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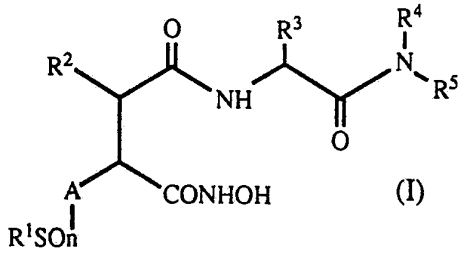
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(54) Title: HYDROXAMIC ACID BASED COLLAGENASE AND CYTOKINE INHIBITORS



(57) Abstract

Hydroxamic acid derivatives of formula (I) wherein R^1 represents hydrogen or a (C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl, phenyl, substituted phenyl, phenyl(C_1-C_6)alkyl, heterocyclyl, (C_1-C_6)alkylcarbonyl, phenacyl or substituted phenacyl group; R^2 represents hydrogen or a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, phenyl (C_1-C_6)alkyl, cycloalkyl (C_1-C_6)alkyl or cycloalkenyl (C_1-C_6)alkyl group, R^3 represents a group $-CH_2CO_2(C_1$-$C_4)$alkyl or $-CH_2CH_2CO_2(C_1$-$C_4)$alkyl; R^4 represents hydrogen or a (C_1-C_6)alkyl or phenyl(C_1-C_6)alkyl group; R^5 represents hydrogen or a methyl group; n is 0, 1 or 2; and A represents a (C_1-C_6)hydrocarbon chain optionally substituted with one or more (C_1-C_6)alkyl, phenyl, or substituted phenyl groups; or salts, solvates or hydrates thereof, are inhibitors of tumour necrosis factor production and of matrix metalloproteinases .

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HYDROXAMIC ACID BASED COLLAGENASZ AND CYTOKINE INHIBITORS

This invention relates to therapeutically active hydroxamic acid derivatives, to processes for their preparation, to pharmaceutical compositions containing them, and to the use of such compounds in medicine. In particular, the compounds are inhibitors of the release of tumour necrosis factor (TNF) from cells, and inhibitors of metalloproteinases involved in tissue degradation.

TNF is a cytokine which is produced initially as a cell-associated 28kD precursor. It is released as an active, 17kD form (Jue, D-M et al., (1990) Biochemistry 29:8371-8377), which can mediate a large number of deleterious effects *in vivo*. When administered to animals or humans it causes inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase responses, similar to those seen during acute infections and shock states. Chronic administration can also cause cachexia and anorexia. Accumulation of excessive TNF can be lethal.

There is considerable evidence from animal model studies that blocking the effects of TNF with specific antibodies can be beneficial in acute infections, shock states, graft versus host reactions and autoimmune disease. TNF is also an autocrine growth factor for some myelomas and lymphomas and can act to inhibit normal haematopoiesis in patients with these tumours.

Preventing the production or action of TNF is, therefore, predicted to be a potent therapeutic strategy for many inflammatory, infectious, immunological or malignant diseases. These include, but are not restricted to, septic shock, haemodynamic shock and sepsis syndrome (Mathison *et al.* (1988) J. Clin. Invest. 81:1925-1937; Miethke *et al.* (1992) J. Exp. Med. 175:91-98), post ischaemic reperfusion injury, malaria (Grau *et al.*, (1989) Immunol. Rev. 112:49-70); mycobacterial infection (Barnes *et al.* (1992) Infect. Imm. 60:1441-6), meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, rheumatoid arthritis, multiple sclerosis, radiation damage, toxicity following administration of immunosuppressive monoclonal antibodies such as OKT3 or CAMPATH-1 and hyperoxic alveolar injury.

Current clinical anti-TNF strategies involve the use of corticosteroids such as dexamethasone, and the use of cyclosporin-A or FK506, which are non-specific inhibitors of cytokine gene transcription. Phosphodiesterase inhibitors such as pentoxyfilline have been shown to be more specific inhibitors of TNF gene transcription (Endres S *et al.* (1991) Immunol. 72:56-60, Schandene *et al.* (1992) Immunol. 76:30-34, Alegre ML, *et al.* (1991); Transplantation 52:674-679, Bianco *et al.* (1991) Blood 78:1205-1211). Thalidomide has also been shown to inhibit TNF production by leucocytes (Sampajo *et al,* (1991) J. Exp. Med. 173:699-703). In experimental settings, anti-TNF monoclonal antibodies, soluble TNF receptors and soluble TNF receptor/immunoadhesins have been shown to specifically inhibit the effects of TNF action (Bagby *et al.* (1991) J. Infect. Dis. 163:83-88, Charpentier *et al.* (1991) Presse-med. 20:2009-2011, Silva *et al.* (1990) J. Infect. Dis. 162:421-427; Franks *et al.* (1991) Infect. Immun. 59:2609-2614, Tracey *et al.* (1987) Nature 330:662-664; Fischer *et al.* (1992) PNAS USA in press, Lesslauer *et al.* (1991) Eur. J. Immunol. 21:2883-2886, Ashkenazi *et al.* (1991) PNAS USA 88:10535-10539)

It has recently been shown that the effects of TNF are mediated by two peptides, TNF α and TNF ß. Although these peptides have only 30% homology with each other, they activate the same receptors and are encoded by immediately adjacent genes. As used herein, the term tumour necrosis factor or TNF therefore means tumour necrosis factor α and peptides having a high degree of sequence homology with, or substantially similar physiological effects to, TNF α, for example TNF ß.

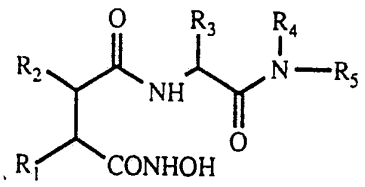
It is an object of the present invention to provide compounds which substantially inhibit the release of TNF from cells, and therefore may be used in the treatment of conditions mediated by TNF. Such uses include, but are not limited to, the treatment of inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infections, shock states, graft versus host reactions and autoimmune disease.

Compounds which have the property of inhibiting the action of metalloproteinases

involved in connective tissue breakdown such as collagenase, stromelysin and gelatinase (known as "matrix metalloproteinases", and herein referred to as MMPs) are thought to be potentially useful for the treatment or prophylaxis of conditions involving such tissue breakdown, for example rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, corneal epidermal or gastric ulceration, and tumour metastasis or invasion. Several classes of MMP inhibitors have been proposed, including derivatives of hydroxamic acid. The following patent publications disclose hydroxamic acid-based MMP inhibitors, but disclose nothing concerning inhibition of TNF release:

US 4599361	(Searle)
EP-A-0236872	(Roche)
EP-A-0274453	(Bellon)
WO 90/05716	(British Bio-technology)
WO 90/05719	(British Bio-technology)
WO 91/02716	(British Bio-technology)
EP-A-0489577	(Celltech)
EP-A-0489579	(Celltech)
EP-A-0497192	(Roche)
WO 92/13831	(British Bio-technology)

The MMP inhibiting hydroxamic acid derivatives disclosed in those publications can be regarded as having the following basic structure (IA):



(IA)

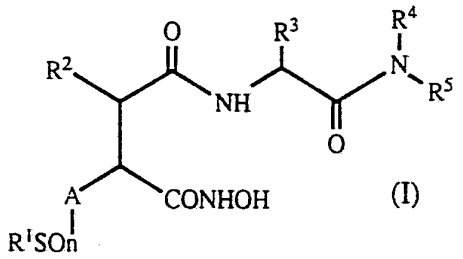
wherein the five substituents R_1 - R_5 may vary according to the detailed disclosure of each publication. For compounds falling within the broad categories disclosed in those publications, the balance of intrinsic level of activity, degree of specificity of activity for a particular category of MMP, and pharmacokinetic properties can vary

in an unpredictable way as the substituents R_1 - R_5 are varied. Their intrinsic potency against particular MMPs can be high. For example, many have a collagenase IC_{50} by the *in vitro* test method of Cawston and Barrett, (Anal. Biochem., **99**, 340-345, 1979) of less than 50 nM. Unfortunately, however, many of the specific compounds disclosed in those publications have poor water solubility, leading to severe formulation difficulties, and/or have generally poor pharmacokinetic properties. Identifying hydroxamic acid-based MMP inhibitors having a good balance of high intrinsic activity, good water solubility and acceptable pharmacokinetic properties, such that the compounds are easy to formulate and have high *in vivo* activity in the target disease or condition, remains a much sought after goal in the art.

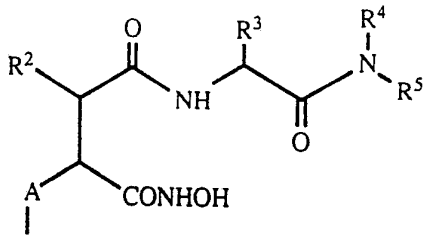
It is a further object of this invention to provide compounds which, in addition to inhibiting TNF release, also inhibit the action of MMPs, and therefore may be used in the treatment of patients who suffer from conditions mediated by TNF and/or MMPs.

It is also an object of the invention to provide compounds having good water solubility and an acceptable pharmacokinetic profile.

WO-A-90 05719 (British Bio-technology), mentioned above, discloses compounds of general formula



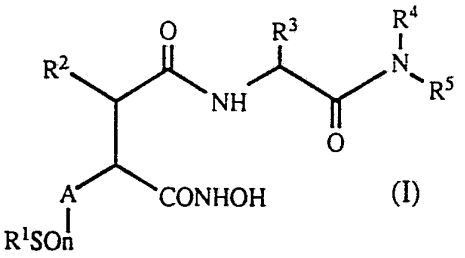
where R^1 represents hydrogen or an alkyl, phenyl, thienyl, substituted phenyl, phenylalkyl, heterocyclyl, alkylcarbonyl, phenacyl or substituted phenacyl group; or, when n=0, R^1 represents SR^x wherein R^x represents a group



R^2 represents a hydrogen atom or an alkyl, alkenyl, phenylalkyl, cycloalkylalkyl or cycloalkenylalkyl group, R^3 represents an amino acid residue with R or S stereochemistry or an alkyl, benzyl, (C_1-C_6 alkoxy) benzyl or benzyloxy (C_1-C_6 alkyl) group; R^4 represents a hydrogen atom or an alkyl group; R^5 represents a hydrogen atom or a methyl group; n is an integer having the value 0, 1 or 2; and A represents a hydrocarbon chain optionally substituted with one or more alkyl, phenyl, or substituted phenyl groups, and their salts and N-oxides. In WO-A-90 05719 such compounds are disclosed as having collagenase inhibitory activity, with consequent utility in the management of diseases involving tissue degradation and/or the promotion of wound healing.

The compounds of the present invention differ in structure from those of WO-A-9005719 principally in the identity of the substituent R^3. In the compounds generically disclosed in WO-A-9005719, R^3 is an amino acid side chain or a (C_1-C_6)alkyl, benzyl, (C_1-C_6)alkoxybenzyl, benzyloxy (C_1-C_6)alkyl or benzyloxybenzyl group. However, compounds in which R^3 is the side chain of aspartic or glutamic acid are not specifically disclosed or their properties specifically characterised in WO-A- 9005719. In the compounds of the present invention, R^3 represents an ester of the side chains of aspartic acid or glutamic acid, as is explained further below. Data suggests that the esters of this invention are more potent than the carboxylic acid analogues as inhibitors of TNF production.

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



(I)

wherein:

R1 represents hydrogen or an (C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl, phenyl, substituted phenyl, phenyl (C_1-C_6)alkyl, heterocyclyl, (C_1-C_6)alkylcarbonyl, phenacyl or substituted phenacyl group;

R2 represents hydrogen or a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, phenyl (C_1-C_6)alkyl, cycloalkyl (C_1-C_6)alkyl or cycloalkenyl (C_1-C_6)alkyl group;

R3 represents a group $-CH_2CO_2$ (C_1-C_4)alkyl or $-CH_2CH_2CO_2$ (C_1-C_4)alkyl;

R4 represents hydrogen or a (C_1-C_6)alkyl or phenyl(C_1-C_6)alkyl group;

R5 represents hydrogen or a methyl group;

n is 0, 1 or 2;

and A represents a (C_1-C_6)hydrocarbon chain optionally substituted with one or more (C_1-C_6)alkyl, phenyl, or substituted phenyl groups;

or a salt solvate or hydrate thereof.

As used herein the term "C_1-C_6 alkyl" refers to a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl and hexyl.

The term "C_2-C_6 alkenyl" refers to a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms and having in addition one double bond of either E or Z stereochemistry where applicable. This term would include, for example, vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

The term "cycloalkyl" refers to a saturated alicyclic moiety having from 3-6 carbon atoms and includes, for example, cyclohexyl, cyclopentyl, cyclobutyl and cyclopropyl.

The term "cycloalkenyl" refers to an alicyclic moiety having from 4-8 carbon atoms and includes, for example, cyclohexenyl, cyclopentenyl, cycloheptenyl and cyclooctenyl.

The term "heterocyclyl" refers to a 5-7 membered heterocyclic ring containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzene ring, including for example, pyrollyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperizinyl, indolyl and benzimidazolyl.

The term "substituted" as applied to any moiety means substituted with up to four substituents, each of which independently may be C_1-C_6 alkoxy, hydroxy, mercapto, C_1-C_6 alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, carboxylic acid, C_1-C_4 alkylcarboxy or nitro.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

There are several chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereomers with R or S

stereochemistry at each chiral centre. General formula (I), and (unless specified otherwise) all other formulae in this specification are to be understood to include all such stereoisomers and mixtures (for example racemic mixtures) thereof.

In the compounds of the invention, the preferred stereochemistry is in general as follows:

C atom adjacent the -CONHOH moiety - S,

C atom adjacent the R_2 group - R,

C atom adjacent the R_3 group - S,

but mixtures in which the above configurations predominate are also contemplated.

Preferred compounds of the invention include those in which, independently or in any combination:

R1 represents hydrogen or an (C_1-C_6)alkyl, phenyl, thienyl, benzyl, acetyl, phenacyl or substituted phenyl, for example 4-hydroxy-, 4-amino- or 4-methoxyphenyl group;

R2 represents a (C_2-C_6)alkyl group, for example a *sec*-butyl group;

R3 represents a group $-CH_2CO_2$ (C_1-C_4)alkyl or $-CH_2CH_2CO_2$ (C_1-C_4)alkyl, the (C_1-C_4)alkyl moiety being for example a methyl or *tert*-butyl group;

R4 represents a (C_1-C_4)alkyl group;

R5 represents a hydrogen atom;

n is 0;

A is $-CH_2-$;

or salts solvates or hydrates thereof.

Specific compounds of the invention are:

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-phenylsulfanylmethyl hexanohydroxamic acid;

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-(thien-2-ylsulfanylmethyl)-hexanohydroxamic acid;

2S-(4-Methoxy-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Amino-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Ethylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Acetylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Benzylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(*tert*-Butylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-Thiomethyl-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(2-*tert*-butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxy-phenylsulphinylmethyl)-3R-(3-methoxycarbonyl-1S-

methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxy-phenylsulphonylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

and salts, hydrates and solvates thereof.

Compounds of the invention which are presently particularly preferred, inter alia for their potency in inhibiting TNF release, and their water solubility are:

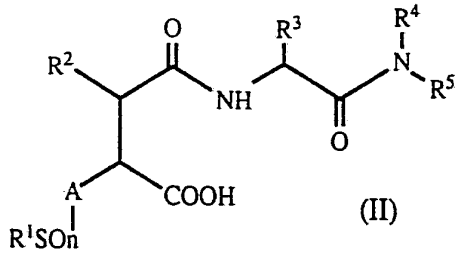
2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid and

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-*tert* butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

and salts (for example the hydrochloride), hydrates and solvates thereof.

Compounds of general formula (I) may be prepared by any suitable method known in the art and/or by the following process, which itself forms part of the invention, namely a process for preparing a compound of general formula (I) as defined above, comprising:

(a) coupling an acid of general formula (II)

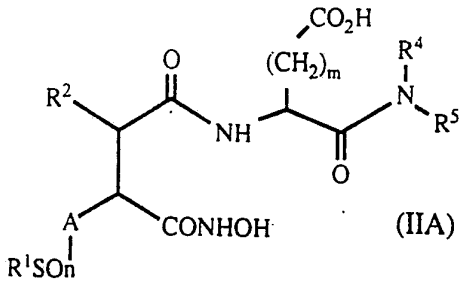


(II)

or an activated derivative thereof with hydroxylamine, O-protected

hydroxylamine, or a salt thereof, R^1, R^2, R^3, R^4, R^5, A and n being as defined in general formula (I) except that any substituents in R^1, R^2, R^3, and A which are potentially reactive with hydroxylamine, O-protected hydroxylamine or their salts may themselves be protected from such reaction, then removing any protecting groups from the resultant hydroxamic acid moiety and from any protected substituents in R^1, R^2, R^3 and A; or

(b) esterifying a compound of formula (IIA)



(IIA)

wherein m=1 or 2 and R^1, R^2, R^4, R^5 and A are as defined in formula (I), with an alcohol of formula $HO(C_1\text{-}C_4)$alkyl; and

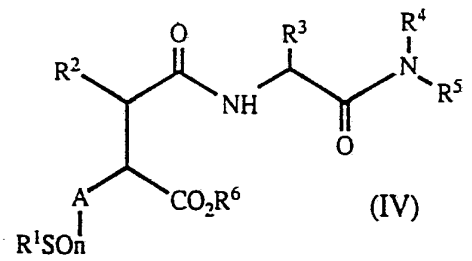
(c) optionally after step (a) or (b) converting a compound of general formula (I) into another compound of general formula (I).

Compounds of general formula (I) which are sulphoxides or sulphones can be prepared from sulphanyl compounds of general formula (I) (n=0) by oxidation.

Conversion of (II) to an activated intermediate such as the pentafluorophenyl, hydroxysuccinyl, or hydroxybenztriazyl ester may be effected by reaction with the appropriate alcohol in the presence of a dehydrating agent such as dicyclohexyl dicarbodiimide (DCC), N,N-dimethylaminopropyl-N'-ethyl carbodiimide (WSCDI), or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ). Esterification of (IIA) may be effected by standard methods.

Protecting groups as referred to above are well known *per se*, for example from the techniques of peptide chemistry. Amino groups are often protectable by benzyloxycarbonyl, t-butoxycarbonyl or acetyl groups, or in the form of a phthalimido group. Hydroxy groups are often protectable as readily cleavable ethers such as the t-butyl, t-butyldimethylsilyl, tetrahydropyranyl or benzyl ether, or as readily cleavable esters such as the acetate. Carboxy groups are often protectable as readily cleavable esters, such as the t-butyl or benzyl ester.

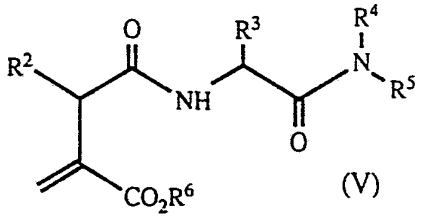
A compound of formula (II) may be prepared by de-esterification (such as by hydrolysis) of an ester of formula (IV)



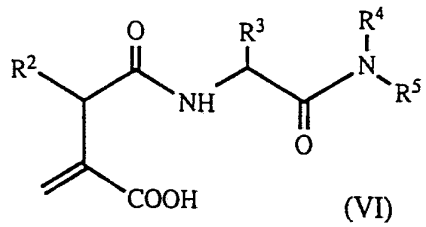
(IV)

wherein R^1, R^2, R^3, R^4, R^5, A and n are as defined in general formula (I) and R^6 represents C_1-C_6 alkyl, 2-trimethylsilylethyl, phenyl C_1-C_6 alkyl or substituted phenyl C_1-C_6 alkyl.

A compound of formula (IV) can be prepared from an ester of formula (V) or an acid of formula (VI)



(V)



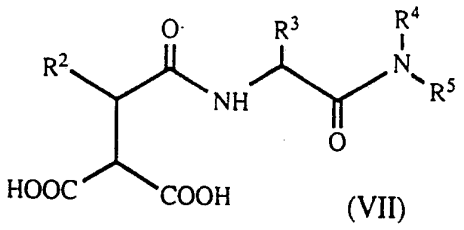
(VI)

wherein R^2, R^3, R^4, and R^5, are as defined in general formula (I) and R^6 represents C_1-C_6 alkyl, phenyl C_1-C_6 alkyl or substituted phenyl C_1-C_6 alkyl, by reaction with a

thiol R^1SH, wherein R^1 is as defined in formula (I), to give compounds wherein A represents a methylene group, or by reaction with a cuprate of formula $(R^1\text{-}S\text{-}A^1)_2CuLi$ wherein R^1 is as defined in formula (I), and A^1 is such that $-A^1\text{-}CH_2-$ is identical to -A- as defined in formula (I).

Esters of formula (V) can be prepared by esterifying acids of formula (VI) with an appropriate alcohol R^6OH or other esterifying agent.

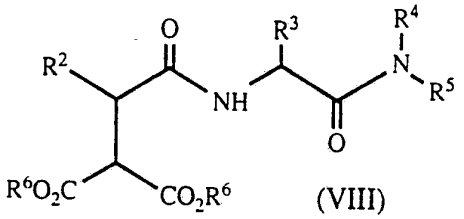
An acid of formula (VI) can be prepared by reacting a malonic acid derivative of formula (VII)



(VII)

wherein R^2, R^3, R^4, and R^5, are as defined in general formula (I), with formaldehyde in the presence of piperidine.

An acid of general formula (VII) can in turn be prepared by de-esterifying (for example by hydrolysis) a compound of formula (VIII)

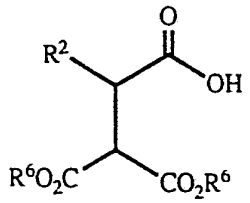


(VIII)

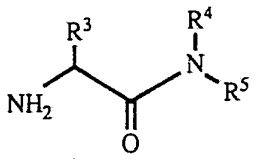
wherein R^2, R^3, R^4, and R^5 are as defined in general formula (I) and R^6 represents C_1-C_6 alkyl, phenyl C_1-C_6 alkyl or substituted phenyl C_1-C_6 alkyl.

A compound of general formula (VIII) can be prepared by coupling a compound of

formula (IX) with a compound of formula (X)



(IX)

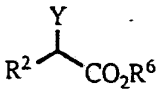


(X)

wherein R^2, R^3, R^4, and R^5 are as defined in general formula (I) and R^6 represents C_1-C_6 alkyl, phenyl C_1-C_6 alkyl or substituted phenyl C_1-C_6 alkyl.

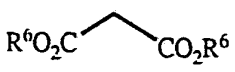
The starting materials and other reagents are either available commercially or can be synthesised by simple chemical procedures.

For example, a substituted acid of formula (IX) may be prepared by reacting an ester of formula (XI)



(XI)

wherein Y represents halo and R^2 and R^6 are as defined above, with a malonate derivative of formula (XII)



(XII)

wherein R^6 is as defined above, with the proviso that when R^6 is benzylic in formula (XI) it is aliphatic in formula (XII), or vice versa, and selectively de-esterifying.

Compounds of general formula (XI) can simply be derived from amino acids, which can be obtained in enantiomerically pure form, enabling a choice of optically active compounds of formula (I) to be prepared.

Compounds of formula (II) and (IIA) are valuable intermediates in the preparation of compounds of formula (I), and in that respect form part of the present invention.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine since they are active as inhibitors of TNF and MMPs. Accordingly in another aspect, this invention concerns:

(i) a method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective, amount of a compound of formula (I) above, or a pharmaceutically acceptable salt thereof; and

(ii) a compound of formula (I) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs; and

(iii) the use of a compound of formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs.

The diseases or conditions referred to above include inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infections, shock states, graft versus host reactions and autoimmune disease; and those involving tissue breakdown such as bone resorption, inflammatory diseases, dermatological conditions, tumour growth, angiogenesis and invasion by secondary metastases, in particular rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, tumour growth, angiogenesis and invasion by secondary metastases.

In a further aspect of the invention there is provided a pharmaceutical or veterinary composition comprising a compound of formula (I) together with a pharmaceutically or veterinarily acceptable excipient or carrier.

One or more compounds of general formula (I) may be present in the composition together with one or more excipient or carrier.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their physicochemical and pharmacokinetic properties. The compositions thus may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions, as appropriate. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. 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 reconstitution 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 syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

The dosage unit for oral administration may contain from about 1 to 250mg, for example from about 25 to 250mg of a compound of general formula I. A suitable daily dose for a mammal may vary widely depending on the condition of the patient. However, a dose of a compound of general formula I of about 0.1 to 300mg/kg body weight, particularly from about 1 to 100mg/kg body weight may be appropriate.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The dosage for topical administration will of course depend on the size of the area being treated. For the eyes, each dose may typically be in the range from 10 to 100mg of the drug.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

For use in the treatment of rheumatoid arthritis, the drug can be administered by the oral route or by injection intra-articularly into the affected joint. The daily dosage for a 70kg mammal may be in the range 10mgs to 1gram.

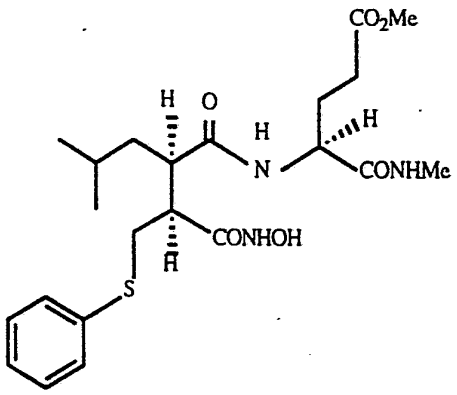
The following examples 1-14 illustrate the invention in more detail, but are not intended to limit the scope in any way. Biological Examples A-C illustrate the activity of some of the compounds of the invention. The comparative example describes the preparation of a compound related in structure to those of the invention, said comparative compound being an example of the class of intermediates of formula (IIA) above for the preparation of compounds of the invention.

Abbreviations

WSCDI	N,N-dimethylaminopropyl-N'-ethyl carbodiimide
DMF	N,N-dimethylformamide
NMM	N-methylmorpholine
DCM	Dichloromethane
HOBT	Hydroxybenztriazole

Example 1

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-phenylsulfanylmethyl hexanohydroxamic acid.



a) N-Methyl-4-methoxycarbonyl-2S-aminobutanamide trifluoroacetic acid salt (12.55g, 72mmol) was taken up in DMF and stirred at 0°C, 2-benzyloxycarbonyl-3R-isobutyl succinic acid-4-pentafluorophenyl-1-benzyl diester (56.98g, 143.8mmol) and N-methyl morpholine (31.56g, 312mmol) were added and the mixture gradually allowed to warm to room temperature and stirred overnight. Solvent was removed under vacuum and the residue taken up in DCM then washed with 1M sodium carbonate, 1M hydrochloric acid and brine, then dried over magnesuim sulphate. Solvent was removed under vacuum and the crude product purified by column chomatography (silica gel, DCM). The product was then further purified by column chromatography (silica gel, DCM/ethyl acetate, 1:1) to provide a white solid.

The title compound was recrystallized from ethyl acetate/hexane (12.01g, 21.65 mmol, 30%):^{1}H-NMR; δ($CDCl_3$), 7.29 (10H, m, Aryl-H), 6.82 (1H, d, J=7.4 Hz, CONHCH), 6.43 (1H, q, J=4.5 Hz, $CNHCH_3$), 5.11 (4H, m, CH_2Ph), 4.36 (1H, m, NHCHCO), 3.81 (1H, d, J=9.8 Hz, $CH(CO_2Bn)_2$), 3.65 (3H, s, CO_2CH_3), 2.96 (1H, dt, J=3.9 Hz, ^{i}BuCH), 2.78 (3H, d, J=4.8 Hz, $NHCH_3$), 2.49 (1H, m, $CH_2CH_2CO_2CH_3$), 2.35 (1H, m, $CH_2CH_2CO_2CH_3$), 2.10 (1H, m, $CH_2CH_2CO_2CH_3$), 1.92 (1H, m, $CH_2CH_2CO_2CH_3$), 1.60 (2H, m, $(CH_3)_2CHCH_2$), 1.04 (1H, m, $CH(CH_3)_2$), 0.82 (6H, 2 x d, J=5.8 Hz, $CH(CH_3)_2$).

b) 2-[1R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-3-methyl-butyl]-acrylic acid.

2-[1R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-3-methyl-butyl]-malonic acid dibenzyl ester (12.01g, 21.65 mmol) was dissolved in ethanol (200 ml), 20% palladium on charcoal (2.4 g) added and the mixture subjected to an atmosphere of hydrogen for 1.5 hours. The catalyst was removed by filtration and the solvent removed under vacuum to give the diacid as a white solid (about 8.5 g). This crude diacid was taken up in ethanol (250 ml) and piperidine (2.03g, 23.81 mmol) was added. After 15 minutes the solution was cooled to 0°C and formaldehyde (37% aqueous solution, 16.2 ml, 216 mmol) was added and the reaction stirred at room temperature overnight. Solvent was removed under vacuum and the residue taken up in ethyl acetate and washed with 1M hydrochloric acid then brine. The organic layer was separated and dried over magnesuim sulphate then the solvent was removed to give the title compound as a white solid (3.89, 11.37 mmol, 53%): ^{1}H-NMR, δ($CDCl_3$), 8.10 (1H, d, J=8.8 Hz, CONHCH), 7.10 (1H, q, J=4.8 Hz, $CONHCH_3$), 6.47 (1H, s, CH_2=C), 5.95 (1H, s, CH_2=C), 4.65 (1H, m, NHCHCO), 3.79 (1H, t, J=6.9 Hz, ^{i}BuCH), 3.63 (3H, s, CO_2CH_3), 2.84 (3H, d, J=4.7 Hz, $NHCH_3$), 2.32 (2H, m, $CH_2CH_2CO_2CH_3$), 2.01 (1H, m, $CH_2CH_2CO_2CH_3$), 1.90 (1H, m, $CHCH_2CH_2CO_2CH_3$), 1.78 (1H, m, $(CH_3)_2CHCH_2$), 1.51 (2H, m,

$(CH_3)_2C\underline{H}CH_2$ and $(CH_3)_2CHC\underline{H_2}$), and 0.87 (6H, 2 x d, J=6.2 Hz, $CH(C\underline{H_3})_2$).

c) 3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-phenylsulfanylmethyl hexanoic acid.

2-[1R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-3-methyl-butyl]-acrylic acid (0.2g, 0.58mmol) was taken up in thiophenol (5ml) and the mixture heated at 60°C under argon with the exclusion of light overnight. Crude product was purified by column chromatography (silica gel, hexane then ethyl acetate) to provide the title compound as a white solid (37mg, 0.08mmol, 14%): ^{1}H-NMR; δ ($CDCl_3$), 7.96 (1H, d, J=7.8Hz, CON$\underline{H}$CH), 7.27 (5H, m, aryl-H), 6.79 (1H, q, J=4.8Hz, CON$\underline{H}CH_3$), 4.54 (1H, m, NHC$\underline{H}$CO), 3.64 (3H, s, $CO_2C\underline{H_3}$), 3.30 (1H, dd, J=13.2, 8.3 Hz, CHC$\underline{H_2}$S), 3.02 (1H, dd, J=13.0, 5.5 Hz, CHC$\underline{H_2}$S), 2.81 (5H, m, ^{i}BuC$\underline{H}$, C$\underline{H}CH_2$S and CONHC$\underline{H_3}$), 2.42 (2H, m, $CH_2C\underline{H_2}CO_2CH_3$), 2.11 (1H, m, C$\underline{H_2}CH_2CO_2CH_3$), 1.97 (1H, m, C$\underline{H_2}CH_2CO_2CH_3$), 1.74 (1H, m, $(CH_3)_2CHC\underline{H_2}$), 1.39 (1H, m, $(CH_3)_2CHC\underline{H_2}$), 1.17 (1H, m, $(CH_3)_2C\underline{H}CH_2$), and 0.84 (6H, d, J=6.4Hz, $(C\underline{H_3})_2CHCH_2$): ^{13}C-NMR; ($CDCl_3$), 174.6, 173.1, 171.9, 171.2, 133.8, 128.2, 127.6, 125.0, 50.7, 50.4, 46.4, 45.0, 38.4, 32.5, 28.6, 25.7, 25.0, 24.5, 22.2, and 19.0.

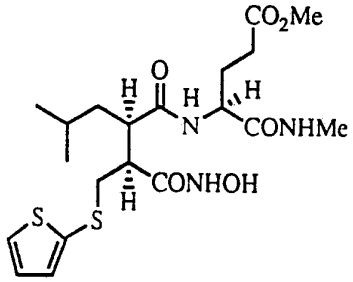
d) 3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-phenylsulfanylmethyl hexanohydroxamic acid.

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-phenylsulfanylmethyl hexanoic acid (37 mg, 0.082 mmol) was taken up in DCM and cooled to 0°C while HOBT (14.3 mg, 0.106 mmol), NMM (10.6 mg, 0.106 mmol) and N-(dimethylaminoethyl)-N'-ethylcarbodiimide (WSCDI, 20.3 mg, 0.106 mmol) were added. The reaction was stirred at 0°C while hydroxylamine hydrochloride (9.2 mg, 0.132 mmol) and NMM (13.3 mg, 0.132 mmol) were added and the reaction stirred at room temperature for two days. Solvent was removed under vacuum and the residue partitioned

between diethyl ether/water and the title compound collected by filtration as a white solid (19.2 mg, 0.041 mmol, 50%): ^{1}H-NMR; δ (methanol-d_4), 7.24 (5H, m, Aryl-H), 4.34 (1H, m, NHC<u>H</u>CO), 3.56 (3H, s, $CO_2C\underline{H_3}$), 2.98 (2H, m, $CHC\underline{H_2}S$), 2.69 (3H, s, $CONHC\underline{H_3}$), 2.58 (1H, m, ^{i}BuC<u>H</u>), 2.38 (3H, m, $C\underline{H}CH_2S$ and $CH_2C\underline{H_2}CO_2CH_3$), 1.95 (2H, m, $C\underline{H_2}CH_2CO_2CH_3$), 1.51 (2H, m, $(CH_3)_2CHC\underline{H_2}$), 1.04 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 0.86 (3H, d, J=6.4 Hz, $CH(C\underline{H_3})_2$), and 0.80 (3H, d, J=6.4 Hz, $CH(C\underline{H_3})_2$):^{13}C NMR; δ (methanol-d_4), 176.1, 174.6, 173.5, 171.4, 130.1, 129.6, 129.6, 53.8, 53.2, 41.6, 35.0, 31.1, 28.1, 26.8, 25.2, 24.5, and 22.2.

Example 2

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-(thien-2-ylsulfanylmethyl)-hexanohydroxamic acid.



a) 3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-(thien-2-ylsulfanylmethyl)-hexanoic acid.

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-3-methyl-butyl]-acrylic acid (1.18g, 3.47 mmol) was treated with thiophene-2-thiol as described in example 1c. Crude product was purified by column chromatography (silica gel, DCM then 10% MeOH/DCM) to provide the title compound as a white solid (1.21g, 2.64 mmol, 76%): ^{1}H-NMR δ (methanol-d_4), 7.41 (1H, m, thienyl-H5), 7.12 (1H, m, thienyl-H3), 6.94 (1H, m, thienyl-H4), 4.27 (1H, m, NHC<u>H</u>CO), 3.63 (3H, s, $CO_2C\underline{H_3}$), 2.94 (2H, m, $CHC\underline{H_2}S$),

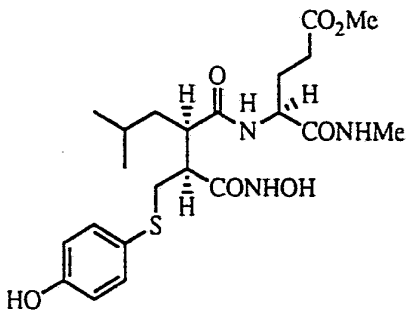
2.69 (5H, m, $CONHC\underline{H}_3$ and $^iBuC\underline{H}$ and $C\underline{H}CH_2S$), 2.36 (2H, m, $C\underline{H}_2CH_2CO_2CH_3$), 1.61 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.39 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.10 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.88 (3H, d, J=6.6 Hz, $CH(C\underline{H}_3)_2$), and 0.79 (3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$).

b) 3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-(thien-2-ylsulfanylmethyl)-hexanohydroxamic acid

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-(thien-2-ylsulfanylmethyl)-hexanoic acid (1.0g, 2.2 mmol) was coupled with hydroxylamine as described in example 1d to produce the title compound which was purified by column chromatography (acid washed silica gel, 10% MeOH/DCM) then triturated with diethyl ether to provide a white solid (170 mg, 0.4 mmol, 17%): ^{1}H-NMR; δ (methanol-d_4), 7.4 (1H, d, J=5.3 Hz, thienyl-H5), 7.1 (1H, d, J=2.5 Hz, thienyl-H3), 6.94 (1H, m, thienyl-H4), 4.26 (1H, m, $NHC\underline{H}CO$), 3.63 (3H, s, $CO_2C\underline{H}_3$), 2.96 (1H, dd, J=12.9, 11.2 Hz, $CHC\underline{H}_2S$), 2.75 (1H, dd, J=12.8, 3.4 Hz, $CHC\underline{H}_2S$), 2.67 (3H, s, $CONHC\underline{H}_3$), 2.55 (1H, dd, J=10.9, 3.1 Hz, $C\underline{H}CH_2S$), 2.37 (3H, m, $^iBuC\underline{H}$ and $CH_2C\underline{H}_2CO_2CH_3$), 1.92 (2H, m, $C\underline{H}_2CH_2CO_2CH_3$), 1.50 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.34 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.05 (1H, m, $(CH_3)_2CHC\underline{H}_2$), and 0.80 (6H, 2 x d, J=6.6, 6.5 Hz, $CH(C\underline{H}_3)_2$).

Example 3

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.



a) 2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid.

2-[1R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-3-methyl-butyl]-acrylic acid (2.18g, 6.37 mmol) was taken up in methanol (10 ml) and 4-hydroxythiophenol (5 ml) added then the mixture stirred at reflux under argon over night. Solvent removal gave a yellow solid which was purified by column chromatography (silica gel, 0-10% methanol/DCM) to give the title compound as a yellow foam (2.02 g, 4.32 mmol, 68%): ^{1}H-NMR; δ (methanol-d_4), 7.19 (2H, d, J=8.7 Hz, Aryl-H), 6.69 (2H, d, J=8.7 Hz, Aryl-H), 4.29 (1H, m, COC<u>H</u>NH), 3.62 (3H, s, $CO_2C\underline{H}_3$), 2.96 (1H, m, $CHC\underline{H}_2S$), 2.81 (1H, m, $CHC\underline{H}_2S$), 2.69 (3H, s, $NHC\underline{H}_3$), 2.61 (1H, m, C<u>H</u>), 2.33 (3H, m, $CH_2C\underline{H}_2CO_2CH_3$ and $C\underline{H}CH_2S$), 2.04 (2H, m, $C\underline{H}_2CH_2CO_2CH_3$), 1.65 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.85 (3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), and 0.79 (3H, d, J=6.6Hz, $CH(C\underline{H}_3)_2$).

b) 2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.

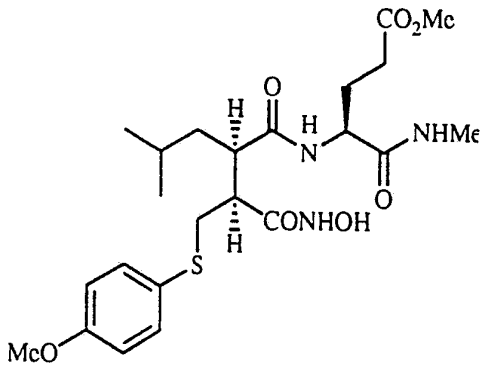
2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid (1.18 g, 2.5 mmol) was taken up in DCM and a small amount of DMF added. The solution was cooled to 0°C while pentafluorophenol (0.93, 5 mmol), NMM (0.3 g, 3 mmol) and WSCDI (0.58 g, 3 mmol) were added. The reaction was stirred at 0°C for 2 hours then room temperature for 1 hour. Solvent was removed under reduced pressure and the residue taken up in DCM then washed with 2M hydrochloric acid, saturated soduim bicarbonate soluton and brine, then dried over magnesuim sulphate. Solvent was removed under reduced pressure and the residue taken up in DCM, to which hydroxylamine hydrochloride (0.23 g, 3.25 mmol) and NMM (0.33 g, 3.25 mmol) were added and the reaction stirred at room temperature over night. The resulting precipitate was collected by filtration, washed with water and

dried under reduced pressure to provide 2S-(4-hydroxy-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid as a white solid (0.56 g, 1.16 mmol, 46%): ^{1}H-NMR, δ (methanol-d_4), 7.18 (2H, d, J=8.6 Hz, Aryl-H), 6.68 (2H, d, J=8.6 Hz, Aryl-H), 4.29 (1H, dd, J=5.6, 5.4 Hz, COC<u>H</u>NH), 3.62 (3H, s, $CO_2C\underline{H}_3$) 2.89 (1H, m, $CHC\underline{H}_2S$), 2.76 (1H, dd, J=12.9, 3.6 Hz, $CHC\underline{H}_2S$), 2.67 (3H, s, $NHC\underline{H}_3$), 2.55 (1H, m, ^{i}BuC<u>H</u>), 2.34 (3H, m, $CH_2C\underline{H}_2CO_2CH_3$ and C<u>H</u>CH_2S), 1.97 (2H, m, $C\underline{H}_2CH_2CO_2CH_3$), 1.48 (2H, m, $(CH_3)_2CHC\underline{H}_2$), 1.01 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 0.83 (3H, d, J=6.4 Hz, $CH(C\underline{H}_3)_2$), and 0.79 (3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$): ^{13}C-NMR; δ (methanol-d_4), 175.9, 174.7, 173.7, 171.3, 158.2, 134.3, 125.6, 117.1, 53.7, 52.2, 41.5, 37.4, 31.1, 28.1, 26.8, 26.2, 24.3, and 21.6.

The mother liquor was purified by column chromatography (acid washed silica gel, 10% methanol/DCM) and recrystallization of the resultant white solid from methanol/diisopropyl ether provided 2R-(4-Hydroxy-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid as the minor diastereoisomer: Analysis for $C_{22}H_{33}N_3O_7S$; requires C 54.64, H 6.88, N 8.70: Found C 53.79 H 6.78 N 8.54: ^{1}H-NMR; (methanol-d_4), 7.17 (2H, d, J=8.7 Hz, Aryl-H), 4.22 (1H, dd, J=9.6, 5.3Hz, NHC<u>H</u>CO), 3.62 (3H, s, $CO_2C\underline{H}_3$), 2.99 (1H, dd, J=13.4, 3.6Hz, $CHC\underline{H}_2S$), 2.87 (1H, m, $CHC\underline{H}_2S$), 2.67 (3H, s, $NHC\underline{H}_3$), 2.55 (1H,m, ^{i}BuC<u>H</u>), 2.33 (3H, m, C<u>H</u>CH_2S and $CH_2C\underline{H}_2CO_2CH_3$), 2.06 (1H, m, $CH_2C\underline{H}_2CO_2CH_3$), 1.85 (1H, m, $CH_2C\underline{H}_2CO_2CH_3$), 1.51 (1H,m, $(CH_3)_2C\underline{H}CH_2$), 0.84 (3H, d, J=7.1 Hz, $CH(C\underline{H}_3)_2$), 0.79 (3H, d, J=6.9 Hz, $C\underline{H}(CH_3)_2$); ^{13}C-NMR; (methanol-d_4), 172.1, 171.2, 168.0, 155.7, 130.8, 123.7, 115.4, 51.41, 50.9, 45.8, 45.4, 33.9, 29.4, 26.1, 25.0, 23.5, 20.7.

Example 4

2S-(4-Methoxy-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.



a) 2S-(4-Methoxy-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid.

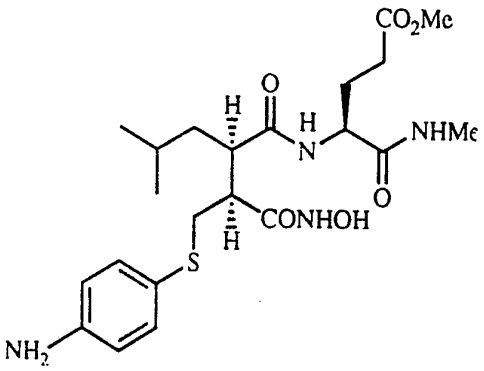
p-Methoxythiophenol (4 ml) and methanol (2 ml) were added to 2-[1R-(3-methoxycarbonyl-1S-methylcarbamoyl)-3-methylbutyl]-acrylic acid (1.01g, 2.9 mmol) and the mixture stirred for 2 days in the dark at 60°C, under argon. Diethyl ether (30 ml) was added to the mixture and resulting white precipitate filtered and thoroughly washed in cold ether to provide the title compound (0.88g, 1.8 mmole, 62%); ^{1}H NMR δ_H; (Methanol-d_4), 7.30 (2H, d, J=8.7 Hz, Ar-H), 6.82 (2H, d, J=8.8 Hz, Ar-H), 4.29 (1H, dd, J=5.7, 8.7 Hz, C<u>H</u>CH_2CH_2), 3.74 (3H, s, $COC\underline{H}_3$), 3.62 (3H, s, $CO_2C\underline{H}_3$), 2.87 (2H, m, $CHC\underline{H}_2S$), 2.67 (3H, s, $CONHC\underline{H}_3$), 2.64 (2H, m, C<u>H</u>C<u>H</u>CH_2S), 2.33 (2H, m, $CH_2C\underline{H}_2CO_2CH_3$), 2.09 - 1.79 (2H, bm, $C\underline{H}_2CH_2CO_2CH_3$), 1.57 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.36 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.07 (1H, m, $(CH_3)_2$ $CHC\underline{H}_2$), 0.83 (3H, d, J=6.5 Hz, $(C\underline{H}_3)_2CH$) and 0.79 (3H, d, J=6.5 Hz, $(C\underline{H}_3)_2CH$).

b) 2S-(4-Methoxy-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.

2S-(4-Methoxy-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid (0.88g, 1.8 mmol) was taken up in DMF (5 ml) and stirred in an ice bath. HOBT (0.28g, 2.1 mmol) and WSCDI (0.40g, 2.1 mmol) were added and the mixture stirred for about 30 minutes in the ice bath followed by 2 hours at room temperature. The mixture was once again cooled in an ice bath and hydroxylamine hydrochloride (0.18g, 2.6 mmol) and NMM (0.26g, 2.6 mmol) added, before stirring at room temperature overnight. DMF was removed under high vacuum and the residue slurried in ether/H_20 (1:1, 50 ml). The resulting white precipitate was filtered and thoroughly washed with ether and water, before drying in-vacuo (0.45g, 0.9 mmol, 52%). m.p. 188 - 189°C; ^{1}H-NMR δ_H; (Methanol-d_4), 7.26 (2H, d, J=8.8 Hz, Ar-H), 6.82 (2H, d, J=8.9 Hz, Ar-H), 4.31 (1H, dd, J=5.6, 8.7 Hz, C<u>H</u>CH_2CH_2), 3.74 (3H, s, $COCH_3$), 3.60 (3H, CO_2CH_3), 2.96 (1H, dd, J=11.3, 12.9 Hz, $CHCHCH_2S$), 2.80 (1H, dd, J=3.6, 13.0 Hz, $CHCHCH_2S$), 2.68 (3H, s, $CONHCH_3$), 2.57 (1H, dt, J=3.5, 10.8 Hz, $CHCHCH_2S$), 2.36 (3H, m, $CH_2CH_2CO2CH_3$ + $CHCHCH_2S$), 2.09 - 1.79 (2H, bm, $CH_2CH_2CO_2CH_3$), 1.51 (1H, m, $(CH_3)_2CHCH_2$), 1.38 (1H, m, $(CH_3)_2CHCH_2$), 1.05 (1H, m, $(CH_3)_2CHCH_2$), 0.84 (3H, d, J=6.4 Hz, $(CH_3)_2CH$) and 0.79 (3H, d, J=6.6 Hz, $(CH_3)_2CH$);^{13}C-NMR; δ_C (Methanol-d_4), 175.9, 174.7, 173.7, 171.3, 160.6, 133.8, 127.5, 115.8, 55.8, 53.8, 52.2, 48.2, 37.1, 31.2, 28.2, 26.9, 24.3 and 21.7.

Example 5

2S-(4-Amino-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.



a) 2S-(4-Amino-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid.

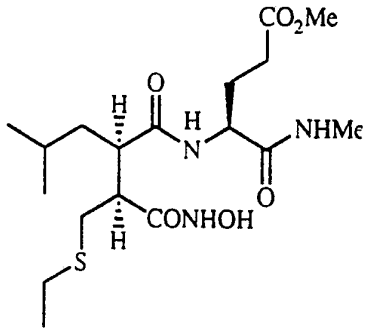
p-Aminothiophenol (4 ml) and methanol (3 ml) were added to 2-[1R-(3-methoxycarbonyl-1S-methylcarbamoyl)-3-methylbutyl]-acrylic acid (0.78g, 2.3 mmol) and the mixture stirred overnight in the dark at 60°C, under argon. The mixture was purified by column chromatography (silica gel, 2-10% methanol/DCM) to give a white solid which was further purified by recrystallisation from EtOAc/EtOH/hexane (0.52g, 1.1 mmole, 49%); ^{1}H-NMR δ_H; (Methanol-d_4), 7.14 (2H, d, J=6.5 Hz, Ar-H), 6.60 (2H, d, J=6.7 Hz, Ar-H), 4.27 (1H, dd, J=5.6, 8.7 Hz, C<u>H</u>CH_2CH_2), 3.63 (3H, s, $CO_2C\underline{H}_3$), 2.80 (2H, m, CHC<u>H</u>$_2$S), 2.66 (3H, s, CONHC<u>H</u>$_3$), 2.68 - 2.52 (2H, bm, C<u>H</u>C<u>H</u>CH_2S), 2.35 (2H, m, $CH_2C\underline{H}_2CO_2CH_3$), 2.08 - 1.76 (2H, bm, $C\underline{H}_2CH_2CO_2CH_3$), 1.57 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.35 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.04 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.83 (3H, d, J=6.4 Hz, $(C\underline{H}_3)_2CH$) and 0.79 (3H, d, J=6.6 Hz, $(C\underline{H}_3)_2CH$).

b) 2S-(4-Amino-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.

2S-(4-Amino-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid (0.50g, 1.1 mmol) was dissolved in DMF (5 ml) and stirred in an ice bath. HOBT (0.17g, 1.3 mmole) and WSCDI (0.24g, 1.3 mmol) were added and the mixture stirred for 30 minutes in the ice bath and 2 hours at room temperature. The mixture was then re-cooled in an ice bath and hydroxylamine hydrochloride (0.11 g, 1.6 mmol) and NMM (0.16g, 1.6 mmol) added, before stirring at room temperature overnight. DMF was evaporated under high vacuum and the residue dissolved in 1:1 ether/H_20 (1:1, 30 ml). The water was separated and evaporated, the resulting residue was purified by column chromatography (acid washed silica gel, 5% methanol/DCM) to give the product as a yellow solid (0.14g, 0.3 mmole, 27%). m.p. 178.0-180°C (decomp.); ^{1}H-NMR δ_H; (Methanol-d_4), 7.12 (2H, d, J=8.4 Hz, Ar-H), 6.62 (2H, d, J=8.5 Hz, Ar-H), 4.30 (1H, m, C<u>H</u>CH_2CH_2), 4.79 (3H, s, CO_2C<u>H_3</u>), 2.91 (1H, m, CHCHC<u>H_2</u>S), 2.74 (1H, m, CHCHC<u>H_2</u>S), 2.67 (3H, s, CONHC<u>H_3</u>), 2.57 (1H, m, C<u>H</u>CHCH_2S), 2.33 (3H, m, CHC<u>H</u>CH_2S + CH_2C<u>H_2</u>CO_2CH_3), 1.81 - 2.08 (2H, bm, C<u>H_2</u>$CH_2CO_2CH_3$), 1.50 (1H, m, $(CH_3)_2$CHC<u>H_2</u>), 1.37 (1H, m, $(CH_3)_2$C<u>H</u>CH_2), 1.02 (1H, m, $(CH_3)_2$CHC<u>H_2</u>), 0.84 (3H, d, J=6.3 Hz, (C<u>H_3</u>$)_2$CH), and 0.79 (3H, d, J=6.5 Hz, (C<u>H_3</u>$)_2$CH); ^{13}C-NMR δ_C; (Methanol-d_4), 175.9, 174.8, 173.7, 171.4, 148.0, 134.4, 123.9, 117.2, 65.2, 53.8, 52.3, 48.2, 41.5, 37.7, 31.2, 28.2, 26.9, 26.3, 24.3 and 21.8.

Example 6

2S-(Ethylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.



a) 2S-(Ethylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid.

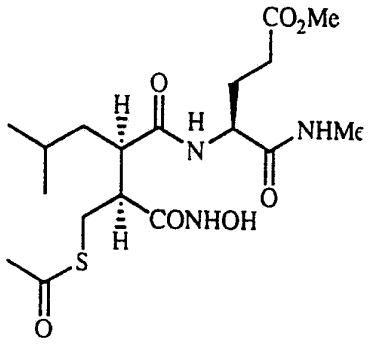
Ethanethiol (5 ml) and triethylamine (0.40 ml, 2.9 mmol) were added to 2-[1R-(3-methoxycarbonyl-1S-methylcarbamoyl)-3-methylbutyl]-acrylic acid (1.98g, 5.8 mmol) and the mixture stirred at 35°C, in the dark, under argon overnight. The bulk of the excess thiol was removed in-vacuo and cold ether added to the residue. The resulting white solid was filtered and thoroughly washed in cold ether. This was dissolved in EtOAc (20 ml) and washed in 1M hydrochloric acid (2 x 15 ml), then the ethyl acetate layer was dried over magnesium sulphate and evaporated under vacuum. Recrystallisation of the resultant white solid from EtOAc/hexane provided the product (1.09g, 2.7 mmol, 47%): ^{1}H NMR δ_H; (Methanol-d_4), 4.33 (1H, dd, J=5.7, 8.8 Hz, C<u>H</u>CH_2CH_2), 3.63 (3H, s, $CO_2C\underline{H}_3$), 2.69 (3H, s, CONHC<u>H</u>$_3$), 2.73 - 2.56 (4H, bm, C<u>H</u>C<u>H</u>$C\underline{H}_2$S), 2.49 (2H, q, J=7.3 Hz, $SC\underline{H}_2CH_3$), 2.39 (2H, m, $CH_2C\underline{H}_2CO_2CH_3$), 2.11 - 1.80 (2H, bm, $C\underline{H}_2CH_2CO_2CH_3$), 1.63 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.43 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.14 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.86 (3H, d, J=6.5 Hz, $(C\underline{H}_3)_2CH$) and 0.82 (3H, d, J=6.6 Hz, $(C\underline{H}_3)_2CH$).

b) 2S-(Ethylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.

2S-(Ethylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid (1.04g, 2.6 mmol) was taken in DMF (7 ml) and stirred in an ice bath. HOBT (0.42g, 3.1 mmol) and WSCDI (0.59g, 3.1 mmol) were added and the mixture stirred for about 30 minutes in an ice bath and a further 2 hours at room temperature. Hydroxylamine hydrochloride (0.26g, 3.9 mmol) and NMM (0.39g, 3.9 mmol) were then added at 0°C, and the mixture stirred overnight at room temperature. DMF was evaporated under high vacuum and the resulting residue slurried in ether/water (1:1, 30 ml). The resulting white precipitate was filtered and dried *in vacuo*. The water layer was separated and evaporated under vacuum and more product isolated from the resulting residue by column chromatography (acid washed silica gel, 5% methanol/DCM). Yield of the combined solids 0.59g, 1.4 mmol, 55%); m.p 204.5 - 206.0°C (decomp.); 1H-NMR δ_H; (Methanol-d_4), 4.37 (1H, dd, J=5.7, 8.7 Hz, C<u>H</u>CH_2CH_2), 3.64 (3H, s, $CO_2C\underline{H}_3$), 2.68 (3H, s, $CONHC\underline{H}_3$), 2.73 - 2.28 (8H, bm, C<u>H</u>C<u>H</u>$C\underline{H}_2SC\underline{H}_2CH_3$ + $CH_2C\underline{H}_2CO_2CH_3$), 2.12 - 1.83 (2H, bm, $C\underline{H}_2CH_2CO_2CH_3$), 1.51 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.39 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.16 (3H, t, J=7.4 Hz, $SCH_2C\underline{H}_3$), 1.05 (1H, m, $(CH_3)_2CHC\underline{H}_2$) 0.85 (3H, d, J=6.4 Hz, $(C\underline{H}_3)_2CH$), and 0.80 (3H, d, J=6.5 Hz, $(C\underline{H}_3)_2CH$); ^{13}C-NMR δ_C; (Methanol-d_4), 175.7, 174.3, 173.4, 171.2, 53.4, 51.9, 48.2, 47.8, 41.3, 32.3, 30.8, 27.8, 26.5, 26.5, 25.9, 24.0, 21.4 and 14.6.

Example 7

2S-(Acetylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.



a) 2S-(Acetylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid.

To 2-[1R-(3-methoxycarbonyl-1S-methylcarbamoyl)-3-methylbutyl]-acrylic acid (1.53g, 4.5 mmol) was added thiolacetic acid (4 ml) and the mixture stirred at room temperature, overnight, in the dark, under argon. Diethyl ether (30 ml) was added to the mixture and the resulting white precipitate filtered and thoroughly washed in cold ether to give the product (1.54g, 3.7 mmol, 82%); ^{1}H NMR δ_H; (Methanol-d_4), 4.34 (1H, dd, J=5.7, 8.5 Hz, C<u>H</u>CH_2CH_2), 3.62 (3H, s, $CO_2C\underline{H}_3$), 3.14 (1H, dd, J=3.4, 13.7 Hz, CHCH$C\underline{H}_2$S), 2.91 (1H, m, CHCH$C\underline{H}_2$S), 2.69 (3H, s, CONH$C\underline{H}_3$), 2.67 (2H, m, C<u>H</u>C<u>H</u>CH_2S), 2.30 (2H, m, $CH_2C\underline{H}_2CO_2CH_3$), 2.27 (3H, s, SCO$C\underline{H}_3$), 2.11 - 1.81 (2H, bm, $C\underline{H}_2CH_2CO_2CH_3$), 1.67 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.44 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.02 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.87 (3H, d, J=6.5 Hz, $(C\underline{H}_3)_2CH$), and 0.83 (3H, d, J=6.5 Hz, $(C\underline{H}_3)_2CH$).

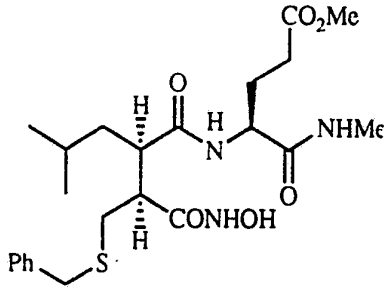
b) 2S-(Acetylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.

2S-(Acetylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-

propylcarbamoyl)-5-methyl-hexanoic acid (1.49g, 3.6 mmol) was dissolved in DMF (10 ml) and stirred in an ice bath. HOBT (0.58g, 4.3 mmol) and WSCDI (0.82g, 4.3 mmol were added and the mixture stirred for about 30 minutes in the ice bath and a further 2 hours at room temperature. Hydroxylamine hydrochloride (0.37g, 5.4 mmol) and NMM (0.54g, 5.4 mmol) were then added at 0°C, and the mixture stirred overnight at room temperature. DMF was evaporated under high vacuum and the resulting residue slurried in ether/H_20 (1:1, 50 ml). The resulting white precipitate was filtered and dried *in vacuo*. A second batch of product was isolated from the aqueous layer following column chromatography (acid washed silica gel, 5% methanol/DCM) to give (0.59g, 1.4 mmol, 38%); m.p. 179.0°C-180.0°C; ^{1}H NMR δ_H;(Methanol-d_4), 4.38 (1H, dd, J=5.8, 8.6 Hz, C<u>H</u>CH_2CH_2), 3.61 (3H, s, $CO_2C\underline{H}_3$), 3.04 (1H, dd, J=4.0, 13.2 Hz, CHCHC<u>H_2</u>S), 2.89 (1H, dd, J=10.7, 13.2 Hz, CHCHC<u>H_2</u>S), 2.69 (3H, s, CONHC<u>H_3</u>), 2.51 (1H, m, CHC<u>H</u>CH_2S), 2.40 (2H, m, $CH_2C\underline{H}_2CO_2CH_3$), 2.35 (1H, m, C<u>H</u>$CHCH_2$S), 2.25 (3H, s, SCOC<u>H_3</u>), 2.13 -1.83 (2H, bm, C<u>H_2</u>$CH_2CO_2CH_3$), 1.53 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.42 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.03 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.85 (3H, d, J=6.4 Hz, $(C\underline{H}_3)_2CH$), and 0.81 (3H, d, J=6.6 Hz, $(C\underline{H}_3)_2CH$); ^{13}C-NMR δ_C; (Methanol-d_4), 196.4, 176.0, 175.2, 174.2, 171.4, 54.3, 52.3, 48.4, 48.1, 41.7, 31.5, 30.8, 30.6, 28.5, 27.2, 26.6, 24.6 and 22.1.

Example 8

2S-(Benzylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.



a) 2S-(Benzylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid.

Benzyl mercaptan (4 ml), methanol (1 ml) and triethylamine (0.21 ml, 1.5 mmol) were added to 2-[1R-(3-methoxycarbonyl-1S-methylcarbamoyl)-3-methylbutyl]-acrylic acid (1.05g, 3.1 mmol) and the mixture stirred overnight in the dark under argon at 60°C. The crude mixture was purified by column chromatography (silica gel, 2-10% methanol/DCM) to give the desired product (0.35g, 0.7 mmol, 24%); ^{1}H NMR δ_H; (Methanol-d_4), 7.21 (5H, m, Ph-H), 4.30 (1H, dd, J=6.0, 8.5 Hz, C<u>H</u>CH_2CH_2), 3.65 (2H, m, C<u>H_2</u>Ph), 3.59 (3H, s, $CO_2C\underline{H_3}$), 2.67 (3H, s, CONHC<u>H_3</u>), 2.81 - 2.18 (6H, bm, C<u>H</u>C<u>H</u>C<u>H_2</u>S + $CH_2C\underline{H_2}CO_2CH_3$), 2.04 - 1.73 (2H, bm, C<u>H_2</u>$CH_2CO_2CH_3$), 1.65 (1H, m, $(CH_3)_2CHC\underline{H_2}$), 1.41 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.08 (1H, m, $(CH_3)_2CHC\underline{H_2}$), 0.83 (3H, d, J=6.5 Hz, $(C\underline{H_3})_2CH$) and 0.80 (3H, d, J=6.6 Hz, $(C\underline{H_3})_2CH$).

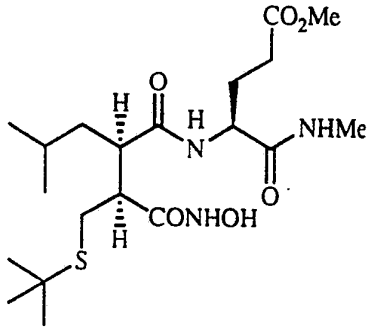
b) 2S-(Benzylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.

2S-(Benzylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid (0.35g, 0.7 mmol) was dissolved in DMF

(5 ml) and stirred in an ice bath. HOBT (0.12g, 0.9 mmol) and WSCDI (0.17g, 0.9 mmol) were added and the mixture stirred for a further about 30 minutes in the ice bath, followed by 2 hours at room temperature. Hydroxylamine hydrochloride (0.08g, 1.1 mmol) and NMM (0.11g, 1.1 mmol) were added whilst stirring in an ice bath, then the mixture allowed to warm to room temperature overnight. DMF was evaporated under high vacuum and the crude residue slurried in ether/H_20 (1:1, 30 ml). The resulting white precipitate was filtered and thoroughly washed in water and ether, before drying in vacuo (0.17g, 0.4 mmol, 47%); m.p. 187-188°C (decomposition); ^{1}H-NMR δ_H;(methanol-d_4), 7.20 (5H, m, Ph-H), 4.25 (1H, dd, J=6.0, 8.4 Hz, C<u>H</u>CHCH$_2$), 3.61 (5H, m, $CO_2C\underline{H}_3$ + $C\underline{H}_2$Ph), 2.67 (3H, s, CONHC<u>H</u>$_3$), 2.62 - 2.35 (3H, bm, CHC<u>H</u>C<u>H</u>$_2$S), 2.33 - 2.05 (3H, bm, C<u>H</u>CHCH$_2$S + $CH_2C\underline{H}_2CO_2CH_3$), 1.99-1.66 (2H, bm, $C\underline{H}_2CH_2CO_2CH_3$), 1.54 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.39 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 0.84 (3H, d, J=6.4 Hz, $(C\underline{H}_3)_2$CH) and 0.80 (3H, d, J=6.5 Hz, $(C\underline{H}_3)_2$CH); ^{13}C NMR δ_C; (Methanol-d_4), 176.2, 175.0, 174.0, 171.9, 140.0, 130.5, 129.8, 128.7, 54.2, 52.6, 42.0, 37.0, 32.4, 31.6, 28.4, 27.2, 26.6, 24.7 and 22.1.

Example 9

2S-(*tert*-Butylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.



a) 2S-(*tert*-Butylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid.

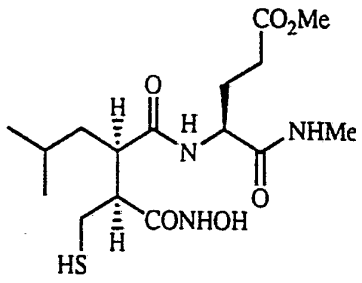
2-[1R-(3-Methoxycarbonyl-1S-methylcarbamoyl)-3-methylbutyl]-acrylic acid (1.28g, 3.7 mmol) was taken up in methanol (5 ml) and treated with tert-butyl mercaptan (5 mL) and triethylamine (0.26 mL, 1.9 mmol) and stirred at 50°C, in the dark, under argon for 72 hours. The bulk of the excess thiol was removed in-vacuo and the residue purified by column chromatography (silica gel, 0 to 10% methanol in DCM) provided the product as a white foam (0.26g, 0.6 mmol, 16%): ^{1}H NMR δ_H; (Methanol-d_4), 4.55 (1H, m, C<u>H</u>CH_2CH_2), 3.70 (3H, s, CO_2C<u>H_3</u>), 2.98 - 2.67 (6H, bm, CHC<u>H</u>C<u>H_2</u>S and CONHC<u>H_3</u>), 2.58 (1H, m, C<u>H</u>$CHCH_2S$), 2.45 (2H, m, CH_2C<u>H_2</u>CO_2CH_3), 2.20 - 1.86 (2H, bm, C<u>H_2</u>$CH_2CO_2CH_3$), 1.70 (1H, m, $(CH_3)_2CHC$<u>H_2</u>), 1.42 (1H, m, $(CH_3)_2C$<u>H</u>CH_2), 1.25 (9H, s, SC(C<u>H_3</u>)$_3$), 1.18 (1H, m, $(CH_3)_2CHC$<u>H_2</u>), and 1.00 - 0.78 (6H, bm, (C<u>H_3</u>)$_2$CH).

b) 2S-(*tert*-Butylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.

2S-(*tert*-Butylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid (0.24g, 0.6 mmol) was taken in DMF (3 ml) and stirred in an ice bath. HOBT (0.09g, 0.7 mmol) and WSCDI (0.12g, 0.7 mmol) were added and the mixture stirred for about 30 minutes in an ice bath and a further 2 hours at room temperature. Hydroxylamine hydrochloride (0.06g, 0.8 mmol) and NMM (0.39g, 3.9 mmol) were then added at 0°C, and the mixture stirred overnight at room temperature. DMF was evaporated under high vacuum and the resulting residue slurried in ether/water (1:1, 30 ml). The resulting white precipitate was filtered and dried *in vacuo* (0.07g, 0.2 mmol, 29%): m.p 195.0 - 196.0°C (decomp.); 1H NMR δ_H; (Methanol-d_4), 4.37 (1H, dd, J=5.7, 8.6 Hz, C<u>H</u>CH_2CH_2), 3.62 (3H, s, $CO_2C\underline{H}_3$), 2.69 (3H, s, CONHC<u>H</u>$_3$), 2.48 - 2.22 (5H, bm, C<u>H</u>CHC<u>H</u>$_2$SC<u>H</u>$_2$CH$_3$ + $CH_2C\underline{H}_2CO_2CH_3$), 1.97 (2H, bm, C<u>H</u>$_2CH_2CO_2CH_3$), 1.52 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.40 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.23 (9H, s, SC(C<u>H</u>$_3)_3$), 1.04 (1H, m, $(CH_3)_2CHC\underline{H}_2$) 0.85 (3H, d, J=6.4 Hz, $(C\underline{H}_3)_2CH$), and 0.80 (3H, d, J=6.5 Hz, $(C\underline{H}_3)_2CH$); ^{13}C NMR δ_C; (Methanol-d_4), 176.5, 174.9, 174.0, 171.9, 54.2, 52.5, 49.2, 48.8, 48.3, 43.6, 41.9, 31.6, 30.1, 28.7, 27.2, 26.6, 24.7, and 22.1.

Example 10

2S-Thiomethyl-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.

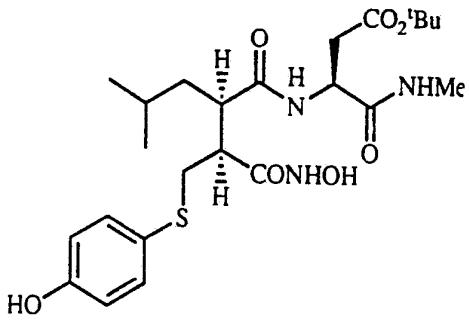


2S-(Acetylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-

propylcarbamoyl)-5-methyl-hexanohydroxamic acid (0.12g, 0.3 mmol) was dissolved in dry methanol (10 mL) and to this solution was added sodium methoxide in methanol (prepared by dissolving sodium metal (0.01g, 0.6 mmol) in dry methanol (5 mL)). The resultant solution was stirred at room temperature for 3 hours then ion exchange resin added to neutralise excess base. The resin was removed by filtration and washed with methanol then the combined filtrates evaporated under vacuum to give the product as a white solid (0.01g, 0.3 mmol, 95%); m.p. 183.5 - 185.5°C; ^{1}H NMR δ_H; (Methanol-d_4), 4.33 (1H, m, C<u>H</u>CH_2CH_2), 3.52 (3H, s, $CO_2C\underline{H}_3$), 2.75 - 2.49 (6H, bm, CHC<u>H</u>$C\underline{H}_2$S and CONHC<u>H</u>$_3$), 2.45 - 2.20 (3H, bm, C<u>H</u>$CHCH_2$S and $CH_2C\underline{H}_2CO_2CH_3$), 2.12 -1.78 (2H, bm, $C\underline{H}_2CH_2CO_2CH_3$), 1.71 - 1.33 (2H, bm, $(CH_3)_2C\underline{H}C\underline{H}_2$), 1.07 (1H, m, $(CH_3)_2CHC\underline{H}_2$), and 0.95 - 0.72 (6H, bm, $(C\underline{H}_3)_2$CH); ^{13}C-NMR δ_C; (Methanol-d_4), 175.9, 174.5, 173.3, 171.3, 53.5, 52.0, 41.8, 32.9, 31.1, 27.9, 26.7, 26.1, 24.4, and 21.7.

<u>Example 11</u>

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(2-*tert*-butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid.



a) N-methyl-2S-(N-Benzyloxycarbonylamino)-3-tert-butoxycarbonyl propionamide.

2S-(N-Benzyloxycarbonylamino)-3-*tert*-butoxycarbonyl propionic acid (9.96, 29.2 mmol) was taken up in DCM (80 ml). The solution was cooled to 0°C, while pentafluorophenol (6.44g, 35.0 mmol) and WSCDI (6.71g, 35.0 mmol) were added. The reaction was stirred for 0°C for about 30 minutes then room temperature for 2 hours. Mixture was then cooled to 0°C and methylamine in abs. ethanol (7.3 ml, 58.4 mmol) added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. Further DCM (70 ml) was added, and the mixture washed with 1M sodium carbonate (2 x 70 ml), 1M hydrochloric acid (2 x 70 ml) and brine (1 x 70 ml). The organic layer was dried over magnesium sulphate and the solvent removed under reduced pressure to give the product as a white solid (9.8g, 29.2 mmol, 100%): ^{1}H-NMR; δ_H ($CDCl_3$), 7.36 (5H, s, Ph-H), 6.52 (1H, bm, $N\underline{H}CH_3$), 5.12 (2H, s, $C\underline{H}_2Ph$), 4.50 (1H, m, $C\underline{H}CH_2CO_2$), 2.91 (1H, dd, J=4.6, 16.9 Hz, $CHC\underline{H}_2CO_2$), 2.79 (3H, d, J=4.9 Hz, $NHC\underline{H}_3$), 2.63 (1H, dd, J=6.5, 17.0 Hz, $CHC\underline{H}_2CO_2$), and 1.43 (9H, s, $CO_2C(C\underline{H}_3)_3$).

b) N-methyl-2S-amino-3-*tert*-butoxycarbonyl propionamide.

N-Methyl-2S-(N-benzyloxycarbonylamino)-3-*tert*-butoxycarbonyl propionamide (5.21g, 15.4 mmol) was taken up in methanol (100 ml), and the resultant solution purged with argon. 10% Pd/C catalyst (1g) was added as a slurry in EtOAc, and hydrogen gas bubbled through the mixture for about 30 minutes. The catalyst was filtered off and the filterate evaporated under reduced pressure to give the product as a white solid (3.13g, 15.4 mmol, 100%); ^{1}H-NMR δ_H; (DMSO-d_6), 7.80 (1H, m, $N\underline{H}CH_3$), 3.43 (1H, m, $C\underline{H}CH_2CO_2$), 2.59(1H, d, J=4.6 Hz, $NHC\underline{H}_3$), 2.54 (1H, m, $CHC\underline{H}_2CO_2$), 2.30 (1H, dd, J=7.7, 15.5 Hz, $CHC\underline{H}_2CO_2$), 1.86 (1H, bs, $\underline{H}_2NCH$), and 1.39 (9H, s, $CO_2C(C\underline{H}_3)_3$).

c) 2-[1R-(2-*tert*-Butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-3-methylbutyl]-malonic acid dibenzylester.

N-methyl-2S-amino-3-*tert*-butoxycarbonyl propionamide (3.10g, 15.3 mmol) was taken up in DMF (80 ml) and 2-benzyloxycarbonyl-3R-isobutyl succinic acid 4-pentafluorophenyl-1-benzyl diester (7.87g, 13.9 mmol) added and the mixture was stirred at 20°C for 72 hours. Solvent was removed under reduced pressure, the residue taken up in DCM (200 ml) and washed in 1M sodium carbonate (2 x 150 ml), 1M hydrochloric acid (1 x 150 ml) and brine (1 x 150 ml). The organic layer was dried over magnesium sulphate and evaporated under reduced pressure to a yellow oil, which was purified by column chromatography (silica gel, 0-5% methanol/DCM) to give a white, foamy solid (6.64g, 12.0 mmol, 86%); ^{1}H NMR δ_H; ($CDCl_3$), 7.32 (10H, bm, Ph-H), 7.06 (1H, m, CONHCH), 5.30 - 5.00 (4H, bm, 2 x $C\underline{H}_2Ph$), 4.60 (1H, m, $C\underline{H}CH_2CO_2{}^tBu$), 3.83 (1H, d, J=9.2 Hz, $CHC\underline{H}(CO_2Bzl)_2$), 2.97 (1H, m, $C\underline{H}CH(CO_2Bzl)_2$), 2.78 (1H, m, $CHC\underline{H}_2CO_2{}^tBu$), 2.50 (1H, dd, J=6.6, 17.2 Hz, $CHC\underline{H}_2CO_2{}^tBu$), 1.68 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.60 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.46 (9H, s, $CO_2C(C\underline{H}_3)_3$), 1.10 (1H, m, $(CH_3)_2CHC\underline{H}_2$), and 0.83 (6H, m, $(C\underline{H}_3)_2CH$).

d) 2-[1R-(2-*tert*-Butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-3-methylbutyl]-acrylic acid.

2-[1R-(2-*tert*-Butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-3-methylbutyl]-malonic acid dibenzylester (6.60g, 11.9 mmol) was taken up in EtOH (100 ml) and the resultant solution purged with argon. 10% Pd/C catalyst (2g) was added as a slurry in EtOAc. Hydrogen was bubbled through the mixture for about 30 minutes, before removal of the catalyst by filtration. The filtrate was cooled to 0°C and piperidine (1.07g, 12.6 mmol) added followed by aqueous formaldehyde (8.6 ml, 115 mmol). This mixture was stirred overnight, warming to room temperature. Solvent was removed under reduced pressure and the residue taken up in EtOAc (100 ml). This was washed in 1M hydrochloric acid (1 x 50 ml) and extracted with 1M sodium carbonate (2 x 70 ml). The aqueous extracts were combined and acidified to pH3 by dropwise additon of 2M hydrochloric acid. The product was extracted from the acidified aqueous layer with EtOAc (2 x 100 ml). This was dried over magnesium sulphate and evaporated under reduced pressure to a white solid

(2.75g, 7.5 mmol, 65%); ^{1}H NMR δ_H; ($CDCl_3$), 7.95 (1H, d, J=8.6 Hz, CONHCH), 6.98 (1H, m, $CONHCH_3$), 6.46 (1H, s, $C=CH_2$), 5.91 (1H, s, $C=CH_2$), 4.84 (1H, m, $CHCH_2CO_2{}^tBu$), 3.71 (1H, m, CH_2CHCCH_2), 2.81 (3H, d, J=4.8 Hz, $CONHCH_3$), 2.64 (2H, m, $CHCH_2CO_2{}^tBu$), 1.79 (1H, m, $(CH_3)_2CHCH_2$), 1.56 - 1.42 (2H, bm, $(CH_3)_2CHCH_2$), 1.40 (9H, s, $CO_2C(CH_3)_3$), and 0.88 (6H, m, $(CH_3)_2CH$).

e) 2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(2-*tert* butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanoic acid.

2-[1R-(2-*tert*-Butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-3-methylbutyl]-acrylic acid (2.70g, 7.3 mmol) was taken up in methanol (5 ml), 4-hydroxythiophenol (2.50g, 20.0 mmol) added and the mixture was then stirred at 60°C, under argon, in the dark for 72 hours. Solvent removal gave a yellow oil which was purified by column chromatography (silica gel, 2-10% methanol/DCM) to give the title compound as a white solid (2.92g, 5.9 mmol, 80%). ^{1}H NMR δ_H; (methanol-d_4), 7.24 (2H, d, J=8.6 Hz, Ar-H), 6.68 (2H, d, J=8.5 Hz, Ar-H), 4.62 (1H, m, $CHCH_2CO_2{}^tBu$), 2.82 (1H, m, $CHCHCH_2S$), 2.76 - 2.49 (6H, bm, $CHCHCH_2S$ and $CHCH_2CO_2{}^tBu$), 2.66 (3H, s, $CONHCH_3$), 1.60 (1H, m, $(CH_3)_2CHCH_2$), 1.41 (9H, s, $CO_2C(CH_3)_3$), 1.18 (1H, m, $(CH_3)_2CHCH_2$), 1.01 (1H, m, $(CH_3)_2CHCH_2$), 0.82 (3H, d, J=6.6 Hz, $(CH_3)_2CH$), and 0.79 (3H, d, J=6.7 Hz, $(CH_3)_2CH$).

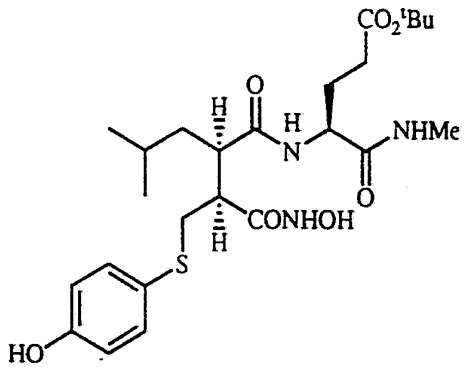
f) 2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(2-*tert* butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid.

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(2-*tert* butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanoic acid (2.21g, 4.4 mmol) was taken up in 10% DMF in DCM (40 ml) and the solution cooled to 0°C, while pentafluorophenol (0.98g, 5.3 mmol) and WSCDI (1.02g, 5.3 mmol) added. The reaction mixture was stirred for 2 hours at room temperature. Solvent was removed under reduced pressure and the residue taken up in DCM and washed in 1M sodium carbonate (2 x 50 ml), 1M hydrochloric acid (1 x 50 ml) and brine (1 x 50 ml). The organic layer was dried over magnesium sulphate and the solvent removed under reduced pressure to give a foamy solid (1.5g, 2.3 mmol, 52%). This

solid was taken up in DMF (20 ml) and hydroxylamine hydrochloride (0.48g, 7 mmol) added, followed by NMM (0.52g, 5.1 mmol) and the mixture was stirred for 1 hour. DMF was evaporated under reduced pressure (high vacuum), the resulting residue was taken up in DCM (50 ml) and the product extracted with water (4 x 50 ml). Aqueous extractions were combined and evaporated under reduced pressure, the resulting residue was purified by column chromatography (acid washed silica gel, 5% methanol/DCM), to give the product as a white power (0.28g, 0.6 mmol, 24%); m.p. 153.0°C; Analysis for $C_{24}H_{37}N_3O_7S$; requires C 56.34 H 7.29 N 8.21: Found C 55.31 H 7.24 N 7.96; ^1H NMR δ_H; (methanol-d_4), 7.21 (2H, d, J=8.6 Hz, Ar-H), 6.68 (2H, d, J=8.7 Hz, Ar-H), 4.61 (1H, dd, J=5.5, 8.7 Hz, C<u>H</u>$CH_2CO_2{}^tBu$), 2.91 (1H, dd, J=3.6, 13.1 Hz, $CHCHC\underline{H}_2S$), 2.79 (1H, m, $CHCHC\underline{H}_2S$), 2.70 - 2.55 (2H, bm, $CHC\underline{H}_2CO_2{}^tBu$), 2.67 (3H, s, $CONHC\underline{H}_3$), 2.51 (1H, m, $CHC\underline{H}CH_2S$), 2.32 (1H, dt, J=3.6, 10.9 Hz, $CH_2C\underline{H}CH$), 1.50 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.43 - 1.25 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.40 (9H, s, $CO_2(C\underline{H}_3)_3$), 1.00 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.83 (3H, d, J=6.6 Hz, $(C\underline{H}_3)_2CH$), and 0.79 (3H, d, J=6.6 Hz, $(C\underline{H}_3)_2CH$); ^{13}C NMR δ_C; (methanol-d_4), 175.7, 173.0, 171.4, 171.2, 158.1, 134.3, 125.8, 117.1, 82.4, 51.4, 48.2, 48.1, 41.4, 37.9, 36.9, 28.4, 26.9, 26.3, 24.2 and 21.8.

Example 12

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-*tert* butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.



a) N-methyl-2S-(N-Benzyloxycarbonylamino)-4-*tert*-butoxycarbonyl butanamide.

2S-(N-Benzyloxycarbonylamino)-4-*tert*-butoxycarbonyl butanoic acid (7.43, 22.0 mmol) was taken up in DCM (70 ml) and the solution cooled to 0°C, while pentafluorophenol (4.9g, 26.5 mmol) and WSCDI (5.05g, 26.5 mmol) were added. The reaction was stirred at 0°C for about 30 minutes then at room temperature for 2 hours. The mixture was then cooled to 0°C and methylamine in absolute ethanol (5.5 ml, 44.1 mmol) added dropwise. The mixture was warmed to room temperature overnight, DCM (60 ml) was added, and the mixture washed with 1M sodium carbonate (2 x 70 ml), 1M hydrochloric acid (2 x 70 ml) and brine (1 x 70 ml). The organic layer was dried over magnesium sulphate and the solvent removed under reduced pressure to give the product as a white solid (7.74g, 22.1 mmol, 100%): ^{1}H NMR δ_H; ($CDCl_3$), 7.32 (5H, s Ar-H), 6.52 (1H, bm, CONHMe), 5.85 (1H, d, J=7.9 Hz, ZNHCH), 5.17 - 5.02 (2H, bm, $PhCH_2O$), 4.19 (1H, m, HNCHCONHMe), 2.77 (3H, d, J=4.7 Hz, $CONHCH_3$), 2.32 (2H, m, $CH_2CH_2CO_2{}^tBu$), 1.99 (2H, m, $CH_2CH_2CO_2{}^tBu$), and 1.43 (9H, s, $CO_2C(CH_3)_3$).

b) N-methyl-2S-amino-4-*tert*-butoxycarbonyl butanamide.

N-methyl-2S-(N-Benzyloxycarbonylamino)-4-*tert*-butoxycarbonyl butanamide

(7.70g, 21.9 mmol) was taken up in methanol (150 ml) and the resultant solution purged with argon. 10% Pd/C catalyst (1:1g) was added as a slurry in EtOAc and hydrogen gas bubbled through the mixture for about 30 minutes. The catalyst was filtered off and the filtrate evaporated under reduced pressure to the product as a white solid (4.75g, 21.9 mmol, 100%): ^{1}H NMR δ_H; (DMSO-d_6), 7.77 (1H, m, CONHCH$_3$), 3.08 (1H, dd, J=5.2, 7.9 Hz, H$_2$NCHCO), 2.58 (3H, d, J=4.6 Hz, CONHCH$_3$), 2.22 (2H, m, CH$_2$CH$_2$CO$_2$^{t}Bu), 1.89 - 0.97 (2H, bm, CH$_2$CH$_2$CO$_2$^{t}Bu) and 1.39 (9H, s, CO$_2$C(CH$_3$)$_3$).

c) 2-[1R-(3-*tert*-Butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-3-methylbutyl]-malonic acid dibenzylester.

N-methyl 2S-amino-4-*tert*-butoxycarbonyl butanamide (4.70g, 21.7 mmol) was taken up in DMF (80 ml), 2-benzyloxycarbonyl-3R-isobutyl succinic acid 4-pentafluorophenyl-1-benzyl diester (11.15g, 19.8 mmol) added and the mixture was stirred at 22°C for 72 hours. Solvent was removed under reduced pressure and the residue taken up in DCM (200 ml) and washed in 1M sodium carbonate (2 x 150 ml), 1M hydrochloric acid (1 x 150 ml) and brine (1 x 150 ml). The organic layer was dried over magnesium sulphate and evaporated under vacuum to a yellow oil, which was purified by column chromatography (silica gel, 1:1 EtOAc/Hexane) to give a white solid, which was recrystallised from EtOAc/hexane (6.8g, 12.0 mmol, 60.9%); ^{1}H NMR δ_H; ($CDCl_3$), 7.27 (10H, bm, Ar-H), 6.91 (1H, m, CONHCH), 6.48 (1H, m, CONHCH$_3$), 5.13 (4H, bm, 2 x CH$_2$Ph), 4.33 (1H, m, CHCH$_2$CH$_2$), 3.82 (1H, d, J=9.7 Hz, CHCH(CO$_2$BzI)$_2$), 2.96 (1H, dt, J=3.9, 10.0 Hz, CHCH(CO$_2$BzI)$_2$), 2.78 (3H, d, J=4.8 Hz, CONHCH$_3$), 2.51 - 2.22 (2H, m, CH$_2$CH$_2$CO$_2$^{t}Bu), 2.12 - 1.83 (2H, m, CH$_2$CH$_2$CO$_2$^{t}Bu), 1.61 (1H, m, (CH$_3$)$_2$CHCH$_2$), 1.46 (1H, m, (CH$_3$)$_2$CHCH$_2$), 1.44 (9H, s, CO$_2$C(CH$_3$)$_3$), 1.10 (1H, m, (CH$_3$)$_2$CHCH$_2$) and 0.83 (6H, m, (CH$_3$)$_2$CH).

d) 2-[1R-(3-*tert*-Butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-3-methylbutyl]-acrylic acid.

2-[1R-(3-*tert*-Butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-3-methylbutyl]-malonic acid dibenzylester (6.65g, 11.8 mmol) was taken up in EtOH (100 ml) and the resultant solution purged with argon. 10% Pd/C catalyst (1.5g) was added as a slurry in EtOAc. Hydrogen gas was bubbled through the mixture for about 30 minutes, before removal of the catalyst by filtration. To the filtrate was added piperidine (1.09g, 12.8 mmol) at 0°C followed by aqueous formaldehyde (8.7 ml, 116 mmol) dropwise. The mixture was stirred overnight, at room temperature. Solvent was removed under reduced pressure and the residue taken up in EtOAc (100 ml). This was washed in 1M hydrochloric acid (1 x 50 ml) and extracted with 1M sodium carbonate (2 x 70 ml). The extractions were combined and acidified to pH3 by the dropwise addition of 2M hydrochloric acid. The product was extracted from the aqueous by EtOAc (2 x 100 ml), the combined organic phases were dried over magnesium sulphate and evaporated under reduced pressure to a white solid (3.36, 8.7 mmol, 75%); ^{1}H NMR δ_H; ($CDCl_3$), 7.96 (1H, d, J=8.6 Hz, CONHCH), 7.01 (1H, m, $CONHCH_3$), 6.45 (1H, s, $C=CH_2$), 5.94 (1H, s, $C=CH_2$), 4.61 (1H, m, COCHNH), 3.78 (1H, m, $CH_2CHCCCH_2$), 2.84 (3H, d, J=4.8 Hz, $CONHCH_3$), 2.24 (2H, m, $CH_2CH_2CO_2{}^tBu$), 2.09 - 1.77 (2H, bm, $CH_2CH_2CO_2{}^tBu$), 1.79 (1H, m, $(CH_3)_2CHCH_2$), 1.58 - 1.35 (2H, bm, $(CH_3)_2CHCH_2$), 1.42 (9H, s, $CO_2C(CH_3)_3$), and 0.88 (6H, m, $(CH_3)_2CH$).

e) 2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(2-*tert* butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid.

2-[1R-(3-*tert*-Butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-3-methylbutyl]-acrylic acid (3.34g, 8.68 mmol) was taken up in methanol (7 ml) and 4-hydroxythiophenol (2.74g, 21.7 mmol) added, the mixture was then stirred at 60°C under argon, in the dark for 60 hours. Solvent was removed by evaporation under vacuum and the resulting crude oil purified by column chromatography (silica gel, 0-10% methanol/DCM). The resulting product was further purified by column chromatography (silica gel, 60-100% EtOAc/hexane) to give the title compound as a white solid (2.22g, 4.3 mmol, 50%); ^{1}H NMR δ_H; (methanol-d_4), 7.23 (2H, d, J=8.6 Hz, Ar-H), 6.69 (2H, d, J=8.7 Hz, Ar-H), 4.25 (1H, dd, J=5.7, 8.7 Hz,

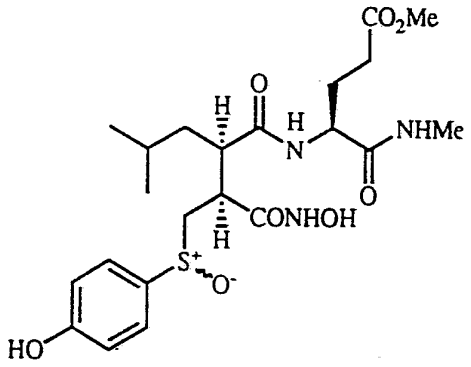
C<u>H</u>$CH_2CH_2CO_2{}^tBu$), 2.85 (2H, m, CHCHC<u>H_2</u>S), 2.67 (3H, s, CONHC<u>H_3</u>), 2.61 (2H, m, C<u>H</u>C<u>H</u>CH_2S), 2.24 (2H, m, CH_2C<u>H_2</u>$CO_2{}^tBu$), 2.04 - 1.73 (2H, bm, C<u>H</u>$CH_2CO_2{}^tBu$), 1.59 (1H, m, $(CH_3)_2$CHC<u>H_2</u>), 1.41 (9H, s, $CO_2C(C\underline{H_3})_3$), 1.36 (1H, m, $(CH_3)_2$C<u>H</u>CH_2), 1.05 (1H, m, $(CH_3)_2$CHC<u>H_2</u>) 0.83 (3H, d, J=6.5 Hz, $(C\underline{H_3})_2$CH), and 0.78 (3H, d, J=6.6 Hz, $(C\underline{H_3})_2$CH).

f) 2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-*tert* butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(2-*tert* butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanoic acid (1.17g, 2.3 mmol) was taken up in DMF (10 ml) and the solution cooled to 0°C, HOBT (0.34g, 2.5 mmol) and WSCDI (0.48g, 2.5 mmol) were added. The reaction mixture was stirred for 2 hours at room temperature. The mixture was once again cooled to 0°C and hydroxylamine hydrochloride (0.24g, 3.4 mmol) and NMM (0.35, 3.4 mmol) were added. The mixture was stirred at room temperature overnight. DMF was evaporated under high vacuum and the residue slurried in ether/$H_2$0 (1:1, 100 ml). The resulting white precipitate was filtered and dried in vacuo. Further product was isolated by separating the ether layer, evaporating and purifying by column chromatography (acid washed silica gel, 5% methanol/DCM) to yield the title compound (1.02g, 1.9 mmol, 46%); m.p. 168.9 - 168.3°C; ^{1}H NMR δ_H; (methanol-d_4), 7.18 (2H, d, J=8.7 Hz, Ar-H), 6.68 (2H, d, J=8.7 Hz, Ar-H), 4.28 (1H, dd, J=5.7, 8.6 Hz, C<u>H</u>CH_2CH_2), 2.94 (1H, m, CHCHC<u>H_2</u>S), 2.78 (1H, dd, J= 3.7, 12.9 Hz, CHCHC<u>H_2</u>S), 2.68 (3H, s, CONHC<u>H_3</u>), 2.56 (1H, dt, J= 3.4, 10.9 Hz, CHC<u>H</u>CH_2S), 2.35 (1H, dt, J= 3.7, 10.9 Hz, C<u>H</u>CHCH_2S), 2.25 (2H, m, CH_2C<u>H_2</u>$CO_2{}^tBu$), 2.06 - 1.75 (2H, bm, C<u>H_2</u>$CH_2CO_2{}^tBu$), 1.53 (1H, m, $(CH_3)_2$CHC<u>H_2</u>), 1.41 (1H, m, $(CH_3)_2$C<u>H</u>CH_2), 1.40 (9H, s, $CO_2C(C\underline{H_3})_3$), 1.02 (1H, m, $(CH_3)_2$CHC<u>H_2</u>), 0.84 (3H, d, J=6.4 Hz, $(C\underline{H_3})_2$CH), and 0.79 (3H, d, J=6.5 Hz, $(C\underline{H_3})_2$CH); ^{13}C NMR δ_C; (methanol-d_4), 175.9, 173.8, 173.7, 171.4, 158.2, 134.3, 125.8, 117.1, 81.9, 53.9, 49.7, 48.1, 41.5, 37.6, 32.7, 28.4, 28.3, 26.9, 26.3, 24.3 and 21.7.

Example 13

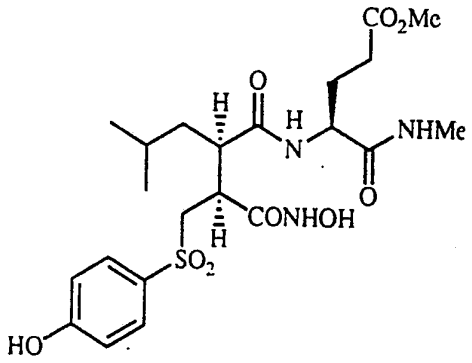
2S-(4-Hydroxy-phenylsulphinylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.



2S-(4-Hydroxy-phenylsulphanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid (0.1g, 0.207 mmol) was dissolved in methanol (5 ml) and m-chloroperbenzoic acid (0.066g, 0.227 mmol) added. The resulting solution was allowed to stir at room temperature overnight. Solvent was removed under high vacuum and the residue triturated, with DCM (10 ml). The resulting white precipitate was filtered and washed thoroughly with DCM to provide the title compound (0.07g, 0.14 mmol, 68%); ^{1}H NMR δ_H; (methanol-d_4, mixture of diastereomers), 7.52 and 7.46 (2H, d, J=8.7 Hz, Ar-H), 6.91 (2H, d, J=8.8 Hz, Ar-H), 4.27 (1H, m, COC<u>H</u>NH), 3.64 and 3.62 (3H, s, $CO_2C\underline{H}_3$), 3.32 (0.5H, m, $CHC\underline{H}_2SO$), 3.27 (1H, m, $CHC\underline{H}_2SO$), 3.05 (0.5H, m, $CHC\underline{H}_2SO$), 2.75 (1H, m, $CH_2C\underline{H}CONHOH$), 2.67 (3H, s, $CONHC\underline{H}_3$), 2.63 (1H, m, $C\underline{H}CHCH_2S$), 2.29 (2H, m, $C\underline{H}_2CH_2CO_2Me$), 1.93 (2H, m, $CH_2C\underline{H}_2CO_2Me$) 1.46 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.37 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.01 (1H, m, $(CH_3)_2CHC\underline{H}_2$), and 0.82 (6H, m, $(C\underline{H}_3)_2CH$); ^{13}C NMR δ_C; (methanol-d_4), 175.2, 175.1,174.9, 174.7, 174.6, 173.7, 173.6, 170.3, 162.8, 133.7, 132.7, 131.5, 128.3, 127.4, 117.7, 117.1, 60.0, 58.5, 54.0, 52.3, 47.7, 43.1, 43.0, 41.1, 41.0, 31.2, 28.2, 26.9, 26.8, 26.3, 24.2, and 21.7.

Example 14

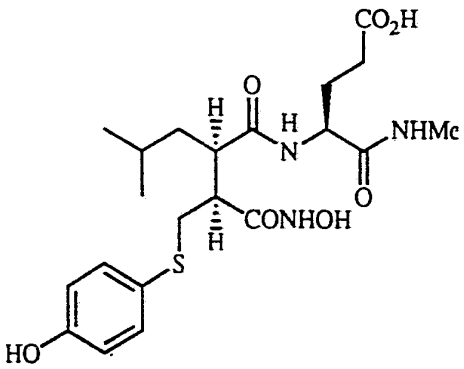
2S-(4-Hydroxy-phenylsulphonylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid



2S-(4-Hydroxy-phenylsulphanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-S-methyl-hexanohydroxamic acid (0.1g, 0.207 mmol) was dissolved in methanol (5 ml) and m-chloroperbenzoic acid (0.0.151g, 0.517 mmol) added. The resulting solution was allowed to stir at room temperature overnight. Solvent was removed under high vacuum and the residue triturated, with DCM (10 ml). The resulting white precipitate was filtered and washed thoroughly with DCM to provide the title compound (0.05g, 0.97 mmol, 48%); ^{1}H NMR δ_H; (methanol-d_4), 7.67 (2H, d, J=8.7 Hz, Ar-H), 6.91 (2H, d, J=8.8 Hz, Ar-H), 4.22 (1H, m, COC<u>H</u>NH), 3.65 (3H, s, $CO_2C\underline{H}_3$), 3.59 (1H, dd, J=14.4, 10.7 Hz, $CHC\underline{H}_2SO_2$), 3.00 (1H, d, J=12.7 Hz, $CHC\underline{H}_2SO_2$), 2.66 (3H, s, $CONHC\underline{H}_3$), 2.63 (1H, m, $C\underline{H}CH_2SO_2$), 2.51 (1H, m, $C\underline{H}CHCH_2SO_2$), 2.30 (2H, t, J=7.3 Hz, $CH_2C\underline{H}_2CO_2Me$), 1.97 (1H, m, $C\underline{H}_2CH_2CO_2Me$), 1.87 (1H, m, $C\underline{H}_2CH_2CO_2Me$), 1.53 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.33 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.01 (1H, m, $(CH_3)_2CHC\underline{H}_2$), and 0.80 (6H, t, J=5.9 Hz, $(C\underline{H}_3)_2CH$); ^{13}C NMR δ_C; (methanol-d_4), 174.9, 174.7, 173.8, 170.0, 164.2, 131.5, 130.5, 117.1, 57.0, 53.9, 52.3, 47.7, 42.4, 40.8, 31.2, 28.1, 26.8, 26.3, 24.1, and 21.8.

Comparative Example

2S-(4-Hydroxy-phenylsulphanylmethyl)-3R-(3-carboxy-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid.



2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-*tert* butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid (0.2g, 0.38 mmol) was dissolved in a mixture of DCM and trifluoroacetic acid (1:1, 10 ml) and the resulting solution stirred at room temperature for 1.5 hours. Solvents were evaporated, azeotroping with toluene then chloroform, and the residue triturated with diethyl ether. The resulting white precipitate was filtered and purified by column chromatography (acid washed silica gel, 10% methanol/DCM) to provide the product as a white solid (0.05g, 0.106 mmol, 28%); ^{1}H NMR δ_H; (methanol-d_4), 7.20 (2H, d, J=8.7 Hz, Ar-H), 6.68 (2H, d, J=8.7 Hz, Ar-H), 4.28 (1H, m, COC<u>H</u>NH), 2.91 (1H, dd, J=13.0, 11.2 Hz, CHCHC<u>H</u>$_2$S), 2.79 (1H, dd, J= 3.7, 13.0 Hz, CHCHC<u>H</u>$_2$S), 2.67 (3H, s, CONHC<u>H</u>$_3$), 2.55 (1H, dt, J= 3.3, 10.6 Hz, CHC<u>H</u>CH$_2$S), 2.32 (3H, m, C<u>H</u>CHCH$_2$S and CH$_2$C<u>H</u>$_2$CO$_2$H), 1.93 (2H, bm, C<u>H</u>$_2$CH$_2$CO$_2$H), 1.48 (1H, m, (CH$_3$)$_2$CHC<u>H</u>$_2$), 1.39 (1H, m, (CH$_3$)$_2$C<u>H</u>CH$_2$), 1.01 (1H, m, (CH$_3$)$_2$CHC<u>H</u>$_2$), 0.84 (3H, d, J=6.4 Hz, (C<u>H</u>$_3$)$_2$CH), and 0.79 (3H, d, J=6.5 Hz, (C<u>H</u>$_3$)$_2$CH); ^{13}C NMR δ_C; (methanol-d_4), 176.2, 175.9, 173.8, 171.3, 158.2, 134.5, 125.7, 117.1, 54.0, 48.1, 41.5, 37.4, 31.3, 28.2, 26.8, 26.2, 24.3, and 21.7.

Biological Example A

The ability of example compounds of the invention to inhibit the release of TNF was investigated. The assay is based on the ability of phorbol myristate acetate (PMA) to stimulate the release of TNF α from a human monocytic cell line, U937.

U937 cells cultured in RPMI 1640 medium + 5% foetal calf serum are centifuged at 1000 x g for 5 minutes and then resuspended in medium at 2 x 10^6 / ml. 1 ml of cell suspension is aliquoted into individual wells of 24-well plates. Test compounds are dissolved in dimethyl sulphoxide (DMSO) at a stock concentration of 100mM, then diluted to 50x the final required concentration with RPMI 1640 medium. 20µl of the diluted compounds are added to U937 cells in duplicate wells. TNF α release is stimulated by addition of PMA to the cells at a final concentration of 50nM. Appropriate control cultures are set up in duplicate. The plates are incubated for 18 hours at 37°C, 5% CO_2, then centrifuged at 1000 x g for 5 minutes. A specific ELISA for TNF α obtained from British Bio-technology Products Limited, Abingdon, England is used to measure TNF α levels in the culture supernatants

The average concentration of test compound which inhibits the release of TNF α by 50% relative to the control culture was assessed. The compounds of examples 2, 3 and 12 above were tested and had IC_{50} values less than 50 µM.

Biological Example B

The compound of Example 3 was assessed for its ability to inhibit release of endotoxin induced TNF production *in vivo*.

Male New Zealand rabbits, 2.5 - 3.0 kg, were anaesthetised with sodium pentobarbitone, 30 mg.kg^{-1} via a marginal ear vein which was maintained by infusion at 18 mg.kg^{-1}.hr^{-1} via a jugular vein. Following tracheotomy, the animals were ventilated, to maintain arterial blood PO_2 between 35 and 40 mmHg, and oxygen was added to the inspired air to maintain arterial blood PO_2 above 100 mmHg. Both femoral veins were cannulated for the administration of endotoxin (LPS) and the infusion of test compound, 2.5 mg.kg^{-1}.hr^{-1} at a rate of 6 ml.hr^{-1}, 15 minutes before the administration of LPS, 40 µg.kg^{-1} i.v. bolus. Blood samples were collected from a femoral artery just before and at 30 minute intervals after the administration of LPS for a period of 4 hours.

The biological activity of TNF in serum test samples was determined using a cytotoxicity assay as described in Mathews, N. and Neale, M.L. in Lymphokines and Interferons, a Practical Approach, Eds. M.J. Clements, A.G. Morris, and A.J.H. Gearing, IRL Press, Oxford, UK.

100 µl volumes of L929 cell suspension at 10^5 cells/ml were dispensed into 96-well microtitre plates. The plates were incubated overnight to allow formation of an even monolayer. A series of dilutions of the test rabbit serum was made in a culture medium containing 2 µg/ml of actinomycin D to give a final concentration of 1 µg/ml when added to the cells. The L929 cells were incubated for 24 hours in the presence of test samples, and serially diluted human TNF α was used as the assay standard. After the incubation period, dead cells were removed by washing briefly with phosphate buffered saline, and remaining cells were fixed with 4% formaldehyde for 10 minutes. After washing the plates with water to remove the fixative, the cells were stained by the addition of 50 µl of 1% crystal violet to each well for 5 minutes. The plates were washed extensively with water and dried. Cells

were solubilised by the addition of 100 µl/well of 30% acetic acid and the OD at 550 nm was determined. The TNF level in units/ml in the test samples was determined from the human TNF α standard curve, where 1 unit is the equivalent of 1 pg/ml human TNF α.

Results:

Time (hrs) from from LPS bolus IV injection	Average % change in serum TNF level	
	LPS (n=5)	LPS + test compound (n=4)
0	0	0
1	+65	-58
2	+55	-65
3	-30	-99
4	-100	-100

Biological Example C

The potency of compounds of Examples 1, 2, 3 and 12 to act as inhibitors of collagenase was determined by the procedure of Cawston and Barrett, (Anal. Biochem., 99, 340-345, 1979), hereby incorporated by reference, whereby a 1mM solution of the compound being tested, or a dilution thereof, was incubated at 37° for 16 hours with collagen and collagenase (buffered with 25mM Hepes, pH 7.5 containing 5mM $CaCl_2$, 0.05% Brij 35 and 0.02% NaN_3). The collagen was acetylated ^{14}C collagen prepared by the method of Cawston and Murphy, (Methods in Enzymology, **80**, 711, 1981), hereby incorporated by reference. The samples were centrifuged to sediment undigested collagen, and an aliquot of the radioactive supernatant removed for assay on a scintillation counter as a measure of hydrolysis. The collagenase activity in the presence of 1mM of the test compound, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the result reported below as that of inhibitor concentration effecting 50% inhibition of the collagenase activity (IC_{50}).

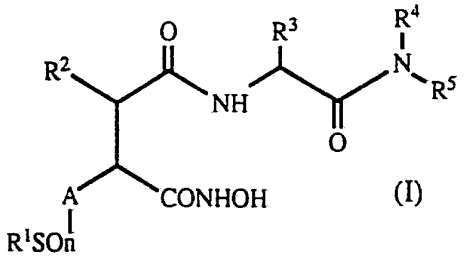
The potency of compounds of Examples 1, 3 and 12 to act as inhibitors of stromelysin was determined by the procedure of Cawston et al, (Biochem. J., **195**, 159-165, 1981), hereby incorporated by reference, whereby a 1mM solution of the compound being tested, or a dilution thereof, was incubated at 37° for 16 hours with stromelysin and ^{14}C acetylate casein (buffered with 25mM Hepes, pH 7.5 containing 5mM $CaCl_2$, 0.05% Brij 35 and 0.02% NaN_3). The casein was acetylated ^{14}C casein prepared by the method of Cawston et al (ibid). The stromelysin activity in the presence of 1mM of the test compound, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the result reported below as that of inhibitor concentration effecting 50% inhibition of the stromelysin activity (IC_{50}).

Results:

Compound	Collagenase IC50	Stromelysin IC50
Example 1	20 nM	250 nM
Example 2	15 nM	--
Example 3	9 nM	50 nM
Example 12	20 nM	40 nM

Claims:

1. A compound of formula (I):



(I)

wherein:

R^1 represents hydrogen or an (C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl, phenyl, substituted phenyl, phenyl (C_1-C_6)alkyl, heterocyclyl, (C_1-C_6)alkylcarbonyl, phenacyl or substituted phenacyl group;

R^2 represents hydrogen or a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, phenyl (C_1-C_6)alkyl, cycloalkyl (C_1-C_6)alkyl or cycloalkenyl (C_1-C_6)alkyl group,

R^3 represents a group $-CH_2CO_2$ (C_1-C_4)alkyl or $-CH_2CH_2CO_2$ (C_1-C_4)alkyl;

R^4 represents hydrogen or a (C_1-C_6)alkyl or phenyl(C_1-C_6)alkyl group;

R^5 represents hydrogen or a methyl group;

n is 0, 1 or 2;

and A represents a (C_1-C_6)hydrocarbon chain optionally substituted with one or more (C_1-C_6)alkyl, phenyl, or substituted phenyl groups;

or a salt, solvate or hydrate thereof.

2. A compound as claimed in claim 1 wherein the chiral centre adjacent to the substituent R^3 has S stereochemistry.

3. A compound as claimed in claim 1 or claim 2 wherein the chiral centre adjacent to the substituent R^2 has R stereochemistry.

4. A compound as claimed in any one of claims 1 to 3 wherein the chiral centre adjacent to the -CONHOH moeity has S stereochemistry..

5. A compound as claimed in any one of claims 1 to 4 wherein R^1 represents hydrogen or an (C_1-C_6)alkyl, phenyl, thienyl, substituted phenyl, benzyl, acetyl or phenacyl group.

6. A compound as claimed in claim 5 wherein R^1 is 4-methoxyphenyl, 4-hydroxyphenyl, 4-aminophenyl, thien-2-yl, or t-butyl.

7. A compound as claimed in any one of claims 1 to 6 wherein R^2 represents a (C_3-C_6)alkyl group.

8. A compound as claimed in any one of claims 1 to 7 wherein R^4 represents a (C_1-C_4)alkyl group.

9. A compound as claimed in any one of claims 1 to 8 wherein R^5 represents a hydrogen atom.

10. A compound as claimed in any one of claims 1 to 9 wherein A represents a methylene group $-CH_2-$.

11. A compound as claimed in any one of claims 1 to 10 wherein n=0.

12. A compound as claimed in claim 1, selected from the group consisting of:

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-

phenylsulfanylmethyl hexanohydroxamic acid;

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-(thien-2-ylsulfanylmethyl)-hexanohydroxamic acid;

2S-(4-Methoxy-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Amino-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Ethylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Acetylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Benzylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(*tert*-Butylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-Thiomethyl-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(2-*tert*-butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxy-phenylsulphinylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxy-phenylsulphonylmethyl)-3R-(3-methoxycarbonyl-1S-

methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

and salts hydrates and solvates thereof.

13. 2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid and salts hydrates and solvates thereof.

14. 2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-*tert* butoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid and salts hydrates and solvates thereof.

15. A compound as claimed in any one of claims 1 to 14 for use in human or veterinary medicine.

16. A method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective, amount of a compound as claimed in any one of claims 1 to 14 .

17. The use of a compound as claimed in any one of claims 1 to 14 in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs.

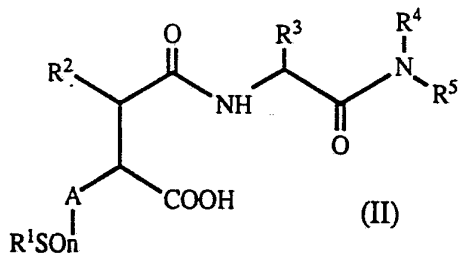
18. A method as claimed in claim 16, or a use as claimed in claim 17 wherein the disease or condition referred to is inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infections, shock states, graft versus host reactions or autoimmune disease.

19. A method as claimed in claim 16, or a use as claimed in claim 17 wherein the disease or condition referred to is rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, tumour growth, tumour angiogenisis or tumour invasion by secondary metastases.

20. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of claims 1 to 14 together with a pharmaceutically or veterinarily acceptable excipient or carrier.

21. A process for preparing a compound of general formula (I) as defined in claim 1, comprising:

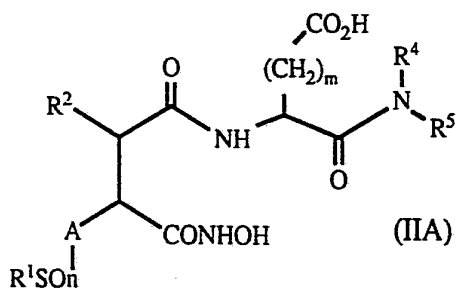
(a) coupling an acid of general formula (II)



(II)

or an activated derivative thereof with hydroxylamine, O-protected hydroxylamine, or a salt thereof, R^1, R^2, R^3, R^4, R^5, A and n being as defined in any of claims 1 to 11 except that any substituents in R^1, R^2, R^3, and A which are potentially reactive with hydroxylamine, O-protected hydroxylamine or their salts may themselves be protected from such reaction, then removing any protecting groups from the resultant hydroxamic acid moiety and from any protected substituents in R^1, R^2, R^3 and A; or

(b) esterifying a compound of formula (IIA)



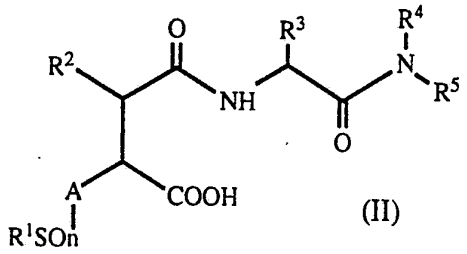
(IIA)

wherein m=1 or 2, and R^1, R^2, R^4, R^5, A and n are as defined in any of claims 1 to 11, with an alcohol of formula $HO(C_1\text{-}C_4)$alkyl; and

(c) optionally after step (a) or (b) converting a compound of general formula (I) into another compound of general formula (I).

22. A process as claimed in claim 21 wherein an activated derivative of the acid (II) is used, and that activated derivative is the pentafluorophenyl, hydroxysuccinyl, or hydroxybenztriazyl ester.

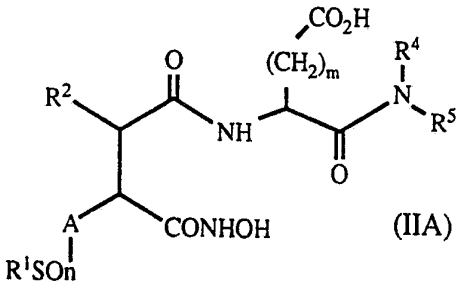
23. An acid of general formula (II)



(II)

wherein R^1, R^2, R^3, R^4, R^5, A and n, and the stereochemistry of the chiral centres adjacent the R^2, R^3 and -COOH groups, are as defined in any of claims 1 to 11.

24. An acid of general formula (IIA)



(IIA)

wherein m=1 or 2, and R^1, R^2, R^4, R^5, A and n, and the steroechemistry of the chiral centres adjacent the R^2, -CONHOH and $-(CH_2)_mCOOH$ groups, are as defined in any of claims 1 to 11.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00706

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C317/44; A61K31/22; C07C323/52; C07C323/60
C07C327/32; C07D333/34; A61K31/265; A61K31/38

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C ; C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 236 872 (F. HOFFMAN-LA ROCHE) 16 September 1987 cited in the application see page 2 - page 3, line 9 see page 8, line 29 - line 31	1,15,16
X	WO,A,9 005 719 (BRITISH BIO-TECHNOLOGY) 31 May 1990 cited in the application see page 10, line 13 - line 20; claims 1,17	23,24
A	see page 1, line 7 - line 29; claim 1	1,15,16

° Special categories of cited documents :[10]

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06 JULY 1993	19. 07. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	HEYWOOD C.J.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB93/00706

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16,18,19 are dircted to a method of treatment of the human/ animal body, the search has been carried out and based on the alleged effects of the compounds.

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:

The use of a term such as heterocyclyl is in contradiction to the requirements of Art. 6 PCT. The search was performed on the basis of those claims which are clear and concise.
Claims searched incompletely: 1-4, 7-11, 15-25

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 searches 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.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300706
SA 73102

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/07/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0236872	16-09-87	AU-B- 588437	14-09-89
		AU-A- 6990287	17-09-87
		CA-A- 1314655	16-03-93
		DE-A- 3782751	07-01-93
		JP-A- 62230757	09-10-87
		US-A- 4996358	26-02-91
WO-A-9005719	31-05-90	AU-A- 4800390	12-06-90
		EP-A- 0446267	18-09-91
		JP-T- 4502008	09-04-92