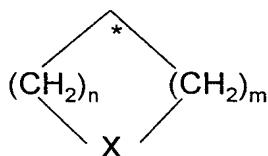


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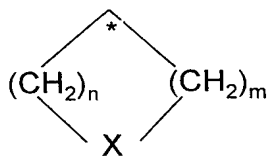


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wherein the carbon atom bearing the asterisk is the carbon to which R³ and R⁴ are attached, "n" and "m" are independently selected from the integers one and two, and X is CF₂, O, SO₂ or NR⁹, wherein R⁹ is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy(C=O)-, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryloxy(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)- or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-; wherein each of said (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl or (C₃-C₆)cycloalkyl moieties of said (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C=O)NH(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)NH(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)NH(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-, (C₃-C₆)cycloalkyl, or benzo-fused(C₃-C₆)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

25

or when R³ and R⁴ are taken together with the carbon atom to which they are attached to form a group of the formula



30

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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

5 R⁵ is R⁶O or R⁶R⁷N wherein R⁶ and R⁷ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₂-C₉)heteroaryl(C₁-C₆)alkyl; wherein each of said (C₆-C₁₀)aryl and (C₂-C₉)heteroaryl moieties of said (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₂-C₉)heteroaryl(C₁-C₆)alkyl groups may be optionally substituted by one or more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, 10 perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

or R⁶ and R⁷ taken together with the nitrogen atom to which they are attached form an optionally substituted heterocycle selected from piperaziny, (C₁-C₆)alkylpiperaziny, (C₆-C₁₀)arylpiperaziny, (C₂-C₉)heteroarylpiperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperaziny, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperaziny, (C₁-C₆)alkyl(C=O)-piperaziny, (C₁-C₆)alkoxy(C=O)-piperaziny, (C₆-C₁₀)aryl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperaziny, morpholiny, piperidiny, pyrrolidiny or azetidiny; 15 wherein each of said piperaziny, (C₁-C₆)alkylpiperaziny, (C₆-C₁₀)arylpiperaziny, (C₂-C₉)heteroarylpiperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperaziny, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperaziny, (C₁-C₆)alkyl(C=O)-piperaziny, (C₁-C₆)alkoxy(C=O)-piperaziny, (C₆-C₁₀)aryl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperaziny, morpholiny, piperidiny, pyrrolidiny or azetidiny 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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, or perfluoro(C₁-C₃)alkoxy and 25 (C₆-C₁₀)aryloxy;

R⁶ is piperaziny, (C₁-C₆)alkylpiperaziny, (C₆-C₁₀)arylpiperaziny, (C₂-C₉)heteroarylpiperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperaziny, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperaziny, (C₁-C₆)alkyl(C=O)-piperaziny, (C₁-C₆)alkoxy(C=O)-piperaziny, (C₆-C₁₀)aryl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperaziny, morpholiny, piperidiny, pyrrolidiny, azetidiny, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)arylpiperidyl, (C₂-C₉)heteroarylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperidyl, (C₁-C₆)alkyl(C=O)-piperidyl, (C₁-C₆)alkoxy(C=O)-piperidyl, (C₆-C₁₀)aryl(C=O)-piperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperidyl, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperidyl; wherein 30 each of said piperaziny, (C₁-C₆)alkylpiperaziny, (C₆-C₁₀)arylpiperaziny, (C₂-C₉)heteroarylpiperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperaziny, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperaziny, (C₁-C₆)alkyl(C=O)-piperaziny, (C₁-C₆)alkoxy(C=O)-piperaziny, (C₆-C₁₀)aryl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperaziny, morpholiny, piperidiny, pyrrolidiny, azetidiny, 35 (C₆-C₁₀)aryloxy;

5 piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)arylpiperidyl, (C₂-C₉)heteroarylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperidyl (C₁-C₆)alkyl(C=O)-piperidyl, (C₁-C₆)alkoxy(C=O)-piperidyl, (C₆-C₁₀)aryl(C=O)-piperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperidyl, and (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperidyl may be optionally substituted on any ring carbon atom capable of forming an additional bond with a

10 substituent (preferably one to three substituents per ring) independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, or perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

Q is (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl or (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl wherein each (C₆-C₁₀)aryl or (C₂-C₉)heteroaryl moieties of said (C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl or (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₂-C₉)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

35

with the proviso that if either R³ or R⁴ is hydrogen, or if both R³ and R⁴ are hydrogen, then R¹ and R² can not both be hydrogen or R¹ must be hydroxy, (C₁-C₆)alkoxy, (C₆-C₁₀)aryl(C₁-C₆)alkoxy, (C₁-C₆)alkyl(C=O)O-(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C=O)O-(C₁-C₆)alkyl,

- 5 (C₆-C₁₀)aryl(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C=O)O- (C₆-C₁₀)arylalkyl(C=O)O-(C₁-C₆)alkyl
or (C₆-C₁₀)arylalkoxy(C=O)O-(C₁-C₆)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
10 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,
15 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
20 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)-
25 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.

30 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
35 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.

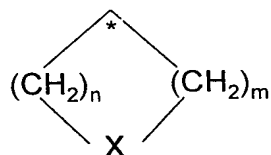
5 The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkoxy and the terms "alkyl" or "aryl" are as defined above.

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

10 The compound of formula I may have chiral centers and therefore exist in different diastereomeric 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 R¹ is OH and R² is hydrogen.

15 Other preferred compounds of formula I include those wherein both R³ and R⁴ are (C₁-C₆)alkyl or R³ and R⁴ are taken together to form an optionally substituted (C₃-C₆)cycloalkyl ring or a benzo-fused(C₃-C₆)cycloalkyl ring or a group of the formula



20 wherein the carbon atom bearing the asterisk is the carbon to which R³ and R⁴ are attached, "n" and "m" are independently selected from the integers one and two, and X is CF₂, O, SO₂ or NR⁹, wherein R⁹ is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroalkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy(C=O)-, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-; wherein each of said (C₆-C₁₀)aryl and (C₂-C₉)heteroaryl moieties of said (C₆-C₁₀)aryl, (C₂-C₉)heteroalkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-, and (C₆-C₁₀)aryl(C₁-C₆)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy.

30 More preferred compounds of formula I include those wherein R³ and R⁴ are taken together to form an optionally substituted (C₃-C₆)cycloalkyl ring.

Other preferred compounds of formula I include those wherein R¹ is hydroxy.

35 Other preferred compounds of formula I include those wherein Q is (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, wherein each (C₆-C₁₀)aryl moieties of said is (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl groups may be optionally substituted with one or more substituents

5 independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl, more preferably the
 10 substituents are selected from fluoro, chloro, (C₁-C₆)alkoxy or (C₁-C₆)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,
 15 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
 20 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
 25 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,

30 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.

35 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

5 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.

10 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.

15 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)
20 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.

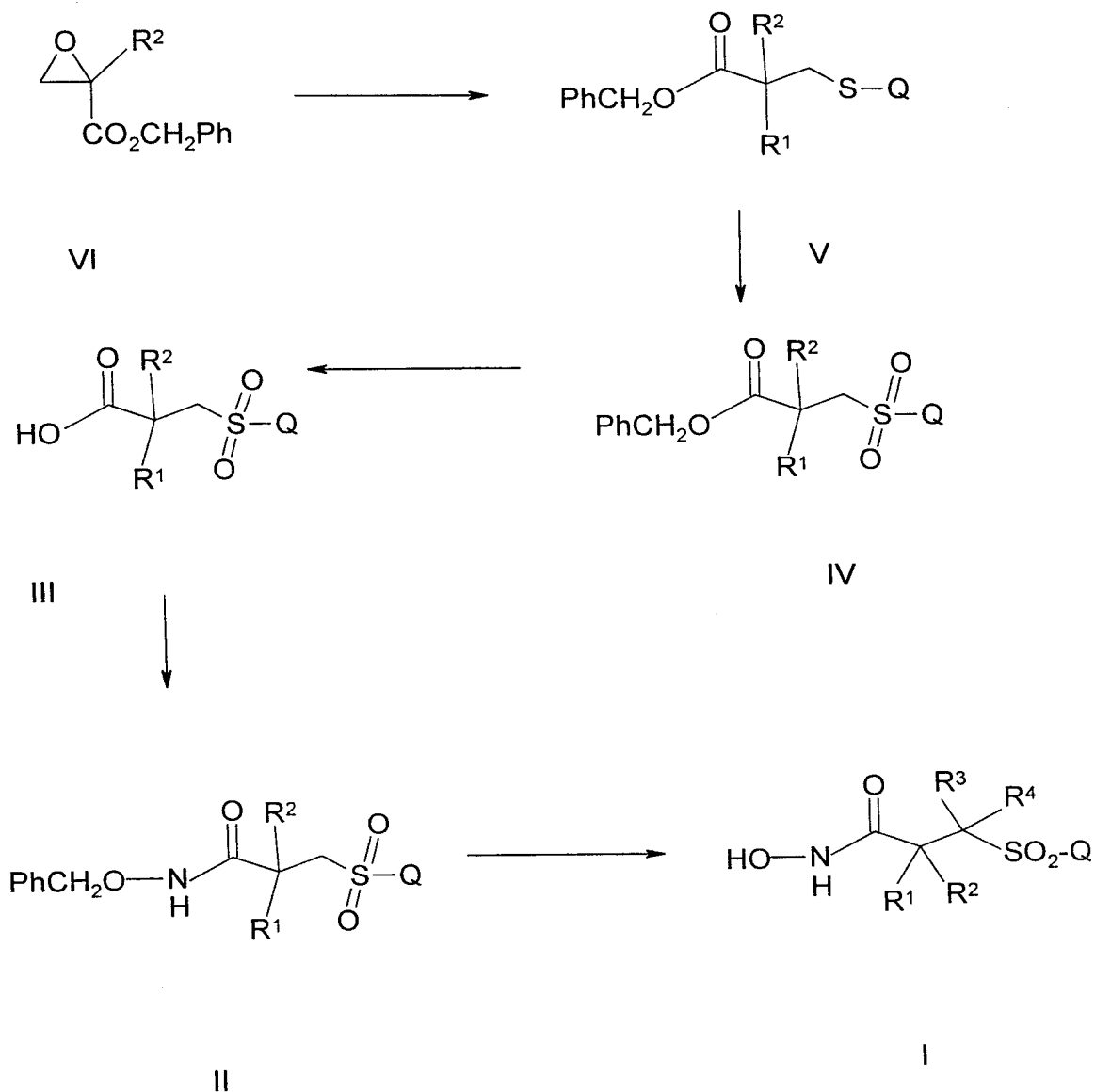
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Detailed Description of the Invention

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.

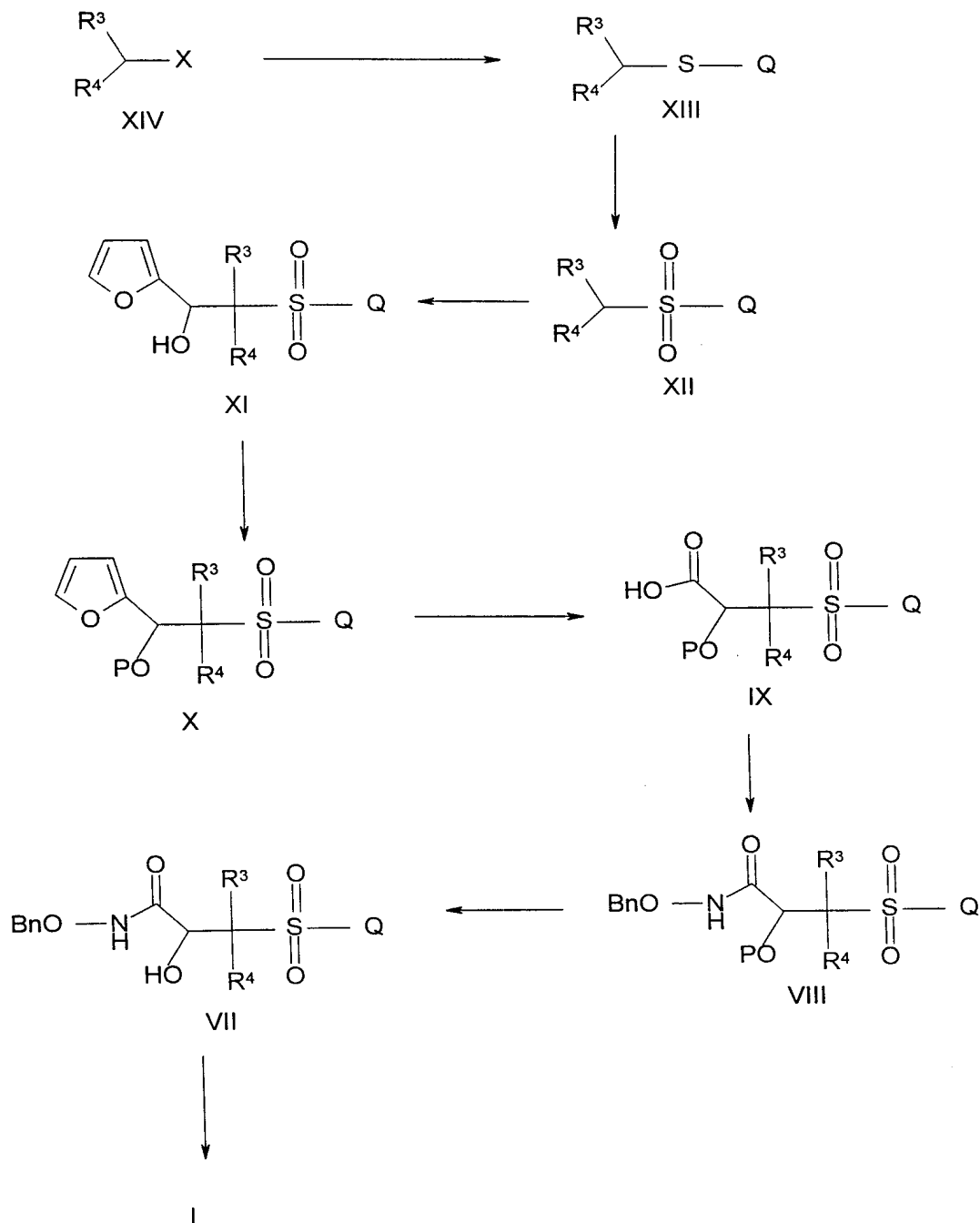
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SCHEME 1



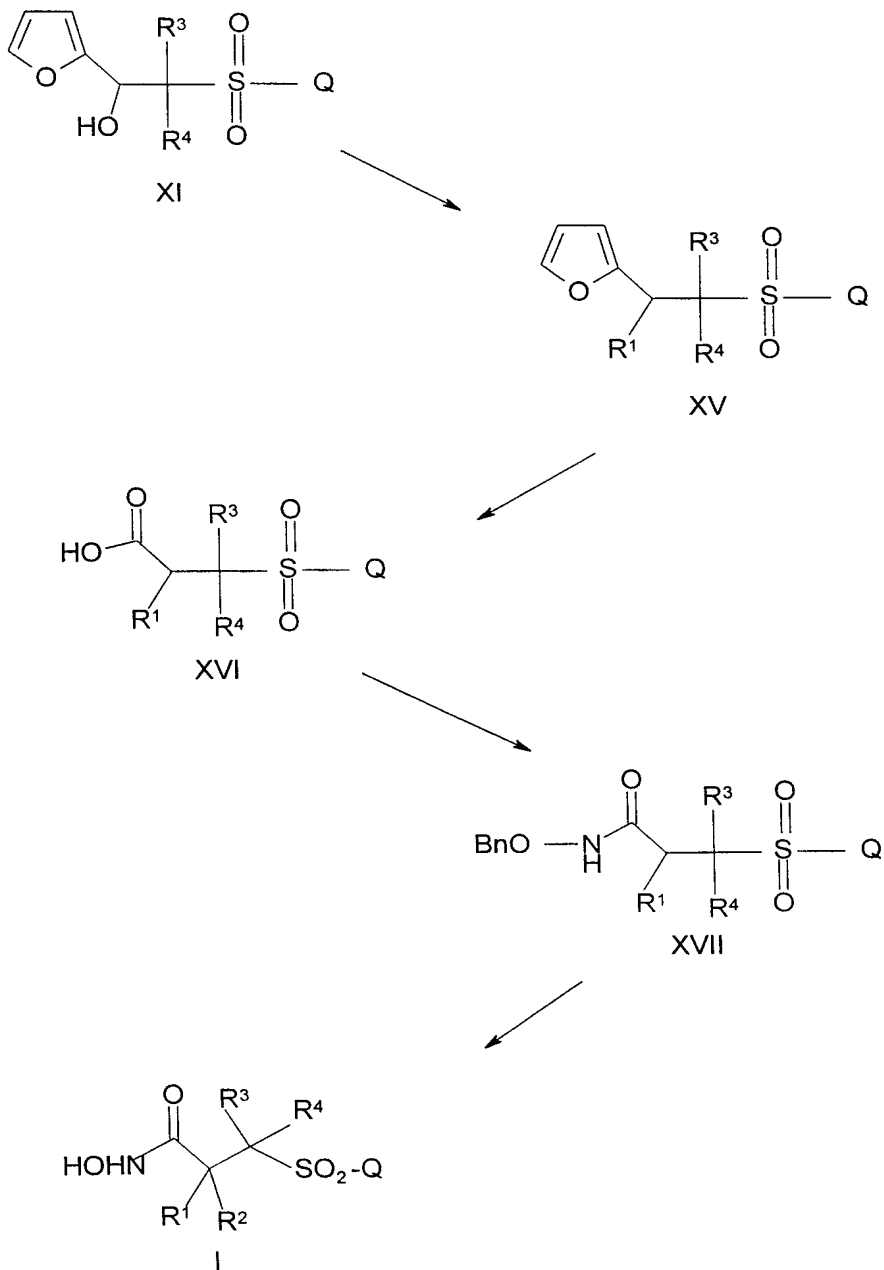
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SCHEME 2



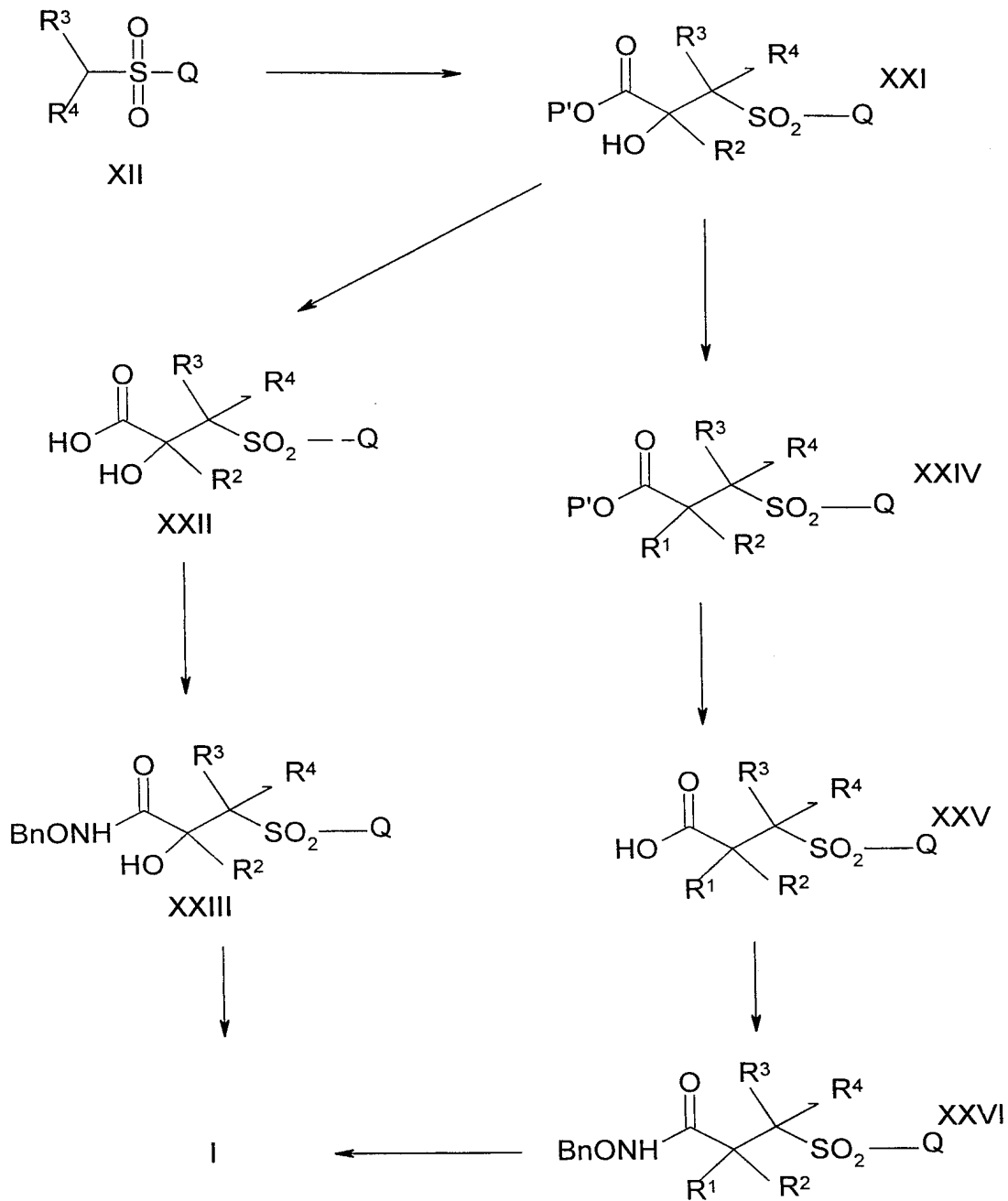
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SCHEME 3



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SCHEME 4



5 Scheme 1 refers to the preparation of compounds of the formula I, wherein R³ and R⁴ 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.
10 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
15 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
20 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
25 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
30 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
35 (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-

5 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
10 hours to about 24 hours, preferably about 3 hours.

Compounds of the formula V, wherein R¹ 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
15 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.

20 Compounds of the formula V, wherein R¹ is (C₆-C₁₀)aryl(C₁-C₆)alkoxy or (C₁-C₆)alkoxy, can be prepared from compounds of the formula V, wherein R¹ is hydroxy, by reaction with a compound of the formula R^{1a}L, wherein L is a leaving group and R^{1a} is (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₁-C₆)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
25 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.

30 Compounds of the formula V, wherein R¹ is (C₁-C₆)alkyl(C=O)O-, (C₁-C₆)alkoxy-(C=O)O-, (C₆-C₁₀)aryl(C=O)O-, (C₆-C₁₀)aryloxy(C=O)O-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)O- or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)O-, can be prepared from compounds of the formula V, wherein R¹ is hydroxy, by reaction with a compound of the formula R^{1b}L, wherein L is a leaving group and R^{1b} is (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy(C=O)-, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryloxy(C=O)-,
35 (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)- or (C₆-C₁₀)aryl(C₁-C₆)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

5 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
10 (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 Knoevenagel condensation between a malonate monobenzyl ester and paraformaldehyde in the presence of piperidine as described in
15 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
20 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
25 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.

30 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
35 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.

5 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.

15 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 acetonitrile, carbon tetrachloride and water. The reaction is conducted from about 0.5 to about 2 hours, preferably about 1.25 hours.

20 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 chloride 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.

30 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.

5 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
10 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.
15 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
20 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 sulfhydryde as described in
Jerry March, Advanced Organic Chemistry, 360 and 589 (3rd ed., 1985). Alternatively,
25 compounds of the formula QSH can also be prepared by reaction of an aryl diazonium salt with
sodium sulfhydryde 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.

30 Scheme 3 refers to the preparation of compounds of the formula I, wherein R¹ is other
than hydroxy and R² 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.

35 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.

5 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.

10 Compounds of the formula XV, wherein R¹ is (C₆-C₁₀)aryl(C₁-C₆)alkoxy or (C₁-C₆)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 (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₁-C₆)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.

15 Compounds of the formula XV, wherein R¹ is (C₁-C₆)alkyl(C=O)O-, (C₁-C₆)alkoxy(C=O)O-, (C₆-C₁₀)aryl(C=O)O-, (C₆-C₁₀)aryloxy(C=O)O-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)O- or (C₆-C₁₀)aryl(C₁-C₆)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 (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy(C=O)-, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryloxy(C=O)O-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)- or (C₆-C₁₀)aryl(C₁-C₆)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.

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

25 Scheme 4 refers to the preparation of compounds of the formula I, wherein R² is other than hydrogen and R³ and R⁴ are other than hydrogen.

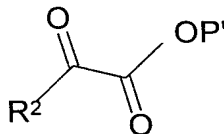
30 Referring to Scheme 4, compounds of the formula I are prepared from compounds of the formula XXIII by hydrogenolysis under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include 5% palladium on barium sulfate or 5% palladium on carbon, preferably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

5 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
10 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
15 conducted from about 4 hours to about 48 hours, preferably about 16 hours.
20

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.
25 The aforesaid reaction may be 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
30 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

5 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
10 reaction is conducted from about 0.25 hours to about 6 hours, preferably about 0.33 hours.

Alternatively, compounds of the formula I, wherein R¹ is other than hydroxy, R² is other than hydrogen and R³ and R⁴ 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.

15 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,
20 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.

25 Compounds of the formula XXIV, wherein R¹ is (C₆-C₁₀)aryl(C₁-C₆)alkoxy, (C₁-C₆)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
30 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 R¹ is (C₁-C₆)alkyl(C=O)O-,
35 (C₁-C₆)alkoxy(C=O)O-, (C₆-C₁₀)aryl(C=O)O-, (C₆-C₁₀)aryloxy(C=O)O-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)O- or (C₆-C₁₀)aryl(C₁-C₆)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

5 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.

10 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
15 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
20 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,
25 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
30 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
35 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

5 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.

10 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

15 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.

20 10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM -----> 120 μ M -----> 12 μ M -----> 1.2 μ M -----> 0.12 μ M

25 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 μ l is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

30 Substrate (DNP-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) 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 μ l substrate per well of the microfluor plate to give a final concentration of 10 mM.

35 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 IC₅₀ values. The zero time is used as a blank for each compound at each

5 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). IC₅₀'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

10 If IC₅₀'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)-NH₂ substrate (10 mM) under the same conditions as inhibition of human collagenase (MMP-1).

15 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.

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

IC₅₀'s are determined as per inhibition of human collagenase (MMP-1). If IC₅₀'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)

25 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 thiopeptolide substrate [Ac-Pro-Leu-Gly-SCH[CH₂CH(CH₃)₂]CO-Leu-Gly-OC₂H₅] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

30 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.

35 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.

5 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
10 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.

 IC₅₀ values were determined in the same manner as for collagenase.

Inhibition of MMP-13

15 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
20 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.

25 Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) 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
30 substrate only.

 IC₅₀'s are determined as per inhibition of human collagenase (MMP-1). If IC₅₀'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
35 had IC₅₀'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:

5 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 $2 \times$
 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
10 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
CO₂ incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and
15 the supernatants removed and assayed for TNF α 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
20 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.

25 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
30 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 tableting purposes.
35 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,

5 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.

10 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.

15 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.

20 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

25 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

30 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

35 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 (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

5 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

10 (2S)-2,N-DIHYDROXY-3-(4-METHOXYBENZENESULFONYL)PROPIONAMIDE

(A) (2S)-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 (2S)-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, (2S)-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) (2S)-2-Hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid benzyl ester

25 A solution of (2S)-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. 30 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 (2S)-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid benzyl ester (3.2 grams, 84%) as a white crystalline solid.

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

35 A solution of (2S)-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

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

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

To a solution of (2S)-2-hydroxy-3-(4-methoxybenzenesulfonyl)propionic acid (800 mg, 3.0 mmole), O-benzylhydroxylamine hydrochloride (526 mg, 3.3 mmole) and triethylamine (1.2
10 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
15 drying over magnesium sulfate, the solvent was evaporated to afford an oil. The desired product, (2S)-N-benzoyloxy-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) (2S)-2,N-Dihydroxy-3-(4-methoxybenzenesulfonyl)propionamide

20 A solution of (2S)-N-benzoyloxy-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 μ m nylon filter and the filtrate was concentrated. The desired product, (2S)-2,N-dihydroxy-3-(4-methoxybenzenesulfonyl) propionamide (180 mg, 65%),
25 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 C₁₀H₁₃NO₆S: C, 43.63; H, 4.76; N, 5.09. Found: C, 43.51; H, 4.68; N, 4.95.

Example 2

30 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
35 C₁₅H₁₄FNO₆S.0.75H₂O: 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

5 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
10 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-Cyclobutylsulfanyl-4-methoxybenzene

15 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
20 bicarbonate solution, water and brine. After drying over magnesium sulfate, the solution was
concentrated to a white solid. Recrystallization from ethyl acetate afforded
1-cyclobutylsulfanyl-4-methoxybenzene (7.28 grams, 79%) as a white crystalline solid.

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

25 A solution of 1-cyclobutylsulfanyl-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
30 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)cyclo-
butyl]-methyl ester

35 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
40 MgSO₄, the solvent was evaporated to leave an oil from which the desired product, 2,2-

5 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)-
10 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
15 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-
20 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
25 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
30 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-
35 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

5 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)-
10 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
15 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
20 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

25 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
30 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
35 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

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5 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

10 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

15 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

20 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

25 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
30 was dried in the air.

Preparation B

4-(4-FLUOROPHENOXY)BENZENETHIOL

35 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

5 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

10 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
15 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

20 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
25 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

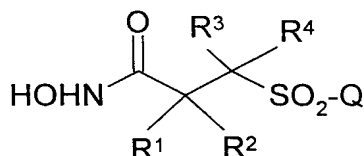
1-BUTOXY-4-CYCLOBUTYLSULFANYLBENZENE

30 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.
35 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.

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CLAIMS

1. A compound of the formula



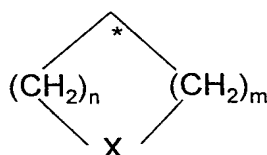
10 wherein R¹ is hydrogen, hydroxy, (C₆-C₁₀)aryl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy, (C₁-C₆)alkyl(C=O)O-, (C₁-C₆)alkoxy(C=O)O-, (C₆-C₁₀)aryl(C=O)O-, (C₆-C₁₀)aryloxy(C=O)O-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)O- or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)O-; wherein said aryl moiety of said (C₆-C₁₀)aryl(C₁-C₆)alkoxy, (C₆-C₁₀)aryl(C=O)O-, (C₆-C₁₀)aryloxy(C=O)O-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)O- or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)O- groups is optionally substituted by one or more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

15 R² is hydrogen or (C₁-C₆)alkyl;

R³ and R⁴ are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkyl(difluoromethylene), (C₁-C₃)alkyl(difluoromethylene)(C₁-C₃)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)O-(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)O-(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂amino(C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)NH(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C=O)NH(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C=O)NH(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C=O)NH(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)NH(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)NH(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, R⁵CO(C₁-C₆)alkyl or R⁸(C₁-C₆)alkyl; or R³ and R⁴ may be taken together with the carbon atom to which they are attached to form a (C₃-C₆)cycloalkyl or benzo-fused(C₃-C₆)cycloalkyl ring or a group of the formula

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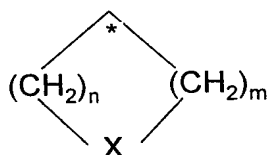
-37-



5

wherein the carbon atom bearing the asterisk is the carbon to which R³ and R⁴ are attached, "n" and "m" are independently selected from the integers one and two, and X is CF₂, O, SO₂ or NR⁹, wherein R⁹ is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy(C=O)-, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryloxy(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)- or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-; wherein each of said (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl or (C₃-C₆)cycloalkyl moieties of said (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C=O)NH(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)NH(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)NH(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl, (C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-, (C₃-C₆)cycloalkyl, or benzo-fused(C₃-C₆)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

25 or when R³ and R⁴ are taken together with the carbon atom to which they are attached to form a group of the formula



30 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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

5 R⁵ is R⁶O or R⁶R⁷N wherein R⁶ and R⁷ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₂-C₉)heteroaryl(C₁-C₆)alkyl; wherein each of said (C₆-C₁₀)aryl and (C₂-C₉)heteroaryl moieties of said (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₂-C₉)heteroaryl(C₁-C₆)alkyl groups may be optionally substituted by one or more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

10 or R⁶ and R⁷ taken together with the nitrogen atom to which they are attached form an optionally substituted heterocycle selected from piperaziny, (C₁-C₆)alkylpiperaziny, (C₆-C₁₀)arylpiperaziny, (C₂-C₉)heteroarylpiperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperaziny, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperaziny, (C₁-C₆)alkyl(C=O)-piperaziny, (C₁-C₆)alkoxy(C=O)-piperaziny, (C₆-C₁₀)aryl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperaziny, morpholiny, piperidiny, pyrrolidiny or azetidiny; wherein each of said piperaziny, (C₁-C₆)alkylpiperaziny, (C₆-C₁₀)arylpiperaziny, (C₂-C₉)heteroarylpiperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperaziny, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperaziny, (C₁-C₆)alkyl(C=O)-piperaziny, (C₁-C₆)alkoxy(C=O)-piperaziny, (C₆-C₁₀)aryl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperaziny, morpholiny, piperidiny, pyrrolidiny or azetidiny 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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, or perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

25 R⁸ is piperaziny, (C₁-C₆)alkylpiperaziny, (C₆-C₁₀)arylpiperaziny, (C₂-C₉)heteroarylpiperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperaziny, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperaziny, (C₁-C₆)alkyl(C=O)-piperaziny, (C₁-C₆)alkoxy(C=O)-piperaziny, (C₆-C₁₀)aryl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperaziny, morpholiny, piperidiny, pyrrolidiny, azetidiny, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)arylpiperidyl, (C₂-C₉)heteroarylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperidyl, (C₁-C₆)alkyl(C=O)-piperidyl, (C₁-C₆)alkoxy(C=O)-piperidyl, (C₆-C₁₀)aryl(C=O)-piperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperidyl, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperidyl; wherein each of said piperaziny, (C₁-C₆)alkylpiperaziny, (C₆-C₁₀)arylpiperaziny, (C₂-C₉)heteroarylpiperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperaziny, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperaziny, (C₁-C₆)alkyl(C=O)-piperaziny, (C₁-C₆)alkoxy(C=O)-piperaziny, (C₆-C₁₀)aryl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperaziny, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperaziny, morpholiny, piperidiny, pyrrolidiny, azetidiny,

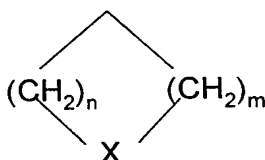
5 piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)aryl piperidyl, (C₂-C₉)heteroaryl piperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl piperidyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl piperidyl (C₁-C₆)alkyl(C=O)-piperidyl, (C₁-C₆)alkoxy(C=O)-piperidyl, (C₆-C₁₀)aryl(C=O)-piperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-piperidyl, and (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-piperidyl may be optionally substituted on any ring carbon atom capable of forming an additional bond with a
 10 substituent independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, or perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

Q is (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl or (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl wherein each (C₆-C₁₀)aryl or (C₂-C₉)heteroaryl moieties of said (C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl or (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₂-C₉)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

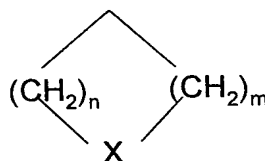
with the proviso that if either R³ or R⁴ is hydrogen, or if both R³ and R⁴ are hydrogen,
 35 then R¹ and R² can not both be hydrogen or R¹ must be hydroxy, (C₁-C₆)alkoxy, (C₆-C₁₀)aryl(C₁-C₆)alkoxy, (C₁-C₆)alkyl(C=O)O-(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C=O)O-(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C=O)O-(C₆-C₁₀)arylalkyl(C=O)O-(C₁-C₆)alkyl or (C₆-C₁₀)arylalkoxy(C=O)O-(C₁-C₆)alkyl;

and the pharmaceutically acceptable salts thereof.

- 5 2. A compound according to claim 1, wherein R¹ is OH and R² is hydrogen.
3. A compound according to claim 1, wherein both R³ and R⁴ are (C₁-C₆)alkyl or R³ and R⁴ are taken together with the carbon atom to which they are attached to form an optionally substituted (C₃-C₆)cycloalkyl ring or benzo-fused(C₃-C₆)cycloalkyl ring or a group of the formula



- 10 wherein "n" and "m" are independently selected from the integers one and two, and X is CF₂, O, SO₂ or NR⁹, wherein R⁹ is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroalkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy(C=O)-, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-; wherein each of said (C₆-C₁₀)aryl and (C₂-C₉)heteroaryl
- 15 moieties of said (C₆-C₁₀)aryl, (C₂-C₉)heteroalkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-, and (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)- groups may be optionally independently substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy.
- 20 4. A compound according to claim 2, wherein both R³ and R⁴ are (C₁-C₆)alkyl or R³ and R⁴ are taken together with the carbon atom to which they are attached to form a (C₃-C₆)cycloalkyl ring or benzo-fused(C₃-C₆)cycloalkyl ring or a group of the formula



- 25 wherein "n" and "m" are independently selected from the integers one and two, and X is CF₂, O, SO₂ or NR⁹, wherein R⁹ is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroalkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, (C₆-C₁₀)arylsulfonyl, (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy(C=O)-, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)-; wherein each of said (C₆-C₁₀)aryl and (C₂-C₉)heteroaryl moieties of said (C₆-C₁₀)aryl, (C₂-C₉)heteroalkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-, and (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C=O)- groups may be optionally independently substituted with one or more substituents independently selected from the group
- 30

5 consisting of fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy.

5. A compound according to claim 1, wherein R³ and R⁴ are taken together to form an optionally substituted (C₃-C₆)cycloalkyl ring.

6. A compound according to claim 2, wherein R³ and R⁴ are taken together to form
10 an optionally substituted (C₃-C₆)cycloalkyl ring.

7. A compound according to claim 1, wherein Q is (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, wherein each (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.
15

8. A compound according to claim 2, wherein Q is (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, wherein each (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.
20

9. A compound according to claim 3, wherein Q is (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, wherein each (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.
25

10. A compound according to claim 4, wherein Q is (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, wherein each (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.
30

11. A compound according to claim 5, wherein Q is (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, wherein each (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl group may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.
35

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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.

- 5 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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)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,
10 bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.
16. A compound according to claim 5, wherein Q is phenyl or phenoxyphenyl
15 optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.
- 20 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, (C₁-C₆)alkoxy or (C₁-C₆)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,
25 (C₁-C₆)alkoxy or (C₁-C₆)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, (C₁-C₆)alkoxy or (C₁-C₆)alkyl.
21. A compound according to claim 8, wherein Q is phenyl or phenoxyphenyl
30 optionally substituted with one or more substituents independently selected from fluoro, chloro, (C₁-C₆)alkoxy or (C₁-C₆)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, (C₁-C₆)alkoxy or (C₁-C₆)alkyl and wherein the substituent is in the 4-position.
- 35 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, (C₁-C₆)alkoxy or (C₁-C₆)alkyl and wherein the substituent is in the 4-position.

5 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, (C₁-C₆)alkoxy or (C₁-C₆)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,
10 (C₁-C₆)alkoxy or (C₁-C₆)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:

(2S)-2,N-dihydroxy-3-(4-methoxybenzenesulfonyl)propionamide,
3-[4-(4-fluorophenoxy)phenylsulfonyl]-2,N-dihydroxypropionamide,
15 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
20 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
25 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.

30 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,
35 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

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

INTERNATIONAL SEARCH REPORT

International 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

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search 22 April 1998	Date of mailing of the international search report 08.05.98
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INTERNATIONAL SEARCH REPORT

Inter nal Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>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</p>	<p>1-3,26, 27</p>
P, X	<p style="text-align: center;">----</p> <p>WO 97 24117 A (RHONE-POULENC) 10 July 1997 compound with CN(RN):193547-69-2 see claims 1,22,61,62</p>	<p>1-3,27</p>
P, A	<p style="text-align: center;">----</p> <p>EP 0 780 386 A (F. HOFFMANN- LA ROCHE) 25 June 1997 see claims 1,28,30</p> <p style="text-align: center;">-----</p>	<p>1-3,26, 27</p>

INTERNATIONAL SEARCH REPORT

International 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. 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

International Application No

PCT/IB 98/00101

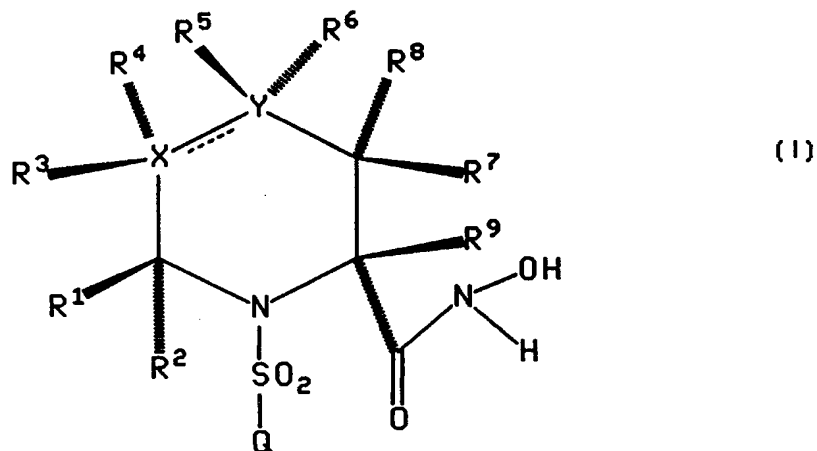
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 0634998 A	25-01-95
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		ZA 9302501 A	08-11-93
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		EP 0722438 A	24-07-96
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		PL 317604 A	23-06-97



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 211/62, 241/24, 279/12, 211/60, 211/90, A61K 31/445</p>	A1	<p>(11) International Publication Number: WO 98/34918</p> <p>(43) International Publication Date: 13 August 1998 (13.08.98)</p>
<p>(21) International Application Number: PCT/IB98/00064</p> <p>(22) International Filing Date: 16 January 1998 (16.01.98)</p> <p>(30) Priority Data: 60/037,600 11 February 1997 (11.02.97) US</p> <p>(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): McCLURE, Kim, Francis [US/US]; Apartment #4, 6 School Street, Mystic, CT 06355 (US).</p> <p>(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).</p>	<p>(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).</p> <p>Published With international search report.</p>	

(54) Title: ARYLSULFONYL HYDROXAMIC ACID DERIVATIVES



(57) Abstract

A compound of formula (I) wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ 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 DERIVATIVESBackground 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.

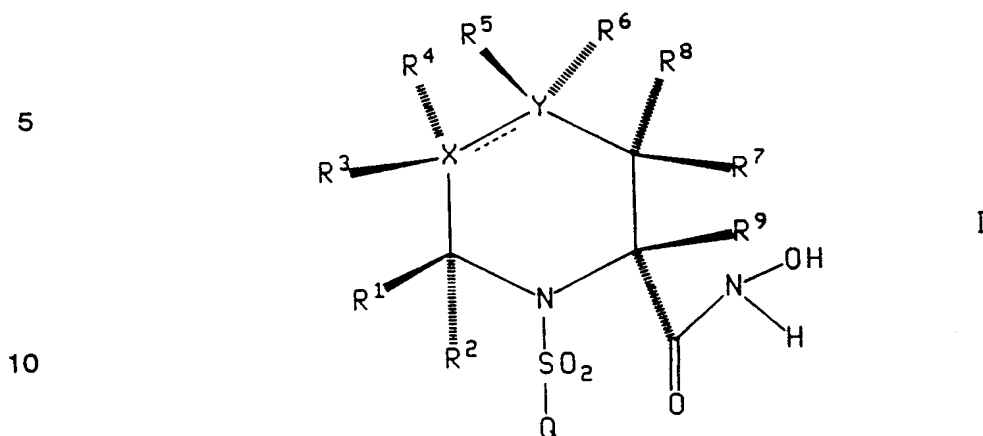
There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated 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).

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Summary of the Invention

The present invention relates to a compound of the formula



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

15 X is carbon, oxygen or sulfur;

Y is carbon, oxygen, sulfur, SO, SO₂ or nitrogen;

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are selected from the group consisting of hydrogen, (C₁-C₆)alkyl optionally substituted by one or two groups selected from (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, trifluoromethyl, halo, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₅-C₉)heteroarylamino, (C₅-C₉)heteroarylthio, (C₅-C₉)heteroaryloxy, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, hydroxy, piperazinyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy, (C₅-C₉)heteroaryl(C₁-C₆)alkoxy, (C₁-C₆)acylamino, (C₁-C₆)acylthio, (C₁-C₆)acyloxy, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, amino, (C₁-C₆)alkylamino or ((C₁-C₆)alkylamino)₂; (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₅-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₅-C₉)heteroaryl(C₂-C₆)alkynyl, (C₁-C₆)alkylamino, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₅-C₉)heteroaryl, (C₅-C₉)heteroarylthio, (C₅-C₉)heteroaryloxy, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl(hydroxymethylene), piperidyl, (C₁-C₆)alkylpiperidyl, (C₁-C₆)acylamino, (C₁-C₆)acylthio, (C₁-C₆)acyloxy, R¹⁰(C₁-C₆)alkyl wherein R¹⁰ is (C₁-C₆)acylpiperazino, (C₆-C₁₀)arylpiperazino, (C₅-C₉)heteroarylpiperazino, (C₁-C₆)alkylpiperazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperazino, (C₅-C₉)heteroaryl(C₁-C₆)alkylpiperazino, morpholino, thiomorpholino,

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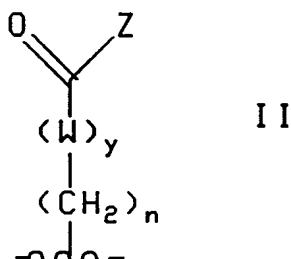
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pyrrolidino, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)aryl piperidyl, (C₅-C₉)heteroaryl piperidyl, (C₁-C₆)alkyl piperidyl (C₁-C₆)alkyl, (C₆-C₁₀)aryl piperidyl (C₁-C₆)alkyl, (C₅-C₉)heteroaryl piperidyl (C₁-C₆)alkyl or (C₁-C₆)acylpiperidyl;

or a group of the formula

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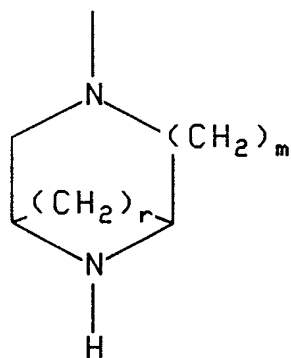
wherein n is 0 to 6;

y is 0 or 1;

W is oxygen or NR²⁴ wherein R²⁴ is hydrogen or (C₁-C₆)alkyl;

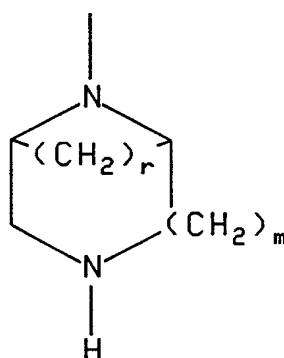
Z is OR¹¹ or NR²⁴R¹¹ wherein R²⁴ is as defined above and R¹¹ is as defined below; azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, thiomorpholiny, indoliny, isoindoliny, tetrahydroquinoliny, tetrahydroisoquinoliny or a bridged diazabicycloalkyl ring selected from the group consisting of

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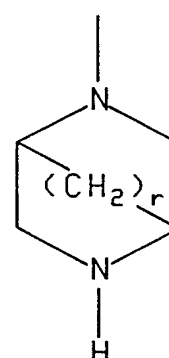


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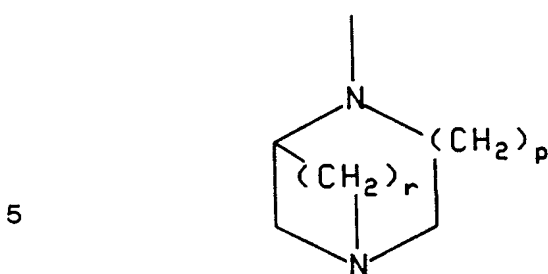
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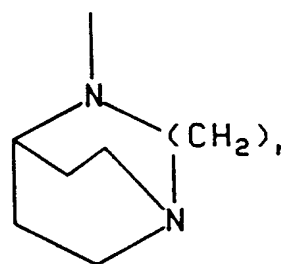
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d



e

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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
 15 selected from hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₅-C₉)heteroaryl(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀)arythio, (C₆-C₁₀)arylthio(C₁-C₆)alkyl, R¹²R¹³N, R¹²R¹³NSO₂, R¹²R¹³NCO, R¹²R¹³NCO(C₁-C₆)alkyl wherein R¹² and R¹³ are each
 20 independently hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₆-C₁₀)aryl (C₁-C₆)alkyl or (C₅-C₉)heteroaryl (C₁-C₆)alkyl or R¹² and R¹³ may be taken together with the nitrogen to which they are attached to form an azetidiny, pyrrolidiny, piperidiny, morpholinyl or thiomorpholinyl ring; R¹⁴SO₂, R¹⁴SO₂NH wherein R¹⁴ is trifluoromethyl, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₅-C₉)heteroaryl
 25 (C₁-C₆)alkyl; R¹⁵CONR¹² wherein R¹² is as defined above and R¹⁵ is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₁-C₆)aryl(C₁-C₆)alkyl(C₆-C₁₀)aryl(C₁-C₆)alkoxy or (C₅-C₉)heteroaryl(C₁-C₆)alkyl; R¹⁶OOC, R¹⁶OOC(C₁-C₆)alkyl wherein R¹⁶ is (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₆-C₁₀)aryl (C₁-C₆)alkyl, 5-indany, CHR¹⁷OCOR¹⁸ wherein R¹⁷ is hydrogen or (C₁-C₆)alkyl and R¹⁸ is (C₁-C₆)alkyl,
 30 (C₁-C₆)alkoxy or (C₆-C₁₀)aryl; CH₂CONR¹⁹R²⁰ wherein R¹⁹ and R²⁰ are each independently hydrogen or (C₁-C₆)alkyl or may be taken together with the nitrogen to which they are attached to form an azetidiny, pyrrolidiny, piperidiny, morpholinyl or

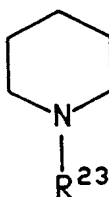
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thiomorpholinyl ring; or $R^{21}O$ (C_1-C_8)alkyl wherein R^{21} is $H_2N(CHR^{22})CO$ wherein R^{22} is the side chain of a natural D- or L-amino acid;

R^{11} is hydrogen, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_8)alkyl, (C_5-C_9)heteroaryl(C_1-C_8)alkyl, (C_1-C_8)alkyl(C_6-C_{10})aryl(C_1-C_8)alkyl, (C_1-C_8)alkyl(C_5-C_9)heteroaryl(C_1-C_8)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_8)acyl, (C_1-C_8)alkyl, (C_6-C_{10})aryl(C_1-C_8)alkyl, (C_5-C_9)heteroaryl(C_1-C_8)alkyl or (C_1-C_8)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_8)alkyl, (C_6-C_{10})aryl(C_1-C_8)alkoxy(C_1-C_8)alkyl, (C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryl, (C_1-C_8)alkyl(C_6-C_{10})aryl, (C_1-C_8)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_8)alkoxy(C_6-C_{10})aryl, (C_5-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_8)alkyl(C_5-C_9)heteroaryl, (C_1-C_8)alkoxy(C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_8)alkoxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryloxy(C_5-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_8)alkyl, (C_5-C_9)heteroaryloxy(C_1-C_8)alkyl, (C_1-C_8)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_8)alkyl(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_8)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_8)alkoxy(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_8)alkoxy(C_6-C_{10})aryloxy(C_5-C_9)heteroaryl optionally substituted by fluoro, chloro, (C_1-C_8)alkyl, (C_1-C_8)alkoxy or perfluoro(C_1-C_3)alkyl;

with the proviso that Z must be substituted when defined as azetidiny, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl, (C_1-C_{10})acylpiperazinyl, (C_1-C_8)alkylpiperazinyl, (C_6-C_{10})aryl piperazinyl, (C_5-C_9)heteroaryl piperazinyl or a bridged diazabicycloalkyl ring;

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- with the proviso that R⁷ is other than hydrogen only when R⁸ is other than hydrogen;
- with the proviso that R⁶ is other than hydrogen only when R⁵ is other than hydrogen;
- 5 with the proviso that R³ is other than hydrogen only when R⁴ is other than hydrogen;
- with the proviso that R² is other than hydrogen only when R¹ is other than hydrogen;
- with the proviso that when R¹, R² and R⁹ are a substituent comprising a
- 10 heteroatom, the heteroatom cannot be directly bonded to the 2- or 6- positions;
- with the proviso that when X is nitrogen, R⁴ is not present;
- with the proviso that when X is oxygen, sulfur, SO, SO₂ or nitrogen and when one or more of the group consisting of R¹, R², R⁵ and R⁶, is a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 4- or 6- positions;
- 15 with the proviso that when Y is oxygen, sulfur, SO, SO₂ or nitrogen and when one or more of the group consisting of R³, R⁴, R⁷ and R⁸, 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 SO₂, R³ and R⁴ are not
- 20 present;
- with the proviso that when y is 1 and W is NR²⁴ or oxygen, Z cannot be hydroxy;
- with the proviso that when Y is oxygen, sulfur, SO or SO₂, R⁵ and R⁶ are not present;
- with the proviso that when Y is nitrogen, R⁹ is not present;
- 25 with the proviso that when the broken line represents a double bond, R⁴ and R⁶ are not present;
- with the proviso that when R³ and R⁵ 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;
- 30 with the proviso that when either the X or Y position is oxygen, sulfur, SO, SO₂ 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;

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with the proviso that at least one of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ 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, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy and (C₁-C₆)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, pyrolyl, 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, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy and (C₁-C₆)alkyl.

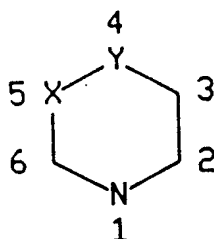
The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy (such as methyloxy carbonyl), aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

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:

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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
10 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 (C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl wherein each terminal aryl group is optionally substituted by fluoro.
15

Other preferred compounds of formula I include those wherein R², R³, R⁶, R⁷ and R⁹ are hydrogen.

More preferred compounds of formula I include those wherein Y is carbon; Q
20 is (C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl.

Specific preferred compounds of formula I include the following:

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

25 (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;

30 (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;

5 (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:

10 (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;

15 (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;

20 (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;

25 (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;

30 (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;

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- (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;
- 5 (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;
- 10 (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;
- 15 (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-20 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;
- 25 (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-30 piperidine-2-carboxylic acid hydroxyamide;
- (2R,3S)-3-Hydroxy-3-methyl-1-[4-(thiazol-5-ylmethoxy)-benzenesulfonyl]-piperidine-2-carboxylic acid hydroxyamide;

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(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;

5 (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;

10 (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;

15 (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;

20 (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;

25 (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;

30 (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;

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(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;

5 (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;

10 (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;

15 (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;

20 (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-Fluorobenzoyloxy)-benzenesulfonyl]-3-methyl-morpholine-3-carboxylic acid hydroxyamide;

25 (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;

30 (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;

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- (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;
- 5 (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-
- 10 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;
- 15 (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-
- 20 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;
- 25 (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
- 30 hydroxyamide;
- (2R,4R)-1-(4-Benzyloxy-benzenesulfonyl)-4-hydroxy-piperidine-2-carboxylic acid hydroxyamide;

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- (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;
- 5 (2R,5S)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-5-hydroxy-piperidine-2-carboxylic acid hydroxyamide;
- (2R,5S)-1-(4-Benzyloxy-benzenesulfonyl)-5-hydroxy-piperidine-2-carboxylic acid hydroxyamide;
- (2R,5R)-1-(4-Benzyloxy-benzenesulfonyl)-5-hydroxy-piperidine-2-carboxylic acid hydroxyamide;
- 10 (2R,5R)-1-[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-5-hydroxy-piperidine-2-carboxylic acid hydroxyamide;
- (2R,3S)-1-(4-Benzyloxy-benzenesulfonyl)-3-hydroxy-piperidine-2-carboxylic acid hydroxyamide;
- 15 (2R,4S)-1-(4-Benzyloxy-benzenesulfonyl)-4-hydroxy-piperidine-2-carboxylic acid 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;
- 20 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;
- 25 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
- 30 1-[4-(4-Fluoro-benzyloxy)-benzenesulfonyl]-2-hydroxycarbamoyl-piperidine-4-carboxylic acid.

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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
5 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
10 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.

15 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
20 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.

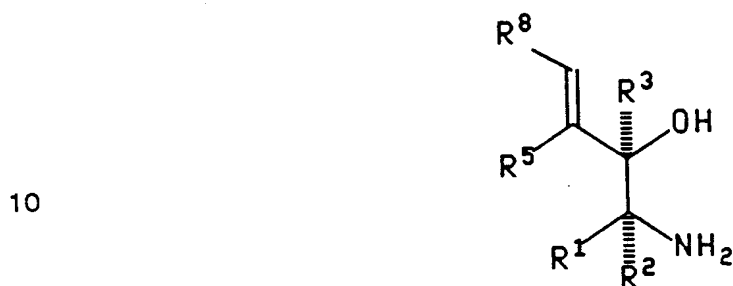
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Detailed Description of the Invention

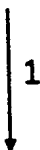
The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, n and Ar in the reaction Schemes and the discussion that follow are defined as above.

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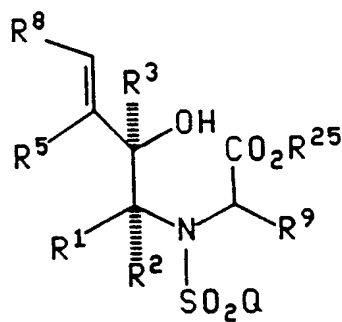
Preparation 1

XVI

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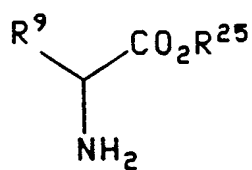
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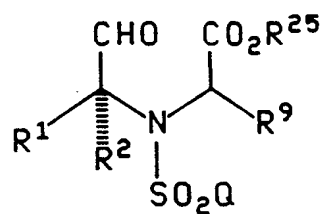
VI

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Preparation 2

XVIII



XVII



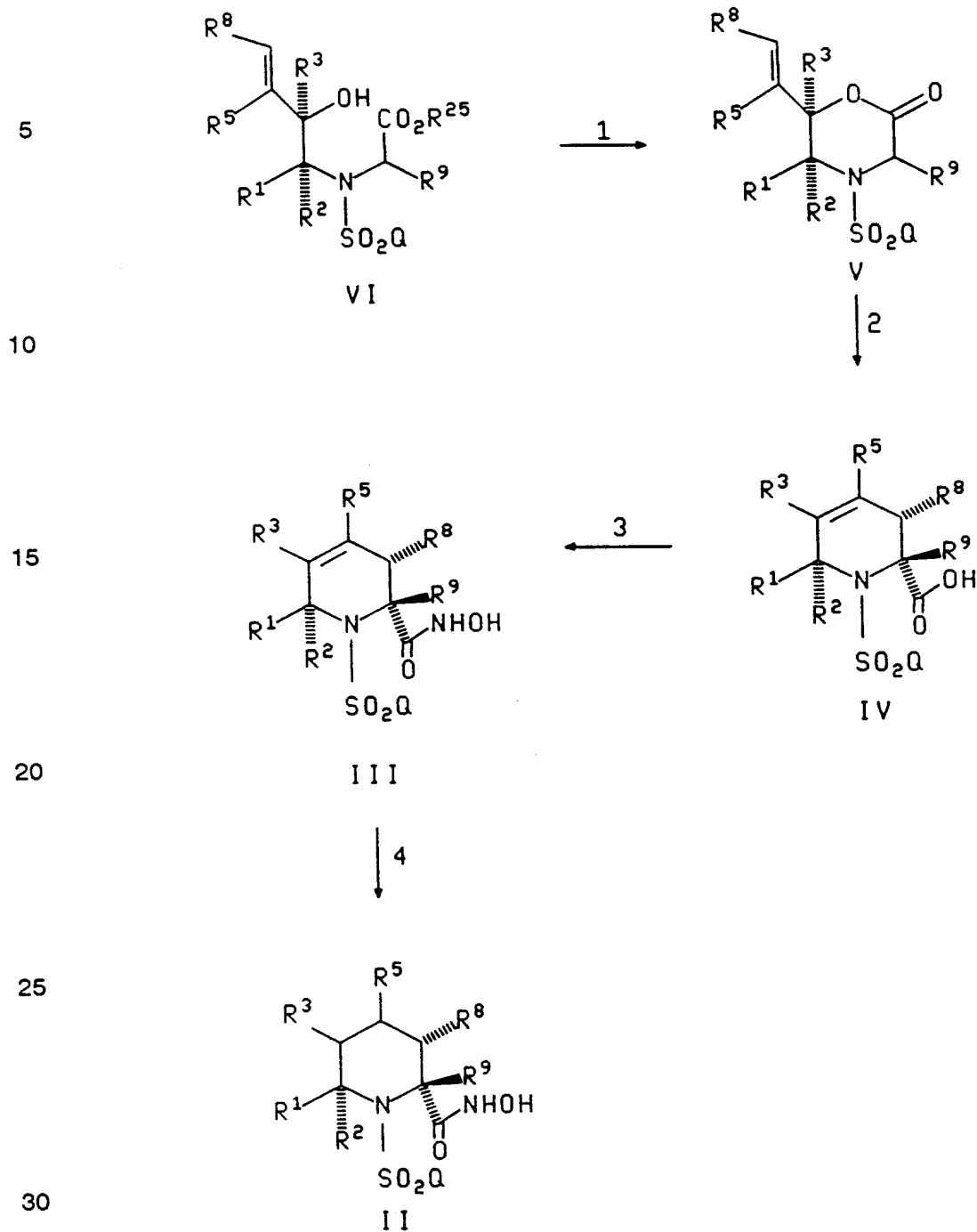
VI

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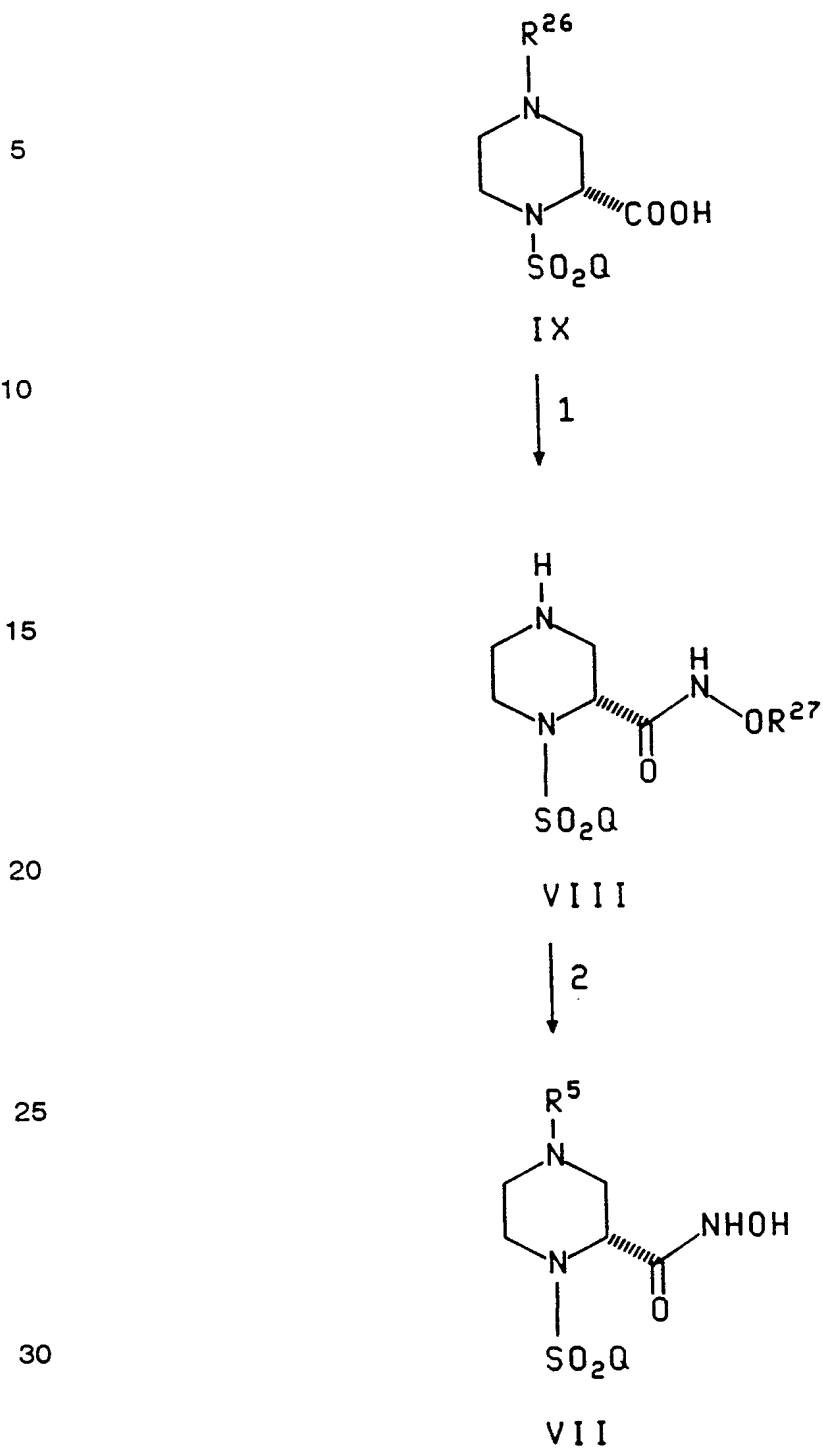
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Scheme 1



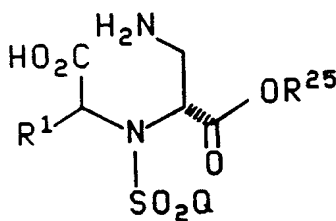
-19-

Scheme 2

-20-

Scheme 3

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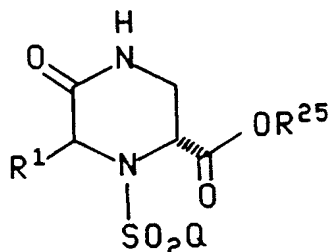


XII

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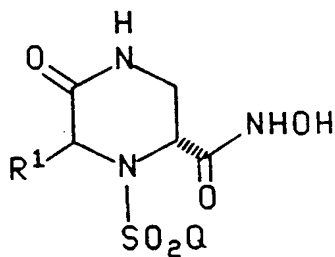


XI

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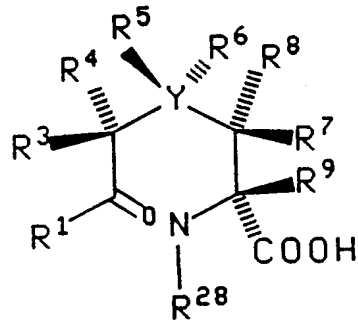
X

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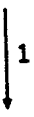
Scheme 4

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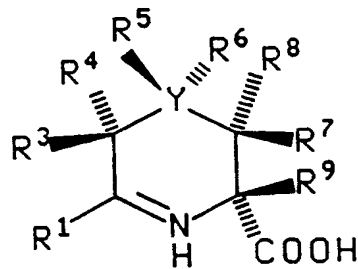


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XXII

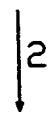


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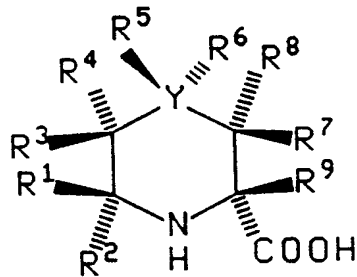


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XXI



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XX

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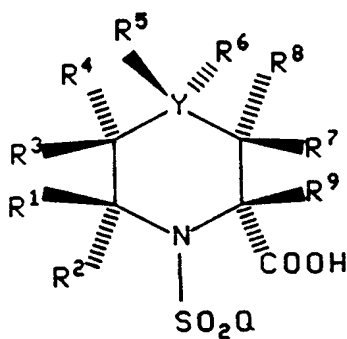
Scheme 4 continued

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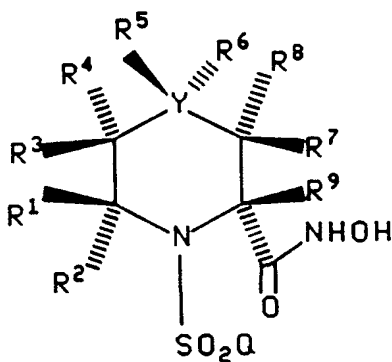


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XIX



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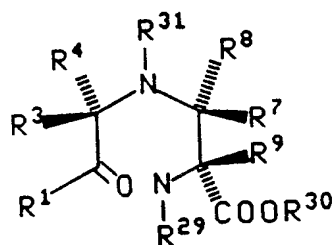
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XIII

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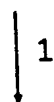
Scheme 5

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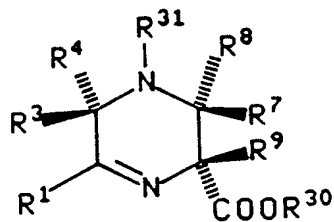


XXVI

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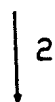


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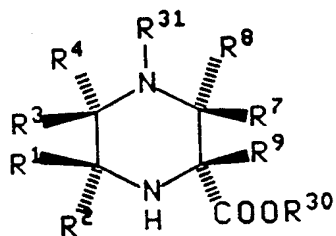


XXV

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XXIV

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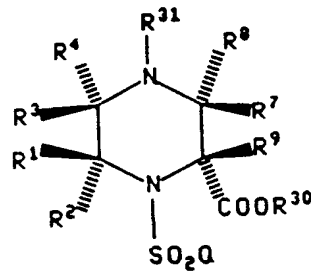
-24-

Scheme 5 continued

XXIV



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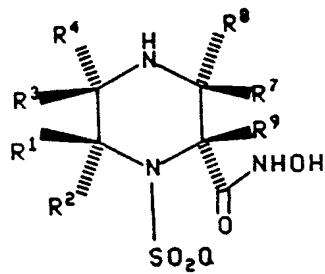


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XXIII



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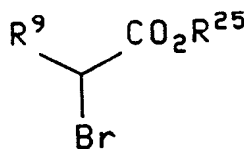
XIV

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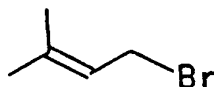
Preparation 1 refers to the preparation of intermediates of the formula VI. Compounds of the formula VI are converted to compounds of the formula I according to the methods of Scheme 1. The starting materials of formula XVI can be prepared according to methods well known to those of ordinary skill in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

5 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
10 reacted with a compound of the formula



15 wherein R²⁵ is carbobenzyloxy, (C₁-C₆)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
20 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 R²⁵ 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
25 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



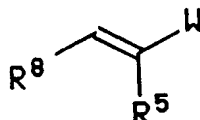
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in the presence of sodium hexamethyldisilazane and a tetrahydrofuran-dimethylformamide solvent mixture at a temperature between about -20°C to about 20°C, preferably about 0°C, and (3) further reacting the compound so formed with ozone in a methylene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

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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

5 by reacting XVII with a compound of the formula



10 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)

15 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

20 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

25 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

30 is then added to the reaction mixture and the solvent, tetrahydrofuran, is removed in vacuo and replaced with toluene. The resulting 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.

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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-hydroxybenzotriazole 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 hexafluorophosphate 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 catalyst, such as 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; R¹, R², R³, R⁴, R⁷ and R⁸ are hydrogen, and R⁶ 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 R²⁶ 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



wherein R²⁷ is tertbutyl, benzyl or allyl, in the presence of dicyclohexylcarbodiimide, dimethylaminopyridine and an aprotic solvent, such as methylene chloride. The R²⁶ protecting group is chosen such that it may be selectively removed in the presence of an without loss of the R²⁷ protecting group, therefore, R²⁶ cannot be the same as R²⁷.

Removal of the R²⁶ protecting group from the compound of formula IX is carried out under conditions appropriate for that particular R²⁶ protecting group in use. Such conditions include; (a) treatment with a hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon, where R²⁶ is carbobenzyloxy, (b) hydrogenolysis where
5 R²⁶ is benzyl or (c) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid where R²⁶ 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 R⁵ is hydrogen or (C₁-C₆)alkyl, by reacting, if desired, VIII with an alkylhalide when R⁵ is (C₁-C₆)alkyl.
10 Subsequent removal of the R²⁷ 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.

15 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; R², R⁷, R⁸ and R⁹ are hydrogen; R³ and R⁴ taken together are carbonyl; R⁵ is hydrogen, and R⁶ is absent. In reaction 1 of Scheme 3, the arylsulfonylamine compound of formula XII, wherein R²⁵ is as defined above, is converted to the corresponding piperazine compound of formula
20 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
25 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 R²⁸ 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
30 appropriate for that particular R²⁸ protecting group in use. Such conditions include those used above for removal of the R²⁶ 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 R²M 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 give 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, $(\text{C}_1\text{-C}_6)$ 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 $(\text{C}_1\text{-C}_6)$ alkyl and R^{31} is tert-butyl, (c) hydrogenolysis where R^{29} is benzyl and R^{31} is $(\text{C}_1\text{-C}_6)$ 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 $(\text{C}_1\text{-C}_6)$ 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 $(\text{C}_1\text{-C}_6)$ 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.

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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 salts, 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.

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Biological AssayInhibition 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
5 incubated at room temperature for 10 minutes then a five fold excess (50 $\mu\text{g}/10 \mu\text{g}$ 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 \longrightarrow 120 μM \longrightarrow 12 μM \longrightarrow 1.2 μM \longrightarrow 0.12 μM

10 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.

15 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)-NH₂) 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
20 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
25 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 IC₅₀ 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
30 fluorescence divided by fluorescence of collagenase alone \times 100). IC₅₀'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

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

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 ($10 \mu\text{M}$) 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 $30 \mu\text{M}$, $3 \mu\text{M}$, $0.3 \mu\text{M}$ and $0.03 \mu\text{M}$. 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 $0.03 \mu\text{M}$, then the inhibitors are assayed at final concentrations of $0.3 \mu\text{M}$, $0.03 \mu\text{M}$, $0.003 \mu\text{M}$ and $0.003 \mu\text{M}$.

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[$\text{CH}_2\text{CH}(\text{CH}_3)_2$] 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 $\mu\text{g}/\text{ml}$. 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

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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, 20 μM 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 , 3 μM , 0.3 μM , and 0.03 μM .

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) 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:

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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 2×10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes

5 ranged from 17 to 24% of the total cells in these preparations.

180 μ l 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 200 μ l. All conditions were performed in triplicate. After a four hour

10 incubation at 37°C in an humidified CO₂ 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.

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of

15 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

20 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

25 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,

30 together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting 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

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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

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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.

5 (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
10 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
15 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
20 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,
25 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
30 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.

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- (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.
- 5 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
10 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
15 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
20 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-carboxylic acid, which
25 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-butylloxycarbonyl piperazine (226 mg, 1.21 mmol), and triethylamine (0.47 mL, 3.33 mmol) was added benzotriazol-1-yloxy-tris(dimethylamino)phosphonium
30 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.

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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; ¹H 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

25 (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

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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 trifluoroacetic 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 μ m nylon filter and the filtrate was concentrated to give 650 mg of (2R,4R)-1-[3-(4-fluorophenoxy)-propane-1-sulfonyl]-2-

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hydroxycarbamoyl-piperidine-4-carboxylic acid methyl ester as a white foam: MS (atmospheric pressure chemical ionization) acidic mode, 417 (M-1); ¹H NMR (400 MHz, CDCl₃) 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

10 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
15 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

20

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

25 (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-4 α ,9 α ,9 $\alpha\alpha$]-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 μ m 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-4 α ,9 α ,9 $\alpha\alpha$]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-4 α ,9 α ,9 $\alpha\alpha$]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 chromatography (eluting with 3:1 hexanes/ethyl acetate) to give 402 mg of [4S-4 α ,9 α ,9 $\alpha\alpha$](1-oxo-4-phenyl-octahydro-pyrido[2,1-c][1,4]oxazin-9-yl)-carbamic acid isopropyl ester as white solid.

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(c) A mixture of [4S-4 α ,9 α ,9 $\alpha\alpha$](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 μ m 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 partitioned 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-trimethylsilyanyl-ethoxycarbonyl)-piperidin-3-yl]-carbamic acid isopropyl ester as a white foam. MS: 610 (M+1).

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(f) To a stirred, cold (0 °C) solution of 2R,3S-[1-[4-(4-fluorobenzyloxy)-benzenesulfonyl]-2-(2-trimethylsilyl-ethoxycarbonyl)-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-hydroxycarbonyl-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)-dimethylhexylsilyl-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+NH₄).

(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-(trimethylsilyl)hydroxylamine hydrochloride (376 mg, 2.22 mmol) was added. The ice bath was removed and the mixture was

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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-trimethylsilyl-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-trimethylsilyl-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-

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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 tetrahydrofuran 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). ¹H NMR (400 MHz, dmso-d₆) 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).

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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: ¹H NMR (400 MHz, CDCl₃) 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

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sodium sulfate. Filtration and concentration gave 1.75 g of 3-(4-fluoro-phenoxy)-propane-1-sulfonyl chloride as a yellow oil: $^1\text{H NMR}$ (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).

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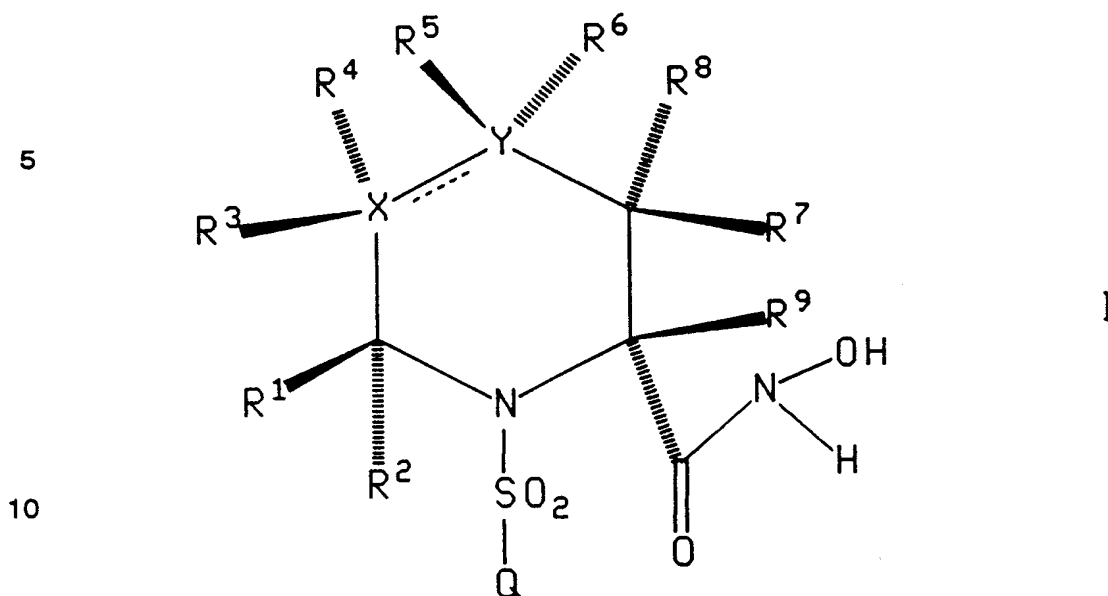
Preparation 3

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
10 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



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

15 X is carbon, oxygen or sulfur;

Y is carbon, oxygen, sulfur, SO, SO₂ or nitrogen;

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are selected from the group consisting of hydrogen, (C₁-C₆)alkyl optionally substituted by one or two groups selected from (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, trifluoromethyl, halo, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₂-C₉)heteroarylamino, (C₂-C₉)heteroarylthio, (C₂-C₉)heteroaryloxy, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, hydroxy, piperazinyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy, (C₁-C₆)acylamino, (C₁-C₆)acylthio, (C₁-C₆)acyloxy, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, amino, (C₁-C₆)alkylamino or ((C₁-C₆)alkyl)₂amino; (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₂-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₂-C₉)heteroaryl(C₂-C₆)alkynyl, (C₁-C₆)alkylamino, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl,

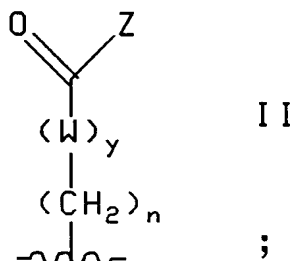
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(C₂-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₂-C₉)heteroarylamino, (C₂-C₉)heteroarylthio, (C₂-C₉)heteroaryloxy, (C₃-C₈)cycloalkyl, (C₁-C₆)alkyl(hydroxymethylene), piperidyl, (C₁-C₆)alkylpiperidyl, (C₁-C₆)acylamino, (C₁-C₆)acylthio, (C₁-C₆)acyloxy, R¹⁰(C₁-C₆)alkyl or a group of the formula

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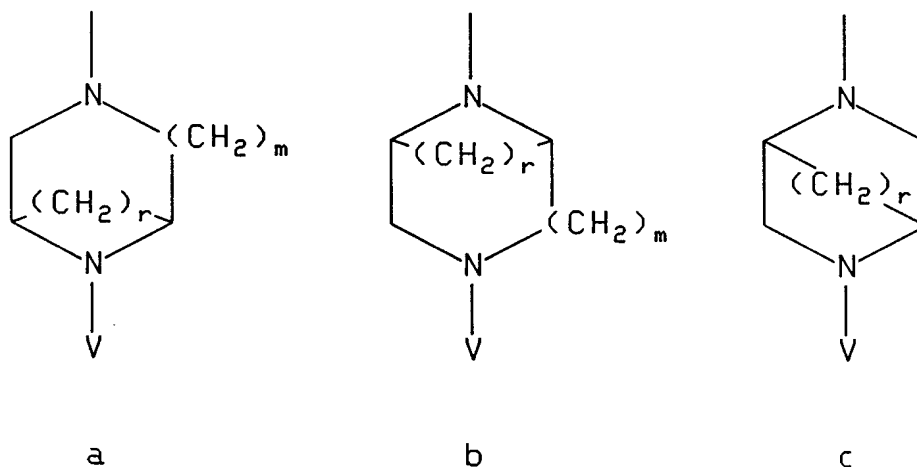
10 wherein n is 0 to 6;

y is 0 or 1;

W is oxygen or >NR²⁴;

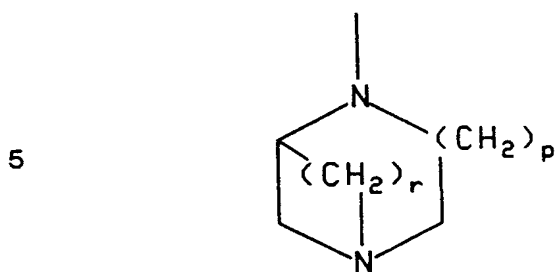
Z is -OR¹¹, -NR²⁴R¹¹, azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, thiomorpholiny, indoliny, isoindoliny, tetrahydroquinoliny, tetrahydroisoquinoliny or a bridged diazabicycloalkyl ring selected from the group consisting of

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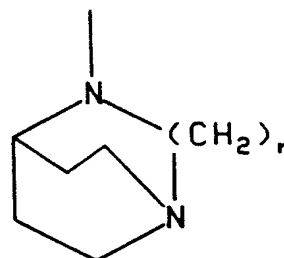


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d



e

10 wherein r is 1, 2 or 3;

m is 1 or 2;

p is 0 or 1; and

V is hydrogen, (C₁-C₃)alkyl, (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy(C=O)-, (C₆-C₁₀)aryl(C=O)-, (C₆-C₁₀)aryloxy(C=O)-, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C=O)-, (C₆-C₁₀)aryl-
 15 (C₁-C₆)alkoxy(C=O)-, or (C₁-C₆)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀)arylthio, (C₆-C₁₀)arylthio(C₁-C₆)alkyl, R¹²R¹³N-, R¹²R¹³NSO₂-, R¹²R¹³N(C=O)-, R¹²R¹³N(C=O)-(C₁-C₆)alkyl, R¹⁴SO₂-, R¹⁴SO₂NH-, R¹⁵(C=O)-[N(R¹²)]-, R¹⁶O(C=O)-, or R¹⁶O(C=O)-(C₁-C₆)alkyl;

25 wherein R¹⁰ is (C₁-C₆)acylpiperazinyl, (C₆-C₁₀)arylpiperazinyl, (C₂-C₉)heteroarylpiperazinyl, (C₁-C₆)alkylpiperazinyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperazinyl, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperazinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl,

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piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)arylpiperidyl, (C₂-C₉)heteroarylpiperidyl, (C₁-C₆)alkylpiperidyl(C₁-C₆)alkyl, (C₆-C₁₀)arylpiperidyl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl-piperidyl-(C₁-C₆)alkyl or (C₁-C₆)acylpiperidyl;

R¹¹ is hydrogen, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkyl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₁-C₆)alkyl(C₂-C₉)heteroaryl(C₁-C₆)alkyl, 5-indanyl, -CHR¹⁷O-(C=O)-R¹⁸ or -CH₂(C=O)-NR¹⁹R²⁰;

R¹² and R¹³ are each independently hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₂-C₉)heteroaryl(C₁-C₆)alkyl or R¹² and R¹³ may be taken together with the nitrogen to which they are attached to form an azetidiny, pyrrolidiny, piperidiny, morpholiny or thiomorpholiny ring;

R¹⁴ is trifluoromethyl, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₂-C₉)heteroaryl(C₁-C₆)alkyl;

R¹⁵ is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₁-C₆)aryl(C₁-C₆)alkyl(C₆-C₁₀)aryl(C₁-C₆)alkoxy or (C₂-C₉)heteroaryl(C₁-C₆)alkyl;

R¹⁶ is (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, 5-indanyl, -[CH(R¹⁷)]O-(C=O)-R¹⁸, -CH₂(C=O)-NR¹⁹R²⁰, or R²¹O(C₁-C₆)alkyl;

R¹⁷ is hydrogen or (C₁-C₆)alkyl;

R¹⁸ is (C₁-C₆)alkyl, (C₁-C₆)alkoxy or (C₆-C₁₀)aryl;

R¹⁹ and R²⁰ are each independently hydrogen or (C₁-C₆)alkyl or may be taken together with the nitrogen to which they are attached to form an azetidiny, pyrrolidiny, piperidiny, morpholiny or thiomopholiny ring;

R²¹ is H₂N(CHR²²)(C=O)-;

R²² is the side chain of a natural D- or L-amino acid;

R²³ is hydrogen, (C₁-C₆)acyl, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl or (C₁-C₆)alkylsulfonyl;

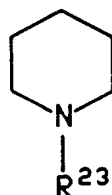
R²⁴ wherever it occurs is independently hydrogen or (C₁-C₆)alkyl;

or R¹ and R², or R³ and R⁴, or R⁵ and R⁶ may be taken together to form a carbonyl;

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or R¹ and R², or R³ and R⁴, or R⁵ and R⁶, or R⁷ and R⁸ may be taken together to form a (C₃-C₆)cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula

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Q is (C₁-C₁₀)alkyl, (C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl or (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl optionally substituted by fluoro, chloro, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl;

20 with the proviso that when y is zero, Q is other than (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₉)heteroaryl, and anyone of R¹-R⁹ is a group of formula II then Z must be substituted when defined as azetidiny, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl, (C₁-C₁₀)acylpiperazinyl, (C₁-C₆)alkylpiperazinyl, (C₆-C₁₀)arylpiperazinyl, (C₂-C₉)heteroarylpiperazinyl or a bridged diazabicycloalkyl ring;

25 with the proviso that when y is zero, Q is other than (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₉)heteroaryl, then at least one of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ must be defined as the
30 group of formula II;

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with the proviso that when Q is (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)heteroaryl, then R¹-R⁹ may be other than formula II but when R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are all defined by hydrogen or (C₁-C₆)alkyl, either X or Y is oxygen, sulfur, SO, -SO₂- or nitrogen, or the broken line represents a double bond;

with the proviso that R⁷ is other than hydrogen only when R⁸ is other than hydrogen;

with the proviso that R⁶ is other than hydrogen only when R⁵ is other than hydrogen;

10 with the proviso that R³ is other than hydrogen only when R⁴ is other than hydrogen;

with the proviso that R² is other than hydrogen only when R¹ is other than hydrogen;

15 with the proviso that when R¹, R² and R⁹ 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, R⁴ is not present;

20 with the proviso that when X is oxygen, sulfur, SO, SO₂ or nitrogen and when one or more of the group consisting of R¹, R², R⁵ and R⁶, 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, SO₂ or nitrogen and when one or more of the group consisting of R³, R⁴, R⁷ and R⁸, are independently a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 3- or 5- positions;

25 with the proviso that when X is oxygen, sulfur, SO or SO₂, R³ and R⁴ are not present;

with the proviso that when y is 1 and W is NR²⁴ or oxygen, Z cannot be hydroxy;

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with the proviso that when Y is oxygen, sulfur, SO or SO₂, R⁵ and R⁶ are not present;

with the proviso that when Y is nitrogen, R⁶ is not present;

with the proviso that when the broken line represents a double bond, R⁴ and
5 R⁶ are not present;

with the proviso that when R³ and R⁵ 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,
10 SO₂ 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, SO₂, or oxygen.
- 15 3. A compound according to claim 1, wherein Q is (C₆-C₁₀)aryl-(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl wherein each terminal aryl group is optionally substituted by fluoro.
4. A compound according to claim 1, wherein R², R³, R⁶, R⁷ and R⁹ are
20 hydrogen.
5. A compound according to claim 1, wherein Y is carbon; Q is (C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl.
6. A compound according to claim 1, wherein Y is oxygen, sulfur, SO, or
25 SO₂.
7. A compound according to claim 3, wherein Y is oxygen, sulfur, SO or SO₂.

8. A compound according to claim 1, wherein at least one of R⁷-R⁹ is other than hydrogen.
9. A compound according to claim 3, wherein at least one of R⁷-R⁹ is other than hydrogen.
- 5 10. A compound according to claim 6, wherein at least one of R⁷-R⁹ is other than hydrogen.
11. A compound according to claim 7, wherein at least one of R⁷-R⁹ is other than hydrogen.
12. A compound according to claim 1, wherein at least one of R⁷-R⁹ is
10 (C₁-C₆)alkyl.
13. A compound according to claim 3, wherein at least one of R⁷-R⁹ is (C₁-C₆)alkyl.
14. A compound according to claim 6, wherein at least one of R⁷-R⁹ is (C₁-C₆)alkyl.
- 15 15. A compound according to claim 7, wherein at least one of R⁷-R⁹ is (C₁-C₆)alkyl.
16. A compound according to claim 1, wherein at least one of R⁷-R⁹ is methyl.
17. A compound according to claim 3, wherein at least one of R⁷-R⁹ is
20 methyl.
18. A compound according to claim 6, wherein at least one of R⁷-R⁹ is methyl.
19. A compound according to claim 7, wherein at least one of R⁷-R⁹ is methyl.
- 25 20. A compound according to claim 1, wherein R⁷ and R⁸ are taken together to form a carbonyl and R⁹ is (C₁-C₆)alkyl.
21. A compound according to claim 3, wherein R⁷ and R⁸ are taken together to form a carbonyl and R⁹ is (C₁-C₆)alkyl.

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22. A compound according to claim 6, wherein R⁷ and R⁸ are taken together to form a carbonyl and R⁹ is (C₁-C₆)alkyl.
23. A compound according to claim 7, wherein R⁷ and R⁸ are taken together to form a carbonyl and R⁹ is (C₁-C₆)alkyl.
- 5 24. A compound according to claim 1 wherein R⁷ and R⁸ are each methyl.
25. A compound according to claim 3 wherein R⁷ and R⁸ are each methyl.
26. A compound according to claim 6 wherein R⁷ and R⁸ are each methyl.
27. A compound according to claim 7 wherein R⁷ and R⁸ are each methyl.
28. A compound according to claim 1 wherein R⁷ and R⁸ are taken
10 together to form a (C₃-C₆)cycloalkyl group.
29. A compound according to claim 3 wherein R⁷ and R⁸ are taken together to form a (C₃-C₆)cycloalkyl group.
30. A compound according to claim 6 wherein R⁷ and R⁸ are taken together to form a (C₃-C₆)cycloalkyl group.
- 15 31. A compound according to claim 8 wherein R⁷ and R⁸ are taken together to form a (C₃-C₆)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-
20 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;
- 25 (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;

5 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

10 (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
15 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
20 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.

25 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
30 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 :

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Date of the actual completion of the international search <p style="text-align: center; font-size: 1.2em;">27 April 1998</p>	Date of mailing of the international search report <p style="text-align: center; font-size: 1.2em;">11. 05. 98</p>
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Name and mailing address of the ISA 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	Authorized officer <p style="text-align: center; font-size: 1.2em;">Luyten, H</p>
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2

INTERNATIONAL SEARCH REPORT

International 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. 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

Information on patent family members

International Application No

PCT/IB 98/00064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9633172 A	24-10-96	AU 5080296 A	31-10-96
		CN 1140165 A	15-01-97
		CZ 9601130 A	13-11-96
		EP 0821671 A	04-02-98
		FI 973974 A	16-10-97
		NO 961585 A	21-10-96
		SG 43350 A	17-10-97



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

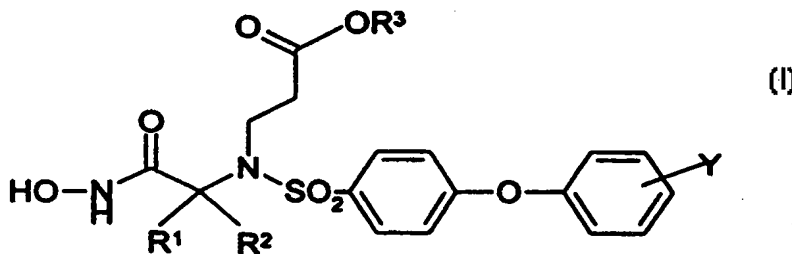
(51) International Patent Classification ⁶ : C07C 311/29, C07D 309/14, 211/66, A61K 31/19, 31/215, 31/35, 31/445	A1	(11) International Publication Number: WO 99/07675 (43) International Publication Date: 18 February 1999 (18.02.99)
(21) International Application Number: PCT/IB98/01113 (22) International Filing Date: 21 July 1998 (21.07.98) (30) Priority Data: 60/055,207 8 August 1997 (08.08.97) US (71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): ROBINSON, Ralph, Pelton [US/US]; 30 Friar Tuck Drive, Gales Ferry, CT 06335 (US). (74) Agents: SPIEGEL, A., J. et al.; c/o Green, Mark, Charles, 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, GE, GH, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	

(54) Title: ARYLOXYARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES

(57) Abstract

A compound of formula (I) or the pharmaceutically acceptable salts thereof, wherein R¹ is (C₁-C₆)alkyl; R² is (C₁-C₆)alkyl; or R¹ and R² taken together with the carbon atom to which they are attached form a ring selected from (C₅-C₇)cycloalkyl, 4-tetrahydropyranyl and 4-piperidinyl; R³ is hydrogen or (C₁-C₆)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, (C₁-C₆)alkoxy, trifluoromethoxy, difluoromethoxy and (C₁-C₆)alkyl.



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5 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, ocular angiogenesis (for example macular degeneration) and other diseases characterized by matrix metalloproteinase activity.

10 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.

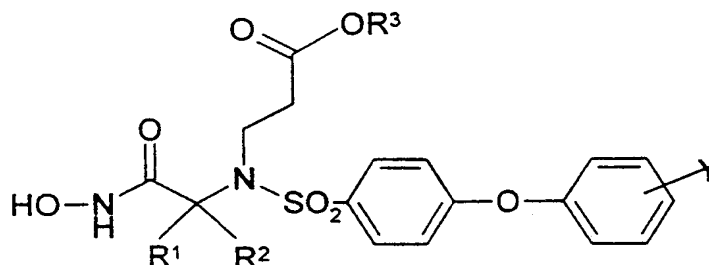
 There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated 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).

20 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).

30 Summary of the Invention

 The present invention relates to a compound of the formula

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I

5

or the pharmaceutically acceptable salts thereof, wherein

R¹ is (C₁-C₆)alkyl;

R² is (C₁-C₆)alkyl;

or R¹ and R² taken together with the carbon atom to which they are attached form a ring
10 selected from (C₅-C₇)cycloalkyl, 4-tetrahydropyranyl and 4-piperidinyl;

R³ is hydrogen or (C₁-C₆)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
15 hydrogen, fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, trifluoromethoxy, difluoromethoxy and
(C₁-C₆)alkyl.

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

20 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
25 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-
30 naphthoate)]salts.

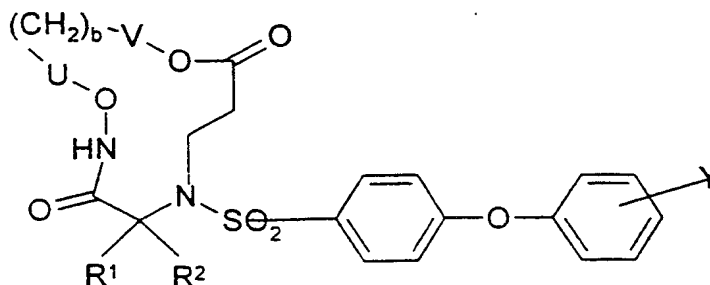
The invention also relates to base addition salts of formula I. The chemical bases that
may be used as reagents to prepare pharmaceutically acceptable base salts of those

-3-

5 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
10 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
15 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
20 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
25 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



30

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.

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5 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 R¹ and R² taken together with the carbon atom to which they are attached form a cyclopentyl or 4-tetrahydropyranyl ring.

10 Other preferred compounds of formula I include those wherein R¹ and R² are both methyl.

Other preferred compounds of formula I include those wherein R³ is hydrogen.

Specific preferred compounds of formula I include the following:

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

15 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

20 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,

25 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,

30 3-[(4-hydroxycarbamoyltetrahydropyran-4-yl)-(4-phenoxybenzenesulfonyl)amino]-propionic acid.

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

35 3-[[4-(4-fluorophenoxy)benzenesulfonyl]-(4-hydroxycarbamoylpiperidin-4-yl)-amino]propionic acid ethyl ester,

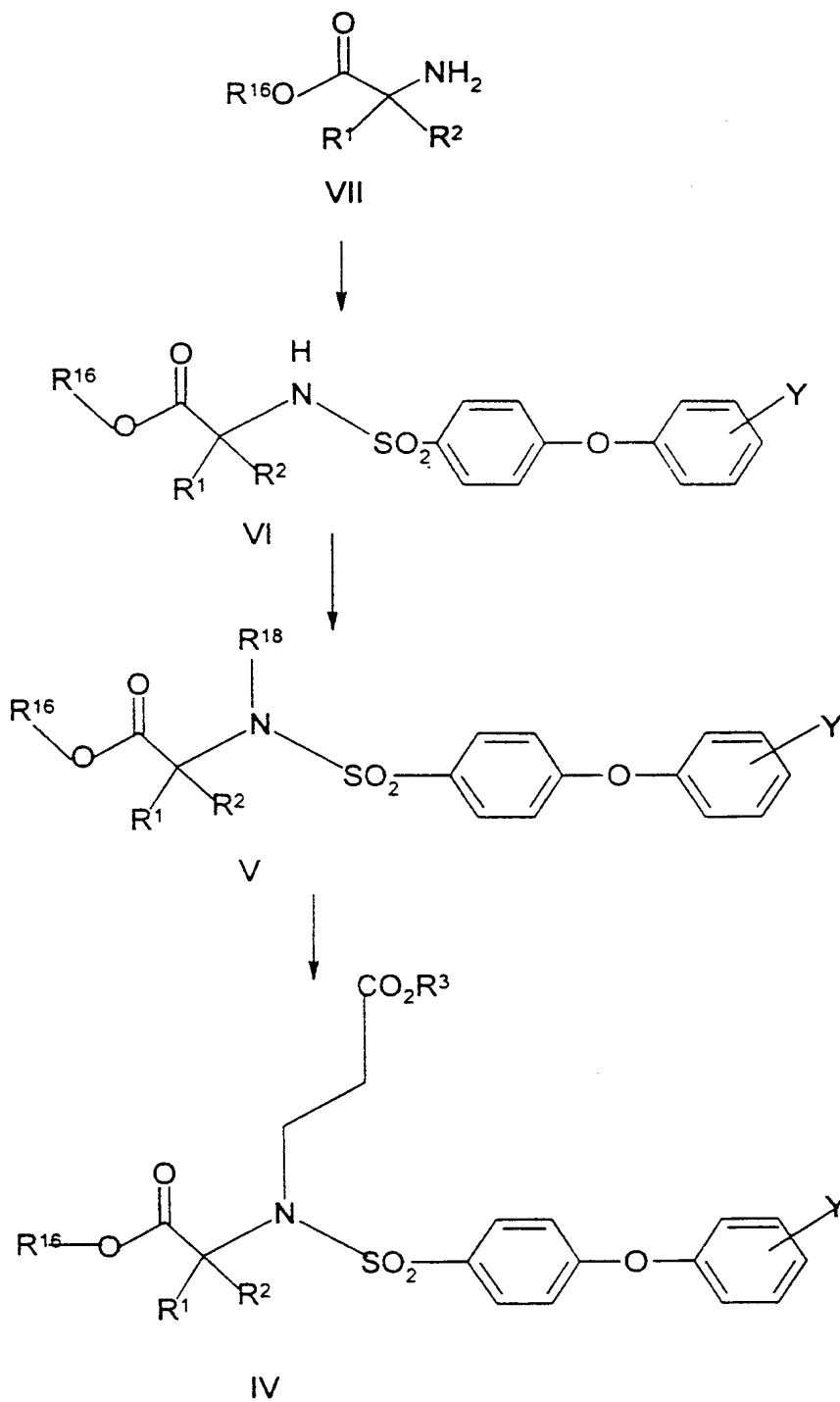
3-[[4-(4-chlorophenoxy)benzenesulfonyl]-(1-hydroxycarbamoyl-1-methylethyl)amino]-propionic acid,

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

-6-

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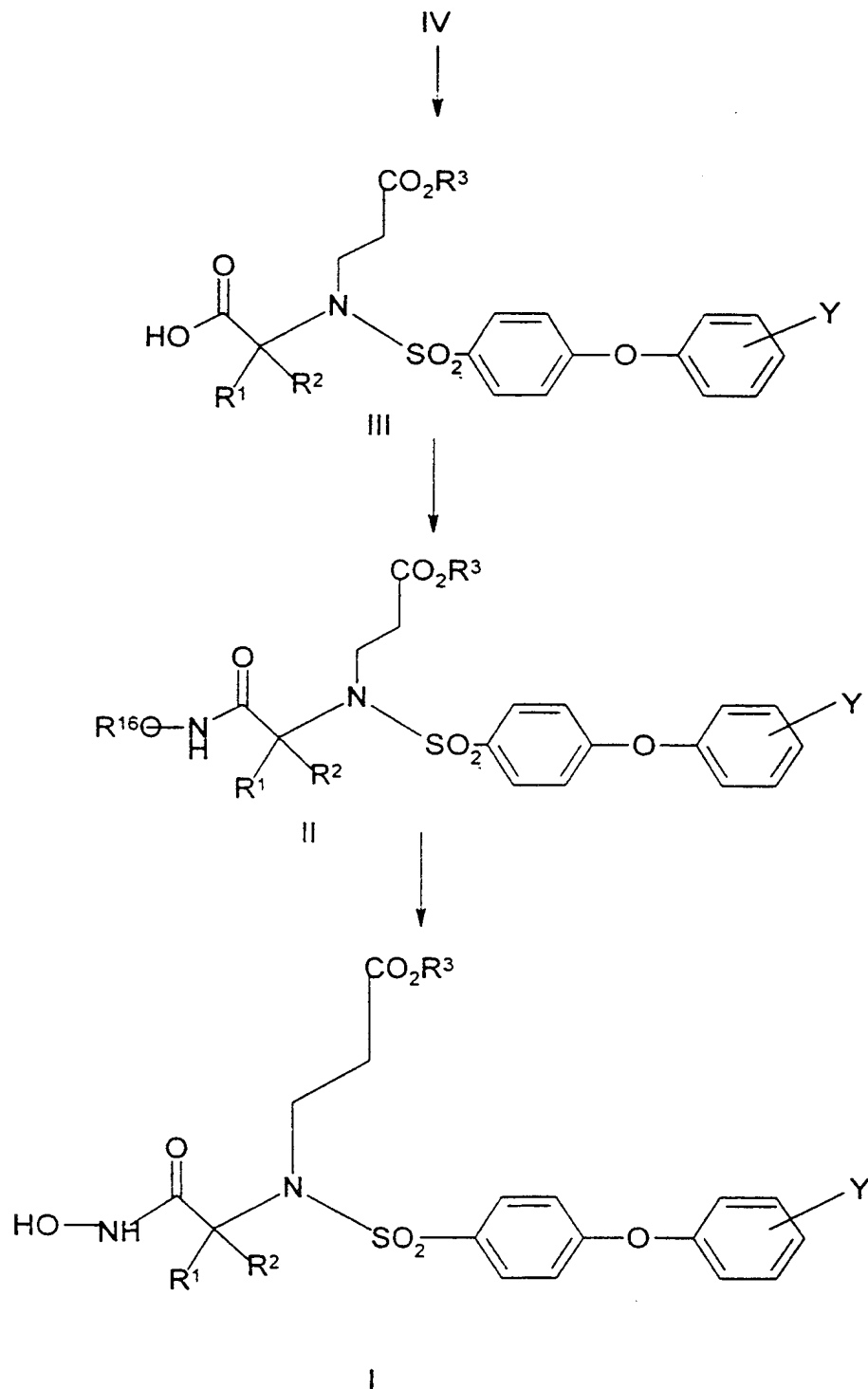
Scheme 1



-7-

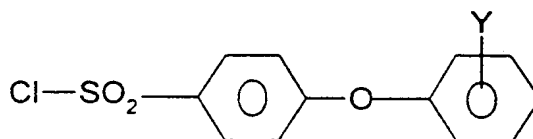
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Scheme 1 Cont'd



-8-

- 5 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 R¹⁶ 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

- 10 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 R¹⁶ is benzyl, is converted to the corresponding compound of formula V, wherein R¹⁸ is the group 3-tert-butyl-dimethylsilanyloxypropyl 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 R³-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.

5 The compound of formula IV is converted to a compound of formula III by removal of the R¹⁶ 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.

10 The carboxylic acid compound of formula III is converted to the hydroxamic acid derivative of formula II, wherein R¹⁶ 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
15 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
20 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
25 period of about 1 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
30 sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, 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
35 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
40 pharmaceutically unacceptable salt and then simply convert the latter back to the free base

5 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
10 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,
15 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 R³ is hydrogen, are capable of forming base salts with various pharmacologically acceptable
20 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
25 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
30 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
35 (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.

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Biological AssayInhibition 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 μ M —> 12 μ M —> 1.2 μ M —> 0.12 μ M

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 μ l is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) 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 μ l 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 IC₅₀ 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). IC₅₀'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC₅₀'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

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5 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 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.

15 Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) 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.

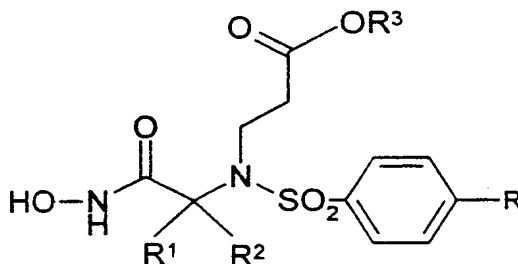
20 IC₅₀'s are determined as per inhibition of human collagenase (MMP-1). If IC₅₀'s are reported to be less than 0.03 mM, inhibitors are then assayed at final concentrations of 0.3 mM, 0.03 mM, 0.003 mM and 0.0003 mM.

25 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 IC₅₀'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.

-13-

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TABLE 1



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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

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5 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, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting 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

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

Example 1

10 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
15 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
20 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
25 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
30 washed with water and brine. After drying over magnesium sulfate, the diethyl ether was
evaporated to afford crude 1-[[3-(tert-butyl-dimethylsilyloxy)-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-dimethylsilyloxy)-propyl]-[4-(4-
35 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

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5 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
10 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 trituated with a mixture of diethyl ether and hexane to provide 1-[(2-carboxyethyl)-[4-(4-
15 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
20 (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-
25 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
30 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
40 diisopropylethylamine (91 mL, 0.52 mole) and O-benzylhydroxylamine hydrochloride (53.8

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5 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
10 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
15 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
20 chromatographed on silica gel eluting with 40% ethyl acetate hexane to provide more of the desired product (32.5 grams).

Mp: 79-83°C. ¹H NMR (DMSO-d₆): 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
25 (M-1). Analysis calculated for C₂₃H₂₇FN₂O₇S.H₂O: C, 53.90; H, 5.70; N, 5.47. Found: C, 54.52; H, 5.63; N, 5.27.

5

Example 2**3-[[4-(4-FLUOROPHENOXY)BENZENESULFONYL]-(1-HYDROXY-CARBAMOYL)CYCLOPENTYL] 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. ¹H NMR (DMSO-d₆): 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 C₂₁H₂₃FN₂O₇S: C, 54.07; H, 4.97; N, 6.00. Found: C, 54.17; H, 5.02; N, 6.05.

20

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. ¹H NMR (DMSO-d₆) 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 C₂₁H₂₅FN₂O₇S: C, 53.84; H, 5.38; N, 5.98. Found: C, 54.00; H, 5.12; N, 5.87.

30

5

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

10 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.

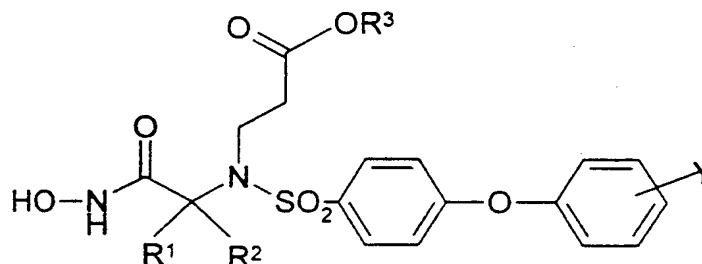
Mp: 162-162.5°C. MS: 439 (M-1). ¹H NMR (DMSO-d₆) δ 12.26 (s, 1 H) 10.10.38 (s, 1 H), 8.75 (s, 1 H), 7.86-7.88 (m, 2 H), 7.16-7.7.30 (m, 4 H), 7.03-7.06 (m, 2 H), 3.29-3.35 (m, 2 H), 2.47-2.59 (m, 2 H), 1.40 (s, 6 H).

5

CLAIMS

1.

A compound of the formula



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or the pharmaceutically acceptable salts thereof, wherein

 R^1 is (C₁-C₆)alkyl;

10

 R^2 is (C₁-C₆)alkyl;or R^1 and R^2 taken together with the carbon atom to which they are attached form a ring selected from (C₅-C₇)cycloalkyl, 4-tetrahydropyranyl and 4-piperidinyl; R^3 is hydrogen or (C₁-C₆)alkyl; and15 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, (C₁-C₆)alkoxy, trifluoromethoxy, difluoromethoxy and (C₁-C₆)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.

20 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.25 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.

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

5 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-
10 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
15 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
20 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 :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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.</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 23 September 1998	Date of mailing of the international search report 14/10/1998
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Name and mailing address of the ISA 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	Authorized officer Van Geyt, J
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INTERNATIONAL SEARCH REPORT

International 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. 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 98/01113

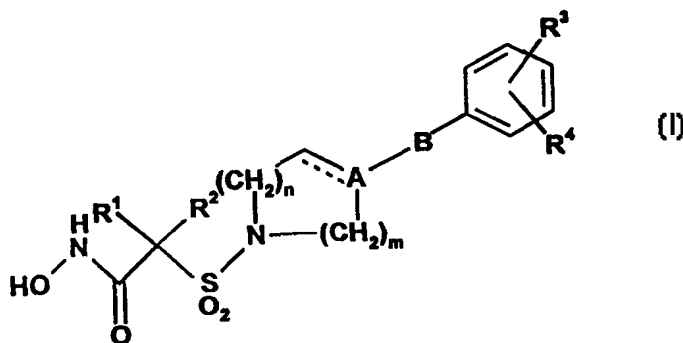
Patent document cited in search report	Classification	Publication date	Patent family member(s)	Publication date
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			PL 322131 A	05-01-1998



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 211/16, 211/22, A61K 31/44, C07D 211/70, 405/12, 401/10, 405/10	A1	(11) International Publication Number: WO 99/29667 (43) International Publication Date: 17 June 1999 (17.06.99)
(21) International Application Number: PCT/EP98/06640 (22) International Filing Date: 9 October 1998 (09.10.98) (30) Priority Data: 9725782.8 5 December 1997 (05.12.97) GB (71) Applicant (for GB only): PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). (71) Applicant (for all designated States except GB US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DACK, Kevin, Neil [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). WHITLOCK, Gavin, Alistair [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). (74) Agents: RUDDOCK, Keith, Stephen et al.; Pfizer Limited, European Patent Dept., Ramsgate Road, Sandwich, Kent CT13 9NJ (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, 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 <i>With international search report.</i>	

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

**(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 CH₂, O or absent; R¹ and R² are each independently selected from hydrogen, C₁ to C₆ alkyl optionally substituted with C₁ to C₄ alkoxy or phenyl, and C₁ to C₆ alkenyl; or, together with the carbon atom to which they are attached, form a C₃ to C₆ cycloalkyl group which optionally incorporates a heteroatom linkage selected from O, SO, SO₂ and NR⁶ or which is optionally benzo-fused; R³ is hydrogen, halo, R⁷ or OR⁷; R⁴ is hydrogen, C₁ to C₄ alkyl, C₁ to C₄ alkoxy, trifluoromethyl or halo; R⁶ is hydrogen or C₁ to C₄ alkyl; R⁷ 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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HYDROXAMIC ACID DERIVATIVES AS MATRIX METALLOPROTEASE
(MMP) INHIBITORS

This invention relates to a series of substituted α -aminosulphonyl-
5 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
10 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,
15 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
20 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
25 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.

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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

5 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

10 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.

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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,
5 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).

10 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
15 may find utility in the prevention of heart attack and stroke.

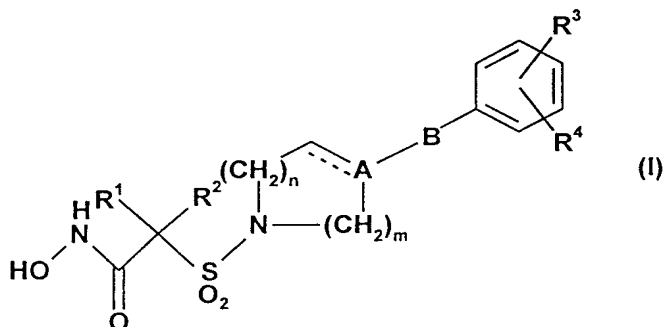
Studies of human cancers have shown that MMP-2 is activated on the invasive tumour cell surface (see J. Biol.Chem., 1993, 268, 14033) and BB-94, a non-selective peptidic hydroxamate MMP inhibitor, has been reported to decrease the tumour burden and prolong the survival of mice carrying human
20 ovarian 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
25 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
30 over other MMPs, such as MMP-1, MMP-2 and MMP-9. Certain of the compounds are potent MMP-2 inhibitors.

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Thus, according to the present invention, there is provided a compound of formula (I):



5 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;

10 B is CH₂, O or absent;

R¹ and R² are each independently selected from hydrogen, C₁ to C₆ alkyl optionally substituted with C₁ to C₄ alkoxy or phenyl, and C₁ to C₆ alkenyl; or, together with the carbon atom to which they are attached, form a C₃ to C₆ cycloalkyl group which optionally
 15 incorporates a heteroatom linkage selected from O, SO, SO₂ and NR⁶ or which is optionally benzo-fused;

R³ is hydrogen, halo, R⁷ or OR⁷;

R⁴ is hydrogen, C₁ to C₄ alkyl, C₁ to C₄ alkoxy, trifluoromethyl or halo;

20 R⁶ is hydrogen or C₁ to C₄ alkyl;

R⁷ 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,
 25 benzothiazolyl and benzodioxanyl, any of which ring systems

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is optionally substituted with one or two substituents selected from C₁ to C₄ alkyl optionally substituted with C₁ to C₄ alkoxy or hydroxy, C₁-C₄ alkoxy optionally substituted with C₁ to C₄ alkoxy or hydroxy, C₁ to C₄ 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.

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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; R¹ is hydrogen, C₁ to C₄ alkyl optionally substituted with methoxy or phenyl, or C₁ to C₅ alkenyl; R² is hydrogen or C₁ to C₄ alkyl; or R¹ and R², together with the carbon atom to which they are attached, form a C₄ to C₅ cycloalkyl group which optionally incorporates a heteroatom linkage selected from O and NR⁶ or which is optionally benzo-fused; R³ 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 C₁ to C₃ alkyl optionally substituted with methoxy or hydroxy, C₁ to C₃ alkoxy optionally substituted with methoxy or hydroxy, methylthio, trifluoromethyl, trifluoromethoxy, fluoro, chloro and cyano; R⁴ is hydrogen, methyl, ethyl, methoxy, trifluoromethyl, fluoro or chloro; R⁶ is methyl; m is 2; and n is 1.

A more preferred group of compounds of formula (I) is that wherein R¹ is hydrogen, methyl, ethyl, 2-methylprop-1-yl, but-1-yl, 2-methoxyethyl, benzyl, 3-phenylprop-1-yl, allyl, 2-methylallyl, 3,3-dimethylallyl; R² is hydrogen, methyl or ethyl; or R¹ and R², 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; R³ is 4-phenyl, 4-(2-methylphenyl), 4-(3-

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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),
 5 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-
 10 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 R⁴ is hydrogen, 2-methyl, 3-methyl, 3-ethyl, 3-methoxy, 3-trifluoromethyl, 3-fluoro or 3-chloro.

15 A particularly preferred group of compounds of formula (I) is that wherein R¹ and R² 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; R³ is 4-phenyl, 4-(3-methoxyphenyl), 4-(3-ethoxyphenyl), 4-[3-(2-methoxyethoxy)phenyl], 4-[3-(2-hydroxyethoxy)phenyl]
 20 or 4-(6-ethoxypyridin-2-yl); and R⁴ 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;

25 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;

30

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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.

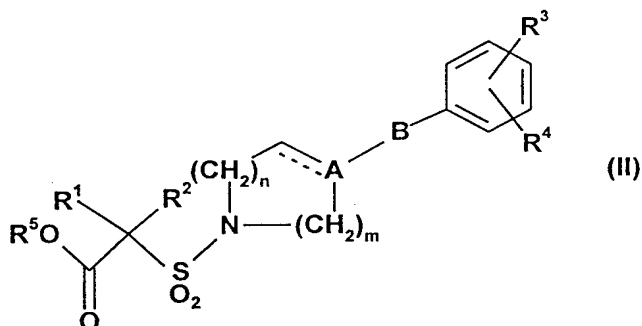
Illustrative of protecting group strategies are the synthetic routes to Example 64, in which an O-benzyl protected hydroxamate is formed prior to the required Suzuki reaction step, and to Example 66, in which alcohol protection using a t-butylidiphenylsilyl group is employed.

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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):



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 via 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 in situ 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.

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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).

5 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-
10 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
15 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 R⁵ is hydrogen may be
20 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
25 suitable solvent such as dichloromethane or dimethylformamide, optionally in the presence of a tertiary amine such as N-methylmorpholine or N-ethyl-diisopropylamine (for example when either the hydroxylamine or the

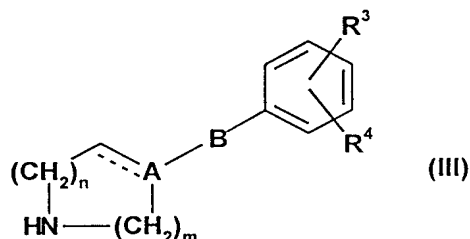
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activating reagent is presented in the form of an acid addition salt), at from about 0°C to about room temperature. Typically, from 1.1 to 2.0 molecular equivalents of the activating reagent and from 1.0 to 4.0 molecular equivalents of any tertiary amine present are employed.

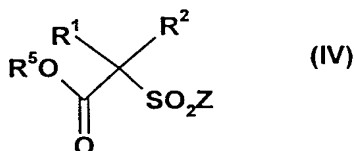
A preferred reagent for mediating the coupling reaction is O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU).

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):



wherein the broken line, A, B, R³, R⁴, m and n are as previously defined for formula (II), by sulphonylation with a compound of formula (IV):



wherein Z is halo, R⁵ is C₁ to C₃ alkyl and R¹ and R² are as previously defined for formula (II). Preferably, Z is chloro.

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When R⁶ 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
5 temperature. For example, when both R¹ and R² 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
10 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.

15 Further routes to the preparation of an ester of formula (II), wherein R³ is R⁷, rely on exploitation of either a Suzuki reaction or a Stille reaction with an ester of formula (II) wherein R³ (but not R⁴) 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 R⁷B(OH)₂, in the
20 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)-
25 dipalladium(0) and the solvent is degassed 1,2-dimethoxyethane optionally with 1-methylpyrrolidin-2-one as co-solvent.

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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):



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).

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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.

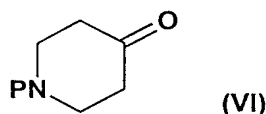
Clearly, when dialkylation is required and R¹ and R² are different, the substituents may be introduced in tandem in a "one-pot reaction" or in separate steps.

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.

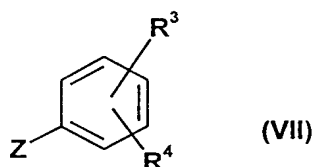
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Clearly, an alternative variation for preparing a compound of formula (II) is to introduce R^1 and/or R^2 into a suitable bromo or iodo intermediate before further elaboration via, for example, a Suzuki or Stille reaction.

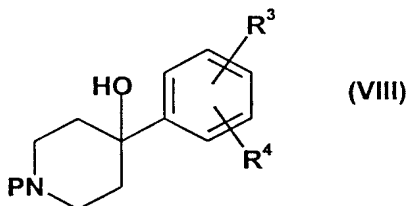
5 An amine of formula (III) may be obtained by standard chemical procedures. For example, when B is absent, m is 2 and n is 1, a suitably N-protected piperidin-4-one of formula (VI):



wherein P is a conventional amine protecting group, is reacted with a carbanion
10 derivative of a compound of formula (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):



15

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.

20

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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 R³ and R⁴ 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 R³ and R⁴ 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.

30

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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
5 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
10 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.

15

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.

20 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

25 Catalytic domain MMP-1 was prepared in Pfizer Central Research laboratories. A stock solution of MMP-1 (1 μ M) was activated 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 CaCl₂, 20 μ M ZnSO₄ and 0.05% Brij 35, pH 7.5) to a
30 concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

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Substrate

The fluorogenic substrate used in this assay was Dnp-Pro- β -cyclohexyl-Ala-Gly-Cys(Me)-His-Ala-Lys-(N-Me-Ala)-NH₂ as originally described in Anal. Biochem., 1993, 212, 58. The final substrate concentration used in the assay was 10 μ M.

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 IC₅₀ 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 (1 μ M) 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 CaCl₂ and 0.16% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assays was 1nM.

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Substrate

The fluorogenic substrate used in this screen was Mca-Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met-Lys(Dnp)-NH₂ (Bachem Ltd., Essex, UK) as originally
5 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

10 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
15 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 IC₅₀ value (the
20 concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-13

Enzyme Preparation

25 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 CaCl₂, 20µM ZnCl₂ and 0.02% Brij 35, pH 7.5) to a concentration of
30 5.3nM. The final concentration of enzyme used in the assay was 1.3nM.

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Substrate

The fluorogenic substrate used in this screen was Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂. The final substrate concentration used in the
5 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
10 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
15 concentrations and, from the resulting dose-response curve, an IC₅₀ value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-14

Enzyme Preparation

20 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
25 solution in Tris-HCl assay buffer (100mM Tris, 100nM NaCl, 10mM CaCl₂, 0.16% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

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Substrate

The fluorogenic substrate used in this screen was Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂ (Bachem Ltd., Essex, UK) as described in J.Biol.Chem.,
5 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
10 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
15 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
20 example enough salts or monosaccharides 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
25 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

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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
5 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
10 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
15 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
20 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
25 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.

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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
5 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
10 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
15 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
20 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
25 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,

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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
5 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
10 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 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
20 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,
25 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

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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.

5 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.

10 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.

15 ¹H 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.

20 Mass spectra were recorded using a Finnigan Mat. TSQ 7000 or a Fisons Instruments 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.

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EXAMPLE 1N-Hydroxy-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetamide

5 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

10 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)⁺.

20

EXAMPLE 2N-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:

25 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)⁺.

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EXAMPLE 3N-Hydroxy-2-[4-(4-phenylphenyl)piperidin-1-ylsulphonyl]acetamide

- Obtained as a colourless solid (62%), m.p. 200-201°C, from the title
5 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%.
 δ (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).
10 LRMS (Thermospray): 375 (M+H)⁺.

EXAMPLE 4N-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
15 compound of Preparation 11, using the procedure of Example 1. Found:
C,52.41; H,5.39; N,9.35. $C_{13}H_{16}N_2O_4S$ requires C,52.69; H,5.44; N,9.45%.
 δ (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).

20

EXAMPLE 5N-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%.
25 δ (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).

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EXAMPLE 6N-Hydroxy-2-(4-benzylpiperidin-1-ylsulphonyl)acetamide

Obtained as a colourless solid (35%), m.p. 132-135°C, from the title
5 compound of Preparation 13, using the procedure of Example 1. Found:
C,53.66; H,6.43; N,8.82. C₁₄H₂₀N₂O₄S requires C,53.83; H,6.45; N,8.97%.
δ(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).

10

EXAMPLE 7N-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
15 the title compound of Preparation 15 (70 mg, 0.18 mmol) and N-
ethyl-diisopropylamine (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-ethyl-diisopropylamine
(0.12 ml, 0.7 mmol) in anhydrous dimethylformamide (0.5 ml) was added and
20 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 (MgSO₄) 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)
25 as a colourless, amorphous solid. δ(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)⁺.

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EXAMPLE 8N-Hydroxy-2(R,S)-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enamide

5 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. δ (CDCl₃): 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).

10 LRMS (APCI): 427 (M+H)⁺.

EXAMPLE 9N-Hydroxy-5-phenyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pentanamide

15 Obtained as a colourless solid (35%), m.p. 150°C (decomp.), from the title compound of Preparation 18, using the procedure of Example 1. δ (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).

20 LRMS (Thermospray): 492 (M+H)⁺.

EXAMPLE 10N-Hydroxy-2-methyl-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]propanamide

25 Obtained as an amorphous solid (41%) from the title compound of Preparation 19, using the procedure of Example 7. δ (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).

30

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EXAMPLE 11N-Hydroxy-1-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]cyclopentanecarboxamide

5 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. $\delta(\text{CDCl}_3)$: 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).

10

EXAMPLE 12N-Hydroxy-2-ethyl-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-sulphonyl]butanamide

15 Obtained as a solid (56%) from the title compound of Preparation 23, using the procedure of Example 7. $\delta(\text{DMSO}_{d6})$: 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

20 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
25 diisopropyl ether:ethyl acetate, rather than flash chromatography, as the purification technique. Found: C,63.03; H,6.60; N,6.43. $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_4\text{S}$; 0.50 H_2O requires C,63.13; H,6.68; N,6.40%. $\delta(\text{DMSO}_{d6})$: 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

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(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)⁺.

5

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
10 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. δ (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).
15 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

20 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 (CDCl₃): 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
25 (m,8H).
LRMS (APCI): 441 (M+H)⁺.

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EXAMPLE 16N-Hydroxy-2-[3-(4-phenylphenoxy)azetidin-1-ylsulphonyl]acetamide

Obtained as a colourless solid (66%) from the title compound of

- 5 Preparation 32, using the procedure of EXAMPLE 1. δ (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)⁺.

10

EXAMPLE 17N-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
15 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 (MgSO₄) and evaporated under reduced pressure, then the residue trituated with diisopropyl ether and crystallised from ethyl acetate to yield the
20 title compound (148 mg, 34%) as a colourless solid, m.p. 151-153°C. Found: C,61.01; H, 6.04; N, 6.48. C₂₂H₂₆N₂O₅S 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).
25 LRMS (APCI): 431 (M+H)⁺.

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EXAMPLE 18N-Hydroxy-2-[4-(3-methoxy-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetamide

5 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
10 combined organic phases were dried (MgSO₄) 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. C₂₀H₂₀N₂O₅S; 0.10 CH₂Cl₂ 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),
15 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+NH₄)⁺.

EXAMPLE 19

20 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-
25 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

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organic phase was separated, washed with water, dried (MgSO₄) 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. C₂₂H₂₆N₂O₅S; 0.10 H₂O 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. C₁₉H₁₉FN₂O₄S 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+NH₄)⁺.

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+NH₄)⁺.

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EXAMPLE 22N-Hydroxy-2-{4-[4-(3-methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

5 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. C₂₁H₂₄N₂O₅S requires C, 60.56; H, 5.81; N, 6.73%. δ (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).
10 LRMS (APCI): 416 (M)⁺.

EXAMPLE 23N-Hydroxy-2-{4-[4-(3-ethylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

15 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. C₂₂H₂₆N₂O₄S; 0.50 H₂O requires C, 62.39; H, 6.43; N, 6.61%. δ (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).
20 LRMS (APCI): 414 (M)⁺.

EXAMPLE 24N-Hydroxy-4-{4-[4-(3-Methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxamide

25 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. δ (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),

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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)⁺.

5

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

10 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. C₂₅H₃₂N₂O₆S; CH₃OH requires C, 59.98; H, 6.97; N, 5.38%. δ(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
15 (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

20 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)
25 as eluant. Found: C,59.39; H, 6.58; N, 6.13. C₂₃H₃₀N₂O₆S requires C, 59.72; H, 6.54; N, 6.06%. δ(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+NH₄)⁺.

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EXAMPLE 27N-Hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]piperidin-1-ylsulphonyl}-
2-methylpropanamide

5 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. C₂₄H₃₂N₂O₆S 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),
10 7.27 (t,1H), 9.00 (brs,1H), 10.76 (brs,1H).
LRMS (Thermospray): 494 (M+NH₄)⁺.

EXAMPLE 28N-Hydroxy-4-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-
15 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. C₂₆H₃₂N₂O₆S 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),
20 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 29N-Hydroxy-4-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]piperidin-1-
25 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-

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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
5 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
10 (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 ($M+NH_4$)⁺.

15

EXAMPLE 30N-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,
20 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 ($M+H$)⁺.

25

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EXAMPLE 31N-Hydroxy-2-[4-[4-(3-ethoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl]acetamide

5 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

15 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)⁺.

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EXAMPLE 33N-Hydroxy-2-{4-[3-methyl-4-(pyridin-2-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

5 Obtained as a colourless amorphous solid (50%) from the title compound of Preparation 85, using the procedure of Example 17. $\delta(\text{DMSO}_{d6})$: 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).

10 LRMS (APCI): 388 (M+H)⁺.

EXAMPLE 34N-Hydroxy-2-{4-[3-methyl-4-(pyridin-3-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

15 Obtained as a colourless solid (57%), m.p. 132-136°C, from the title compound of Preparation 86, using the procedure of Example 31. $\delta(\text{DMSO}_{d6})$: 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).

20 LRMS (APCI): 388 (M+H)⁺.

EXAMPLE 35N-Hydroxy-2-{4-[3-methyl-4-(pyridin-4-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

25 Obtained as a colourless solid (20%), m.p. 165-167° C, from the title compound of Preparation 87, using the procedure of Example 31. $\delta(\text{DMSO}_{d6})$: 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)⁺.

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EXAMPLE 36N-Hydroxy-2-[4-[4-(6-ethoxypyridin-2-yl)-3-methylphenyl]piperidin-1-ylsulphonyl]-2-methylpropanamide

5 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. δ (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),
10 6.72 (d,1H), 7.05 (d,1H), 7.15 (m,2H), 7.34 (q,1H), 7.73 (t,1H), 9.00 (brs,1H), 10.75 (brs,1H).
HRMS (positive ion electrospray): 462.206 (M+H)⁺.

EXAMPLE 37

15 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. δ (DMSO_{d6}): 1.93 (m,2H), 2.40
20 (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)⁺.

25

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
30 crystallisation of the residue from dichloromethane-diisopropyl ether.

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δ (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
5 (brs,1H), 11.05 (brs,1H).
LRMS (Thermospray): 515 (M+NH₄)⁺.

EXAMPLE 39

N-Hydroxy-2-{4-[4-(3-hydroxymethylphenyl)-3-methylphenyl]-1,2,3,6-
10 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. C₂₁H₂₄N₂O₅S
requires C,60.56; H,5.81; N,6.73%. δ (DMSO_{d6}): 2.22 (s,3H), 2.60 (m,2H), 3.47
15 (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-
20 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. δ (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),
25 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)⁺.

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EXAMPLE 41N-Hydroxy-2-{4-[3-methyl-4-(3-methylthiophenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

- 5 Obtained as a colourless solid (17%), from the title compound of Preparation 102, using the procedure of Example 1. $\delta(\text{DMSO}_{d6})$: 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).
- 10 LRMS (APCI): 432 (M)⁺.

EXAMPLE 42N-Hydroxy-2-{4-[4-(3-methoxymethylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

- 15 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. $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$; 0.10 H_2O requires C,60.11; H,6.19; N,6.37%. $\delta(\text{DMSO}_{d6})$: 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).
- 20 LRMS (Thermospray): 432 (M+H)⁺.

EXAMPLE 43

- 25 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. $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_6\text{S}$ requires

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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).

5 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

10 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. C₂₂H₂₆N₂O₅S; 0.60 CH₂Cl₂ 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
15 (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

20 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. C₂₁H₂₁F₃N₂O₄S; 0.25 H₂O
25 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)⁺.

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EXAMPLE 46N-Hydroxy-2-[4-(4-phenoxyphenyl)piperidin-1-ylsulphonyl]acetamide

Obtained as a colourless solid (13%), m.p. 176-179°C, from the title
5 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 10.80 (brs,1H).
LRMS (Thermospray): 392 (M+H)⁺.

EXAMPLE 47N-Hydroxy-2-{4-[4-(3-[2-methoxyethoxy]phenyl)-3-methylphenyl]piperidin-1-
15 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
20 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)⁺.

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EXAMPLE 48N-Hydroxy-4-methoxy-2(R,S)-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]butanamide

5 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.

δ (DMSO_{d6}): 2.10 (m,2H), 2.23 (s,3H), 2.57 (m,2H), 3.20 (s,4H), 3.36 (m,1H),
10 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

15 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. C₂₄H₂₈N₂O₅S; 0.50 H₂O requires C,61.91; H,6.28;
20 N,6.02%. δ (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)⁺.

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EXAMPLE 50N-Hydroxy-2-[4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl]indane-2-carboxamide

5 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),
10 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 51N-Hydroxy-1-[4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl]cyclobutanecarboxamide

15 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),
20 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 52N-Hydroxy-4-[4-[4-(3-methoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl]-1-methylpiperidine-4-carboxamide

25 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:

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concentrated aqueous ammonia solution (90:10:1) as eluant. $\delta(\text{CDCl}_3)$: 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).
5 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
10

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. $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$; 0.50 H_2O requires C,66.22; H,5.77; N,5.94%.
15 $\delta(\text{DMSO}_{d6})$: 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
20

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
25 the residue was purified by flash chromatography using dichloromethane:methanol (98:2) as eluant, followed by trituration with diisopropyl ether. $\delta(\text{DMSO}_{d6})$: 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).
30 LRMS (APCI): 463 (M+H)⁺.

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EXAMPLE 55N-Hydroxy-2-[4-[4-(3-chloro-4-fluorophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetamide

5 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%. δ (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).
10 LRMS (APCI): 439 (M+H)⁺.

EXAMPLE 56

15 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%.
20 δ (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)⁺.

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EXAMPLE 57N-Hydroxy-2-{4-[4-(2-fluorophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

- 5 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. δ (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).
- 10 LRMS (APCI): 405 (M+H)⁺.

EXAMPLE 58N-Hydroxy-2-{4-[4-(3,4-dimethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

- 15 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. C₂₂H₂₆N₂O₆S requires C,59.18; H,5.87; N,6.27%. δ (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).
- 20 LRMS (APCI): 447 (M+H)⁺.

EXAMPLE 59N-Hydroxy-2-{4-[4-(indan-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetamide

- 25 Obtained as a colourless solid (58%), m.p. 149-152°C, from the title compound of Preparation 152, using the procedure of Example 17. δ (DMSO_{d6}):

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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).

5 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

10 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. δ (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).

15 LRMS (Thermospray): 488 (M+NH₄)⁺.

EXAMPLE 61

N-Hydroxy-2-[4-(4-phenyl-3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetamide

20 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. C₂₀H₁₉F₃N₂O₄S requires C,54.54; H,4.35; N,6.36%. δ (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).

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LRMS (Thermospray): 458 (M+NH₄)⁺.

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EXAMPLE 62N-Hydroxy-2-{4-[4-(2,2-dimethyl-1,3-benzodioxol-5-yl)-3-methylphenyl]-piperidin-1-ylsulphonyl}-2-methylpropionamide

- 5 Obtained as a colourless solid (52%), m.p. 184-186°C, from the title compound of Preparation 161, using the procedure of Example 19. δ (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).
- 10 LRMS (APCI): 489 (M+H)⁺.

EXAMPLE 63N-Hydroxy-2-{4-[4-(1,2-dimethylbenzimidazol-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropionamide

- 15 Obtained as a colourless solid (22%), m.p. 213-215°C, from the title compound of Preparation 165, using the procedure of Example 19. δ (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).
- 20 LRMS (Thermospray): 485 (M+H)⁺.

EXAMPLE 64N-Hydroxy-2-{4-[4-(3-cyanophenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropionamide

- 25 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

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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

10 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)⁺.

20 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-ethyl-diisopropylamine (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-ethyl-diisopropylamine (0.6 ml, 2.7 mmol) were added and the reaction mixture stirred for about 16 hours, then

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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.

10 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. $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_6\text{S}$ requires C,60.48; H,6.77; N,5.88%. $\delta(\text{DMSO}_{d6})$: 1.49

15 (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).

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PREPARATION 1t-Butyl 4-hydroxy-4-(4-phenylphenyl)piperidin-1-carboxylate

A 2.5M solution of n-butyllithium in hexane (8 ml, 20 mmol) was added
5 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
10 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 (MgSO₄) and evaporated under
reduced pressure. Crystallisation of the residue from diisopropyl ether gave the
15 title compound (4.29 g) as a colourless solid, m.p. 144-146°C. δ (CDCl₃): 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)⁺.

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PREPARATION 24-(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
25 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 (MgSO₄) and evaporated
under reduced pressure to yield the title compound (2.79 g) as a colourless

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solid. $\delta(\text{CDCl}_3)$: 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)⁺.

5

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 (MgSO₄) and evaporated under reduced pressure, then the residue crystallised from ethyl acetate to provide the title compound (13.9 g) as a colourless solid.

$\delta(\text{DMSO}_{d6})$: 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).

15
20

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

25

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extracted with dichloromethane (4 x 200 ml), then the combined extracts dried (MgSO₄) and evaporated under reduced pressure to furnish the title compound (10.6 g) as an off-white solid. δ (CDCl₃): 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 (MgSO₄) and evaporated under pressure to afford the title compound (3.5 g) as an off-white solid, m.p. 104-107°C. δ (CDCl₃): 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).

20

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-oxopiperidine-1-carboxylate, using the procedure of Preparation 1. δ (CDCl₃): 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)⁺.

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PREPARATION 74-(3-Methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridine

Obtained as a colourless solid (90%) from the title compound of

5 Preparation 6, using the procedure of Preparation 2. $\delta(\text{CDCl}_3)$: 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)⁺.

10

PREPARATION 8Methyl 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
15 [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 (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography, using
20 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. C₂₀H₂₁NO₄S requires C, 64.66; H, 5.70; N, 3.77%. $\delta(\text{CDCl}_3)$: 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).

25 LRMS (APCI): 372 (M+H)⁺.

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PREPARATION 9Methyl 2-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetate

5 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).
10 LRMS (Thermospray): 386 (M+H)⁺.

PREPARATION 10Methyl 2-[4-(4-phenylphenyl)piperidin-1-ylsulphonyl]acetate

15 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).
20

PREPARATION 11Methyl 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
25 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).

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PREPARATION 12Methyl 2-(4-phenylpiperidin-1-ylsulphonyl)acetate

Obtained as a colourless solid (35%), m.p. 98-100°C, from 4-
5 phenylpiperidine and methyl chlorosulphonylacetate, using the procedure of
Preparation 8. Found: C,56.43; H,6.41; N,4.64. C₁₄H₁₉NO₄S requires C,56.55;
H,6.44; N,4.71%. δ (CDCl₃): 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).

10

PREPARATION 13Methyl 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
15 chromatographic purification step. δ (CDCl₃): 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)⁺.

20

PREPARATION 14Methyl 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
25 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

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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 ($\text{M}+\text{H}$)⁺.

10

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 ($\text{M}+\text{NH}_4$)⁺.

25

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PREPARATION 16Methyl 2(R,S)-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoate

5 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. $\delta(\text{CDCl}_3)$: 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), 5.10-10 5.22 (m,2H), 5.73 (m,1H), 6.06 (brs,1H), 7.20-7.45 (m,8H).
LRMS (Thermospray): 426 (M+H)⁺.

PREPARATION 172(R,S)-[4-(3-Methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoic acid

15 Obtained as an amorphous solid (46%) from the title compound of Preparation 16, using the procedure of Preparation 15. $\delta(\text{CDCl}_3)$: 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).
20 LRMS (Thermospray): 368 (M+H-CO₂)⁺.

PREPARATION 18Methyl 5-phenyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pentanoate

25 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. $\delta(\text{CDCl}_3)$: 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).
30 LRMS (Thermospray): 490 (M+H)⁺.

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PREPARATION 192-Methyl-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]propanoic acid

5 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

10 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 (MgSO₄) and evaporated under reduced pressure, then the residue purified by flash chromatography, using

15 dichloromethane:methanol:glacial acetic acid (89:10:1) as eluant, to furnish the title compound (60 mg) as a pale yellow, amorphous solid. δ (CDCl₃): 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

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

25 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 (MgSO₄) and

30 evaporated under reduced pressure. The residue was purified by flash chromatography, using hexane:ethyl acetate (9:1) as eluant, to afford the title

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compound (340 mg) as an amorphous solid. $\delta(\text{CDCl}_3)$: 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).

5 LRMS (Thermospray): 440 (M+H)⁺.

PREPARATION 21

1-[4-(3-Methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-yl-ylsulphonyl]cyclopentanecarboxylic acid

10 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. $\delta(\text{CDCl}_3)$: 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).

15 LRMS (Thermospray): 426 (M+H)⁺.

PREPARATION 22

Methyl 2-ethyl-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-yl-ylsulphonyl]butanoate

20 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
25 compound (125 mg) as a white amorphous solid. $\delta(\text{CDCl}_3)$: 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).

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PREPARATION 232-Ethyl-2-[4-(4-phenylphenyl)-1,2,3,6-tetrahydroimidin-1-ylsulphonyl]-
butanoic acid

5 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
10 dichloromethane (3 x 20 ml). The combined extracts were dried (MgSO₄) and
evaporated under reduced pressure to yield the title compound (95 mg) as a
pale yellow, amorphous solid. δ (CDCl₃): 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).

15

PREPARATION 24Methyl 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
20 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. C₂₄H₂₉NO₄S requires C, 67.42;
H, 6.84; N, 3.28%. δ (CDCl₃): 0.90 (t,3H), 1.30 (m,4H), 2.05 (m,1H), 2.15
25 (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)⁺.

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PREPARATION 274-Methyl-2(R,S)-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoic acid

- 5 Obtained as a colourless solid (94%), m.p. 153-155°C, from the title compound of Preparation 26, using the procedure of Preparation 15. $\delta(\text{CDCl}_3)$: 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).
- 10 LRMS (Thermospray): 368 (M+H-CO₂)⁺.

PREPARATION 28Methyl 2(R,S)-methyl-2-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridine-1-ylsulphonyl]pent-4-enoate

- 15 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
- 20 (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 (MgSO₄) and evaporated under reduced pressure, then the residue purified by flash chromatography, using hexane:ethyl acetate (92.5:7.5)
- 25 as eluant, to afford the title compound (263 mg) as a colourless gum. $\delta(\text{CDCl}_3)$: 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)⁺.

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PREPARATION 292(R,S)-Methyl-2-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]pent-4-enoic acid

5 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. $\delta(\text{CDCl}_3)$: 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).

10 LRMS (Thermospray): 382 (M+H-CO₂)⁺, 426 (M+H)⁺.

PREPARATION 301-Benzhydryl-3-(4-phenylphenoxy)azetidine

 Potassium carbonate (2.39 g, 17.4 mmol) was added to a stirred mixture
15 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 (MgSO₄) and
20 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. $\delta(\text{CDCl}_3)$: 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)⁺.

25

PREPARATION 313-(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
30 ml), ethyl acetate (20 ml) and glacial acetic acid (10 ml) was hydrogenated at

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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 (MgSO₄) and evaporated under reduced pressure to yield the title compound containing 1 mol.equiv. of diphenylmethane* (456 mg) as a colourless, amorphous solid. δ (CDCl₃): 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)azetid-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. δ (CDCl₃): 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.

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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. $\delta(\text{CDCl}_3)$: 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 ($\text{M}+\text{H}$)⁺.

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.

$\text{C}_{17}\text{H}_{24}\text{BrNO}_3$ requires C,55.14; H,6.53; N,3.78%. $\delta(\text{CDCl}_3)$: 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 ($\text{M}+\text{H}$)⁺.

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

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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
5 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-
10 butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 33.

$\delta(\text{CDCl}_3)$: 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)⁺.

15

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
20 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 (MgSO₄) and evaporated
under reduced pressure to give the title compound (13.6 g) as a low melting
solid. $\delta(\text{CDCl}_3)$: 1.60 (brs,1H), 2.40 (m,5H), 3.10 (t,2H), 3.52 (m,2H), 6.10
25 (brs,1H), 7.05 (dd,1H), 7.22 (d,1H), 7.46 (d,1H).

LRMS (Thermospray): 251/253 (M+H)⁺.

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PREPARATION 364-(4-Bromophenyl)-1,2,3,6-tetrahydropyridine

Obtained as a solid (87%), m.p. 76-78°C, from the title compound of
5 Preparation 34 and trifluoroacetic acid, using the procedure of Preparation 35.
 $\delta(\text{CDCl}_3)$: 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)⁺.

10

PREPARATION 37Methyl 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
15 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
20 bicarbonate solution, then the organic phase separated, washed with water,
dried (MgSO₄) 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.
25 C₁₅H₁₈BrNO₄S requires C,46.40; H,4.67; N,3.61%. $\delta(\text{CDCl}_3)$: 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+NH₄)⁺.

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PREPARATION 38Methyl 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
5 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+NH₄)⁺.

10

PREPARATION 39Methyl 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
15 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 (MgSO₄) and evaporated under reduced pressure. The residue
20 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),
25 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+NH₄)⁺.

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PREPARATION 40Methyl 2-[4-(4-bromo-3-methylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-2-methylpropanoate

5 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 (MgSO₄) and
10 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. C₁₇H₂₂BrNO₄S requires C,49.04; H,5.33; N,3.36%. δ(CDCl₃): 1.67
15 (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 41Methyl 2-[4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetate

20 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)
25 (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 (MgSO₄) and evaporated under reduced pressure, then the residue purified by flash chromatography, using dichloromethane as

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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%.

5 $\delta(CDCl_3)$: 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+NH₄)⁺.

PREPARATION 42

10

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
15 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),
20 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
25 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

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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 (MgSO₄) 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. δ (CDCl₃): 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 (MgSO₄) and evaporated under reduced pressure to provide the title compound (2.79 g) as a pale yellow viscous oil. δ (CDCl₃): 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

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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
5 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
10 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. $\text{C}_{21}\text{H}_{23}\text{NO}_5\text{S}$ requires C,62.82; H,5.77; N,3.49%. $\delta(\text{CDCl}_3)$: 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),
15 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

20 Obtained as a colourless oil (67%), from 4-bromo-3-fluorobiphenyl and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43. $\delta(\text{CDCl}_3)$: 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).

25

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

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Preparation 44. $\delta(\text{CDCl}_3)$: 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)⁺.

5

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

10 Preparation 47 and methyl chlorosulphonylacetate, using the procedure of Preparation 45. $\delta(\text{DMSO-}d_6)$: 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+NH₄)⁺.

15

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
20 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 (MgSO₄) and evaporated under reduced pressure to afford the title compound (540 mg) as a pale yellow oil.

25 $\delta(\text{CDCl}_3)$: 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)⁺.

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PREPARATION 502-[4-(3-Methoxy-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-2-methylpropanoic acid

5 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
10 dried (MgSO₄) and evaporated under reduced pressure to give the title compound (210 mg) as a pale yellow, semi-solid. δ (CDCl₃): 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+NH₄)⁺.

15

PREPARATION 514-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
20 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
25 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.
 δ (CD₃CN): 4.20 (s,3H), 7.58 (d,1H), 7.80 (s,1H), 8.16 (d,1H).
LRMS (Thermospray): 301 (M)⁺.

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PREPARATION 524-(3-Ethoxyphenyl)-3-methoxybromobenzene

Anhydrous 1,4-dioxan (80 ml) was added to a mixture of the title
5 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 (MgSO₄)
10 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. δ (CDCl₃): 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)⁺.

15

PREPARATION 53t-Butyl 4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]-4-hydroxypiperidine-1-
carboxylate

Obtained as a colourless oil (60%), from the title compound of
20 Preparation 52 and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure
of Preparation 43. δ (CDCl₃): 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).

25

PREPARATION 544-[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.

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$\delta(\text{CDCl}_3)$: 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)⁺.

5

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
10 Preparation 54 and methyl chlorosulphonylacetate, using the procedure of Preparation 45. $\delta(\text{CDCl}_3)$: 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)⁺.

15

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-
20 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
25 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

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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+NH₄)⁺.

PREPARATION 57

10 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).

15 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

25 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).
30 LRMS (Thermospray): 399 (M+H)⁺.

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PREPARATION 604-[4-(3-Methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridine

Obtained as a pale yellow semi-solid (93%), from the title compound of

- 5 Preparation 59 and trifluoroacetic acid, using the procedure of Preparation 44.
 $\delta(\text{CDCl}_3)$, 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)⁺.

10

PREPARATION 61Methyl 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
15 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
20 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. $\delta(\text{CDCl}_3)$: 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).
25 LRMS (Thermospray): 416 (M+H)⁺.

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PREPARATION 623-Ethylphenylboronic acid

n-Butyllithium (11 ml of a 2.5M solution in hexane, 28 mmol) was added
5 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
10 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
15 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%). $\delta(\text{DMSO}_{d_6})$:
1.17 (t,3H), 2.57 (q,2H), 7.22 (t,2H), 7.57 (t,1H), 7.61 (s,1H), 7.93 (s,2H).

20

PREPARATION 63Methyl 2-{4-[4-(3-ethylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-
ylsulphonyl}acetate

Obtained as a yellow solid (75%), m.p. $58-60^{\circ}\text{C}$, from the title
compounds of Preparation 62 and Preparation 37, using the procedure of
25 Preparation 41. $\delta(\text{CDCl}_3)$: 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 ($\text{M}+\text{NH}_4$)⁺.

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PREPARATION 64Methyl 4-{4-[4-(3-methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxylate

5 Obtained as a glassy solid (20%), from the title compound of Preparation 61 and bis-2-iodoethyl ether, using the procedure of Preparation 39. $\delta(\text{CDCl}_3)$: 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).

10 LRMS (APCI): 486 (M+H)⁺.

PREPARATION 654-{4-[4-(3-Methoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxylic acid

15 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. $\delta(\text{CDCl}_3)$: 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).

20

PREPARATION 66Methyl 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 (MgSO₄) and evaporated under reduced pressure, then the residue crystallised

25

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from methanol to yield the title compound (215 mg) as a white solid, m.p. 137-139°C. $\delta(\text{CDCl}_3)$: 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

10 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:
15 C,63.04; H, 6.59; N, 2.91. $\text{C}_{25}\text{H}_{31}\text{NO}_6\text{S}$ requires C, 63.40; H, 6.60; N, 2.96%.
 $\delta(\text{DMSO}_{d6})$: 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)⁺.

20

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
25 Preparation 52. Found: C, 57.77; H, 4.51. $\text{C}_{14}\text{H}_{13}\text{BrO}_2$ requires C, 57.36; H, 4.47. $\delta(\text{CDCl}_3)$: 3.82 (s,3H), 3.86 (s,3H), 6.91 (d,1H), 7.03-7.39 (m,6H).
LRMS (Thermospray): 311 (M+NH₄)⁺.

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PREPARATION 69t-Butyl 4-hydroxy-4-[3-methoxy-4-(3-methoxyphenyl)phenyl]piperidine-1-carboxylate

5 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. $\delta(\text{CDCl}_3)$: 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)⁺.

10

PREPARATION 704-[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

15 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 (MgSO₄) and evaporated under reduced pressure to provide the title compound (3.3 g) as a yellow oil.

20 $\delta(\text{CDCl}_3)$: 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

25 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

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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%. $\delta(CDCl_3)$: 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%. $\delta(CDCl_3)$: 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%.

$\delta(CDCl_3)$: 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)⁺.

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PREPARATION 742-{4-[3-Methoxy-4-(3-methoxyphenyl)phenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

5 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).
10 LRMS (Thermospray): 465 (M+NH₄)⁺.

PREPARATION 75Methyl 2-{4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

15 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),
20 7.02 (d,1H), 7.10 (m,2H), 7.31 (m,2H).
LRMS (Thermospray): 474 (M+H)⁺.

PREPARATION 76Methyl 2-{4-[4-(3-ethoxyphenyl)-3-methoxyphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

25 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).
30 LRMS (Thermospray): 476 (M+H)⁺.

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PREPARATION 772-{4-[4-(3-Ethoxyphenyl)-3-methoxyphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

- 5 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).
- 10 LRMS (Thermospray): 479 (M+NH₄)⁺.

PREPARATION 78Methyl 4-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxylate

- 15 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),
- 20 7.20-7.36 (m, 4H).
- LRMS (Thermospray): 500 (M+H)⁺.

PREPARATION 794-{4-[4-(3-Ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}tetrahydropyran-4-carboxylic acid

- 25 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

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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
5 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. $\text{C}_{26}\text{H}_{31}\text{NO}_6\text{S}$ requires C, 64.31; H, 6.44; N, 2.89%. $\delta(\text{CDCl}_3)$: 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).
10 LRMS (Thermospray): 486 (M+H)⁺.

PREPARATION 80

Methyl 2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

15 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. $\text{C}_{25}\text{H}_{31}\text{NO}_5\text{S}$ requires C, 65.62; H, 6.83; N, 3.06%. $\delta(\text{CDCl}_3)$: 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-
20 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

25 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).

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$\delta(\text{CDCl}_3)$: 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)⁺.

5

PREPARATION 82Methyl 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. $\delta(\text{CDCl}_3)$:
10 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)⁺.

15

PREPARATION 83Methyl 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.
20 $\delta(\text{CDCl}_3)$: 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)⁺.

25

PREPARATION 842-{4-[4-(3-Ethoxyphenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

Obtained as a colourless solid (72%), m.p. 125-128°C, from the title

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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:

5 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)⁺.

10

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 Preparation 37 (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)⁺.

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PREPARATION 86Methyl 2-{4-[3-methyl-4-(pyridin-3-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

5 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

15 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 886-Ethoxy-2-(tri-n-butylstannyl)-pyridine

25 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

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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
5 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. δ (CDCl₃): 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
10 (dd,1H).

PREPARATION 89

Methyl 2-{4-[4-(6-ethoxypyridin-2-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

15 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
20 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 (MgSO₄) 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
25 (290 mg, 52%) as a colourless foam. δ (CDCl₃): 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)⁺.

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PREPARATION 90Methyl 2-{4-[4-(6-ethoxypyridin-2-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

5 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
10 (90:10 to 70:30), to provide the title compound (70 mg, 25%) as a colourless foam. $\delta(\text{CDCl}_3)$: 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)⁺.

15

PREPARATION 912-{4-[4-(6-Ethoxypyridin-2-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

A solution of the title compound of Preparation 91 (68 mg, 0.15 mmol) in
20 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 (MgSO₄) and evaporated under reduced pressure to furnish the title compound (60 mg, 87%)
25 as a colourless solid, m.p. 178-179°C. Found: C, 61.53; H, 6.81; N, 6.09. C₂₃H₃₀N₂O₅S requires C, 61.86; H, 6.77; N, 6.27%. $\delta(\text{CDCl}_3)$: 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).

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PREPARATION 92Methyl 4-[4-(4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]tetrahydropyran-4-carboxylate

- 5 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. $\delta(\text{CDCl}_3)$: 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).
- 10 LRMS (Thermospray): 442 (M+H)⁺.

PREPARATION 934-[4-(4-Phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]tetrahydropyran-4-carboxylic acid

- 15 Obtained as a colourless solid (66%), m.p. 214°C, from the title compound of Preparation 92, using the procedure of Preparation 79. $\delta(\text{CDCl}_3)$: 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)⁺.

20

PREPARATION 94Methyl 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
- 25 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. $\text{C}_{27}\text{H}_{33}\text{NO}_6\text{S}$ requires C, 64.91; H, 6.66; N, 2.80%. $\delta(\text{DMSO}_{d6})$: 1.34 (t,3H), 2.00 (m,2H), 2.22 (s,3H), 2.28 (d,2H), 2.55

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(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).

5 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

10 Obtained as a colourless solid (56%), m.p. 212-214°C, from the title compound of Preparation 94, using the procedure of Preparation 79. δ (CDCl₃): 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).

15 LRMS (Thermospray): 486 (M+H)⁺.

PREPARATION 96

Methyl 2-{4-[4-(3-formylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

20 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. δ (CDCl₃): 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).

25 LRMS (APCI): 414 (M+H)⁺.

PREPARATION 97

Methyl 2-{4-[4-(3-hydroxymethylphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

30 The title compound of Preparation 96 (303 mg, 0.73 mmol) was

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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

5 resin was removed by filtration and the filtrate evaporated under reduced pressure to afford the title compound as a colourless foam (270 mg, 90%).
 $\delta(\text{CDCl}_3)$: 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)⁺.

10

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
15 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
20 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 (MgSO₄) and
25 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. C₉H₈BNO₂ requires C, 62.49; H, 4.66; N, 8.10%. $\delta(\text{DMSO}_{d6})$: 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).

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PREPARATION 99Methyl 2-methyl-2-{4-[3-methyl-4-(quinolin-3-yl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}propanoate

5 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)⁺.

15

PREPARATION 1002-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. 25 222-224°C. Found: C, 66.17; H, 5.77; N, 6.15. $C_{25}H_{26}N_2O_4S$ requires C, 66.64; H, 6.582; 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)⁺.

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PREPARATION 1013-Methylthiophenylboronic acid

A solution of 3-bromothiobanisole (10.3 g, 50.9 mmol) in anhydrous
5 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
10 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
15 aqueous sodium hydroxide solution. The combined aqueous extracts were
acidified with concentrated hydrochloric acid and extracted with ether. The
combined ether extracts were dried (MgSO₄) and evaporated under reduced
pressure to provide the title compound (7.8 g, 100%) as a white solid.
δ(DMSO_{db}): 2.45 (s,3H), 7.27 (m,2H), 7.54 (m,1H), 7.67 (s,1H), 8.05 (brs,2H).

20

PREPARATION 102Methyl 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
25 Preparation 101 and Preparation 37, using the procedure of Preparation 41, but
using dichloromethane:hexane (3:1) as eluant. δ(CDCl₃): 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)⁺.

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PREPARATION 1033-Methoxymethylphenylboronic acid

Obtained as a yellow solid (100%), from 1-bromo-3-
5 methoxymethylbenzene (J. Amer. Chem. Soc., 1989, 111, 6311; Tetrahedron
1985, 41, 1435) and trimethyl borate, using the procedure of Preparation 101.
 $\delta(\text{DMSO}_{d6})$: 3.27 (s,3H), 4.38 (s,2H), 7.31 (m,2H), 7.68 (m,2H), 7.98 (brs,2H).

PREPARATION 104

10 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. $\delta(\text{CDCl}_3)$: 2.27 (s,3H), 2.68 (m,2H), 3.42
15 (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

20 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
25 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

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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
5 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%). $\delta(\text{CDCl}_3)$: 3.43 (s,3H), 3.74 (t,2H), 4.10 (t,2H), 6.87 (d,1H), 7.10 (m,3H).

PREPARATION 106

10 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. $\text{C}_9\text{H}_{13}\text{BO}_4$ requires C, 55.15; H, 6.69%. $\delta(\text{DMSO}_{d6})$: 3.30 (s,3H), 3.63 (t,2H), 4.06 (t,2H), 6.94 (dd,1H), 7.22
15 (t,1H), 7.32 (m,2H), 7.98 (brs,2H).
LRMS (Thermospray): 214 ($\text{M}+\text{NH}_4$)⁺.

PREPARATION 107

20 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. $\delta(\text{CDCl}_3)$: 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
25 (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-

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bromo-2,3-dihydrobenzofuran (Synthesis, 1988, 952) and trimethyl borate, using the procedure of Preparation 101. δ (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).

5

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 (MgSO₄) 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. δ (CDCl₃): 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)⁺.

20

PREPARATION 110

t-Butyl 4-[4-(2,3-dihydrobenzofuran-5-yl)-3-methylphenyl]-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. δ (CDCl₃): 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)⁺.

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PREPARATION 1114-[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
5 Preparation 110 and trifluoroacetic acid, using the procedure of Preparation 44.
 $\delta(\text{CDCl}_3)$: 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)⁺.

10

PREPARATION 112Methyl 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
15 the procedure of Preparation 61. $\delta(\text{CDCl}_3)$: 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)⁺.

20

PREPARATION 1133-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. $\delta(\text{CDCl}_3)$: 2.23 (s,3H), 7.08 (d,1H), 7.40-7.64 (m, 6H).

25

PREPARATION 114t-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

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113 and t-butyl 4-oxopiperidine-1-carboxylate, using the procedure of Preparation 43, but with hexane:ethyl acetate (85:15) as eluant. $\delta(\text{CDCl}_3)$: 1.50 (s,9H), 1.77 (m,2H), 2.04 (m,2H), 2.27 (s,3H), 3.26 (m,2H), 4.05 (m,2H),
5 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

10 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. $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}$; 0.25 H_2O requires C, 70.90; H, 5.79; N, 4.35%. $\delta(\text{CDCl}_3)$: 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).
15 LRMS (APCI): 318 (M)⁺.

PREPARATION 116

Methyl 2-{4-[3-methyl-4-(3-trifluoromethylphenyl)phenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}acetate

20 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. $\text{C}_{22}\text{H}_{22}\text{F}_3\text{NO}_4\text{S}$; 0.25 CH_2Cl_2 requires C, 56.30; H, 4.78; N, 2.95%. $\delta(\text{CDCl}_3)$: 2.27 (s,3H), 2.70 (m,2H), 3.64 (t,2H), 3.82 (s,3H), 4.03
25 (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

30 Obtained as a white foam (54%), from 4-phenoxybromobenzene and t-

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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. $\delta(\text{CDCl}_3)$: 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

10 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 15 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 20 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 25 reduced pressure to give the title compound as a yellow oil (550 mg, 100%).
 $\delta(\text{CDCl}_3)$: 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)⁺.

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PREPARATION 119Methyl 2-[4-(4-phenoxyphenyl)piperidin-1-ylsulphonyl]acetate

Obtained as a colourless solid (38%), from the title compound of

- 5 Preparation 118 and methyl chlorosulphonylacetate, using the procedure of Preparation 45. $\delta(\text{CDCl}_3)$: 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+NH₄)⁺.

10

PREPARATION 120Methyl 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
15 with ethyl acetate:hexane (1:3) as eluant. $\delta(\text{CDCl}_3)$: 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

20

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. $\delta(\text{CDCl}_3)$: 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
25 (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)⁺.

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PREPARATION 1222-[4-[4-(3-[2-Methoxyethoxy]phenyl)-3-methylphenyl]piperidin-1-ylsulphonyl]-2-methylpropionic acid

5 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. C₂₅H₃₃NO₆S requires C, 63.14; H, 6.99; N, 2.95%. δ (CDCl₃): 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
10 (d,1H), 7.30 (t,1H).
LRMS (Thermospray): 475 (M+H)⁺.

PREPARATION 123Methyl 4-methoxy-2(R,S)-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]butanoate

15 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)
20 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 (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography, using dichloromethane as eluant, followed by trituration with diisopropyl ether, to yield
25 the title compound (148 mg) as a colourless solid, m.p. 95-96°C. δ (CDCl₃): 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)⁺.

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PREPARATION 1244-Methoxy-2(R,S)-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]butanoic acid

5 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
10 with water, then the resulting mixture acidified with glacial acetic acid and extracted with ethyl acetate. The combined organic phases were dried (MgSO₄) and evaporated under reduced pressure to provide the title compound (145 mg) as a colourless solid, m.p. 108-109°C. δ (CDCl₃): 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),
15 6.07 (brs, 1H), 7.19-7.47 (m,8H).
LRMS (APCI): 429 (M+H)⁺.

PREPARATION 125Methyl 4-[4-(3-methyl-4-phenylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]tetrahydropyran-4-carboxylate

20 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
25 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 (MgSO₄) and evaporated under reduced pressure. The residue was

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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

10 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
15 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
20 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)⁺.

25

PREPARATION 127

4-[4-(3-Methoxyphenyl)-3-methylphenyl]piperidine

Obtained as a pink oil (74%), from the title compound of Preparation 59,

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using the procedure of Preparation 118. $\delta(\text{CDCl}_3)$: 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).

5 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
10 compound of Preparation 127 and methyl chlorosulphonylacetate, using the procedure of Preparation 45. $\delta(\text{CDCl}_3)$: 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)⁺.

15

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
20 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)
25 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 (MgSO₄) and evaporated under reduced pressure to give a yellow oil. Purification by flash chromatography, using an

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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%.

5 $\delta(CDCl_3)$: 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)⁺.

10

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:

15 C,68.17; H,6.22; N,2.74. $C_{29}H_{31}NO_5S$; 0.30 H₂O 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+NH₄)⁺.

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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
25 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

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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. $\delta(\text{CDCl}_3)$: 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)⁺.

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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.

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$\delta(\text{CDCl}_3)$: 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)⁺.

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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

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(MgSO₄) 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 (MgSO₄) and evaporated under reduced pressure to furnish the title compound as a yellow gum (175 mg). δ (CDCl₃): 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. δ (CDCl₃): 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

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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 (MgSO₄) 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 (CDCl₃): 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)⁺.

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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 (CDCl₃): 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)⁺.

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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

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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
5 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
10 successively with water and aqueous sodium chloride solution, dried (MgSO₄) 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 (CDCl₃): 2.60 (m,2H), 3.56 (m,2H), 3.75-3.88 (m,4H),
15 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

20 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 (CDCl₃): 2.60 (m,2H), 3.56-3.84 (m,6H),
25 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

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Preparation 57 and 3-chloro-4-fluorophenylboronic acid, using the procedure of Preparation 109. $\delta(\text{CDCl}_3)$: 2.22 (s,3H), 7.04 (d,1H), 7.10-7.20 (m,2H), 7.28-7.39 (m,2H), 7.42 (s,1H).

5

PREPARATION 140

t-Butyl 4-[4-(3-chloro-4-fluorophenyl)-3-methylphenyl]-4-hydroxypiperidine-1-carboxylate

10 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. $\text{C}_{23}\text{H}_{27}\text{ClFNO}_3$ requires C, 65.79; H, 6.48; N, 3.34%. $\delta(\text{CDCl}_3)$: 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).

15 LRMS (APCI): 420 (M+H)⁺.

PREPARATION 141

4-[4-(3-Chloro-4-fluorophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridine

20 Obtained as a pale yellow oil (99%), from the title compound of Preparation 140 and trifluoroacetic acid, using the procedure of Preparation 35. $\delta(\text{CDCl}_3)$: 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)⁺.

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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

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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),
5 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

10 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).

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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
20 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).

25 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
30 compound of Preparation 144 and trifluoroacetic acid, using the procedure of

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Preparation 35. $\delta(\text{CDCl}_3)$: 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).

5 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

10 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. $\text{C}_{22}\text{H}_{23}\text{NO}_6\text{S}$ requires C, 61.52; H, 5.40; N, 3.26%. $\delta(\text{CDCl}_3)$: 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
15 (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

20 Obtained as a colourless oil (33%), from the title compound of Preparation 57 and 3-fluorophenylboronic acid, using the procedure of Preparation 109. $\delta(\text{CDCl}_3)$: 2.20 (s,3H), 7.06-7.25 (m,4H), 7.30-7.40 (m,2H), 7.43 (s,1H).

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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

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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)⁺.

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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)⁺.

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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

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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

10 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), 15 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+NH₄)⁺.

PREPARATION 153

20 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), 25 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)⁺.

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PREPARATION 1544-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 155t-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 1564-(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)⁺.

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PREPARATION 157Methyl 2-[4-(4-phenyl-3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]acetate

5 Obtained as a pale yellow oil (59%), from the title compound of Preparation 156 and methyl chlorosulphonylacetate, using the procedure of Preparation 37. $\delta(\text{CDCl}_3)$: 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)⁺.

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PREPARATION 1582,2-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
15 procedure of Preparation 101. $\delta(\text{DMSO}_{d6})$: 1.60 (s,6H), 6.77 (d,1H), 7.17 (s,1H), 7.28 (d,1H), 7.80 (s,2H).

PREPARATION 159Methyl 2-[4-[4-(2,2-dimethyl-1,3-benzodioxol-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl]-2-methylpropanoate

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 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. $\delta(\text{CDCl}_3)$: 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),
25 6.05 (brs,1H), 6.70-6.78 (m,3H), 7.19-7.30 (m,3H). LRMS (Thermospray): 486 (M+H)⁺.

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PREPARATION 160Methyl 2-{4-[4-(2,2-dimethyl-1,3-benzodioxol-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

- 5 Obtained as a colourless, amorphous solid (96%), from the title compound of Preparation 159, using the procedure of Preparation 90.
- $\delta(\text{CDCl}_3)$: 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).
- 10 LRMS (Thermospray): 488 (M+H)⁺.

PREPARATION 1612-{4-[4-(2,2-Dimethyl-1,3-benzodioxol-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

- 15 Obtained as a colourless, amorphous solid (47%) from the title compound of Preparation 160, using the procedure of Preparation 79.
- $\delta(\text{CDCl}_3)$: 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)⁺.

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PREPARATION 1621,2-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 25 44 hours, then allowed to cool and partitioned between ethyl acetate and water.

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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 (MgSO₄) and evaporated under reduced pressure, then
5 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. δ (CDCl₃): 1.37 (s,12H), 2.60 (s,3H), 3.72 (s,3H), 7.27 (d,1H), 7.70 (d,1H), 8.15 (s,1H).
10 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

15 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
20 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 (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography,
25 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. δ (CDCl₃): 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).
30 LRMS (Thermospray): 482 (M+H)⁺.

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PREPARATION 164Methyl 2-{4-[4-(1,2-dimethylbenzimidazol-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

- 5 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.
- $\delta(\text{CDCl}_3)$: 1.65 (s,6H), 1.78-1.88 (m,4H), 2.27 (s,3H), 2.62 (s,3H), 2.65 (m,1H),
- 10 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

- 15 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.
- $\delta(\text{DMSO}_{d6})$: 1.50 (s,6H), 1.62 (m,2H), 1.82 (m,2H), 2.20 (s,3H), 2.70 (m,1H),
- 20 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

- 25 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

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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
5 poured into ethyl acetate. The mixture was washed with 2M hydrochloric acid, then the organic phase dried (MgSO₄) and evaporated under reduced pressure to afford the title compound (439 mg, 91%) as a colourless, amorphous solid.
δ(CDCl₃): 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).
10 LRMS (Electrospray): 425 (M+Na)⁺.

PREPARATION 167

N-Benzyloxy 2-[4-(4-bromo-3-methylphenyl)-1,2,3,6-tetrahydropyridin-1-
15 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-benzyloxyhydroxylamine hydrochloride (200 mg, 1.25 mmol), N-methylmorpholine
20 (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 (MgSO₄) and evaporated under reduced pressure. The residue was flash chromatographed, using an elution
25 gradient of methanol:dichloromethane (1:99 to 2:98), to give the title compound (553 mg, 91%) as a colourless oil. δ(CDCl₃): 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)⁺.

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PREPARATION 168N-Benzyloxy 2-{4-[4-(3-cyanophenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropionamide

5 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

10 step. $\delta(\text{CDCl}_3)$: 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 1693-Ethoxy-5-(tri-n-butylstannyl)pyridine

15 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),

20 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,

25 32%) as a colourless oil. $\delta(\text{CDCl}_3)$: 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).

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PREPARATION 170Methyl 2-{4-[4-(3-ethoxypyridin-5-yl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanoate

5 Obtained as a gum (30%), from the title compounds of Preparation 169 and Preparation 40, using the procedure of Preparation 89. $\delta(\text{CDCl}_3)$: 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).

10 LRMS (APCI): 459 (M+H)⁺.

PREPARATION 171Methyl 2-{4-[4-(3-ethoxypyridin-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

15 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. $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5\text{S}$ requires C, 62.59; H, 7.00; N, 6.08%. $\delta(\text{CDCl}_3)$: 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),
20 8.17 (s,1H), 8.27 (s,1H).

LRMS (Electrospray): 461 (M+H)⁺.

PREPARATION 1722-{4-[4-(3-Ethoxypyridin-5-yl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

25

Obtained as a colourless solid (98%), m.p. 202-203°C, from the title compound of Preparation 171, using the procedure of Preparation 91.

$\delta(\text{CDCl}_3)$: 1.44 (t,3H), 1.70 (s,6H), 1.80 (m,4H), 2.18 (s,3H), 2.60 (m,1H), 3.08

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(m,2H), 3.96 (m,2H), 4.13 (q,2H), 7.05-7.15 (m,3H), 7.26 (obscured by CHCl₃, 1H), 8.22 (s,1H), 8.33 (s,1H).

LRMS (Thermospray): 447 (M+H)⁺.

5

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
10 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
15 dried (MgSO₄) 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%). δ (CDCl₃): 1.98 (t,1H), 3.95 (t,2H), 4.07 (m,2H), 6.87 (d,1H), 7.08-7.17 (m,3H).

20

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
25 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

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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%).

$\delta(\text{CDCl}_3)$: 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 ($\text{M}+\text{NH}_4$)⁺.

10

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 15 -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 20 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%). $\delta(\text{CDCl}_3)$: 1.08 (s,9H), 4.06 (t,2H), 4.19 (t,2H), 25 7.12 (m,1H), 7.36-7.45 (m,8H), 7.74 (m,6H), 7.82 (m,1H).
LRMS (Thermospray): 438 ($\text{M}+\text{NH}_4$)⁺.

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PREPARATION 176Methyl 2-{4-[4-(3-[2-t-butylidiphenylsilyloxyethoxy]phenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropionate

5 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). $\delta(\text{CDCl}_3)$: 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),
10 6.08 (brs,1H), 6.90 (m,3H), 7.19-7.42 (m,10H), 7.71 (d,4H).
LRMS (Thermospray): 438 (M+NH₄)⁺.

PREPARATION 177Methyl 2-{4-[4-(3-[2-t-butylidiphenylsilyloxyethoxy]phenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoate

15 Obtained as a colourless oil (88%), from the title compound of Preparation 176, using the procedure of Preparation 66. $\delta(\text{CDCl}_3)$: 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
20 (d,1H), 7.34-7.47 (m,6H), 7.71 (d,4H).
LRMS: (Thermospray): 438 (M+NH₄)⁺.

PREPARATION 1782-{4-[4-(3-[2-t-Butylidiphenylsilyloxyethoxy]phenyl)-3-methylphenyl]piperidin-1-ylsulphonyl}-2-methylpropanoic acid

25 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. $\delta(\text{CDCl}_3)$: 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
30 (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).

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Biological activity

The following Table illustrates the in vitro activities for a range of the compounds of the invention as MMP inhibitors.

5

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

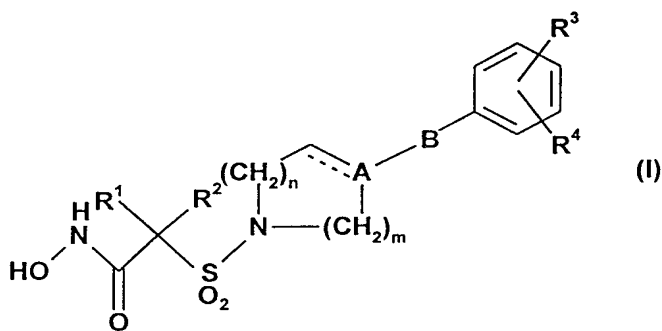
10

NR = no result

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CLAIMS

1. A compound of formula (I):



5

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;

10

A is C or CH;

B is CH₂, O or absent;

R¹ and R² are each independently selected from hydrogen, C₁ to C₆ alkyl optionally substituted with C₁ to C₄ alkoxy or phenyl, and C₁ to C₆ alkenyl; or, together with the carbon atom to which they are attached, form a C₃ to C₆ cycloalkyl group which optionally incorporates a heteroatom linkage selected from O, SO, SO₂ and NR⁶ or which is optionally benzo-fused;

15

R³ is hydrogen, halo, R⁷ or OR⁷;

R⁴ is hydrogen, C₁ to C₄ alkyl, C₁ to C₄ alkoxy, trifluoromethyl or halo;

20

R⁶ is hydrogen or C₁ to C₄ alkyl;

R⁷ is a monocyclic or bicyclic ring system selected from phenyl,

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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 C₁ to C₄ alkyl optionally substituted with C₁ to C₄ alkoxy or hydroxy, C₁-C₄ alkoxy optionally substituted with C₁ to C₄ alkoxy or hydroxy, C₁ to C₄ 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; R¹ is hydrogen, C₁ to C₄ alkyl optionally substituted with methoxy or phenyl, or C₁ to C₅ alkenyl; R² is hydrogen or C₁ to C₄ alkyl; or R¹ and R², together with the carbon atom to which they are attached, form a C₄ to C₅ cycloalkyl group which optionally incorporates a heteroatom linkage selected from O and NR⁶ or which is optionally benzo-fused; R³ 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 C₁ to C₃ alkyl optionally substituted with methoxy or hydroxy, C₁ to C₃ alkoxy optionally substituted with methoxy or hydroxy, methylthio, trifluoromethyl, trifluoromethoxy, fluoro, chloro and cyano; R⁴ is hydrogen, methyl, ethyl, methoxy, trifluoromethyl, fluoro or chloro; R⁶ is methyl; m is 2; and n is 1.

3. A compound according to claim 2 wherein R¹ is hydrogen, methyl, ethyl,

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2-methylprop-1-yl, but-1-yl, 2-methoxyethyl, benzyl, 3-phenylprop-1-yl, allyl, 2-methylallyl, 3,3-dimethylallyl; R² is hydrogen, methyl or ethyl; or R¹ and R², 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; R³ 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 R⁴ is hydrogen, 2-methyl, 3-methyl, 3-ethyl, 3-methoxy, 3-trifluoromethyl, 3-fluoro or 3-chloro.

20

4. A compound according to claim 3 wherein R¹ and R² 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; R³ 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 R⁴ is 3-methyl or 3-methoxy.

25

5. A compound according to claim 4 wherein the compound of formula (I) is selected from

30

N-hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-

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tetrahydropyridin-1-ylsulphonyl}acetamide;

N-hydroxy-2-{4-[4-(3-ethoxyphenyl)-3-methylphenyl]-1,2,3,6-tetrahydropyridin-1-ylsulphonyl}-2-methylpropanamide;

5 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;

10 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;

15 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.

20 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.

25 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.

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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
5 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
10 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 acceptable solvate of either entity, according to any one of claims 1 to 5, for the manufacture of a human
15 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
20 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
25 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

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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

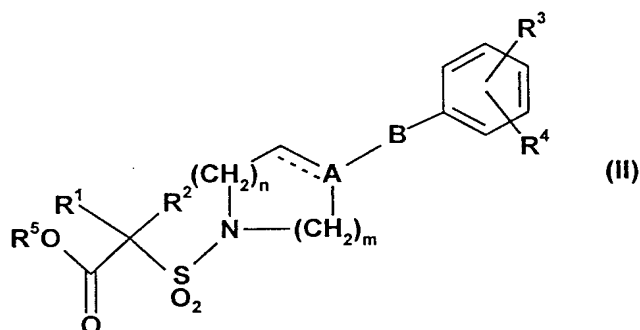
5 angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

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

10 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

15 angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

15. A compound of formula (II):



20

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.

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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
5 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.

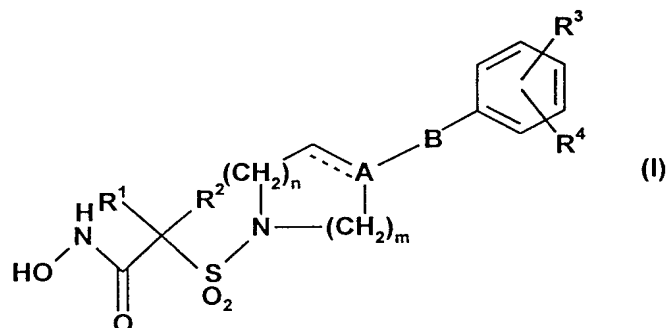
10

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,
15 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
20 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
25 claim 7 respectively.

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19. A process for the preparation of a compound of formula (I):



5

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;

10

B is CH₂, O or absent;

R¹ and R² are each independently selected from hydrogen, C₁ to C₆ alkyl optionally substituted with C₁ to C₄ alkoxy or phenyl, and C₁ to C₆ alkenyl; or, together with the carbon atom to which they are attached, form a C₃ to C₆ cycloalkyl group which optionally incorporates a heteroatom linkage selected from O, SO, SO₂ and NR⁶ or which is optionally benzo-fused;

15

R³ is hydrogen, halo, R⁷ or OR⁷;

R⁴ is hydrogen, C₁ to C₄ alkyl, C₁ to C₄ alkoxy, trifluoromethyl or halo;

20

R⁶ is hydrogen or C₁ to C₄ alkyl;

R⁷ is a monocyclic or bicyclic ring system selected from phenyl, thienyl, furyl, pyridinyl, pyrimidinyl, naphthyl, indanyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, quinolinyl,

-143-

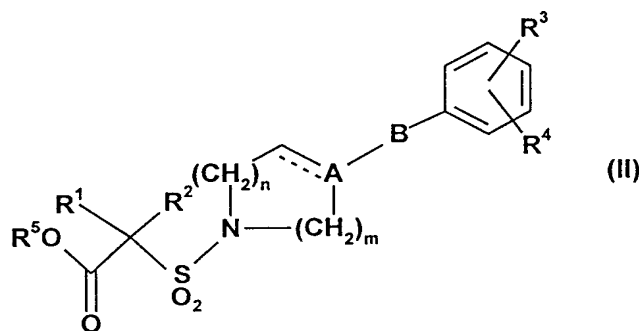
isoquinolinyl, benzodioxolyl, benzimidazolyl, benzoxazolyl,
 benzothiazolyl and benzodioxanyl, any of which ring systems
 is optionally substituted with one or two substituents selected from
 5 C₁ to C₄ alkyl optionally substituted with C₁ to C₄ alkoxy or
 hydroxy, C₁-C₄ alkoxy optionally substituted with C₁ to C₄ alkoxy
 or hydroxy, C₁ to C₄ alkylthio, trifluoromethyl, trifluoromethoxy,
 halo and cyano;

m is 1 or 2;

10 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):



15

wherein R⁵ is hydrogen or C₁ to C₃ alkyl, and the broken line, A, B, R¹, R², R³,
 R⁴, m and n are as previously defined for formula (I), with hydroxylamine,
 optionally followed by formation of a pharmaceutically or veterinarily acceptable
 20 solvate of either entity.

25

20. A process according to claim 19 wherein, when R⁵ is C₁ to C₃ 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 .

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21. A process according to claim 20 wherein the base is an alkali metal carbonate or bicarbonate, the solvent is methanol, optionally combined with
5 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 R⁵ is hydrogen, the acid of formula (II) in the presence of from 1.1 to 2.0 molecular equivalents of an
10 activating agent and from 1.0 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.

15 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-ethyl-diisopropylamine, the solvent is anhydrous dimethylformamide or anhydrous 1-methylpyrrolidin-2-one and the reaction temperature is about room temperature.

INTERNATIONAL SEARCH REPORT

International 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.

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- "&" document member of the same patent family

Date of the actual completion of the international search

27 January 1999

Date of mailing of the international search report

04/02/1999

Name and mailing address of the ISA

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Authorized officer

De Jong, B

INTERNATIONAL SEARCH REPORT

International 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. 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

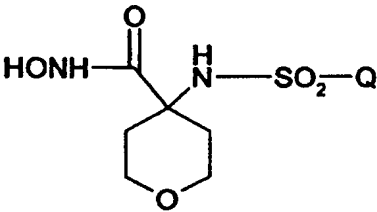
International Application No

PCT/EP 98/06640

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 309/14, 405/12, A61K 31/35	A1	(11) International Publication Number: WO 99/52889 (43) International Publication Date: 21 October 1999 (21.10.99)
(21) International Application Number: PCT/IB99/00505 (22) International Filing Date: 24 March 1999 (24.03.99) (30) Priority Data: 60/081,364 10 April 1998 (10.04.98) US (71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): REITER, Lawrence, Alan [US/US]; 32 West Mystic Avenue, Mystic, CT 06355 (US). (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 <i>With international search report.</i>
(54) Title: (4-ARYLSULFONYLAMINO)-TETRAHYDROPYRAN-4-CARBOXYLIC ACID HYDROXAMIDES		
<div style="text-align: center;">  </div> <p style="text-align: right;">(I)</p>		
(57) Abstract <p>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 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 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.</p>		

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5 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
10 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,
15 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
20 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
25 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
30 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
35 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
40 arthritis is an inflammatory joint disease characterized by excessive TNF levels and the loss

5 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.

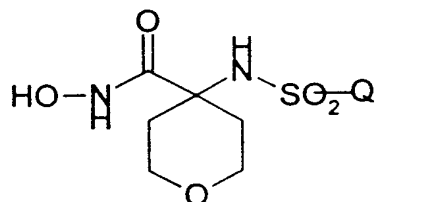
The present inventors have also discovered that it is possible to design inhibitors with
10 differential metalloprotease activity. Specifically, for example, the inventors have been able to design molecules which selectively inhibit matrix metalloprotease-13 (MMP-13) preferentially over MMP-1.

Matrix metalloproteinase and reprotysin inhibitors are well known in the literature. Specifically, PCT Publication WO 96/33172, published October 24, 1996, refers to cyclic
15 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,
20 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
25 "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.
30 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.
35 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.

5

Summary of the Invention

The present invention relates to a compound of the formula



or the pharmaceutically acceptable salts thereof, wherein

Q is (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₆-C₁₀)aryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl or (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl;

wherein each (C₆-C₁₀)aryl or (C₂-C₉)heteroaryl moieties of said (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₆-C₁₀)aryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl or (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₂-C₉)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)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.

5 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(C₁-C₆)alkyl (including trifluoromethyl), (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, perfluoro(C₁-C₃)alkoxy (including trifluoromethoxy and difluoromethoxy) and (C₁-C₆)alkyl.

10 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, pyrrolyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, 15 optionally substituted by 1 to 2 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy and (C₁-C₆)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 (C₆- 20 C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₆-C₁₀)aryl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, or (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl.

Other preferred compounds of formula I include those wherein Q is optionally 25 substituted (C₆-C₁₀)aryloxy(C₆-C₁₀)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
30 hydroxyamide;
- 4-[4-(Phenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid
hydroxyamide;
- 4-[4-(4-Pyridyloxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid
hydroxyamide;
- 35 4-[4-(4-Fluorophenyl)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid
hydroxyamide;
- 4-[4-(4-Fluorophenylmethoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid
hydroxyamide;
- 40 4-[4-(Phenylmethoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid
hydroxyamide; and

5 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
10 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 prostate cancer and hematopoietic malignancies including leukemias and lymphomas), tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including
15 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.
20 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 reprotolysin activity in a mammal, including a human, comprising an amount of a compound of
25 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 reprotolysin (such as aggrecanase or ADAM's TS-1, 10, 12, 15 and 17, most
30 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
35 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,
40 neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease,

5 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
10 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
15 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
20 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
25 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
30 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
35 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,
40 lefunimide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

5 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,
10 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,
15 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
20 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,
25 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.

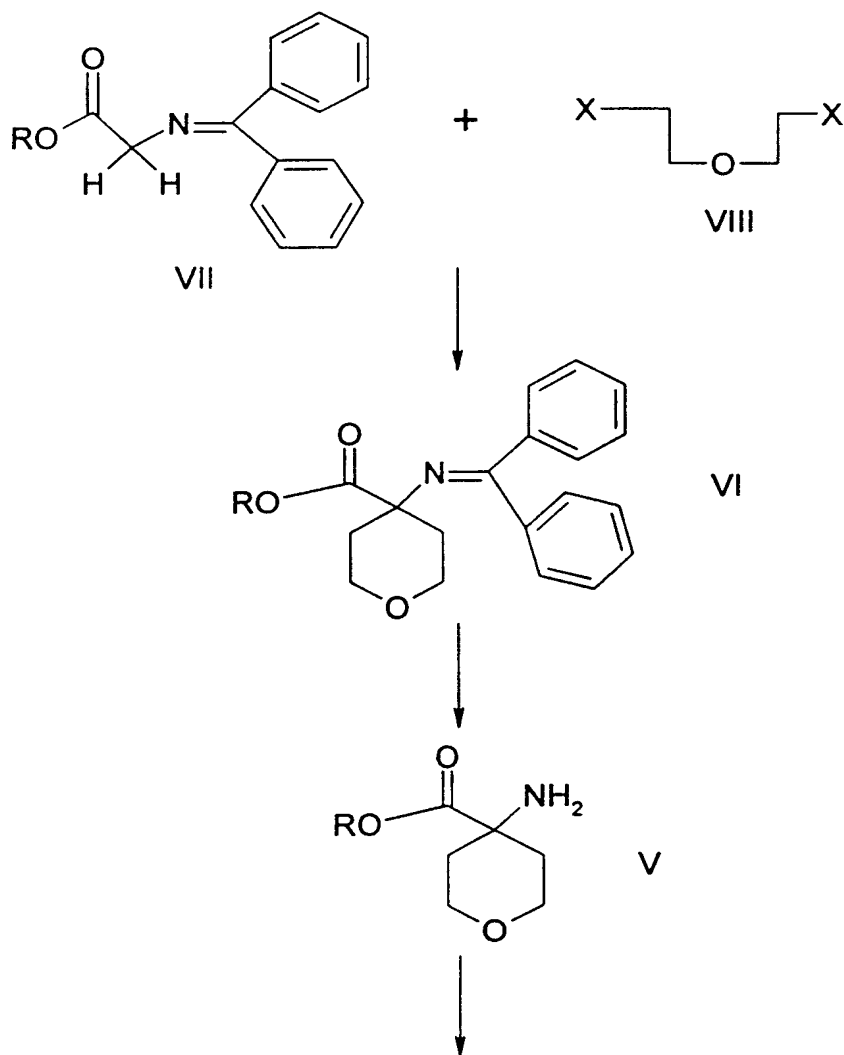
 The compounds of the present invention may also be used in combination with
osteoporosis agents such as droloxifene or fosomax and immunosuppressant agents such as
30 FK-506 and rapamycin.

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.

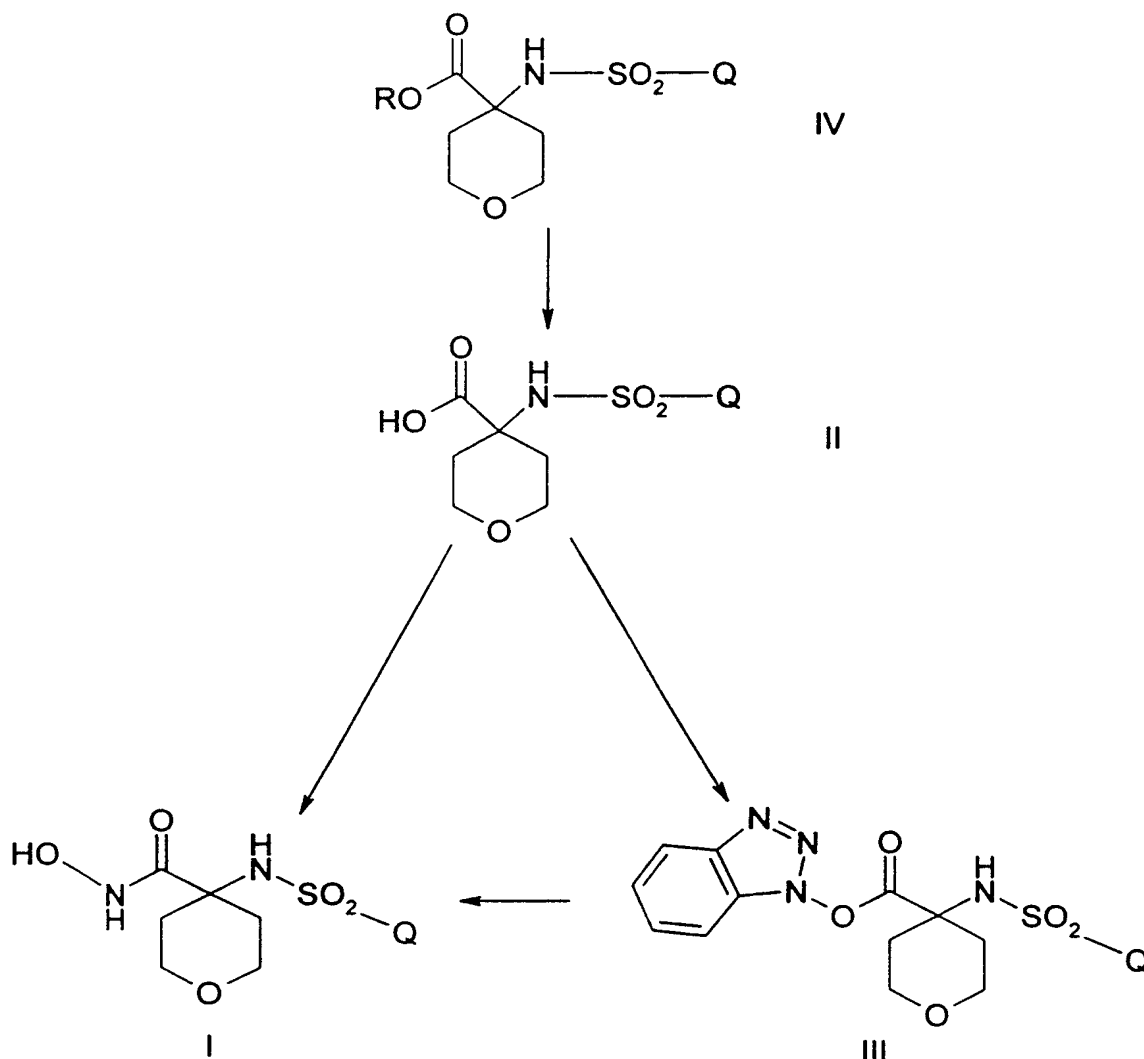
5

Scheme 1



5

Scheme 1 (continued)



5 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-hydroxybenzotriazole 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
10 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%
15 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
20 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 (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate and a
25 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
30 (benzotriazol-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
35 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 hydroxylamine hydrochloride
40 with chlorotrimethyl-silane in pyridine at 0°C to room temperature. The product of formula I is

5 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
10 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
15 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
20 formula IV. The reaction is carried out 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.

25 The compound of formula IV is prepared by reacting a compound of formula V with a reactive functional derivative of a sulfonic acid (QSO₂OH), such as the sulfonyl chloride (QSO₂Cl), 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
30 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
35 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.

5 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 ethylene glycol, sodium hydride, lithium diisopropylamide, or sodium hexamethyl disilazide. Suitable solvents include dimethylether, dimethylformamide, tetrahydrofuran or dimethylsulfoxide. The reaction mixture is
10 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
15 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
20 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
25 (hereinafter also referred to as the compounds of the present invention) to inhibit metalloproteinases or mammalian reprotolysin 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)

30

 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
35 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
40 a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after

5 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 μ l is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 60 ng/ml.

10 Substrate (DNP-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is made as a 5 mM stock in dimethylsulfoxide and then diluted to 20 μ M in assay buffer. The assay is initiated by the addition of 50 μ l substrate per well of the microfluor plate to give a final concentration of 10 mM.

15 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 IC₅₀ 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). IC₅₀'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

25 If IC₅₀'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.

30 10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM CaCl₂, 20 μ M ZnCl₂ and 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM \longrightarrow 120 μ M \longrightarrow 12 μ M \longrightarrow 1.2 μ M \longrightarrow 0.12 μ M

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 μ L 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 μ L, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μ M \longrightarrow 3 μ M \longrightarrow 0.3 μ M \longrightarrow 0.03 μ M, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

40

5 Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 μ L 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-NH₂) is diluted in assay buffer to 20 μ M. The assay is initiated by addition of 50 μ L of diluted substrate yielding a final assay concentration of 10 μ M 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 IC₅₀ 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. IC₅₀'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.

25 10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 150 mM NaCl, 10 mM CaCl₂ and 0.05% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM \longrightarrow 120 μ M \longrightarrow 12 μ M \longrightarrow 1.2 μ M \longrightarrow 0.12 μ M

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 μ L 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 μ L, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μ M \longrightarrow 3 μ M \longrightarrow 0.3 μ M \longrightarrow 0.03 μ M, 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 μ L per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 50 ng/mL (0.875 nM).

40 A ten mM dimethylsulfoxide stock solution of substrate (Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH₂) is diluted in assay buffer to 6 μ M. The assay is initiated by

5 addition of 50 μ L of diluted substrate yielding a final assay concentration of 3 μ M 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.

10 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 \times 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC_{50} 's are defined as the concentration of inhibitor that
15 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-
20 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-
25 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, 0.3m mM, and 0.03 mM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is prepared as for inhibition of human collagenase (MMP-1) and 50 μ l is added to each well to give a final assay concentration of 10 μ M. Fluorescence readings (360 nM excitation; 450 nM emission) are taken
30 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,
35 0.03 mM, 0.003 mM and 0.0003 mM.

5

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 2×10^6 /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.

15 180 μ l 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 μ l. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO₂ 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.

20

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 dysregulation of soluble TNF- α is shown by the following in vitro assay:

Method for the evaluation of recombinant TNF- α Converting Enzyme Activity

25

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.

30

Preparation of fluorescent quenched substrate:

35

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 (E₅₆₀, 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

5 proteinase." Bioconjugate Chem. 7, 385-391 (1995). This peptide encompasses the cleavage site 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
10 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
15 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 µM ZnCl₂), 10 µl of 100 µM fluorescent quenched substrate, 10 µl of a DMSO (5%) solution of test compound, and an amount of r-TACE
20 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
25 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
30 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 IC₅₀ value determined.

All of the compounds of the invention have IC₅₀ 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

35 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 10⁶ /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn

5 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
 10 CO₂ 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
 15 at 2 X 10⁵ cells per well into 48 well plates with 5 µCi / ml ³⁵S (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% CO₂.

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.

20 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	<p>Make all compounds stocks at 10 mM in DMSO.</p> <p>Make a 100 uM stock of each compound in DMEM in 96 well plate.</p> <p>Store in freezer overnight.</p> <p>The next day perform serial dilutions in DMEM with IL-1 to 5 uM, 500 nM. and 50 nM.</p> <p>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.</p> <p>Final compound concentrations equal 500 nM, 50 nM, and 5 nM.</p> <p>All samples completed in triplicate with Control and IL-1 alone samples on each plate.</p>

25 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

5 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% CO₂ 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).

15 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, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting 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

5 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.

10 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.

15 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

20 divided doses.

25 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.

30 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

35 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.

5 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
10 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
15 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 20 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
25 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
30 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
35 ester as a clear yellow oil (16.114 g, 64 %).

¹HNMR (CDCl₃) 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).

5 **(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.
10 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.

$^1\text{H NMR}$ (CDCl_3) δ 4.15 (q, 2H), 3.82 (m, 2H), 3.62 (m, 2H), 2.07 (m, 2H), 1.60 (s, 2H),
15 1.44 (m, 2H), 1.24 (t, 3H). $^{13}\text{C NMR}$ (CDCl_3) δ 176.48, 63.70, 61.09, 54.78, 35.05, 14.15. MS Atmospheric Pressure Chemical Ionization Mass Spectra: 210 ($\text{M}^+ + 1$).

(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
25 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-
30 fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid ethyl ester as an off-white crystalline solid (12.15 grams, 71%, mp 116-117°C).

$^1\text{H NMR}$ (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 ($\text{M}^+ + 1$).

35 **(D) 4-[4-(4-Fluorophenoxy)-benzenesulfonylamino]tetrahydropyran-4-carboxylic acid**

Method A

A solution of 4-[4-(4-fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid ethyl ester (12.1 grams, 0.0286 mole) in tetrahydrofuran (190 mL) was treated
40 with aqueous 3 M sodium hydroxide solution (95 mL, 0.286 mole) and stirred at room

5 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-
10 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.
15 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 sulfate, and concentrated to give 4-[4-(4-fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid (31.26 grams, 98%)
20 as a white crystalline solid.

¹HNMR (CDCl₃) 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).

25 **(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).
30 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
35 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).

5 ^1H NMR (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 ($\text{M}^+ + 1$).

(F) 4-[4-(4-Fluorophenoxy)benzenesulfonylamino]-tetrahydropyran-4-carboxylic acid hydroxyamide

10 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 ParrTM shaker at 3 atmospheres pressure for 18 hours. After filtration through nylon (pore size 0.45 mm) to
15 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-
20 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
25 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,
30 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
35 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
40 point a large amount of white crystalline solid had precipitated. This was cooled overnight in a

5 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).

¹HNMR (d₆ 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). ¹³CNMR (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

15 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

20 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

30 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

35 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

40

5 vacuum. The titled compound, 4.7 grams (57%), was collected by filtration and washed with isopropanol.

Preparation E

4-(3-Methylbutoxy)benzenesulfonyl chloride

10 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%).

15

Preparation F

4-Fluorobiphenylsulfonyl chloride

20 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.

25

Preparation G

Sodium 4-(4-fluorobenzyloxy)benzenesulfonate

30 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

35 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-
40 fluorobenzyloxy)benzenesulfonyl chloride a white solid (130 mg, 26%).

5

Preparation I**4-(4-Chlorophenoxy)benzenesulfonyl chloride**

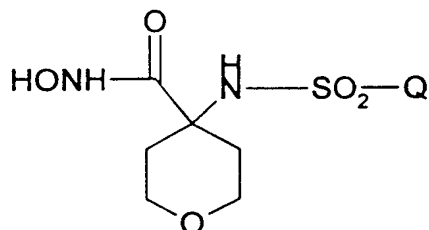
Chlorosulfonic acid (9.7 mL, 0.147 mole) was added dropwise to 4-chlorophenoxybenzene (12.6 mL, 73.4 mmole) at room temperature with stirring. When addition was complete, the mixture was stirred at room temperature for 1 hour and then poured into ice water. The solid was collected by filtration, dried in the air, and recrystallized from petroleum ether and ethyl acetate to give 4-(4-chlorophenoxy)benzenesulfonylchloride (7.43 grams, 33%).

10

5

CLAIMS

1. A compound of the formula



or the pharmaceutically acceptable salts thereof, wherein

Q is (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₆-C₁₀)aryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl or (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl;

wherein each (C₆-C₁₀)aryl or (C₂-C₉)heteroaryl moieties of said (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₆-C₁₀)aryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl or (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₂-C₉)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl, perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)aryloxy;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein Q is optionally substituted (C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₂-C₉)-

- 5 heteroaryl(C₆-C₁₀)aryl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)-aryl, or (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl.
3. A compound according to claim 1, wherein Q is optionally substituted (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl.
4. A compound according to claim 3, wherein the (C₆-C₁₀)aryloxy ring of said (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl group is optionally mono-substituted in the 4-position of the ring.
- 10 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;
- 15 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
20 hydroxyamide;
- 4-[4-(4-fluorophenyl)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid
hydroxyamide;
- 4-[4-(4-fluorophenylmethoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid
hydroxyamide;
- 25 (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
30 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),
35 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
40 sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing,

5 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 reprotolysin 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 reprotolysin in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International 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; -----	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
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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 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	Authorized officer <p style="text-align: center;">Francois, J</p>
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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. 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

International 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
			AT 159012 T	15-10-1997
			AU 684255 B	11-12-1997
			AU 5265593 A	04-05-1995
			CA 2112779 A	07-07-1994
			DE 69314456 D	13-11-1997
			DE 69314456 T	26-02-1998
			DK 606046 T	04-05-1998
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			MX 9400276 A	29-07-1994
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			US 5552419 A	03-09-1996
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			US 5672615 A	30-09-1997
			ZA 9400048 A	11-08-1994



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 493/08, A61K 31/35 // (C07D 493/08, 311:00, 307:00)</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/52910</p> <p>(43) International Publication Date: 21 October 1999 (21.10.99)</p>
<p>(21) International Application Number: PCT/IB99/00503</p> <p>(22) International Filing Date: 24 March 1999 (24.03.99)</p> <p>(30) Priority Data: 60/081,309 10 April 1998 (10.04.98) US</p> <p>(71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): ROBINSON, Ralph, Pelton [US/US]; 30 Friar Tuck Drive, Gales Ferry, CT 06335 (US).</p> <p>(74) Agents: SPIEGEL, Allen, J. et al.; c/o Simpson, Alison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB).</p>	<p>(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).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: BICYCLIC HYDROXAMIC ACID DERIVATIVES</p>		
<div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>		
<p>(57) Abstract</p> <p>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.</p>		

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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.

10

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)).

15

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.

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The mammalian reprolysin 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.

35

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

40

5 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
10 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,
15 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
20 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
25 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
30 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
35 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
40 arthritis is an inflammatory joint disease characterized by excessive TNF levels and the loss

5 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.

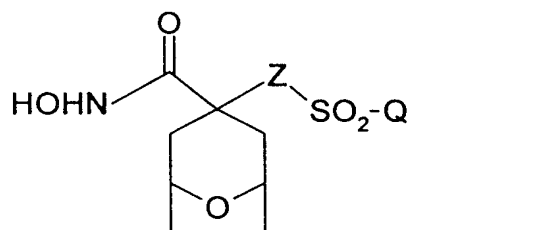
10 The present inventors have also discovered that it is possible to design inhibitors with differential metalloprotease activity. Specifically, for example, the inventors have been able to design molecules which selectively inhibit matrix metalloprotease-13 (MMP-13) preferentially over MMP-1.

15 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 20 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 25 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, 30 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 35 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.

5

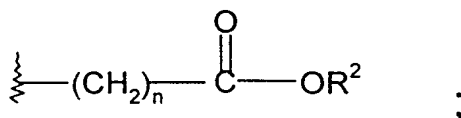
Summary of the Invention

The present invention relates to a compound of the formula



wherein Z is $>CH_2$ or $>NR^1$;

10 R^1 is hydrogen, (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



n is an integer from one to six;

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

15 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, (C_2-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;

25 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, (C_2-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;

30

5 C₉)heteroaryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₆-
C₁₀)aryloxy(C₁-C₆)alkyl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl(C₆-C₁₀)aryl or (C₂-
C₉)heteroaryloxy(C₁-C₆)alkyl(C₂-C₉)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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, perfluoro(C₁-C₃)alkyl,
10 perfluoro(C₁-C₃)alkoxy and (C₆-C₁₀)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
15 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-
20 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
25 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.

30 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.

35 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, isothiazoyl, imidazolyl, benzimidazolyl, tetrazoyl, pyrazinyl,
40 pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothieryl, pyrazoyl, indolyl,

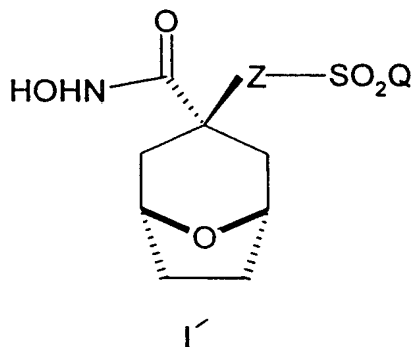
5 isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl. Preferred heteroaryls include pyridyl, furyl, thienyl, isothiazolyl, pyrazinyl, pyrimidyl, pyrazolyl, isoxazolyl, thiazolyl or oxazolyl. Most preferred heteroaryls include pyridyl, furyl or thienyl.

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
10 "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 diastereomeric or enantiomeric forms. This invention relates to all optical isomers, tautomers and
15 stereoisomers of the compounds of formula I and mixtures thereof.

Preferably, compounds of the formula I exist as the exo isomer of the formula



Other preferred compounds of formula I are those wherein Q is (C₆-C₁₀)aryl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, wherein each aryl or heteroaryl
20 moiety of said (C₆-C₁₀)aryl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl or (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl groups may be optionally substituted with one or more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)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
25 more substituents independently selected from fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl, more preferably the substituents are selected from fluoro, chloro, (C₁-C₆)alkoxy or (C₁-C₆)alkyl, most preferably the substituent is in the 4-position.

Specific preferred compounds of formula I include the following:

30 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;

- 5 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-
- 10 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-
- 15 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,
- 20 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-
- 25 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,
- 30 3-*exo*-{[4-(4-Fluorophenoxy)benzenesulfonyl]pyridin-3-ylmethylamino}-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,
- 3-*exo*-[4-(4-Fluorobenzoyloxy)benzenesulfonylamino]-8-oxabicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide,
- 3-*exo*-(4-Benzyloxybenzenesulfonylamino)-8-oxabicyclo[3.2.1]octane-3-carboxylic
- 35 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,

- 5 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-
- 10 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-
- 15 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-
- 20 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-
- 25 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,
- 30 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-
- 35 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.

35 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

40 breast cancer, lung cancer and prostate cancer and hematopoietic malignancies including

5 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
10 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
15 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
20 (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
25 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),
30 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
35 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
40 pharmaceutically acceptable salt thereof effective in treating such a condition.

5 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.

10 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
15 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,
20 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
25 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
30 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
35 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
40 corticosteroids and hyaluronic acids such as hyalgan and synvisc.

5 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.

10 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.

15 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.

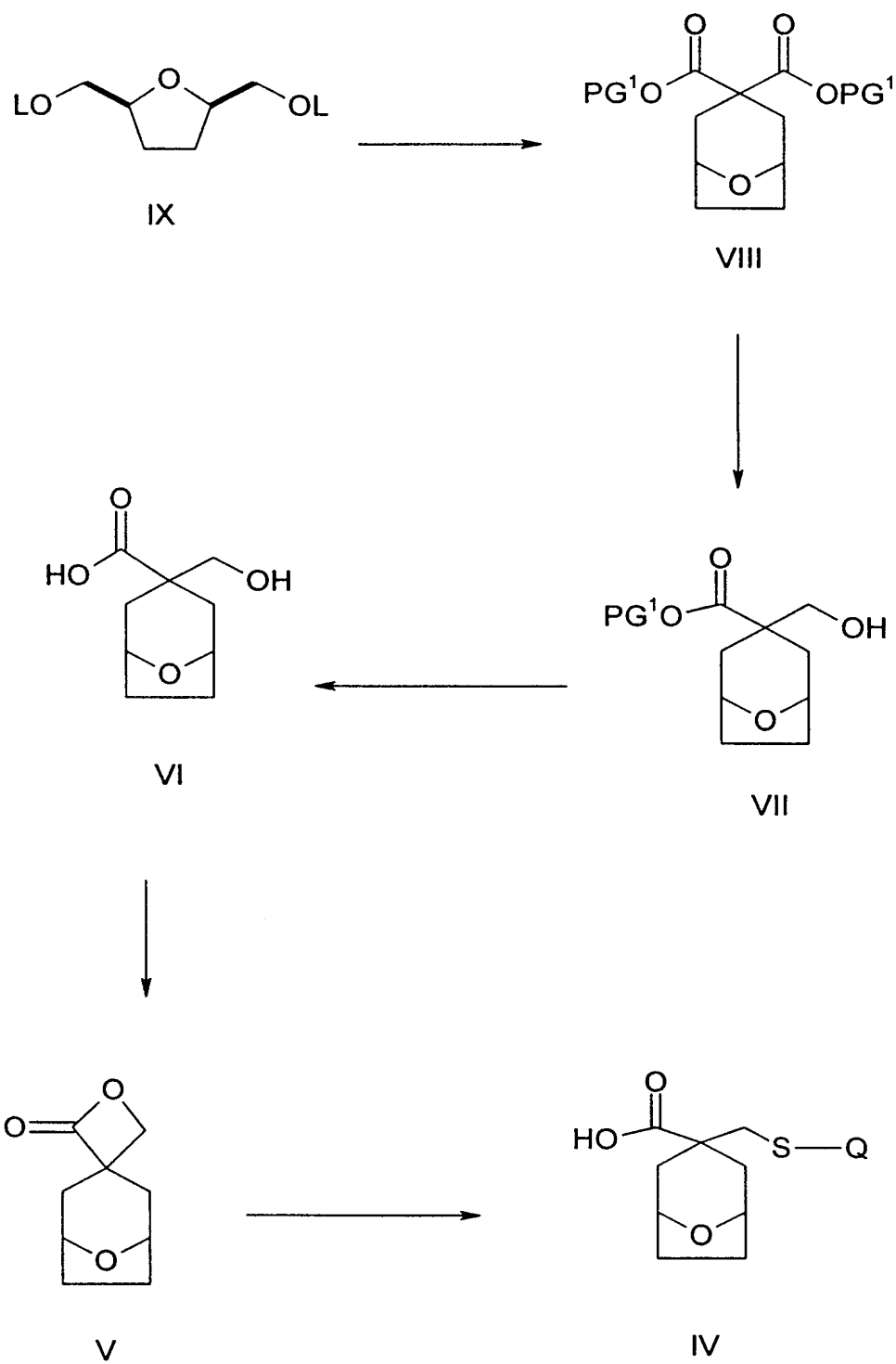
20 The compounds of the present invention may also be used in combination with osteoporosis agents such as droloxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

Detailed Description of the Invention

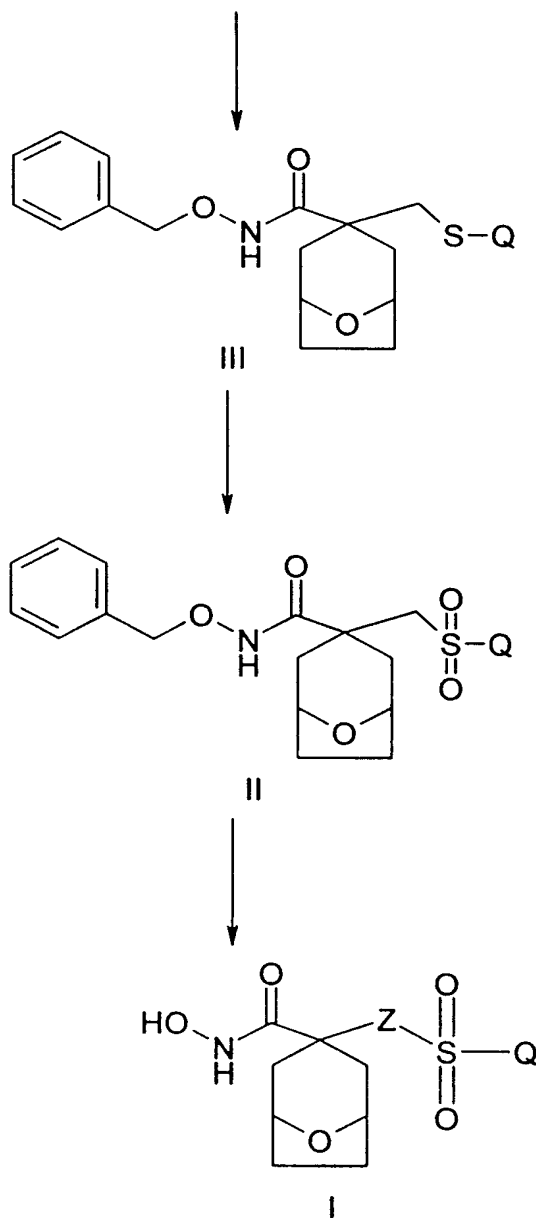
25 The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated n, R¹, R², Q and Z in the reaction Schemes and the discussion that follow are defined as above.

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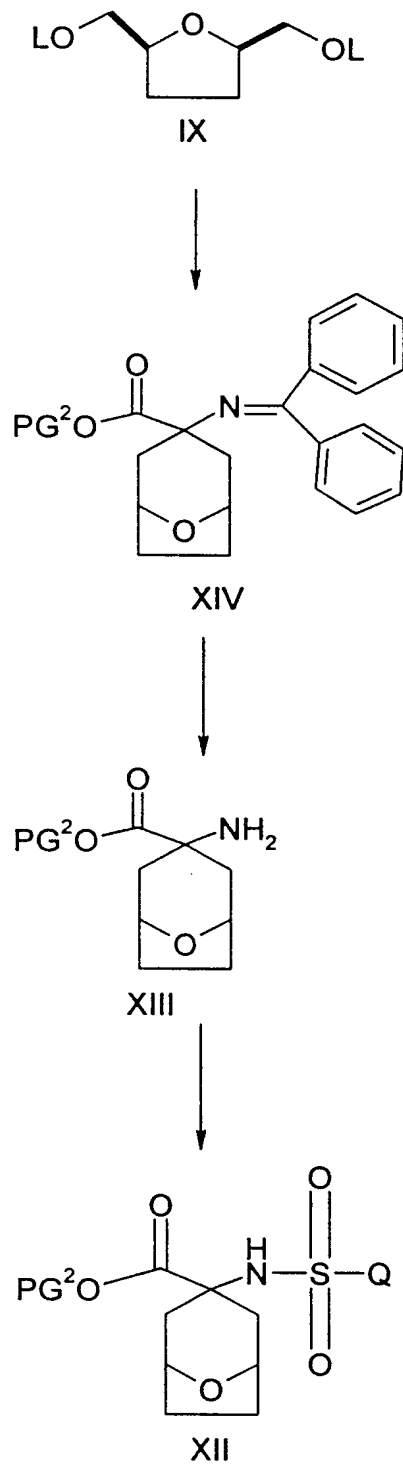
SCHEME 1



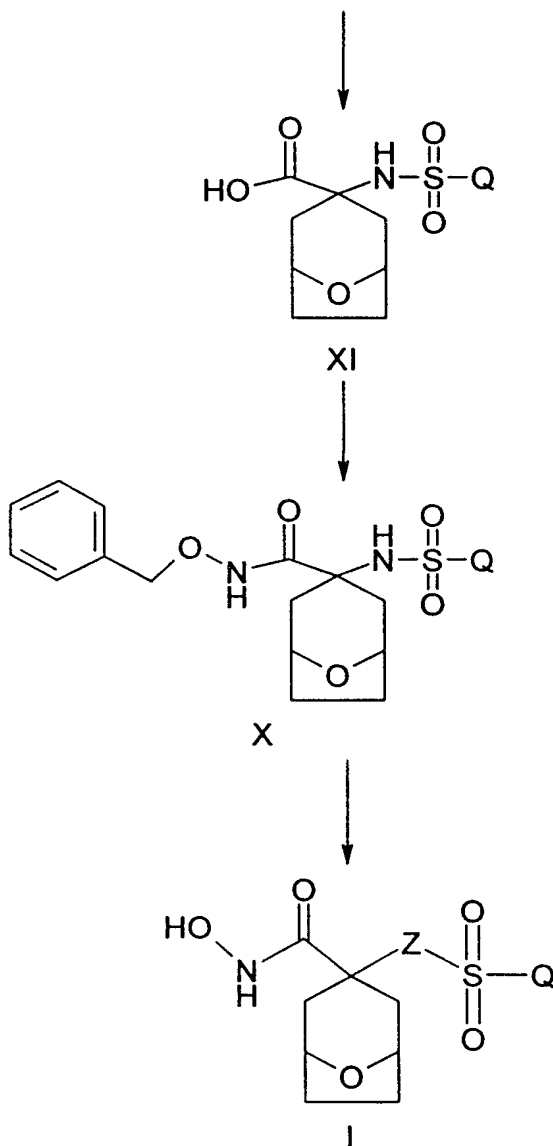
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SCHEME 1 CONTINUED

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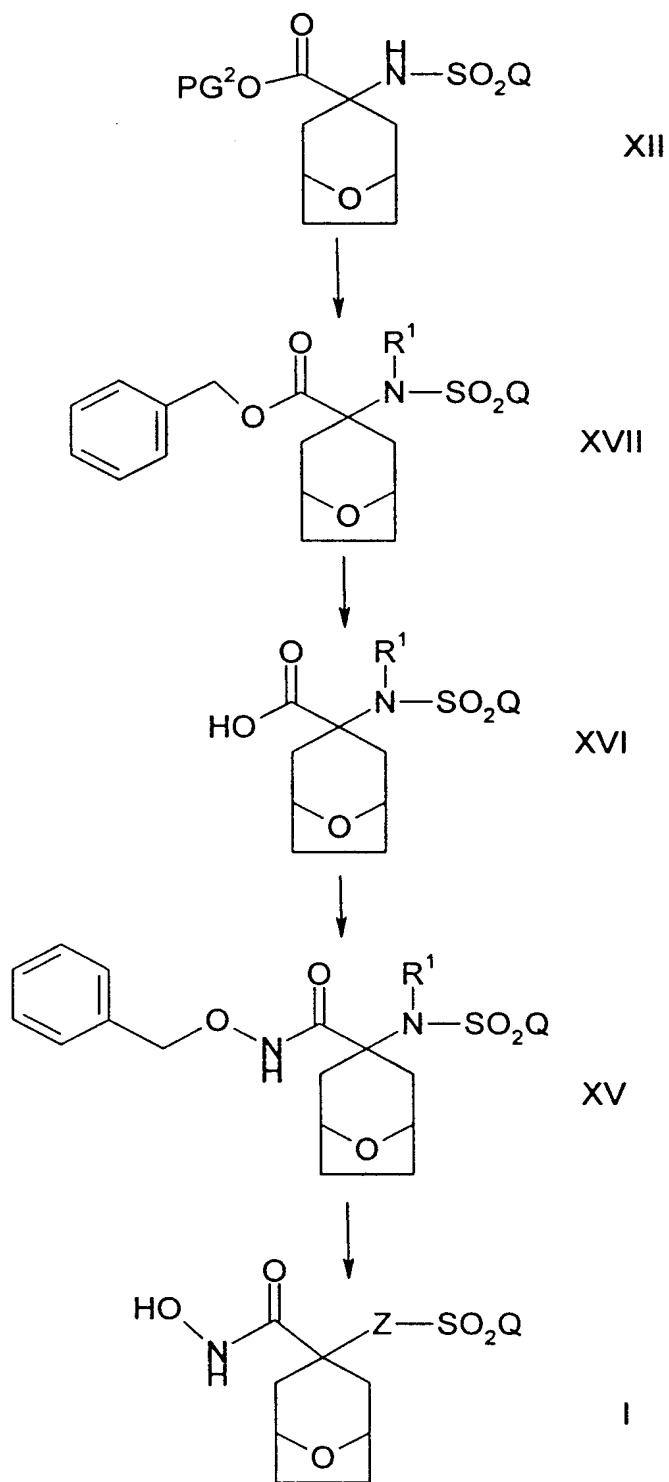
SCHEME 2

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SCHEME 2 CONTINUED

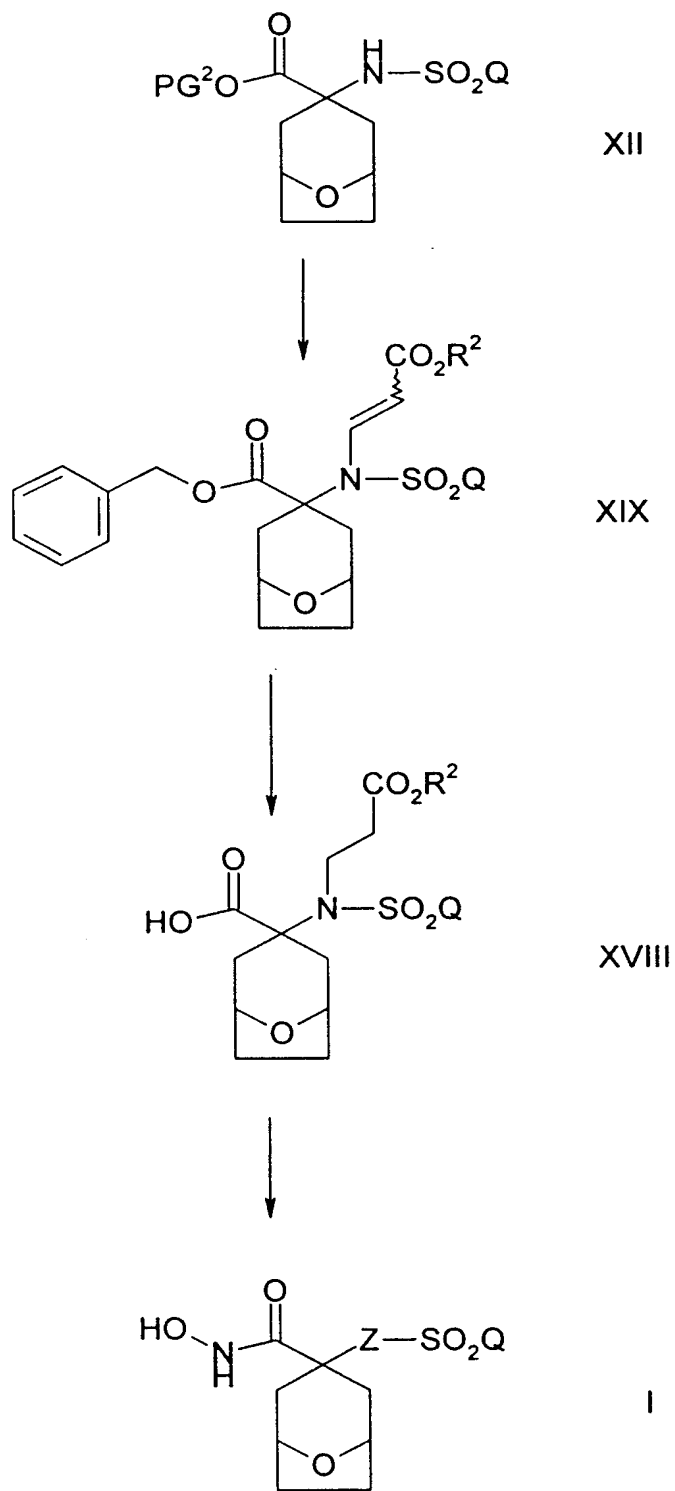
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SCHEME 3



5

SCHEME 4



5 Scheme 1 refers to the preparation of compounds of formula I, wherein Z is CH₂.
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
10 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
15 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
20 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
25 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,
30 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
35 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
40 sodium hydride. Suitable solvents include ethers (such as THF, diethyl ether or 1,2-

5 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.

15 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 PG¹ 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.

20

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 diisobutylaluminum 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.

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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 stereochemistry 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.

35

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5 The compounds formula VIII, wherein PG¹ 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
10 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 sulfhydryde as described in Jerry March, Advanced Organic Chemistry, 360 and 589
15 (3rd ed., 1985). Alternatively, compounds of the formula QSH can also be prepared by reaction
of an aryl diazonium salt with sodium sulfhydryde 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
20 id. at 1107 and 1110.

 Scheme 2 refers to the preparation of compounds of the formula I, wherein Z is >NR¹,
and R¹ 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
25 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
30 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-
35 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,
40 preferably about 50° C. Suitable solvents include N,N-dimethylformamide or halogenated

5 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 PG² 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
10 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 PG² is methyl or ethyl, are prepared from compounds of the formula XIII, wherein PG² is methyl or ethyl, by reaction with a compound of the formula QSO₂Cl in the presence of a base, such as triethylamine, and a polar solvent.
15 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.

20 Compounds of the formula XIII, wherein PG² is methyl or ethyl, are prepared from compounds of the formula XIV, wherein PG² 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
25 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 PG² 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
30 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 PG² is methyl, ethyl or benzyl, are obtained as mixtures of diastereomers which can be separated by chromatographic means.

35 Compounds of the formula QSO₂Cl 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 NR¹ and R¹ is (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl or a group of the formula -(CH₂)_nCO₂R², wherein n is 1, 3, 4, 5, or 6 and R² is (C₁-C₆)alkyl.

5 Referring to Scheme 3, compounds of the formula I, wherein Z is NR¹ and R¹ is (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl or a group of the formula
10 -(CH₂)_nCO₂R², wherein n is 1, 3, 4, 5, or 6 and R² is (C₁-C₆)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
15 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
20 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,
25 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
30 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
35 PG² is benzyl, by reaction with a reactive derivative of an alcohol of the formula R¹OH 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
40 about 16 hours.

5 The compounds of formula XII, wherein PG² 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 >NR¹, R¹ is a group of the formula -(CH₂)₂CO₂R² (i.e. n is 2) and R² is (C₁-C₆)alkyl.

10 Referring to Scheme 4, compounds of said formula I are prepared from compounds of the formula XVIII, wherein R² is (C₁-C₆)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
15 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 R² is (C₁-C₆)alkyl, can be prepared from compounds of the formula XIX, wherein R² is (C₁-C₆)alkyl, by reduction in a polar solvent. Suitable reducing agents include hydrogen over palladium and hydrogen over palladium on
20 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 R² is (C₁-C₆)alkyl, can be prepared from
25 compounds of the formula XII, wherein PG² is benzyl, by Michael addition of a propiolate ester and a base in a polar solvent. Suitable propiolates are of the formula H-C≡C-CO₂R², wherein R² is (C₁-C₆)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.

30 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 PG² is benzyl, can be prepared according to the
35 methods of Scheme 2.

 Compounds of said formula I, wherein Z is >NR¹, R¹ is a group of the formula -(CH₂)_nCO₂R², n is 1 to 6 and R² is hydrogen are prepared from compounds of formula I, wherein Z is >NR¹, R¹ is a group of the formula -(CH₂)_nCO₂R², n is 1 to 6 and R² is (C₁-C₆)alkyl, by saponification using a base such as sodium hydroxide in a protic solvent such as ethanol,
40 methanol or water or a mixture such as water and ethanol, water and toluene, or water and THF.

5 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
10 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
15 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
20 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.

25 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
30 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
35 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
40 product yields.

5 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 reprotolysin 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.

10

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 μ g trypsin per 100 μ g of collagenase. The trypsin and collagenase are incubated at room temperature for 15 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 \longrightarrow 120 μ M \longrightarrow 12 μ M \longrightarrow 1.2 μ M \longrightarrow 0.12 μ M

20 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 μ l is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 60 ng/ml.

25 Substrate (DNP-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is made as a 5 mM stock in dimethylsulfoxide and then diluted to 20 μ M in assay buffer. The assay is initiated by the addition of 50 μ l substrate per well of the microfluor plate to give a final concentration of 10 mM.

30 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

35 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 IC₅₀ 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). IC₅₀'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

5 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 10 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 \rightarrow 120 μM \rightarrow 12 μM \rightarrow 1.2 μM \rightarrow 0.12 μM

15 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 \rightarrow 3 μM \rightarrow 0.3 μM \rightarrow 0.03 μM , etc.). A blank (no enzyme, no 20 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).

25 A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂) 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 30 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 35 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.

5 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.

10 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

15 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 microfluo 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
20 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 microfluo plate. The final concentrations in the assay are 30 mM, 3mmM, 0.3m mM, and 0.03 mmM.

25 Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) 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.

30 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

35 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
40 in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2