution was stirred for 2 days. Aqueous 8% sodium bicarbonate solution (12ml) was added, with vigorous stirring. The aqueous phase was separated and extracted with dichloromethane (15ml). The organic phases were combined and dried (Na_2SO_4). The solvent was removed *in vacuo* to leave a semi-solid, which was triturated in diethyl ether (10ml) to give a solid suspension. Cyclohexane (10ml) was added to the suspension and the solvent was decanted. The residual solid was dried *in vacuo* to leave a white solid which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a cream powder (51mg). Melting Point 130-134°C Mass Spec MH^+ (found) = 441 MH^+ (calculated) = 441

The following Examples 28-35 were prepared in a similar manner to Example 27 from Intermediate 18:

Example 28

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-morpholin-4-ylmethyl-thiazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Pale buff powder, Melting Point 138-143°C

Mass Spec MH^+ (found) = 457 MH^+ (calculated) = 457

Example 29

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-piperidin-1-ylmethyl-thiazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream powder, Melting Point 153-158°C

Mass Spec MH^+ (found) = 455 MH^+ (calculated) = 455

Example 30

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-[2-(4-methyl-piperazin-1-ylmethyl)-thiazole-4-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

White powder, Melting Point 153-158°C

Mass Spec MH^+ (found) = 470 MH^+ (calculated) = 470

Example 31

rel-(3S,3aS,6aR)-4-(2-Cyclopropylaminomethyl-thiazole-4-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Pale grey powder, Melting Point 160-163°C

Mass Spec MH^+ (found) = 427 MH^+ (calculated) = 427

Example 32

rel-(3S,3aS,6aR)-4-{2-[(4-Fluoro-benzylamino)-methyl]-thiazole-4-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Pale yellow powder, Melting Point 141-145°C

Mass Spec MH^+ (found) = 495 MH^+ (calculated) = 495

Example 33

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-[2-(4-phenyl-piperazin-1-ylmethyl)-thiazole-4-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Cream powder, Melting Point 156-161°C

Mass Spec MH^+ (found) = 532 MH^+ (calculated) = 532

Example 34

rel-(3S,3aS,6aR)-4-(2-Dibutylaminomethyl-thiazole-4-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Pale yellow powder, Melting Point 81-86°C

Mass Spec MH^+ (found) = 499 MH^+ (calculated) = 499

Example 35

rel-(3R,3aR,6aS)-3-Isopropyl-4-{2-[(1-isopropyl-2-methyl-propylamino)-methyl]-thiazole-4-carbonyl}-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream powder, Melting Point 192-195°C

Mass Spec MH^+ (found) = 485 MH^+ (calculated) = 485

Example 36

rel-(3S,3aS,6aR)-4-(2-Dimethylaminomethyl-thiazole-4-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Oxalyl chloride (127mg) was added to a stirred suspension of Intermediate 19 (125mg) in dichloromethane (10ml), followed by dimethylformamide (1 drop). The reaction mixture was stirred for 1.0h. then concentrated *in vacuo*. The residue was suspended in dichloromethane (15ml) and treated, with stirring, with Intermediate 10 (43mg) and sodium bicarbonate (175mg). After stirring the reaction mixture for 16h aqueous 8% sodium bicarbonate solution (12ml) was added. The aqueous phase was separated and extracted with dichloromethane (15ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give a brown gum. The gum was chromatographed on silica (Merck 9385), using a mixture of dichloromethane, ethanol and ammonia (160:8:1) as the eluent, to

give a brown gum, which was treated with 1.0M. hydrogen chloride in ether to give the title compound (23mg) as a cream solid. Melting Point 122-127°C
Mass Spec MH^+ (found) = 415 MH^+ (calculated) = 415

Example 37
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-morpholin-4-ylmethyl-isoxazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride
A mixture of Intermediate 21 (50mg) and morpholine (13mg) in dichloromethane (5ml) was stirred for 1.5h. Sodium triacetoxyborohydride (43mg) was added and stirring was continued for 2.5h. The reaction mixture was washed with 8% aqueous sodium bicarbonate solution. The organic phase was passed through a Varian SPE bond elution silica cartridge (which had been pre-conditioned by eluting a column volume of dichloromethane), eluting sequentially with dichloromethane, chloroform, diethyl ether, ethyl acetate, acetonitrile and methanol. Fractions containing the required product were combined and evaporated to give a foam which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a white solid (39mg).
Mass Spec MH^+ (found) = 441 MH^+ (calculated) = 441
T.l.c. (dichloromethane:methanol 9:1): Rf = 0.65.

The following Examples 38-44 were prepared in a similar manner to Example 37 from Intermediate 21:

Example 38
rel-(3R,3aR,6aS)-4-(5-Dimethylaminomethyl-isoxazole-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride
White solid. Mass Spec MH^+ (found) = 399 MH^+ (calculated) = 399
T.l.c. (dichloromethane:methanol 9:1): Rf = 0.58.

Example 39

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-pyrrolidin-1-ylmethyl-isoxazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 425 MH^+ (calculated) = 425

T.l.c. (dichloromethane:methanol 9:1): Rf = 0.55.

Example 40

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-piperidin-1-ylmethyl-isoxazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

White solid. Mass Spec MH^+ (found) = 439 MH^+ (calculated) = 439

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.52.

Example 41

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-methyl-piperazin-1-ylmethyl)-isoxazole-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

White solid. Mass Spec MH^+ (found) = 454 MH^+ (calculated) = 454

T.l.c. (dichloromethane:methanol 9:1): Rf = 0.13.

Example 42

rel-(3R,3aR,6aS)-4-{5-[(4-Fluoro-benzylamino)-methyl]-isoxazole-3-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 479 MH^+ (calculated) = 479

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.59.

Example 43

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-phenyl-piperazin-1-ylmethyl)-isoxazole-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 516 MH^+ (calculated) = 516
T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.62.

Example 44

rel-(3R,3aR,6aS)-4-(5-Dibutylaminomethyl-isoxazole-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 483 MH^+ (calculated) = 483
T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.75.

Example 45

rel-(3R,3aR,6aS)-4-(5-Dimethylaminomethyl-1-methyl-1H-pyrazole-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A mixture of Intermediate 26 (50mg) and dimethylammonium chloride (32mg) in dichloromethane (5ml) was stirred for 2h. Sodium triacetoxyborohydride (55mg) was added and stirring was continued for 3h. The reaction mixture was washed with 8% aqueous sodium bicarbonate solution. The organic phase was passed through a Varian SPE cartridge (which had been pre-conditioned by eluting through a column volume of dichloromethane), eluting with dichloromethane, chloroform, diethyl ether, ethyl acetate, acetonitrile and methanol. Fractions containing the required product were combined and evaporated to give a pale brown oil which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a cream solid (28mg). Mass Spec MH^+ (found) = 412 MH^+ (calculated) = 412 T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.68.

The following Examples 46-49 were prepared in a similar manner to Example 45 from Intermediate 26:

Example 46

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-pyrrolidin-1-ylmethyl-1H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 438 MH^+ (calculated) = 438

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.65.

Example 47

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-morpholin-4-ylmethyl-1H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 454 MH^+ (calculated) = 454

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.69.

Example 48

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-piperidin-1-ylmethyl-1H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 452 MH^+ (calculated) = 452

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.67.

Example 49

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[1-methyl-5-(4-methyl-piperidin-1-ylmethyl)-1H-pyrazole-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid. Mass Spec MH^+ (found) = 466 MH^+ (calculated) = 466

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.78.

Example 50

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[2-methyl-5-(4-phenyl-piperazin-1-ylmethyl)-2H-pyrazole-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A mixture of Intermediate 29 (50mg) and phenylpiperazine (28mg) in dichloromethane (5ml) was stirred for 2h. Sodium triacetoxyborohydride (50mg) was added and stirring was continued overnight. The reaction mixture was washed with 8% aqueous sodium bicarbonate solution. The organic phase was passed through a Varian SPE cartridge (which had been pre-conditioned by eluting through a column volume of dichloromethane), eluting sequentially with dichloromethane, chloroform, diethyl ether, ethyl acetate, acetonitrile and methanol. Fractions containing the required product were combined and evaporated to give a gum which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a dark yellow solid (16mg). Mass Spec MH^+ (found) = 529 MH^+ (calculated) = 529 T.l.c. (dichloromethane: ethanol:ammonia 100:8:1): Rf = 0.77.

The following Examples 51-55 were prepared in a similar manner to Example 50 from Intermediate 29:

Example 51

rel-(3R,3aR,6aS)-4-(5-Dimethylaminomethyl-2-methyl-2H-pyrazole-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Yellow solid. Mass Spec MH^+ (found) = 412 MH^+ (calculated) = 412 T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.66.

Example 52

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-methyl-5-pyrrolidin-1-ylmethyl-2H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Yellow solid. Mass Spec MH^+ (found) = 438 MH^+ (calculated) = 438

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.63.

Example 53

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-methyl-5-morpholin-4-ylmethyl-2H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Yellow solid. Mass Spec MH^+ (found) = 454 MH^+ (calculated) = 454

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.65.

Example 54

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-methyl-5-piperidin-1-ylmethyl-2H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Yellow solid. Mass Spec MH^+ (found) = 452 MH^+ (calculated) = 452

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.65.

Example 55

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[2-methyl-5-(4-methyl-piperazin-1-ylmethyl)-2H-pyrazole-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Yellow solid. Mass Spec MH^+ (found) = 467 MH^+ (calculated) = 467

T.l.c. (dichloromethane:ethanol:ammonia 100:8:1): Rf = 0.29.

Example 56

rel-(3R,3aR,6aS)-4-{6-[(Dicyclohexylamino)-methyl]-pyridine-3-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

A mixture of Intermediate 31 (90mg), dicyclohexylamine (104.6µl), sodium iodide (79mg) and potassium carbonate (169mg) in acetonitrile (2ml) was stirred for 5 days. The solvent was evaporated and the residue was partitioned between 2M sodium carbonate solution (2ml) and dichloromethane (3ml). The phases were separated. The organic phase was passed through a Varian SPE cartridge (which had been pre-conditioned by eluting through a column volume of dichloromethane), eluting sequentially with dichloromethane, chloroform, diethyl ether, ethyl acetate, acetonitrile and methanol. Fractions containing the required product were combined and evaporated to give a colourless oil which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a cream solid (60mg). Mass Spec MH^+ (found) = 545 MH^+ (calculated) = 545 T.l.c. (ethyl acetate): Rf = 0.47.

The following Examples 57-64 were prepared in a similar manner to Example 56 from Intermediate 31:

Example 57

rel-(3R,3aR,6aS)-4-(6-Dibutylaminomethyl-pyridine-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Brown glass. Mass Spec MH^+ (found) = 493 MH^+ (calculated) = 493

T.l.c. (ethyl acetate) Rf = 0.49

Example 58

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(6-morpholin-4-ylmethyl-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Orange glass. Mass Spec MH^+ (found) = 451 MH^+ (calculated) = 451

T.l.c. (ethyl acetate) Rf = 0.38

Example 59

rel-(3R,3aR,6aS)-4-(6-Cyclopropylaminomethyl-pyridine-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Pale brown solid. Mass Spec MH^+ (found) = 421 MH^+ (calculated) = 421

T.l.c. (ethyl acetate) Rf = 0.36

Example 60

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(6-piperidin-1-ylmethyl-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Green solid. Mass Spec MH^+ (found) = 449 MH^+ (calculated) = 449

T.l.c. (ethyl acetate) Rf = 0.36

Example 61

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[6-(4-methyl-piperazin-1-ylmethyl)-pyridine-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Orange glass. Mass Spec MH^+ (found) = 464 MH^+ (calculated) = 464

T.l.c. (ethyl acetate) Rf = 0.05

Example 62

rel-(3R,3aR,6aS)-3-Isopropyl-4-{6-[(1-isopropyl-2-methyl-propylamino)-methyl]-pyridine-3-carbonyl}-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Yellow solid. Mass Spec MH^+ (found) = 479 MH^+ (calculated) = 479

T.l.c. (ethyl acetate) Rf = 0.42

Example 63

rel-(3R,3aR,6aS)-4-(6-Dimethylaminomethyl-pyridine-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Pale yellow glass. Mass Spec MH^+ (found) = 409 MH^+ (calculated) = 409

T.l.c. (ethyl acetate) Rf = 0.21

Example 64

rel-(3R,3aR,6aS)-4-{6-[(4-Fluoro-benzylamino)-methyl]-pyridine-3-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Yellow/brown solid. Mass Spec MH^+ (found) = 489 MH^+ (calculated) = 489

T.l.c. (ethyl acetate) Rf = 0.41

Example 65

rel-(3R,3aR,6aS)-4-(5-Cyclopropylaminomethyl-pyrazine-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

A mixture of Intermediate 34 (45mg), cyclopropylamine (23.3μl) and sodium iodide (25mg) in dichloromethane (1ml) was stirred for 18h. More cyclopropylamine (23.3μl) was added and stirring was continued for a further 24h. The reaction mixture was partitioned between 2M sodium carbonate solution (3ml) and dichloromethane (3ml). The phases were separated. The organic phase was passed through a Varian SPE cartridge (which had been pre-conditioned by eluting through a column volume of dichloromethane), eluting sequentially with dichloromethane, chloroform, diethyl ether, ethyl acetate, acetonitrile and methanol. Fractions containing the required product were combined and evaporated to give a pale brown oil (17mg) which was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a brown solid (20mg). Mass Spec MH^+ (found) = 422 MH^+ (calculated) = 422

T.l.c. (ethyl acetate): Rf = 0.12.

The following Examples 66-75 were prepared in a similar manner to Example 65 from Intermediate 34:

Example 66

rel-(3R,3aR,6aS)-4-(5-Dibutylaminomethyl-pyrazine-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Pale brown solid. Mass Spec MH^+ (found) = 494 MH^+ (calculated) = 494

T.l.c. (ethyl acetate) Rf = 0.63

Example 67

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-morpholin-4-ylmethyl-pyrazine-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Cream solid. Mass Spec MH^+ (found) = 452 MH^+ (calculated) = 452

T.l.c. (ethyl acetate) Rf = 0.12

Example 68

rel-(3R,3aR,6aS)-4-{5-[(Dicyclohexylamino)-methyl]-pyrazine-2-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Cream solid. Mass Spec MH^+ (found) = 546 MH^+ (calculated) = 546

T.l.c. (ethyl acetate) Rf = 0.65

Example 69

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-piperidin-1-ylmethyl-pyrazine-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Cream solid. Mass Spec MH^+ (found) = 450 MH^+ (calculated) = 450

T.l.c. (ethyl acetate) Rf = 0.12

Example 70

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-methyl-piperazin-1-ylmethyl)-pyrazine-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Brown glass. Mass Spec MH^+ (found) = 465 MH^+ (calculated) = 465

T.l.c. (ethyl acetate) Rf = 0.02

Example 71

rel-(3R,3aR,6aS)-3-Isopropyl-4-{5-[(1-isopropyl-2-methyl-propylamino)-methyl]-pyrazine-2-carbonyl}-1-methanesulfonyl-hexahydro-pyrrolo[3,2-]pyrrol-2-one hydrochloride (1:2)

Cream solid. Mass Spec MH^+ (found) = 480 MH^+ (calculated) = 480

T.l.c. (ethyl acetate) Rf = 0.45

Example 72

rel-(3R,3aR,6aS)-4-(5-Dimethylaminomethyl-pyrazine-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Pale brown solid. Mass Spec MH^+ (found) = 410 MH^+ (calculated) = 410

T.l.c. (ethyl acetate) Rf = 0.06

Example 73

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-phenyl-piperazin-1-ylmethyl)-pyrazine-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Pale yellow glass. Mass Spec MH^+ (found) = 527 MH^+ (calculated) = 527

T.l.c. (ethyl acetate) Rf = 0.27

Example 74

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-pyrrolidin-1-ylmethyl-pyrazine-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Orange/brown solid. Mass Spec MH^+ (found) = 436 MH^+ (calculated) = 436

T.l.c. (ethyl acetate) Rf = 0.05

Example 75

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-methylaminomethyl-pyrazine-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride (1:2)

Pale brown solid. Mass Spec MH^+ (found) = 396 MH^+ (calculated) = 396

T.l.c. (ethyl acetate) Rf = 0.02

Example 76

(3S,3aS,6aR)-4-(5-Cyclopropylaminomethyl-pyrazine-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A solution of Intermediate 48 (21.53g) and 4.0M HCl in 1,4-dioxan (200ml) was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* to give an off-white solid. The solid was recrystallised from hot 5% water/2-propanol (2.3l) to give the title (single enantiomer) compound (15.54g) as a white solid.

T.l.c. (Silica, eluent 200:8:1 dichloromethane:ethanol:0.880 ammonia) Rf = 0.21.

Mass spec. MH^+ (found) 422.19, MH^+ (calc) 422.19

$[\alpha]_D^{20}$ +51.3 (c = 0.9, 1:1 H_2O/MeCN)

M.pt. 183-185°C

Circular Dichroism: λ_{max}250.2nm (ΔE -1.34$M^{-1}cm^{-1}$)

λ_{max}285.4nm (ΔE +0.99$M^{-1}cm^{-1}$), (MeCN/H_2O)

Elemental analysis: Found C, 47.4; H, 6.4; N, 14.3; S, 6.5; Cl, 7.8; water, 4.9% ($C_{19}H_{27}Cl\ N_5O_4S$ .HCl.1.3H_2O requires C, 47.4; H, 6.4; N, 14.6; S, 6.7; Cl, 7.4; water, 4.9%).

Example 76 (alternative preparation)

A mixture of Intermediate 46 (1.056g), cyclopropylamine (0.73ml) and potassium iodide (481mg) in acetonitrile (25ml) was stirred for 3 hours. The solvent was evaporated *in vacuo* and the mixture partitioned between sat. sodium bicarbonate solution (20ml) and dichloromethane (20ml). The phases were separated. The aqueous phase was further extracted with dichloromethane (2x20ml) The combined organics were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave an oil. The oil was purified by flash column chromatography (Merck 9385 silica) and eluted with 200:8:1 dichloromethane:ethanol:0.880 ammonia. Fractions containing the required product were combined and evaporated to give a white solid (924mg) which was dissolved in dichloromethane (10ml) and treated with 1.0M. hydrogen chloride in diethyl ether (10ml) to give the title (single enantiomer) compound as a white solid (1.00g).

Example 77:

(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-pyrrolidin-1-ylmethyl-oxazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Intermediate 56 (32.2g) was added rapidly to a stirred solution of 1-hydroxybenzotriazole (13.0g) in acetonitrile (350ml). A solution of (3S,3aS,6aR)-3-isopropyl-1-methanesulfonyl-hexahydropyrrolo[3,2-b]pyrrol-2-one (Intermediate 122 from International Patent Application WO97/36903) (21.7g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (37.0g) in acetonitrile (70ml) was then added and the reaction mixture was stirred for 20h. The solvent was removed *in vacuo* and the residue was partitioned between dichloromethane (900ml) and 1.0M. sodium carbonate solution (600ml). The aqueous phase was separated and extracted with dichloromethane (150ml). The combined organics were washed with brine (250ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown solid. The solid was purified by flash column chromatography (Merck 9385 silica; eluent

dichloromethane:ethanol:ammonia 150:8:1 to 135:8:1) to give a cream solid (29.3g). The solid was dissolved in dichloromethane (150ml) and treated with 1.0M. hydrogen chloride in ether (75ml). The solvent was removed *in vacuo* to leave a solid which was again dissolved in dichloromethane (150ml) and treated with 1.0M. hydrogen chloride in ether (75ml). The solvent was removed *in vacuo* to leave a solid which was recrystallised from acetone to give the title compound (26.3g) as a white solid.

Melting point 156-158^{0}C.

T.l.c. (Silica; dichloromethane:ethanol:ammonia 100:8:1; double elution) Rf = 0.66.

^{1}H NMR (400 MHz; D-6 DMSO): d 8.78 (s, 1H), 4.68 (s, 2H), 4.13 (ddd, J= 11,11,7 Hz, 1H), 4.08 (dd, J=11,10 Hz, 1H), 3.80 (ddd, J=12,10.5,5.5 Hz, 1H), 3.60 (m, 2H), 3.55 (dd, J=12,10.5 Hz, 1H), 3.31 (s, 3H), 3.20 (m, 2H), 3.03 (dd, J=12,2.5 Hz, 1H), 2.88 (md, J=2.5 Hz, 1H), 2.34 (m, 1H), 2.12 (m, 1H), 1.96 (m, 4H), 1.19 (d, J=7 Hz, 3H), 0.98 (d, J=7 Hz, 3H). Contains 0.16 Mol. % acetone.

Infra-red (KBr diffuse reflectance) 3633, 3474, 3149, 3102, 2956, 2882, 2668, 2576, 2475, 1747, 1709, 1639, 1634, 1567, 1442, 1380, 1347, 1161, 1146, 967, 810, 547 cm^{-1}.

Mass spec MH^+ (found) = 425.186372. MH^+ (calculated) = 425.185867 (error 1.2ppm).

Combustion analysis.

Found: C, 48.65; H, 6.39; N, 11.41; S, 6.19; Cl, 7.13%.

$C_{19}H_{28}N_4O_5S.HCl.0.75H_2O.0.2Me_2CO$ requires: C, 48.43; H, 6.57; N, 11.53; S, 6.60; Cl, 7.29%.

Example 78:

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-pyrrolidin-1-ylmethyl-oxazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A stirred suspension of Intermediate 56 (second preparation: 40mg) in dichloromethane (4ml) was treated with oxalyl chloride (63mg) followed by dimethylformamide (1 drop). The reaction mixture was stirred for 1.5h. The solvent was removed in vacuo and replaced by toluene (10 ml). The resultant suspension was triturated vigorously for 10 min. The toluene was removed in vacuo to leave a gum which was suspended in dichloromethane (5 ml) and treated with Intermediate 10 (20mg) and sodium bicarbonate (35mg). The reaction mixture was stirred for 3.75h. then partitioned between dichloromethane (2x10ml) and water (5ml). The combined organics were dried (Na_2SO_4) and concentrated in vacuo to leave a solid. The solid was triturated in ether (4ml) for 10 min. The ether was decanted. The residue was dried in vacuo to leave a white powder. The powder was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a cream powder (17mg).
Melting point 116-120°C.
Mass spec MH^+ (found) = 425. MH^+ (calculated) = 425.

The following Examples 79-81 were prepared in a similar manner to Example 78 from Intermediate 10 and Intermediates 57-59 respectively:

Example 79:
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-piperidin-1-ylmethyl-oxazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride
White powder, melting point 140-143°C.
Mass spec MH^+ (found) = 439. MH^+ (calculated) = 439

Example 80:
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-[2-(4-phenyl-piperazin-1-ylmethyl)-oxazole-4-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

Cream solid, melting point 156-160°C.

Mass spec MH^+ (found) = 516. MH^+ (calculated) = 516.

Example 81:

rel-(3S,3aS,6aR)-4-(2-Dibutylaminomethyl-oxazole-4-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

White powder, melting point 122-126°C.

Mass spec MH^+ (found) = 483. MH^+ (calculated) = 483.

Example 82:

rel-(3S,3aS,6aR)-4-{2-[(Cyclopropyl-methyl-amino)-methyl]-oxazole-4-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride

A solution of Intermediate 51 (21mg) in dioxan (1.5ml) and 1.0M. sodium hydroxide (0.4ml) was stirred for 3.5h. Hydrochloric acid (0.35ml) was added with stirring. The solvents were removed in vacuo. The residue was triturated in dioxan (3ml) for 5 min. The solvent was removed in vacuo. The trituration was repeated using more dioxan (3ml). The solvent was removed in vacuo and the residue dried under vacuum to give a solid. A stirred suspension of this solid in dichloromethane (3ml) was treated with oxalyl chloride (50mg) followed by dimethylformamide (1 drop). The reaction mixture was stirred for 1.0h. The solvent was removed in vacuo and the residue was triturated vigorously in a (1:1) mixture of dichloromethane and toluene (10ml) for 5 min. The solvents were removed in vacuo to leave a gum which was suspended in dichloromethane (5 ml) and treated with Intermediate 10 (18mg) and sodium bicarbonate (35mg). The reaction mixture was stirred for 0.75h., left at room temperature for 3 days, diluted with dichloromethane (10ml) and washed with water (10ml). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to leave a gum. The gum was purified by flash column chromatography (Merck

9385 silica; eluent dichloromethane:ethanol:ammonia 150:8:1) to give a white powder. The powder was treated with 1.0M. hydrogen chloride in diethyl ether to give the title compound as a white powder (7mg).
Melting point 116-119°C.
Mass spec MH^+ (found) = 425. MH^+ (calculated) = 425.

The following Example 83 was prepared in a similar manner to Example 82 from Intermediate 10 and Intermediate 52:

Example 83:
rel-(3S,3aS,6aR)-4-{2-[(Dicyclohexylamino)-methyl]-oxazole-4-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride
White powder, melting point 130-133°C.
Mass spec MH^+ (found) = 535. MH^+ (calculated) = 535.

Biological Data

1. The compounds of Examples 1-83 were tested in the in vitro elastase test described earlier in the description. The IC_{50} values are given in the following table:

Example	IC_{50} (μM)	Example	IC_{50} (μM)
1	0.123	39	0.021
2	0.081	40	0.030
3	0.164	41	0.014
4	0.065	42	0.057
5	0.039	43	0.051
6	0.071	44	0.099
7	0.082	45	0.019
8	0.086	46	0.014
9	0.129	47	0.024
10	0.114	48	0.030
11	0.139	49	0.051
12	0.104	50	0.054
13	0.032	51	0.021
14	0.021	52	0.012
15	0.021	53	0.015
16	0.019	54	0.011
17	0.068	55	0.020
18	0.022	56	0.038
19	0.057	57	0.041
20	0.013	58	0.045
21	0.029	59	0.028
22	0.043	60	0.037
23	0.026	61	0.030
24	0.024	62	0.041
25	0.009	63	0.025
26	0.017	64	0.048
27	0.008	65	0.013
28	0.011	66	0.076
29	0.014	67	0.019
30	0.017	68	0.087
31	0.016	69	0.022
32	0.009	70	0.013
33	0.005	71	0.050
34	0.013	72	0.012
35	0.056	73	0.074
36	0.013	74	0.012
37	0.017	75	0.093
38	0.014	76	0.011

Example	IC_{50} (μM)
77	0.010
78	0.014
79	0.016
80	0.100
81	0.076
82	0.084
83	0.137

2. Compounds of Examples 1, 2, 11, 12, 13, 15, 16, 17, 27, 28, 29, 31, 33, 34, 35, 37-50, 56, 57, 59, 60, 62-69, 72, 73, 76, 78, 80 and 81 were tested in an *in vivo* hamster test described above at an effective dose of less than 10mg/kg, and gave a duration of effect lasting at least 6 hours.

3. The compounds of Examples 1 to 83 were tested in the human whole blood elastase inhibition assay described earlier in the description. The IC_{50} values are given in the table below.

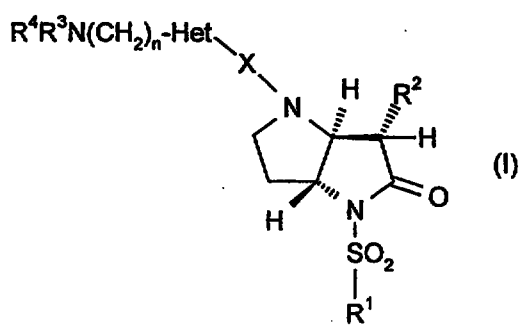
Example	IC_{50} (μM)	Example	IC_{50} (μM)
1	0.355	41	1.76
2	1.882	42	0.43
3	2.195	43	0.429
4	4.185	44	0.528
5	3	45	0.518
6	4.015	46	0.524
7	3.04	47	1.043
8	3.46	48	0.414
9	3.615	49	0.539
10	5.565	50	1.92
11	1.16	51	>10
12	2.4	52	7.637
13	1.103	53	8.23
14	1.885	54	4.205
15	0.452	55	>10
16	0.774	56	0.293
17	0.316	57	0.193
18	2.925	58	2.44
19	0.408	59	0.394
20	6.405	60	0.605
21	0.317	61	5.898
22	0.453	62	0.252
23	0.364	63	1.62
24	0.306	64	0.521
25	1.64	65	0.333
26	>10	66	0.217
26	0.704	67	0.878
28	1.125	68	0.221
29	0.311	69	0.264
30	1.683	70	3.215
31	0.896	71	0.205
32	0.427	72	0.322
33	0.257	73	0.282
34	0.546	74	0.205
35	0.81	75	5.025
36	0.296	76	0.139
37	1.187	77	0.245
38	0.224	78	0.411
39	0.358	79	0.502
40	0.222	80	0.4

Example	IC50 (μM)
81	0.296
82	0.717
83	0.55

* C L M S *

Claims

1. A compound of formula (I)



(I)

(relative stereochemistry indicated)

wherein:

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

R^2 represents C_{2-4}alkyl or C_{2-4}alkenyl;

X represents CO or SO_2;

Het represents an optionally substituted 5 to 10 membered monocylic or bicyclic aromatic ring system containing 1 to 4 heteroatoms selected from O, N and S;

n represents an integer 0 to 4;

R^3 and R^4 independently represent hydrogen, C_{1-8}alkyl, $-(CH_2)_{1-4}CONR^5R^6$, COC_{1-4}alkyl or $(CH_2)_{0-2}$ Ph where Ph represents phenyl optionally substituted by one or more C_{1-4}alkyl or halogen groups or NR^3 R^4 together represents azetidinyl, pyrrolidinyl, piperidinyl, azepinyl, morpholinyl, piperazinyl optionally N-substituted by C_{1-6}alkyl, phenyl (optionally substituted by halogen or C_{1-4}alkyl) or benzyl (optionally substituted on the benzene ring by halogen or C_{1-4}alkyl) or NR^3R^4 together represents a ring as just described save that it is substituted on carbon by one or more C_{1-4}alkyl, $CONR^5R^6$ or $COOR^6$ groups;

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

and salts and solvates thereof.



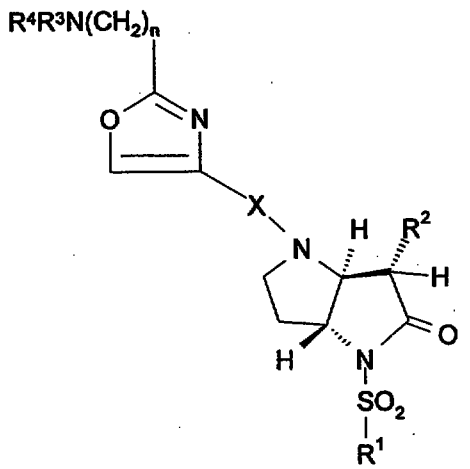
2. A compound of formula (I) according to claim 1 herein Het represents a 5 or 6 membered monocyclic aromatic ring containing 1 or 2 heteroatoms selected from O, N and S.

3 A compound of formula (I) according to claim 2 wherein Het represents thiazolyl, isoxazolyl, pyrazolyl or pyrazinyl.

4. A compound of formula (I) according to claim 2 wherein Het represents pyridin-3-yl.

5. A compound of formula (I) according to claim 2 wherein Het represents oxazolyl.

6. A compound of formula (I) according to claim 1, 2 or 5 which is a compound of formula (IA)



(IA)

(relative stereochemistry indicated).

7. A compound of formula (I) according to any one of the preceding claims wherein R^2 represents isopropyl or propyl.

8. A compound of formula (I) according to to any one of the preceding claims wherein R^2 represents isopropyl.

9. A compound of formula (I) according to any one of the preceding claims wherein R^1 represents methyl or ethyl.

10. A compound of formula (I) according to claim 9 wherein R^1 represents methyl.



11. A compound of formula (I) according to any one of the preceding claims wherein X represents CO.

12. A compound of formula (I) according to any one of the preceding claims wherein n represents 1 to 3.

13. A compound of formula (I) according to any one of the preceding claims wherein R^3 and R^4 independently represent hydrogen or C_{1-8}alkyl or NR^3R^4 represents pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl optionally N-substituted by C_{1-8}alkyl or phenyl (optionally substituted by halogen or C_{1-4}alkyl).

14. A compound of formula (I) according to claim 1 which is

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-pyrrolidin-1-ylmethyl-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-morpholin-4-ylmethyl-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-phenyl-piperazin-1-ylmethyl)-furan-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-methyl-piperazin-1-ylmethyl)-furan-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-morpholin-4-ylmethyl-furan-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-4-(2-Dimethylaminomethyl-furan-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-piperidin-1-ylmethyl-furan-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-pyrrolidin-1-ylmethyl-furan-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[2-(4-phenyl-piperazin-1-ylmethyl)-furan-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[2-(4-methyl-piperazin-1-ylmethyl)-furan-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;



rel-(3R,3aR,6aS)-4-(5-Dimethylaminomethyl-thiophene-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-piperidin-1-ylmethyl-thiophene-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(5-morpholin-4-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-4-(5-Dimethylaminomethyl-1H-pyrrole-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(5-piperidin-1-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(5-pyrrolidin-1-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-phenyl-piperazin-1-ylmethyl)-1H-pyrrole-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-methyl-piperazin-1-ylmethyl)-1H-pyrrole-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-4-(5-Dibutylaminomethyl-1H-pyrrole-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(5-methylaminomethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-piperidin-1-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-morpholin-4-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-4-(5-Dimethylaminomethyl-1-methyl-1H-pyrrole-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-pyrrolidin-1-ylmethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;



rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-methylaminomethyl-1H-pyrrole-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-4-(4-Dimethylaminomethyl-1H-pyrrole-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-pyrrolidin-1-ylmethyl-thiazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-morpholin-4-ylmethyl-thiazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-piperidin-1-ylmethyl-thiazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-[2-(4-methyl-piperazin-1-ylmethyl)-thiazole-4-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-4-(2-Cyclopropylaminomethyl-thiazole-4-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-4-{2-[(4-Fluoro-benzylamino)-methyl]-thiazole-4-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-[2-(4-phenyl-piperazin-1-ylmethyl)-thiazole-4-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-4-(2-Dibutylaminomethyl-thiazole-4-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-3-Isopropyl-4-{2-[(1-isopropyl-2-methyl-propylamino)-methyl]-thiazole-4-carbonyl}-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-4-(2-Dimethylaminomethyl-thiazole-4-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-morpholin-4-ylmethyl-isoxazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3R,3aR,6aS)-4-(5-Dimethylaminomethyl-isoxazole-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;



rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-pyrrolidin-1-ylmethyl-isoxazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-piperidin-1-ylmethyl-isoxazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-methyl-piperazin-1-ylmethyl)-isoxazole-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-{5-[(4-Fluoro-benzylamino)-methyl]-isoxazole-3-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-phenyl-piperazin-1-ylmethyl)-isoxazole-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-(5-Dibutylaminomethyl-isoxazole-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-(5-Dimethylaminomethyl-1-methyl-1H-pyrazole-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-pyrrolidin-1-ylmethyl-1H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-morpholin-4-ylmethyl-1H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(1-methyl-5-piperidin-1-ylmethyl-1H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[1-methyl-5-(4-methyl-piperidin-1-ylmethyl)-1H-pyrazole-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[2-methyl-5-(4-phenyl-piperazin-1-ylmethyl)-2H-pyrazole-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-(5-Dimethylaminomethyl-2-methyl-2H-pyrazole-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;



rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-methyl-5-pyrrolidin-1-ylmethyl-2H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-methyl-5-morpholin-4-ylmethyl-2H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(2-methyl-5-piperidin-1-ylmethyl-2H-pyrazole-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[2-methyl-5-(4-methyl-piperazin-1-ylmethyl)-2H-pyrazole-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-{6-[(Dicyclohexylamino)-methyl]-pyridine-3-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-(6-Dibutylaminomethyl-pyridine-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(6-morpholin-4-ylmethyl-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-(6-Cyclopropylaminomethyl-pyridine-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(6-piperidin-1-ylmethyl-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[6-(4-methyl-piperazin-1-ylmethyl)-pyridine-3-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-4-{6-[(1-isopropyl-2-methyl-propylamino)-methyl]-pyridine-3-carbonyl}-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-(6-Dimethylaminomethyl-pyridine-3-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-{6-[(4-Fluoro-benzylamino)-methyl]-pyridine-3-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-(5-Cyclopropylaminomethyl-pyrazine-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;



rel-(3R,3aR,6aS)-4-(5-Dibutylaminomethyl-pyrazine-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-morpholin-4-ylmethyl-pyrazine-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-{5-[(Dicyclohexylamino)-methyl]-pyrazine-2-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-piperidin-1-ylmethyl-pyrazine-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-methyl-piperazin-1-ylmethyl)-pyrazine-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-4-{5-[(1-isopropyl-2-methyl-propylamino)-methyl]-pyrazine-2-carbonyl}-1-methanesulfonyl-hexahydro-pyrrolo[3,2-]pyrrol-2-one;
rel-(3R,3aR,6aS)-4-(5-Dimethylaminomethyl-pyrazine-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-[5-(4-phenyl-piperazin-1-ylmethyl)-pyrazine-2-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-pyrrolidin-1-ylmethyl-pyrazine-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3R,3aR,6aS)-3-Isopropyl-1-methanesulfonyl-4-(5-methylaminomethyl-pyrazine-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
or a salt or solvate of any one thereof.

15. A compound of formula (I) according to claim 1 which is (3S,3aS,6aR)-4-(5-Cyclopropylaminomethyl-pyrazine-2-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one
or a salt or solvate thereof.

16. A compound of formula (I) according to claim 1 which is rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-pyrrolidin-1-ylmethyl-oxazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;

rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-piperidin-1-ylmethyl-oxazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-[2-(4-phenyl-piperazin-1-ylmethyl)-oxazole-4-carbonyl]-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-4-(2-Dibutylaminomethyl-oxazole-4-carbonyl)-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-4-{2-[(Cyclopropyl-methyl-amino)-methyl]-oxazole-4-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one;
rel-(3S,3aS,6aR)-4-{2-[(Dicyclohexylamino)-methyl]-oxazole-4-carbonyl}-3-isopropyl-1-methanesulfonyl-hexahydro-pyrrolo[3,2-b]pyrrol-2-one
or a salt or solvate of any one thereof.

17. A compound of formula (I) according to claim 1 which is (3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-pyrrolidin-1-ylmethyl-oxazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one
or a salt or solvate thereof.

18. A compound of formula (I) according to claim 1 which is (3S,3aS,6aR)-3-Isopropyl-1-methanesulfonyl-4-(2-pyrrolidin-1-ylmethyl-oxazole-4-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-2-one hydrochloride.

19. A purified single enantiomer of a compound of formula (I) according to any one of claims 1 to 14 and 16 having the absolute stereochemistry as illustrated in formula (I).

20. A compound of formula (I) according to any one of claims 1 to 19 for use as a pharmaceutical.

21. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 19 in admixture with one or more physiologically acceptable diluents or carriers.

22. Use of a compound of formula (I) according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment of chronic bronchitis or chronic obstructive pulmonary disease.

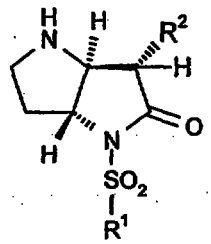
23. A method of treatment of chronic bronchitis or chronic obstructive pulmonary disease in a human or animal subject which comprises administering to said human or animal subject an effective amount of a compound of formula (I) according to any one of claims 1 to 19.

24. Use of a compound of formula (I) according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment of asthma.

25. A method of treatment of asthma in a human or animal subject which comprises administering to said human or animal subject an effective amount of a compound of formula (I) according to any one of claims 1 to 19.

26. A process for preparing a compound of formula (I) as defined in claim 1 which comprises:

(i) condensation of a compound of formula (II):

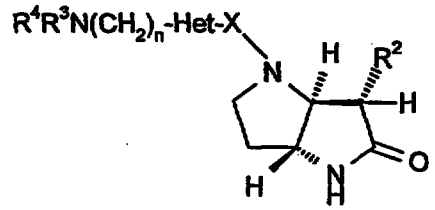


(II)

(relative stereochemistry indicated)

with a compound $R^4R^3N(CH_2)_nHetCOOH$ or an acid derivative thereof such as an acid chloride, activated ester, acid anhydride, or a mixed anhydride or with a compound $R^4R^3N(CH_2)_nHetXY$, where Y is a reactive group such as halogen, e.g. chlorine, or a protected derivative thereof; or

(ii) sulphonylation of a compound of formula (III):



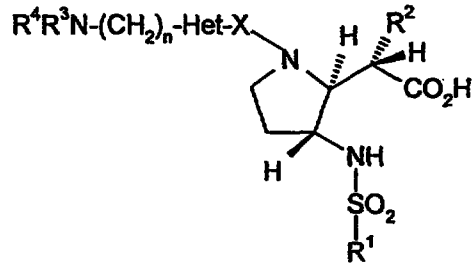
(III)

(relative stereochemistry indicated)

or a protected derivative thereof

with a compound YO_2SR^1 wherein Y is a reactive group such as halogen, e.g. chlorine; or

(iii) cyclising a compound of formula (IV):

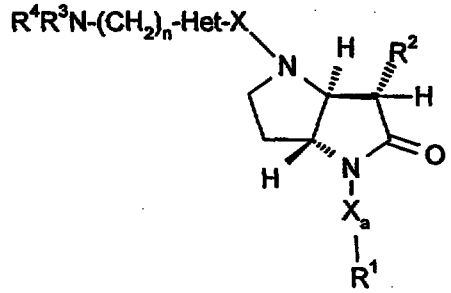


(IV)

(relative stereochemistry indicated)

or a carboxylic acid ester thereof; or

(iv) oxidation of a corresponding compound of formula (V)

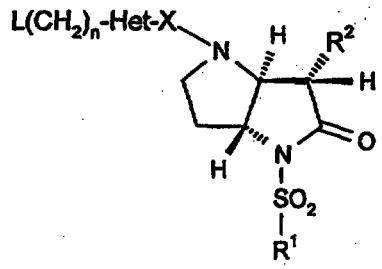


(V)

(relative stereochemistry indicated)

wherein X_a is sulphur or SO; or

(v) reaction of a corresponding compound of formula (VI)



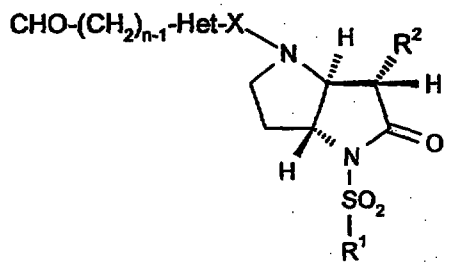
(VI)

(relative stereochemistry indicated)

wherein L is a leaving group

with a compound of formula R^4R^3NH; or

(vi) preparation of a compound of formula I in which n represents an integer 1 to 4 by reduction of the product of reaction of a corresponding compound of formula (VII)

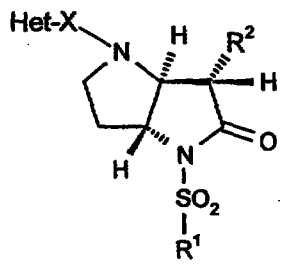


(VII)

(relative stereochemistry indicated)

with a compound of formula R^4R^3NH; or

(vii) preparation of a compound of formula I in which n represents 1 by reaction of a corresponding compound of formula (VIII)



(VIII)

(relative stereochemistry indicated)

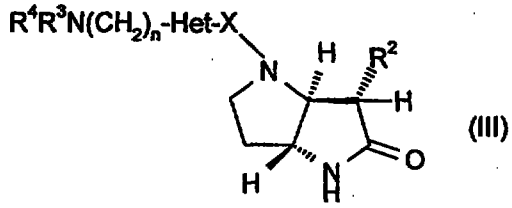
with formaldehyde or paraformaldehyde together with a compound of formula R^4R^3NH under acidic conditions; or

(viii) deprotecting a compound of formula (I) which is protected; or

(ix) purifying one enantiomer of the compound of formula (I) from a mixture of enantiomers;

and where desired or necessary converting a resultant free base compound of formula I into a physiologically acceptable salt form or vice versa or converting one salt form into another physiologically acceptable salt form.

27. A compound of formula (III)

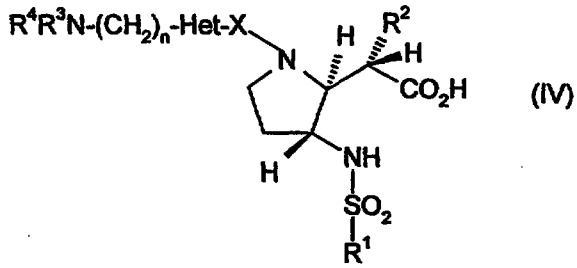


(III)

(relative stereochemistry indicated)

wherein R^2, R^3, R^4, n, Het and X are as defined in claim 1 or a protected derivative thereof.

28. A compound of formula (IV)

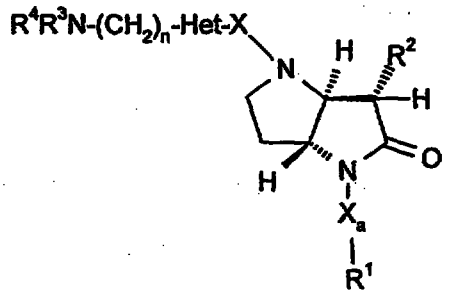


(IV)

(relative stereochemistry indicated)

wherein R^1, R^2, R^3, R^4, n, Het and X are as defined in claim 1 or a carboxylic acid ester thereof.

29. A compound of formula (V)

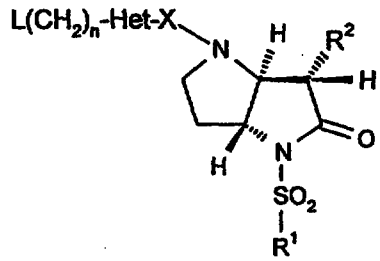


(V)

(relative stereochemistry indicated)

wherein R^1, R^2, R^3, R^4, n, Het and X are as defined in claim 1 and X_a represents sulphur or SO.

30. A compound of formula (VI)

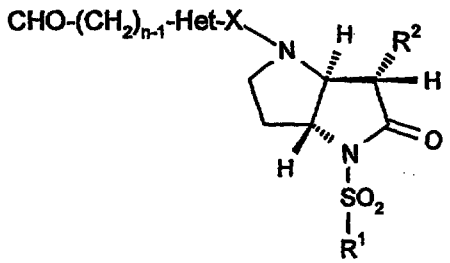


(VI)

(relative stereochemistry indicated)

wherein R^1, R^2, n, Het and X are as defined in claim 1 and L represents a leaving group.

31. A compound of formula (VII)

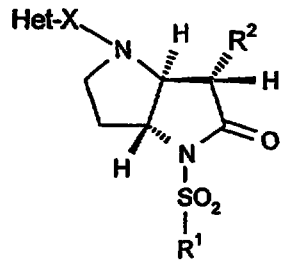


(VII)

(relative stereochemistry indicated)

wherein R^1, R^2, Het and X are as defined in claim 1 and n represents an integer 1 to 4.

32. A compound of formula (VIII)



(VIII)

(relative stereochemistry indicated)

wherein R^1, R^2, X and Het are as defined in claim 1.