OXA- AND THIADIAZOLES AND THEIR USE AS METALLOPROTEINASE INHIBITORS

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ABSTRACT
Compounds formula (IA) or (IB), wherein W represents HO(C==O)—, HONH(C==O)— or H(C==O)N(OH)—; X represents —O— or —S—; and R1, R2, and R3 are as defined in the description and claims, are inhibitors of matrix metalloproteinases, in particular MMP9 and/or MMP12.
Figure 1

![Graph showing enzyme levels in different conditions.](image)

- **Sham**
- **CCl₄ alone**
- **CCl₄ + 2 mg/kg Example 12**
- **CCl₄ + 10 mg/kg Example 12**
- **CCl₄ + 20 mg/kg Example 12**

Legend:
- ■ Aspartate transaminase (ASAT)
- □ Alanine transaminase (ALAT)
Figure 2

Percentage of fibrotic liver tissue

<table>
<thead>
<tr>
<th>sham</th>
<th>CCl₄ alone</th>
<th>CCl₄ + 2 mg/kg Example 12</th>
<th>CCl₄ + 10 mg/kg Example 12</th>
<th>CCl₄ + 20 mg/kg Example 12</th>
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OXAZO- AND THIADIAZOLES AND THEIR USE AS METALLOPROTEINASE INHIBITORS

[0001] The present invention relates to therapeutically active hydroxamic and carboxylic 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 matrix metalloproteinases.

BACKGROUND TO THE INVENTION

[0002] The matrix metalloproteinases (MMP's) are a family of zinc containing endopeptidases which are capable of cleaving large biomolecules such as the collagens, proteoglycans and gelatins. Imbalance between active MMPs and endogenous inhibitors, leads to excessive tissue disruption. The three main groups of MMPs are the collagenases, the gelatinases, and the stromelysins. Collagenases include fibroblast collagenase (MMP-1), neutrophil collagenase (MMP-8), and collagenase 3 (MMP-13). Gelatinases include 72 kDa gelatinase (gelatibase A; MMP-2) and 92 kDa gelatinase (gelatibase B; MMP-9). Stromelysins include stromelysin 1 (MMP-3), stromelysin 2 (MMP-10) and matrilysin (MMP-7). However there are MMPs which do not fit neatly into the above groups, for example metalloelastase (MMP-12), membrane-type MMP (MT-MMP or MMP-14) and stromelysin 3 (MMP-11).

[0003] Over-expression and activation of MMPs have been linked with a wide range of diseases such as cancer, rheumatoid arthritis; osteoarthritis; chronic inflammatory disorders, such as asthma, bronchitis and emphysema; cardiovascular disorders, such as atherosclerosis; corneal ulceration; dental diseases such as gingivitis and periodontal disease; neurological disorders, such as multiple sclerosis and restenosis. For example, MMP-12 is required for the development of cigarette smoke-induced emphysema in mice. Science, 277, 2002 (1997). Inhibition of MMPs is therefore a strategy for treatment of such disease states. However, there is evidence that non-selective inhibition of matrix metalloproteinase activity may affect normal physiological process leading to dose limiting side effects. Selective inhibition of MMP-12 and/or MMP-9 is thought to be a particularly relevant strategy for intervention in inflammatory conditions.

[0004] MMPs can hydrolyse the membrane-bound precursor of the pro-inflammatory cytokine tumour necrosis factor α (TNF-α). This cleavage yields mature soluble TNF-α and the inhibitors of MMPs can block production of TNF-α both in vitro and in vivo. This pharmacological action is a probable contributor to the anti-inflammatory action of this class of compounds.

[0005] For a recent review of MMP inhibition as reflected in the patent literature, see Doherty et al. Therapeutic Developments in Matrix Metalloproteinase Inhibition; Expert Opinions on Therapeutic Patents, 2002, 12, 665-707.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIG. 1 is a bar graph illustrating the average ASAT and ALAT levels for control animals and those treated with the compound of Example 13 at three different dosages.

[0008] FIG. 2 is a bar graph illustrating the average area percentages of fibrosis in the livers of animals.

DETAILED DESCRIPTION OF THE INVENTION

[0009] According to the present invention there is provided compound formula (IA or (IB))

\[
W \quad R_2 \quad N-X \quad W. \quad N \quad 2 \quad N \quad R_4 \quad R_3 \quad R_4 \quad R_2 \quad R_3 \quad W
\]

wherein

[0010] W represents HO(C=O) — , HONH(C=O) — , or H(C=O)N(OH) — ;

[0011] X represents —O— or —S—;

[0012] R, represents —O or —S—;

[0013] hydrogen;

[0014] —OH or —SH;

[0015] fluoro or chloro;

[0016] –CF3;

[0017] (C1–C6)alkyl;

[0018] (C1–C6)alkoxy;

[0019] (C1–C6)alkenyl;

[0020] phenyl or substituted phenyl;

[0021] phenyl(C1–C6)alkyl or substituted phenyl(C1–C6)alkyl; phenyl(C1–C6)alkenyl or substituted phenyl(C1–C6)alkenyl heterocyclic or substituted heterocyclic;

[0022] heterocyclic(C1–C6)alkyl or substituted heterocyclic(C1–C6)alkyl; a group BSOA– wherein is 0, 1 or 2 and B is hydrogen or a (C1–C6)alkyl, phenyl, substituted phenyl, heterocyclic substituted heterocyclic, (C1–C6)acyl, phenoxyl or substituted phenacyl group, and A represents (C1–C6)alkylene;

[0023] —NH2, (C1–C6)alkylamino or di(C1–C6)alkylamino; amino(C1–C6)alkyl, (C1–C6)alkylamino(C1–C6)alkyl, di(C1–C6)alkylamino(C1–C6)alkyl, hydroxy(C1–C6)alkyl, mercapto(C1–C6)alkyl or carboxy(C1–C6)alkyl wherein the amino-, hydroxy-, mercapto- or carboxyl-group are optionally protected or the carboxyl-group amidated; or

[0024] a cycloalkyl, cycloalkenyl or non-aromatic heterocyclic ring containing up to 3 heteroatoms, any of which may be (i) substituted by one or more substituents selected from C1–C6 alkyl, C2–C5 alkenyl, halo, cyano...
As used herein the term “divalent (C₂₋₃₆)alkylene radical” means a hydrocarbon chain having from 2 to 6 carbon atoms, at least one triple bond, and two unsatisfied valences.

As used herein the term “cycloalkyl” means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term “cycloalkenyl” means an unsaturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. In the case of cycloalkenyl rings of from 5-8 carbon atoms, the ring may contain more than one double bond.

As used herein the term “aryl” refers to a mono-, bi- or tri-cyclic carbocyclic aromatic group, and to groups consisting of two or more covalently linked monocyclic carbocyclic aromatic groups. Illustrative of such groups are phenyl, biphenyl and naphthyl.

As used herein the unqualified term “heterocyclic” or “heterocyclic” includes “heteroaryl” as defined below, and in particular means a 5-8 membered aromatic or non-aromatic heterocyclic ring containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzyl or second heterocyclic ring, and the term includes, for example, pyrrolyl, furyl, thiophenyl, pyridindinyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, thiazapinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, and benzimidazolyl rings.

As used herein the term “heteroaryl” refers to a 5- or 6-membered aromatic ring containing one or more heteroatoms, and optionally fused to a benzyl or pyridyl ring, and to groups consisting of two covalently linked 5- or 6-membered aromatic rings each containing one or more heteroatoms; and to groups consisting of a monocyclic carbocyclic aromatic group covalently linked to a 5- or 6-membered aromatic ring containing one or more heteroatoms. Illustrative of such groups are thiophenyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, 4-((1,2,3)-thiadiazol-4-y)phenyl and 5-isoxazol-3-ylthiophenyl.

As used herein the unqualified term “carbocyclic” or “carbocyclic” refers to a 5-8 membered ring whose ring atoms are all carbon.

Unless otherwise specified in the context in which it occurs, the term “substituted” as applied to any moiety herein means substituted with up to four substituents, each of which independently may be (C₆H₄)alkyl, phenyl, benzyl, (C₂₋₃₆)alkyl, alkoxy, phenoxy, hydroxy, mercapto, (C₁₋₃₆)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, oxo, —COOH, —CONH₂, —COR, —CONH—COR, —CONH—CONHR, —CONHR₂, —OH, —OR, oxo, —SH, —SR, —NHCOR, and NHCOR wherein R is C₁₋₄ alkyl or benzyl and/or (ii) fused to a cycloalkyl or heterocyclic ring: R₃ represents a group R₁₀=—(X)₉=—(AI,K)₉=— wherein A is heterocyclic group.

As used herein the term “divalent (C₂₋₃₆)alkylene radical” means a hydrocarbon chain having from 2 to 6 carbon atoms, at least one triple bond, and two unsatisfied valences.

As used herein the term “cycloalkyl” means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term “cycloalkenyl” means an unsaturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. In the case of cycloalkenyl rings of from 5-8 carbon atoms, the ring may contain more than one double bond.

As used herein the term “aryl” refers to a mono-, bi- or tri-cyclic carbocyclic aromatic group, and to groups consisting of two covalently linked monocyclic carbocyclic aromatic groups. Illustrative of such groups are phenyl, biphenyl and naphthyl.

As used herein the unqualified term “heterocyclic” or “heterocyclic” includes “heteroaryl” as defined below, and in particular means a 5-8 membered aromatic or non-aromatic heterocyclic ring containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzyl or second heterocyclic ring, and the term includes, for example, pyrrolyl, furyl, thiophenyl, pyridindinyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, thiazapinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, and benzimidazolyl rings.

As used herein the term “heteroaryl” refers to a 5- or 6-membered aromatic ring containing one or more heteroatoms, and optionally fused to a benzyl or pyridyl ring, and to groups consisting of two covalently linked 5- or 6-membered aromatic rings each containing one or more heteroatoms; and to groups consisting of a monocyclic carbocyclic aromatic group covalently linked to a 5- or 6-membered aromatic ring containing one or more heteroatoms. Illustrative of such groups are thiophenyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, 4-((1,2,3)-thiadiazol-4-y)phenyl and 5-isoxazol-3-ylthiophenyl.

As used herein the unqualified term “carbocyclic” or “carbocyclic” refers to a 5-8 membered ring whose ring atoms are all carbon.

Unless otherwise specified in the context in which it occurs, the term “substituted” as applied to any moiety herein means substituted with up to four substituents, each of which independently may be (C₆H₄)alkyl, phenyl, benzyl, (C₂₋₃₆)alkyl, alkoxy, phenoxy, hydroxy, mercapto, (C₁₋₃₆)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, oxo, —COOH, —CONH₂, —COR, —CONH—COR, —CONH—CONHR, —CONHR₂, —OH, —OR, oxo, —SH, —SR, —NHCOR, and NHCOR wherein R is C₁₋₄ alkyl or benzyl and/or (ii) fused to a cycloalkyl or heterocyclic ring: R₃ represents a group R₁₀=—(X)₉=—(AI,K)₉=— wherein A is heterocyclic group.

As used herein the term “divalent (C₂₋₃₆)alkylene radical” means a hydrocarbon chain having from 2 to 6 carbon atoms, at least one triple bond, and two unsatisfied valences.
amino acid mean the group R in respectively a natural and non-natural amino acid of formula NH₂—CH(R)—COOH.

Examples of side chains of natural alpha amino acids include those of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α-aminoadipic acid, α-amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α-methylserine, ornithine, picolinic acid, and threonine.

In natural alpha-amino acid side chains which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups as in arginine, lysine, glutamic acid, aspartic acid, tryptophan, histidine, serine, threonine, tyrosine, and cysteine, such functional substituents may optionally be protected.

Likewise, in the side chains of non-natural alpha amino acids which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups, such functional substituents may optionally be protected.

The term “protected” when used in relation to a functional substituent in a side chain of a natural or non-natural alpha-amino acid means a derivative of such a substituent which is substantially non-functional. The widely used handbook by T. W. Greene and P. G. Wuts “Protective Groups in Organic Synthesis” Second Edition, Wiley, New York, 1991 reviews the subject. For example, carboxyl groups may be esterified (for example as a C₆H₄O₂alkyl ester), amino groups may be converted to amides (for example as a NHCOCONH₂alkyl amide) or carbamates (for example as an NHCONH₂alkyl amide) or NHCOC₂H₅carbamate, hydroxy groups may be converted to ethers (for example as an OCH₂alkyl or O(alkyl)OH), or thiol groups may be converted to thioethers (for example as a tert-butyl or benzyl thioether) or thiosters (for example as a OOC₂H₅alkyl thioester).

There are at least two actual or potential 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 diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof. Currently, the preferred stereo configuration of the carbon atom carrying the R₃ group is R; that of the carbon atom carrying the R₂ group (when asymmetric) is R; and that of the carbon atom carrying the R₂ group (when asymmetric) is S.

The Group R₃

R₃ may be, for example,

hydrogen, hydroxy, methyl, methoxy, trifluoromethyl, ethyl, n-propyl, allyl phenylpropyl, cyclopropylmethyl, phenylprop-2-enyl, thienylsulphonylmethyl, thienylsulphonylmethyl), or thienylsulphonylmethyl, or

C₃H₅Cl alkyl, eg methyl, ethyl n-propyl or n-butyl, substituted by a phthalimidino, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3-methyl-2,5-dioxo-1-imidazolidinyl, 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, 2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl, 3-methyl-2,4,5-trioxo-1-imidazolidinyl, 2,5-dioxo-3-phenyl-1-imidazolidinyl, 2-oxo-1-pyrolidinyl, 2,5-dioxo-1-pyrolidinyl or 2,6-dioxopiperidinyl, 5,5-dimethyl-2,4-dioxo-3-oxazolidinyl, hexahydro-1,3-dioxopyrazol[1,2a][1,2,4]triazolo[1,2-a][1,2,4]-triazol-2-yl, or a naphthalimidino (i.e. 1,3-dihydro-1,3-dioxo-2H-benzo[f]isoindol-2-yl), 1,3-dihydro-1-oxo-2H-benzo[f]isoindol-2-yl, 1,3-dihydro-1,3-dioxo-2H-pyrrolo[3,4-b]quinolin-2-yl, or 2,3-dihydro-1,3-dioxo-1H-benz[e]isoquinolin-2-yl group, or

cyclohexyl, cyclooctyl, cycloheptyl, cyclopentyl, cyclobutyl, cyclopentyl, tetrahydropropyryl or morpholynyl.

Presently preferred R₃ groups include hydrogen, hydroxy, methoxy, cyclopropyl, n-propyl, and allyl. Of these, hydrogen, hydroxy, methoxy and allyl are presently more preferred.

The Group R₄

R₄ may for example be

C₆H₄C₃H₅alkenyl or C₆H₄alkynyl;

cycloalkyl(C₆H₄alkyl)ₙ;

phenyl(C₆H₄alkenyl)-, phenyl(C₆H₄alkynyl)- or phenyl(C₆H₄alkynyl)-optionally substituted in the phenyl ring;

eheterocyclic(C₆H₄alkenyl)-, heterocyclic(C₆H₄alkynyl)- or heterocyclic(C₆H₄alkynyl)-optionally substituted in the heterocyclic ring;

4-phenylphenyl(C₆H₄alkyl), 4-phenylphenyl(C₆H₄alkenyl)-, 4-phenylphenyl(C₆H₄alkynyl)-, 4-heterocyclicphenyl(C₆H₄alkenyl)-, 4-heterocyclicphenyl(C₆H₄alkynyl)-, 4-heterocyclicphenyl(C₆H₄alkynyl)- optionally substituted in the terminal phenyl or heterocyclic ring;

phenoxy(C₆H₄alkenyl)- or heteroaryloxy(C₆H₄alkenyl)-optionally substituted in the phenyl or heterocyclic ring;

Specific examples of such groups include methyl, ethyl, n- or iso-propyl, n-, iso- or tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-nonyl, n-decyl, prop-2-ynyl-1-yl, cyclohexylethyl, cyclopropylmethyl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, benzyl phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, phenoxybutyl, 3-(4-pyridylphenyl)propyl, 3-(4-pyridylphenyl)propyl, 3-(4-pyridylphenyl)propyl, 3-(4-pyridylphenyl)propyl, 3-(4-pyridylphenyl)propyl-2-yn-1-yl and 3-(4-chlorophenyl)phenylpropyl-.

Presently preferred R₄ groups include benzyl, n-buty, iso-buty, n-hexyl, ethoxyphenylpropyl, preferably 4-ethoxyphenylpropyl and 1 and cyclopentylmethyl. Of these, isobutyl and ethoxyphenylpropyl, particularly 4-ethoxyphenylpropyl, are presently more preferred.

The Group R₅

R₅ may for example be C₆H₄alkyl, phenyl, 2-3-, or 4-pyridyl, 2- or 3-thienyl, 2-3-, or 4-hydroxyphenyl, 2-3-, or 4-methoxyphenyl, 2-3-, or 4-pyridylmethyl, benzyl, 2-3-, or 4-hydroxybenzyl, 2-3-, or 4-benzoxylbenzyl, 2-3-, or 4-C₆H₄alkoxycarbonyl, or benzoxycarbonyl(C₆H₄alkyl)-; or

the characterising group of a natural α-amino acid, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; or

a group -[Alk]ₙR₆, where Alk is a (C₆H₄alkyl) or (C₆H₄alkenyl) group optionally interrupted by one or more —O—, or —S— atoms or —N(R₆)₂ groups (where R₆ is a hydrogen atom or a (C₆H₄alkyl) group), n is 0 or 1, and R₆ is an optionally substituted cycloalkyl or cycloalkenyl group; or

a benzyl group substituted in the phenyl ring of a group of formula —OCH₃COR₆ where R₆ is hydroxyl,
amino, \((C_1-C_8)alkoxy\), phenyl\((C_1-C_8)alkoxy\), (C\(_1\)-C\(_8\))alkylamino, di\((C_1-C_8)alkyl\)amino, phenyl\((C_1-C_8)alkylamino\), the residue of an amino acid or acid halide, ester or amide derivative thereof, said residue being linked via an amide bond, said amino acid being selected from glycine, \(\alpha\) or \(\beta\) alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid, and aspartic acid; or

[a0083] a heterocyclic\((C_1-C_8)alkyl\) group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, \((C_1-C_8)alkoxy\), cyano, \((C_1-C_8)alkanoyl\), trifluoromethyl\((C_1-C_8)alkyl\), hydroxy, formyl, amino, \((C_1-C_8)alkylamino\), di\((C_1-C_8)alkylamino\), mercapto, \((C_1-C_8)alkylthio\), hydroxy\((C_1-C_8)alkyl\), mercapto\((C_1-C_8)alkyl\) or \((C_1-C_8)alkyl\)phenylmethyl; or

[a0084] a group —CR\(_2\)R\(_3\)R\(_4\), in which:

[a0085] each of R\(_2\), R\(_3\) and R\(_4\) is independently hydrogen, \((C_1-C_8)alkyl\), \((C_1-C_8)alkenyl\), \((C_1-C_8)alkylamino\), \((C_1-C_8)cycloalkyl\); or

[a0086] R\(_2\) is hydrogen and R\(_3\) and R\(_4\) are independently phenyl or heteroaryl such as pyridyl; or

[a0087] R\(_2\) is hydrogen, \((C_1-C_8)alkyl\), \((C_1-C_8)alkenyl\), \((C_1-C_8)cycloalkyl\), and R\(_3\) and R\(_4\) together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

[a0088] R\(_2\), R\(_3\), and R\(_4\) together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

[a0089] R\(_2\) and R\(_3\) are each independently \((C_1-C_8)alkyl\), \((C_1-C_8)alkenyl\), \((C_1-C_8)alkylamino\), \((C_1-C_8)cycloalkyl\) or a group as defined for R\(_2\) below other than hydrogen, or R\(_2\) and R\(_3\) together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R\(_4\) is hydrogen, \(-\text{SH}\), halogen, \(-\text{CN}\), \(-\text{CO}_2\text{H}\), \(-\text{C}_2\text{H}_4\text{perfluoroalkyl}\), \(-\text{CH}_3\text{OH}\), \(-\text{CO}_2\text{(C}_1\text{-C}_8\text{)alkyl}\), \(-\text{O}(\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{O}(\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{S}(\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{S}(\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{SO}_2\text{(C}_1\text{-C}_8\text{)alkyl}\), \(-\text{SO}_2\text{(C}_1\text{-C}_8\text{)alkyl}\), or a group —Q-W wherein Q represents a bond or \(-\text{O}\), \(-\text{S}\), \(-\text{SO}\), or \(-\text{SO}_2\), and W represents a phenyl, phenylalkyl, \((C_1-C_8)cycloalkyl\), \((C_1-C_8)cycloalkylalkyl\), \((C_1-C_8)cycloalkylalkyl\), heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxy, halogen, \(-\text{CN}\), \(-\text{CO}_2\text{H}\), \(-\text{CO}_2\text{(C}_1\text{-C}_8\text{)alkyl}\), \(-\text{CONH}_2\), \(-\text{CONH(C}_1\text{-C}_8\text{)alkyl}\), \(-\text{CONH(C}_1\text{-C}_8\text{)alkyl}\), \(-\text{CHO}\), \(-\text{CH}_3\text{OH}\), \(-\text{C}_2\text{H}_4\text{perfluoroalkyl}\), \(-\text{O}(\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{S}(\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{SO}(\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{SO}_2\text{(C}_1\text{-C}_8\text{)alkyl}\), \(-\text{NO}_2\), \(-\text{NH}_2\), \(-\text{NH}(\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{N}(\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{NHO}(\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{C}_2\text{H}_4\text{perfluoroalkyl}\), \(-\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{C}_2\text{-C}_8\text{alkyl}\), \(-\text{C}_1\text{-C}_8\text{)alkyl}\), \(-\text{C}_1\text{-C}_8\text{)alkenyl}\), \(-\text{C}_2\text{-C}_8\text{alkenyl}\), \(-\text{C}_1\text{-C}_8\text{)cycloalkyl}\), \(-\text{phenyl}\), and \(-\text{benzyl}\).

[a0090] Examples of particular R\(_2\) groups include benzyl, phenyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, 1-benzothio-1-methylthyl, 1-methylthio-1-methylthyl, and 1-mercapto-1-methylthyl.

[a0091] Presently preferred R\(_2\) groups include phenyl, benzyl, tert-butoxymethyl, isopropyl, tert-butyl, and iso-butyl. Of these, tert-butyl and benzyl are presently more preferred.

The Group R\(_2\)

[a0092] R\(_2\) may be, for example, \((C_1-C_8)alkyl\) such as methyl, ethyl, \(n\)-or isoo-propyl, prop-2-yl, and tert-butyl; \((C_1-C_8)alkoxy\) such as cyclopropyl or cyclopentyl; phenyl; \((C_1-C_8)alkyl\)-such as benzyl; heteroaryl\((C_1-C_8)alkyl\)-such as thienylmethyl; monocyclic heterocyclic such as morpholino; or monocyclic heteroaryl such as thienyl or furanyl. Any of the foregoing may be optionally substituted, for example by methyl, trifluoromethyl, hydroxy, mercapto, amino or carboxy.

[a0093] As mentioned above, the present compounds are useful in human or veterinary medicine since they are active as inhibitors of MMPs. Accordingly in another aspect, this invention concerns:

[a0094] (i) a method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound which is a member of the group defined above, or a pharmaceutically acceptable salt thereof; and

[a0095] (ii) a compound which is a member of the group defined above, for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMP; and

[a0096] (iii) the use of a compound which is a member of the group defined above in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs.

[a0097] Diseases or conditions mediated by MMPs include those involving tissue breakdown such as bone resorption, inflammatory diseases, dermatological conditions and tumour growth or invasion by secondary metastases; in particular rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, neuroinflammatory disorders, including those involving myelin degradation, for example multiple sclerosis; restenosis, emphysema, bronchitis and asthma.

[a0098] In a further aspect of the invention there is provided a pharmaceutical or veterinary composition comprising a compound which is a member of the group defined above together with a pharmaceutically or veterinarily acceptable excipient or carrier.

[a0099] It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy. Optimum dose levels and frequency of dosing will be determined by clinical trial.

[a1000] With the compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetico properties. The orally administrable compositions 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. 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 glycerine; tableting 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 hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

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 pharmacetics 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 edetate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hydroxypropyl may also be included.

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.

Compounds according to the present invention in which $W$ is a hydroxamic acid group $\text{HONH(C=O)}$ — may be prepared from corresponding compounds of the invention in which $W$ is a carboxyl group $\text{COOH}$ or from the corresponding protected hydroxamic acid derivatives. That process, which forms another aspect of the invention, comprises an acid of general formula (IIA) or (IIB)

or an activated derivative thereof to react with hydroxylamine, $\text{O}$-protected hydroxylamine, or an $\text{N,O}$-diprotected hydroxylamine, or a salt thereof, $X, R_1, R_2, R_3,$ and $R_4$ being as defined in general formula (IIA) or (IIB) except that any substituents in $R_1, R_2, R_3,$ and $R_4$ which are potentially reactive with hydroxylamine, $\text{O}$-protected hydroxylamine, or $\text{N,O}$-diprotected 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 $R_4$.

Conversion of (IIA) or (IIB) to an activated derivative such as the pentfluorophenyl, hydroxysuccinyl, or hydroxybenzotriazolyl ester may be affected by reaction with the appropriate alcohol in the presence of a dehydrating agent such as dicyclohexyl carbodiimide (DCC), $\text{N,N}$-dimethylaminoethyl-$\text{N}$-ethyl carbodiimide (EDC), or 2-ethoxy-1-ethoxycarbonyl-1,2-di-hydroquinoline (EDQ).

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 benzoylcarbonyl, $\text{t}$-butoxycarbonyl or acetyl groups, or in the form of a phthalalimido group. Hydroxy groups are often protectable as readily cleavable ethers such as the $\text{t}$-butyl or benzyl ether, or as readily cleavable esters such as the acetate. Carboxyl groups are often protectable as readily cleavable esters, such as the $\text{t}$-butyl or benzyl ester.

Examples of $\text{O}$-protected hydroxylamines for use in method (a) above include $\text{O}$-benzylhydroxylamine, $\text{O,4}$-methoxybenzylhydroxylamine, $\text{O}$-trimethysilylhydroxylamine, and $\text{O}$-tert-butoxycarbonylhydroxylamine. $\text{N}$, $\text{O}$-bis($\text{4}$-methoxybenzyl)hydroxylamine, $\text{N}$-tert-butoxycarbonyl-$\text{O}$-tert-$\text{t}$-butyl(dimethyl)silylhydroxylamine, $\text{N}$-tert-butoxycarbonyl — $\text{O}$ — tetrahydropranylhydroxylamine, and $\text{N}$, $\text{O}$-bis(tert-butoxycarbonyl)hydroxylamine.

Compounds of the invention wherein $W$ is an $\text{N}$-formylhydroxylaminogroup $\text{H(C=O)}\text{NH(OH)}$ — may be prepared by $\text{N}$-formylation of the corresponding $\text{O}$-protected compound in which $W$ is $\text{—NH(OH)}$, then removal of the $\text{O}$-protecting group.

Compounds according to the present invention in which $W$ is a carboxylic acid group $\text{—COOH}$, i.e compounds of formula (IIA) or (IIB) above, may be prepared by a process comprising: coupling an acid of formula (III) or an activated derivative thereof

with an amine of formula (IVA) or (IVB)
wherein X, R, R₂, R₃, and R₄ are as defined in general formula (IA) and (IB) except that any substituents in R₁, R₂, R₃, and R₄ which are potentially reactive in the coupling reaction may themselves be protected from such reaction, and R₁₁ represents a hydroxy protecting group, and subsequently removing the protecting group R₁, and any protecting groups from R₂, R₃, R₄, and R₅.

Active derivatives of acids (III) include activated esters such as the pentafluorophenyl ester, acid anhydrides and acid halides, eg chlorides. Suitable hydroxy protecting groups may be selected from those known in the art.

Compounds of formula (IVA) and (IVB) may be prepared by methods analogous to the general methods for oxadiazole ring formation illustrated in Schemes 1 and 2 in Examples 1 and 2 below.

The following preparative Examples describe the preparation of compounds useful in accordance with the invention.

The following abbreviations have been used in the examples

DCM—Dichloromethane
DMF N,N-Dimethylformamide

Example 1

3R-[2,2-Dimethyl-1S-(5-phenyl-1,2,4-oxadiazol-3-yl)-propylcarbamoyl]-2S-hydroxy-5-methyl-hexanoic acid

Scheme 1.

[0117] HOBT—1-Hydroxybenzotriazole
[0118] Pfp—Pentafluorophenol
[0119] WSCDI—N-(3-Dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride
[0120] HCl—Hydrochloric acid
[0121] THF—Tetrahydrofuran
[0122] TFA—Trifluoroacetic acid
[0123] P(O-Tol)₃—Tri-O-tolylphosphine
[0124] AcOEt—Ethyl acetate
[0125] CH₃CN—Acetonitrile
Example 1 was prepared as outlined in Scheme 1 using procedures described below.

Step A. (1S-carbamoyl-2,2-dimethyl-propyl)-carbamic acid benzyl ester

[0127] N-benzylloxycarbonyl-L-tert-butylglycine (50 g, 189 mmol) was dissolved in DMF (500 mL) and cooled in an ice-water bath before addition of HOBT (28.05 g, 208 mmol) andWSCDI (39.8 g, 208 mmol). Reaction was stirred at 0°C for 1 hour before addition of 0.880 ammonia solution (21 mL, 377 mmol). The reaction was allowed to warm to room temperature and stirred for 18 hours. DMF was removed under reduced pressure and the residue partitioned between ethyl acetate and 1M HCl. The organic layer was separated and washed with 1M HCl, saturated aqueous sodium bicarbonate solution and brine before drying over magnesium sulphate, filtration and concentration under reduced pressure. Column chromatographic on silica gel using ethyl acetate/hexane as eluent leads to isolation of the desired product as an orange oil (36.72 g, 89%).

[0131] 1H-NMR: δ (CDCl3), 7.42 (5H, m), 5.28 (2H, m), 4.55 (2H, d, J=6.5 Hz) and 1.11 (9H, s).

[0132] LRMS; +ve ion 269 (M+Na), 247.2 (M+H).

Step B. (1S-cyano-2,2-dimethyl-propyl)-carbamic acid benzyl ester

[0130] (1S-carbamoly-2,2-dimethyl-propyl)-carbamic acid benzyl ester (44.1 g, 167 mmol) was dissolved in anhydrous pyridine (203 mL, 2.5 mol) under an inert atmosphere and cooled in an ice-water bath. Phosphorus oxychloride (21.8 mL, 234 mmol) was added slowly over 15 minutes and the reaction allowed to stir in the ice-water bath for 2 hours before warming to room temperature and stirred for 12 hours. The reaction mixture was treated with ice-water (400 mL) and extracted with ethyl acetate (2×300 mL). The organic layer was separated and washed with 1M HCl, saturated aqueous sodium bicarbonate solution and brine before drying over magnesium sulphate, filtration and concentration under reduced pressure. Column chromatography on silica gel using ethyl acetate/hexane as eluent leads to isolation of the desired product as an orange oil (36.72 g, 89%).

[0133] 1H-NMR: δ (CDCl3), 7.32 (5H, m), 6.21 (1H, bs), 5.95 (1H, bs), 5.81 (1H, d, J=6.4 Hz), 5.08 (2H, m), 4.79 (1H, bs), 4.05 (1H, d, J=6.5 Hz) and 0.95 (9H, s).

[0135] LRMS; +ve ion 279.8 (M+H).

Step D. [2,2-dimethyl-1S-[(5-phenyl-1,2,4]oxadiazo-3-yl)-propyl]-carbamic acid benzyl ester

[0136] 1S–(N-hydroxycarbamimidoyl)-2,2-dimethyl-propyl]-carbamic acid benzyl ester (0.21 g, 0.75 mmol) was
dissolved in DMF (5 mL) and treated with pyridine (0.1 mL, 1.28 mmol), benzoyl chloride (0.13 mL, 1.1 mmol) and DMAP (catalytic). The reaction mixture was stirred at room temperature for 4 hours before heating to 100° C. and stirring for 16 hours. The reaction was cooled back to room temperature and concentrated under reduced pressure. The reaction was diluted with ethyl acetate and washed with 1M HCl, saturated aqueous sodium bicarbonate solution and brine before drying over magnesium sulphate, filtration and concentration under reduced pressure. The desired product was isolated as an orange oil (0.22 g, 78%).

[0137] 1H-NMR; delta (CDCl3), 8.12 (2H, m), 7.55 (3H, m), 7.32 (5H, m), 5.55 (1H, d, J=6.4 Hz), 5.12 (2H, m), 4.95 (1H, d, J=6.5 Hz) and 1.10 (9H, s).

[0138] LRMS; +ve ion 366.2 (M+H), 388.2 (M+Na).

Step E. 2,2-dimethyl-1S-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propylamine

[0139] 2,2-dimethyl-1S-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propylamine (0.13 g, 0.6 mmol) was dissolved in DMF (5 mL) and cooled in an ice-water bath before the addition 2R-(2,2-Dimethyl-SS-o xo-[1,3]dioxolan-4-yl)-4-methyl-pentanoic acid pentafluorophenyl ester (0.22 g, 0.6 mmol). Reaction was allowed to warm to room temperature and stirred for 15 hours. The DMF was removed under reduced pressure and the reaction diluted with ethyl acetate and washed with 1M HCl, saturated aqueous sodium bicarbonate solution and brine before drying over magnesium sulphate, filtration and concentration under reduced pressure. The product was isolated as a yellow oil (0.13 g, 98%).

[0140] LRMS; +ve ion 232 (M+H).

Step F. 2R-(2,2-Dimethyl-5-oxo-[1,3]dioxolan-4S-yl)-4-methyl-pentanoic acid [2,2-dimethyl-1S-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propyl]-amide

[0141] 2R-(2,2-Dimethyl-5-oxo-[1,3]dioxolan-4S-yl)-4-methyl-pentanoic acid [2,2-dimethyl-1S-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propyl]-amide (0.05 g, 0.11 mmol) was dissolved in methanol (2 mL) and treated with 50% aqueous hydroxylamine (0.04 mL, 0.5 mmol). Reaction was stirred at room temperature for 2 hours before evaporation under reduced pressure. The reaction product was separated by preparative reverse phase chromatography to yield the required product as a white solid (0.02 g, 44%).

[0145] 1H-NMR; delta (CDCl3), 8.13 (2H, m), 7.65 (1H, m), 7.58 (2H, m), 5.14 (1H, s), 4.01 (1H, d, J=7.1 Hz), 2.94 (1H, m), 1.60 (1H, m), 1.45 (1H, m), 1.16 (1H, m), 1.07 (7H, s), 0.89 (3H, d, J=6.5 Hz) and 0.86 (3H, d, J=6.6 Hz).

[0146] 13C-NMR; delta (CDCl3), 177.1, 176.3, 172.0, 171.6, 134.6, 130.8, 129.4, 125.7, 73.7, 55.8, 49.6, 39.7, 36.2, 27.4, 27.2, 24.2 and 22.5.

[0147] LRMS; +ve ion 419 (M+H), -ve ion 417 (M-H).

Step H. 2R-(2,2-Dimethyl-5-oxo-[1,3]dioxolan-4S-yl)-4-methyl-pentanoic acid pentafluorophenyl ester

[0148] 2R-(2,2-Dimethyl-5-oxo-[1,3]dioxolan-4S-yl)-4-methyl-pentanoic acid (prepared according to WO94/02447) (30 g, 130 mmol) was dissolved in ethyl acetate (300 ml) and treated with pentafluorophenol (28.8 g, 156 mmol) and WSCDI (30 g, 156 mmol). Reaction was heated to reflux for 2 hours and then allowed to stir at room temperature for 12 hours. The reaction mixture was washed with 1M Na2CO3 and brine before drying over magnesium sulphate, filtration and concentration under reduced pressure. The product was recrystallised from ethyl acetate/hexane to yield the desired product as a single diastereomer (21.2 g, 42%).

[0149] 1H-NMR; delta (CDCl3), 4.55 (1H, d, J=6.7 Hz), 3.31 (1H, m), 1.85 (3H, m), 1.65 (3H, s), 1.65 (3H, s), 1.05 (3H, d, J=6.5 Hz) and 0.99 (3H, d, J=6.5 Hz).

[0150] Also prepared, the diastereomer 3R-[2,2-dimethyl-1S-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propylcarbamoyl]-2R-hydroxy-5-methyl-hexahydroxamic acid.

[0151] M+H=420.0, M+Na=441.5, M-H=417.5.

[0152] The corresponding carboxylic acid was prepared as outlined in Scheme 1 and the procedure below.

Step I. 3R-[1S-(5-Furan-2-yl-[1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propylcarbamoyl]-2S-hydroxy-5-methyl-hexahydroxamic acid

[0153] 2R-(2,2-Dimethyl-SS-o xo-[1,3]dioxolan-4-yl)-4-methyl-pentanoic acid [2,2-dimethyl-1S-(5-Furan-2-yl-[1,2,4]oxadiazol-3-yl)-propyl]-amide (0.05 g, 0.12 mmol) was dissolved in tetrahydrofuran (5 ml) and cooled to 4°C during the addition of 1M hydrochloric acid (5 ml). The solution was allowed to warm to room temperature and then stirred for 18 hours. The bulk of the solvent was removed under reduced pressure before drying under high vacuum to a white foam (0.045 g, ca. quant.).

[0154] 1H-NMR; delta (CDCl3), 7.88 (1H, s), 7.45 (1H, d, J=3.6 Hz), 6.74 (1H, m), 5.15 (1H, s), 4.18 (2H, d, J=6.4 Hz), 2.91 (1H, m), 1.65 (1H, m), 1.50 (1H, m), 1.31 (1H, m), 1.06 (9H, s), 0.88 (3H, d, J=6.4 Hz) and 0.82 (3H, d, J=6.5 Hz).

[0155] LRMS; +ve ion 392.2 (M-H).
Example 2
3R-[2,2-Dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yld)-propylcarbamoyl]-2S-hydroxy-5-methyl-hexano-hydroxyamic acid

Scheme 2:

Reagents and conditions.
A. HOBT,WSC/DMF.
B. Tosamine, 100°C.
C. Aq.NH₂OH, ethanol, 70°C.
D. TFA, DCM.
E. HOBT, WSC/DMF.
F. Aq.NH₂OH, methanol.
Example 2 was prepared as outlined in scheme 2 using procedures described below.

Step A.
2S-tert-Butoxycarbonylamino-3,3-dimethyl-butyric acid benzotriazol-1-yl ester

A solution of N-tert-Butoxycarbonyl-L-tert-butyl glycine (5 g, 21.6 mmol) in ethyl acetate (80 ml) was cooled in an ice-water bath. HOBt (3.22 g, 23.8 mmol) andWSCDI (4.56 g, 23.8 mmol) were added and the reaction allowed to stir at room temperature for 12 hours. The reaction mixture was washed with 1M Na2CO3 and brine, before drying over magnesium sulphate, filtration and concentration to a white foam (5.74 g, 76%).

1H-NMR; delta (CDCl3), 8.05 (1H, m), 7.65 (2H, m), 7.41 (1H, m), 5.10 (1H, d, J=6.6 Hz), 4.45 (1H, d, J=6.5 Hz), 1.55 (9H, s) and 1.21 (9H, s).

LRMS; +ve ion 349 (M+H).

Step B. [2,2-Dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propyl]-carboxylic acid tert-butyl ester

2S-tert-Butoxycarbonyl amino-3,3-dimethyl-butyric acid benzotriazol-1-yl ester (3.71 g, 10.7 mmol) was dissolved in toluene (80 ml) and treated with N-hydroxy-benzamidine (2.9 g, 21.3 mmol). The reaction mixture was stirred at 110°C for 18 hours. The solution was concentrated under reduced pressure and partitioned between ethyl acetate and 1M Na2CO3. The organic layer was further washed with 1M Na2CO3 and brine before drying over magnesium sulphate, filtration and concentration under reduced pressure. Column chromatography on silica gel using ethyl acetate and hexane (1:4) lead to isolation of the desired product (2.58 g, 73%).

1H-NMR; delta (CDCl3), 8.10 (2H, m), 7.50 (3H, m), 5.30 (1H, d, J=6.5 Hz), 4.95 (1H, d, J=6.6 Hz), 1.44 (9H, s) and 1.03 (9H, s).

LRMS; +ve ion 354.2 (M+Na).

Step C. N-hydroxy-benzamidine

Benzonitrile (5 g, 48 mmol) was dissolved in ethanol (100 ml) and treated with 50% aqueous hydroxylamine (16 ml, 242 mmol). Reaction was heated to reflux for 3 hours before concentration under reduced pressure to give a clear foam (4.5 g, 68%).

LRMS; +ve ion 137 (M+H).

Step D. 2,2-Dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propionamide

[2,2-Dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propyl]-carboxylic acid tert-butyl ester (1 g, 3.0 mmol) was dissolved in DCM (5 ml) and treated with TFA (5 ml). Reaction stirred at room temperature for 3 hours. The reaction was concentrated under reduced pressure and partitioned between ethyl acetate and 1M Na2CO3. The organic layer was further washed with 1M Na2CO3 and brine before drying over magnesium sulphate, filtration and concentration under reduced pressure to give the desired product (0.65 g, 93%).

1H-NMR; delta (CH3OD), 8.10 (2H, m), 7.55 (3H, m), 4.81 (1H, s) and 1.19 (9H, s).

LRMS; +ve ion 232 (M+H).

Step E. 2R-(2,2-Dimethyl-5-oxo-[1,3]dioxolan-4-yl)-4-methyl-pentanoic acid-[2,2-dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propyl]-amide

2R-(2,2-Dimethyl-5-oxo-[1,3]dioxolan-4-yl)-4-methyl-pentanoic acid (0.27 g, 1.17 mmol) was dissolved in DMF (5 ml) and cooled in an ice-water bath before addition of HOBT (0.17 g, 1.29 mmol) andWSCDI (0.25 g, 1.29 mmol). Reaction was stirred at 0°C for 1 hour before addition of 2,2-Dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propionlamine (0.3 g, 1.29 mmol). The reaction was allowed to warm to room temperature and stirred for 18 hours. DMF was removed under reduced pressure and the residue partitioned between ethyl acetate and 1M HCl. The organic layer was separated and washed with 1M HCl, saturated aqueous sodium bicarbonate solution and brine before drying over magnesium sulphate, filtration and concentration under reduced pressure. Column chromatography on silica gel using ethyl acetate and hexane (1:4) lead to isolation of the desired product (0.26 g, 46%).

LRMS; +ve ion 444 (M+H).

Step F. 3R-[2,2-Dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propyl]carbonyl]-2S-hydroxy-5-methyl-hexamethyl-hydroxamic acid

2R-(2,2-Dimethyl-5-oxo-[1,3]dioxolan-4-yl)-4-methyl-pentanoic acid-[2,2-dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propyl]-amide (0.26 g, 0.6 mmol) was dissolved in methanol (5 ml) and treated with 50% aqueous hydroxylamine (0.2 ml, 2.95 mmol). Reaction stirred at room temperature for 3 hrs before concentration under reduced pressure. The product was recrystallised from ethyl acetate/ hexane to yield the desired product (0.11 g, 41%).

1H-NMR; delta (CD3OD), 8.06 (2H, m), 7.53 (3H, m), 5.21 (1H, s), 4.01 (1H, d, J=7.5 Hz), 2.99 (1H, m), 1.60 (1H, m), 1.50 (1H, m), 1.15 (1H, m), 1.10 (9H, s), 0.92 (3H, d, J=6.6 Hz) and 0.81 (3H, d, J=6.5 Hz).

13C-NMR; delta (CD3OD), 180.3, 176.7, 172.0, 169.7, 132.9, 130.5, 128.8, 128.4, 73.7, 57.1, 49.5, 39.5, 36.5, 27.3, 24.3 and 22.5.

LRMS; +ve ion 419 (M+H); -ve ion 417 (M+1).

Example 3

2R-[3-(4-Ethoxy-phenyl)-propyl]-N4,1S-[3-(5-thiophen-2-yl)-[1,2,4]oxadiazol-3-yl]-2,2-dimethyl-propyl]-5S,N4-di hydroy-succinamide
Example 3 was prepared as outlined in Scheme 3 using procedures described below.

Step A: 2R-allyl-3S-hydroxy-succinic acid disopropyl ester

[0176] To a cold (−78°C) solution of 25-Hydroxy-succinic acid disopropyl ester (19.70 mL, 95 mmol) in THF (35 mL) was added LiHMDS (200 mL, 0.2 mol, 2.1 eq.) dropwise. The reaction mixture was stirred at −78°C for two hours and then at −30°C for 30 min. The reaction mixture was then cooled to −78°C and allyl bromide (12.36 mL, 0.14 mol, 1.5 eq.) was added dropwise. The reaction mixture was allowed to warm to RT overnight. It was poured into a saturated solution of NHaCl/ice (200 mL). Extraction with AcOEt (3×200 mL) followed by a wash with water (50 mL) and with brine (50 mL) afforded a yellow oil after removal of the solvents under vacuum. Purification by flash chromatography gave 2R-allyl-3S-hydroxy-succinic acid disopropyl ester as a colourless oil (7.76 g, de−80%, 40% yield).

[0177] 1H-NMR; δ (CDCl3), 5.77-5.88 (1H, m), 4.98-5.21 (4H, m), 4.22 (1H, brs), 3.18 (1H, bs), 2.87-2.94 (1H, m), 2.56-2.65 (1H, m), 2.40-2.48 (1H, m), 1.29 (6H, d, J=6.3 Hz) and 1.22 (6H, d, J=6.3 Hz).

[0178] LRMS: +ve ion 281 (M+Na).

Step B:

2R-[3-(4-ethoxy-phenyl)-allyl]-3S-hydroxy-succinic acid disopropyl ester

[0179] To a solution of 2R-allyl-3S-hydroxy-succinic acid disopropyl ester (4.79 g, 18.5 mmol), 4-bromo phenetole (3.19 mL, 22.2 mmol, 1.2 eq.) and NEt3 (6.22 mL, 44.6 mmol, 2.4 eq.) in CH3CN (40 mL), was added a sonicated (for 2 min) suspension of P(O-Tol)3 (0.57 g, 2.22 mmol, 0.1 eq.) and Pd(OAc)2 (209 mg, 5%) in CH3CN (5 mL). The reaction mixture was heated to reflux for 2 hrs. CH3CN was removed under vacuum. The crude was extracted with AcOEt (3×200 mL), washed with water (50 mL) and with brine (50 mL). A purification by flash chromatography afforded the desired 2R-[3-(4-ethoxy-phenyl)-allyl]-3S-hydroxy-succinic acid disopropyl ester (5.92 g, 84% yield).

[0180] 1H-NMR; δ (CDCl3), 7.28 (2H, d, J=8.8 Hz), 6.83 (2H, d, J=8.8 Hz), 6.46 (1H, d, J=15.7 Hz), 6.02-6.12 (1H, m), 4.98-5.13 (2H, m), 4.26 (1H, dd, J=7.1, 3.0 Hz), 4.02 (2H, q, J=7.0 Hz), 3.23 (1H, d, J=7.1 Hz), 2.92-2.97 (1H, m), 2.68-2.79 (1H, m), 2.49-2.62 (1H, m), 1.41 (3H, t, J=7.0 Hz) and 1.19-1.30 (12H, m).

[0181] LRMS: +ve ion 404 (M+Na).

Step C: 2R-[3-(4-ethoxy-phenyl)-propyl]-3S-hydroxy-succinic acid disopropyl ester

[0182] To a solution of 2R-[3-(4-ethoxy-phenyl)-allyl]-3S-hydroxy-succinic acid disopropyl ester (129 mg, 0.34 mmol) in MeOH (10 mL) under an inert atmosphere, was added 10% Pd/C (13 mg). H2 was bubbled through the resulting suspension for 30 min. The reaction mixture was then stirred under 1 atmosphere of H2 for 16 hrs. Pd/C was filtered off and the solvent removed under reduced pressure to give 2R-[3-(4-ethoxy-phenyl)-propyl]-3S-hydroxy-succinic acid disopropyl ester (115 mg, 88% yield).

[0183] 1H-NMR; δ (CDCl3), 7.08 (2H, d, J=8.6 Hz), 6.81 (2H, d, J=8.6 Hz), 4.97-5.14 (2H, m), 4.20 (1H, dd, J=7.3, 3.5 Hz), 4.01 (2H, q, J=7.0 Hz), 3.18 (1H, d, J=7.3 Hz),...
2.77-2.83 (1H, m), 2.55-2.62 (2H, m), 1.45-1.94 (4H, m), 1.40 (3H, t, J=7.0 Hz) and 1.12-1.30 (12H, m).

[0184] LRMS: +ve ion 402.0 (M+Na).

Step D: 2R-[3-(4-ethoxy-phenyl)-propyl]-3S-hydroxy-succinic acid.

[0185] To a solution of 2R-[3-(4-ethoxy-phenyl)-propyl]-3S-hydroxy-succinic acid diisopropyl ester (4.78 g, 12.6 mmol) in THF/water (3:1, 120 ml) was added NaOH (1.66 g, 41.5 mmol, 5.5 eq.). The reaction mixture was then stirred for 16 hrs at RT. The mixture was concentrated under reduced pressure and acidified to pH=3 by addition of HCI 1 N. The hydroxy diacid was extracted with AcOEt. The organic layer was dried over MgSO4 and the solvent removed under reduced pressure to give the desired 2R-[3-(4-ethoxy-phenyl)-propyl]-3S-hydroxy-succinic acid (3.66 g, 85% yield).

[0186] 1H-NMR: delta (CD3OD), 7.07 (2H, d, J=8.6 Hz), 6.79 (2H, d, J=8.6 Hz), 4.23 (1H, d, J=5.8 Hz), 3.98 (2H, q, J=7.0 Hz), 2.76-2.81 (1H, m), 2.52-2.59 (2H, m), 1.55-1.72 (4H, m), 1.35 (3H, t, J=7.0 Hz).

[0187] LRMS: +ve ion 319 (M+Na); –ve ion 295 (M–H).

Step E: 2R-(2,2-dimethyl-5-oxo-[1,3]dioxolane-4S-yl)-5-(4-ethoxy-phenyl)-pentanoic acid

[0188] To a solution of 2R-[3-(4-ethoxy-phenyl)-propyl]-3S-hydroxy-succinic acid (3.66 g, 12.3 mmol) in acetonitrile (50 ml) under an inert atmosphere were added dimethyl oxalate (2.58 ml, 21 mmol, 1.7 eq.) and copper chloride (165 mg, 1.2 mmol, 0.1 eq.). The reaction mixture was stirred at RT for 16 hrs. The solvent was then removed under vacuum to give 2R-(2,2-dimethyl-5-oxo-[1,3]dioxolane-4S-yl)-5-(4-ethoxy-phenyl)-pentanoic acid (4.03 g, 97% yield).

[0189] 1H-NMR: delta (CDCl3), 7.08 (2H, d, J=8.5 Hz), 6.82 (2H, d, J=8.5 Hz), 4.48 (1H, d, J=4.8 Hz), 4.01 (2H, q, J=7.0 Hz), 2.91-2.98 (1H, m), 2.54-2.64 (3H, m), 1.23-2.20 (4H, m), 1.58 (3H, s), 1.53 (3H, s) and 1.40 (3H, t, J=7.0 Hz).

[0190] LRMS: +ve ion 359 (M+Na); –ve ion 335 (M–H).

Step F: 2R-(2,2-dimethyl-5-oxo-[1,3]dioxolane-4S-yl)-5-(4-ethoxy-phenyl)-pentanoic acid pentafluorophenyl ester

[0190] To a cold (0°C) solution of 2R-(2,2-dimethyl-5-oxo-[1,3]dioxolane-4S-yl)-5-(4-ethoxy-phenyl)-pentanoic acid (4.05 g, 12 mmol) and pentafluorophenol (2.43 g, 13.2 mmol, 1.1 eq.) in CH2Cl2 (50 ml) was added WSC (2.54 g, 13.2 mmol, 1.1 eq.). The reaction mixture was allowed to warm to RT overnight. CH2Cl2 was removed under vacuum and the resulting crude reaction mixture was dissolved in AcOEt (200 ml). The organic layer was washed with water (50 ml), NaHCO3 sat (20 ml) and finally with brine (20 ml). Solvent was removed under reduced pressure to give an oil which was purified by flash chromatography to furnish the 2R-(2,2-dimethyl-5-oxo-[1,3]dioxolane-4S-yl)-5-(4-ethoxy-phenyl)-pentanoic acid pentafluorophenyl ester (3.94 g, 65% yield).

[0191] 1H-NMR: delta (CDCl3), 7.09 (2H, d, J=8.4 Hz), 6.83 (2H, d, J=8.4 Hz), 4.56 (1H, d, J=6.0 Hz), 4.01 (2H, q, J=7.0 Hz), 3.20-3.28 (1H, m), 2.64 (2H, t, J=7.6 Hz), 1.98-2.08 (2H, m), 1.70-1.86 (2H, m), 1.62 (3H, s), 1.57 (3H, s) and 1.40 (3H, t, J=7.0 Hz).

Step G: 2R-[3-(4-Ethoxy-phenyl)-propyl]-N1-[1S-(5-thiophen-2-yl)-1,2,4-oxadiazol-3-yl]-2,2-dimethyl-propyl]-[1,3]dioxolane-4S-one

[0192] To a solution of 2R-(2,2-dimethyl-5-oxo-[1,3]dioxolane-4S-yl)-5-(4-ethoxy-phenyl)-pentanoic acid pentafluorophenyl ester (150 mg, 0.53 mmol) in CH2Cl2 (10 ml) was added 2.2-dimethyl-1S-(5-thiophen-2-yl)-1,2,4-oxadiazol-3-yl-propylamine (100 mg, 0.42 mmol, 1.4 eq.). The reaction mixture was stirred for 16 hrs and the solvent was removed under vacuum. The crude was taken-up in AcOEt (70 ml) and washed with water (10 ml), then with Na2CO3 (10 ml) and finally with brine (10 ml). The solvent was dried over MgSO4 and removed under reduced pressure to give the desired 2R-[3-(4-Ethoxy-phenyl)-propyl]-N1-[1S-(5-thiophen-2-yl)-1,2,4-oxadiazol-3-yl]-2,2-dimethyl-propyl]-[1,3]dioxolane-4S-one (82 mg, 33% crude).

[0193] 1H-NMR: delta (CDCl3), 7.88 (1H, m), 7.62 (1H, m), 7.20 (1H, m), 6.95 (2H, d, J=8.4 Hz), 6.71 (2H, d, J=8.4 Hz), 6.55 (1H, d, J=9.7 Hz), 5.19 (1H, d, J=9.7 Hz), 4.56 (1H, d, J=6.4 Hz), 3.95 (2H, q, J=7.0 Hz), 2.64 (3H, bm), 1.84 (2H, m), 1.70 (2H, m), 1.62 (3H, s), 1.54 (3H, s), 1.38 (3H, t, J=6.9 Hz) and 1.02 (9H, s).

[0194] LRMS: +ve ion 556.0 (M+H).

Step H: 2R-[3-(4-Ethoxy-phenyl)-propyl]-N1-[1S-(5-thiophen-2-yl)-1,2,4-oxadiazol-3-yl]-2,2-dimethyl-propyl]-[3S,Nα]-di-hydroxy-succinamide

[0195] To a solution of 2R-[3-(4-Ethoxy-phenyl)-propyl]-N1-[1S-(5-thiophen-2-yl)-1,2,4-oxadiazol-3-yl]-2,2-dimethyl-propyl]-[1,3]dioxolane-4S-one (82 mg, 0.15 mmol) in iPrOH (5 ml), was added an aqueous solution of hydroxyamine (50%, 48 µl, 0.7 mmol, 5 eq.). The reaction mixture was allowed to stir at RT for 16 hrs. The solvent was removed under reduced pressure to yield an oil which was purified by preparative reverse phase chromatography to give the required product (25.5 mg, 32%).

[0196] 1H-NMR: delta (CH3OD), 1H-NMR: delta (CD3OD), 7.86 (2H, m), 7.25 (1H, d, J=3.81 Hz), 6.83 (2H, d, J=8.6 Hz), 6.54 (2H, d, J=8.6 Hz), 5.14 (1H, s), 4.03 (1H, d, J=7.6 Hz), 3.87 (2H, q, J=6.96), 2.85 (1H, m), 2.45 (2H, bm), 1.53 (4H, bm), 1.33 (3H, t, J=7.0 Hz) and 1.06 (9H, s).

[0197] LRMS: +ve ion 553.2 (M+Na); –ve ion 529.2 (M–H).

[0198] The compounds of Examples 4-17 were prepared by the method of Example 1 by parallel synthesis, using the appropriate acid chloride in Step D. The products were purified by preparative HPLC:

Example 4

2S-Hydroxy-3R-[1S-(5-isopropyl-[1,2,4]oxadiazol-3-yl]-2,2-dimethyl-propyl]carbonyl]-5-methyl hexahydroxyacid

[0199]
Example 5
2S-Hydroxy-3R-[1S-(5-furan-2-yl)-1,2,4]oxadiazol-3-yl]-2,2-dimethyl-propylcarbamoyl]-5-methyl hexahydroxamic acid

LRMS; +ve ion 431 (M+Na), –ve ion 407 (M–H).

Example 6
2S-Hydroxy-3R-[1S-(5-cyclopentylmethylene-1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propylcarbamoyl]-5-methyl hexahydroxamic acid

LRMS; +ve ion 425 (M+H), –ve ion 423 (M–H).

Example 7
2S-Hydroxy-3R-[1S-(5-thiopen-2-ylmethylene-1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propylcarbamoyl]-5-methyl hexahydroxamic acid

LRMS; +ve ion 461 (M+Na), –ve ion 437 (M–H).

Example 8
2S-Hydroxy-3R-[1S-(5-ethyl-1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propylcarbamoyl]-5-methyl hexahydroxamic acid

LRMS; +ve ion 393 (M+Na), –ve ion 369 (M–H).

Example 9
2S-Hydroxy-3R-[1S-(5-cyclopentyl-1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propylcarbamoyl]-5-methyl hexahydroxamic acid

LRMS; +ve ion 411 (M+H), –ve ion 409 (M–H).

Example 10
2S-Hydroxy-3R-[1S-(5-benzyl-1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propylcarbamoyl]-5-methyl hexahydroxamic acid

LRMS; +ve ion 433 (M+H), –ve ion 431 (M–H).
Example 11
2S-Hydroxy-3R-[1S-(5-isobutyl-[1,2,4]oxadiazol-3-yl]-2,2-dimethyl-propylcarbamoyl]-5-methyl hexanoxydramic acid

Example 14
2S-Hydroxy-3R-[1S-(5-thiophen-2-yl-[1,2,4]oxadiazol-3-yl]-2,2-dimethyl-propylcarbamoyl]-5-methyl hexanoxydramic acid

Example 15
2S-Hydroxy-3R-[1S-(5-p-tolyl-[1,2,4]oxadiazol-3-yl]-2,2-dimethyl-propylcarbamoyl]-5-methyl hexanoxydramic acid
Example 16
2S-Hydroxy-3R-[1S-(5-cyclopropyl[1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propylcarbamoyl]-5-methyl hexa-nohydroxamic acid

Example 18
2S-Hydroxy-3R-[1S-(3-isopropyl-[1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propylcarbamoyl]-5-methyl hexa-nohydroxamic acid

Example 17
2S-Hydroxy-3R-[1S-(5-methyl-[1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propylcarbamoyl]-5-methyl hexa-nohydroxamic acid

Example 19
2S,N2-Dihydroxy-3R-isobutyl-N2-methyl-1S-(3-phenyl[1,2,4]oxadiazol-5-yl)-propyl]-succinamide

[0225] LRMS; +ve ion 405 (M+Na), –ve ion 381 (M–H).

[0226] 1H-NMR; delta(CH3OD), 8.26 (1H, d, J=9.4 Hz), 5.02 (1H, d, J=9.5 Hz), 4.02 (1H, d, J=6.4 Hz), 2.89 (1H, m), 2.57 (3H, s), 1.61 (1H, m), 1.44 (1H, m), 1.22 (1H, m), 1.00 (9H, s)

[0227] 13C-NMR; delta (CH3OD), 178.6, 176.1, 171.9, 170.7, 73.5, 55.6, 49.5, 39.9, 36.2, 27.6, 26.6, 24.2, 22.7 and 12.4.

[0228] LRMS; +ve ion 379 (M+Na), –ve ion 355 (M–H).

[0229] The compounds of Examples 18-19 were prepared by the method of Example 2, by using the appropriate nitrile in Step C and/or the appropriate amino acid residue in Step A:

[0230] 1H-NMR; delta(CH3OD), 8.05 (2H, m), 7.52 (3H, m), 5.14 (1H, d, J=7.2 Hz), 4.00 (1H, d, J=7.7 Hz), 2.91 (1H, m), 2.36 (1H, m), 1.63 (1H, m), 1.54 (1H, m), 1.16 (1H, m), 1.00 (3H, d, J=6.8 Hz), 0.95 (3H, d, J=6.3 Hz), 0.84 (3H, d, J=6.3 Hz).

[0231] LRMS; +ve ion 427 (M+Na), –ve ion 403 (M–H).

[0232] The compounds of Examples 20-23 were prepared by the method of Example 2, by using the appropriate nitrile in Step C and/or the appropriate amino acid residue in Step A. The synthesis to the appropriate chiral succinate in Step E is detailed within WO 94/21625.
Example 20

2S-Alllyl-5-methyl-3R-[2-phenyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-ethylcarbamoyl]-hexanohydroxamic acid

Example 22

2S-Alllyl-5-methyl-3R-[2-phenyl-1S-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylcarbamoyl]-hexanohydroxamic acid

[0241]

[0246]

[0242] 1H-NMR; delta (CD3OD), 9.13 (1H, d, J=8.26 Hz), 8.05 (2H, m), 7.55 (3H, m), 7.25 (5H, m), 5.66 (1H, m), 5.45 (1H, m), 4,90 (2H, m), 4.50 (1H, s), 3.51 (1H, dd, J=13.92, 4.84 Hz), 3.17 (1H, dd, J=13.92, 10.90 Hz), 2.50 (1H, m), 2.0 (2H, m), 1.50 (3H, m), 1.0 (3H, d, J=6.5 Hz), 0.96 (3H, d, J=6.6 Hz).

[0243] 13C-NMR; delta (CD3OD), 181.0, 177.0, 172.7, 138.0, 136.5, 133.0, 130.8, 130.6, 130.5, 130.1, 128.7, 128.7, 117.7, 48.4, 48.3, 42.1, 39.5, 36.2, 27.1, 24.9 and 22.0.

Example 21

2S-Alllyl-5-methyl-3R-[2-phenyl-1S-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-ethylcarbamoyl]-hexanohydroxamic acid

[0244]

[0245] 1H-NMR; delta (DMSO), 10.28 (1H, s), 8.64 (1H, d, J=6.2 Hz), 8.64 (1H, br s), 7.25 (5H, m), 5.45 (2H, m), 4.51 (1H, m), 4.30 (2H, m), 3.15 (1H, m), 2.85 (2H, m), 2.20 (1H, dt, J=10.6, 3.12 Hz), 1.70 (2H, m), 1.25 (6H, d, J=6.91 Hz), 0.70 (1H, m), 0.52 (3H, d, J=6.4 Hz), 0.48 (3H, d, J=6.4 Hz).

13C-NMR; delta (MeOD), 179.0, 175.6, 175.5, 171.3, 136.6, 135.0, 129.2, 128.6, 127.3, 116.4, 48.7, 46.9, 40.6, 38.1, 34.8, 26.9, 25.6, 23.5, 20.7 and 19.9.

Example 23

2S-Alllyl-3R-[2,2-dimethyl-1S-(3-methyl-[1,2,4]oxadiazol-5-yl)-propylcarbamoyl]-5-methyl-hexanohydroxamic acid

[0249]

[0250] 1H-NMR; delta (CD3OD), 8.81 (1H, d, J=8.59 Hz), 7.65 (1H, m), 5.70 (1H, m), 5.15 (1H, d, J=8.62 Hz), 4.95 (2H, m), 2.60 (1H, dt, J=11.10, 3.16 Hz), 2.39 (3H, s), 1.38 (1H, dt, J=13.10, 3.33 Hz), 1.31 (1H, m), 0.98 (1H, m), 0.98 (9H, s), 0.86 (3H, d, J=6.6 Hz), 0.84 (3H, d, J=6.6 Hz).
The compound of Example 24 was prepared by the method of Example 2. The synthesis to the appropriate chiral succinate in Step E is detailed within WO 95/19956.

Example 24
3R-[2,2-Dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propylcarbamoyl]-5-methyl-hexanohydroxamic acid

LRMS: +ve ion 403.5 (M+H), -ve ion 401.3 (M-H).

The compound of Example 25 was prepared by the method of Example 2, by using the appropriate nitrile in Step C and/or the appropriate amino acid residue in Step A. The synthesis to the appropriate chiral succinate in Step E is detailed within WO 97/02239.

Example 25
2S-Methoxy-5-methyl-3R-1S-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-phenyl-ethylcarbamoyl]-hexanohydroxamic acid

1H-NMR; delta (CD3OD), 7.14 (5H, m), 5.34 (1H, m), 3.38 (1H, d, J=9.68 Hz), 3.20 (2H, m), 3.02 (3H, s), 2.65 (1H, m), 2.22 (3H, s), 1.35 (2H, m), 0.90 (1H, m), 0.75 (3H, d, J=6.55 Hz) and 0.70 (3H, d, J=6.57 Hz).

The compounds of Example 26 and 27 were prepared by the method of Example 2. The synthesis to the appropriate chiral succinate in Step E is detailed within WO 92/13831 using methods analogous to those described in WO 95/32944.

Example 26
3R-[2,2-Dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propylcarbamoyl]-heptadecanoic acid

1H-NMR; delta (CD3OD), 8.05 (2H, m), 7.49 (3H, m), 5.22 (1H, s), 2.93 (1H, m), 2.65 (1H, dd, J=9.8, 16.7 Hz), 2.38 (1H, dd, J=4.6, 16.6 Hz), 1.52 (1H, m), 1.43 (1H, m), 1.26 (24H, m), 1.10 (9H, s) and 0.89 (3H, m).

LRMS; +ve ion 524.4 (M+H).
Example 27
3R-[2,2-Dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propylcarbamoyl]-nonadecanoic acid

[0261]

LRMS; +ve ion 556.2 (M+H).

[0262] The compound of Example 28 was prepared by the method of Example 1. The synthesis to the appropriate chiral succinate in Step H is detailed within WO 92/13831 using methods analogous to those described in WO 95/32944.

Example 28
6-(4-Chloro-phenyl)-3R-[2,2-dimethyl-1S-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propylcarbamoyl]-hexanoic acid

[0263]

LRMS; +ve ion 506.2 (M+Na), -ve ion 482.4 (M–H).

[0264] 1H-NMR; delta(CH3OD), 8.07 (2H, m), 7.61 (3H, m), 6.93 (4H, m), 5.15 (1H, s), 2.94 (1H, m), 2.5 (4H, m), 1.5 (4H, m) and 1.07 (9H, s).

[0265] 13C-NMR; delta (CH3OD), 178.0, 177.1, 142.6, 134.6, 132.7, 131.0, 130.8, 129.5, 129.4, 125.7, 55.7, 43.8, 39.0, 36.3, 36.1, 34.1, 30.3 and 27.4.

[0266] LRMS; +ve ion 506.2 (M+Na), -ve ion 482.4 (M–H).

[0267] Also prepared, the diastereomer 6-(4-Chloro-phenyl)-3R-[2,2-dimethyl-1R-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propylcarbamoyl]-hexanoic acid

[0268] 1H-NMR; delta (CH3OD), 7.95 (1H, m), 7.87 (1H, d, J=5.0 Hz), 7.28 (1H, m), 5.15 (1H, s), 4.18 (2H, d, J=6.4 Hz), 2.94 (1H, m), 1.68 (1H, m), 1.48 (1H, m), 1.31 (1H, m), 1.06 (9H, s), 0.88 (3H, d, J=6.4 Hz) and 0.82 (3H, d, J=6.5 Hz).


[0270] The compounds of Examples 29 and 30 were prepared by the method of Example 1.

Example 29
3R-[2,2-Dimethyl-1S-(5-thiophen-2-yl-[1,2,4]oxadiazol-3-yl)-propylcarbamoyl]-2S-hydroxy-5-methyl-hexanoic acid

[0271]

LRMS; -ve ion 408.2 (M–H).
Example 30

3R-[1S-(5-Furan-2-yl][1,2,4]oxadiazol-3-yl]-2,2-dimethyl-propyl-carbamoyl]-2S-hydroxy-5-methyl-hexanoicacid

[0275] 1H-NMR; delta(CH3OD), 7.88 (1H, s), 7.45 (1H, d, J=3.6 Hz), 6.74 (1H, m), 5.15 (1H, s), 4.18 (2H, d, J=6.4 Hz), 2.91 (1H, m), 1.65 (1H, m), 1.50 (1H, m), 1.31 (1H, m), 1.06 (9H, s), 0.88 (3H, d, J=6.4 Hz) and 0.82 (3H, d, J=6.5 Hz).

[0276] LRMS: +ve ion 392.2 (M-H).

[0277] The compounds of Example 31 and 32 were prepared by the method of Example 2. The synthesis to the appropriate chiral succinate in Step E is detailed within WO 94/02446 using the appropriate cinnanyl bromide or cyclopentylmethyl iodide instead of the methallyl iodide as detailed in the aforementioned patent.

Example 31

N,N-[2,2-Dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propyl]-2S,N,N-dihydroxy-3R-(3-phenyl-allyl)-succinamide

[0278] 1H-NMR; delta(CH3OD), 7.95 (2H, d, J=7.2 Hz), 7.53 (1H, m), 7.48 (2H, m), 7.09 (2H, d, J=6.4 Hz), 6.91 (3H, m), 6.31 (1H, d, J=15.8 Hz), 6.04 (1H, m), 5.26 (1H, s), 4.14 (1H, d, J=7.6 Hz), 3.02 (1H, m), 2.46 (1H, m), 2.37 (1H, m) and 1.07 (9H, s).

[0280] 13C-NMR; delta(CH3OD), 179.8, 175.9, 172.0, 169.6, 138.8, 134.0, 132.8, 130.4, 129.7, 128.9, 128.4, 128.4, 127.3, 73.2, 56.5, 51.3, 36.8 and 34.0.

[0281] LRMS; +ve ion 501.2 (M+Na), -ve ion 477.4 (M-H).

Example 32

2R-Cyclopentylmethyl-3S,N,N-dihydroxy-N1S-[3-isopropyl-[1,2,4]oxadiazol-5-yl]-2,2-dimethyl-propyl]-succinamide

[0282] 1H-NMR; delta(CH3OD), 5.13 (1H, s), 3.99 (1H, d, J=7.7 Hz), 3.06 (1H, m), 2.87 (1H, m), 1.83 (1H, m), 1.72 (1H, m), 1.63-1.39 (6H, bm), 1.31 (6H, d, J=6.9 Hz), 1.27 (1H, m), 1.03 (9H, s) and 1.02 (2H, m).

[0284] 13C-NMR; delta(CH3OD), 179.6, 176.6, 176.5, 172.0, 73.6, 56.8, 50.8, 39.6, 36.7, 36.5, 34.7, 33.6, 28.3, 27.2, 26.5 and 21.2.

[0285] LRMS; +ve ion 411.2 (M+H), -ve ion 409.6 (M-H).

[0286] The compounds of Examples 33-35 were prepared by the method of Example 3 using the appropriate aryl bromide in Step B.

Example 33

2R-[3-(3,5-Bis-trifluoromethyl-phenyl)-propyl]-N,N-[2,2-dimethyl-1S-(5-thiophen-2-yl][1,2,4]oxadiazol-3-yl]-propyl]-3S,N,N-dihydroxy-succinamide

[0287] 1H-NMR; delta(CH3OD), 8.38 (1H, d, J=9.4 Hz), 7.86 (1H, s), 7.75 (3H, bs), 7.4 (1H, d, J=3.5 Hz), 6.7 (1H, m), 5.12 (1H, d, J=9.4 Hz), 4.26 (1H, d, J=4.0 Hz), 2.83 (3H, bm), 1.8 (4H, bm) and 1.0 (9H, s).

[0289] LRMS; +ve ion 623.2 (M+H), -ve ion 621.0 (M-H).
Example 34

2R-[3-(3,5-Bis-trifluoromethyl-phenyl)-propyl]-N₁-[1S-(5-furan-2-yl-[1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propyl]-3S,N₄-dihydroxy-succinamide

Example 35

2R-[3-(4-Ethoxy-phenyl)-propyl]-N₁-[1S-(5-furan-2-yl-[1,2,4]oxadiazol-3-yl)-2,2-dimethyl-propyl]-3S,N₄-dihydroxy-succinamide

Example 36

3-Cyclopentyl-N-[2,2-dimethyl-1S-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propyl]-2R-[(formyl-hydroxy-amino)methyl]-propionamide

1H-NMR; delta(CH3OD), 8.26 (0.3H, s), 8.05 (2H, d, J=6.9 Hz), 7.84 (0.7H, s), 7.52 (3H, m), 5.20 (1H, m), 3.75 (1H, m), 3.63 (0.3H, dd, J=13.9, 5.5 Hz), 3.43 (0.7H, dd, J=14.2, 4.6 Hz), 3.18 (0.7H, m), 3.00 (0.3H, m), 1.92 (1H, m), 1.47 (8H, m), 1.10 (3H, s), 1.08 (6H, s) and 0.98 (2H, m).

13C-NMR; delta (CH3OD), 179.9, 176.9, 176.6, 169.3, 163.8, 159.2, 132.5, 130.0, 129.6, 128.9, 128.3, 127.9, 56.8, 56.7, 53.9, 50.3, 44.8, 44.6, 39.1, 38.9, 37.9, 37.7, 35.9, 35.8, 34.1, 33.4, 33.3, 26.9, 26.1 and 25.9.

LRMS; +ve ion 451 (M+Na), –ve ion 427 (M–H).

The compound of Example 37 was prepared by the method of Example 1. The synthesis to the appropriate chiral succinate in Step E is detailed within WO 01/10834.

Example 37

3-Cyclopentyl-N-[2,2-dimethyl-1S-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propyl]-2R-[(formyl-hydroxy-amino-methyl]-propionamide

1H-NMR; delta(CH3OD), 8.49 (0.6H, d, J=8.7 Hz), 8.37 (0.4H, d, J=8.1 Hz), 8.28 (0.4H, s), 8.14 (2H, m), 7.85 (0.6H, s), 7.65 (1H, m), 7.59 (2H, m), 4.31 (1H, s), 3.79 (1H, m), 3.63 (0.4H, m), 3.43 (0.6H, m), 3.13 (0.6H, m), 2.97 (0.4H, m), 1.55 (9H, m), 1.08 (3H, s), 1.07 (6H, s) and 1.04 (2H, m).

13C-NMR; delta (CH3OD), 176.6, 171.6, 164.2, 159.7, 134.8, 132.8, 130.8, 130.3, 129.4, 125.7, 69.5, 56.0, 54.3, 50.8, 45.4, 45.3, 40.6, 39.5, 38.3, 38.2, 35.9, 34.5, 33.8, 33.7, 32.0, 27.5, 26.4 and 26.3.

LRMS; +ve ion 429 (M+H).
Biological Results

A. Enzyme Inhibition Assays

Compounds of the invention were tested to assess their activities as inhibitors of MMP9 and MMP12.

MMP9 Assay Protocol

Compounds were tested for inhibitory activity against 92 kDa gelatinase (MMP9) in an assay using a coumarin-labelled peptide substrate, (7-methoxycoumarin-4-yl)acetyl-Pro-Leu-Gly-Leu-(3-[2,4-dinitrophenyl]-L-2,3-diaminopropionyl)-Ala-Arg-NH2 (McP-GLD.PapAR) (Knight et al, FEBS Lett. 1992: 263-266). The protocol for this assay was as described for the MMP9 assay above.

Results:

Key to Biological Data

<table>
<thead>
<tr>
<th>Example</th>
<th>MMP9 IC50(nM)</th>
<th>MMP12 IC50 (nM)</th>
<th>MMP1 IC50(nM)</th>
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<tr>
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<tr>
<td>35</td>
<td>A</td>
<td>A</td>
<td>D</td>
</tr>
</tbody>
</table>

These results show that in general, the compounds tested were active as inhibitors of MMP12, with certain examples showing selective inhibition of both MMP9 and 12 relative to MMP-1.

B. CCL4-induced Liver Fibrosis Model

Carbon tetrachloride (CCL4) induces liver fibrosis when administered intraperitoneal (Bulpina O, Cutal J, Bravo M L., Inflammation 1997 Oct.; 21(5):475-88). Compounds of the invention can be evaluated for their ability to prevent the CCL4-induced formation of fibrotic tissue.

Animals

Male Sprague-Dawley rats, 7 weeks old, weight approx. 300 g from Charles River/Ha-Credo, St-Germain/ l’Arbresle, France.
Rats were acclimatised for 5 days before commencing experiments, in air-conditioned rooms, 2 animals per cage. Temperature: 22° C ± 2, Relative humidity: 55% ± 10. Light: 12 hour cycle (7 a.m.-7 p.m.), Cage: Makrolon® cage 42.5x26.6x15 on each fitted with a stainless steel cover-feed rack.

The study involved the following groups of 8 animals each, as indicated below.

- **Group 1**: “Sham” animals received CCl₄ vehicle (i.p.) and once daily, the vehicle of test substance (s.c.)
- **Group 2**: Positive control group received CCl₄ (i.p.), and once daily, the vehicle of the test substance (s.c.)
- **Group 3**: Experimental group received CCl₄ (i.p.), and once daily, 2 mg/kg s.c. of the compound of Example 13.
- **Group 4**: Experimental group received CCl₄ (i.p.), and once daily, 10 mg/kg s.c. of the compound of Example 13.
- **Group 5**: Experimental group received CCl₄ (i.p.) and once daily, 20 mg/kg s.c. of the compound of Example 13.
- **Rats**: Rats were labelled on their tails. The labels were checked and renewed, if necessary, after every CCl₄ injection.

Procedure

- **CCl₄ (Prolabo)** in olive oil was administered every 3 days for three weeks by intraperitoneal injection (0.25 ml CCl₄/kg body weight, diluted in oil 1:1 vol/vol for a total volume of 0.5 ml/kg). Animals were weighed daily. If body weight decreased by more than 10% of the initial weight, the animal was excluded from the study.

Vehicles and compound were used as follows:

- **Group 3**: CCl₄ was administered in olive oil (prolabo) at a 1:1 dilution;
- **Group 3**: The compound of Example 13 was suspended in 0.25% Tween-80 and 0.25% carboxymethylcellulose in sterile 0.9% NaCl. The solution was kept at 4°C throughout the experiment and used each day to prepare the suspensions.
- **Group 3**: The compound of Example 13 was administered daily by subcutaneous (s.c.) injection at a volume of administration of 5 ml/kg. Groups 1 and 2 were dosed s.c. with 5 ml/kg of vehicle. Freshly prepared solutions were used on each day of the experiment. Administrations were carried out each day at the same time.
- **Group 3**: The treatment of groups of this study was started for each animal at the time of the first CCl₄ administration and was continued for 21 consecutive days. The last administration of test substances or vehicle was done 1 day before the sacrifice of the animals.

**Results**

- **Group 3**: Death was reported for 16 animals. Date and supposed cause are reported in Table 1.

**Serum Enzyme Levels**

- **Group 3**: Animals were killed 21 days following the first CCl₄ administration by isoflurane inhalation. Blood was withdrawn individually at the time of sacrifice, i.e. one day after the last administration of test substance or vehicle. Blood was centrifuged at 4°C. Plasma was carefully collected and aliquoted in 3 fractions. Plasma aspartate amino transferase (ASAT) and alanine amino transferase (ALAT) levels were measured in order to assess liver necrosis. Increased ASAT and ALAT levels in serum are associated with liver impairment. Average ASAT and ALAT levels for control animals and those treated with the compound of Example 13 at three different dosages are shown in FIG. 1 (Y-axis is units of enzyme activity per litre, IU/L). Subcutaneous treatment with the compound of Example 13 clearly decreases ASAT and ALAT levels compared to animals treated with vehicle. This demonstrates that the compound of Example 13 has a protective effect on the liver.

**Histological Evaluation of Liver Fibrosis**

- **Group 3**: Liver fibrosis was evaluated by measuring the area of fibrosis in the liver using microtomy. Results are reported as percentage area that was fibrotic.
- **Group 3**: The liver was removed, the three lobes were dissected and samples were removed and either fixed in 10% formaldehyde or frozen at -80°C.
- **Group 3**: Liver sections were embedded in paraffin blocks. Sectioning and staining with Sirius red was performed. Quantification of the fibrosis in liver was carried out on a minimum of 3 sections taken from different locations in the liver. The quantitative analysis was performed using an image analyser (Imstra) and software Morpho12.
- **Group 3**: Average area percentages of fibrosis in the livers of animals in the different groups were calculated, and the results are shown in FIG. 2.
- **Group 3**: B. IL2-induced Peritoneal Recruitment of Lymphocytes
- **Group 3**: Administration of IL2 intraperitoneally causes migration of lymphocytes into the intraperitoneal cavity. This is a model for the cellular migration that occurs during inflammation.
- **Group 3**: Compounds of the invention inhibit IL2-induced lymphocyte recruitment. Protocol
- **Group 3**: CSH/HEK mice (Elevage Janvier, France) were intraperitoneally injected with IL2 (Serono Pharmaceutical Research Institute, 20 μg/kg, in saline).
- **Group 3**: Compounds of the invention were suspended in 0.5% carboxymethylcellulose (CMC)/0.25% tween-20 and were administered by sc or po route (10 ml/kg) 15 min prior to administration of IL2.
- **Group 3**: Twenty-four hours after administration of IL2, peritoneal white blood cells were collected by 3 successive lavages of the peritoneal cavity with 5 ml phosphate buffered saline (PBS)-1 mM EDTA (4°C). The suspension was centrifuged (1700 g×10 min at 4°C). The resulting pellet was suspended in 1 ml PBS-1 mM EDTA.
- **Group 3**: Lymphocytes were identified and counted using a Beckman/Coulter counter.

**Experimental Design**

- **Group 3**: The animals were divided into 5 groups (6 mice each group):
- **Group 3**: Group 1: (baseline) received 0.5% CMC/0.25% tween-20 (vehicle of compound of the invention) and saline (vehicle of IL2);
- **Group 3**: Group 2: (control IL2) received 0.5% CMC/0.25% tween-20 and injection of IL2;
- **Group 3**: Group 3: Experimental group (Compound of the invention Dose 1) received a compound of the invention and injection of IL2;
- **Group 3**: Group 4: Experimental group (Compound of the invention Dose 2) received a compound of the invention and injection of IL2;
Group 5: Experimental group (Compound of the invention Dose 3) received a compound of the invention and injection of IL-2;

Group 6: Reference group received reference compound dexamethasone and injection of IL-2.

Calculation

Inhibition of lymphocyte recruitment was calculated as follows:

\[
\% \text{ inhibition} = \frac{1 - (L_2 - L_1)}{(L_2 - L_1)} \times 100\%
\]

Where \( L_1 \) = Number of lymphocytes in group 1 (E3/µl), \( L_2 \) = Number of lymphocytes in group 2 (E3/µl), \( L_X \) = Number of lymphocytes in group X (3-5) (E3/µl)

The dose of compound of the invention required to inhibit lymphocyte recruitment by 50% (ID50) was calculated using a curve-fitting routine. Results are listed in Table 1.

### TABLE 1

<table>
<thead>
<tr>
<th>Example</th>
<th>Dose range or routes (mg/kg)</th>
<th>Route</th>
<th>ID50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 13</td>
<td>0.03, 0.3, 3, 30</td>
<td>Subcutaneous</td>
<td>0.05</td>
</tr>
<tr>
<td>Example 13</td>
<td>0.3, 3, 30</td>
<td>Oral</td>
<td>0.1</td>
</tr>
<tr>
<td>Example 5</td>
<td>0.3, 1, 3, 10, 30</td>
<td>Subcutaneous</td>
<td>1</td>
</tr>
</tbody>
</table>

1. A method of treatment or prophylaxis of diseases mediated by MMPs in mammals comprising administering to the mammal an effective amount of a compound having formula (IA) or (IB)

\[
\begin{align*}
\text{(C}_1\text{-C}_6\text{)alkoxy;} \\
\text{(C}_1\text{-C}_6\text{)alkenyl; phenyl or substituted phenyl;} \\
\text{phenyl(C}_1\text{-C}_6\text{)alkyl or substituted phenyl(C}_1\text{-C}_6\text{)alkyl;} \\
\text{phenyl(C}_2\text{-C}_6\text{)alkenyl or substituted phenyl(C}_2\text{-C}_6\text{)alkenyl heterocyclic or substituted heterocyclic;} \\
\text{heterocyclic(C}_2\text{-C}_6\text{)alkyl or substituted heterocyclic(C}_1\text{-C}_6\text{)alkyl;} \\
\text{a group BSO}_{2n}\text{A} - \text{wherein n is 0, 1 or 2 and B is hydrogen or} \\
\text{a(C}_1\text{-C}_6\text{)alkyl, phenyl, substituted phenyl, heterocyclic, substituted heterocyclic, (C}_1\text{-C}_6\text{)acyl, phe} \\
\text{necyl or substituted phenacyl group, and A represents (C}_1\text{-C}_6\text{)alkyl-} \\
\text{lene; } \\
\text{—NH}_2\text{, (C}_1\text{-C}_6\text{)alkylamino or di(C}_1\text{-C}_6\text{)alkylamino;} \\
\text{amino(C}_1\text{-C}_6\text{)alkyl, (C}_1\text{-C}_6\text{)alkyl amino(C}_1\text{-C}_6\text{)alkyl;} } \\
\text{di(C}_1\text{-C}_6\text{)alkylamino(C}_1\text{-C}_6\text{)alkyl, hydroxy(C}_1\text{-C}_6\text{)alkyl;} } \\
\text{mercapto(C}_1\text{-C}_6\text{)alkyl or carboxy(C}_1\text{-C}_6\text{)alkyl} \\
\text{wherein the amino-, hydroxy-, mercapto- or carboxyl-} \\
\text{group are optionally protected or the carboxyl-} \\
\text{group amidated; or} \\
\text{a cyclooalkyl, cycloalkenyl or non-aromatic heterocyclic ring containing up to 3 heteroatoms, any of which may be} \\
\text{(i) substituted by one or more substituents selected from} \\
\text{C}_1\text{-C}_6\text{alkyl, C}_2\text{-C}_6\text{alkenyl, halo, cyano (—CN), —CO}_2\text{H, —CO}_2\text{R, —CONH}_2\text{, —CONHR, —CON(R)} \\
\text{2, —OH, —OR, oxo, —SH, SR, NHCOR, and} \\
\text{NICOOR wherein R is C}_1\text{-C}_6\text{alkyl or benzy} \\
\text{and/or} \\
\text{(ii) fused to a cyclooalkyl or heterocyclic ring;} \\
\text{R}_2 \text{represents a group R}_1\text{—(X)}_1\text{—(ALK)}_2, \text{wherein} \\
\text{R}_1 \text{represents hydrogen, or a C}_1\text{-C}_6\text{alkyl, C}_2\text{-C}_6\text{alkenyl,} \\
\text{C}_2\text{-C}_6\text{alkynyl, cycloalkyl, aryl, or heterocyclic group, any of which may be} \\
\text{unsubstituted or substituted by} \\
\text{(C}_1\text{-C}_6\text{)alkyl, (C}_1\text{-C}_6\text{)alkoxy, hydroxy, mercapto, (C}_1\text{-C}_6\text{)alkylthio, amino, halo (including} \\
\text{fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, oxo,} \\
\text{—COON, —CONH}_2\text{, —COOR, —NHCOR, —CONHR, —CON(R)} \\
\text{2, —NR}_2\text{, or —CONR}_2\text{ wherein R}^4 \text{and} \\
\text{R}^5 \text{are independently a C}_1\text{-C}_6\text{alkyl group and} \\
\text{ALK represents a straight or branched divalent C}_1\text{-C}_6\text{alky} \\
\text{lene, C}_2\text{-C}_6\text{alkynylene, or C}_2\text{-C}_6\text{alkylene radical, and may be interrupted by one or more non-adjacent} \\
\text{—NH,—O— or—S—linkages,} \\
\text{X}_1 \text{represents —NH,—O— or—S—, NR}_2\text{ or} \\
\text{—NCOR wherein R}^4 \text{is a C}_1\text{-C}_6\text{alkyl group, and} \\
\text{m and p are independently 0 or 1;} \\
\text{R}_3 \text{is C}_1\text{-C}_6\text{alkyl, phenyl, 2-3-, or 4-pyridyl, 2- or 3-thionyl,} \\
\text{2-3-, or 4-methoxyphenyl, 2-3-, or 4-pyridyl(methyl)benzyl, 2-3-, or 4-hydroxybenzyl,} \\
\text{2-3-, or 4-benzoxoxybenzyl, 2-3-, or 4-C}_1\text{-C}_6\text{alkoxybenzyl, or benzyl(C}_1\text{-C}_6\text{alkyl); or} \\
\text{the characterizing group of a natural } \alpha \text{-amino acid, in} \\
\text{which any functional group may be protected, any} \\
\text{amino group may be acylated and any carboxyl group} \\
\text{present may be amidated; or} \\
\text{a group [-ALK]}_p \text{where Alk is a C}_1\text{-C}_6\text{alkyl or (C}_1\text{-C}_6\text{)alkenyl} \\
\text{group optionally interrupted by one or more} \\
\text{—O— or—S—atoms or—N(R)}_p \text{groups [where} \\
\text{R}_3 \text{is a hydrogen atom or a C}_1\text{-C}_6\text{alkyl group], n is 0 or 1, and} \\
\text{R}_5 \text{is an optionally substituted cycloalkyl or cycloalkenyl} \\
\text{group; or} \\
\text{a benzyl group substituted in the phenyl ring by a group of} \\
\text{formula —OH}_2\text{COR} \text{where} \\
\text{R}_3 \text{is hydroxyl, amino,} \\
\text{(C}_1\text{-C}_6\text{)alkoxy, phenyl(C}_1\text{-C}_6\text{)alkoxy, (C}_1\text{-C}_6\text{)alkylamino, di(C}_1\text{-C}_6\text{)alkylamino, phenyl(C}_1\text{-C}_6\text{)alkylamino, the residue of an amino acid or acid halide, ester}
or amide derivative thereof, said residue being linked via an amide bond, said amino acid being selected from glycine, α or β alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid, and aspartic acid; or a heterocyclic(C1-C6 alkyl) group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C1-C6) alkoxy, cyano, (C1-C6) alkanyl, (trifluoromethyl)(C1-C6) alkyl, hydroxy, formyl, amino, (C1-C6) alkyllamino, di-(C1-C6) alkyllamino, mercapto, (C1-C6) alkythio, hydroxy(C1-C6) alkyl, mercapto(C1-C6) alkyl or (C1-C6) alkylphenylmethyl; or a group —CR1 R2 R3 R4 in which:

each of R1, R2 and R4 is independently hydrogen, (C1-C6) alkyl, (C2-C6) alkenyl, (C2-C6) alkylnyl, phenyl(C1-C6) alkyl, (C3-C6) cycloalkyl; or R3 is hydrogen and R1 and R4 are independently phenyl or heteroaryl such as pyridyl; or R1 is hydrogen, (C2-C6) alkyl, (C2-C6) alkenyl, (C2-C6) alkylnyl, phenyl(C1-C6) alkyl, (C3-C6) cycloalkyl, and R2 and R4 together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring;

or R1, R2 and R4 together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or R2 and R3 are each independently (C1-C6) alkyl, (C2-C6) alkenyl, (C2-C6) alkylnyl, phenyl(C1-C6) alkyl, or a group as defined for R2 below other than hydrogen, or R2 and R3 together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R1 is hydrogen, —OH, —SH, halogen, —CN, —CO2H, (C1-C6) perfluoroalkyl, —CH2OH, —CO2(C1-C6) alkyl, —O(C1-C6) alkyl, —O(C2-C6) alkenyl, —O(C2-C6) alkylnyl, —(C1-C6) alkyl, —(SO2(C1-C6) alkyl, —SO2(C2-C6) alkyl, —SO2(C2-C6) alkenyl, —SO2(C2-C6) alkylnyl, —SO2(C1-C6) alkyl, or —SO2(C1-C6) alkenyl or a group Q-W wherein Q represents a bond or —O—, —S—, —O— or —S— and W represents a phenyl, phenylalkyl, (C1-C6) cycloalkyl, (C2-C6) cycloalkylalkyl, (C2-C6) cycloalkylalkylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxy, halogen, —CN, —CO2H, —CO2(C1-C6) alkyl, —CONH2, —CONH(C1-C6) alkyl, —CONH(C1-C6) alkyl, —CH2OH, —CH2OH, (C1-C6) perfluoroalkyl, —O(C1-C6) alkyl, —O(C1-C6) alkyl, —S(C1-C6) alkyl, —SO(C1-C6) alkyl, —SO2(C1-C6) alkyl, —NO2, —NR2, —(NH(C1-C6) alkyl), —N(C1-C6) alkyl, —NHCO(C1-C6) alkyl, —(C1-C6) alkenyl, (C2-C6) alkenyl, (C2-C6) alkylnyl, (C3-C6) cycloalkyl, (C4-C6) cycloalkylalkyl, (C4-C6) cycloalkylalkylalkyl, phenyl or benzyl; R4 represents optionally substituted C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkylnyl, C1-C6 perfluoroalkyl, cycloalkyl, cycloalkyl(C1-C6 alkyl), cycloalkylalkyl, cycloalkylalkylalkyl, phenyl, naphthyl,

non-aryl heterocyclyl,

non-aryl heterocyclyl(C1-C6 alkyl),

heteroaryl; or heteroaryl(C1-C6 alkyl); or a pharmaceutically acceptable salt, hydrate or solvate thereof.

2. A method for the preparation of a medicament for the treatment or prophylaxis of diseases mediated by MMPs comprising adding to a medicament formulation a compound having formula (IA) or (IB)

\[
\begin{align*}
R2 & \quad N-O \quad X \quad N- \quad W \quad N \quad R4 \\
R3 & \quad R \quad O \quad R3
\end{align*}
\]

wherein

W represents HO(C=O) —, HONH(C=O) — or H(C=O)N(OH); X represents —O— or —S—; R1 represents hydrogen; —OH or —SH; fluoro or chloro; —CF3; (C1-C6) alkyl; (C1-C6) alkoxy; (C2-C6) alkenyl; phenyl or substituted phenyl; phenyl(C1-C6) alkyl or substituted phenyl(C1-C6) alkyl; phenyl(C2-C6) alkenyl or substituted phenyl(C2-C6) alkenyl heterocyclyl or substituted heterocyclyl; heterocyclyl(C1-C6) alkyl or substituted heterocyclyl (C1-C6) alkyl;

group BSO2A wherein n is 0, 1 or 2 and B is hydrogen or a (C1-C6) alkyl, phenyl, substituted phenyl, heterocyclyl, substituted heterocyclyl, (C1-C6) acyl, phenacyl or substituted phenacyl group, and A represents (C1-C6) alkylen; —NH2, (C1-C6) alkyllamino or di(C1-C6) alkyllamino; amino(C1-C6) alkyl, (C1-C6) alkyllamino(C1-C6) alkyl, (C1-C6) alkyllamino(C1-C6) alkyl, hydroxy(C1-C6) alkyl, mercapto(C1-C6) alkyl or carboxy(C1-C6) alkyl wherein the amino- , hydroxy-, mercapto- or carboxyl- group are optionally protected or the carboxyl- group amidated; or a cycloalkyl, cycloalkenyl or non-aromatic heterocyclic ring containing up to 3 heteroatoms, any of which may be (i) substituted by one or more substituents selected from C1-C6 alkyl, C2-C6 alkenyl, halo, cyano (—CN), —CO2H, —CO2R, —CONH2, —CONHR, —CONRR (R2), —OH, —OR, oxo—, —SH, —SR, —NHCOR, and
—NHCO₂R wherein R is C₁-C₈ alkyl or benzyl and/or (ii) fused to a cycloalkyl or heterocyclic ring;  
R₆ represents a group R₆-o-(X₆)ₗ-thioalkyl, wherein  
R₆ represents hydrogen, or a C₁-C₈ alkyl, C₂-C₈ alkenyl,  
C₂-C₈ alkynyl, cycloalkyl, aryl, or heterocyclic group,  
any of which may be un-substituted or substituted by  
(C₁-C₈)alkyl, (C₁-C₈)alkoxy, hydroxy, mercapto,  
(C₁-C₈)alkylthio, amino, halo (including fluoro, chloro,  
bromo and iodo), trifluoromethyl, cyano, nitro, oxo,  
—COOH, —CONH₂, —COOR₂, —NRCO₂R₂,  
—CONHR₂, —NR₂, —NR₃, or —CONR₂R₃  
wherein R₆ and R₇ are independently a (C₁-C₁₂)alkyl  

ALK represents a straight or branched divalent C₁-C₈  
alkylene, C₃-C₈ alkenylene, or C₃-C₈ alkynylene radical,  
and may be interrupted by one or more non-adjacent  
—N—, —O—, or —S— linkages,  
X₇ represents —NH—, —O—, or —S—, —NR₃—, or  
—NCO₂R— wherein R is a (C₁-C₁₂)alkyl group,  
and m and p are independently 0 or 1;  

R₆ is C₁-C₈ alkyl, phenyl, 2,3- or 4-pyridyl, 2- or 3-thienyl,  
2-, 3- or 4-hydroxyphenyl, 2-, 3- or 4-methoxyphenyl,  
2,3- or 4-pyridylmethyl, benzyl, 2,3- or 4-hydroxybenzyl,  
2,3- or 4-benzoxylbenzyl, 2-, 3- or 4-C₁-C₈  
alkoxybenzyl, or benzoxyl(C₁-C₈ alkyl);  

and the characterizing group of a natural α-amino acid,  
in which any functional group may be protected,  
any amino group may be acylated and any carboxyl group  
present may be amidated; or  
a group —Alk Lₐₐk wherein Alk is a (C₁-C₈)alkyl  
or (C₂-C₈)  
alcohol group optionally interrupted by one or more  
—O—, —S—, —N— atoms or —N(R₉)₂ groups [where  
R₉ is a hydrogen atom or a (C₁-C₈)alkyl group],  
n or is 0 or 1, and  
Rₖ is an optionally substituted cycloalkyl or cycloalkyl-  

enityl group, or  
a benzyl group substituted in the phenyl ring by a group of  
formula —OCH₂COR, wherein R is hydroxy, amino,  
(C₁-C₈)alkoxy, phenyl(C₁-C₈)alkoxy, (C₁-C₈)alkyl-  
ylamino, di(C₁-C₈)alkylamino, phenyl(C₁-C₈)alkyl-  
ylamino, the residue of an amino acid or acid halide,  
ester or amide derivative thereof, said residue being  
linked via an amide bond, said amino acid being  
selected from glycine, α or β alanine, valine,  
leucine, isoleucine, phenylalanine, tyrosine,  
tryptophan, serine, threonine,  
cysteine, methionine, asparagine, glutamine,  
lysine, histidine, arginine, glutamic acid,  
and aspartic acid; or  
a heterocyclic(C₁-C₈)alkyl group, either being  
unsubstituted or mono- or di-substituted in the heterocyclic  
ring with halo, nitro, carboxy, (C₁-C₈)alkoxy,  
(cyano, (C₁-C₈)alkanoyl, trifluoromethyl(C₁-C₈)alkyl,  
hydroxy, formyl, amino, (C₁-C₈)alkylaminoo, di(C₁-C₈)alkyl-  
yn amino, mercapto, (C₁-C₈)alkylthio, hydroxy(C₁-C₈)  
alkyl mercapto(C₁-C₈)alkyl or (C₁-C₈)alkylphosphinyl-  
ethyl; or  
a group —CR₆R₇Rₘₐk, in which:  
each of R₆, R₇, and Rₘ is independently hydrogen, (C₁-C₈)  
alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, phenyl(C₁-C₈)  
alkyl, (C₂-C₈)cycloalkyl; or  
R₆ is hydrogen and R₇ and Rₘ are independently  
phenyl or heteroaryl such as pyridyl; or  
R₆ is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)  
alkynyl, phenyl(C₁-C₈)alkyl, or (C₂-C₈)cycloalkyl, and  
R₇ and Rₘ together with the carbon atom to which they  
are attached form a 3 to 8 membered cycloalkyl or a 5-  
to 6-membered heterocyclic ring;  
or R₆, R₇, and Rₘ together with the carbon atom to which  
they are attached form a tricyclic ring (for example adaman-  
tyl); or  
R₆ and Rₗ are each independently (C₁-C₈)alkyl, (C₂-C₈)  
alkenyl, (C₂-C₈)alkynyl, phenyl(C₁-C₈)alkyl, or a group  
as defined for R₆ below other than hydrogen, and  
R₆ and Rₗ together with the carbon atom to which they  
are attached form a cycloalkyl or heterocyclic ring, and  
R₆ is hydrogen, —OH, —SH, halogen, —CN, —CO₂H,  
(C₁-C₈)perthoroalkyl, —CH₂OH, —CO₂(C₁-C₈)alkyl,  
—O(C₁-C₈)alkyl, —O(C₂-C₈)alkenyl, —S(C₁-C₈)  
alkyl, —SO(C₁-C₈)alkyl, —SO₂(C₁-C₈)alkyl, —S(C₁-C₈)  
alkenyl, —SO₂(C₁-C₈)alkenyl, —SO₂(C₂-C₈)alkyl,  
—SO₂(C₂-C₈)alkenyl or a group O-W wherein W  
represents a bond or  
—O—, —S—, —SO— or —SO₂— and W represents a  
phenyl, phenylalkyl, (C₁-C₈)cycloalkyl, (C₁-C₈)cy-  
cloalkylalkyl, (C₂-C₈)cycloalkenyl, (C₂-C₈)cycloalkyl-  
ealkenyl, heteroaryl or heteroaralkyl group, which  
which group W may optionally be substituted by one  
or more substituents independently selected from,  
hydroxyl, halogen, —CN, —CO₂H, —CO₂(C₁-C₈)alkyl,  
—CONH₂, —CONH(C₁-C₈)alkyl, —CONH(C₁-C₈)  
alkyl, —CH₂OH, (C₁-C₈)perthoroalkyl, —O(C₁-C₈)  
alkyl, —S(C₁-C₈)alkyl, —SO(C₁-C₈)alkyl, —SO₂(C₁-C₈)  
alkyl, —NO₂, —NH₂, —NH(C₁-C₈)alkyl, —N(C₁-C₈)  
alkyl, —NHC(O)(C₁-C₈)alkyl, —NHC(O)(C₁-C₈)  
alkenyl, —NHC(O)(C₂-C₈)alkyl, —NHC(O)(C₂-C₈)  
alkenyl, (C₂-C₈)cycloalkyl, (C₂-C₈)cycloalkenyl,  
phenyl or benzyl;  
Rₖ represents optionally substituted  
C₁-C₈ alkyl,  
C₂-C₈ alkenyl,  
C₂-C₈ alkynyl,  
C₁-C₈ perthoroalkyl,  
cycloalkyl,  
cycloalkyl(C₁-C₈ alkyl),  
cycloalkenyl,  
cycloalkenyl(C₁-C₈ alkyl),  
phenyl,  
phenyl(C₁-C₈ alkyl),  
naphthyl,  
non-aryl heterocyclyl,  
non-aryl heterocyclyl(C₁-C₈ alkyl),  
heteroaryl; or  
heteroaryl(C₁-C₈ alkyl);  

and a pharmaceutically acceptable salt, hydrate or solvate  
thereof.

3. The method according to claim 1 wherein the disease  
selected from the group consisting of bone resorption,  
tumour growth or invasion by secondary metasastes,  
rheumatoid arthritis, septic arthritis, osteoarthritis,  
periodontitis, gingivitis, corneal ulceration,  
neuroinflammatory disorders, restenosis,  
emphysema, fibrotic diseases, chronic obstructive  
pulmonary disease, bronchitis, asthma, autoimmune  
disease, transplant rejection, cystic fibrosis, psoriasis,  
psoriatic arthritis, degenerative cartilage loss,  
inflammatory gastric conditions,  
inflammatory bowel disease, and ulcerative colitis,  
atopic dermatitis, epidermolysis bullous,  
epidermic ulceration, a neuropathy or nephropathy,  
lomerononephritis and renal failure; ocular  
inflammation; liver cirrhosis, Sjoegren’s syndrome;  
and an inflammatory condition of the nervous  

system.
4. The method according to claim 1 wherein the disease is selected from the group consisting of multiple sclerosis, emphysema, liver fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, Crohn’s disease, inflammatory bowel disease, and liver sclerosis.

5. The method according to claim 1 wherein the disease is hepatitis.

6. The method according to claim 2, wherein the disease is selected from the group consisting of bone resorption, tumour growth or invasion by secondary metastases, rheumatoid arthritis, septic arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, neuroinflammatory disorders, restenosis, emphysema, fibrotic disease, chronic obstructive pulmonary disease, bronchitis, asthma, autoimmune disease, transplant rejection, cystic fibrosis, psoriasis, psoriatic arthritis, degenerative cartilage loss, inflammatory gastric conditions, inflammatory bowel disease, and ulcerative colitis, atopic dermatitis, epidermolysis bullosa, epidermic ulceration, a neuropathy or nephropathy, glomerulonephritis and renal failure, ocular inflammation, liver cirrhosis, Sjögren’s syndrome, and an inflammatory condition of the nervous system.

7. The method according to claim 2, wherein the disease is selected from the group consisting of multiple sclerosis, emphysema, liver fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, Crohn’s disease, inflammatory bowel disease, and liver sclerosis.

8. The method according to claim 2, wherein the disease is hepatitis.

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