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(71) Applicant *(for all designated States except US)*: BRITISH BIOTECH PHARMACEUTICALS LIMITED [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HUNTER, Michael, George [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). BECKETT, Raymond, Paul [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). CLEMENTS, John, Martin [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). WHITTAKER, Mark [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). SPAVOLD, Zoe, Marie [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).

(74) Agent: WALLS, Alan, J.; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).

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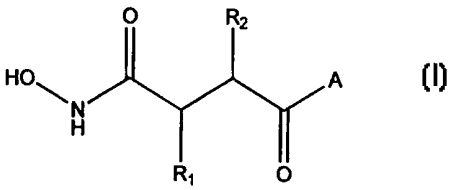
(57) Abstract



(I)

Compounds of formula (I) are antibacterials wherein: R_1 represents hydrogen, or C_1–C_6 alkyl or C_1–C_6 alkyl substituted by one or more halogen atoms; R_2 represents a group R_{10}–$(X)_n$–$(ALK)_m$– wherein R_{10} represents hydrogen, or a C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, cycloalkyl, aryl, or heterocyclyl group, any of which may be unsubstituted or substituted by (C_1–C_6)alkyl, (C_1–C_6)alkoxy, hydroxy, mercapto, (C_1–C_6)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, –COOH, $-CONH_2$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1–C_6)alkyl group, and ALK represents a straight or branched divalent C_1–C_6 alkylene, C_2–C_6 alkenylene, or C_2–C_6 alkynylene radical, and may be interrupted by one or more non-adjacent –NH–, –O– or –S– linkages, X represents –NH–, –O– or –S–, and m and n are independently 0 or 1; and A represents a group as defined in the specification.

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HYDROXAMIC ACID DERIVATIVES AS ANTIBACTERIALS

This invention relates to the use of hydroxamic acid derivatives as antibacterial agents.

Background to the Invention

In general, bacterial pathogens are classified as either Gram-positive or Gram-negative. Many antibacterial agents (including antibiotics) are specific against one or other Gram-class of pathogens. Antibacterial agents effective against both Gram-positive and Gram-negative pathogens are therefore generally regarded as having broad spectrum activity.

Many classes of antibacterial agents are known, including the penicillins and cephalosporins, tetracyclines, sulfonamides, monobactams, fluoroquinolones and quinolones, aminoglycosides, glycopeptides, macrolides, polymyxins, lincosamides, trimethoprim and chloramphenicol. The fundamental mechanisms of action of these antibacterial classes vary.

Bacterial resistance to many known antibacterials is a growing problem. Accordingly there is a continuing need in the art for alternative antibacterial agents, especially those which have mechanisms of action fundamentally different from the known classes.

Amongst the Gram-positive pathogens, such as Staphylococci, Streptococci, Mycobacteria and Enterococci, resistant strains have evolved/arisen which makes them particularly difficult to eradicate. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative Staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium*.

Pathogenic bacteria are often resistant to the aminoglycoside, β-lactam (penicillins

and cephalosporins), and chloramphenicol types of antibiotic. This resistance involves the enzymatic inactivation of the antibiotic by hydrolysis or by formation of inactive derivatives. The β-lactam (penicillin and cephalosporin) family of antibiotics are characterised by the presence of a β-lactam ring structure. Resistance to this family of antibiotics in clinical isolates is most commonly due to the production of a "penicillinase" (β-lactamase) enzyme by the resistant bacterium which hydrolyses the β-lactam ring thus eliminating its antibacterial activity.

Recently there has been an emergence of vancomycin-resistant strains of enterococci (Woodford N. 1998 Glycopeptide-resistant enterococci: a decade of experience. Journal of Medical Microbiology. 47(10):849-62). Vancomycin-resistant enterococci are particularly hazardous in that they are frequent causes of hospital based infections and are inherently resistant to most antibiotics. Vancomycin works by binding to the terminal D-Ala-D-Ala residues of the cell wall peptidioglycan precursor. The high-level resistance to vancomycin is known as VanA and is conferred by a genes located on a transposable element which alter the terminal residues to D-Ala-D-lac thus reducing the affinity for vancomycin.

In view of the rapid emergence of multidrug-resistant bacteria, the development of antibacterial agents with novel modes of action that are effective against the growing number of resistant bacteria, particularly the vancomycin resistant enterococci and β-lactam antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus,* is of utmost importance.

Brief Description of the Invention

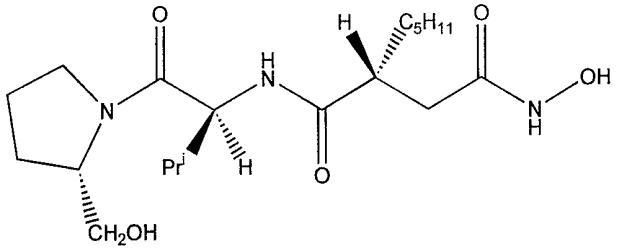
This invention is based on the finding that certain hydroxamic acid derivatives have antibacterial activity, and makes available a new class of antibacterial agents. The inventors have found that the compounds with which this invention is concerned are antibacterial with respect to a range of Gram-positive and Gram-negative organisms.

Although it may be of interest to establish the mechanism of action of the

compounds with which the invention is concerned, it is their ability to inhibit bacterial growth which makes them useful. However, it is presently believed that their antibacterial activity is due, at least in part, to intracellular inhibition of bacterial polypeptide deformylase (PDF) enzyme.

Bacterial polypeptide deformylases (PDF) (EC 3.5.1.31), are a conserved family of metalloenzymes (Reviewed: Meinnel T, Lazennec C, Villoing S, Blanquet S, 1997, Journal of Molecular Biology 267, 749-761) which are essential for bacterial viability, their function being to remove the formyl group from the N-terminal methionine residue of ribosome-synthesised proteins in eubacteria. Mazel et al. (EMBO J. **13(4)**:914-923, 1994) have recently cloned and characterised an *E. coli* PDF. As PDF is essential to the growth of bacteria and there is no eukaryotic counterpart to PDF, Mazel et al. (ibid), Rajagopalan et al. (J. Am. Chem. Soc. 119:12418-12419, 1997) and Becker et al., (J. Biol Chem. 273(19):11413-11416, 1998) have each proposed that PDF is an excellent anti-bacterial target.

The natural antibiotic actinonin (see for example J.C.S Perkin I, 1975, 819) is a hydroxamic acid derivative of Structure (A):



(A)

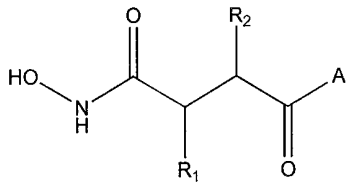
In addition, various structural analogues of actinonin have also been shown to have antibacterial activity (see for example Broughton et al. (Devlin et al. Journal of the Chemical Society. Perkin Transactions 1 (9):830-841, 1975; Broughton et al. Journal of the Chemical Society. Perkin Transactions 1 (9):857-860, 1975).

Hydroxamic acid derivatives are also known in the field of matrix metalloproteinase

(MMP) inhibition. Many examples of the class have been synthesised and their MMP inhibitory properties reported. A smaller number have been reported to be active in animal models of diseases mediated by MMPs, for example various cancers and rheumatoid arthritis. For reviews of the patent literature on hydroxamate MMP inhibitors, see for example Beckett, Exp. Opin. Ther. Patents (1996) 6, 1305-1315, and Beckett & Whittaker, Exp. Opin. Ther. Patents (1998), 8(3), 259-282, and the documents cited therein.

Description of the invention

According to the present invention there is provided the use of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof in the preparation of an antibacterial composition:



(I)

wherein:

R_1 represents hydrogen, or C_1-C_6 alkyl, C_1-C_6 alkyl substituted by one or more halogen atoms, amino, hydroxy, or C_1-C_6 alkoxy;

R_2 represents a group R_{10}-$(X)_n$-$(ALK)_m$- wherein

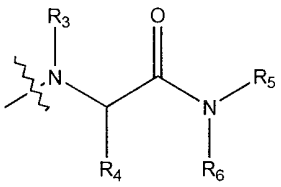
R_{10} represents hydrogen, or a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, aryl, or heterocyclyl group, any of which may be unsubstituted or substituted by (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, -COOH, -$CONH_2$, -$COOR^A$, -$NHCOR^A$, -$CONHR^A$, -NHR^A, -NR^AR^B, or -$CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group, and

ALK represents a straight or branched divalent C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene radical, and may be interrupted by one or more non-adjacent -NH-, -O- or -S- linkages,

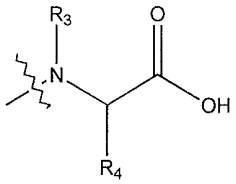
X represents -NH-, -O- or -S-, and

m and n are independently 0 or 1; and

A represents (i) a group of formula (IA), (IB), (IC) or (ID)



(IA)



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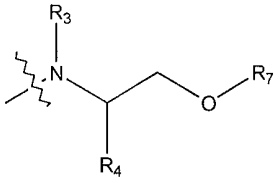

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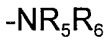


(ID)

wherein:

R_3 represents hydrogen or C_1-C_6 alkyl and R_4 represents the side chain of a natural or non-natural alpha amino acid or R_3 and R_4 when taken together with the nitrogen and carbon atoms to which they are respectively attached form an optionally substituted saturated heterocyclic ring of 5 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring,

R_5 and R_6, independently represent hydrogen, or optionally substituted C_1-C_8 alkyl, cycloalkyl, aryl, aryl(C_1-C_6 alkyl), heterocyclic, or heterocyclic(C_1-C_6 alkyl), or R_5 and R_6 when taken together with the nitrogen atom to which they are attached form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring, and

R_7 represents hydrogen, C_1-C_6 alkyl, or an acyl group.

PROVIDED THAT (a) R_5 and R_6 taken together with the nitrogen atom to which they are attached do not form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms when R_1 and R_3 are hydrogen, R_2 is hydrogen, C_1-C_6 alkyl, phenyl, benzyl, 4-chlorophenylmethyl, 4-nitrophenylmethyl, or 4-aminophenylmethyl and R_3 is hydrogen, methyl, isopropyl, isobutyl or benzyl; and (b) R_5 is not 2-pyridyl or 2-thiazolyl when R_1, R_3 and R_6 are hydrogen, R_2 is n-pentyl and R_4 is isopropyl; and (c) R_5 and R_6 are not both ethyl when R_1 and R_3 are hydrogen, R_2 is n-pentyl and R_4 is methyl or isopropyl.

In another aspect, the invention provides a method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound of formula (I) as defined above.

In a further aspect of the invention there is provided a method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound of formula (I) as defined above to the site of contamination.

The compounds of formula (I) as defined above may be used as component(s) of antibacterial cleaning or disinfecting materials.

According to a preferred embodiment, the various aspects of the invention can be applied against vancomycin-, quinolone- and "β-lactam"-resistant bacteria and the infections they cause.

On the hypothesis that the compounds (I) act by inhibition of intracellular PDF, the most potent antibacterial effect may be achieved by using compounds which efficiently pass through the bacterial cell wall. Thus, compounds which are highly active as inhibitors of PDF in vitro and which penetrate bacterial cells are preferred

for use in accordance with the invention. It is to be expected that the antibacterial potency of compounds which are potent inhibitors of the PDF enzyme in vitro, but are poorly cell penetrant, may be improved by their use in the form of a prodrug, ie a structurally modified analogue which is converted to the parent molecule of formula (I), for example by enzymic action, after it has passed through the bacterial cell wall.

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

As used herein the term "divalent (C_1-C_6)alkylene radical" means a saturated hydrocarbon chain having from 1 to 6 carbon atoms and two unsatisfied valencies.

As used herein the term "(C_2-C_6)alkenyl" means a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "divalent (C_2-C_6)alkenylene radical" means a hydrocarbon chain having from 2 to 6 carbon atoms, at least one double bond, and two unsatisfied valencies.

As used herein the term "C_2-C_6 alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "divalent (C_2-C_6)alkynylene radical" means a hydrocarbon chain having from 2 to 6 carbon atoms, at least one triple bond, and two unsatisfied valencies.

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 napthyl.

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 rings containing one or more heteroatoms;. Illustrative of such groups are thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, 4-([1,2,3]-thiadiazoly-4-yl)phenyl and 5-isoxazol-3-ylthienyl.

As used herein the unqualified term “heterocyclyl” or “heterocyclic” includes "heteroaryl" as defined above, and in particular means a 5-7 membered aromatic or non-aromatic heterocyclic ring containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzene ring, including for example, pyrrolyl, furyl, thienyl, piperidinyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, benzimidazolyl, maleimido, succinimido, phthalimido and 1,3-dioxo-1,3-dihydro-isoindol-2-yl groups.

As used herein the term "acyl" means a group $R_{20}C(O)$- where R_{20} is $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_3$-$C_7)$cycloalkyl, phenyl, heterocyclyl, phenyl$(C_1$-$C_6)$alkyl, heterocyclyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl$(C_1$-$C_6)$alkyl, phenyl$(C_2$-$C_6)$alkenyl, heterocyclyl$(C_2$-$C_6)$alkenyl, $(C_3$-$C_7)$cycloalkyl$(C_2$-$C_6)$alkenyl, any of which R_{20} groups may be substituted.

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 $(C_1$-$C_6)$alkyl, benzyl, $(C_1$-$C_6)$alkoxy, phenoxy, hydroxy, mercapto, $(C_1$-$C_6)$alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COR^A$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1$-$C_6)$alkyl group. In the case where "substituted" means benzyl, the phenyl ring thereof may itself be substituted with any of the foregoing, except benzyl.

As used herein the terms "side chain of a natural alpha-amino acid" and "side chain of a non-natural alpha-amino acid" mean the group R^x in respectively a natural and non-natural amino acid of formula NH_2-CH(R^x)-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, pipecolic acid, and thyroxine.

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 C_1-C_6 alkyl ester), amino groups may be converted to amides (for example as a $NHCOC_1$-C_6 alkyl amide) or carbamates (for example as an $NHC(=O)OC_1$-C_6 alkyl or $NHC(=O)OCH_2Ph$ carbamate), hydroxyl groups may be converted to ethers (for example an OC_1-C_6 alkyl or a $O(C_1$-C_6 alkyl)phenyl ether) or esters (for example a $OC(=O)C_1$-C_6 alkyl ester) and thiol groups may be converted to thioethers (for example a tert-butyl or benzyl thioether) or thioesters (for example a $SC(=O)C_1$-C_6 alkyl thioester).

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 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 stereoconfiguration of the carbon atom carrying the R_2 group is R; that of the carbon atom carrying the R_4 group (when asymmetric) is S; and that of the carbon atom carrying the R_1 group

(when asymmetric) is R.

In the compounds for use according to the invention and in the novel compounds of the invention:

R_1 may be, for example, hydrogen, hydroxy, methoxy, methyl, or trifuoromethyl. Hydrogen is currently preferred.

R_2 may be, for example:

optionally substituted C_1-C_8 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl or cycloalkyl;

phenyl(C_1-C_6 alkyl)-, phenyl(C_3-C_6 alkenyl)- or phenyl(C_3-C_6 alkynyl)- optionally substituted in the phenyl ring;

cycloalkyl(C_1-C_6 alkyl)-, cycloalkyl(C_3-C_6 alkenyl)- or cycloalkyl(C_3-C_6 alkynyl)- optionally substituted in the cycloalkyl ring;

heterocyclyl(C_1-C_6 alkyl)-, heterocyclyl(C_3-C_6 alkenyl)- or heterocyclyl(C_3-C_6 alkynyl)- optionally substituted in the heterocyclyl ring; or

$CH_3(CH_2)_pO(CH_2)_q$- or $CH_3(CH_2)_pS(CH_2)_q$-, wherein p is 0, 1, 2 or 3 and q is 1, 2 or 3.

Specific examples of R_2 groups include

methyl, ethyl, n- and iso-propyl, n- and iso-butyl, n-pentyl, iso-pentyl 3-methyl-but-1-yl, n-hexyl, n-heptyl, n-acetyl, n-octyl, methylsulfanylethyl, ethylsulfanylmethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-ethoxymethyl, 3-hydroxypropyl, allyl, 3-phenylprop-3-en-1-yl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, furan-2-ylmethyl, furan-3-

methyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylmethyl, piperidinylmethyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, and 4-methoxybenzyl.

Presently preferred groups at R_2 are n-propyl, n-butyl, n-pentyl, benzyl and cyclopentylmethyl.

R_3 may be, for example, hydrogen or methyl, with hydrogen presently preferred.

R_4 may be, for example

the characterising group of a natural α-amino acid, for example isopropyl, benzyl, or 4-hydroxyphenylmethyl, 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 $-[Alk]_nR_9$ where Alk is a (C_1-C_6)alkylene or (C_2-C_6)alkenylene group optionally interrupted by one or more -O-, or -S- atoms or $-N(R_{12})-$ groups [where R_{12} is a hydrogen atom or a (C_1-C_6)alkyl group], n is 0 or 1, and R_9 is hydrogen or an optionally substituted phenyl, aryl, heterocyclyl, cycloalkyl or cycloalkenyl group or (only when n is 1) R_9 may additionally be hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group; or

a benzyl group substituted in the phenyl ring by a group of formula $-OCH_2COR_8$ where R_8 is hydroxyl, amino, (C_1-C_6)alkoxy, phenyl(C_1-C_6)alkoxy, (C_1-C_6)alkylamino, di$((C_1-C_6)$alkyl)amino, phenyl(C_1-C_6)alkylamino; or

a heterocyclic(C_1-C_6)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C_1-C_6)alkoxy,

cyano, (C_1-C_6)alkanoyl, trifluoromethyl (C_1-C_6)alkyl, hydroxy, formyl, amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, mercapto, (C_1-C_6)alkylthio, hydroxy(C_1-C_6)alkyl, mercapto(C_1-C_6)alkyl or (C_1-C_6)alkylphenylmethyl; or

a group $-CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, and R_a and R_b 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

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, $-CO_2H$, (C_1-C_4)perfluoroalkyl, $-CH_2OH$, $-CO_2$(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -O(C_2-C_6)alkenyl, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, $-SO_2$(C_1-C_6) alkyl, -S(C_2-C_6)alkenyl, -SO(C_2-C_6)alkenyl, $-SO_2$(C_2-C_6)alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or $-SO_2$- and W represents a phenyl, phenylalkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkylalkyl, (C_4-C_8)cycloalkenyl, (C_4-C_8)cycloalkenylalkyl, heteroaryl or heteroarylalkyl

group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO_2H, -CO_2(C_1-C_6)alkyl, -$CONH_2$, -CONH(C_1-C_6)alkyl, -CONH(C_1-C_6alkyl)$_2$, -CHO, -CH_2OH, (C_1-C_4)perfluoroalkyl, -O(C_1-C_6)alkyl, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -NO_2, -NH_2, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NHCO(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, phenyl or benzyl.

Examples of particular R_4 groups include methyl, ethyl, isopropyl, benzyl, 4-chlorobenzyl, 4-hydroxybenzyl, phenyl, cyclohexyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, naphthylmethyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, 1-methoxy-1-methylethyl, 1-hydroxy-1-methylethyl, 1-fluoro-1-methylethyl, 4,4-dimethyl-prop-1-en-4-yl, 4,4-dimethyl-prop-4-yl hydroxymethyl, 2-hydroxethyl, 2-carboxyethyl, 2-methylcarbamoylethyl, 2-carbamoylethyl, and 4-aminobutyl. Presently preferred R_4 groups include tert-butyl, iso-butyl, benzyl and methyl.

R_3 and R_4 when taken together with the nitrogen and carbon atoms to which they are respectively attached may form an optionally substituted saturated heterocyclic ring of 5 to 8 atoms. For example, R_3 and R_4 may form a bridge between the nitrogen and carbon atoms to which they are attached, said bridge being represented by the divalent radical -$(CH_2)_{3-6}$-, or -$(CH_2)_r$-O-$(CH_2)_s$-, or -$(CH_2)_r$-S-$(CH_2)_s$-, wherein r and s are each independently 1, 2 or 3 with the proviso that r+s = 2, 3, 4, or 5.

R_5 and R_6 may independently be, for example, hydrogen, methyl, ethyl, tert-butyl, n-heptyl, cyclopentyl, cyclohexyl, phenyl,2-ethoxycarbonyl-eth-2-yl, pyrid-2-yl, 1,1,3,3-tetramethylbutyl, benzyl, 2,6-dimethyl-4-tert-butyl-phenyl,diphenylmethyl, 4-chlorophenyl-phenylmethyl, 2-fluorophenyl-phenylmethyl, 1-(4-fluorophenyl)-1-phenyl-1-amino-methyl, 1,1-diphenylprop-3-yl, 3-phenyl-thiazolyl, or 2-hydroxyethyl;

or R_5 and R_6 when taken together with the nitrogen atom to which they are attached may form a saturated 5- to 8-membered monocyclic N-heterocyclic ring which is attached via the N atom and which optionally contains -N(R_{11})- wherein R_{11} is hydrogen or C_1-C_6 alkyl, benzyl, acyl, or an amino protecting group, O, S, SO or SO_2 as a ring member, and/or is optionally substituted on one or more C atoms by hydroxy, C_1-C_6 alkyl, hydroxy(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, oxo, ketalised oxo, amino, mono(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, carboxy, C_1-C_6 alkoxycarbonyl, hydroxymethyl, C_1-C_6 alkoxymethyl, carbamoyl, mono(C_1-C_6 alkyl)carbamoyl, di(C_1-C_6 alkyl)carbamoyl, or hydroxyimino.

Examples of such rings are substituted or unsubstituted 1-pyrrolidinyl, piperidin-1-yl, 1-piperazinyl, hexahydro-1-pyridazinyl, morpholin-4-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl 1-oxide, tetrahydro-1,4-thiazin-4-yl 1,1-dioxide, hexahydroazipino, or octahydroazocino. Substituted examples of the foregoing are 2-(methylcarbamoyl)-1-pyrrolidinyl, 2-(hydroxymethyl)-1-pyrrolidinyl, 4-hydroxypiperidino, 2-(methylcarbamoyl)piperidino, 4-hydroxyiminopiperidino, 4-methoxypiperidino, 4-methylpiperidin-1yl, 4-benzylpiperidin-1-yl, 4-acetylpiperidin-1-yl,4-methyl-1-piperazinyl, 4-phenyl-1-piperazinyl, 1,4-dioxa-8-azaspiro[4,5]decan-8-yl, hexahydro-3-(methylcarbamoyl)-2-pyridazinyl, and hexahydro-1-(benzyloxycarbonyl)-2-pyridazinyl, decahydroisoquinolin-2-yl, and 1,2,3,4-tetrahydroisoquinolin-2-yl.

When A is a group of formula (IA), it is currently preferred that R_5 be methyl or hydrogen, and R_6 be methyl.

R_7 may be, for example, hydrogen, or a group $R_{20}C(O)$- where R_{20} is a (C_1-C_6)alkyl group such as methyl or ethyl.

A specific example of a compound having PDF inhibiting and antibacterial activity in accordance with the invention is:

N^1-(1S-dimethylcarbamoyl-2,2-dimethyl-1-propyl)-N^4-hydroxy-2R-butyl-succinamide

and pharmaceutically acceptable salts, hydrates and solvates thereof.

Compounds for use in accordance with the invention may be prepared by methods described in the literature for the preparation of hydroxamate MMP inhibitors, for example the patent publications relating to such compounds cited in Beckett, Exp. Opin. Ther. Patents (1996) 6, 1305-1315, and Beckett & Whittaker, Exp. Opin. Ther. Patents (1998), 8(3), 259-282.

Compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

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 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.

For topical application to the skin, the active ingredient(s) 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.

The active ingredient(s) 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.

Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. 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.

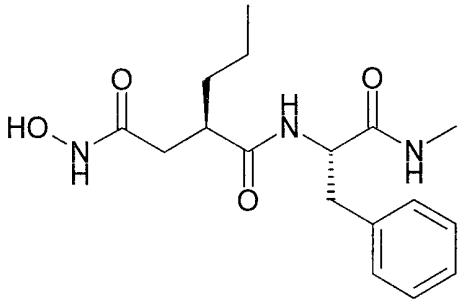
The following examples are of compounds of formula (I) above having PDF inhibiting activity and antibacterial activity in accordance with the invention

^{1}H and ^{13}C NMR spectra were recorded using a Bruker AC 250E spectrometer at 250.1 and 62.9 MHz, respectively. Elemental microanalyses were performed by MEDAC Ltd. Department of Chemistry, Brunel University, Uxbridge, Middlesex UB8 3PH. L-Tert-leucine-N-methylamide was prepared according to established

literature methods.

Example 1

N^1-(1S-Methylcarbamoyl-2-phenyl-ethyl)-N^4-hydroxy-2R-propyl-succinamide



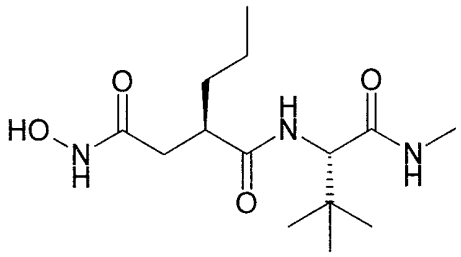
The title compound was prepared by the method described in WO 92/13831 (Example 1), substituting valeryl chloride for 4-methylvaleryl chloride.

m.p. = 191 - 193°C. ^{1}H-NMR δ (CD_3OD, partial D exchange); 8.12 (0.5H, d, J=8.1Hz), 7.96-7.87 (5H, m), 4.55-4.40 (1H, m), 3.11 (1H, dd, J=6.4, 13.7Hz), 2.89 (1H, dd, J=8.9, 13.7Hz), 2.65, 2.63 (3H, 2s), 2.60-2.50 (1H, m), 2.20 (1H, dd, J=8.0, 14.6Hz), 2.06 (1H, dd, J=6.7, 14.6Hz), 1.48-1.00 (4H, m) and 0.78 (3H, t, J=7.1Hz). ^{13}C-NMR δ (CD_3OD); 177.0, 174.0, 170.8, 138.8, 130.3, 129.4, 127.7, 56.3, 44.4, 38.7, 36.4, 35.6, 26.3 21.3 and 14.3. IR (KBr, ν_{max} cm^{-1}); 3292, 2957, 1637, 1560 and 1541. Found: C 60.18, H 7.45, N 12.52%; $C_{17}H_{25}N_3O_4 0.2H_20$ requires C 60.23, H 7.55, N 12.39%.

The compounds of Examples 2 and 3 were prepared by analogy with Example 1.

Example 2

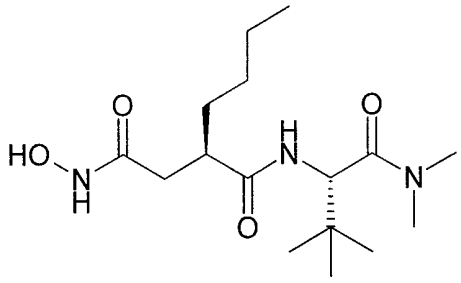
N^1-(1S-Methylcarbamoyl-2,2-dimethyl-propyl)-N^4-hydroxy-2R-propyl-succinamide



m.p. 200°C. ^{1}H-NMR (CD_3OD); 4.19 (1H, s), 2.90-2.76 (1H, m), 2.68 (3H, s), 2.31 (1H, dd, J=7.9, 14.6Hz), 2.15 (1H, dd, J=6.5, 14.6Hz), 1.60-1.40 (1H, m), 1.40-1.14 (3H, m), 0.95 (9H, s) and 0.85 (3H, t, J=7.0Hz). ^{13}C-NMR (CD_3OD); 176.9, 173.3, 170.7, 62.2, 43.6, 36.5, 35.7, 35.3, 27.17, 26.0, 21.4 and 14.4. IR (KBr, v_{max} cm^{-1}); 1682, 1634, 1544, 1470, 1413, 1369 and 1248. Found C 55.35 H 8.84 N 13.92%; $C_{14}H_{27}N_3O_4$ requires C 55.79, H 9.03, N 13.94%.

Example 3

N^1-(1S-Dimethylcarbamoyl-2,2-dimethyl-1-propyl)-N^4-hydroxy-2R-butyl-succinamide



Off white solid. m.p. 165-166°C. ^{1}H-NMR; δ ($CDCl_3$), 4.87 (1H, s), 3.19 (3H, s), 2.93 (3H, s), 2.83 (1H, m), 2.35 (1H, dd, J=7.8, 14.6Hz), 2.19 (1H, dd, J=6.3, 14.5Hz), 1.59-1.06 (6H, br m), 1.01 (9H, s) and 0.87 (3H, t, J=6.9Hz). ^{1}H-NMR; δ ($CDCl_3$), 177.5, 173.6, 171.1, 71.1, 56.6, 42.3, 39.2, 36.6, 36.4, 33.6, 30.8, 27.5, 24.0 and 14.7. LRMS: +ve ion 352 [M+Na], -ve ion 328 [M-H].

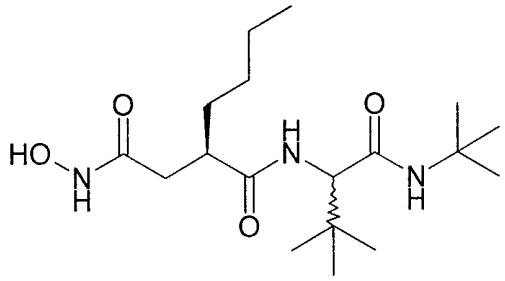
Example 4

By methods described in the literature analogous to those used for Example 1-3 above, the following compounds of formula (I) above, wherein A is a group of formula (IA) were prepared:

R_1	R_2	R_3	R_4	R_5	R_6
H	cyclopentylmethyl	H	benzyl	H	methyl
H	iso-butyl	H	iso-propyl	H	methyl
H	iso-butyl	H	benzyl	H	phenyl
H	iso-butyl	H	tert-butyl	H	phenyl
H	iso-butyl	H	1-methyl-1-methylthio-ethyl	H	methyl
H	$HO(CH_2)_{14}$-	H	tert-butyl	H	methyl
H	cyclopentylmethyl	H	tert-butyl	H	tert-butyl
H	cyclopentylmethyl	H	4,4-dimethyl-prop-1-en-4-yl	H	cyclohexyl
H	cyclopentylmethyl	H	4,4-dimethyl-prop-4-yl	H	cyclohexyl
H	iso-butyl	H	tert-butyl	H	methyl
H	iso-butyl	H	iso-butyl	H	2-ethoxycarbonyl-eth-2-yl
H	iso-butyl	H	tert-butyl	H	tert-butyl
H	iso-butyl	H	tert-butyl	methyl	methyl
H	iso-butyl	H	tert-butyl	H	pyrid-2-yl
H	cyclopentylmethyl	H	tert-butyl	H	benzyl
OH	iso-butyl	H	tert-butyl	H	2,6-dimethyl-4-tert-butyl-phenyl
OH	iso-butyl	H	tert-butyl	H	diphenylmethyl
OH	iso-butyl	H	tert-butyl	H	4-chlorophenyl-phenylmethyl
OH	iso-butyl	H	tert-butyl	H	1,1-diphenylprop-3-yl
OH	iso-butyl	H	tert-butyl	H	3-phenyl-thiazolyl
OH	iso-butyl	H	tert-butyl	H	1-(4-fluorophenyl)-1-phenyl-1-amino-methyl
OH	iso-butyl	H	tert-butyl	H	2-fluorophenyl-phenylmethyl

Example 5

N^1-(1R,S-*tert*-Butylcarbamoyl-2,2-dimethyl-1-propyl)-N^4-hydroxy-2R-butyl-succinamide

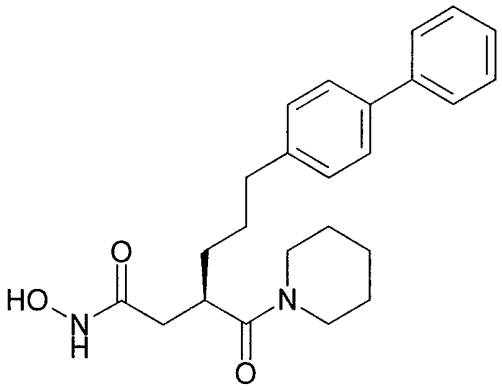


The title compound was prepared by Ugi reaction of the appropriate homochiral succinate ester with trimethylacetaldehyde and ammonia, followed by conversion to the desired hydroxamic acid, as described in GB-2298423-A. The starting succinates were prepared by the method described in WO 92/13831.

^{1}H-NMR: δ (CD_3OD; mixture of diastereoisomers); 7.39 (0.5 H, s), 7.32 (0.5 H, s), 4.08 (0.5 H, s) 4.02 (0.5H, 2s), 2.80-2.70 (1H, m), 2.32-2.19 (1H, m), 2.18-2.00 (1H, m), 1.60-1.04 (6H, m), 1.22 (4.5H, s), 1.21 (4.5H, s), 0.90 (4.5H, s), 0.87 (4.5H, s) and 0.85-0.76 (3H, m). ^{13}C-NMR (CD_3OD); 177.0, 176.8, 171.8, 170.9, 62.8, 62.2, 52.2, 52.1, 43.8, 43.7, 36.6, 36.4, 35.8, 35.4, 35.3, 35.1, 28.9, 28.8, 27.4, 27.2, 21.5, 21.4, 14.3 and 14.3. IR (KBr, ν_{max} cm^{-1}); 3313, 2963, 1637, 1546, 1456, 1395, 1364, 1264, 1225 and 1188.

Example 6

6-Biphenyl-4-yl-3R-(piperidine-1-carbonyl)-hexanoic acid hydroxyamide



The title compound was prepared by a method analogous to that used for the preparation of compounds of Examples 1-4, except that piperidine was used in the coupling reaction in place of the amino acid derivative.

m.p. 149-150°C. ^{1}H-NMR: δ ($(CD_3)_2SO$), 10.37 (1H, s), 8.69 (1H, s), 7.69-7.19 (9H, m), 3.59-3.24 (4H, m), 3.24-3.08 (1H, m), 2.65-2.43 (2H, m), 2.25 (1H, dd, J=7.8, 14.6Hz), 2.01 (1H, dd, J=6.0, 14.7Hz) and 1.64-1.20 (10H, m). ^{13}C-NMR; δ ($(CD_3)_2SO$), 172.3, 168.0, 141.6, 140.5, 138.0, 129.3, 127.5, 126.9, 126.8, 46.4, 42.6, 36.3, 35.4, 35.1, 31.8, 28.5, 26.5, 25.8 and 24.5. IR (reflection disc, ν_{max}, cm^{-1}); 3230, 2939, 2855, 1659, 1612, 1461.

Biological Example A

i) *Cloning of the Escherichia coli PDF gene.*

The *E. coli* PDF gene was cloned in pET24a(+) (designated pET24-PDF) and was used to transform BL21 DE3 cells from Novagen Inc, (Madison, Wisconsin). Clones were selected at 37°C on YT agar plates (8g/l typtone, 5g/yeast extract, NaCl 5g/l, agar 15g/l) supplemented with 30μg/ml kanamycin.

ii) *Expression of PDF*

A 20ml overnight culture of BL21 DE3 cells harbouring pET24-PDF was used to infect 500ml 2xYT broth (16g/l typtone, 10g/l yeast extract, NaCl 5g/l) containing 30ug/ml kanamycin in a 2 litre baffled flask and grown at 37°C with shaking to an OD_{600} 0.6. The culture was then induced by adjusting the medium to 1.0mM isopropyl β-D thiogalactopyranoside (IPTG). The induction was allowed to proceed for a further 3 hours at 37°C, the cells were harvested by centrifugation and the cell pellet washed with 250ml phosphate buffered saline (PBS) and the pellet stored at -70°C.

iii) *Preparation of soluble protein fraction.*

The cells from a 1 litre expression were resuspeneded in 2x 25ml of ice cold phosphate buffered saline. The cell suspension was sonicated on ice using an MSE Soniprep 150 fitted with a medium probe and at an amplitude of 20-25 microns in 6x20 second pluses. The resulting suspension was then cleared by centrifugation at 20,000 xg for 15 minutes. The supernatant was then used for further purification of the enzyme.

iv) *PDF Purification*

E. coli lysate from a 1l culture in phosphate buffered saline (PBS) were adjusted to 2M ammonium sulphate. A 15ml phenyl sepharose column was equilibrated with PBS/2M ammonium sulphate at 4°C. The lysate was loaded on the column and washed with equilibration buffer. The column was eluted by reducing the ammonium sulphate concentration from 2M to 0M over 10 column volumes. 5ml fractions were collected and analysed by SDS-PAGE. The fractions containing the majority of the 20kDa PDF were pooled. The pooled fractions were concentrated using a 3kDa cutoff membrane to a volume of 5ml. The fraction was then loaded onto a Superdex 75 (size exclusion chromatography) column equilibrated in PBS. The concentrated PDF pool eluted at one ml/min at 4°C and 5ml fractions collected and analysed by SDS-PAGE. The purest fractions were pooled and stored at -70°C.

(v) *PDF in vitro assay*

The assay was performed in a single 96 well plate in a final volume of 100µl containing:

- 20µl PDF (4µg/ml)
- 20µl 100mM Hepes pH 7.0 + 1M KCl + 0.05% Brij
- 10µl serial dilution of test compound in 20% DMSO
- 50µl formyl-Met-Ala-Ser (8mM)

The assay was incubated at 37°C for 30 minutes. The free amino group of the deformylated (Met-Ala-Ser) product was detected using fluorescamine, by the following additions:

- 50µl 0.2M borate pH 9.5
- 50µl fluorescamine (150µg/ml in dry dioxane)

Fluorescence was quantified on SLT Fluostar plate reader using an excitation wavelength of 390nM and an emission wavelength of 485nM. Standard control reactions are a no inhibitor reaction which provides the zero inhibition figure and a no enzyme and no inhibitor reaction which provides the 100% inhibition figure. The data was analysed by conversion of the fluorescence units to % inhibition and the inhibitor concentration plotted against % inhibition. The data was fitted to a sigmoidal function : $y = A+((B-A)/(1+((C/x)^D)))$, wherein A represents zero inhibition, B represents 100% inhibition and C represents the $IC_{50,}$ D represents the slope. The IC_{50} represents the concentration of inhibitor (nM) required to decrease enzyme activity by 50%.

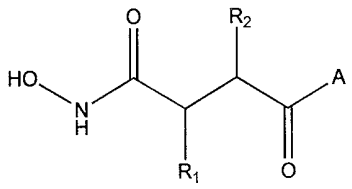
The test compounds were found to inhibit bacterial PDF *in vitro*.

Biological Example B

Minimal inhibitory concentrations (MIC) of the test compounds against *E. coli* strain DH5α (Genotype; F-ϕ80d*lac*ZΔM15Δ(*lac*ZYA-*arg*F)U169 *deo*R *rec*A1 *end*A1 *hsd*R17(r_k^-,m_k^+)*pho*A *sup*E44λ$^-$ *thi*-1 *gyr*A96 *rel*A1) obtained from GibcoBRL Life Technologies, were determined as follows. Stock solutions of test compound were prepared by dissolution of each compound in dimethylsulfoxide at 10mM. For the determination of the minimal inhibitory concentration, two fold serial dilutions were prepared in 2xYT broth (typtone 16g/l, yeast extract 10g/l, sodium chloride 5g/l obtained from BIO 101 Inc, 1070 Joshua Way, Vista, CA92083, USA) to yield 0.05 ml compound-containing medium per well. Inocula were prepared from cultures grown overnight in 2xYT broth at 37°C. Cell densities were adjusted to absorbance at 660nm (A_{660}) = 0.1; the optical density-standardized preparations were diluted 1:1000 in 2xYT broth; and each well inoculated with 0.05ml of the diluted bacteria. Microtiter plates were incubated at 37°C for 18 hours in a humidified incubator. The test compounds had MIC's of 200μM or less against one or both of the test organisms.

Claims

1. The use of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof in the preparation of an antibacterial composition:



(I)

wherein:

R_1 represents hydrogen, or C_1-C_6 alkyl, C_1-C_6 alkyl substituted by one or more halogen atoms, amino, hydroxy, or C_1-C_6 alkoxy;

R_2 represents a group R_{10}-$(X)_n$-$(ALK)_m$- wherein

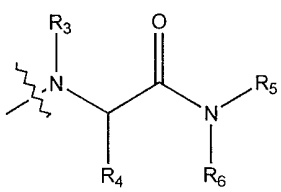
R_{10} represents hydrogen, or a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, aryl, or heterocyclyl group, any of which may be unsubstituted or substituted by $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy, mercapto, $(C_1$-$C_6)$alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, -COOH, $-CONH_2$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein R^A and R^B are independently a $(C_1$-$C_6)$alkyl group, and

ALK represents a straight or branched divalent C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene radical, and may be interrupted by one or more non-adjacent -NH-, -O- or -S- linkages,

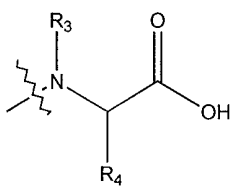
X represents -NH-, -O- or -S-, and

m and n are independently 0 or 1; and

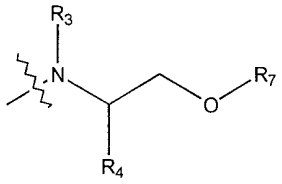
A represents (i) a group of formula (IA), (IB), (IC) or (ID)



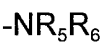
(IA)



(IB)



(IC)



(ID)

wherein:

R_3 represents hydrogen or C_1-C_6 alkyl and R_4 represents the side chain of a natural or non-natural alpha amino acid or R_3 and R_4 when taken together with the nitrogen and carbon atoms to which they are respectively attached form an optionally substituted saturated heterocyclic ring of 5 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring,

R_5 and R_6, independently represent hydrogen, or optionally substituted C_1-C_8 alkyl, cycloalkyl, aryl, aryl(C_1-C_6 alkyl), heterocyclic, or heterocyclic(C_1-C_6 alkyl), or R_5 and R_6 when taken together with the nitrogen atom to which they are attached form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring, and

R_7 represents hydrogen, C_1-C_6 alkyl, or an acyl group.

PROVIDED THAT (a) R_5 and R_6 taken together with the nitrogen atom to which they are attached do not form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms when R_1 and R_3 are hydrogen, R_2 is hydrogen, C_1-C_6 alkyl, phenyl, benzyl, 4-chlorophenylmethyl, 4-nitrophenylmethyl, or 4-aminophenylmethyl and R_3 is hydrogen, methyl, isopropyl, isobutyl or benzyl; and (b) R_5 is not 2-pyridyl or 2-thiazolyl when R_1, R_3 and R_6 are hydrogen, R_2 is n-pentyl and R_4 is isopropyl; and (c) R_5 and R_6 are not both ethyl when R_1 and R_3 are hydrogen, R_2 is n-pentyl and R_4 is methyl or isopropyl.

2. The use as claimed in claim 1 wherein R_1 represents hydrogen, or C_1-C_6 alkyl; R_3 represents hydrogen or C_1-C_6 alkyl; R_4 represents the side chain of a natural or non-natural alpha amino acid; R_5 and R_6, independently represent hydrogen, C_1-C_6 alkyl, or cycloalkyl or R_5 and R_6 taken together with the nitrogen atom to which they are attached form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms; and R_7 represents hydrogen or an acyl group.

3. A method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound of formula (I) as defined in claim 1 or claim 2

4. The use or method as claimed in any of claims 1 to 3 wherein R_1 is hydrogen or methyl.

5. The use or method as claimed in any of claims 1 to 4 wherein R_2 is:

C_1-C_6 alkyl, C_3-C_6 alkenyl or C_3-C_6 alkynyl;

phenyl(C_1-C_6 alkyl)-, phenyl(C_3-C_6 alkenyl)- or phenyl(C_3-C_6 alkynyl)- optionally substituted in the phenyl ring;

cycloalkyl(C_1-C_6 alkyl)-, cycloalkyl(C_3-C_6 alkenyl)- or cycloalkyl(C_3-C_6 alkynyl)- optionally substituted in the phenyl ring;

heterocyclyl(C_1-C_6 alkyl)-, heterocyclyl(C_3-C_6 alkenyl)- or heterocyclyl(C_3-C_6 alkynyl)- optionally substituted in the heterocyclyl ring;

4-phenylphenyl(C_1-C_6 alkyl)-, 4-phenylphenyl(C_3-C_6 alkenyl)-, 4-phenylphenyl(C_3-C_6 alkynyl)- , 4-heteroarylphenyl(C_1-C_6 alkyl)-, 4-heteroarylphenyl(C_3-C_6 alkenyl)-, 4-heteroarylphenyl(C_3-C_6 alkynyl)-,

optionally substituted in the terminal phenyl or heteroaryl ring.

6. The use or method as claimed in claim 4 wherein R_2 is methyl, ethyl, n- and iso-propyl, n- , iso- or tert-butyl, n-pentyl, n-hexyl, 2-ethylsulfanylethyl, 2-methoxyethyl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, 3-(4-pyridylphenyl)propyl-, 3-(4-(4-pyridyl)phenyl)prop-2-yn-1-yl, 3-(4-phenylphenyl)propyl-, 3-(4-phenyl)phenyl)prop-2-yn-1-yl, 3-[(4-chlorophenyl)phenyl]propyl- or 1,3-dioxo-1,3-dihydro-isoindoyl-2-ylbutyl

7. The use or method as claimed in claim 4 wherein R_2 is n-butyl, benzyl or cyclopentylmethyl.

8. The use or method as claimed in any of claims 1 to 7 wherein R_3 is hydrogen or methyl.

9. The use or method as claimed in any of claims 1 to 8 wherein R_4 is:

C_1-C_6 alkyl, phenyl, 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-benzyloxybenzyl, 2,- 3-, or 4-C_1-C_6 alkoxybenzyl, or benzyloxy(C_1-C_6alkyl)-group; or

a group -$[Alk]_nR_9$ where Alk is a (C_1-C_6)alkyl or (C_2-C_6)alkenyl group optionally interrupted by one or more -O-, or -S- atoms or -$N(R_{12})$- groups [where R_{12} is a hydrogen atom or a (C_1-C_6)alkyl group], n is 0 or 1, and R_9 is an optionally substituted cycloalkyl or cycloalkenyl group; or

a benzyl group substituted in the phenyl ring by a group of formula -OCH_2COR_8 where R_8 is hydroxyl, amino, (C_1-C_6)alkoxy, phenyl(C_1-C_6)alkoxy,

(C_1-C_6)alkylamino, di((C_1-C_6)alkyl)amino, phenyl(C_1-C_6)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(C_1-C_6)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C_1-C_6)alkoxy, cyano, (C_1-C_6)alkanoyl, trifluoromethyl (C_1-C_6)alkyl, hydroxy, formyl, amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, mercapto, (C_1-C_6)alkylthio, hydroxy(C_1-C_6)alkyl, mercapto(C_1-C_6)alkyl or (C_1-C_6)alkylphenylmethyl; or

a group $-CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, and R_a and R_b 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

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or a group as defined for R_c below other

than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, -CO_2H, (C_1-C_4)perfluoroalkyl, -CH_2OH, -CO_2(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -O(C_2-C_6)alkenyl, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, -SO_2(C_1-C_6) alkyl, -S(C_2-C_6)alkenyl, -SO(C_2-C_6)alkenyl, -SO_2(C_2-C_6)alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO_2- and W represents a phenyl, phenylalkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkylalkyl, (C_4-C_8)cycloalkenyl, (C_4-C_8)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO_2H, -CO_2(C_1-C_6)alkyl, -$CONH_2$, -CONH(C_1-C_6)alkyl, -CONH(C_1-C_6alkyl)$_2$, -CHO, -CH_2OH, (C_1-C_4)perfluoroalkyl, -O(C_1-C_6)alkyl, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -NO_2, -NH_2, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NHCO(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, phenyl or benzyl.

10. The use or method as claimed in claim 8 wherein R_4 is phenyl, tert-butyl, iso-butyl, benzyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, or 1-mercapto-1-methylethyl.

11. The use or method as claimed in claim 8 wherein R_4 is tert-butyl.

12. The use or method as claimed in any of claims 1 to 11 wherein R_5 and R_6 are independently hydrogen methyl, ethyl or cyclohexyl..

13. The use or method as claimed in claim 11 wherein R_5 and R_6 when taken together with the nitrogen atom to which they are attached form a saturated 5- to 8-membered monocyclic N-heterocyclic ring which is attached via the N atom and which optionally contains NR_{11} wherein R_{11} is hydrogen, C_1-C_6 alkyl, benzyl, acyl, or

an amino protecting group, O, S, SO or SO_2 as a ring member, and/or is optionally substituted on one or more C atoms by hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, oxo, ketalised oxo, amino, mono(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, carboxy, C_1-C_6 alkoxycarbonyl, hydroxymethyl, C_1-C_6 alkoxymethyl, carbamoyl, mono(C_1-C_6 alkyl)carbamoyl, di(C_1-C_6 alkyl)carbamoyl, or hydroxyimino.

14. The use or method as claimed in claim 11 wherein R_5 and R_6 when taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted 1-pyrrolidinyl, piperidin-1-yl, 1-piperazinyl, hexahydro-1-pyridazinyl, morpholin-4-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl 1-oxide, tetrahydro-1,4-thiazin-4-yl 1,1-dioxide, thiazolidin-3-yl, hexahydroazipino, or octahydroazocino ring.

15. The use or method as claimed in claim 11 wherein R_5 and R_6 when taken together with the nitrogen atom to which they are attached form a 2-(methylcarbamoyl)-1-pyrrolidinyl, 2-(hydroxymethyl)-1-pyrrolidinyl, 4-hydroxypiperidino, 2-(methylcarbamoyl)piperidino, 4-hydroxyiminopiperidino, 4-methoxypiperidino, 4-methyl-1-piperazinyl, 4-phenyl-1-piperazinyl, 1,4-dioxa-8-azaspiro[4,5]decan-8-yl, hexahydro-3-(methylcarbamoyl)-2-pyridazinyl, hexahydro-1-(benzyloxycarbonyl)-2-pyridazinyl, 5,5-dimethyl-4-methylcarbamoyl-thiazolidin-3-yl, or 5,5-dimethyl-4-propylcarbamoyl-thiazolidin-3-yl ring.

16. The use or method as claimed in any of claims 1 to 10 wherein R_7 is hydrogen, or a group $R_{20}C(O)$- where R_{20} is a (C_1-C_6)alkyl group.

17. The use or method as claimed in claim 16 wherein R_7 is a group $R_{20}C(O)$- where R_{20} is methyl or ethyl.

18. The use or method as claimed in claim 16 wherein the compound is N^1-(1S-dimethylcarbamoyl-2,2-dimethyl-1-propyl)-N^4-hydroxy-2R-butyl-succinamide or a pharmaceutically acceptable salt, hydrate or solvate thereof.

INTERNATIONAL SEARCH REPORT

Inter >nal Application No
PCT/GB 99/01541

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/165 A61K31/16 A61K31/22 A61K31/44 A61K31/425 A61K31/445

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 24474 A (NIELSEN JOHN ROEMER ;BRUENNER NILS (DK); STEPHENS ROSS (DK); DANOE) 11 June 1998 (1998-06-11) abstract page 1, line 1 - line 11 page 4, line 13 - line 25 page 11, line 35 -page 12, line 14 page 14, line 3 - line 11 page 24, line 19 - line 35 page 28, line 6 - line 12; claims 1,4,6,28,30,32,33,50 ---	1-6,8,9, 12
X	WO 94 10990 A (GALLOWAY WILLIAM ALAN ;BRITISH BIO TECHNOLOGY (GB); CRIMMIN MICHAE) 26 May 1994 (1994-05-26) whole document, in particular page 14 paragraph 1- paragraph 2 --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 1999	03/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 33165 A (BRITISH BIOTECH PHARM ;BECKETT RAYMOND PAUL (GB); MILLER ANDREW (G) 24 October 1996 (1996-10-24) abstract page 3, last paragraph -page 4, paragraph 1; claims; examples ---	1-15
X	WO 95 06031 A (IMMUNEX CORP) 2 March 1995 (1995-03-02) abstract page 2, last paragraph -page 4, line 15; claims; examples ---	1-6,8-11
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US SATO, TSUTOMU ET AL: "Manufacture of antibiotic YL 01869P with Streptomyces as collagenase inhibitor, antibacterial, and antitumor agent" retrieved from STN Database accession no. 115:239709 HCA XP002119639 abstract & JP 03 157372 A (YAMANOUCHI PHARMACEUTICAL CO., LTD., JAPAN) 5 July 1991 (1991-07-05) ---	1-6
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US AMANO, SHOICHI ET AL: "Antibiotic SF2197C manufacture with Actinomadura" retrieved from STN Database accession no. 115:230518 HCA XP002119640 abstract & JP 03 053891 A (MEIJI SEIKA KAISHA, LTD., JAPAN) 7 March 1991 (1991-03-07) ---	1-6
X	TANZAWA, KAZUHIKO ET AL: "Matlystatins, new inhibitors of type IV collagenases from Actinomadura atramentaria. II. Biological activities" J. ANTIBIOT. (1992), 45(11), 1733-7 , XP002119635 whole document, in particular Table 1 ---	1-6
X	US 5 532 265 A (GIJBELS KOENRAAD ET AL) 2 July 1996 (1996-07-02) abstract column 2, line 60 - line 65 column 5, line 4 - line 6; claims; examples --- -/--	1-6,8,9, 12

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 99/01541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	COTTER C.S. ET AL: "Inhibition of proteases in Pseudomonas otitis media in chinchillas." OTOLARYNGOLOGY - HEAD AND NECK SURGERY, (1996) 115/4 (342-351). , XP002119636 the whole document	1-6,8,9, 12
X	WO 92 22523 A (RES CORP TECHNOLOGIES INC) 23 December 1992 (1992-12-23) abstract page 2, line 19 - line 33; claims 1-96,102,103,105; examples	1-6, 8-10,12
A	"Antibiotic Actinonin. I to VIII" J. CHEM. SOC., PERKIN TRANS. 1, vol. 9, 1975, pages 819-860, XP002119637 the whole document	1-18
A	GALARDY R.E.: "Galardin(TM). Antiinflammatory protease inhibitor." DRUGS OF THE FUTURE, (1993) 18/12 (1109-1111). , XP002119638 the whole document	1-18
A	GB 1 028 921 A (RANJEET BHAGWAN SINGH ET AL.) 11 May 1966 (1966-05-11) the whole document	1-18

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01541

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. [X] Claims Nos.: 3-18
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 3-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] 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:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-17 relate to the use of an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds mentioned in the examples, closely related compounds and to the general idea underlying the application.

Claim searched completely: 18
Claims seached incompletely: 1-17

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 99/01541

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9824474 A	11-06-1998	AU 5187698 A	29-06-1998
		EP 0942746 A	22-09-1999
WO 9410990 A	26-05-1994	AT 150300 T	15-04-1997
		AU 5430194 A	08-06-1994
		DE 69309094 D	24-04-1997
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		EP 0667770 A	23-08-1995
		ES 2101358 T	01-07-1997
		JP 8505605 T	18-06-1996
		US 5691382 A	25-11-1997
WO 9633165 A	24-10-1996	AU 5343696 A	07-11-1996
		EP 0821666 A	04-02-1998
		EP 0821668 A	04-02-1998
		WO 9633161 A	24-10-1996
		JP 11503746 T	30-03-1999
		JP 11503748 T	30-03-1999
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