COMPOUNDS

The present invention relates to compounds useful in the inhibition of metalloproteinases and in particular to pharmaceutical compositions comprising them, as well as their use.

The compounds of this invention are inhibitors of one or more metalloproteinase enzymes and are particularly effective as inhibitors of TACE (TNFα Converting Enzyme). 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 (MMP) 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 biologically 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 disease conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these disease 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 and 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; and extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atheroscelerosis.

A number of metalloproteinase inhibitors are known; different classes of compounds may have different degrees of potency and selectivity for inhibiting various metalloproteinases. We have discovered a class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting TACE. The compounds of this invention have beneficial potency and/or pharmacokinetic properties.

TACE (also known as ADAM17) which has been isolated and cloned [R.A. Black *et al.* (1997) Nature 385:729-733; M.L. Moss *et al.* (1997) Nature 385:733-736] is a member of the admalysin family of metalloproteins. TACE has been shown to be responsible for the cleavage of pro-TNFα, a 26kDa membrane bound protein to release 17kDa biologically active soluble TNFα. [Schlondorff *et al.* (2000) Biochem. J. 347: 131-138]. TACE mRNA is found in most tissues, however TNFα is produced primarily by activated monocytes, macrophages and T lymphocytes. TNFα has been implicated in a wide range of pro-inflammatory biological processes including induction of adhesion molecules and chemokines to promote cell trafficking, induction of matrix destroying enzymes, activation of fibroblasts to produce prostaglandins and activation of the immune system [Aggarwal *et al* (1996) Eur. Cytokine Netw. 7: 93-124]. Clinical use of the anti-TNF biologicals has shown TNFα to play an important role in a range of inflammatory diseases including rheumatoid arthritis, Crohn's disease and psoriasis [Onrust *et al* (1998) Biodrugs 10: 397-422, Jarvis et al (1999) Drugs 57:945-964]. TACE activity has also been implicated in the shedding of other membrane bound proteins including TGFα, p75 & p55 TNF receptors, L-selectin and amyloid precursor protein [Black (2002) Int. J. Biochem. Cell Biol. 34: 1-5]. The biology of TACE inhibition has recently been reviewed and shows TACE to have a central role in TNFα production and

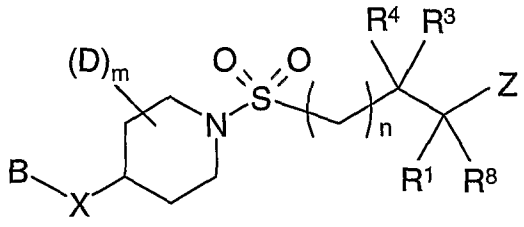
selective TACE inhibitors to have equal, and possibly greater, efficacy in the collagen induced arthritis model of RA than strategies that directly neutralise TNFα [Newton et al (2001) Ann. Rheum. Dis. 60: iii25-iii32].

A TACE inhibitor might therefore be expected to show efficacy in all disease where TNFα has been implicated including, but not limited to, inflammatory diseases including rheumatoid arthritis and psoriasis, autoimmune diseases, allergic/atopic diseases, transplant rejection and graft versus host disease, cardiovascular disease, reperfusion injury, malignancy.

Compounds that inhibit matrix metalloproteinases are already known in the art. WO 00/12477 discloses hydroxamic acids and carboxylic acid derivatives that are inhibitors of matrix metalloproteinases; WO 00/12478 discloses arylpiperazines that are useful in the inhibition of matrix metalloproteinase and are of particular interest as regards the inhibition of MMP13 and MMP9; and WO 01/87870 discloses hydroxamic acid derivatives which are inhibitors of matrix metalloproteinases including ADAM or ADAM-TS enzymes.

Surprisingly we have found a series of sulphonylpiperidine compounds comprising an alkenyl or alkynyl substituents which have metalloproteinase inhibitory activity, and are in particular, inhibitors of TACE (ADAM17).

According to one aspect of the present invention there is provided a compound of formula (1):



formula (1)

wherein Z is selected from $-CONR^{15}OH$ and $-N(OH)CHO$;

R^{15} is hydrogen or C_{1-3}alkyl;

wherein R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{17}), aryl (optionally substituted by one or more R^{17}),

heteroaryl (optionally substituted by one or more R^{17}), heterocyclyl, C_{1-4}alkoxycarbonyl, –OR^5, –SR^2, –SOR^2, –SO_2R^2, –COR^2, –CO_2R^5, –$CONR^5R^6$, –$NR^{16}COR^5$, –$SO_2NR^5R^6$ and –$NR^{16}SO_2R^2$;

R^{16} is hydrogen or C_{1-3}alkyl;

R^{17} is selected from halo, C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{1-6}alkoxy;

R^2 is group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^5 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^6 is hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

or R^5 and R^6 together with the nitrogen to which they are attached form a heterocyclic 4- to 7-membered ring;

wherein R^8 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy and C_{1-4}alkyl;

or R^1 and R^8 together form a carbocyclic or saturated heterocyclic 3- to 6-membered ring;

wherein R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocyclyl, aryl or heteroaryl;

wherein n is 0 or 1;

wherein m is 0 or 1;

wherein D is hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl or fluoro;

wherein X is $–(CR^9R^{10})–Q–(CR^{11}R^{12})_u–$ where u is 0 or 1;

Q is O, S, SO or SO_2;

R^9, R^{10}, $R^{11}$and R^{12} are independently selected from hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

wherein B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally independently substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heterocyclyl whereby the group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, –$CONHR^{13}$, –$CONHR^{13}R^{14}$, –SO_2R^{13}, –SO_2NHR^{13}, –$SO_2NR^{13}R^{14}$, –$NHSO_2R^{13}$, C_{1-4}alkyl and C_{1-4}alkoxy;

R^{13} and R^{14} are independently hydrogen, C_{1-4}alkyl or C_{3-5}cycloalkyl;

or R^{13} and R^{14} together with the nitrogen to which they are attached form a heterocyclic 4 to 7-membered ring.

Another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pharmaceutically acceptable salt thereof.

It is to be understood that, insofar as certain of the compounds of formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon or sulphur atoms, the invention includes in its definition any such optically active or racemic form which possesses metalloproteinases inhibition activity and in particular TACE inhibition activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Compounds of formula (1) are therefore provided as enantiomers, diastereomers, geometric isomers and atropisomers.

Within the present invention it is to be understood that a compound of formula (1) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has metalloproteinases inhibition activity and in particular TACE inhibition activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have metalloproteinases inhibition activity and in particular TACE inhibition activity.

It is also to be understood that certain compounds of formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess metalloproteinases inhibition activity and in particular TACE inhibition activity.

The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include but are not limited to hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In addition where the compounds of formula (1) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine or tris-(2-hydroxyethyl)amine

The compounds of formula (1) may also be provided as *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (1) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example formyl, acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for

example ethoxycarbonyl; di-(C_{1-4})alkylcarbamoyl and *N*-(di-(C_{1-4})alkylaminoethyl)-*N*-(C_{1-4})alkylcarbamoyl (to give carbamates); di-(C_{1-4})alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, (C_{1-4})alkylaminomethyl and di-((C_{1-4})alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting *in vivo* hydrolysable esters include, for example, $R^AC(O)O(C_{1-6})$alkyl-CO-, wherein R^A is for example, benzyloxy-(C_{1-4})alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(C_{1-4})piperazino-(C_{1-4})alkyl, piperazino-(C_{1-4})alkyl and morpholino-(C_{1-4})alkyl.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *tert*-butyl are specific for the branched chain version only. For example, "C_{1-3}alkyl" includes methyl, ethyl, propyl and isopropyl, examples of "C_{1-4}alkyl" include the examples of "C_{1-3}alkyl", butyl and *tert*-butyl and examples of "C_{1-6}alkyl" include the examples of "C_{1-4}alkyl"and additionally pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. Examples of "C_{1-20}alkyl" include the examples of "C_{1-6}alkyl" and other straight chain and branched alkyl groups. An analogous convention applies to other generic terms, for example "C_{2-4}alkenyl" includes vinyl, allyl and 1-propenyl and examples of "C_{2-6}alkenyl" include the examples of "C_{2-4}alkenyl" and additionally 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl. Examples of "C_{2-4}alkynyl" includes ethynyl, 1-propynyl and 2-propynyl and examples of "C_{2-6}alkynyl"include the examples of "C_{2-4}alkynyl" and additionally 3-butynyl, 2-pentynyl and 1-methylpent-2-ynyl.

The term "C_{3-6}cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "C_{3-7}cycloalkyl" includes "C_{3-6}cycloalkyl" and additionally cycloheptyl. The term "C_{3-10}cycloalkyl" includes "C_{3-7}cycloalkyl" and additionally cyclooctyl, cyclononyl and cyclodecyl.

"Heterocycloalkyl" is a monocyclic saturated 3- to 10-membered ring containing 1 or 2 heteroatoms selected from nitrogen, sulphur or oxygen wherein a ring nitrogen or sulphur may be oxidised to the N-oxide or S-oxide(s).

"C_{5-7}cycloalkenyl" is a monocyclic 5 to 7-membered ring containing 1, 2 or 3 double bonds. Examples are cyclopentenyl and cyclohexenyl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

Examples of "C_{1-4}alkoxy" include methoxy, ethoxy, propoxy and isopropoxy. Examples of "C_{1-6}alkoxy" include the examples of "C_{1-4}alkoxy" and additionally pentyloxy, 1-ethylpropoxy and hexyloxy. Examples of "C_{1-4}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and isopropoxycarbonyl .

Examples of "aryl" are phenyl and naphthyl.

Examples of "arylC_{1-4}alkyl" are benzyl, phenylethyl, naphthylmethyl and naphthylethyl.

"Heteroaryl" is monocyclic or bicyclic aryl ring containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen where a ring nitrogen may be oxidised. Examples of heteroaryl are pyridyl, imidazolyl, quinolinyl, cinnolyl, pyrimidinyl, thienyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl and pyrazinyl. Preferably heteroaryl is pyridyl, imidazolyl, quinolinyl, pyrimidinyl, thienyl, pyrazolyl, thiazolyl, oxazolyl and isoxazolyl.

Examples of "heteroarylC_{1-4}alkyl" are pyridylmethyl, pyridylethyl, pyrimidinylethyl, pyrimidinylpropyl, quinolinylpropyl and oxazolylmethyl.

"Heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic or bicycylic ring containing 4 to 12 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-; a ring nitrogen or sulphur atom may be optionally oxidised to form the N-oxide or S-oxide(s); and a ring –NH may be optionally substituted by acetyl, formyl, methyl or mesyl. Examples and suitable values of the term "heterocyclyl" are piperidinyl, *N*-acetylpiperidinyl, *N*-methylpiperidinyl, *N*-formylpiperazinyl, *N*-mesylpiperazinyl, homopiperazinyl, piperazinyl, azetidinyl, oxetanyl, morpholinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl, pyranyl, dihydro-*2H*-pyranyl, tetrahydrofuranyl, 2,2-dimethyl-1,3-dioxolanyl and 3,4-dimethylenedioxybenzyl. Preferred values are 3,4-dihydro-*2H*-pyran-5-yl, tetrahydrofuran-2-yl, 2,2-dimethyl-1,3-dioxolan-2-yl and 3,4-dimethylenedioxybenzyl.

Heterocyclic rings are rings containing 1, 2 or 3 rings atoms selected nitrogen, oxygen and sulphur. "Heterocyclic 5 to 7-membered" rings are pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl, homopiperazinyl, thiomorpholinyl , thiopyranyl and morpholinyl.

"Heterocyclic 4 to 7-membered" rings include the examples of "heterocyclic 5 to 7-membered" and additionally azetidinyl.

"Saturated heterocyclic 3 to 6-membered" rings are oxiranyl, aziridinyl, thiirane azetidinyl, oxetanyl, thietanyl, tetrahydrothienyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-2*H*-pyranyl, tetrahydro-2*H*-thiopyranyl and piperidinyl and a ring nitrogen may be substituted by a group selected from formyl, acetyl and mesyl.

A "carbocyclic 3 to 6-membered" ring is a saturated, partially saturated or unsaturated ring containing 3 to 6 ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopent-3-enyl, cyclohexyl and cyclopent-2-enyl.

Where optional substituents are chosen from "one of more" groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. Preferably "one or more" means "1, 2 or 3" and this is particularly the case when the group or substituent is halo. "One or more" may also means "1 or 2".

Compounds of the present invention have been named with the aid of computer software (ACD/Name version 5.09).

Preferred values of Z, R^1, R^3, R^4, R^8, n, m, D, X and B are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one aspect of the present invention there is provided a compound of formula (1) as depicted above wherein Z is $-CONR^{15}OH$. In another aspec Z is –N(OH)CHO.

In one aspect of the invention R^{15} is hydrogen, methyl, ethyl or isopropyl. In another aspect R^{15} is hydrogen.

In one aspect of the invention R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-6}cycloalkyl (optionally substituted by R^{17}), aryl (optionally substituted by R^{17}), heteroaryl (optionally substituted by R^{17}), C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$, $-CONR^5R^6$, $-NR^{16}COR^5$, $-SO_2NR^5R^6$ and $-NR^{16}SO_2R^2$. In another aspect R^1 is hydrogen, C_{1-6}alkyl or aryl where C_{1-6}alkyl or aryl are optionally substituted by one or more substituents independently

selected from C_{1-4}alkyl, aryl (optionally substituted by R^{17}) and heteroaryl (optionally substituted by R^{17}). In a further aspect R^1 is aryl, C_{1-6}alkyl or C_{1-6}alkyl substituted by aryl or heteroaryl. In another aspect R^1 is methyl, ethyl, propyl, isobutyl or phenyl where each is optionally substituted by phenyl or pyrimidinyl. In yet another aspect R^1 is methyl, isobutyl, phenyl, 2-phenylethyl or 3-pyrimidin-2-ylpropyl. In a further aspect R^1 is methyl, phenyl, phenylethyl or pyrimidin-2-ylpropyl.

In one aspect of the invention R^{16} is hydrogen, methyl or ethyl. In another aspect R^{16} is methyl or ethyl. In another aspect R^{16} is hydrogen.

In one aspect of the invention R^{17} is halo or C_{1-4}alkyl. In another aspect R^{17} is fluoro, chloro, bromo or methyl. In another aspect R^{17} is fluoro or methyl.

In one aspect of the invention R^2 is a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo. In another aspect R^2 is a group selected from methyl, phenyl and benzyl where the group is optionally substituted by chloro. In one aspect of the invention R^2 is methyl.

In one aspect of the invention R^5 is hydrogen or a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo. In another aspect R^5 is hydrogen or a group selected from methyl, phenyl and benzyl where the group is optionally substituted by chloro.

In one aspect of the invention R^8 is hydrogen, methyl, ethyl, propyl or isopropyl. In another aspect R^8 is hydrogen.

In one aspect of the invention R^3 is hydrogen.

In one aspect of the invention R^4 is hydrogen.

In one aspect of the invention n is 0. In another aspect n is 1.

In one aspect of the invention m is 0. In another aspect m is 1.

In one aspect of the invention D is hydrogen, methyl or fluoro. In another aspect D is hydrogen.

In one aspect of the invention X is $-CR^9R^{10}-Q-$ or $-CR^9R^{10}-Q-CR^{11}R^{12}-$. In another aspect of the invention X is $-(CH_2)-Q-$ or $-(CH_2)-Q-(CH_2)-$. In a further aspect X is $-(CH_2)-O-$ or $-(CH_2)-O-(CH_2)-$.

In one aspect of the invention u is 1. In another aspect u is 0.

In one aspect of the invention Q is O.

In one aspect of the invention R^9 is hydrogen.

In one aspect of the invention R^{10} is hydrogen.

In one aspect of the invention R^{11} is hydrogen.

In one aspect of the invention R^{12} is hydrogen.

In one aspect of the invention B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally independently substituted by C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocycloalkyl. In another aspect B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally independently substituted by C_{1-4}alkyl, C_{3-6}cycloalkyl, or heterocycloalkyl. In a further aspect B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally independently substituted by C_{1-4}alkyl or aryl. In yet another aspect B is vinyl or ethynyl where each is optionally independently substituted by methyl, ethyl or phenyl. In yet a further aspect B is vinyl, ethynyl, prop-1-enyl, prop-1-ynyl, but-1-ynyl or 2-phenylvinyl. In a further aspect B is vinyl, ethynyl, prop-1-enyl, prop-1-ynyl or but-1-ynyl.

A preferred class of compound is of formula (1) wherein:

Z is –N(OH)CHO;

R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-6}cycloalkyl (optionally substituted by R^{17}), aryl (optionally substituted by R^{17}), heteroaryl (optionally substituted by R^{17}), C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$, $-CONR^5R^6$, $-NR^{16}COR^5$, $-SO_2NR^5R^6$ and $-NR^{16}SO_2R^2$;

R^{16} is hydrogen, methyl or phenyl;

R^{17} is halo or C_{1-4}alkyl;

R^2 is a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo;

R^5 is hydrogen or a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo;

R^8 is hydrogen, methyl, ethyl, propyl or isopropyl;

R^3 is hydrogen, methyl, ethyl or phenyl;

R^4 is hydrogen, methyl, ethyl or phenyl;

n is 0;

m is 1;

D is hydrogen, methyl or fluoro;

X is $-(CH_2)-O-$ or $-(CH_2)-O-(CH_2)-$; and

B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally independently substituted by C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocycloalkyl.

Another preferred class of compound is of formula (1) wherein:

Z is –N(OH)CHO;

R^1 is hydrogen, C_{1-6}alkyl or aryl where C_{1-6}alkyl or aryl are optionally substituted by one or more substituents independently selected from C_{1-4}alkyl, aryl (optionally substituted by R^{17}) and heteroaryl (optionally substituted by R^{17});

R^{17} is halo or C_{1-4}alkyl;

R^8 is hydrogen;

R^3 is hydrogen;

R^4 is hydrogen;

n is 0;

m is 1;

D is hydrogen, methyl or fluoro;

X is $-(CH_2)-O-$ or $-(CH_2)-O-(CH_2)-$; and

B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally independently substituted by C_{1-4}alkyl or aryl.

Another preferred class of compound is of formula (1) wherein:

Z is $-CONR^{15}OH$;

R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-6}cycloalkyl (optionally substituted by R^{17}), aryl (optionally substituted by R^{17}), heteroaryl (optionally substituted by R^{17}), C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$, $-CONR^5R^6$, $-NR^{16}COR^5$, $-SO_2NR^5R^6$ and $-NR^{16}SO_2R^2$;

R^{15} is hydrogen, methyl, ethyl or isopropyl;

R^{16} is hydrogen, methyl or phenyl;

R^{17} is halo or C_{1-4}alkyl;

R^2 is a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo;

R^5 is hydrogen or a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo;

R^8 is hydrogen, methyl, ethyl, propyl or isopropyl;

R^3 is hydrogen, methyl, ethyl or phenyl;

R^4 is hydrogen, methyl, ethyl or phenyl;

n is 0;

m is 1;

D is hydrogen, methyl or fluoro;

X is $-(CH_2)-O-$ or $-(CH_2)-O-(CH_2)-$; and

B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally independently substituted by C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocycloalkyl.

Another preferred class of compound is of formula (1) wherein:

Z is $-CONR^{15}OH$;

R^1 is hydrogen, C_{1-6}alkyl or aryl where C_{1-6}alkyl or aryl are optionally substituted by one or more substituents independently selected from C_{1-4}alkyl, aryl (optionally substituted by R^{17}) and heteroaryl (optionally substituted by R^{17});

R^{17} is halo or C_{1-4}alkyl;

R^{15} is hydrogen, methyl, ethyl or isopropyl;

R^8 is hydrogen;

R^3 is hydrogen;

R^4 is hydrogen;

n is 0;

m is 1;

D is hydrogen, methyl or fluoro;

X is $-(CH_2)-O-$ or $-(CH_2)-O-(CH_2)-$; and

B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally independently substituted by C_{1-4}alkyl or aryl.

Another preferred class of compound is of formula (1) wherein:

Z is $-CONR^{15}OH$ or $-N(OH)CHO$;

R^{15} is hydrogen;

R^1 is methyl, ethyl, propyl, isobutyl or phenyl where each is optionally substituted by phenyl or pyrimidinyl;

R^8 is hydrogen;

R^3 is hydrogen;

R^4 is hydrogen;

n is 0;

m is 1;

D is hydrogen;

X is $-(CH_2)-O-$ or $-(CH_2)-O-(CH_2)-$; and

B is vinyl or ethynyl where each is optionally independently substituted by methyl, ethyl or phenyl.

In another aspect of the invention, preferred compounds of the invention are any one of:

(1-phenyl-2-{[4-(prop-2-ynyloxy)piperidin-1-yl]sulphonyl}ethyl)hydroxyformamide;

2-{[4-(allyloxy)piperidin-1-yl]sulphonyl}-1-phenylethyl(hydroxy)formamide;

2-({4-[but-2-enyloxy]piperidin-1-yl}sulphonyl)-1-phenylethyl(hydroxy)formamide;

2-{[4-(but-2-ynyloxy)piperidin-1-yl]sulphonyl}-1-phenylethyl(hydroxy)formamide;

(2-{[4-(pent-2-ynyloxy)piperidin-1-yl]sulphonyl}-1-phenylethyl)hydroxyformamide;

1-({[4-(but-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-3-phenylpropyl(hydroxy)formamide;

2-{[4-(but-2-ynyloxy)piperidin-1-yl]sulphonyl}-1-methylethyl(hydroxy)formamide;

1-({[4-(but-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl(hydroxy)formamide;

1-[({4-[(but-2-ynyloxy)methyl]piperidin-1-yl}sulphonyl)methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide; and

2-({4-[(but-2-ynyloxy)methyl]piperidin-1-yl}sulphonyl)-1-methylethyl(hydroxy)formamide.

Further preferred compounds of the invention are any one of :

(R/S)-1-({[4-(but-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl(hydroxy)formamide;

(R/S)-1-[({4-[(but-2-ynyloxy)methyl]piperidin-1-yl}sulphonyl)methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide;

(R/S)-2-({4-[(but-2-ynyloxy)methyl]piperidin-1-yl}sulphonyl)-1-methylethyl(hydroxy)formamide;

2-(4-But-2-ynyloxymethylpiperidin-1-ylsulphonylmethyl)-4-methyl-pentanoic acid hydroxyamide;

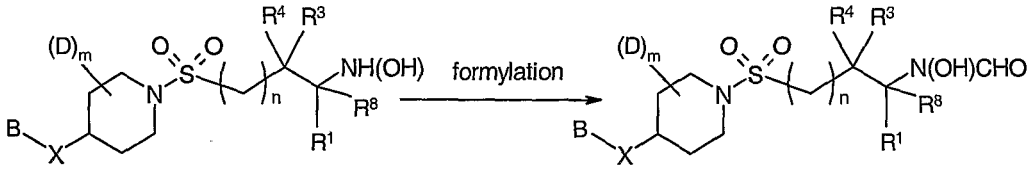
(R/S)-2-({4-[prop-2-enyloxy]piperidin-1-yl}sulphonyl)-1-phenylethyl(hydroxy)formamide;

(R/S)-2-({4-[but-2-enyloxy]piperidin-1-yl}sulphonyl)-1-phenylethyl(hydroxy)formamide; and

(R/S)-2-({4-[3-phenyl-prop-2-enyloxy]piperidin-1-yl}sulphonyl)-1-phenylethyl(hydroxy)formamide.

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof wherein Z is –N(OH)CHO, which process comprises the steps of:

a) converting a hydroxylamine of formula (2) into a compound of formula (1);



formula (2) formula (1)

Scheme 1

and thereafter if necessary:

i) converting a compound of formula (1) into another compound of formula (1);

ii) removing any protecting groups;

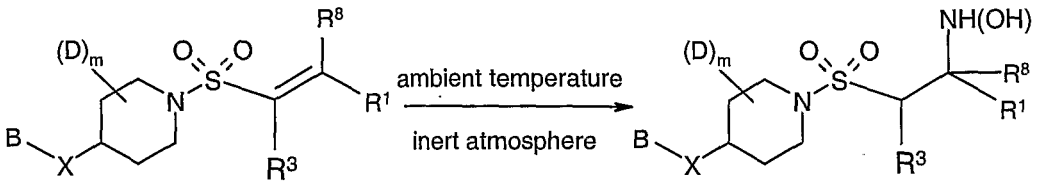
iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

Formylation may be suitably performed by adding a preformed mixture of acetic acid (8 equivalents) and formic acid (excess) to formula (2) in tetrahydrofuran or dichloromethane and stirring the solution for 15 hours at temperatures ranging from 0°C to room temperature followed by stirring in methanol. Alternatively a formylation method described in *J.Med.Chem.*, 2002, *45*, 219 using trifluoroethylformate can be used.

This process may further comprise a process for the preparation of a hydroxylamine of formula (2):

- when n is 0 and R^4 is hydrogen (indicated as a compound of formula (2')),which process comprises:

b) converting an alkene of formula (3) into a hydroxylamine of formula (2') ;



formula (3) formula (2')

Scheme 2

Suitable reagents for such a conversion include aqueous hydroxylamine in tetrahydrofuran under an argon atmosphere.

The alkene of formula (3) where R^8 is hydrogen can be prepared by the reaction of a compound of formula (4') with a compound of formula (5) under Wadsworth-Emmons or Peterson reaction conditions;

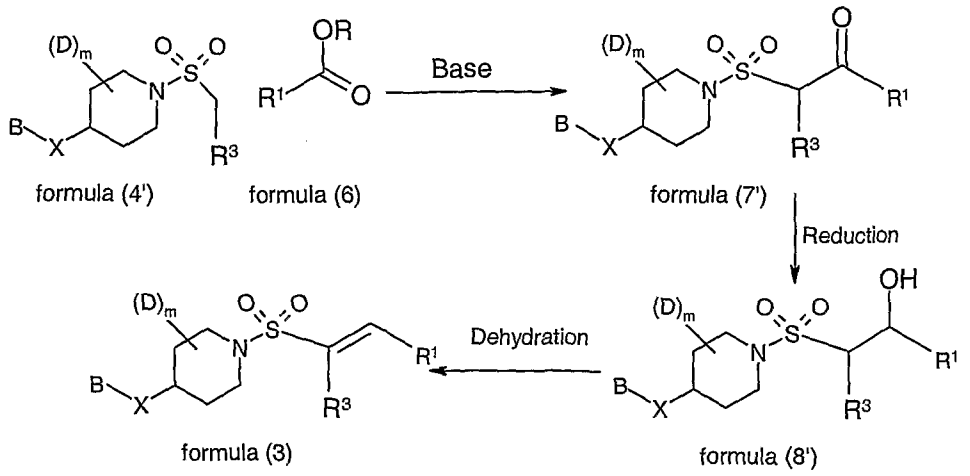


formula (4') formula (5) formula (3)

Scheme 3

Wadsworth-Emmons or Peterson reactions involve the forming of the anion of formula (4') with 2 equivalents of lithium bis(trimethylsilyl)amide, sodium hydride or lithium diisopropylamide in tetrahydrofuran at temperatures of –78°C to 0°C and reacting this with 1 equivalent of diethylchlorophosphate (Wadsworth Emmons) or 1 equivalent of trimethylsilyl chloride (Peterson). After 1 hour an aldehyde (1.1 equivalent) in tetrahydrofuran is added to the resultant anion described and reacted at room temperature over 15 hours.

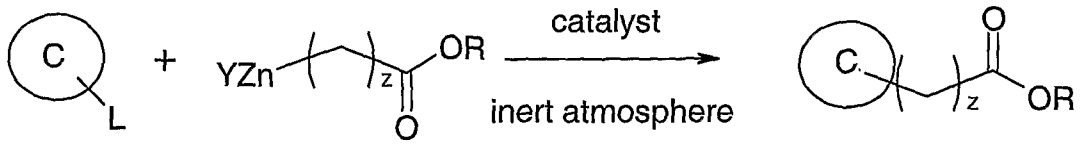
The alkene of formula (3) where R^8 is hydrogen can also be prepared by the reaction of a compound of formula (4') with a compound of formula (6) as illustrated by scheme 4;



Scheme 4

Suitable bases include lithium bis(trimethylsilyl)amide, sodium hydride or lithium diisopropylamide in tetrahydrofuran at temperatures of –78°C to 0°C to form the anion. Suitable reducing agents for the reduction step include sodium borohydride in ethanol or borane-dimethylsulphide complex or borane- tetrahydrofuran complex in tetrahydrofuran at room temperature. Suitable dehydration reagents for the dehydration step include methanesulphonyl chloride or tosyl chloride and triethylamine in dichloromethane at room temperature.

The present invention provides a process for the preparation of a compound of formula (6) wherein R^1 is C_{1-6}alkyl substituted by aryl or heteroaryl where the aryl and heteroaryl groups are optionally substituted by one or more R^{17}. Such a process is outlined in the scheme below:



wherein C is aryl or heteroaryl each being optionally substituted by one or more R^{17}; L is a suitable leaving group such as halo, tosyl, mesyl or triflate; Y is such that a zinc metal salt is formed i.e. Y is for example bromo or iodo; and z is an integer of 1 to 6 such that $(\ )_z$ represents C_{1-6}alkylene; it is to be understood that in this aspect of the invention R^1 is represented by  so that the C_{1-6}alkyl group represented by $(\ )_z$ may be a straight or branched chain. In another aspect of the invention $(\ )_z$ may represent C_{1-20}alkyl.

The reaction is performed under an inert atmosphere, which ensures consistent catalytic activity and in a non-protic solvent such as tetrahydrofuran. Suitable catalysts include nickel based and palladium (0) based catalysts. Preferable a palladium (0) based catalyst is used. The palladium (0) based catalyst may be generated from palladium (II) based compounds when used in conjunction with a promoter such as triphenylphosphine.

A specific example of a compound of formula (6) is ethyl 4-(pyrimidin-2-yl)butanoate. This compound is formed by the reaction of 2-bromopyrimidine with 4-ethoxy-4-oxo-butylzinc bromide in the presence of bis(acetonitrile)palladium (II) chloride (2.5mmol) and triphenylphosphine in a non-protic solvent and under an inert atmosphere. The stoiciometric amount of zinc salt produced as a by-product can be removed from the reaction mixture by washing with an aqueous solution of ethylenediamine tetraacetic acid tetrasodium salt. Preferably the non-protic solvent is tetrahydrofuran. Preferably the inert atmosphere is a nitrogen atmosphere.

Alternatively a process for the preparation of a hydroxylamine of formula (2):

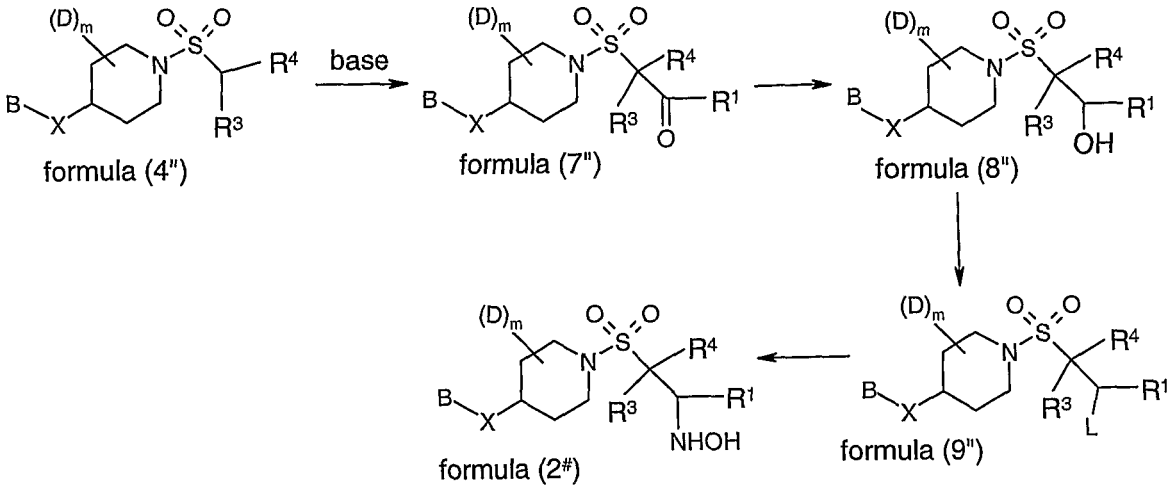
- when n is 0 (indicated as a compound of formula ($2^{\#}$)) may comprise;

c) i) reacting a compound of formula (4") (see scheme 13 for its preparation) with R^1COOR, R^1COCl or activated R^1COOR to yield a ketone of formula (7") (where R is C_{1-20}alkyl e.g. methyl, ethyl or arylC_{1-4}alkyl e.g. benzyl);

ii) reducing the ketone of formula (7") to yield an alcohol of formula (8");

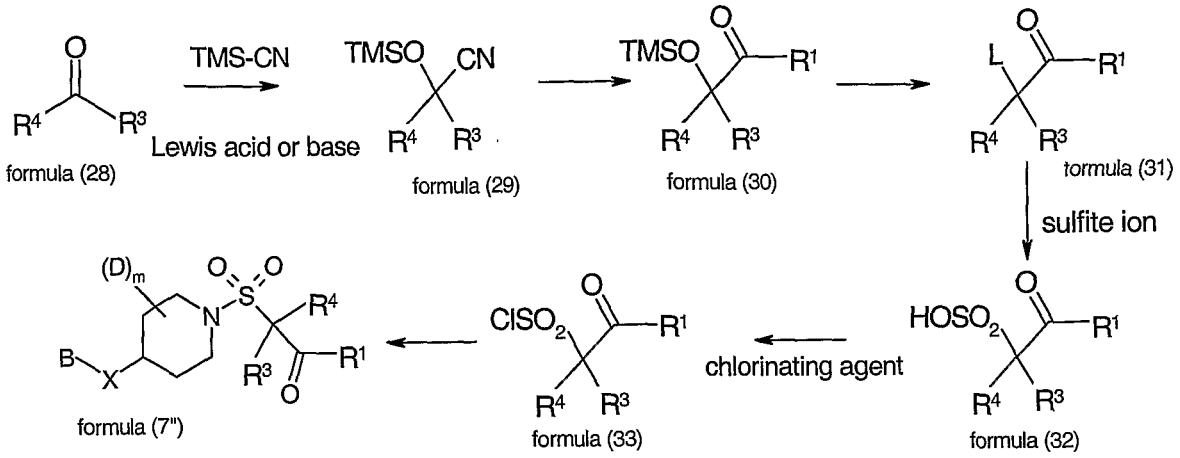
iii) converting –OH group of the alcohol of formula (8") into a leaving group (L) such as a halide, mesylate, tosylate etc. (see compound of formula (9");

iv) displacing the leaving group with aqueous hydroxylamine to yield a hydroxylamine of formula ($2^{\#}$);



Scheme 5

A ketone of formula (7") may additionally be prepared by the process illustrated in scheme 6:



Scheme 6

The silyl group present in the compound of formula (30) can be removed by tetrabutylammonium fluoride. Suitable leaving groups (L) are halo, mesyl and tosyl. A suitable chlorinating agent is $POCl_3$. A compound of formula (7") is prepared in the last stage by reacting the compound of formula (33) with the appropriate piperidine reagent.

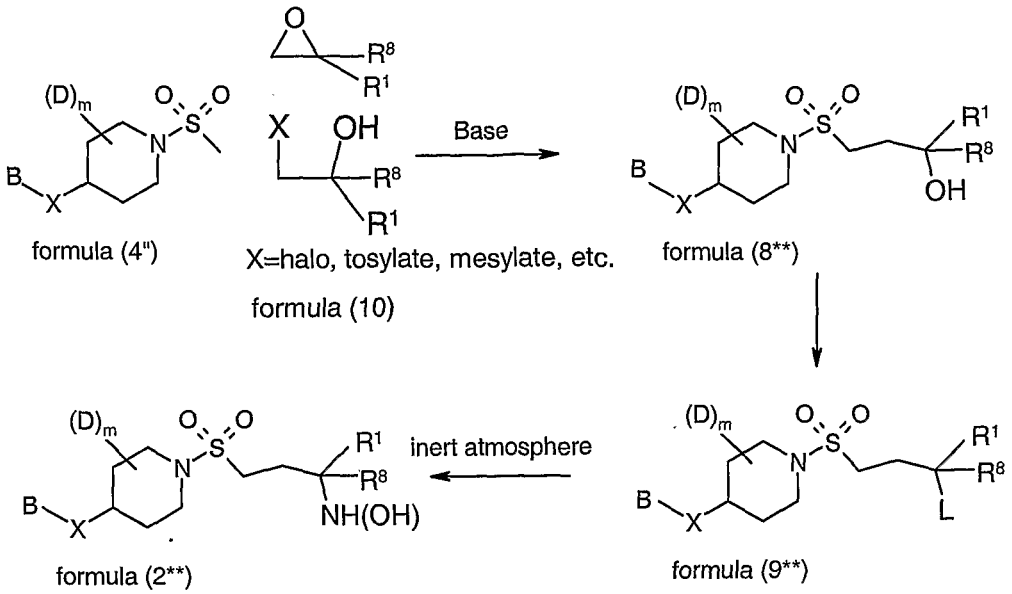
Or a process for the preparation of a hydroxylamine of formula (2):

- when n is 1 and R^3 and R^4 are both hydrogen (indicated as a compound of formula (2**)) may further comprise:

d) i) reacting a compound of formula (4") with a compound of formula (10) (either an epoxide or equivalent) to yield an alcohol of formula (8**);

ii) converting –OH group of the alcohol of formula (8**) into a leaving group such as a halide, mesylate, tosylate etc. (see compound of formula (9**);

iii) displacing the leaving group with aqueous hydroxylamine to yield a hydroxylamine of formula (2**);



Scheme 7

Suitable bases are lithium bis(trimethylsilyl)amide and lithium diisopropylamide at temperatures from –78°C to 0°C. Suitable leaving groups (L) are chloro, bromo, iodo, methanesulphonyl and tosyl and these would be formed from the alcohol by treatment with methanesulphonyl chloride and pyridine in dichloromethane (mesylate), tosyl chloride and pyridine in dichloromethane (tosylate), triphenylphosphine and carbon tetrabromide (bromo); the chloro, bromo and iodo derivatives could also be prepared from the mesylate or tosylate by addition of a suitable halide source, e.g. tetrabutylammonium iodide or sodium iodide or lithium chloride in a solvent such as acetone.

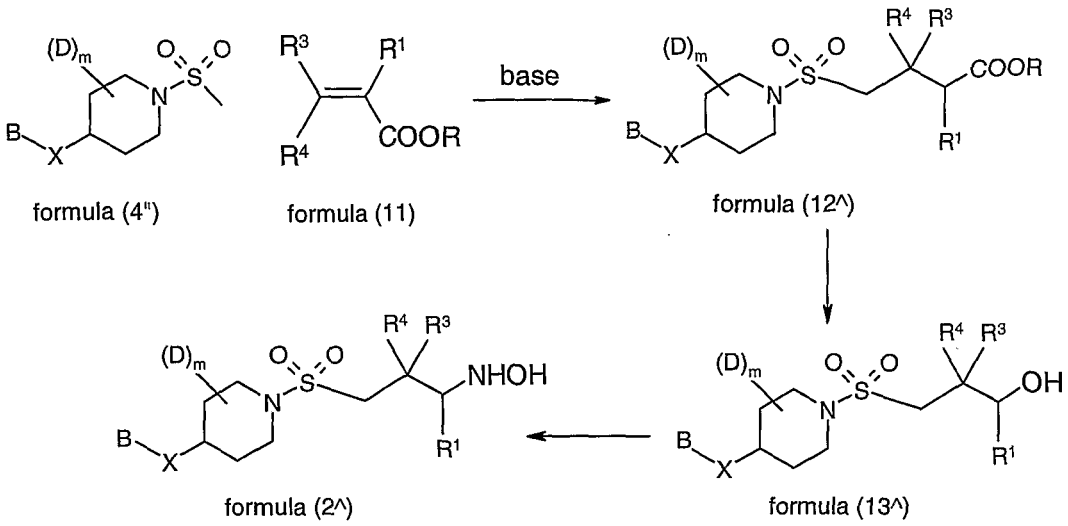
Or a process for the preparation of a hydroxylamine of formula (2):

- when n is 1 and R^8 is hydrogen, indicated as a compound of formula (2^), may further comprise:

e) i) reacting a compound of formula (4") with a compound of formula (11) to yield an ester of formula (12^);

ii) converting the ester of formula (12^) into an alcohol of formula (13^);

iii) displacing the –OH group with aqueous hydroxylamine to yield a hydroxylamine of formula (2^);

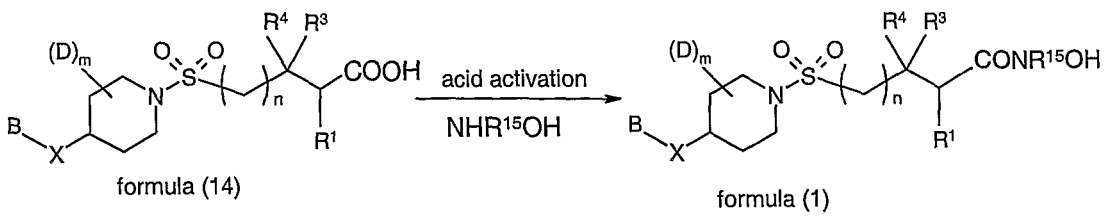


Scheme 8

The group –COOR of formula (12^) is representative of an ester wherein R may be C_{1-20} alkyl, e.g. methyl, ethyl or arylC_{1-4}alkyl, e.g. benzyl and B is a protecting group such as trimethylsilyl or tertiarybutyldimethylsilyl. Baeyer-Villiger reaction conditions such as a peracid e.g. *m*-CPBA (meta-chloroperbenzoic acid) in dichloromethane are suitable for the conversion of the ester group into the alcohol group. After the Baeyer-Villiger reaction, it will be necessary to remove the protecting group which is B in formula (12^) and replace it with a B group as defined in relation to formula (1) as illustrated herein. It may be appropriate to convert the alcohol group into a leaving group such as bromo, iodo, mesyl and tosyl, before displacement with aqueous hydroxylamine.

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof wherein Z is $-CONR^{15}OH$, which process comprises:

a) converting an acid of formula (14) into a compound of formula (1);



Scheme 9

and thereafter if necessary:

i) converting a compound of formula (1) into another compound of formula (1);

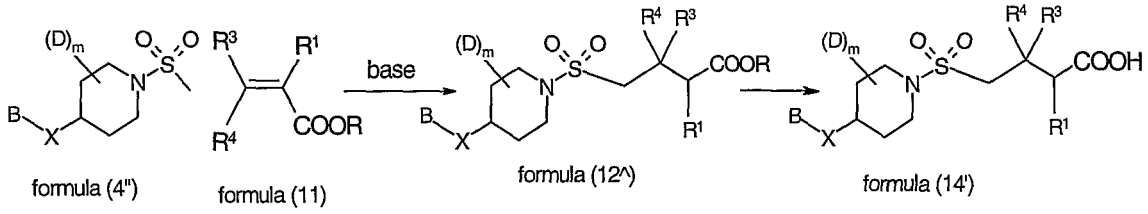
ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

The acid of formula (14) may be suitably activated by conversion to an acid halide, such as the acid chloride or to an activated ester using carbonyldiimidazole, a carbodiimide or a pentafluorophenyl ester. Alternatively when the acid of formula (14) is an ester e.g. the methyl or ethyl ester, it can be converted directly to a compound of formula (1) by reaction with $NHR^{15}OH$.

Also provided is a process for the preparation of an acid of formula (14) which process comprises;

b) reacting a compound of formula (4") with an alkene of formula (11) to yield an ester of formula (12^) which is hydrolysed to an acid of formula (14') where an acid of formula (14') is an acid of formula (14) wherein n is 1;

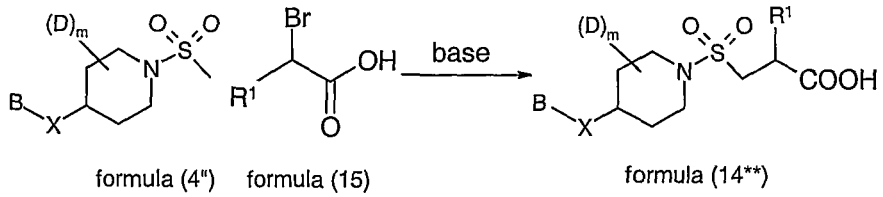


Scheme 10

Suitable bases able to deprotonate a compound of formula (4") are butyllithium, lithium diisopropylamide and lithium bis(trimethylsilyl)amide followed by the addition of a copper salt e.g. copper bromide-dimethylsulphide complex, copper iodide, in solvents such as dimethylsulphide, ether, tetrahydrofuran at temperatures from –78°C to room temperature.

Or a process for the preparation of an acid of formula (14) comprises;

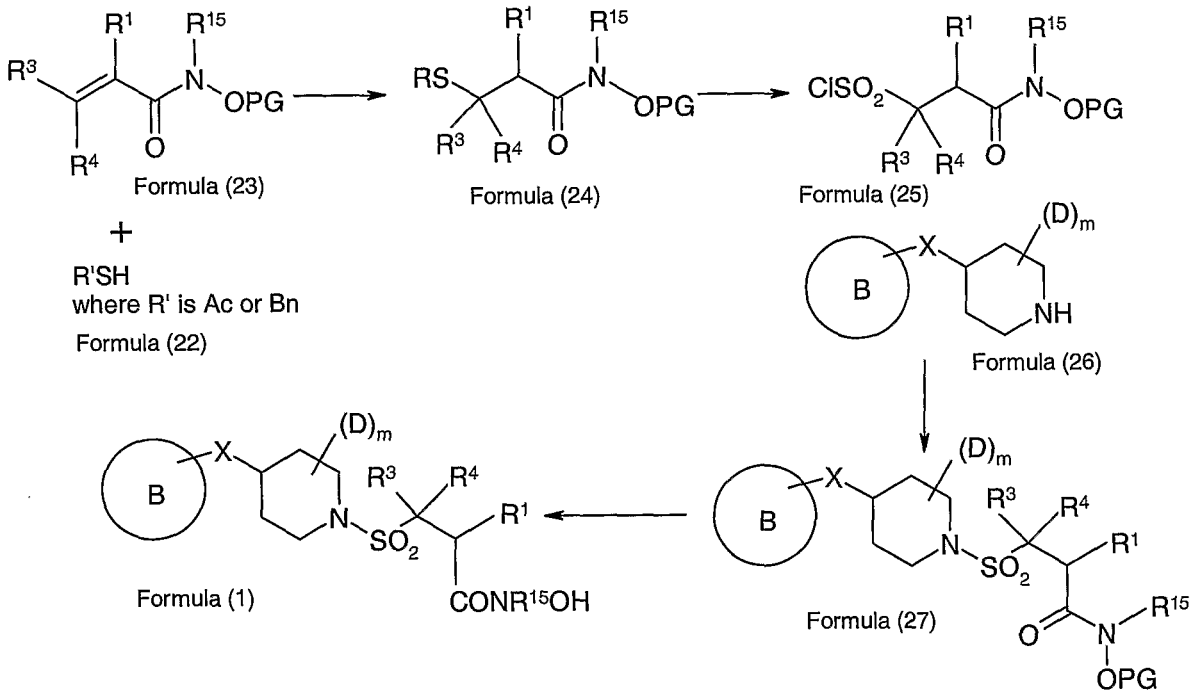
c) reacting a compound of formula (4") with a compound of formula (15) to yield an acid of formula (14**) which is an acid of formula (14) wherein n is 0, R^3 is hydrogen and R^4 is hydrogen;



Scheme 11

Suitable bases to deprotonate formula (4") include lithium bis(trimethylsilyl)amide, lithium diisopropylamide and sodium hydride in solvents such as tetrahydrofuran and ether at temperatures from –78°C to 0°C.

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof wherein Z is $-CONR^{15}OH$, R^8 is hydrogen and n is 0, which process comprises steps as outlined in scheme 12:



Scheme 12

The process of scheme 12 comprises the steps of:

a) reacting a thiol of formula (22) with an acrylate of formula (23) at temperatures of 0°C to 70°C to yield a thioether of formula (24);

b) oxidising the thioether of formula (24) to a sulphonyl chloride of formula (25) by bubbling chlorine gas onto a solution of the thioether in acetic acid at temperatures of 0°C to room temperature;

c) reacting the sulphonyl chloride of formula (25) with a piperidine of formula (26) under standard sulphonamide conditions (e.g. triethylamine in dichloromethane at temperatures from 0°C to 50°C) to yield a compound of formula (27);

d) removing the protecting group to yield a compound of formula (1.)

The protecting group (PG) may be 2,4-dimethoxybenzyl which can be removed with mild acid (see Tetrahedron Letters, 1998, 39(43), 7865). The process of scheme 12 may further comprise if necessary:

i) converting a compound of formula (1) into another compound of formula (1);

ii) removing any other protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

In another aspect of the invention, there is provided a process for the preparation of a compound of formula (4), formula (4') and formula (4") which process comprises;

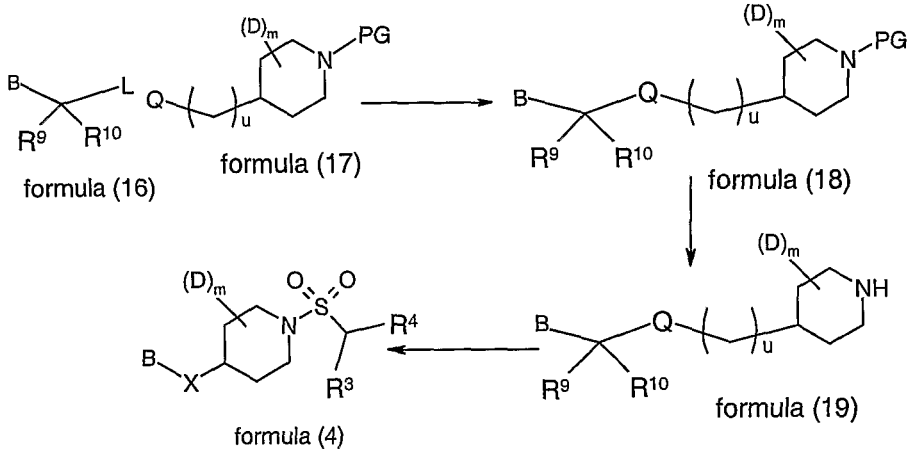
a) reacting a compound of formula (16) with a compound of formula (17) (wherein Q is O or S), in the presence of a base to deprotonate the compound of formula (17), to yield a compound of formula (18);

b) removing the protecting group (PG) from the compound of formula (18) to yield a compound of formula (19);.

c) reacting the compound of formula (19) with a suitable reagent to yield a compound of formula (4) wherein X is $-(CR^9R^{10})-Q-(CR^{11}R^{12})_u$; and

d) oxidising Q where Q is S as required.

When R^4 is hydrogen a compound of formula (4') is produced and when R^3 and R^4 are both hydrogen compound of formula (4") is produced



Scheme 13

Compounds of formula (4), formula (4') and formula (4") may also be prepared by a process which comprises;

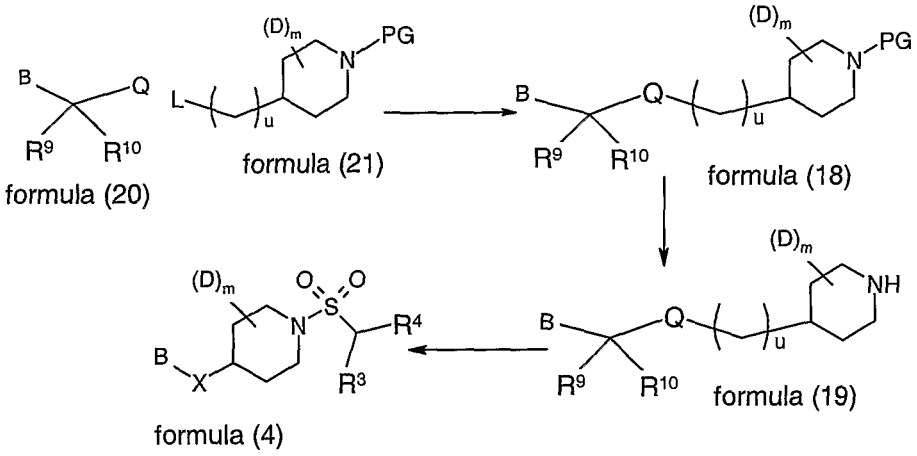
a) reacting a compound of formula (20) (wherein Q is O or S) with a compound of formula (21), in the presences of a base to yield a compound of formula (18);

b) removing the protecting group (PG) from the compound of formula (18) to yield a compound of formula (19);.

c) reacting the compound of formula (19) with a suitable reagent to yield a compound of formula (4) wherein X is $-(CR^9R^{10})-Q-(CR^{11}R^{12})_u$; and

d) oxidising Q where Q is S as required.

When R^4 is hydrogen a compound of formula (4') is produced and when R^3 and R^4 are both hydrogen compound of formula (4") is produced

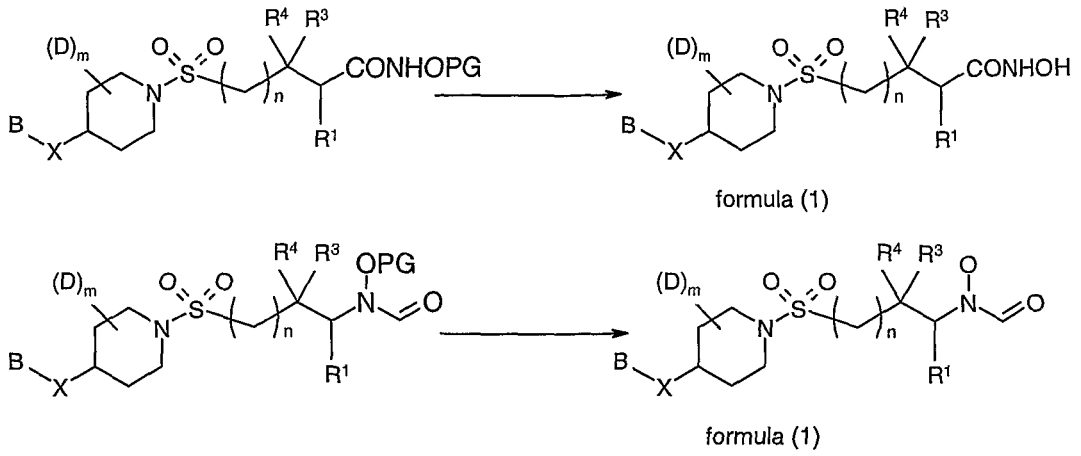


Scheme 14

In both schemes 13 and 14; L is a suitable leaving group such as halo (chloro, bromo, iodo), mesyl, tosyl; suitable bases to deprotonate compounds of formula (17) and formula (20) include sodium hydride, lithium diisopropylamide, butyllithium and lithium bis(trimethylsilyl)amide; suitable reaction conditions for a) are temperatures ranging from –78°C to 70°C and an aprotic solvent, e.g. tetrahydrofuran under argon; suitable protecting groups (PG) include Boc (t-butoxycarbonyl), CBz (carbonyloxybenzyl) groups and mesyl or another alkylsulphonyl. In the case where PG is alkylsulphonyl, reaction of formula (16) and (17) and of formula (20) and formula (21) directly produces a compound of formula (4). A compound of formula (18) can be converted to formula (19) by treatment with acid (Boc) boron trifluoride diethyl etherate in dichloromethane in the presence of dimethylsulphite (CBz). A compound of formula (19) can be converted to a compound of formula (4) by treatment with an alkylsulphonyl chloride in the presence of a base such as pyridine in a solvent such as dichloromethane.

A compound of formula (1) can be prepared by removal of a protecting group on the zinc binding group directly. The protecting group (PG) can be 2,4-dimethoxybenzyl which

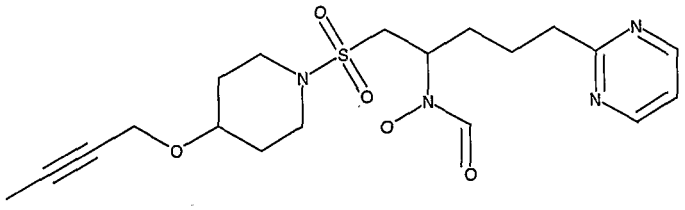
can be removed with mild acid (see Tetrahedron Letters, 1998, 39(43), 7865). The required protected hydroxamic acid or reverse hydroxamate can be obtained by using a suitably protected hydroxylamine earlier in the synthesis.



Scheme 15

As discussed herein compounds that inhibit metalloproteinases and in particular TACE, are of great importance and it is thus apparent that any intermediate (and process for it manufacture) involved in the manufacture of such a compound will be of commercial value.

One such metalloproteinase inhibitor and TACE inhibitor, disclosed herein, is (R/S)-1-({[4-(but-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl(hydroxy)formamide:



This compound can be made by a process that comprises the steps of :

a) reacting 4-hydroxypiperidine with methanesulphonyl chloride in the presence of a base to yield 4-hydroxy-1-(methanesulphonyl)piperidine;

b) adding a solution of 4-hydroxy-1-(methanesulphonyl)piperidine to sodium hydride, followed by addition of 1-bromobut-2-yne to yield 4-(but-2-ynyloxy)-1-methanesulphonylpiperidine;

c) adding lithium bis(trimethylsilyl)amide to a solution of 4-(but-2-ynyloxy)-1-methanesulphonylpiperidine followed by ethyl 4-(pyrimidin-2-yl)butanoate to yield 1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pentan-2-one;

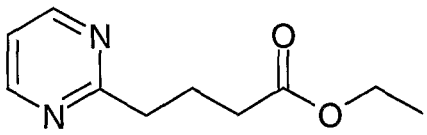
d) reducing 1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pentan-2-one with a reagent such as sodium borohydride to yield (R/S)-1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pentan-2-ol;

e) dehydrating (R/S)-1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pentan-2-ol using methanesulphonyl chloride to yield E-1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pent-1-ene;

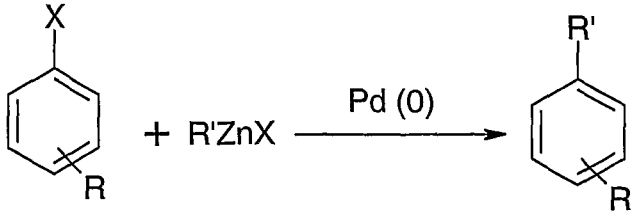
f) reacting a solution of E-1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pent-1-ene with hydroxylamine to yield (R/S)-[1-({[4-(4-but-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl]hydroxylamine; and

g) adding a mixture of acetic anhydride and formic acid to a solution of (R/S)-[1-({[4-(4-but-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl]hydroxylamine to yield (R/S)-1-({[4-(but-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl(hydroxy)formamide.

A further embodiment of the invention thus provides ethyl 4-(pyrimidin-2-yl)butanoate, which is an intermediate used in the synthesis of (R/S)-1-({[4-(but-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl(hydroxy)formamide (see part c) of the above process).



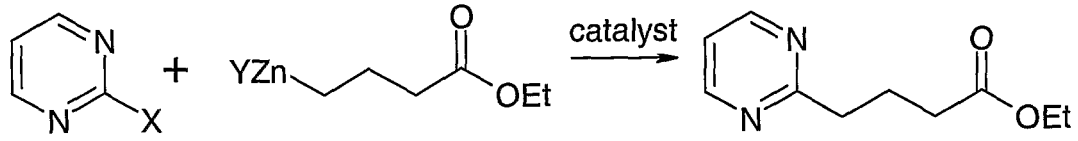
Also provided is a process for the preparation of ethyl 4-(pyrimidin-2-yl)butanoate. This process uses Negishi coupling. Negishi coupling involves the cross coupling of an organozinc reagent with an aryl halide to form carbon-carbon bonds (Baba S., Negishi E., *J. Am. Chem. Soc.*, **1976**, 98, 6729-6731; Negishi E., King A., Okukado N., *J Org, Chem.*, **1977**, 42, 1821-1823).



Negishi coupling has several advantages over other coupling methods that employ organometal reagents other than organozinc reagents. Firstly it allows the direct coupling of

an sp^3 centre to an aryl group. Secondly, the organozinc reagent can be easily prepared from the corresponding organohalide, and finally the mild nature of organozinc reagents means that sensitive functional groups such as esters, ketones, nitriles and halides can be tolerated. For further details of Negishi coupling and other transition-metal catalysed cross coupling reactions, the reader is directed to Yamamoto Y., Negishi E., *J. Organomet. Chem.*, **1999**, 576, 1-317 and references cited therein and Tsuji J., Palladium reagents and Catalysts, Wiley, New York (1995) and references cited therein.

This process of the invention comprises the reaction of a 2-halopyrimidine, 2-tosylpyrimidine, 2-pyrimidinyl triflate or 2-pyrimidinyl mesylate with 4-ethoxy-4-oxo-butylzinc bromide or 4-ethoxy-4-oxo-butylzinc iodide in the presence of a catalyst;



wherein X is halo, triflate or mesylate and Y is bromide or iodide.

The process may further comprise the step of removing the zinc salt by-products by washing the crude resultant product with an aqueous solution of the tetrasodium salt of ethylenediamine tetraacetic acid. This step removes >99.9% of the zinc salt by-products.

It is preferred that the reaction is performed under an inert atmosphere to ensures consistent catalytic activity. It is also preferred that the reaction is performed in a non-protic solvent. Preferably the non-protic solvent is tetrahydrofuran, diethyl ether or dimethoxyethylglycol dimethylether and more preferably the solvent is tetrahydrofuran. Preferably the inert atmosphere is a nitrogen atmosphere.

Suitable catalysts for use in the process include nickel based and palladium (0) based catalysts. However it is preferred that a palladium (0) based catalyst is used. Preferably the palladium (0) based catalyst is generated by the action of a promoter such as triphenylphosphine on a palladium (II) based compound. More preferably the catalyst is generated from bis(acetonitrile) palladium (II) dichloride and triphenylphosphine.

A further aspect of the invention is the use of a pro catalyst comprising bis(acetonitrile) palladium (II) dichloride and triphenylphosphine in a Negishi coupling reaction.

2-Halopyrimidine, 2-tosylpyrimidine, 2-pyrimidinyl triflate and 2-pyrimidinyl mesylate are readily available or can be easily derived made by the skilled person from the art.

4-Ethoxy-4-oxo-butylzinc bromide is readily available and can, for example, be purchased from Rieke Metals Inc. who are known to use a reduction of zinc (II) cyanide with lithium and naphthalene for the preparation of their reagents (WO 93/15086). Alternatively 4-ethoxy-4-oxo-butylzinc bromide can be prepared from 4-bromobutyrate with diethylzinc and a manganese (II)/copper (I) catalyst system in DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) (I. Klement, P Knochel, *Tetrahedron Lett.*, 1994, **35**, 1177 – the contents of which are incorporated herein by reference). 4-Ethoxy-4-oxo-butylzinc iodide can be similarly prepared but may also be made by the use of a zinc/copper couple activation reaction with chlorotrimethylsilane/1,2-dibromoethane (P. Knochel, M.C.P. Yeh, S.C. Berk, J. Talbert; *J. Org. Chem.*, 1988, **53**, 2392) or the use of sonication (E. Erdik, *Tetrahedron*, 1987, **43**, 2203)

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard

practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid such as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possesses metalloproteinases inhibitory activity, and in particular TACE inhibitory activity. This property may be assessed, for example, using the procedure set out below.

Isolated Enzyme Assays

Matrix Metalloproteinase family including for example MMP13.

Recombinant human proMMP13 may be expressed and purified as described by Knauper *et al.* [V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550 (1996)]. The purified enzyme can be used to monitor inhibitors of activity as follows: purified proMMP13 is activated using 1mM amino phenyl mercuric acid (APMA), 20 hours at 21°C; the activated MMP13 (11.25ng per assay) is incubated for 4-5 hours at 35°C in assay buffer (0.1M Tris-HCl, pH 7.5 containing 0.1M NaCl, 20mM $CaCl_2$, 0.02 mM ZnCl and 0.05% (w/v) Brij 35 using the synthetic substrate 7-methoxycoumarin-4-yl)acetyl.Pro.Leu.Gly.Leu.N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl.Ala.Arg.NH_2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. 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 similar protocol can be used for other expressed and purified pro MMPs using substrates and buffers conditions optimal for the particular MMP, for instance as described in C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

Adamalysin family including for example TNF convertase

The ability of the compounds to inhibit proTNFα convertase enzyme (TACE) may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) Nature 370:218-220. The purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1%

(w/v) Triton X-100 and 2mM $CaCl_2$), at 26°C for 4 hours. The amount of inhibition is determined as for MMP13 except λex 485nm and λem 538nm were used. The substrate was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser^1 and Pro^2 were double-coupled. The following side chain protection strategy was employed; Ser^1(But), Gln^5(Trityl), $Arg^{8,12}$(Pmc or Pbf), $Ser^{9,10,11}$(Trityl), Cys^{13}(Trityl). Following assembly, the N-terminal Fmoc-protecting group was removed by treating the Fmoc-peptidyl-resin with in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2 hours at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) Anal Biochem. 108:156-161) which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF]. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

The compounds of the invention have been found to be active against TACE at 0.1nM to 50μM, and in particular 10μM of compound 1 gave 72% inhibition, and 10μM of compound 3 gave 72% inhibition.

Natural Substrates

The activity of the compounds of the invention as inhibitors of aggrecan degradation may be assayed using methods for example based on the disclosures of E. C. Arner *et al.*, (1998) Osteoarthritis and Cartilage 6:214-228; (1999) Journal of Biological Chemistry, 274 (10), 6594-6601 and the antibodies described therein. The potency of compounds to act as inhibitors against collagenases can be determined as described by T. Cawston and A. Barrett (1979) Anal. Biochem. 99:340-345.

Inhibition of metalloproteinase activity in cell/tissue based activity

Test as an agent to inhibit membrane sheddases such as TNF convertase

The ability of the compounds of this invention to inhibit the cellular processing of TNFα production may be assessed in THP-1 cells using an ELISA to detect released TNF essentially as described K. M. Mohler *et al.*, (1994) Nature 370:218-220. In a similar fashion the processing or shedding of other membrane molecules such as those described in N. M. Hooper *et al.*, (1997) Biochem. J. 321:265-279 may be tested using appropriate cell lines and with suitable antibodies to detect the shed protein.

Test as an agent to inhibit cell based invasion

The ability of the compound of this invention to inhibit the migration of cells in an invasion assay may be determined as described in A. Albini *et al.*, (1987) Cancer Research 47:3239-3245.

Test as an agent to inhibit whole blood TNF sheddase activity

The ability of the compounds of this invention to inhibit TNFα production is assessed in a human whole blood assay where LPS is used to stimulate the release of TNFα. 160μl of heparinized (10Units/ml) human blood obtained from volunteers, was added to the plate and incubated with 20μl of test compound (duplicates), in RPMI1640 + bicarbonate, penicillin, streptomycin, glutamine and 1% DMSO, for 30 minutes at 37°C in a humidified (5%CO_2/95%air) incubator, prior to addition of 20μl LPS (E. coli. 0111:B4; final concentration 10μg/ml). Each assay includes controls of neat blood incubated with medium alone or LPS (6 wells/plate of each). The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged (2000rpm for 10 min; 4°C), plasma harvested (50-100μl) and stored in 96 well plates at -70°C before subsequent analysis for TNFα concentration by ELISA.

Test as an agent to inhibit in vitro cartilage degradation

The ability of the compounds of this invention to inhibit the degradation of the aggrecan or collagen components of cartilage can be assessed essentially as described by K. M. Bottomley *et al.*, (1997) Biochem J. 323:483-488.

In vivo assessment

Test as an anti-TNF agent

The ability of the compounds of this invention as *in vivo* TNFα inhibitors is assessed in the rat. Briefly, groups of female Wistar Alderley Park (AP) rats (90-100g) are dosed with

compound (5 rats) or drug vehicle (5 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.) 1 hour prior to lipopolysaccharide (LPS) challenge (30μg/rat i.v.). Sixty minutes following LPS challenge rats are anaesthetised and a terminal blood sample taken via the posterior vena cavae. Blood is allowed to clot at room temperature for 2hours and serum samples obtained. These are stored at –20°C for TNFα ELISA and compound concentration analysis.

Data analysis by dedicated software calculates for each compound/dose:

Percent inhibition of TNFα= Mean TNFα (Vehicle control) – Mean TNFα (Treated) X 100

Mean TNFα (Vehicle control)

Test as an anti-arthritic agent

Activity of a compound as an anti-arthritic is tested in the collagen-induced arthritis (CIA) as defined by D. E. Trentham *et al.*, (1977) J. Exp. Med. 146,:857. In this model acid soluble native type II collagen causes polyarthritis in rats when administered in Freunds incomplete adjuvant. Similar conditions can be used to induce arthritis in mice and primates.

Pharmaceutical Compositions

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The composition may also be in a form suitable for inhalation.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease

condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

Therefore in a further aspect of the present invention there is provided a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treatment of a warm-blooded animal such as man by therapy.

Also provided is a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treating a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNFα.

Further provided is a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treating inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use in a method of treating rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis. A compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use in a method of treating a respiratory disorder such as asthma or COPD.

According to an additional aspect of the invention there is provided a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

Also provided is a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNFα.

Further provided is a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy.

in a warm-blooded animal such as man. In particular a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use as a medicament in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis. A compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is also provided for use as a medicament in the treatment of a respiratory disorder such as asthma or COPD.

According to another aspect of the invention there is provided the use of a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNFα in a warm-blooded animal such as man.

Also provided is the use of a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular the use of a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided in the manufacture of a medicament in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis. The use of a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is also provided in the manufacture of a medicament in the treatment of a respiratory disorder such as asthma or COPD.

According to a further feature of this aspect of the invention there is provided a method of producing a metalloproteinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to a further feature of this aspect of the invention there is provided a method of producing a TACE inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating autoimmune disease, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

Also provided is a method of treating rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1). Further provided is a method of treating a respiratory disorder such as asthma or COPD in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

In addition to their use in therapeutic medicine, the compounds of formula (1) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc,

obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "Isolute™ SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industrial Estate, Ystrad Mynach, Hengoed, Mid Glamorgan, UK. Where Flashmaster II is referred to, this means a UV driven automated chromatography unit supplied by Jones;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$ and

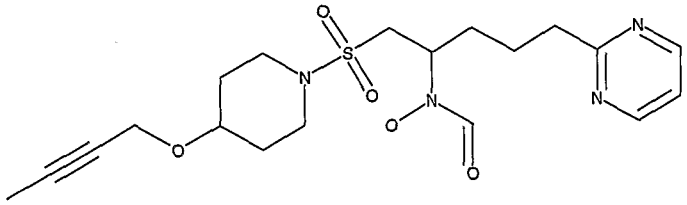
(xi) the following abbreviations are used:

DMSO	dimethyl sulphoxide;
DMF	*N*-dimethylformamide;

DCM	dichloromethane;
NMP	*N*-methylpyrrolidinone;
DIAD	Di-*iso*propylazodicarboxylate
LHMDS or LiHMDS	Lithium bis(trimethylsilyl)amide
MeOH	Methanol
RT	Room temperature
TFA	Trifluoroacetic acid
EtOH	ethanol
EtOAc	ethyl acetate.
EDTA	ethylenediaminetetraacetic acid
THF	tetrahydrofuran
TBDMS	tertiarybutyldimethylsilyl
DIPEA	diisopropylethylamine
MTBE	methyltertiarybutylether

EXAMPLE 1

(R/S)-1-({[4-(But-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl(hydroxy)formamide



To a stirred solution of (R/S)-[1-({[4-(4-but-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl]hydroxylamine (170mg, 0.43mmol) in THF (5.0ml), was added a preformed mixture of acetic anhydride (200µl, 2.1mmol) and formic acid (0.75ml). The mixture was stirred at RT for 23 hours. The solvents were removed by rotary evaporation, EtOAc (15ml) followed by saturated sodium hydrogen carbonate was added and the reaction mixture was stirred for 4 hours. The mixture was diluted with EtOAc (15ml) and washed with brine (10ml), dried (Na_2SO_4) and evaporated to give a colourless film. The aqueous layer was re-extracted with DCM (3x10ml), dried (Na_2SO_4) and combined with the previous product. This residue was purified by chromatography (Flashmaster II, eluent 0→10% MeOH/ DCM) to give a mixture. The mixture was redissolved in MeOH (5ml) and K_2CO_3 was

added. After 16h the solution was concentrated, partitioned between DCM and brine, the organic layer was dried (Na_2CO_3) and concentrated to give the title compound as a pure oil (84mg, 46%). NMR($CDCl_3$): 8.69 (d, 2H), 8.22 & 7.90 (br s, 1H), 7.3 (t, 1H), 4.1 (q, 2H), 3.58 (m, 1H), 3.3 (m, 4H), 3.02 (m, 2H), 2.83 (m, 2H), and 1.8-1.47 (m, 11H); MS: 425.

The starting material (R/S)-[1-({[4-(4-but-2-ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl]hydroxylamine was prepared as follows :

i) To solution of 4-hydroxypiperidine (20g, 198mmol) in 2M aqueous sodium hydroxide (350ml) was added methanesulphonyl chloride (25ml, 323mmol) over 10 minutes. The solution was stirred at ambient temperature for a further 1 hour. The reaction mixture was poured into EtOAc (300ml) and the organic phase separated. The aqueous phase was extracted with EtOAc (2 x 300ml). The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was treated with SCX-2 resin (20g) for 15 minutes before filtration and evaporation to give 4-hydroxy-1-(methanesulphonyl)piperidine as a white solid, (6.62g, 19%). NMR($CDCl_3$):3.95 (m, 1H), 3.45 (m, 2H), 3.10 (m, 2H), 2.75 (s, 3H), 1.95 (m, 2H), 1.70 (m, 2H).

ii) To a suspension of sodium hydride (60% dispersion, 1.5g, 37.5mmol) in DMF (350ml) was added a solution of 4-hydroxy-1-(methanesulphonyl)piperidine (6.4g, 35.7mmol) in DMF (50ml). After 20 minutes at RT, 1-bromobut-2-yne (3.0ml, 34.3mmol) was added rapidly. After 4 hours, at RT water (5ml) was added and the mixture left to stand for 16 hours. The solvent was concentrated and the resultant brown oil was partitioned between brine (200ml) and EtOAc (200ml). The aqueous phase was extracted with EtOAc (2x200ml) and the organic layers combined. The combined extracts were dried (Na_2SO_4) and concentrated to give a brown oil which was purified by chromatography (Flashmaster II, 70g silica column, eluted with 0→100% EtOAc / *iso*-Hexane gradient) to give 4-(but-2-ynyloxy)-1-methanesulphonylpiperidine (1.8g, 22%Yield). NMR($CDCl_3$): 4.14 (q, 2H), 3.75 (m, 1H), 3.35 (m, 2H), 3.21 (m, 2H), 2.77 (s, 3H), 1.90 (m, 2H), 1.85 (t, 3H), 1.82 (m, 2H).

iii) To a stirred solution of the 4-(but-2-ynyloxy)-1-methanesulphonylpiperidine (461mg, 2mmol) in THF (15ml) at -15°C was added LiHMDS (4.4ml, 1.0M solution in THF, 4.4mmol). The solution was then stirred at this temperature for 30 minutes. A solution of ethyl 4-(pyrimidin-2-yl)butanoate§ (400 mg, 2.1 mmol) in THF (1 ml) was then added dropwise. The reaction was slowly allowed to warm to 5°C, then after 20 minutes, water

(2ml) was added. The solution was partitioned between brine (20ml) and EtOAc (10ml), then the aqueous layer was re-extracted with EtOAc (10ml). The combined organic extracts were dried, (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography (silica gel, 50% EtOAc in hexane) gave 1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pentan-2-one as a yellow oil (286 mg, 38%). NMR($CDCl_3$): 8.67 (d, 2H), 7.13 (t, 1H), 4.13 (q, 2H), 3.96 (s, 2 H), 3.72 (m, 1H), 3.47 (m, 2H), 3.22 (m, 2H), 3.0 (t, 2H), 2.84 (t, 2H), 2.16 (m, 2H), 1.98 (m, 2H), 1.85 (t, 3H), 1.76 (m, 2H); MS: 380.

iv) To a stirred solution of 1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pentan-2-one (286mg, 0.75mmol) in EtOH (5ml) was added sodium borohydride (15mg) and the mixture stirred at RT. After 25 minutes the reaction mixture was concentrated and EtOAc (20ml) was added. The organic layer was washed with brine (20ml) and the aqueous fraction re-extracted with EtOAc (20ml). The combined organics were dried (Na_2SO_4) and evaporated to give (R/S)-1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pentan-2-ol (286mg, 100% yield). NMR: 8.67 (d, 2H), 7.14 (t, 1H), 4.24 (m, 1H), 4.13 (q, 2H), 3.74 (m, 1H), 3.56 (br s, 1H), 3.42 (m, 2H), 3.24 (m, 2H), 3.02 (m, 4H), 1.85 (t, 3H), 1.81 (m, 8H); MS: 382.

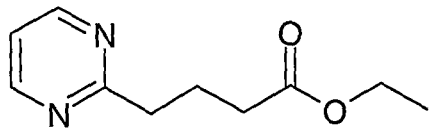
v) To a stirred solution of (R/S)-1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pentan-2-ol (286mg, 0.75mmol) in DCM (5ml) was added triethylamine (260µl, 1.9mmol) followed by methanesulphonyl chloride (65µl, 0.83mmol) and the mixture stirred at RT. After 21 hours the reaction mixture was poured into brine, diluted with DCM (20ml) and partitioned. The organic layer was dried (Na_2SO_4), evaporated and purified by chromatography (Flashmaster II, 10g silica column, 0→100% hexane to EtOAc) to give E-1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pent-1-ene (158mg, 58% yield). NMR: 8.68 (d, 2H), 7.15 (t, 1H), 6.76 (dt, 1H), 6.12 (d, 1H), 4.12 (q, 2H), 3.68 (m, 1H), 3.30 (m, 2H), 3.05 (m, 4H), 2.35 (m, 2H), 2.04 (m, 2H), 1.89 (m, 2H), 1.84 (t, 3H), 1.76 (m, 2H); MS: 364.

vi) To a stirred solution of the E-1-{[4-(but-2-ynyloxy)piperidinyl]sulphonyl}-5-(pyrimidin-2-yl)pent-1-ene (158mg, 0.43mmol) in THF (5ml) under argon was added hydroxylamine (50% solution in water, 450µl) and the mixture stirred overnight. The mixture was poured into water (5ml) and EtOAc (15ml) and the partitioned organic layer was washed with brine (5ml), dried (Na_2SO_4) and concentrated to give (R/S)-[1-({[4-(4-but-2-

ynyloxy)piperidin-1-yl]sulphonyl}methyl)-4-pyrimidin-2-ylbutyl]hydroxylamine (170mg, 100%), this was used immediately in the final step.

§Ethyl 4-(pyrimidin-2-yl)butanoate was prepared as follows:

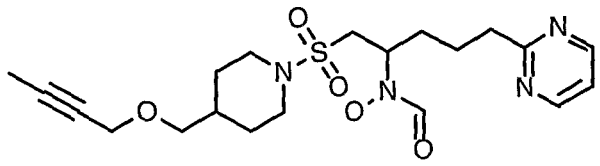
Ethyl 4-(pyrimidin-2-yl)butanoate



2-Bromopyrimidine (80g, 500mmol) was slurried in THF (400ml). An inert atmosphere was created by displacing the air atmosphere with nitrogen, followed by degassing the slurry by nitrogen purging. Bis(acetonitrile)palladium (II) chloride (2.5mmol) and triphenylphosphine (7.5mmol) were charged, followed by 4-ethoxy-4-oxo-butylzinc bromide (0.5M in THF, approximately 600mmol) in 9 portions. The mixture was stirred until the reaction was complete at which point water was added and the solution rotary evaporated to an oil. DCM was added and this solution was washed with 1M EDTA tetrasodium salt, water and brine. The DCM solution was then rotary evaporated to an oil, causing the precipitation of an impurity. This mixture was dissolved in THF, filtered to remove the impurity, then the solvent removed on a rotary evaporator affording the desired ethyl 4-(pyrimidin-2-yl)butanoate as an orange oil (95.4g, 492mmol). ^{1}H NMR (400MHz): δ 8.73-8.72 (d, 2H), 7.35-7.33 (t, 1H), 4.07-4.02 (q, 2H), 2.91-2.88 (t, 2H), 2.38-2.34 (t, 2H), 2.05-1.97 (m, 2H), 1.20-1.16 (t, 3H)

EXAMPLE 2

(R/S)-1-[({4-[(but-2-ynyloxy)methyl]piperidin-1-yl}sulphonyl)methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide



The procedure described in Example 1 was followed except that 4-(but-2-ynyloxymethyl)-1-(methanesulphonyl)piperidine (360mg, 1.47mmol) was used (synthesis described below) in

place of 4-(but-2-ynyloxy)-1-methanesulphonylpiperidine to give (R/S)-1-[({4-[(but-2-ynyloxy)methyl]piperidin-1-yl}sulphonyl)methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide (169mg, 0.38mmol). NMR: 8.68 (d, 2H), 8.48 (s, 0.5H), 8.04 (d, 0.5H), 7.23 (t, 0.5H), 7.19 (t, 0.5H), 4.08 (m, 2H), 3.78 (m, 2H), 3.3 (m, 4H), 3.06 (m, 4H), 2.78 (m, 2H), 1.92 (m, 2H), 1.85 (t, 3H), 1.7 (m, 7H) ; MS: 439

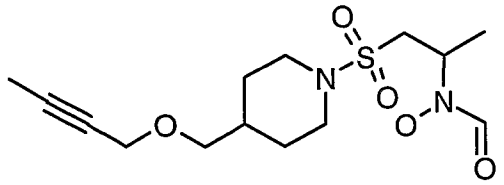
The starting 4-(but-2-ynyloxymethyl)-1-(methanesulphonyl)piperidine was prepared as follows:

i) To a stirred solution of piperidin-4-ylmethanol (2g, 17.4mmol) dissolved in DCM (250ml) was added triethylamine (6ml, 43.5mmol) followed by methanesulphonyl chloride (3.0ml, 38.2mmol). After 2.5 hours at RT the reaction mixture was diluted with EtOAc (500ml) and the organic layer washed with 2M HCl (100ml), $NaHCO_3$ (100ml), brine (100ml), dried (Na_2SO_4) and evaporated to give 4-(methanesulphonyloxymethyl)-1-methanesulphonylpiperidine as an off-white solid (4.5g, 96%). NMR($CDCl_3$): 4.1 (d, 2H), 3.86 (m, 2H), 3.02 (s, 3H), 2.79 (s, 3H), 2.67 (m, 2H), 1.89 (m, 3H), 1.43 (m, 2H).

ii) To a stirred solution of but-2-yn-1-ol (550ul, 7.4mmol) in DMF (25ml) was added sodium hydride (300mg, 8.1mmol). After 90 minutes a solution of 4-(methanesulphonyloxymethyl)-1-methanesulphonylpiperidine (2.0g, 7.4mmol) in DMF (30ml) was added. After 2 hours stirring at RT water (5ml) was added and the mixture concentrated to a brown oil. This was partitioned between EtOAc (100ml) and brine (150ml). The aqueous layers were re-extracted with EtOAc (2x50ml) and the combined organic fractions were dried (Na_2SO_4), evaporated and purified by chromatography (Flashmaster II, 50g silica, 50→100% hexane to EtOAc) to give 4-(but-2-ynyloxymethyl)-1-(methanesulphonyl)piperidine(680mg, 2.8mmol, 37%). NMR($CDCl_3$): 4.07 (q, 2H), 3.81 (br m, 2H), 3.35 (d, 2H), 2.76 (s, 3H), 2.64 (m, 2H), 1.8 (m, 5H), 1.71 (m, 1H), 1.35 (m, 2H).

EXAMPLE 3

(R/S)-2-({4-[(But-2-ynyloxy)methyl]piperidin-1-yl}sulphonyl)-1-methylethyl(hydroxy)formamide



To a stirred solution of (R/S)-2-{[4-(but-2-ynyloxymethyl)piperidin-1-yl]sulphonyl}-1-methylethylhydroxylamine (112mg, 0.37mmol) in THF (5.0ml), was added a preformed mixture of acetic anhydride (200µl, 2.1mmol) and formic acid (0.75ml). The mixture was stirred at RT overnight. The solvents were removed by rotary evaporation, EtOAc (10ml) followed by saturated sodium hydrogen carbonate and the reaction mixture was stirred for 2 hours. The mixture was washed with brine (10ml), dried (Na_2SO_4) and evaporated to give a pale yellow oil. This residue was purified by chromatography (Flashmaster II, eluent 0→60% EtOAc / DCM) to give (R/S)-2-({4-[(but-2-ynyloxy)methyl]piperidin-1-yl}sulphonyl)-1-methylethyl(hydroxy)formamide (75mg, 0.22mmol). NMR($CDCl_3$): 7.96 (s, 1H), 4.36 (m, 1H), 4.08 (q, 2H), 3.77 (m, 2H), 3.47 (dd, 1H), 3.34 (d, 2H), 2.90 (dd, 2H), 2.75 (m, 2H), 1.85 (t, 3H), 1.82 (m, 2H), 1.74 (m, 1H), 1.48 (d, 3H), 1.34 (m, 2H); MS: 333.

The starting material (R/S)-2-{[4-(but-2-ynyloxymethyl)piperidin-1-yl]sulphonyl}-1-methylethylhydroxylamine was prepared as follows:

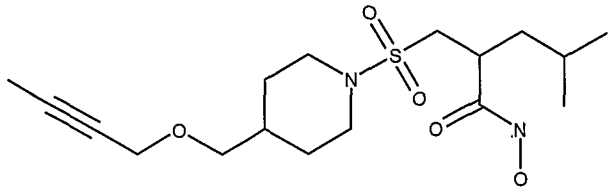
i) To a stirred solution of the 4-(but-2-ynyloxymethyl)-1-methanesulphonylpiperidine (prepared above) (320mg, 1.3mmol) in THF (10ml) at -17°C under argon was added LiHMDS (2.8ml, 1.0M solution in THF, 2.8mmol). The solution was then stirred at this temperature for 30 minutes. A solution of diethylchlorophosphate (190µl, 1.31mmol) was then added and the reaction mixture stirred at 0°C for a further 50 minutes. Acetaldehyde (100µL, 1.8mmol) was then added. After 15 hours the reaction was quenched with saturated ammonium chloride (10ml). The organic phase was separated and the aqueous layer extracted with EtOAc (30ml). The combined organics were combined, washed with brine (10ml), dried (Na_2SO_4), concentrated and chromatographed (Flashmaster II, 50g silica, 50→100% hexane to EtOAc) to give E/Z-{1-[4-(4-but-2-ynyloxymethyl)piperidin-1-yl]sulphonyl}prop-1-ene as a yellow oil (100 mg, 0.37mmol). MS: 272.

ii) To a stirred solution of the E/Z-{1-[4-(4-but-2-ynyloxymethyl)piperidin-1-yl]sulphonyl}prop-1-ene (100mg, 0.37mmol) in THF (5ml) under argon was added hydroxylamine (50% solution in water, 450µl) and the mixture stirred over the weekend. The

mixture was poured into water (5ml) and EtOAc (15ml) and the partitioned organic layer was washed with brine (5ml), dried (Na_2SO_4) and concentrated to give (R/S)-2-{[4-(but-2-ynyloxymethyl)piperidin-1-yl]sulphonyl}-1-methylethylhydroxylamine (112mg, 0.37mmol). This was used immediately in the final step.

EXAMPLE 4

2-(4-But-2-ynyloxymethylpiperidin-1-ylsulphonylmethyl)-4-methyl-pentanoic acid hydroxyamide



To a stirred solution of 2-(4-but-2-ynyloxymethylpiperidin-1-ylsulphonylmethyl)-4-methylpentanoic acid (350mg, 0.97mmol) in DCM (20ml) was added DMF (2 drops) and oxalyl chloride (0.1ml, 1.16mmol). The reaction was stirred for 1 hour at RT and then evaporated to dryness at RT to give a yellow solid. The solid was redissolved in DCM (6ml) and added dropwise, over 5 minutes, to a solution of hydroxylamine (50% aq., 1.0ml) in THF (15ml). The resultant solution was stirred at RT for 1hour and then evaporated under reduced pressure. The crude product was purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 50% to 80% EtOAc / isohexane) to give the product, as a white solid (160mg, 0.43mmol). NMR (400MHz, $CDCl_3$) 0.91 (d, 3H), 0.93 (d, 3H), 1.34 (m, 2H), 1.71 (m, 2H), 1.81 (m, 1H), 1.85 (t, 3H), 2.71 (m, 2H), 2.83 (dd, 1H), 3.35 (d, 2H), 3.42 (dd, 1H), 3.72 (m, 2H), 4.08 (q, 2H); MS: 375.

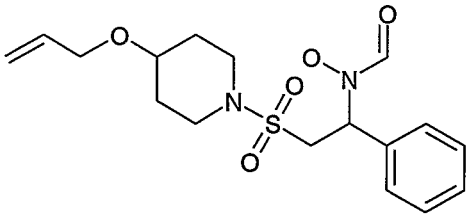
The starting material 2-(4-but-2-ynyloxymethylpiperidin-1-ylsulphonylmethyl)-4-methyl-pentanoic acid was prepared as follows :

i) To a solution of 4-but-2-ynyloxymethyl-1-methanesulphonylpiperidine (520mg, 2.12mmol) in THF (7ml) cooled to -16°C was added LiHMDS (1.0M in THF, 2.2ml, 2.2mmol). The solution was stirred at -16°C for 10 minutes. To this solution was added a solution of 3-isobutyl-oxiran-2-one in THF, dropwise, at -16°C, (prepared by addition of LiHMDS (1.0M in THF, 2.3ml, 2.3mmol) to a solution of 2-bromoisocaproic acid (431mg, 2.2mmol) in THF (7ml) at -16°C). Stirring was continued at RT for 1 hours. The reaction

was quenched with ammonium chloride solution (saturated aqueous, 5ml). 2M HCl (8ml) and EtOAc (20ml) were added. The organic phase was separated. The aqueous phase extracted with EtOAc (20ml). The combined organic phases were washed with brine (20ml), dried (Na_2SO_4), evaporated and purified by chromatography (Flashmaster II, 50g, eluent 50→80% EtOAc / isohexane) to give 2-(4-but-2-ynyloxymethylpiperidin-1-ylsulphonylmethyl)-4-methyl-pentanoic acid (350mg, 0.97mmol) as a yellow oil. NMR (400MHz, $CDCl_3$) 0.94(d, 3H), 0.97 (d, 3H), 1.30-1.74 (8H, m), 1.85 (t, 3H), 2.65 (td, 1H), 2.75 (m, 1H), 2.90 (dd, 1H), 3.02 (m, 1H), 3.45 (d, 1H), 3.78 (m, 2H), 4.08 (m, 2H); MS 360.

EXAMPLE 5

(R/S)-2-({4-[Prop-2-enyloxy]piperidin-1-yl}sulphonyl)-1-phenylethyl(hydroxy)formamide



To a solution of (R/S)-2-{[4-[prop-2-enyloxy]piperidin-1-yl]sulphonyl}-1-phenylethylhydroxylamine (described below) (0.75mmol) in DCM (1ml) was added a pre-mixture of formic acid (2ml) and acetic anhydride (1ml) and stirred at RT overnight. Methanol (5ml) was then added and, after stirring for 30 minutes, the mixture was evaporated. The residue was re-dissolved in methanol (2ml) and allowed to stand at RT overnight. After evaporation, the mixture was purified by BondElut chromatography (10g Silica), eluting with a gradient from DCM to 5% methanol in DCM to give (R/S)-2-[prop-2-enyloxy]piperidin-1-yl}sulphonyl)-1-phenylethyl(hydroxy)formamide (0.16mmol, 0.059g) as a solid. MS: 369.

The starting (R/S)-2-{[4-[prop-2-enyloxy]piperidin-1-yl]sulphonyl}-1-phenylethylhydroxylamine was prepared as follows:

i) Triethylamine (8.0g, 0.079mol) was added to a stirred solution of *E*-β-styrenesulphonyl chloride (12.0g, 0.059mol) and 4-hydroxypiperidine (8.0g, 0.079mol) in THF (100ml) at RT. Stirring was continued overnight before the reaction mixture was reduced to low volume and partitioned between EtOAc followed by aqueous 1M HCl, saturated $NaHCO_3$ and brine. The organic fraction was then dried (Na_2SO_4) and evaporated to give E-[4-hydroxypiperidin-1-ylsulphonyl]-2-phenylethene. (12.75g; 0.046mol); NMR

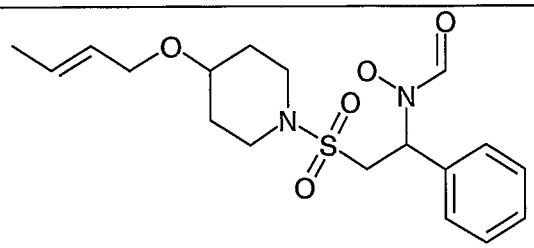
($CDCl_3$): 1.5–1.8 (m, 4H), 1.9–2.1 (m, 2H), 3.0–3.2 (m, 2H), 3.4–3.6 (m, 2H), 3.85 (s, 1H), 6.65 (s, 1H), 7.3–7.6 (m, 6H); MS: 268.

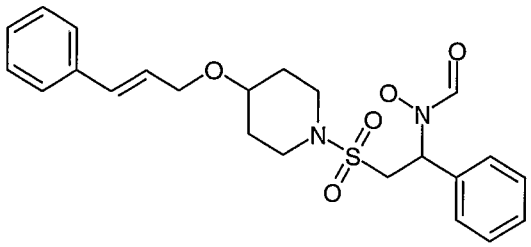
ii) E-[4-hydroxypiperidin-1-ylsulphonyl]-2-phenylethene (0.2g, 0.75mmol) was dissolved in DMF (3ml) and added to allyl bromide (1.5mmol). A covering of argon gas was introduced to the tube before solid sodium hydride (0.1g; incl. oil) was carefully added, in three portions to the stirred reaction. Stirring was continued overnight. Water (5ml) was added (dropwise initially) and the resultant mixture extracted with EtOAc (5ml). The organic layer was separated and the aqueous layer washed again with EtOAc (3ml). The combined organics were evaporated, re-dissolved in DCM (5ml) and applied to a 10g Silica BondElut column and eluted with a gradient from DCM to 2.5% MeOH in DCM to give E-[4-[prop-2-enyloxy]piperidin-1-ylsulphonyl]-2-phenylethene which was carried through to the next step.

iii) E-[4-[prop-2-enyloxy]piperidin-1-ylsulphonyl]-2-phenylethene was dissolved in THF (1ml) and the air in the tubes excluded with argon before hydroxylamine in water (50% solution, 1ml) was added and the mixture stirred vigorously overnight. EtOAc (1ml) was added and the aqueous layer separated. The organic layers were washed with brine and dried (Na2SO4) and concentrated to give (R/S)-2-{[4-[prop-2-enyloxy]piperidin-1-yl]sulphonyl}-1-phenylethylhydroxylamine which was carried through to the final step.

EXAMPLES 6 and 7

The method described in Example 5 was followed except allyl bromide was replaced with the appropriate halide to give the products shown below.

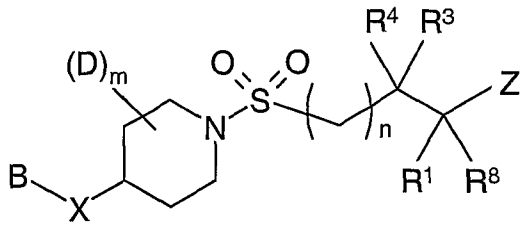
Example Number	Structure and Name	Starting phenol	MH+
6	 (R/S)-2-({4-[but-2-enyloxy]piperidin-1-yl}sulphonyl)-1-phenylethyl(hydroxy)formamide	1-bromo-but-2-ene	383

7	 (R/S)-2-({4-[3-phenyl-prop-2-enyloxy]piperidin-1-yl}sulphonyl)-1-phenylethyl(hydroxy)formamide	1-bromo, 3-phenyl-prop-2-ene	439

CLAIMS:

What we claim is :-

1. A compound of formula (1):



formula (1)

wherein Z is selected from $-CONR^{15}OH$ and $-N(OH)CHO$;

R^{15} is hydrogen or C_{1-3}alkyl;

wherein R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{17}), aryl (optionally substituted by one or more R^{17}), heteroaryl (optionally substituted by one or more R^{17}), heterocyclyl, C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$, $-CONR^5R^6$, $-NR^{16}COR^5$, $-SO_2NR^5R^6$ and $-NR^{16}SO_2R^2$;

R^{16} is hydrogen or C_{1-3}alkyl;

R^{17} is selected from halo, C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{1-6}alkoxy;

R^2 is group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^5 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^6 is hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

or R^5 and R^6 together with the nitrogen to which they are attached form a heterocyclic 4- to 7-membered ring;

wherein R^8 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy and C_{1-4}alkyl;

or R^1 and R^8 together form a carbocyclic or saturated heterocyclic 3- to 6-membered ring;

wherein R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocyclyl, aryl or heteroaryl;

wherein n is 0 or 1;

wherein m is 0 or 1;

wherein D is hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl or fluoro;

wherein X is $-(CR^9R^{10})-Q-(CR^{11}R^{12})_u-$ where u is 0 or 1;

Q is O, S, SO or SO_2;

R^9, R^{10}, $R^{11}$and R^{12} are independently selected from hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

wherein B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally independently substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heterocyclyl whereby the group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^{13}$, $-CONHR^{13}R^{14}$, $-SO_2R^{13}$, $-SO_2NHR^{13}$, $-SO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, C_{1-4}alkyl and C_{1-4}alkoxy;

R^{13} and R^{14} are independently hydrogen, C_{1-4}alkyl or C_{3-5}cycloalkyl;

or R^{13} and R^{14} together with the nitrogen to which they are attached form a heterocyclic 4 to 7-membered ring.

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

2. A compound according to claim 1 wherein X is $-(CH_2)-O-$ or $-(CH_2)-O-(CH_2)-$.

3. A compound according to claim 1 or 2 wherein B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally independently substituted by C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocycloalkyl.

4. A compound according to any one of claims 1 to 3 wherein R^1 is hydrogen, C_{1-6}alkyl or aryl where C_{1-6}alkyl or aryl are optionally substituted by one or more substituents independently selected from C_{1-4}alkyl, aryl (optionally substituted by R^{17}) and heteroaryl (optionally substituted by R^{17}) and wherein R^{17} is halo or C_{1-4}alkyl.

5. A compound according to any one of claims 1 to 4 for use as a medicament.

6. The use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament in the treatment of a disease condition mediated by one or more metalloproteinase enzymes.

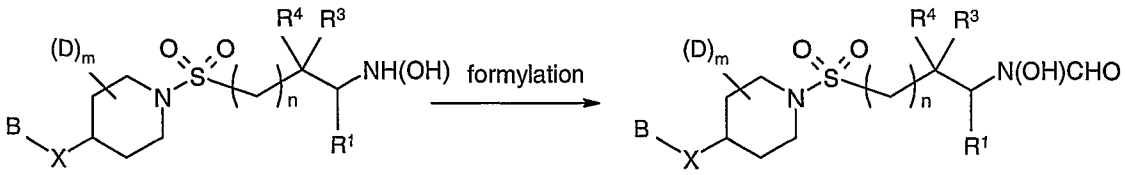
7. The use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament in the treatment of a disease condition mediated TNFα.

8. A method of treating autoimmune disease, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound according to claim 1.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4; and a pharmaceutically-acceptable diluent or carrier.

10. A process for preparing a compound according to claim 1 comprising, when Z is –N(OH)CHO, the step of:

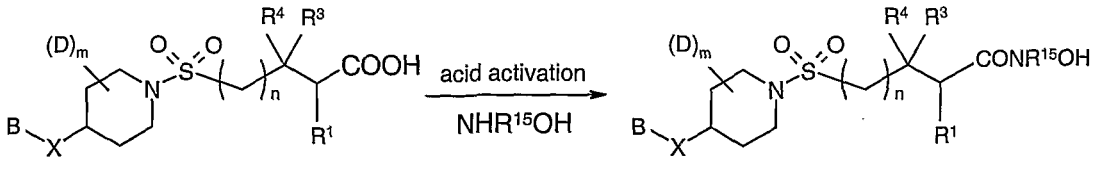
a) converting a hydroxylamine of formula (2) into a compound of formula (1);



formula (2) formula (1)

or when Z is –CONR^{15}OH, the step of:

b) converting an acid of formula (14) into a compound of formula (1);



formula (14) formula (1)

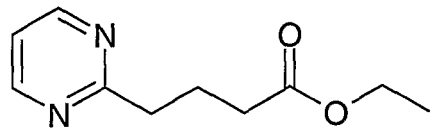
and thereafter if necessary:

i) converting a compound of formula (1) into another compound of formula (1);

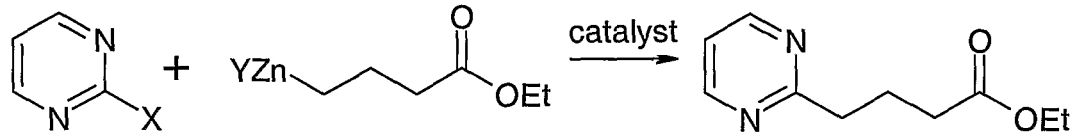
ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

11. Ethyl 4-(pyrimidin-2-yl)butanoate.



12. A process comprising the reaction of a 2-halopyrimidine, 2-tosylpyrimidine, 2-pyrimidinyl triflate or 2-pyrimidinyl mesylate with 4-ethoxy-4-oxo-butylzinc bromide or 4-ethoxy-4-oxo-butylzinc iodide in the presence of a catalyst;



wherein X is halo, triflate or mesylate and Y is bromide or iodide.

13. A process according to claim 11 wherein the catalyst is generated from bis(acetonitrile) palladium (II) dichloride and triphenylphosphine.

14. The use of bis(acetonitrile) palladium (II) dichloride and triphenylphosphine in a Negishi coupling reaction.