COMPOUNDS

The present invention relates to novel hydantoin derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMPs) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biological important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem. J. 321:265-279).

Metalloproteinases have been associated with many diseases or conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these diseases or conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the

gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atherosclerosis; asthma; rhinitis; and chronic obstructive pulmonary diseases (COPD).

MMP12, also known as macrophage elastase or metalloelastase, was initially cloned in the mouse by Shapiro *et al* [1992, Journal of Biological Chemistry 267: 4664] and in man by the same group in 1995. MMP12 is preferentially expressed in activated macrophages, and has been shown to be secreted from alveolar macrophages from smokers [Shapiro *et al*, 1993, Journal of Biological Chemistry, 268: 23824] as well as in foam cells in atherosclerotic lesions [Matsumoto *et al*, 1998, Am. J. Pathol. 153: 109]. A mouse model of COPD is based on challenge of mice with cigarette smoke for six months, two cigarettes a day six days a week. Wild-type mice developed pulmonary emphysema after this treatment. When MMP12 knock-out mice were tested in this model they developed no significant emphysema, strongly indicating that MMP12 is a key enzyme in the COPD pathogenesis. The role of MMPs such as MMP12 in COPD (emphysema and bronchitis) is discussed in Anderson and Shinagawa, 1999, Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs 1(1): 29-38. It was recently discovered that smoking increases macrophage infiltration and macrophage-derived MMP-12 expression in human carotid artery plaques Kangavari [Matetzky S, Fishbein MC *et al.*, Circulation 102:(18), 36-39 Suppl. S, Oct 31, 2000].

MMP9 (Gelatinase B; 92kDa TypeIV Collagenase; 92kDa Gelatinase) is a secreted protein which was first purified, then cloned and sequenced, in 1989 [S.M. Wilhelm *et al* (1989) J. Biol. Chem. 264 (29): 17213-17221; published erratum in J. Biol. Chem. (1990) 265

(36): 22570]. A recent review of MMP9 provides an excellent source for detailed information and references on this protease: T.H. Vu & Z. Werb (1998) (In : Matrix Metalloproteinases, 1998, edited by W.C. Parks & R.P. Mecham, pp. 115 – 148, Academic Press. ISBN 0-12-545090-7). The following points are drawn from that review by T.H. Vu & Z. Werb (1998).

The expression of MMP9 is restricted normally to a few cell types, including trophoblasts, osteoclasts, neutrophils and macrophages. However, the expression can be induced in these same cells and in other cell types by several mediators, including exposure of the cells to growth factors or cytokines. These are the same mediators often implicated in initiating an inflammatory response. As with other secreted MMPs, MMP9 is released as an inactive Pro-enzyme which is subsequently cleaved to form the enzymatically active enzyme. The proteases required for this activation *in vivo* are not known. The balance of active MMP9 versus inactive enzyme is further regulated *in vivo* by interaction with TIMP-1 (Tissue Inhibitor of Metalloproteinases -1), a naturally-occurring protein. TIMP-1 binds to the C-terminal region of MMP9, leading to inhibition of the catalytic domain of MMP9. The balance of induced expression of ProMMP9, cleavage of Pro- to active MMP9 and the presence of TIMP-1 combine to determine the amount of catalytically active MMP9 which is present at a local site. Proteolytically active MMP9 attacks substrates which include gelatin, elastin, and native Type IV and Type V collagens; it has no activity against native Type I collagen, proteoglycans or laminins.

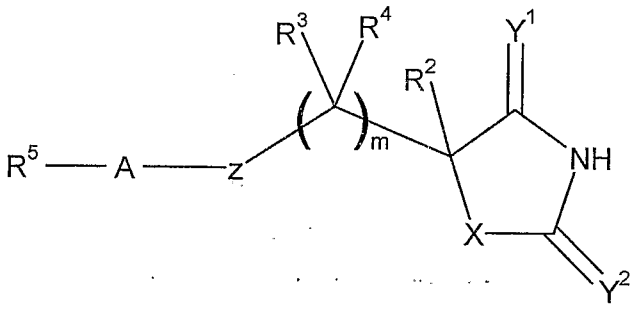
There has been a growing body of data implicating roles for MMP9 in various physiological and pathological processes. Physiological roles include the invasion of embryonic trophoblasts through the uterine epithelium in the early stages of embryonic implantation; some role in the growth and development of bones; and migration of inflammatory cells from the vasculature into tissues.

MMP9 release, measured using enzyme immunoassay, was significantly enhanced in fluids and in AM supernantants from untreated asthmatics compared with those from other populations [Am. J. Resp. Cell & Mol. Biol., Nov 1997, 17 (5):583-591]. Also, increased MMP9 expression has been observed in certain other pathological conditions, thereby

implicating MMP9 in disease processes such as COPD, arthritis, tumour metastasis, Alzheimer's disease, multiple sclerosis, and plaque rupture in atherosclerosis leading to acute coronary conditions such as myocardial infarction.

A number of metalloproteinase inhibitors are known (see, for example, the reviews of MMP inhibitors by Beckett R.P. and Whittaker M., 1998, Exp. Opin. Ther. Patents, 8(3):259-282; and by Whittaker M. *et al*, 1999, Chemical Reviews 99(9):2735-2776).

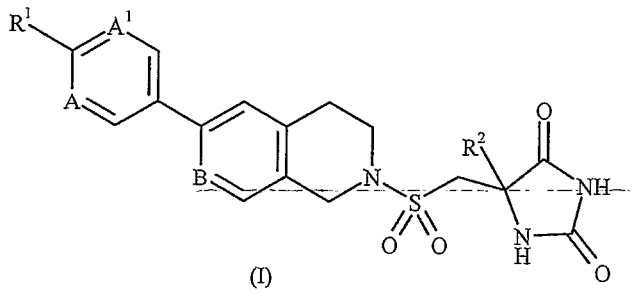
WO 02/074767 discloses hydantoin derivatives of formula



that are useful as MMP inhibitors, particularly as potent MMP12 inhibitors.

We now disclose a further group of hydantoin derivatives that are inhibitors of metalloproteinases and are of particular interest in inhibiting MMPs such as MMP12 and MMP9. The compounds of the present invention have beneficial potency, selectivity and/or pharmacokinetic properties. The compounds of the present invention are within the generic scope of WO 02/074767 but are of a type not specifically exemplified therein.

In accordance with the present invention, there are provided compounds of formula (I)



(I)

wherein

R^1 represents H, halogen, CF_3 or CH_2CN;

R^2 represents C1 to 3 alkyl; and

A, A^1 and B each independently represent CH or N;

and pharmaceutically acceptable salts thereof.

The compounds of formula (I) may exist in enantiomeric forms. It is to be understood that all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention.

Compounds of formula (I) may also exist in various tautomeric forms. All possible tautomeric forms and mixtures thereof are included within the scope of the invention.

In one embodiment, R^1 represents chloro.

In one embodiment, R^1 represents CF_3.

In one embodiment, R^2 represents methyl or ethyl. In one embodiment, R^2 represents methyl.

In one embodiment, A and A^1 each represent N. In another embodiment, A represents N and A^1 represents CH. In another embodiment, A and A^1 each represent CH.

In one embodiment, B represents N. In another embodiment, B represents CH.

In one embodiment, R^1 represents CF_3; R^2 represents methyl or ethyl; A and A^1 each represent N; and B represents CH.

In one embodiment, R^1 represents CF_3; R^2 represents methyl or ethyl; A and A^1 each represent N; and B represents N.

In one embodiment, R^1 represents chloro; R^2 represents methyl or ethyl; A represents N and A^1 represents CH; and B represents N.

In one embodiment, R^1 represents chloro; R^2 represents methyl or ethyl; and A, A^1 and B each represent CH.

Unless otherwise indicated, the term "C1 to 3 alkyl" referred to herein denotes a straight or branched chain alkyl group having from 1 to 3 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl and i-propyl.

Unless otherwise indicated, the term "halogen" referred to herein denotes fluoro, chloro, bromo and iodo.

Examples of compounds of the invention include:
(5*S*)-5-methyl-5-({[6-[2-(trifluoromethyl)pyrimidin-5-yl]-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)imidazolidine-2,4-dione;
(5*S*)-5-({[6-(4-chlorophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione;
{4-[2-({[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]phenyl}acetonitrile;
(5*S*)-5-methyl-5-{[(6-pyridin-3-yl-3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl]methyl}imidazolidine-2,4-dione;

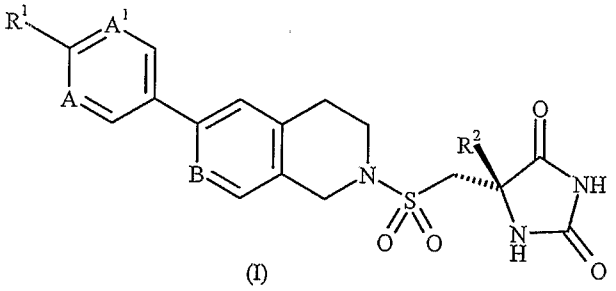
(5*S*)-5-({[6-(4-chlorophenyl)-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione;
and pharmaceutically acceptable salts thereof.

Each exemplified compound represents a particular and independent aspect of the invention.

The compounds of formula (I) may exist in enantiomeric forms. Therefore, all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation, or HPLC. Alternatively the optical isomers may be obtained by asymmetric synthesis, or by synthesis from optically active starting materials.

Where optically isomers exist in the compounds of the invention, we disclose all individual optically active forms and combinations of these as individual specific embodiments of the invention, as well as their corresponding racemates.

Preferably the compounds of formula (I) have (5S)-stereochemistry as shown below:



(I)

Where tautomers exist in the compounds of the invention, we disclose all individual tautomeric forms and combinations of these as individual specific embodiments of the invention.

The present invention includes compounds of formula (I) in the form of salts. Suitable salts include those formed with organic or inorganic acids or organic or inorganic bases. Such salts will normally be pharmaceutically acceptable salts although non-pharmaceutically acceptable salts may be of utility in the preparation and purification of particular compounds. Such salts include acid addition salts such as hydrochloride, hydrobromide, citrate, tosylate and maleate salts and salts formed with phosphoric acid or sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt, for example, sodium or potassium, an alkaline earth metal salt, for example, calcium or magnesium, or an organic amine salt, for example, triethylamine.

Salts of compounds of formula (I) may be formed by reacting the free base or another salt thereof with one or more equivalents of an appropriate acid or base.

The compounds of formula (I) are useful because they possess pharmacological acivity in animals and are thus potentially useful as pharmaceuticals. In particular, the compounds of the invention are metalloproteinase inhibitors and may thus be used in the treatment of diseases or conditions mediated by MMP12 and/or MMP9 such as asthma, rhinitis, chronic obstructive pulmonary diseases (COPD), arthritis (such as rheumatoid arthritis and osteoarthritis), atherosclerosis and restenosis, cancer, invasion and metastasis, diseases involving tissue destruction, loosening of hip joint replacements, periodontal disease, fibrotic disease, infarction and heart disease, liver and renal fibrosis, endometriosis, diseases related to the weakening of the extracellular matrix, heart failure, aortic aneurysms, CNS related diseases such as Alzheimer's disease and multiple sclerosis (MS), and haematological disorders.

In general, the compounds of the present invention are potent inhibitors of MMP9 and MMP12. The compounds of the present invention also show good selectivity with respect to a relative lack of inhibition of various other MMPs such as MMP14.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in the treatment of diseases or conditions in which inhibition of MMP12 and/or MMP9 is beneficial.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in the treatment of inflammatory disease.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in the treatment of an obstructive airways disease such as asthma or COPD.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in the treatment of rheumatoid arthritis, osteoarthritis, atherosclerosis, cancer or multiple sclerosis.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or

those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

The invention further provides a method of treating a disease or condition in which inhibition of MMP12 and/or MMP9 is beneficial which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

The invention also provides a method of treating an obstructive airways disease, for example, asthma or COPD, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder to be treated. The daily dosage of the compound of formula (I)/salt (active ingredient) may be in the range from 0.001 mg/kg to 75 mg/kg, in particular from 0.5 mg/kg to 30 mg/kg. This daily dose may be given in divided doses as necessary. Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

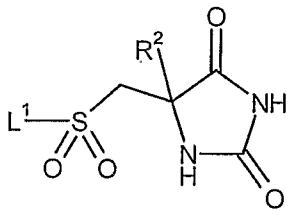
The pharmaceutical compositions of this invention may be administered in a standard manner for the disease or condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more diseases or conditions referred to hereinabove such as "Symbicort" (trade mark) product.

The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which, comprises:

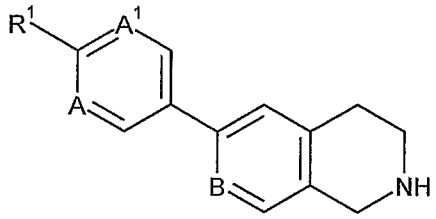
a) reaction of a compound of formula (II)

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(II)

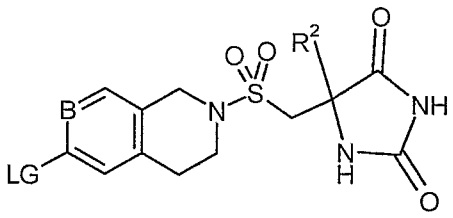
wherein R^2 is as defined in formula (I) and L^1 represents a leaving group, with a compound of formula (III) (or a salt thereof)



(III)

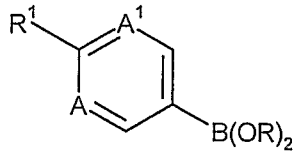
wherein R^1, A, A^1 and B are as defined in formula (I); or

b) reaction of a compound of formula (V)



(V)

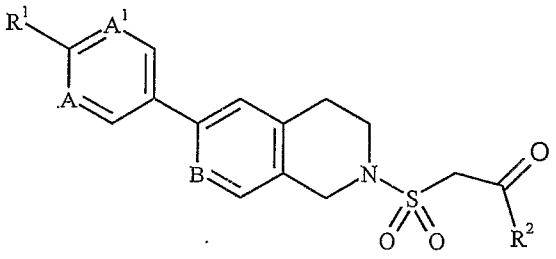
wherein R^2 and B are as defined in formula (I) and LG is a leaving group; with a boronic acid derivative of formula ~~(XII)~~



(XII)

wherein R^1, A and A^1 are as defined in formula (I); or

c) reaction of a compound of formula (IX)



(IX)

wherein R^1, R^2, A, A^1 and B are as defined in formula (I); with ammonium carbonate and potassium cyanide;

and optionally thereafter forming a pharmaceutically acceptable salt thereof.

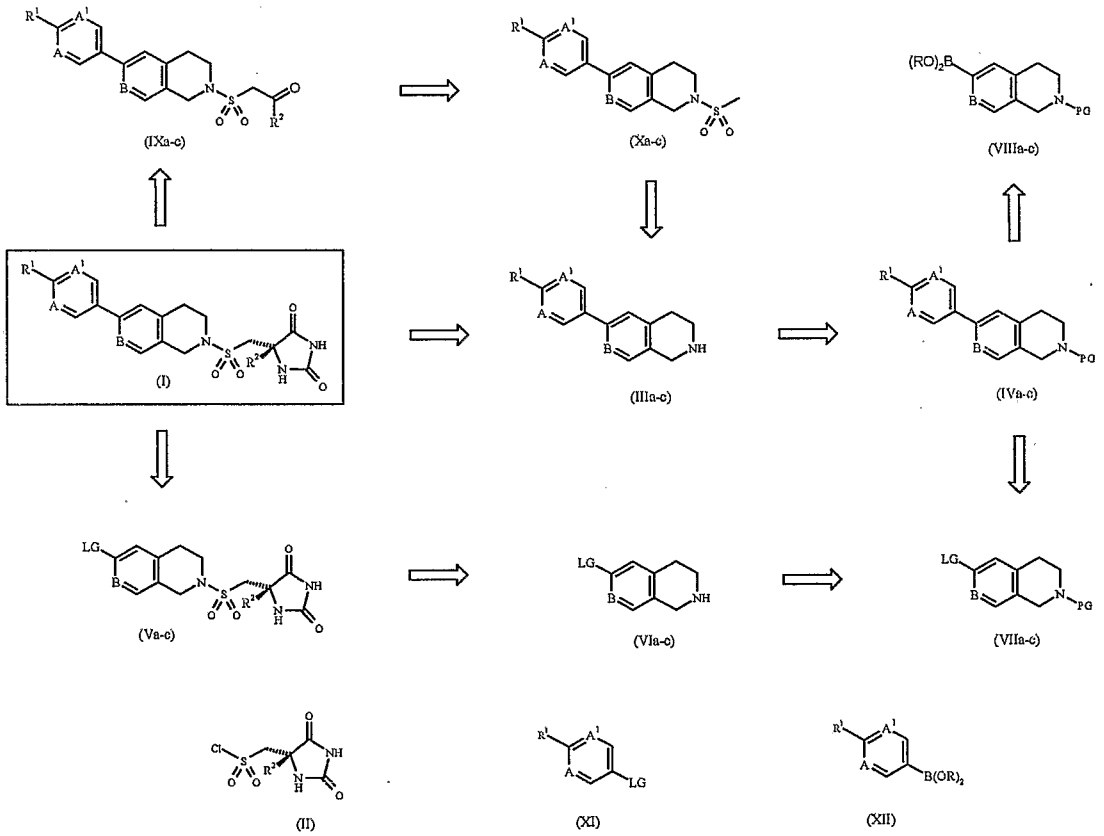
In the above process (a), suitable leaving groups L^1 include halo, particularly chloro or trifluoromethylsulfonate. The reaction is preferably performed in a suitable solvent optionally in the presence of an added base for a suitable period of time, typically 0.5 to 16 h, at ambient to reflux temperature. Typically solvents such as N,N-dimethylformamide, pyridine, tetrahydrofuran, acetonitrile, N-methylpyrrolidine or dichloromethane are used. When used, the added base may be an organic base such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine or pyridine, or an inorganic base such as an alkali metal carbonate. The reaction is typically conducted at ambient temperature for 0.5 to 16 h, or until completion of the reaction has been achieved, as determined by chromatographic or spectroscopic methods. Reactions of sulfonyl halides with various

primary and secondary amines are well known in the literature, and the variations of the conditions will be evident for those skilled in the art.

Sulfonylchlorides of formula (II) wherein L^1 represents chloro and R^2 represents Me are disclosed in WO 02/074767 and references cited therein. Corresponding compounds wherein R^2 represents C1 to 3 alkyl may be prepared using analogous methods.

Suitable processes for the preparation of compounds of formula (I) are described in a retrosynthetic way in Scheme 1.

Scheme 1



In Scheme 1, protecting groups (PG) can be either carbamates (e.g. *tert*-butoxycarbamate), amides (e.g. trifluoroacetyl) or alkyl (e.g. *tert*-butyl or benzyl). Leaving groups (LG) can

be either chloride, bromide, iodide or trifluoromethylsulfonate. In the palladium-catalysed Suzuki couplings, either boronic acids or pinacolboronates may be used. Intermediate (IVa-c) can be prepared by standard Suzuki coupling (*Chem. Rev.* **1995**, *95*, 2457) between an electrophile (VIIa-c) and a boron reagent (XII), or the other way around, between an electrophile (XI) and a boron reagent (VIIIa-c). The latter can be obtained from (VIIa-c) using standard Miyaura conditions (*J. Org. Chem.* **1995**, *60*, 7508-7510). Deprotection of (IVa-c) either by hydrogen chloride in methanol (PG = *tert*-butoxycarbonyl) or refluxing 1-chloroethyl chloroformate/ refluxing methanol (PG = *tert*-butyl or benzyl) (*Synlett.* **1993**, 195-196) gives amine (IIIa-c) as a hydrochloride salt. The free base can be obtained by treatment of (IIIa-c) with base and extraction with an organic solvent such as ethyl acetate or toluene. Reacting (IIIa-c) either as a salt or base in a suitable solvent (e.g. acetonitrile, tetrahydrofuran, *N*-methylpyrrolidine or *N*,*N*-dimethylformamide) with the sulfonyl chloride (II) in the presence of a tertiary amine (e.g. triethylamine, pyridine or *N*,*N*-diisopropylethylamine) for 0.5 to 16 hours produces compounds of formula (I).

An alternative route to compounds of formula (I) from intermediate (IIIa-c) via methanesulfonamide (Xa-c) and ketone (IXa-c) has been previously described (WO 02/074767). Briefly, treatment of (IIIa-c) with methansulfonyl chloride and a tertiary amine (e.g. triethylamine, pyridine or *N*,*N*-diisopropylethylamine) in a suitable solvent (e.g. dichloromethane or tetrahydrofuran) produces the methansulfonamide (Xa-c) which in turn can be transformed into the ketone (IXa-c) using standard procedures. Heating ketone (IXa-c) with ammonium carbonate and potassium cyanide in 50% aqueous ethanol in a sealed vial at 80-90 °C for 1 to 5 hours gives a racemic hydantoin that can be resolved by chiral chromatography (e.g. on OD-H with 100% ethanol).

In a third route, intermediate (VIIa-c) is deprotected as described above to give amine (VIa-c) as a hydrochloride salt. The free base can be isolated by treatment with base and extraction with an organic solvent e.g. ethyl acetate or toluene. Reacting (VIa-c) either as a salt or base in a suitable solvent (e.g. acetonitrile, tetrahydrofuran, *N*-methylpyrrolidine or *N*,*N*-dimethylformamide) with sulfonyl chloride (II) in the presence of a tertiary amine (e.g. triethylamine, pyridine or *N*,*N*-diisopropylethylamine) for 0.5 to 16 hours produces

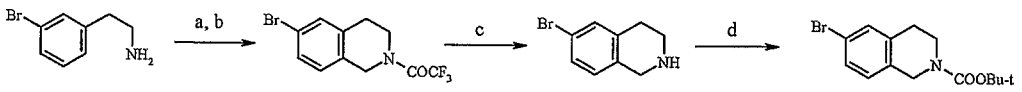
chiral sulfonamide (Va-c). The latter can be coupled with boron reagent (XII) using standard Suzuki conditions to give compounds of formula (I).

Intermediates (VIIa-b) are conveniently prepared using the following methods.

The 1,2,3,4-tetrahydroisoquinoline intermediate (VIIa)

Methods for the synthesis of 1,2,3,4-tetrahydroisoquinolines are well known in the literature. The classical route is the Pomeranz-Fritz reaction of benzaldehydes with a diacetal protected aminoacetaldehyde (*Org. React.* **1951**, *6*, 191) yielding the isoquinoline nucleus which upon catalytical reduction gives 1,2,3,4-tetrahydro-isoquinolines. Another route is the Bischler-Napieralski reaction (*Org. React.* **1951**, *6*, 74) of a carbamate of 2-phenylethanamines with phosphoryl chloride in refluxing toluene or xylenes. Reduction of the resulting cyclic benzamide with lithium aluminium hydride in tetrahydrofuran (*J. Med. Chem.* **1987**, *30(12)*, 2208-2216) or diborane in tetrahydrofuran (*J. Med. Chem.* **1980**, *23(5)*, 506-511) affords the 1,2,3,4-tetrahydroisoquinoline. A variation of the Bischler-Napieralski reaction is the Pictet-Spengler synthesis (*Org. React.* **1951**, *6*, 151). In this reaction amides, carbamates or sulfonamides of 2-phenylethanamines are heated with paraformaldehyde and strong proton acids (e.g. trifluoroacetic acid, sulfuric acid) or Lewis acids in a solvent (e.g. dichloromethane, toluene, formic acid) to give the 1,2,3,4-tetrahydroisoquinoline in a single step (*Tetrahedron* **2002**, *58(8)*, 1471-1478).

Scheme 2



Route A

(+ 8-Br-isomer)

VIIa (B and B¹ = CH and LG = Br)

Reagents:
a) $(CF_3CO)_2O$, Et_3N; +4°C. b) $(HCHO)_n$, H_2SO_4, HOAc; RT. c) $NaBH_4$, EtOH; RT or NH_3 (conc), EtOH, heat.
d) $(t\text{-}BuOCO)_2O$, Et_3N, DCM, RT.

Preferably the 1,2,3,4-tetrahydroisoquinoline intermediate (VIIa) is synthesised by Route A shown in Scheme 2. This route is a Friedel-Craft-type reaction of *N*-[2-(3-

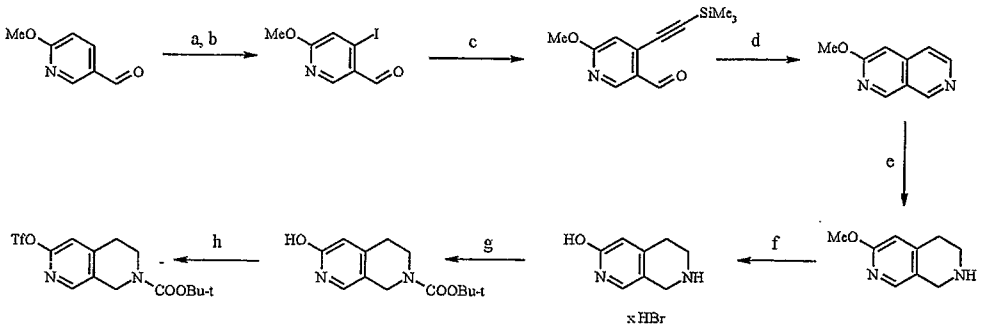
bromophenyl)ethyl]-2,2,2-trifluoroacetamide with formaldehyde and sulfuric acid in acetic acid (*Tetrahedron Lett.* **1996**, *37(31)*, 5453-5456) giving a mixture of the 6-bromo- and 8-bromoisomer in a ratio of 3 to 1. Replacement of the trifluoroacetamide group with a BOC-group gives (VIIa). The regioisomers are not conveniently separated at this stage.

The 1,2,3,4-tetrahydro-2,7-naphthyridine intermediate (VIIb)

In contrast to the 1,2,3,4-tetrahydroisoquinolines, there are rather few examples of synthetic methods for 1,2,3,4-tetrahydro-2,7-naphthyridines in the literature. One important method to prepare 1,2,3,4-tetrahydro-2,7-naphthyridine is the regio-selective catalytic reduction of 2,7-naphthyridine (*Eur. J. Med. Chem. Ther.* **1996**, *31(11)*, 875-888). The synthesis of 2,7-naphthyridine and some derivatives thereof has been described in the literature. One classical route involves several steps and starts with the acid catalysed condensation of malononitrile with diethyl 1,3-acetonedicarboxylate (*J. Chem. Soc.* **1960**, 3513-3515; see also *J. Heterocycl. Chem.* **1970**, 7, 419-421). A slightly different route to 2,7-naphthyridine involves oxidation of 4-formyl-2,7-naphthyridine to give 2,7-naphthyridine-4-carboxylic acid followed by decarboxylation (*Synthesis* **1973**, 46-47). A completely different method is based on the internal Diels-Alder reaction of *N*-(ethoxycarbonyl)-*N*-(but-3-ynyl)amino-methylpyrazine and gives a mixture of 1,2,3,4-tetrahydro-2,7-naphthyridine and 5,6,7,8-tetrahydro-1,7-naphthyridine after hydrolysis of the carbamate group (WO 02/064574).

Scheme 3

Route B

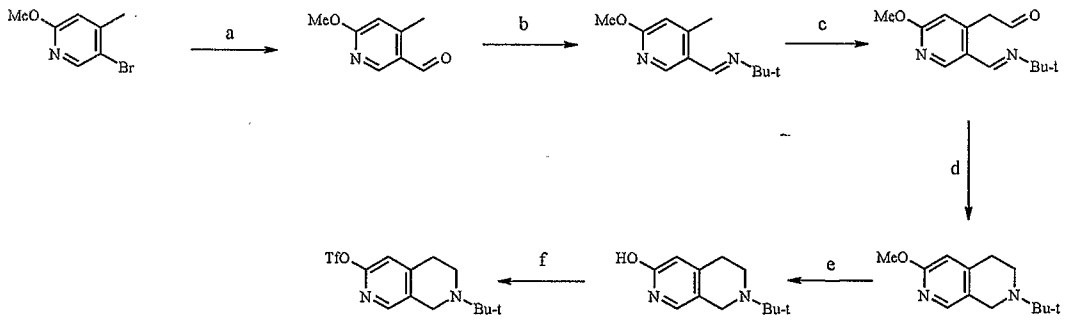


Reagents:
a) $LiCH_3NCH_2CH_2N(CH_3)_2$, THF, -70°C, b) n-BuLi in hexanes, -70°C, then I_2. c) TMS-acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 60°C. d) 7 M NH_3, EtOH, 80°C. e)H_2, PtO_2, HOAc. f) 48% HBr (aq), 120°C. g) $(BOC)_2O$, Et_3N, H_2O, THF. h) Tf_2O, PhMe, 30% K_3PO_4.

Preferably the 1,2,3,4-tetrahydro-2,7-naphthyridine intermediate (VIIb) can be synthesised as shown in Schemes 3 and 4. In Route B, commercially available 6-methoxynicotinaldehyde is treated successively with the lithium salt of *N,N,N'*-trimethylethylenediamine, then *n*-BuLi in hexanes and finally iodine to afford the 4-iodo-6-methoxynicotinaldehyde (cf. *Tetrahedron Lett.* **1993**, *34(39)*, 6173-6176). The iodo compound is coupled with trimethylsilylacetylene under usual Sonagashira-Hagihara conditions (*Synthesis* **1980**, 627-630) and the resulting 6-methoxy-4-[(trimethylsilyl)ethynyl]nicotinaldehyde is condensed with ammonium hydroxide in ethanol to give 3-methoxy-2,7-naphthyridine (*Synthesis* **1999**, *2*, 306-311). Regioselective catalytical reduction (cf. *Eur. J. Med. Chem. Ther.* **1996**, *31(11)*, 875-888) affords 6-methoxy-1,2,3,4-tetrahydro-2,7-naphthyridine. Demethylation and N-protection with BOC-anhydride and finally treatment of the resulting *tert*-butyl 6-hydroxy-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate with triflic anhydride in a two-phase system gives (VIIb).

Scheme 4

Route C



Reagents:
a) n-BuLi, THF, -70°C then DMF, -70°C to RT. b) t-BuNH$_2$, DCM, 3Å mol. sieves. c) Li-TMP, -20°C then DMF, -20 to -10°C.
d) NaBH$_3$CN, MeOH, HOAc; RT. e) 48% HBr (aq), reflux; work-up with K_2CO_3 (aq). f) Tf_2O, pyridine +4°C.

In Route C, commercially available 5-bromo-2-methoxy-4-methylpyridine in anhydrous tetrahydrofuran is metallated with *n*-BuLi and then treated with *N,N*-dimethylformamide to afford 6-methoxy-4-methylnicotinaldehyde. This was converted to the *tert*-butylimine with

tert-butylamine in dichloromethane. Metallation with lithium 2,2,6,6-tetramethylpiperidide (Li-TMP) (cf. *J. Org. Chem.* **1993**, *58*, 2463-2467) and addition of *N,N*-dimethylformamide affords the iminoacetaldehyde which is reduced with sodium cyanoborohydride in methanol to give 2-*tert*-butyl-6-methoxy-1,2,3,4-tetrahydro-2,7-naphthyridine. Cleavage of the methyl group with refluxing 48% hydrobromic acid and treatment with triflic anhydride in the presence of base gives (VIIb) protected as the *tert*-butylamine.

It will be appreciated by those skilled in the art that in the processes of the present invention certain potentially reactive functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by suitable protecting groups. Thus, the preparation of the compounds of the invention may involve, at various stages, the addition and removal of one or more protecting groups.

Suitable protecting groups and details of processes for adding and removing such groups are described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The compounds of the invention and intermediates thereto may be isolated from their reaction mixtures and, if necessary further purified, by using standard techniques.

The present invention will now be further explained by reference to the following illustrative examples.

General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian *Inova* 400 MHz or a Varian *Mercury*-VX 300 MHz instrument. The central peaks of chloroform-*d* (δ_H 7.27 ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm), acetonitrile-d_3 (δ_H 1.95 ppm) or methanol-d_4 (δ_H 3.31 ppm) were used as internal references. Column chromatography was carried out using silica gel (0.040-0.063 mm, Merck) with a slight over-pressure (0.2-0.4 bars) applied on the column. A Kromasil KR-100-5-C_{18} column (250 × 20 mm, Akzo Nobel) and mixtures

of acetonitrile/water with 0.1 % TFA at a flow rate of 10 mL/min were used for preparative HPLC. Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received. The organic phases from extractions were dried over anhydrous sodium sulfate if not stated otherwise. Organic phases or solutions were concentrated by rotary evaporation. Yields were not optimised.

The following method was used for LC-MS analysis:
Instrument *Agilent 1100*; Column *Waters Symmetry* 2.1 × 30 mm; Mass APCI; Flow rate 0.7 mL/min; Wavelength 254 or 220 nm; Solvent A: water + 0.1% TFA; Solvent B: acetonitrile + 0.1% TFA ; Gradient 15-95% /B 2.7 min, 95% B 0.3 min.

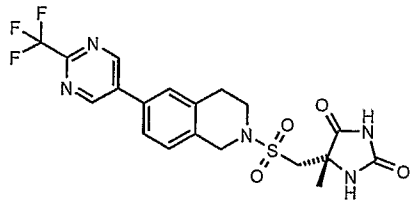
The following method was used for GC-MS analysis:
Instrument *Hewlett Packard 5890 Series II*; Column *Agilent HP-5* (30 m x 0.32 mm ID); Mass selective detector *Hewlett Packard 5971 Series* ; Pressure 55 kPa He; Oven program 100°C (3 min) to 300°C, 25°C/ min.

Abbreviations:

BOC-anhydride	di-*tert*-butyl dicarbonate
n-BuLi	*n*-butyl lithium
DCM	dichloromethane
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
GC-MS	gas chromatography- mass spectrometry
LDA	lithium diisopropylamide
MeOH	methanol
LC-MS	liquid chromatography- mass spectroscopy
$PdCl_2$ x dppf	1,1′-bis(diphenylphosphino)ferrocene palladium(II)dichloride

RT	room temperature, normally 20 to 22 °C
TEA	triethylamine
THF	tetrahydrofuran
TBME	*tert*-butyl methyl ether
TFA	trifluoroacetic acid
Triflic anhydride	trifluoromethanesulfonic anhydride (Tf_2O)

Example 1 (5*S*)-5-Methyl-5-({[6-[2-(trifluoromethyl)pyrimidin-5-yl]-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)imidazolidine-2,4-dione



[(4*S*)-4-Methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride (0.0295 g, 0.13 mmol) in dry THF (0.60 mL) was added dropwise to a stirred solution of 6-[2-(trifluoromethyl)pyrimidin-5-yl]-1,2,3,4-tetrahydroisoquinoline (0.039 g, 0.14 mmol), DIPEA (0.034 mL, 0.20 mmol) and dry THF (0.60 mL) at ice-bath temperature. After the addition was complete the solution was stirred at RT for 2 h and then taken up in water-brine and extracted twice with EtOAc. The combined organic phases were washed with brine, dried, filtered and concentrated to give a crude product. Purification by preparative HPLC afforded 0.050 g (76%) of the title compound as a white solid.

LC-MS *m/z* 470 (M+1);

^{1}H NMR (CD_3CN) δ 9.19 (s, 2H), 8.51 (br s, 1H), 7.62 (s, 1H), 7.61 (dd, 1H), 7.36 (d, 1H), 6.33 (br s, 1H), 4.51 (s, 2H), 3.57 (t, 2H), 3.52 (d, 1H), 3.42 (d, 1H), 3.04 (t, 2H) and 1.48 (s, 3H) ppm.

The starting materials were prepared as follows:

6-[2-(Trifluoromethyl)pyrimidin-5-yl]-1,2,3,4-tetrahydroisoquinoline

tert-Butyl 6-[2-(trifluoromethyl)pyrimidin-5-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (0.051 g, 0.13 mmol) was stirred in TFA (1.0 mL) and DCM (1.0 mL) at RT overnight, then concentrated twice, the second time with added toluene (5 mL), to afford the trifluoroacetate salt.

LC-MS *m/z* 280 (M+1);

^{1}H NMR (CD_3CN) δ 9.25 (s, 2H), 7.73 (m, 2H), 7.44 (d, 1H), 4.45 (s, 2H), 3.56 (t, 2H) and 3.24 (t, 2H) ppm.

The crude product was taken up in 1M sodium carbonate solution (10 mL) and extracted twice with EtOAc. The combined organic phases were washed with brine, dried, filtered and concentrated to give 0.039 g (100%) of the title product as a white solid.

2-(Trifluoromethyl)pyrimidin-5-yl trifluoromethanesulfonate

Triflic anhydride (13.9 g, 85 mmol) in dry DCM (70 mL) was added slowly to an ice-cold solution of 2-(trifluoromethyl)pyrimidin-5-ol (13.9, 85 mmol) (US 4,558,039), DIPEA (16 mL, 93 mmol) and dry DCM (260 mL) at such a rate that the temperature was kept between 4 °C and 6 °C. After the addition was complete, the solution was stirred for 2.5 h at 4 °C and then allowed to warm to RT. Water (50 mL) and 1M phosphoric acid (4.5 mL) were added and the phases were washed and separated. The organic phase was washed successively with water and saturated sodium bicarbonate, dried, filtered and carefully concentrated by rotary evaporation (pressure 300-400 mbar). The dark-red oil was purified by column chromatography with EtOAc-heptanes (1:8 through 1:4) as eluent to give 22.5 g (90%) of the title product as a colourless oil that crystallised in the cold. Alternatively, the product could be purified by distillation, b.p. 75-77 °C/10 mbar.

^{1}H NMR ($CDCl_3$) δ 8.90 (s, 2H) ppm.

tert-Butyl 6-[2-(trifluoromethyl)pyrimidin-5-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxylate

A 4:1 mixture (0.10 g, 0.28 mmol) of *tert*-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate and *tert*-butyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate,

2-(trifluoromethyl)pyrimidin-5-yl trifluoromethanesulfonate (0.083 g, 0.28 mmol), $PdCl_2$ x dppf (0.0048 g), 2M sodium carbonate (1.1 mL), toluene (4.0 mL) and EtOH (1.0 mL) was purged with dry argon for ten minutes then heated in a sealed vial at 81 °C for 6 h. The black solution was filtered through glass-wool, taken up in water-brine and washed twice with EtOAc. The combined organic phases were dried, filtered and concentrated with silica (5 g). Column chromatography with EtOAc-heptanes (1:8 through 1:5) gave 0.051 g (48%) of the title product as white solid.

LC-MS *m/z* 380 (M+1);

^{1}H NMR ($CDCl_3$) δ 9.06 (s, 2H), 7.44 (dd, 1H), 7.38 (br s, 1H), 7.30 (d, 1H), 4.66 (s, 2H), 3.71 (t, 2H), 2.95 (t, 2H), and 1.51 (s, 9H) ppm.

tert-Butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate

A 3:1 mixture (0.49 g, 1.6 mmol) of *tert*-butyl 6-bromo-3,4-dihydroisoquinoline-2(1*H*)-carboxylate and *tert*-butyl 8-bromo-3,4-dihydroisoquinoline-2(1*H*)-carboxylate, bis(pinacolato)diborane (0.45 g, 1.8 mmol), $PdCl_2$ x dppf (0.039 g, 0.048 mmol), potassium acetate (0.48 g, 4.8 mmol) and DMF (8.0 mL) was heated at 81 °C overnight. The solvent was evaporated, the residue taken up in water-brine and washed twice with EtOAc. The organic phase was dried, filtered and concentrated. Column chromatography with EtOAc-heptanes (1:10 through 1:4) gave 0.24 g of a 4:1 mixture of the title product and *tert*-butyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate.

^{1}H NMR ($CDCl_3$) δ 7.62 (d, 1H), 7.60 (s, 1H), 7.13 (d, 1H), 4.59 (s, 2H), 3.64 (t, 2H), 2.85 (t, 2H), 1.50 (s, 9H) and 1.35 (s, 12H) ppm (6-isomer).

^{1}H NMR ($CDCl_3$) δ 7.69 (d, 1H), 7.24-7.14 (m, 2H), 4.88 (s, 2H), 3.64 (t, 2H), 2.85 (t, 2H), 1.50 (s, 9H) and 1.35 (s, 12H) ppm (8-isomer).

tert-Butyl 6-bromo-3,4-dihydroisoquinoline-2(1*H*)-carboxylate

6-Bromo-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline was prepared in two steps from [2-(3-bromophenyl)ethyl]amine (4.0 g, 20 mmol) following the procedure of Stokker (*Tetrahedron Lett.* **1996**, *37(31)*, 5453-5456). Column chromatography with EtOAc-

heptanes (1:10 through 1:6) gave 2.3 g (7.5 mmol) of a 3:1 mixture of 6-bromo-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline and 8-bromo-2-(trifluoro-acetyl)-1,2,3,4-tetrahydroisoquinoline.

^{1}H NMR ($CDCl_3$) δ 7.62 (d, 1H), 7.60 (s, 1H), 7.13 (d, 1H), 4.59 (s, 2H), 3.64 (t, 2H), 2.85 (t, 2H) and 1.50 (s, 9H) and 1.35 (s, 12H) ppm (6-isomer).

^{1}H NMR ($CDCl_3$) δ 7.69 (d, 1H), 7.24-7.14 (m, 2H), 4.88 (s, 2H), 3.64 (t, 2H), 2.85 (t, 2H) and 1.50 (s, 9H) and 1.35 (s, 12H) ppm (8-isomer).

The above material was stirred with absolute EtOH (100 mL) and 25% ammonium hydroxide (10 mL) at 60 °C for 4 h. More 25% ammonium hydroxide (15 mL) was added and stirring continued at RT overnight. The volatiles were evaporated to leave the crude amine as a white solid.

LC-MS *m/z* 212, 214 (M+1).

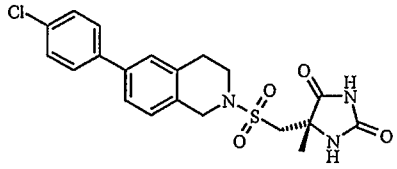
Dry THF (50 mL) and DIPEA (1.3 mL, 7.5 mmol) were added followed by BOC-anhydride (1.8 g, 8.2 mmol). The mixture was stirred at RT overnight. The volatiles were evaporated and the residue was taken up in water. The pH was adjusted to 2 with 1M phosphoric acid and the product was extracted twice with EtOAc. The combined organic phases were washed with brine made slightly alkaline with saturated sodium bicarbonate, dried, filtered and concentrated. The crude product was purified by column chromatography with EtOAc-heptanes (1:50 through 1:20) to give 2.24 g (96%) of a 3:1 mixture of the title product and *tert*-butyl 8-bromo-3,4-dihydroisoquinoline-2(1*H*)-carboxylate.

LC-MS *m/z* 256, 258 (M-56);

^{1}H NMR ($CDCl_3$) δ 7.31 (dd, 1H), 7.30 (br s, 1H), 6.98 (d, 1H), 4.52 (s, 2H), 3.63 (t, 2H), 2.81 (t, 2H) and 1.50 (s, 9H) ppm (6-isomer).

^{1}H NMR ($CDCl_3$) δ 7.42 (dd, 1H), 7.12-7.01 (m, 2H), 4.55 (s, 2H), 3.64 (t, 2H), 2.84 (t, 2H) and 1.51 (s, 9H) ppm (8-isomer).

Example 2 (5*S*)-5-({[6-(4-Chlorophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione



(5*S*)-5-{[(6-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl]methyl}-5-methyl-imidazolidine-2,4-dione (0.016 g, 0.040 mmol), 4-chlorophenylboronic acid (0.0072 g, 0.045 mmol), $PdCl_2$ x dppf (0.0030 g), 2M sodium carbonate (0.15 mL), toluene (0.80 mL) and EtOH (0.20 mL) were stirred in a sealed vial at 95 °C for 17 h. The solvent was evaporated and the residue was taken up in water. The solution was acidified with 10% HOAc to pH 6 and then extracted twice with EtOAc. The combined organic phases were washed with brine-saturated sodium bicarbonate, dried, filtered and concentrated to give a crude product.

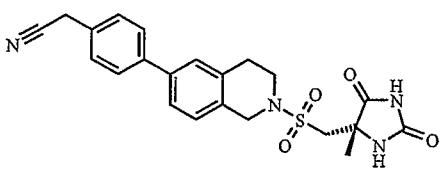
LC-MS *m/z* 434 (M+1).

Purification by preparative HPLC afforded 0.0080 g (46%) of the title compound as a white solid.

^{1}H NMR (CD_3CN) δ 8.53 (br s, 1H), 7.62 (m, 2H), 7.46 (m, 4H), 7.23 (d, 1H), 6.34 (br s, 1H), 4.45 (s, 2H), 3.53 (m, 2H), 3.49 (d, 1H), 3.39 (d, 1H), 2.99 (m, 2H) and 1.46 (s, 3H) ppm.

The compounds of Examples 3 and 4 were prepared using the general method of Example 2.

Example 3 {4-[2-({[(4*S*)-4-Methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]phenyl}acetonitrile

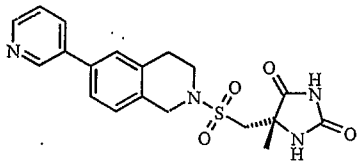


White solid.

LC-MS *m/z* 439 (M+1);

^{1}H NMR (CD_3CN) δ 8.61 (br s, 1H), 7.65 (m, 2H), 7.48 (m, 2H), 7.43 (m, 2H), 7.23 (d, 1H), 6.38 (br s, 1H), 4.46 (s, 2H), 3.87 (s, 2H), 3.53 (m, 2H), 3.50 (d, 1H), 3.40 (d, 1H), 3.00 (m, 2H) and 1.46 (s, 3H) ppm.

Example 4 (5*S*)-5-Methyl-5-{[(6-pyridin-3-yl-3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl]methyl}imidazolidine-2,4-dione



White solid.

LC-MS *m/z* 401 (M+1);

^{1}H NMR (CD_3CN) δ 8.98 (br s, 1H), 8.71 (m, 1H), 8.54 (d, 2H), 7.89 (m, 1H), 7.56 (m, 2H), 7.34 (m, 1H), 6.34 (br s, 1H), 4.49 (s, 2H), 3.55 (m, 2H), 3.52 (d, 1H), 3.41 (d, 1H), 3.03 (m, 2H) and 1.47 (s, 3H) ppm.

The starting material was prepared as follows:

(5*S*)-5-({[6-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione

A 3:1 mixture (0.44 g, 1.4 mmol) of 6-bromo-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline and 8-bromo-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (prepared according to *Tetrahedron Lett.* **1996**, *37(31)*, 5453-5456) was stirred in ethanol (10 mL) containing a few drops of 25% ammonium hydroxide at RT. After 2.5 h, the solution was concentrated, dissolved in dry THF (1.0 mL) under argon and cooled on an ice-bath. DIPEA (0.41 mL, 2.4 mmol) was added followed by a solution of [(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl-chloride (0.27 g, 1.2 mmol) and dry THF (1.0 mL). The mixture was stirred at RT for 1 h and then concentrated. The crude product was taken up in water and extracted twice with EtOAc. The combined organic phases were

washed with brine, dried, filtered and concentrated to give 0.55 g of a mixture of (5*S*)-5-({[6-bromo-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione and (5*S*)-5-({[8-bromo-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione. The regioisomers were separated by preparative HPLC.

(5*S*)-5-({[8-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione (eluting first)

Yield: 0.13 g of a white solid.

LC-MS *m/z* 402/404 (M+1), 419/421 (M+18);

^{1}H NMR (CD_3CN) δ 8.48 (br s, 1H), 7.48 (m, 1H), 7.21 (m, 1H), 7.14 (m, 1H), 6.31 (br s, 1H), 4.36 (s, 2H), 3.48 (m, 4H), 2.95 (m, 2H) and 1.46 (s, 3H) ppm.

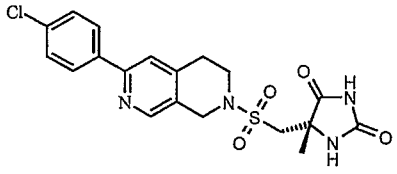
(5*S*)-5-({[6-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione (eluting second)

Yield: 0.25 g of a white solid.

LC-MS *m/z* 402/404 (M+1), 419/421 (M+18);

^{1}H NMR (CD_3CN) δ 8.47 (br s, 1H), 7.38 (m, 1H), 7.36 (m, 1H), 7.08 (m, 1H), 6.29 (br s, 1H), 4.36 (s, 2H), 3.48 (m, 2H), 3.47 (d, 1H), 3.37 (d, 1H), 2.92 (m, 2H) and 1.45 (s, 3H) ppm.

Example 5 (5*S*)-5-({[6-(4-Chlorophenyl)-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione



[(4*S*)-4-Methyl-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride (0.086 g, 0.38 mmol) in anhydrous NMP (0.50 mL) was added dropwise to a stirred solution of 6-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,7-naphthyridine (0.046 g, 0.19 mmol),

DIPEA (0.066 mL, 0.38 mmol) and anhydrous NMP (1.5 mL) at RT. After the addition was complete the solution was stirred at RT for 1.5 h, then diluted with water (1 mL) and purified by preparative HPLC to afford 0.0070 g (8%) of the title compound as a white solid.

LC-MS *m/z* 435, 436 (M+1);

^{1}H NMR (DMSO-d_6) δ 10.8 (s, 1H), 8.49 (s, 1H), 8.10 (d, 2H), 8.06 (s, 1H), 7.84 (s, 1H), 7.54 (d, 2H), 4.45 (s, 2H), 3.61 (d, 1H), 3.48 (d, 1H), 3.47 (t, 2H), 2.98 (t, 2H) and 1.34 (s, 3H) ppm.

The starting materials were prepared as follows:

6-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,7-naphthyridine

tert-Butyl 6-{[(trifluoromethyl)sulfonyl]oxy}-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate (0.69 g, 1.8 mmol), 4-chlorophenylboronic acid (0.39 g, 2.5 mmol), $PdCl_2$ x dppf (0.050 g), saturated sodium carbonate (2 mL), EtOH (4 mL) and toluene (4 mL) were stirred at 80 °C for 6 h. The solution was cooled to RT, taken up in water (10 mL) and extracted with EtOAc (25 mL). The combined organic phases were washed with brine, dried, filtered and concentrated. Purification by column chromatography with EtOAc-heptanes (1:1) as eluent gave 0.065 g (10%) of *tert*-butyl 6-(4-chlorophenyl)-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate.

LC-MS *m/z* 345 (M+1).

This material was dissolved in MeOH (2 mL) and acetyl chloride (0.2 mL) was slowly added. After stirring at 40 °C overnight, the solution was concentrated, the residue was taken up in 1M sodium hydroxide (10 mL) and extracted with EtOAc-ether (1:1) (4 x 30 mL). The combined organic phases were dried, filtered and concentrated to give 0.046 g (100%) of the crude title compound.

LC-MS *m/z* 245 (M+1).

tert-Butyl 6-{[(trifluoromethyl)sulfonyl]oxy}-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate

Crude 3-methoxy-2,7-naphthyridine (prepared from 4.4 mmol of 6-methoxy-4-[(trimethylsilyl)ethynyl]nicotinaldehyde) was hydrogenated (30 psi pressure) at RT over

PtO_2 (approx. 0.1 g) in HOAc (25 mL) for 2.5 h. The solution was filtered through a Celite pad and the clear filtrate was concentrated by freeze-drying to give crude 6-methoxy-1,2,3,4-tetrahydro-2,7-naphthyridine as the acetate salt.

LC-MS *m/z* 165 (M+1).

This material was refluxed in 48% hydrobromic acid for 10 h. The volatiles were evaporated and the residue was dried under vacuum and 45 °C to give approx. 0.70 g. of crude 5,6,7,8-tetrahydro-2,7-naphthyridin-3-ol hydrobromide.

LC-MS *m/z* 151 (M+1).

This material (approx. 4.8 mmol) was dissolved in water (13 mL) and treated with THF (33 mL), Et_3N (0.85 mL, 6.0 mmol) and BOC-anhydride (1.6 g, 7.3 mmol) at RT. After stirring at the same temperature for 6 h the solution was concentrated to one third of its original volume and the residue was taken up in water and extracted three times with EtOAc. The combined organic phases were dried, filtered and concentrated to give 0.80 g (67% crude yield) of *tert*-butyl 6-hydroxy-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate as a white solid.

LC-MS *m/z* 251 (M+1), 195 (M-55).

This material (approx. 5.4 mmol) was dissolved in a two-phase system of toluene (20 mL) and 30% aqueous tripotassium orthophosphate (20 mL) and treated with triflic anhydride (1.6 mL, 6.8 mmol) at 4 °C [*Org. Lett.* **2002**, *4(26)*, 4717-4718]. The ice-bath was removed and the stirring was continued for 2 h at RT after which the two phases were separated. The aqueous phase was washed once with toluene. The combined organic phases were washed with brine, dried and concentrated. Purification by column chromatography with EtOAc-heptanes (2:1) as eluent gave 0.45 g (17 % yield) of the title product.

LC-MS *m/z* 383 (M+1), 283 (M-99).

3-Methoxy-2,7-naphthyridine

To a stirred solution of *N,N,N'*-trimethylethylenediamine (1.9 mL, 15 mmol) in anhydrous THF (65 mL) under argon at –70 °C was slowly added 1.6M *n*-BuLi in hexanes (9.0 mL, 14 mmol). After stirring at –70 °C for 15 minutes, 6-methoxy-nicotinaldehyde (1.3 g, 9.8 mmol) was added dropwise. After the addition was complete, stirring was continued at -70 °C for another 15 minutes. Then 1.6M *n*-BuLi in hexanes (10 mL, 16 mmol) was added dropwise and stirring continued at –45 °C for 4 h. The solution was cooled to

–70 °C and then a solution of iodine (3.0 g, 12 mmol) and anhydrous THF (25 mL) was added dropwise. When the addition was complete, stirring was continued at –70 °C for 30 minutes and then at RT for 3 h. The crude product was taken up in ether (40 mL) and washed successively with saturated ammonium chloride (2 x 40 mL) and 5% sodium thiosulfate (2 x 20 mL). The organic phase was dried, filtered and concentrated. Purification by column chromatography with EtOAc-heptanes (1:1) as eluent gave 0.41 g (15% yield) of 4-iodo-6-methoxynicotinaldehyde.

LC-MS *m/z* 264 (M+1);

^{1}H NMR ($CDCl_3$) δ 9.95 (s, 1H), 8.53 (s, 1H), 7.32 (s, 1H) and 3.98 (s, 3H) ppm.

4-Iodo-6-methoxynicotinaldehyde (0.41 g, 1.6 mmol), trimethylsilylacetylene (0.35 mL, 2.8 mmol), $PdCl_2(PPh_3)_2$ (catalytic amount), CuI (catalytic amount), TEA (2 mL) and THF (10 mL) were stirred at 60 °C for 2 h. The volatiles were evaporated and the residue was taken up in water and extracted with ether. The organic phase was dried, filtered and concentrated. Purification by column chromatography with EtOAc-heptanes (1:3) as eluent gave 0.25 g (68% yield) of 6-methoxy-4-[(trimethylsilyl)ethynyl]nicotinaldehyde.

LC-MS *m/z* 234 (M+1);

^{1}H NMR ($CDCl_3$) δ 10.4 (s, 1H), 8.73 (s, 1H), 6.84 (s, 1H), 4.03 (s, 3H) and 0.30 (s, 9H) ppm.

6-Methoxy-4-[(trimethylsilyl)ethynyl]nicotinaldehyde (0.25 g, 1.1 mmol) and 7M ammonia in MeOH (5 mL) were stirred in a sealed vial at 80 °C overnight. The solution was concentrated, taken up in saturated sodium carbonate and extracted with ether. The organic phase was dried, filtered and concentrated to give 0.20 g of the title product.

GC-MS *m/z* 160 (M);

^{1}H NMR ($CDCl_3$) δ 9.41 (s, 1H), 9.27 (s, 1H), 8.47 (d, 1H), 7.64 (d, 1H), 7.03 (s, 1H) and 4.12 (s, 3H) ppm.

Pharmacological Example

Isolated Enzyme Assays

MMP12

Recombinant human MMP12 catalytic domain may be expressed and purified as described by Parkar A.A. *et al*, (2000), Protein Expression and Purification, 20, 152. The purified enzyme can be used to monitor inhibitors of activity as follows: MMP12 (50 ng/ml final concentration) is incubated for 60 minutes at room temperature with the synthetic substrate Mca-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH_2 (10 μM) in assay buffer (0.1M "Tris-HCl" (trade mark) buffer, pH 7.3 containing 0.1M NaCl, 20mM $CaCl_2$, 0.020 mM ZnCl and 0.05% (w/v) "Brij 35" (trade mark) detergent) in the presence (10 concentrations) or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 320 nm and λem 405 nm. Percent inhibition is calculated as follows:

% Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

MMP8

Purified pro-MMP8 is purchased from Calbiochem. The enzyme (at 10 μg/ml) is activated by p-amino-phenyl-mercuric acetate (APMA) at 1 mM for 2.5 h, 35 °C. The activated enzyme can be used to monitor inhibitors of activity as follows: MMP8 (200 ng/ml final concentration) is incubated for 90 minutes at 35 °C (80% H_2O) with the synthetic substrate Mca-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH_2 (12.5 μM) in assay buffer (0.1M "Tris-HCl" (trade mark) buffer, pH 7.5 containing 0.1M NaCl, 30mM $CaCl_2$, 0.040 mM ZnCl and 0.05% (w/v) "Brij 35" (trade mark) detergent) in the presence (10 concentrations) or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 320 nm and λem 405 nm. Percent inhibition is calculated as follows:

% Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

MMP9

Recombinant human MMP9 catalytic domain was expressed and then purified by Zn chelate column chromatography followed by hydroxamate affinity column chromatography. The enzyme can be used to monitor inhibitors of activity as follows: MMP9 (5 ng/ml final concentration) is incubated for 30 minutes at RT with the synthetic substrate Mca-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH_2 (5 μM) in assay buffer (0.1M "Tris-HCl" (trade mark) buffer, pH 7.3 containing 0.1M NaCl, 20mM $CaCl_2$, 0.020 mM ZnCl and 0.05% (w/v) "Brij 35" (trade mark) detergent) in the presence (10 concentrations) or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 320 nm and λem 405 nm. Percent inhibition is calculated as follows:

% Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

MMP14

Recombinant human MMP14 catalytic domain may be expressed and purified as described by Parkar A.A. *et al*, (2000), Protein Expression and Purification, 20, 152. The purified enzyme can be used to monitor inhibitors of activity as follows: MMP14 (10 ng/ml final concentration) is incubated for 60 minutes at room temperature with the synthetic substrate Mca-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH_2 (10 μM) in assay buffer (0.1M "Tris-HCl" (trade mark) buffer, pH 7.5 containing 0.1M NaCl, 20mM $CaCl_2$, 0.020 mM ZnCl and 0.05% (w/v) "Brij 35" (trade mark) detergent) in the presence (5 concentrations) or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 320 nm and λem 405 nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

A protocol for testing against other matrix metalloproteinases, including MMP9, using expressed and purified pro MMP is described, for instance, by C. Graham Knight *et al.*, (1992) FEBS Lett., 296(3), 263-266.

MMP19

Recombinant human MMP19 catalytic domain may be expressed and purified as described by Parkar A.A. *et al*, (2000), Protein Expression and Purification, 20:152. The purified enzyme can be used to monitor inhibitors of activity as follows: MMP19 (40 ng/ml final concentration) is incubated for 120 minutes at 35 °C with the synthetic substrate Mca-Pro-Leu-Ala-Nva-Dpa-Ala-Arg-NH_2 (5 μM) in assay buffer (0.1M "Tris-HCl" (trade mark) buffer, pH 7.3 containing 0.1M NaCl, 20mM $CaCl_2$, 0.020 mM ZnCl and 0.05% (w/v) "Brij 35" (trade mark) detergent) in the presence (5 concentrations) or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 320 nm and λem 405 nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

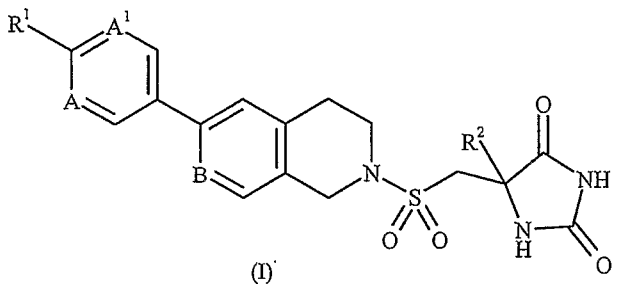
The following table shows data for a representative selection of the compounds of the present invention.

Table

Compound	hMMP12 IC_{50} (nM)	hMMP9 IC_{50} (nM)	hMMP14 IC_{50} (nM)
Example 1	10.4	29.3	> 10000
Example 2	1.4	3.5	415
Example 5	7	8.3	1990

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof



(I)

wherein

R^1 represents H, halogen, CF_3 or CH_2CN;

R^2 represents C1 to 3 alkyl; and

A, A^1 and B each independently represent CH or N;

2. A compound according to Claim 1, wherein R^1 represents chloro.

3. A compound according to Claim 1, wherein R^1 represents CF_3.

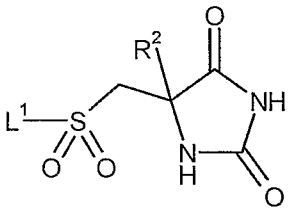
4. A compound according to any one of Claims 1 to 3, wherein R^2 represents methyl or ethyl.

5. A compound according to any one of Claims 1 to 4, wherein A and A^1 each represent N.

6. A compound according to Claim 1 which is selected from the group consisting of:
(5*S*)-5-methyl-5-({[6-[2-(trifluoromethyl)pyrimidin-5-yl]-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)imidazolidine-2,4-dione;
(5*S*)-5-({[6-(4-chlorophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione;
{4-[2-({[(4*S*)-4-methyl-2,5-dioxoimidazolidin-4-yl]methyl}sulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]phenyl}acetonitrile;
(5*S*)-5-methyl-5-{[(6-pyridin-3-yl-3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl]methyl}imidazolidine-2,4-dione;
(5*S*)-5-({[6-(4-chlorophenyl)-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl]sulfonyl}methyl)-5-methylimidazolidine-2,4-dione;
and pharmaceutically acceptable salts thereof.

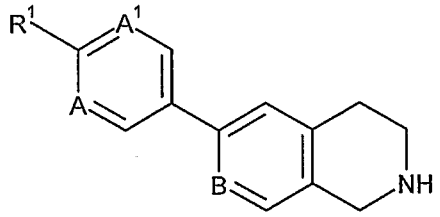
7. A process for the preparation of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof which comprises:

a) reaction of a compound of formula (II)



(II)

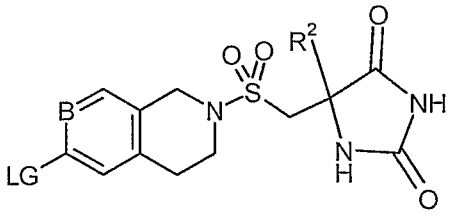
wherein R^2 is as defined in formula (I) and L^1 represents a leaving group, with a compound of formula (III) (or a salt thereof)



(III)

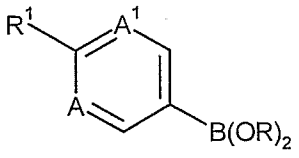
wherein R^1, A, A^1 and B are as defined in formula (I); or

b) reaction of a compound of formula (V)



(V)

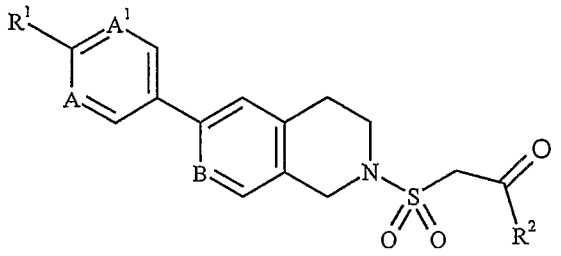
wherein R^2 and B are as defined in formula (I) and LG is a leaving group; with a boronic acid derivative of formula (XII)



(XII)

wherein R^1, A and A^1 are as defined in formula (I); or

c) reaction of a compound of formula (IX)



(IX)

wherein R^1, R^2, A, A^1 and B are as defined in formula (I); with ammonium carbonate and potassium cyanide;

and optionally thereafter forming a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 6 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A process for the preparation of a pharmaceutical composition as claimed in claim 8 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 6 with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 6 for use in therapy.

11. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 6 in the manufacture of a medicament for use in the treatment of an obstructive airways disease.

12. Use according to claim 11, wherein the obstructive airways disease is asthma or chronic obstructive pulmonary disease.

13. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 6 in the manufacture of a medicament for use in the treatment of rheumatoid arthritis, osteoarthritis, atherosclerosis, cancer or multiple sclerosis.

14. A method of treating a disease or condition mediated by MMP12 and/or MMP9 which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 6.

15. A method of treating an obstructive airways disease which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 6.