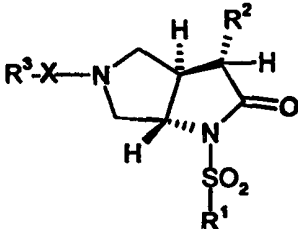




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(21) International Application Number: PCT/EP98/05743 (22) International Filing Date: 7 September 1998 (07.09.98) (30) Priority Data: 9719172.0 9 September 1997 (09.09.97) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): DOWLE, Michael, Dennis [GB/GB]; (GB). FINCH, Harry [GB/GB]; (GB). HARRISON, Lee, Andrew [GB/GB]; (GB). INGLIS, Graham, George, Adam [GB/GB]; (GB). JOHNSON, Martin, Redpath [GB/GB]; (GB). MACDONALD, Simon, John, Fawcett [GB/GB]; (GB). SHAH, Pritom [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). (74) Agent: TEUTEN, Andrew, J.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.		
(54) Title: PYRROLOPYRROLONE DERIVATIVES (57) Abstract According to the invention there are provided compounds of formula (I), (relative stereochemistry indicated), wherein R¹, R² and R³ are as defined in the specification. Compounds of formula (I) are useful <i>inter alia</i> in the treatment or chronic bronchitis.  (I)		

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Pyrrolopyrrolone derivatives

5 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.

10 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.

15 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
20 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.

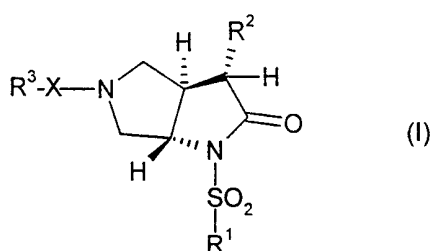
25 One of the enzymes found in the azurophilic granules is neutrophil elastase. Neutrophil elastase has a wide spectrum of activities in the body. For example, within the lung the enzyme increases mucus production and changes the cellular composition of the epithelium. The enzyme also causes vascular 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,
 5 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
 10 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
 15 activity is implicated.

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



20 (relative stereochemistry indicated)

wherein:

R¹ represents C₁₋₆alkyl;

R² represents C₂₋₄alkyl or C₂₋₄alkenyl;

X represents CO or SO₂;

25 R³ represents: (a) C₂₋₈alkenyl NR⁴R⁵;

- (b) phenyl substituted by $(\text{CH}_2)_a\text{Q}(\text{CH}_2)_b\text{NR}^4\text{R}^5$;
- (c) a 5 or 6 membered heterocyclic aromatic ring containing 1 or 2 heteroatoms selected from N, S and O substituted by $(\text{CH}_2)_a\text{Q}(\text{CH}_2)_b\text{NR}^4\text{R}^5$;
- 5 (d) phenyl substituted by $\text{NHCOC}_{1-8}\text{alkyl}$;
- (e) a group as defined in (b), (c), or (d) further substituted on the phenyl or heterocyclic ring by one or more groups selected from $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxy}$, halogen and nitro; or
- (f) $\text{C}_{1-8}\text{alkylNR}^4\text{R}^5$;
- 10 R^4 and R^5 independently represent hydrogen, $\text{C}_{1-8}\text{alkyl}$, $-(\text{CH}_2)_{1-4}\text{CONR}^6\text{R}^7$, $\text{COC}_{1-4}\text{alkyl}$ or $(\text{CH}_2)_{0-2}\text{Ph}$ where Ph represents phenyl optionally substituted by one or more $\text{C}_{1-4}\text{alkyl}$ or halogen groups or NR^4R^5 together represents azetidiny, pyrrolidinyl, piperidinyl, azepinyl, morpholinyl, piperazinyl or $\text{N-C}_{1-6}\text{alkyl-piperazinyl}$ or such a heterocyclic ring optionally substituted by one or
- 15 more $\text{C}_{1-4}\text{alkyl}$, CONR^6R^7 or COOR^6 groups;
- Q represents a bond, S, O or NR^8 ;
- a represents 0 to 4 and b represents 2 to 4 save that $a+b$ lies in the range 2 to 6 except when Q represents a bond in which case b may also represent 0 or 1 and $a+b$ may lie in the range 0 to 6;
- 20 R^6 , R^7 and R^8 independently represent hydrogen or $\text{C}_{1-4}\text{alkyl}$;
- 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
- 25 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 absolute stereochemistry as illustrated in formula (I).

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

- 5 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.

When R^3 represents C_{2-8} alkenyln R^4R^5 , examples include $CH=CHCH_2NR^4R^5$.

10

When R^3 represents phenyl substituted by $NHCOC_{1-8}$ alkyl, examples include phenyl substituted by $NHCOMe$.

When R^3 represents C_{1-8} alkyln R^4R^5 , examples include $(CH_2)_3NR^4R^5$.

15

When R^3 represents a substituted 5 or 6 membered heterocyclic aromatic ring, examples of heterocycles include furan, pyrrole, thiophene, imidazole, thiazole, isoxazole, pyrazole, pyrazine and pyridine.

- 20 When R^4 and R^5 independently represent C_{1-8} alkyl, examples include methyl and cyclopropyl.

When R^4 and R^5 independently represent $(CH_2)_{1-4}CONR^6R^7$ examples include CH_2CONMe_2 .

25

When R^4 and R^5 independently represent COC_{1-4} alkyl, examples include $COMe$.

Suitable R_1 alkyl groups include methyl, ethyl and propyl.

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

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

5

We prefer X to represent CO.

We prefer R^3 to represent

- 10 (a) C_{2-8} alkenyl NR^4R^5 ;
(b) phenyl substituted by $(CH_2)_aQ(CH_2)_bNR^4R^5$;
(c) a 5 or 6 membered heterocyclic aromatic ring
containing 1 or 2 heteroatoms selected from
N, S and O substituted by
 $(CH_2)_aQ(CH_2)_bNR^4R^5$;
15 (d) phenyl substituted by $NHCOC_{1-8}$ alkyl; or
(e) a group as defined in (b), (c), or (d) further
substituted on the phenyl or heterocyclic ring
by one or more groups selected from
 C_{1-4} alkyl, C_{1-4} alkoxy, halogen and nitro.

20

We particularly prefer R^3 to represent:

- (a) C_{2-8} alkenyl NR^4R^5 ;
(b) phenyl substituted by $(CH_2)_aQ(CH_2)_bNR^4R^5$;
(c) a 5 or 6 membered heterocyclic aromatic ring
25 containing 1 or 2 heteroatoms selected from
N, S and O substituted by
 $(CH_2)_aQ(CH_2)_bNR^4R^5$; or
(d) a group as defined in (b) or (c) further
substituted on the phenyl or heterocyclic

ring by one or more groups selected from
C₁₋₄alkyl, C₁₋₄alkoxy, halogen and nitro.

5 We prefer R⁴ and R⁵ independently to represent hydrogen or C₁₋₈alkyl or for
NR⁴R⁵ to represent pyrrolidiny, piperidiny, morpholiny or piperaziny
optionally N-substituted by C₁₋₈alkyl or phenyl (optionally substituted by
halogen or C₁₋₄alkyl).

10 We prefer Q to represent a bond and for a+b to represent 1 or 2.

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:

15 In vitro assays of human neutrophil elastase

Assay contents:

20 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).

25 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 IC₅₀ 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

10

Adult hamsters (100-150g) are randomised into groups (n=4) and fasted overnight. Under gaseous anaesthetic (3% isoflurane) 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.

15

20 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.

25

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).

5 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
10 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
15 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.

20 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.

25 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 bronchitis 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.

5 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
10 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
15 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
20 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.

25 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
5 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
10 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
15 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
20 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
25 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.

5 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
10 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
15 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
20 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
25 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.

5 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.

10 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.

15 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-tetrafluoroethane, carbon dioxide or other suitable gas.

20 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.

25 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.

- 5 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.

10 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.

- 15 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.

- 20 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
25 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.

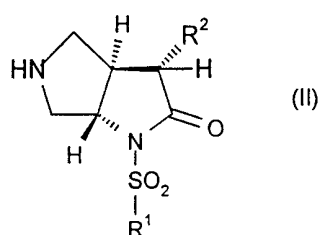
The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

5

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

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

10

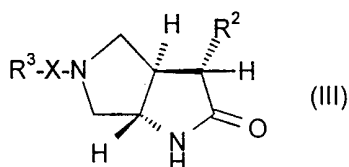


(relative stereochemistry indicated)

with a compound $R^3\text{COOH}$ or $R^3\text{XY}$, where Y is a reactive group such as halogen, e.g. chlorine, or a protected derivative thereof; or

15

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

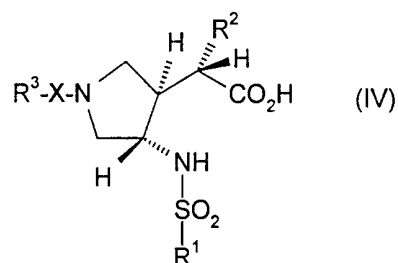


20 (relative stereochemistry indicated)

or a protected derivative thereof,

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

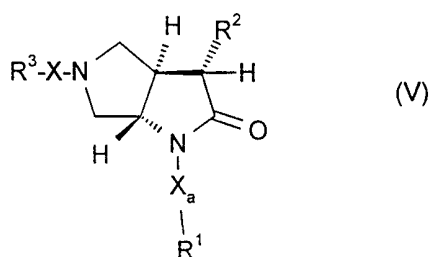
(iii) cyclising a compound of formula (IV):



(relative stereochemistry indicated)

5 or a carboxylic acid ester thereof; or

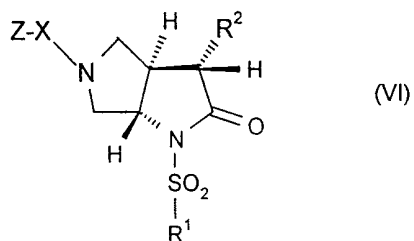
(iv) oxidation of a corresponding compound of formula (V)



(relative stereochemistry indicated)

10 wherein X_a is sulphur or SO; or

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



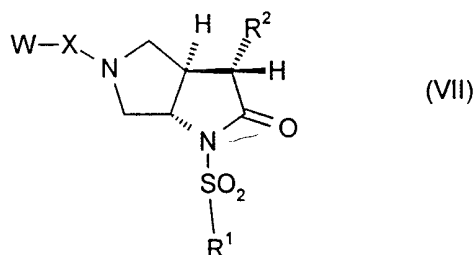
(relative stereochemistry indicated)

15 wherein Z represents

(a) C₂₋₈alkenyl-L

(b) phenyl substituted by (CH₂)_aQ(CH₂)_b-L;

- (c) a 5 or 6 membered heterocyclic aromatic ring containing 1 or 2 heteroatoms selected from N, S and O substituted by $(\text{CH}_2)_a\text{Q}(\text{CH}_2)_b\text{-L}$, or
- (d) a group as defined in (b) or (c) further substituted by one or more groups selected from C_{1-4} alkyl, C_{1-4} alkoxy, halogen and nitro; or
- 5 (e) C_{1-8} alkyl-L
- and L represents a leaving group, save that when Q represents a bond, a and b do not both represent 0;
- with a compound of formula $\text{R}^4\text{R}^5\text{NH}$; or
- 10 (vi) reduction of the product of reaction of a corresponding compound of formula (VII)



(relative stereochemistry indicated)

- 15 wherein W represents:
- (a) C_{2-7} alkenyl-CHO;
- (b) phenyl substituted by $(\text{CH}_2)_a\text{Q}(\text{CH}_2)_c\text{CHO}$;
- (c) a 5 or 6 membered heterocyclic aromatic ring containing 1 or 2 heteroatoms selected from N, S and O substituted by $(\text{CH}_2)_a\text{Q}(\text{CH}_2)_c\text{-CHO}$;
- 20 (d) a group as defined in (b) or (c) further substituted by one or more groups selected from C_{1-4} alkyl, C_{1-4} alkoxy, halogen and nitro; or
- (e) C_{1-7} alkylCHO
- wherein c represents b-1 save that it may not be less than zero,
- with a compound of formula $\text{R}^4\text{R}^5\text{NH}$; or

25

(vii) conversion of one compound of formula (I) into another compound of formula I; or

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

5

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

10 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)

15 The condensation reaction with R^3COOH is suitably carried out in the presence of a coupling agent such as 1-(3-N,N-dimethylaminopropyl)-3-ethylcarbodiimide, and a solvent such as dichloromethane, DMF or tetrahydrofuran at a temperature of suitably between $0^\circ C$ and ambient. It will be appreciated that as an alternative to using R^3COOH , acid derivatives such as the acid chloride, activated ester, acid anhydride, or a mixed

20 anhydride may be used. Reaction conditions will be modified accordingly, for instance by inclusion of a base. If one or both R^3 , R^4 represents hydrogen, it will generally be preferred to protect the nitrogen, e.g. with BOC.

25 With R^3XY the reaction is suitably carried out in the presence of a base such as triethylamine and a solvent such as DCM, suitably at $0^\circ C$ -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 0°C.

A nitrogen in the R³ sidechain may require protecting, e.g. with BOC.

5

Process (iii)

The cyclisation reaction is suitably carried out in the presence of 2-chloro-1-methylpyridinium iodide, or 1-(3-N,N-dimethylaminopropyl)-3-

ethylcarbodiimide (EDC), in a solvent such as dichloromethane, at a

10 temperature of suitably 0°C - reflux. This reaction may also be performed using a carboxylic acid thioester derivative of the compound of formula (IV).

Process (iv)

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

15 by peracid oxidation.

Process (v)

Leaving groups include halogen (e.g. chlorine, bromine) mesylate and tosylate.

20 This reaction may be performed by combining the reactants optionally in the presence of a base such as triethylamine or potassium carbonate in an inert aprotic solvent such as DMF or MeCN.

Process (vi)

25 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 NaBH₃CN or NaBH(OAc)₃.

Process (vii)

Conversion may be performed by conventional methods. For example, compounds of formula I in which R³ represents phenyl substituted by NHCOC₁₋₈alkyl may be prepared by acylating a corresponding compound of formula I in which R³ represents phenyl substituted by NH₂.

Process (viii)

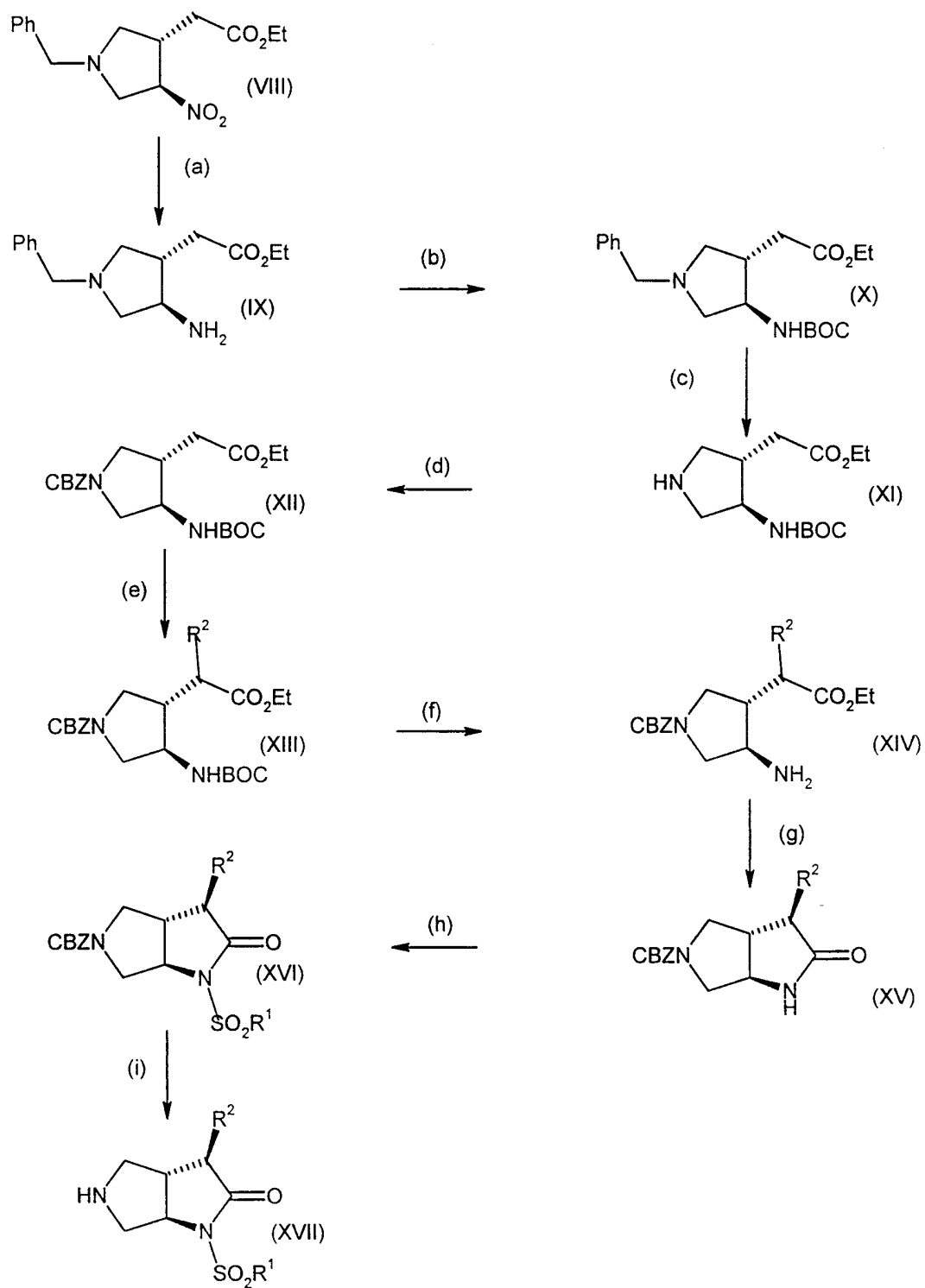
Protecting groups, especially nitrogen protecting groups, and means for deprotection are described in T W Greene "Protective Groups in Organic Synthesis", 2nd Ed (1991) J Wiley & Sons.

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 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 (compounds are drawn with relative stereochemistry):

Scheme 1

Step a

This is a standard nitro group reduction which may be achieved using hydrogen in the presence of a metal catalyst, e.g. palladium supported on carbon, in a suitable solvent such as ethanol.

5

Step b

This is a conventional protection reaction which may be performed by reacting with BOC_2O in the presence of a base, e.g. triethylamine, in an inert solvent such as acetonitrile or dichloromethane.

10

Step c

This is a conventional deprotection reaction which may be achieved by reacting with hydrogen or ammonium formate in the presence of a metal catalyst, e.g. palladium supported on carbon, in a suitable solvent such as ethanol.

15

Step d

This is a conventional protection reaction which may be performed by reacting with benzyl chloroformate in the presence of a base, e.g. triethylamine, in an inert solvent such as acetonitrile or dichloromethane.

20

Step e

This alkylation reaction may be achieved by the sequential reactions with a strong base, e.g. LHMDs, in the presence of DMPU in an inert solvent such as THF or diethyl ether at -70°C , followed by alkyl halide, e.g. bromide or iodide, at -70°C -room temperature.

25

Step f

This is a conventional deprotection reaction which may be performed by reacting with an acid, e.g. trifluoroacetic acid or hydrogen chloride in a suitable solvent such as dichloromethane or dioxane.

5

Step g

This cyclisation may be achieved using t-butyl magnesium chloride in the presence of TMEDA in an inert solvent such as THF or diethyl ether. The use of TMEDA is optional.

10

Step h

This standard sulphonylation reaction may be achieved by sequential reactions with a strong base, e.g. LHMDs, in an inert solvent such as THF or diethyl ether at -70° – 0° C, followed by the appropriate alkylsulphonylhalide (eg methanesulfonyl chloride) at -70° C - room temperature.

15

Step i

This conventional deprotection reaction can be achieved by reacting with hydrogen in the presence of a metal catalyst, e.g. palladium supported on carbon, and a proton source, e.g. ethereal hydrogen chloride, in a suitable solvent such as ethyl acetate or ethanol. The use of a proton source is optional.

20

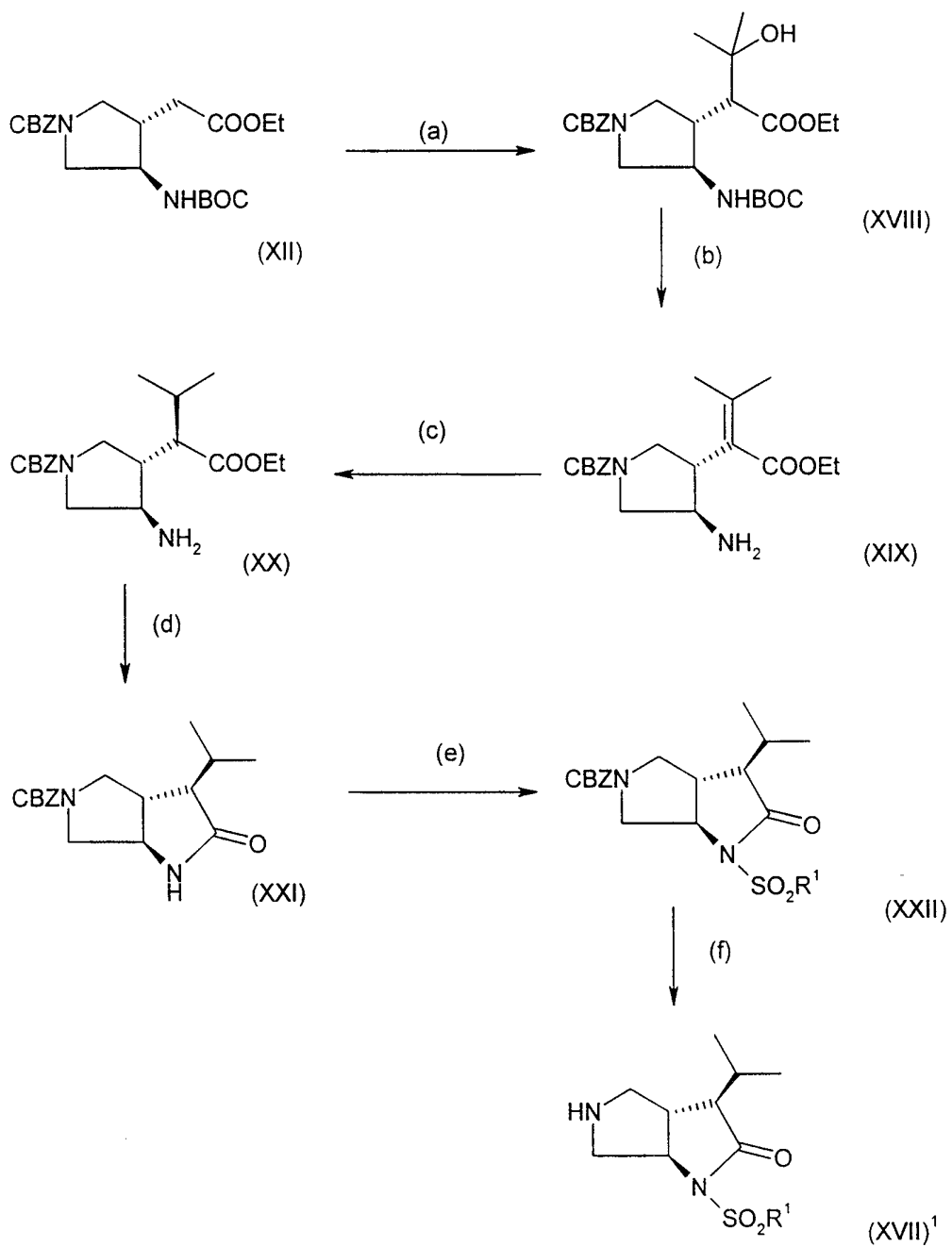
A chiral resolution step (see main process (viii) above) may also be introduced into Scheme 1 at a convenient point in order to produce enantiomerically pure products, if desired.

25

Certain compounds of formula (XVII) in which R^2 represents isopropyl may alternatively be prepared by following an alternative Scheme 2 from

compounds of formula (XII) (compounds are drawn with relative stereochemistry):

Scheme 2



Step (a)

For this reaction, the anion of the compound of formula (XII) is first prepared by treatment with a strong base, e.g. LHMDs, followed by treatment with acetone.

5

Step (b)

Standard dehydration conditions may be used for this reaction, e.g. treatment with concentrated sulphuric acid. These conditions will remove the BOC deprotecting group, otherwise the deprotection can be performed as an additional step.

10

Step (c)

This is a reduction reaction which will be performed under mild conditions so as not to remove the CBZ protecting group. Hydrogenation over Pd/C in ethanol or ethyl acetate for a short period of time (eg <1hr) will be suitable.

15

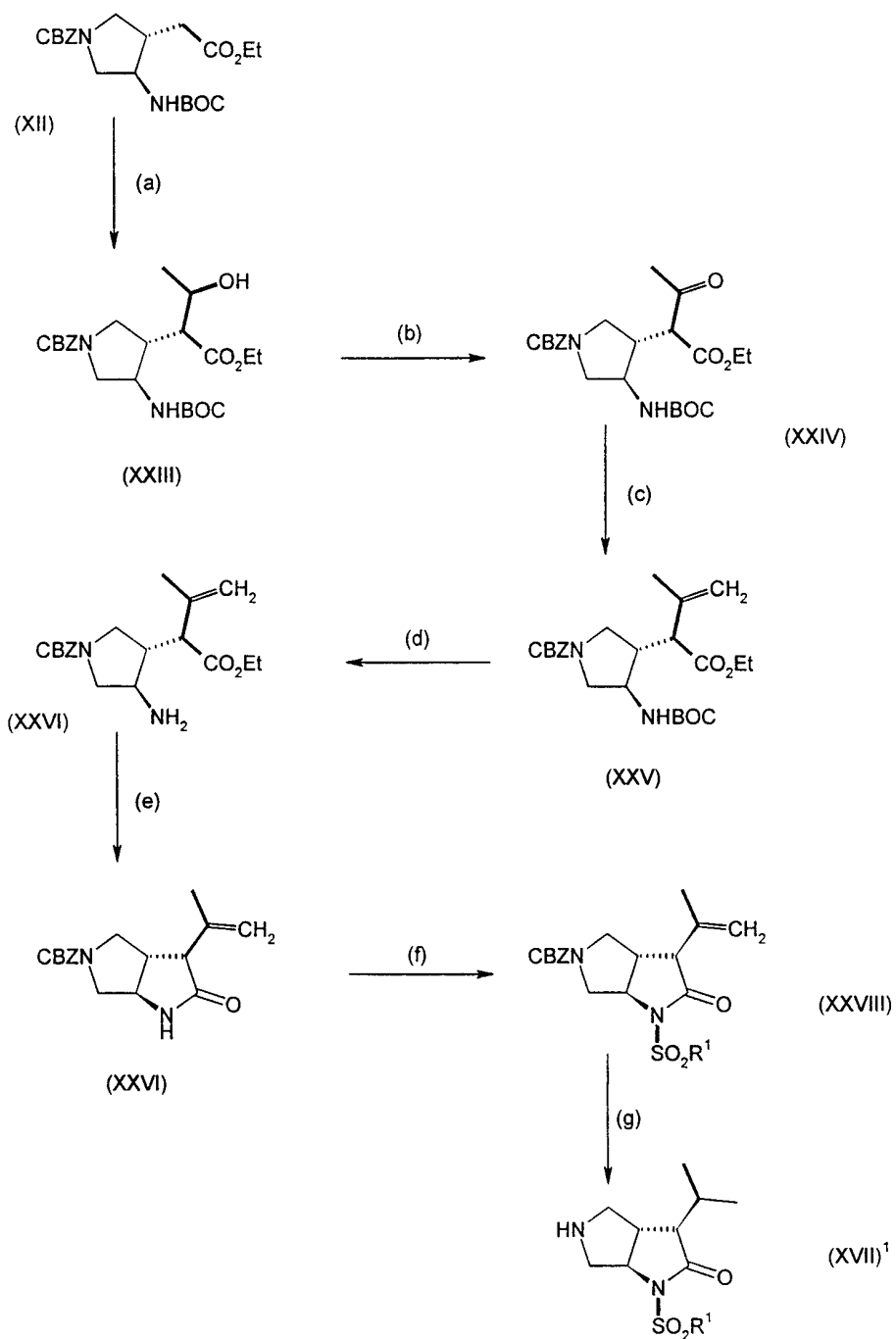
Steps (d)-(f)

These processes are analogous to Scheme I, steps (g)-(i).

20

A further alternative method for preparation of compounds of formula (XVII) in which R² represents isopropyl is given in Scheme 3 (compounds are drawn with relative stereochemistry):

Scheme 3



Step (a)

For this reaction, the anion of compound of formula (XII) is prepared by treatment with a strong base, e.g. LHMDs, followed by treatment with
5 acetaldehyde.

Step (b)

This oxidation may be suitably carried out under nitrogen using Swern oxidation conditions, e.g. oxalyl chloride and DMSO at -80°-0° in
10 dichloromethane, followed by triethylamine.

Step (c)

This methylenation may be achieved using Tebbe reaction conditions, e.g. m-chlorobis(h⁵-2,4-cyclopentadien-1-yl)(dimethylaluminium)-m-
15 methylenetitanium in THF at around 0°- room temperature.

Step (d)

This standard deprotection may be performed using an acid, e.g. trifluoroacetic acid or hydrogen chloride, in a suitable solvent such as
20 dichloromethane or dioxane.

Step (e)

This cyclisation may be achieved using t-butyl magnesium chloride in an inert solvent such as THF or diethyl ether.

25

Step (f)

This process is analogous to Scheme 1, step (h).

Step (g)

This is a conventional deprotection reaction which may be achieved by reacting with hydrogen in the presence of a metal catalyst catalyst, e.g. palladium on carbon, in a suitable solvent such as ethanol.

- 5 In Schemes 1, 2 and 3, a diastereomeric separation may be necessary to obtain the compound of desired stereochemistry.

The protecting groups CBZ and BOC used in Schemes 1, 2 and 3 are preferred illustrations and alternative protecting groups can be
10 contemplated.

The route shown in Scheme 2 may also be followed for the preparation of compounds having different R^2 , especially bulky R^2 . A different ketone reagent will then be used in step (a).
15

Scheme 3 may also be adapted to produce compounds of formula (XVII) having other branched R^2 alkyl or alkenyl sidechains.

The intermediate compounds of formula (III) may be prepared by reacting a deprotected compound of formula (XV) from Scheme 1 with R^3COOH or R^3XY in the manner described above in relation to main process (i) above.
20

The intermediate compounds of formula (IV) may be prepared from a compound of formula (XIV) in an analogous manner to that described above for preparing a compound of formula (III) from a compound of formula (XV) together with main process (ii) above.
25

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 in the presence of base. Compounds of formula (V) wherein X_a represents SO may be prepared by peracid oxidation of a corresponding compound wherein X_a represents S.

5

Compounds of formula (VI) and (VII) may be prepared from compounds of formula (II) following conventional methods known *per se*.

10 The compound of formula (VIII) may be prepared by the method of Archille Barco *et al* (1992) J. Org. Chem. 57, 6279.

Compounds of formula R_3COOH and R^3XY are either known or may be prepared by conventional methods known *per se*.

15 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
20 of routine optimisation of experimental conditions.

Certain of the intermediate compounds herein described are novel and form an important aspect of the invention. We provide intermediates as racemic mixtures or in the form of a purified single enantiomer.

25

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

The following non-limiting Example illustrates the present invention.

ABBREVIATIONS

BOC	t-butyloxycarbonyl
CBZ	Benzyloxycarbonyl
(BOC) ₂ O	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
DCM	dichloromethane
DMSO	dimethylsulphoxide
TMEDA	tetramethylethylene diamine

5

Intermediates

Intermediate I

rel-(3S,4R)-(1-Benzyl-4-nitro-pyrrolidin-3-yl)-acetic acid ethyl ester

- 10 This compound was prepared by the method of Archille Barco *et al*
J.Org.Chem.1992, 57, 6279 as a medium brown oil. Tlc silica
(cyclohexane:ethyl acetate:3:1) Rf 0.26.

Intermediate IIrel-(3S,4R)-(4-Amino-1-benzyl-pyrrolidin-3-yl)-acetic acid ethyl ester

A solution of Intermediate I (397g) in absolute ethanol (1.4l) was reduced at room temperature with stirring over a platinum/carbon catalyst (5% 115g) under a hydrogen atmosphere. The reaction proceeded to completion over 5h (H₂ uptake 99.7l). The reaction mixture was filtered through celite and evaporated *in vacuo* to give the title compound as a light brown oil (303g). Tlc Silica, cyclohexane:ethyl acetate (3:1); R_f 0.15

10 Intermediate IIIrel-(3S,4R)-(1-Benzyl-4-tert-butoxycarbonylamino-pyrrolidin-3-yl)-acetic acid ethyl ester

A solution of (BOC)₂O (289g) in acetonitrile (1.5l) was added below 25°C with stirring over 25 min to a solution of Intermediate II (288.8) and triethylamine (111.2g) in acetonitrile (1.5l). After 2.5 days the solvent was removed *in vacuo* and the resultant brown oil partitioned between ethyl acetate (2.5l) and water (2l). The aqueous layer was further extracted with ethyl acetate (2l). The combined organics were washed with brine, dried (MgSO₄), filtered and evaporated. The residual light brown solid was 15 triturated with ether and then collected by filtration. The title compound was obtained as a white solid (233g). Tlc Silica, hexane:ethylacetate (3:1); R_f 0.27

Intermediate IV25 rel-(3S,4R)-(4-tert-Butoxycarbonylamino-pyrrolidin-3-yl)-acetic acid ethyl ester

A solution of Intermediate III (100g) in absolute ethanol (1.25l) was reduced over palladium on carbon catalyst (10%, 20g) under a hydrogen atmosphere at room temperature and with stirring (Hydrogen uptake 7.5l). After 20h the

reaction mixture was filtered through hyflo and evaporated *in vacuo* to give the title compound as a colourless oil (71g) which crystallised to a white solid on standing. Tlc silica (dichloromethane; ethanol; ammonia 80:20:2) Rf 0.4.

5

Intermediate V

rel-(3S,4R)-3-tert-Butoxycarbonylamino-4-ethoxycarbonylmethyl-pyrrolidine-1-carboxylic acid benzyl ester

Triethylamine (156ml) was added slowly to a cooled solution of Intermediate IV (100.7g) and benzyl chloroformate (74ml) in dichloromethane (3l) at 10°C with stirring. The temperature during the addition was maintained below 15°C. The reaction mixture was stirred overnight and then washed with water (3l). The solvent was removed *in vacuo* and the residual oil purified by chromatography on silica (Merck 9385) eluting with hexane:ethyl acetate (3:1). The resultant white solids were combined and triturated with hexane:ethyl acetate (2:1) (400ml), to give the title compound 155g. Mass spec. (found) $MH^+ = 407$ (calc) $MH^+ = 407$.

20

Intermediate VI

rel-(3S,4R)-3-tert-Butoxycarbonylamino-4-(1-ethoxycarbonyl-but-3-enyl)-pyrrolidine-1-carboxylic acid benzyl ester

A solution of lithium bis (trimethylsilyl) amide in tetrahydrofuran (1M, 80ml) was added dropwise over 1h with stirring under a nitrogen atmosphere at -70°C to a solution of the Intermediate V (9.8g) in a mixture of dry tetrahydrofuran (54ml) and 1,3-dimethyl-3,4,5,6-tetrahydro 2 (1H) pyrimidinone (120ml). After a further 1h allyl iodide (2.8ml) was added dropwise over 10 min and the mixture was stirred below -70°C for 2h. The reaction was quenched with saturated aqueous ammonium chloride (30ml)

which was added dropwise over 30 min. The mixture was extracted with ethyl acetate (4x100ml). The combined extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to give an orange oil (26g). The oil was partitioned between toluene (200ml) and water (100ml). The organics were washed with water (2x100ml) and brine (80ml), dried (Na₂SO₄), filtered and evaporated to give a clear orange oil (15g). Purification of this oil by flash column chromatography on silica (Merck 9385) using gradient elution [ethyl acetate:hexane from (1:9) to (2:3)]. The title compound was thereby obtained as a white crystalline solid (8.6g). Mass spec MH⁺ (found) 447
MH⁺ (calc) 447

Intermediate VII

rel-(3R,4S)-3-Amino-4-(1-ethoxycarbonyl-but-3-enyl)-pyrrolidine-1-carboxylic acid benzyl ester

Intermediate VI (5g) was dissolved in 4M hydrogen chloride in dioxan (53ml) at room temperature. The solution was stirred for 3h and evaporated. The residue was partitioned between water (100ml) and ether (50ml). The aqueous layer was washed with ether (50ml) and then basified with saturated aqueous sodium hydrogen carbonate (100ml). The mixture was extracted with ethyl acetate (3x50ml). The combined extracts were dried (Na₂SO₄) filtered and evaporated to give the title compound as a clear, pale yellow, viscous oil (3.7g). Mass spec MH⁺ (found) 347 MH⁺ (calc) 347.

Intermediate VIII

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

A solution of Intermediate VII (3.5g) in a mixture of dry tetrahydrofuran (35ml) and dry tetramethylethylenediamine (35ml) was cooled to 5°C. A solution of t-butyl magnesium chloride (1M, 32ml) in tetrahydrofuran was

added over 25 min and the mixture was allowed to warm to room temperature over 1.5h. After a further 1.5h the reaction was quenched with saturated aqueous ammonium chloride (10ml). Chilled 2M hydrochloric acid (100ml) was then added with cooling. The resultant mixture was acidified (pH1-2) using concentrated hydrochloric acid (40ml). The mixture was extracted with ethyl acetate (3x100ml). The combined extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the title compound as a white crystalline solid (3g). Mass spec MH^+ (found) 301 MH^+ (calc) 301.

Intermediate IX

rel-(3R,3aS,6aR)-3-allyl-methanesulfonyl-2-oxo-hexahydropyrrolo[3,4-b]pyrrole-5-carboxylic acid benzyl ester

A solution of lithium hexamethyldisilazide in tetrahydrofuran (1M, 13ml) was added at -10°C over 10 min to a stirred solution of Intermediate VIII (3g). After 5 min the reaction was allowed to warm to around 0°C , at which temperature it was held for 35 min. The mixture was recooled to -70°C and methanesulphonyl chloride (1.93ml) was added dropwise over 15 min. After a further 3.5h the reaction was quenched with saturated aqueous ammonium carbonate (20ml) at below -50°C . It was then allowed to attain ambient, when it was diluted with water (100ml) and extracted with ethyl acetate (3x100ml). The combined extracts were washed with brine (100ml), dried (Na_2SO_4), filtered and evaporated. The resultant oil was purified by flash column chromatography on silica using gradient elution. The eluent was initially ethyl acetate hexane (4:1) and increased in polarity to ethyl acetate:hexane (5:1). The title compound was obtained as a viscous gum/glass (3.1g). Mass spec MH^+ (found) 379 MH^+ (calc) 379 MNH_4^+ (found) 396 MNH_4^+ (found) 396.

Intermediate Xrel-(3R,3aS,6aR)-1-Methanesulfonyl-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one hydrochloride

A solution of Intermediate IX (3g) in ethyl acetate (150ml) containing
5 ethereal hydrogen chloride (1.0M, 12ml) was stirred over 5% palladium on
activated carbon (wet 1.5g) under a hydrogen atmosphere. After 5h more
catalyst (0.5g) was added and the reaction was stirred for a further 16h.
(Hydrogen uptake 470ml). The reaction mixture was diluted with an equal
volume of absolute ethanol and then filtered through celite. The filtrate was
10 evaporated, redissolved in a mixture of ethyl acetate and dichloromethane
(1:10, 100ml) and extracted with water (2x50ml). The combined extracts
were washed with ethyl acetate (50ml), basified with saturated aqueous
sodium hydrogen carbonate and extracted with dichloromethane (4x50ml).
The combined extracts were dried (Na_2SO_4) filtered and evaporated to give
15 a pale yellow foam (1.2g). Ethereal hydrogen chloride (1.0M, 5ml) was
added and the mixture reevaporated to give the title compound as a glass.
Tlc silica (dichloromethane; ethanol: ammonia, 100:8:1) Rf 0.1.

Intermediate XI20 4-(Piperidin-1-yl)-but-2-enoic Acid Anhydride Dihydrochloride

Oxalyl chloride (4.2ml) was added to a stirred solution of 4-(piperidin-1-yl)-
but-2-enoic acid hydrochloride (10g) in dichloromethane (200ml).
Dimethylformamide (2 drops) was then added. The resultant suspension
was stirred for 4h and then concentrated to ~25ml. The slurry obtained was
25 stirred a further 1h and then filtered. The filter pad was washed with
dichloromethane (50ml) and dried *in vacuo* to give the title compound as a
white solid (4.95g). M.p. 120-124°C (decomposition).

Intermediate XII

rel-(3R,3aS,6aR)-5-(4-Bromomethyl-benzoyl)-1-methanesulfonyl-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one

Intermediate X (150mg), 4-(bromomethyl) benzoyl chloride (161mg) and sodium hydrogen carbonate (223 mg) were suspended in dichloromethane (15ml) and stirred at room temperature overnight. the mixture was diluted with dichloromethane, washed with saturated sodium hydrogen carbonate solution and evaporated to leave an orange solid from which the product was extracted using a pre-packed silica cartridge. The columns were eluted with vacuum suction using the following solvents; dichloromethane, chloroform, diethyl ether, ethyl acetate and acetonitrile to give the title compound as a cream solid (174mg) Mass spec. MH^+ (found) 444, MH^+ (calc) 444.

Intermediate XIII

15 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. (Silica, eluent dichloromethane:methanol 9:1) R_f = 0.32.

Intermediate XIV

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

Intermediate X (279mg), Intermediate XIII (181mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (378mg) were dissolved in acetonitrile (30ml) and the solution stirred at room temperature for 6 hours. The solvent was removed *in vacuo*, the residue dissolved in

dichloromethane, washed with saturated sodium hydrogen carbonate and the product extracted using a pre-packed silica cartridge, eluting sequentially with dichloromethane, chloroform, diethyl ether, ethyl acetate, acetonitrile and methanol to leave the title compound as a white solid
5 (216mg). Mass spec MH^+ (found) 370, MH^+ (calc) 370.

Examples

10 Example 1

rel-(3R,3aS,6aR)-1-Methanesulfonyl-5-(4-piperidin-1-yl-but-2-enoyl)-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one hydrochloride

Intermediate XI (0.44g) was added at room temperature to a solution of Intermediate X (0.28g) containing solid sodium hydrogen carbonate (0.34g).
15 The reaction was stirred for 4h. The mixture was washed with saturated aqueous sodium hydrogen carbonate (20ml). The aqueous phase was separated and extracted with dichloromethane (20ml). The combined organics were washed with water (2 x 30ml), dried over sodium sulphate and evaporated *in vacuo*. The resultant gum was purified by flash column
20 chromatography on silica gel (Merck 9385) using gradient elution. The initial eluent, dichloromethane:ethanol:ammonia (200:8:1), was increased in polarity to dichloromethane:ethanol:ammonia (150:8:1). The resultant viscous oil (0.42g) was dissolved in ethyl acetate (30ml) and treated with ethereal hydrogen chloride. The resultant white solid suspension was
25 evaporated and dried *in vacuo* to give the title compound. T.l.c. silica, dichloromethane:ethanol:ammonia (100:8:1); Rf. 0.55. Mass spec. MH^+ (found) 398, MH^+ (calc) 398.

Example 2

rel-(3R,3aS,6aR)-1-Methanesulfonyl-5-(4-piperidin-1-yl-butyryl)-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one

A solution of Example 1 free base (0.2g) in ethyl acetate 40ml was stirred over a 10% palladium on carbon catalyst (0.1g) under a hydrogen atmosphere at room temperature for 2h. Hydrogen uptake 15ml. The mixture was filtered through celite and the filtrate concentrated to ~15ml. The concentrate was treated with ethereal hydrogen chloride (1M, 5ml) precipitating a white solid. The mixture was evaporated and dried to give the title compound (0.15g) as a white solid. Mass spec MH^+ (found) 400 MH^+ (calc) 400

Example 3

rel-N-[4-(1-Methanesulfonyl-2-oxo-3R-propylhexahydro-(3aS,6aR)-pyrrolo[3,4-b]pyrrole-5-sulfonyl)-phenyl]acetamide

Triethylamine (246ml) and N-acetylsulfanilyl chloride (108mg) were added to a solution of Intermediate X (100mg) in dichloromethane (3.3ml). The solution was stirred at room temperature for 5h. Sodium hydrogen carbonate (150mg) was added and the reaction stirred overnight. The resultant suspension was washed with saturated sodium hydrogen carbonate solution. The solvent was removed *in vacuo*. The resultant solid was purified using pre-packed silica cartridges. The columns were eluted with vacuum suction using the following solvents; dichloromethane (2 x column volume), chloroform (2 x column volume), diethyl ether (4 x column volume), ethyl acetate (4 x column volume) and acetonitrile (4 x column volume) to give the title compound (48mg) as a white solid. T.l.c. silica, dichloromethane:methanol, 9:1; Rf. 0.61. Mass spec. MH^+ (found) 444, MH^+ (calc) 444.

Example 4

rel-(3R,3aS,6aR)-1-Methanesulfonyl-5-(4-piperidin-1-ylmethyl-benzoyl)-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one hydrochloride

Piperidine (47mg) and sodium iodide (33mg) were added to a solution of Intermediate XII (70mg) in dichloromethane (5ml) and the suspensions stirred at room temperature overnight. The reactions were washed with saturated sodium hydrogen carbonate solution and the products extracted using a pre-packed silica cartridge, eluting sequentially with dichloromethane, chloroform, diethyl ether, ethyl acetate, acetonitrile and methanol to leave a gum which was treated with ethereal hydrogen chloride and evaporated to leave the title compound as a yellow solid (44mg).
T.l.c. (Silica, eluent dichloromethane:methanol 9:1) R_f = 0.29.
Mass spec. MH⁺ (found) 448, MH⁺ (calc) 448

The following Example was prepared in a similar manner to Example 4 from Intermediate XII:

Example 5

rel-(3R,3aS,6aR)-1-Methanesulfonyl-5-(4-morpholin-4-ylmethyl-benzoyl)-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one hydrochloride

White solid

T.l.c. (Silica, eluent dichloromethane:methanol 9:1) R_f = 0.54.

Mass spec. MH⁺ (found) 450, MH⁺ (calc) 450

Example 6

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

Morpholine was added to a solution of Intermediate XIV (50mg) in dichloromethane (5ml) and the solution stirred for two hours at room temperature. Sodium triacetoxyborohydride (43mg) was added to the

solution and the reaction stirred at room temperature overnight. the reaction was washed with saturated sodium hydrogen carbonate solution and the product extracted using a pre-packed silica cartridge, eluting sequentially with dichloromethane, chloroform, diethyl ether, ethyl acetate, acetonitrile and methanol to leave a gum which was treated with ethereal hydrogen chloride and evaporated to leave the title compound as a white solid (24mg).
T.l.c. (Silica, eluent dichloromethane:methanol 9:1) Rf = 0.48.
Mass spec. MH⁺ (found) 441, MH⁺ (calc) 441

10 The following Example was prepared in a similar manner to Example 6 from Intermediate XIV:

Example 7

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

Yellow solid

T.l.c. (Silica, eluent dichloromethane:methanol 9:1) Rf = 0.40.

Mass spec. MH⁺ (found) 399, MH⁺ (calc) 399

20

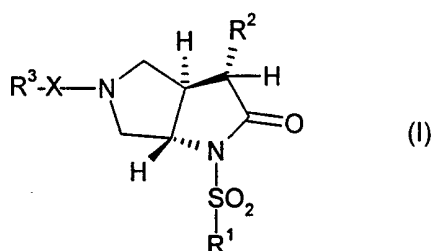
Biological Data

1. The compounds of Examples 1 to 7 were tested in the in vitro elastase test described earlier in the description. The IC₅₀ values are given
- 5 in the table below:

Example	IC ₅₀ (μM)
1	0.227
2	0.9
3	0.229
4	0.296
5	0.222
6	0.146
7	0.399

Claims

1. A compound of formula (I)



5 (relative stereochemistry indicated)

wherein:

R¹ represents C₁₋₆alkyl;

R² represents C₂₋₄alkyl or C₂₋₄alkenyl;

X represents CO or SO₂;

- 10 R³ represents: (a) C₂₋₈alkenyl NR⁴R⁵;
 (b) phenyl substituted by (CH₂)_aQ(CH₂)_bNR⁴R⁵
 (c) a 5 or 6 membered heterocyclic aromatic ring containing
 1 or 2 heteroatoms selected from N, S and O
 substituted by (CH₂)_aQ(CH₂)_bNR⁴R⁵;
 15 (d) phenyl substituted by NHCOC₁₋₈alkyl;
 (e) a group as defined in (b), (c), or (d) further substituted
 on the phenyl or heterocyclic ring by one or more
 groups selected from C₁₋₄alkyl, C₁₋₄alkoxy, halogen and
 nitro; or
 20 (f) C₁₋₈alkylNR⁴R⁵;

R⁴ and R⁵ independently represent hydrogen, C₁₋₈alkyl, -(CH₂)₁₋₄CONR⁶R⁷, COC₁₋₄alkyl or (CH₂)₀₋₂Ph where Ph represents phenyl optionally substituted by one or more C₁₋₄alkyl or halogen groups or NR⁴R⁵ together represents azetidiny, pyrrolidinyl, piperidinyl, azepinyl, morpholinyl, piperazinyl or N-C₁₋₆alkyl-piperazinyl or such a heterocyclic ring optionally substituted by one or
 25 more C₁₋₄alkyl, CONR⁶R⁷ or COOR⁶ groups;

Q represents a bond, S, O or NR^8 ;

a represents 0 to 4 and b represents 2 to 4 save that a+b lies in the range 2 to 6 except when Q represents a bond in which case b may also represent 0 or 1 and a+b may lie in the range 0 to 6;

- 5 R^6 , R^7 and R^8 independently represent hydrogen or C_{1-4} alkyl; and salts and solvates thereof.

2. A compound of formula I as defined in claim 1 wherein R^3 represents:

- 10 (a) C_{2-8} alkenyl NR^4R^5 ;
 (b) phenyl substituted by $(\text{CH}_2)_a\text{Q}(\text{CH}_2)_b\text{NR}^4\text{R}^5$;
 (c) a 5 or 6 membered heterocyclic aromatic ring containing 1 or 2 heteroatoms selected from N, S and O substituted by $(\text{CH}_2)_a\text{Q}(\text{CH}_2)_b\text{NR}^4\text{R}^5$;
 (d) phenyl substituted by NHCOC_{1-8} alkyl; or
 15 (e) a group as defined in (b), (c), or (d) further substituted on the phenyl or heterocyclic ring by one or more groups selected from C_{1-4} alkyl, C_{1-4} alkoxy, halogen and nitro.

3. A compound of formula (I) as defined in claim 1 or claim 2 wherein
 20 R^3 represents

- 25 (a) C_{2-8} alkenyl NR^4R^5 ;
 (b) phenyl substituted by $(\text{CH}_2)_a\text{Q}(\text{CH}_2)_b\text{NR}^4\text{R}^5$;
 (c) a 5 or 6 membered heterocyclic aromatic ring containing 1 or 2 heteroatoms selected from N, S and O substituted by $(\text{CH}_2)_a\text{Q}(\text{CH}_2)_b\text{NR}^4\text{R}^5$; or
 (d) a group as defined in (b) or (c) further substituted on the phenyl or heterocyclic ring by one or more groups selected from

C₁₋₄alkyl, C₁₋₄alkoxy, halogen and nitro.

4. A compound of formula (I) according to any one of the preceding claims wherein X represents CO.
5. A compound of formula (I) according to any one of the preceding claims wherein R² represents isopropyl or propyl.
6. A compound of formula (I) according to claim 5 wherein R² represents isopropyl.
7. A compound of formula (I) according to any one of the preceding claims wherein R¹ represents methyl or ethyl.
8. A compound of formula (I) according to claim 7 wherein R¹ represents methyl.
9. A compound of formula (I) which is:
 rel-(3R,3aS,6aR)-1-Methanesulfonyl-5-(4-piperidin-1-yl-but-2-enoyl)-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one;
 rel-(3R,3aS,6aR)-1-Methanesulfonyl-5-(4-piperidin-1-yl-butyryl)-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one;
 rel-N-[4-(1-Methanesulfonyl-2-oxo-3R-propylhexahydro-(3aS,6aR)-pyrrolo[3,4-b]pyrrole-5-sulfonyl)-phenyl]acetamide;
 rel-(3R,3aS,6aR)-1-Methanesulfonyl-5-(4-piperidin-1-ylmethyl-benzoyl)-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one;
 rel-(3R,3aS,6aR)-1-Methanesulfonyl-5-(4-morpholin-4-ylmethyl-benzoyl)-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one;
 rel-(3R,3aS,6aR)-1-Methanesulfonyl-5-(5-morpholin-4-ylmethyl-isoxazole-3-carbonyl)-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one;
 rel-(3R,3aS,6aR)-5-(5-Dimethylaminomethyl-isoxazole-3-carbonyl)-1-methanesulfonyl-3-propyl-hexahydro-pyrrolo[3,4-b]pyrrol-2-one;
 or a salt or solvate of any one thereof.
10. A purified single enantiomer of a compound of formula (I) according to any one of claims 1 to 9 having the absolute stereochemistry as illustrated in formula (I).

11. A compound of formula (I) according to any one of claims 1 to 10 for use as a pharmaceutical.
12. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 10 in admixture with one or more physiologically acceptable diluents or carriers.
13. Use of a compound of formula (I) according to any one of claims 1 to 10 in the manufacture of a medicament for the treatment of chronic bronchitis or chronic obstructive pulmonary disease.
14. A method of treatment of chronic bronchitis 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 10.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/05743

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D487/04 A61K31/40 //(C07D487/04,209:00,209:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 21855 A (ZENECA) 17 August 1995 see page 1, line 1 - page 2, paragraph 1 -----	1,11
A	WO 93 24519 A (ZENECA) 9 December 1993 see page 1, paragraph 1 -----	1,11
P,A	WO 97 36903 A (GLAXO) 9 October 1997 see claims 1,20,22 -----	1,11

☐ Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

25 January 1999

Date of mailing of the international search report

03/02/1999

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/05743

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 14
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/05743

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9521855 A	17-08-1995	AT 174034 T AU 692515 B AU 1583995 A CA 2180006 A CN 1140455 A DE 69506380 D EP 0743953 A FI 963132 A JP 9508902 T NO 963329 A NZ 279265 A US 5739157 A ZA 9501061 A	15-12-1998 11-06-1998 29-08-1995 17-08-1995 15-01-1997 14-01-1999 27-11-1996 09-08-1996 09-09-1997 09-10-1996 26-01-1998 14-04-1998 11-08-1995
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WO 9736903 A	09-10-1997	AU 2291797 A EP 0891362 A	22-10-1997 20-01-1999