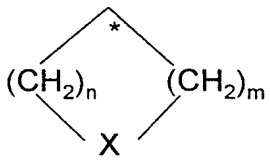
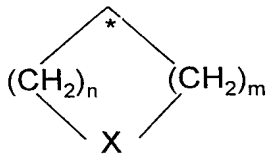


wherein the carbon atom bearing the asterisk is the carbon to which R^3 and R^4 are atttached, "n" and "m" are independently selected from the integers one and two, and X is CF_2, O, SO_2 or NR^9, wherein R^9 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, (C_1-C_6)alkyl(C=O)-, (C_1-C_6)alkoxy(C=O)-, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryloxy(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)- or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-; wherein each of said (C_6-C_{10})aryl, (C_2-C_9)heteroaryl or (C_3-C_6)cycloalkyl moieties of said (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-, (C_3-C_6)cycloalkyl, or benzo-fused(C_3-C_6)cycloalkyl ring may be optionally substituted on any ring atom capable of forming an additional bond by a substituent (preferably one to three substituents per ring) independently selected from the group consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

or when R^3 and R^4 are taken together with the carbon atom to which they are attached to form a group of the formula



then any of the carbon atoms of said ring, capable of forming an additional bond, may be optionally substituted by a substituent (preferably zero to three substituents) independently selected from the group consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

R^5 is R^6O or R^6R^7N wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_2-C_9)heteroaryl(C_1-C_6)alkyl; wherein each of said (C_6-C_{10})aryl and (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_2-C_9)heteroaryl(C_1-C_6)alkyl groups may be optionally substituted by one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

or R^6 and R^7 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocycle selected from piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl or azetidinyl; wherein each of said piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl or azetidinyl may be optionally substituted on any ring carbon atom capable of forming an additional bond with a substituent (preferably one to three substituents per ring) independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, or perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

R^8 is piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl, azetidinyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_2-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_2-C_9)heteroaryl(C_1-C_6)alkylpiperidyl, (C_1-C_6)alkyl(C=O)-piperidyl, (C_1-C_6)alkoxy(C=O)-piperidyl, (C_6-C_{10})aryl(C=O)-piperidyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperidyl, or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperidyl; wherein each of said piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl, azetidinyl,

piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_2-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_2-C_9)heteroaryl(C_1-C_6)alkylpiperidyl (C_1-C_6)alkyl(C=O)-piperidyl, (C_1-C_6)alkoxy(C=O)-piperidyl, (C_6-C_{10})aryl(C=O)-piperidyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperidyl, and (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperidyl may be optionally substituted on any ring carbon atom capable of forming an additional bond with a substituent (preferably one to three substituents per ring) independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, or perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

Q is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl wherein each (C_6-C_{10})aryl or (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents (preferably one to three substituents) independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

with the proviso that if either R^3 or R^4 is hydrogen, or if both R^3 and R^4 are hydrogen, then R^1 and R^2 can not both be hydrogen or R^1 must be hydroxy, (C_1-C_6)alkoxy, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl,

$(C_6$-$C_{10})$aryl(C=O)O-$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryloxy(C=O)O- $(C_6$-$C_{10})$arylalkyl(C=O)O-$(C_1$-$C_6)$alkyl or $(C_6$-$C_{10})$arylalkoxy(C=O)O-$(C_1$-$C_6)$alkyl;

or a pharmaceutically acceptable salt thereof.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), trimethyl-ammonium or diethylammonium, and the lower alkanolammonium salts such tris-(hydroxymethyl)-methylammonium and other base salts of pharmaceutically acceptable organic amines.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl.

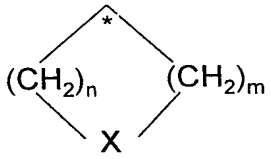
The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkoxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

The compound of formula I may have chiral centers and therefore exist in different diasteriomeric or enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferred compounds of formula I include those wherein R^1 is OH and R^2 is hydrogen.

Other preferred compounds of formula I include those wherein both R^3 and R^4 are $(C_1\text{-}C_6)$alkyl or R^3 and R^4 are taken together to form an optionally substituted $(C_3\text{-}C_6)$cycloalkyl ring or a benzo-fused$(C_3\text{-}C_6)$cycloalkyl ring or a group of the formula



wherein the carbon atom bearing the asterisk is the carbon to which R^3 and R^4 are atttached, "n" and "m" are independently selected from the integers one and two, and X is CF_2, O, SO_2 or NR^9, wherein R^9 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroalkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_1\text{-}C_6)$alkyl(C=O)-, $(C_1\text{-}C_6)$alkoxy(C=O)-, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)-, or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)-; wherein each of said $(C_6\text{-}C_{10})$aryl and $(C_2\text{-}C_9)$heteroaryl moieties of said $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroalkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)-, and $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)- groups may be optionally independently substituted with one or more substituents (preferably one to three substituents) independently selected from the group consisting of fluoro, chloro, bromo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, perfluoro$(C_1\text{-}C_3)$alkyl, perfluoro$(C_1\text{-}C_3)$alkoxy and $(C_6\text{-}C_{10})$aryloxy.

More preferred compounds of formula I include those wherein R^3 and R^4 are taken together to form an optionally substituted $(C_3\text{-}C_6)$cycloalkyl ring.

Other preferred compounds of formula I include those wherein R^1 is hydroxy.

Other preferred compounds of formula I include those wherein Q is $(C_6\text{-}C_{10})$aryl or $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, wherein each $(C_6\text{-}C_{10})$aryl moieties of said is $(C_6\text{-}C_{10})$aryl or $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl groups may be optionally substituted with one or more substituents

independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

More preferred compounds of formula I include those wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl, more preferably the substituents are selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl, most preferably the substituent is in the 4-position.

Specific preferred compounds of formula I include the following:

(2S)-2,N-dihydroxy-3-(4-methoxybenzenesulfonyl)propionamide,

3-[4-(4-fluorophenoxy)phenylsulfonyl]-2,N-dihydroxypropionamide,

2,N-dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclobutyl]acetamide.

2,N-dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclopentyl]acetamide,

2-[1-(4-cyclobutoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide,

2-[1-(4-butoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide,

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclobutyl}-2,N-dihydroxyacetamide, or

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclopentyl}-2,N-dihydroxyacetamide.

Other specific compounds of formula I include the following:

2,N-dihydroxy-2-[1-(4-phenoxybenzenesulfonyl)cyclopentyl]acetamide,

2,N-dihydroxy-2-[1-(4-phenoxybenzenesulfonyl)cyclobutyl]acetamide,

acetic acid {1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclopentyl}hydroxycarbamoyl methyl ester,

acetic acid {1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclobutyl}hydroxycarbamoyl methyl ester,

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclopentyl}-N-hydroxy-2-methoxy-acetamide,

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclobutyl}-N-hydroxy-2-methoxyacetamide,

2-[1-(4-butoxybenzenesulfonyl)cyclohexyl]-2,N-dihydroxyacetamide,

2-[1-(4-butoxybenzenesulfonyl)cyclopentyl]-2,N-dihydroxyacetamide, or

2-[1-(4-butoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, osteoporosis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic

shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

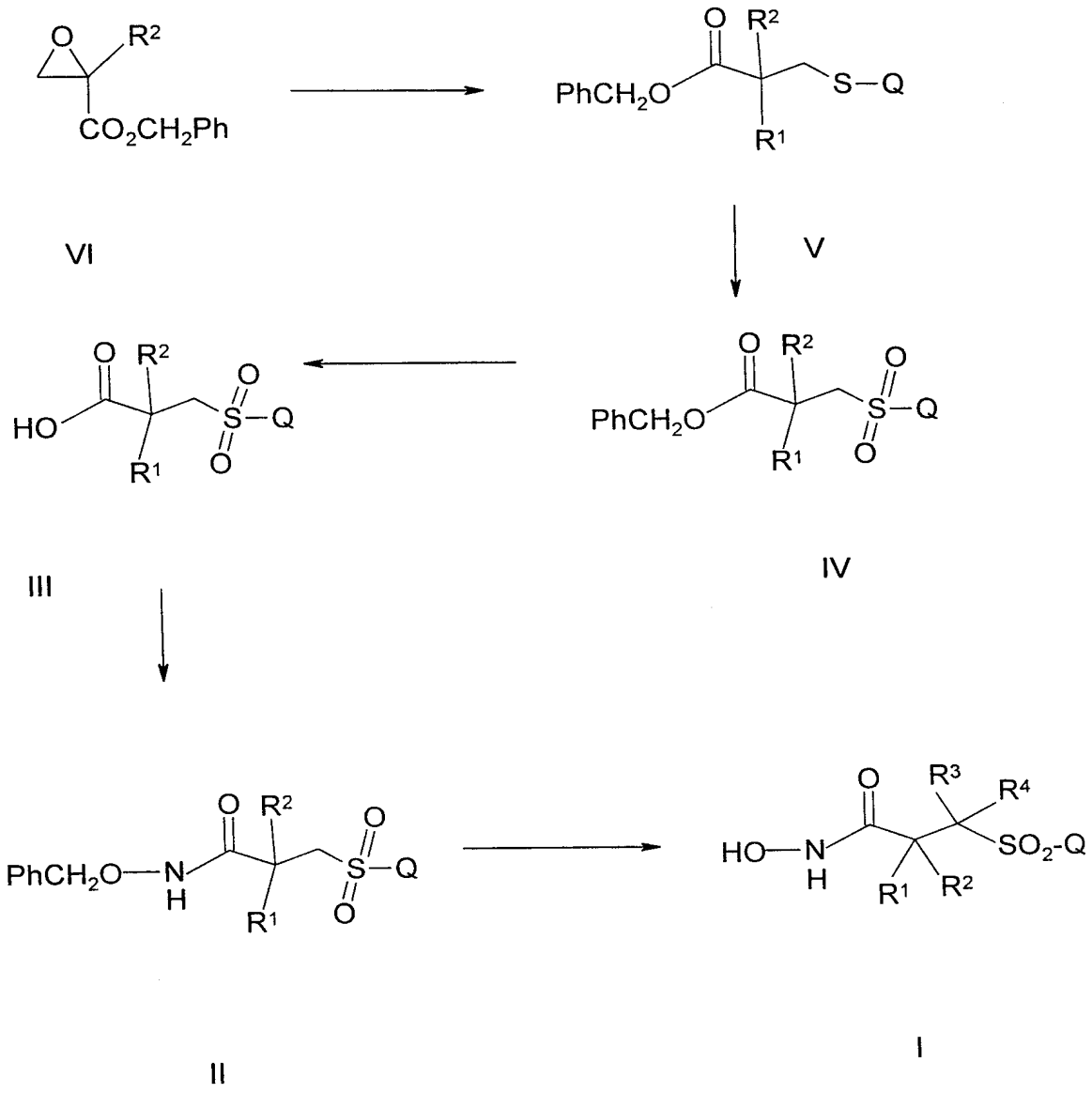
The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, osteoporosis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

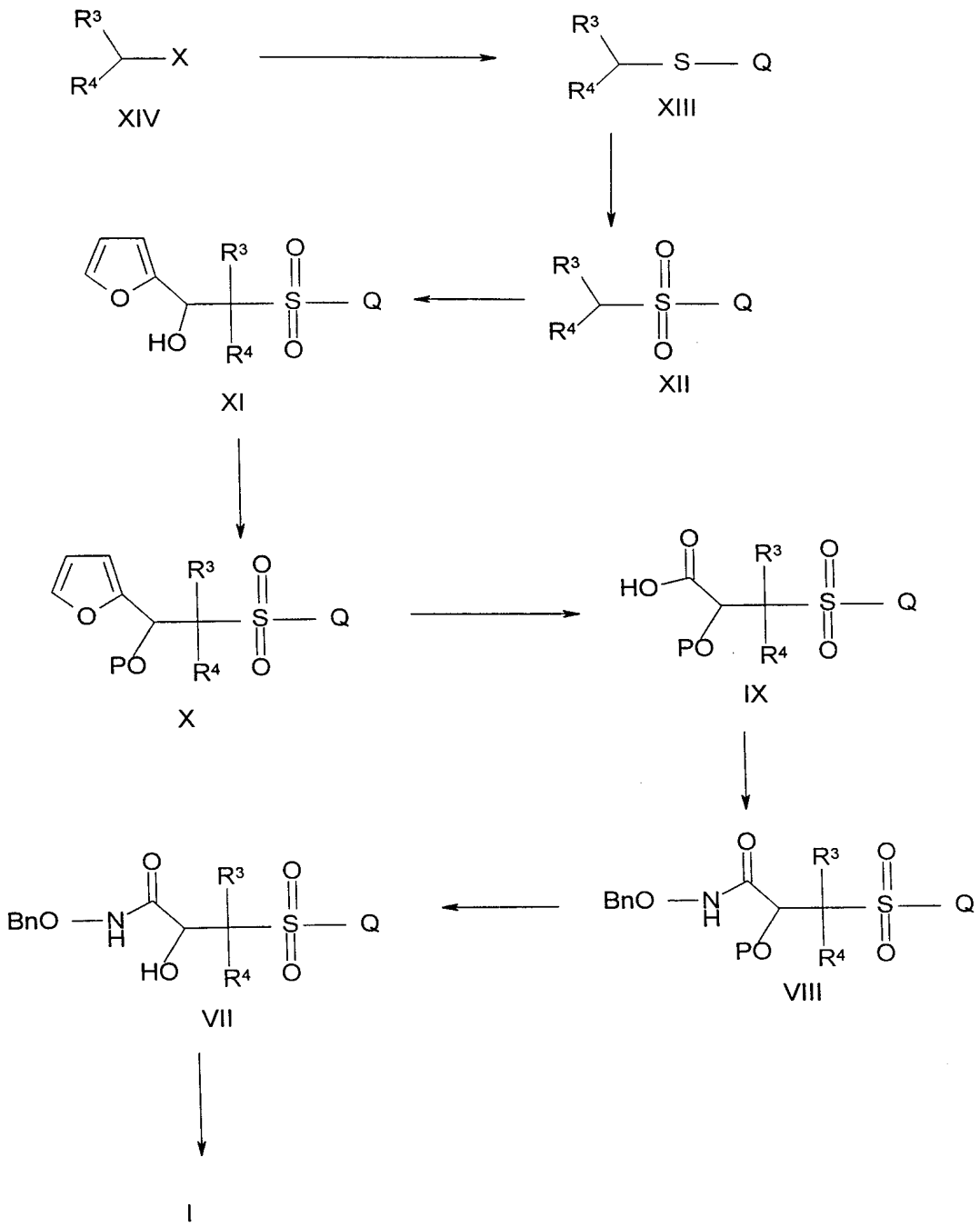
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated n, m, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, Q and X in the reaction Schemes and the discussion that follow are defined as above.

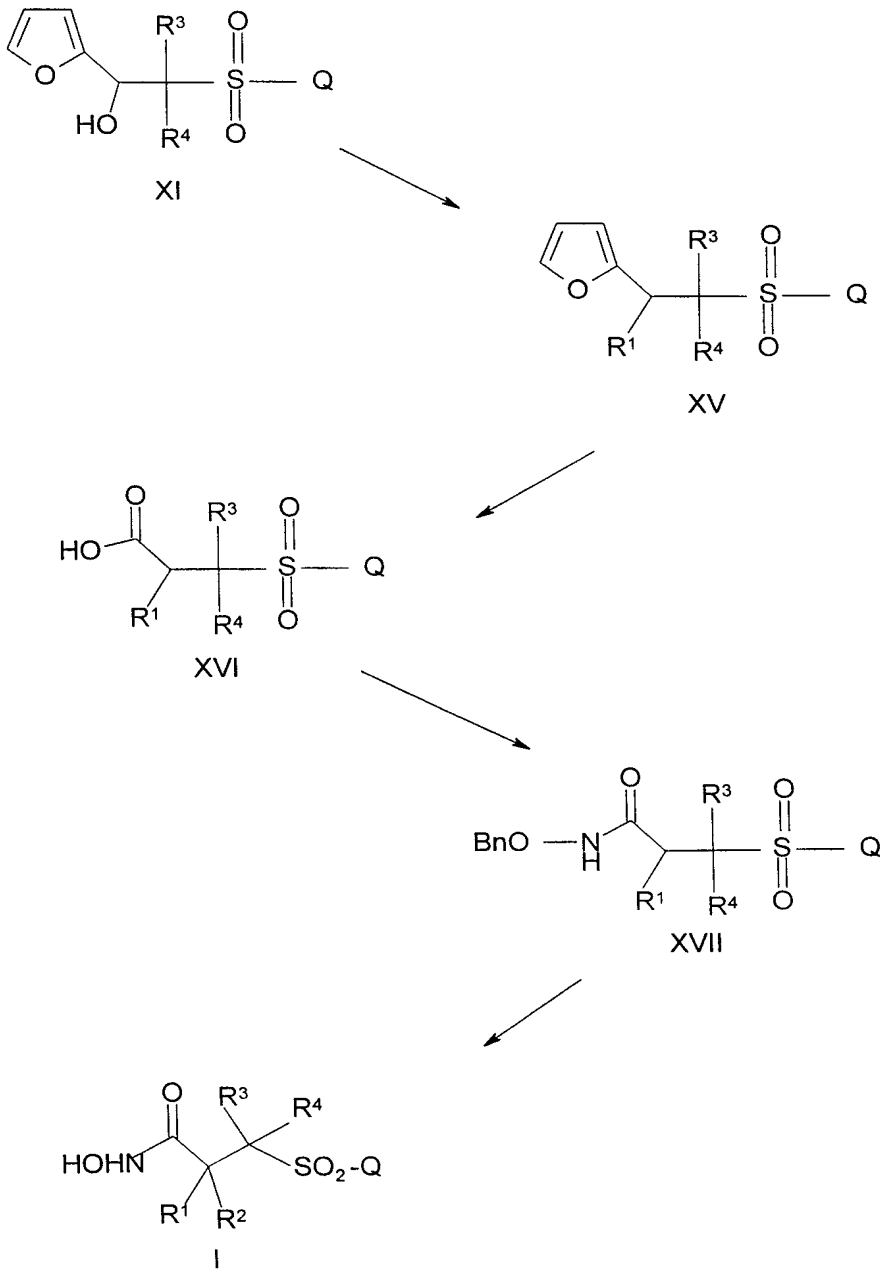
SCHEME 1



SCHEME 2



SCHEME 3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S
Q
HO
R4
O
XI
R3
O
S
Q
O
R1
R4
XV
O
HO
R3
O
S
Q
R1
R4
XVI
O
R3
O
BnO
N
H
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R3
R4
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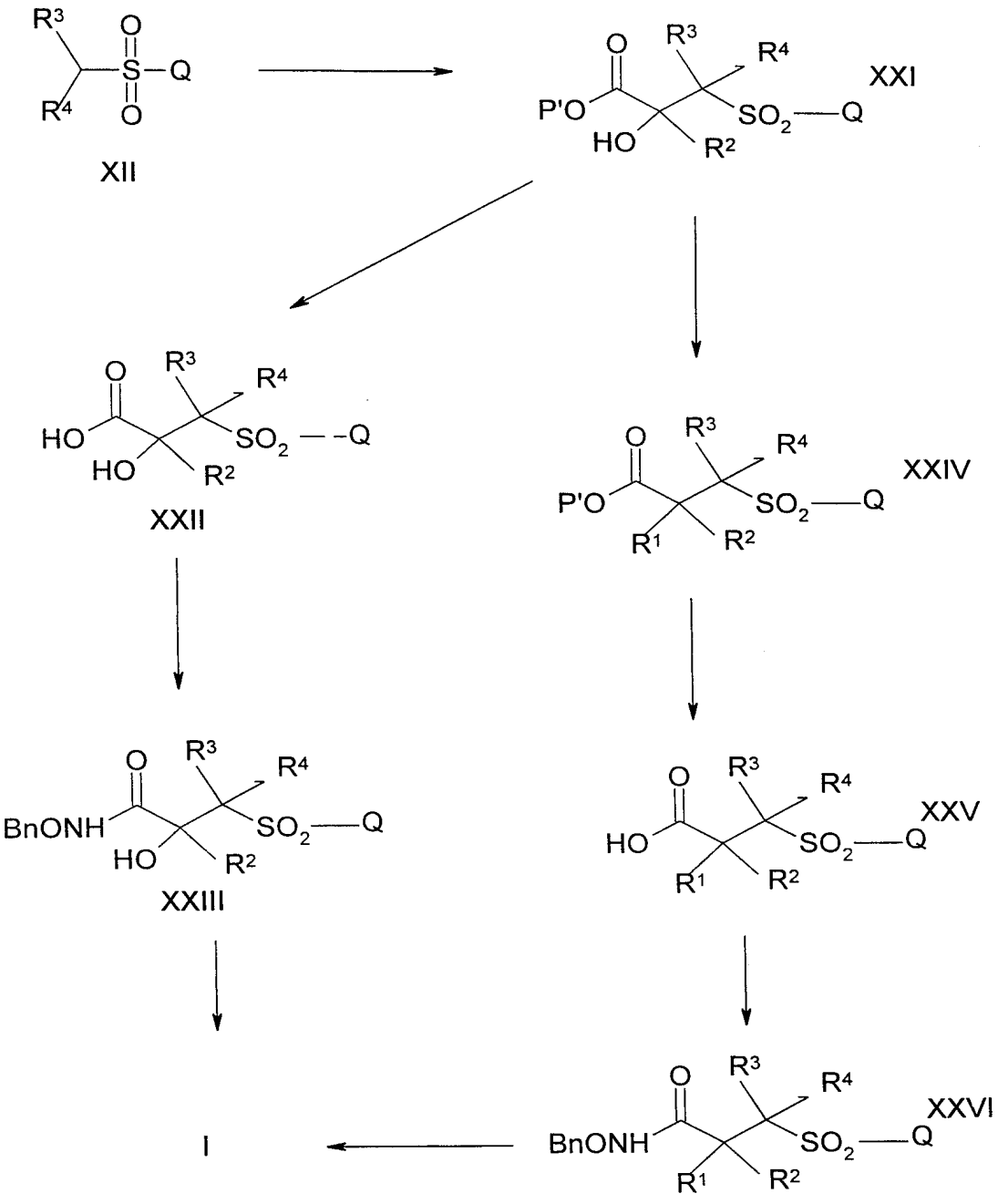
R1
R2
I

SCHEME 4



Scheme 1 refers to the preparation of compounds of the formula I, wherein R^3 and R^4 are hydrogen. Referring to Scheme I, a compound of the formula I is prepared from a compound of the formula II by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include 5% palladium on barium sulfate or 5% palladium on carbon, preferably 5% palladium on barium sulfate. Suitable solvents include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours.

The compound of formula II is prepared from a compound of formula III by reaction with O-benzylhydroxylamine hydrochloride, an activating agent, and a base in a reaction inert solvent. Suitable activating agents include (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate or 1-(3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, preferably (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate. Suitable bases include tertiary amines such as triethylamine, diisopropylethylamine or 4-N,N-dimethylaminopyridine, preferably triethylamine. The temperature of the aforesaid reaction may range from about 0°C to about 60°C, preferably about 20°C (room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, or ethers such as THF or diethyl ether, preferably the solvent is methylene chloride. The reaction is complete in about 4 hours to about 48 hours, preferably about 16 hours.

The compound of formula III is prepared from a compound of formula IV by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include palladium or 5-10% palladium on activated charcoal, preferably 10% palladium on activated charcoal. Suitable solvents include acetic acid, alcohols such as ethanol, methanol, or isopropanol, preferably ethanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 24 hours, preferably about 3 hours.

Compounds of the formula IV can be prepared from compounds of the formula V by reaction with an oxidant in a reaction inert solvent. Suitable oxidants include meta-

chloroperbenzoic acid, hydrogen peroxide or sodium perborate, preferably meta-chloroperbenzoic acid. Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. Suitable temperatures for the aforesaid reaction range from about 0°C to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 24 hours, preferably about 3 hours.

Compounds of the formula V, wherein R^1 is hydroxy, can be prepared from compounds of the formula VI by reaction with a Grignard reagent and a thiol of the formula QSH in a reaction inert solvent. Suitable Grignard reagents include ethyl magnesium bromide or phenyl magnesium bromide, preferably ethyl magnesium bromide. Suitable solvents include ethers such as diethyl ether, tetrahydrofuran or 1,2-dimethoxyethane, preferably the solvent is a mixture of tetrahydrofuran and diethyl ether. Suitable temperatures for the aforesaid reaction are from about -78°C to about 50°C , preferably from about 0°C to about 25°C (i.e. room temperature). The reaction is complete in about 1 to about 24 hours, preferably about 3 hours.

Compounds of the formula V, wherein R^1 is $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy or $(C_1\text{-}C_6)$alkoxy, can be prepared from compounds of the formula V, wherein R^1 is hydroxy, by reaction with a compound of the formula $R^{1a}L$, wherein L is a leaving group and R^{1a} is $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkyl, in the presence of a strong base in an aprotic polar solvent. Suitable leaving groups include chloro, fluoro, bromo, mesylate, triflate or tosylate. Preferably, the leaving group is iodo. Suitable bases include sodium hydride, lithium dialkyl amides such as lithium N-isopropyl-N-cyclohexylamide or lithium diisopropyl amide, potassium t-butoxide, sodium amide, or potassium hydride, preferably sodium hydride. Suitable solvents include ethers (such as THF, diethyl ether or 1,2-dimethoxyethane), preferably THF. The aforesaid reaction is conducted at about -78°C to about 0°C, preferably at about 0°C.

Compounds of the formula V, wherein R^1 is $(C_1\text{-}C_6)$alkyl(C=O)O-, $(C_1\text{-}C_6)$alkoxy-(C=O)O-, $(C_6\text{-}C_{10})$aryl(C=O)O-, $(C_6\text{-}C_{10})$aryloxy(C=O)O-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)O- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)O-, can be prepared from compounds of the formula V, wherein R^1 is hydroxy, by reaction with a compound of the formula $R^{1b}L$, wherein L is a leaving group and R^{1b} is $(C_1\text{-}C_6)$alkyl(C=O)-, $(C_1\text{-}C_6)$alkoxy(C=O)-, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryloxy(C=0)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)-, in the presence of a base in a reaction inert solvent. Suitable leaving groups include chloro, fluoro, bromo, or $R^{1b}O$ (i.e. an anhydride). Preferably, the leaving group is chloro. Suitable bases include tertiary amine bases such as triethylamine, pyridine or 4-dimethylaminopyridine, preferably triethylamine. The temperature of the aforesaid reaction is from about 0°C to about 30°C, preferably from

about 20°C to about 25°C (i.e. room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. The reaction is conducted from about 1 hour to about 24 hours, preferably for about 2 hours.

Compounds of the formula VI can be prepared by methods well known to those of ordinary skill in the art. Compounds of the formula VI can also be prepared by peracid oxidation (e.g., meta-chloroperbenzoic acid) of the corresponding α,β-unsaturated benzyl esters as described in Jerry March, Advanced Organic Chemistry, 735 (3rd ed., 1985). The corresponding α,β-unsaturated benzyl esters may be prepared by Knovenagel condensation between a malonate monobenzyl ester and paraformaldehyde in the presence of piperidine as described in H.O. House, Modern Synthetic Reactions, 649-651 (2nd ed., W.A. Benjamin, Menlo Park, California, 1972).

Compounds of the formula VI, wherein R^2 is hydrogen, can also be prepared in racemic or enantiomerically pure form by conversion of L-, D-, or D,L-serine as reported by W. Roush and B. Brown, J. Org. Chem., 47, 3387 (1992).

Scheme 2 refers to the preparation of compounds of the formula I, wherein R^2 is hydrogen and R^1 is OH. Referring to Scheme 2, compounds of formula I can be prepared from compounds of the formula VII by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include 5% palladium on barium sulfate or 5% palladium on carbon, preferably 5% palladium on barium sulfate. Suitable solvents include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours.

Compounds of the formula VII can be prepared from compounds of the formula VIII by reaction with an alkali metal hydroxide in a polar solvent. Suitable alkali metal hydroxides include lithium hydroxide, sodium hydroxide or potassium hydroxide, preferably lithium hydroxide, most preferably about 5 equivalents of the alkali metal hydroxide. The aforesaid reaction may conducted at a temperature from about 0°C to about 60°C, preferably from about 20°C to about 25°C (i.e. room temperature). Suitable solvents include a mixture of water and an alcohol such as methanol or ethanol and, optionally an water miscible ether such as tetrahydrofuran or 1,2-dimethoxyethane. Preferably, the solvent system is methanol/water/tetrahydrofuran. The reaction is conducted from about 1 to about 72 hours, preferably about 24 hours.

The compound of formula VIII is prepared from a compound of the formula IX by reaction with O-benzylhydroxylamine hydrochloride in the presence of a catalyst and a base in a reaction inert solvent. Suitable catalysts include (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate or 1-(3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, preferably (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate. Suitable bases include tertiary amines such as triethylamine. diisopropylethylamine or dimethylaminopyridine, preferably triethylamine. The aforesaid reaction temperature is from about 0° C to about 60°C, preferably from about 20° C to about 25°C (i.e. room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. The reaction is conducted from about 4 hours to about 48 hours, preferably about 16 hours.

The compound of formula IX is prepared from a compound of the formula X by reaction with an excess of sodium periodate in the presence of catalytic ruthenium trichloride hydrate. The aforesaid reaction is conducted at a temperature from about 0°C to about 35°C, preferably from about 20°C to about 25°C (i.e. room temperature). Suitable solvents include acetone or a mixture of acetonitrile, carbon tetrachloride and water, preferably a 1:1:2 mixture of acetonitile, carbon tetrachloride and water. The reaction is conducted from about 0.5 to about 2 hours, preferably about 1.25 hours.

The compound of the formula X, wherein "P" is pivaloyl, acetyl or benzoyl, is prepared by reaction of a compound of the formula XI with a protecting group reagent in the presence of a base in a reaction inert solvent. Suitable protecting group reagents include pivaloyl chloride, pivaloic anhydride, acetyl chloride, acetic anhydride, benzoyl cloride or benzoic anhydride, preferably acetic anhydride. Suitable bases include tertiary amine bases such as pyridine or 4-N,N-dimethylaminopyridine, preferably 4-N, N-dimethylaminopyridine. The temperature of the aforesaid reaction is from about 0°C to about 30°C, preferably from about 20°C to about 25°C (i.e. room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. The reaction is conducted from about 1 hour to about 24 hours, preferably for about 2 hours.

The compound of formula XI is prepared from a compound of the formula XII by reaction with 2-furaldehyde and a strong base in a polar aprotic solvent. Suitable bases include potassium-tert.-butoxide, lithium diisopropylamide, and butyl lithium, preferably 2.5 M n-butyllithium in hexane. The temperature of the aforesaid reaction is from about -78°C to about 0°C, preferably about -78°C. Suitable solvents include diethyl ether, tetrahydrofuran, or 1,2-dimethoxyethane, preferably the solvent is tetrahydrofuran. The reaction is conducted from about 0.25 hours to about 6 hours, preferably about 0.33 hours.

The compound of formula XII is prepared from a compound of the formula XIII by reaction with an oxidant in a reaction inert solvent. Suitable oxidants include meta-chloroperbenzoic acid, hydrogen peroxide or sodium perborate, preferably meta-chloroperbenzoic acid. Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. Suitable temperatures for the aforesaid reaction range from about 0°C to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 24 hours, preferably about 3 hours.

The compound of the formula XIII is prepared from a compound of the formula XIV by reaction with a thiol of the formula QSH in the presence of a base in an aprotic solvent. Suitable bases include sodium hydride, ethyl magnesium bromide, lithium diisopropyl amide, potassium hydride, or sodium methoxide, preferably sodium hydride. The temperature of the aforesaid reaction is from about 0°C to about 60°C, preferably 20°C to about 25°C (i.e. room temperature). Suitable solvents include aprotic solvents such as methylene chloride, tetrahydrofuran or N,N-dimethylformamide, preferably N,N-dimethylformamide. The reaction is conducted for about 1 hour to about 48 hours, preferably about 16 hours.

Compounds of the formula XIV and QSH are commercially available or can be made by methods well known to those of ordinary skill in the art. Compounds of the formula QSH can also be prepared by reaction of an alkyl or aryl halide with sodium sulfhydride as described in Jerry March, Advanced Organic Chemistry, 360 and 589 (3rd ed., 1985). Alternatively, compounds of the formula QSH can also be prepared by reaction of an aryl diazonium salt with sodium sulfhydride as described in March id. at 601. Alternatively, compounds of the formula QSH can also be prepared by reaction of a Grignard reagent with sulfur as described in March id. at 550. Alternatively, compounds of the formula QSH can also be prepared by reduction of a sulfonyl chloride, sulfonic acid or disulfide as described in March id. at 1107 and 1110.

Scheme 3 refers to the preparation of compounds of the formula I, wherein R^1 is other than hydroxy and R^2 is hydrogen.

Referring to Scheme 3, compounds of the formula I are prepared from compounds of the formula XVII by hydrogenolysis according to methods analogous to the methods described for converting compounds of formula VII to compounds of formula I in Scheme 2.

Compounds of the formula XVII are prepared from compounds of the formula XVI by reaction with O-benzylhydroxylamine hydrochloride in the presence of a catalyst and a base in a reaction inert solvent according to methods analogous to the conversion of compounds of the formula IX to formula VIII as described above in Scheme 2.

Compounds of the formula XVI are prepared from compounds of the formula XV by reaction with an excess of sodium periodate in the presence of a catalyst according to methods analogous to those used for the conversion of compounds of the formula X to formula IX as described above in Scheme 2.

Compounds of the formula XV, wherein R^1 is $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy or $(C_1\text{-}C_6)$alkoxy, can be prepared from compounds of the formula XI by reaction with a compound of the formula $R^{1a}L$, wherein L is a leaving group and R^{1a} is $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkyl, in the presence of a strong base in an aprotic polar solvent. Suitable leaving groups include chloro, fluoro, bromo, mesylate, triflate or tosylate. Preferably, the leaving group is iodo. Suitable bases include lithium dialkyl amides such as lithium N-isopropyl-N-cyclohexylamide or lithium diisopropyl amide, potassium t-butoxide, sodium amide, potassium hydride or sodium hydride, preferably sodium hydride. Suitable solvents include ethers (such as THF, diethyl ether or 1,2-dimethoxyethane), preferably THF. The aforesaid reaction is conducted at about -78°C to about 0°C, preferably at about 0°C.

Compounds of the formula XV, wherein R^1 is $(C_1\text{-}C_6)$alkyl(C=O)O-, $(C_1\text{-}C_6)$alkoxy(C=O)O-, $(C_6\text{-}C_{10})$aryl(C=O)O-, $(C_6\text{-}C_{10})$aryloxy(C=O)O-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)O- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)O-, can be prepared from compounds of the formula XI by reaction with a compound of the formula $R^{1b}L$, wherein L is a leaving group and R^{1b} is $(C_1\text{-}C_6)$alkyl(C=O)-, $(C_1\text{-}C_6)$alkoxy(C=O)-, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryloxy(C=O)O-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)-, in the presence of a base in a reaction inert solvent. Suitable leaving groups include chloro, fluoro, bromo or (R^{1b})O- (i.e. an anhydride). Preferably, the leaving group is chloro. Suitable bases include tertiary amine bases such as triethylamine, pyridine or 4-dimethylaminopyridine, preferably triethylamine. The temperature of the aforesaid reaction is from about 0°C to about 30°C, preferably from about 20°C to about 25°C (i.e. room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. The reaction is conducted from about 1 hour to about 24 hours, preferably for about 2 hours.

Compounds of the formula XI can be made according to the methods of Scheme 2.

Scheme 4 refers to the preparation of compounds of the formula I, wherein R^2 is other than hydrogen and R^3 and R^4 are other than hydrogen.

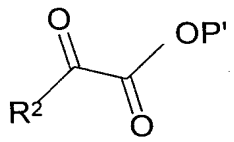
Referring to Scheme 4, compounds of the formula I are prepared from compounds of the formula XXIII by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include 5% palladium on barium sulfate or 5% palladium on carbon, preferably 5% palladium on barium sulfate. Suitable solvents

include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours.

The compound of the formula XXIII is prepared from a compound of the formula XXII by reaction with O-benzylhydroxylamine hydrochloride in the presence of a catalyst and a base in a reaction inert solvent. Suitable catalysts include (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate or 1-(3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, preferably (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate. Suitable bases include tertiary amines such as triethylamine. diisopropylethylamine or dimethylaminopyridine, preferably triethylamine. The aforesaid reaction temperature is from about 0° C to about 60°C, preferably from about 20° C to about 25°C (i.e. room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. The reaction is conducted from about 4 hours to about 48 hours, preferably about 16 hours.

The compound of the formula XXII can be prepared by deprotection of a compound of the formula XXI by reaction with an alkali metal hydroxide in a polar solvent. Suitable alkali metal hydroxides include lithium hydroxide, sodium hydroxide or potassium hydroxide, preferably lithium hydroxide, most preferably about 5 equivalents of the alkali metal hydroxide. The aforesaid reaction may conducted at a temperature from about 0°C to about 60°C, preferably from about 20°C to about 25°C (i.e. room temperature). Suitable solvents include a mixture of water and an alcohol such as methanol or ethanol and, optionally an water miscible ether such as tetrahydrofuran or 1,2-dimethoxyethane. Preferably, the solvent system is methanol/water/tetrahydrofuran. The reaction is conducted from about 1 to about 72 hours, preferably about 24 hours.

Compounds of the formula XXI can be prepared from compounds of the formula XII by reaction with a compound of the formula



XXVII

wherein P' is methyl, ethyl or benzyl, and a strong base in a polar aprotic solvent. Suitable bases include sodium hydride (NaH), potassium-tert.-butoxide, lithium diisopropylamide, and butyl lithium, preferably 2.5 M n-butyllithium in hexane. The temperature of the aforesaid reaction is from about -78°C to about 0°C, preferably about -78°C. Suitable solvents include diethyl ether, tetrahydrofuran, or 1,2-dimethoxyethane, preferably the solvent is tetrahydrofuran. The reaction is conducted from about 0.25 hours to about 6 hours, preferably about 0.33 hours.

Alternatively, compounds of the formula I, wherein R^1 is other than hydroxy, R^2 is other than hydrogen and R^3 and R^4 are other than hydrogen, can be prepared from compounds of the formula XXV by methods analogous to the conversion of compounds of the formula XXII to compounds of formula I, as described above in Scheme 4.

Compounds of the formula XXV can be prepared from compounds of the formula XXIV, wherein P' is benzyl, by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include palladium or 5-10% palladium on activated charcoal, preferably 10% palladium on activated charcoal. Suitable solvents include acetic acid, alcohols such as ethanol, methanol, or isopropanol, preferably ethanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 24 hours, preferably about 3 hours.

Compounds of the formula XXIV, wherein R^1 is $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy, can be prepared from compounds of the formula XXI by reaction with an arylalkyl or alkyl halide in the presence of a base in an aprotic solvent. Suitable bases include sodium hydride, ethyl magnesium bromide, lithium diisopropyl amide, potassium hydride, or sodium methoxide, preferably sodium hydride. The temperature of the aforesaid reaction is from about 0°C to about 60°C, preferably 20°C to about 25°C (i.e. room temperature). Suitable solvents include aprotic solvents such as methylene chloride, tetrahydrofuran or N,N-dimethylformamide, preferably N,N-dimethylformamide. The reaction is conducted for about 1 hour to about 48 hours, preferably about 16 hours.

Alternatively, compounds of the formula XXIV, wherein R^1 is $(C_1\text{-}C_6)$alkyl(C=O)O-, $(C_1\text{-}C_6)$alkoxy(C=O)O-, $(C_6\text{-}C_{10})$aryl(C=O)O-, $(C_6\text{-}C_{10})$aryloxy(C=O)O-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)O- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)O-, can be prepared from compounds of the formula XXI by reaction with an arylacyl or acyl halide in the presence of a base in an aprotic solvent. Suitable bases include tertiary amines such as triethylamine, diisopropylethylamine or 4-N,N-dimethylaminopyridine, preferably triethylamine. The

temperature of the aforesaid reaction may range from about 0°C to about 60°C, preferably about 20°C (room temperature). Suitable solvents include halogenated solvents such as methylene chloride or chloroform, or ethers such as THF or diethyl ether, preferably the solvent is methylene chloride. The reaction is complete in about 4 hours to about 48 hours, preferably about 16 hours.

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic

compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 mg trypsin per 100 mg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ------> 120 μM ------> 12 μM ------> 1.2 μM ------> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 ml is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 mM in assay buffer. The assay is initiated by the addition of 50 ml substrate per well of the microfluor plate to give a final concentration of 10 mM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each

concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 mM then the inhibitors are assayed at concentrations of 0.3 mM, 0.03 mM, 0.03 mM and 0.003 mM.

Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2 substrate (10 mM) under the same conditions as inhibition of human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 mM, 3 mM, 0.3 mM and 0.03 mM. Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 mM, then the inhibitors are assayed at final concentrations of 0.3 mM, 0.03 mM, 0.003 mM and 0.003 mM.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-SCH[$CH_2CH(CH_3)_2$]CO-Leu-Gly-OC_2H_5] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1 ml of a 10 mg/ml trypsin stock per 26 mg of stromelysin. The trypsin and stromelysin are incubated at 37°C for 15 minutes followed by 10 ml of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250 ml of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25 mg/ml. Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50 ml per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50 mL to the appropriate wells yields final concentrations of 3 mM, 0.3 mM, 0.003 mM, and 0.0003 mM. All conditions are completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50 ml to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20mM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 mM, 3mM, 0.3 mM, and 0.03 mM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 ml is added to each well to give a final assay concentration of 10 mM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 mM, inhibitors are then assayed at final concentrations of 0.3 mM, 0.03 mM, 0.003 mM and 0.0003 mM.

All of the compounds of the invention that were tested in the Inhibition of MMP-13 assay had IC_{50}'s of less than 50nm.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180m of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200ml. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFα using the R&D ELISA Kit®.

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be used including oral, parenteral (e.g., intravenous, intramuscular or subcutaneous), buccal, anal and topical. In general, the active compound will be administered at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. Preferably the active compound will be administered orally or parenterally. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes. and, if so desired, emulsifying and/or suspending agents as well,

together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (d) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under

nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used.

Example 1

(2*S*)-2,N-DIHYDROXY-3-(4-METHOXYBENZENESULFONYL)PROPIONAMIDE

(A) (2*S*)-2-Hydroxy-3-(4-methoxyphenylsulfanyl)propionic acid benzyl ester

A solution of 1 M ethylmagnesium bromide in diethyl ether (16.6 mL, 16.7 mmole) was diluted with tetrahydrofuran (32 mL) and cooled in an ice bath. A solution of 4-methoxybenzenethiol (2.3 grams, 16.7 mmole) in anhydrous tetrahydrofuran (5 mL) was added dropwise. The resulting mixture was allowed to stir at 0°C for 1 hour and then a solution of benzyl (2*S*)-glycidate (2.3 grams, 12.9 mmole) in tetrahydrofuran (5 mL) was added. The mixture was stirred at room temperature for 3 hours. After quenching with water, the mixture was extracted with ether. The aqueous layer was acidified to pH 5 and again extracted with diethyl ether. The combined diethyl ether extracts were washed with water and brine, dried over magnesium sulfate and concentrated to an oil. The product, (2*S*)-2-hydroxy-3-(4-methoxyphenylsulfanyl)propionic acid benzyl ester (3.6 grams, 88%) was isolated as a light yellow oil by chromatography on silica gel using 1:1 diethyl ether/hexane as eluant.

(B) (2*S*)-2-Hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid benzyl ester

A solution of (2*S*)-2-hydroxy-3-(4-methoxyphenylsulfanyl)propionic acid benzyl ester (3.6 grams, 11 mmole) in methylene chloride (25 mL) was cooled in an ice bath and a solution of 50% m-chloroperbenzoic acid (8.4 grams, 24 mmole) in methylene chloride (75 mL) was added dropwise. The resulting mixture was stirred at room temperature for 4 hours. After quenching with saturated aqueous sodium bisulfite solution, the mixture was extracted with diethyl ether. The extract was washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated to a white solid. Recrystallization from 1:1 hexane/ethyl acetate afforded (2*S*)-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid benzyl ester (3.2 grams, 84%) as a white crystalline solid.

(C) (2*S*)-2-Hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid

A solution of (2*S*)-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid benzyl ester (1.0 grams, 2.8 mmole) in methanol (70 mL) was treated with 10% palladium on activated carbon (100 mg) and hydrogenated at 3 atmospheres pressure for 3 hours in a Parr shaker. The catalyst was removed by filtration through diatomaceous earth and the filtrate was concentrated

to afford (2*S*)-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid as a white foam (729 mg, 100%).

(D) (2*S*)-N-Benzyloxy-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionamide

To a solution of (2*S*)-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid (800 mg, 3.0 mmole), O-benzylhydroxylamine hydrochloride (526 mg, 3.3 mmole) and triethylamine (1.2 mL, 9.0 mmole) in methylene chloride (80 mL) was added (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (1.4 grams, 3.3 mmole). The reaction mixture was stirred at room temperature for 16 hours and was then diluted with methylene chloride. The solution was washed successively with saturated aqueous sodium bicarbonate solution, water, 0.5 M aqueous hydrochloric acid solution and saturated brine. After drying over magnesium sulfate, the solvent was evaporated to afford an oil. The desired product, (2*S*)-N-benzyloxy-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionamide (400 mg, 36%), was isolated by flash chromatography on silica gel eluting successively with chloroform, 1% methanol in chloroform and 2% methanol in chloroform.

(E) (2*S*)-2,N-Dihydroxy-3-(4-methoxybenzenesulfonyl)propionamide

A solution of (2*S*)-N-benzyloxy-2-hydroxy-3-(4-methoxybenzenesulfonyl) propionamide (400 mg, 1.0 mmole) in methanol (30 mL) was treated with 5% palladium on barium sulfate (200 mg) and hydrogenated at 3 atmospheres pressure for 4 hours in a Parr shaker. The catalyst was removed by passage through a 0.45 µm nylon filter and the filtrate was concentrated. The desired product, (2*S*)-2,N-dihydroxy-3-(4-methoxybenzenesulfonyl) propionamide(180 mg, 65%), was isolated by flash chromatography on silica gel eluting with 5% methanol in chloroform followed by recrystallization from chloroform/methanol.

Melting point 138-144°C; MS m/z 276 (M+1); analysis calculated for $C_{10}H_{13}NO_6S$: C, 43.63; H, 4.76; N, 5.09. Found: C, 43.51; H, 4.68; N, 4.95.

Example 2

3-[4-(4-FLUOROPHENOXY)PHENYLSULFONYL]-2,N-DIHYDROXYPROPIONAMIDE

3-[4-(4-Fluorophenoxy)phenylsulfonyl]-2,N-dihydroxypropionamide was prepared by a method analogous to that described in Example 1 using (4-fluorophenoxy)phenylthiol as starting material. Recrystallized from chloroform.

Melting point 129-130°C; MS m/z 356 (M+1); analysis calculated for $C_{15}H_{14}FNO_6S.0.75H_2O$: C, 48.84; H, 4.24; N, 3.80. Found: C, 49.03; H, 4.06; N, 3.86.

Example 3

2,N-DIHYDROXY-2-[1-(4-METHOXYBENZENESULFONYL)CYCLOBUTYL]ACETAMIDE

(A) 1-Cyclobutylsulfanyl-4-methoxybenzene

4-Methoxybenzenethiol (5.7 g, 40.7 mmole) was added to a suspension of sodium hydride (1.17 grams, 49 mmole) in dry N,N-dimethylformamide (50 mL). After stirring for 1 hour, cyclobutylbromide (6.0 grams, 44.4 mmole) was added. The reaction mixture was stirred for 16 hours and was quenched by addition of saturated aqueous ammonium chloride solution. The solvents were evaporated. The residue was taken up in diethyl ether and washed successively with 0.5 N aqueous hydrochloric acid solution, water and brine. After drying over magnesium sulfate, the diethyl ether was evaporated to afford 1-cyclobutylsulfanyl-4-methoxybenzene as an oil (7.9 grams, 100%).

(B) 1-Cyclobutylsulfonyl-4-methoxybenzene

A solution of 1-cyclobutylsulfanyl-4-methoxybenzene (7.9 grams, 40.7 mmole) in methylene chloride (50 mL) was cooled in an ice bath and a solution of 57% m-chloroperbenzoic acid (28 grams, 92 mmole) in methylene chloride (100 mL) was added dropwise. The resulting mixture was stirred at room temperature for 7 days. After quenching with saturated aqueous sodium bisulfite solution, the mixture was filtered to remove a white precipitate and extracted with methylene chloride. The extract was washed successively with saturated aqueous sodium bicarbonate solution, water and brine. After drying over magnesium sulfate, the solution was concentrated to a white solid. Recrystallization from ethyl acetate afforded 1-cyclobutylsulfonyl-4-methoxybenzene (7.28 grams, 79%) as a white crystalline solid.

(C) Furan-2-yl-[1-(4-methoxybenzenesulfonyl)cyclobutyl]methanol

A solution of 1-cyclobutylsulfonyl-4-methoxybenzene (4.0 grams, 17.7 mmole) in dry tetrahydrofuran (80 mL) was cooled to -78°C and a 2.5 M solution of n-butyllithium in hexane was added. The mixture was allowed to warm to -50°C and was again cooled to -78°C. 2-Furaldehyde (4 mL, 48 mmole) was then added. After stirring for 20 minutes at -78°C, the reaction was quenched by addition of saturated aqueous ammonium chloride solution. The resulting mixture was extracted with ethyl acetate. The organic extract was washed with water and brine and was dried over magnesium sulfate. Evaporation of the solvent gave an oil from which furan-2-yl-[1-(4-methoxybenzenesulfonyl)cyclobutyl]-methanol (4.3 grams, 75%) was isolated by flash chromatography on silica gel eluting with 1:3 ethyl acetate/hexane.

(D) 2,2-Dimethylpropionic acid furan-2-yl[1-(4-methoxybenzenesulfonyl)cyclobutyl]-methyl ester

A solution of furan-2-yl-[1-(4-methoxybenzenesulfonyl)cyclobutyl]methanol (1.57 grams, 4.9 mmole) and 4-dimethylaminopyridine (0.89 grams, 7.3 mmole) in methylene chloride (50 mL) was cooled in an ice bath. Pivaloyl chloride (0.66 mL, 5.4 mmole) was added. The mixture was stirred at 0°C for 2 hours, diluted with methylene chloride and extracted successively with 0.5 N aqueous hydrochloric acid and brine. After drying over $MgSO_4$, the solvent was evaporated to leave an oil from which the desired product, 2,2-

dimethylpropionic acid furan-2-yl[1-(4-methoxybenzenesulfonyl)cyclobutyl]methyl ester (1.60 grams, 81%), was isolated by flash chromatography eluting with 16% ethyl acetate in hexane.

(E) 2,2-Dimethylpropionic acid carboxy[1-(4-methoxybenzenesulfonyl)cyclobutyl] methyl ester

To a solution of 2,2-dimethylpropionic acid furan-2-yl[1-(4-methoxybenzenesulfonyl)-cyclobutyl]methyl ester (1.6 grams, 3.94 mmol) in acetonitrile (12 mL), carbon tetrachloride (12 mL) and water (22 mL) at room temperature were added, sequentially, sodium periodate (6.73 grams, 31 mmole) and ruthenium (III) chloride hydrate (21 mg). The mixture was stirred at room temperature for 1.25 hours and was then diluted with water and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate. The combined organic fractions were dried over magnesium sulfate to yield the crude product, 2,2-dimethylpropionic acid carboxy[1-(4-methoxybenzenesulfonyl)cyclobutyl]-methyl ester, as an oil.

(F) 2,2-Dimethylpropionic acid benzyloxycarbamoyl-[1-(4-methoxybenzene sulfonyl)-cyclobutyl]methyl ester

The entire crude sample of 2,2-dimethylpropionic acid carboxy[1-(4-methoxybenzene-sulfonyl)cyclobutyl]methyl ester obtained in Step E was dissolved in methylene chloride (60 mL). O-Benzylhydroxylamine hydrochloride (0.69 grams, 4.3 mmol), triethylamine (1.6 mL, 11.5 mmole) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (1.91 grams, 4.3 mmole) were then added sequentially. The mixture was stirred at room temperature for 16 hours and was then concentrated under vacuum. The residue was taken up in ethyl acetate and the resulting solution was washed successively with 0.5 M aqueous hydrochloric acid solution, saturated aqueous sodium bicarbonate solution and brine. After drying over magnesium sulfate, the solvent was evaporated to afford an oil. The desired product, 2,2-dimethylpropionic acid benzyloxycarbamoyl-[1-(4-methoxybenzenesulfonyl)cyclobutyl]methyl ester (0.87 grams, 46%), was isolated by flash chromatography on silica gel eluting with 30% ethyl acetate in hexane.

(G) N-Benzyloxy-2-hydroxy-2[1-(4-methoxybenzenesulfonyl)cyclobutyl] acetamide

To a solution of 2,2-dimethylpropionic acid benzyloxycarbamoyl-[1-(4-methoxybenzenesulfonyl)cyclobutyl]methyl ester (0.87 grams, 1.78 mmol) in methanol (10 mL), tetrahydrofuran (5 mL) and water (5 mL) was added lithium hydroxide hydrate (0.37 grams, 8.8 mmol). The mixture was stirred at room temperature for 24 hours. Methanol-washed Amberlite IR-120 ion exchange resin (6 grams) was then added. After stirring for 15 minutes, the mixture was filtered. The filtrate was concentrated and the residue was taken up in ethyl acetate. The resulting solution was washed with saturated sodium bicarbonate

solution and brine, dried over magnesium sulfate and concentrated to afford the desired product, N-benzyloxy-2-hydroxy-2[1-(4-methoxybenzenesulfonyl)-cyclobutyl]acetamide, as an oil (0.72 grams, 100%).

(H) 2,N-Dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclobutyl]acetamide

A solution of N-benzyloxy-2-hydroxy-2[1-(4-methoxybenzenesulfonyl)-cyclobutyl]acetamide (0.13 grams, 0.32 mmole) in methanol (30 mL) was treated with 5% palladium on barium sulfate (0.07 grams) and hydrogenated at 3 atmospheres pressure for 4 hours in a Parr shaker. The catalyst was removed by passage through a 0.45 μm nylon filter and the filtrate was concentrated. The desired product, 2,N-dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclobutyl]acetamide (0.061 grams, 65%), was isolated as a foam by flash chromatography on silica gel eluting successively with chloroform, 1% methanol in chloroform and 2% methanol in chloroform. MS m/z 314 (M-1).

Example 4

2,N-DIHYDROXY-2-[1-(4-METHOXYBENZENESULFONYL)CYCLOPENTYL]ACETAMIDE

2,N-Dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclopentyl]acetamide was prepared by a method analogous to that described in Example 3 using 4-methoxybenzenethiol and cyclopentyl bromide as starting materials. MS m/z 328 (M-1).

Example 5

2-{1-[4-(4-FLUOROPHENOXY)BENZENESULFONYL]CYCLOBUTYL}-2,N-DIHYDROXYACETAMIDE

2-{1-[4-(4-Fluorophenoxy)benzenesulfonyl]cyclobutyl}-2,N-dihydroxyacetamide was prepared by a method analogous to that described in Example 3 using 4-(4-fluorophenoxy)benzenethiol and cyclobutyl bromide as starting materials. MS m/z 394 (M-1).

4-(4-Fluorophenoxy)benzenethiol was obtained as follows. Chlorosulfonic acid (26 mL, 0.392 mole) was added dropwise to ice-cooled 4-fluorophenoxybenzene (36.9 grams, 0.196 mole) with mechanical stirring. When addition was complete, the mixture was stirred at room temperature for 4 hours. The mixture was then poured into ice water. The product, 4-(4-fluorophenoxy)benzenesulfonylchloride (18.6 grams, 33%) was collected by filtration and was dried in the air.

4-(4-Fluorophenoxy)benzene-sulfonylchloride (5.1 grams, 17.7 mmole) was added to an ice-cooled mixture of concentrated sulfuric acid (7 mL) and water (37 mL) with mechanical stirring. Zinc dust (6.2 grams, 95 mmole) was then added in portions. The cooling bath was removed and the mixture was allowed to stir at room temperature for 2 hours and at reflux for 3 hours. After cooling to room temperature, the mixture was quenched by addition of ice. The resulting mixture was extracted with toluene. The organic layer was washed with water and

saturated brine, dried over magnesium sulfate and evaporated to afford 4-(4-fluorophenoxy)benzenethiol as a white solid (3.3 grams, 84%).

Example 6

2-{1-[4-(4-FLUOROPHENOXY)BENZENESULFONYL]CYCLOPENTYL}-2,N-DIHYDROXYACETAMIDE

2-{1-[4-(4-Fluorophenoxy)benzenesulfonyl]cyclopentyl}-2,N-dihydroxyacetamide was prepared by a method analogous to that described in Example 3 using (4-fluorophenoxy)benzenethiol and cyclopentyl bromide as starting materials. MS m/z 408 (M-1).

Example 7

2-[1-(4-CYCLOBUTOXYBENZENESULFONYL)CYCLOBUTYL]-2,N-DIHYDROXYACETAMIDE

2-[1-(4-Cyclobutoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide was prepared by a method analogous to that described in Example 3 using 1-cyclobutoxy-4-cyclobutylsulfanylbenzene as starting material in step B. MS: 354 (M-1).

Example 8

2-[1-(4-BUTOXYBENZENESULFONYL)CYCLOBUTYL]-2,N-DIHYDROXYACETAMIDE

2-[1-(4-Butoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide was prepared by a method analogous to that described in Example 3 using 1-butoxy-4-cyclobutylsulfanylbenzene as starting material as starting material in step B. MS: 356 (M-1).

Preparation A

4-(4-FLUOROPHENOXY)BENZENESULFONYLCHLORIDE

Chlorosulfonic acid (26 mL, 0.392 mole) was added dropwise to ice-cooled 4-fluorophenoxybenzene (36.9 grams, 0.196 mole) with mechanical stirring. When addition was complete, the mixture was stirred at room temperature for 4 hours. The mixture was then poured into ice water. The titled compound (18.6 grams, 33%) was collected by filtration and was dried in the air.

Preparation B

4-(4-FLUOROPHENOXY)BENZENETHIOL

4-(4-Fluorophenoxy)benzene-sulfonylchloride (5.1 grams, 17.7 mmole) was added to an ice-cooled mixture of concentrated sulfuric acid (7 mL) and water (37 mL) with mechanical stirring. Zinc dust (6.2 grams, 95 mmole) was then added in portions. The cooling bath was removed and the mixture was allowed to stir at room temperature for 2 hours and at reflux for 3 hours. After cooling to room temperature, the mixture was quenched by addition of ice. The resulting mixture was extracted with toluene. The organic layer was washed with water and

saturated brine, dried over magnesium sulfate and evaporated to afford the titled compound as a white solid (3.3 grams, 84%).

Preparation C

4-CYCLOBUTYLSULFANYLPHENOL

4-Hydroxybenzenethiol (10.0 grams, 79.3 mmole) was added to a suspension of sodium hydride (1.9 grams, 79.2 mmole) in N,N-dimethylformamide (50 mL). When evolution of hydrogen was complete and the mixture had cooled to room temperature, cyclobutylbromide (11.4 grams, 84.4 mmole) was added. The reaction mixture was stirred at room temperature for 2.5 hours and was then quenched by addition of water and 6 N aqueous hydrochloric acid solution. The mixture was extracted with diethyl ether. The organic extract was washed with brine, dried over magnesium sulfate and concentrated to afford a yellow oil. Roughly half of this material was chromatographed on silica gel eluting with 9:1:1 hexane/ethyl acetate/methylene chloride to afford the titled compound as a clear oil (8.85 grams).

Preparation D

1-CYCLOBUTOXY-4-CYCLOBUTYLSULFANYLBENZENE

A 60% suspension of sodium hydride in oil (1.97 grams, 49 mmole) was added to a solution of 4-cyclobutylsulfanylphenol(7.2 grams, 40 mmole) in N,N-dimethylformamide (25 mL). After hydrogen evolution was complete, cyclobutylbromide (6.4 grams, 47 mmole) was added. The reaction mixture was stirred at room temperature for 4 hours and then at 70°C in an oil bath for 16 hours. After cooling and quenching with water, the mixture was extracted with diethyl ether. The organic extract was washed with water and brine, dried over magnesium sulfate and concentrated to give an impure sample of the titled compound, an oil. This was used without without purification.

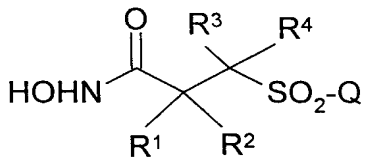
Preparation E

1-BUTOXY-4-CYCLOBUTYLSULFANYLBENZENE

A 60% suspension of sodium hydride in oil (2.2 grams, 55 mole) was added to an ice-cooled solution of 4-cyclobutylsulfanylphenol(8.85 grams, 49.1 mmole) in N,N-dimethylformamide (35 mL). After hydrogen evolution was complete, 1-bromobutane (6.7 mL, 58.9 mmole) was added. The reaction mixture was then stirred at room temperature for 16 hours. After cooling and quenching with water, the mixture was extracted with diethyl ether. The organic extract was washed with water and brine, dried over magnesium sulfate and concentrated to give an impure sample of the titled compound, an oil (11.2 grams). This was used without without purification.

CLAIMS

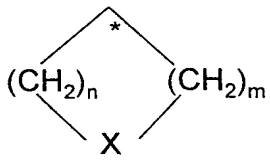
1. A compound of the formula



wherein R^1 is hydrogen, hydroxy, $(C_6-C_{10})aryl(C_1-C_6)alkoxy$, $(C_1-C_6)alkoxy$, $(C_1-C_6)alkyl(C=O)O-$, $(C_1-C_6)alkoxy(C=O)O-$, $(C_6-C_{10})aryl(C=O)O-$, $(C_6-C_{10})aryloxy(C=O)O-$, $(C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O-$ or $(C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-$; wherein said aryl moiety of said $(C_6-C_{10})aryl(C_1-C_6)alkoxy$, $(C_6-C_{10})aryl(C=O)O-$, $(C_6-C_{10})aryloxy(C=O)O-$, $(C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O-$ or $(C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-$ groups is optionally substituted by one or more substituents independently selected from fluoro, chloro, bromo, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $perfluoro(C_1-C_3)alkyl$, $perfluoro(C_1-C_3)alkoxy$ and $(C_6-C_{10})aryloxy$;

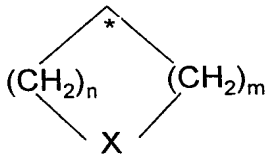
R^2 is hydrogen or $(C_1-C_6)alkyl$;

R^3 and R^4 are independently selected from the group consisting of hydrogen, $(C_1-C_6)alkyl$, trifluoromethyl, $trifluoromethyl(C_1-C_6)alkyl$, $(C_1-C_6)alkyl(difluoromethylene)$, $(C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl$, $(C_6-C_{10})aryl$, $(C_2-C_9)heteroaryl$, $(C_6-C_{10})aryl(C_1-C_6)alkyl$, $(C_2-C_9)heteroaryl(C_1-C_6)alkyl$, $(C_6-C_{10})aryl(C_6-C_{10})aryl$, $(C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl$, $hydroxy(C_1-C_6)alkyl$, $(C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl$, $(C_6-C_{10})aryl(C=O)O-(C_1-C_6)alkyl$, $(C_6-C_{10})aryloxy(C=O)O-(C_1-C_6)alkyl$, $(C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl$, $(C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, $(C_6-C_{10})aryloxy(C_1-C_6)alkyl$, $(C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl$, $(C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl$, $amino(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]_2amino(C_1-C_6)alkyl$, $(C_1-C_6)alkyl(C=O)NH(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C=O)NH(C_1-C_6)alkyl$, $(C_6-C_{10})aryl(C=O)NH(C_1-C_6)alkyl$, $(C_6-C_{10})aryloxy(C=O)NH(C_1-C_6)alkyl$, $(C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)NH(C_1-C_6)alkyl$, $(C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)NH(C_1-C_6)alkyl$, $(C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl$, $(C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl$, $R^5CO(C_1-C_6)alkyl$ or $R^8(C_1-C_6)alkyl$; or R^3 and R^4 may be taken together with the carbon atom to which they are attached to form a $(C_3-C_6)cycloalkyl$ or $benzo\text{-}fused(C_3-C_6)cycloalkyl$ ring or a group of the formula



wherein the carbon atom bearing the asterisk is the carbon to which R^3 and R^4 are atttached, "n" and "m" are independently selected from the integers one and two, and X is CF_2, O, SO_2 or NR^9, wherein R^9 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, (C_1-C_6)alkyl(C=O)-, (C_1-C_6)alkoxy(C=O)-, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryloxy(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)- or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-; wherein each of said (C_6-C_{10})aryl, (C_2-C_9)heteroaryl or (C_3-C_6)cycloalkyl moieties of said (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)NH(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-, (C_3-C_6)cycloalkyl, or benzo-fused(C_3-C_6)cycloalkyl ring may be optionally substituted on any ring atom capable of forming an additional bond by a substituent independently selected from the group consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

or when R^3 and R^4 are taken together with the carbon atom to which they are attached to form a group of the formula



then any of the carbon atoms of said ring, capable of forming an additional bond, may be optionally substituted by a substituent independently selected from the group consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

R^5 is R^6O or R^6R^7N wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_2-C_9)heteroaryl(C_1-C_6)alkyl; wherein each of said (C_6-C_{10})aryl and (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_2-C_9)heteroaryl(C_1-C_6)alkyl groups may be optionally substituted by one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

or R^6 and R^7 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocycle selected from piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl or azetidinyl; wherein each of said piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl or azetidinyl may be optionally substituted on any ring carbon atom capable of forming an additional bond with a substituent (preferably one to three substituents per ring) independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, or perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

R^8 is piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl, azetidinyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_2-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_2-C_9)heteroaryl(C_1-C_6)alkylpiperidyl, (C_1-C_6)alkyl(C=O)-piperidyl, (C_1-C_6)alkoxy(C=O)-piperidyl, (C_6-C_{10})aryl(C=O)-piperidyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperidyl, or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperidyl; wherein each of said piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazinyl, (C_2-C_9)heteroaryl(C_1-C_6) alkylpiperazinyl, (C_1-C_6)alkyl(C=O)-piperazinyl, (C_1-C_6)alkoxy(C=O)-piperazinyl, (C_6-C_{10})aryl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperazinyl, morpholinyl, piperidinyl, pyrrolidinyl, azetidinyl,

piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_2-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_2-C_9)heteroaryl(C_1-C_6)alkylpiperidyl (C_1-C_6)alkyl(C=O)-piperidyl, (C_1-C_6)alkoxy(C=O)-piperidyl, (C_6-C_{10})aryl(C=O)-piperidyl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C=O)-piperidyl, and (C_6-C_{10})aryl(C_1-C_6)alkoxy(C=O)-piperidyl may be optionally substituted on any ring carbon atom capable of forming an additional bond with a substituent independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, or perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

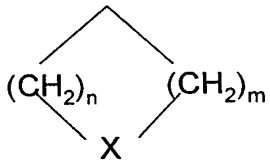
Q is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl wherein each (C_6-C_{10})aryl or (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl. perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

with the proviso that if either R^3 or R^4 is hydrogen, or if both R^3 and R^4 are hydrogen, then R^1 and R^2 can not both be hydrogen or R^1 must be hydroxy, (C_1-C_6)alkoxy, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_1-C_6)alkyl(C=O)O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryl(C=O)O-(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C=O)O- (C_6-C_{10})arylalkyl(C=O)O-(C_1-C_6)alkyl or (C_6-C_{10})arylalkoxy(C=O)O-(C_1-C_6)alkyl;

and the pharmaceutically acceptable salts thereof.

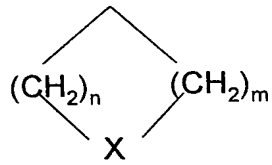
2. A compound according to claim 1, wherein R^1 is OH and R^2 is hydrogen.

3. A compound according to claim 1, wherein both R^3 and R^4 are $(C_1\text{-}C_6)$alkyl or R^3 and R^4 are taken together with the carbon atom to which they are attached to form an optionally substituted $(C_3\text{-}C_6)$cycloalkyl ring or benzo-fused$(C_3\text{-}C_6)$cycloalkyl ring or a group of the formula



wherein "n" and "m" are independently selected from the integers one and two, and X is CF_2, O, SO_2 or NR^9, wherein R^9 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroalkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_1\text{-}C_6)$alkyl(C=O)-, $(C_1\text{-}C_6)$alkoxy(C=O)-, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)-, or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)-; wherein each of said $(C_6\text{-}C_{10})$aryl and $(C_2\text{-}C_9)$heteroaryl moieties of said $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroalkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)-, and $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)- groups may be optionally independently substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, bromo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, perfluoro$(C_1\text{-}C_3)$alkyl, perfluoro$(C_1\text{-}C_3)$alkoxy and $(C_6\text{-}C_{10})$aryloxy.

4. A compound according to claim 2, wherein both R^3 and R^4 are $(C_1\text{-}C_6)$alkyl or R^3 and R^4 are taken together with the carbon atom to which they are attached to form a $(C_3\text{-}C_6)$cycloalkyl ring or benzo-fused$(C_3\text{-}C_6)$cycloalkyl ring or a group of the formula



wherein "n" and "m" are independently selected from the integers one and two, and X is CF_2, O, SO_2 or NR^9, wherein R^9 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroalkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_1\text{-}C_6)$alkyl(C=O)-, $(C_1\text{-}C_6)$alkoxy(C=O)-, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)-, or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)-; wherein each of said $(C_6\text{-}C_{10})$aryl and $(C_2\text{-}C_9)$heteroaryl moieties of said $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroalkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)-, and $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy(C=O)- groups may be optionally independently substituted with one or more substituents independently selected from the group

consisting of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy.

5. A compound according to claim 1, wherein R^3 and R^4 are taken together to form an optionally substituted (C_3-C_6)cycloalkyl ring.

6. A compound according to claim 2, wherein R^3 and R^4 are taken together to form an optionally substituted (C_3-C_6)cycloalkyl ring.

7. A compound according to claim 1, wherein Q is (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl, wherein each (C_6-C_{10})aryl moiety of said (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

8. A compound according to claim 2, wherein Q is (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl, wherein each (C_6-C_{10})aryl moiety of said (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

9. A compound according to claim 3, wherein Q is (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl, wherein each (C_6-C_{10})aryl moiety of said (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

10. A compound according to claim 4, wherein Q is (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl, wherein each (C_6-C_{10})aryl moiety of said (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

11. A compound according to claim 5, wherein Q is (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl, wherein each (C_6-C_{10})aryl moiety of said (C_6-C_{10})aryl or (C_6-C_{10})aryloxy(C_6-C_{10})aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

12. A compound according to claim 1, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

13. A compound according to claim 2, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

14. A compound according to claim 3, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

15. A compound according to claim 4, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

16. A compound according to claim 5, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

17. A compound according to claim 8, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

18. A compound according to claim 1, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.

19. A compound according to claim 2, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.

20. A compound according to claim 5, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.

21. A compound according to claim 8, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.

22. A compound according to claim 1, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl and wherein the substituent is in the 4-position.

23. A compound according to claim 2, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl and wherein the substituent is in the 4-position.

24. A compound according to claim 5, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl and wherein the substituent is in the 4-position.

25. A compound according to claim 8, wherein Q is phenyl or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, (C_1-C_6)alkoxy or (C_1-C_6)alkyl and wherein the substituent is in the 4-position.

26. A compound according to claim 1, wherein said compound is selected from the group consisting of:

(2*S*)-2,N-dihydroxy-3-(4-methoxybenzenesulfonyl)propionamide,

3-[4-(4-fluorophenoxy)phenylsulfonyl]-2,N-dihydroxypropionamide,

2,N-dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclobutyl]acetamide;

2,N-dihydroxy-2-[1-(4-methoxybenzenesulfonyl)cyclopentyl]acetamide,

2-[1-(4-cyclobutoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide,

2-[1-(4-butoxybenzenesulfonyl)cyclobutyl]-2,N-dihydroxyacetamide,

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclobutyl}-2,N-dihydroxyacetamide, and

2-{1-[4-(4-fluorophenoxy)benzenesulfonyl]cyclopentyl}-2,N-dihydroxyacetamide.

27. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, osteoporosis, cancer, tissue ulceration, muscular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

28. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

29. A method for treating a condition selected from the group consisting of arthritis, osteoporosis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a

human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/IB 98/00101

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C317/44 C07C317/46 A61K31/16

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 C07C A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 20047 A (BRITISH BIOTECHNOLOGY) 14 October 1993 see claims 1,20 ---	1-3,26, 27
A	WO 95 09841 A (BRITISH BIOTECH) 13 April 1995 see claims 1,20 --- -/--	1-3,26, 27

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

[X] Patent family members are listed in annex.

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

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2

Date of the actual completion of the international search	Date of mailing of the international search report
22 April 1998	08. 05. 98

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 98/00101

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Week 9207 Derwent Publications Ltd., London, GB; AN 92-051997 XP002063103 "Amide cpds. which inhibit collagenase - useful for treating bone resorption diseases, epidermolysis bullosa, etc." & JP 03 294 252 A (YAMANOUCHI) , 25 December 1991 see abstract	1-3,26, 27
P,X	WO 97 24117 A (RHONE-POULENC) 10 July 1997 compound with CN(RN):193547-69-2 see claims 1,22,61,62	1-3,27
P,A	EP 0 780 386 A (F. HOFFMANN- LA ROCHE) 25 June 1997 see claims 1,28,30	1-3,26, 27

AQUESTIVE EXHIBIT 1004 page 1094

INTERNATIONAL SEARCH REPORT

Im tional application No.
PCT/IB 98/00101

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

Remark: Although claims 28-29 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. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

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

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/IB 98/00101

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9320047 A	14-10-93	AT 150452 T	15-04-97
		AU 3899193 A	08-11-93
		DE 69309047 D	24-04-97
		EP 0634998 A	25-01-95
		JP 7505387 T	15-06-95
		US 5525629 A	11-06-96
		ZA 9302501 A	08-11-93
WO 9509841 A	13-04-95	AU 7787594 A	01-05-95
		EP 0722438 A	24-07-96
		JP 9503222 T	31-03-97
		ZA 9407799 A	10-07-95
WO 9724117 A	10-07-97	AU 1529897 A	28-07-97
EP 780386 A	25-06-97	AU 7548296 A	31-07-97
		CA 2193178 A	21-06-97
		JP 9249638 A	22-09-97
		NO 965413 A	23-06-97
		PL 317604 A	23-06-97

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A1

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(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
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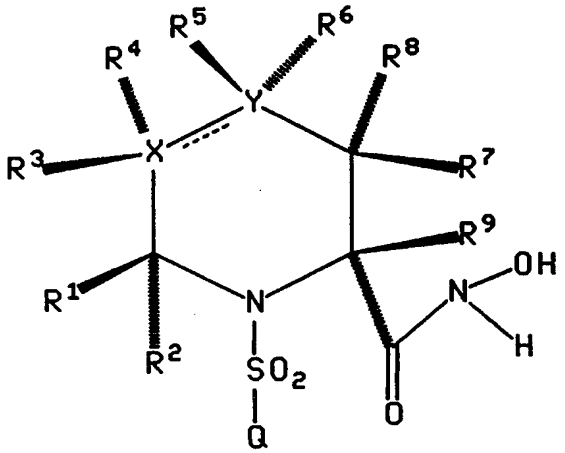
(54) Title: ARYLSULFONYL HYDROXAMIC ACID DERIVATIVES



(I)

(57) Abstract

A compound of formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and Q are as defined above, useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non–steroidal anti–inflammatory drugs (NSAID'S) and analgesics, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis–platinum, etoposide, taxol, taxotere and other alkaloids, such as vincristine, in the treatment of cancer.

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ARYLSULFONYL HYDROXAMIC ACID DERIVATIVES

Background of the Invention

The present invention relates to arylsulfonyl hydroxamic acid derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (hereinafter NSAID'S) and analgesics for the treatment of arthritis, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, in the treatment of cancer.

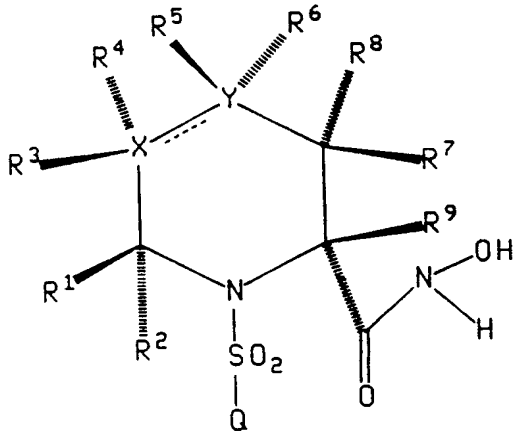
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Fiers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

Summary of the Invention

The present invention relates to a compound of the formula



I

or the pharmaceutically acceptable salt thereof, wherein the broken line represents an optional double bond;

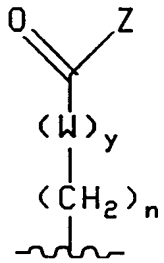
X is carbon, oxygen or sulfur;

Y is carbon, oxygen, sulfur, SO, SO_2 or nitrogen;

R^1, R^2 R^3, R^4 R^5, R^6, R^7, R^8 and R^9 are selected from the group consisting of hydrogen, (C_1-C_6)alkyl optionally substituted by one or two groups selected from (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, halo, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino, (C_5-C_9)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, hydroxy, piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_5-C_9)heteroaryl(C_1-C_6)alkoxy, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, amino, (C_1-C_6)alkylamino or ((C_1-C_6)alkylamino)$_2$; (C_2-C_6)alkenyl, (C_6-C_{10})aryl(C_2-C_6)alkenyl, (C_5-C_9)heteroaryl(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-C_{10})aryl(C_2-C_6)alkynyl, (C_5-C_9)heteroaryl(C_2-C_6)alkynyl, (C_1-C_6)alkylamino,(C_1-C_6)alkylthio,(C_1-C_6)alkoxy,perfluoro(C_1-C_6)alkyl,(C_6-C_{10})aryl,(C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino, (C_5-C_9)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkyl(hydroxymethylene), piperidyl, (C_1-C_6)alkylpiperidyl, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, R^{10}(C_1-C_6)alkyl wherein R^{10} is (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino,(C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino,morpholino,thiomorpholino,

pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl,(C_1-C_6)alkylpiperidyl(C_1-C_6)alkyl,(C_6-C_{10})arylpiperidyl(C_1-C_6)alkyl, (C_5-C_9)heteroarylpiperidyl(C_1-C_6)alkyl or (C_1-C_6)acylpiperidyl;

or a group of the formula



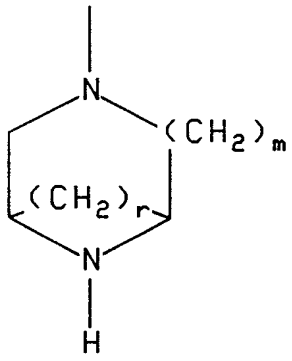
II

wherein n is 0 to 6;

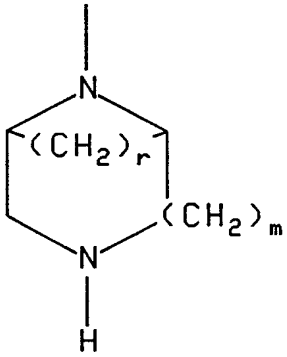
y is 0 or 1;

W is oxygen or NR^{24} wherein R^{24} is hydrogen or (C_1-C_6)alkyl;

Z is OR^{11} or $NR^{24}R^{11}$ wherein R^{24} is as defined above and R^{11} is as defined below; azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl or a bridged diazabicycloalkyl ring selected from the group consisting of



a



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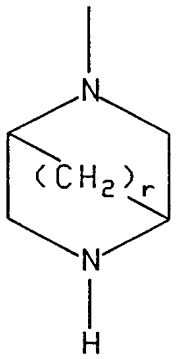

c

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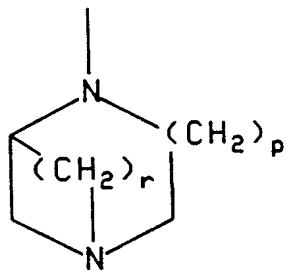
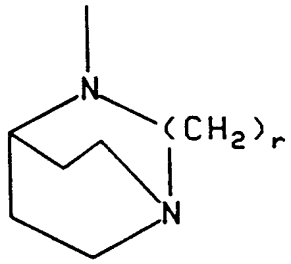


d



e

wherein r is 1, 2 or 3;

m is 1 or 2;

p is 0 or 1; and

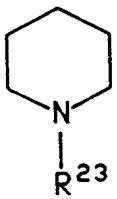
wherein each heterocyclic group may optionally be substituted by one or two groups selected from hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_{10})$acyl, $(C_1$-$C_{10})$acyloxy, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acyloxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylthio, $(C_1$-$C_6)$alkylthio$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylthio, $(C_6$-$C_{10})$arylthio$(C_1$-$C_6)$alkyl, $R^{12}R^{13}N$, $R^{12}R^{13}NSO_2$, $R^{12}R^{13}NCO$, $R^{12}R^{13}NCO(C_1$-$C_6)$alkyl wherein R^{12} and R^{13} are each independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl $(C_1$-$C_6)$alkyl or $(C_5$-$C_9)$heteroaryl $(C_1$-$C_6)$alkyl or R^{12} and R^{13} may be taken together with the nitrogen to which they are attached to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or thiomorpholinyl ring; $R^{14}SO_2$, $R^{14}SO_2NH$ wherein R^{14} is trifluoromethyl, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl or $(C_5$-$C_9)$heteroaryl $(C_1$-$C_6)$alkyl; $R^{15}CONR^{12}$ wherein R^{12} is as defined above and R^{15} is hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_1$-$C_6)$aryl$(C_1$-$C_6)$alkyl$(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxy or $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl; $R^{16}OOC$, $R^{16}OOC(C_1$-$C_6)$alkyl wherein R^{16} is $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl $(C_1$-$C_6)$alkyl, 5-indanyl, $CHR^{17}OCOR^{18}$ wherein R^{17} is hydrogen or $(C_1$-$C_6)$alkyl and R^{18} is $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy or $(C_6$-$C_{10})$aryl; $CH_2CONR^{19}R^{20}$ wherein R^{19} and R^{20} are each independently hydrogen or $(C_1$-$C_6)$alkyl or may be taken together with the nitrogen to which they are attached to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or

thiomopholinyl ring; or $R^{21}O$ (C_1C_6)alkyl wherein R^{21} is $H_2N(CHR^{22})CO$ wherein R^{22} is the side chain of a natural D- or L-amino acid;

R^{11} is hydrogen, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl$(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl$(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl, 5-indanyl, $CHR^{17}OCOR^{18}$ or $CH_2CONR^{19}R^{20}$ wherein R^{17}, R^{18}, R^{19} and R^{20} are as defined above;

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6 may be taken together to form a carbonyl;

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, or R^7 and R^8 may be taken together to form a $(C_3$-$C_6)$cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula



wherein R^{23} is hydrogen, $(C_1$-$C_6)$acyl, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkylsulfonyl; and

Q is $(C_1$-$C_{10})$alkyl, $(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryloxy$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryloxy$(C_5$-$C_9)$heteroaryl, $(C_5$-$C_9)$heteroaryl, $(C_1$-$C_6)$alkyl$(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxy$(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryloxy$(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkyl$(C_5$-$C_9)$heteroaryl, $(C_1$-$C_6)$alkoxy$(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxy$(C_5$-$C_9)$heteroaryl, $(C_5$-$C_9)$heteroaryloxy$(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryloxy$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryloxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl$(C_6$-$C_{10})$aryloxy$(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkyl$(C_5$-$C_9)$heteroaryloxy$(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkyl$(C_6$-$C_{10})$aryloxy$(C_5$-$C_9)$heteroaryl, $(C_1$-$C_6)$alkoxy$(C_6$-$C_{10})$aryloxy$(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkoxy$(C_5$-$C_9)$heteroaryloxy$(C_6$-$C_{10})$aryl or $(C_1$-$C_6)$alkoxy$(C_6$-$C_{10})$aryloxy$(C_5$-$C_9)$heteroaryl optionally substituted by fluoro, chloro, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy or perfluoro$(C_1$-$C_3)$alkyl;

with the proviso that Z must be substituted when defined as azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl, $(C_1$-$C_{10})$acylpiperazinyl, $(C_1$-$C_6)$alkylpiperazinyl, $(C_6$-$C_{10})$arylpiperazinyl, $(C_5$-$C_9)$heteroarylpiperazinyl or a bridged diazabicycloalkyl ring;

with the proviso that R^7 is other than hydrogen only when R^8 is other than hydrogen;

with the proviso that R^6 is other than hydrogen only when R^5 is other than hydrogen;

with the proviso that R^3 is other than hydrogen only when R^4 is other than hydrogen;

with the proviso that R^2 is other than hydrogen only when R^1 is other than hydrogen;

with the provisio that when R^1, R^2 and R^9 are a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 2- or 6- positions;

with the proviso that when X is nitrogen, R^4 is not present;

with the proviso that when X is oxygen, sulfur, SO, SO_2 or nitrogen and when one or more of the group consisting of R^1, R^2, R^5 and R^6, is a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 4- or 6- positions;

with the proviso that when Y is oxygen, sulfur, SO, SO_2 or nitrogen and when one or more of the group consisting of R^3, R^4, R^7 and R^8, are independently a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 3- or 5- positions;

with the proviso that when X is oxygen, sulfur, SO or SO_2, R^3 and R^4 are not present;

with the proviso that when y is 1 and W is NR^{24} or oxygen, Z cannot be hydroxy;

with the proviso that when Y is oxygen, sulfur, SO or SO_2, R^5 and R^6 are not present;

with the proviso that when Y is nitrogen, R^6 is not present;

with the proviso that when the broken line represents a double bond, R^4 and R^6 are not present;

with the proviso that when R^3 and R^5 are independently a substituent comprising a heteroatom when the broken line represents a double bond, the heteroatom cannot be directly bonded to positions X and Y;

with the proviso that when either the X or Y position is oxygen, sulfur, SO, SO_2 or nitrogen, the other of X or Y is carbon;

with the proviso that when X or Y is defined by a heteroatom, the broken line does not represent a double bond;

with the proviso that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 must be defined as the group of formula II.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents independently selected from the group consisting of fluoro, chloro, cyano, nitro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl.

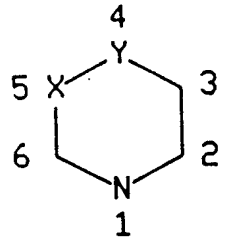
The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents independently selected from the group consisting of fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl.

The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy (such as methyloxy carbonyl), aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

The term "D- or L-amino acid", as used herein, unless otherwise indicated, includes glycine, alanine, valine, leucine, isoleucine, phenylalanine, asparagine, glutamine, tryptophan, proline, serine, threonine, tyrosine, hydroxyproline, cysteine, cystine, methionine, aspartic acid, glutamic acid, lysine, arginine or histidine.

The positions on the ring of formula I, as used herein, are defined as follows:



The preferred conformation of the compound of formula I includes hydroxamic acid axially disposed in the 2-position.

The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferred compounds of formula I include those wherein Y is carbon.

Other preferred compounds of formula I include those wherein Q is (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl wherein each terminal aryl group is optionally substituted by fluoro.

Other preferred compounds of formula I include those wherein R^2, R^3, R^6, R^7 and R^9 are hydrogen.

More preferred compounds of formula I include those wherein Y is carbon; Q is (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl.

Specific preferred compounds of formula I include the following:

(2R,4R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid;

(2R,4R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid methyl ester;

(2R,4R)-1-[3-(4-Fluorophenoxy)-propane-1-sulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid;

(2R,4R)-1-[3-(4-Fluorophenoxy)-propane-1-sulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid methyl ester;

(2R,3S)-{1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidin-3-yl}-carbamic acid isopropyl ester;

3-(S)-4-(4'-Fluorobiphenyl-4-sulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

3-(S)-4-[4-(4-Fluorobenzyloxy)benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

(2R,4S)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-4-hydroxy-piperidine-2-carboxylic acid hydroxyamide; and

(2R,4R)-1-(4-Methoxybenzenesulfonyl)-4-(piperazine-1-carbonyl)-piperidine-2-carboxylic acid hydroxyamide hydrochloride.

Other compounds of the invention include:

(3S)-4-[4-(2-Chloro-thiazol-5-ylmethoxy)-benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

(3S)-2,2-Dimethyl-4-[4-(thiazol-5-ylmethoxy)-benzenesulfonyl]-thiomorpholine-3-carboxylic acid hydroxyamide;

(3S)-2,2-Dimethyl-4-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-thiomorpholine-3-carboxylic acid hydroxyamide;

(3S)-4-{4-[2-(4-Fluorophenyl)-ethoxy]-benzenesulfonyl}-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

(3S)-2,2-Dimethyl-4-[4-(2-pyridin-4-yl-ethoxy)-benzenesulfonyl]-thiomorpholine-3-carboxylic acid hydroxyamide;

(3S)-4-[4-(Benzothiazol-2-ylmethoxy)-benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

(3S)-2,2-Dimethyl-4-[4-(5-trifluoromethyl-benzothiazol-2-ylmethoxy)-benzenesulfonyl]-thiomorpholine-3-carboxylic acid hydroxyamide;

(3S)-2,2-Dimethyl-4-[4-(1H-tetrazol-5-ylmethoxy)-benzenesulfonyl]-thiomorpholine-3-carboxylic acid hydroxyamide;

(2R,3S)-{1-[4-(2-Chloro-thiazol-5-ylmethoxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidin-3-yl}-carbamic acid methyl ester;

(2R,3S)-{2-Hydroxycarbamoyl-1-[4-(thiazol-5-ylmethoxy)-benzenesulfonyl]-piperidin-3-yl}-carbamic acid methyl ester;

(2R,3S)-{2-Hydroxycarbamoyl-1-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-piperidin-3-yl}-carbamic acid methyl ester;

(2R,3S)-{1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidin-3-yl}-carbamic acid methyl ester;

(2R,3S)-(1-{4-[2-(4-Fluorophenyl)-ethoxy]-benzenesulfonyl}-2-hydroxycarbamoyl-piperidin-3-yl)-carbamic acid methyl ester;

(2R,3S)-{2-Hydroxycarbamoyl-1-[4-(2-pyridin-4-yl-ethoxy)-benzenesulfonyl]-piperidin-3-yl}-carbamic acid methyl ester;

(2R,3S)-{1-[4-(Benzothiazol-2-ylmethoxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidin-3-yl}-carbamic acid methyl ester;

(2R,3S)-{2-Hydroxycarbamoyl-1-[4-(5-trifluoromethyl-benzothiazol-2-ylmethoxy)-benzenesulfonyl]-piperidin-3-yl}-carbamic acid methyl ester;

(2R,3S)-{2-Hydroxycarbamoyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzenesulfonyl]-piperidin-3-yl}-carbamic acid methyl ester;

(2R,3S)-1-[4-(2-Chloro-thiazol-5-ylmethoxy)-benzenesulfonyl]-3-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-3-Hydroxy-1-[4-(thiazol-5-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-3-Hydroxy-1-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-3-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-1-{4-[2-(4-Fluorophenyl)-ethoxy]-benzenesulfonyl}-3-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-3-Hydroxy-1-[4-(2-pyridin-4-yl-ethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-1-[4-(Benzothiazol-2-ylmethoxy)-benzenesulfonyl]-3-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-3-Hydroxy-1-[4-(5-trifluoromethyl-benzothiazol-2-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-3-Hydroxy-1-[4-(1H-tetrazol-5-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-1-[4-(2-Chloro-thiazol-5-ylmethoxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-3-Hydroxy-3-methyl-1-[4-(thiazol-5-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-3-Hydroxy-3-methyl-1-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-1-{4-[2-(4-Fluorophenyl)-ethoxy]-benzenesulfonyl}-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-3-Hydroxy-3-methyl-1-[4-(2-pyridin-4-yl-ethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-1-[4-(Benzothiazol-2-ylmethoxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-3-Hydroxy-3-methyl-1-[4-(5-trifluoromethyl-benzothiazol-2-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-3-Hydroxy-3-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(3R)-4-[4-(2-Chloro-thiazol-5-ylmethoxy)-benzenesulfonyl]-2,2-dimethyl-morpholine-3-carboxylic acid hydroxyamide;

(3R)-2,2-Dimethyl-4-[4-(thiazol-5-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

(3R)-2,2-Dimethyl-4-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

(3R)-4-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2,2-dimethyl-morpholine-3-carboxylic acid hydroxyamide;

(3R)-4-{4-[2-(4-Fluorophenyl)-ethoxy]-benzenesulfonyl}-2,2-dimethyl-morpholine-3-carboxylic acid hydroxyamide;

(3R)-2,2-Dimethyl-4-[4-(2-pyridin-4-yl-ethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

(3R)-4-[4-(Benzothiazol-2-ylmethoxy)-benzenesulfonyl]-2,2-dimethyl-morpholine-3-carboxylic acid hydroxyamide;

(3R)-2,2-Dimethyl-4-[4-(5-trifluoromethyl-benzothiazol-2-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

(3R)-2,2-Dimethyl-4-[4-(1H-tetrazol-5-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

(2R,4R)-1-[4-(2-Chloro-thiazol-5-ylmethoxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid;

(2R,4R)-2-Hydroxycarbamoyl-1-[4-(thiazol-5-ylmethoxy)-benzenesulfonyl]-piperidine-4-carboxylic acid;

(2R,4R)-2-Hydroxycarbamoyl-1-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-piperidine-4-carboxylic acid;

(2R,4R)-1-{4-[2-(4-Fluorophenyl)-ethoxy]-benzenesulfonyl}-2-hydroxycarbamoyl-piperidine-4-carboxylic acid;

(2R,4R)-2-Hydroxycarbamoyl-1-[4-(2-pyridin-4-yl-ethoxy)-benzenesulfonyl]-piperidine-4-carboxylic acid;

(2R,4R)-1-[4-(Benzothiazol-2-ylmethoxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid;

(2R,4R)-2-Hydroxycarbamoyl-1-[4-(5-trifluoromethyl-benzothiazol-2-ylmethoxy)-benzenesulfonyl]-piperidine-4-carboxylic acid;

(2R,4R)-2-Hydroxycarbamoyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzenesulfonyl]-piperidine-4-carboxylic acid;

(3R)-4-[4-(2-Chloro-thiazol-5-ylmethoxy)-benzenesulfonyl]-3-methyl-morpholine-3-carboxylic acid hydroxyamide;

(3R)-3-Methyl-4-[4-(thiazol-5-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

(3R)-3-Methyl-4-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

(3R)-4-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-3-methyl-morpholine-3-carboxylic acid hydroxyamide;

(3R)-4-{4-[2-(4-Fluorophenyl)-ethoxy]-benzenesulfonyl}-3-methyl-morpholine-3-carboxylic acid hydroxyamide;

(3R)-3-Methyl-4-[4-(2-pyridin-4-yl-ethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

(3R)-4-[4-(Benzothiazol-2-ylmethoxy)-benzenesulfonyl]-3-methyl-morpholine-3-carboxylic acid hydroxyamide;

(3R)-3-Methyl-4-[4-(5-trifluoromethyl-benzothiazol-2-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

(3R)-3-Methyl-4-[4-(1H-tetrazol-5-ylmethoxy)-benzenesulfonyl]-morpholine-3-carboxylic acid hydroxyamide;

(2R)-1-[4-(2-Chloro-thiazol-5-ylmethoxy)-benzenesulfonyl]-2-methyl-3-oxo-piperidine-2-carboxylic acid hydroxyamide;

(2R)-2-Methyl-3-oxo-1-[4-(thiazol-5-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R)-2-Methyl-3-oxo-1-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-methyl-3-oxo-piperidine-2-carboxylic acid hydroxyamide;

(2R)-1-{4-[2-(4-Fluorophenyl)-ethoxy]-benzenesulfonyl}-2-methyl-3-oxo-piperidine-2-carboxylic acid hydroxyamide;

(2R)-2-Methyl-3-oxo-1-[4-(2-pyridin-4-yl-ethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R)-1-[4-(Benzothiazol-2-ylmethoxy)-benzenesulfonyl]-2-methyl-3-oxo-piperidine-2-carboxylic acid hydroxyamide;

(2R)-2-Methyl-3-oxo-1-[4-(5-trifluoromethyl-benzothiazol-2-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R)-2-Methyl-3-oxo-1-[4-(1H-tetrazol-5-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R,4S)-1-(4-Benzyloxy-benzenesulfonyl)-4-butylaminomethyl-4-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

(2R,4S)-4-Butylaminomethyl-1-[4-(4-fluorobenzyloxy)-benzenesulfonyl]-4-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

(2R,4S)-4-Benzylamino-1-(4-benzyloxy-benzenesulfonyl)-piperidine-2-carboxylic acid hydroxyamide;

(2R,4S)-4-Benzylamino-1-[4-(4-fluorobenzyloxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

(2R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-4-oxo-piperidine-2-carboxylic acid hydroxyamide;

(2R,4R)-1-(4-Benzyloxy-benzenesulfonyl)-4-hydroxy-piperidine-2-carboxylicacid hydroxyamide;

(2R,4R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-4-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

(2R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-4-methyl-piperazine-2-carboxylic acid hydroxyamide;

(2R,5S)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-5-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

(2R,5S)-1-(4-Benzyloxy-benzenesulfonyl)-5-hydroxy-piperidine-2-carboxylicacid hydroxyamide;

(2R,5R)-1-(4-Benzyloxy-benzenesulfonyl)-5-hydroxy-piperidine-2-carboxylicacid hydroxyamide;

(2R,5R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-5-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

(2R,3S)-1-(4-Benzyloxy-benzenesulfonyl)-3-hydroxy-piperidine-2-carboxylicacid hydroxyamide;

(2R,4S)-1-(4-Benzyloxy-benzenesulfonyl)-4-hydroxy-piperidine-2-carboxylicacid hydroxyamide;

(2R,4S)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-4-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

1-(4-Butoxy-benzenesulfonyl)-3-(morpholine-4-carbonyl)-piperidine-2-carboxylic acid hydroxyamide;

1-[4-(4-Fluoro-benzyloxy)-benzenesulfonyl)-3-(morpholine-4-carbonyl)-piperidine-2-carboxylic acid hydroxyamide;

1-[3-(Fluoro-benzyloxy)-propane-1-sulfonyl]-3-(morpholine-4-carbonyl)-piperidine-2-carboxylic acid hydroxymide;

1-(4-Butoxy-benzenesulfonyl)-3-(pyrrolidine-1-carbonyl)-piperidine-2-carboxylic acid hydroxyamide;

1-[4-(4-Fluoro-benzyloxy)-benzenesulfonyl)-3-(pyrrolidine-1-carbonyl)-piperidine-2-carboxylic acid hydroxyamide;

1-[3-(4-Fluoro-benzyloxy)-propane-1-sulfonyl)-3-(pyrrolidine-1-carbonyl)-piperidine-2-carboxylic acid hydroxyamide; and

1-[4-(4-Fluoro-benzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

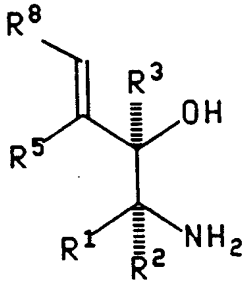
The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

Detailed Description of the Invention

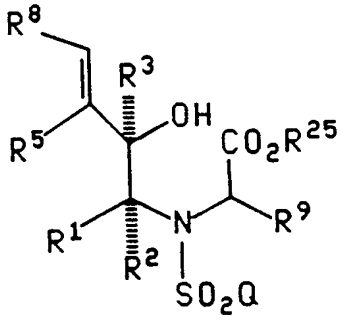
The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, n and Ar in the reaction Schemes and the discussion that follow are defined as above.

Preparation 1



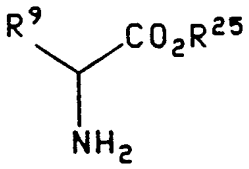
XVI

1



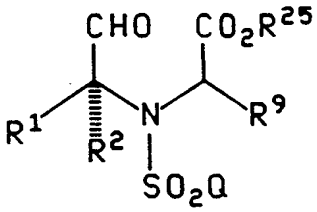
VI

Preparation 2



XVIII

1

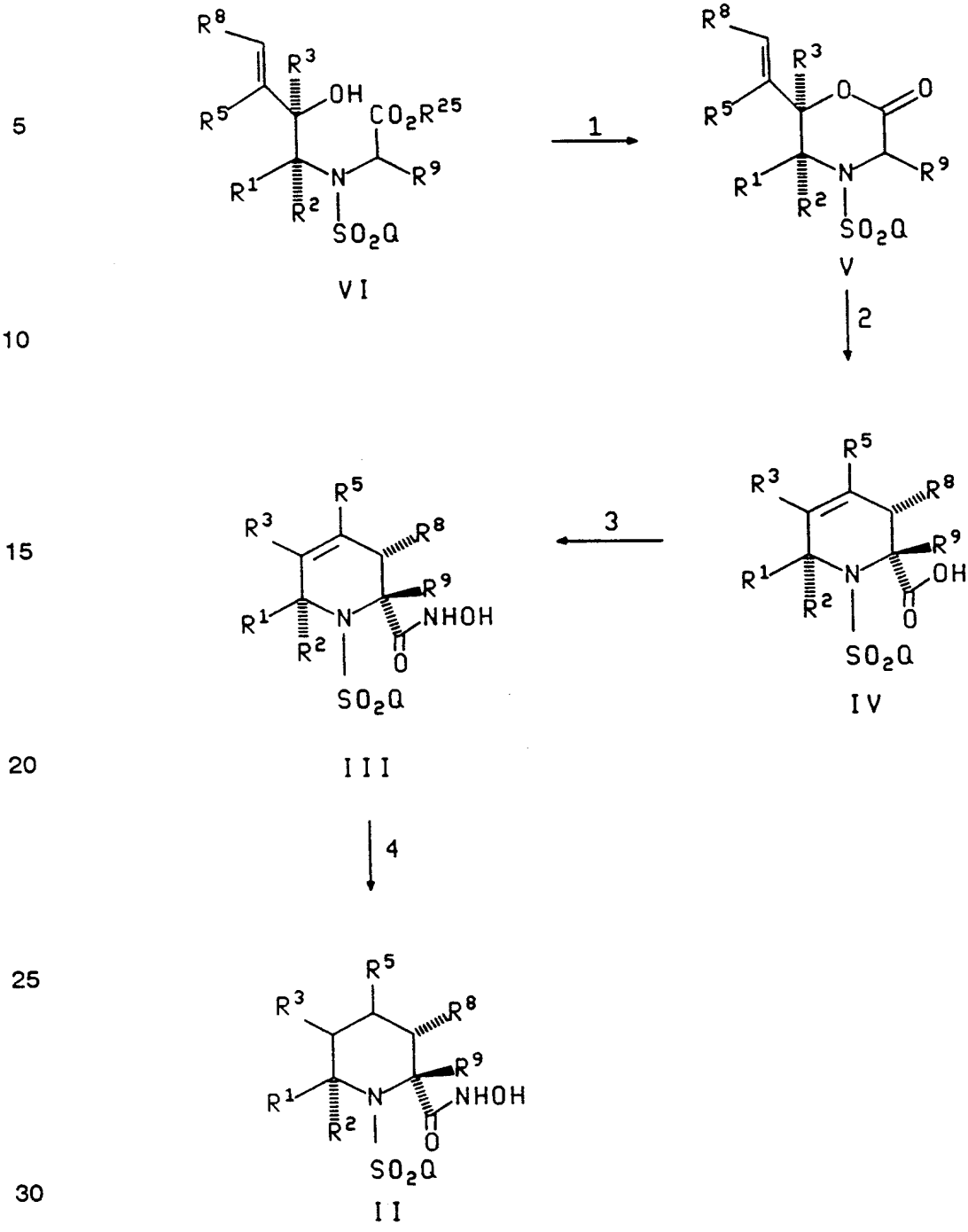


XVII

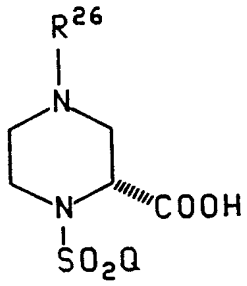
2

VI

Scheme 1

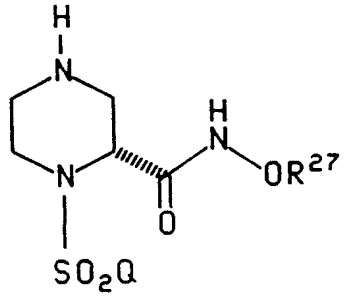


Scheme 2



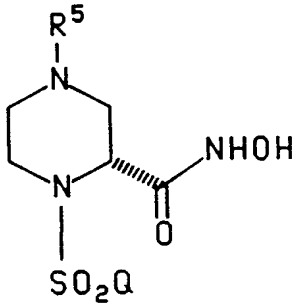
IX

1



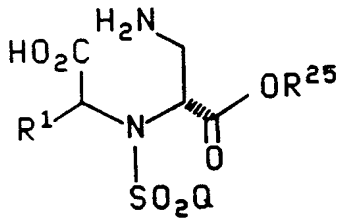
VIII

2



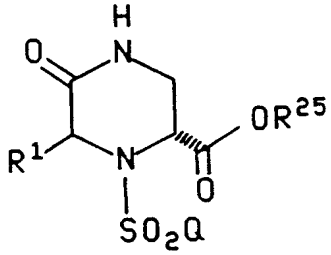
VII

Scheme 3



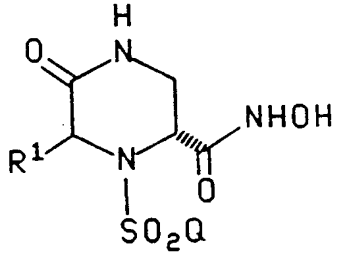
XII

1



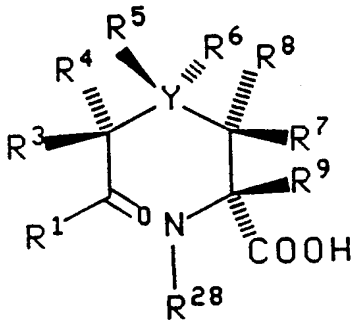
XI

2



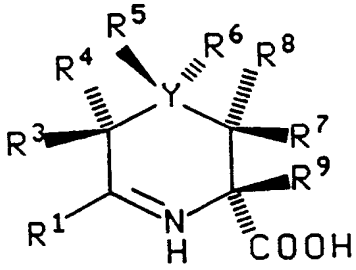
X

Scheme 4



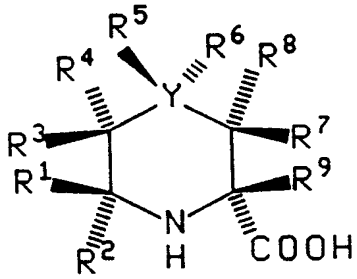
XXII

1



XXI

2

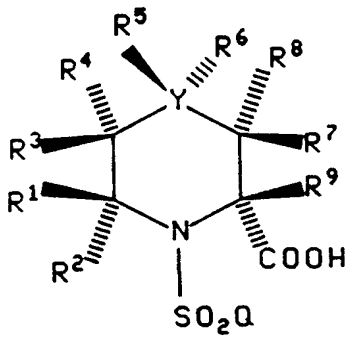


XX

Scheme 4 continued

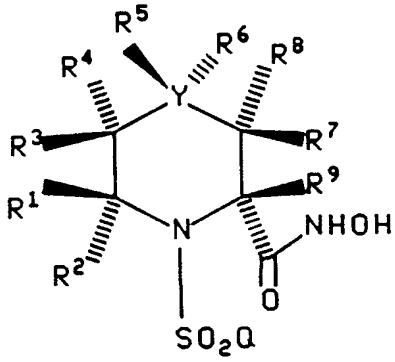
XX

3



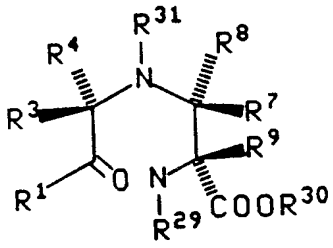
XIX

4



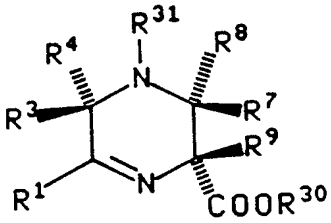
XIII

Scheme 5



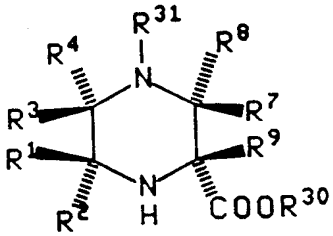
XXVI

1



XXV

2

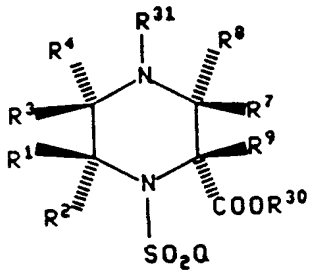


XXIV

Scheme 5 continued

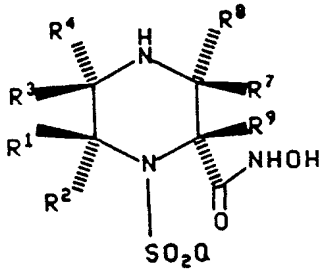
XXIV

3



XXIII

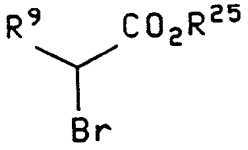
4



XIV

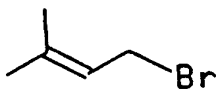
Preparation 1 refers to the preparation of intermediates of the formula VI. Compounds of the formula VI are converted to compounds of the formula I according to the methods of Scheme 1. The starting materials of formula XVI can be prepared according to methods well known to those of ordinary skill in the art.

In reaction 1 of Preparation 1, the compound of formula **XVI** is converted to the corresponding hydroxy ester compound of formula **VI** by first reacting **XVI** with an arylsulfonylhalide in the presence of triethylamine and an aprotic solvent, such as methylene chloride, tetrahydrofuran or dioxane, at a temperature between about 20°C to about 30°C, preferably at room temperature. The compound so formed is further reacted with a compound of the formula



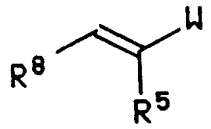
wherein R^{25} is carbobenzyloxy, (C_1-C_6)alkyl, benzyl, allyl or tert-butyl, in the presence of sodium hexamethyldisilazane and a tetrahydrofuran-dimethylformamide solvent mixture at a temperature between about -20°C to about 20°C, preferably about 0°C, to form the hydroxy ester compound of formula **VI**.

Preparation 2 refers to an alternate method of preparing compounds of the formula VI. The starting materials of formula XVIII can be prepared according to methods well known to those of ordinary skill in the art. In reaction 1 of Preparation 2, the amine compound of formula **XVIII**, wherein R^{25} is as defined above, is converted to the corresponding arylsulfonyl amine compound of formula **XVII** by (1) reacting **XVIII** with an arylsulfonylhalide in the presence of triethylamine and an aprotic solvent, such as methylene chloride, tetrahydrofuran, or dioxane, at a temperature between about 20°C to about 30°C, preferably at room temperature, (2) reacting the compound so formed with a compound of the formula



in the presence of sodium hexamethyldisilazane and a tetrahydrofuran-dimethylformamide solvent mixture at a temperature between about -20°C to about 20°C, preferably about 0°C, and (3) further reacting the compound so formed with ozone in a methylene chloride-methanol solution at a temperature between about -90°C

to about -70°C, preferably about -78°C. The unstable ozonide compound so formed is then reacted with triphenylphosphine to form the arylsulfonyl amine compound formula **XVII**. In Reaction 2 of Preparation 2, the arylsulfonyl amine compound of formula **XVII** is converted to the corresponding hydroxy ester compound of formula **VI** by reacting **XVII** with a compound of the formula



wherein W is lithium, magnesium, copper or chromium.

Scheme 1 refers to the preparation of compounds of the formula II, which are compounds of the formula I, wherein X and Y are carbon; R^4, R^6 and R^7 are hydrogen; and the dashed line between X and Y is absent. In reaction 1 of Scheme 1, the compound of formula **VI**, wherein the R^{25} protecting group is carbobenzyloxy, (C_1-C_6) alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding morpholinone compound of formula **V** by lactonization and subsequent Claisen rearrangement of the compound of formula **VI**. The reaction is facilitated by the removal of the R^{25} protecting group from the compound of formula **VI** and is carried out under conditions appropriate for that particular R^{25} protecting group in use. Such conditions include: (a) treatment with hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon, where R^{25} is carbobenzyloxy, (b) saponification where R^{25} is lower alkyl, (c) hydrogenolysis where R^{25} is benzyl, (d) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid, where R^{25} is tert-butyl, or (e) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R^{25} is allyl.

In reaction 2 of Scheme 1, the morpholinone compound of formula **V** is converted to the carboxylic acid compound of formula **IV** by reacting **V** with lithium hexamethyldisilazane in an aprotic solvent, such as tetrahydrofuran, at a temperature between about -90°C to about -70°C, preferably about -78°C. Trimethylsilyl chloride is then added to the reaction mixture and the solvent, tetrahydrofuran, is removed in vacuo and replaced with toluene. The resuling reaction mixture is heated to a temperature between about 100°C to about 120°C, preferably about 110°C, and treated with hydrochloric acid to form the carboxylic acid compound of formula **IV**.

In reaction 3 of Scheme 1, the carboxylic acid compound of formula IV is converted to the corresponding hydroxamic acid compound of formula III by treating IV with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenztriazole in a polar solvent, such as dimethylformamide, followed by the addition of hydroxylamine to the reaction mixture after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The hydroxylamine is preferably generated in situ from a salt form, such as hydroxylamine hydrochloride, in the presence of a base, such as N-methylmorpholine. Alternatively, a protected derivative of hydroxylamine or its salt form, where the hydroxyl group is protected as a tert-butyl, benzyl or allyl ether, may be used in the presence of (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorphosphate and a base, such as N-methylmorpholine. Removal of the hydroxylamine protecting group is carried out by hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride. N,O-bis(4-methoxybenzyl)hydroxylamine may also be used as the protected hydroxylamine derivative where deprotection is achieved using a mixture of methanesulfonic acid and trifluoroacetic acid.

In reaction 4 of Scheme 1, the hydroxamic acid compound of formula III is converted, if desired, to the corresponding piperidine compound of formula II by treating III with hydrogen and a hydrogenation catayst, such a 10% palladium on carbon.

Scheme 2 refers to the preparation of compounds of the formula VII, which are compound of the formula I wherein Y is nitrogen; X is carbon; R^1, R^2, R^3, R^4, R^7 and R^8 are hydrogen, and R^6 is absent. The starting materials of formula IX can be prepared according to methods well known to those of ordinary skill in the art. In reaction 1 of Scheme 2, the arylsulfonylpiperazine compound of formula IX, wherein R^{26} is carbobenzyloxy, benzyl or carbotertbutyloxy, is converted to the compound of formula VIII by reacting IX with a protected derivative of hydroxylamine of the formula

$$R^{27}ONH_2 \bullet HCl$$

wherein R^{27} is tertbutyl, benzyl or allyl, in the presence of dicyclohexylcarbodiimide, dimethylaminopyridine and an aprotic solvent, such as methylene chloride. The R^{26} protecting group is chosen such that it may be selectively removed in the presence of an without loss of the R^{27} protecting group, therefore, R^{26} cannot be the same as R^{27}.

Removal of the R^{26} protecting group from the compound of formula **IX** is carried out under conditions appropriate for that particular R^{26} protecting group in use. Such conditions include; (a) treatment with a hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon, where R^{26} is carbobenzyloxy, (b) hydrogenolysis where R^{26} is benzyl or (c) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid where R^{26} is carbotertbutyloxy.

In reaction 2 of Scheme 2, the compound of formula **VIII** is converted to the corresponding hydroxamic acid compound of formula **VII**, wherein R^5 is hydrogen or $(C_1\text{-}C_6)$alkyl, by reacting, if desired, **VIII** with an alkylhalide when R^5 is $(C_1\text{-}C_6)$alkyl. Subsequent removal of the R^{27} hydroxylamine protecting group is carried out by hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride.

Scheme 3 refers to the preparation of compounds of the formula X, which are compounds of the formula I wherein Y is nitrogen; X is carbon; R^2, R^7, R^8 and R^9 are hydrogen; R^3 and R^4 taken together are carbonyl; R^5 is hydrogen, and R^6 is absent. In reaction 1 of Scheme 3, the arylsulfonylamine compound of formula **XII**, wherein R^{25} is as defined above, is converted to the corresponding piperazine compound of formula **XI** by reacting **XII** with a carbodiimide and a base, such as triethylamine. The compound of formula **XI** is further reacted to give the hydroxamic acid compound of formula **X** according to the procedure described above in reaction 3 of Scheme 1.

Scheme 4 refers to the preparation of compounds of the formula XIII. The starting materials of formula XVIII can be prepared according to methods well known to those of ordinary skill in the art. Compounds of the formula XIII are compounds of the formula I wherein X is carbon, and the dotted line between X and Y is absent. In reaction 1 of Scheme 4, removal of the R^{28} protecting group and subsequent reductive amination of the compound of formula **XXII**, wherein Y is oxygen, sulfur or carbon, to give the corresponding imine compound of formula **XXI** is carried out under conditions appropriate for that particular R^{28} protecting group in use. Such conditions include those used above for removal of the R^{26} protecting group in reaction 1 of Scheme 2.

In reaction 2 of Scheme 4, the imine compound of formula **XXI** is converted to the corresponding piperidine compound of formula **XX** by reacting **XXI** with a nucleophile of the formula R^2M wherein M is lithium, magnesium halide or cerium

halide. The reaction is carried out in ether solvents, such as diethyl ether or tetrahydrofuran, at a temperature between about -78°C to about 0°C, preferably about -70°C.

In reaction 3 of Scheme 4, the sulfonation of the piperidine compound of formula **XX** to given the corresponding arylsulfonylpiperidine compound of formula **XIX** is carried out by reacting **XX** with an arylsulfonylhalide in the presence of triethylamine and an aprotic solvent, such as methylene chloride, tetrahydrofuran or dioxane, at a temperature between about 20°C to about 30°C, preferably at room temperature.

In reaction 4 of Scheme 4, the arylsulfonylpiperidine compound of formula **XIX** is converted to the hydroxamic acid compound of formula **XIII** according to the procedure described above in reaction 3 of Scheme 1.

Scheme 5 refers to the preparation of compounds of the formula XIV, which are compounds of formula I wherein Y is nitrogen, X is carbon, the dotted line between X and Y is absent, R^5 is hydrogen and R^6 is absent. In reaction 1 of Scheme 5, the compound of formula **XXVI**, wherein the R^{29} and R^{31} protecting groups are each independently selected from the group consisting of carbobenzyloxy, benzyl and carbotertbutyloxy and R^{30} is carbobenzyloxy, (C_1-C_6)alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding imine compound of formula **XXV** by the removal of the R^{29} protecting group and subsequent reductive amination of the compound of formula **XXVI**. The R^{29} protecting group is chosen such that it may be selectively removed in the presence of and without loss of the R^{31} protecting group. Removal of the R^{29} protecting group from the compound of formula **XXVI** is carried out under conditions appropriate for that particular R^{29} protecting group in use which will not affect the R^{31} protecting group. Such conditions include; (a) treatment with hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon, where R^{29} is carbobenzyloxy and R^{31} is tert-butyl, (b) saponification where R^{29} is (C_1-C_6)alkyl and R^{31} is tert-butyl, (c) hydrogenolysis where R^{29} is benzyl and R^{31} is (C_1-C_6) alkyl or tert-butyl, (d) treatment with a strong acid such as trifluoroacetic acid or hydrochloric acid where R^{29} is tert-butyl and R^{31} is (C_1-C_6)alkyl, benzyl or allyl, or (e) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R^{29} is allyl and R^{31} is (C_1-C_6)alkyl, benzyl or tert-butyl. The R^{30} protective group may be selected such that it is removed in the same reaction step as the R^{29} protecting group.

In reaction 2 of Scheme 5, the imine compound of formula **XXV** is converted to the corresponding compound of formula **XXIV** by reacting **XXV** with a nucleophile of the formula R^2M wherein M is lithium, magnesium halide or calcium halide. The reaction is carried out in ether solvents, such as diethyl ether or tetrahydrofuran, at a temperature between about -78°C to about 0°C, preferably about -70°C.

In reaction 3 of Scheme 5, the sulfonation of the piperidine compound of formula **XXIV** to give the corresponding arylsulfonylpiperidine compound of formula **III** is carried out according to the procedure described above in reaction 3 of Scheme 4.

In reaction 4 of Scheme 5, the arylsulfonylpiperidine compound of formula **XXIII** is converted to the hydroxamic acid compound of formula **XIV** by (1) removing the R^{30}, if needed, and R^{31} protecting groups from **XXIII** followed by (2) reacting **XXIII** according to the procedure described above in reaction 3 of Scheme 1. Removal of the R^{30} and R^{31} protecting groups from the compound of formula **XXIII** is carried out under conditions appropriate for that particular R^{30} and R^{31} protecting group in use. Such conditions include those used above for removal of the R^{25} protecting group in reaction 1 of Scheme 1.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium slats, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (the compounds of the invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 μg trypsin per 100 μg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 μg/10 μg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ——> 120 μM ——> 12 μM ——> 1.2 μM ——> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 μl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 μM in assay buffer. The assay is initiated by the addition of 50 μl substrate per well of the microfluor plate to give a final concentration of 10 μM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 μM then the inhibitors are assayed at concentrations of 0.3 μM, 0.03 μM, 0.03 μM and 0.003 μM.

Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2 substrate (10 μM) under the same conditions as inhibition of human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 μM, 3 μM, 0.3 μM and 0.03 μM. Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, then the inhibitors are assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.003 μM.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-$SCH[CH_2CH(CH_3)_2]CO$-Leu-Gly-OC_2H_5] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1 μl of a 10 mg/ml trypsin stock per 26 μg of stromelysin. The trypsin and stromelysin are incubated at 37°C for 15 minutes followed by 10 μl of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250 μl of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25 μg/ml. Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50 μl per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50 μL to the appropriate wells yields final

concentrations of 3 μM, 0.3 μM, 0.003 μM, and 0.0003 μM. All conditions are completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50 μl to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20μM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μM, 3μM, 0.3 μM, and 0.03 μM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, inhibitors are then assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.0003 μM.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180μ of the cell suspension was aliquoted into flate bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200μl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFα using the R&D ELISA Kit.

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be used including orally, parenterally and topically. In general, the compound of the invention will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the invention can be administered in a wide variety of different dosage forms. In general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight

polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

EXAMPLE 1

(2R, 4R)-1-(4-Methoxy-benzenesulfonyl)-4-(piperazine-1-carbonyl)-piperidine-2-carboxylic acid hydroxyamide hydrochloride

(a) To a stirred, cold (-78 °C) solution of (2R)-2-benzyloxycarbonylamino-pentanedioic acid 1-tert-butyl ester 5-methyl ester (5.6g, 15.9 mmol), prepared as described in J. Org. Chem., 55, 1711-1721 (1990) and J. Med. Chem., 39, 73-85 (1996), in 30 mL of tetrahydrofuran was added lithium bis(trimethylsilyl)amide (40 mL, 1 M in tetrahydrofuran, 39.8 mmol). The resulting mixture was stirred for 1 hour at-45 °C and then recooled to -78 °C. Allyl bromide (5.2 mL, 63.7 mmol) was then added. After 2 hours the reaction was quenched by the addition of 1 M aqueous hydrogen chloride at -78 °C. The mixture was then extracted with diethyl ether. The combined ethereal

extracts were washed with brine and the mixture was dried over sodium sulfate. After filtration and concentration of the filtrate, the crude product was purified by silica gel chromatography (elution with 1:5 ethyl acetate/hexanes) to provide (2R,4R)-4-allyl-2-benzyloxycarbonylamino-pentanedioic acid 1-tert-butyl ester 5-methyl ester.

(b) Ozone gas was bubbled through a stirred, cold (-78 °C) solution of (2R,4R)-4-allyl-2-benzyloxycarbonylamino-pentanedioic acid 1-tert-butyl ester 5-methyl ester (5.0 g, 12.8 mmol) in 100 mL of 10:1 methanol/methylene chloride, and 0.73 mL of acetic acid until a blue color persisted. Nitrogen gas was then bubbled through the solution until the blue color dissipated. The mixture was warmed to ambient temperature and dimethyl sulfide (2.8 mL, 3.83 mmol) was added. The mixture was stirred for 48 hours, diluted with methylene chloride, and washed with 10% aqueous sodium carbonate, brine, and the mixture was dried over sodium sulfate. Filtration and concentration of the filtrate provided (2R,4S)-6-methoxy-piperidine-1,2,4-tricarboxylic acid 1-benzyl ester 2-tert-butyl ester 4-methyl ester as a clear oil, which was used in the subsequent step without purification.

(c) A mixture of (2R,4S)-6-methoxy-piperidine-1,2,4-tricarboxylic acid 1-benzyl ester 2-tert-butyl ester 4-methyl ester (4.85 g, 11.9 mmol) and 10% palladium on carbon (500 mg) in 100 mL of ethanol was shaken under a 45 psi atmosphere of hydrogen gas for 1.5 hours. The mixture was filtered through nylon and the filtrate was concentrated to provide (2R,4R)-piperidine-2,4-dicarboxylic acid 2-tert-butyl ester 4-methyl ester as light yellow oil, which was used in the subsequent step without further purification.

(d) To a stirred, cold (0 °C) solution of (2R,4R)-piperidine-2,4-dicarboxylic acid 2-tert-butyl ester 4-methyl ester (2.7 g, 11.1 mmol) and triethylamine (4.6 ml, 33.3 mmol) in 30 mL of methylene chloride was added 4-methoxy-benzenesulfonyl chloride (2.3 g, 11.1 mmol). The mixture was warmed to ambient temperature and stirred for 4 hours. The reaction was quenched by the addition of aqueous ammonium chloride and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, and the organic mixture was dried over sodium sulfate. After filtration and concentration of the filtrate, the resulting crude product was purified by silica gel chromatography (elution with 3:8 ethyl acetate/hexanes) to provide (2R,4R)-1-(4-methoxy-benzenesulfonyl)-piperidine-2,4-dicarboxylic acid 2-tert-butyl ester 4-methyl ester.

(e) To a stirred, cold (0 °C) solution of (2R,4R)-1-(4-methoxy-benzenesulfonyl)-piperidine-2,4-dicarboxylic acid 2-tert-butyl ester 4-methyl ester (4.4 g, 10.6 mmol) in 30 mL of methylene chloride was added 10 mL of trifluoroacetic acid dropwise. The mixture was stirred for 1 hour at 0 °C and for 8 hours at ambient temperature. Concentration provided (2R,4R)-1-(4-methoxy-benzenesulfonyl)-piperidine-2,4-dicarboxylic acid 4-methyl ester, which was used in the subsequent step without purification.

(f) To a stirred solution of (2R,4R)-1-(4-methoxy-benzenesulfonyl)-piperidine-2,4-dicarboxylic acid 4-methyl ester (4.4 g, 12.3 mmol), O-benzylhydroxylamine hydrochloride (2.15 g, 13.5 mmol), and triethylamine (5.15 mL, 36.9 mmol) was added benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (6.0 g, 12.3 mmol) at ambient temperature. The resulting mixture was stirred for 24 hours. The mixture was diluted with ethyl acetate and washed with 1 M aqueous hydrogen chloride, aqueous sodium bicarbonate, and brine. The organic mixture was dried over magnesium sulfate, filtered, and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (elution with 5% methanol in methylene chloride) to provide (2R,4R)-2-benzyloxycarbamoyl-1-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid methyl ester as a colorless solid.

(g) To a stirred cold (0 °C) solution of (2R,4R)-2-benzyloxycarbamoyl-1-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid methyl ester (4.0 g, 8.6 mmol) in 10 mL of 9:1 methanol/water was added lithium hydroxide monohydrate (1.8 g, 43 mmol). The mixture was stirred for 2 hours before Amberlite IR-120 resin (96 g) was added. After 15 minutes, the mixture was filtered and the filtrate was concentrated to give (2R,4R)-2-benzyloxycarbamoyl-1-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylicacid,which was used in the subsequent reaction without purification.

(h) To a stirred solution of (2R,4R)-2-benzyloxycarbamoyl-1-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid (500 mg, 1.11 mmol), tert-butyloxycarbonyl piperazine (226 mg, 1.21 mmol), and triethylamine (0.47 mL, 3.33 mmol) was added benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (535 mg, 1.21 mmol) at ambient temperature. The resulting mixture was stirred for 24 hours. The mixture was diluted with ethyl acetate and washed with 1 M aqueous hydrogen chloride, aqueous sodium bicarbonate, and brine.

The organic mixture was dried over magnesium sulfate, filtered, and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (elution with 2% methanol in methylene chloride) to provide (2R,4R)-4-[2-benzyloxycarbamoyl-1-(4-methoxy-benzenesulfonyl)-piperidine-4-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester as a colorless solid.

(i) A mixture of (2R,4R)-4-[2-benzyloxycarbamoyl-1-(4-methoxy-benzene- sulfonyl)-piperidine-4-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester (500 mg, 0.81 mmol) and 5% palladium on barium sulfate (250 mg) in 10 mL of methanol was shaken under a 40 psi atmosphere of hydrogen gas for 1.5 hours. Filtration through nylon and concentration of the filtrate provided (2R,4R)-4-[2-hydroxycarbamoyl-1-(4-methoxy-benzenesulfonyl)-piperidine-4-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester as a colorless solid, which was used in the subsequent step without purification.

(j) Hydrogen chloride gas was bubbled through a cold (0°C) solution of (2R,4R)-4-[2-hydroxycarbamoyl-1-(4-methoxy-benzenesulfonyl)-piperidine-4-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester (420 mg, 0.8 mmol) for 10 minutes. After an additional 20 minutes the mixture was concentrated to provide (2R, 4R)-1-(4-methoxy-benzenesulfonyl)-4-(piperazine-1-carbonyl)-piperidine-2-carboxylic acid hydroxyamide hydrochloride as a colorless solid: Mass spectrum (atmospheric pressure chemical ionization; basic mode) m/z (M+H) 427, 366; ^{1}H NMR (dimethyl sulfoxide-d_6, 400 MHz, ppm) δ 10.70 (bd, 1 H, J = 2.7 Hz), 9.06 (bs, 2 H), 8.84 (bs, 1 H), 7.70 (dd, 2 H, J = 8.9, 2.9 Hz), 7.06 (dd, 2 H, J = 8.9, 2.9 Hz), 4.42 (bs, 1 H), 3.80 (s, 3 H), 3.80-3.20 (m, 6 H), 3.04 (m, 4 H), 2.76 (m, 1 H), 1.79 (bd, 1 H, J = 13.5 Hz), 1.52 (bd, 1 H, J = 12.6 Hz), 1.32 (m, 1 H) 1.14 (m 1H).

Example 2

(2R,4R)-1-[3-(4-Fluorophenoxy)-propane-1-sulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid methyl ester

(a) To a stirred solution of (2R,4R)-piperidine-2,4-dicarboxylic acid 2-tert-butyl ester 4-methyl ester (920 mg, 3.78 mmol) and triethylamine (1.58ml, 11.3 mmol) in 10 mL of methylene chloride was added a solution of 3-(4-fluorophenoxy)-propane-1-sulfonyl chloride (1.05 g, 4.16 mmol) in 2 mL of methylene chloride under a nitrogen atmosphere. The mixture was stirred for 16 hours at ambient temperature (22 °C), then

diluted with 20 mL of 1 N hydrochloric acid and 20 mL of methylene chloride. The organic layer was removed and washed with brine and dried over sodium sulfate. Filtration and concentration of the filtrate gave 2.8 g of a yellow oil, which was purified by flash chromatography (3:2 hexanes/ethyl acetate elution) to give 1.15 g (2R,4R)-1-[3-(4-fluoro-phenoxy)-propane-1-sulfonyl]-piperidine-2,4-dicarboxylic acid 2-tert-butyl ester 4-methyl ester of as a yellow oil.

(b) To a stirred, cold (0 °C) solution of (2R,4R)-1-[3-(4-fluorophenoxy)-propane-1-sulfonyl]-piperidine-2,4-dicarboxylic acid 2-tert-butyl ester 4-methyl ester (1.15 g, 2.5 mmol) in 10 mL of methylene chloride was added 10 mL of trifluroacetic acid. The mixture was allowed warm to ambient temperature (22 °C) over 16 hours. The mixture was concentrated in vacuo to give 970 mg of crude (2R,4R)-1-[3-(4-fluorophenoxy)-propane-1-sulfonyl]-piperidine-2,4-dicarboxylic acid 4-methyl ester as a orange solid.

(c) To a stirred solution of (2R,4R)-1-[3-(4-fluorophenoxy)-propane-1-sulfonyl]-piperidine-2,4-dicarboxylic acid 4-methyl ester (970 mg, 2.4 mmol) in 5 mL of methylene chloride was added triethylamine (1.0 mL, 7.2 mmol) and O-benzylhydroxylamine hydrochloride (410 mg, 2.64 mmol) at ambient temperature (22 °C). To the resulting solution was added benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (1.17 g, 2.64 mmol) and the mixture was stirred for 16 hours under a nitrogen atmosphere. The mixture was diluted with 25 mL of 1 N hydrochloric acid and 25 mL of ethyl acetate. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (2 x). The combined organic layers were washed with saturated aqueous sodium carbonate (1 x) and brine (1 x). The organic layer was dried (sodium sulfate), filtered, and the filtrate was concentrated in vacuo. Purification of the viscous yellow residue by flash chromatography (eluting with 1:1 ethyl acetate/hexanes) gave 810 mg of (2R,4R)-2-benzyloxycarbamoyl-1-[3-(4-fluorophenoxy)-propane-1-sulfonyl]-piperidine-4-carboxylic acid methyl ester as a clear oil.

(d) A mixture of (2R,4R)-2-benzyloxycarbamoyl-1-[3-(4-fluorophenoxy)-propane-1-sulfonyl]-piperidine-4-carboxylic acid methyl ester (800 mg, 1.57 mmol) and 200 mg of 5% palladium on barium sulfate in 15 mL of methanol was shaken in a Parr apparatus under a 40 psi hydrogen gas atmosphere for 2 hours. The catalyst was removed by passage of the mixture through a 0.45 μm nylon filter and the filtrate was concentrated to give 650 mg of (2R,4R)-1-[3-(4-fluorophenoxy)-propane-1-sulfonyl]-2-

hydroxycarbamoyl-piperidine-4-carboxylic acid methyl ester as a white foam: MS (atmospheric pressure chemical ionization) acidic mode, 417 (M-1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94-6.97 (m, 2 H), 6.80-6.83 (m, 2 H), 4.56 (s, 1 H), 4.03 (t, 2 H, J = 5.3 Hz), 3.83 (d, 1 H, J = 12.9 Hz), 3.68 (s, 3 H), 3.15-3.28 (m, 3 H), 2.76 (t, 1 H, J = 11.5 Hz), 2.54 (d, 1 H, J = 13.5 Hz), 2.26 (d, 2 H , J = 5.9 Hz), 2.02 (m, 1 H, J = 13.0 Hz), 1.73-1.78 (m, 1 H), 1.56-1.62 (m, 1 H).

Example 3

(2R,4R)-1-[3-(4-Fluorophenoxy)-propane-1-sulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid

To a stirred, cold (0 °C) solution of (2R,4R)-1-[3-(4-fluorophenoxy)-propane-1-sulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid methyl ester (400 mg, 0.96 mmol) in 5 mL of a methanol/water mixture (10:1) was added lithium hydroxide monohydrate (120 mg, 2.88 mmol). After 3 hours at 0 °C, prerinsed (methanol) Amberlite resin (4.1g) was added. The mixture was filtered and the filtrate was concentrated to give 370 mg of (2R,4R)-1-[3-(4-fluorophenoxy)-propane-1-sulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid as a white foam: MS (atmospheric pressure chemical ionization) acidic mode, 403 (M-1).

Example 4

(2R,4R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid methyl ester

4-(4-Fluoro-benzyloxy)-benzenesulfonyl chloride. MS: 465 (M-1).

The titled compound of example 4 was prepared by a method analogous to that described in example 2 using the reagents.

Example 5

(2R,4R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid. MS: 451 (M-1).

The titled compound of example 5 was prepared by a method analogous to that described in example 3 starting with 1-[4-(4-Fluoro-benzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid methyl ester.

Example 6

2R,3S-{1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidin-3-yl}-carbamic acid isopropyl ester

(a) To a stirred, cold (0 °C) solution of the known (Agami, C.; Hamon, L.; Kadouri-Puchot, C.; Le Guen, V J. Org. Chem. 1996, 61, 5736-5742) [4S-4α,9α,9aα]-1-oxo-4-phenyl-octahydro-pyrido[2,1-c][1,4]oxazine-9-carboxylic acid methyl ester (8.28 g, 2.86 mmol) in 100 mL of tetrahydrofuran was added 2.39 mL of concentrated hydrochloric acid. After 5 minutes the mixture was concentrated to dryness. The resulting solid was suspended in ethyl acetate and the mixture was stirred for an hour. The solids were collected by filtration, rinsed with ethyl acetate, and dried to give 9.04 g of a white solid.

Two grams of this solid was dissolved in 26 mL of 6 N hydrochloric acid and heated at reflux for 6 hours. The mixture was cooled to 0 °C and neutralized with 3 N sodium hydroxide and concentrated in vacuo. The resulting solids were suspended in chloroform and passed through a 45 μm nylon filter. The filtrate was concentrated to a yellow oil which was purified by flash chromatography (eluting with 2:1 hexanes/ethyl acetate with 1% acetic acid) to give 802 mg of [4S-4α,9α,9aα]1-oxo-4-phenyl-octahydro-pyrido[2,1-c][1,4]oxazine-9-carboxylic acid as white solid.

(b) To a stirred solution of [4S-4α,9α,9aα]1-oxo-4-phenyl-octahydro-pyrido[2,1-c][1,4]oxazine-9-carboxylic acid (568 mg, 2.06 mmol) in 15 mL of benzene was added triethylamine (0.28 mL, 2.06 mmol) and diphenylphosphoryl azide (0.44 mL, 2.06 mmol) at 22 °C under a nitrogen atmosphere. The mixture was stirred at 22 °C for 45 minutes and at reflux for 50 minutes before 2-propanol (3.2 mL, 41.2 mmol) was added. After an additional 20 hours at reflux the mixture was cooled to 22 °C and concentrated in vacuo. The residue was taken up in ethyl acetate and the resulting solution was washed with 5% citric acid, water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried (sodium sulfate), filtered, and the filtrate was concentrated in vacuo. The yellow residue was purified by flash chromatrography (eluting with 3:1 hexanes/ethyl acetate) to give 402 mg of [4S-4α,9α,9aα](1-oxo-4-phenyl-octahydro-pyrido[2,1-c][1,4]oxazin-9-yl)-carbamic acid isopropyl ester as white solid.

(c) A mixture of [4S-4a,9a,9aa](1-oxo-4-phenyl-octahydro-pyrido[2,1-c][1,4]oxazin-9-yl)-carbamic acid isopropyl ester (900 mg , 2.71 mmol) and 20% palladium hydroxide on carbon (920 mg) in 77 mL of ethanol/water (10:1) was shaken in a Parr apparatus under a 45 psi hydrogen gas atmosphere for 72 hours. The catalyst was removed by passage of the mixture through a 0.45 μm nylon filter and the filtrate was concentrated to give 610 mg of 2R,3S-3-isopropoxycarbonylamino-piperidine-2-carboxylic acid as white solid. MS: 229 (M-1).

(d) To a stirred solution of 2R,3S-3-isopropoxycarbonylamino-piperidine-2-carboxylic acid (320 mg, 1.39 mmol) in 5 mL of methylene chloride was added triethylamine (0.58 mL, 4.17 mmol) followed by 4-(4-fluorobenzyloxy)-benzenesulfonyl chloride (460 mg, 1.53 mmol). After 16 hours at 22 °C the mixture was partioned between 1 N hydrochloric acid and ethyl acetate. The organic layer was removed and washed with brine and dried over sodium sulfate. Filtration and concentration of the filtrate gave 480 mg of crude 2R,3S-1-[4-(4-fluorobenzyloxy)-benzenesulfonyl]-3-isopropoxycarbonylamino-piperidine-2-carboxylic acid as a light yellow solid.

(e) To a stirred, cold (0 °C) solution of crude 2R,3S-1-[4-(4-fluorobenzyloxy)-benzenesulfonyl]-3-isopropoxycarbonylamino-piperidine-2-carboxylic acid (380 mg, 0.77 mmol) in 5 mL of methylene chloride was added triethylamine (0.32 mL, 2.31 mmol) followed by benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (510 mg, 1.15 mmol). The resulting solution was stirred for 2 minutes at 0 °C under a nitrogen atmosphere before O-(trimethylsilylethyl)hydroxylamine hydrochloride (195 mg, 1.15 mmol) was added. The mixture was allowed to warm slowly to 22 °C over 14 hours. The mixture was concentrated in vacuo and the residue was diluted with water and extracted with ethyl acetate/diethyl ether (1:1; 3 x). The combined organic extracts were washed with saturated aqueous carbonate (2 x), water (2 x), and brine (1 x). The organic layer was dried (magnesium sulfate), filtered, and the filtrate was concentrated in vacuo. The yellow residue was purified by flash chromatography (eluting with 65:35 hexanes/ethyl acetate) to give 300 mg of 2R,3S-[1-[4-(4-fluorobenzyloxy)-benzenesulfonyl]-2-(2-trimethylsilanyl-ethoxycarbamoyl)-piperidin-3-yl]-carbamic acid isopropyl ester as a white foam. MS: 610 (M+1).

(f) To a stirred, cold (0 °C) solution of 2R,3S-[1-[4-(4-fluorobenzyloxy)-benzenesulfonyl]-2-(2-trimethylsilanyl-ethoxycarbamoyl)-piperidin-3-yl]-carbamic acid isopropyl ester (265 mg, 0.44 mmol) in 4 mL of methylene chloride was added 3 mL of trifluoroacetic acid. The resulting colorless solution was allowed to warm to 23 °C over 2 hours and was stirred for an additional 28 hours. The mixture was concentrated in vacuo to a solid/foam, which was suspended in ethyl acetate hexanes (1:6) and stirred for 10 hours. The white solids were collected by filtration, rinsed with hexanes, and purified further by flash chromatography (eluting with 7:3 ethyl acetate/hexanes with 1% acetic acid) to give 130 mg of 2R,3S-1-[4-(4-fluorobenzyloxy)benzenesulfonyl]-2-hydroxycarbamoyl-piperidin-3-yl}-carbamic acid isopropyl ester as a white solid/foam. MS: 510 (M+1).

Example 7

3-(S)-4-(4'-Fluorobiphenyl-4-sulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide

(a) To a stirred solution of the known (PCT Publication WO 97/20824) 3-(S)-dimethylthexylsilyl-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylate (1.17 g, 3.70 mmol) in 6 mL of methylene chloride was added triethylamine (1.02 mL, 7.40 mmol) followed by 4'-fluorobiphenylsulfonyl chloride (1.0 g, 3.70 mmol). The resulting solution was stirred for 56 hours at 23 °C. The reaction mixture was diluted with methylene chloride and washed with water. The organic layer was concentrated in vacuo; the residue was dissolved in methanol, and the mixture was heated at reflux for 6 hours. The mixture was cooled to 23 °C and concentrated in vacuo. The residue was purified by flash chromatography (eluting with 3:7 ethyl acetate/hexanes with 0.1% acetic acid) to give 670 mg of 3-(S)-4-(4'-fluorobiphenyl-4-sulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid as a white foam/solid. MS: 427 ($M+NH_4$).

(b) To a stirred, cold (0 °C) solution of 3-(S)-4-(4'-fluorobiphenyl-4-sulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid (605 mg, 1.48 mmol) in 5 mL of methylene chloride was added triethylamine (0.62 mL, 4.43 mmol) under a nitrogen atmosphere. Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (980 mg, 2.22 mmol) was added and the resulting solution was stirred for 5 minutes before O-(trimethylsilylethyl)hydroxylamine hydrochloride (376 mg, 2.22 mmol) was added. The ice bath was removed and the mixture was

stirred for 20 hours at 23 °C. The mixture was diluted with aqueous ammonium chloride and extracted with 1:1 ethyl acetate/diethyl ether (3 x). The combined organic extracts were washed with saturated aqueous sodium carbonate (2 x), water (1 x), and brine (1 x). The organic layer was dried (magnesium sulfate), filtered, and the filtrate was concentrated in vacuo. The residual yellow oil was purified by flash chromatography (eluting with 3:7 ethyl acetate/hexanes) to give 650 mg of 3-(S)-4-(4'-fluorobiphenyl-4-sulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid (2-trimethylsilanyl-ethoxy)-amide as a white foam. MS: 523 (M-1).

(c) A solution of 3-(S)-4-(4'-fluorobiphenyl-4-sulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid (2-trimethylsilanyl-ethoxy)-amide (650 mg, 1.24 mmol) in 8 mL of trifluoroacetic acid was stirred for at 22 °C for 16 hours. The mixture was concentrated in vacuo and the residue was triturated with methylene chloride and diethyl ether. The solvent was removed to give 550 mg of a tan solid. The solid was suspended in 1:1 diethyl ether/hexanes and stirred gently for 20 hours. The solids were collected by filtration (1:1 diethyl ether/hexanes rinsing) and dried to give 470 mg of 3-(S)-4-(4'-fluorobiphenyl-4-sulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide as white solid. MS: 423 (M-1).

Example 8

3-(S)-4-[4-(4-Fluorobenzyloxy)benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3 -carboxylic acid hydroxyamide

(a) To a stirred, cold (0 °C) solution of the known (Belgian Patent Publication BE 893025) 2,2-dimethyl-thiomorpholine-3-carboxylic acid (600 mg, 3.42 mmol) in 10 mL of 1:1 water/dioxane was added 6 N sodium hydroxide (1.2 mL, 7.1 mmol). To the resulting solution 4-(4-fluorobenzyloxy)benzenesulfonyl chloride (1.08 g, 3.77 mmol) was added. After 30 and 60 minutes an additional 1 gram of 4-(4-fluorobenzyloxy)benzenesulfonyl chloride and 1.2 mL of 6 N sodium hydroxide was added. The mixture (pH ca. 12) was diluted with water and extracted with diethyl ether (1 x). The ethereal layer was washed with 1 N sodium hydroxide; the combined basic aqueous layers were acidified to pH 3 using concentrated hydrochloric acid, and the acidic mixture was extracted with ethyl acetate (3 x). The combined organic extracts were dried (sodium sulfate), filtered, and the filtrate was concentrated in vacuo to give 820 mg of 3-(S)-4-[4-(4-

fluorobenzyloxy)benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3-carboxylic acid as a white solid. MS: 438 (M-1).

(b) To a stirred, cold (0 °C) solution of 3-(S)-4-[4-(4-fluorobenzyloxy)-benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3-carboxylic acid (820 mg, 1.87 mmol) in 5 mL of methylene chloride was added triethylamine (0.52 mL, 3.74 mmol) under a nitrogen atmosphere. Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (1.24 g, 2.81 mmol) was added and the resulting solution was stirred for 5 minutes before O-(tert-butyldimethylsilyl)hydroxylamine (550 mg, 3.74 mmol) was added.The ice bath was removed and the mixture was stirred for 16 hours at 23 °C. The mixture was diluted with aqueous ammonium chloride and extracted with ethyl acetate (3 x). The combined organic extracts were washed with water, brine, and dried over sodium sulfate. Filtration and concentration of the filtrate gave a viscous yellow oil, which was purified by flash chromatography (eluting with 1:3 ethyl acetate/hexanes) to give 270 mg of 3-(S)-4-[4-(4-fluorobenzyloxy)benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3-carboxylic acid (tert-butyldimethylsiloxy)-amide as a white foam. MS: 569 (M+1).

(c) To a stirred, cold (0 °C) solution of 3-(S)-4-[4-(4-fluorobenzyloxy)-benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3-carboxylic acid (tert-butyldimethylsiloxy)-amide (270 mg, 0.47 mmol) in 10 mL of tetrahydrofuran was added two drops of concentrated hydrochloric acid. After 30 minutes the mixture was diluted with 15 mL of tetrahydrofuran and the mixture was concentrated in vacuo to a volume of ca. 5 mL. The volume was adjusted to ca. 25 mL with tetrahyrofuran and the mixture was concentrated again to ca. 5 mL. This process was repeated twice more before the mixture was finally concentrated to dryness. The resulting solids were suspended in a mixture of hexanes and diethyl ether and the mixture was stirred for 16 hours. The solid were collected by filtration, rinsed with diethyl ether,and dried to give 180 mg of 3-(S)-4-[4-(4-fluorobenzyloxy)benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3 -carboxylic acid hydroxyamide as a white solid. MS: 453 (M-1). ^{1}H NMR (400 MHz, dmso-d_6) δ 10.63 (s, 1 H), 8.80 (bs, 1 H) 7.59-7.61 (m, 2 H), 7.46-7.50 (m, 2 H), 7.17-7.21 (m, 2 H), 7.09-7.12 (m, 2 H), 5.12 (s, 2 H), 3.99 (s, 1 H), 3.87-3.93 (m, 1 H), 3.69 (d, 1 H, J = 12.7 Hz), 2.78-2.86 (m, 1 H), 2.44-2.50 (m, 1 H), 1.35 (s, 3 H), 1.12 (s, 3H).

Preparation 1

4-(4-Fluorobenzyloxy)benzenesulfonyl chloride

To a stirred solution of 4-hydroxybenzenesulfonic acid sodium salt dihydrate (5.13 g, 22.1 mmol) in 23 mL of 1 N sodium hydroxide was added a solution of 4-fluorobenzyl bromide (3.3 mL, 26.5 mmol) in 20 mL of ethanol. The mixture was heated at reflux for two days, then cooled to ambient temperature (22 °C), whereupon a white precipitate formed. The flaky white solids were collected by filtration, rinsed with ethyl acetate and diethyl ether, and dried to give 4. 95 g of 4-(4-fluoro-benzyloxy)-benzenesulfonic acid sodium salt. A stirred solution of 4-(4-fluoro-benzyloxy)-benzenesulfonic acid sodium salt (13.0 g, 42.7 mmol) in 50 mL of thionyl chloride and two drops of dimethylformamide was heated at a gentle reflux for 8 hours. The mixture was concentrated to a yellow solid which was suspended in ethyl acetate and filtered. The filtrate was concentrated to 11.2 g of 4-(4-fluorobenzyloxy)benzenesulfonyl chloride as a light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.98 (m, 2 H), 7.38-7.41 (m, 2 H), 7.08-7.12 (m, 4 H), 5.12 (s, 2 H).

Preparation 2

3-(4-Fluorophenoxy)-propane-1-sulfonyl chloride

To a stirred solution of 4-fluorophenol (5.0 g, 44.6 mmol) in 50 mL of toluene was added sodium hydride (60% dispersion in mineral oil, 1.78 g, 44.6 mmol) at ambient temperature (22 °C). After 20 minutes, a solution of 1,3-propane sulfone (3.9 mL, 44.6 mmol) in toluene was added slowly and the mixture was stirred for 16 hours. The reaction was quenched by the addition of methanol and the mixture was concentrated in vacuo to an off-white solid. This solid was suspended in ethyl acetate, filtered, and the solids were collected and dried to give 10.9 g of 3-(4-fluorophenoxy)-propane-1-sulfonic acid sodium salt as an off-white powder. A stirred solution of 3-(4-fluorophenoxy)-propane-1-sulfonic acid sodium salt (2.0 g, 7.8 mmol) in 10 mL of thionyl chloride and one drops of dimethylformamide was heated at reflux for 16 hours. The mixture was then cooled to 0 °C, diluted with 25 mL of diethyl ether, and the reaction was quenched by the slow addition of water. The organic layer was removed and the aqueous layer was extracted with 25 mL of diethyl ether. The combined organic layers were washed with brine and dried over

sodium sulfate. Filtration and concentration gave 1.75 g of 3-(4-fluoro-phenoxy)-propane-1-sulfonyl chloride as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96-7.00 (m, 2 H), 6.80-6.84 (m, 2 H), 4.10 (t, 2 H, J = 5.5 Hz), 3.91 (t, 2 H, J = 7.5 Hz) 2.47-2.54 (m, 2 H).

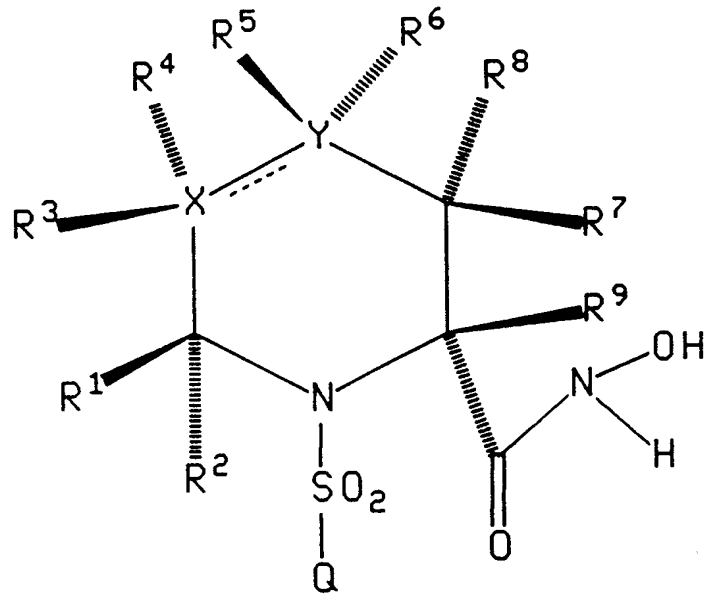
Preparation 3

4'-Fluorobiphenylsulfonyl chloride

Chlorosulfonic acid (8.7 mL, 0.13 mole) was added dropwise to stirred cold (0 °C) 4-fluorobiphenyl (10.2 g, 59 mmol). After 30 minutes at 0 °C the reaction mixture was poured onto ice. The resulting white precipitate was collected by filtration and dissolved in chloroform. The chloroform solution was washed with water, brine, dried over magnesium sulfate, and concentrated to afford a white solid. The desired 4'-fluorobiphenylsulfonyl chloride (4.3 g), was separated from 4'-fluorobiphenylsulfonic acid by crystallization of the latter from ethyl acetate and crystallization of the remaining material from hexanes.

CLAIMS

1. A compound of the formula



I

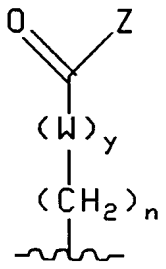
or the pharmaceutically acceptable salt thereof, wherein the broken line represents an optional double bond;

X is carbon, oxygen or sulfur;

Y is carbon, oxygen, sulfur, SO, SO_2 or nitrogen;

R^1, R^2 R^3, R^4 R^5, R^6, R^7, R^8 and R^9 are selected from the group consisting of hydrogen, (C_1-C_6)alkyl optionally substituted by one or two groups selected from (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, halo, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_2-C_9)heteroarylamino, (C_2-C_9)heteroarylthio, (C_2-C_9)heteroaryloxy, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, hydroxy, piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, amino, (C_1-C_6)alkylamino or ((C_1-C_6)alkyl)$_2$amino; (C_2-C_6)alkenyl, (C_6-C_{10})aryl(C_2-C_6)alkenyl, (C_2-C_9)heteroaryl(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-C_{10})aryl(C_2-C_6)alkynyl, (C_2-C_9)heteroaryl(C_2-C_6)alkynyl, (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, perfluoro(C_1-C_6)alkyl, (C_6-C_{10})aryl,

$(C_2$-$C_9)$heteroaryl, $(C_6$-$C_{10})$arylamino, $(C_6$-$C_{10})$arylthio, $(C_6$-$C_{10})$aryloxy, $(C_2$-$C_9)$heteroarylamino, $(C_2$-$C_9)$heteroarylthio, $(C_2$-$C_9)$heteroaryloxy, $(C_3$-$C_6)$cycloalkyl, $(C_1$-$C_6)$alkyl(hydroxymethylene), piperidyl, $(C_1$-$C_6)$alkylpiperidyl, $(C_1$-$C_6)$acylamino, $(C_1$-$C_6)$acylthio, $(C_1$-$C_6)$acyloxy, $R^{10}(C_1$-$C_6)$alkyl or a group of the formula



II

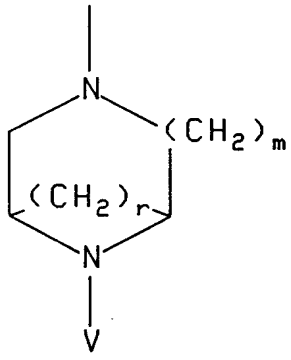
;

wherein n is 0 to 6;

y is 0 or 1;

W is oxygen or $>NR^{24}$;

Z is $-OR^{11}$, $-NR^{24}R^{11}$, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl or a bridged diazabicycloalkyl ring selected from the group consisting of



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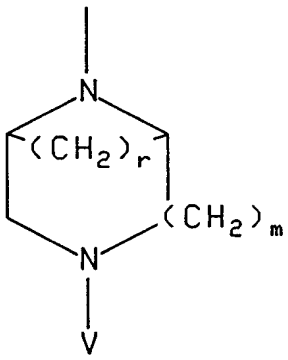

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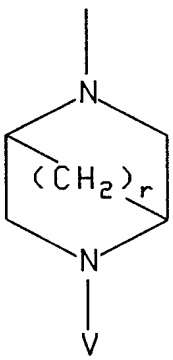

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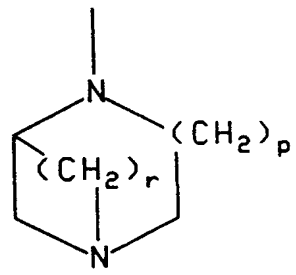

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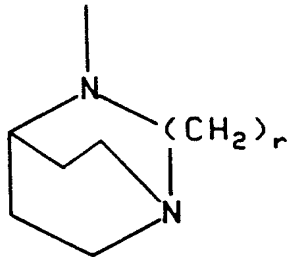


e

wherein r is 1, 2 or 3;

m is 1 or 2;

p is 0 or 1; and

V is hydrogen, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_6)$alkyl(C=O)-, $(C_1\text{-}C_6)$ alkoxy(C=O)-, $(C_6\text{-}C_{10})$aryl(C=O)-, $(C_6\text{-}C_{10})$aryloxy(C=O)-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl(C=O)-, $(C_6\text{-}C_{10})$aryl-$(C_1\text{-}C_6)$alkoxy(C=O)-, or $(C_1\text{-}C_6)$alkoxy(C=O)-O-;

wherein each heterocyclic group (i.e., each Z cyclic group containing one or more heteroatoms) may optionally be independently substituted by one or two groups selected from hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_{10})$acyl, $(C_1\text{-}C_{10})$acyloxy, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$acyloxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkylthio$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylthio, $(C_6\text{-}C_{10})$arylthio$(C_1\text{-}C_6)$alkyl, $R^{12}R^{13}N$-, $R^{12}R^{13}NSO_2$-, $R^{12}R^{13}N(C=O)$-, $R^{12}R^{13}N(C=O)$-$(C_1\text{-}C_6)$alkyl, $R^{14}SO_2$-, $R^{14}SO_2NH$-, $R^{15}(C=O)$-$[N(R^{12})]$-, $R^{16}O(C=O)$-, or $R^{16}O(C=O)$-$(C_1\text{-}C_6)$alkyl;

wherein R^{10} is $(C_1\text{-}C_6)$acylpiperazinyl, $(C_6\text{-}C_{10})$arylpiperazinyl, $(C_2\text{-}C_9)$heteroarylpiperazinyl, $(C_1\text{-}C_6)$alkylpiperazinyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylpiperazinyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkylpiperazinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl,

piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_2-C_9)heteroarylpiperidyl, (C_1-C_6)alkylpiperidyl(C_1-C_6)alkyl, (C_6-C_{10})arylpiperidyl(C_1-C_6)alkyl, (C_2-C_9)heteroarylpiperidyl-(C_1-C_6)alkyl or (C_1-C_6)acylpiperidyl;

R^{11} is hydrogen, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_2-C_9)heteroaryl(C_1-C_6)alkyl, 5-indanyl, -CHR^{17}O-(C=O)-R^{18} or -CH_2(C=O)-$NR^{19}R^{20}$;

R^{12} and R^{13} are each independently hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_2-C_9)heteroaryl(C_1-C_6)alkyl or R^{12} and R^{13} may be taken together with the nitrogen to which they are attached to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or thiomorpholinyl ring;

R^{14} is trifluoromethyl, (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_2-C_9)heteroaryl(C_1-C_6)alkyl;

R^{15} is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_1-C_6)aryl(C_1-C_6)alkyl(C_6-C_{10})aryl(C_1-C_6)alkoxy or (C_2-C_9)heteroaryl(C_1-C_6)alkyl;

R^{16} is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, 5-indanyl, -[$CH(R^{17})$]O-(C=O)-R^{18}, -CH_2(C=O)-$NR^{19}R^{20}$, or R^{21}O(C_1-C_6)alkyl;

R^{17} is hydrogen or (C_1-C_6)alkyl;

R^{18} is (C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_6-C_{10})aryl;

R^{19} and R^{20} are each independently hydrogen or (C_1-C_6)alkyl or may be taken together with the nitrogen to which they are attached to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or thiomopholinyl ring;

R^{21} is $H_2N(CHR^{22})$(C=O)-;

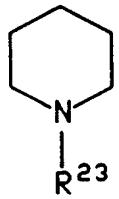
R^{22} is the side chain of a natural D- or L-amino acid;

R^{23} is hydrogen, (C_1-C_6)acyl, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl or (C_1-C_6)alkylsulfonyl;

R^{24} wherever it occurs is independently hydrogen or (C_1-C_6)alkyl;

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6 may be taken together to form a carbonyl;

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, or R^7 and R^8 may be taken together to form a (C_3-C_6)cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula



Q is (C_1-C_{10})alkyl, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_2-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_2-C_9)heteroaryl optionally substituted by fluoro, chloro, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl;

with the proviso that when y is zero, Q is other than (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_9)heteroaryl, and anyone of R^1-R^9 is a group of formula II then Z must be substituted when defined as azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl, (C_1-C_{10})acylpiperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_2-C_9)heteroarylpiperazinyl or a bridged diazabicycloalkyl ring;

with the proviso that when y is zero, Q is other than (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_9)heteroaryl, then at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 must be defined as the group of formula II;

with the proviso that when Q is $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_9)$heteroaryl, then R^1-R^9 may be other than formula II but when R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are all defined by hydrogen or $(C_1\text{-}C_6)$alkyl, either X or Y is oxygen, sulfur, SO, $-SO_2-$ or nitrogen, or the broken line represents a double bond;

with the proviso that R^7 is other than hydrogen only when R^8 is other than hydrogen;

with the proviso that R^6 is other than hydrogen only when R^5 is other than hydrogen;

with the proviso that R^3 is other than hydrogen only when R^4 is other than hydrogen;

with the proviso that R^2 is other than hydrogen only when R^1 is other than hydrogen;

with the provisio that when R^1, R^2 and R^9 are a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 2- or 6- positions of the ring;

with the proviso that when X is nitrogen, R^4 is not present;

with the proviso that when X is oxygen, sulfur, SO, SO_2 or nitrogen and when one or more of the group consisting of R^1, R^2, R^5 and R^6, is a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 4- or 6- positions;

with the proviso that when Y is oxygen, sulfur, SO, SO_2 or nitrogen and when one or more of the group consisting of R^3, R^4, R^7 and R^8, are independently a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 3- or 5- positions;

with the proviso that when X is oxygen, sulfur, SO or SO_2, R^3 and R^4 are not present;

with the proviso that when y is 1 and W is NR^{24} or oxygen, Z cannot be hydroxy;

with the proviso that when Y is oxygen, sulfur, SO or SO_2, R^5 and R^6 are not present;

with the proviso that when Y is nitrogen, R^6 is not present;

with the proviso that when the broken line represents a double bond, R^4 and R^6 are not present;

with the proviso that when R^3 and R^5 are independently a substituent comprising a heteroatom when the broken line represents a double bond, the heteroatom cannot be directly bonded to positions X and Y;

with the proviso that when either the X or Y position is oxygen, sulfur, SO, SO_2 or nitrogen, the other of X or Y is carbon;

with the proviso that when X or Y is defined by a heteroatom, the broken line does not represent a double bond.

2. A compound according to claim 1, wherein Y is carbon, SO, SO_2, or oxygen.

3. A compound according to claim 1, wherein Q is $(C_6\text{-}C_{10})$aryl-$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl wherein each terminal aryl group is optionally substituted by fluoro.

4. A compound according to claim 1, wherein R^2, R^3, R^6, R^7 and R^9 are hydrogen.

5. A compound according to claim 1, wherein Y is carbon; Q is $(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl.

6. A compound according to claim 1, wherein Y is oxygen, sulfur, SO, or SO_2.

7. A compound according to claim 3, wherein Y is oxygen, sulfur, SO or SO_2.

8. A compound according to claim 1, wherein at least one of R^7-R^9 is other than hydrogen.

9. A compound according to claim 3, wherein at least one of R^7-R^9 is other than hydrogen.

10. A compound according to claim 6, wherein at least one of R^7-R^9 is other than hydrogen.

11. A compound according to claim 7, wherein at least one of R^7-R^9 is other than hydrogen.

12. A compound according to claim 1, wherein at least one of R^7-R^9 is $(C_1$-$C_6)$alkyl.

13. A compound according to claim 3, wherein at least one of R^7-R^9 is $(C_1$-$C_6)$alkyl.

14. A compound according to claim 6, wherein at least one of R^7-R^9 is $(C_1$-$C_6)$alkyl.

15. A compound according to claim 7, wherein at least one of R^7-R^9 is $(C_1$-$C_6)$alkyl.

16. A compound according to claim 1, wherein at least one of R^7-R^9 is methyl.

17. A compound according to claim 3, wherein at least one of R^7-R^9 is methyl.

18. A compound according to claim 6, wherein at least one of R^7-R^9 is methyl.

19. A compound according to claim 7, wherein at least one of R^7-R^9 is methyl.

20. A compound according to claim 1, wherein R^7 and R^8 are taken together to form a carbonyl and R^9 is $(C_1$-$C_6)$alkyl.

21. A compound according to claim 3, wherein R^7 and R^8 are taken together to form a carbonyl and R^9 is $(C_1$-$C_6)$alkyl.

22. A compound according to claim 6, wherein R^7 and R^8 are taken together to form a carbonyl and R^9 is $(C_1\text{-}C_6)$alkyl.

23. A compound according to claim 7, wherein R^7 and R^8 are taken together to form a carbonyl and R^9 is $(C_1\text{-}C_6)$alkyl.

24. A compound according to claim 1 wherein R^7 and R^8 are each methyl.

25. A compound according to claim 3 wherein R^7 and R^8 are each methyl.

26. A compound according to claim 6 wherein R^7 and R^8 are each methyl.

27. A compound according to claim 7 wherein R^7 and R^8 are each methyl.

28. A compound according to claim 1 wherein R^7 and R^8 are taken together to form a $(C_3\text{-}C_6)$cycloalkyl group.

29. A compound according to claim 3 wherein R^7 and R^8 are taken together to form a $(C_3\text{-}C_6)$cycloalkyl group.

30. A compound according to claim 6 wherein R^7 and R^8 are taken together to form a $(C_3\text{-}C_6)$cycloalkyl group.

31. A compound according to claim 8 wherein R^7 and R^8 are taken together to form a $(C_3\text{-}C_6)$cycloalkyl group.

32. A compound according to claim 1, wherein said compound is selected from the group consisting of:

(2R,4R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid;

(2R,4R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid methyl ester;

(2R,4R)-1-[3-(4-Fluorophenoxy)-propane-1-sulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid;

(2R,4R)-1-[3-(4-Fluorophenoxy)-propane-1-sulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid methyl ester;

(2R,3S)-{1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidin-3-yl}-carbamic acid isopropyl ester;

3-(S)-4-(4'-Fluorobiphenyl-4-sulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

3-(S)-4-[4-(4-Fluorobenzyloxy)benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

(2R,4S)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-4-hydroxy-piperidine-2-carboxylic acid hydroxyamide; and

(2R,4R)-1-(4-Methoxybenzenesulfonyl)-4-(piperazine-1-carbonyl)-piperidine-2-carboxylic acid hydroxyamide hydrochloride.

33. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, mucular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

34. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

35. A method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human,

comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/IB 98/00064

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/62 C07D241/24 C07D279/12 C07D211/60 C07D211/90
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 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 33172 A (PFIZER INC) 24 October 1996 see the whole document	1-33

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 1998	11. 05. 98

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	Luyten, H

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

INTERNATIONAL SEARCH REPORT

Inte onal application No.
PCT/IB 98/00064

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.: 34-35
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 34-35 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. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

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

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Intern ...al Application No
PCT/IB 98/00064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 0821671 A	04-02-98
		FI 973974 A	16-10-97
		NO 961585 A	21-10-96
		SG 43350 A	17-10-97

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(51) International Patent Classification 6 :
C07C 311/29, C07D 309/14, 211/66, A61K 31/19, 31/215, 31/35, 31/445

A1

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(30) Priority Data:
60/055,207 8 August 1997 (08.08.97) US

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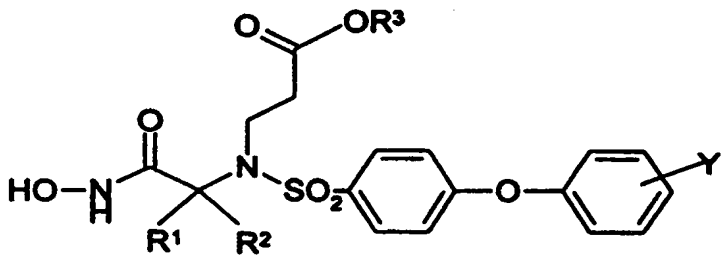
(54) Title: ARYLOXYARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES

(57) Abstract

A compound of formula (I) or the pharmaceutically acceptable salts thereof, wherein R^1 is $(C_1–C_6)$alkyl; R^2 is $(C_1–C_6)$alkyl; or R^1 and R^2 taken together with the carbon atom to which they are attached form a ring selected from $(C_5–C_7)$cycloalkyl, 4–tetrahydropyranyl and 4–piperidinyl; R^3 is hydrogen or $(C_1–C_6)$alkyl; and Y is a substituent of any of the carbon atoms of the phenyl ring capable of supporting an additional bond, preferably from 1 to 2 substituents (more preferably one substituent, most preferably one substituent in the 4–position) on the phenyl ring, independently selected from hydrogen, fluoro, chloro, trifluoromethyl, $(C_1–C_6)$alkoxy, trifluoromethoxy, difluoromethoxy and $(C_1–C_6)$alkyl.



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ARYLOXYARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES

Background of the Invention

The present invention relates to aryloxyarylsulfonylamino hydroxamic acid derivatives. These compounds are selective inhibitors of matrix metalloproteinase-13 and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, bone resorption, loosening of artificial joint implants, atherosclerosis, multiple sclerosis, occular angiogenisis (for example macular degeneration) and other diseases characterized by matrix metalloproteinase activity.

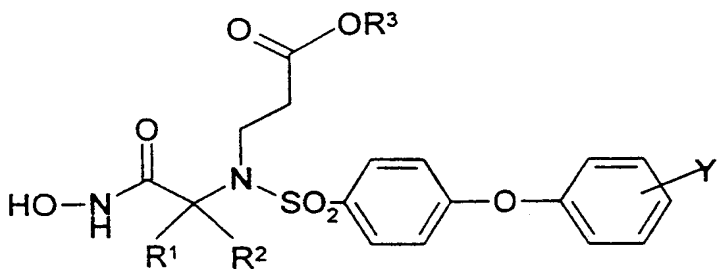
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to the pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Friers, FEBS Letters, 1991, 285. 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

Summary of the Invention

The present invention relates to a compound of the formula



I

or the pharmaceutically acceptable salts thereof, wherein

R^1 is $(C_1\text{-}C_6)$alkyl;

R^2 is $(C_1\text{-}C_6)$alkyl;

or R^1 and R^2 taken together with the carbon atom to which they are attached form a ring selected from $(C_5\text{-}C_7)$cycloalkyl , 4-tetrahydropyranyl and 4-piperidinyl;

R^3 is hydrogen or $(C_1\text{-}C_6)$alkyl; and

Y is a substituent on any of the carbon atoms of the phenyl ring capable of supporting an additional bond, preferably from 1 to 2 substituents (more preferably one substituent, most preferably one substituent in the 4-position) on the phenyl ring, independently selected from hydrogen, fluoro, chloro, trifluoromethyl, $(C_1\text{-}C_6)$alkoxy. trifluoromethoxy, difluoromethoxy and $(C_1\text{-}C_6)$alkyl.

The term "alkyl", as used herein. unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein. includes O-alkyl groups wherein "alkyl" is defined above.

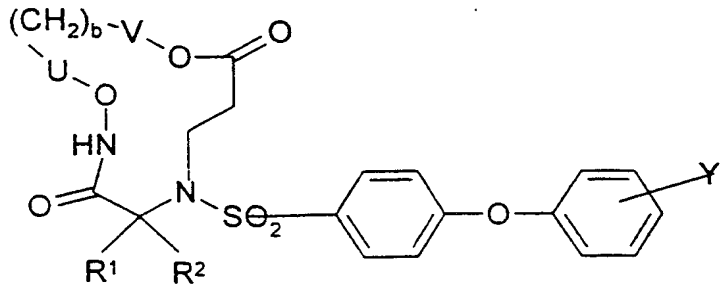
The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those

compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

This invention also encompasses pharmaceutical compositions containing and methods of treating or preventing comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain. Prodrugs also include compounds of formula I in which the hydroxamic acid and carbonyl moiety when taken together form a group of the formula



wherein R^1, R^2 and Y are as defined in formula I and U and V are independently carbonyl, methylene, SO_2 or SO_3, and b is an integer from one to three wherein each methylene group is optionally substituted with hydroxy.

Preferred compounds of formula I include those wherein Y is hydrogen, fluoro or chloro, preferably 4-fluoro or 4-chloro.

Other preferred compounds of formula I include those wherein R^1 and R^2 taken together with the carbon atom to which they are attached form a cyclopentyl or 4-tetrahydropyranyl ring.

Other preferred compounds of formula I include those wherein R^1 and R^2 are both methyl.

Other preferred compounds of formula I include those wherein R^3 is hydrogen.

Specific preferred compounds of formula I include the following:

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxy-carbamoylcyclopentyl)amino]-propionic acid ethyl ester,

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxy-carbamoylcyclopentyl) amino]propionic acid,

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxycarbamoyl-1-methylethyl)amino]propionic acid ethyl ester, and

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxy-carbamoyl-1-methylethyl)amino]propionic acid.

Other compounds of formula I include the following:

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid,

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid ethyl ester,

3-[[4-(4-chlorophenoxy)benzenesulfonyl]-(4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid,

3-[[4-(4-chlorophenoxy)benzenesulfonyl]-(4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid ethyl ester,

3-[(4-hydroxycarbamoyltetrahydropyran-4-yl)-(4-phenoxybenzenesulfonyl)amino]-propionic acid,

3-[(4-hydroxycarbamoyltetrahydropyran-4-yl)-(4-phenoxybenzenesulfonyl)amino]-propionic acid ethyl ester,

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(4-hydroxycarbamoylpiperidin-4-yl)-amino]propionic acid ethyl ester,

3-[[4-(4-chlorophenoxy)benzenesulfonyl]-(1-hydroxycarbamoyl-1-methylethyl)amino]-propionic acid,

3-[[4-(4-chlorophenoxy)benzenesulfonyl]-(1-hydroxycarbamoyl-1-methylethyl)amino]-propionic acid ethyl ester,

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxycarbamoylcyclohexyl)amino]-propionic acid,

3-[(1-hydroxycarbamoylcyclopentyl)-(4-phenoxybenzenesulfonyl)amino]propionic acid, and

3-[[4-(4-chlorophenoxy)benzenesulfonyl]-(1-hydroxycarbamoylcyclopentyl)amino]-propionic acid.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, bone resorption, loosening of artificial joint implants, atherosclerosis, multiple sclerosis, occular angiogenisis (for example macular degeneration) and other diseases characterized by matrix metalloproteinase activity, or (b) the selective inhibition of matrix metalloproteinase-13 in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments and a pharmaceutically acceptable carrier.

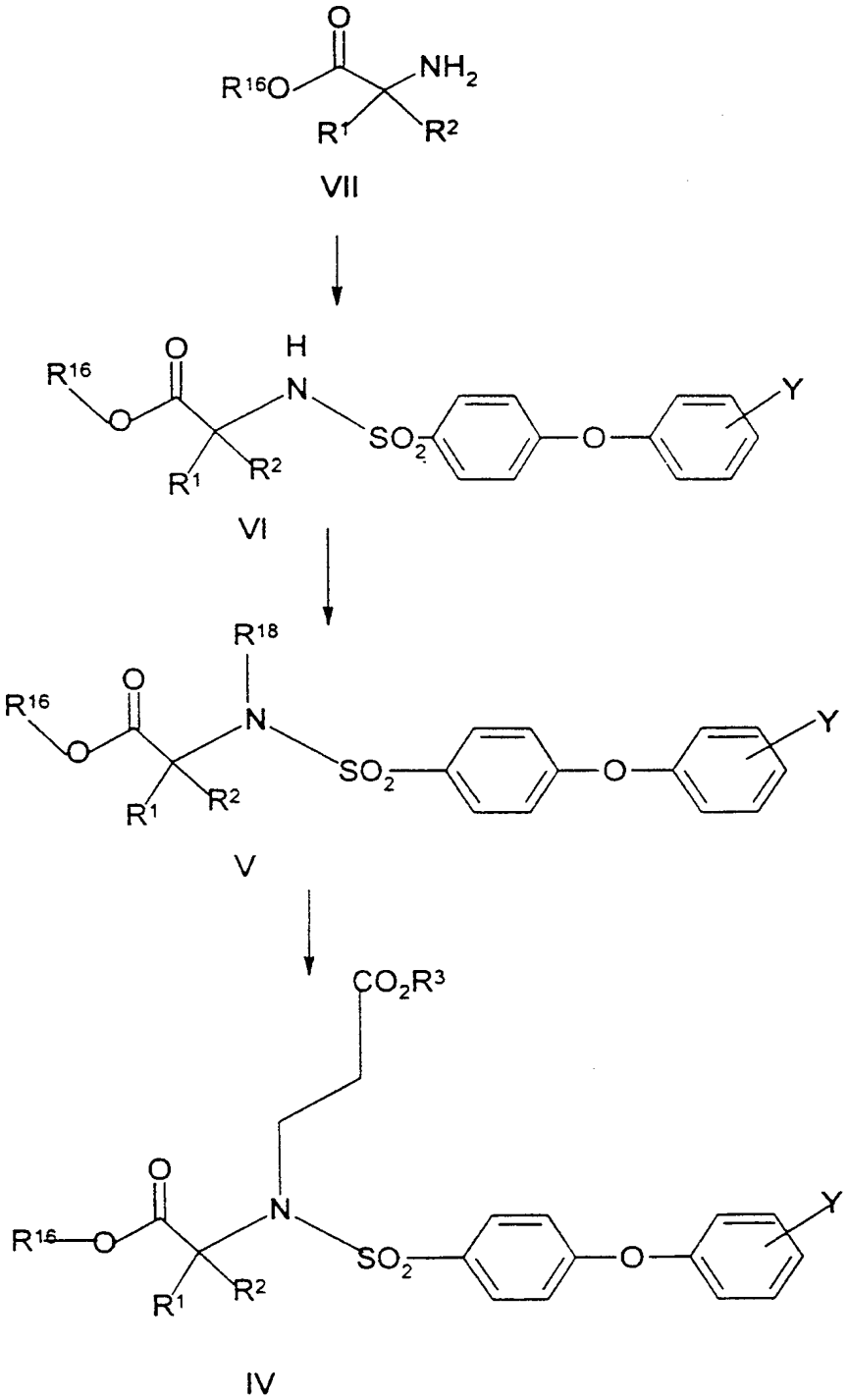
The present invention also relates to a method for the selective inhibition of matrix metalloproteinase-13 or in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, bone resorption, loosening of artificial joint implants, atherosclerosis, multiple sclerosis, occular angiogenisis (for example macular degeneration) and other diseases characterized by matrix metalloproteinase-13 activity in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

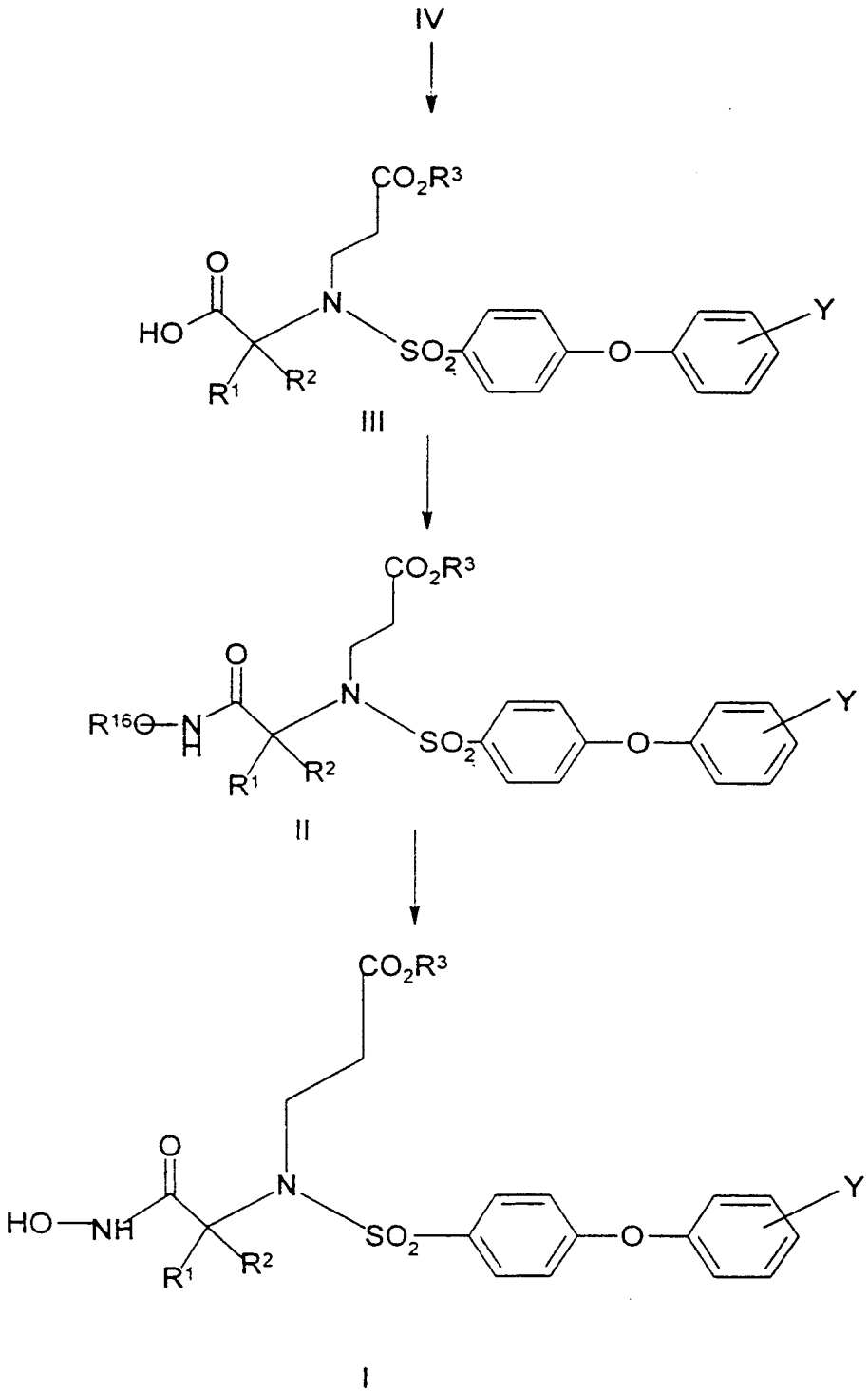
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated Y, R^1, R^2 and R^3 in the reaction Schemes and the discussion that follow are defined as above.

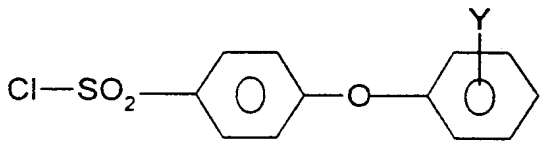
Scheme 1



Scheme 1 Cont'd



Scheme 1 refers to the preparation of compounds of the formula I from compounds of the formula VII. Referring to Scheme 1, the amino acid compound of formula **VII**, wherein R^{16} is benzyl, is converted to the corresponding compound of formula **VI** by reaction with a reactive functional derivative of an arylsulfonic acid compound of the formula



VIII

in the presence of a base, such as triethylamine, and a polar solvent, such as tetrahydrofuran, 1,2-dimethoxyethane, dioxane, water or acetonitrile, preferably 1,2-dimethoxyethane. The reaction mixture is stirred, at room temperature, for a time period between about 10 minutes to about 24 hours, preferably about 60 minutes.

The arylsulfonylamino compound of formula **VI**, wherein R^{16} is benzyl, is converted to the corresponding compound of formula **V**, wherein R^{18} is the group 3-tert-butyl-dimethylsilanyloxypropanyl by reaction with tert-butyl-(3-halo-propoxy)dimethylsilane, preferably the iodide derivative, in the presence of a base, such as potassium carbonate, cesium carbonate, potassium hexamethyldisilazide, or sodium hydride, preferably potassium hexamethyldisilazide. The reaction is stirred in a polar solvent, such as dimethylformamide or N-methylpyrrolidin-2-one, at room temperature, for a time period between about 2 hours to about 48 hours, preferably about 18 hours.

The compound of formula **V** is converted to a carboxylic acid derivative of formula **IV** by reaction with boron trifluoride-etherate complex to form an intermediate alcohol, followed by oxidation and protection by esterification. Specifically, the reaction with boron trifluoride-etherate complex is performed in an inert solvent such as methylene chloride, chloroform, preferably methylene chloride, at room temperature for about 15 minutes to about 4 hours, preferably about one hour. Oxidation of the alcohol is facilitated by using chromium trioxide in aqueous sulfuric acid (Jones Reagent) at about 0°C for about one to about 6 hours, preferably about 2 hours. Protection of the carboxylic acid is facilitated by treatment of the free acid with an alkylating agent such as R^3-L, wherein L is a leaving group such as iodo, bromo, mesylate, or tosylate, preferably iodo, with a base, such potassium carbonate or cesium carbonate, preferably potassium carbonate, in a polar solvent such as dimethylformamide, N-methylpyrrolidin-2-one or tetrahydrofuran, preferably dimethyl formamide, for about 1 to about 24 hours, preferably 16 hours, at about room temperature.

The compound of formula IV is converted to a compound of formula III by removal of the R^{16} protecting group by hydrogenolysis using palladium on carbon in a solvent such as methanol or ethanol, for a period from about 30 minutes to about 48 hours, preferably 16 hours, at a temperature of about 20°C to about 25°C, i.e. room temperature.

The carboxylic acid compound of formula **III** is converted to the hydroxamic acid derivative of formula **II**, wherein R^{16} is benzyl, by activation of the compound of formula III followed by reaction with benzylhydroxylamine. The compound of formula III is activated by treatment with (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate in the presence of a base, at room temperature, in a polar solvent. The aforesaid reaction is conducted for a period of about 15 minutes to about 4 hours, preferably about 1 hour. The activated compound derived from formula III is converted *in situ* to the compound of formula II by reaction with benzylhydroxylamine hydrochloride. The reaction with benzylhydroxylamine hydrochloride is conducted for about 1 hour to about 5 days, preferably for about 16 hours, at a temperature of about 40°C to about 80°C, preferably about 60°C. Suitable bases include N-methylmorpholine or diisopropylethylamine, preferably diisopropylethylamine. Suitable solvents include N,N-dimethylformamide or N-methylpyrrolidin-2-one, preferably N,N-dimethylformamide.

The compound of formula II is converted into a compound I by removal of the hydroxyl amine protecting group. Removal of the hydroxylamine protecting group is carried out by hydrogenolysis of the benzyl protecting group using catalytic palladium on barium sulfate in a polar solvent at a temperature from about 20°C to about 25°C, i.e. room temperature, for a period of about I hour to about 5 hours, preferably about 3 hours.

Compounds of formula VII and VIII are commercially available or can be made by methods well known to those of ordinary skill in the art.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium slats.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base

compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, e.g., where R^3 is hydrogen, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the MMP-13 selective compounds of the present invention) to inhibit matrix metalloproteinase-13 (collagenase 3) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase-13 is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 mg trypsin per 100 mg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ——> 120 μM ——> 12 μM ——> 1.2 μM ——> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 ml is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 mM in assay buffer. The assay is initiated by the addition of 50 ml substrate per well of the microfluor plate to give a final concentration of 10 mM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 mM then the inhibitors are assayed at concentrations of 0.3 mM, 0.03 mM, 0.03 mM and 0.003 mM.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20mM zinc chloride, 0.02% brij). Twenty-five

microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 mM, 3mM, 0.3 mM, and 0.03 mM.

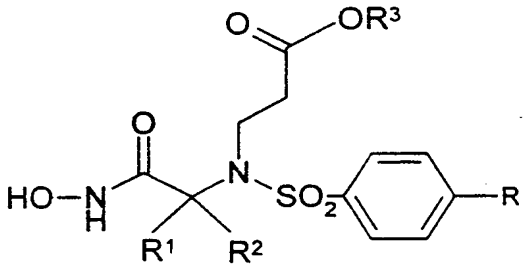
Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 ml is added to each well to give a final assay concentration of 10 mM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 mM, inhibitors are then assayed at final concentrations of 0.3 mM, 0.03 mM, 0.003 mM and 0.0003 mM.

The compounds of the present invention possess surprisingly selective activity against matrix metalloproteinase-13 (collagenase 3) as compared to matrix metalloproteinase-1 (collagenase 1). Specifically, the compounds of the formula I are 100 times more selective for matrix metalloproteinase-13 (collagenase 3) than matrix metalloproteinase-1 (collagenase 1) and have IC_{50}'s of less than 10nM against matrix metalloproteinase-13 (collagenase 3). Table 1 lists several compounds that demonstrate the unexpected selectivity of the compounds of the invention.

TABLE 1



I

Ex.	R^1	R^2	R^3	R	MMP-1 IC_{50}(nM)	MMP-13 IC_{50}(nM)
1	cyclopentyl	-	ethyl	4-fluorophenoxy	100	0.9
1	cyclopentyl	-	ethyl	4-fluorophenoxy	100	0.9
2	cyclopentyl	-	hydrogen	4-fluorophenoxy	360	1.2
2	cyclopentyl	-	hydrogen	4-fluorophenoxy	200	0.6
3	methyl	methyl	ethyl	4-fluorophenoxy	1200	1.6
3	methyl	methyl	ethyl	4-fluorophenoxy	1800	2.3
4	methyl	methyl	hydrogen	4-fluorophenoxy	3500	5.7
4	methyl	methyl	hydrogen	4-fluorophenoxy	2000	2.3
4	methyl	methyl	hydrogen	4-fluorophenoxy	4800	8
	cyclopentyl	-	hydrogen	methoxy	800	21
	cyclopentyl	-	hydrogen	methoxy	700	25
	methyl	methyl	hydrogen	methoxy	12000	590
	methyl	methyl	hydrogen	methoxy	12000	730
	cyclohexyl	hydrogen	hydrogen	methoxy	18	4
	cyclohexyl	hydrogen	hydrogen	methoxy	22	2

For administration to humans for the inhibition of matrix metalloproteinase-13 or the production of tumor necrosis factor (TNF), a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person

responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriodimethylsulfoxide unless otherwise specified). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20 to 25°C. All non-aqueous reactions were run under

a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used.

Example 1

3-[[4-(4-FLUOROPHENOXY)BENZENESULFONYL]-(1-HYDROXY-CARBAMOYL CYCLOPENTYL)AMINO]-PROPIONIC ACID ETHYL ESTER

(A) To a solution of 1-aminocyclopentanecarboxylic acid benzyl ester p-toluenesulfonic acid salt (200 grams, 0.51 mole) and triethylamine (177 mL, 1.27 mole) in water (1 L) and 1,2-dimethoxyethane (1 L) was added 4-(4-fluorophenoxy)benzenesulfonyl-chloride (161 grams, 0.56 moles). The mixture was stirred at room temperature for 16 hours and then most of the solvent was removed by evaporation under vacuum. The mixture was diluted with ethyl acetate and was washed successively with dilute hydrochloric acid solution, water, and brine. The solution was dried over magnesium sulfate and concentrated to leave a brown solid. Trituration with diethyl ether to afforded 1-[4-(4-fluorophenoxy)benzenesulfonylamino]-cyclopentanecarboxylic acid benzyl ester as a tan solid, 167 grams (70%).

(B) To a solution of 1-[4-(4-fluorophenoxy)benzenesulfonylamino]-cyclopentanecarboxylic acid benzyl ester (199 grams, 0.42 mole) in dry N,N-dimethylformamide (2.5 L) at room temperature was added potassium hexamethyldisilazide (100 grams, 0.50 mole) and, after 3 hours, tert-butyl-(3-iodopropoxy)dimethylsilane (150 grams, 0.50 mole). The resulting mixture was stirred at room temperature for 16 hours. Additional tert-butyl-(3-iodopropoxy)-dimethylsilane (20 grams, 0.067 mole) was then added. Stirring at room temperature was continued for a further 3.5 hours. The mixture was quenched by addition of saturated ammonium chloride solution. The N,N-dimethylformamide was removed by evaporation under vacuum. The residue was taken up in diethyl ether and washed with water and brine. After drying over magnesium sulfate, the diethyl ether was evaporated to afford crude 1-{[3-(tert-butyl-dimethylsilanyloxy)-propyl]-[4-(4-fluorophenoxy)benzenesulfonyl]-amino}cyclopentanecarboxylic acid benzyl ester as an amber oil (279.6 grams).

(C) To a solution of the crude 1-{[3-(tert-butyl-dimethylsilanyloxy)-propyl]-[4-(4-fluorophenoxy)benzenesulfonyl]-amino}cyclopentanecarboxylic acid benzyl ester (279 grams) in methylene chloride (1 L) at room temperature was added boron trifluoride etherate (103 mL, 0.84 mole). After 1 hour, the reaction was quenched by sequential addition of saturated ammonium chloride solution and water. The organic phase was separated, washed with water and brine and dried over magnesium sulfate. Evaporation of the solvent under vacuum

provided crude 1-[[4-(4-fluorophenoxy)benzenesulfonyl]-(3-hydroxypropyl)amino] cyclopentanecarboxylic acid benzyl ester as an amber oil (235 grams).

(D) A solution of the crude 1-[[4-(4-fluorophenoxy)benzenesulfonyl]-(3-hydroxypropyl)amino]cyclopentanecarboxylic acid benzyl ester (235 grams) in acetone (2 L) was cooled in an ice bath and treated with Jones reagent (about 200 mL) until an orange color persisted. The mixture was stirred from 0°C to room temperature over 1 hour. After quenching excess oxidant with isopropanol (10 mL), the mixture was filtered and the filtrate was concentrated under vacuum. The residue was taken up in ethyl acetate, washed with water and brine, dried over magnesium sulfate and concentrated to afford a solid which was triturated with a mixture of diethyl ether and hexane to provide 1-{(2-carboxyethyl)-[4-(4-fluorophenoxy)benzenesulfonyl]amino}cyclopentane carboxylic acid benzyl ester as a white solid (147 grams).

(E) To a solution of 1-{(2-carboxyethyl)-[4-(4-fluorophenoxy)benzenesulfonyl] amino}-cyclopentanecarboxylic acid benzyl ester (147 grams) in N,N-dimethyl formamide (3 L) at room temperature was added potassium carbonate (150 grams, 1.08 mole) and ethyl iodide (32.4 mL, 0.405 mole). The mixture was stirred for 16 hours at room temperature. After filtration, most of the solvent was removed under vacuum. The residue was taken up in water and acidified using 6N aqueous hydrogen chloride solution. The resulting mixture was extracted with diethyl ether. The organic extract was washed with water and brine, dried over magnesium sulfate, and concentrated to yield 1-{(2-ethoxycarbonylethyl)-[4-(4-fluorophenoxy)benzenesulfonyl] amino}cyclopentane carboxylic acid benzyl ester as a yellow semi-solid (149.1 grams, 96%).

(F) A solution of 1-{(2-ethoxycarbonylethyl)-[4-(4-fluorophenoxy)benzene sulfonyl]-amino}cyclopentanecarboxylic acid benzyl ester (74.5 grams, 0.13 mole) in ethanol (1.8 L) was treated with 10% palladium on activated carbon (7.4 grams) and hydrogenated in a Parr™ shaker at 3 atmospheres pressure for 16 hours. After filtration through nylon (pore size 0.45 µm) to remove the catalyst, the solvent was evaporated to afford 1-{(2-ethoxycarbonylethyl)-[4-(4-fluorophenoxy)benzenesulfonyl]amino} cyclopentanecarboxylic acid as a white foam. The reaction was repeated on the same scale to provide, in total, 125.2 grams of the desired product.

(G) Diisopropylethylamine (50 mL, 0.286 mole) and (benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate (126.5 grams, 0.286 mole) were added sequentially to a solution of 1-{(2-ethoxycarbonylethyl)-[4-(4-fluorophenoxy)benzene-sulfonyl]amino}cyclopentanecarboxylic acid (125.2 grams, 0.26 mole) in N,N-dimethylformamide (2 L). The mixture was stirred for 1 hour. Additional diisopropylethylamine (91 mL, 0.52 mole) and O-benzylhydroxylamine hydrochloride (53.8

grams, 0.338 mole) were then added and the resulting mixture was stirred at 60°C for 96 hours. After concentration under vacuum, the residue was taken up in water and acidified with 1N aqueous hydrogen chloride solution. The mixture was extracted with ethyl acetate and the extract was washed sequentially with water, saturated aqueous sodium bicarbonate solution and brine. The solution was dried over magnesium sulfate and concentrated to give crude 3-{(1-benzyloxycarbamoylcyclopentyl)-[4-(4-fluorophenoxy)benzenesulfonyl]-amino}propionic acid ethyl ester as a yellow oil (164 grams).

F) A solution of crude 3-{(1-benzyloxycarbamoylcyclopentyl)-[4-(4-fluorophenoxy)-benzenesulfonyl]amino}propionic acid ethyl ester (164 grams) in ethanol (2.4 L) was treated with 5% palladium on barium sulfate (50 grams) and hydrogenated in a Parr™ shaker at 3 atmospheres pressure for 3 hours. After filtration through nylon (pore size 0.45 µm) to remove the catalyst, the solvent was evaporated to afford an oil. After addition of ethyl acetate and hexane, 3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxy-carbamoylcyclopentyl)amino]-propionic acid ethyl ester, a white crystalline solid (73.5 grams) was collected by filtration. The filtrate was concentrated and the residue was chromatographed on silica gel eluting with 40% ethyl acetate hexane to provide more of the desired product (32.5 grams).

Mp: 79-83°C. ^{1}H NMR (DMSO-d_6): δ 10.40 (br s, 1 H), 8.78 (br s, 1 H), 7.80-7.77 (m, 2 H), 7.31-7.03 (m, 6 H), 4.02 (q, J = 7.3 Hz, 2 H), 3.49-3.45 (m, 2 H), 2.70-2.67 (m, 2 H), 2.24-2.21 (m, 2 H), 1.86-1.83 (m, 2 H), 1.53-1.50 (m, 4 H), 1.16 (t, J = 7.3 Hz, 3 H). MS 493 (M-1). Analysis calculated for $C_{23}H_{27}FN_2O_7S.H_2O$: C, 53.90; H, 5.70; N, 5.47. Found: C, 54.52; H, 5.63; N, 5.27.

Example 2

3-[[4-(4-FLUOROPHENOXY)BENZENESULFONYL]-(1-HYDROXY-CARBAMOYLCYCLOPENTYL) AMINO]PROPIONIC ACID

A solution of 3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxycarbamoyl cyclopentyl)-amino]propionic acid ethyl ester (106 grams, 0.214 mole) in ethanol (2.5 L) was treated with aqueous 1 N sodium hydroxide solution (856 mL, 0.856 mole) and stirred at room temperature for 2 hours. The mixture was concentrated to remove ethanol, diluted with water, acidified with 6 N aqueous hydrochloric acid solution and extracted with ethyl acetate. After washing with water and brine, the organic extract was dried over magnesium sulfate and concentrated to a foam. Crystallization from 30% ethyl acetate in hexane gave 3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxy carbamoylcyclopentyl)-amino]propionic acid as a white crystalline solid (81.5 grams, 81%).

Mp: 170-172°C. ^{1}H NMR (DMSO-d_6): δ 12.25 (br s, 1 H), 10.40 (br s, 1 H), 8.74 (br s, 1 H), 7.79-7.77 (m, 2 H), 7.29-7.03 (m, 6 H), 3.45-3.41 (m, 2 H), 2.61-2.57 (m, 2 H), 2.24-2.21 (m, 2 H), 1.88-1.82 (m, 2 H), 1.53-1.50 (m, 4 H). MS 465 (M-1). Analysis calculated for $C_{21}H_{23}FN_2O_7S$: C, 54.07; H, 4.97; N, 6.00. Found: C, 54.17; H, 5.02; N, 6.05.

Example 3

3-[[4-(4-FLUOROPHENOXY)BENZENESULFONYL]-(1-HYDROXYCARBAMOYL-1-METHYLETHYL)AMINO]PROPIONIC ACID ETHYL ESTER

The title compound was prepared according to a procedure analogous to that outlined in Example 1 starting with 2-amino-2-methyl-propionic acid benzyl ester p-toluenesulfonic acid salt.

Mp: 124.8-125° C. ^{1}H NMR (DMSO-d_6) δ 10.37 (s, 1 H), 8.74 (s,1 H), 7.86 (d, 2 H, J = 8.9 Hz), 7.16-7.30 (m, 4 H), 7.04 (d, 2 H, J = 8.7 hz), 3.99 (q, 2 H, J = 7.1 Hz), 3.33-3.37 (m, 2 H), 2.62-2.66 (m, 2 H), 1.40 (s, 6 H), 1.13 (t, 3 H, J = 7.1 Hz). MS: 467 (M-1). Analysis calculated for $C_{21}H_{25}FN_2O_7S$: C, 53.84; H, 5.38; N, 5.98. Found: C, 54.00; H, 5.12; N, 5.87.

Example 4

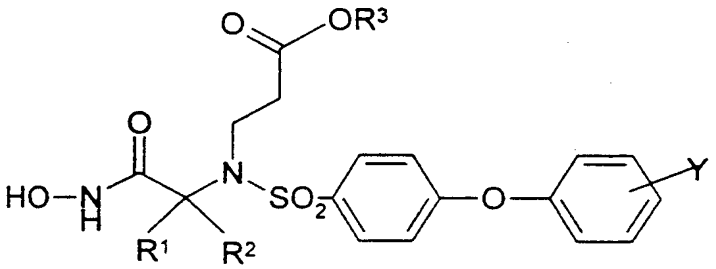
3-[[4-(4-FLUOROPHENOXY)BENZENESULFONYL]-(1-HYDROXY-CARBAMOYL-1-METHYLETHYL)AMINO]PROPIONIC ACID

The title compound was prepared from 3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxycarbamoyl-1-methylethyl)amino]propionic acid ethyl ester according to a procedure analogous to that described in Example 2.

Mp: 162-162.5°C. MS: 439 (M-1). ^{1}H NMR (DMSO-d_6) δ 12.26 (s, 1 H) 10.10.38 (s, 1 H), 8.75 (s,1 H), 7.86-7.88 (m, 2 H), 7.16-7.7.30 (m, 4 H), 7.03-7.06 (m, 2 H), 3.29-3.35 (m, 2 H), 2.47-2.59 (m, 2 H), 1.40 (s, 6 H).

CLAIMS

1. A compound of the formula



I

or the pharmaceutically acceptable salts thereof, wherein

R^1 is $(C_1\text{-}C_6)$alkyl;

R^2 is $(C_1\text{-}C_6)$alkyl;

or R^1 and R^2 taken together with the carbon atom to which they are attached form a ring selected from $(C_5\text{-}C_7)$cycloalkyl , 4-tetrahydropyranyl and 4-piperidinyl;

R^3 is hydrogen or $(C_1\text{-}C_6)$alkyl; and

Y is a substituent on any of the carbon atoms of the phenyl ring capable of supporting an additional bond, independently selected from fluoro, chloro, trifluoromethyl, $(C_1\text{-}C_6)$alkoxy, trifluoromethoxy, difluoromethoxy and $(C_1\text{-}C_6)$alkyl.

2. A compound according to claim 1, wherein Y is hydrogen, fluoro or chloro.

3. A compound according to claim 1, wherein Y is 4-fluoro or 4-chloro.

4. A compound according to claim 1, wherein R^1 and R^2 taken together with the carbon atom to which they are attached form a cyclopentyl ring.

5. A compound according to claim 3, wherein R^1 and R^2 taken together with the carbon atom to which they are attached form a cyclopentyl ring.

6. A compound according to claim 1, wherein R^1 and R^2 taken together with the carbon atom to which they are attached form a 4-tetrahydropyranyl ring.

7. A compound according to claim 1, wherein R^1 and R^2 are both methyl.

8. A compound according to claim 3, wherein R^1 and R^2 are both methyl.

9. A compound according to claim 1, wherein R^3 is hydrogen.

10. A compound according to claim 3, wherein R^3 is hydrogen.

11. A compound according to claim 4, wherein R^3 is hydrogen.

12. A compound according to claim 1, wherein said compound is selected from the group consisting of:

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxy-carbamoylcyclopentyl)amino]-propionic acid ethyl ester,

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxy-carbamoylcyclopentyl) amino]propionic acid,

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxycarbamoyl-1-methylethyl)amino]propionic acid ethyl ester, and

3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(1-hydroxy-carbamoyl-1-methylethyl)amino]propionic acid.

13. A pharmaceutical composition for (a) the treatment of arthritis or cancer and other diseases characterized by matrix metalloproteinase-13 activity or (b) the selective inhibition of matrix metalloproteinase-13 in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments or inhibition and a pharmaceutically acceptable carrier.

14. A method for the selective inhibition of matrix metalloproteinases-13 in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

15. A method for treating arthritis or cancer and other diseases characterized by matrix metalloproteinase-13 activity in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/IB 98/01113

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C311/29 C07D309/14 C07D211/66 A61K31/19 A61K31/215
A61K31/35 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 C07C C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 606 046 A (CIBA-GEIGY AG) 13 July 1994 see claims ---	1-15
X	WO 96 27583 A (PFIZER) 12 September 1996 see claims -----	1-15

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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Date of the actual completion of the international search	Date of mailing of the international search report
23 September 1998	14/10/1998

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	Van Geyt, J

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AQUESTIVE EXHIBIT 1004 page 1183

INTERNATIONAL SEARCH REPORT

Ir. national application No.
PCT/IB 98/01113

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.: 14 and 15
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 14 and 15 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. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

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

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

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

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

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

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

Remark on Protest

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

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

AQUESTIVE EXHIBIT 1004 page 1184

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ›nal Application No
PCT/IB 98/01113

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A1

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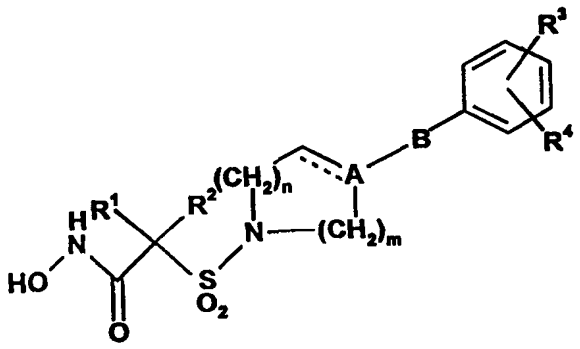
With international search report.

(54) Title: HYDROXAMIC ACID DERIVATIVES AS MATRIX METALLOPROTEASE (MMP) INHIBITORS



(I)

(57) Abstract

Compounds of formula (I) or pharmaceutically or veterinarily acceptable salts thereof, or pharmaceutically or veterinarily acceptable solvates of either entity, wherein the broken line represents an optional bond; A is C or CH; B is CH_2, O or absent; R^1 and R^2 are each independently selected from hydrogen, C_1 to C_6 alkyl optionally substituted with C_1 to C_4 alkoxy or phenyl, and C_1 to C_6 alkenyl; or, together with the carbon atom to which they are attached, form a C_3 to C_6 cycloalkyl group which optionally incorporates a heteroatom linkage selected from O, SO, SO_2 and NR^6 or which is optionally benzo–fused; R^3 is hydrogen, halo, R^7 or OR^7; R^4 is hydrogen, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, trifluoromethyl or halo; R^6 is hydrogen or C_1 to C_4 alkyl; R^7 is an optionally substituted monocyclic or bicyclic ring system; m is 1 or 2; and n is 0, 1 or 2; with the proviso that B is not O when A is C; are MMP inhibitors useful in the treatment of, *inter alia*, tissue ulceration, wound repair and skin diseases.

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BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
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CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
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HYDROXAMIC ACID DERIVATIVES AS MATRIX METALLOPROTEASE (MMP) INHIBITORS

This invention relates to a series of substituted α-aminosulphonyl-acetohydroxamic acids which are inhibitors of zinc-dependent metalloprotease enzymes. In particular, the compounds are inhibitors of certain members of the matrix metalloprotease (MMP) family.

Matrix metalloproteases (MMPs) constitute a family of structurally similar zinc-containing metalloproteases, which are involved in the remodelling and degradation of extracellular matrix proteins, both as part of normal physiological processes and in pathological conditions. Since they have high destructive potential, MMPs are usually under close regulation and failure to maintain MMP regulation may be a component of a number of diseases and pathological conditions, including atherosclerotic plaque rupture, heart failure, restenosis, periodontal disease, tissue ulceration, wound repair, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

Another important function of certain MMPs is to activate various enzymes, including other MMPs, by cleaving the pro-domains from their protease domains. Thus some MMPs act to regulate the activities of other MMPs, so that over-production of one MMP may lead to excessive proteolysis of extracellular matrix by another. Moreover, MMPs have different substrate preferences (shown in the following Table for selected family members) and different functions within normal and pathological conditions. For recent reviews of MMPs, see Current Pharmaceutical Design, 1996, 2, 624 and Exp. Opin. Ther. Patents, 1996, 6, 1305.

TABLE

Enzyme	Other Names	Preferred Substrates
MMP-1	collagenase-1; interstitial collagenase	collagens I, II, III, VII, X; gelatins
MMP-2	gelatinase A; 72kDa gelatinase	gelatins; collagens IV, V, VII, X; elastin; fibronectin; activates pro-MMP-13
MMP-3	stromelysin-1	proteoglycans; laminin; fibronectin; gelatins
MMP-8	collagenase-2; neutrophil collagenase	collagens I, II, III
MMP-9	gelatinase B; 92kDa gelatinase	gelatins; collagens IV, V; elastin
MMP-13	collagenase-3	collagens I, II, III; gelatins
MMP-14	MT-MMP-1	activates pro-MMP-2 & 13; gelatins

Excessive production of MMP-3 is thought to be responsible for pathological tissue breakdown which underlies a number of diseases and conditions. For example, MMP-3 has been found in the synovium and cartilage of osteoarthritis and rheumatoid arthritis patients, thus implicating MMP-3 in the joint damage caused by these diseases: see Biochemistry, 1989, 28, 8691 and Biochem. J., 1989, 258, 115. MMP-13 is also thought to play an important role in the pathology of osteoarthritis and rheumatoid arthritis: see Lab. Invest., 1997, 76, 717 and Arthritis Rheum., 1997, 40, 1391. The compounds of the present invention inhibit both MMP-3 and MMP-13 and thus may be of utility in treating these diseases.

The over-expression of MMP-3 is also thought to be responsible for much of the tissue damage and chronicity of chronic wounds, such as venous ulcers, diabetic ulcers and pressure sores: see Brit. J. Dermatology, 1996, 135, 52.

Furthermore, the production of MMP-3 may also cause tissue damage in conditions where there is ulceration of the colon (as in ulcerative colitis and Crohn's disease: see J. Immunol., 1997 158, 1582 and J. Clin. Pathol., 1994, 47, 113) or of the duodenum (see Am. J. Pathol., 1996, 148, 519).

Moreover, MMP-3 may also be involved in skin diseases such as dystrophic epidermolysis bullosa (see Arch. Dermatol. Res., 1995, 287, 428) and dermatitis herpetiformis (see J. Invest. Dermatology, 1995, 105, 184).

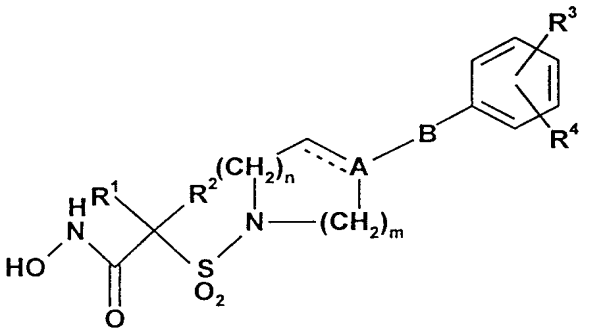
Finally, rupture of atherosclerotic plaques by MMP-3 may lead to cardiac or cerebral infarction: see Circulation, 1997, 96, 396. Thus, MMP-3 inhibitors may find utility in the prevention of heart attack and stroke.

Studies of human cancers have shown that MMP-2 is activated on the invasive tumour cell surface (see J. Biol.Chem., 1993, 268, 14033) and BB-94, a non-selective peptidic hydroxamate MMP inhibitor, has been reported to decrease the tumour burden and prolong the survival of mice carrying human ovarian carcinoma xenografts (see Cancer Res., 1993, 53, 2087). Certain compounds of the present invention inhibit MMP-2 and therefore may be useful in the treatment of cancer metastasis and tumour angiogenesis.

Various series of MMP inhibitors have appeared in the patent literature. For example, α-arylsulphonamido-substituted acetohydroxamic acids are disclosed in EP-A-0606046, WO-A-9627583 and WO-A-9719068, whilst EP-A-0780386 discloses certain related sulphone-substituted hydroxamic acids.

The compounds of the present invention are inhibitors of some of the members of the MMP family. In particular, they are potent inhibitors of MMP-3 and MMP-13, with certain compounds exhibiting varying degrees of selectivity over other MMPs, such as MMP-1, MMP-2 and MMP-9. Certain of the compounds are potent MMP-2 inhibitors.

Thus, according to the present invention, there is provided a compound of formula (I):



(I)

or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate (including hydrate) of either entity,

wherein the broken line represents an optional bond;

A is C or CH;

B is CH_2, O or absent;

R^1 and R^2 are each independently selected from hydrogen, C_1 to C_6 alkyl optionally substituted with C_1 to C_4 alkoxy or phenyl, and C_1 to C_6 alkenyl; or, together with the carbon atom to which they are attached, form a C_3 to C_6 cycloalkyl group which optionally incorporates a heteroatom linkage selected from O, SO, SO_2 and NR^6 or which is optionally benzo-fused;

R^3 is hydrogen, halo, R^7 or OR^7;

R^4 is hydrogen, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, trifluoromethyl or halo;

R^6 is hydrogen or C_1 to C_4 alkyl;

R^7 is a monocyclic or bicyclic ring system selected from phenyl, thienyl, furyl, pyridinyl, pyrimidinyl, naphthyl, indanyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, quinolinyl, isoquinolinyl, benzodioxolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl and benzodioxanyl, any of which ring systems

is optionally substituted with one or two substituents selected from C_1 to C_4 alkyl optionally substituted with C_1 to C_4 alkoxy or hydroxy, C_1-C_4 alkoxy optionally substituted with C_1 to C_4 alkoxy or hydroxy, C_1 to C_4 alkylthio, trifluoromethyl, trifluoromethoxy, halo and cyano;

m is 1 or 2;

and n is 0, 1 or 2;

with the proviso that B is not O when A is C.

In the above definition, unless otherwise indicated, alkyl, alkoxy, alkylthio and alkenyl groups having three or more carbon atoms may be straight chain or branched chain. Halo means fluoro, chloro, bromo or iodo.

The compounds of formula (I) may contain one or more chiral centres and therefore can exist as stereoisomers, i.e. as enantiomers or diastereoisomers, as well as mixtures thereof. The invention includes both the individual stereoisomers of the compounds of formula (I) and any mixture thereof. Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation or chromatography (including HPLC) of a diastereoisomeric mixture of a compound of formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of formula (I) may be prepared from a corresponding optically pure intermediate or by resolution, either by HPLC of the racemate using a suitable chiral support or, where appropriate, by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active base or acid.

Furthermore, compound of formula (I) which contain alkenyl groups can exist as cis-stereoisomers or trans-stereoisomers. Again, the invention includes both the separated individual stereoisomers as well as mixtures thereof.

Also included in the invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

Compounds of formulae (I) may provide pharmaceutically or veterinarily acceptable base salts, in particular non-toxic alkali metal salts, with bases. Examples include the sodium and potassium salts. The pharmaceutically or veterinarily acceptable salts of the compounds of formula (I) which contain a basic centre are, for example, non toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with organo-carboxylic acids, or with organo-sulphonic acids.

A preferred group of compounds of formula (I) is that wherein B is absent; R^1 is hydrogen, C_1 to C_4 alkyl optionally substituted with methoxy or phenyl, or C_1 to C_5 alkenyl; R^2 is hydrogen or C_1 to C_4 alkyl; or R^1 and R^2, together with the carbon atom to which they are attached, form a C_4 to C_5 cycloalkyl group which optionally incorporates a heteroatom linkage selected from O and NR^6 or which is optionally benzo-fused; R^3 is selected from 4-phenyl, 4-pyridinyl, 4-(indan-5-yl), 4-(2,3-dihydrobenzofuran-5-yl), 4-(quinolin-3-yl), 4-(benzodioxol-5-yl) and 4-(benzimidazol-5-yl), any of which is optionally substituted with one or two substituents selected from C_1 to C_3 alkyl optionally substituted with methoxy or hydroxy, C_1 to C_3 alkoxy optionally substituted with methoxy or hydroxy, methylthio, trifluoromethyl, trifluoromethoxy, fluoro, chloro and cyano; R^4 is hydrogen, methyl, ethyl, methoxy, trifluoromethyl, fluoro or chloro; R^6 is methyl; m is 2; and n is 1.

A more preferred group of compounds of formula (I) is that wherein R^1 is hydrogen, methyl, ethyl, 2-methylprop-1-yl, but-1-yl, 2-methoxyethyl, benzyl, 3-phenylprop-1-yl, allyl, 2-methylallyl, 3,3-dimethylallyl; R^2 is hydrogen, methyl or ethyl; or R^1 and R^2, together with the carbon atom to which they are attached, form a cyclobutyl, cyclopentyl, tetrahydropyran-4,4-diyl, 1-methylpiperidin-4,4-diyl or indan-2,2-diyl group; R^3 is 4-phenyl, 4-(2-methylphenyl), 4-(3-

methylphenyl), 4-(3-ethylphenyl), 4-[3-(prop-2-yl)phenyl], 4-(3,5-dimethylphenyl), 4-(3-methoxymethylphenyl), 4-(3-hydroxymethylphenyl), 4-(2-methoxyphenyl), 4-(3-methoxyphenyl), 4-(3-ethoxyphenyl), 4-(4-ethoxyphenyl), 4-[3-(prop-1-oxy)phenyl], 4-[3-(prop-2-oxy)phenyl], 4-[4-(prop-2-oxy)phenyl], 4-(3,4-dimethoxyphenyl), 4-[3-(2-methoxyethoxy)phenyl], 4-[3-(2-hydroxyethoxy)phenyl], 4-(3-methylthiophenyl), 4-(3-trifluoromethylphenyl), 4-(3-trifluoromethoxyphenyl), 4-(2-fluorophenyl), 4-(3-chloro-4-fluorophenyl), 4-(3-cyanophenyl), 4-(pyridin-2-yl), 4-(pyridin-3-yl), 4-(pyridin-4-yl), 4-(6-ethoxypyridin-2-yl), 4-(5-ethoxypyridin-3-yl), 4-(indan-5-yl), 4-(2,3-dihydrobenzofuran-5-yl), 4-(quinolin-3-yl), 4-(benzodioxol-5-yl), 4-(2,2-dimethylbenzodioxol-5-yl) and 4-(1,2-dimethylbenzimidazol-5-yl); and R^4 is hydrogen, 2-methyl, 3-methyl, 3-ethyl, 3-methoxy, 3-trifluoromethyl, 3-fluoro or 3-chloro.

A particularly preferred group of compounds of formula (I) is that wherein R^1 and R^2 are both hydrogen or methyl or, together with the carbon atom to which they are attached, form a cyclobutyl, cyclopentyl, tetrahydropyran-4,4-diyl or 1-methylpiperidin-4,4-diyl group; R^3 is 4-phenyl, 4-(3-methoxyphenyl), 4-(3-ethoxyphenyl), 4-[3-(2-methoxyethoxy)phenyl], 4-[3-(2-hydroxyethoxy)phenyl] or 4-(6-ethoxypyridin-2-yl); and R^4 is 3-methyl or 3-methoxy.

Especially preferred individual compounds of the invention include

N-hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide;

N-hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanamide;

N-hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide;

N-hydroxy-1-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}cyclopentanecarboxamide;

N-hydroxy-1-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}cyclobutanecarboxamide;

N-hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide;

N-hydroxy-2-{4-[4-(6-ethoxypyridin-2-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide;

N-hydroxy-2-{4-[4-(3-[2-methoxyethoxy]phenyl)-3-methylphenyl]-piperidin-1-ylsulphonyl}-2-methylpropanamide; and

N-hydroxy-2-{4-[4-(3-[2-hydroxyethoxy]phenyl)-3-methylphenyl]piperidine-1-ylsulphonyl}-2-methylpropanamide.

In a further aspect, the present invention provides processes for the preparation of a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate (including hydrate) of either entity, as illustrated below.

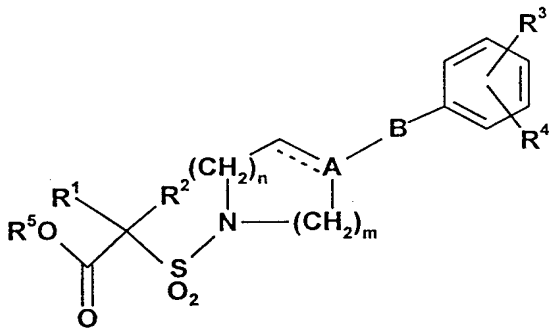
It will be appreciated by persons skilled in the art that, within certain of the processes described, the order of the synthetic steps employed may be varied and will depend inter alia on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, such factors will also influence the choice of reagent for use in the said synthetic steps.

Illustrative of protecting group strategies are the synthetic routes to Example 64, in which an O-benzyl protected hydroxamate is formed prior to the required Suzuki reaction step, and to Example 66, in which alcohol protection using a t-butyldiphenylsilyl group is employed.

It will also be appreciated that various standard substituent or functional group interconversions and transformations within certain compounds of formula (I) will provide other compounds of formula (I). An example is the conversion of the tetrahydropyridine derivative (Example 28) to the piperidine derivative (Example 29) by hydrogenation.

The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

A compound of formula (I) may be prepared directly from an ester of formula (II):



(II)

wherein R^5 is C_1 to C_3 alkyl, and the broken line, A,B, R^1, R^2, R^3, R^4, m and n are as previously defined for formula (I), or <u>via</u> the intermediacy of the corresponding carboxylic acid of formula (II) wherein R^5 is hydrogen.

When prepared directly from an ester of formula (II), the reaction may be carried out by treatment of the ester with up to a 3-fold excess of hydroxylamine in a suitable solvent at from about room temperature to about 85°C. The hydroxylamine is conveniently generated <u>in situ</u> from its hydrochloride salt by conducting the reaction in the presence of a molar equivalent amount of a suitable base such as an alkali metal carbonate or bicarbonate, e.g. potassium carbonate. Preferably the solvent is methanol , optionally combined with tetrahydrofuran or dichloromethane as co-solvent, and the reaction temperature is from about 65 to 70°C.

Alternatively, the ester may be converted by conventional hydrolysis to the corresponding carboxylic acid which is then transformed to the required hydroxamic acid of formula (I).

Preferably the hydrolysis is effected under basic conditions using up to about a 6-fold excess of an alkali metal hydroxide in aqueous solution, optionally in the presence of a co-solvent, at from about room temperature to about 85°C. Typically the co-solvent is selected from methanol, 1,4-dioxan, a mixture of methanol and tetrahydrofuran and a mixture of methanol and 1,4-dioxan and the reaction temperature is from about 40 to about 70°C.

The subsequent coupling step may be achieved using conventional amide-bond forming techniques, e.g. via the acyl chloride derivative and hydroxylamine hydrochloride in the presence of an excess of a tertiary amine such as triethylamine or pyridine to act as acid-scavenger, optionally in the presence of a catalyst such as 4-dimethylaminopyridine, in a suitable solvent such as dichloromethane, at from about 0°C to about room temperature. For convenience, pyridine may also be used as the solvent.

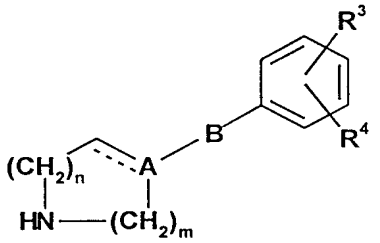
In particular, any one of a host of amino acid coupling variations may be used. For example, the acid of formula (II) wherein R^5 is hydrogen may be activated using a carbodiimide such as 1,3-dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminoprop-1-yl)carbodiimide optionally in the presence of 1-hydroxybenzotriazole and/or a catalyst such as 4-dimethylaminopyridine, or by using a halotrisaminophosphonium salt such as bromotris(pyrrolidino)-phosphonium hexafluorophosphate. Either type of coupling is conducted in a suitable solvent such as dichloromethane or dimethylformamide, optionally in the presence of a tertiary amine such as N-methylmorpholine or N-ethyldiisopropylamine (for example when either the hydroxylamine or the

activating reagent is presented in the form of an acid addition salt), at from about 0°C to about room temperature. Typically, from 1.1 to 2.0 molecular equivalents of the activating reagent and from 1.0 to 4.0 molecular equivalents of any tertiary amine present are employed.

A preferred reagent for mediating the coupling reaction is O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU).

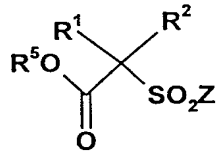
Preferably a solution of the acid and from 1.0 to 1.2 molecular equivalents of N-ethyldiisopropylamine in a suitable solvent such as anhydrous dimethylformamide or anhydrous 1-methylpyrrolidin-2-one, under nitrogen, is treated with up to a 50% excess of HATU at about room temperature followed, after about 15 to 30 minutes, with up to about a 3-fold excess of hydroxylamine hydrochloride and up to about a 4-fold excess of N-ethyldiisopropylamine, optionally in the same solvent, at the same temperature.

An ester of formula (II) may be prepared from an amine of formula (III):



(III)

wherein the broken line, A,B, R^3, R^4, m and n are as previously defined for formula (II), by sulphonylation with a compound of formula (IV):



(IV)

wherein Z is halo, R^5 is C_1 to C_3 alkyl and R^1 and R^2 are as previously defined for formula (II). Preferably, Z is chloro.

When R^6 is hydrogen, it will normally be advantageous to protect this secondary amino linkage with a conventional amine protecting group.

The reaction may be effected in the presence of up to a 50% excess of an appropriate base in a suitable solvent at from about 0°C to about room temperature. For example, when both R^1 and R^2 are hydrogen, an appropriate base is 1,8-diazabicyclo[5.4.0]undec-7-ene and a suitable solvent is dichloromethane.

Alternatively, the anion of (III) may be generated initially using up to a 20% excess of a strong base in a suitable solvent, under nitrogen, and then the sulphonylation with from 1.0 to 1.2 molecular equivalents of (IV) effected.

Conveniently, such a coupling may be carried out at room temperature with N,O-bis(trimethylsilyl)acetamide as base and anhydrous tetrahydrofuran as solvent.

Further routes to the preparation of an ester of formula (II), wherein R^3 is R^7, rely on exploitation of either a Suzuki reaction or a Stille reaction with an ester of formula (II) wherein R^3 (but not R^4) is either bromo or iodo.

Thus, in the Suzuki reaction, the latter ester is treated with from 1.0 to 1.5 molecular equivalents of a boronic acid of formula $R^7B(OH)_2$, in the presence of from 2.0 to 3.0 molecular equivalents of an alkali metal fluoride, about 0.1 molecular equivalents of a triarylphosphine and about 0.05 molecular equivalents of a palladium catalyst in a suitable solvent, under nitrogen, at from about 65 to about 100°C. Typically, the fluoride is cesium fluoride, the phosphine is tri-o-tolylphosphine, the catalyst is tris(dibenzylideneacetone)-dipalladium(0) and the solvent is degassed 1,2-dimethoxyethane optionally with 1-methylpyrrolidin-2-one as co-solvent.

In the Stille reaction, the aforementioned ester starting material of formula (II) is treated with from 1.0 to 2.0 molecular equivalents of a suitable trialkylstannane derivative of formula $R^7Sn(alkyl)_3$ wherein alkyl is, for example, n-butyl, in the presence of from 2.0 to 3.0 molecular equivalents of a tertiary base, from 0.3 to 0.6 molecular equivalents of a triarylphosphine and from 0.05 to 0.2 molecular equivalents of a palladium catalyst in a suitable solvent, under nitrogen, at from about 65 to about 100°C. Typically, the base is triethylamine, the phosphine is tri-o-tolylphosphine, the catalyst is palladium(II) acetate optionally in the presence of tetrakis(triphenylphosphine)palladium(0) and the solvent is anhydrous acetonitrile.

Certain esters of formula (II) wherein at least one of R^1 and R^2 is other than hydrogen may be conveniently obtained from the α-carbanion of an ester of formula (II) wherein at least one of R^1 and R^2 is hydrogen by conventional C-alkylation procedures using an alkylating agent of formula (VA) or (VB):

RX	X-W-Y
(VA)	(VB)

wherein R is as previously defined for R^1 or R^2 but is not hydrogen, X and Y may be the same or different and are suitable leaving groups, and W is a C_2 to C_5 alkylene group which optionally incorporates a heteroatom linkage selected from O, SO, SO_2 and NR^6 or which is optionally benzo-fused. When R^6 is to be hydrogen in a compound of formula (I), then a conventional amine protecting group strategy may be of advantage during this alkylation procedure.

A suitable leaving group may be selected from halo (e.g. chloro, bromo or iodo), C_1-C_4 alkanesulphonyloxy, trifluoromethanesulphonyloxy and arylsulphonyloxy (e.g. benzenesulphonyloxy or p-toluenesulphonyloxy).

Preferably, X and Y are selected from bromo, iodo and p-toluenesulphonyloxy.

The carbanion may be generated using an appropriate base in a suitable solvent. Typical base-solvent combinations may be selected from lithium, sodium or potassium hydride, lithium, sodium or potassium bis(trimethylsilyl)amide, lithium diisopropylamide and butyllithium, together with toluene, ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxan, dimethylformamide, N,N-dimethylacetamide, 1-methylpyrrolidin-2-one and any mixture thereof.

Preferably the base is sodium hydride and the solvent is anhydrous dimethylformamide, optionally with anhydrous tetrahydrofuran as co-solvent, or anhydrous 1-methylpyrrolidin-2-one. For monoalkylation, up to about a 10% excess of base is employed whilst, for dialkylation, from about 2 to about 3 molar equivalents are generally appropriate.

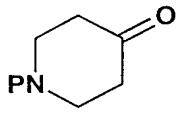
Typically, the carbanion is generated at about room temperature, under nitrogen, and subsequently treated with up to about a 30% excess of the required alkylating agent at the same temperature.

Clearly, when dialkylation is required and R^1 and R^2 are different, the substituents may be introduced in tandem in a "one-pot reaction" or in separate steps.

A particularly convenient, alternative alkylation method involves treatment of the substrate with the required alkylating agent in the presence of from 3.0 to 3.5 molecular equivalents of anhydrous potassium carbonate in anhydrous dimethyl sulphoxide or anhydrous 1,2-dimethoxyethane, under nitrogen, at about room temperature.

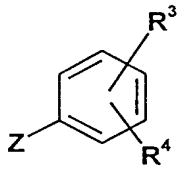
Clearly, an alternative variation for preparing a compound of formula (II) is to introduce R^1 and/or R^2 into a suitable bromo or iodo intermediate before further elaboration via, for example, a Suzuki or Stille reaction.

An amine of formula (III) may be obtained by standard chemical procedures. For example, when B is absent, m is 2 and n is 1, a suitably N-protected piperidin-4-one of formula (VI):



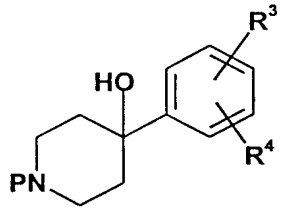
(VI)

wherein P is a conventional amine protecting group, is reacted with a carbanion derivative of a compound of formula (VII):



(VII)

wherein Z is as previously defined for formula (IV) and R^3 and R^4 are as previously defined for formula (III), to provide a compound of formula (VIII):



(VIII)

Preferably, Z is chloro, bromo or iodo.

Conveniently (VII) is converted to an aryllithium or aryl Grignard derivative whilst, of the plethora of amine protecting groups available, P is typically t-butoxycarbonyl (Boc) or benzyl.

When P is Boc, (VIII) may be transformed directly to a compound of formula (III), wherein the broken line represents a bond, A is C, B is absent, m is 2, n is 1 and R^3 and R^4 are as previously defined for formula (III), using trifluoroacetic acid optionally in a suitable solvent such as dichloromethane at about room temperature. Alternatively, when P is benzyl, (VIII) may be converted in two steps to the same compound of formula (III). For example, in the first step, dehydration may be effected in refluxing toluene using p-toluenesulphonic acid and a Dean-Stark apparatus. N-Deprotection of the resulting alkene (1,2,3,6-tetrahydropyridine derivative), in the second step, may be achieved using 1-chloroethyl chloroformate in refluxing toluene followed by treatment of the reaction mixture, at room temperature, with either methanol or ethanol.

This unsaturated piperidine may be converted to a compound of formula (III) wherein the broken line does not represent a bond, A is CH, B is absent, m is 2, n is 1 and R^3 and R^4 are as previously defined for formula (III) under conventional catalytic, or catalytic transfer, hydrogenation conditions. Alternatively, these hydrogenation conditions may be employed to convert the previously described N-benzyl alkene (1,2,3,6-tetrahydropyridine derivative) to the same piperidine derivative, directly in one step. Furthermore, this fully saturated piperidine is also available in one step from (VIII) when P is Boc by standard ionic hydrogenation using, for example, triethylsilane and trifluoroacetic acid in dichloromethane.

Other amines of formula (III), when neither commercially available nor subsequently described, can be obtained either by analogy with the processes described in the Preparations section or by conventional synthetic procedures, in accordance with standard textbooks on organic chemistry or literature precedent, from readily accessible starting materials using appropriate reagents and reaction conditions.

Moreover, persons skilled in the art will be aware of variations of, and alternatives to, those processes described hereinafter in the Examples and Preparations sections which allow the compounds defined by formula (I) to be obtained.

The pharmaceutically and veterinarily acceptable base salts of the compounds of formula (I) may also be prepared in a conventional manner. For example a solution of the hydroxamic acid is treated with the appropriate base, either neat or in a suitable solvent, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically and veterinarily acceptable acid addition salts can be obtained in an analogous manner by treating a solution of a basic compound of formula (I) with the appropriate acid. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

The biological activities of the compounds of the present invention were determined by the following test methods, which are based on the ability of the compounds to inhibit the cleavage of various fluorogenic peptides by MMPs 1, 2, 3, 9, 13 and 14.

The assays for MMPs 2, 3, 9 and 14 are based upon the original protocol described in FEBS, 1992, 296, 263, with the minor modifications described below.

Inhibition of MMP-1

Enzyme Preparation

Catalytic domain MMP-1 was prepared in Pfizer Central Research laboratories. A stock solution of MMP-1 (1μM) was activiated by the addition of aminophenylmercuric acetate (APMA), at a final concentration of 1mM, for 20 minutes at 37°C. MMP-1 was then diluted in Tris-HCl assay buffer (50mM Tris, 200mM NaCl, 5mM $CaCl_2$, 20μM $ZnSO_4$ and 0.05% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

Substrate

The fluorogenic substrate used in this assay was Dnp-Pro-β-cyclohexyl-Ala-Gly-Cys(Me)-His-Ala-Lys-(N-Me-Ala)-NH_2 as originally described in Anal. Biochem., 1993, 212, 58. The final substrate concentration used in the assay was 10μM.

Determination of Enzyme Inhibition

The test compound was dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate and allowed to equilibrate for 15 minutes at 37°C in an orbital shaker prior to the addition of substrate. Plates were then incubated for 1 hour at 37°C prior to determination of fluorescence (substrate cleavage) using a fluorimeter (Fluostar; BMG LabTechnologies, Aylesbury, UK) at an excitation wavelength of 355 nm and emission wavelength of 440 nm. The potency of inhibition was measured from the amount of substrate cleavage obtained using a range of test compound concentrations and, from the resulting dose-response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-2, MMP-3 and MMP-9

Enzyme Preparation

Catalytic domains MMP-2, MMP-3 and MMP-9 were prepared in Pfizer Central Research laboratories. A stock solution of MMP-2, MMP-3 or MMP-9 (1μM) was activated by the addition of APMA. For MMP-2 and MMP-9, a final concentration of 1mM APMA was added, followed by incubation for 1 hour at 37°C. MMP-3 was activated by the addition of 2mM APMA, followed by incubation for 3 hours at 37°C. The enzymes were then diluted in Tris-HCl assay buffer (100mM Tris, 100mM NaCl, 10mM $CaCl_2$ and 0.16% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assays was 1nM.

Substrate

The fluorogenic substrate used in this screen was Mca-Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met-Lys(Dnp)-NH_2 (Bachem Ltd., Essex, UK) as originally described in J.Biol.Chem., 1994, 269, 20952. This substrate was selected because it has a balanced hydrolysis rate against MMPs 2, 3 and 9 (k_{cat}/k_m of 54,000, 59,400 and 55,300 s^{-1} M^{-1} respectively). The final substrate concentration used in the assay was 5μM.

Determination of Enzyme Inhibition

The test compound was dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate and allowed to equilibrate for 15 minutes at 37°C in an orbital shaker prior to the addition of substrate. Plates were then incubated for 1 hour at 37°C, prior to determination of fluorescence using a fluorimeter (Fluostar; BMG LabTechnologies, Aylesbury, UK) at an excitation wavelength of 328nm and emission wavelength of 393nm. The potency of inhibition was measured from the amount of substrate cleavage obtained using a range of test compound concentrations and, from the resulting dose-response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-13

Enzyme Preparation

Human recombinant MMP-13 was prepared by PanVera Corporation (Madison, Wisconsin) and characterised at Pfizer Central Research laboratories. A 1.9 mg/ml stock solution was activated with 2mM APMA for 2 hours at 37°C. MMP-13 was then diluted in assay buffer (50mM Tris, 200mM NaCl, 5mM $CaCl_2$, 20μM $ZnCl_2$ and 0.02% Brij 35, pH 7.5) to a concentration of 5.3nM. The final concentration of enzyme used in the assay was 1.3nM.

Substrate

The fluorogenic substrate used in this screen was Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2. The final substrate concentration used in the assay was 10μM.

Determination of Enzyme Inhibition

The test compound was dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate. The addition of substrate to each well initiated the reaction. Fluorescence intensity was determined using a 96 well plate fluorimeter (Cytofluor II; PerSeptive Biosystems, Inc., Framingham, MA) at an excitation wavelength of 360nm and emission wavelength of 460nm. The potency of inhibition was measured from the amount of substrate cleavage obtained using a range of test compound concentrations and, from the resulting dose-response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-14

Enzyme Preparation

Catalytic domain MMP-14 was prepared in Pfizer Central Research laboratories. A 10μM enzyme stock solution was activated for 20 minutes at 25°C following the addition of 5μg/ml of trypsin (Sigma, Dorset, UK). The trypsin activity was then neutralised by the addition of 50μg/ml of soyabean trypsin inhibitor (Sigma, Dorset, UK), prior to dilution of this enzyme stock solution in Tris-HCl assay buffer (100mM Tris, 100nM NaCl, 10mM $CaCl_2$, 0.16% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

Substrate

The fluorogenic substrate used in this screen was Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2 (Bachem Ltd., Essex, UK) as described in J.Biol.Chem., 1996, 271, 17119.

Determination of enzyme inhibition

This was performed as described for MMPs 2, 3 and 9.

In human therapy, the compounds of formula (I), their pharmaceutically acceptable salts, and pharmaceutically acceptable solvates of either entity, can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

They may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solution or suspensions containing flavouring or colouring agents. They can also be injected, for example intravenously, intramuscularly or subcutaneously, and are best used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or monosaccarides to make the solution isotonic with blood. For other routes of parenteral administration, such as buccal or sublingual, they may be administered in the form of tablets or lozenges which can be formulated in a conventional manner.

In addition, the compounds and their salts may be administered topically in the form of sterile creams, gels, suspensions, lotions, ointments, dusting powders, sprays, drug-incorporated dressings or via a skin patch. For example, they can be incorporated into a cream consisting of an aqueous or oily emulsion of polyethylene glycols or liquid paraffin, or they can be incorporated into an ointment consisting of a white wax soft paraffin base, or as a hydrogel

with cellulose or polyacrylate derivatives or other viscosity modifiers, or as a dry powder or liquid spray or aerosol with butane/propane, HFA or CFC propellants, or as a drug-incorporated dressing either as a tulle dressing, with white soft paraffin or polyethylene glycol impregnated gauze dressings or with hydrogel, hydrocolloid, alginate or film dressings. Moreover, the compounds and salts may be administered intraocularly as an eye drop with appropriate buffers, viscosity modifiers (e.g. cellulose derivatives), preservatives (e.g. benzalkonium chlorides (BZK)) and agents to adjust tonicity (e.g. sodium chloride).

All such formulations may also contain stabilisers and preservatives.

Depending on the route of administration to human patients, the daily dosage level of the compounds of formula (I) and their salts may be from 0.001 to 20 mg/kg, in single or divided doses. Thus, for example, tablets or capsules could contain from 0.02 to 500 mg of active compound for administration singly or two or more at a time as appropriate.

The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can of course be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

For veterinary use, a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

Thus the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, together with a pharmaceutically acceptable diluent or carrier.

It further provides a veterinary formulation comprising a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, together with a veterinarily acceptable diluent or carrier.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, or a pharmaceutical composition containing any of the foregoing, for use as a human medicament.

In addition, it provides a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, or a veterinary formulation containing any of the foregoing, for use as an animal medicament.

In yet another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, for the manufacture of a human medicament for the curative or prophylactic treatment of a medical condition for which a MMP inhibitor is indicated.

It also provides the use of a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, for the manufacture of an animal medicament for the curative or prophylactic treatment of a medical condition for which a MMP inhibitor is indicated.

Moreover, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate containing either entity, for the manufacture of a human medicament for the curative or prophylactic treatment of atherosclerotic plaque rupture,

myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

It also provides the use of a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate containing either entity, for the manufacture of an animal medicament for the curative or prophylactic treatment of atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

Additionally, the invention provides a method of treating or preventing a medical condition for which a MMP inhibitor is indicated, in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, or a pharmaceutical composition or veterinary formulation containing any of the foregoing.

Still further, the invention provides a method of treating or preventing atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells, in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically or

veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, or a pharmaceutical composition or veterinary formulation containing any of the foregoing.

The invention also includes any novel intermediates described herein, for example those of formula (II).

The syntheses of the compound of the invention and of the intermediates for use therein are illustrated by the following Examples and Preparations.

Room temperature means 20 to 25°C.

Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230-400 mesh).

Melting points are uncorrected.

^{1}H Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AC300, a Varian Unity Inova-300 or a Varian Unity Inova-400 spectrometer and were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Mass spectra were recorded using a Finnigan Mat. TSQ 7000 or a Fisons Intruments Trio 1000 mass spectrometer. LRMS means low resolution mass spectrum and the calculated and observed ions quoted refer to the isotopic composition of lowest mass.

EXAMPLE 1

N-Hydroxy-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetamide

Potassium carbonate (207mg, 1.5 mmol) was added to a stirred mixture of the title compound of Preparation 8 (186 mg, 0.5 mmol), hydroxylamine hydrochloride (104 mg, 1.5 mmol), tetrahydrofuran (2 ml) and methanol (3 ml). The reaction mixture was heated under reflux for 20 hours, allowed to cool, diluted with water (15 ml) and ethyl acetate (10 ml) and acidified with concentrated hydrochloric acid. This mixture was then briefly heated at 100°C, allowed to cool and filtered. The material thus obtained was washed sequentially with water and ethyl acetate, then dried under vacuum to provide the title compound (125 mg, 67%) as a colourless solid, m.p. 216-218°C. Found: C,61.05; H, 5.35; N, 7.41. $C_{19}H_{20}N_2O_4S$ requires C, 61.27; H, 5.41; N, 7.52%. δ ($DMSO_{d6}$): 2.62 (m,2H), 3.50 (m,2H), 3.92 (s,2H), 3.98 (m,2H), 6.24 (brs, 1H), 7.35 (m,1H), 7.41-7.48 (m,2H), 7.52-7.58 (m,2H), 7.62-7.73 (m,4H), 9.22 (s,1H), 10.82 (s,1H).
LRMS (APCI): 373 $(M+H)^+$.

EXAMPLE 2

N-Hydroxy-2-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetamide

Obtained as a colourless solid (58%), m.p. 190-191°C, from the title compound of Preparation 9, using the procedure of Example 1. Found: C,62.05; H,5.74; N,7.12. $C_{20}H_{22}N_2O_4S$ requires C,62.16; H,5.74; N,7.25%. δ($DMSO_{d6}$): 2.23 (s,3H), 2.60 (m,2H), 3.47 (t,2H), 3.90 (s,2H), 3.95 (m,2H), 6.20 (brs, 1H), 7.17 (d,1H), 7.30-7.48 (m,7H), 9.20 (s,1H), 10.80 (s,1H).
LRMS (Thermospray): 388$(M+H)^+$.

EXAMPLE 3

N-Hydroxy-2-[4-(4-phenylphenyl)piperidin-1-ylsulphonyl]acetamide

Obtained as a colourless solid (62%), m.p. 200-201°C, from the title compound of Preparation 10, using the procedure of Example 1. Found: C,60.96; H,5.86; N,6.97. $C_{19}H_{22}N_2O_4S$ requires C,60.94; H,5.92; N,7.48%. $\delta(DMSO_{d6})$: 1.63 (m,2H), 1.83 (m,2H), 2.66 (m,1H), 2.98 (t,2H), 3.70 (m,2H), 3.83 (s,2H), 7.30 (m,3H), 7.40 (t,2H), 7.54-7.60 (m,4H), 9.18 (s,1H), 10.75 (s,1H).

LRMS (Thermospray): 375 $(M+H)^+$.

EXAMPLE 4

N-Hydroxy-2-(4-phenyl-1,2,3,6-tetrahydropyridin-1-ylsulphonyl)acetamide

Obtained as a colourless solid (76%), m.p. 175-176°C, from the title compound of Preparation 11, using the procedure of Example 1. Found: C,52.41; H,5.39; N,9.35. $C_{13}H_{16}N_2O_4S$ requries C,52.69; H,5.44; N,9.45%. $\delta(DMSO_{d6})$: 2.58 (m,2H), 3.46 (t,2H), 3.90 (s,2H), 3.95 (m,2H), 6.18 (brs, 1H), 7.23-7.48 (m,5H), 9.20 (s,1H), 10.80 (s,1H).

EXAMPLE 5

N-Hydroxy-2-(4-phenylpiperidin-1-ylsulphonyl)acetamide

Obtained as a colourless solid (44%), m.p. 185-187°C, from the title compound of Preparation 12, using the procedure of Example 1. Found: C,52.08; H,6.04; N,9.23. $C_{13}H_{18}N_2O_4S$ requires C,52.33; H,6.08; N,9.39%. $\delta(DMSO_{d6})$: 1.62 (m,2H), 1.82 (m,2H), 2.62 (m,1H), 2.98 (t,2H), 3.70 (m,2H), 3.84 (s,2H), 7.15-7.33 (m,5H), 9.20 (s,1H), 10.78 (s,1H).

EXAMPLE 6

N-Hydroxy-2-(4-benzylpiperidin-1-ylsulphonyl)acetamide

Obtained as a colourless solid (35%), m.p. 132-135°C, from the title compound of Preparation 13, using the procedure of Example 1. Found: C,53.66; H,6.43; N,8.82. $C_{14}H_{20}N_2O_4S$ requires C,53.83; H,6.45; N,8.97%. $\delta(DMSO_{d6})$: 1.13 (m,2H), 1.58 (m,3H), 2.49 (d,2H), 2.75 (t,2H), 3.50 (d,2H), 3.73 (s,2H), 7.10 (m,3H), 7.22 (m,2H), 9.10 (s,1H), 10.70 (s,1H).

EXAMPLE 7

N-Hydroxy-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enamide

O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (100 mg, 0.26 mmol) was added to a stirred solution of the title compound of Preparation 15 (70 mg, 0.18 mmol) and N-ethyldiisopropylamine (0.03 ml, 0.18 mmol) in anhydrous dimethylformamide (1 ml), under nitrogen, at room temperature. After 15 minutes, a solution of hydroxylamine hydrochloride (37 mg, 0.53 mmol) and N-ethyldiisopropylamine (0.12 ml, 0.7 mmol) in anhydrous dimethylformamide (0.5 ml) was added and the reaction mixture stirred for 20 hours, then partitioned between ethyl acetate and aqueous phosphate buffer (pH 7). The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using dichloromethane:methanol (97:3) as eluant, to give the title compound (55 mg) as a colourless, amorphous solid. $\delta(DMSO_{d6})$: 2.50-2.80 (m,4H), 3.50 (m,2H), 3.80 (dd,1H), 4.00 (m,2H), 5.03-5.18 (m,2H), 5.62 (m,1H), 6.23 (brs, 1H), 7.37 (m,1H), 7.45 (m,2H), 7.53 (m,2H), 7.67 (m,4H), 9.22 (s,1H), 10.85 (s,1H). LRMS (Thermospray): 413 $(M+H)^+$.

EXAMPLE 8

N-Hydroxy-2(R,S)-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enamide

Obtained as a solid (13%) from the title compound of Preparation 17, using the procedure of Example 7, but with an elution gradient of dichloromethane:methanol (100:0 to 90:10) for the chromatographic purification step. $\delta(CDCl_3)$: 2.25 (s,3H), 2.62 (m,2H), 2.82 (m,2H), 3.62 (m,2H), 3.80 (dd,1H), 4.10 (m,2H), 5.10-5.22 (m,2H), 5.75 (m,1H), 6.03 (brs, 1H), 7.20-7.43 (m,8H).

LRMS (APCI): 427 $(M+H)^+$.

EXAMPLE 9

N-Hydroxy-5-phenyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pentanamide

Obtained as a colourless solid (35%), m.p. 150°C (decomp.), from the title compound of Preparation 18, using the procedure of Example 1. $\delta(DMSO_{d6})$: 1.50 (m,2H), 1.80 (m,1H), 2.00 (m,1H), 2.54 (m,4H), 3.45 (m,2H), 3.75 (dd,1H), 3.98 (m,2H), 6.10 (brs,1H), 7.10-7.54 (m,10H), 7.63 (m,4H), 9.10 (s,1H), 10.88 (s,1H).

LRMS (Thermospray): 492 $(M+H)^+$.

EXAMPLE 10

N-Hydroxy-2-methyl-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]propanamide

Obtained as an amorphous solid (41%) from the title compound of Preparation 19, using the procedure of Example 7. $\delta(DMSO_{d6})$: 1.50 (s,6H), 2.66 (m,2H), 3.50 (m,2H), 4.00 (m,2H), 6.10 (brs,1H), 7.30-7.70 (m,9H), 9.00 (s,1H), 10.78 (s,1H).

EXAMPLE 11

N-Hydroxy-1-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]cyclopentanecarboxamide

Obtained as a solid (44%) from the title compound of Preparation 21, using the procedure of Example 7, but with dichloromethane:methanol (99:1) as eluant for the chromatographic purification step. $\delta(CDCl_3)$: 1.70 (m,2H), 1.86 (m,2H), 2.27 (s,3H), 2.37 (m,2H), 2.48 (m,2H), 2.62 (m,2H), 3.60 (t,2H), 4.05 (m,2H), 6.02 (brs,1H), 7.20-7.43 (m,8H).

EXAMPLE 12

N-Hydroxy-2-ethyl-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-sulphonyl]butanamide

Obtained as a solid (56%) from the title compound of Preparation 23, using the procedure of Example 7. $\delta(DMSO_{d6})$: 0.90 (m,6H), 1.95-2.13 (m,4H), 2.52 (m,2H), 3.48 (m,2H), 3.98 (m,2H), 6.10 (brs,1H), 7.35 (m,1H), 7.44 (m,2H), 7.52 (m,2H), 7.64 (m,4H), 9.03 (brs,1H), 10.70 (brs,1H).

EXAMPLE 13

N-Hydroxy-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]hexanamide

Obtained as a colourless solid (72%), m.p. 186-189°C, from the title compound of Preparation 25, using the procedure of Example 7, but with 1-methylpyrrolidin-2-one as reaction solvent and with crystallisation from diisopropyl ether:ethyl acetate, rather than flash chromatography, as the purification technique. Found: C,63.03; H,6.60; N,6.43. $C_{23}H_{28}N_2O_4S$; 0.50 H_2O requires C,63.13; H,6.68; N,6.40%. $\delta(DMSO_{d6})$: 0.83 (t,3H), 1.10-1.35 (m,4H), 1.78 (m,1H), 1.98 (m,1H), 2.55 (m,2H), 3.50 (m,2H), 3.70 (dd,1H), 3.98

(m,2H), 6.12 (brs, 1H), 7.32 (m,1H), 7.44 (m,2H), 7.52 (m,2H), 7.64 (m,4H), 9.20 (brs, 1H), 10.85 (brs,1H).

LRMS (APCI): 429 $(M+H)^+$.

EXAMPLE 14

N-Hydroxy-4-methyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enamide

Obtained as a colourless solid (33%), m.p. 170-171°C, from the title compound of Preparation 27, using the procedure of Example 7, but with an elution gradient of dichloromethane:methanol (100:0 to 98:2) for the chromatographic purification step. $\delta(DMSO_{d6})$: 1.65 (s,3H), 2.40-2.80 (m,4H), 3.52 (m,2H), 3.90 (dd,1H), 4.00 (m,2H), 4.70 (s,1H), 4.78 (s,1H), 6.23 (brs,1H), 7.35 (m,1H), 7.44 (m,2H), 7.52 (d,2H), 7.65 (m,4H), 9.22 (s,1H), 10.85 (s,1H).

LRMS (APCI): 427 $(M+H)^+$.

EXAMPLE 15

N-Hydroxy-2(R,S)-methyl-2-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enamide

Obtained as a colourless gum (20%) from the title compound of Preparation 29, using the procedure of Example 7, but with an elution gradient of dichloromethane:methanol (100:0 to 98:2 to 95:5) for the chromatographic purification step. δ ($CDCl_3$): 1.60 (s,3H), 2.28 (s,3H), 2.64 (m,3H), 3.00 (m,1H), 3.62 (m,2H), 4.10 (m,2H), 5.21 (m,2H), 5.70 (m,1H), 6.03 (brs,1H), 7.20-7.44 (m,8H).

LRMS (APCI): 441 $(M+H)^+$.

EXAMPLE 16

N-Hydroxy-2-[3-(4-phenylphenoxy)azetidin-1-ylsulphonyl]acetamide

Obtained as a colourless solid (66%) from the title compound of Preparation 32, using the procedure of EXAMPLE 1. $\delta(DMSO_{d6})$: 4.03 (s,2H), 4.05 (dd,2H), 5.09 (m,1H), 6.94 (d,2H), 7.30 (m,1H), 7.40 (m,2H), 7.60 (m,4H), 9.25 (s,1H), 10.80 (brs,1H).

LRMS (Thermospray): 364 $(M+H)^+$.

EXAMPLE 17

N-Hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Potassium carbonate (406 mg, 3 mmol) was added to a stirred mixture of the title compound of Preparation 41 (429 mg, 1 mmol), hydroxylamine hydrochloride (212 mg, 3 mmol) and methanol (20 ml). The reaction mixture was heated under reflux for about 6 hours, allowed to cool and partitioned between ethyl acetate and 1M hydrochloric acid. The separated organic phase was dried ($MgSO_4$) and evaporated under reduced pressure, then the residue triturated with diisopropyl ether and crystallised from ethyl acetate to yield the title compound (148 mg, 34%) as a colourless solid, m.p. 151-153°C. Found: C,61.01; H, 6.04; N, 6.48. $C_{22}H_{26}N_2O_5S$ requires C, 61.38; H, 6.09; N, 6.51%. δ $(DMSO_{d6})$: 1.33 (t,3H), 2.23 (s,3H), 2.60 (m,2H), 3.46 (t,2H), 3.91 (s,2H), 3.96 (m,2H), 4.03 (q,2H), 6.10 (brs,1H), 6.80-6.95 (m,3H), 7.17 (d,1H), 7.28-7.38 (m,3H), 9.20 (brs,1H), 10.8 (brs,1H).

LRMS (APCI): 431 $(M+H)^+$.

EXAMPLE 18

N-Hydroxy-2-[4-(3-methoxy-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetamide

Potassium carbonate (95 mg, 0.7 mmol) was added to a stirred mixture of the title compound of Preparation 45 (170 mg, 0.4 mmol), hydroxylamine hydrochloride (49 mg, 0.7 mmol) and methanol (3 ml). The reaction mixture was heated under reflux for about 2 hours, allowed to cool, diluted with phosphate buffer (15 ml) and extracted with ethyl acetate (2 x 15 ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue was triturated with ethyl acetate to furnish the title compound (50 mg, 30%) as a colourless solid, m.p. 175-177°C. Found: C,58.84; H, 5.51; N, 6.70. $C_{20}H_{20}N_2O_5S$; 0.10 CH_2Cl_2 requires C, 58.75; H, 5.45; N, 6.82%. δ ($DMSO_{d6}$): 2.63 (m,2H), 3.50 (t,2H), 3.80 (s,3H), 3.93 (s,2H), 3.99 (s,2H), 6.27 (s,1H), 7.10 (d,1H), 7.16 (s,1H), 7.27 (d,1H), 7.31 (d,1H), 7.41 (t,2H), 7.47 (d,2H), 9.23 (brs,1H), 10.80 (brs,1H).
LRMS (Thermospray): 420 $(M+NH_4)^+$.

EXAMPLE 19

N-Hydroxy-2-[4-(3-methoxy-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-2-methylpropanamide

O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (274 mg, 0.72 mmol) was added to a stirred solution of the title compound of Preparation 50 (200 mg, 0.48 mmol) and N-ethyldiisopropylamine (0.08 ml, 0.48 mmol) in anhydrous dimethylformamide (4 ml), under nitrogen, at room temperature. After 15 minutes, hydroxylamine hydrochloride (100 mg, 1.44 mmol) and N-ethyldiisopropylamine (0.33 ml, 1.9 mmol) were added and the reaction mixture stirred for about 3 hours, then partitioned between ethyl acetate and aqueous phosphate buffer (pH 7). The

organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure, then the residue was triturated with diisopropyl ether to give the title compound (71 mg, 36%) as a colourless, amorphous solid, m.p. 156-158°C. Found: C,60.80; H, 6.17; N, 6.25. $C_{22}H_{26}N_2O_5S$; 0.10 H_2O requires C, 61.12; H, 6.11; N, 6.48%. δ($DMSO_{d6}$): 1.51 (s,6H), 2.57 (m,2H), 3.43 (t,2H), 3.80 (s,3H), 4.03 (m,2H), 6.25 (brs,1H), 7.09 (d,1H), 7.13 (s,1H), 7.26 (d,1H), 7.31 (d,1H), 7.39 (t,2H), 7.46 (d,2H), 9.24 (brs,1H), 10.79 (brs,1H).

LRMS (APCI): 431 $(M+H)^+$.

EXAMPLE 20

N-Hydroxy-2-[4-(3-fluoro-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetamide

Obtained as a colourless solid (40%), m.p. 184-188°C, from the title compound of Preparation 47, using the procedure of Example 1. Found: C,58.39; H,4.90; N,6.84. $C_{19}H_{19}FN_2O_4S$ requires C,58.45; H,4.91; N,7.17%. δ($DMSO_{d6}$): 2.61 (m,2H), 3.47 (t,2H), 3.94 (s,2H), 4.00 (s,2H), 6.35 (brs,1H), 7.33-7.60 (m,8H), 9.23 (brs,1H), 10.80 (brs,1H).

LRMS (Thermospray): 408 $(M+NH_4)^+$.

EXAMPLE 21

N-Hydroxy-2-{4-[4-(3-ethoxyphenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (76%), m.p. 168-170°C, from the title compound of Preparation 56, using the procedure of Example 1. δ($DMSO_{d6}$): 1.34 (t,3H), 2.61 (m,2H), 3.49 (t,2H), 3.94 (s,2H), 3.98 (s,2H), 4.10 (q,2H), 6.25 (brs,1H), 6.91 (d,1H), 7.17 (s,1H), 7.22 (d,1H), 7.33 (t,1H), 7.52 (d,2H), 7.66 (d,2H), 9.22 (brs,1H), 10.80 (brs,1H).

LRMS (Thermospray): 434 $(M+NH_4)^+$.

EXAMPLE 22

N-Hydroxy-2-{4-[4-(3-methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (76%), m.p. 162-165°C, from the title compound of Preparation 61, using the procedure of Example 1. Found: C,60.26; H, 5.86; N, 6.43. $C_{21}H_{24}N_2O_5S$ requires C, 60.56; H, 5.81; N, 6.73%. $\delta(DMSO_{d6})$: 2.23 (s,3H), 2.60 (m,2H), 3.47 (t,2H), 3.77 (s,3H), 3.93 (s,2H), 3.97 (s,2H), 6.20 (brs,1H), 6.83-6.94(m,3H), 7.18 (d,1H), 7.27-7.39 (m, 3H), 9.22 (brs,1H), 10.80 (brs,1H).

LRMS (APCI): 416 $(M)^+$.

EXAMPLE 23

N-Hydroxy-2-{4-[4-(3-ethylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (58%), m.p. 151-154°C, from the title compound of Preparation 63, using the procedure of Example 1. Found: C,62.75; H, 6.24; N, 6.26. $C_{22}H_{26}N_2O_4S$; 0.50 H_2O requires C, 62.39; H, 6.43; N, 6.61%. $\delta(DMSO_{d6})$: 1.20 (t,3H), 2.24 (s,3H), 2.61 (m,4H), 3.47 (t,2H), 3.92 (s,2H), 3.97 (s,2H), 6.20 (brs,1H), 7.10-7.23 (m,4H), 7.27-7.38 (m,3H), 9.22 (brs,1H), 10.81 (brs,1H).

LRMS (APCI): 414 $(M)^+$.

EXAMPLE 24

N-Hydroxy-4-{4-[4-(3-Methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxamide

Obtained as a pale yellow solid (47%), m.p. 160-170°C, from the title compound of Preparation 65, using the procedure of Example 19. $\delta(DMSO_{d6})$: 1.93 (m,2H), 2.23 (s,3H), 2.39 (m,2H), 2.43 (m,2H), 3.20 (t,2H), 3.49 (m,2H),

3.77 (s,3H), 3.86 (m,2H), 4.00 (m,2H), 6.16 (brs,1H), 6.83-6.94 (m,3H), 7.17 (d,1H), 7.36 (m,3H), 9.21 (brs,1H), 11.00 (brs,1H).
LRMS (APCI) 487 $(M+H)^+$.

EXAMPLE 25

N-Hydroxy-4-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}tetrahydropyran-4-carboxamide

Obtained as a white solid (82%), m.p. 200-202°C, from the title compound of Preparation 67, using the procedure of Example 19, except that the residue was crystallised from methanol. Found: C,60.02; H, 6.78; N, 5.45. $C_{25}H_{32}N_2O_6S$; CH_3OH requires C, 59.98; H, 6.97; N, 5.38%. $\delta(DMSO_{d6})$: 1.60 (m,2H), 1.78 (m,2H), 1.90 (m,2H), 2.20 (s,3H), 2.38 (m,2H), 2.64 (m,1H), 3.04 (t,2H), 3.20 (t,2H), 3.70 (m,2H), 3.77 (s,3H), 3.86 (m,2H), 6.87 (m,3H), 7.13 (m,3H), 7.33 (t,1H), 9.16 (brs,1H), 10.97 (brs,1H).
LRMS (APCI) 489 $(M+H)^+$.

EXAMPLE 26

N-Hydroxy-2-{4-[3-methoxy-4-(3-methoxyphenyl)phenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide

Obtained as a white solid (47%), m.p. 161-163°C, from the title compound of Preparation 74, using the procedure of Example 19, except that the residue was purified by flash chromatography using dichloromethane:methanol:concentrated aqueous ammonia solution (90:10:1) as eluant. Found: C,59.39; H, 6.58; N, 6.13. $C_{23}H_{30}N_2O_6S$ requires C, 59.72; H, 6.54; N, 6.06%. $\delta(DMSO_{d6})$: 1.49 (s,6H), 1.64 (m,2H), 1.81 (m,2H), 2.70 (m,1H), 3.06 (t,2H), 3.75 (s,8H), 6.87 (m,2H), 6.98 (m,3H), 7.20 (d,1H), 7.27 (t,1H), 8.99 (brs,1H), 10.75 (brs,1H).
LRMS (Thermospray): 480 $(M+NH_4)^+$.

EXAMPLE 27

N-Hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide

Obtained as a white solid (39%), m.p. 134-136°C, from the title compound of Preparation 77, using the procedure of Example 26. Found: C,60.60; H, 6.80; N, 5.82. $C_{24}H_{32}N_2O_6S$ requires C, 60.48; H, 6.77; N, 5.88%. δ($DMSO_{d6}$): 1.32 (t,3H), 1.49 (s,6H), 1.66 (m,2H), 1.81 (m,2H), 2.70 (m,1H), 3.07 (t,2H), 3.76 (s,5H), 4.02 (q,2H), 6.85 (m,2H), 6.98 (m,3H), 7.20 (d,1H), 7.27 (t,1H), 9.00 (brs,1H), 10.76 (brs,1H).
LRMS (Thermospray): 494 $(M+NH_4)^+$.

EXAMPLE 28

N-Hydroxy-4-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxamide

Obtained as a colourless solid (87%), m.p. 152-154°C, from the title compound of Preparation 79, using the procedure of Example 19. Found: C,61.99; H, 6.47; N, 5.54. $C_{26}H_{32}N_2O_6S$ requires C, 62.38; H, 6.44; N, 5.60%. δ($DMSO_{d6}$): 1.33 (t,3H), 1.93 (m,2H), 2.24 (s,3H), 2.40 (d,2H), 2.52 (m,2H), 3.21 (dd,2H), 3.50 (m,2H), 3.88 (m,2H), 3.98-4.10 (m,4H), 6.18 (brs,1H), 6.80-6.95 (m,3H), 7.18 (d,1H), 7.26-7.37 (m,3H), 9.22 (brs,1H), 11.05 (brs,1H).
LRMS (APCI): 501 $(M+H)^+$.

EXAMPLE 29

N-Hydroxy-4-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}tetrahydropyran-4-carboxamide

Palladium on barium sulfate (5%, 5 mg) was added to a stirred solution of the title compound of Example 28 (50 mg, 0.1 mmol) in a mixture of 1,2-

dimethoxyethane (1 ml) and methanol (3 ml), then the reaction mixture hydrogenated at 345 kPa (50 psi) pressure for about 20 hours. A further portion of palladium on barium sulfate (5%, 5 mg) was added and hydrogenation continued for an additional 20 hours. The catalyst was removed by filtration, the solvent evaporated under reduced pressure and the residue crystallised from ether-hexane to afford the title compound (34 mg, 66%) as a colourless solid, m.p. 165-167°C. Found: C,60.81; H, 6.76; N, 5.35. $C_{26}H_{34}N_2O_6S$; 0.50 H_2O requires C, 61.03; H, 6.89; N, 5.47%. δ ($DMSO_{d6}$): 1.35 (t,3H), 1.60 (m,2H), 1.78 (m,2H), 1.92 (m,2H), 2.20 (s,3H), 2.40 (d,2H), 2.62 (m,1H), 3.03 (dd,2H), 3.20 (dd,2H), 3.73 (m,2H), 3.86 (m,2H), 4.04 (q,2H), 6.80-6.92 (m,3H), 7.07-7.17 (m,3H), 7.30 (t,1H), 9.18 (brs,1H), 11.0 (brs,1H).
LRMS (Thermospray): 520 $(M+NH_4)^+$.

EXAMPLE 30

N-Hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanamide

Obtained as a colourless solid (33%), m.p. 116-118°C, from the title compound of Preparation 81, using the procedure of Example 19. Found: C,62.52; H, 6.47; N, 6.00. $C_{24}H_{30}N_2O_5S$ requires C, 62.86; H, 6.59; N, 6.11%. δ($DMSO_{d6}$): 1.34 (t,3H), 1.52 (s,6H), 2.23 (s,3H), 2.53 (m,2H), 3.50 (m,2H), 4.00-4.10 (m,4H), 6.18 (brs,1H), 6.80-6.95 (m,3H), 7.18 (d,1H), 7.28-7.38 (m,3H), 9.03 (brs,1H), 10.8 (brs,1H).
LRMS (Thermospray): 459 $(M+H)^+$.

EXAMPLE 31

N-Hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (48%), m.p. 179-180°C (crystallised from diisopropyl ether), from the title compound of Preparation 82, using the procedure of Example 17. Found: C,60.72; H,6.49; N,6.36. $C_{22}H_{28}N_2O_5S$ requires C,61.09; H,6.53; N,6.48%. δ($DMSO_{d6}$): 1.31 (t,3H), 1.68 (m,2H), 1.86 (m,2H), 2.20 (s,3H), 2.65 (m,1H), 3.00 (m,2H), 3.72 (m,2H), 3.86 (s,2H), 4.03 (q.2H), 6.80-6.90 (m,3H), 7.10 (s,2H), 7.17 (s,1H), 7.30 (t,1H), 9.20 (brs,1H), 10.8 (brs,1H).

LRMS (APCI): 433 $(M+H)^+$.

EXAMPLE 32

N-Hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide

Obtained as a colourless solid (53%), m.p. 172-174°C (crystallised from diisopropyl ether), from the title compound of Preparation 84, using the procedure of Example 19. Found: C,62.20; H,6.99; N,6.02. $C_{24}H_{32}N_2O_5S$ requires C,62.58; H,7.00; N,6.08%. δ($DMSO_{d6}$): 1.31 (t,3H), 1.50 (s,6H), 1.61 (m,2H), 1.79 (m,2H), 2.20 (s,3H), 2.65 (m,1H), 3.05 (m,2H), 3.75 (m,2H), 4.03 (q,2H), 6.80-6.90 (m,3H), 7.08-7.18 (m,3H), 7.30 (dd,1H), 8.98 (brs,1H), 10.75 (brs,1H).

LRMS (APCI): 461 $(M+H)^+$.

EXAMPLE 33

N-Hydroxy-2-{4-[3-methyl-4-(pyridin-2-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless amorphous solid (50%) from the title compound of Preparation 85, using the procedure of Example 17. $\delta(DMSO_{d6})$: 2.33 (s,3H), 2.60 (m,2H), 3.46 (t,2H), 3.91 (s,2H), 3.97 (m,2H), 6.12 (brs,1H), 7.30-7.40 (m,4H), 7.50 (d,1H), 7.84 (dd,1H), 8.63 (d,1H), 9.20 (brs,1H), 10.8 (brs,1H).

LRMS (APCI): 388 $(M+H)^+$.

EXAMPLE 34

N-Hydroxy-2-{4-[3-methyl-4-(pyridin-3-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (57%), m.p. 132-136°C, from the title compound of Preparation 86, using the procedure of Example 31. $\delta(DMSO_{d6})$: 2.23 (s,3H), 2.60 (m,2H), 3.46 (t,2H), 3.91 (s,2H), 3.97 (m,2H), 6.12 (brs,1H), 7.21 (d,1H), 7.35 (d,1H), 7.40 (s,1H), 7.45 (dd,1H), 7.78 (d,1H), 8.55 (m,2H), 9.20 (brs,1H), 10.8 (brs,1H).

LRMS (APCI): 388 $(M+H)^+$.

EXAMPLE 35

N-Hydroxy-2-{4-[3-methyl-4-(pyridin-4-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (20%), m.p. 165-167° C, from the title compound of Preparation 87, using the procedure of Example 31. $\delta(DMSO_{d6})$: 2.26 (s,3H), 2.60 (m,2H), 3.47 (t,2H), 3.92 (s,2H), 3.97 (m,2H), 6.12 (brs,1H), 7.22 (d,1H), 7.35-7.42 (m,4H), 8.62 (d,2H), 9.20 (brs,1H), 10.8 (brs,1H).

LRMS (APCI): 388 $(M+H)^+$.

EXAMPLE 36

N-Hydroxy-2-{4-[4-(6-ethoxypyridin-2-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide

Obtained as a colourless solid (30%), m.p. 184-187° C, from the title compound of Preparation 91, using the procedure of Example 19, except that the residue was purified by flash chromatography using dichloromethane: ethanol (98:2) as eluant. $\delta(DMSO_{d6})$: 1.30 (t,3H), 1.48 (s,6H), 1.63 (m,2H), 1.79 (m,2H), 2.35 (s,3H), 2.67 (m,1H), 3.05 (t,2H), 3.75 (d,2H), 4.30 (q,2H), 6.72 (d,1H), 7.05 (d,1H), 7.15 (m,2H), 7.34 (o,1H), 7.73 (t,1H), 9.00 (brs,1H), 10.75 (brs,1H).

HRMS (positive ion electrospray): 462.206 $(M+H)^+$.

EXAMPLE 37

N-Hydroxy-4-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]tetrahydropyran-4-carboxamide

Obtained as a colourless solid (68%), m.p. 191-193°C, from the title compound of Preparation 93, using the procedure of Example 19, but with crystallisation of the residue from methanol. $\delta(DMSO_{d6})$: 1.93 (m,2H), 2.40 (d,2H), 2.55 (m,2H), 3.20 (t,2H), 3.48 (m,2H), 3.85 (m,2H), 4.00 (m,2H), 6.11 (brs,1H), 7.35 (t,1H), 7.44 (m,2H), 7.52 (d,2H), 7.65 (m,4H), 9.22 (brs,1H), 11.05 (brs,1H).

LRMS (APCI): 443 $(M+H)^+$.

EXAMPLE 38

N-Hydroxy-4-{4-[4-(4-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxamide

Obtained as a colourless solid (36%), m.p. 159-161°C, from the title compound of Preparation 95, using the procedure of Example 19, but with crystallisation of the residue from dichloromethane-diisopropyl ether.

$\delta(DMSO_{d6})$: 1.35 (t,3H), 1.94 (m,2H), 2.22 (s,3H), 2.38 (d,2H), 2.50 (brs,2H), 3.20 (t,2H), 3.50 (brs,2H), 3.87 (dd,2H), 3.98 (brs,2H), 4.04 (q,2H), 6.15 (brs,1H), 6.96 (d,2H), 7.13 (d,1H), 7.22 (d,2H), 7.28 (d,1H), 7.33 (s,1H), 9.20 (brs,1H), 11.05 (brs,1H).

LRMS (Thermospray): 515 $(M+NH_4)^+$.

EXAMPLE 39

N-Hydroxy-2-{4-[4-(3-hydroxymethylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (63%), m.p. 174-176°C (crystallised from methanol-diisopropyl ether), from the title compound of Preparation 97, using the procedure of Example 17. Found: C,60.35; H,5.75; N,6.70. $C_{21}H_{24}N_2O_5S$ requires C,60.56; H,5.81; N,6.73%. $\delta(DMSO_{d6})$: 2.22 (s,3H), 2.60 (m,2H), 3.47 (t,2H), 3.93 (s,2H), 3.97 (s,2H), 4.53 (d,2H), 5.19 (t,1H exchangeable), 6.20 (brs,1H), 7.15-7.42 (m,7H), 9.20 (brs,1H), 10.80 (brs,1H).

LRMS (APCI): 417 $(M+H)^+$.

EXAMPLE 40

N-Hydroxy-2-methyl-2-{4-[3-methyl-4-(quinolin-3-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}propanamide

Obtained as a colourless solid (51%), m.p. 158-160°C, from the title compound of Preparation 100, using the procedure of Example 19. $\delta(DMSO_{d6})$: 1.50 (s,6H), 2.32 (s,3H), 2.57 (m,2H), 3.53 (m,2H), 4.03 (m,2H), 6.23 (brs,1H), 7.34-7.48 (m,3H), 7.63 (t,1H), 7.79 (t,1H), 8.04 (t,2H), 8.37 (s,1H), 8.91 (s,1H), 9.04 (brs,1H), 10.8 (brs,1H).

LRMS (APCI): 466 $(M+H)^+$.

EXAMPLE 41

N-Hydroxy-2-{4-[3-methyl-4-(3-methylthiophenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (17%), from the title compound of Preparation 102, using the procedure of Example 1. $\delta(DMSO_{d6})$: 2.23 (s,3H), 2.49 (s,3H), 2.60 (m,2H), 3.47 (t,2H), 3.91 (s,2H), 3.97 (s,2H), 6.22 (brs,1H), 7.08 (d,1H), 7.17 (m,2H), 7.24 (d,1H), 7.34 (m, 3H), 9.22 (brs,1H), 10.80 (brs,1H).

LRMS (APCI): 432 $(M)^+$.

EXAMPLE 42

N-Hydroxy-2-{4-[4-(3-methoxymethylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (28%), m.p. 151-153°C (crystallised from ethyl acetate-diisopropyl ether), from the title compound of Preparation 104, using the procedure of Example 17. Found: C,60.16; H,6.00; N,6.28. $C_{22}H_{26}N_2O_5S$; 0.10 H_2O requires C,60.11; H,6.19; N,6.37%. $\delta(DMSO_{d6})$: 2.22 (s,3H), 2.60 (m,2H), 3.30 (s,3H), 3.47 (t,2H), 3.93 (s,2H), 3.97 (s,2H), 4.04 (s,2H), 6.20 (brs,1H), 7.17 (d,1H), 7.21-7.42 (m,6H), 9.20 (brs,1H), 10.80 (brs,1H).

LRMS (Thermospray): 432 $(M+H)^+$.

EXAMPLE 43

N-Hydroxy-2-{4-[4-(3-[2-methoxyethoxy]phenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (64%), m.p. 158-160°C (crystallised from ethyl acetate), from the title compound of Preparation 107, using the procedure of Example 17. Found: C,59.78; H,6.10; N,6.01. $C_{23}H_{28}N_2O_6S$ requires

C,59.98; H,6.13; N,6.08%. δ($DMSO_{d6}$): 2.24 (s,3H), 2.60 (m,2H), 3.30 (s,3H), 3.47 (t,2H), 3.66 (m,2H), 3.92 (s,2H), 3.97 (m,2H), 4.12 (t,2H), 6.20 (brs,1H), 6.89 (m,3H), 7.18 (d,1H), 7.34 (m,3H), 9.20 (brs,1H), 10.80 (brs,1H).
LRMS (Thermospray): 460 $(M)^+$.

EXAMPLE 44

N-Hydroxy-2-{4-[4-(2,3-dihydrobenzofuran-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (56%), m.p. 158-162°C, from the title compound of Preparation 112, using the procedure of Example 17. Found: C,57.01; H,5.47; N,5.26. $C_{22}H_{26}N_2O_5S$; 0.60 CH_2Cl_2 requires C,56.61; H,5.30; N,5.84%. δ($DMSO_{d6}$): 2.23 (s,3H), 2.58 (m,2H), 3.20 (t,2H), 3.44 (t,2H), 3.92 (s,2H), 3.96 (s,2H), 4.55 (t,2H), 6.20 (brs,1H), 6.78 (d,1H), 7.01 (d,1H), 7.12 (d,1H), 7.17 (s,1H), 7.27 (d,1H), 7.33 (s,1H), 9.20 (brs,1H), 10.80 (brs,1H).
LRMS (APCI): 428 $(M+H)^+$.

EXAMPLE 45

N-Hydroxy-2-{4[3-methyl-4-(3-trifluoromethylphenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (50%), m.p. 168-170°C (crystallised from diisopropyl ether), from the title compound of Preparation 116, using the procedure of Example 17, except that tetrahydrofuran was used as a co-solvent for the reaction. Found: C,54.96; H,4.73; N,5.97. $C_{21}H_{21}F_3N_2O_4S$; 0.25 H_2O requires C,54.96; H,4.72; N,6.10%. δ($DMSO_{d6}$): 2.24 (s,3H), 2.60 (m,2H), 3.47 (t,2H), 3.93 (s,2H), 3.97 (m,2H), 6.22 (brs,1H), 7.23 (d,1H), 7.36 (d,1H), 7.41 (s,1H), 7.68 (m,4H), 9.20 (brs,1H), 10.80 (brs,1H).
LRMS (APCI): 455 $(M+H)^+$.

EXAMPLE 46

N-Hydroxy-2-[4-(4-phenoxyphenyl)piperidin-1-ylsulphonyl]acetamide

Obtained as a colourless solid (13%), m.p. 176-179°C, from the title compound of Preparation 119, using the procedure of Example 17, except that dichloromethane was used as a co-solvent for the reaction. Found: C,57.92; H,5.62; N,6.97. $C_{19}H_{22}N_2O_5S$; 0.20 H_2O requires C,57.91; H,5.73; N,7.11%. $\delta(DMSO_{d6})$: 1.63 (m,2H), 1.84 (m,2H), 2.63 (m,1H), 2.98 (t,2H), 3.69 (m,2H), 3.85 (s,2H), 6.96 (m,4H), 7.10 (t,1H), 7.27 (d,2H), 7.36 (t,2H), 9.20 (brs,1H), 10.80 (brs,1H).

LRMS (Thermospray): 392 $(M+H)^+$.

EXAMPLE 47

N-Hydroxy-2-{4-[4-(3-[2-methoxyethoxy]phenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide

Obtained as a colourless solid (42%), m.p. 155-156°C, from the title compound of Preparation 122, using the procedure of Example 19, except that the residue was purified by flash chromatography, using dichloromethane:methanol (97:3) as eluant, prior to crystallisation from dichloromethane-diisopropyl ether. $\delta(DMSO_{d6})$: 1.50 (s,6H), 1.60 (m,2H), 1.80 (m,2H), 2.20 (s,3H), 2.65 (m,1H), 3.05 (t,2H), 3.30 (s,3H), 3.62 (t,2H), 3.74 (d,2H), 4.10 (t,2H), 6.80-6.92 (m,3H), 7.10-7.17 (m,3H), 7.30 (t,1H), 9.02 (brs,1H), 10.7 (brs,1H).

LRMS (Electrospray): 513 $(M+Na)^+$.

EXAMPLE 48

N-Hydroxy-4-methoxy-2(R,S)-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]butanamide

Obtained as a colourless solid (39%), m.p. 135-136°C, from the title compound of Preparation 124, using the procedure of Example 19, except that the residue was purified by flash chromatography using dichloromethane: methanol (97:3) as eluant, prior to crystallisation from diisopropyl ether. $\delta(DMSO_{d6})$: 2.10 (m,2H), 2.23 (s,3H), 2.57 (m,2H),3.20 (s,4H), 3.36 (m,1H), 3.48 (m,2H), 3.87 (dd,1H), 3.98 (m,2H), 6.20 (brs,1H), 7.16 (d,1H), 7.32 (m,5H), 7.43 (m,2H), 9.22 (brs,1H), 10.95 (brs,1H).
LRMS (Thermospray): 444 $(M)^+$.

EXAMPLE 49

N-Hydroxy-4-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]tetrahydropyran-4-carboxamide

Obtained as a colourless solid (91%), m.p. 188-190°C, from the title compound of Preparation 126, using the procedure of Example 38. Found: C,61.89; H,6.15; N,5.94. $C_{24}H_{28}N_2O_5S$; 0.50 H_2O requires C,61.91; H,6.28; N,6.02%. $\delta(DMSO_{d6})$: 1.95 (m,2H), 2.22 (s,3H), 2.39 (d,2H), 2.50 (m,2H), 3.20 (t,2H), 3.48 (brs,2H), 3.87 (dd,2H), 4.00 (brs,2H), 6.17 (brs,1H), 7.16 (d,1H), 7.31 (m,5H), 7.42 (m,2H).9.22 (brs,1H), 11.05 (brs,1H).
LRMS (APCI): 457 $(M+H)^+$.

EXAMPLE 50

N-Hydroxy-2-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}indane-2-carboxamide

Obtained as a colourless solid (63%), m.p. 199-202°C, from the title compound of Preparation 130, using the procedure of Example 19, but with crystallisation of the residue from diisopropyl ether. Found: C,66.25; H,6.18; N,5.18. $C_{29}H_{32}N_2O_5S$; 0.30 H_2O requires C,61.21; H,6.25; N,5.33%. δ($DMSO_{d6}$): 1.55 (m,2H), 1.76 (m,2H), 2.20 (s,3H), 2.54 (m,1H), 2.89 (t,2H), 3.48 (m,2H), 3.77 (m,7H), 6.87 (m,3H), 7.07-7.35 (m,8H), 9.10 (brs,1H), 11.05 (brs,1H).

EXAMPLE 51

N-Hydroxy-1-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}cyclobutanecarboxamide

Obtained as a colourless solid (52%), m.p. 157-160°C, from the title compound of Preparation 132, using the procedure of Example 50. Found: C,62.79; H,6.60; N,5.93. $C_{24}H_{30}N_2O_5S$ requires C,62.86; H,6.59; N,6.11%. δ($DMSO_{d6}$): 1.60 (m,2H), 1.78 (m,3H), 1.93 (m,1H), 2.20 (s,3H), 2.57 (m,5H), 2.97 (t,2H), 3.72 (m,2H), 3.77 (s,3H), 6.87 (m,3H), 7.11 (s,2H), 7.15 (s,1H), 7.36 (t,1H), 9.10 (brs,1H), 10.92 (brs,1H).
LRMS (Thermospray): 459 $(M+H)^+$.

EXAMPLE 52

N-Hydroxy-4-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-1-methylpiperidine-4-carboxamide

Obtained as a colourless solid (13%), from the title compound of Preparation 134, using the procedure of Example 19, except that the residue was purified by flash chromatography using dichloromethane:methanol:

concentrated aqueous ammonia solution (90:10:1) as eluant. $\delta(CDCl_3)$: 1.79 (m,2H), 1.90 (m,2H), 2.16 (m,2H), 2.27 (s,3H), 2.30 (s,3H), 2.33 (m,4H), 2.64 (m,1H), 2.91 (brd,2H), 3.10 (t,2H), 3.83 (s,3H), 3.91 (m,2H), 6.88 (m,3H), 7.08 (m,2H), 7.18 (d,1H), 7.30 (t,1H).

LRMS (Thermospray): 502 $(M+H)^+$.

EXAMPLE 53

N-Hydroxy-3-phenyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]propanamide

Obtained as a colourless solid (31%), m.p. 202-205°C, from the title compound of Preparation 136, using the procedure of Example 19, except that the residue was triturated with dichloromethane. Found: C,66.05; H,5.82; N,6.15. $C_{26}H_{26}N_2O_4S$; 0.50 H_2O requires C,66.22; H,5.77; N,5.94%.

$\delta(DMSO_{d6})$: 2.60 (m,2H), 3.15 (m,2H), 3.57 (m,2H), 4.03 (m,3H), 6.07 (brs,1H), 7.16-7.36 (m,6H), 7.45 (m,2H), 7.57 (m,2H), 7.65 (m,4H), 9.17 (brs,1H), 10.70 (brs,1H).

LRMS (APCI): 463 $(M+H)^+$.

EXAMPLE 54

N-Hydroxy-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]indane-2-carboxamide

Obtained as a colourless solid (27%), m.p. 159-161°C, from the title compound of Preparation 138, using the procedure of Example 19, except that the residue was purified by flash chromatography using dichloromethane:methanol (98:2) as eluant, followed by trituration with diisopropyl ether. $\delta(DMSO_{d6})$: 2.55 (m,2H), 3.41 (m,2H), 3.53 (d,2H), 3.77 (d,2H), 3.96 (m,2H), 6.18 (brs,1H), 7.16 (m,2H), 7.23 (m,2H), 7.34-7.53 (m,5H), 7.65 (m,4H), 9.15 (brs,1H), 11.10 (brs,1H).

LRMS (APCI): 463 $(M+H)^+$.

EXAMPLE 55

N-Hydroxy-2-{4-[4-(3-chloro-4-fluorophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (60%), m.p. 181-183°C (crystallised from ether), from the title compound of Preparation 142, using the procedure of Example 17, except that tetrahydrofuran was used as a co-solvent for the reaction. Found: C,54.65; H,4.61; N,6.13. $C_{20}H_{20}ClFN_2O_4S$ requires C,54.73; H,4.59; N,6.38%. $\delta(DMSO_{d6})$: 2.24 (s,3H), 2.60 (m,2H), 3.47 (t,2H), 3.90 (s,2H), 3.97 (m,2H), 6.22 (brs,1H), 7.20 (d,1H), 7.30-7.40 (m,3H), 7.45 (t,1H), 7.56 (m,1H), 9.20 (brs,1H), 10.80 (brs,1H).
LRMS (APCI): 439 $(M+H)^+$.

EXAMPLE 56

N-Hydroxy-2-{4-[4-(1,3-benzodioxol-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (69%), m.p. 165-167°C, from the title compound of Preparation 146, using the procedure of Example 45. Found: C,58.60; H,5.10; N,6.01. $C_{21}H_{22}N_2O_6S$ requires C,58.59; H,5.15; N,6.51%. $\delta(DMSO_{d6})$: 2.22 (s,3H), 2.59 (m,2H), 3.46 (t,2H), 3.90 (s,2H), 3.96 (m,2H), 6.04 (s,2H), 6.20 (brs,1H), 6.76 (d,1H), 6.89 (s,1H), 6.95 (d,1H), 7.15 (d,1H), 7.28 (d,1H), 7.35 (s,1H), 9.20 (brs,1H), 10.80 (brs,1H).
LRMS (APCI): 431 $(M+H)^+$.

EXAMPLE 57

N-Hydroxy-2-{4-[4-(2-fluorophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (32%), m.p. 160-163°C, from the title compound of Preparation 150, using the procedure of Example 17, except that tetrahydrofuran was used as a co-solvent for the reaction. $\delta(DMSO_{d6})$: 2.12 (s,3H), 2.60 (m,2H), 3.48 (t,2H), 3.84 (s,2H), 3.98 (m,2H), 6.21 (brs,1H), 7.17 (d,1H), 7.23-7.35 (m,4H), 7.40 (s,1H), 7.42 (m,1H).
LRMS (APCI): 405 $(M+H)^+$.

EXAMPLE 58

N-Hydroxy-2-{4-[4-(3,4-dimethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (61%), m.p. 172-174°C, from the title compound of Preparation 151, using the procedure of Example 57. Found: C,59.36; H,6.08; N,5.87. $C_{22}H_{26}N_2O_6S$ requires C,59.18; H,5.87; N,6.27%. $\delta(DMSO_{d6})$: 2.25 (s,3H), 2.60 (m,2H), 3.48 (t,2H), 3.75 (s,3H), 3.78 (s,3H), 3.90 (s,2H), 3.96 (m,2H), 6.19 (brs,1H), 6.82 (d,1H), 6.88 (s,1H), 7.00 (d,1H), 7.19 (d,1H), 7.29 (d,1H), 7.36 (s,1H), 9.20 (brs,1H), 10.80 (brs,1H).
LRMS (APCI): 447 $(M+H)^+$.

EXAMPLE 59

N-Hydroxy-2-{4-[4-(indan-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (58%), m.p. 149-152°C, from the title compound of Preparation 152, using the procedure of Example 17. $\delta(DMSO_{d6})$:

2.03 (m,2H), 2.22 (s,3H), 2.59 (m,2H), 2.90 (m,4H), 3.47 (m,2H), 3.90 (s,2H), 3.96 (m,2H), 6.19 (brs,1H), 7.05 (d,1H), 7.15 (m,2H), 7.23-7.30 (m,2H), 7.36 (s,1H), 9.20 (brs,1H), 10.80 (brs,1H).

LRMS (APCI): 427 $(M+H)^+$.

EXAMPLE 60

N-Hydroxy-2-{4-[3-methyl-4-(3-trifluoromethoxyphenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

Obtained as a colourless solid (13%), m.p. 154°C (crystallised from dichloromethane-diisopropyl ether), from the title compound of Preparation 153, using the procedure of Example 17. $\delta(DMSO_{d6})$: 2.23 (s,3H), 2.59 (m,2H), 3.47 (t,2H), 3.90 (s,2H), 3.96 (m,2H), 6.22 (brs,1H), 7.20 (d,1H), 7.30-7.40 (m,5H), 7.58 (t,1H), 9.20 (brs,1H), 10.80 (brs,1H).

LRMS (Thermospray): 488 $(M+NH_4)^+$.

EXAMPLE 61

N-Hydroxy-2-[4-(4-phenyl-3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetamide

Obtained as a colourless solid (43%), m.p. 143-145°C, from the title compound of Preparation 157, using the procedure of Example 17. Found: C,54.63; H,4.35; N,5.90. $C_{20}H_{19}F_3N_2O_4S$ requires C,54.54; H,4.35; N,6.36%. $\delta(DMSO_{d6})$: 2.66 (m,2H), 3.50 (m,2H), 3.93 (s,2H), 4.00 (m,2H), 6.38 (brs,1H), 7.30 (m,2H), 7.35-7.47 (m,4H), 7.79 (d,1H), 7.82 (s,1H), 9.20 (brs,1H), 10.80 (brs,1H).

LRMS (Thermospray): 458 $(M+NH_4)^+$.

EXAMPLE 62

N-Hydroxy-2-{4-[4-(2,2-dimethyl-1,3-benzodioxol-5-yl)-3-methylphenyl]-piperidin-1-ylsulphonyl}-2-methylpropionamide

Obtained as a colourless solid (52%), m.p. 184-186°C, from the title compound of Preparation 161, using the procedure of Example 19. $\delta(DMSO_{d6})$: 1.47 (s,6H), 1.60 (m,2H), 1.65 (s,6H), 1.78 (m,2H), 2.20 (s,3H), 2.65 (m,1H), 3.04 (m,2H), 3.73 (m,2H), 6.68 (d,1H), 6.77 (s,1H), 6.83 (d,1H), 7.07 (s,2H), 7.12 (s,1H), 9.00 (brs,1H), 10.75 (brs,1H).

LRMS (APCI): 489 $(M+H)^+$.

EXAMPLE 63

N-Hydroxy-2-{4-[4-(1,2-dimethylbenzimidazol-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl]-2-methylpropionamide

Obtained as a colourless solid (22%), m.p. 213-215°C, from the title compound of Preparation 165, using the procedure of Example 19. $\delta(DMSO_{d6})$: 1.48 (s,6H), 1.62 (m,2H), 1.80 (m,2H), 2.20 (s,3H), 2.52 (s,3H), 2.67 (m,1H), 3.08 (t,2H), 3.73 (s,3H), 3.75 (m,2H), 7.08-7.15 (m,4H), 7.39 (s,1H), 7.47 (d,1H), 9.00 (brs,1H), 11.75 (brs,1H).

LRMS (Thermospray): 485 $(M+H)^+$.

EXAMPLE 64

N-Hydroxy-2-{4-[4-(3-cyanophenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropionamide

Palladium on barium sulfate (5%, 10 mg) was added to a stirred solution of the title compound of Preparation 168 (70 mg, 0.13 mmol) in methanol (2 ml), then the reaction mixture hydrogenated at 345 kPa (50 psi) pressure for about 20 hours. A further portion of palladium on barium sulfate (5%, 10 mg) was added and hydrogenation continued for an additional 4 days. The catalyst was

removed by filtration, the solvent evaporated under reduced pressure and the residue flash chromatographed, using methanol:dichloromethane (5:95) as eluant, to give the title compound (13 mg, 23%) as a colourless amorphous solid. δ ($CDCl_3$): 1.63 (s,6H), 1.63-1.95 (m,4H), 2.26 (s,3H), 2.67 (m,1H), 3.10 (m,2H), 3.96 (m,2H), 7.04-7.20 (m,3H), 7.50-7.70 (m,4H)
IR (KBr) 2240 cm^{-1} for cyano.

EXAMPLE 65

N-Hydroxy-2-{4-[4-(5-ethoxypyridin-3-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropionamide

Obtained as a colourless foam (62%), from the title compound of Preparation 172, using the procedure of Example 19, except that the residue was purified by flash chromatography, using dichloromethane:ethanol (95:5) as eluant. δ($DMSO_{d6}$): 1.32 (t,3H), 1.48 (s,6H), 1.61 (m,2H), 1.79 (m,2H), 2.21 (s,3H), 2.67 (m,1H), 3.05 (t,2H), 3.75 (d,2H), 4.13 (q,2H), 7.15-7.20 (m,3H), 7.30 (s,1H), 8.10 (s,1H), 8.23 (s,1H), 8.98 (brs,1H), 10.75 (brs,1H).
LRMS (Thermospray): 462 $(M+H)^+$.

EXAMPLE 66

N-Hydroxy-2-{4-[4-(3-[2-hydroxyethoxy]phenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide

O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (510 mg, 1.15 mmol) was added to a stirred solution of the title compound of Preparation 178 (530 mg, 0.76 mmol) and N-ethyldiisopropylamine (0.20 ml, 0.9 mmol) in anhydrous dimethylformamide (4 ml), under nitrogen, at room temperature. After 15 minutes, hydroxylamine hydrochloride (188 mg, 2.2 mmol) and N-ethyldiisopropylamine (0.6 ml, 2.7 mmol) were added and the reaction mixture stirred for about 16 hours, then

partitioned between ethyl acetate and aqueous phosphate buffer (pH 7). The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in anhydrous tetrahydrofuran (15 ml), tetra-n-butylammonium fluoride (1.4 ml of a 1.0M solution in tetrahydrofuran; 1.4 mmol) added and the resulting solution stirred at room temperature for 1.5 hours, then partitioned between ethyl acetate and aqueous phosphate buffer (pH 7). The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography, using dichloromethane:methanol: concentrated aqueous ammonia solution (90:10:1) as eluant, followed by crystallisation from methanol-water, provided the product as a colourless solid (155mg, 43%), m.p. 147-150°C. Found: C,60.26; H,6.81; N,5.76. $C_{24}H_{32}N_2O_6S$ requires C,60.48; H,6.77; N,5.88%. $\delta(DMSO_{d6})$: 1.49 (s,6H), 1.63 (m,2H), 1.80 (m,2H), 2.21 (s,3H), 2.67 (m,1H), 3.08 (t,2H), 3.74 (m,4H), 4.02 (t,2H), 4.83 (t,1H), 6.82-6.92 (m,3H), 7.10 (s,2H), 7.16 (s,1H), 7.30 (t,1H), 9.00 (brs,1H), 10.75 (brs,1H).

PREPARATION 1

t-Butyl 4-hydroxy-4-(4-phenylphenyl)piperidin-1-carboxylate

A 2.5M solution of n-butyllithium in hexane (8 ml, 20 mmol) was added over about 10 minutes to a stirred mixture of 4-bromobiphenyl (4.66 g, 20 mmol), anhydrous ether (100 ml) and anhydrous tetrahydrofuran (10 ml), under nitrogen, at about -75°C. After a further 1 hour, a solution of t-butyl 4-oxopiperidin-1-carboxylate (3.98 g, 20 mmol) in anhydrous tetrahydrofuran (10 ml) was added at such a rate that the reaction temperature was maintained below -60°C.

The reaction mixture was stirred at about -75°C for 3 hours and quenched with aqueous ammonium chloride solution, then the organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Crystallisation of the residue from diisopropyl ether gave the title compound (4.29 g) as a colourless solid, m.p. 144-146°C. $\delta(CDCl_3)$: 1.50 (s,9H), 1.78 (d,2H), 2.06 (m,2H), 3.28 (dd,2H), 4.06 (m,2H), 7.35 (t,1H), 7.43 (m,2H), 7.50-7.65 (m,6H).

LRMS (APCI): 354 $(M+H)^+$.

PREPARATION 2

4-(4-Phenylphenyl)-1,2,3,6-tetrahydropyridine

Trifluoroacetic acid (20 ml) was added to a stirred solution of the title compound of Preparation 1 (4.2 g, 11.9 mmol) in dichloromethane (20 ml) at room temperature. After a further 3 hours, the reaction mixture was evaporated under reduced pressure and the residue basified with 1M aqueous sodium hydroxide solution. The resulting mixture was extracted with dichloromethane, then the combined extracts washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to yield the title compound (2.79 g) as a colourless

solid. $\delta(CDCl_3)$: 1.53 (s,1H), 2.50 (m,2H), 3.14 (t,2H), 3.58 (m,2H), 6.20 (brs,1H), 7.34 (t,1H), 7.45 (m,4H), 7.60 (m,4H).

LRMS (Thermospray): 236 $(M+H)^+$.

PREPARATION 3

1-Benzyl-4-hydroxy-4-(4-phenylphenyl)piperidine

A 1.6M solution of n-butyllithium in hexane (39 ml, 63 mmol) was added to a stirred solution of 4-bromobiphenyl (11.7 g, 50 mmol) in anhydrous tetrahydrofuran (50 ml), under nitrogen, at about -50°C, whilst ensuring that the reaction temperature was kept below -40°C. After a further 1 hour, a solution of 1-benzyl-4-oxopiperidine (10.4 g, 55 mmol) in anhydrous tetrahydrofuran (30 ml) was added at such a rate that the reaction temperature was maintained below -40°C. The cooling bath was then removed and, after a further 1 hour, the reaction mixture was partitioned between dichloromethane (400 ml) and brine (200 ml). The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure, then the residue crystallised from ethyl acetate to provide the title compound (13.9 g) as a colourless solid. $\delta(DMSO_{d6})$: 1.80 (d,2H), 2.52 (m,2H), 3.24 (m,4H), 4.33 (d,2H), 7.28-7.75 (m,14H), 11.30 (brs, 1H).

PREPARATION 4

1-Benzyl-4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridine

A solution of the title compound of Preparation 3 (13.8 g, 40.2 mmol) and p-toluenesulphonic acid (15.3 g, 80.4 mmol) in toluene (100 ml) was heated under reflux in a Dean-Stark apparatus until water removal was complete (ca. 2 hours), then allowed to cool and diluted with water (200 ml). The resulting mixture was basified with concentrated aqueous ammonia solution and

extracted with dichloromethane (4 x 200 ml), then the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure to furnish the title compound (10.6 g) as an off-white solid. $\delta(CDCl_3)$: 2.57 (m,2H), 2.70 (m,2H), 3.18 (m,2H), 3.62 (s,2H), 6.10 (brs, 1H), 7.20-7.60 (m,14H).

PREPARATION 5

4-(4-Phenylphenyl)piperidine

A stirred mixture of the title compound of Preparation 4 (5.07 g, 15.6 mmol), ammonium formate (4 g, 62 mmol), palladium hydroxide on carbon (500 mg) and methanol (50 ml) was heated under reflux for 4.5 hours, allowed to cool and filtered. The filtrate was evaporated under reduced pressure and the residue partitioned between 2M aqueous sodium hydroxide solution and dichloromethane. The organic phase was separated and combined with dichloromethane extracts (3 x 100 ml) of the aqueous phase, then the combined dichloromethane solutions dried ($MgSO_4$) and evaporated under pressure to afford the title compound (3.5 g) as an off-white solid, m.p. 104-107°C. $\delta(CDCl_3)$: 1.50 (brs,1H), 1.63 (m,2H), 1.83 (m,2H), 2.62 (m,1H), 2.75 (m,2H), 3.19 (d,2H), 7.25 (m,3H), 7.40 (m,2H), 7.53 (m,4H).

PREPARATION 6

t-Butyl 4-hydroxy-4-(3-methyl-4-phenylphenyl)piperidine-1-carboxylate

Obtained as a colourless solid (60%), m.p. 142-144°C, from 4-bromo-2-methylbiphenyl (J.Amer.Chem.Soc., 1926, 48, 1372) and t-butyl 4-oxopiperidin-1-carboxylate, using the procedure of Preparation 1. $\delta(CDCl_3)$: 1.48 (s,9H), 1.78 (m,2H), 2.04 (m,2H), 2.30 (s,3H), 3.28 (m,2H), 4.05 (m,2H), 7.20-7.42 (m,8H).

LRMS (Thermospray): 468 $(M+H)^+$.

PREPARATION 7

4-(3-Methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridine

Obtained as a colourless solid (90%) from the title compound of Preparation 6, using the procedure of Preparation 2. $\delta(CDCl_3)$: 1.85 (s,1H), 2.28 (s,3H), 2.50 (m,2H), 3.14 (t,2H), 3.57 (m,2H), 6.18 (brs, 1H), 7.20-7.42 (m,8H).

LRMS (APCI): 250 $(M+H)^+$.

PREPARATION 8

Methyl 2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetate

A solution of methyl chlorosulphonylacetate (0.35 g, 2 mmol) in dichloromethane (2 ml) was added dropwise to a stirred solution of the title compound of Preparation 2 (470 mg, 2 mmol) and 1,8-diazabicyclo [5.4.0]undec-7-ene (0.3 ml, 2 mmol) in dichloromethane (8 ml) at about 0°C, the cooling bath removed and the reaction mixture stirred at room temperature for 4 hours, then diluted with dichloromethane. The resulting mixture was washed with 0.1 M hydrochloric acid, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using dichloromethane as eluant, followed by crystallisation from diisopropyl ether, to give the title compound (250 mg) as a colourless solid, m.p. 182-183°C. Found: C,64.32; H,5.59; N,3.77. $C_{20}H_{21}NO_4S$ requires C,64.66; H,5.70; N,3.77%. $\delta(CDCl_3)$: 2.66 (m,2H), 3.62 (t,2H), 3.78 (s,3H), 3.99 (s,2H), 4.08 (m,2H), 6.08 (brs, 1H), 7.32 (m,1H), 7.38-7.44 (m,4H), 7.53-7.60 (m,4H).

LRMS (APCI): 372 $(M+H)^+$.

PREPARATION 9

Methyl 2-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetate

Obtained as a colourless solid (30%), m.p. 104-105°C, from the title compound of Preparation 7 and methyl chlorosulphonylacetate, using the procedure of Preparation 8. Found: C,65.18; H,6.03; N,3.59. $C_{21}H_{23}NO_4S$ requires C,65.43; H,6.01; N,3.63%. $\delta(CDCl_3)$: 2.28 (s,3H), 2.68 (m,2H), 3.64 (t,2H), 3.81 (s,3H), 4.02 (s,2H), 4.10 (m,2H), 6.08 (brs,1H), 7.20-7.47 (m,8H). LRMS (Thermospray): 386 $(M+H)^+$.

PREPARATION 10

Methyl 2-[4-(4-phenylphenyl)piperidin-1-ylsulphonyl]acetate

Obtained as a colourless solid (27%), m.p. 169-170°C, from the title compound of Preparation 5 and methyl chlorosulphonylacetate, using the procedure of Preparation 8. Found: C,63.99; H,6.18; N,3.69. $C_{20}H_{23}NO_4S$ requires C,64.32; H, 6.21; N,3.75. $\delta(CDCl_3)$: 1.83 (m,2H), 1.95 (m,2H), 2.68 (m,1H), 3.00 (t,2H), 3.80 (s,3H), 3.95 (s,2H), 3.97 (m,2H), 7.20-7.35 (m,3H), 7.40 (t,2H), 7.50-7.60 (m,4H).

PREPARATION 11

Methyl 2-(4-phenyl-1,2,3,6-tetrahydropyridin-1-ylsulphonyl)acetate

Obtained as a colourless solid (20%), m.p. 93-94°C, from 4-phenyl-1,2,3,6-tetrahydropyridine and methyl chlorosulphonylacetate, using the procedure of Preparation 8. Found: C,56.86; H,5.79; N,4.76, $C_{14}H_{17}NO_4S$ requires C,56.93; H,5.80; N,4.74%. $\delta(CDCl_3)$: 2.62 (m,2H), 3.60 (t,2H), 3.78 (s,3H), 3.99 (s,2H), 4.05 (m,2H), 6.00 (brs,1H), 7.22-7.35 (m,5H).

PREPARATION 12

Methyl 2-(4-phenylpiperidin-1-ylsulphonyl)acetate

Obtained as a colourless solid (35%), m.p. 98-100°C, from 4-phenylpiperidine and methyl chlorosulphonylacetate, using the procedure of Preparation 8. Found: C,56.43; H,6.41; N,4.64. $C_{14}H_{19}NO_4S$ requires C,56.55; H,6.44; N,4.71%. $\delta(CDCl_3)$: 1.80 (m,2H), 1.90 (m,2H), 2.60 (m,1H), 2.97 (m,2H), 3.80 (s,3H), 3.92 (s,2H), 3.93 (m,2H), 7.15-7.33 (m,5H).

PREPARATION 13

Methyl 2-(4-benzylpiperidin-1-ylsulphonyl)acetate

Obtained as an amorphous solid (24%) from 4-benzylpiperidine and methyl chlorosulphonylacetate, using the procedure of Preparation 8, but with an elution gradient of dichloromethane:methanol (100:0 to 95:5) for the chromatographic purification step. $\delta(CDCl_3)$: 1.30 (m,2H), 1.62 (m,1H), 1.70 (m,2H), 2.54 (d,2H), 2.78 (t,2H), 3.73 (s,3H), 3.76 (m,2H), 3.88 (s,2H), 7.08 (d,2H), 7.17 (t,1H), 7.24 (m,2H).
LRMS (APCI): 312 $(M+H)^+$.

PREPARATION 14

Methyl 2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoate

60% Sodium hydride in a mineral oil dispersion (21 mg, 0.53 mmol) was added to a stirred solution of the title compound of Preparation 8 (180 mg, 0.48 mmol) in a mixture of anhydrous tetrahydrofuran (1 ml) and anhydrous dimethylformamide (1 ml), under nitrogen, at room temperature. After 30 minutes, allyl bromide (0.05 ml, 0.53 mmol) was added and stirring continued

for a further 2 hours, then the resulting mixture was partitioned between ethyl acetate and aqueous phosphate buffer (pH 7). The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure, then the residue triturated with diisopropyl ether to yield the title compound (170 mg) as a colourless solid. δ ($CDCl_3$): 2.60-2.85 (m,4H), 3.55-3.77 (m,2H), 3.79 (s,3H), 4.03 (dd,1H), 4.12 (m,2H), 5.10-5.22 (m,2H), 5.74 (m,1H), 6.08 (brs, 1H), 7.36 (m,1H), 7.43 (m,4H), 7.60 (m,4H).
LRMS (APCI): 411 $(M+H)^+$.

PREPARATION 15

2(R,S)-[4-(4-Phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoic acid

1M Aqueous sodium hydroxide solution (1.2 ml, 1.2 mmol) was added to a stirred solution of the title compound of Preparation 14 (160 mg, 0.39 mmol) in a mixture of tetrahydrofuran (5 ml) and methanol (10 ml). The resulting solution was heated at 50°C for 3 hours, then evaporated under reduced pressure and the residue dissolved in water. This aqueous solution was acidified with concentrated hydrochloric acid and the resulting emulsion extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using an elution gradient of ethyl acetate:methanol:glacial acetic acid (100:0:0 to 97:3:0 to 96:3:1), followed by trituration with hexane, to provide the title compound (90 mg) as a colourless, amorphous solid. δ($CDCl_3$): 2.60-2.87 (m,4H), 3.60-3.72 (m,2H), 4.05 (dd,1H), 4.12 (s,2H), 5.10-5.23 (m,2H), 5.79 (m,1H), 6.06 (brs,1H), 7.30-7.43 (m,5H), 7.50-7.60 (m,4H).
LRMS (Thermospray): 415 $(M+NH_4)^+$.

PREPARATION 16

Methyl 2(R,S)-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoate

Obtained as a solid (67%) from the title compound of Preparation 9 and allyl bromide, using the procedure of Preparation 14, but with flash chromatography, employing an elution gradient of hexane:ethyl acetate (100:0 to 80:2)), as the purification step. $\delta(CDCl_3)$: 2.30 (s,3H), 2.68 (m,2H), 2.85 (m,2H), 3.56 (m,1H), 3.70 (m,1H), 3.80 (s,3H), 4.03 (dd,1H), 4.10 (m,2H), 5.10-5.22 (m,2H), 5.73 (m,1H), 6.06 (brs,1H), 7.20-7.45 (m,8H).

LRMS (Thermospray): 426 $(M+H)^+$.

PREPARATION 17

2(R,S)-[4-(3-Methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoic acid

Obtained as an amorphous solid (46%) from the title compound of Preparation 16, using the procedure of Preparation 15. $\delta(CDCl_3)$: 2.30 (s,3H), 2.66 (m,2H), 2.87 (m,2H), 3.60 (m,1H), 3.70 (m,1H), 4.03 (dd,1H), 4.12 (m,2H), 5.13-5.25 (m,2H), 5.78 (m,1H), 6.04 (brs,1H), 7.20-7.43 (m,8H).

LRMS (Thermospray): 368 $(M+H-CO_2)^+$.

PREPARATION 18

Methyl 5-phenyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pentanoate

Obtained as a colourless solid (65%), m.p. 146-148°C, from the title compound of Preparation 8 and 1-bromo-3-phenylpropane, using the procedure of Preparation 14. $\delta(CDCl_3)$: 1.70 (m,2H), 2.15 (m,2H), 2.64 (m,4H), 3.52 (m,1H), 3.63 (m,1H), 3.79 (s,3H), 3.98 (dd,1H), 4.06 (m,2H), 6.05 (m,1H), 7.10-7.50 (m,10H), 7.60 (m,4H).

LRMS (Thermospray): 490 $(M+H)^+$.

PREPARATION 19

2-Methyl-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]propanoic acid

60% Sodium hydride in a mineral oil dispersion (48 mg, 1.2 mmol) was added to a stirred solution of the title compound of Preparation 8 (150 mg, 0.4 mmol) in a mixture of anhydrous tetrahydrofuran (3 ml) and anhydrous dimethylformamide (1 ml), under nitrogen, at room temperature. After 30 minutes, methyl p-toluenesulphonate (220 mg, 1.2 mmol) was added and stirring continued for a further 20 hours, then the resulting mixture was partitioned between ethyl acetate and water. The aqueous phase was acidified with 2M hydrochloric acid and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using dichloromethane:methanol:glacial acetic acid (89:10:1) as eluant, to furnish the title compound (60 mg) as a pale yellow, amorphous solid. $\delta(CDCl_3)$: 1.70 (s,6H), 2.63 (m,2H), 3.67 (m,2H), 4.17 (m,2H), 6.08 (brs,1H), 7.25-7.70 (m,9H).

PREPARATION 20

Methyl 1-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl] cyclopentanecarboxylate

60% Sodium hydride in a mineral oil dispersion (43 mg, 1.07 mmol) was added to a stirred solution of the title compound of Preparation 9 (380 mg, 0.99 mmol) in anhydrous dimethylformamide (5 ml), under nitrogen, at room temperature. After 30 minutes, 1,4-diiodobutane (0.14 ml, 1.06 mmol) was added and stirring continued for 18 hours, then more 60% sodium hydride dispersion (43 mg, 1.07 mmol) was added and stirring continued for a further 4 hours. The resulting mixture was partitioned between ethyl acetate and water, then the organic phase separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using hexane:ethyl acetate (9:1) as eluant, to afford the title

compound (340 mg) as an amorphous solid. $\delta(CDCl_3)$: 1.64 (m,2H), 1.88 (m,2H), 2.28 (s,3H), 2.37 (m,2H), 2.52 (m,2H), 2.63 (m,2H), 3.60 (t,2H), 3.80 (s,3H), 4.10 (m,2H), 6.03 (brs,1H), 7.20-7.43 (m,8H).

LRMS (Thermospray): 440 $(M+H)^+$.

PREPARATION 21

1-[4-(3-Methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-yl-ylsulphonyl]cyclopentanecarboxylic acid

Obtained as a solid (54%) from the title compound of Preparation 20, using the procedure of Preparation 15, but with an elution gradient of hexane:ethyl acetate (75:25 to 0:100) for the chromatographic purification step. $\delta(CDCl_3)$: 1.65 (m,2H), 1.88 (m,2H), 2.27 (s,3H), 2.39 (m,2H), 2.50 (m,2H), 2.63 (m,2H), 3.64 (t,2H), 4.12 (m,2H), 6.03 (brs,1H), 7.20-7.43 (m,8H).

LRMS (Thermospray): 426 $(M+H)^+$.

PREPARATION 22

Methyl 2-ethyl-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-yl-ylsulphonyl]butanoate

This was conducted as for Preparation 19 and on the same molar scale, using the title compound of Preparation 8 and ethyl iodide. However, in this case, no concomitant ester hydrolysis was apparent and therefore the required product was isolated from the organic phase during work-up and purified by flash chromatography, using dichloromethane as eluant, to give the title compound (125 mg) as a white amorphous solid. $\delta(CDCl_3)$: 1.04 (t,6H), 2.08-2.26 (m,4H), 2.66 (m,2H), 3.60 (m,2H), 3.80 (s,3H), 4.10 (m,2H), 6.08 (brs,1H), 7.35 (m,1H), 7.43 (m,4H), 7.60 (m,4H).

PREPARATION 23

2-Ethyl-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydroyridin-1-ylsulphonyl]-butanoic acid

1M Aqueous sodium hydroxide solution (1.5 ml, 1.5 mmol) was added to a stirred solution of the title compound of Preparation 22 (120 mg, 0.28 mmol) in a mixture of tetrahydrofuran (5 ml) and methanol (2 ml). The resulting mixture was heated under reflux for 70 hours, allowed to cool to room temperature, acidified with 2M hydrochloric acid and extracted with dichloromethane (3 x 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield the title compound (95 mg) as a pale yellow, amorphous solid. $\delta(CDCl_3)$: 1.10 (t,6H), 2.10-2.28 (m,4H), 2.64 (m,2H), 3.65 (m,2H), 4.15 (m,2H), 6.08 (brs,1H), 7.35 (m,1H), 7.43 (m,4H), 7.58 (m,4H).

PREPARATION 24

Methyl 2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]hexanoate

This was conducted essentially as for Preparation 14, using the title compound of Preparation 8 and n-butyl iodide, but employing 1.0 mol.equiv. of sodium hydride, 1-methylpyrrolidin-2-one as solvent and an alkylation reaction time of 70 hours, to provide the title compound (78%) as a colourless solid, m.p. 152-154°C. Found: C, 67.09; H, 6.76; N, 3.22. $C_{24}H_{29}NO_4S$ requires C, 67.42; H, 6.84; N, 3.28%. $\delta(CDCl_3)$: 0.90 (t,3H), 1.30 (m,4H), 2.05 (m,1H), 2.15 (m,1H), 2.60-2.75 (m,2H), 3.55 (m,1H), 3.70 (m,1H), 3.80 (s,3H), 3.95 (dd,1H), 4.10 (m,2H), 6.08 (brs, 1H), 7.35 (m,1H), 7.43 (m,4H), 7.58 (m,4H). LRMS (Thermospray): 428 $(M+H)^+$.

PREPARATION 25

2(R,S)-[4-(4-Phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-hexanoic acid

1M Aqueous sodium hydroxide solution (1.5 ml, 1.5 mmol) was added to a stirred solution of the title compound of Preparation 24 (220 mg, 0.51 mmol) in a mixture of 1,4-dioxan (3 ml) and methanol (10 ml). The resulting mixture was heated under reflux for 45 minutes, diluted with water and acidified with concentrated hydrochloric acid, then the precipitate collected and dried under vacuum to furnish the title compound (200 mg) as a colourless, crystalline solid, m.p. 180-182°C. Found: C, 65.64; H, 6.42; N, 3.30. $C_{23}H_{27}NO_4S$; 0.50 H_2O requires C, 65.38; H, 6.68; N, 3.32%. $\delta(DMSO_{d6})$: 0.83 (t,3H), 1.27 (m,4H), 1.81 (m,1H), 1.93 (m,1H), 2.58 (m,2H), 3.50 (m,2H), 4.00 (m,2H), 4.05 (dd,1H), 6.22 (brs, 1H), 7.33 (m,1H), 7.43 (m,2H), 7.52 (m,2H), 7.64 (m,4H), 13.30 (brs,1H).

LRMS (Thermospray): 387 $(M+NH_4-CO_2)^+$.

PREPARATION 26

Methyl 4-methyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoate

Obtained as a solid (79%), m.p. 149-151°C after crystallisation from diisopropyl ether, from the title compound of Preparation 8 and 3-bromo-2-methylprop-1-ene, using the procedure of Preparation 14. $\delta(CDCl_3)$: 1.77 (s,3H), 2.60-2.75 (m,3H), 2.80 (dd,1H), 3.57 (m,1H), 3.70 (m,1H), 3.78 (s,3H), 4.10 (m,2H), 4.18 (dd,1H), 4.75 (s,1H), 4.82 (s,1H), 6.10 (brs,1H), 7.35 (m,1H), 7.44 (m,4H), 7.60 (m,4H).

LRMS (Thermospray): 426 $(M+H)^+$.

PREPARATION 27

4-Methyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoic acid

Obtained as a colourless solid (94%), m.p. 153-155°C, from the title compound of Preparation 26, using the procedure of Preparation 15. $\delta(CDCl_3)$: 1.79 (s,3H), 2.65 (m,2H), 2.75 (dd,1H), 2.90 (dd,1H), 3.60 (m,1H), 3.70 (m,1H), 4.13 (m,2H), 4.20 (dd,1H), 4.80 (s,1H), 4.88 (s,1H), 6.08 (s,1H), 7.35 (m,1H), 7.44 (m,4H), 7.60 (m,4H).

LRMS (Thermospray): 368 $(M+H-CO_2)^+$.

PREPARATION 28

Methyl 2(R,S)-methyl-2-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridine-1-ylsulphonyl]pent-4-enoate

60% Sodium hydride in a mineral oil dispersion (70 mg, 1.75 mmol) was added to a stirred solution of the title compound of Preparation 9 (600 mg, 1.56 mmol) in anhydrous dimethylformamide (5 ml), under nitrogen, at room temperature. After 20 minutes, allyl bromide (0.145 ml, 1.72 mmol) was added and stirring continued for 2 hours, then more 60% sodium hydride dispersion (70 mg, 1.75 mmol) was added followed, after 20 minutes, by methyl iodide (0.11 ml, 1.72 mmol). The reaction mixture was stirred for a further 20 hours, then partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using hexane:ethyl acetate (92.5:7.5) as eluant, to afford the title compound (263 mg) as a colourless gum. $\delta(CDCl_3)$: 1.62 (s,3H), 2.30 (s,3H), 2.59 (m,1H), 2.66 (m,2H), 3.14 (m,1H), 3.62 (m,2H), 3.80 (s,3H), 4.10 (m,2H), 5.20 (m,2H), 5.62 (m,1H), 6.08 (brs,1H), 7.20-7.44 (m,8H).

LRMS (Thermospray): 440 $(M+H)^+$.

PREPARATION 29

2(R,S)-Methyl-2-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoic acid

Obtained as a colourless gum (90%) from the title compound of Preparation 28, using the procedure of Preparation 15, but with a reaction duration of 24 hours. $\delta(CDCl_3)$: 1.63 (s,3H), 2.30 (s,3H), 2.62 (m,3H), 3.13 (m,1H), 3.68 (m,2H), 4.18 (m,2H), 5.22 (m,2H), 5.70 (m,1H), 6.07 (brs,1H), 7.17-7.45 (m,8H).

LRMS (Thermospray): 382 $(M+H-CO_2)^+$, 426 $(M+H)^+$.

PREPARATION 30

1-Benzhydryl-3-(4-phenylphenoxy)azetidine

Potassium carbonate (2.39 g, 17.4 mmol) was added to a stirred mixture of 1-benzhydryl-3-methanesulphonyloxyazetidine (J.Org.Chem., 1972, 37, 3953; 5 g, 15.8 mmol), 4-phenylphenol (2.95 g, 17.4 mmol) and anhydrous dimethylformamide (65 ml), then the resulting mixture heated under reflux for 4 hours, allowed to cool and partitioned between ethyl acetate and water. The organic phase was separated, washed with saturated brine, dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using hexane:ethyl acetate (95:5) as eluant, to give the title compound (1.32 g) as a colourless, amorphous solid. $\delta(CDCl_3)$: 3.17 (dd,2H), 3.75 (dd,2H), 4.43 (s,2H), 4.83 (m,1H), 6.81 (d,1H), 7.16-7.55 (m,17H).
LRMS (Thermospray): 392 $(M+H)^+$.

PREPARATION 31

3-(4-Phenylphenoxy)azetidine

A stirred mixture of the title compound of Preparation 30 (1.03 g, 2.63 mmol), 10% palladium hydroxide on activated carbon (100 mg), ethanol (100 ml), ethyl acetate (20 ml) and glacial acetic acid (10 ml) was hydrogenated at

345 kPa (50 psi) and 50°C for 20 hours, then filtered. The filter pad was washed with ethanol and the combined washings and filtrate evaporated under reduced pressure, then the residue was basified with 2M aqueous sodium hydroxide solution. This mixture was extracted with ethyl acetate and the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure to yield the title compound containing 1 mol.equiv. of diphenylmethane* (456 mg) as a colourless, amorphous solid. $\delta(CDCl_3)$: 1.75 (brs,1H), 3.83 (m,2H), 3.94 (m,2H), 3.98 (s,2H)*, 6.82 (d,2H), 7.20-7.55 (m,17H)*.

LRMS (Thermospray): 226 $(M+H)^+$.

PREPARATION 32

Methyl 2-[3-(4-phenylphenoxy)azetidin-1-ylsulphonyl]acetate

Obtained as a colourless, amorphous solid (22%) from the title compound of Preparation 31 and methyl chlorosulphonylacetate, using the procedure of Preparation 8. $\delta(CDCl_3)$: 3.81 (s,3H), 4.07 (s,2H), 4.23 (dd,2H), 4.42 (dd,2H), 4.98 (m,1H), 6.80 (d,2H), 7.34 (m,1H), 7.42 (m,2H), 7.54 (m,4H). LRMS (APCI): 362 $(M+H)^+$.

PREPARATION 33

t-Butyl 4-(4-bromo-3-methylphenyl)-4-hydroxypiperidine-1-carboxylate

A. A 2.5M solution of n-butyllithium in hexane (3.8 ml, 9.4 mmol) was added over about 10 minutes to a stirred mixture of 2,5-dibromotoluene (2.35 g, 9.4 mmol) in anhydrous ether (50 ml), under nitrogen, at about -75°C. After a further 1 hour, a solution of t-butyl 4-oxopiperidine-1-carboxylate (1.7 g, 8.5 mmol) in anhydrous tetrahydrofuran (5 ml) was added at such a rate that the reaction temperature was maintained below -60°C.

The reaction mixture was stirred at about -75°C for 1 hour, allowed to warm to about 0°C and quenched with aqueous ammonium chloride solution.

The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using ether:hexane (50:50) as eluant, to provide two isomeric products.

The less polar isomer (0.6 g, 20%) was isolated as a colourless foam and identified as t-butyl 4-(4-bromo-2-methylphenyl)-4-hydroxypiperidine-1-carboxylate. $\delta(CDCl_3)$: 1.46 (s,9H), 1.55 (s,1H), 1.82-2.03 (m,4H), 2.58 (s,3H), 3.23 (m,2H), 4.01 (m,2H), 7.20-7.33 (m,3H).

LRMS (Thermospray): 369/371 $(M+H)^+$.

The more polar isomer, was collected as a 4:1 mixture of the title compound:t-butyl 4-oxopiperidine-1-carboxylate (2.15 g), a portion of which was crystallised from diisopropyl ether to furnish the pure title compound (570 mg) as a colourless solid, m.p. 102-103°C. Found: C,55.14; H,6.58; N,3.76. $C_{17}H_{24}BrNO_3$ requires C,55.14; H,6.53; N,3.78%. $\delta(CDCl_3)$: 1.48 (s,9H), 1.51 (s,1H), 1.70 (d,2H), 1.96 (m,2H), 2.40 (s,3H), 3.22 (t,2H), 4.02 (m,2H), 7.15 (dd,1H), 7.36 (d,1H), 7.50 (d,1H).

LRMS (Thermospray): 369/371 $(M+H)^+$.

B. A 2.5M solution of n-butyllithium in hexane (38 ml, 94 mmol) was added over about 10 minutes to a stirred mixture of 2-bromo-5-iodo-toluene (28 g, 94 mmol) in anhydrous ether (500 ml), under nitrogen, at about -75°C. After a further 15 minutes, a solution of t-butyl 4-oxopiperidine-1-carboxylate (17 g, 85 mmol) in anhydrous tetrahydrofuran (50 ml) was added at such a rate that the reaction temperature was maintained below -60°C.

The reaction mixture was stirred at about -75°C for 1 hour, allowed to warm to 0°C and quenched with aqueous ammonium chloride solution. The organic phase was separated, washed with water, dried ($MgSO_4$) and

evaporated under reduced pressure. The residue was dissolved in pentane and the resulting solution cooled to 0°C, when the title compound crystallised. It was collected and dried to afford a colourless solid (20.1 g, 64%), identical with that obtained in Preparation 33A.

PREPARATION 34

t-Butyl 4-(4-bromophenyl)-4-hydroxypiperidine-1-carboxylate

Obtained as an amorphous solid (74%) from 1,4-dibromobenzene and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 33.
$\delta(CDCl_3)$: 1.50 (s,9H), 1.69 (m,2H), 1.95 (m,2H), 3.22 (t,2H), 4.02 (m,2H), 7.34 (d,2H), 7.47 (d,2H).
LRMS (Thermospray): 357 $(M+H)^+$.

PREPARATION 35

4-(4-Bromo-3-methylphenyl)-1,2,3,6-tetrahydropyridine

Trifluoroacetic acid (100 ml) was added to a stirred solution of the title compound of Preparation 33 (20 g) in dichloromethane (100 ml) at room temperature. After a further 18 hours, the reaction mixture was evaporated under reduced pressure and the residue basified with 2M aqueous sodium hydroxide solution to pH>12. The resulting mixture was extracted with ether, then the combined extracts washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound (13.6 g) as a low melting solid. $\delta(CDCl_3)$: 1.60 (brs,1H), 2.40 (m,5H), 3.10 (t,2H), 3.52 (m,2H), 6.10 (brs,1H), 7.05 (dd,1H), 7.22 (d,1H), 7.46 (d,1H).
LRMS (Thermospray): 251/253 $(M+H)^+$.

PREPARATION 36

4-(4-Bromophenyl)-1,2,3,6-tetrahydropyridine

Obtained as a solid (87%), m.p. 76-78°C, from the title compound of Preparation 34 and trifluoroacetic acid, using the procedure of Preparation 35. $\delta(CDCl_3)$: 2.43 (m,2H), 3.12 (t,2H), 3.53 (m,2H), 6.13 (s,1H), 7.25 (d,2H), 7.44 (d,2H).

LRMS (Thermospray): 239 $(M+H)^+$.

PREPARATION 37

Methyl 2-[4-(4-bromo-3-methylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetate

N,O-Bis(trimethylsilyl)acetamide (0.9 ml, 4.0 mmol) was added to a stirred solution of the title compound of Preparation 35 (2 g, 7.9 mmol) in anhydrous tetrahydrofuran (40 ml), under nitrogen, at room temperature. A solution of methyl chlorosulphonylacetate (1.64 g, 9.5 mmol) in anhydrous tetrahydrofuran (15 ml) was then added and the reaction mixture stirred at room temperature for 18 hours. The resulting mixture was evaporated under reduced pressure, the residue partitioned between ethyl acetate and aqueous sodium bicarbonate solution, then the organic phase separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using dichloromethane as eluant, followed by crystallisation from diisopropyl ether, to yield the title compound (1.65 g, 55%) as a colourless solid, m.p. 110-112°C. Found: C,46.32; H,4.62; N,3.55. $C_{15}H_{18}BrNO_4S$ requires C,46.40; H,4.67; N,3.61%. $\delta(CDCl_3)$: 2.40 (s,3H), 2.60 (m,2H), 3.60 (t,2H), 3.80 (s,3H), 4.01 (s,2H), 4.07 (m,2H), 6.02 (brs,1H), 7.02 (dd,1H), 7.21 (d,1H), 7.50 (d,1H).

LRMS (Thermospray): 404/406 $(M+NH_4)^+$.

PREPARATION 38

Methyl 2-[4-(4-bromophenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetate

Obtained as a colourless solid (32%), m.p. 100-102°C, from the title compound of Preparation 36 and methyl chlorosulphonylacetate, using the procedure of Preparation 37. Found: C,44.95; H,4.26; N,3.65. $C_{14}H_{16}BrNO_4S$ requires C,44.93; H,4.31; N,3.74%. $\delta(DMSO_{d6})$: 2.47 (m,2H), 3.46 (t,2H), 3.70 (s,3H), 3.94 (m,2H), 4.37 (s,2H), 6.03 (s,1H), 7.40 (d,2H), 7.55 (d,2H).
LRMS (Thermospray): 393 $(M+NH_4)^+$.

PREPARATION 39

Methyl 4-[4-(4-bromo-3-methylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-tetrahydropyran-4-carboxylate

Bis-2-iodoethyl ether (3.9 g, 12 mmol) was added to a stirred mixture of the title compound of Preparation 37 (3.6 g, 9.3 mmol), anhydrous potassium carbonate (3.8 g, 27.8 mmol) and anhydrous dimethylsulfoxide (50 ml), under nitrogen, at room temperature. After 18 hours, the reaction mixture was partitioned between ether and water, then the organic phase washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using dichloromethane : methanol (99:1) as eluant, followed by crystallisation from diisopropyl ether, to provide the title compound (3.43 g, 80%) as a colourless solid, m.p. 128-130°C. Found: C,49.92; H,5.40; N,2.90. $C_{19}H_{24}BrNO_5S$ requires C,49.78; H,5.28; N,3.06%. $\delta(CDCl_3)$: 2.23 (m,2H), 2.40 (s,3H), 2.42 (m,2H), 2.58 (m,2H), 3.30 (m,2H), 3.58 (m,2H), 3.87 (s,3H), 4.00-4.10 (m,4H), 6.00 (brs,1H), 7.02 (dd,1H), 7.21 (d,1H), 7.49 (d,1H).
LRMS (Thermospray): 477 $(M+NH_4)^+$.

PREPARATION 40

Methyl 2-[4-(4-bromo-3-methylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-2-methylpropanoate

Iodomethane (2 ml, 32.1 mmol) was added to a stirred mixture of the title compound of Preparation 37 (5 g, 12.9 mmol), anhydrous potassium carbonate (5.4 g, 39.1 mmol) and anhydrous dimethylsulfoxide (50 ml), under nitrogen, at room temperature. After 24 hours, the reaction mixture was partitioned between ether and water, then the organic phase washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using an elution gradient of ether:pentane (40:60 to 100:0), followed by crystallisation from diisopropyl ether, to furnish the title compound (4.7 g, 87%) as a colourless solid, m.p. 100-101°C. Found: C,49.00; H,5.33; N,3.28. $C_{17}H_{22}BrNO_4S$ requires C,49.04; H,5.33; N,3.36%. $\delta(CDCl_3)$: 1.67 (s,6H), 2.40 (s,3H), 2.58 (m,2H), 3.60 (t,2H), 3.80 (s,3H), 4.08 (m,2H), 6.00 (brs,1H), 7.03 (dd,1H), 7.21 (d,1H), 7.49 (d,1H).

PREPARATION 41

Methyl 2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

To a solution of the title compound of Preparation 37 (776 mg, 2 mmol) in degassed 1,2-dimethoxyethane (20 ml) was added 3-ethoxyphenylboronic acid (430 mg, 2.6 mmol), cesium fluoride (790 mg, 5.2 mmol), tri-o-tolylphosphine (61 mg, 0.2 mmol) and tris(dibenzylideneacetone)dipalladium(0) (91 mg, 0.1 mmol), then the reaction mixture heated under reflux for about 3 hours under nitrogen. The resulting mixture was allowed to cool to room temperature, then diluted with dichloromethane and washed with water. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using dichloromethane as

eluant, followed by crystallisation from diisopropyl ether, to afford the title compound (665 mg, 78%) as a colourless solid, m.p. 79-81°C. Found: C,64.40; H,6.37; N,3.17. $C_{23}H_{27}NO_5S$ requires C,64.31; H,6.34; N,3.26%. $\delta(CDCl_3)$: 1.43 (t,3H), 2.31 (s,3H), 2.70 (m,2H), 3.63 (t,2H), 3.82 (s,3H), 4.03 (s,2H), 4.10 (m,4H), 6.08 (brs,1H), 6.84-6.93 (m,3H), 7.20-7.37 (m,4H). LRMS (Thermospray): 447 $(M+NH_4)^+$.

PREPARATION 42

4-Bromo-2-methoxybiphenyl

n-Amyl nitrite (8.1 ml, 60 mmol) was slowly added to a stirred mixture of 4-bromo-2-methoxyaniline (J.Med.Chem., 1989, 32, 1936; 8.1 g, 60 mmol) and benzene (175 ml), under nitrogen, at about 50°C. When the addition was complete, the reaction mixture was heated under reflux for about 3 hours, then allowed to cool to room temperature and evaporated under reduced pressure. The residue was azeotroped with tetrahydrofuran, then with ethyl acetate, and purified by flash chromatography, using an elution gradient of hexane:ethyl acetate (100:0 to 95:5) to give the title compound (1.66 g) as a colourless solid, m.p. 50-52°C. $\delta(CDCl_3)$: 3.77 (s,3H), 7.08 (s,1H), 7.14 (s,2H), 7.30 (m,1H), 7.36-7.41 (m,2H), 7.41-7.49 (m,2H).

PREPARATION 43

t-Butyl 4-hydroxy-4-(3-methoxy-4-phenylphenyl)piperidine-1-carboxylate

A 2.5M solution of n-butyllithium in hexane (4.4 ml, 11 mmol) was added over about 10 minutes to a stirred mixture of the title compound of Preparation 42 (2.6 g, 10 mmol) in anhydrous tetrahydrofuran (30 ml), under nitrogen, at about -75°C. After a further 1 hour, a solution of t-butyl 4-oxopiperidine-1-carboxylate (2.2 g, 11 mmol) in anhydrous tetrahydrofuran (10 ml) was added

at such a rate that the reaction temperature was maintained below -60°C. The reaction mixture was stirred at about -75°C for 1 hour, then slowly warmed to room temperature and quenched with aqueous sodium chloride solution. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography, using hexane:ethyl acetate (3:1) as eluant, yielded the title compound (3.4 g) as a colourless semi-solid. $\delta(CDCl_3)$: 1.50 (s,9H), 1.78 (m,2H), 2.04 (m,2H), 3.27 (m,2H), 3.83 (s,3H), 4.08 (m,2H), 7.09 (d,1H), 7.16 (s,1H), 7.27-7.37 (m,2H), 7.40 (m,2H), 7.52 (d, 2H).

PREPARATION 44

4-(3-Methoxy-4-phenylphenyl)-1,2,3,6-tetrahydropyridine

Trifluoroacetic acid (20 ml) was added to a stirred solution of the title compound of Preparation 43 (3.4 g, 11.9 mmol) in dichloromethane (20 ml) at room temperature. After a further 72 hours, the reaction mixture was evaporated under reduced pressure and the residue basified with 1M aqueous sodium hydroxide solution. The resulting mixture was extracted with dichloromethane, then the combined extracts washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to provide the title compound (2.79 g) as a pale yellow viscous oil. $\delta(CDCl_3)$: 1.73 (s,1H), 2.51 (m,2H), 3.14 (t,2H), 3.57 (m,2H), 3.83 (s,3H), 6.19 (s,1H), 7.01 (s,1H), 7.05 (d,2H), 7.27-7.37 (m,2H), 7.40 (t,2H), 7.52 (d, 2H).

LRMS (Thermospray): 266 $(M+H)^+$.

PREPARATION 45

Methyl 2-[4-(3-methoxy-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetate

N,O-Bis(trimethylsilyl)acetamide (1.0 ml, 4.4 mmol) was added dropwise

to a stirred solution of the title compound of Preparation 44 (1.95 g, 7.3 mmol) in anhydrous tetrahydrofuran (40 ml) at room temperature. The reaction mixture was stirred at room temperature for 1 hour, then a solution of methyl chlorosulphonylacetate (1.5 g, 8.8 mmol) in tetrahydrofuran (10 ml) was added. The resulting mixture was stirred at room temperature for about 1.5 hours and then saturated aqueous sodium bicarbonate solution (50 ml) added. The mixture was extracted with dichloromethane (3 x 100 ml), then the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using dichloromethane as eluant, to furnish the title compound (1.0 g) as a pale yellow solid solid, m.p. 92-95°C. Found: C,62.24; H,5.70; N,3.42. $C_{21}H_{23}NO_5S$ requires C,62.82; H,5.77; N,3.49%. $\delta(CDCl_3)$: 2.73 (m,2H), 3.67 (t,2H), 3.84 (s,3H), 3.86 (s,3H), 4.06 (s,2H), 4.08 (m,2H), 6.12 (s,1H), 6.98 (s,1H), 7.04 (d,2H), 7.27-7.37 (m,2H), 7.44 (t,2H), 7.56 (d,2H).

LRMS (Thermospray): 402 $(M)^+$.

PREPARATION 46

t-Butyl 4-(3-fluoro-4-phenylphenyl)-4-hydroxypiperidine-1-carboxylate

Obtained as a colourless oil (67%), from 4-bromo-3-fluorobiphenyl and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43. $\delta(CDCl_3)$:): 1.50 (s,9H), 1.78 (m,2H), 2.03 (m,2H), 3.26 (t,2H), 4.05 (m,2H), 7.27-7.51 (m,6H), 7.57 (d, 2H).

PREPARATION 47

4-(3-Fluoro-4-phenylphenyl)-1,2,3,6-tetrahydropyridine

Obtained as a colourless solid (90%), m.p. 79-82°C, from the title compound of Preparation 46 and trifluoroacetic acid, using the procedure of

Preparation 44. $\delta(CDCl_3)$: 1.85 (s,1H), 2.49 (m,2H), 3.13 (t,2H), 3.58 (m,2H), 6.24 (brs, 1H), 7.12-7.27 (m,2H), 7.35-7.52 (m,4H), 7.59 (d,2H).
LRMS (Thermospray): 253 $(M)^+$.

PREPARATION 48

Methyl 2-[4-(3-fluoro-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetate

Obtained as a colourless solid (38%), from the title compound of Preparation 47 and methyl chlorosulphonylacetate, using the procedure of Preparation 45. $\delta(DMSO_{d6})$: 2.60 (m,2H), 3.47 (t,2H), 3.68 (s,3H), 3.96 (s,2H), 4.37 (s,2H), 6.33 (brs,1H), 7.34-7.57 (m,8H).
LRMS (Thermospray): 407 $(M+NH_4)^+$.

PREPARATION 49

Methyl 2-[4-(3-methoxy-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-2-methylpropanoate

Iodomethane (0.2 ml, 3.4 mmol) was added to a stirred mixture of the title compound of Preparation 45 (0.54 g, 1.4 mmol), anhydrous potassium carbonate (0.56 g, 4.1 mmol) and anhydrous dimethylsulphoxide (5 ml), then the reaction mixture stirred at room temperature for about 16 hours. The resulting mixture was partitioned between ethyl acetate and water, then the organic phase washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound (540 mg) as a pale yellow oil.
$\delta(CDCl_3)$: 1.69 (s,6H), 2.67 (m,2H), 3.64 (t,2H), 3.82 (s,3H), 3.84 (s,3H), 4.14 (m,2H), 6.09 (s,1H), 6.98 (s,1H), 7.03 (d,2H), 7.27-7.37 (m,2H), 7.42 (t,2H), 7.54 (d,2H).
LRMS (Thermospray): 430 $(M+H)^+$.

PREPARATION 50

2-[4-(3-Methoxy-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-2-methylpropanoic acid

1M Aqueous sodium hydroxide solution (1.2 ml, 1.2 mmol) was added to a stirred solution of the title compound of Preparation 49 (250 mg, 0.58 mmol) in methanol (5 ml). The resulting solution was heated at 50°C for about 2 hours, then allowed to cool to room temperature and poured into ethyl acetate. This mixture was washed with 2M hydrochloric acid, then the organic phase dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound (210 mg) as a pale yellow , semi- solid. $\delta(CDCl_3)$: 1.69 (s,6H), 2.67 (m,2H), 3.64 (t,2H), 3.83 (s,3H), 4.17 (m,2H), 6.08 (s,1H), 6.97 (s,1H), 7.03 (d,2H), 7.27-7.36 (m,2H), 7.40 (t,2H), 7.53 (d,2H).
LRMS (Thermospray): 433 $(M+NH_4)^+$.

PREPARATION 51

4-Bromo-2-methoxyphenyldiazonium tetrafluoroborate

A solution of 4-bromo-2-methoxyaniline (J. Med.Chem., 1989, 32, 1936; 17.9 g, 88.6 mmol) in anhydrous ether (350 ml) was added over about 1 hour to boron trifluoride etherate (27 ml, 212 mmol) at -15°C. The resulting solution was stirred at -15°C for about 5 minutes and then a solution of t-butyl nitrite (11.4 ml, 106 mmol) in anhydrous ether (100 ml) was added slowly, keeping the internal temperature at around -15°C. The reaction mixture was stirred at -15°C for a further 15 minutes and then at 4°C for about 4 hours. Pentane was added and the resulting precipitate collected, washed with pentane and dried under reduced pressure to yield the title compound (20.1 g) as a purple solid.
$\delta(CD_3CN)$: 4.20 (s,3H), 7.58 (d,1H), 7.80 (s,1H), 8.16 (d,1H).
LRMS (Thermospray): 301 $(M)^+$.

PREPARATION 52

4-(3-Ethoxyphenyl)-3-methoxybromobenzene

Anhydrous 1,4-dioxan (80 ml) was added to a mixture of the title compound Preparation 51 (8.0 g, 26.6 mmol), 3-ethoxyphenylboronic acid (5.3 g, 31.9 mmol) and palladium(II) acetate (0.35 g, 1.3 mmol) and the reaction mixture stirred at room temperature for about 16 hours. The resulting mixture was diluted with water (100 ml) and ether (100 ml), filtered and the filtrate extracted with ether (2 x 100 ml). The combined extracts were dried ($MgSO_4$) and then evaporated under reduced pressure. Purification of the residue by flash chromatography, using pentane:ether (20:1) as eluant, provided the title compound (6.9 g) as a colourless oil. $\delta(CDCl_3)$: 1.45 (t,3H), 3.83 (s,3H), 4.10 (q,2H), 6.89 (d,1H), 7.06 (d,2H), 7.10-7.24 (m,3H), 7.27-7.38 (m,1H). LRMS (APCI): 308 $(M+H)^+$.

PREPARATION 53

t-Butyl 4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]-4-hydroxypiperidine-1-carboxylate

Obtained as a colourless oil (60%), from the title compound of Preparation 52 and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43. $\delta(CDCl_3)$: 1.44 (t,3H), 1.50 (s,9H), 1.79 (m,2H), 2.03 (m,2H), 3.27 (t,2H), 3.83 (s,3H), 4.06 (m,4H), 6.86 (d,1H), 7.08 (m,3H), 7.15 (s, 1H), 7.31 (m,2H).

PREPARATION 54

4-[4-(3-Ethoxyphenyl)-3-methoxyphenyl]-1,2,3,6-tetrahydropyridine

Obtained as a pale yellow viscous oil (91%), from the title compound of Preparation 53 and trifluoroacetic acid, using the procedure of Preparation 44.

$\delta(CDCl_3)$: 1.44 (t,3H), 2.53 (m,2H), 3.16 (t,2H), 3.58 (s,2H), 3.83 (s,3H), 4.07 (q,2H), 6.19 (brs,1H), 6.86 (d,1H), 7.00 (s,1H), 7.07 (m,3H), 7.31 (m,2H).
LRMS (Thermospray): 310 $(M+H)^+$.

PREPARATION 55

Methyl 2-{4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a yellow semi-solid (22%), from the title compound of Preparation 54 and methyl chlorosuphonylacetate, using the procedure of Preparation 45. $\delta(CDCl_3)$: 1.43 (t,3H), 2.69 (m,2H), 3.65 (t,2H), 3.81 (s,3H), 3.84 (s,3H), 4.04 (s,2H), 4.08 (m,4H), 6.10 (brs,1H), 6.87 (d,1H), 6.96 (s,1H), 7.02 (d,1H), 7.09 (m,2H), 7.31 (m,2H).
LRMS (Thermospray): 446 $(M+H)^+$.

PREPARATION 56

Methyl 2-{4-[4-(3-ethoxyphenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

To a solution of the title compound of Preparation 38 (250 mg, 0.7 mmol) in 1,2-dimethoxyethane (8 ml) was added 3-ethoxyphenylboronic acid (168 mg, 1.0 mmol), cesium fluoride (226 mg, 1.5 mmol), tri-o-tolylphosphine (21 mg, 0.07 mmol) and tris(dibenzylideneacetone)dipalladium(0) (31 mg, 0.035 mmol), then the reaction mixture heated under reflux for about 4 hours under nitrogen. The resulting mixture was allowed to cool to room temperature, then diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure, then the residue triturated with hexane-ether to furnish the title

compound (222 mg) as a pale yellow solid, m.p. 120-122°C. Found: C,64.25; H,6.01; N,2.99. $C_{22}H_{25}NO_5S$ requires C,63.60; H,6.06; N,3.37%. $\delta(DMSO_{d6})$: 1.32 (t,3H), 2.62 (m,2H), 3.50 (t,2H), 3.71 (s,3H), 3.98 (d,2H), 4.10 (q,2H), 4.37 (s,2H), 6.27 (brs,1H), 6.91 (d,1H), 7.18 (s,1H), 7.22 (d,1H), 7.36 (t,1H), 7.52 (d,2H), 7.66 (d,2H).

LRMS (Thermospray): 433 $(M+NH_4)^+$.

PREPARATION 57

4-Bromo-2-methylphenyldiazonium tetrafluoroborate

Obtained as a yellow solid (93%), from 4-bromo-2-methylaniline and t-butyl nitrite, using the procedure of Preparation 51. $\delta(CD_3CN)$: 2.70 (s,3H), 7.93 (d,1H), 8.04 (s,1H), 8.50 (d,1H).

PREPARATION 58

4-(3-Methoxyphenyl)-3-methylbromobenzene

Obtained as a pale yellow oil (25%), from the title compound of Preparation 57 and 3-methoxyphenylboronic acid, using the procedure of Preparation 52. $\delta(CDCl_3)$: 2.15 (s,3H), 3.84 (s,3H), 6.79-6.94 (m,3H), 7.09 (s,1H), 7.33 (d,1H), 7.37 (d,1H), 7.43 (s,1H).

PREPARATION 59

t-Butyl 4-hydroxy-4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidine-1-carboxylate

Obtained as a colourless oil (63%), from the title compound of Preparation 58 and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43. $\delta(CDCl_3)$: 1.50 (s,9H), 1.79 (m,2H), 2.04 (m,2H), 2.19 (s,3H), 3.27 (t,2H), 3.83 (s,3H), 4.06 (m,2H), 6.85 (s,1H), 6.90 (d,2H), 7.26 (m, 1H), 7.34 (t,2H), 7.38 (s,1H).

LRMS (Thermospray): 399 $(M+H)^+$.

PREPARATION 60

4-[4-(3-Methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridine

Obtained as a pale yellow semi-solid (93%), from the title compound of Preparation 59 and trifluoroacetic acid, using the procedure of Preparation 44. $\delta(CDCl_3)$, 2.30 (s,3H), 2.42 (s,2H), 3.15 (t,2H), 3.57 (s,2H), 3.83 (s,3H), 6.18 (brs,1H), 6.90 (m,3H), 7.16-7.36 (m, 4H).

LRMS (Thermospray): 280 $(M+H)^+$.

PREPARATION 61

Methyl 2-{4-[4-(3-methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

A solution of methyl chlorosulphonylacetate (0.65 g, 3.7 mmol) in dichloromethane (10 ml) was added dropwise to a stirred solution of the title compound of Preparation 60 (0.92 g, 3.3 mmol) and 1,8-diazabicyclo [5.4.0]undec-7-ene (0.76 g, 4.9 mmol) in dichloromethane (20 ml) at about 0°C, the cooling bath removed and the reaction mixture stirred at room temperature for 4 hours, then diluted with dichloromethane. The resulting mixture was washed with 0.1 M hydrochloric acid, dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using dichloromethane as eluant, to afford the title compound (250 mg) as a colourless solid, m.p. 83-85°C. $\delta(CDCl_3)$: 2.30 (s,3H), 2.69 (m,2H), 3.66 (t,2H), 3.85 (s,3H), 3.86 (s,3H), 4.03 (s,2H), 4.11 (m,2H), 6.09 (brs,1H), 6.83-6.97(m,3H), 7.17-7.35 (m, 4H).

LRMS (Thermospray): 416 $(M+H)^+$.

PREPARATION 62

3-Ethylphenylboronic acid

n-Butyllithium (11 ml of a 2.5M solution in hexane, 28 mmol) was added to a stirred solution of 3-ethylbromobenzene (Chem. Pharm. Bull., 1968, 16, 2456; 4.6 g, 25 mmol) in anhydrous tetrahydrofuran (50 ml), whilst keeping the internal temperature below -60°C. The mixture was stirred at about -70°C for 1 hour, then trimethylborate (4.4 ml, 38 mmol) added dropwise, again whilst keeping the internal temperature below -60°C. The reaction mixture was stirred at -70°C for 30 minutes, then slowly allowed to warm to room temperature. 2M Hydrochloric acid was added, the mixture was extracted with dichloromethane (3 x 50 ml) and the combined extracts concentrated under reduced pressure The residue was dissolved in ether (50 ml), the solution extracted with 1M aqueous sodium hydroxide solution (2 x 30 ml) and the aqueous phase acidified with 2M hydrochloric acid, then extracted with ether (3 x 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound as a white solid (0.9 g, 24%). $\delta(DMSO_{d6})$: 1.17 (t,3H), 2.57 (q,2H), 7.22 (t,2H), 7.57 (t,1H), 7.61 (s,1H), 7.93 (s,2H).

PREPARATION 63

Methyl 2-{4-[4-(3-ethylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a yellow solid (75%), m.p. 58-60°C, from the title compounds of Preparation 62 and Preparation 37, using the procedure of Preparation 41. $\delta(CDCl_3)$: 1.27 (t,3H), 2.50 (s,3H), 2.68 (m,4H), 3.64 (t,2H), 3.82 (s,3H), 4.03 (s,2H), 4.10 (s,2H), 6.08 (brs,1H), 7.14-7.37 (m,7H). LRMS (Thermospray): 431 $(M+NH_4)^+$.

PREPARATION 64

Methyl 4-{4-[4-(3-methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxylate

Obtained as a glassy solid (20%), from the title compound of Preparation 61 and bis-2-iodoethyl ether, using the procedure of Preparation 39. $\delta(CDCl_3)$: 2.20-2.34 (m,5H), 2.45 (m,2H), 2.67 (m,2H), 3.33 (t,2H), 3.62 (m,2H), 3.83 (s,3H), 3.89 (s,3H), 4.01 (m,2H), 4.10 (m,2H), 6.05 (brs,1H), 6.91 (m,3H), 7.23-7.36 (m,4H).

LRMS (APCI): 486 $(M+H)^+$.

PREPARATION 65

4-{4-[4-(3-Methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxylic acid

Obtained as a pale yellow solid (93%), m.p. 180-190°C, from the title compound of Preparation 64, using the procedure of Preparation 50. $\delta(CDCl_3)$: 2.20-2.33 (m,5H), 2.43 (m,2H), 2.65 (m,2H), 3.43 (t,2H), 3.67 (m,2H), 3.82 (s,3H), 4.04 (m,2H), 4.14 (m,2H), 6.04 (brs,1H), 6.88 (m,3H), 7.21-7.36 (m,4H).

PREPARATION 66

Methyl 4-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-tetrahydropyran-4-carboxylate

A stirred mixture of the title compound of Preparation 64 (315 mg, 0.65 mmol), ammonium formate (200 mg, 3.2 mmol), 10% palladium on carbon (50 mg) and methanol (5 ml) was heated under reflux for 1.5 hours, then allowed to cool and filtered. The filtrate was evaporated under reduced pressure and the residue partitioned between ether and water. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure, then the residue crystallised

from methanol to yield the title compound (215 mg) as a white solid, m.p. 137-139°C. $\delta(CDCl_3)$: 1.75-1.94 (m,4H), 2.19 (d,1H), 2.22 (d,1H), 2.27 (s,3H), 2.43 (m,2H), 2.66 (m,1H), 3.07 (t,2H), 3.32 (t,2H), 3.83 (s,3H), 3.90 (s,3H), 3.96 (m,2H), 4.00 (d,1H), 4.02 (d,1H), 6.87 (m,3H), 7.08 (m,2H), 7.19 (d,1H), 7.32 (m,1H).

LRMS (APCI): 486 $(M+H)^+$.

PREPARATION 67

4-{4-[4-(3-Methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}tetrahydropyran-4-carboxylic acid

Obtained as a white solid (84%), m.p. 225-228°C, from the title compound of Preparation 66, using the procedure of Preparation 50, but with a mixture of methanol (5 ml) and tetrahydrofuran (10 ml) as solvent. Found: C,63.04; H, 6.59; N, 2.91. $C_{25}H_{31}NO_6S$ requires C, 63.40; H, 6.60; N, 2.96%. $\delta(DMSO_{d6})$: 1.60 (m,2H), 1.80 (m,2H), 1.93 (dt,2H), 2.20 (s,3H), 2.24 (m,2H), 2.68 (m,1H), 3.05 (t,2H), 3.20 (t,2H), 3.75 (s,3H), 3.77 (m,2H), 3.88 (d,1H), 3.92 (d,1H), 6.86 (m,3H), 7.11 (m,3H), 7.31 (m,1H), 13.80 (brs,1H).

LRMS (APCI): 474 $(M)^+$.

PREPARATION 68

3-Methoxy-4-(3-methoxyphenyl)bromobenzene

Obtained as a pale yellow oil (78%), from the title compound of Preparation 51 and 3-methoxyphenylboronic acid, using the procedure of Preparation 52. Found: C, 57.77; H, 4.51. $C_{14}H_{13}BrO_2$ requires C, 57.36; H, 4.47. $\delta(CDCl_3)$: 3.82 (s,3H), 3.86 (s,3H), 6.91 (d,1H), 7.03-7.39 (m,6H).

LRMS (Thermospray): 311 $(M+NH_4)^+$.

PREPARATION 69

t-Butyl 4-hydroxy-4-[3-methoxy-4-(3-methoxyphenyl)phenyl]piperidine-1-carboxylate

Obtained as a colourless oil (67%), from the title compound of Preparation 68 and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43. $\delta(CDCl_3)$: 1.50 (s,9H), 1.79 (m,2H), 2.06 (m,2H), 3.28 (t,2H), 3.83 (s,6H), 4.06 (m,2H), 6.88 (d,1H), 7.08 (m,3H), 7.14 (s, 1H), 7.32 (m,2H).
LRMS (Thermospray): 436 $(M+Na)^+$.

PREPARATION 70

4-[3-Methoxy-4-(3-methoxyphenyl)phenyl]-1,2,3,6-tetrahydropyridine

A stirred solution of the title compound of Preparation 69 (6.7 g, 16.2 mmol) and p-toluenesulphonic acid (6.17 g, 32.5 mmol) in toluene (70 ml) was heated under reflux in a Dean-Stark apparatus until water removal was complete (ca. 4 hours), then allowed to cool and diluted with ethyl acetate (100 ml). The resulting mixture was washed with 1M aqueous sodium hydroxide solution (3 x 50 ml), then the organic phase dried ($MgSO_4$) and evaporated under reduced pressure to provide the title compound (3.3 g) as a yellow oil.
$\delta(CDCl_3)$: 1.80 (brs,1H), 2.50 (m,2H), 3.14 (t,2H), 3.57 (m,2H), 3.84 (s,6H), 6.20 (brs,1H), 6.88 (d,1H), 6.98-7.36 (m, 6H).
LRMS (Thermospray): 296 $(M+H)^+$.

PREPARATION 71

Methyl 2-{4-[3-methoxy-4-(3-methoxyphenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a yellow semi-solid (40%), from the title compound of Preparation 70 and methyl chlorosulphonylacetate, using the procedure of

Preparation 45. Found: C,58.87; H, 5.65; N, 3.11. $C_{22}H_{25}NO_6S$; 1.00 H_2O requires C, 58.78; H, 6.05; N, 3.12%. δ($CDCl_3$): 2.71 (m,2H), 3.64 (t,2H), 3.81 (s,3H), 3.84 (s,6H), 4.02 (s,2H), 4.11 (m,2H), 6.10 (brs,1H), 6.88 (d,1H), 6.97 (s,1H), 7.02 (d,1H), 7.12 (m,2H), 7.32 (m,2H).
LRMS (Thermospray): 449 $(M+H)^+$.

PREPARATION 72

Methyl 2-{4-[3-methoxy-4-(3-methoxyphenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a colourless semi-solid (40%), from the title compound of Preparation 71 and iodomethane, using the procedure of Preparation 49. Found: C,62.30; H, 6.29; N, 3.00. $C_{24}H_{29}NO_6S$ requires C, 62.73; H, 6.36; N, 3.05%. δ($CDCl_3$): 1.68 (s,6H), 2.67 (m,2H), 3.64 (t,2H), 3.82 (s,3H), 3.84 (s,3H), 3.85 (s,3H), 4.13 (m,2H), 6.07 (brs,1H), 6.88 (d,1H), 6.97 (s,1H), 7.02 (d,1H), 7.13 (m,2H), 7.31 (m,2H).
LRMS (Thermospray): 460 $(M+H)^+$.

PREPARATION 73

Methyl 2-{4-[3-methoxy-4-(3-methoxyphenyl)phenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a colourless solid (80%), m.p. 140-142°C, from the title compound of Preparation 72, using the procedure of Preparation 66. Found: C,62.31; H, 6.87; N, 2.91. $C_{24}H_{31}NO_6S$ requires C, 62.45; H, 6.77; N, 3.03%. δ($CDCl_3$): 1.66 (s,6H), 1.87 (m,4H), 2.49 (m,1H), 3.09 (t,2H), 3.82 (s,6H), 3.84 (s,3H), 3.93 (m,2H), 6.81 (s,1H), 6.86 (d,2H), 7.08 (m,2H), 7.29 (m,2H).
LRMS (Thermospray): 462 $(M+H)^+$.

PREPARATION 74

2-{4-[3-Methoxy-4-(3-methoxyphenyl)phenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

Obtained as a colourless solid (80%), m.p. 164-165°C, from the title compound of Preparation 73, using the procedure of Preparation 50. Found: C,61.64; H, 6.53; N, 3.06. $C_{23}H_{29}NO_6S$ requires C, 61.73; H, 6.53; N, 3.13%. $\delta(CDCl_3)$: 1.69 (s,6H), 1.87 (m,4H), 2.69 (m,1H), 3.10 (t,2H), 3.81 (s,3H), 3.82 (s,3H), 4.02 (m,2H), 6.80 (s,1H), 6.87 (m,2H), 7.07 (m,2H), 7.27 (m,2H). LRMS (Thermospray): 465 $(M+NH_4)^+$.

PREPARATION 75

Methyl 2-{4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a pale yellow oil (29%), from the title compound of Preparation 55 and iodomethane, using the procedure of Preparation 49. Found: C,62.99; H, 6.64; N, 2.88. $C_{25}H_{31}NO_6S$ requires C, 63.40; H, 6.60; N, 2.96%. $\delta(CDCl_3)$: 1.43 (t,3H), 1.67 (s,6H), 2.66 (m,2H), 3.63 (t,2H), 3.81 (s,3H), 3.83 (s,3H), 4.07 (q,2H), 4.13 (m,2H), 6.07 (brs,1H), 6.87 (d,1H), 6.96 (s,1H), 7.02 (d,1H), 7.10 (m,2H), 7.31 (m,2H).
LRMS (Thermospray): 474 $(M+H)^+$.

PREPARATION 76

Methyl 2-{4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a colourless semi-solid (83%) from the title compound of Preparation 75, using the procedure of Preparation 66. Found: C,62.86; H, 7.12; N, 2.68. $C_{25}H_{33}NO_6S$ requires C, 63.14; H, 6.99; N, 2.95%. $\delta(CDCl_3)$: 1.43 (t,3H), 1.67 (s,6H), 1.86 (m,4H), 2.70 (m,1H), 3.09 (t,2H), 3.82 (s,6H), 3.97 (m,2H), 4.06 (q,2H), 6.80 (s,1H), 6.86 (m,2H), 7.08 (m,2H), 7.27 (m,2H).
LRMS (Thermospray): 476 $(M+H)^+$.

PREPARATION 77

2-{4-[4-(3-Ethoxyphenyl)-3-methoxyphenyl]piperidin-1-ylsulphonyl}-2-methyl-propanoic acid

Obtained as a colourless solid (95%), from the title compound of Preparation 76, using the procedure of Preparation 50. Found: C,61.92; H, 7.00; N, 2.72. $C_{24}H_{31}NO_6S$ requires C, 62.45; H, 6.77; N, 3.03%. $\delta(CDCl_3)$: 1.42 (t,3H), 1.70 (s,6H), 1.87 (m,4H), 2.70 (m,1H), 3.11 (t,2H), 3.80 (s,3H), 4.04 (m,4H), 6.80 (s,1H), 6.85 (d,2H), 7.08 (m,2H), 7.27 (m,2H).

LRMS (Thermospray): 479 $(M+NH_4)^+$.

PREPARATION 78

Methyl 4-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxylate

Obtained as a colourless foam (86%), from the title compound of Preparation 39 and 3-ethoxyphenylboronic acid, using the procedure of Preparation 41, but with methanol:dichloromethane (1:99) as eluant. $\delta(CDCl_3)$: 1.42 (t,3H), 2.22 (m,2H), 2.28 (s,3H), 2.44 (d,2H), 2.65 (m,2H), 3.34 (dd,2H), 3.60 (m,2H), 3.90 (s,3H), 4.00-4.15 (m,6H), 6.03 (brs,1H), 6.83-6.92 (m,3H), 7.20-7.36 (m,4H).

LRMS (Thermospray): 500 $(M+H)^+$.

PREPARATION 79

4-{4-[4-(3-Ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxylic acid

1M Aqueous sodium hydroxide solution (2.3 ml, 2.3 mmol) was added to a stirred solution of the title compound of Preparation 78 (290 mg, 0.58 mmol) in a mixture of methanol (10 ml) and 1,4-dioxan (2 ml). The resulting solution was heated at 80°C for about 5 hours, then allowed to cool to room

temperature and evaporated under reduced pressure. The residue was partitioned between 1M hydrochloric acid and ethyl acetate, then the organic phase dried ($MgSO_4$) and evaporated under reduced pressure. The residue was crystallised from diisopropyl ether to furnish the title compound (220 mg) as a colourless solid, m.p. 203-205°C. Found: C,64.14; H, 6.47; N, 2.87. $C_{26}H_{31}NO_6S$ requires C, 64.31; H, 6.44; N, 2.89%. $\delta(CDCl_3)$: 1.43 (t,3H), 2.27 (m,2H), 2.29 (s,3H), 2.42 (d,2H), 2.68 (m,2H), 3.42 (dd,2H), 3.67 (m,2H), 4.00-4.18 (m,6H), 6.04 (brs,1H), 6.82-6.93 (m,3H), 7.20-7.35 (m,4H).
LRMS (Thermospray): 486 $(M+H)^+$.

PREPARATION 80

Methyl 2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a colourless solid (80%), m.p. 75-76°C, from the title compound of Preparation 41 and iodomethane, using the procedure of Preparation 40. Found: C,65.55; H, 6.82; N, 2.98. $C_{25}H_{31}NO_5S$ requires C, 65.62; H, 6.83; N, 3.06%. $\delta(CDCl_3)$: 1.43 (t,3H), 1.68 (s,6H), 2.28 (s,3H), 2.65 (m,2H), 3.62 (m,2H), 3.81 (s,3H), 4.06 (q,2H), 4.12 (m,2H), 6.06 (brs,1H), 6.83-6.92 (m,3H), 7.20-7.35 (m,4H).
LRMS (Thermospray): 458 $(M+H)^+$.

PREPARATION 81

2-{4-[4-(3-Ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoic acid

Obtained as a colourless amorphous solid (50%), from the title compound of Preparation 80, using the procedure of Preparation 79, but with purification by flash chromatography using methanol:dichloromethane (2:98).

$\delta(CDCl_3)$: 1.43 (t,3H), 1.68 (s,6H), 2.25 (s,3H), 2.60 (m,2H), 3.62 (m,2H), 4.05 (q,2H), 4.15 (m,2H), 6.03 (brs,1H), 6.78-6.90 (m,3H), 7.20-7.35 (m,4H).
LRMS (APCI): 444 $(M+H)^+$.

PREPARATION 82

Methyl 2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}acetate

Obtained as a colourless amorphous solid (99%), from the title compound of Preparation 41, using the procedure of Preparation 66. $\delta(CDCl_3)$: 1.43 (t,3H), 1.85 (m,2H), 1.97 (m,2H), 2.28 (s,3H), 2.67 (m,1H), 3.01 (m,2H), 3.84 (s,3H), 3.98 (s,2H), 4.01 (m,2H), 4.05 (q,2H), 6.80-6.90 (m,3H), 7.05-7.34 (m,4H).
LRMS (Thermospray): 432 $(M+H)^+$.

PREPARATION 83

Methyl 2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a colourless gum (91%), from the title compound of Preparation 82 and iodomethane, using the procedure of Preparation 40.
$\delta(CDCl_3)$: 1.42 (t,3H), 1.67 (s,6H), 1.80-1.95 (m,4H), 2.29 (s,3H), 2.67 (m,1H), 3.10 (m,2H), 3.82 (s,3H), 3.97 (m,2H), 4.06 (q,2H), 6.82-6.90 (m,3H), 7.06-7.35 (m,4H).
LRMS (Thermospray): 460 $(M+H)^+$.

PREPARATION 84

2-{4-[4-(3-Ethoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methyl-propanoic acid

Obtained as a colourless solid (72%), m.p. 125-128°C, from the title

compound of Preparation 83, using the procedure of Preparation 79, except that the crude product was flash chromatographed using methanol : dichloromethane (3:97), before crystallisation from diisopropyl ether. Found: C,64.14; H, 7.01; N, 3.06. $C_{24}H_{31}NO_5S$ requires C, 64.69; H, 7.01; N, 3.14%. $\delta(CDCl_3)$: 1.41 (t,3H), 1.68 (s,6H), 1.77-1.97 (m,4H), 2.26 (s,3H), 2.66 (m,1H), 3.10 (m,2H), 4.00-4.10 (m,4H), 6.80-6.90 (m,3H), 7.03-7.35 (m,4H).
LRMS (APCI): 446 $(M+H)^+$.

PREPARATION 85

Methyl 2-{4-[3-methyl-4-(pyridin-2-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

A stirred solution of the title compound of Preparation37 (206 mg, 0.53 mmol), 2-(tri-n-butylstannyl)pyridine (Tetrahedron, 1997 53, 859; 295 mg, 0.80 mmol), tri-o-tolylphosphine (50 mg, 0.16 mmol), palladium(II) acetate (12 mg, 0.05 mmol) and triethylamine (0.2 ml, 1.44 mmol) in anhydrous acetonitrile (6 ml), under nitrogen, was heated under reflux for 6 hours. Additional portions of tri-o-tolylphosphine (50 mg, 0.16 mmol) and palladium(II) acetate (12 mg, 0.05 mmol) were added, then reflux continued for a further 24 hours. The resulting, cool mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate solution, then the separated organic phase washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using an elution gradient of hexane:ethyl acetate (100:0 to 55:45), to afford the title compound (20 mg, 10%) as a colourless amorphous solid. $\delta(CDCl_3)$: 2.39 (s,3H), 2.68 (m,2H), 3.65 (t,2H), 3.81 (s,3H), 4.02 (s,2H), 4.10 (m,2H), 6.10 (brs,1H), 7.23-7.30 (m,3H), 7.40 (m,2H), 7.75 (dd,1H), 8.70 (d,1H).
LRMS (APCI): 387 $(M+H)^+$.

PREPARATION 86

Methyl 2-{4-[3-methyl-4-(pyridin-3-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a colourless foam (78%), from the title compound of Preparation 37 and 3-(tri-n-butylstannyl)pyridine, using the procedure of Preparation 85, except that the reaction time was 5 hours at reflux followed by 72 hours at room temperature. Found: C, 62.07; H, 5.78; N, 7.09. $C_{20}H_{22}N_2O_4S$ requires C, 62.16; H, 5.74; N, 7.25%. $\delta(CDCl_3)$: 2.30 (s,3H), 2.70 (m,2H), 3.68 (t,2H), 3.83 (s,3H), 4.03 (s,2H), 4.14 (m,2H), 6.10 (brs,1H), 7.20-7.40 (m,4H), 7.66 (d,1H), 8.60 (m,2H).
LRMS (APCI): 387 $(M+H)^+$.

PREPARATION 87

Methyl 2-{4-[3-methyl-4-(pyridin-4-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a colourless foam (54%), from the title compound of Preparation 37 and 4-(tri-n-butylstannyl)pyridine, using the procedure of Preparation 85. Found: C, 61.98; H, 5.80; N, 7.13. $C_{20}H_{22}N_2O_4S$ requires C, 62.16; H, 5.74; N, 7.25%. $\delta(CDCl_3)$: 2.30 (s,3H), 2.70 (m,2H), 3.64 (t,2H), 3.81 (s,3H), 4.02 (s,2H), 4.10 (m,2H), 6.10 (brs,1H), 7.20-7.30 (m,5H), 8.66 (d,2H).
LRMS (APCI): 387 $(M+H)^+$.

PREPARATION 88

6-Ethoxy-2-(tri-n-butylstannyl)-pyridine

A 2.5M solution of n-butyllithium in hexane (4.5 ml, 11.3 mmol) was added to a stirred solution of 2-bromo-6-ethoxypyridine (Rec. Trav. chim., 1965, 84, 53; 2.1g, 11.3 mmol) in anhydrous ether (25 ml), under nitrogen, at about -40°C. After about 20 minutes, tri-n-butyltin chloride (3.1 ml, 11.4 mmol) was

slowly added and, after a further 15 minutes, the reaction mixture was allowed to warm to room temperature. The resulting mixture was quenched by the addition of aqueous ammonium chloride solution, then the organic phase separated, washed with water, dried (MgSO4) and evaporated under reduced pressure. The residue was purified by flash chromatography, using an elution gradient of pentane:dichloromethane (100:0 to 80:20), to give the title compound (1.6 g, 34%) as a colourless oil. $\delta(CDCl_3)$: 0.90 (t,9H), 1.08 (t,6H), 1.30-1.42 (m,9H), 1.58 (m,6H), 4.40 (q,2H), 6.53 (d,1H), 6.97 (d,1H), 7.39 (dd,1H).

PREPARATION 89

Methyl 2-{4-[4-(6-ethoxypyridin-2-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

A stirred mixture of the title compounds of Preparation 40 (500 mg, 1.2 mmol) and Preparation 88 (745 mg, 1.8 mmol), tri-o-tolylphosphine (109 mg, 0.36 mmol), palladium(II) acetate (30 mg, 0.13 mmol), tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.025mmol), triethylamine (0.45 ml, 3.2 mmol) and anhydrous acetonitrile (15 ml), under nitrogen, was heated under reflux for 18 hours. The cool mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate solution, then the organic phase separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using an elution gradient of pentane:ether (95:5 to 80:20), to yield the title compound (290 mg, 52%) as a colourless foam. $\delta(CDCl_3)$: 1.40 (t,3H), 1.68 (s,6H), 2.46 (s,3H), 2.66 (m,2H), 3.63 (m,2H), 3.81 (s,3H), 4.12 (m,2H), 4.40 (q,2H), 6.07 (brs,1H), 6.68 (d,1H), 6.98 (d,1H), 7.26 (m,2H), 7.40 (d,1H), 7.60 (dd,1H). LRMS (APCI): 459 $(M+H)^+$.

PREPARATION 90

Methyl 2-{4-[4-(6-ethoxypyridin-2-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}- 2-methylpropanoate

A stirred solution of the title compound of Preparation 89 (280 mg, 0.6 mmol) in methanol (12 ml) was hydrogenated at 345 kPa (50psi) pressure over 10% palladium on carbon (50 mg) for 18 hours, then the resulting mixture filtered. The filtrate was evaporated under reduced pressure and the residue purified by flash chromatography, using an elution gradient of pentane:ether (90:10 to 70:30), to provide the title compound (70 mg, 25%) as a colourless foam. $\delta(CDCl_3)$: 1.40 (t,3H), 1.67 (s,6H), 1.82 (m,2H), 1.89 (m,2H), 2.43 (s,3H), 2.67 (m,1H), 3.08 (m,2H), 3.81 (s,3H), 3.95 (brd,2H), 4.38 (q,2H), 6.67 (d,1H), 6.96 (d,1H), 7.10 (m,2H), 7.38 (d,1H), 7.60 (dd,1H).
LRMS (APCI): 461 $(M+H)^+$.

PREPARATION 91

2-{4-[4-(6-Ethoxypyridin-2-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methyl-propanoic acid

A solution of the title compound of Preparation 91 (68 mg, 0.15 mmol) in a mixture of 1,4-dioxan (2 ml) and 1M aqueous sodium hydroxide solution (0.26 ml, 0.26 mmol) was stirred at room temperature for 18 hours. The resulting solution was diluted with water (20 ml), acidified with glacial acetic acid to pH ~4 and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated under reduced pressure to furnish the title compound (60 mg, 87%) as a colourless solid, m.p. 178-179°C. Found: C, 61.53; H, 6.81; N, 6.09. $C_{23}H_{30}N_2O_5S$ requires C, 61.86; H, 6.77; N, 6.27%. $\delta(CDCl_3)$: 1.39 (t,3H), 1.68 (s,6H), 1.82 (m,2H), 1.90 (m,2H), 2.43 (s,3H), 2.67 (m,1H), 3.10 (m,2H), 4.00 (brd,2H), 4.38 (q,2H), 6.65 (d,1H), 6.96 (d,1H), 7.10 (m,2H), 7.38 (d,1H), 7.60 (dd,1H).

PREPARATION 92

Methyl 4-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]tetrahydropyran-4-carboxylate

Obtained as a colourless solid (67%), m.p. 203-206°C, from the title compound of Preparation 8 and bis-2-iodoethyl ether, using the procedure of Preparation 39. $\delta(CDCl_3)$: 2.25 (m,2H), 2.44 (d,2H), 2.66 (m,2H), 3.32 (t,2H), 3.61 (m,2H), 3.90 (s,3H), 4.01 (dd,2H), 4.10 (m,2H), 6.08 (brs,1H), 7.30-7.62 (m,9H).

LRMS (Thermospray): 442 $(M+H)^+$.

PREPARATION 93

4-[4-(4-Phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]tetrahydropyran-4-carboxylic acid

Obtained as a colourless solid (66%), m.p. 214°C, from the title compound of Preparation 92, using the procedure of Preparation 79. $\delta(CDCl_3)$: 2.27 (m,2H), 2.42 (d,2H), 2.66 (m,2H), 3.41 (t,2H), 3.62 (m,2H), 4.04 (dd,2H), 4.15 (m,2H), 6.08 (brs,1H), 7.30-7.48 (m,5H), 7.58 (m,4H).

LRMS (APCI): 427 $(M+H)^+$.

PREPARATION 94

Methyl 4-{4-[4-(4-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxylate

Obtained as a colourless solid (66%), 140-141°C, from the title compound of Preparation 39 and 4-ethoxyphenylboronic acid, using the procedure of Preparation 41, but with ethyl acetate:hexane (30:70) as eluant. Found: C, 64.59; H, 6.60; N, 2.74. $C_{27}H_{33}NO_6S$ requires C, 64.91; H, 6.66; N, 2.80%. δ($DMSO_{d6}$): 1.34 (t,3H), 2.00 (m,2H), 2.22 (s,3H), 2.28 (d,2H), 2.55

(brs,2H), 3.19 (t,2H), 3.50 (brs,2H), 3.80 (s,3H), 3.90 (dd,2H), 3.99 (brs,2H), 4.06 (q,2H), 6.17 (brs,1H), 6.96 (d,2H), 7.14 (d,1H), 7.22 (d,2H), 7.28 (d,1H), 7.33 (s,1H).

LRMS (Thermospray): 500 $(M+H)^+$.

PREPARATION 95

4-{4-[4-(4-Ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxylic acid

Obtained as a colourless solid (56%), m.p. 212-214°C, from the title compound of Preparation 94, using the procedure of Preparation 79. $\delta(CDCl_3)$: 1.34 (t,3H), 1.98 (m,2H), 2.22 (s,3H), 2.24 (d,2H), 2.55 (brs,2H), 3.19 (t,2H), 3.52 (brs,2H), 3.90 (dd,2H), 4.01 (brs,2H), 4.04 (q,2H), 6.17 (brs,1H), 6.96 (d,2H), 7.13 (d,1H), 7.22 (d,2H), 7.28 (d,1H), 7.33 (s,1H).

LRMS (Thermospray): 486 $(M+H)^+$.

PREPARATION 96

Methyl 2-{4-[4-(3-formylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a colourless gum (86%),from the title compound of Preparation 37 and 3-formylphenylboronic acid, using the procedure of Preparation 41, but with methanol:dichloromethane (1:99) as eluant. $\delta(CDCl_3)$: 2.30 (s,3H), 2.70 (m,2H), 3.64 (t,2H), 3.82 (s,3H), 4.02 (s,2H), 4.12 (m,2H), 6.10 (brs,1H), 7.20-7.33 (m,3H), 7.60 (m,2H), 7.85 (m,2H), 10.08 (s,1H).

LRMS (APCI): 414 $(M+H)^+$.

PREPARATION 97

Methyl 2-{4-[4-(3-hydroxymethylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

The title compound of Preparation 96 (303 mg, 0.73 mmol) was

dissolved in a mixture of methanol (15 ml) and 1,2-dimethoxyethane (5 ml), polymer-supported borohydride on Amberlite™ IRA-400 (360 mg, 0.91 mmol) added and the reaction mixture stirred for 3 hours at room temperature. The resin was removed by filtration and the filtrate evaporated under reduced pressure to afford the title compound as a colourless foam (270 mg, 90%). $\delta(CDCl_3)$: 2.30 (s,3H), 2.70 (m,2H), 3.64 (t,2H), 3.82 (s,3H), 4.02 (s,2H), 4.12 (m,2H), 4.77 (brs,2H), 6.10 (brs,1H), 7.20-7.50 (m,7H).
LRMS (Thermospray): 416 $(M+H)^+$.

PREPARATION 98

Quinolin-3-ylboronic acid

A 2.5M solution of n-butyllithium in hexane (4.4 ml, 11 mmol) was slowly added to a stirred solution of 3-bromoquinoline (2.08 g, 10 mmol) in anhydrous ether (20 ml), under nitrogen, at -75°C. After a further 20 minutes at -75°C, trimethylborate (1.46 ml, 13 mmol) was added, whereupon the red colour changed to yellow. The reaction mixture was allowed to warm to room temperature and quenched with water, followed by 1M aqueous sodium hydroxide solution (10 ml). The resulting mixture was stirred for 30 minutes and then glacial acetic acid added until a pH ~5-6 was attained, which generated a gummy precipitate. Diisopropyl ether was added to this mixture, stirring continued for 1 hour and then the clear aqueous and organic phases were decanted from the solid and discarded. The solid residue was dissolved in ethyl acetate and the solution washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound as a pale yellow solid (580 mg, 34%). Found: C, 62.74; H, 4.11; N, 7.92. $C_9H_8BNO_2$ requires C, 62.49; H, 4.66; N, 8.10%. $\delta(DMSO_{d6})$: 7.59 (t,1H), 7.76 (t,1H), 7.98 (m,2H), 8.42 (brs,2H,exchangeable), 8.70 (s,1H), 9.18 (s,1H).

PREPARATION 99

Methyl 2-methyl-2-{4-[3-methyl-4-(quinolin-3-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}propanoate

Obtained as a colourless solid (82%), m.p. 149-151°C, from the title compounds of Preparation 40 and Preparation 98, using the procedure of Preparation 41, but using 25% 1-methylpyrrolidin-2-one in 1,2-dimethoxyethane as the reaction solvent and ether:pentane (80:20) as eluant for flash chromatography. Found: C, 67.02; H, 6.20; N, 5.78. $C_{26}H_{28}N_2O_4S$ requires C, 67.22; H, 6.08; N, 6.03%. $\delta(CDCl_3)$: 1.67 (s,6H), 2.36 (s,3H), 2.67 (m,2H), 3.65 (m,2H), 3.82 (s,3H), 4.13 (m,2H), 6.10 (brs,1H), 7.32 (m,3H), 7.60 (t,1H), 7.75 (t,1H), 7.87 (d,1H), 8.10 (s,1H), 8.16 (d,1H), 8.93 (s,1H).
LRMS (Thermospray): 465 $(M+H)^+$.

PREPARATION 100

2-Methyl-2-{4-[3-methyl-4-(quinolin-3-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}propionic acid

A solution of the title compound of Preparation 99 (500 mg, 1.08 mmol) in a mixture of 1,4-dioxan (5 ml), methanol (10 ml) and 1M aqueous sodium hydroxide solution (3.2 ml, 3.2 mmol) was stirred under reflux for 30 minutes. The resulting solution was allowed to cool, acidified with glacial acetic acid to pH ~4, diluted with water (15 ml) and the resulting mixture partially evaporated under reduced pressure until crystallisation occurred. The solid was collected and dried to yield the title compound (440 mg, 90%) as a colourless solid, m.p. 222-224°C. Found: C, 66.17; H, 5.77; N, 6.15. $C_{25}H_{26}N_2O_4S$ requires C, 66.64; H, 65.82; N, 6.22%. $\delta(DMSO_{d6})$: 1.51 (s,6H), 2.31 (s,3H), 2.59 (m,2H), 3.58 (m,2H), 4.08 (m,2H), 6.26 (brs,1H), 7.33-7.50 (m,3H), 7.65 (t,1H), 7.78 (t,1H), 8.05 (t,2H), 8.37 (s,1H), 8.90 (s,1H), 13.4 (brs,1H).
LRMS (APCI): 451 $(M+H)^+$.

PREPARATION 101

3-Methylthiophenylboronic acid

A solution of 3-bromothioanisole (10.3 g, 50.9 mmol) in anhydrous tetrahydrofuran (15 ml) was added dropwise to a stirred mixture of magnesium turnings (1.86 g, 75 mmol) and a crystal of iodine under nitrogen. Once the reaction was initiated, the remainder of the solution was added at such a rate as to keep the reaction mixture under reflux. When the addition was complete, the mixture was stirred under reflux for a further 1 hour, allowed to cool to room temperature and then added to a solution of trimethyl borate (5.8 ml, 51 mmol) in anhydrous tetrahydrofuran (25 ml), whilst keeping the internal temperature at about -10°C. The reaction mixture was allowed to warm to about 0°C, stirred for 30 minutes and then quenched with 2M hydrochloric acid. The resulting mixture was extracted with ether, then the combined extracts extracted, in turn, with 2M aqueous sodium hydroxide solution. The combined aqueous extracts were acidified with concentrated hydrochloric acid and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated under reducted pressure to provide the title compound (7.8 g, 100%) as a white solid.

$\delta(DMSO_{d6})$: 2.45 (s,3H), 7.27 (m,2H), 7.54 (m,1H), 7.67 (s,1H), 8.05 (brs,2H).

PREPARATION 102

Methyl 2-{4-[3-methyl-4-(3-methylthiophenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a colourless solid (83%), from the title compounds of Preparation 101 and Preparation 37, using the procedure of Preparation 41, but using dichloromethane:hexane (3:1) as eluant. $\delta(CDCl_3)$: 2.28 (s,3H), 2.50 (s,3H), 2.68 (m,2H), 3.64 (t,2H), 3.81 (s,3H), 4.02 (s,2H), 4.10 (m,2H), 6.08 (brs,1H), 7.07 (d,1H), 7.20-7.36 (m, 6H).

LRMS (APCI): 432 $(M+H)^+$.

PREPARATION 103

3-Methoxymethylphenylboronic acid

Obtained as a yellow solid (100%), from 1-bromo-3-methoxymethylbenzene (J. Amer. Chem. Soc., 1989, 111, 6311; Tetrahedron 1985, 41, 1435) and trimethyl borate, using the procedure of Preparation 101. $\delta(DMSO_{d6})$: 3.27 (s,3H), 4.38 (s,2H), 7.31 (m,2H), 7.68 (m,2H), 7.98 (brs,2H).

PREPARATION 104

Methyl 2-{4-[4-(3-methoxymethylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a colourless oil (35%), from the title compounds of Preparation 103 and Preparation 37, using the procedure of Preparation 41, but using ether:hexane (60:40) as eluant. $\delta(CDCl_3)$: 2.27 (s,3H), 2.68 (m,2H), 3.42 (s,3H), 3.64 (t,2H), 3.81 (s,3H), 4.02 (s,2H), 4.10 (m,2H), 4.51 (s,2H), 6.08 (brs,1H), 7.20-7.32 (m, 7H).
LRMS (Thermospray): 430 $(M+H)^+$.

PREPARATION 105

1-Bromo-3-(2-methoxyethoxy)benzene

Anhydrous potassium carbonate (4.2 g, 30.4 mmol) was added to a stirred solution of 3-bromophenol (5.0 g, 28.9 mmol) in anhydrous dimethylformamide (100 ml). After 5 minutes, 1-iodo-2-methoxyethane (Annalen, 1967, 710, 59; 5.9 g, 31.8 mmol) was added and the reaction mixture stirred at room temperature for about 16 hours. At this point the mixture was heated at about 50°C for approximately 72 hours, before 1-chloro-2-methoxyethane (1.8 ml, 19.8 mmol) was added and heating continued for a further 24 hours. The resulting mixture was evaporated under reduced pressure and the residue partitioned between ethyl acetate and water. The layers were

separated and the aqueous layer was further extracted with ethyl acetate. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated to a red oil, which was purified by flash chromatography using hexane:ethyl acetate (3:1) as eluant, to furnish the title compound as a colourless oil (1.7 g, 25%). $\delta(CDCl_3)$: 3.43 (s,3H), 3.74 (t,2H), 4.10 (t,2H), 6.87 (d,1H), 7.10 (m,3H).

PREPARATION 106

3-(2-Methoxyethoxy)phenylboronic acid

Obtained as a colourless solid (74%), m.p. 101-103°C, from the title compound of Preparation 105 and trimethyl borate, using the procedure of Preparation 101. Found: C, 55.09; H, 6.70. $C_9H_{13}BO_4$ requires C, 55.15; H, 6.69%. $\delta(DMSO_{d6})$: 3.30 (s,3H), 3.63 (t,2H), 4.06 (t,2H), 6.94 (dd,1H), 7.22 (t,1H), 7.32 (m,2H), 7.98 (brs,2H).
LRMS (Thermospray): 214 $(M+NH_4)^+$.

PREPARATION 107

Methyl 2-{4-[4-(3-[2-methoxyethoxy]phenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a colourless oil (59%), from the title compounds of Preparation 106 and Preparation 37, using the procedure of Preparation 41, but using ether:hexane (1:1) as eluant. $\delta(CDCl_3)$: 2.28 (s,3H), 2.67 (m,2H), 3.45 (s,3H), 3.63 (t,2H), 3.77 (t,2H), 3.80 (s,3H), 4.02 (s,2H), 4.09 (s,2H), 4.15 (s,2H), 6.07 (brs,1H), 6.90 (m,3H), 7.19-7.34 (m, 4H).

PREPARATION 108

2,3-Dihydrobenzofuran-5-ylboronic acid

Obtained as a colourless solid (38%), m.p. >240°C (decomp.), from 5-

bromo-2,3-dihydrobenzofuran (Synthesis, 1988, 952) and trimethyl borate, using the procedure of Preparation 101. $\delta(DMSO_{d6})$: 3.33 (t,2H), 4.48 (t,2H), 6.68 (d,1H), 7.56 (d,1H), 7.63 (s,1H), 7.70 (brs,2H).

PREPARATION 109

5-(4-Bromo-2-methylphenyl)-2,3-dihydrobenzofuran

The title compound of Preparation 108 (2.0 g, 12.2 mmol) was added portionwise over 5 minutes to a stirred mixture of the title compound of Preparation 57 (3.4 g, 12.0 mmol) and palladium(II) acetate (0.15 g, 0.6 mmol) in anhydrous methanol (30 ml) and the reaction mixture heated under reflux for 1.5 hours. The resulting mixture was allowed to cool to room temperature, filtered, then the filtrate diluted with water (100 ml) and extracted with ether (2 x 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using hexane as eluant, to afford the title compound (1.7 g) as a pale orange oil.
$\delta(CDCl_3)$: 2.25 (s,3H), 3.25 (t,2H), 4.62 (t,2H), 6.83 (d,1H), 7.02 (d,1H), 7.09 (m,2H), 7.34 (d, 1H), 7.60 (s,1H).
LRMS (APCI): 289 $(M)^+$.

PREPARATION 110

t-Butyl 4-[4-(2,3-dihydrobenzofuran-5-yl)-3-methyphenyl]-4-hydroxypiperidine-1-carboxylate

Obtained as a white solid (66%), from the title compound of Preparation 109 and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43. $\delta(CDCl_3)$: 1.50 (s,9H), 1.78 (m,2H), 2.06 (m,2H), 2.29 (s,3H), 3.26 (m,4H), 4.05 (m,2H), 4.62 (t,2H), 6.82 (d,1H), 7.05 (d,1H), 7.15 (s,1H), 7.21 (d, 1H), 7.30 (m,1H), 7.36 (s,1H).
LRMS (Thermospray): 432 $(M+Na)^+$.

PREPARATION 111

4-[4-(2,3-Dihydrobenzofuran-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridine

Obtained as a colourless viscous oil (98%), from the title compound of Preparation 110 and trifluoroacetic acid, using the procedure of Preparation 44. $\delta(CDCl_3)$: 2.30 (s,3H), 2.49 (m,2H), 3.12 (t,2H), 3.26 (t,2H), 3.56 (s,2H), 4.62 (t,2H), 6.17 (brs,1H), 6.82 (d,1H), 7.07 (d,1H), 7.16(m,2H), 7.26 (m,2H).
LRMS (Thermospray): 292 $(M+H)^+$.

PREPARATION 112

Methyl 2-{4-[4-(2,3-dihydrobenzofuran-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a pale yellow, foamy solid (45%), m.p. 118-122°C, from the title compound of Preparation 111 and methyl chlorosulphonylacetate, using the procedure of Preparation 61. $\delta(CDCl_3)$: 2.30 (s,3H), 2.67 (m,2H), 3.24 (t,2H), 3.62 (t,2H), 3.79 (s,3H), 4.01 (s,2H), 4.06 (s,2H), 4.62 (t,2H), 6.08 (brs,1H), 6.82 (d,1H), 7.05 (d,1H), 7.26 (m,4H).
LRMS (Thermospray): 428 $(M+H)^+$.

PREPARATION 113

3-Methyl-4-(3-trifluoromethylphenyl)bromobenzene

Obtained as a colourless oil (66%), from the title compound of Preparation 57 and 3-trifluoromethylphenylboronic acid, using the procedure of Preparation 109. $\delta(CDCl_3)$: 2.23 (s,3H), 7.08 (d,1H), 7.40-7.64 (m, 6H).

PREPARATION 114

t-Butyl 4-hydroxy-4-[3-methyl-4-(3-trifluoromethylphenyl)phenyl]piperidine-1-carboxylate

Obtained as a yellow oil (54%), from the title compound of Preparation

113 and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43, but with hexane:ethyl acetate (85:15) as eluant. $\delta(CDCl_3)$: 1.50 (s,9H), 1.77 (m,2H), 2.04 (m,2H), 2.27 (s,3H), 3.26 (m,2H), 4.05 (m,2H), 7.04 (d,1H), 7.15 (s,1H), 7.37 (m,2H), 7.55 (m,4H).
LRMS (Thermospray): 436 $(M+H)^+$.

PREPARATION 115

4-[3-Methyl-4-(3-trifluoromethylphenyl)phenyl]-1,2,3,6-tetrahydropyridine

Obtained as a colourless oil (98%), from the title compound of Preparation 114 and trifluoroacetic acid, using the procedure of Preparation 44. Found: C, 70.90; H, 5.84; N, 4.38. $C_{19}H_{18}F_3N$; 0.25 H_2O requires C, 70.90; H, 5.79; N, 4.35%. $\delta(CDCl_3)$: 2.26 (s,3H), 2.49 (brs,2H), 3.12 (brs,2H), 3.56 (brs,2H), 6.20 (brs,1H), 7.18 (d,1H), 7.26 (m,2H), 7.55 (m,4H).
LRMS (APCI): 318 $(M)^+$.

PREPARATION 116

Methyl 2-{4-[3-methyl-4-(3-trifluoromethylphenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a pale yellow foam (31%), from the title compound of Preparation 115 and methyl chlorosulphonylacetate, using the procedure of Preparation 61, but with dichloromethane:hexane (80:20) as eluant. Found: C, 56.38; H, 4.77; N, 2.96. $C_{22}H_{22}F_3NO_4S$; 0.25 CH_2Cl_2 requires C, 56.30; H, 4.78; N, 2.95%. $\delta(CDCl_3)$: 2.27 (s,3H), 2.70 (m,2H), 3.64 (t,2H), 3.82 (s,3H), 4.03 (s,2H), 4.11 (s,2H), 6.10 (brs,1H), 7.24 (m,3H), 7.55 (m,4H).
LRMS (APCI): 453 $(M)^+$.

PREPARATION 117

t-Butyl 4-hydroxy-4-(4-phenoxyphenyl)piperidine-1-carboxylate

Obtained as a white foam (54%), from 4-phenoxybromobenzene and t-

butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43, but with a mixture of anhydrous ether and anhydrous tetrahydrofuran as solvent and ether:hexane (60:40) as eluant. $\delta(CDCl_3)$: 1.50 (s,9H), 1.75 (m,2H), 1.99 (m,2H), 3.25 (m,2H), 4.04 (m,2H), 7.00 (m,4H), 7.12 (t,1H), 7.37 (t,2H), 7.44 (d,2H).

PREPARATION 118

4-(4-Phenoxyphenyl)piperidine

Triethylsilane (3.0 ml, 18.9 mmol) was added to a stirred solution of the title compound of Preparation 117 (775 mg, 2.1 mmol) in anhydrous dichloromethane (10 ml), the resulting solution was cooled to about 0°C and then trifluoroacetic acid (10 ml) was slowly added. The reaction mixture was allowed to warm to room temperature and then stirred for about 1.5 hours. The resulting mixture was evaporated under reduced pressure, then the residue dissolved in methanol and this solution basified with 2M aqueous sodium hydroxide solution. The mixture was extracted with ethyl acetate and the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure.

This residue was dissolved in glacial acetic acid (20 ml) and the solution hydrogenated over palladium on carbon (60 mg) at 345 kPa (50psi) and room temperature for 2 hours. The mixture was filtered, the filtrate evaporated under reduced pressure and the residue dissolved in methanol. This solution was then basified with 2M aqueous sodium hydroxide solution, extracted with ethyl acetate and the combined extracts dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound as a yellow oil (550 mg, 100%). $\delta(CDCl_3)$: 1.63 (m,2H), 1.84 (m,2H), 2.60 (m,1H), 2.74 (t,2H), 3.20 (m,2H), 6.95 (d,2H), 7.00 (d,2H), 7.07 (t,1H), 7.18 (d,2H), 7.33 (m,2H).
LRMS (Thermospray): 254 $(M+H)^+$.

PREPARATION 119

Methyl 2-[4-(4-phenoxyphenyl)piperidin-1-ylsulphonyl]acetate

Obtained as a colourless solid (38%), from the title compound of Preparation 118 and methyl chlorosulphonylacetate, using the procedure of Preparation 45. $\delta(CDCl_3)$: 1.80 (m,2H), 1.94 (m,2H), 2.64 (m,1H), 3.00 (t,2H), 3.83 (s,3H), 3.95 (m,4H), 6.95 (m,4H), 7.10 (t,1H), 7.16 (d,2H), 7.33 (m,2H). LRMS (Thermospray): 407 $(M+NH_4)^+$.

PREPARATION 120

Methyl 2-{4-[4-(3-[2-methoxyethoxy]phenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropionate

Obtained as a pale yellow oil (97%), from the title compounds of Preparation 106 and Preparation 40, using the procedure of Preparation 41, but with ethyl acetate:hexane (1:3) as eluant. $\delta(CDCl_3)$: 1.67 (s,6H), 2.28 (s,3H), 2.65 (m,2H), 3.45 (s,3H), 3.62 (m,2H), 3.76 (m,2H), 3.80 (s,3H), 4.13 (m,4H), 6.06 (brs,1H), 6.90 (m,3H), 7.19-7.35 (m,4H).

PREPARATION 121

Methyl 2-{4-[4-(3-[2-methoxyethoxy]phenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a pale yellow oil (83%), from the title compound of Preparation 120, using the procedure of Preparation 90. $\delta(CDCl_3)$: 1.66 (s,6H), 1.78-1.88 (m,4H), 2.27 (s,3H), 2.68 (m,1H), 3.09 (m,2H), 3.45 (s,3H), 3.77 (t,2H), 3.81 (s,3H), 3.96 (d,2H), 4.15 (t,2H), 6.90 (m,3H), 7.10 (m,2H), 7.18 (d,1H), 7.30 (t,1H).

LRMS (Thermospray): 490 $(M+H)^+$.

PREPARATION 122

2-{4-[4-(3-[2-Methoxyethoxy]phenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropionic acid

Obtained as a colourless solid (78%), m.p. 140-141°C, from the title compound of Preparation 121, using the procedure of Preparation 79. Found: C, 62.89; H, 7.06; N, 2.85. $C_{25}H_{33}NO_6S$ requires C, 63.14; H, 6.99; N, 2.95%. $\delta(CDCl_3)$: 1.68 (s,6H), 1.78-1.88 (m,4H), 2.27 (s,3H), 2.68 (m,1H), 3.11 (m,2H), 3.45 (s,3H), 3.77 (t,2H), 4.00 (d,2H), 4.15 (t,2H), 6.90 (m,3H), 7.10 (m,2H), 7.18 (d,1H), 7.30 (t,1H).

LRMS (Thermospray): 475 $(M+H)^+$.

PREPARATION 123

Methyl 4-methoxy-2(R,S)-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]butanoate

60% Sodium hydride dispersion in mineral oil (23 mg, 0.57 mmol) was added to a stirred solution of the title compound of Preparation 9 (200 mg, 0.52 mmol) in anhydrous 1-methylpyrrolidin-2-one (3 ml), under nitrogen, at room temperature. After 30 minutes, 1-iodo-2-methoxyethane (101 mg, 0.57 mmol) was added and stirring continued for a further 16 hours, then the resulting mixture was partitioned between ethyl acetate and water The organic phase was separated, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using dichloromethane as eluant, followed by trituration with diisopropyl ether, to yield the title compound (148 mg) as a colourless solid, m.p. 95-96°C. δ $(CDCl_3)$: 2.28 (s,3H), 2.39 (m,2H), 2.67 (m,2H), 3.30 (s,3H), 3.40 (m,1H), 3.54 (m,2H), 3.67 (m,1H), 3.80 (s,3H), 4.10 (brs,2H), 4.17 (dd,1H), 6.07 (brs, 1H), 7.22 (m,3H), 7.32 (m,3H), 7.41 (m,2H).

LRMS (APCI): 444 $(M+H)^+$.

PREPARATION 124

4-Methoxy-2(R,S)-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]butanoic acid

1M Aqueous sodium hydroxide solution (1.0 ml, 1.0 mmol) was added to a stirred solution of the title compound of Preparation 123 (148 mg, 0.33 mmol) in a mixture of methanol (5 ml) and 1,4-dioxan (2 ml). The resulting solution was heated at 80°C for about 4 hours, then allowed to cool to room temperature and evaporated under reduced pressure. The residue was diluted with water, then the resulting mixture acidified with glacial acetic acid and extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to provide the title compound (145 mg) as a colourless solid, m.p. 108-109°C. δ ($CDCl_3$): 2.28 (s,3H), 2.39 (m,2H), 2.67 (m,2H), 3.36 (s,3H), 3.53-3.73 (m,5H), 4.12 (brs,2H), 4.20 (dd,1H), 6.07 (brs, 1H), 7.19-7.47 (m,8H).

LRMS (APCI): 429 $(M+H)^+$.

PREPARATION 125

Methyl 4-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]tetrahydropyran-4-carboxylate

60% Sodium hydride dispersion in mineral oil (34 mg, 0.86 mmol) was added to a stirred solution of the title compound of Preparation 9 (300 mg, 0.78 mmol) in anhydrous 1-methylpyrrolidin-2-one (3 ml), under nitrogen, at room temperature. After 30 minutes, bis-2-iodoethyl ether (380 mg, 0.78 mmol) was added and stirring continued for a further 4 hours, then more 60% sodium hydride dispersion in mineral oil (34 mg, 0.86 mmol) was added and the mixture stirred for a further 16 hours. The resulting mixture was partitioned between ethyl acetate and water, then the organic phase separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was

purified by crystallisation from diisopropyl ether to furnish the title compound (188 mg) as a colourless solid, m.p. 117-119°C. Found: C,65.70; H,6.44; N,2.98. $C_{25}H_{29}NO_5S$ requires C,65.91; H,6.42; N,3.08%. $\delta(CDCl_3)$: 2.22 (m,2H), 2.29 (s,3H), 2.47 (m,2H), 2.64 (m,2H), 3.33 (t,2H), 3.60 (m,2H), 3.87 (s,3H), 4.00 (dd,2H), 4.10 (m,2H), 6.07 (brs,1H), 7.20-7.43 (m,8H).
LRMS (Thermospray): 456 $(M+H)^+$.

PREPARATION 126

4-[4-(3-Methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]tetrahydropyran-4-carboxylic acid

1M Aqueous sodium hydroxide solution (1.4 ml, 1.4 mmol) was added to a stirred solution of the title compound of Preparation 125 (160 mg, 0.35 mmol) in a mixture of methanol (5 ml) and 1,4-dioxan (2 ml). The resulting solution was heated at 80°C for 4 hours, then allowed to cool to room temperature, diluted with water and concentrated under reduced pressure. The resulting mixture was acidified with 1M hydrochloric acid and the precipitate thus obtained was collected, washed with water and dried to afford the title compound (135 mg) as a colourless solid, m.p. 211-213°C. Found: C,64.89; H,6.14; N,3.07. $C_{24}H_{27}NO_5S$ requires C,65.28; H,6.14; N,3.17%. $\delta(DMSO_{d6})$: 1.96 (m,2H), 2.03 (s,3H), 2.10 (m,2H), 2.53 (m,2H), 3.23 (t,2H), 3.54 (m,2H), 3.92 (dd,2H), 4.03 (m,2H), 6.18 (brs,1H), 7.16 (d,1H), 7.28-7.43 (m,7H), 13.7 (brs,1H).
LRMS (APCI): 442 $(M+H)^+$.

PREPARATION 127

4-[4-(3-Methoxyphenyl)-3-methylphenyl]piperidine

Obtained as a pink oil (74%), from the title compound of Preparation 59,

using the procedure of Preparation 118. $\delta(CDCl_3)$: 1.67 (m,2H), 1.88 (m,2H), 2.29 (s,3H), 2.63 (m,1H), 2.57 (t,2H), 3.22 (m,2H), 3.83 (s,3H), 6.89 (m,3H), 7.10 (m,2H), 7.18 (d,1H), 7.32 (t,1H).

LRMS (Thermospray): 282 $(M+H)^+$.

PREPARATION 128

Methyl 2-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}acetate

Obtained as a colourless solid (47%), m.p. 96-98°C, from the title compound of Preparation 127 and methyl chlorosulphonylacetate, using the procedure of Preparation 45. $\delta(CDCl_3)$: 1.83 (m,2H), 1.96 (m,2H), 2.28 (s,3H), 2.63 (m,1H), 3.02 (t,2H), 3.83 (s,6H), 4.01 (m,4H), 6.89 (m,3H), 7.10 (m,2H), 7.20 (d,1H), 7.34 (t,1H).

LRMS (Thermospray): 418 $(M+H)^+$.

PREPARATION 129

Methyl 2-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}indane-2-carboxylate

1,2-Di(bromomethyl)benzene (409 mg, 1.55 mmol) was added to a stirred mixture of the title compound of Preparation 128 (500 mg, 1.2 mmol) and anhydrous potassium carbonate (497 mg, 3.6 mmol) in anhydrous 1,2-dimethoxyethane (5 ml) and the resulting mixture stirred at room temperature for 17 hours. Little reaction had occurred, so the solvent was evaporated under reduced pressure and the residue dissolved in 1-methylpyrrolidin-2-one (5 ml) and the solution heated at 100°C for 2 hours. This mixture was allowed to cool to room temperature, partitioned between ether and water, then the organic phase washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. Purification by flash chromatography, using an

elution gradient of pentane:ethyl acetate (10:1 to 3:1), yielded the title compound as a white crystalline solid (160 mg), m.p. 174-176°C. Found: C,68.95; H,6.48; N,2.56. $C_{30}H_{33}NO_5S$ requires C,69.34; H,6.40; N,2.70%. $\delta(CDCl_3)$: 1.74 (m,2H), 1.85 (m,2H), 2.27 (s,3H), 2.57 (m,1H), 2.89 (t,2H), 3.73-3.86 (m,4H), 3.83 (s,6H), 3.96 (m,2H), 6.87 (m,3H), 7.06 (m,2H), 7.18-7.33 (m,6H).

LRMS (Thermospray): 520 $(M+H)^+$.

PREPARATION 130

2-{4-[4-(3-Methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}indane-2-carboxylic acid

Obtained as a colourless solid (83%), m.p. 204-206°C, from the title compound of Preparation 129, using the procedure of Preparation 79. Found: C,68.17; H,6.22; N,2.74. $C_{29}H_{31}NO_5S$; 0.30 H_2O requires C,68.16; H,6.23; N,2.74%. $\delta(DMSO_{d6})$: 1.54 (m,2H), 1.76 (m,2H), 2.21 (s,3H), 2.57 (m,1H), 2.89 (t,2H), 3.55 (d,2H), 3.72 (d,2H), 3.77 (s,3H), 3.81 (m,2H), 6.87 (m,3H), 7.07 (m,3H), 7.19 (m,2H), 7.28 (m,3H), 13.65 (brs,1H).

LRMS (Thermospray): 520 $(M+NH_4)^+$.

PREPARATION 131

Methyl 1-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}cyclobutanecarboxylate

1,3-Diiodopropane (513 mg, 1.73 mmol) was added to a stirred mixture of the title compound of Preparation 128 (557 mg, 1.33 mmol), anhydrous potassium carbonate (553 mg, 4.0 mmol) and anhydrous 1,2-dimethoxyethane (8 ml), then the mixture was stirred at room temperature for 17 hours and at reflux for 72 hours. The resulting mixture was allowed to cool to room

temperature and partitioned between ethyl acetate and water, then the organic phase dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. Purification by flash chromatography, using pentane:ethyl acetate (3:1) as eluant, provided the title compound (472 mg) as a white crystalline solid, m.p. 97-101°C. $\delta(CDCl_3)$: 1.75-2.02 (m,5H), 2.13 (m,1H), 2.28 (s,3H), 2.59-2.75 (m,3H), 2.90 (m,2H), 3.00 (t,2H), 3.82 (s,3H), 3.87 (s,3H), 3.93 (m,2H), 6.87 (m,3H), 7.06 (m,2H), 7.18 (d,1H), 7.32 (t,1H).
LRMS (Thermospray): 458 $(M+H)^+$.

PREPARATION 132

1-{4-[4-(3-Methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}cyclobutanecarboxylic acid

Obtained as a colourless solid (100%), m.p. 155-160°C, from the title compound of Preparation 131, using the procedure of Preparation 79.
$\delta(CDCl_3)$: 1.80 (m,2H), 1.91 (m,2H), 2.12 (m,2H), 2.27 (s,3H), 2.62 (m,1H), 2.74 (m,2H), 2.91 (m,2H), 3.04 (t,2H), 3.82 (s,3H), 3.99 (m,2H), 6.87 (m,3H), 7.06 (m,2H), 7.18 (d,1H), 7.32 (t,1H).
LRMS (Thermospray): 444 $(M+H)^+$.

PREPARATION 133

Methyl 4-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-1-methylpiperidine-4-carboxylate

The title compound of Preparation 128 (500 mg, 1.2 mmol) and anhydrous potassium carbonate (553 mg, 4.0 mmol), followed by anhydrous 1,2-dimethoxyethane (8 ml), were added to N-methyl-bis(2-chloroethyl)amine hydrochloride (231 mg, 1.2 mmol) and the mixture was heated under reflux for 48 hours. The resulting mixture was allowed to cool to room temperature, diluted with ethyl acetate, washed with 5% aqueous citric acid solution, dried

($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. The residual oil was dissolved in ethyl acetate and the solution washed successively with aqueous sodium bicarbonate solution/aqueous sodium hydroxide solution (pH 12) and aqueous sodium chloride solution, then dried ($MgSO_4$) and evaporated under reduced pressure to furnish the title compound as a yellow gum (175 mg). $\delta(CDCl_3)$: 1.87 (m,6H), 2.20 (m,2H), 2.25 (s,3H), 2.27 (s,3H), 2.53 (m,2H), 2.66 (m,1H), 2.90 (m,2H), 3.07 (t,2H), 3.82 (s,3H), 3.88 (s,3H), 3.93 (m,2H), 6.88 (m,3H), 7.08 (m,2H), 7.20 (d,1H), 7.32 (t,1H).

LRMS (Thermospray): 501 $(M+H)^+$.

PREPARATION 134

4-{4-[4-(3-Methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-1-methylpiperidine-4-carboxylic acid hydrochloride

1M Aqueous sodium hydroxide solution (1.4 ml, 1.4 mmol) was added to a stirred solution of the title compound of Preparation 133 (172 mg, 0.34 mmol) in a mixture of methanol (5 ml) and 1,4-dioxan (3 ml). The reaction solution was heated at 80°C for 10 hours, then allowed to cool to room temperature and concentrated under reduced pressure. The resulting mixture was acidified with 1M hydrochloric acid, washed with dichloromethane and evaporated under reduced pressure, then the residue was washed with water to afford the title compound (143 mg) as a colourless solid. $\delta(CDCl_3)$: 1.67 (m,2H), 1.84 (m,2H), 2.20 (s,3H), 2.30 (m,2H), 2.62-2.90 (m,7H), 3.12 (t,2H), 3.48 (m,2H), 3.77 (brs,6H), 6.88 (m,3H), 7.10 (brs,2H), 7.18 (brs,1H), 7.32 (t,1H).

LRMS (Thermospray): 523 $(M+HCl)^+$.

PREPARATION 135

Methyl 3-phenyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]propanoate

60% Sodium hydride dispersion in mineral oil (34 mg, 0.77 mmol) was

added to a stirred solution of the title compound of Preparation 8 (288 mg, 0.77 mmol) in anhydrous dimethylformamide (5 ml), under nitrogen, at room temperature. After 30 minutes, benzyl bromide (0.1 ml, 0.82 mmol) was added and stirring continued for a further 16 hours, then the resulting mixture was partitioned between ethyl acetate and water The organic phase was separated and the aqueous phase washed with ethyl acetate. The combined organic solutions were washed sequentially with water and aqueous sodium chloride solution, dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was triturated with diisopropyl ether to give the title compound (170 mg) as a colourless solid, m.p. 137-138°C. δ ($CDCl_3$): 2.68 (m,2H), 3.42 (m,2H), 3.59 (m,1H), 3.67 (s,3H), 3.72 (m,1H), 4.14 (brs,2H), 4.21 (dd,1H), 6.10 (brs,1H), 7.18-7.37 (m,6H), 7.44 (m,4H), 7.59 (m,4H).
LRMS (Thermospray): 462 $(M+H)^+$.

PREPARATION 136

3-Phenyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]propanoic acid

Obtained as a colourless solid (50%), m.p. 164-165°C, from the title compound of Preparation 135, using the procedure of Preparation 79. δ ($CDCl_3$): 2.68 (m,2H), 3.41 (m,2H), 3.60 (m,1H), 3.72 (m,1H), 4.14 (brs,2H), 4.24 (dd,1H), 6.08 (brs,1H), 7.20-7.37 (m,6H), 7.43 (m,4H), 7.59 (m,4H).
LRMS (APCI): 447 $(M+H)^+$.

PREPARATION 137

Methyl 2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]indane-2-carboxylate

60% Sodium hydride dispersion in mineral oil (30 mg, 0.73 mmol) was added to a stirred solution of the title compound of Preparation 8 (250 mg, 0.67

mmol) in anhydrous dimethylformamide (5 ml), under nitrogen, at room temperature. After 30 minutes, 1,2-di(bromomethyl)benzene (267 mg, 1.0 mmol) was added and stirring continued for a further 16 hours. Next, an additional quantity of sodium hydride dispersion in mineral oil (30 mg, 0.73 mmol) was added and the reaction mixture stirred at room temperature for a further 2 hours. The resulting mixture was partitioned between ethyl acetate and water, the organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic solutions were washed successively with water and aqueous sodium chloride solution, dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using pentane:ether (3:1) as eluant, followed by trituration with diisopropyl ether, to yield the title compound (154 mg) as a colourless solid, m.p. 186-188°C. δ ($CDCl_3$): 2.60 (m,2H), 3.56 (m,2H), 3.75-3.88 (m,4H), 3.82 (s,3H), 4.07 (brs,2H), 6.05 (brs,1H), 7.19-7.28 (m,4H), 7.34-7.45 (m,5H), 7.59 (m,4H).

LRMS (APCI): 474 $(M+H)^+$.

PREPARATION 138

2-[4-(4-Phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]indane-2-carboxylic acid

Obtained as a colourless solid (67%), from the title compound of Preparation 137, using the procedure of Preparation 50, except that the residue was triturated with diisopropyl ether. δ ($CDCl_3$): 2.60 (m,2H), 3.56-3.84 (m,6H), 4.07 (brs,2H), 6.05 (brs,1H), 7.19-7.60(m,13H).

PREPARATION 139

4-(3-Chloro-4-fluorophenyl)-3-methylbromobenzene

Obtained as a colourless oil (20%), from the title compound of

Preparation 57 and 3-chloro-4-fluorophenylboronic acid, using the procedure of Preparation 109. $\delta(CDCl_3)$: 2.22 (s,3H), 7.04 (d,1H), 7.10-7.20 (m,2H), 7.28-7.39 (m,2H), 7.42 (s,1H).

PREPARATION 140

t-Butyl 4-[4-(3-chloro-4-fluorophenyl)-3-methylphenyl]-4-hydroxypiperidine-1-carboxylate

Obtained as a colourless gum (39%), from the title compound of Preparation 139 and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43. Found: C, 65.96; H, 6.64; N, 3.36. $C_{23}H_{27}ClFNO_3$ requires C, 65.79; H, 6.48; N, 3.34%. $\delta(CDCl_3)$: 1.50 (s,9H), 1.76 (m,2H), 2.04 (m,2H), 2.28 (s,3H). 3.28 (t,2H), 4.07 (m,2H), 7.16-7.20 (m,3H), 7.30-7.40 (m,3H). LRMS (APCI): 420 $(M+H)^+$.

PREPARATION 141

4-[4-(3-Chloro-4-fluorophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridine

Obtained as a pale yellow oil (99%), from the title compound of Preparation 140 and trifluoroacetic acid, using the procedure of Preparation 35. $\delta(CDCl_3)$: 2.26 (s,3H), 2.50 (m,2H), 3.12 (t,2H), 3.56 (m,2H), 6.16 (brs,1H), 7.15 (m,3H), 7.27 (m,2H), 7.35 (d,1H).
LRMS (APCI): 302 $(M+H)^+$.

PREPARATION 142

Methyl 2-{4-[4-(3-chloro-4-fluorophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a colourless solid (37%), m.p. 125-126°C, from the title

compound of Preparation 141 and methyl chlorosulphonylacetate, using the procedure of Preparation 61. Found: C, 57.46; H, 4.83; N, 3.14. $C_{21}H_{21}ClFNO_4S$ requires C, 57.60; H, 4.83; N, 3.20%. $\delta(CDCl_3)$: 2.28 (s,3H), 2.67 (m,2H), 3.62 (t,2H), 3.80 (s,3H), 4.01 (s,2H), 4.06 (s,2H), 6.08 (brs,1H), 7.17 (m,3H), 7.23 (m,2H), 7.36 (d,1H).
LRMS (Thermospray): 438 $(M+H)^+$.

PREPARATION 143

4-(1,3-Benzodioxol-5-yl)-3-methylbromobenzene

Obtained as a colourless oil (34%), from the title compound of Preparation 57 and 1,3-benzodioxol-5-ylboronic acid, using the procedure of Preparation 109. $\delta(CDCl_3)$: 2.22 (s,3H), 6.00 (s,2H), 6.70 (d,1H), 6.75 (s,1H), 6.85 (d,1H), 7.06 (d,1H), 7.33 (d,1H), 7.40 (s,1H).

PREPARATION 144

t-Butyl 4-[4-(1,3-benzodioxol-5-yl)-3-methylphenyl]-4-hydroxypiperidine-1-carboxylate

Obtained as a colourless solid (39%), m.p. 135-138°C, from the title compound of Preparation 143 and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43. Found: C, 69.82; H, 7.15; N, 3.44. $C_{24}H_{29}NO_5$ requires C, 70.05; H, 7.10; N, 3.40%. $\delta(CDCl_3)$: 1.50 (s,9H), 1.76 (m,2H), 2.04 (m,2H), 2.29 (s,3H). 3.28 (t,2H), 4.04 (m,2H), 6.00 (s,2H), 6.76 (d,1H), 6.79 (s,1H), 6.87 (d,1H), 7.20 (d,1H), 7.30 (d,1H), 7.37 (s,1H).
LRMS (APCI): 412 $(M+H)^+$.

PREPARATION 145

4-[4-(1,3-Benzodioxol-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridine

Obtained as a pale yellow solid (96%), m.p. 105-108°C, from the title compound of Preparation 144 and trifluoroacetic acid, using the procedure of

Preparation 35. $\delta(CDCl_3)$: 2.28 (s,3H), 2.50 (m,2H), 3.12 (t,2H), 3.56 (m,2H), 6.00 (s,2H), 6.17 (brs,1H), 6.75-6.82 (m,2H), 6.87 (d,1H), 7.17 (d,1H), 7.22-7.30 (m,2H).

LRMS (APCI): 294 $(M+H)^+$.

PREPARATION 146

Methyl 2-{4-[4-(1,3-benzodioxol-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a colourless solid (57%), m.p. 133-134°C, from the title compound of Preparation 145 and methyl chlorosulphonylacetate, using the procedure of Preparation 61. Found: C, 61.15; H, 5.41; N, 3.15. $C_{22}H_{23}NO_6S$ requires C, 61.52; H, 5.40; N, 3.26%. $\delta(CDCl_3)$: 2.28 (s,3H), 2.67 (m,2H), 3.62 (t,2H), 3.80 (s,3H), 4.01 (s,2H), 4.06 (s,2H), 6.00 (s,2H), 6.08 (brs,1H), 6.78 (m,2H), 6.87 (d,1H), 7.20 (m,2H), 7.26 (m,1H).

LRMS (APCI): 430 $(M+H)^+$.

PREPARATION 147

4-(2-Fluorophenyl)-3-methylbromobenzene

Obtained as a colourless oil (33%), from the title compound of Preparation 57 and 3-fluorophenylboronic acid, using the procedure of Preparation 109. $\delta(CDCl_3)$: 2.20 (s,3H), 7.06-7.25 (m,4H), 7.30-7.40 (m,2H), 7.43 (s,1H).

PREPARATION 148

t-Butyl 4-[4-(2-fluorophenyl)-3-methylphenyl]-4-hydroxypiperidine-1-carboxylate

Obtained as a pale yellow, amorphous solid (53%), from the title compound of Preparation 147 and t-butyl 4-oxopiperidine-1-carboxylate, using

the procedure of Preparation 43. Found: C, 71.39; H, 7.37; N, 3.69. $C_{23}H_{28}FNO_3$ requires C, 71.67; H, 7.32; N, 3.63%. $\delta(CDCl_3)$: 1.50 (s,9H), 1.78 (d,2H), 2.04 (m,2H), 2.22 (s,3H). 3.28 (t,2H), 4.04 (m,2H), 7.12 (t,1H), 7.16-7.26 (m,3H), 7.35 (m,2H), 7.40 (s,1H).

LRMS (APCI): 386 $(M+H)^+$.

PREPARATION 149

4-[4-(2-Fluorophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridine

Obtained as a pale yellow oil (93%), from the title compound of Preparation 148 and trifluoroacetic acid, using the procedure of Preparation 35. $\delta(CDCl_3)$: 1.80 (brs,1H), 2.21 (s,3H), 2.50 (m,2H), 3.12 (t,2H), 3.57 (m,2H), 6.19 (brs,1H), 7.10-7.38 (m,7H).

LRMS (APCI): 268 $(M+H)^+$.

PREPARATION 150

Methyl 2-{4-[4-(2-fluorophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a colourless solid (30%), m.p. 128-130°C, from the title compound of Preparation 149 and methyl chlorosulphonylacetate, using the procedure of Preparation 61. Found: C, 62.57; H, 5.71; N, 3.32. $C_{21}H_{22}FNO_4S$ requires C, 62.52; H, 5.50; N, 3.47%. $\delta(CDCl_3)$: 2.21 (s,3H), 2.69 (m,2H), 3.63 (t,2H), 3.81 (s,3H), 4.01 (s,2H), 4.10 (m,2H), 6.09 (brs,1H), 7.14 (t,1H), 7.17-7.30 (m,5H), 7.35 (m,1H).

LRMS (APCI): 404 $(M+H)^+$.

PREPARATION 151

Methyl 2-{4-[4-(3,4-dimethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a colourless gum (76%), from the title compound of

Preparation 37 and 3,4-dimethoxyphenylboronic acid, using the procedure of Preparation 41. Found: C, 61.71; H, 6.10; N, 2.91. $C_{23}H_{27}NO_6S$ requires C, 62.01; H, 6.11; N, 3.14%. $\delta(CDCl_3)$: 2.30 (s,3H), 2.67 (m,2H), 3.62 (t,2H), 3.82 (s,3H), 3.87 (s,3H), 3.92 (s,3H), 4.02 (s,2H), 4.10 (m,2H), 6.08 (brs,1H), 6.83-6.97 (m,3H), 7.20-7.30 (m,3H).

LRMS (APCI): 446 $(M+H)^+$.

PREPARATION 152

Methyl 2-{4-[4-(indan-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as a pale yellow solid (75%), from the title compound of Preparation 37 and indan-5-ylboronic acid (WO-A-97/32853), using the procedure of Preparation 41. $\delta(CDCl_3)$: 2.10 (m,2H), 2.30 (s,3H), 2.69 (m,2H), 2.98 (m,4H), 3.62 (t,2H), 3.82 (s,3H), 4.02 (s,2H), 4.10 (m,2H), 6.08 (brs,1H), 7.09 (d,1H), 7.18-7.35 (m,5H).

LRMS (Thermospray): 443 $(M+NH_4)^+$.

PREPARATION 153

Methyl 2-{4-[3-methyl-4-(3-trifluoromethoxyphenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

Obtained as an amorphous solid (28%), from the title compound of Preparation 37 and 3-trifluoromethoxyphenylboronic acid (WO-A-96/13500), using the procedure of Preparation 41. $\delta(CDCl_3)$: 2.30 (s,3H), 2.69 (m,2H), 3.64 (t,2H), 3.81 (s,3H), 4.02 (s,2H), 4.10 (m,2H), 6.10 (brs,1H), 7.15-7.30 (m,6H), 7.43 (t,1H).

LRMS (APCI): 471 $(M+H)^+$.

PREPARATION 154

4-Phenyl-3-trifluoromethylbromobenzene

Obtained as an orange oil (37%), from 4-bromo-2-trifluoromethylaniline, using the procedure of Preparation 42. Found: C, 51.70; H, 2.61. $C_{13}H_8BrF_3$ requires C, 51.86; H, 2.68%. $\delta(CDCl_3)$: 7.19 (d,1H), 7.26 (m,2H), 7.38 (m,3H), 7.65 (d,1H), 7.86 (s,1H).

PREPARATION 155

t-Butyl 4-hydroxy-4-(4-phenyl-3-trifluoromethylphenyl)piperidine-1-carboxylate

Obtained as a colourless solid (53%), m.p. 153-155°C (from hexane), from the title compound of Preparation 154 and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43. Found: C, 65.34; H, 6.22; N, 3.26. $C_{23}H_{26}F_3NO_3$ requires C, 65.55; H, 6.22; N, 3.32%. $\delta(CDCl_3)$: 1.50 (s,9H), 1.78 (d,2H), 2.04 (m,2H), 3.28 (t,2H), 4.10 (m,2H), 7.28-7.42 (m,6H), 7.66 (d,1H), 7.88 (s,1H).

LRMS (Thermospray): 422 $(M+H)^+$.

PREPARATION 156

4-(4-Phenyl-3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine

Obtained as a pale brown oil (90%), from the title compound of Preparation 155 and p-toluenesulphonic acid, using the procedure of Preparation 70. $\delta(CDCl_3)$: 2.50 (m,2H), 3.17 (t,2H), 3.58 (m,2H), 6.27 (brs,1H), 7.25-7.42 (m,6H), 7.56 (d,1H), 7.75 (s,1H).

LRMS (Thermospray): 304 $(M+H)^+$.

PREPARATION 157

Methyl 2-[4-(4-phenyl-3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetate

Obtained as a pale yellow oil (59%), from the title compound of Preparation 156 and methyl chlorosulphonylacetate, using the procedure of Preparation 37. $\delta(CDCl_3)$: 2.71 (m,2H), 3.66 (t,2H), 3.82 (s,3H), 4.02 (s,2H), 4.12 (m,2H), 6.18 (brs,1H), 7.28-7.42 (m,6H), 7.55 (d,1H), 7.72 (s,1H). LRMS (APCI): 440 $(M+H)^+$.

PREPARATION 158

2,2-Dimethyl-1,3-benzodioxol-5-ylboronic acid

Obtained as a green solid (47%), m.p. 174-176°C, from 5-bromo-2,2-dimethyl-1,3-benzodioxole (GB-A-2187452) and trimethyl borate, using the procedure of Preparation 101. $\delta(DMSO_{d6})$: 1.60 (s,6H), 6.77 (d,1H), 7.17 (s,1H), 7.28 (d,1H), 7.80 (s,2H).

PREPARATION 159

Methyl 2-{4-[4-(2,2-dimethyl-1,3-benzodioxol-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a colourless, amorphous solid (33%), from the title compounds of Preparation 158 and Preparation 40, using the procedure of Preparation 41, but with ether:hexane (1:4) as eluant. $\delta(CDCl_3)$: 1.67 (s,6H), 1.73 (s,6H), 2.30 (s,3H), 2.65 (m,2H), 3.62 (t,2H), 3.80 (s,3H), 4.13 (m,2H), 6.05 (brs,1H), 6.70-6.78 (m,3H), 7.19-7.30 (m,3H).
LRMS (Thermospray): 486 $(M+H)^+$.

PREPARATION 160

Methyl 2-{4-[4-(2,2-dimethyl-1,3-benzodioxol-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a colourless, amorphous solid (96%), from the title compound of Preparation 159, using the procedure of Preparation 90. $\delta(CDCl_3)$: 1.64 (s,6H), 1.72 (s,6H), 1.78-1.88 (m,4H), 2.27 (s,3H), 2.63 (m,1H), 3.09 (m,2H), 3.81 (s,3H), 3.98 (d,2H), 6.68-6.77 (m,3H), 7.07 (m,2H), 7.17 (d,1H).

LRMS (Thermospray): 488 $(M+H)^+$.

PREPARATION 161

2-{4-[4-(2,2-Dimethyl-1,3-benzodioxol-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

Obtained as a colourless, amorphous solid (47%) from the title compound of Preparation 160, using the procedure of Preparation 79. $\delta(CDCl_3)$: 1.67 (s,6H), 1.72 (s,6H), 1.78-1.88 (m,4H), 2.27 (s,3H), 2.63 (m,1H), 3.10 (m,2H), 4.00 (d,2H), 6.68-6.77 (m,3H), 7.05 (m,2H), 7.16 (d,1H).

LRMS (Thermospray): 474 $(M+H)^+$.

PREPARATION 162

1,2-Dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazole

A mixture of 5-bromo-1,2-dimethylbenzimidazole (J. Chem. Soc., 1931, 1143; 2 g, 8.88 mmol), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.06 ml, 14 mmol), triethylamine (3.9 ml, 28 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium(II) (224 mg, 0.27 mmol) and anhydrous 1,4-dioxan (35ml), under nitrogen, was stirred under reflux for 44 hours, then allowed to cool and partitioned between ethyl acetate and water.

This mixture was filtered to remove palladium residues, the layers separated and the aqueous phase washed with ethyl acetate. The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue was purified by flash chromatography, using methanol:dichloromethane (1:3) as eluant, followed by trituration with diisopropyl ether, to provide the title compound (356 mg, 15%) as a colourless, amorphous solid. $\delta(CDCl_3)$: 1.37 (s,12H), 2.60 (s,3H), 3.72 (s,3H), 7.27 (d,1H), 7.70 (d,1H), 8.15 (s,1H).

LRMS (Thermospray): 273 $(M+H)^+$.

PREPARATION 163

Methyl 2-{4-[4-(1,2-dimethylbenzimidazol-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

To a stirred solution of the title compound of Preparation 40 (400 mg, 0.96 mmol) in degassed 1,2-dimethoxyethane (20 ml) was added the title compound of Preparation 162 (351 mg, 1.29 mmol), cesium fluoride (380 mg, 2.5 mmol), tri-o-tolylphosphine (31 mg, 0.1 mmol) and tris(dibenzylideneacetone)dipalladium(0) (47 mg, 0.05 mmol), then the reaction mixture heated under reflux for about 3 hours, under nitrogen. Because of limited solubility, a portion of 1-methylpyrrolidin-2-one (4 ml) was added and the resulting mixture refluxed for 9 hours, then allowed to cool to room temperature, diluted with ethyl acetate, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using an elution gradient of methanol:dichloromethane (0:100 to 2:98), followed by crystallisation from diisopropyl ether, to furnish the title compound (261 mg, 56%) as a colourless solid, m.p. 148-151°C. $\delta(CDCl_3)$: 1.67 (s,6H), 2.30 (s,3H), 2.63 (s,3H), 2.67 (m,2H), 3.63 (m,2H), 3.77 (s,3H), 3.81 (s,3H), 4.13 (m,2H), 6.07 (brs,1H), 7.19-7.32 (m,5H), 7.62 (s,1H).

LRMS (Thermospray): 482 $(M+H)^+$.

PREPARATION 164

Methyl 2-{4-[4-(1,2-dimethylbenzimidazol-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a pale yellow gum (32%), from the title compound of Preparation 163, using the procedure of Preparation 90, except that the hydrogenation was conducted at 414 kPa (60 psi) and 70°C for 24 hours and methanol:dichloromethane (3:97) was used as chromatography eluant.

$\delta(CDCl_3)$: 1.65 (s,6H), 1.78-1.88 (m,4H), 2.27 (s,3H), 2.62 (s,3H), 2.65 (m,1H), 3.09 (m,2H), 3.75 (s,3H), 3.81 (s,3H), 3.97 (m,2H), 7.05-7.32 (m,5H), 7.61 (s,1H).

LRMS (Thermospray): 484 $(M+H)^+$.

PREPARATION 165

2-{4-[4-(1,2-Dimethylbenzimidazol-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

Obtained as a colourless solid (88%), m.p. 125-127°C, from the title compound of Preparation 164, using the procedure of Preparation 91.

$\delta(DMSO_{d6})$: 1.50 (s,6H), 1.62 (m,2H), 1.82 (m,2H), 2.20 (s,3H), 2.70 (m,1H), 2.78 (s,3H), 3.08 (t,2H), 3.81 (d,2H), 3.92 (s,3H), 7.10-7.20 (m,3H), 7.46 (d,1H), 7.65 (s,1H), 7.88 (d,1H).

LRMS (Thermospray): 471 $(M+H)^+$.

PREPARATION 166

2-[4-(4-Bromo-3-methylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-2-methylpropanoic acid

1M Aqueous sodium hydroxide solution (4.2 ml, 4.2 mmol) was added to

a stirred solution of the title compound of Preparation 40 (500 mg, 1.2 mmol) in a mixture of methanol (3 ml) and 1,4-dioxan (3 ml). The resulting solution was heated at 50°C for 2 hours, then allowed to cool to room temperature and poured into ethyl acetate. The mixture was washed with 2M hydrochloric acid, then the organic phase dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound (439 mg, 91%) as a colourless, amorphous solid. $\delta(CDCl_3)$: 1.67 (s,6H), 2.40 (s,3H), 2.58 (m,2H), 3.64 (t,2H), 4.11 (m,2H), 6.00 (brs,1H), 7.03 (d,1H), 7.21 (d,1H), 7.48 (d,1H).

LRMS (Electrospray): 425 $(M+Na)^+$.

PREPARATION 167

N-Benzyloxy 2-[4-(4-bromo-3-methylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-2-methylpropionamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (274 mg, 1.43 mmol) was added to a stirred mixture of the title compound of Preparation 166 (439 mg, 1.19 mmol), N-hydroxybenzotriazole (176 mg, 1.3 mmol), O-benzylhydroxylamine hydrochloride (200 mg, 1.25 mmol), N-methylmorpholine (0.29 ml, 2.62 mmol) and anhydrous dichloromethane (8 ml). The reaction mixture was stirred at room temperature for 18 hours, diluted with dichloromethane, washed sequentially with dilute aqueous citric acid, water and aqueous sodium bicarbonate solution, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was flash chromatographed, using an elution gradient of methanol:dichloromethane (1:99 to 2:98), to give the title compound (553 mg, 91%) as a colourless oil. $\delta(CDCl_3)$: 1.60 (s,6H), 2.40 (s,3H), 2.53 (m,2H), 3.58 (t,2H), 4.04 (m,2H), 4.93 (s,2H), 5.95 (brs,1H), 7.00 (d,1H), 7.20 (s,1H), 7.36-7.50 (m,6H), 9.20 (brs,1H).

LRMS (Electrospray): 531 $(M+Na)^+$.

PREPARATION 168

N-Benzyloxy 2-{4-[4-(3-cyanophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropionamide

Obtained as an amorphous solid (30%), from the title compound of Preparation 167 and 3-cyanophenylboronic acid (Arch. Pharm. 1996, 329, 73), using the procedure of Preparation 41, but using an elution gradient of ethyl acetate:pentane (10:90 to 50:50) for the flash chromatographic purification step. $\delta(CDCl_3)$: 1.60 (s,6H), 2.24 (s,3H), 2.61 (m,2H), 3.60 (t,2H), 4.08 (m,2H), 4.95 (s,2H), 6.03 (brs,1H), 7.15 (d,1H), 7.25 (m,2H), 7.40 (m,5H), 7.55 (m,2H), 7.62 (m,2H), 9.20 (s,1H).

LRMS (Thermospray): 530 $(M+H)^+$.

PREPARATION 169

3-Ethoxy-5-(tri-n-butylstannyl)pyridine

A stirred mixture of 3-bromo-5-ethoxypyridine (Rec. Trav. chim., 1948, 67, 377; 930 mg, 4.6 mmol), bis(tri-n-butyltin) (3.46 ml, 6.9 mmol), tri-o-tolylphosphine (420 mg, 1.37 mmol), palladium(II) acetate (78 mg, 0.35 mmol), triethylamine (1.23 ml, 8.84 mmol) and acetonitrile (15 ml), under nitrogen, was heated under reflux for 18 hours, then allowed to cool. The solution was decanted from the black, tarry residue and evaporated under reduced pressure, then the resulting residue flash chromatographed, using an elution gradient of ethyl acetate:pentane (0:100 to 5:95), to yield the title compound (600 mg, 32%) as a colourless oil. $\delta(CDCl_3)$: 0.90 (t,9H), 1.08 (t,6H), 1.30-1.42 (m,6H), 1.42 (t,3H), 1.58 (m,6H), 4.08 (q,2H), 7.25 (s,1H), 8.17 (s,1H), 8.19 (s,1H).

PREPARATION 170

Methyl 2-{4-[4-(3-ethoxypyridin-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a gum (30%), from the title compounds of Preparation 169 and Preparation 40, using the procedure of Preparation 89. $\delta(CDCl_3)$: 1.46 (t,3H), 1.68 (s,6H), 2.28 (s,3H), 2.65 (m,2H), 3.63 (m,2H), 3.81 (s,3H), 4.10 (m,4H), 6.08 (brs,1H), 7.12 (s,1H), 7.20 (d,1H), 7.28 (m,2H), 8.18 (s,1H), 8.28 (s,1H).

LRMS (APCI): 459 $(M+H)^+$.

PREPARATION 171

Methyl 2-{4-[4-(3-ethoxypyridin-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a colourless solid (88%), m.p. 110-112°C, from the title compound of Preparation 170, using the procedure of Preparation 66. Found: C, 62.24; H, 6.96; N, 5.97. $C_{24}H_{32}N_2O_5S$ requires C, 62.59; H, 7.00; N, 6.08%. $\delta(CDCl_3)$: 1.44 (t,3H), 1.67 (s,6H), 1.82 (m,2H), 1.89 (m,2H), 2.28 (s,3H), 2.67 (m,1H), 3.08 (m,2H), 3.81 (s,3H), 3.96 (m,2H), 4.12 (q,2H), 7.10-7.20 (m,4H), 8.17 (s,1H), 8.27 (s,1H).

LRMS (Electrospray): 461 $(M+H)^+$.

PREPARATION 172

2-{4-[4-(3-Ethoxypyridin-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methyl-propanoic acid

Obtained as a colourless solid (98%), m.p. 202-203°C, from the title compound of Preparation 171, using the procedure of Preparation 91. $\delta(CDCl_3)$: 1.44 (t,3H), 1.70 (s,6H), 1.80 (m,4H), 2.18 (s,3H), 2.60 (m,1H), 3.08

(m,2H), 3.96 (m,2H), 4.13 (q,2H), 7.05-7.15 (m,3H), 7.26 (obscured by $CHCl_3$, 1H), 8.22 (s,1H), 8.33 (s,1H).

LRMS (Thermospray): 447 $(M+H)^+$.

PREPARATION 173

3-(2-Hydroxyethoxy)bromobenzene

Anhydrous potassium carbonate (18.0 g, 130 mmol) was added to a stirred solution of 3-bromophenol (6.0 ml, 52 mmol) in anhydrous dimethylformamide (120 ml) and the mixture was heated under reflux for 45 minutes, then allowed to cool to about 50°C. 2-Bromoethanol (3.1 ml, 43 mmol) was added and the reaction mixture heated under reflux for a further 2 hours, before being allowed to slowly cool to room temperature. The resulting mixture was poured into ether, the mixture washed with water and the organic phase dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography, using an elution gradient of pentane:ethyl acetate (10:1 to 5:1), to provide the title compound as a colourless oil (6.4 g, 57%). $\delta(CDCl_3)$: 1.98 (t,1H), 3.95 (t,2H), 4.07 (m,2H), 6.87 (d,1H), 7.08-7.17 (m,3H).

PREPARATION 174

3-(2-t-Butyldiphenylsilyloxyethoxy)bromobenzene

Triethylamine (1.7 ml, 9.2 mmol) was added to a stirred solution of the title compound of Preparation 173 (1.8 g, 8.2 mmol) in anhydrous dimethylformamide (30 ml) and the mixture was cooled to about 0°C. t-Butyldiphenylsilyl chloride (2.4 ml, 9.2 mmol) was added and the reaction mixture stirred at 0°C for 1 hour and at room temperature for about 16 hours, then poured into ether. The resulting mixture was washed with 0.5M hydrochloric acid, then the aqueous washings back-washed with ether. The

combined organic solutions were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using an elution gradient of pentane:dichloromethane (3:1 to 2:1 to 1:1), to furnish the title compound as a colourless oil (2.2 g, 62%).
$\delta(CDCl_3)$: 1.10 (s,9H), 4.00 (t,2H), 4.08 (t,2H), 6.82 (m,1H), 7.03-7.29 (m,4H), 7.38-7.48 (m,5H), 7.71 (m,4H).
LRMS (Thermospray): 474 $(M+NH_4)^+$.

PREPARATION 175

3-(2-t-Butyldiphenylsilyloxyethoxy)phenylboronic acid

n-Butyllithium (2.3ml of a 2.5M solution in hexane, 5.9 mmol) was added to a stirred solution of the title compound of Preparation 174 (2.5 g, 5.6 mmol) in anhydrous tetrahydrofuran (25 ml), keeping the internal temperature below -60°C. The reaction mixture was stirred at about -70°C for 1 hour, then trimethylborate (4.4 ml, 38 mmol) was added dropwise, again keeping the internal temperature below -60°C . The reaction mixture was stirred at -70°C for 30 min, allowed to slowly warm to room temperature, quenched with a mixture of concentrated hydrochloric acid (12.5 ml) and water (30 ml), then ether (30 ml) added. The layers were separated and the aqueous layer was washed with ether. The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by flash chromatography, using ether as eluant, to afford the title compound as a colourless oil (1.14 g, 50%). $\delta(CDCl_3)$: 1.08 (s,9H), 4.06 (t,2H), 4.19 (t,2H), 7.12 (m,1H), 7.36-7.45 (m,8H), 7.74 (m,6H), 7.82 (m,1H).
LRMS (Thermospray): 438 $(M+NH_4)^+$.

PREPARATION 176

Methyl 2-{4-[4-(3-[2-t-butyldiphenylsilyloxyethoxy]phenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropionate

Obtained as an oil (73%), from the title compounds of Preparation 175 and Preparation 40, using the procedure of Preparation 41, except that purification by flash chromatography involved an elution gradient of pentane:ethyl acetate (10:1 to 5:1). $\delta(CDCl_3)$: 1.07 (s,9H), 1.67 (s,6H), 2.28 (s,3H), 2.65 (m,2H), 3.62 (m,2H), 3.81 (s,3H), 4.02 (m,2H), 4.08-4.16 (m,4H), 6.08 (brs,1H), 6.90 (m,3H), 7.19-7.42 (m,10H), 7.71 (d,4H).
LRMS (Thermospray): 438 $(M+NH_4)^+$.

PREPARATION 177

Methyl 2-{4-[4-(3-[2-t-butyldiphenylsilyloxyethoxy]phenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

Obtained as a colourless oil (88%), from the title compound of Preparation 176, using the procedure of Preparation 66. $\delta(CDCl_3)$: 1.07 (s,9H), 1.67 (s,6H), 1.80-1.95 (m,4H), 2.28 (s,3H), 2.65 (m,1H), 3.10 (t,2H), 3.81 (s,3H), 3.95 (m,2H), 3.97 (t,2H), 4.11 (t,2H), 6.86 (m,3H), 7.10 (m,2H), 7.19 (d,1H), 7.34-7.47 (m,6H), 7.71 (d,4H).
LRMS: (Thermospray): 438 $(M+NH_4)^+$.

PREPARATION 178

2-{4-[4-(3-[2-t-Butyldiphenylsilyloxyethoxy]phenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

Obtained as a colourless foam (88%), from the title compound of Preparation 177, using the procedure of Preparation 79, but with the reaction being carried out at room temperature. $\delta(CDCl_3)$: 1.07 (s,9H), 1.67 (s,6H), 1.78-1.95 (m,4H), 2.27 (s,3H), 2.65 (m,1H), 3.11 (t,2H), 3.97 (t,2H), 4.02 (m,2H), 4.11 (t,2H), 6.86 (m,3H), 7.10 (m,2H), 7.18 (d,1H), 7.30 (d,1H), 7.34-7.43 (m,6H), 7.71 (d,4H).

Biological activity

The following Table illustrates the in vitro activities for a range of the compounds of the invention as MMP inhibitors.

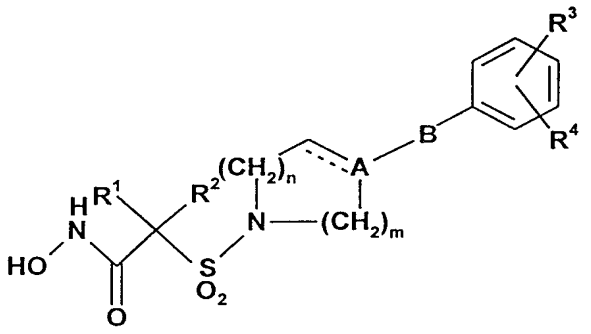
TABLE

EXAMPLE NO.	IC_{50}(nM)		
	MMP-3	MMP-2	MMP-13
2	16	315	28
3	26	38	25
15	20	173	NR
28	24	432	NR
40	18	525	NR
50	23	1907	NR
56	15	387	NR

NR = no result

CLAIMS

1. A compound of formula (I):



(I)

or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity,

wherein the broken line represents an optional bond;

A is C or CH;

B is CH_2, O or absent;

R^1 and R^2 are each independently selected from hydrogen, C_1 to C_6 alkyl optionally substituted with C_1 to C_4 alkoxy or phenyl, and C_1 to C_6 alkenyl; or, together with the carbon atom to which they are attached, form a C_3 to C_6 cycloalkyl group which optionally incorporates a heteroatom linkage selected from O, SO, SO_2 and NR^6 or which is optionally benzo-fused;

R^3 is hydrogen, halo, R^7 or OR^7;

R^4 is hydrogen, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, trifluoromethyl or halo;

R^6 is hydrogen or C_1 to C_4 alkyl;

R^7 is a monocyclic or bicyclic ring system selected from phenyl,

thienyl, furyl, pyridinyl, pyrimidinyl, naphthyl, indanyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, quinolinyl, isoquinolinyl, benzodioxolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl and benzodioxanyl, any of which ring systems is optionally substituted with one or two substituents selected from C_1 to C_4 alkyl optionally substituted with C_1 to C_4 alkoxy or hydroxy, C_1-C_4 alkoxy optionally substituted with C_1 to C_4 alkoxy or hydroxy, C_1 to C_4 alkylthio, trifluoromethyl, trifluoromethoxy, halo and cyano;

m is 1 or 2;

and n is 0, 1 or 2;

with the proviso that B is not O when A is C.

2. A compound according to claim 1 wherein B is absent; R^1 is hydrogen, C_1 to C_4 alkyl optionally substituted with methoxy or phenyl, or C_1 to C_5 alkenyl; R^2 is hydrogen or C_1 to C_4 alkyl; or R^1 and R^2, together with the carbon atom to which they are attached, form a C_4 to C_5 cycloalkyl group which optionally incorporates a heteroatom linkage selected from O and NR^6 or which is optionally benzo-fused; R^3 is selected from 4-phenyl, 4-pyridinyl, 4-(indan-5-yl), 4-(2,3-dihydrobenzofuran-5-yl), 4-(quinolin-3-yl), 4-(benzodioxol-5-yl) and 4-(benzimidazol-5-yl), any of which is optionally substituted with one or two substituents selected from C_1 to C_3 alkyl optionally substituted with methoxy or hydroxy, C_1 to C_3 alkoxy optionally substituted with methoxy or hydroxy, methylthio, trifluoromethyl, trifluoromethoxy, fluoro, chloro and cyano; R^4 is hydrogen, methyl, ethyl, methoxy, trifluoromethyl, fluoro or chloro; R^6 is methyl; m is 2; and n is 1.

3. A compound according to claim 2 wherein R^1 is hydrogen, methyl, ethyl,

2-methylprop-1-yl, but-1-yl, 2-methoxyethyl, benzyl, 3-phenylprop-1-yl, allyl, 2-methylallyl, 3,3-dimethylallyl; R^2 is hydrogen, methyl or ethyl; or R^1 and R^2, together with the carbon atom to which they are attached, form a cyclobutyl, cyclopentyl, tetrahydropyran-4,4-diyl, 1-methylpiperidin-4,4-diyl or indan-2,2-diyl group; R^3 is 4-phenyl, 4-(2-methylphenyl), 4-(3-methylphenyl), 4-(3-ethylphenyl), 4-[3-(prop-2-yl)phenyl], 4-(3,5-dimethylphenyl), 4-(3-methoxymethylphenyl), 4-(3-hydroxymethylphenyl), 4-(2-methoxyphenyl), 4-(3-methoxyphenyl), 4-(3-ethoxyphenyl), 4-(4-ethoxyphenyl), 4-[3-(prop-1-oxy)phenyl], 4-[3-(prop-2-oxy)phenyl], 4-[4-(prop-2-oxy)phenyl], 4-(3,4-dimethoxyphenyl), 4-[3-(2-methoxyethoxy)phenyl], 4-[3-(2-hydroxyethoxy)phenyl], 4-(3-methylthiophenyl), 4-(3-trifluoromethylphenyl), 4-(3-trifluoromethoxyphenyl), 4-(2-fluorophenyl), 4-(3-chloro-4-fluorophenyl), 4-(3-cyanophenyl), 4-(pyridin-2-yl), 4-(pyridin-3-yl), 4-(pyridin-4-yl), 4-(6-ethoxypyridin-2-yl), 4-(5-ethoxypyridin-3-yl), 4-(indan-5-yl), 4-(2,3-dihydrobenzofuran-5-yl), 4-(quinolin-3-yl), 4-(benzodioxol-5-yl), 4-(2,2-dimethylbenzodioxol-5-yl) and 4-(1,2-dimethylbenzimidazol-5-yl); and R^4 is hydrogen, 2-methyl, 3-methyl, 3-ethyl, 3-methoxy, 3-trifluoromethyl, 3-fluoro or 3-chloro.

4. A compound according to claim 3 wherein R^1 and R^2 are both hydrogen or methyl or, together with the carbon atom to which they are attached, form a cyclobutyl, cyclopentyl, tetrahydropyran-4,4-diyl or 1-methylpiperidin-4,4-diyl group; R^3 is 4-phenyl, 4-(3-methoxyphenyl), 4-(3-ethoxyphenyl), 4-[3-(2-methoxyethoxy)phenyl], 4-[3-(2-hydroxyethoxy)phenyl] or 4-(6-ethoxypyridin-2-yl); and R^4 is 3-methyl or 3-methoxy.

5. A compound according to claim 4 wherein the compound of formula (I) is selected from

N-hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-

tetrahydropyridin-1-ylsulphonyl}acetamide;

N-hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanamide;

N-hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide;

N-hydroxy-1-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}cyclopentanecarboxamide;

N-hydroxy-1-{4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}cyclobutanecarboxamide;

N-hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide;

N-hydroxy-2-{4-[4-(6-ethoxypyridin-2-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanamide;

N-hydroxy-2-{4-[4-(3-[2-methoxyethoxy]phenyl)-3-methylphenyl]-piperidin-1-ylsulphonyl}-2-methylpropanamide; and

N-hydroxy-2-{4-[4-(3-[2-hydroxyethoxy]phenyl)-3-methylphenyl]piperidine-1-ylsulphonyl}-2-methylpropanamide.

6. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, according to any one of claims 1 to 5, together with a pharmaceutically acceptable diluent or carrier.

7. A veterinary formulation comprising a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, according to any one of claims 1 to 5, together with a veterinarily acceptable diluent or carrier.

8. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, according to any one of claims 1 to 5, or a pharmaceutical composition containing any of the foregoing according to claim 6, for use as a human medicament.

9. A compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, according to any one of claims 1 to 5, or a veterinary formulation containing any of the foregoing according to claim 7, for use as an animal medicament.

10. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically accceptable solvate of either entity, according to any one of claims 1 to 5, for the manufacture of a human medicament for the curative or prophylactic treatment of a medical condition for which a MMP inhibitor is indicated.

11. The use of a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, according to any one of claims 1 to 5, for the manufacture of an animal medicament for the curative or prophylactic treatment of a medical condition for which a MMP inhibitor is indicated.

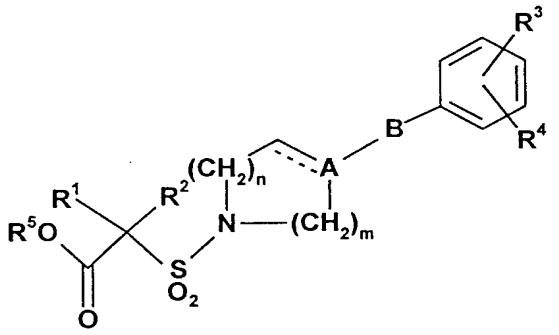
12. The use according to claim 10 or claim 11 wherein the inhibitor is a MMP-3 inhibitor.

13. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, according to any one of claims 1 to 5, for the manufacture of a human medicament for the

curative or prophylactic treatment of atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

14. The use of a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, according to any one of claims 1 to 5, for the manufacture of an animal medicament for the curative or prophylactic treatment of atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

15. A compound of formula (II):



(II)

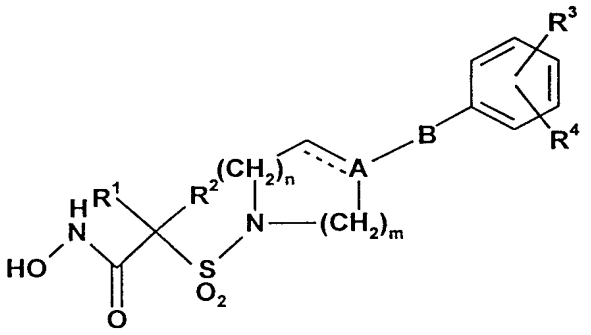
wherein R^5 is hydrogen or C_1 to C_3 alkyl, and the broken line, A,B, R^1, R^2, R^3, R^4, m and n are as previously defined for formula (I) in claim 1.

16. A method of treating or preventing a medical condition for which a MMP inhibitor is indicated, in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, according to any of one claims 1 to 5, or a pharmaceutical composition or veterinary formulation containing any of the foregoing according to claim 6 or claim 7 respectively.

17. A method according to claim 16 wherein the inhibitor is a MMP-3 inhibitor.

18. A method of treating or preventing atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells, in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, according to any one of claim 1 to 5, or a pharmaceutical composition or veterinary formulation containing any of the foregoing according to claim 6 or claim 7 respectively.

19. A process for the preparation of a compound of formula (I):



(I)

or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity,

wherein the broken line represents an optional bond;

A is C or CH;

B is CH_2, O or absent;

R^1 and R^2 are each independently selected from hydrogen, C_1 to C_6 alkyl optionally substituted with C_1 to C_4 alkoxy or phenyl, and C_1 to C_6 alkenyl; or, together with the carbon atom to which they are attached, form a C_3 to C_6 cycloalkyl group which optionally incorporates a heteroatom linkage selected from O, SO, SO_2 and NR^6 or which is optionally benzo-fused;

R^3 is hydrogen, halo, R^7 or OR^7;

R^4 is hydrogen, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, trifluoromethyl or halo;

R^6 is hydrogen or C_1 to C_4 alkyl;

R^7 is a monocyclic or bicyclic ring system selected from phenyl, thienyl, furyl, pyridinyl, pyrimidinyl, naphthyl, indanyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, quinolinyl,

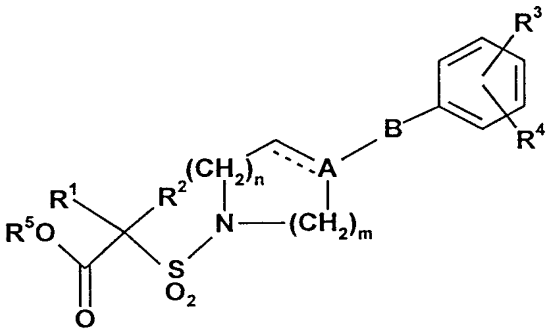
isoquinolinyl, benzodioxolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl and benzodioxanyl, any of which ring systems is optionally substituted with one or two substituents selected from C_1 to C_4 alkyl optionally substituted with C_1 to C_4 alkoxy or hydroxy, C_1-C_4 alkoxy optionally substituted with C_1 to C_4 alkoxy or hydroxy, C_1 to C_4 alkylthio, trifluoromethyl, trifluoromethoxy, halo and cyano;

m is 1 or 2;

and n is 0, 1 or 2;

with the proviso that B is not O when A is C;

which comprises reacting a compound of formula (II):



(II)

wherein R^5 is hydrogen or C_1 to C_3 alkyl, and the broken line, A,B, R^1, R^2, R^3, R^4, m and n are as previously defined for formula (I), with hydroxylamine, optionally followed by formation of a pharmaceutically or veterinarily acceptable salt of the required product or a pharmaceuticallly or veterinarily acceptable solvate of either entity.

20. A process according to claim 19 wherein, when R^5 is C_1 to C_3 alkyl, the ester of formula (II) is treated with up to a 3-fold excess of hydroxylamine hydrochloride in the presence of a molar equivalent amount of a suitable base in a suitable solvent at from about room temperature to about 85°C .

21. A process according to claim 20 wherein the base is an alkali metal carbonate or bicarbonate, the solvent is methanol, optionally combined with tetrahydrofuran or dichloromethane as co-solvent, and the reaction temperature is from about 65 to about 70°C .

22. A process according to claim 19 wherein, when R^5 is hydrogen, the acid of formula (II) in the presence of from 1.1 to 2.0 molecular equivalents of an activating agent and from1.0 to 4.0 molecular equivalents of a tertiary amine, in a suitable solvent, is treated with up to about a 3-fold excess of hydroxylamine hydrochloride, optionally in the same solvent, at from about 0°C to about room temperature.

23. A process according to claim 22 wherein the activating agent is O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), the tertiary amine is N-ethyldiisopropylamine, the solvent is anhydrous dimethylformamide or anhydrous 1-methylpyrrolidin-2-one and the reaction temperature is about room temperature.

INTERNATIONAL SEARCH REPORT

Inte ›nal Application No
PCT/EP 98/06640

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/16 C07D211/22 A61K31/44 C07D211/70 C07D405/12
C07D401/10 C07D405/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 780 386 A (HOFFMANN LA ROCHE ;AGOURON PHARMA (US)) 25 June 1997 cited in the application see abstract	
A	EP 0 606 046 A (CIBA GEIGY AG) 13 July 1994 cited in the application see abstract	

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
27 January 1999	04/02/1999

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	De Jong, B

1

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

INTERNATIONAL SEARCH REPORT

I. .national application No.
PCT/EP 98/06640

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.: 16-18
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 16-18 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 compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

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

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte nal Application No
PCT/EP 98/06640

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		ZA 9400048 A	11-08-1994

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C07D 309/14, 405/12, A61K 31/35

A1

(11) International Publication Number: **WO 99/52889**

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(30) Priority Data:
60/081,364 10 April 1998 (10.04.98) US

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(72) Inventor; and
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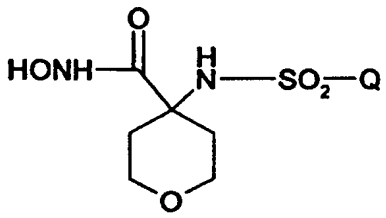
(74) Agents: SPIEGEL, Allen, J. et al.; c/o Simpson, Alison, Urquhart–Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: (4–ARYLSULFONYLAMINO)–TETRAHYDROPYRAN–4–CARBOXYLIC ACID HYDROXAMIDES



(I)

(57) Abstract

A compound of formula (I) wherein Q is as defined, is use in the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro–degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neurophaty, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis and septic shock. In addition, the compounds of the present invention may be used in combination therapy wtih standard non–steroidal anti–inflammatory drugs (NSAID'S) and analgesics, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis–platinum, etoposide, taxol, taxotere and other alkaloids, such as vincristine, in the treatment of cancer.

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BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
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CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
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CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

(4-ARYLSULFONYLAMINO)-TETRAHYDROPYRAN-4-CARBOXYLIC ACID HYDROXAMIDES

Background of the Invention

The present invention relates to (4-arylsulfonylamino)-tetrahydropyran-4-carboxylic acid hydroxamide derivatives , and to pharmaceutical compositions and methods of treatment.

The compounds of the present invention are inhibitors of zinc metalloendopeptidases, especially those belonging to the matrix metalloproteinase (also called MMP or matrixin) and reprolysin (also known as adamylsin) subfamilies of the metzincins (Rawlings, et al., Methods in Enzymology, 248, 183-228 (1995) and Stocker, et al., Protein Science, 4, 823-840 (1995)).

The MMP subfamily of enzymes, currently contains seventeen members (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19, MMP-20). The MMP's are most well known for their role in regulating the turn-over of extracellular matrix proteins and as such play important roles in normal physiological processes such as reproduction, development and differentiation. In addition, the MMP's are expressed in many pathological situations in which abnormal connective tissue turnover is occurring. For example, MMP-13 an enzyme with potent activity at degrading type II collagen (the principal collagen in cartilage), has been demonstrated to be overexpressed in osteoarthritic cartilage (Mitchell, et al., J. Clin. Invest., 97, 761 (1996)). Other MMPs (MMP-2, MMP-3, MMP-8, MMP-9, MMP-12) are also overexpressed in osteoarthritic cartilage and inhibition of some or all of these MMP's is expected to slow or block the accelerated loss of cartilage typical of joint diseases such as osteoarthritis or rheumatoid arthritis.

The mammalian reprolysins are known as ADAMs (A Disintegrin And Metalloproteinase) (Wolfberg, et al., J. Cell Biol., 131, 275-278 (1995)) and contain a disintegrin domain in addition to a metalloproteinase-like domain. To date twenty three distinct ADAM's have been identified.

ADAM-17, also known as tumor necrosis factor-alpha converting enzyme (TACE), is the most well known ADAM. ADAM-17 (TACE) is responsible for cleavage of cell bound tumor necrosis factor-alpha (TNF-α, also known as cachectin). TNF-α is recognized to be involved in many infectious and auto-immune diseases (W. Friers, FEBS Letters, 285, 199 (1991)). Furthermore, it has been shown that TNF-α is the prime mediator of the inflammatory response seen in sepsis and septic shock (Spooner, et al., Clinical Immunology and Immunopathology, 62 S11 (1992)). There are two forms of TNF-α, a type II membrane protein of relative molecular mass 26,000 (26 kD) and a soluble 17 kD form generated from the cell bound protein by specific proteolytic cleavage. The soluble 17 kD form of TNF-α is released by the cell and is associated with the deleterious effects of TNF-α. This form of

TNF-α is also capable of acting at sites distant from the site of synthesis. Thus, inhibitors of TACE prevent the formation of soluble TNF-α and prevent the deleterious effects of the soluble factor.

Select compounds of the invention are potent inhibitors of aggrecanase, an enzyme important in the degradation of cartilage aggrecan. Aggrecanase is also believed to be an ADAM. The loss of aggrecan from the cartilage matrix is an important factor in the progression of joint diseases such as osteoarthritis and rheumatoid arthritis and inhibition of aggrecanase is expected to slow or block the loss of cartilage in these diseases.

Other ADAMs that have shown expression in pathological situations include ADAM TS-1 (Kuno, et al., J. Biol. Chem., 272, 556-562 (1997)), and ADAM's 10, 12 and 15 (Wu, et al., Biochem. Biophys. Res. Comm., 235, 437-442, (1997)). As knowledge of the expression, physiological substrates and disease association of the ADAM's increases the full significance of the role of inhibition of this class of enzymes will be appreciated.

Diseases in which inhibition of MMP's and or ADAM's will provide therapeutic benefit include: arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis, septic shock and other diseases characterized by metalloproteinase or ADAM expression.

This invention also relates to a method of using the compounds of the invention in the treatment of the above diseases in mammals, especially humans, and to the pharmaceutical compositions useful therefore.

It is recognized that different combinations of MMP's and ADAM's are expressed in different pathological situations. As such inhibitors with specific selectivities for individual ADAM's and/or MMP's may be preferred for individual diseases. For example, rheumatoid arthritis is an inflammatory joint disease characterized by excessive TNF levels and the loss

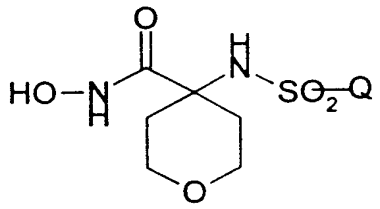
of joint matrix constituents. In this case, a compound that inhibits TACE and aggrecanase as well as MMP's such as MMP-13 may be the preferred therapy. In contrast, in a less inflammatory joint disease such as osteoarthritis, compounds that inhibit matrix degrading MMP's such as MMP-13 but not TACE may be preferred.

The present inventors have also discovered that it is possible to design inhibitors with differential metalloprotease activity. Specifically, for example, the inventors have been able to design molecules which selectively inhibit matrix metalloprotease-13 (MMP-13) preferentially over MMP-1.

Matrix metalloproteinase and reprolysin inhibitors are well known in the literature. Specifically, PCT Publication WO 96/33172, published October 24, 1996, refers to cyclic arylsulfonylamino hydroxamic acids that are useful as MMP inhibitors. United States Patent 5,672,615, PCT Publication WO 97/20824, PCT Publication WO 98/08825, PCT publication WO 98/27069, and PCT Publication WO 98/34918, published August 13, 1998, entitled "Arylsulfonyl Hydroxamic Acid Derivatives" all refer to cyclic hydroxamic acids that are useful as MMP inhibitors. PCT Publications WO 96/27583 and WO 98/07697, published March 7, 1996 and February 26, 1998, respectively, refer to arylsulfonyl hydroxamic acids. PCT Publication WO 98/03516, published January 29, 1998 refers to phosphinates with MMP activity. PCT Publication 98/34915, published August 13, 1998, entitled "N-Hydroxy-b-Sulfonyl Propionamide Derivatives," refers to propionylhydroxamides as useful MMP inhibitors. PCT Publication WO 98/33768, published August 6, 1998, entitled "Arylsulfonylamino Hydroxamic Acid Derivatives," refers to N-unsubstituted arylsulfonylamino hydroxamic acids. PCT Publication WO 98/30566, published July 16, 1998, entitled "Cyclic Sulfone Derivatives," refers to cyclic sulfone hydroxamic acids as MMP inhibitors. United States Provisional Patent Application 60/55208, filed August 8, 1997, refers to biaryl hydroxamic acids as MMP inhibitors. United States Provisional Patent Application Serial No. 60/55207, filed August 8, 1997, entitled "Aryloxyarylsulfonylamino Hydroxamic Acid Derivatives," refers to aryloxyarylsulfonyl hydroxamic acids as MMP inhibitors. United States Provisional Patent Application 60/62766, filed October 24, 1997, entitled "The Use of MMP-13 Selective Inhibitors For The Treatment of Osteoarthritis and Other MMP Mediated Disorders," refers to the use of MMP-13 selective inhibitors to treat inflammation and other disorders. United States Provisional Patent Application Serial No. 60/68261, filed December 19, 1997, refers to the use of MMP inhibitors to treat angiogenesis and other disorders. Each of the above referenced publications and applications is hereby incorporated by reference in its entirety.

Summary of the Invention

The present invention relates to a compound of the formula



I

or the pharmaceutically acceptable salts thereof, wherein

Q is $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl or $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl;

wherein each $(C_6\text{-}C_{10})$aryl or $(C_2\text{-}C_9)$heteroaryl moieties of said $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl or $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents per ring independently selected from fluoro, chloro, bromo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, perfluoro$(C_1\text{-}C_3)$alkyl, perfluoro$(C_1\text{-}C_3)$alkoxy and $(C_6\text{-}C_{10})$aryloxy;

or a pharmaceutically acceptable salt thereof.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents selected from the group consisting of fluoro, chloro, bromo, perfluoro(C_1-C_6)alkyl (including trifluoromethyl), (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, perfluoro(C_1-C_3)alkoxy (including trifluoromethoxy and difluoromethoxy) and (C_1-C_6)alkyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyrroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl. Preferred heteroaryls include pyridyl, furyl, thienyl, isothiazolyl, pyrazinyl, pyrimidyl, pyrazolyl, isoxazolyl, thiazolyl or oxazolyl. Most preferred include pyridyl, furyl or thienyl.

Preferred compounds of formula I include those wherein Q is optionally substituted (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, or (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_6-C_{10})aryl.

Other preferred compounds of formula I include those wherein Q is optionally substituted (C_6-C_{10})aryloxy(C_6-C_{10})aryl.

Specific preferred compounds of formula I include the following:

4-[4-(4-Fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(4-Chlorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(Phenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(4-Pyridyloxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(4-Fluorophenyl)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(4-Fluorophenylmethoxy)bezenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(Phenylmethoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide; and

4-[4-(4-Fluorophenylethoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide.

The present invention also relates to a pharmaceutical composition for the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer breast cancer, lung cancer and prostrate cancer and hematopoietic malignancies including leukemias and lymphomas), tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis, septic shock and other diseases characterized by metalloproteinase activity and other diseases characterized by mammalian reprolysin activity in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition for the inhibition of (a) matrix metalloproteinases or other metalloproteinases involved in matrix degradation, or (b) a mammalian reprolysin (such as aggrecanase or ADAM's TS-1, 10, 12, 15 and 17, most preferably ADAM-17) in a mammal, including a human, comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease,

Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis, septic shock and other diseases characterized by metalloproteinase activity and other diseases characterized by mammalian reprolysin activity in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or other metalloproteinases involved in matrix degradation, or (b) a mammalian reprolysin (such as aggrecanase or ADAM's TS-1, 10, 12, 15 and 17, preferably ADAM-17) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of matrix metalloproteinases or the inhibition of mammalian reprolysin comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF-α inhibitors such as anti-TNF monoclonal antibodies and TNF receptor immunoglobulin molecules (such as Enbrel®), low dose methotrexate, lefunimide, hydroxychloroquine, d-penicilamine, auranofin or parenteral or oral gold.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib and rofecoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, and antimetabolites such as methotrexate.

The compounds of the present invention may also be used in combination with cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

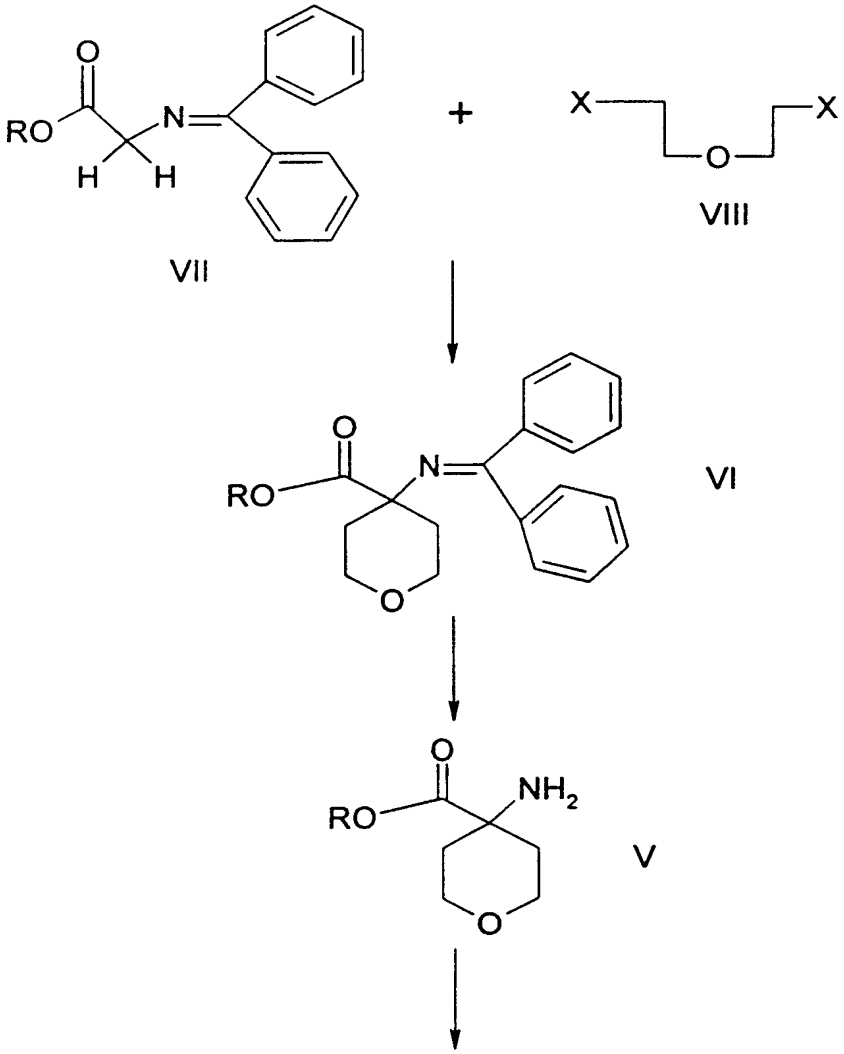
The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, requip, miratex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as Aricept, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The compounds of the present invention may also be used in combination with osteoporosis agents such as droloxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

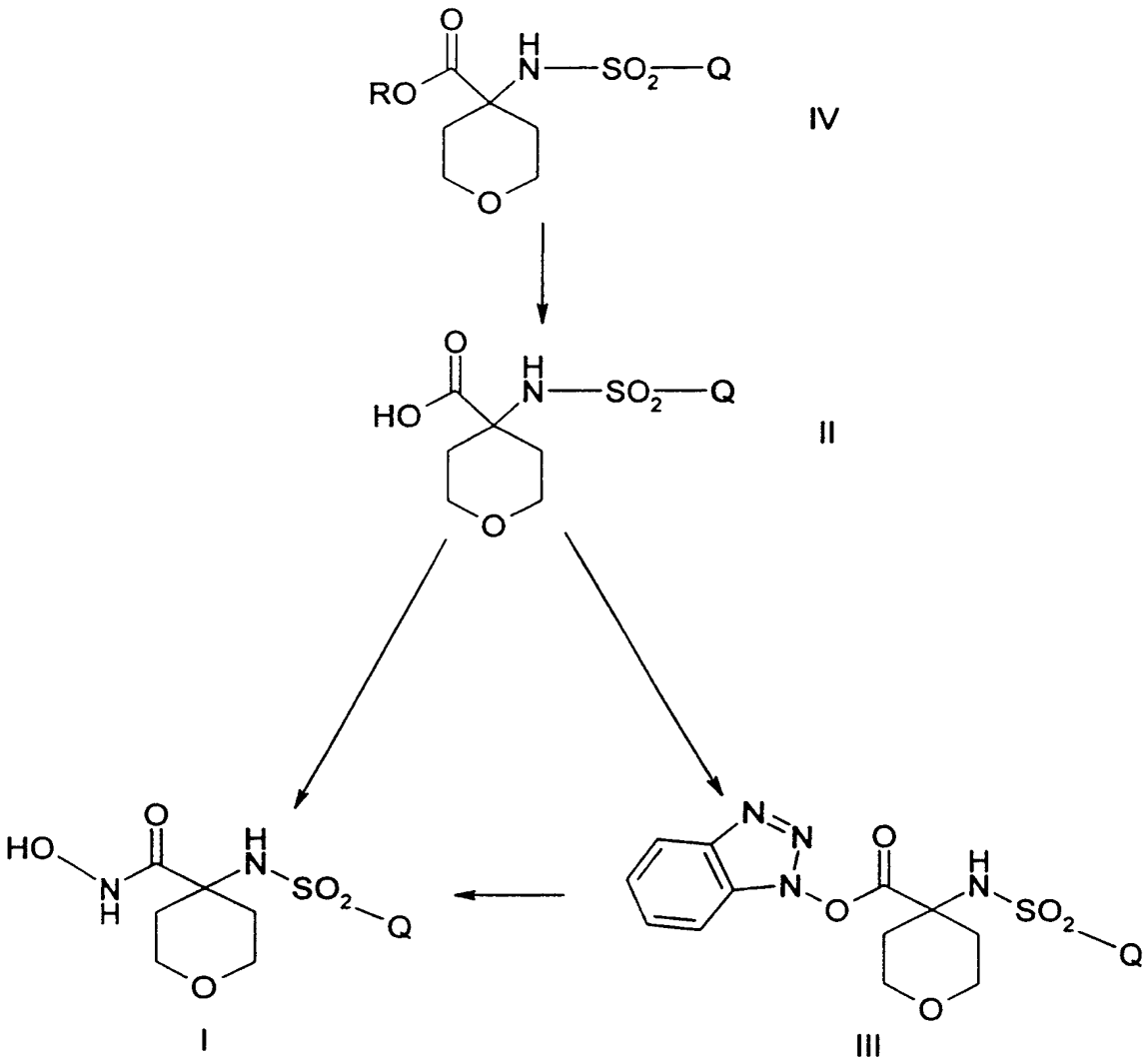
Detailed Description of the Invention

The following reaction Scheme illustrates the preparation of the compounds of the present invention. Unless otherwise indicated, Q in the reaction Schemes and the discussion that follows is defined as above.

Scheme 1



Scheme 1 (continued)



Scheme 1 refers to the preparation of compounds of the formula I.

Referring to Scheme 1, the compound of formula I is prepared from the carboxylic acid of formula II by treatment with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenztriazole in a polar solvent, such as N,N-dimethylformamide, followed by the addition of hydroxylamine to the reaction mixture after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The hydroxylamine is preferably generated in situ from a salt form, such as hydroxylamine hydrochloride, in the presence of a base, such as triethylamine.

Alternatively the compound of formula I can be prepared from a compound of formula II by reaction with a protected derivative of hydroxylamine or its salt form, where the hydroxyl group is protected as a tert-butyl, benzyl, allyl or 2-trimethylsilylethyl ether. Removal of the hydroxyl protecting group is carried out by hydrogenolysis for a benzyl protecting group (5% palladium on barium sulfate is the preferred catalyst) or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium(II)chloride. The 2-trimethylsilylethyl ether may be removed by reaction with a strong acid such as trifluoroacetic acid or by reaction with a fluoride source such as boron trifluoride etherate.

The reaction of II with hydroxylamine, a salt of hydroxylamine, a protected derivative of hydroxylamine or a salt of a protected derivative of hydroxylamine may also be carried out in the presence of (benztriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate and a base such as triethylamine in an inert solvent, such as methylene chloride. The reaction mixture is stirred at a temperature between about 0°C to about 50°C, preferably room temperature, for a time period between about 1 hour to about 3 days, preferably about 1 day.

Another procedure for converting a compound of formula II to a compound of formula I is to react the compound of formula II with O-benzylhydroxylamine hydrochloride in the presence of (benztriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate and triethylamine using methylene chloride as solvent. Subsequent removal of the O-benzyl protecting group to afford a compound of formula I is then carried out by hydrogenolysis under 3 atmospheres hydrogen at room temperature using 5% palladium on barium sulfate as catalyst. The preferred solvent is methanol. The reaction time may vary from about 1 hour to about 2 days (8 hours is preferred).

The preferred procedure for converting a compound of formula II to a compound of formula I is to react the compound of formula II with oxalyl chloride in methylene chloride in the presence of a catalytic amount of DMF for 16 hours. The resulting acid chloride is reacted at 0°C with N, O- bis trimethylsilyl hydroxylamine formed by reacting hydroxyamine hydrochloride with chlorotrimethyl-silane in pyridine at 0°C to room temperature. The product of formula I is

obtained after a few hours reactions at 0°C to room temperature followed by an acidic aqueous workup which removes all trimethyl silyl residues.

In certain instances it is preferred to obtain the compound of formula **I** by reaction of hydroxylamine, a salt of hydroxylamine, a protected derivative of hydroxylamine or a salt of a protected derivative of hydroxylamine with an activated ester of formula **III**. The reaction is carried out in an inert solvent, such as N,N-dimethyl-formamide at a temperature ranging from about room temperature to about 80°C, preferably about 60°C for a time period of about 1 hour to about 2 days. If a protected derivative of hydroxylamine or a salt of a protected derivative of hydroxylamine is used, removal of the protecting group is carried out as described above. The activated ester derivative of formula **III** is obtained by treatment of the compound of formula **II** with (benztriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate and a base such as triethylamine in an inert solvent, such as methylene chloride. The reaction mixture is stirred at a temperature between about 0°C to about 50°C, preferably room temperature, for a time period between about 1 hour to about 3 days, preferably about 1 day.

The intermediate compound of formula **II** is prepared by saponification of a compound of formula **IV**. The reaction is carried out at in a solvent, such as aqueous ethanol, with an excess of a metal hydroxides, such as sodium hydroxide or lithium hydroxide, at a temperature of about 20° C to about 100° C, (i.e. room temperature to the reflux temperature of the solvent), preferably about 80° C. The reaction mixture is normally agitated at room temperature for a time period between about 30 minutes to about 1 week, preferably about 16 hours.

The compound of formula **IV** is prepared by reacting a compound of formula **V** with a reactive functional derivative of a sulfonic acid (QSO_2OH), such as the sulfonyl chloride (QSO_2Cl), in the presence of a base. Suitable bases include sodium hydroxide, triethylamine or diisopropylethylamine, preferably triethylamine. Suitable solvents include dimethylformamide (DMF), methylene chloride, tetrahydrofuran, dioxane, water or acetonitrile, preferably DMF. The reaction mixture is stirred at a temperature between about 0°C to about 50°C, preferably at about 20°C to about 25°C (i.e. room temperature), for a time period between about 10 minutes to about 2 days, preferably about 1 day.

The compound of formula **V** is prepared by hydrolysis of a compound of formula **IV**. Specifically, the compound of formula **VI** is treated with aqueous acid, preferably in the presence of an immiscible organic solvent such ethyl ether, diisopropyl ether or methylene chloride. Suitable acids include hydrochloric and sulfuric. The reaction mixture is stirred at a temperature between about 0°C to about 50°C, preferably at about 20°C to about 25°C (i.e. room temperature), for a time period between about 10 minutes to about 2 days, preferably about 1 day.

The compound of formula **VI** is prepared by reaction of the amino acid derivative of the formula **VII** with a compound of the formula **VIII** in the presence of a base and a solvent, wherein X is Cl, Br, I, tosylate or mesylate. Suitable bases include ethlyene glycol, sodium hydride, lithium diisopropylamide, or sodium hexamethyl disilazide. Suitable solvents include dimethylether, dimethylformamide, tetrahydrofuran or dimethylsulfoxide. The reaction mixture is stirred at a temperature between about -20°C to about 25°C, preferably at about 0°C to about 20°C (i.e. room temperature), for a time period between about 10 minutes to about 2 days, preferably about 1 day.

The compounds of formulae **VII** and **VIII** can be prepared by methods well known to those of ordinary skill in the art. Examples of such compounds include methylglycine benzophenone imine and ethyl glycine benzophenone imine.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium slats.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit metalloproteinases or mammalian reprolysin and, consequently, demonstrate their effectiveness for treating diseases characterized by metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin. The amount of trypsin is optimized for each lot of collagenase-1 but a typical reaction uses the following ratio: 5 μg trypsin per 100 μg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted using the following scheme:

10 mM ——> 120 μM ——> 12 μM ——> 1.2 μM ——> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after

addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D7-D12 and negative controls (no enzyme, no inhibitors) are set in wells D1-D6.

Collagenase-1 is diluted to 240 ng/ml and 25 ml is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 60 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethylsulfoxide and then diluted to 20 μM in assay buffer. The assay is initiated by the addition of 50 ml substrate per well of the microfluor plate to give a final concentration of 10 mM.

Fluorescence readings (360 nM excitation, 460 nm emission) are taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours

Fluorescence versus time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (at least five fold over the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration versus % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be less than 0.03 mM then the inhibitors are assayed at concentrations of 0.3 mM, 0.03 mM, and 0.003 mM.

Inhibition of Gelatinase (MMP-2)

Human recombinant 72 kD gelatinase (MMP-2, gelatinase A) is activated for 16-18 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 4°C, rocking gently.

10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM $CaCl_2$, 20 μM $ZnCl_2$ and 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM ⟶ 120 μM ⟶ 12 μM ⟶ 1.2 μM ⟶ 0.12 μM

Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μL of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μL, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μM ⟶ 3 μM ⟶ 0.3 μM ⟶ 0.03 μM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 µL per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 25 ng/mL (0.34 nM).

A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2) is diluted in assay buffer to 20 µM. The assay is initiated by addition of 50 µL of diluted substrate yielding a final assay concentration of 10 µM substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC_{50}'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of Stromelysin Activity (MMP-3)

Human recombinant stromelysin (MMP-3, stromelysin-1) is activated for 20-22 hours with 2 mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37°C.

10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 150 mM NaCl, 10 mM $CaCl_2$ and 0.05% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM ⟶ 120 µM ⟶ 12 µM ⟶ 1.2 µM ⟶ 0.12 µM

Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 µL of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 µL, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 µM ⟶ 3 µM ⟶ 0.3 µM ⟶ 0.03 µM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

Activated enzyme is diluted to 200 ng/mL in assay buffer, 25 µL per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 50 ng/mL (0.875 nM).

A ten mM dimethylsulfoxide stock solution of substrate (Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH_2) is diluted in assay buffer to 6 µM. The assay is initiated by

addition of 50 µL of diluted substrate yielding a final assay concentration of 3 µM substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC_{50}'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 2.0 hours, at 37°C and is diluted to 240 ng/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20mM zinc chloride, 0.02% brij 35). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 60 ng/ml.

Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase-1 (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 mM, 3mmM, 0.3m mM, and 0.03 mmM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 µl is added to each well to give a final assay concentration of 10 µM. Fluorescence readings (360 nM excitation; 450 nM emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls and negative controls are set up in triplicate as outlined in the MMP-1 assay.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 mM, inhibitors are then assayed at final concentrations of 0.3 mM, 0.03 mmM, 0.003 mmM and 0.0003 mM.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180 µl of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100 ng/ml final concentration) gave a final volume of 200 µl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFa using the R&D ELISA Kit.

Inhibition of Soluble TNF-α Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the cellular release of TNF-α and, consequently, demonstrate their effectiveness for treating diseases involving the disregulation of soluble TNF-α is shown by the following in vitro assay:

Method for the evaluation of recombinant TNF-α Converting Enzyme Activity

Expression of recombinant TACE

A DNA fragment coding for the signal sequence, preprodomain, prodomain and catalytic domain of TACE (amino acids 1-473), can be amplified by polymerase chain reaction using a human lung cDNA library as a template. The amplified fragment is then cloned into pFastBac vector. The DNA sequence of the insert is confirmed for both the strands. A bacmid prepared using pFastBac in E. coli DH10Bac is transfected into SF9 insect cells. The virus particles is then amplified to P1, P2, P3 stages. The P3 virus is infected into both Sf9 and High Five insect cells and grown at 27°C for 48 hours. The medium is collected and used for assays and further purification.

Preparation of fluorescent quenched substrate:

A model peptidic TNF-α substrate (LY-LeucineAlanineGlutamineAlanineValine-ArginineSerine-SerineLysine(CTMR)-Arginine (LY=Lucifer Yellow; CTMR=Carboxytetramethyl-Rhodamine)) is prepared and the concentration estimated by absorbance at 560 nm (E_{560}, 60,000 M-1CM-1) according to the method of Geoghegan, KF, "Improved method for converting an unmodified peptide to an energy-transfer substrate for a

proteinase." Bioconjugate Chem. 7, 385-391 (1995). This peptide encompasses the cleavage cite on pro-TNF which is cleaved in vivo by TACE.

Expression of recombinant TACE

A DNA fragment coding for the signal sequence, preprodomain, prodomain and catalytic domain of TACE (amino acids 1-473), is amplified by polymerase chain reaction using a human lung cDNA library as a template. The amplified fragment is cloned into pFastBac vector. The DNA sequence of the insert is confirmed for both the strands. A bacmid prepared using pFastBac in E. coli DH10Bac is transfected into SF9 insect cells. The virus particles were amplified to P1, P2, P3 stages. The P3 virus is infected into both Sf9 and High Five insect cells and grown at 27°C for 48 hours. The medium is collected and used for assays and further purification.

Enzyme reaction.

The reaction, carried out in a 96 well plate (Dynatech), is comprised of 70 µl of buffer solution (25 mM Hepes-HCl, pH7.5, plus 20 uM $ZnCl_2$), 10 µl of 100 µM fluorescent quenched substrate, 10 µl of a DMSO (5%) solution of test compound, and an amount of r-TACE enzyme which will cause 50% cleavage in 60 minutes - in a total volume of 100 µl. The specificity of the enzyme cleavage at the amide bond between alanine and valine is verified by HPLC and mass spectrometry. Initial rates of cleavage are monitored by measuring the rate of increase in fluorescence at 530 nm (excitation at 409 nm) over 30 minutes. The experiment is controlled as follows: 1) for background fluorescence of substrate; 2) for fluorescence of fully cleaved substrate; 3) for fluorescence quenching or augmentation from solutions containing test compound.

Data is analyzed as follows. The rates from the non-test compound containing "control" reactions were averaged to establish the 100% value. The rate of reaction in the presence of test compound was compared to that in the absence of compound, and tabulated as "percent of non-test compound containing control. The results are plotted as "% of control" vs. the log of compound concentration and a half-maximal point or IC_{50} value determined.

All of the compounds of the invention have IC_{50} of less than 1 µM, preferably less than 50nM. Most preferred compounds of the invention are at least 100 fold less potent against r-MMP-1 than in the above TACE assay.

Human Monocyte Assay

Human mononuclear cells are isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells are washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn

3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180m of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100 ng/ml final concentration) gave a final volume of 200 µl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNF-α using the R&D ELISA Kit.

Aggrecanase Assay

Primary porcine chondrocytes from articular joint cartilage are isolated by sequential trypsin and collagenase digestion followed by collagenase digestion overnight and are plated at 2 X 10^5 cells per well into 48 well plates with 5 µCi / ml ^{35}S (1000 Ci/mmol) sulphur in type I collagen coated plates. Cells are allowed to incorporate label into their proteoglycan matrix (approximately 1 week) at 37°C, under an atmosphere of 5% CO_2.

The night before initiating the assay, chondrocyte monolayers are washed two times in DMEM/ 1% PSF/G and then allowed to incubate in fresh DMEM /1% FBS overnight.

The following morning chondrocytes are washed once in DMEM/1%PSF/G. The final wash is allowed to sit on the plates in the incubator while making dilutions.

Media and dilutions can be made as described in the Table below.

Control Media	DMEM alone (control media)
IL-1 Media	DMEM + IL-1 (5 ng/ml)
Drug Dilutions	Make all compounds stocks at 10 mM in DMSO. Make a 100 uM stock of each compound in DMEM in 96 well plate. Store in freezer overnight. The next day perform serial dilutions in DMEM with IL-1 to 5 uM, 500 nM. and 50 nM. Aspirate final wash from wells and add 50 ul of compound from above dilutions to 450 ul of IL-1 media in appropriate wells of the 48 well plates. Final compound concentrations equal 500 nM, 50 nM, and 5 nM. All samples completed in triplicate with Control and IL-1 alone samples on each plate.

Plates are labeled and only the interior 24 wells of the plate are used. On one of the plates, several columns are designated as IL-1 (no drug) and Control (no IL-1, no drug). These control columns are periodically counted to monitor 35S-proteoglycan release. Control

and IL-1 media are added to wells (450 ul) followed by compound (50 ul) so as to initiate the assay. Plates are incubated at 37°C, with a 5% CO_2 atmosphere.

At 40-50 % release (when CPM from IL-1 media is 4-5 times control media) as assessed by liquid scintillation counting (LSC) of media samples, the assay is terminated (9-12 hours). Media is removed from all wells and placed in scintillation tubes. Scintillate is added and radioactive counts are acquired (LSC). To solubilize cell layers, 500 ul of papain digestion buffer (0.2 M Tris, pH 7.0, 5 mM EDTA, 5 mM DTT, and 1 mg/ml papain) is added to each well. Plates with digestion solution are incubated at 60°C overnight. The cell layer is removed from the plates the next day and placed in scintillation tubes. Scintillate is then added, and samples counted (LSC).

The percent of released counts from the total present in each well is determined. Averages of the triplicates are made with control background subtracted from each well. The percent of compound inhibition is based on IL-1 samples as 0% inhibition (100% of total counts).

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or

flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

For topical ocular administration, direct application to the affected eye may be employed in the form of a formulation as eyedrops, aerosol, gels or ointments, or can be incorporated into collagen (such as poly-2-hydroxyethylmethacrylate and co-polymers thereof), or a hydrophilic polymer shield. The materials can also be applied as a contact lens or via a local reservoir or as a subconjunctival formulation.

For intraorbital administration a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in an aqueous solution or suspension (particle size less than 10 micron) may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH between 5 and 8, if necessary and the liquid diluent first rendered isotonic. Small amounts of polymers can be added to increase viscosity or for sustained release (such as cellulosic polymers, Dextran, polyethylene glycol, or alginic acid). These solutions are suitable for intraorbital injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intraorbitally at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The present invention is illustrated by the following Preparations and Examples, but it is not limited to the details thereof.

Example 1

4-[4-(4-FLUOROPHENOXY)BENZENESULFONYLAMINO]-TETRAHYDRO PYRAN-4-CARBOXYLIC ACID HYDROXYAMIDE

(A) 4-[N-(Diphenylmethylene)amino]tetrahydropyran-4-carboxylic acid ethyl ester

To a suspension of sodium hydride (6.56 grams. 0.164 mole) in ethylene glycol dimethyl ether (150 mL) at 0°C was added a solution of the N-(diphenylmethylene)glycine ethyl ester (20.60 grams, 0.07398 mole) in ethylene glycol dimethyl ether (50 mL) dropwise via addition funnel. A solution of 2-bromoethyl ether (23.21 grams, 0.090 mole) in ethylene glycol dimethyl ether (50 mL) was then added, in 10 mL portions over approximately 5 minutes, to the ethylene glycol dimethyl ether solution. The ice bath was removed and the reaction was stirred at room temperature for 16 hours. The mixture was diluted with diethyl ether and washed with water. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated to afford a cloudy yellow oil (28.692 grams). Chromatography on silica gel eluting first with 4 L of 5% ethyl acetate/hexane followed by 4 liters of 10% ethyl acetate/hexane gave 4-[N-(diphenylmethylene)amino]tetrahydropyran-4-carboxylic acid ethyl ester as a clear yellow oil (16.114 g, 64 %).

^{1}HNMR ($CDCl_3$) δ 7.58 (d, 2H), 7.36 (m, 4H), 7.28 (t, 2H), 7.08 (m, 2H), 3.99 (m, 2H), 3.70, (m, 2H), 3.66 (q, 2H), 2.10 (m, 2H), 1.99 (m, 2H), 1.08 (t, 3H). MS Atmospheric Pressure Chemical Ionization Mass Spectra: 338 (M^++1).

(B) **4-Aminotetrahydropyran-4-carboxylic acid ethyl ester**

To a solution of 4-[N-(diphenylmethylene)amino]tetrahydropyran-4-carboxylic acid ethyl ester (16.0 grams, 0.047 mole) in diethyl ether (120 mL) was added 1M aqueous hydrochloric acid solution (100 mL). The mixture was stirred vigorously at room temperature for 16 hours. The layers were separated and the aqueous layer washed with diethyl ether. The aqueous layer was brought to pH 10 with dilute aqueous ammonium hydroxide solution and extracted with dichloromethane. The organic extract was dried over sodium sulfate and concentrated to give 4-aminotetrahydropyran-4-carboxylic acid ethyl ester (7.128 g, 71.7%) as an oil.

^{1}HNMR ($CDCl_3$) δ 4.15 (q, 2H), 3.82 (m, 2H), 3.62 (m, 2H), 2.07 (m, 2H), 1.60 (s, 2H), 1.44 (m, 2H), 1.24 (t, 3H). ^{13}CNMR ($CDCl_3$) d 176.48, 63.70, 61.09, 54.78, 35.05, 14.15. MS Atmospheric Pressure Chemical Ionization Mass Spectra: 210 (M^++1).

(C) **4-[4-(4-Fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid ethyl ester**

To a solution of 4-aminotetrahydropyran-4-carboxylic acid ethyl ester (7.00 grams, 0.0404 mole) in N,N-dimethylformamide (40 mL) was added triethylamine (5.94 mL, 0.043 mole). Solid 4-(4-fluorophenoxy)benzenesulfonyl chloride (12.165 grams, 0.0424 mole) was added in portions. The resulting mixture was stirred at room temperature for 16 hours and then most of the solvent was removed by evaporation under vacuum. The residue was partitioned between saturated sodium bicarbonate solution and dichloromethane. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent under vacuum provided crude 4-[4-(4-fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid ethyl ester as an amber oil (21.05 grams). Flash chromatography on silica gel eluting with 25% ethyl acetate / hexane followed by 50% ethyl acetate / hexane provided 4-[4-(4-fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid ethyl ester as an off-white crystalline solid (12.15 grams, 71%, mp 116-117°C).

^{1}HNMR ($CDCl_3$) δ 7.79 (d, 2H), 7.09 (t, 2H) 7.02 (m, 2H), 6.97 (d, 2H), 5.10 (s, 1H), 4.01 (q, 2H), 3.60 (m, 4H), 2.08 (m, 2H), 1.84 (br d, 2H), 1.23 (t, 3H). M S Atmospheric Pressure Chemical Ionization Mass Spectra: 424 (M^++1).

(D) **4-[4-(4-Fluorophenoxy)-benzenesulfonylamino]tetrahydropyran-4-carboxylic acid**

Method A

A solution of 4-[4-(4-fluorophenoxy)benzenesulfonylaminó]tetrahydropyran-4-carboxylic acid ethyl ester (12.1 grams, 0.0286 mole) in tetrahydrofuran (190 mL) was treated with aqueous 3 M sodium hydroxide solution (95 mL, 0.286 mole) and stirred at room

temperature for 4 days. The solvent was evaporated under vacuum and the residue partitioned between water and diethyl ether. The aqueous layer was washed with diethyl ether, acidified to pH 1 with 3N aqueous hydrochloric acid solution and extracted with dichloromethane. After washing with water, the organic extract was dried over sodium sulfate, and concentrated to give 4-[4-(4-fluorophenoxy)-benzenesulfonylamino]tetrahydropyran-4-carboxylic acid (11.241 grams, 99%) as a yellowish solid foam.

Method B

A solution of 4-[4-(4-fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid ethyl ester (34.19 grams, 0.807 mole) in ethanol (330 mL) was treated with aqueous 3 M sodium hydroxide solution (330 mL, 0.990 mole) and heated to reflux overnight. The solvent was evaporated under vacuum and the residue partitioned between water and diethyl ether. The aqueous layer was washed with diethyl ether, acidified to pH 1 with 3N aqueous hydrochloric acid solution and extracted with ethyl acetate. After washing with water, the organic extract was dried over sodium soulfate, and concentrated to give 4-[4-(4-fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid (31.26 grams, 98%) as a white crystalline solid.

^{1}HNMR ($CDCl_3$) δ 7.73 (d, 2H), 7.03 (t, 2H) 6.96 (m, 2H), 6.91 (d, 2H), 3.56 (m, 2H), 3.43 (br m, 3H), 2.01 (m, 2H), 1.80 (br d, 2H). MS Atmospheric Pressure Chemical Ionization Mass Spectra: 394 (M^+-1) (-ion).

(E) 4-[4-(4-Fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid N-benzyloxyamide

Diisopropyl ethylamine (3.89 grams, 0.030 mole) and (benzotriazol-1-yloxy)tris-(dimethylamino)-phosphonium hexafluorophosphate (13.27 grams, 0.030 mole) were added sequentially to a solution of 4-[4-(4-fluorophenoxy)-benzenesulfonylamino] tetrahydropyran-4-carboxylic acid (11.22 grams, 0.028 mole) in anhydrous N,N-dimethylformamide (140 mL). The resulting solution was stirred at room temperature for 16 hours. Additional diisopropyl ethylamine (4.0 mL, 0.051 mole) and O-benzyl hydroxylamine hydrochloride (5.46 grams, 0.034 mole) were then added and the resulting mixture was stirred at 60°C for 18 hours. After concentration under vacuum, the residue was treated with 0.5N aqueous hydrochloric acid solution and extracted with ethyl acetate. The organic extract was washed with saturated aqueous sodium bicarbonate solution, water, and brine. The solution was dried over magnesium sulfate, filtered and concentrated to one fourth original volume. Addition of an equal volume of hexane precipitated 4-[4-(4-fluorophenoxy)benzenesulfonylamino]-tetrahydropyran-4-carboxylic acid N-benzyloxyamide (11.595 g, 81.6%) as a white crystalline solid (mp 175-176°C).

^{1}HNMR ($CDCl_3$) δ 7.76 (d, 2H), 7.35 (m, 5H), 7.05 (t, 2H), 6.96 (m, 4H) 5.38 (br s, 1H), 4.86 (s, 2H), 3.57 (m, 2H), 3.44 (m, 2H), 2.01 (m, 2H), 1.77 (br d, 2H), 1.54 (br s, 1H). MS Atmospheric Pressure Chemical Ionization 501 (M^++1).

(F) 4-[4-(4-Fluorophenoxy)benzenesulfonylamino]-tetrahydropyran-4-carboxylic acid hydroxyamide

Method A

A solution of 4-[4-(4-fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid N-benzyloxyamide(11.28 grams, 0.0225 mole) in ethyl acetate (600 mL) was treated with 5% palladium on barium sulfate (5.0 grams) and hydrogenated in a Parr™ shaker at 3 atmospheres pressure for 18 hours. After filtration through nylon (pore size 0.45 mm) to remove the catalyst, the filter pad was rinsed with methanol. Combined filtrate and rinse were evaporated and the residue taken up in hot methanol. Cooling afforded crude 4-[4-(4-fluorophenoxy)benzenesulfonylamino]-tetrahydropyran-4-carboxylic acid hydroxyamide (5.941 grams, 64%, mp 176-177°C) as a white crystalline solid. The mother liquor was evaporated and the residue crystallized from 50% methanol/dichloromethane to give additional 4-[4-(4-fluorophenoxy)benzenesulfonylamino]-tetrahydropyran-4-carboxylic acid hydroxyamide (0.660 grams, mp 184-185°C) as white needles. The mother liquor was again evaporated and the residue crystallized from methanol/dichloromethane to give additional product (1.861 grams, mp 176-177°C). Recrystallization of the first lot from methanol/dichloromethane provided analytically pure 4-[4-(4-fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide (3.091 grams, mp 184-185°C).

Method B

Oxalyl chloride (11.83 grams, 0.0932 mole, 1.1 eq.) and DMF (0.13 mL) were added to a stirred suspension of the carboxylic acid (33.25 grams, 0.0841 mole) in dry methylene chloride (300 mL) at room temperature. Some bubbling was observed. The suspension, which slowly became a yellowish solution was stirred overnight at room temperature. Meanwhile, a solution of hydroxylamine hydrochloride (7.65 grams, 0.110 mole, 1.3 eq.) in dry pyridine (51.4 mL, 0.635 mole, 7.5 eq.) at 0°C was treated with chlorotrimethylsilane causing a white precipitate to form. This suspension was stirred at room temperature overnight. Both flasks were then cooled to 0°C and the solution of acid chloride was added to the suspension of silylated hydroxylamine. The resulting mixture was stirred at 0°C for 1 hour and room temperature for 2 hours. Added 1000 mL aqueous 2N HCl and stirred at room temperature for 1 hour. The layers were separated, the aqueous layer was extracted three times with ethylacetate (500 mL). Combined organic layers were washed with water and brine and dried over magnesium sulfate, filtered and the volume of the filtrate reduced to 300 mL at which point a large amount of white crystalline solid had precipitated. This was cooled overnight in a

refrigerator. The solid was collected by vacuum filtration, rinsed with cold 1:1 ethylacetate/hexane and dried under high vacuum to give 30.311 grams of the desired hydroxamic acid (87.8%) as a white crystalline solid (mp 189-190°C).

^{1}HNMR (d_6 DMSO) δ 10.35 (br s, 1H), 8.68 (br s, 1H), 7.78 (br s, 1H), 7.74 (d, 2H), 7.26 (t, 2H), 7.16 (m, 2H), 7.04 (d, 2H), 3.40 (m, 2H), 3.31 (m, 2H), 1.78 (m, 4H). ^{13}CNMR (DMSO) δ 169.65, 160.66, 137.50, 129.39, 122.34, 122.25, 117.75, 117.44, 117.24, 62.94, 58.45, 33.34. MS Atmospheric Pressure Chemical Ionization Mass Spectra: 409 (M^+-1) (-ion).

Preparation A

4-(4-Fluorophenoxy)benzenesulfonyl chloride

Chlorosulfonic acid (26 mL, 0.392 mole) was added dropwise to ice-cooled 4-fluorophenoxybenzene (36.9 grams, 0.196 mole) with mechanical stirring. When addition was complete, the mixture was stirred at room temperature for 4 hours. The mixture was then poured into ice water. The product, 4-(4-fluorophenoxy)benzene-sulfonylchloride (18.6 grams, 33%) was collected by filtration and dried in the air.

Preparation B

Sodium 4-(3-methylbutoxy)benzenesulfonate

A solution of 4-hydroxybenzenesulfonic acid (10.0 grams, 43.1 mmole) and sodium hydroxide (3.3 grams, 83 mmole) in water (40 mL) was mixed with a solution of 1-iodo-3-methylbutane (11.3 mL, 86.4 mmole) in isopropanol (60 mL) and the resulting mixture was heated at reflux for 2 days. The isopropanol was removed by evaporation under vacuum. The title compound, 10.0 grams (87%), was collected by filtration and washed with isopropanol.

Preparation C

4-(3-Methylbutoxy)benzenesulfonyl chloride

A mixture of sodium 4-(3-methylbutoxy)benzenesulfonate (2.5 grams, 9.4 mmole), thionyl chloride (10 mL), and 5 drops of N,N-dimethylformamide was heated at reflux for 5 hours. After cooling, the excess thionyl chloride was evaporated and the residue was taken up in ethyl acetate. The solution was cooled in an ice bath and water was added. The organic phase was separated and washed with water and brine. After drying over sodium sulfate, the solvent was evaporated to afford the title compound as an oil, 2.34 grams (95%).

Preparation D

Sodium 4-(2-cyclopentylethoxy)benzenesulfonate

A solution of 4-hydroxybenzenesulfonic acid (6.5 grams, 28.2 mmole) and sodium hydroxide (2.2 grams, 55 mmole) in water (15 mL) was mixed with a solution of 2-(bromoethyl)cyclopentane (15.0 grams, 84.7 mmole) in isopropanol (40 mL) and the resulting mixture was heated at reflux for 2 days. The isopropanol was removed by evaporation under

vacuum. The titled compound, 4.7 grams (57%), was collected by filtration and washed with isopropanol.

Preparation E

4-(3-Methylbutoxy)benzenesulfonyl chloride

A mixture of sodium 4-(2-cyclopentylethoxy)-benzenesulfonate (2.5 grams, 8.6 mmole), thionyl chloride (15 mL), and a few drops of N,N-dimethylformamide was heated at reflux for 5 hours. After cooling, the excess thionyl chloride was evaporated and the residue was taken up in ethyl acetate. The solution was cooled in an ice bath and water was added. The organic phase was separated and washed with water and brine. After drying over sodium sulfate, the solvent was evaporated to afford the title compound as an oil, 2.24 grams (90%).

Preparation F

4-Fluorobiphenylsulfonyl chloride

Chlorosulfonic acid (8.7 mL, 0.13 mole) was added dropwise to 4-fluorobiphenyl (10.2 grams, 59 mmol) while stirring in an ice bath. Stirring was continued with ice cooling for 0.5 hours and then the reaction mixture was poured onto ice. The resulting white precipitate was collected by filtration and dissolved in chloroform. The chloroform solution was washed with water and brine, dried over magnesium sulfate and concentrated to afford a white solid. The desired product, 4-fluorobiphenylsulfonyl chloride (4.3 grams, 27%), was separated from 4-fluorobiphenylsulfonic acid (an unwanted side product) by crystallization of the latter from ethyl acetate and crystallization of the remaining material from hexane.

Preparation G

Sodium 4-(4-fluorobenzyloxy)benzenesulfonate

To a solution of 4-hydroxybenzenesulfonic acid (5.13 grams, 22.1 mmole) in 1N aqueous sodium hydroxide solution (23 mL) was added a solution of 4-fluorobenzylbromide (3.3 mL, 26.5 mmole) in ethanol (20 mL). The resulting mixture was heated at reflux for 2 days. Upon cooling and standing, a white solid precipitated. The precipitated product, sodium 4-(4-fluorobenzyloxy)benzenesulfonate, 4.95 grams (74%) was collected by filtration and washed with ethyl acetate and diethyl ether.

Preparation H

4-(4-Fluorobenzyloxy)benzenesulfonyl chloride

To a slurry of sodium 4-(4-fluorobenzyloxy)benzenesulfonate (0.5 grams, 1.64 mmole), in methylene chloride (5 mL) was added phosphorus pentachloride (275 mg, 1.31 mmole). The resulting mixture was heated at reflux for 7 hours. After cooling in an ice bath and quenching with water (15 mL), the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and concentrated to afford 4-(4-fluorobenzyloxy)benzenesulfonyl chloride a white solid (130 mg, 26%).

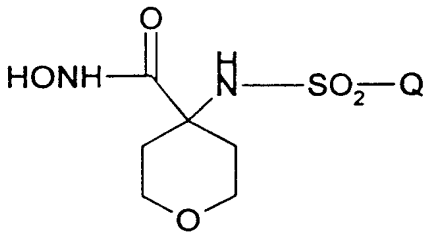
Preparation I

4-(4-Chlorophenoxy)benzenesulfonyl chloride

Chlorosulfonic acid (9.7 mL, 0.147 mole) was added dropwise to 4-chlorophenoxybenzene (12.6 mL, 73.4 mmole) at room temperature with stirring. When addition was complete, the mixture was stirred at room temperature for 1 hour and then poured into ice water. The solid was collected by filtration, dried in the air, and recrystallized from petroleum ether and ethyl acetate to give 4-(4-chlorophenoxy)benzenesulfonylchloride (7.43 grams, 33%).

CLAIMS

1. A compound of the formula



I

or the pharmaceutically acceptable salts thereof, wherein

Q is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_6-C_{10})aryl or (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl;

wherein each (C_6-C_{10})aryl or (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_6-C_{10})aryl or (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents per ring independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein Q is optionally substituted (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)-

heteroaryl(C_6-C_{10})aryl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})-aryl, or (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_6-C_{10})aryl.

3. A compound according to claim 1, wherein Q is optionally substituted (C_6-C_{10})aryloxy(C_6-C_{10})aryl.

4. A compound according to claim 3, wherein the (C_6-C_{10})aryloxy ring of said (C_6-C_{10})aryloxy(C_6-C_{10})aryl group is optionally mono-substituted in the 4-position of the ring.

5. A compound according to claim 1, wherein said compound is selected from the group consisting of:

4-[4-(4-fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(4-chlorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(phenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(4-pyridyloxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(4-fluorophenyl)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

4-[4-(4-fluorophenylmethoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

(phenylmethoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide; and

4-[4-(4-Fluorophenylethoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxyamide;

6. A pharmaceutical composition for the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing,

burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis and septic shock in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

7. A method for treating a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis and septic shock in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

8. A pharmaceutical composition for the treatment of a condition which can be treated by the inhibition of matrix metalloproteinases in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition for the treatment of a condition which can be treated by the inhibition of a mammalian reprolysin in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

10. A method for the inhibition of matrix metalloproteinases in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

11. A method for the inhibition of a mammalian reprolysin in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/IB 99/00505

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D309/14 C07D405/12 A61K31/35

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 606 046 A (CIBA-GEIGY) 13 July 1994 see page 23; claims 1,3,4; figure B	1-3,6,8, 9

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 1999	16/06/1999

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	Francois, J

1

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 99/00505

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.: 7,10,11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7,10,11 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. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

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

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/IB 99/00505

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 606046 A	13-07-1994	US 5455258 A	03-10-1995
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		DE 69314456 T	26-02-1998
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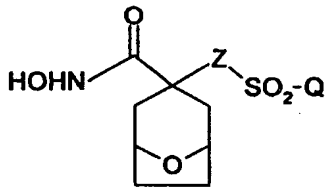

(I)

(57) Abstract

A compound of formula (I), wherein Z and Q are as defined in the specification, to pharmaceutical compositions containing them and to their medicinal use.

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BICYCLIC HYDROXAMIC ACID DERIVATIVES

Background of the Invention

The present invention relates to bicyclic hydroxamic acid derivatives, and to pharmaceutical compositions and methods of treatment.

The compounds of the present invention are inhibitors of zinc metalloendopeptidases, especially those belonging to the matrix metalloproteinase (also called MMP or matrixin) and reprolysin (also known as adamylsin) subfamilies of the metzincins (Rawlings, et al., Methods in Enzymology, 248, 183-228 (1995) and Stocker, et al., Protein Science, 4, 823-840 (1995)). The MMP subfamily of enzymes, currently contains seventeen members (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19, MMP-20). The MMP's are most well known for their role in regulating the turn-over of extracellular matrix proteins and as such play important roles in normal physiological processes such as reproduction, development and differentiation. In addition, the MMP's are expressed in many pathological situations in which abnormal connective tissue turnover is occurring. For example, MMP-13 an enzyme with potent activity at degrading type II collagen (the principal collagen in cartilage), has been demonstrated to be overexpressed in osteoarthritic cartilage (Mitchell, et al., J. Clin. Invest., 97, 761 (1996)). Other MMPs (MMP-2, MMP-3, MMP-8, MMP-9, MMP-12) are also overexpressed in osteoarthritic cartilage and inhibition of some or all of these MMP's is expected to slow or block the accelerated loss of cartilage typical of joint diseases such as osteoarthritis or rheumatoid arthritis.

The mammalian reprolysins are known as ADAMs (A Disintegrin And Metalloproteinase) (Wolfberg, et al., J. Cell Biol., 131, 275-278 (1995)) and contain a disintegrin domain in addition to a metalloproteinase-like domain. To date twenty three distinct ADAM's have been identified.

ADAM-17, also known as tumor necrosis factor-alpha converting enzyme (TACE), is the most well known ADAM. ADAM-17 (TACE) is responsible for cleavage of cell bound tumor necrosis factor-alpha (TNF-α, also known as cachectin). TNF-α is recognized to be involved in many infectious and auto-immune diseases (W. Friers, FEBS Letters, 285, 199 (1991)). Furthermore, it has been shown that TNF-α is the prime mediator of the inflammatory response seen in sepsis and septic shock (Spooner, et al., Clinical Immunology and Immunopathology, 62 S11 (1992)). There are two forms of TNF-α, a type II membrane protein of relative molecular mass 26,000 (26 kD) and a soluble 17 kD form generated from the cell bound protein by specific proteolytic cleavage. The soluble 17 kD form of TNF-α is released by the cell and is associated with the deleterious effects of TNF-α. This form of

TNF-α is also capable of acting at sites distant from the site of synthesis. Thus, inhibitors of TACE prevent the formation of soluble TNF-α and prevent the deleterious effects of the soluble factor.

Select compounds of the invention are potent inhibitors of aggrecanase, an enzyme important in the degradation of cartilage aggrecan. Aggrecanase is also believed to be an ADAM. The loss of aggrecan from the cartilage matrix is an important factor in the progression of joint diseases such as osteoarthritis and rheumatoid arthritis and inhibition of aggrecanase is expected to slow or block the loss of cartilage in these diseases.

Other ADAMs that have shown expression in pathological situations include ADAM TS-1 (Kuno, et al., J. Biol. Chem., 272, 556-562 (1997)), and ADAM's 10, 12 and 15 (Wu, et al., Biochem. Biophys. Res. Comm., 235, 437-442, (1997)). As knowledge of the expression, physiological substrates and disease association of the ADAM's increases the full significance of the role of inhibition of this class of enzymes will be appreciated.

Diseases in which inhibition of MMP's and or ADAM's will provide therapeutic benefit include: arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis, septic shock and other diseases characterized by metalloproteinase or ADAM expression.

This invention also relates to a method of using the compounds of the invention in the treatment of the above diseases in mammals, especially humans, and to the pharmaceutical compositions useful therefore.

It is recognized that different combinations of MMP's and ADAM's are expressed in different pathological situations. As such inhibitors with specific selectivities for individual ADAM's and/or MMP's may be preferred for individual diseases. For example, rheumatoid arthritis is an inflammatory joint disease characterized by excessive TNF levels and the loss

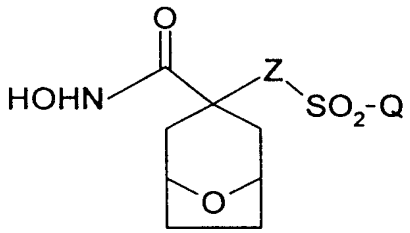
of joint matrix constituents. In this case, a compound that inhibits TACE and aggrecanase as well as MMP's such as MMP-13 may be the preferred therapy. In contrast, in a less inflammatory joint disease such as osteoarthritis, compounds that inhibit matrix degrading MMP's such as MMP-13 but not TACE may be preferred.

The present inventors have also discovered that it is possible to design inhibitors with differential metalloprotease activity. Specifically, for example, the inventors have been able to design molecules which selectively inhibit matrix metalloprotease-13 (MMP-13) preferentially over MMP-1.

Matrix metalloproteinase inhibitors are well known in the literature. Specifically, PCT Publication WO 96/33172, published October 24, 1996, refers to cyclic arylsulfonylamino hydroxamic acids that are useful as MMP inhibitors. United States Patent 5,672,615, PCT Publication WO 97/20824, PCT Publication WO 98/08825, PCT publication WO 98/27069, and PCT Publication WO 98/34918, published August 13, 1998, entitled "Arylsulfonyl Hydroxamic Acid Derivatives" all refer to cyclic hydroxamic acids that are useful as MMP inhibitors. PCT Publications WO 96/27583 and WO 98/07697, published March 7, 1996 and February 26, 1998, respectively, refer to arylsulfonyl hydroxamic acids. PCT Publication WO 98/03516, published January 29, 1998 refers to phosphinates with MMP activity. PCT Publication 98/34915, published August 13, 1998, entitled "N-Hydroxy-b-Sulfonyl Propionamide Derivatives," refers to propionylhydroxamides as useful MMP inhibitors. PCT Publication WO 98/33768, published August 6, 1998, entitled "Arylsulfonylamino Hydroxamic Acid Derivatives," refers to N-unsubstituted arylsulfonylamino hydroxamic acids. PCT Publication WO 98/30566, published July 16, 1998, entitled "Cyclic Sulfone Derivatives," refers to cyclic sulfone hydroxamic acids as MMP inhibitors. United States Provisional Patent Application 60/55208, filed August 8, 1997, refers to biaryl hydroxamic acids as MMP inhibitors. United States Provisional Patent Application Serial No. 60/55207, filed August 8, 1997, entitled "Aryloxyarylsulfonylamino Hydroxamic Acid Derivatives," refers to aryloxyarylsulfonyl hydroxamic acids as MMP inhibitors. United States Provisional Patent Application 60/62766, filed October 24, 1997, entitled "The Use of MMP-13 Selective Inhibitors For The Treatment of Osteoarthritis and Other MMP Mediated Disorders," refers to the use of MMP-13 selective inhibitors to treat inflammation and other disorders. United States Provisional Patent Application Serial No. 60/68261, filed December 19, 1997, refers to the use of MMP inhibitors to treat angiogenesis and other disorders. Each of the above referenced publications and applications is hereby incorporated by reference in its entirety.

Summary of the Invention

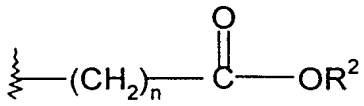
The present invention relates to a compound of the formula



I

wherein Z is $>CH_2$ or $>NR^1$;

R^1 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl or a group of the formula



;

n is an integer from one to six;

R^2 is hydrogen or $(C_1\text{-}C_6)$alkyl;

Q is $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl or $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl$(C_2\text{-}C_9)$heteroaryl;

wherein each $(C_6\text{-}C_{10})$aryl or $(C_2\text{-}C_9)$heteroaryl moieties of said $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}$

C_9)heteroaryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl(C_6-C_{10})aryl or (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl(C_2-C_9)heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents per ring independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy;

or pharmaceutically acceptable salts thereof.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), trimethyl-ammonium or diethylammonium, and the lower alkanolammonium salts such tris-(hydroxymethyl)-methylammonium and other base salts of pharmaceutically acceptable organic amines.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl,

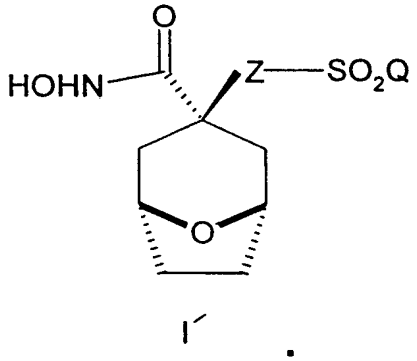
isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl. Preferred heteroaryls include pyridyl, furyl, thienyl, isothiazolyl, pyrazinyl, pyrimidyl, pyrazolyl, isoxazolyl, thiazolyl or oxazolyl. Most preferred heteroaryls include pyridyl, furyl or thienyl.

The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula R-(C=O)- wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkoxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

The compound of formula I may have chiral centers and therefore exist in different diasteriomeric or enantiomeric forms. This invention relates to all optical isomers, tautomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferably, compounds of the formula I exist as the exo isomer of the formula



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Other preferred compounds of formula I are those wherein Q is $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl or $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, wherein each aryl or heteroaryl moiety of said $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl or $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl groups may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy or perfluoro$(C_1\text{-}C_3)$alkyl.

More preferred compounds of formula I include those wherein Q is phenyl, pyridyloxyphenyl (more preferably 4-pyridyl) or phenoxyphenyl optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy or perfluoro$(C_1\text{-}C_3)$alkyl, more preferably the substituents are selected from fluoro, chloro, $(C_1\text{-}C_6)$alkoxy or $(C_1\text{-}C_6)$alkyl, most preferably the substituent is in the 4-position.

Specific preferred compounds of formula I include the following:

3-*exo*-[4-(4-fluorophenoxy)benzenesulfonylamino]-8-oxabicyclo[3.2.1]-octane-3-carboxylic acid hydroxyamide;

3-*exo*-[4-(4-fluorophenoxy)benzenesulfonylmethyl]-8-oxabicyclo-[3.2.1]-octane-3-carboxylic acid hydroxyamide;

3-(4-phenoxybenzenesulfonylmethyl)-8-oxabicyclo[3.2.1]-octane-3-carboxylic acid hydroxyamide;

3-*exo*-(4´-fluorobiphenyl-4-benzenesulfonylmethyl)-8-oxabicyclo-[3.2.1]-octane-3-carboxylic acid hydroxyamide; and

3-*exo*-[4-(4-Chlorophenoxy)benzenesulfonylmethyl]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide.

Other compounds of the invention of formula I include the following:

3-*exo*-(4-Phenoxybenzenesulfonylamino)-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-[4-(Pyridin-4-yloxy)benzenesulfonylamino]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-[4-(4-Chlorophenoxy)benzenesulfonylamino]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-[[4-(4-Chlorophenoxy)benzenesulfonyl]-(3-*endo*-hydroxycarbamoyl-8-oxabicyclo[3.2.1]oct-3-yl)amino]propionic acid,

3-[[4-(4-Chlorophenoxy)benzenesulfonyl]-(3-*endo*-hydroxycarbamoyl-8-oxabicyclo[3.2.1]oct-3-yl)amino]propionic acid ethyl ester,

3-[[4-(4-Fluorophenoxy)benzenesulfonyl]-(3-*endo*-hydroxycarbamoyl-8-oxabicyclo[3.2.1]oct-3-yl)-amino]propionic acid,

3-[[4-(4-Fluorophenoxy)benzenesulfonyl]-(3-*endo*-hydroxycarbamoyl-8-oxabicyclo[3.2.1]oct-3-yl)-amino]propionic acid ethyl ester,

3-*exo*-{[4-(4-Fluorophenoxy)benzenesulfonyl]methylamino}-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*endo*-[4-(4-Fluorophenoxy)benzenesulfonylamino]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-{[4-(4-Fluorophenoxy)benzenesulfonyl]pyridin-3-ylmethylamino}-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-[4-(4-Fluorobenzyloxy)benzenesulfonylamino]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-(4-Benzyloxybenzenesulfonylamino)-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-(4-Benzyloxybenzenesulfonylmethyl)-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-{Methyl-[4-(pyridin-4-yloxy)benzenesulfonyl]amino}-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-(4-Methoxybenzenesulfonylamino)-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-(4-Methoxybenzenesulfonylmethyl)-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-5-Pyridin-2-ylthiophene-2-sulfonylamino)-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-(4-Phenoxybenzenesulfonylamino)-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-[4-(Pyridin-4-yloxy)benzenesulfonylmethyl]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-[4-(Pyridin-4-yloxy)benzenesulfonylamino]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-[4-(4-Chlorophenoxy)benzenesulfonylmethyl]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-[4-(4-Chlorophenoxy)benzenesulfonylamino]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-[[4-(4-Fluorophenoxy)benzenesulfonyl]-(3-*endo*-hydroxycarbamoyl-8-oxabicyclo[3.2.1]oct-3-yl)amino]propionic acid,

3-[(3-*endo*-Hydroxycarbamoyl-8-oxabicyclo[3.2.1]oct-3-yl)-(4-phenoxybenzenesulfonyl)-amino]propionic acid,

3-*exo*-{[4-(4-Fluorophenoxy)benzenesulfonyl]pyridin-3-ylmethylamino}-8-oxabicyclo-[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-[(4-Phenoxybenzenesulfonyl)pyridin-3-ylmethylamino]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-{Methyl[4-(pyridin-4-yloxy)benzenesulfonyl]amino}-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,

3-*exo*-(5-Isoxazol-3-yl-thiophene-2-sulfonylamino)-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide, and

3-*exo*-(5-Phenylthiophene-2-sulfonylamino)-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide.

The present invention also relates to a pharmaceutical composition for the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer breast cancer, lung cancer and prostrate cancer and hematopoietic malignancies including

leukemias and lymphomas), tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis, septic shock and other diseases characterized by metalloproteinase activity and other diseases characterized by mammalian reprolysin activity in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition for the inhibition of (a) matrix metalloproteinases or other metalloproteinases involved in matrix degradation, or (b) a mammalian reprolysin (such as aggrecanase or ADAM's TS-1, 10, 12, 15 and 17, most preferably ADAM-17) in a mammal, including a human, comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis, septic shock and other diseases characterized by metalloproteinase activity and other diseases characterized by mammalian reprolysin activity in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or other metalloproteinases involved in matrix degradation, or (b) a mammalian reprolysin (such as aggrecanase or ADAM's TS-1, 10, 12, 15 and 17, preferably ADAM-17) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of matrix metalloproteinases or the inhibition of mammalian reprolysin comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF-α inhibitors such as anti-TNF monoclonal antibodies and TNF receptor immunoglobulin molecules (such as Enbrel®), low dose methotrexate, lefunimide, hydroxychloroquine, d-penicilamine, auranofin or parenteral or oral gold.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib and rofecoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, and antimetabolites such as methotrexate.

The compounds of the present invention may also be used in combination with cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

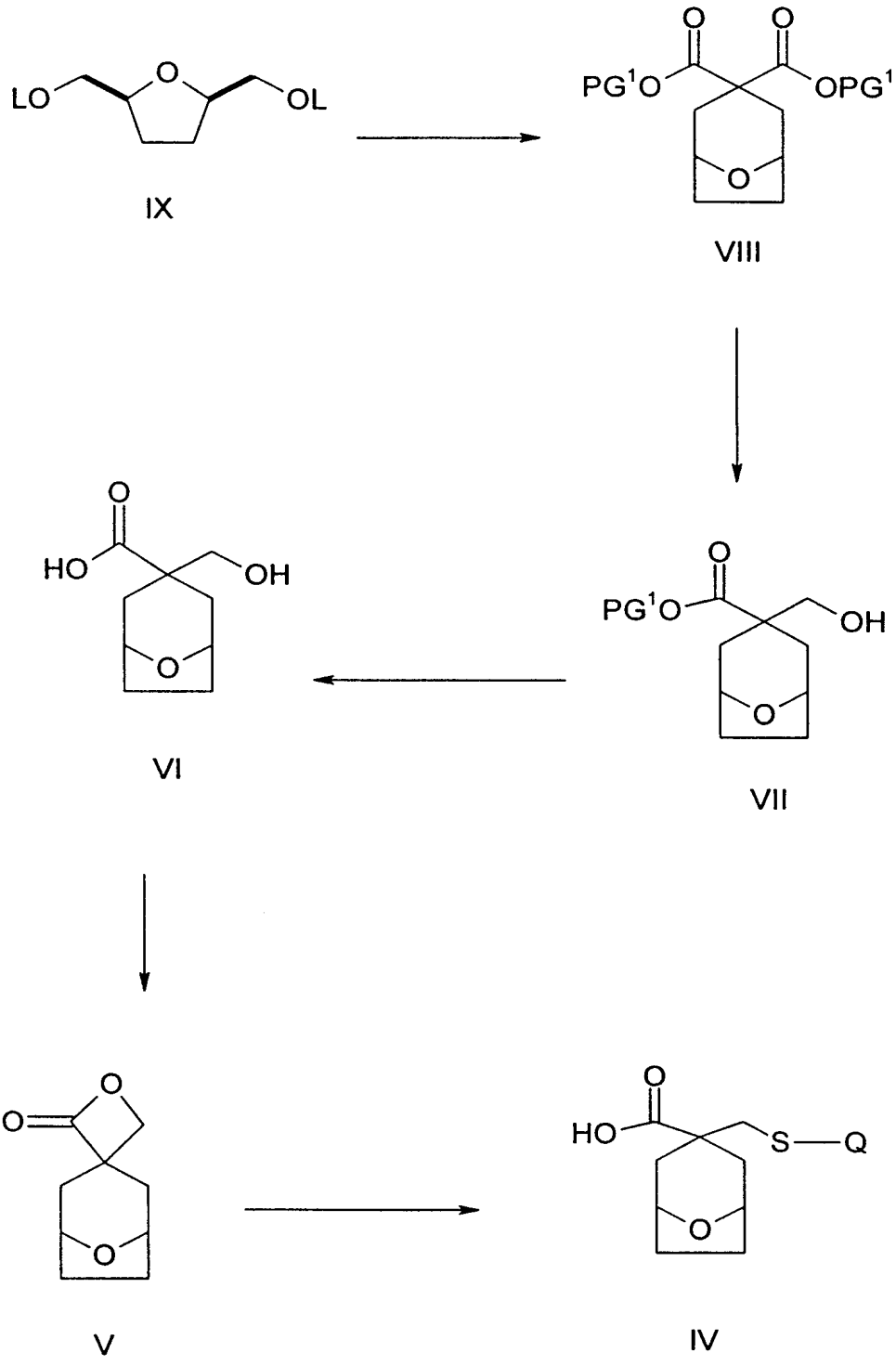
The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, requip, miratex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as Aricept, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The compounds of the present invention may also be used in combination with osteoporosis agents such as droloxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated n, R^1, R^2, Q and Z in the reaction Schemes and the discussion that follow are defined as above.

SCHEME 1


LO
OL
O
IX
PG1O
OPG1
O
O
O
VIII
HO
OH
O
O
VI
PG1O
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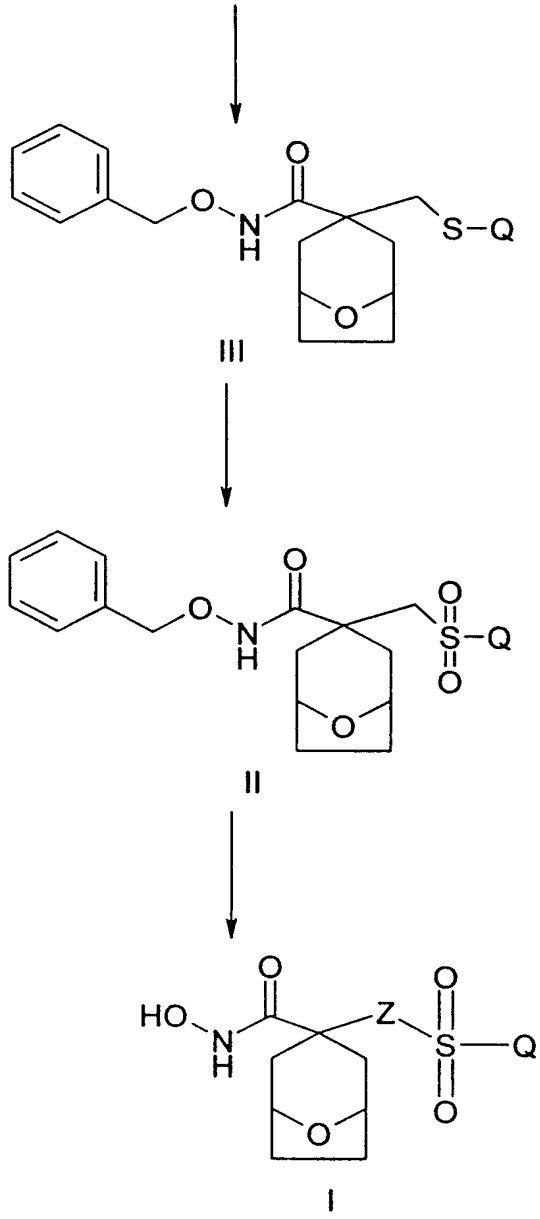
O
VII
O
O
O
V
HO
S—Q
O
O
IV

5

SCHEME 1 CONTINUED



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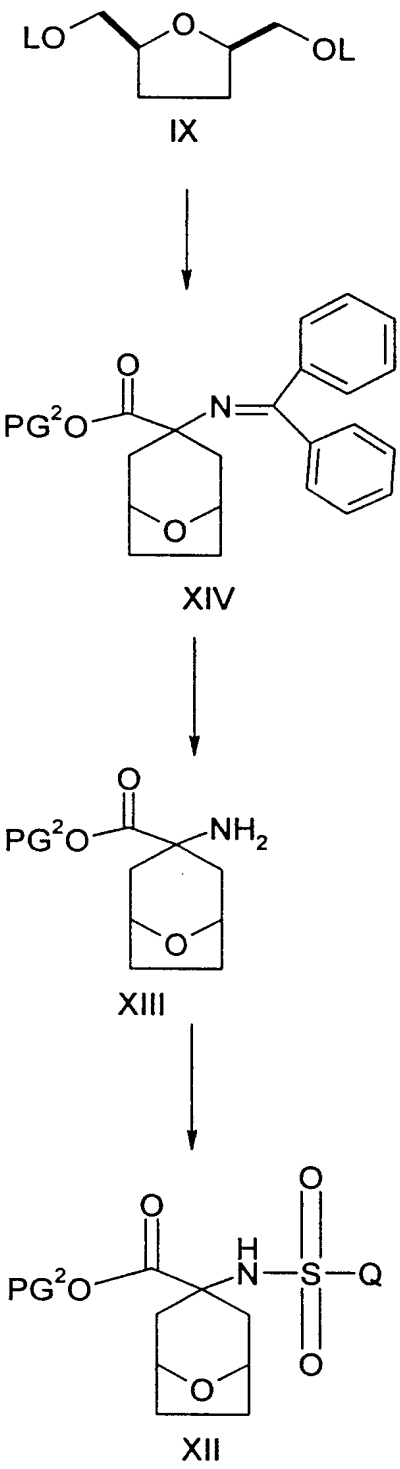
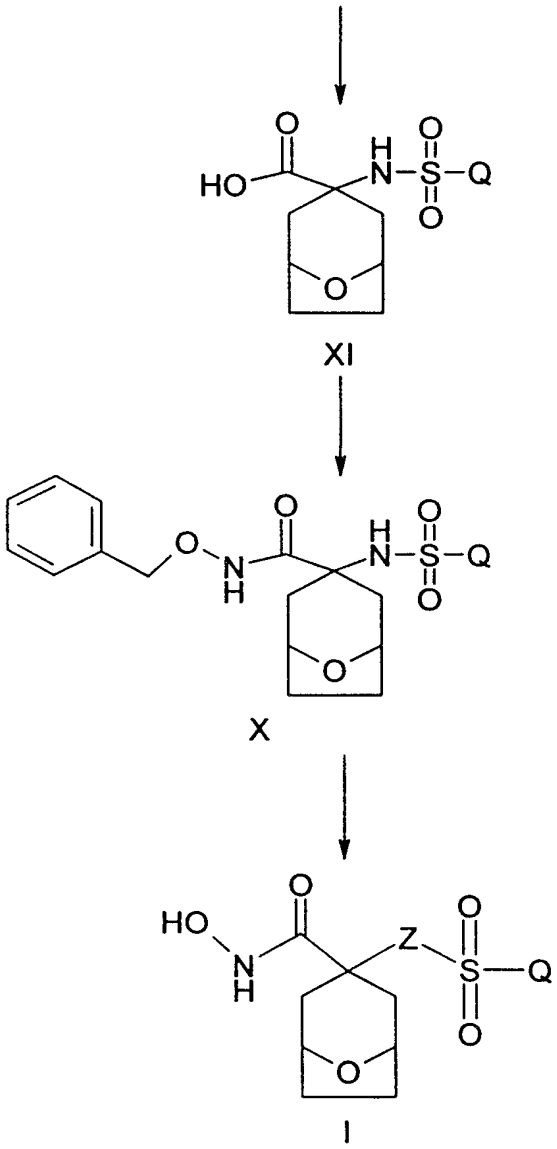


SCHEME 2 CONTINUED



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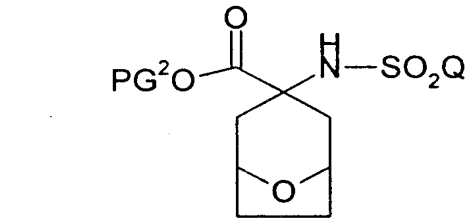
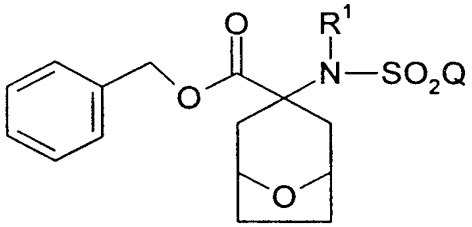


XII



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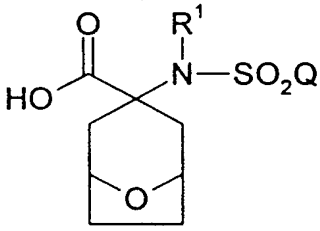

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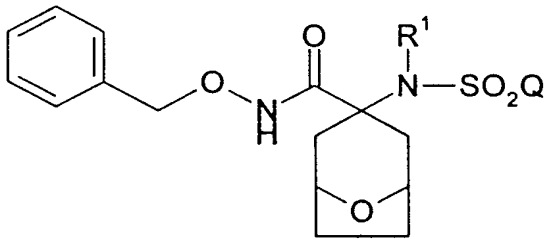

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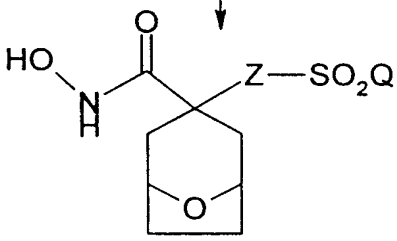
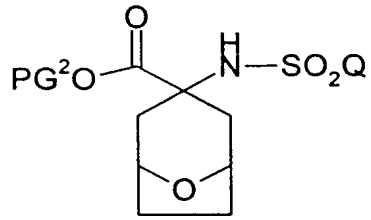
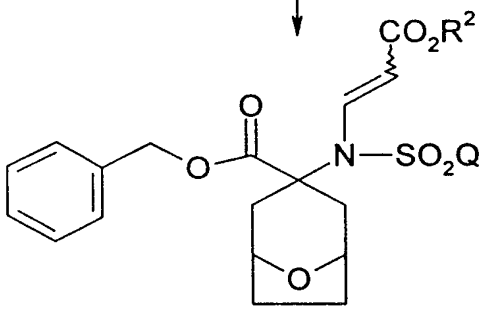


I

SCHEME 4



XII



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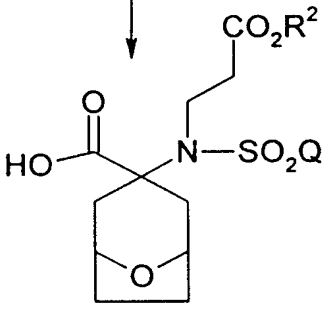
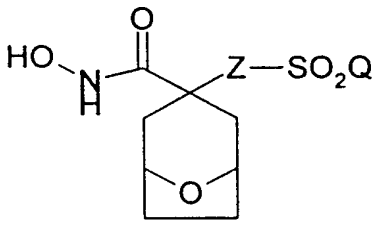


XVIII



I

Scheme 1 refers to the preparation of compounds of formula I, wherein Z is CH_2. Referring to Scheme I, a compound of the formula I is prepared from a compound of the formula II by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include 5% palladium on barium sulfate or 5% palladium on carbon, preferably 5% palladium on barium sulfate. Suitable solvents include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours.

Compounds of the formula II can be prepared from compounds of the formula III by reaction with an oxidant in a reaction inert solvent. Suitable oxidants include meta-chloroperbenzoic acid, hydrogen peroxide or sodium perborate, preferably meta-chloroperbenzoic acid. Suitable solvents include halogenated solvents such as methylene chloride or chloroform, preferably methylene chloride. Suitable temperatures for the aforesaid reaction range from about 0°C to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 24 hours, preferably about 16 hours.

The compound of formula III is prepared from a compound of formula IV by reaction with O-benzylhydroxyamine hydrochloride, an activating agent, and a base in a reaction inert solvent. Suitable activating agents include (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate or 1-(3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, preferably (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate. Suitable bases include tertiary amines such as triethylamine, diisopropylethylamine or 4-N,N-dimethylaminopyridine, preferably diisopropylethylamine. The temperature of the aforesaid reaction may range from about 0°C to about 60°C, preferably about 50°C. Suitable solvents include N,N-dimethylformamide, halogenated solvents such as methylene chloride or chloroform, or ethers such as THF or diethyl ether; preferably the solvent is N,N-dimethylformamide. The reaction is complete in about 4 hours to about 48 hours, preferably about 16 hours.

Compounds of the formula IV, can be prepared from compounds of the formula V, by reaction with a compound of the formula **QSH**, wherein Q is as defined above, in the presence of a strong base in an aprotic polar solvent. Suitable bases include sodium hydride, lithium diisopropylamide, potassium t-butoxide, sodium amide or potassium hydride, preferably sodium hydride. Suitable solvents include ethers (such as THF, diethyl ether or 1,2-

dimethoxyethane), or N, N-dimethylformamide, preferably the solvent is THF. The aforesaid reaction is conducted at about -78°C to about 0°C, preferably at about 22°C (i.e., room temperature) for a period of 30 minutes to about 24 hours, preferably about 2 hours.

Compounds of the formula V are prepared from compounds of the formula VI by dehydration in the presence of a tertiary amine base, preferably triethylamine, optionally in the presence of 4-dimethylaminopyridine, and a dehydrating agent in an inert solvent. Suitable dehydrating agents include trifluoromethanesulfonic anhydride, methanesulfonic anhydride, methanesulfonyl chloride, *p*-toluenesulfonyl chloride or benzenesulfonyl chloride, preferably benzenesulfonyl chloride. Suitable solvents include diethyl ether or dichloromethane. The reaction is performed at a temperature from about -80°C to about 0°C, preferably about 0°C. The reaction is carried out for about 10 minutes to 4 hours, preferably about 1 hour.

The compounds of the formula VI are prepared from a compound of formula VII, wherein PG^1 is methyl or ethyl, by saponification with a base, such as lithium hydroxide, in a solvent mixture. Suitable solvent mixtures include water and methanol or water, methanol and THF. The reaction is performed at a temperature from about 60°C to about 120°C, preferably at about the reflux temperature of the solvent mixture used. The reaction is carried out for about 30 minutes to 24 hours, preferably about 16 hours.

The exo-hydroxymethyl isomer of the compound of the formula VII is prepared from a compound of formula VIII. In general, a solution of a compound of formula VIII is dissolved in an inert aromatic solvent, preferably benzene or toluene, and cooled at about -40° C to -20°C, preferably about -40°C. To the cold solution is added a suitable hindered reducing agent, preferably disobutylaluminum hydride, in an inert aromatic solvent, maintaining the temperature below -25°C. After the addition is complete, the reaction is maintained below 0°C for about 3 hours. At about -15°C, a protic solvent, preferably ethanol, is added. After stirring at about -15°C for about 1 hour, sodium borohydride is added and the reaction is allowed to warm to about room temperature while stirring for a period of 2 to 24 hours, preferably about 16 hours.

The endo-hydroxymethyl isomer of the compound of the formula VII can be prepared from the exo-hydroxymethyl compound of the formula VI by a series of steps which can invert the sterochemistry about the carbon atom bearing the hydroxymethyl and carboxylic acid groups. Specifically, the exo-hydroxymethyl isomer of formula VI is first converted to the corresponding benzyl ester. Subsequent Jones oxidation of the alcohol to the carboxylic acid and alkyl ester formation (methyl or ethyl) provides an intermediate mixed benzyl alkyl ester (i.e. the exo ester is methyl or ethyl and the endo ester is benzyl). The benzyl ester is then removed by hydrogenolysis and the resulting carboxylic acid is reduced to the alcohol by diborane reduction, providing the endo-hydroxymethyl isomer of the compound of the formula VII.

The compounds formula VIII, wherein PG^1 is ethyl or methyl, are prepared from compounds of the formula IX, wherein L is methanesulfonyl, benzenesulfonyl or tosyl, by reaction with dimethyl or diethyl malonate in the presence of a strong base, such as sodium hydride, in a polar solvent, such as N,N-dimethylformamide, for a time period between about 4 hours to about 24 hours, preferably about 16 hours. The aforesaid reaction temperature is between about 70°C to about 150°C, preferably about 140° C.

Compounds of the formula IX are known or can be made by methods well known to those of ordinary skill in the art.

Compounds of the formula QSH can be prepared by reaction of an alkyl or aryl halide with sodium sulfhydride as described in Jerry March, Advanced Organic Chemistry, 360 and 589 (3rd ed., 1985). Alternatively, compounds of the formula QSH can also be prepared by reaction of an aryl diazonium salt with sodium sulfhydride as described in March id. at 601. Alternatively, compounds of the formula QSH can also be prepared by reaction of a Grignard reagent with sulfur as described in March id. at 550. Alternatively, compounds of the formula QSH can also be prepared by reduction of a sulfonyl chloride, sulfonic acid or disulfide as described in March id. at 1107 and 1110.

Scheme 2 refers to the preparation of compounds of the formula I, wherein Z is $>NR^1$, and R^1 is hydrogen. Referring to Scheme 2, compounds of formula I can be prepared from compounds of the formula X by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include 5% palladium on barium sulfate or 5% palladium on carbon, preferably 5% palladium on barium sulfate. Suitable solvents include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours.

The compound of formula X is prepared from a compound of the formula XI by reaction with O-benzylhydroxylamine hydrochloride in the presence of a catalyst and a base in a reaction inert solvent. Suitable catalysts include (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate or 1-(3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, preferably (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate. Suitable bases include tertiary amines such as triethylamine, diisopropylethylamine or 4-N,N-dimethylaminopyridine, preferably diisopropylethylamine. The aforesaid reaction temperature is from about 0° C to about 60°C, preferably about 50° C. Suitable solvents include N,N-dimethylformamide or halogenated

solvents such as methylene chloride or chloroform; preferably, the solvent is N,N-dimethylformamide. The reaction is conducted over a period of about 4 hours to about 48 hours, preferably about 16 hours.

Compounds of the formula XI are prepared from compounds of the formula XII, wherein PG^2 is methyl or ethyl, by saponification with a base such as sodium hydroxide in a solvent mixture such as water and ethanol. The reaction is performed at a temperature from about 60°C to about 100°C, preferably at about the reflux temperature of the solvent mixture used. The reaction is carried out for about 1 day to 10 days, preferably about 6 days.

The compounds of the formula XII, wherein PG^2 is methyl or ethyl, are prepared from compounds of the formula XIII, wherein PG^2 is methyl or ethyl, by reaction with a compound of the formula QSO_2Cl in the presence of a base, such as triethylamine, and a polar solvent. Suitable solvents include N,N-dimethylformamide, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, water or acetonitrile, preferably N,N-dimethylformamide. The reaction mixture is stirred at room temperature for a time period between about 1 hour to about 24 hours, preferably about 16 hours.

Compounds of the formula XIII, wherein PG^2 is methyl or ethyl, are prepared from compounds of the formula XIV, wherein PG^2 is methyl or ethyl, by hydrolysis in the presence of aqueous mineral acid and a solvent such as diethyl ether. Suitable mineral acids include hydrochloric and sulfuric acid, preferably hydrochloric acid. The reaction is carried out at a temperature ranging from about 0°C to 50°C; preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is conducted over a period of about 2 hours to about 48 hours, preferably about 16 hours.

Compounds of the formula XIV, wherein PG^2 is methyl, ethyl or benzyl, are prepared from compounds of the formula IX, wherein L is methanesulfonyl, benzenesulfonyl or tosyl, by reaction with N-diphenylmethylene glycine, methyl, ethyl or benzyl ester, in the presence of a strong base, such as sodium hydride, in a polar solvent, such as N,N-dimethylformamide, for a time period between about 4 hours to about 24 hours, preferably about 16 hours. The aforesaid reaction temperature is between about 70°C to about 140°C, preferably about 100° C. Compounds of the formula XIV, wherein PG^2 is methyl, ethyl or benzyl, are obtained as mixtures of diastereomers which can be separated by chromatographic means.

Compounds of the formula QSO_2Cl and formula IX are known or commercially available or can be made by methods well known to those of ordinary skill in the art.

Scheme 3 refers to the preparation of compounds of the formula I, wherein Z is NR^1 and R^1 is $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl or a group of the formula $-(CH_2)_nCO_2R^2$, wherein n is 1, 3, 4, 5, or 6 and R^2 is $(C_1\text{-}C_6)$alkyl.

Referring to Scheme 3, compounds of the formula I, wherein Z is NR^1 and R^1 is (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl or a group of the formula $-(CH_2)_nCO_2R^2$, wherein n is 1, 3, 4, 5, or 6 and R^2 is (C_1-C_6)alkyl, are prepared from compounds of the formula XV by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include 5% palladium on barium sulfate or 5% palladium on carbon, preferably 5% palladium on barium sulfate. Suitable solvents include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours.

The compound of formula XV is prepared from a compound of the formula XVI by reaction with O-benzylhydroxylamine hydrochloride in the presence of a catalyst and a base in a reaction inert solvent. Suitable catalysts include (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate or 1-(3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, preferably (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate. Suitable bases include tertiary amines such as triethylamine, diisopropylethylamine or 4-N,N-dimethylaminopyridine, preferably diisopropylethylamine. The aforesaid reaction temperature is from about 0° C to about 60°C, preferably about 50° C. Suitable solvents include N,N-dimethylformamide or halogenated solvents such as methylene chloride or chloroform, preferably the solvent is N,N-dimethylformamide. The reaction is conducted over a period of about 4 hours to about 48 hours, preferably about 16 hours.

The compound of formula XVI is prepared from a compound of the formula XVII by removal of the benzyl protecting group. Specifically, the benzyl protecting group is removed by hydrogenolysis using palladium or palladium on carbon in a solvent such as methanol or ethanol, for a period from about 30 minutes to about 48 hours, preferably 16 hours, at a temperature of about 20°C to about 25°C (i.e., room temperature).

The compound of formula XVII is prepared from a compound of the formula XII, wherein PG^2 is benzyl, by reaction with a reactive derivative of an alcohol of the formula $\mathbf{R^1OH}$ such as the methanesulfonate, tosylate, chloro, bromo or iodo derivative, preferably the iodo derivative, in the presence of a base such as potassium carbonate or sodium hydride, preferably sodium hydride, and a polar solvent, such as N,N-dimethylformamide. The reaction mixture is stirred at room temperature for a time period between about 60 minutes to about 48 hours, preferably about 16 hours.

The compounds of formula XII, wherein PG^2 is benzyl, are prepared according to the methods of Scheme 2.

Scheme 4 refers to the preparation of compounds of formula I, wherein Z is $>NR^1$, R^1 is a group of the formula $-(CH_2)_2CO_2R^2$ (i.e. n is 2) and R^2 is $(C_1\text{-}C_6)$alkyl.

Referring to Scheme 4, compounds of said formula I are prepared from compounds of the formula XVIII, wherein R^2 is $(C_1\text{-}C_6)$alkyl, by reaction with oxalyl chloride or thionyl chloride, preferably oxalyl chloride, and a catalyst, preferably about 2% of N,N-dimethylformamide, in an inert solvent, such as methylene chloride, to form an *in situ* acid chloride that is subsequently reacted with O-trimethylsilylhydroxylamine in the presence of a base, such as pyridine, 4-N,N-dimethylaminopyridine or triethylamine, preferably pyridine. The reaction is performed at a temperature of about 22°C (i.e., room temperature) for about 1 to about 12 hours, preferably about 1 hour.

Compounds of the formula XVIII, wherein R^2 is $(C_1\text{-}C_6)$alkyl, can be prepared from compounds of the formula XIX, wherein R^2 is $(C_1\text{-}C_6)$alkyl, by reduction in a polar solvent. Suitable reducing agents include hydrogen over palladium and hydrogen over palladium on carbon, preferably hydrogen over palladium on carbon. Suitable solvents include methanol, ethanol and isopropanol, preferably ethanol. The aforesaid reaction is performed at a temperature of about 22°C (i.e., room temperature) for a period of 1 to 7 days, preferably about 2 days.

Compounds of the formula XIX, wherein R^2 is $(C_1\text{-}C_6)$alkyl, can be prepared from compounds of the formula XII, wherein PG^2 is benzyl, by Michael addition of a propiolate ester and a base in a polar solvent. Suitable propiolates are of the formula $H\text{-}C{\equiv}C\text{-}CO_2R^2$, wherein R^2 is $(C_1\text{-}C_6)$alkyl. Suitable bases include tetrabutylammonium fluoride, potassium carbonate, and cesium carbonate, preferably tetrabutylammonium fluoride. Suitable solvents include tetrahydrofuran, acetonitrile, tert-butanol and N,N-dimethylformamide, preferably tetrahydrofuran. The aforesaid reaction is performed at a temperature of about -10°C to about 60°C, preferably ranging between 0°C and about 22°C (i.e., room temperature). The compounds of formula XIX are obtained as mixtures of geometric isomers about the olefinic double bond; separation of the isomers is not necessary.

Compounds of the formula XII, wherein PG^2 is benzyl, can be prepared according to the methods of Scheme 2.

Compounds of said formula I, wherein Z is $>NR^1$, R^1 is a group of the formula $-(CH_2)_nCO_2R^2$, n is 1 to 6 and R^2 is hydrogen are prepared from compounds of formula I, wherein Z is $>NR^1$, R^1 is a group of the formula $-(CH_2)_nCO_2R^2$, n is 1 to 6 and R^2 is $(C_1\text{-}C_6)$alkyl, by saponification using a base such as sodium hydroxide in a protic solvent such as ethanol, methanol or water or a mixture such as water and ethanol, water and toluene, or water and THF.

The preferred solvent system is water and ethanol. The reaction is conducted for a period of 30 minutes to 24 hours, preferably about 2 hours.

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit metalloproteinases or mammalian reprolysin and, consequently, demonstrate their effectiveness for treating diseases characterized by metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin. The amount of trypsin is optimized for each lot of collagenase-1 but a typical reaction uses the following ratio: 5 μg trypsin per 100 μg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted using the following scheme:

10 mM ------> 120 μM ------> 12 μM ------> 1.2 μM ------> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D7-D12 and negative controls (no enzyme, no inhibitors) are set in wells D1-D6.

Collagenase-1 is diluted to 240 ng/ml and 25 ml is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 60 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethylsulfoxide and then diluted to 20 μM in assay buffer. The assay is initiated by the addition of 50 ml substrate per well of the microfluor plate to give a final concentration of 10 mM.

Fluorescence readings (360 nM excitation, 460 nm emission) are taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours

Fluorescence versus time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (at least five fold over the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration versus % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be less than 0.03 mM then the inhibitors are assayed at concentrations of 0.3 mM, 0.03 mM, and 0.003 mM.

Inhibition of Gelatinase (MMP-2)

Human recombinant 72 kD gelatinase (MMP-2, gelatinase A) is activated for 16-18 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 4°C, rocking gently.

10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM $CaCl_2$, 20 μM $ZnCl_2$ and 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM---→ 120 μM----→ 12 μM----→ 1.2 μM----→ 0.12 μM

Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μL of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μL, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μM ----→ 3 μM ----→ 0.3 μM ----→ 0.03 μM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 μL per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 25 ng/mL (0.34 nM).

A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2) is diluted in assay buffer to 20 μM. The assay is initiated by addition of 50 μL of diluted substrate yielding a final assay concentration of 10 μM substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC_{50}'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of Stromelysin Activity (MMP-3)

Human recombinant stromelysin (MMP-3, stromelysin-1) is activated for 20-22 hours with 2 mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37°C.

10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 150 mM NaCl, 10 mM $CaCl_2$ and 0.05% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM---→ 120 μM----→ 12 μM----→ 1.2 μM----→ 0.12 μM

Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μL of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μL, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μM ----→ 3 μM ----→ 0.3 μM ----→ 0.03 μM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

Activated enzyme is diluted to 200 ng/mL in assay buffer, 25 μL per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 50 ng/mL (0.875 nM).

A ten mM dimethylsulfoxide stock solution of substrate (Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH_2) is diluted in assay buffer to 6 μM. The assay is initiated by addition of 50 μL of diluted substrate yielding a final assay concentration of 3 μM substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC_{50}'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Alternatively, inhibition of stromelysin activity can be assayed using Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH_2 (3 μM) under conditions similar as in inhibition of human collagenase (MMP-1).

Human stromelysin is activated for 20-24 hours at 37°C with 2 mM APMA (p-aminophenyl mercuric acetate) and is diluted to give a final concentration in the assay of 50

ng/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 μM, 3 μM, 0.3 μM, and 0.03 μM. Each concentration is done in triplicate.

Fluorescence readings (320 nm excitation, 390 emission) are taken at time zero and then at 15 minute intervals for 3 hours.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, then the inhibitors are assayed at final concentrations of 0.03 μM, 0.003 μM, 0.0003 μM, and 0.00003 μM.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 2.0 hours, at 37°C and is diluted to 240 ng/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20mM zinc chloride, 0.02% brij 35). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 60 ng/ml.

Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase-1 (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 mM, 3mmM, 0.3m mM, and 0.03 mmM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM. Fluorescence readings (360 nM excitation; 450 nM emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls and negative controls are set up in triplicate as outlined in the MMP-1 assay.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 mM, inhibitors are then assayed at final concentrations of 0.3 mM, 0.03 mmM, 0.003 mmM and 0.0003 mM.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2