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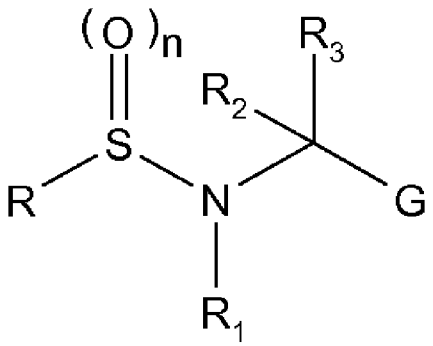
(54) **Title**: ARYL-SULPHONAMIDIC DIMERS AS METALLOPROTEASES INHIBITORS



(II)

(57) **Abstract**: The invention relates to dimeric aryl-sulphonamido compounds endowed with inhibitory activity against metalloproteases MMP, having formula (I) below (M)-L-(M') (I), wherein M and M', the same or different from each other, represent the residues of the metalloproteases inhibitors of formula (II), wherein R, R_1, R_2, R_3, G and n have the meanings reported in the specification; the invention also refers to the process for their preparation, to pharmaceutical compositions comprising them and to their use as therapeutic agents, particularly in the treatment of degenerative disorders.

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TITLE OF THE INVENTION

ARYL-SULPHONAMIDIC DIMERS AS METALLOPROTEASES INHIBITORS

Field of the invention

The present invention finds application in the field of therapy and, more in particular, it relates to aryl-sulphonamido compounds, to a process for their preparation, to pharmaceutical compositions comprising them and to their use as therapeutic agents, particularly in the treatment of degenerative disorders.

Background

Many physiological and pathological processes are known to be characterised by both a significant hyper-proliferation and mobility of cells. Among them are physiological processes like, for instance, embryogenesis or development and differentiation of tissues and, also, pathological processes among which are tumours or, more in general, disorders affecting a variety of body districts or organs: lungs, muscles, bones, skin as well as the nervous, lymphatic, gastrointestinal, renal, maculo-ocular, cardiovascular system, and the like.

In pathological or non-pathological conditions, high cellular proliferation and mobility mainly depends on the activity of zinc metalloproteases, a class of catalytic proteases present in humans (also referred to as proteinases) which are known to coordinate a zinc ion in their catalytic site, and which are able to hydrolyse amidic bonds within the peptidic chain of the proteins.

Among the zinc metalloproteases are extracellular matrix metalloproteases (hereinafter referred to as MMPs), ADAMS (A Disintegrin and Metalloproteases) and ADAMTs (A Disintegrin and Metalloproteases with Trombospondin Type I repeats).

Once produced, these proteases remain anchored onto the cellular membranes or are excreted in the extra-cellular matrix (ECM), an important physiological structure comprising an organized tri-dimensional network of cells of the surrounding tissues which are electrically, chemically and physically connected to each other.

As such, they may play a key role in several extracellular processes including cell-cell and cell-ECM interactions, as well as in physiological intracellular processes; e.g.

growth, development and remodelling of tissues, transduction of intra- and inter-cellular signals and adhesion phenomena.

The proteolytic activity of these zinc metalloproteases, in physiological conditions, is highly and finely tuned by endogenous inhibitors known as tissue inhibitors of metalloproteases (TIMPs), which have been found to exert a fundamental role also in regulating the activity of ADAMs and ADAMTs.

Thus, the delicate equilibrium between MMPs and their inhibitors enables the proper functioning of all of the physiological roles in which MMPs are involved such as, for example, embryonic growth and development, tissue morphogenesis, cell migration and matrix remodelling, reproductive processes, i.e. menstrual cycle and ovulation, bone formation, adipogenesis, wound healing and angiogenesis or even release and processing of bioactive molecules as intra- or inter-cellular peptide signals.

Due to their diffusion in the human body and their exerted role, it is thus evident that any alteration in the regulation of even one of the above mentioned processes, for instance because of pathologies like tumours whose progression may determine either over-expression or under-expression of MMPs, would result, almost inevitably, in the occurrence of degenerative processes leading to an abnormal evolution and/or development of tissues.

Examples of the above pathologies in which over- or under-expression of MMPs may be involved, thus leading to an altered tissutal morphology with uncontrolled cell proliferation, may comprise: arthritis and connective tissue disorders; neurodegenerative disorders such as multiple sclerosis, Alzheimer's disease, stroke and ALS (Amyotrophic Lateral Sclerosis); cardiovascular disorders such as atherosclerosis, aneurism, heart failure, dilated cardiomyopathy; pulmonary diseases such as emphysema or cystic fibrosis; gastric ulcers; sepsis and autoimmune disorders.

In addition, during tissutal degeneration, the altered expression of these zinc proteases may also depend, for instance, from the cells type, the activation of their pro-enzymatic forms, genic transcription pathways as well as excretion and endocytosis mechanisms.

The extracellular and intracellular threshold of active zinc metalloproteases are often regulated onto the cell membrane surface by means of a catalytic shedding by other metalloproteases like the MMPs anchored onto the cellular membrane, known as Membrane-Type MMPs (MT-MMPS), by Tumor Necrosis Factor alpha convertase,

better knows as TACE (and corresponding to ADAM-17), or by even other ADAMs or ADAMTs.

Therefore, for therapeutic purposes, when pathological affections occur as being characterized by a significant activity of metalloproteases on the cell surface of invasive and hyper-proliferating cells, it could be desirable to inhibit those MT-MMPs or some other ADAMs or ADAMTs.

So far, at least 23 different enzymes, which are known to belong to the family of MMPs, have been classified into sub-groups according to their substrate specificity.

Among them are, as an example, MMP-1, MMP-8 and MMP-13 known to act on collagenase; MMP-2 and MMP-9, on the other side, known to target gelatinase; and MMP-3, MMP-10 and MMP-11 known to target stromelysin.

In addition, a fourth sub-group of membrane-type MMPs, called as MT-MMPs, have been identified and characterized so far, namely: MT1-MMP (MMP-14), MT2-MMP (MMP-15), MT3-MMP (MMP-16), MT4-MMP (MMP-17), MT5-MMP (MMP-24) and MT6-MMP (MMP-26); the exerted role, however, has been clarified for only some of them (see, for a reference, HG Munshi et al, *Cancer Metastasis Rev.*, 2006, 25, 45-56; and VS Golubkov et al., *J Biol. Chem*, 2005, 280, 25079-25086).

As an example, MMP-14 is known to be responsible for the activation of pro-MMP-2 on the external surface of some cell types, e.g. smooth muscle cells of vascular tissue in the angiogenetic processes (see, for a reference, N. Koshikawa et al., *J. Cell. Biol.* 2000, 148, 615-624; and Y. Itoh, H. Nagase, *Essays in Biochemistry*, 2002, 38, 21-36).

In addition, MMP-14 is known to be hyper-expressed on the membranes of some types of tumoral cells, such as in melanomas (see, as a reference, NE Sounni et al., *Int. J. Cancer,* 2002, 98, 23-28), breast adenocarcinoma (see, as a reference, NE Sounni, *et al.*, *FASEB J* 2002, 16, 555–564) and in glyomas (AT Belien, et al., *J Cell Biol* 1999, 144, 373–384; and EI Deryugina, et al, *Cancer Res,* 2002; 62:580–588).

MMP-14 may also activate other pro-MMPs like pro-MMP-13, which hyper-expression is known to be correlated, in some cell types, to tumours, inflammation or cardiovascular and neurodegenerative disorders (see, for example, AR Folgueras et al., *Int. J. Dev. Biol.*, 2004, 48, 411-424; and JO Degushi, et al., *Circulation*, 2005, 2708-2715).

Even other MMPs are known to contribute to the activation of pro-MMP-2 and/or pro-MMP-13 and/or pro-MMP9. As an example, MMP-15, MMP-16, MMP-17 and MMP-24 are known to activate pro-MMP-2 and pro-MMP-13; MMP-17 acts only to activate pro-MMP-2, whilst MMP-26 activates pro-MMP-2 and proMMP-9; see, as a reference, AR Folgueras et al., (*Int. J. Dev. Biol.*, 2004, 48, 411-424).

Moreover, MMP-2 and MMP-13 are produced from proliferating and invasive cells and are activated, or anyway activable, in ECM by catalytic activity of the membrane surface MT-MMPs; they represent, therefore, the prior tool for cell motility across the digestive surface permeability of ECM.

Based on previous studies on the so-called "degradomics" (see, as a reference, C Lopez-Otin et al., *Nature Rev.* 2002, 3, 509-519; and CM Overall et al., *Nature Review Cancer*, 2006, 6, 227-239), the possibility of targeting some MMPs as drug delivery candidates for cancer and other pathologies, whilst avoiding interferences with physiological roles exerted by some other MMPs, is nowadays widely acknowledged.

As such, studies are ongoing for the development of MMP inhibitors, to be used in therapy, that are able to selectively address pathological affections without the aforementioned drawbacks.

Therefore, as the activity of some MMPs should be inhibited so as to limit and counteract an occurring degenerative process, the activity of some other types of MMPs regulating physiological processes of development and morphogenesis should not be impaired, as the above may result in undesirable side effects.

Among them is, as an example, the musculoskeletal syndrome with fibroproliferative effects in the join capsule of the knee known to occur upon impairment of the normal tissue remodelling activity exerted by MMP-1. Likewise, the inhibition of some MMPs involved in tumorogenesis control such as, for instance, MMP-3, may cause an increase of cellular proliferation and invasion.

In therapy, therefore, a lack of inhibition on MMP-1 and MMP-3, considered as antitarget, is highly desirable.

On the contrary, an evident selectivity toward MMP-2 and MMP-9 was found to have pro-apoptic effects on tumor cell cultures without showing important side effects.

Therefore, the search for molecules able to specifically regulate the activity of specific MMPs, when normal mechanisms are lost, will provide useful compounds for the treatment of several diseases.

A variety of metalloproteases inhibitors, some of which referring to sulphonamido derivatives, is known in the art.

Among them are, as an example, carbocyclic side chain containing N-substituted metallo protease inhibitors, described in WO 01/70720, and pharmaceutical compositions thereof.

US 6,686,355 discloses biphenyl derivatives possessing a cyclic nitrogen containing sulphonamido group, as MMP inhibitors.

WO 2004/069365 describes diagnostic imaging agents comprising matrix metalloproteases inhibitors bearing substituted N,N-dialkyl chain sulphonamido groups, properly labelled with a γ-emitting radionuclide.

WO 98/39329 describes sulphonamido hydroxamic acid derivatives specifically targeting MMP-2, MMP-9 and MMP-13; the several compounds therein exemplified comprise substituted N,N-dialkyl side chain sulphonamido groups.

US 7,067,670 discloses alkyl-sulphonamido hydroxamic acid derivatives possessing inhibitory activity towards MMP-2 and MMP-13.

US 6,500,948 discloses pyridyloxy- and pyridylthio-arylsulphonamido derivatives having MMP inhibitory activity, wherein the N atom of the sulphonamido group is part of a six membered heterocycle, bearing carbon atoms adjacent to the above N atom.

US 6,495,568 discloses alkyl- or cycloalkyl-sulphonamido hydroxamic acid derivatives as matrix metalloproteases inhibitors.

US 5,985,900 discloses sulphonamido derivatives being characterized by a phenyl- or phenylene-SO_2NH- moiety, possessing MMP inhibitory activity.

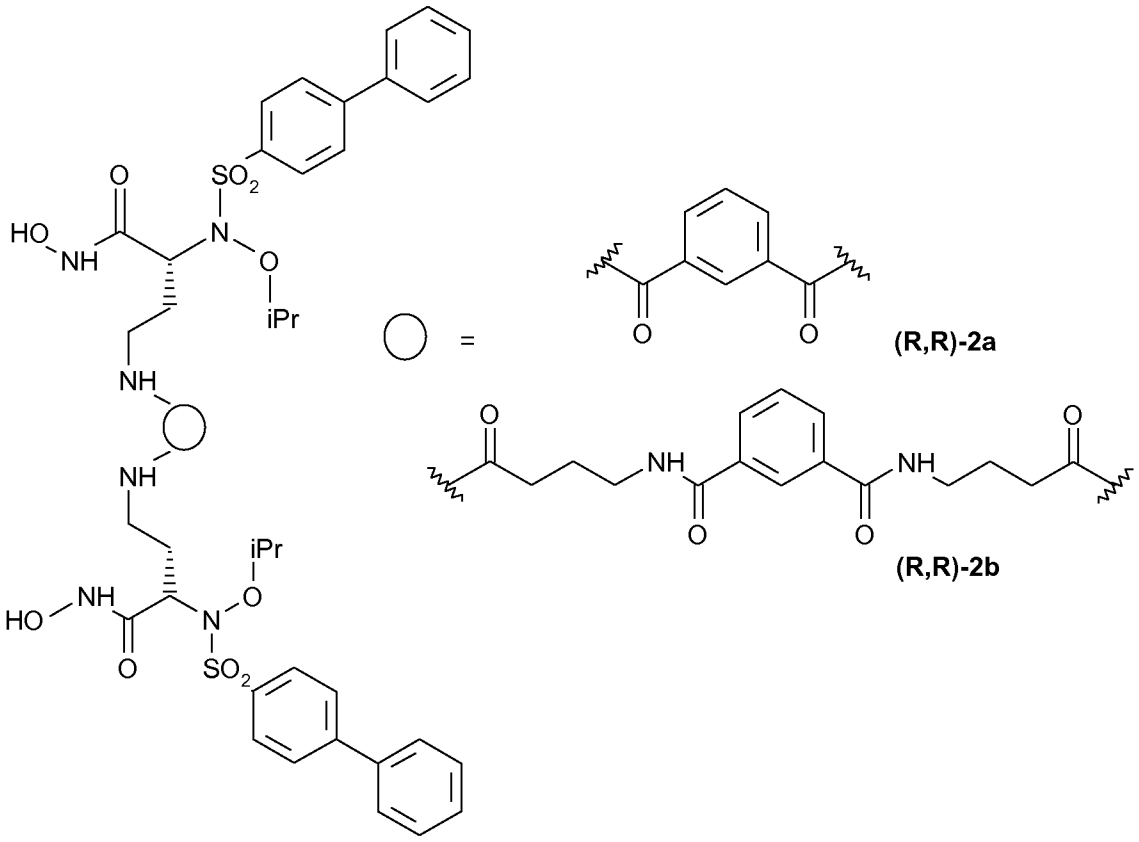
WO 99/42443 discloses sulfonylamino hydroxamic acid derivatives bearing a group aryl-SO_2NH-, therein indicated as matrix-degrading metalloproteinases.

Other sulphonamido MMP inhibitors are known in the art. Among them are selective inhibitors of gelatinase A (MMP-2) being disclosed by Rossello et al. in *Bioorg. & Med. Chem.* 12 (2004) 2441-2450.

Likewise, MMP-2 inhibitors showing a good MMP-2/MMP-1 selectivity were also disclosed by Tuccinardi et al in *Bioorg. & Med. Chem.* 14 (2006) 4260-4276).

In addition to the above, previous works in this field have indicated that the use of selective MMP-2 inhibitors that spare some MMPs such as MMP-1 and MMP-3 enables to block invasion of HT1080 cells (of a highly invasive fibrosarcoma) and HUVEC (Human Umbical Vein Endothelial) cells in models of chemoinvasion and angiogenesis (A. Rossello, et al, *Bioorg & Med. Chem.*, 2004, 12, 2441-2450; and A. Rossello, et al., *Bioorg & Med. Chem. Lett.*, 2005, 15, 1321-1326).

Dimeric sulphonamido MMP inhibitors were also described by Rossello et al. in Bioorganic & Medicinal Chemistry Letters 15, (2005), 2311-2314, and therein referred to as compounds (R,R)-2a and (R,R)-2b, which formulae are reported below:



Corresponding compounds bearing a carboxyl group in place of the hydroxamate group [(R,R)-8a and (R,R)-8b] and intermediate tert-butyl esters thereof, were also disclosed.

Based on the results being obtained on isolated enzymes and according to a method described by CG Knight et al. (see, as a reference, *FEBS Lett.* 1992, *296*, 263; and *Methods Enzymol.* 1995, *248*, 470), the said method comprising the use of the

fluorogenic substrate FS-1 (e.g. Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2) as reported by A. Rossello et al., in Bioorg. Med. Chem. Lett. 12 (2004), 2441-2450, compound (R,R)-2b proved to be a dual inhibitor of MMP-2 (IC_{50} value corresponding to 9.8±2 nM) and of MMP-14 (IC_{50} value corresponding to 34±14 nM).

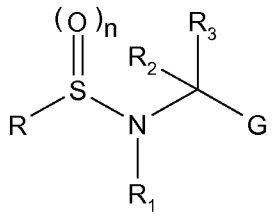
We have now found a new class of dimeric zinc metalloproteases inhibitors having aryl-sulphonamidic structure which, based on IC_{50} values of inhibition tests being in the nano/subnano molar range, resulted to be particularly effective towards target enzymes, in particular MMP-2, MMP-13 and MMP-14.

Object of the invention

Therefore, it is a first object of the present invention a compound having the following general formula (I)

(M)-L-(M') (I)

wherein M and M', the same or different from each other, represent the residues of the metalloproteases inhibitors of formula (II)



(II)

wherein:

R is a group of formula –Ar–X–Ar' (III) wherein Ar is an arylene, heteroarylene, aryl or heteroaryl group and Ar', the same or different and independently from Ar, is an aryl or heteroaryl group or H; the said Ar and Ar' being optionally substituted by one or more groups selected from:

(i) straight or branched alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, amino, aminoalkyl, alkylamino, aminoacyl, acylamino, carboxy or perfluorinated alkyl, each of which having from 1 to 4 carbon atoms in the alkyl chain;

(ii) straight or branched C_2-C_6 alkenyl or alkynyl group;

(iii) halogen or a cyano (–CN) group;

X is a single bond or it is a divalent linker selected from a straight or branched C_1-C_4 alkylene chain, –O–, –S–, –S(O)$_2$–, –CO–, –NR'–, –NR'CO– or –CONR'–, wherein R' is H or a straight or branched C_1-C_4 alkyl group;

R_1 is hydrogen, hydroxy or a group –Ra or –ORa wherein Ra is selected from straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl groups; or Ra is a group of formula (IV)

$$–(CH_2)_p–Z–(CH_2)_r–W \qquad (IV)$$

wherein p is zero or an integer from 1 to 4; Z is a single bond or a divalent linker selected from –O–, –NR'–, –NR'CO– or –CONR'–, wherein R' is as above defined; r is zero or an integer from 1 to 4; and W is phenyl or a 5 or 6 membered heterocycle, each of which being optionally substituted by one or more groups selected from –NH_2, –COR', –CONHR', –COOR' or –SO_2NHR' wherein R' is as above defined, by aryl or heteroaryl or by one or more of the above groups from (i) to (ii);

R_2 and **R_3** are, the same or different and each independently, hydrogen, a straight or branched C_1-C_4 alkyl group optionally substituted by hydroxyl or C_1-C_4 alkoxy groups, or a zinc binding group selected from –COOH, –COORb, –CONHOH, –CONHORb, –CONRbOH, –CONHS(O)$_2$Rb, –$CONH_2$, –CONHRb or –P(O)(OH)$_2$, wherein Rb is a straight or branched alkyl, arylalkyl or heteroarylalkyl group having from 1 to 4 carbon atoms in the alkyl chain; or any of the above R_2 or R_3 groups is linked to R_1 so as to form a 5 to 7 membered heterocyclic ring, optionally substituted by one or more oxo groups (=O);

G is a group selected from straight or branched C_1-C_6 alkyl, aryl, heteroaryl or arylalkyl or it is a group –$(CH_2)_m$-N(R_4)(R_5);

R_4 is H or a group selected from –CORc, –COORc, –S(O)$_2$Rc, –CONHRc or –S(O)$_2$NHRc, wherein Rc is a group selected from C_3-C_6 cycloalkyl, straight or branched alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylaryl, alkylheteroaryl, a 5 or 6 membered heterocyclyl, alkylheterocyclyl or heterocycloalkyl having from 1 to 4 carbon atoms in the alkyl chain;

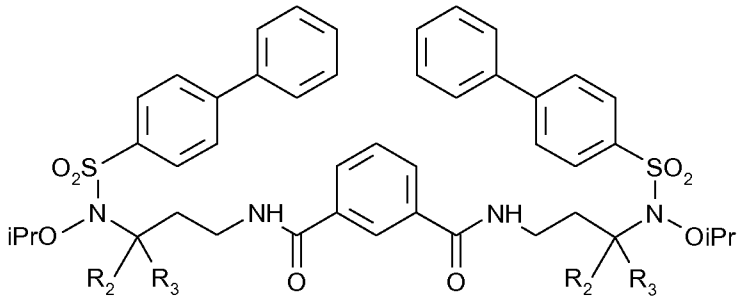
R_5 is H or, together with the N atom to which they are bonded, R_4 and R_5 form an optionally benzocondensed 4 to 6 membered heterocycle, optionally substituted by a group Ra as above defined and/or by one or more oxo (=O) groups;

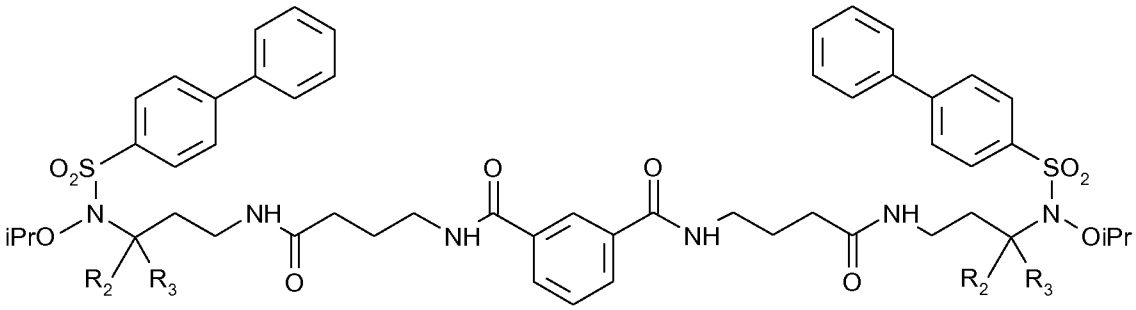
n is 1 or 2;

m is an integer from 1 to 6;

L is a bond or a linker connecting moieties M and M' comprising a hydrocarbon chain with from 1 to 20 carbon atoms, optionally interrupted by one or more groups selected from arylene, heteroarylene, cycloalkylene, heterocycloalkylene, –O–, –S–, –S(O)$_2$–, –CO–, –OCO–, –COO–, –NR'–, –NR'CO– or –CONR'–, wherein R' is as above defined, the said chain being optionally substituted by oxo (=O), amino, hydroxy or carboxy groups;

with the proviso that when the compounds of formula (I) are:





where M and M' are the same, and one of R_2 or R_3 is hydrogen, then the other of R_2 or R_3 is not –COOH, –COO^{t}Bu or –CONHOH;

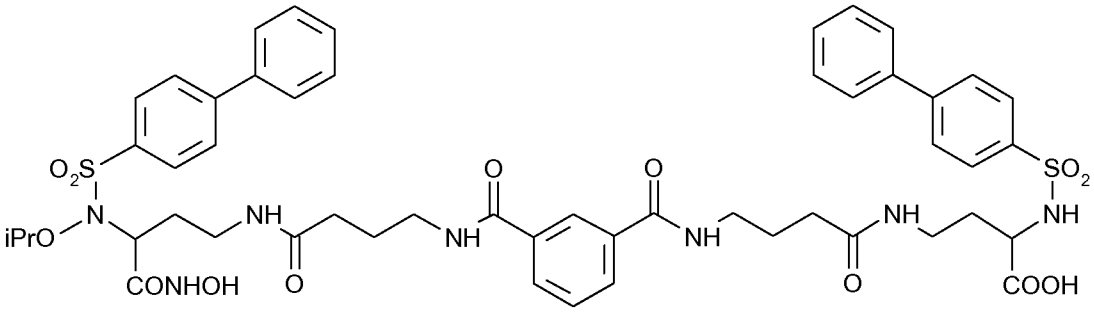
and the pharmaceutically acceptable salts thereof.

The compounds of formula (I) may have one or more asymmetric carbon atom, otherwise referred to as chiral carbon atom, and may thus exist in the form of single enantiomers, racemates, diastereoisomers and any mixture thereof, all to be intended as comprised within the scope of the present invention.

As set forth above, the compounds of formula (I) of the invention comprise two metalloproteases inhibitor moieties M and M', each of which deriving from the compounds having formula (II).

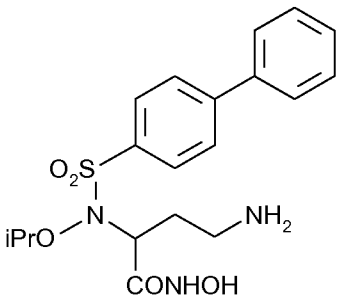
As reported in more details below, the terms "moiety" or "moieties" are herewith intended to define the residual portions of a given molecule of formula (II) once properly attached or conjugated, either directly or through any suitable linker L, to the rest of the molecule.

Just as a non limiting example, a compound of the invention could be thus represented by the following formula (I):

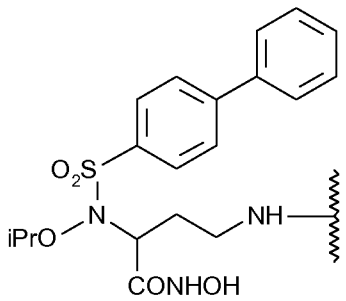


wherein M and M' differ from each other;

M being the residue of a first metalloproteases inhibitor of formula (II) below bearing an amino group as the site of conjugation with the rest of the molecule:



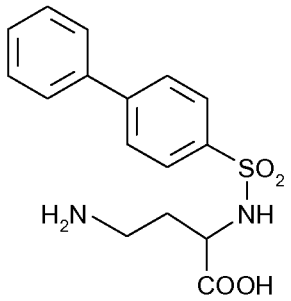
(II)



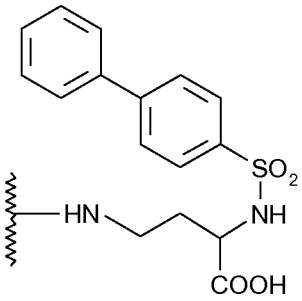
residue M

wherein R is biphenyl-4-yl, n = 2; R_1 = isopropoxy, one of R_2 or R_3 is hydrogen and the other of R_2 or R_3 is a group –CONHOH, m = 2, R_4 and R_5 are both hydrogen atoms, and the line (~~~~~) represents the site of attachment with the rest of the molecule; and

M' being the residue of another metalloproteases inhibitor of formula (II) below also bearing an amino group as the site of conjugation with the rest of the molecule:



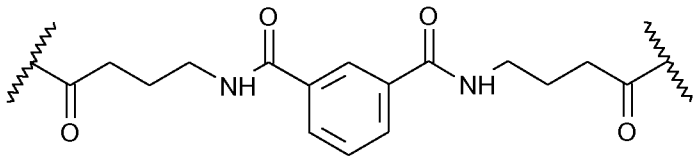
(II)



residue M'

wherein R is biphenyl-4-yl, n = 2; R_1 = hydrogen, one of R_2 or R_3 is hydrogen and the other of R_2 or R_3 is a group –COOH, m = 2, R_4 and R_5 are both hydrogen atoms, and the line (~~~~) represents the site of attachment with the rest of the molecule; and

the linker L being represented by the following divalent group:

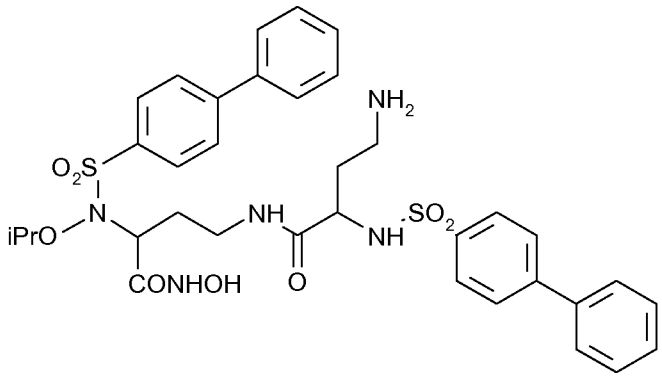


wherein the lines (~~~~) represent the sites of attachment with M, on the left side, and M' on the right side.

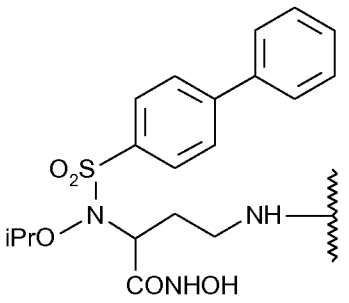
From the above, it should be clear to the skilled person that the compound of formula (I) of the invention is represented by the residues M and M' of the two metalloproteases inhibitors of formula (II), each of them being conjugated with the linker L through a carboxamido bond.

Analogous considerations thus apply, for instance, in case one or both of the metalloproteases inhibitors of formula (II) bear a carboxy group as the site of attachment with the rest of the molecule.

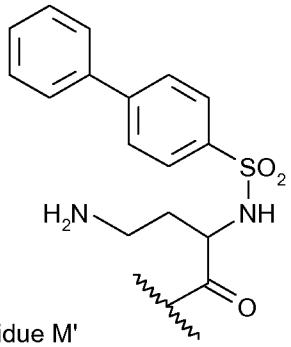
Likewise, for instance in the case of compounds of the invention (I) wherein the linker L is a bond, moieties M and M' are directly linked to each other, for instance as follows:



wherein M and M' have the following meanings:



residue M



residue M'

Details concerning the kind of linker, the means of attachment and, hence, the kind of conjugation between the moieties, and their position of attachment so as to give rise to the compounds of the invention, are all specifically reported below.

As set forth above, within the compounds of formula (I) of the invention and, more particularly, of the moieties M and M', R is a group of formula –Ar–X–Ar' (III) wherein Ar represents an arylene or heteroarylene group linked to –X–Ar' or, when X represents a single bond and Ar' is H, an aryl or heteroaryl group.

In this context, despite the fact that arylene and heteroarylene are presently intended so as to define a divalent radical group (e.g. phenylene $-C_6H_4-$), both terms aryl and arylene (and thus heteroaryl and heteroarylene) are herewith used interchangeably unless otherwise provided.

In the present description, and unless otherwise provided, with the term aryl group (and thus of arylene group) we intend a carbocyclic aromatic group.

With the term heteroaryl (and thus heteroarylene) we intend a 5 or 6 membered aromatic heterocycle with from 1 to 3 heteroatoms or heteroatomic groups selected from N, NH, O or S.

Suitable examples of aryl of heteroaryl groups, when referring to Ar and Ar' and, also, to any other aryl or heteroaryl group being present within the compounds of formula (I), may thus include phenyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyridyl, pyrimidinyl, thiazolyl, and the like.

As far as formula (III) is concerned, it is clear to the skilled person that both Ar and Ar' may be directly linked to each other, when X represents a single bond so as to give rise to a group –Ar–Ar' or, alternatively, they may be linked to each other through any

suitable divalent linker among those above indicated thus providing, as an example, R groups corresponding to –Ar–O–Ar', –Ar–S–Ar', –Ar–CONR'–Ar', and the like.

In addition, and when referring to Ar' as corresponding to a hydrogen atom H, any of the above R groups could be identified, respectively, by –Ar itself (when X is a bond) or by a group –Ar–OH, –Ar–SH, –Ar–CONR'H, and the like.

As formerly reported, any of the above Ar and/or Ar' groups may be optionally further substituted, in any free position, by one or more groups as defined in items from (i) to (iii).

Among the optional substituents, and unless otherwise provided, with straight or branched alkyl with from 1 to 4 carbon atoms in the chain we intend any of the C_1-C_4 alkyl groups thus including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

Likewise, when referring to alkoxy we intend any of the corresponding alkyl-oxy groups such as methoxy, ethoxy, n-propoxy, isopropoxy, and the like.

From the above, the alkyl groups may be further substituted by hydroxyl (–OH), amino ($–NH_2$) or even by the aforementioned alkoxy (–OAlk) groups so as to give rise to hydroxyalkyl (HO–Alk–), aminoalkyl (H_2N–Alk–) or alkoxyalkyl (Alk–O–Alk–) groups, respectively.

By analogy, with the terms alkylamino we refer to an amino group being further substituted by any of the aforementioned alkyl groups, so as to give rise to Alk–NH– groups.

With the term acyl, unless otherwise provided, we intend any of the groups conventionally identifiable as Alk(CO)– groups wherein the Alk residue just represents any straight or branched C_1-C_4 alkyl group.

Suitable examples of acyl groups may thus include acetyl (CH_3CO–), propionyl (CH_3CH_2CO–), butirryl [$CH_3(CH_2)_2CO$–], isobutirryl [$(CH_3)_2CHCO$–], valeryl [$CH_3(CH_2)_3CO$–], and the like.

From the above, aminoacyl groups may thus include H_2NCO– as well as any of the above acyl groups wherein the alkyl chain is properly substituted by amino such as, for instance, aminoacetyl (H_2NCH_2CO–), aminopropionyl [$H_2NCH_2CH_2CO$– or $CH_3CH(NH_2)CO$–], and the like.

By analogy, unless otherwise provided, acylamino groups may be suitably represented by carboxamido groups wherein any of the former acyl groups is bonded to –NH– such as, for instance, acetamido (CH_3CONH–), propionamido (CH_3CH_2CONH–), butirramido [$CH_3(CH_2)_2CONH$–], and the like.

With the term perfluorinated alkyl we intend any of the former alkyl groups wherein all of the hydrogen atoms are replaced by fluorine atoms like, for instance, trifluoromethyl, $-C_2F_5$, $-C_3F_7$ or $-C_4F_9$ groups.

With the term straight or branched C_2-C_6 alkenyl or alkynyl group we intend any of the C_2-C_6 hydrocarbon chains comprising at least one double bond or triple bond, respectively.

Suitable examples of alkenyl or alkynyl groups according to the invention thus comprise vinyl, allyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, ethynyl, propynyl, butynyl, and the like.

Finally, with the term halogen atom we intend any of the fluorine, chlorine, bromine or iodine atoms.

According to a first embodiment of the invention, within the compounds of formula (I), R represents a group of formula (III) wherein Ar represents an optionally substituted phenylene group, X represents a single bond or a divalent linker selected from –O–, –S– or –NH– and Ar' represents H or an optionally substituted phenyl group.

Preferred substituents, in this class, are straight or branched C_1-C_4 alkyl or alkoxy groups or halogen atoms.

Even more preferably, within the compounds of formula (I), R represents a group of formula (III) wherein Ar represents a phenylene group, X represents a single bond or –O– and Ar' represents H or a phenyl group, the phenylene and phenyl groups being optionally substituted by straight or branched C_1-C_4 alkyl or alkoxy groups or by halogen atoms.

Still more preferred, within this class, are the compounds wherein R is a group selected from biphenyl-4-yl, 4-bromophenyl, 4-(4'-methoxyphenyl)-phenyl, 4-(4'-ethoxyphenyl)-phenyl, 4-phenoxy-phenyl, 4-(4'methoxyphenoxy)-phenyl and 4-(4'ethoxyphenoxy)-phenyl.

According to a different aspect of the invention, R_1 is hydrogen, hydroxy, a group –Ra or –ORa wherein Ra is alkyl or alkenyl, or it is a group of formula (IV) wherein p, Z and r are as above defined and W is phenyl or a 5 or 6 membered heterocycle, each of which being optionally further substituted as above indicated.

In the present description, and unless otherwise provided, with the term 5 or 6 membered heterocycle or heterocyclic group we intend any 5 or 6 membered aromatic or non aromatic heterocycle, hence including saturated, partly unsaturated or even fully unsaturated rings, with from 1 to 3 heteroatoms or heteroatomic groups selected from N, NH, O or S.

From the above, it is clear to the skilled person that the aforementioned definition of heterocycle or heterocyclic group also encompasses any fully unsaturated heterocycle, also known as heteroaryl group.

Suitable examples of heterocyclic groups, not including those already reported as falling within the definition of heteroaryl, may thus comprise tetrahydrofuran, pyrroline, pyrrolidine, morpholine, thiomorpholine, piperidine, piperazine, and the like.

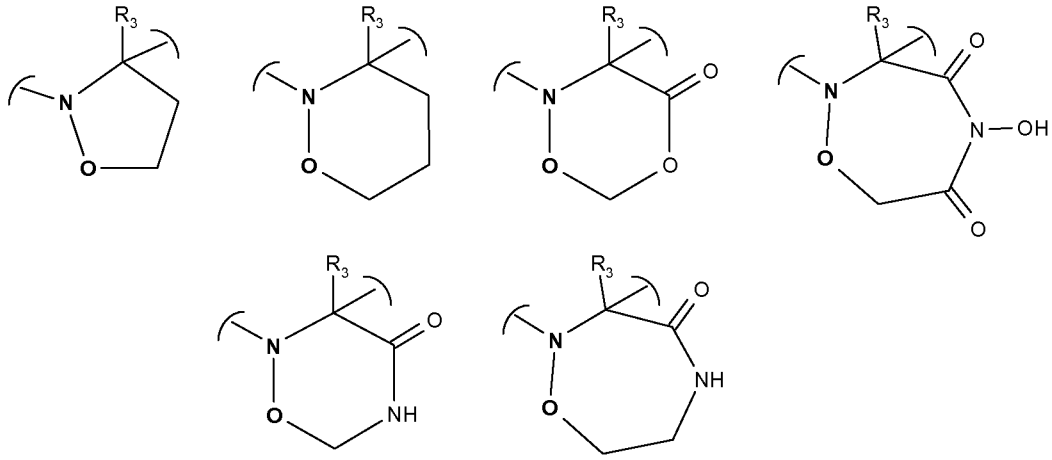
According to a preferred embodiment of the invention, R_1 is hydrogen or a group –Ra or –ORa, wherein Ra is an alkyl or alkenyl group as above defined, or it is a group of formula (IV) wherein p is 1 or 2, Z is a single bond or a divalent group selected from –O– or –NH–, r is 0, 1 or 2, and W is an optionally substituted phenyl or heterocyclic group as above defined.

Still more preferred, within this class, are the compounds wherein R_1 is selected from hydrogen, isopropyl, isopropoxy, benzyloxy, 4-phenyl-benzyloxy, allyloxy, 2-[2(piperazinyl-1-yl)ethoxy]ethoxy or 2-[2(4(ethylcarbonyl)piperazinyl-1-yl)ethoxy] ethoxy.

As far as R_2 and R_3 are concerned, they independently represent H, an optionally substituted alkyl group or a zinc binding group among those formerly reported.

Alternatively, R_2 or R_3 may be linked to R_1 so as to give rise to a 5 to 7 membered heterocyclic ring at least comprising one N heteroatom, e.g. the N atom being bonded to S in formula (II). According to a preferred embodiment, the above 5 to 7 memebred heterocyclic ring at least comprises two adjacent N-O heteroatoms, e.g. the N atom being bonded to S, in formula (II), and the O atom being part of R_1 itself.

As a non limiting example, suitable compounds wherein one of R_2 or R_3 (e.g. R_2) is linked to R_1 so as to give rise to the above heterocyclic structures may thus comprise:



wherein the above adjacent N-O heteroatoms are represented in bold.

According to a preferred embodiment of the invention, R_2 and R_3 are selected, each independently, from H, straight or branched C_1-C_4 alkyl, –COOH, –COORb, –CONHOH or –CONHORb, wherein Rb is a straight or branched alkyl, arylalkyl or heteroarylalkyl group having from 1 to 4 carbon atoms in the alkyl chain.

Still more preferably, within this class, R_2 and R_3 are both H atoms or one of them is H and the remaining one of R_2 or R_3 is –COOH or –CONHOH.

As formerly reported, G is a group selected from straight or branched C_1-C_6 alkyl, aryl, heteroaryl or arylalkyl, the said groups being as above defined or, alternatively, G is a group of formula $–(CH_2)_m$-$N(R_4)(R_5)$, wherein m, R_4 and R_5 are as set forth above.

With respect to the meanings of R_4, the said group may represent a hydrogen atom H or a carbonyl, carboxyl, sulphonyl, carboxamido or sulphonamido group, further derivatized through the above indicated Rc groups.

When referring to Rc, and unless otherwise provided, with the term C_3-C_6 cycloalkyl we intend any 3 to 6 membered cycloaliphatic ring such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

From the above, having defined the meanings of alkyl, aryl, heteroaryl and heterocycle (or heterocyclyl), any composite-name group such as arylalkyl, alkylaryl,

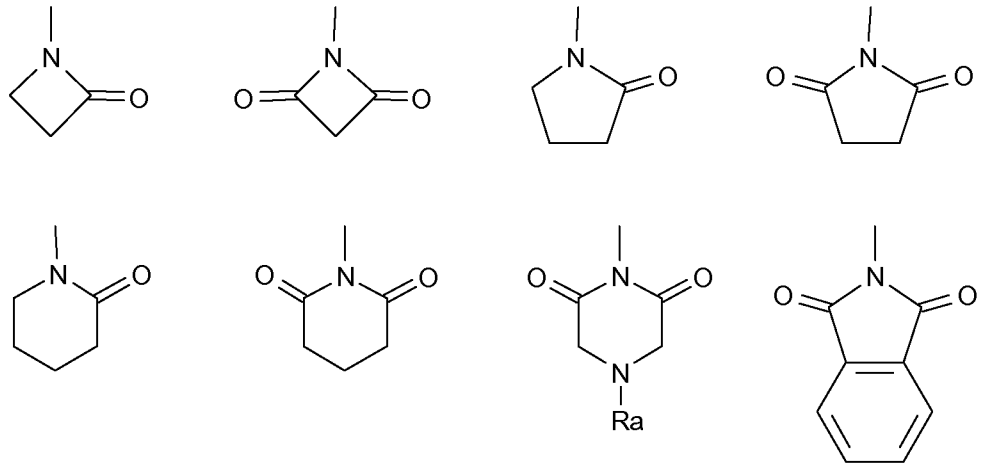
heteroarylalkyl, alkylheteroaryl, alkylheterocyclyl or heterocyclylalkyl, should be clear to the skilled person.

Just as an example, and unless otherwise provided, with the term alkylaryl we intend any aryl group further substituted by alkyl: e.g. p-ethyl-phenyl (pC_2H_5-C_6H_4-); with the term arylalkyl we instead refer to an alkyl group further substituted by aryl: e.g. 2-phenyl-ethyl (C_6H_5-CH_2-CH_2-); and the like.

From all of the above it should be clear to the skilled person that analogous consideration may apply for heteroarylalkyl, alkylheteroaryl, heterocycloalkyl or alkylheterocyclyl groups.

With respect to R_5, it represents H or, alternatively, R_4 and R_5 together with the N atom to which they are bonded form an optionally benzocondensed 4 to 6 membered heterocycle, as above reported.

Suitable examples of the said heterocycles, for instance substituted by Ra and oxo groups, may thus comprise:



According to an additional preferred embodiment of the invention, G is a straight or branched C_1-C_6 alkyl group, preferably isopropyl, or it is a group of formula $-(CH_2)_m$-$N(R_4)(R_5)$, wherein R_4 is selected from –CORc, –COORc or $-S(O)_2Rc$, wherein Rc is aryl, straight or branched alkyl or an arylalkyl group having from 1 to 4 carbon atoms in the alkyl chain; and R_5 is H.

Even more preferred, within this class, are the compounds of formula (II) wherein R_4 is selected from acetyl, benzoyl, phenacetyl, 4-phenylbutanoyl, benzyloxycarbonyl, methanesulphonyl, phenylsulphonyl or benzylsulphonyl, and R_5 is H.

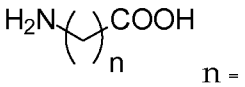
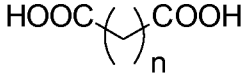
According to a still different embodiment of the invention, R_4 and R_5 together with the N atom to which they are bonded, form an N-phthalimido group.

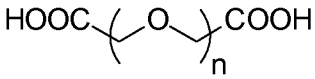
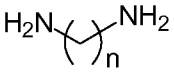
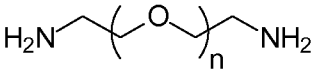
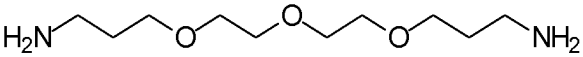
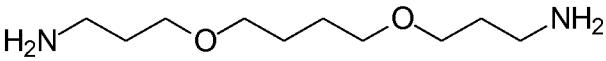
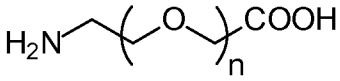
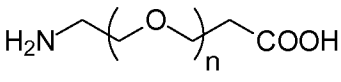
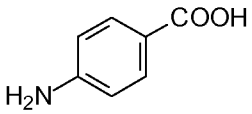
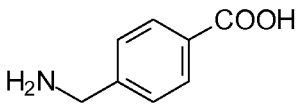
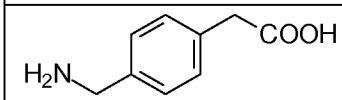
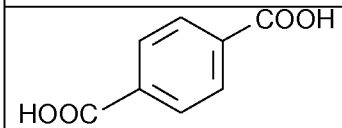
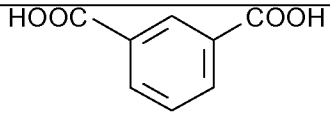
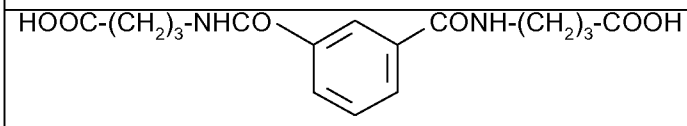
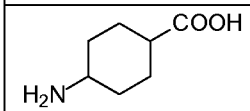
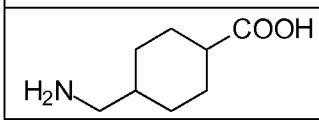
Finally, according to an additional preferred embodiment of the invention, within the compounds of formula (I), n and m are both 2.

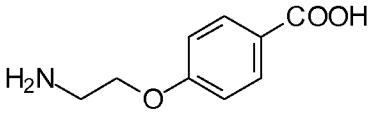
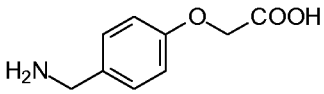
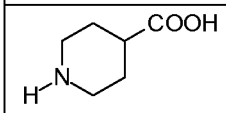
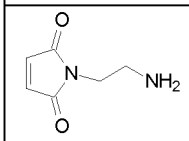
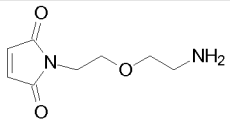
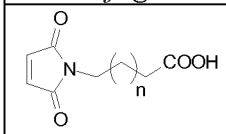
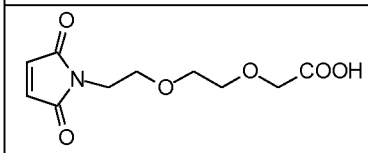
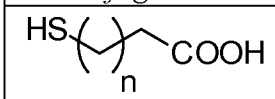
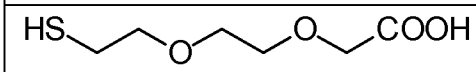
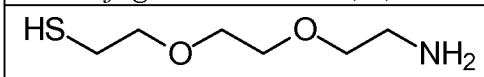
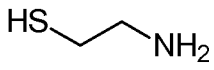
Besides acting as a linking group between the metalloproteases inhibitor moieties M and M', the linker may provide, if present, for a proper distance between them.
In this respect, an optimal distance between these units may represent an important factor so as to get and maintain the targeting capability of the compounds of the invention towards metalloproteases. In fact, any improper or anyway sub-optimal derivatization of the sulphonamido-based targeting moiety may result in a significant loss of the affinity of the resultant dimeric compounds for the targeted objective.
In addition, the above linker(s) may significantly contribute to improve the hydrophilicity of the resultant compound of formula (I), thus providing the desired pharmacokinetic or pharmacodynamic profile of the obtained derivative.

As formerly reported, L is a bond or a linker connecting moieties M and M' and comprising a hydrocarbon chain with from 1 to 20 carbon atoms, optionally interrupted by one or more groups selected from arylene, heteroarylene, cycloalkylene, heterocycloalkylene, –O–, –S–, $–S(O)_2–$, –CO–, –OCO–, –COO–, –NR'–, –NR'CO– or –CONR'–, wherein R' is as above defined, the said chain being optionally substituted by oxo (=O), amino, hydroxy or carboxy groups.

Suitable examples of linkers L according to the invention are reported below, which formula is comprehensive of the reactive functional groups allowing for the conjugation reaction with the rest of the molecule.

 n = 1-6,
 n = 1-4

 n = 1-3
 n = 2-6
 n = 1-5   *Tetrahedron Lett.* **1998**, *39*, *6277; Makromol. Chem.* **1979**, *180*, 2539.


 n = 1-4   *J. Org. Chem.* **2001**, *66*, 4799; *Org. Prep. Proced. Int.* **2002**, *34*, 326
 n = 1-6   *Bioconjugate Chem.* **1999**, *10*, 1021.









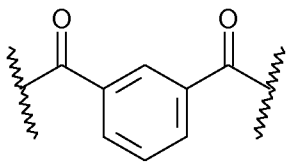



 *Bioconjugate Chem.* **1990**, *1*, 431
 *Bioconjugate Chem.* **1990**, *1*, 431
 n = 0-3
 *Bioconjugate Chem.* **1996**, *7*, 180
 n = 0-1
 *Bioconjugate Chem.* **1996**, *7*, 180
 *Tetrahedron* **1997**, *53*, 10939


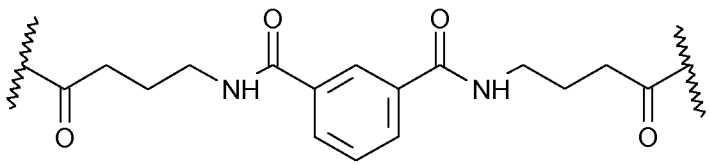
Most of the linkers are known and commercially available whilst other may be prepared according to well known methods, for instance as per the above cited references.

Particularly preferred, among the linkers L, are those represented by hydrocarbon chains interrupted by arylene rings, preferably 1,3-phenylene and 1,4-phenylene rings, the said

chains being further substituted by oxo groups and/or further interrupted by –CONH– or –NHCO– groups.

Even more preferred, among them, are the linkers of formula:





wherein the lines (~~~~) represent the points of attachment with the rest of the molecule.

Moieties M and M', as the residues of the metalloproteases inhibitors of formula (II), are attached to the rest of the molecule at given sites of conjugation so as to give rise to the corresponding carboxamido linkages.

As such, whether the same or different, M and M' may be conjugated to each other, either direcly or through the linker L, by means of reactive functional groups (e.g. carboxy or amino) being part of the metalloproteases inhibitors of formula (II) themselves and of the optional linker.

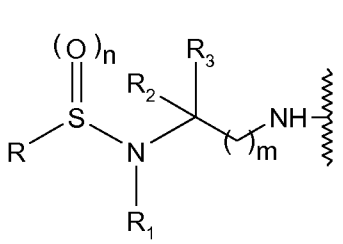
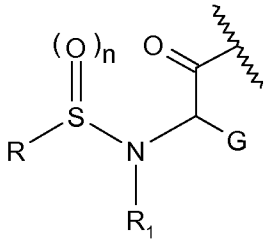
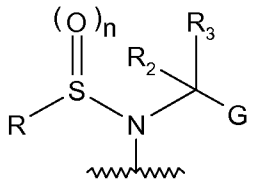
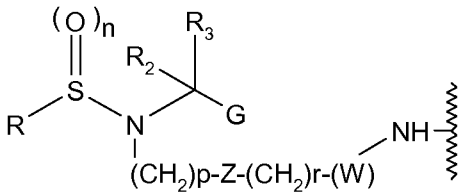
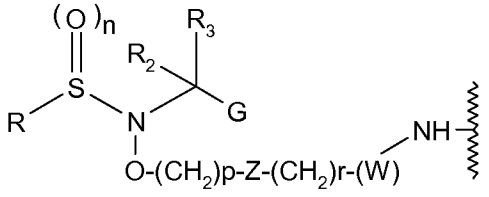
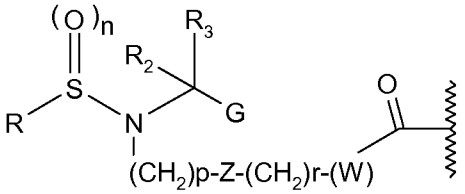
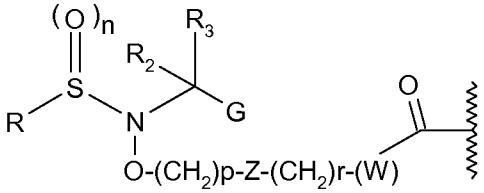
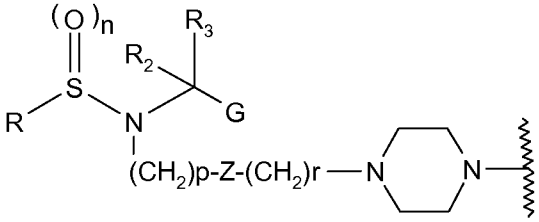
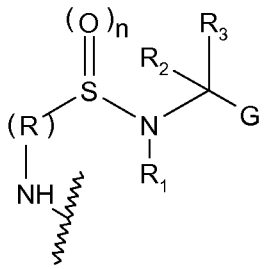
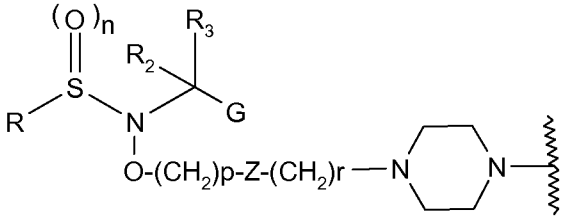
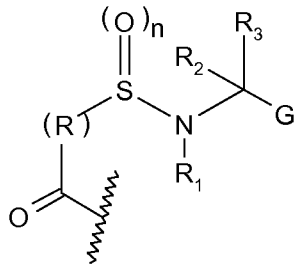
In this respect, preferred points of attachment within both M and M' residues may be thus represented by groups:

- R, when R is a group of formula (III) being suitably substituted by reactive functional groups allowing for the conjugation with the rest of the molecule (e.g. carboxy or amino);
- R_1, for instance when R_1 itself is hydrogen or when it represents a group –Ra or –ORa as formerly reported, the said group being substituted by the aforementioned reactive functional groups (e.g. carboxy, amino or even heterocyclic rings like piperazino);
- any of R_2 and R_3, for instance when representing a carboxy group; and
- G, for instance when representing the group $–(CH_2)_m-N(R_4)(R_5)$ with any of R_4 and/or R_5 being a hydrogen atom or a heteroyclic group bearing the aforementioned reactive functional groups.

From all of the above, a preferred class of compounds of the invention is represented by the derivatives of formula (I)

(M)-L-(M') (I)

wherein M and M', the same or different from each other, are selected from the group consisting of:

wherein R, n, R_1, R_2, R_3, m, G, p, Z, r and W are as above reported, the line (~~~~) represents the point of attachment with the rest of the molecule; and L is as above reported.

According to a preferred embodiment of the invention, M and M' are the same and, even more preferably, their position of attachment or conjugation with the rest of the molecule occurs through the same reactive functional group.

As formerly reported, the compounds of formula (I) of the invention can also be present in the form of a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt", as used herein, refers to derivatives of the compounds of the invention wherein the parent compound is suitably modified by converting any of the free acid or basic groups, if present, into the corresponding addition salt with any base or acid conventionally intended as being pharmaceutically acceptable.

Apart from being non-toxic, the corresponding salts of the compounds of formula (I) of the invention are also characterized by a high stability, including a physiological stability upon usage and administration.

Suitable examples of the said salts may thus include mineral or organic acid addition salts of basic residues such as amino groups, as well as mineral or organic basic addition salts of acidic residues such as carboxylic, phosphonic or sulphuric groups.

Preferred cations of inorganic bases which can be suitably used to prepare salts within the invention comprise ions of alkali or alkaline-earth metals such as potassium, sodium, calcium or magnesium. Preferred cations of organic bases comprise, inter alia, those of primary, secondary and tertiary amines such as ethanolamine, diethanolamine, morpholine, glucamine, N-methylglucamine, N,N-dimethylglucamine.

Preferred anions of inorganic acids which can be suitably used to salify the compounds of the invention comprise the ions of halo acids such as chlorides, bromides, iodides or other suitable ions such as sulfates.

Preferred anions of organic acids comprise those routinely used in pharmaceutical techniques for the salification of basic substances such as, for instance, acetate, trifluoroacetate, succinate, citrate, fumarate, maleate or oxalate.

Preferred amino acids that can be suitably used to salify the compounds of the invention may also comprise, for instance, taurine, glycine, lysine, arginine, ornithine, aspartic and glutamic acid.

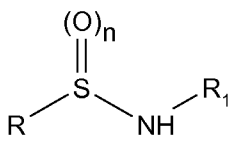
Specific examples of the compounds of formula (I) of the invention, together with the process for their preparation, are reported in the following experimental section.

The process for the preparation of the compounds of the invention may be carried out according to conventional methods well known to those skilled in synthetic organic chemistry techniques.

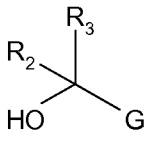
Preferably, the said preparation process comprises, at first, preparing the metalloproteases inhibitors of formula (II) and, then, subsequently subjecting them to a conjugation reaction, either directly, or through the presence of any suitable linker L.

The metalloproteases inhibitors of formula (II) are described in WO 2008/113756 (PCT/EP2008/053078), and their preparation comprises:

a) reacting a compound of formula (V) with a compound of formula (VI)



(V)



(VI)

wherein R, R_1, R_2, R_3, G and n have the above reported meanings so as to obtain a compound of formula (II); and, optionally

b) converting the compound of formula (II) being obtained in step (a) into another compound of formula (II) and/or into a pharmaceutically acceptable salt thereof;

c) conjugating a compound of formula (II) thus obtained in any of the steps (a) or (b) with the same or different compound of formula (II) thus obtained in any of the steps (a) or (b), either directly or through a suitable linker L, as above defined.

The above process is particularly advantageous as it is susceptible of being properly modulated, through any proper variant, so as to obtain any of the desired compounds of formula (I) of the invention.

In step (a) of the process, the reaction between the compounds of formula (V) and (VI) is carried out according to conventional methods for the preparation of sulphonamido or sulphinamido groups with n as 2 or 1, respectively.

Typically, the reaction is carried out under the known Mitsunobu condensation operative conditions, in the presence of suitable solvents including, among others,

tetrahydrofuran, dichloromethane, acetonitrile, N-methylpyrrolidone, benzene, toluene, m-xylene, and mixtures thereof.

In this respect, the above reaction may take place in the presence of a suitable condensing agent, either as such or suitably supported onto polymeric resins and including, for instance, diethyl azodicarboxylate (DEAD), diisopropylazodicarboxylate (DIAD), 1,1'-azodicarbonyldipiperidine (ADDP), N,N,N',N'-tetramethylazodicarboxamide (TMAD), triphenylphosphine (PPh_3), tributylphosphine (PBu_3), and the like.

From all of the above, it should be clear to the skilled person that, in step (a) of the process, any of the R, R_1, R_2, R_3 and G groups, hereinafter shortly referred to as "R" groups, may be present as such or, alternatively, may be present in any properly protected form.

More in particular, functional groups being present in any of the compounds of formula (V) or (VI) and which could give rise to unwanted side reactions and by-products, need to be properly protected before the condensation reaction takes place. Likewise, subsequent deprotection of those same protected groups may follow upon completion of the said reactions.

In the present invention, unless otherwise indicated, the term "protecting group", designates a protective group adapted to preserving the function of the group to which it is bound. Specifically, protective groups are used to preserve amino, hydroxyl or carboxyl functions. Appropriate protective groups may thus include, for example, benzyl, benzyloxycarbonyl, alkyl or benzyl esters, or other substituents commonly used for the protection of such functions, which are all well known to those skilled in the art [see, for a general reference, T. W. Green; Protective Groups in Organic Synthesis (Wiley, N.Y. 1981)].

Likewise, selective protection and deprotection of any of the said groups, for instance including carboxyl, hydroxyl and amino groups, may all be accomplished according to very well known methods commonly employed in organic synthetic chemistry.

In addition to the above, as per step (b) of the process, any of the "R" groups within the compounds of formula (II) that could be easily identified as a derivatized group, for instance any ester or amide, may be prepared from the functional groups from which it derives, by working according to conventional methods.

As a non limiting example, for instance in the case of the preparation of a compound of formula (II) wherein R_2 is a group –COORb, Rb is an alkyl group and R_3 is H, that same compound could be prepared according to the present process: (i) by starting from a compound of formula (VI) wherein R_2 and R_3 are as above defined, as per step (a); or, alternatively, (ii) by starting from a corresponding compound of formula (II) wherein R_2 is –COOH, and by properly converting the carboxyl group into the desired –COORb group, as per step (b) of the process.

The above reaction conditions are well known in the art for the preparation of carboxylic esters.

Analogous considerations may apply, for instance, in the preparation of carboxamides by properly reacting the corresponding carboxyl derivative with any suitable amine, and by working according to well known operative conditions.

Likewise, for instance in the preparation of a compound of formula (II) wherein R_2 is the hydroxamic group –CONHOH, the process may be carried out by first reacting a compound of formula (II) wherein R_2 is carboxyl, being obtained in step (a), in the presence of suitable reactants like, for instance, O-(tert-butyldimethylsilyl)hydroxylamine, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, O-tritylhydroxylamine or O-benzylhydroxylamine, as the case may be.

Subsequent deprotection of the obtained intermediate derivative, for instance under acidic hydrolysis in the presence of trifluoroacetic acid or with trimethylsilyltriflate or by catalytic hydrogenation in the case of O-benzylhydroxylamine, may lead to the desired compound with R_2 as –CONHOH.

Several additional examples are known in the art as allowing to convert a given group within a compound of formula (II) into another group. They may comprise, for instance: the conversion of an amino ($–NH_2$) or caroboxamido ($–CONH_2$) group into the corresponding N-substituted derivative; the conversion of a carboxyl group into the corresponding benzyl ester derivative, by reaction with benzylbromide in the presence of cesium carbonate, as per well known operative conditions; the conversion of a carboxyl group (–COOH) into the corresponding ($–CONHSO_3H$) group, by its first conversion into ($–CONH_2$) followed by reaction with chlorosulfonic acid in the presence of 2-picoline; the conversion of a carboxyl group (–COOH) into the corresponding [$–CH_2PO(OH)_2$] group, by its first reduction to hydroxymethyl

($-CH_2OH$), subsequent conversion into ($-CH_2Cl$) by means of thionyl chloride, followed by reaction with triethylphosphite to give the corresponding $[-CH_2P(OH)_2]$ group finally hydrolyzed to $[-CH_2PO(OH)_2]$.

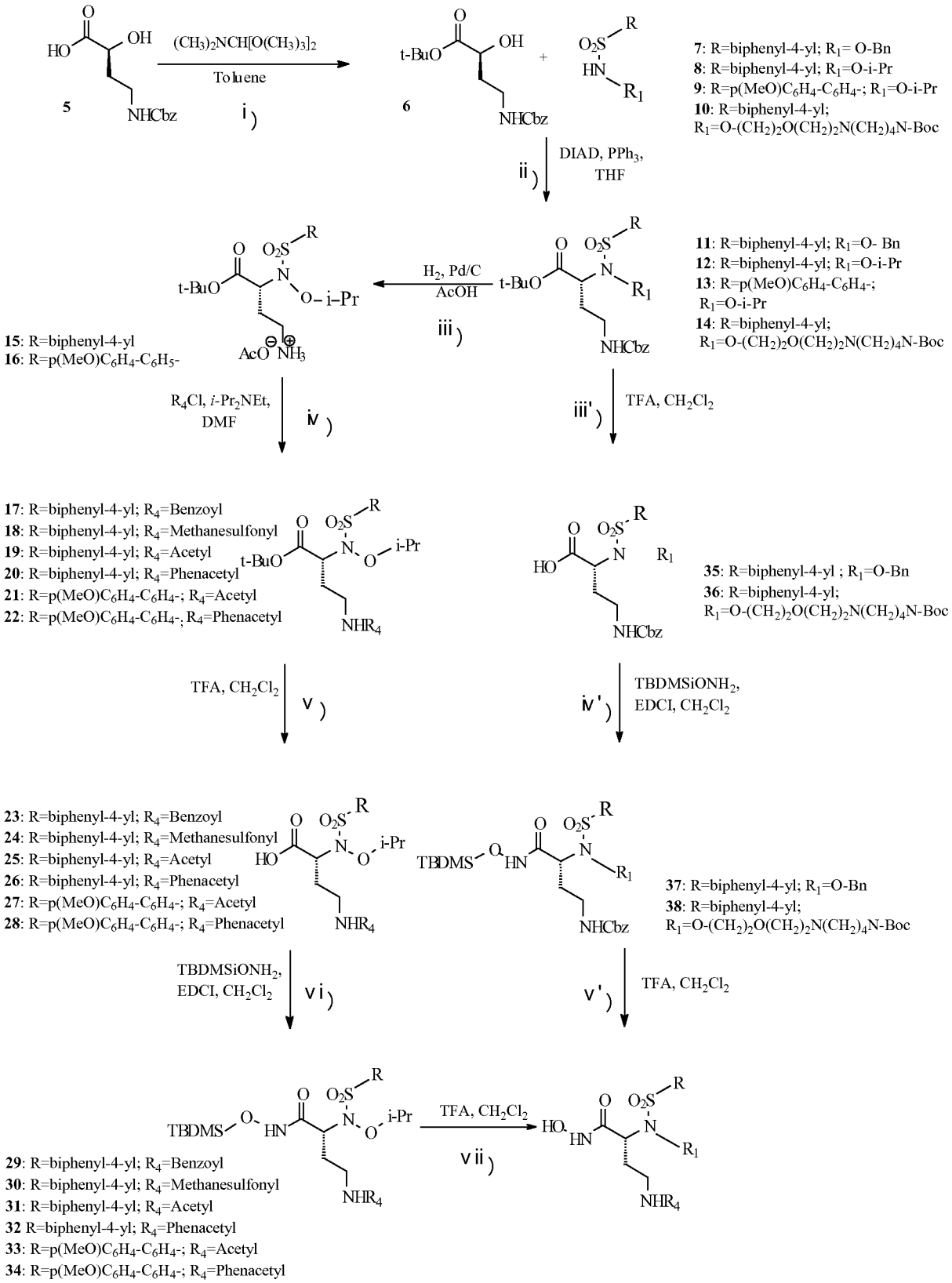
All of the above reactions and operative conditions thereof are well known in the art and allow to obtain a variety of compounds of formula (II).

Clearly, also per step (b) of the process, any functional group within the compounds of formula (II) being obtained in step (a) and that could lead to undesired by-products, need to be properly protected before the reaction takes place, and then deprotected, according to known methods.

For a reference to the specific operative conditions being employed in the preparation of the compounds of formula (II) see, as an example, the following Scheme 1 that provides synthetic pathways for the preparation of some representative compounds. Specific details, however, can be found in the experimental section.

Within the Scheme 1 below, it is reported the preparation of some representative compounds of formula (II) wherein n and m are both 2; R, R_1 and R_4 have the meanings therein reported, one of R_2 or R_3 is H and the remaining one of R_2 or R_3 is a carboxyl or hydroxamic group (-COOH or –CONHOH) and R_5 is H.

Scheme 1


5
6
(CH3)2NCH[O(CH3)3]2
Toluene
i)
DIAD, PPh3, THF
ii)
H2, Pd/C
AcOH
iii)
iii')
TFA, CH2Cl2
R4Cl, i-Pr2NEt, DMF
iv)
TFA, CH2Cl2
v)
TBDMSiONH2, EDCI, CH2Cl2
iv')
TBDMSiONH2, EDCI, CH2Cl2
vi)
v')
TFA, CH2Cl2
TFA, CH2Cl2
vii)
7: R=biphenyl-4-yl; R1= O-Bn
8: R=biphenyl-4-yl; R1=O-i-Pr
9: R=p(MeO)C6H4-C6H4-; R1=O-i-Pr
10: R=biphenyl-4-yl; R1=O-(CH2)2O(CH2)2N(CH2)4N-Boc
11: R=biphenyl-4-yl; R1=O- Bn
12: R=biphenyl-4-yl; R1=O-i-Pr
13: R=p(MeO)C6H4-C6H4-; R1=O-i-Pr
14: R=biphenyl-4-yl; R1=O-(CH2)2O(CH2)2N(CH2)4N-Boc
15: R=biphenyl-4-yl
16: R=p(MeO)C6H4-C6H5-
17: R=biphenyl-4-yl; R4=Benzoyl
18: R=biphenyl-4-yl; R4=Methanesulfonyl
19: R=biphenyl-4-yl; R4=Acetyl
20: R=biphenyl-4-yl; R4=Phenacetyl
21: R=p(MeO)C6H4-C6H4-; R4=Acetyl
22: R=p(MeO)C6H4-C6H4-; R4=Phenacetyl
23: R=biphenyl-4-yl; R4=Benzoyl
24: R=biphenyl-4-yl; R4=Methanesulfonyl
25: R=biphenyl-4-yl; R4=Acetyl
26: R=biphenyl-4-yl; R4=Phenacetyl
27: R=p(MeO)C6H4-C6H4-; R4=Acetyl
28: R=p(MeO)C6H4-C6H4-; R4=Phenacetyl
29: R=biphenyl-4-yl; R4=Benzoyl
30: R=biphenyl-4-yl; R4=Methanesulfonyl
31: R=biphenyl-4-yl; R4=Acetyl
32 R=biphenyl-4-yl; R4=Phenacetyl
33: R=p(MeO)C6H4-C6H4-; R4=Acetyl
34: R=p(MeO)C6H4-C6H4-; R4=Phenacetyl
35: R=biphenyl-4-yl ; R1=O-Bn
36: R=biphenyl-4-yl; R1=O-(CH2)2O(CH2)2N(CH2)4N-Boc
37: R=biphenyl-4-yl; R1=O-Bn
38: R=biphenyl-4-yl; R1=O-(CH2)2O(CH2)2N(CH2)4N-Boc

Essentially, the above preparation process comprises the steps of:

i) protecting the carboxyl group of compound (5) with any suitable protecting group, for instance with N,N-dimethylformamide di-tert-butyl acetal in toluene (see, as a general reference, Rossello et al. *Bioorg. Med. Chem. Lett,* 2005, *15*, 1321), thus providing the compound of formula (6);

ii) reacting any one of the compounds (7-10) with the compound of formula (6) by working according to well known Mitsunobu operative conditions, for instance in the presence of diisopropylazodicarboxylate (DIAD) and triphenylphosphine (PPh_3) as condensing agents, in a suitable solvent like tetrahydrofuran, thus obtaining the corresponding compounds of formula (11-14); and processing them as per the alternative pathways below:

iii) deprotecting the amino group of the compounds (12-13) according to conventional methods including, for instance, catalytic hydrogenation with palladium or platinum catalysts in acetic acid, so as to obtain the compounds (15-16);

iv) properly functionalizing the amino group of compounds (15-16) so as to get any desired $-NHR_4$ group, as per compounds (17-22), for instance through reaction with any suitable acylating agent;

v) deprotecting the carboxylic function so as to get the corresponding compounds (23-28) under suitable hydrolysis conditions, for instance in the presence of trifluoroacetic acid and in a suitable solvent like dichloromethane;

vi) converting that same carboxylic group of compounds (23-28) into a suitable silyl derivative (29-34) according to known methods, for instance by means of O-(tert-butyldimethylsilyl)hydroxylamine in dichloromethane, followed by the addition of 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide;

vii) and hydrolysing compounds (29-34), for instance with trifluoroacetic acid in dichloromethane, so as to lead to the desired compounds of formula (II);

or, alternatively

iii') deprotecting the carboxylic function of compounds (11 and 14) so as to obtain the compounds (35 and 36), for instance by working as per step (v);

iv') converting the compounds thus obtained to the corresponding silyl derivatives (37-38), for instance by working as per step (vi);

v') and hydrolysing compounds (37-38), for instance by working as per step (vii), thus obtaining the desired compounds of formula (II).

Once obtained, the selected metalloproteases inhibitor of formula (II), for instance giving rise to moiety M, is then conjugated with the selected metalloproteases inhibitor of formula (II) giving rise to the other moiety M', so as to lead to to the compounds of the invention.

Conjugation occurs by properly reacting, according to known methods, a metalloproteases inhibitor of formula (II) bearing, in the selected position of attachment with the rest of the molecule, a suitable reactive functional group like amino or carboxy, with the rest of the molecule.

The above conjugation reaction may be carried out according to a variety of methods known in the art, for instance in the presence of suitably activating coupling agents, so as to give rise to the corresponding conjugated compound of the invention, e.g. carboxamides.

Analogous considerations apply when any of the metalloproteases inhibitors of formula (II), giving rise to the moieties M and M', is first reacted with a suitable linker and, then, the obtained compound is reacted with the selected residual moiety M' or M, respectively.

Clearly, any functional group being present in any of the moieties of the metalloproteases inhibitors or the optional linker, and not taking part to the above conjugation reactions, may be suitably protected so as to avoid the formation of unwanted side products and finally deprotected, according to known methods.

From all of the above, it should be clear to the skilled person that the above process, comprehensive of any variant thereof for the preparation of suitable compounds of formula (I) of the invention, may be conveniently modified so as to adapt the reaction conditions to the specific needs, for instance by choosing appropriate condensing agents, solvents and protective groups, as the case may be.

Finally, the optional salification of the compounds of formula (I) may be carried out by properly converting any of the free acidic groups (e.g. carboxylic, sulforic, phosphonic and the like) or free amino groups into the corresponding pharmaceutically acceptable salts. In this case too, the operative conditions being employed for the optional

salification of the compounds of the invention are all within the ordinary knowledge of the skilled person.

The compounds of formula (V) and (VI), as starting materials of the present process, are known or can be easily prepared according to known methods.

The sulphonamido derivatives of formula (V), for instance, may be prepared by reacting any suitable amino compound with any suitable sulphonyl chloride derivative, substantially as follows:

$$R_1\text{-}NH_2 + R\text{-}S(O)_2Cl \rightarrow R\text{-}S(O)_2NHR_1$$

Likewise, if not known per se, both the above amine and the sulphonyl chloride derivative may be easily prepared according to known methods from commercially available compounds.

Analogous consideration may apply to the compounds of formula (VI) that, if not commercially available per, se may be conveniently prepared according to conventional methods well known in the art.

Pharmacology: inhibitory activity

According to the present invention, the compounds of formula (I) are endowed with inhibitory activity against matrix metalloproteases and are therefore useful, in therapy, in the treatment of pathologies in which the regulation of said enzymes is altered.

More in particular, the compounds were tested to prove their activity against MMP-2, MMP-13 and MMP-14, according to the method described in Example 19.

As reported therein, the inhibitory activity of the compounds of the invention was evaluated on the known fluorogenic substrate (Mca-Lys-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2), shortly referred to as FS-6 (see, as a reference, U. Neumann, *Analytical Biochem.* 2004, 328, 166-173).

The said fluorogenic substrate was developed from the analogous FS-1 (see, as a reference, the aforementioned CG Knight et al., in *Febs Lett.* 1992, 296, 263-266) through the insertion of a lysine residue between Mca and Proline residues.

As the elongation of the peptide chain, in FS-6, was reported as improving the ability of the substrate to be hydrolyzed by MMPs, presumably because of the sterically hindered Mca moiety that might have been responsible for the decreased substrate affinity for

some MMPs, present compounds were tested according to this more accurate and highly sensible method, based on FS-6.

Therefore, as per the experimental data thus obtained and comments thereof (see Example 19), the compounds of the invention resulted to be endowed with an inhibitory activity against MMP-2, MMP-13 and MMP-14, markedly superior than that of the structurally close prior art compound, presently identified as Reference Compound (R,R)-2b.

Because of their unexpected activity profile, therefore, the compounds of the invention may be advantageously used, in therapy, in the treatment of those pathologies broadly referred to as degenerative disorders, wherein the above enzymes are involved.

Therefore, it is an additional embodiment of the invention a compound of formula (I) and the pharmaceutically acceptable salts thereof, for use as a medicament.

Additionally, also comprised within the scope of the invention is the use of the above compounds of formula (I) and the pharmaceutically acceptable salts thereof, in the preparation of a medicament for the treatment of degenerative disorders.

The said degenerative disorders comprise tumours and, more in general, patholgies leading to an altered tissutal morphology with uncontrolled cell proliferation.

The said pathologies may thus comprise: arthritis and connective tissue disorders; neurodegenerative disorders such as multiple sclerosis, Alzheimer's disease, stroke and ALS (Amyotrophic Lateral Sclerosis); cardiovascular disorders such as atherosclerosis, aneurism, heart failure, dilated cardiomyopathy; pulmonary diseases such as emphysema or cystic fibrosis; gastric ulcers; sepsis and autoimmune disorders.

In a still another embodiment, the invention concerns pharmaceutical compositions comprising, as an active ingredient, a pharmaceutically effective amount of a compound of formula (I) as set forth above, and the pharmaceutically acceptable salts thereof, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients.

The compositions of the invention can be well prepared according to conventional methods widely known in the art for the preparation of pharmaceutical forms and may comprise any of the carriers, diluents or excipients known in the art for the intended purpose.

In a yet another aspect, the invention provides a method for the treatment of the above degenerative disorders, which method comprises the administration, to a mammal in need thereof, of a therapeutically effective amount of a compound of formula (I), and the pharmaceutically acceptable salts thereof.

From all of the above, it can be easily envisaged that the compounds of this invention may have a wide range of applications, in therapy, and may be thus properly formulated according to conventional methods for the intended administration route: i.e. topical, oral and enteral administration.

With the aim of better illustrate the present invention, without posing any limitation to it, the following examples are now given. In this respect, further applications including possible variants to the preparative process, that will become evident to the skilled person, are thus to be considered as comprised within the scope of the present invention.

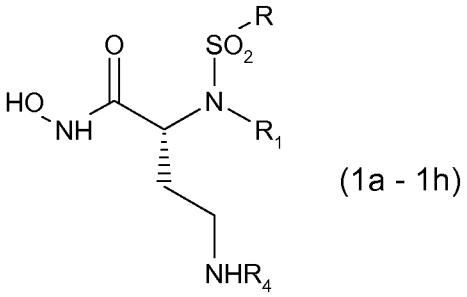
Experimental Section

The following examples from 1 to 15 and corresponding synthetic schemes 1-6 refer to the preparation of metalloproteases inhibitors of formula (II); subsequent examples 16 to 18 and corresponding synthetic schemes 7-10 refer, instead, to the preparation of the compounds of formula (I) of the invention.

Inhibition data of some representative compounds of the invention over selected metalloproteases are also reported in example 19.

Unless otherwise provided, reference to the compounds numbering as reported in the following schemes will be maintained.

Compounds (II) presently numbered as compounds (1a-1h) were prepared by the method outlined in Scheme 1.

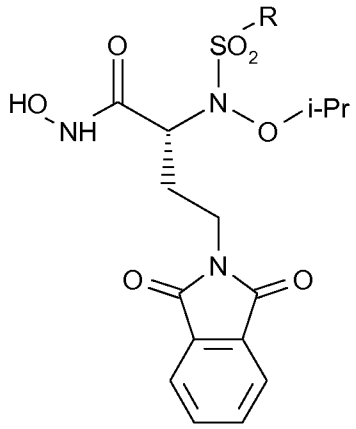


(1a - 1h)

	R	R_1	R_4
1a	biphenyl-4-yl	benzyloxy	benzyloxycarbonyl
1b	biphenyl-4-yl	isopropoxy	benzoyl
1c	biphenyl-4-yl	isopropoxy	methanesulfonyl
1d	biphenyl-4-yl	isopropoxy	acetyl
1e	biphenyl-4-yl	isopropoxy	phenacetyl
1f	p(MeO)C_6H_4-C_6H_4-	isopropoxy	acetyl
1g	p(MeO)C_6H_4-C_6H_4-	isopropoxy	phenacetyl
1h	biphenyl-4-yl	-O-$(CH_2)_2$-O-$(CH_2)_2$- N NH	benzyloxycarbonyl

Optically active α-hydroxy-*tert*-butyl ester (6) was synthesized by direct esterification of commercially available α-hydroxy acid (5) with N,N-dimethylformamide di-tert-butyl acetal (see Rossello, A.et al.; *Bioorg. Med. Chem. Lett,* 2005, *15*, 1321). A Mitsunobu condensation reaction of sulfonamides (7-10) with α-hydroxy-tert-butyl-ester (6), gave tert-butyl esters (11-14). Acid cleavage of esters (11, 14) yielded carboxylic acids (35, 36) which were converted to their O-silylate (37, 38) upon treatment with O-(tert-butyl-dimethylsilyl)hydroxylamine. Hydrolysis with trifluoroacetic acid of tert-butyl O-silylate (37, 38) provided hydroxamic acids (1a, 1h). Tert-butyl esters (17-22) were obtained by Pd-catalyzed hydrogenation of (12, 13) followed by acylation with commercial acyl chlorides. Acid cleavage of esters (17-22) yielded carboxylates (23-28) which were subsequently converted to their respective tert-butyl O-silylate (29, 34). Hydroxamic acids (1b-1g) were then obtained by treatment of (29, 34) with trifluoroacetic acid.

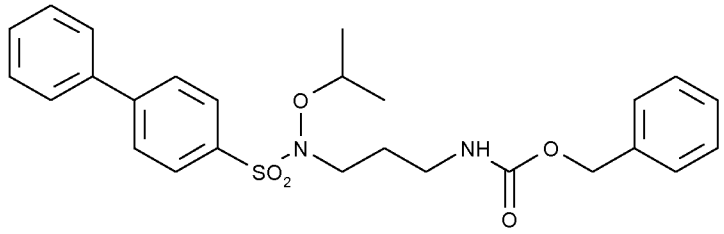
Additional compounds of formula (II), numbered as compounds (2-4) were also prepared according to Scheme 2.



	R
2	p(MeO)C_6H_4-C_6H_5-
3	p(C_6H_5O)C_6H_4-
4	p(EtO)C_6H_4-C_6H_5-

(S)-α-Hydroxy-tert-butyl ester (40) was obtained by direct esterification of commercially available α-hydroxy acid (39) using N,N-dimethylformamide di-tert-butyl acetal. A Mitsunobu coupling of sulfonamides (9, 41, and 42) with α-hydroxy-tert-butyl-ester (40), gave tert-butyl esters (43-45). Acid cleavage of (43, 44) yielded carboxylic acids (46, 47) which were converted to their O-silylate (48, 49) upon treatment with O-(tert-butyl-dimethylsilyl)hydroxylamine. Hydrolysis with trifluoroacetic acid of tert-butyl O-silylate (48, 49) provided hydroxamic acids (2 and 3). Suzuki coupling of commercially available 4-ethoxyphenyl boronic acid with ester (45) gave biphenyl ester (50), which was converted to hydroxamic acid (4) using the procedure described above.

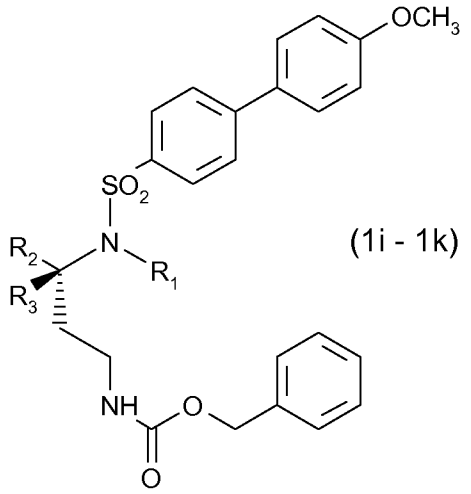
An additional metalloproteases inhibitor of formula (II), presently indicated as compound (64), wherein both R_2 and R_3, in formula (II) are H atoms, was prepared as per Scheme 5 below, through Mitsunobu condensation reaction between commercially available alcohol (63) with sulphonamide (8)



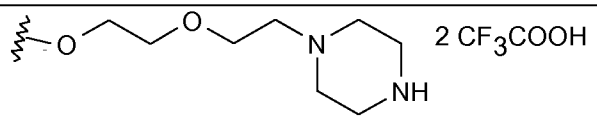
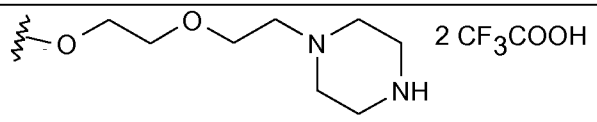
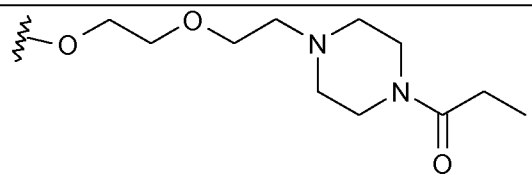
(64)

Sulfonamides (7-10 and 41, 42) used in Schemes 1 and 2 were prepared as shown in Scheme 3. Commercially available arylsulfonyl chlorides (56-59) were coupled with the appropriate O-alkylhydroxylamines (53-55) upon treatment with N-methylmorpholine (see Rossello, A. et al.; *Bioorg. Med. Chem.* 2004, 12, 2441). While O-alkylhydroxylamines (53 and 54) were commercially available, (55) was prepared as described in Scheme 4. N-protection of commercial amino alcohol (60) upon reaction with di-tert-butyldicarbonate gave piperazine derivative (61). Mitsunobu reaction with N-hydroxyphthalimide provided (62) which was converted to (55) by hydrazinolysis with hydrazine hydrate in ethanol.

Additional compounds of formula (II) numbered as compounds (1i – 1k) having the following formulae were also prepared:



(1i - 1k)

One of R_2 or R_3 is H and the other of R_2 or R_3 is:		R_1
1i	-COOH	
1j	-CONHOH	
1k	-CONHOH	

Compounds (1i) and (1j) were prepared as shown in scheme 6 by properly reacting, as formerly reported under Mitsunobu coupling conditions, the sulphonamido derivative (65) with compound (6) of scheme 1. The obtained compound (66) was then deprotected with trifluoroacetic acid so as to obtain compound (1i) as di-trifluoroacetate salt.

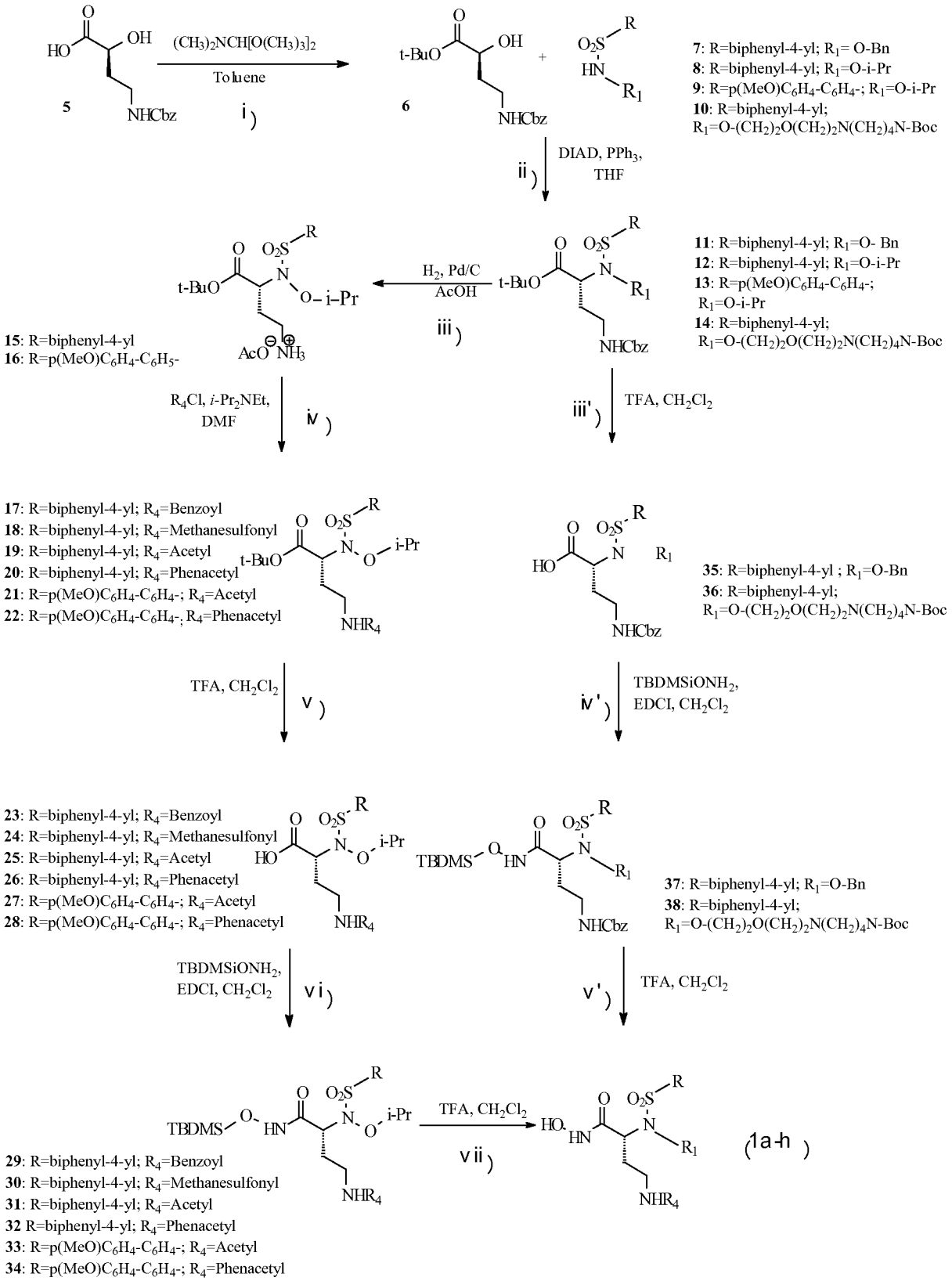
This latter carboxylic acid was then converted into the corresponding hydroxamic acid derivative (1j) di-trifluoroacetate, as formerly reported.

Compound (1j) was then acylated at the piperazino N atom with 2,5-dioxipyrrolidine-1-yl propionate, by working according to conventional methods in the presence of triethylamine, so as to obtain the corresponding compound (1k).

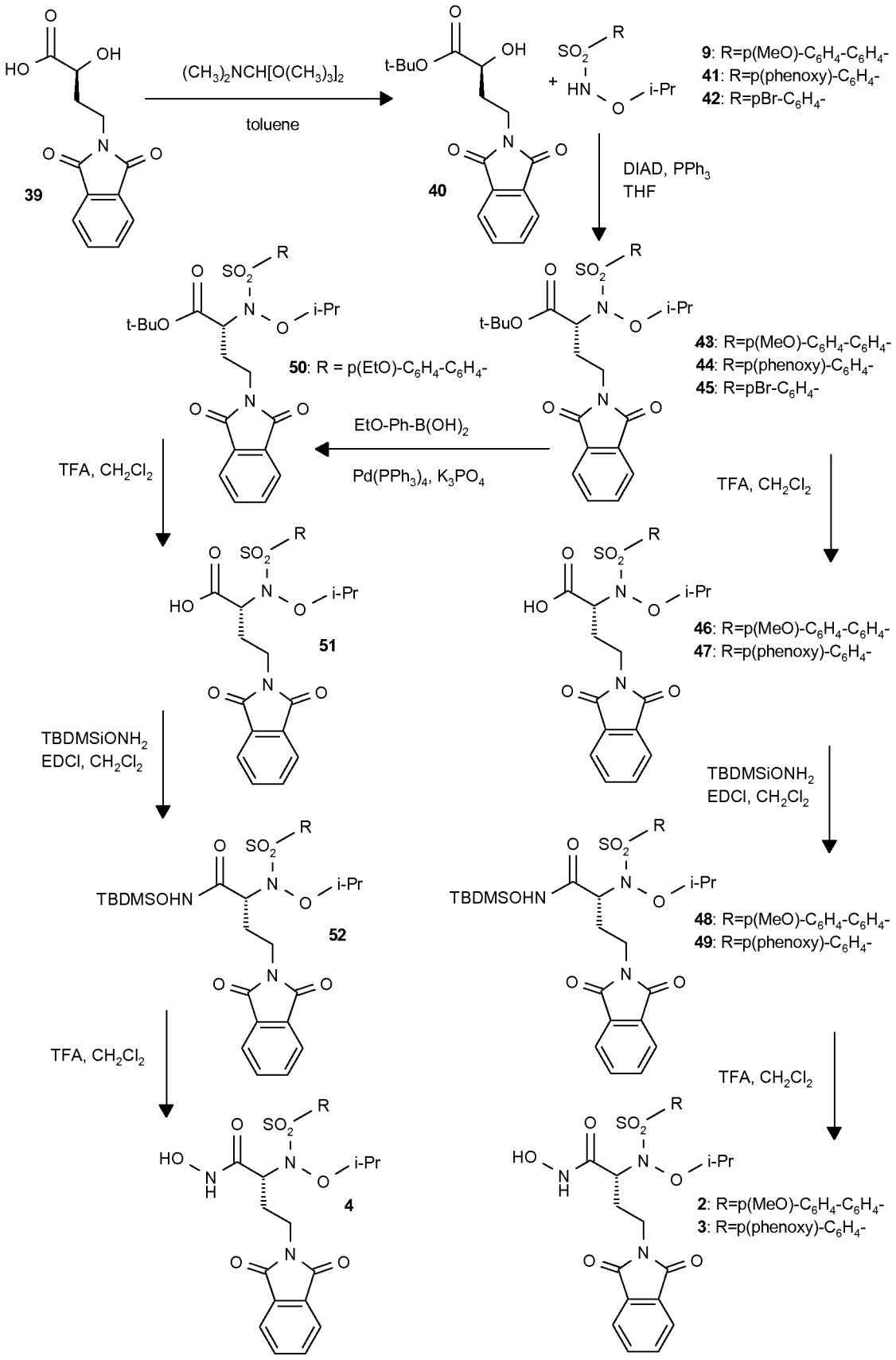
The starting material (65) was obtained, by analogy, as reported in schemes 3 and 4 for the preparation of compound (10).

^{1}H-NMR spectra were recorded on a Varian Gemini 200 (200 MHz) using $CDCl_3$, DMSO-d_6 or $(CD_3)_2CO$ as solvents. Mass spectra were recorded on a GC/MS Trace GCQ Plus Thermo Quest Finnigan spectrometer.

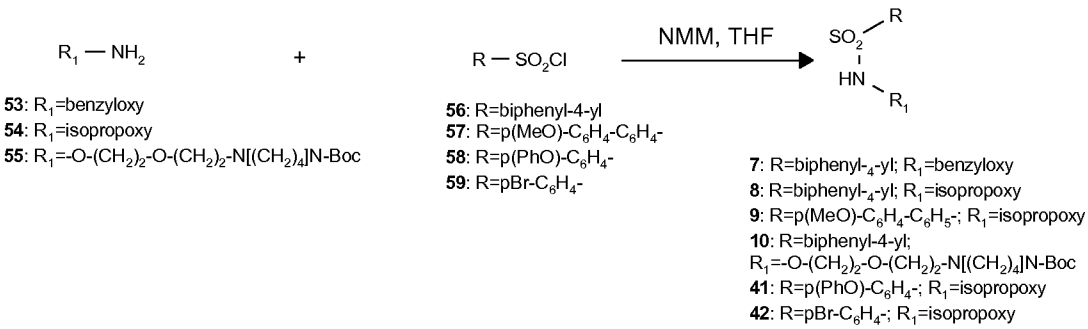
Scheme 1


5
6
(CH3)2NCH[O(CH3)3]2
Toluene
i)
t-BuO
OH
NHCbz
O2S
HN
R1
7: R=biphenyl-4-yl; R1= O-Bn
8: R=biphenyl-4-yl; R1=O-i-Pr
9: R=p(MeO)C6H4-C6H4-; R1=O-i-Pr
10: R=biphenyl-4-yl;
R1=O-(CH2)2O(CH2)2N(CH2)4N-Boc
ii)
DIAD, PPh3,
THF
11: R=biphenyl-4-yl; R1=O- Bn
12: R=biphenyl-4-yl; R1=O-i-Pr
13: R=p(MeO)C6H4-C6H4-;
R1=O-i-Pr
14: R=biphenyl-4-yl;
R1=O-(CH2)2O(CH2)2N(CH2)4N-Boc
H2, Pd/C
AcOH
iii)
t-BuO
O-i-Pr
AcO
NH3
15: R=biphenyl-4-yl
16: R=p(MeO)C6H4-C6H5-
R4Cl, i-Pr2NEt,
DMF
iv)
iii')
TFA, CH2Cl2
17: R=biphenyl-4-yl; R4=Benzoyl
18: R=biphenyl-4-yl; R4=Methanesulfonyl
19: R=biphenyl-4-yl; R4=Acetyl
20: R=biphenyl-4-yl; R4=Phenacetyl
21: R=p(MeO)C6H4-C6H4-; R4=Acetyl
22: R=p(MeO)C6H4-C6H4-; R4=Phenacetyl
i-Pr
NHR4
HO
35: R=biphenyl-4-yl ; R1=O-Bn
36: R=biphenyl-4-yl;
R1=O-(CH2)2O(CH2)2N(CH2)4N-Boc
TFA, CH2Cl2
v)
iv')
TBDMSiONH2,
EDCI, CH2Cl2
23: R=biphenyl-4-yl; R4=Benzoyl
24: R=biphenyl-4-yl; R4=Methanesulfonyl
25: R=biphenyl-4-yl; R4=Acetyl
26: R=biphenyl-4-yl; R4=Phenacetyl
27: R=p(MeO)C6H4-C6H4-; R4=Acetyl
28: R=p(MeO)C6H4-C6H4-; R4=Phenacetyl
TBDMS
37: R=biphenyl-4-yl; R1=O-Bn
38: R=biphenyl-4-yl;
R1=O-(CH2)2O(CH2)2N(CH2)4N-Boc
TBDMSiONH2,
EDCI, CH2Cl2
vi)
v')
TFA, CH2Cl2
29: R=biphenyl-4-yl; R4=Benzoyl
30: R=biphenyl-4-yl; R4=Methanesulfonyl
31: R=biphenyl-4-yl; R4=Acetyl
32 R=biphenyl-4-yl; R4=Phenacetyl
33: R=p(MeO)C6H4-C6H4-; R4=Acetyl
34: R=p(MeO)C6H4-C6H4-; R4=Phenacetyl
TFA, CH2Cl2
vii)
(1a-h)

Scheme 2


39
40
(CH3)2NCH[O(CH3)3]2
toluene
t-BuO
OH
HO
9: R=p(MeO)-C6H4-C6H4-
41: R=p(phenoxy)-C6H4-
42: R=pBr-C6H4-
DIAD, PPh3
THF
50: R = p(EtO)-C6H4-C6H4-
43: R=p(MeO)-C6H4-C6H4-
44: R=p(phenoxy)-C6H4-
45: R=pBr-C6H4-
EtO-Ph-B(OH)2
Pd(PPh3)4, K3PO4
TFA, CH2Cl2
51
46: R=p(MeO)-C6H4-C6H4-
47: R=p(phenoxy)-C6H4-
TBDMSiONH2
EDCl, CH2Cl2
52
TBDMSOHN
48: R=p(MeO)-C6H4-C6H4-
49: R=p(phenoxy)-C6H4-
4
2: R=p(MeO)-C6H4-C6H4-
3: R=p(phenoxy)-C6H4-

Scheme 3

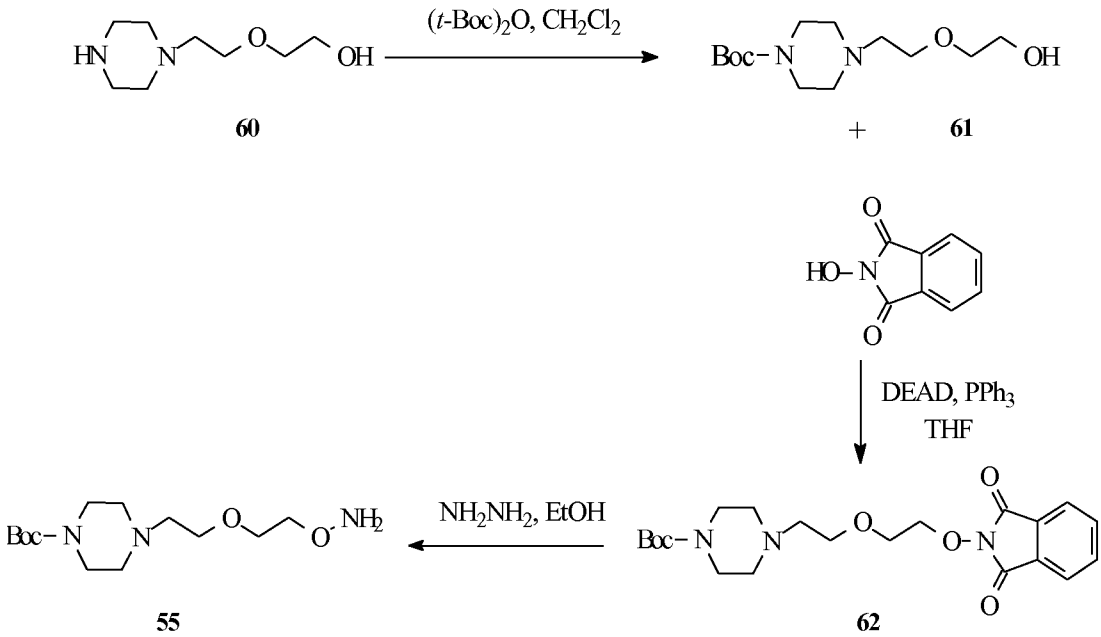


53: R_1=benzyloxy
54: R_1=isopropoxy
55: R_1=-O-$(CH_2)_2$-O-$(CH_2)_2$-N[$(CH_2)_4$]N-Boc

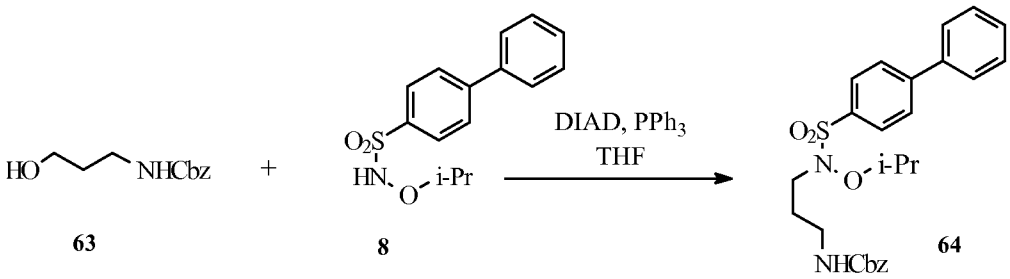
56: R=biphenyl-4-yl
57: R=p(MeO)-C_6H_4-C_6H_4-
58: R=p(PhO)-C_6H_4-
59: R=pBr-C_6H_4-

7: R=biphenyl-$_4$-yl; R_1=benzyloxy
8: R=biphenyl-$_4$-yl; R_1=isopropoxy
9: R=p(MeO)-C_6H_4-C_6H_5-; R_1=isopropoxy
10: R=biphenyl-4-yl;
R_1=-O-$(CH_2)_2$-O-$(CH_2)_2$-N[$(CH_2)_4$]N-Boc
41: R=p(PhO)-C_6H_4-; R_1=isopropoxy
42: R=pBr-C_6H_4-; R_1=isopropoxy

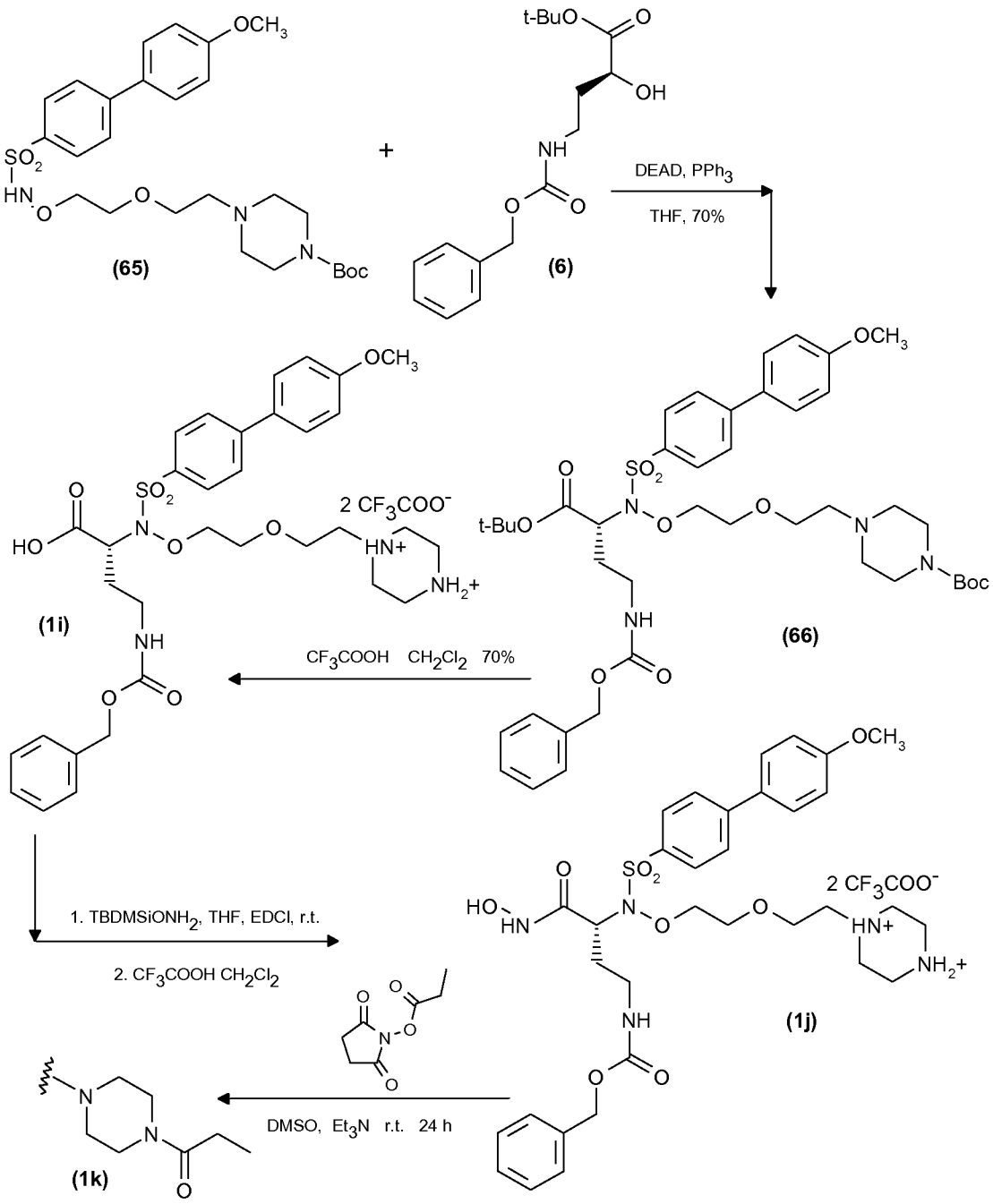
Scheme 4



Scheme 5

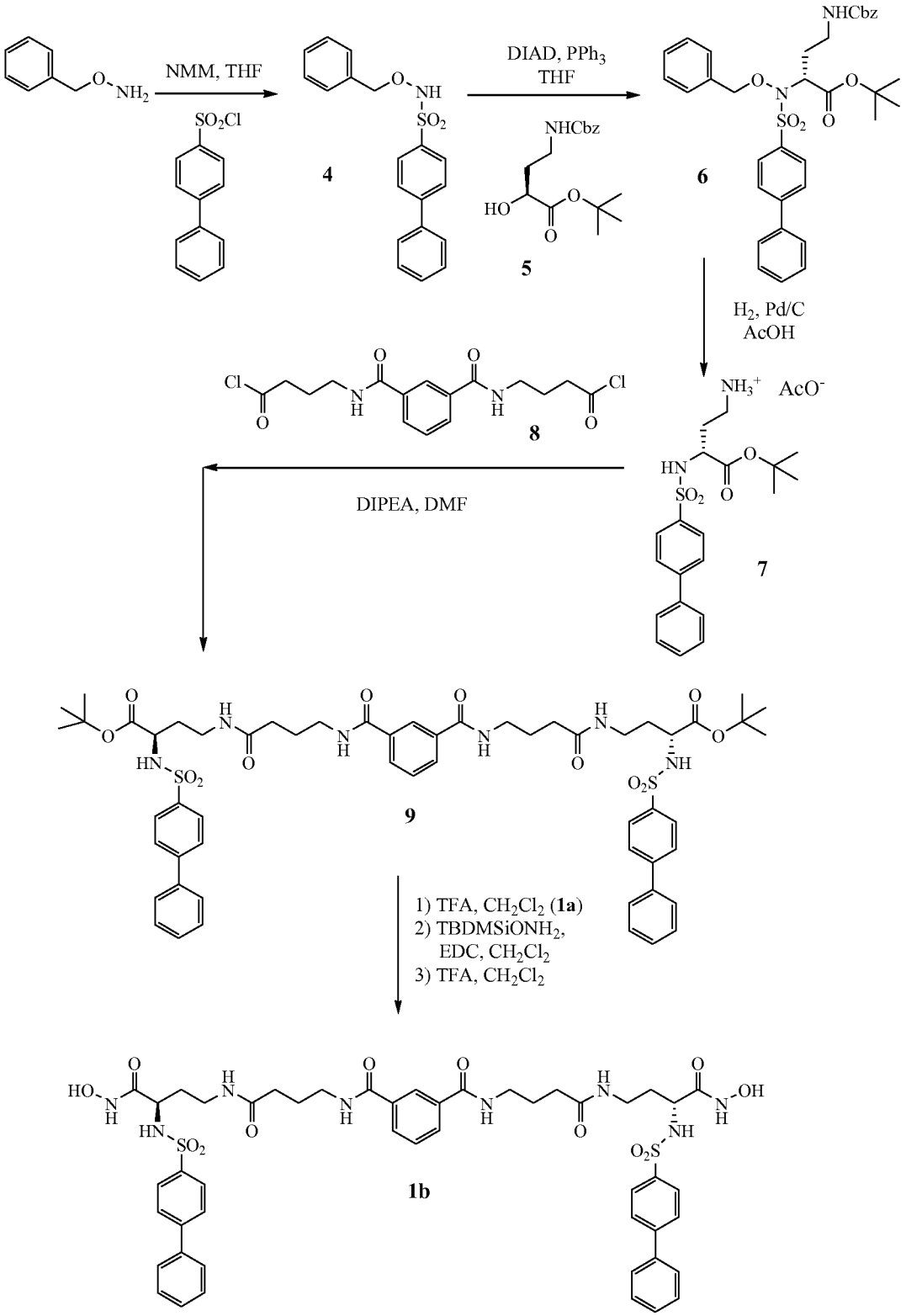


Scheme 6


OCH3
SO2
HN
O
O
N
N
Boc
(65)
+
t-BuO
O
OH
NH
O
O
(6)
DEAD, PPh3
THF, 70%
2 CF3COO-
HO
HN+
NH2+
(1i)
t-BuO
(66)
CF3COOH CH2Cl2 70%
1. TBDMSiONH2, THF, EDCl, r.t.
2. CF3COOH CH2Cl2
(1j)
DMSO, Et3N r.t. 24 h
(1k)

5

Scheme 7

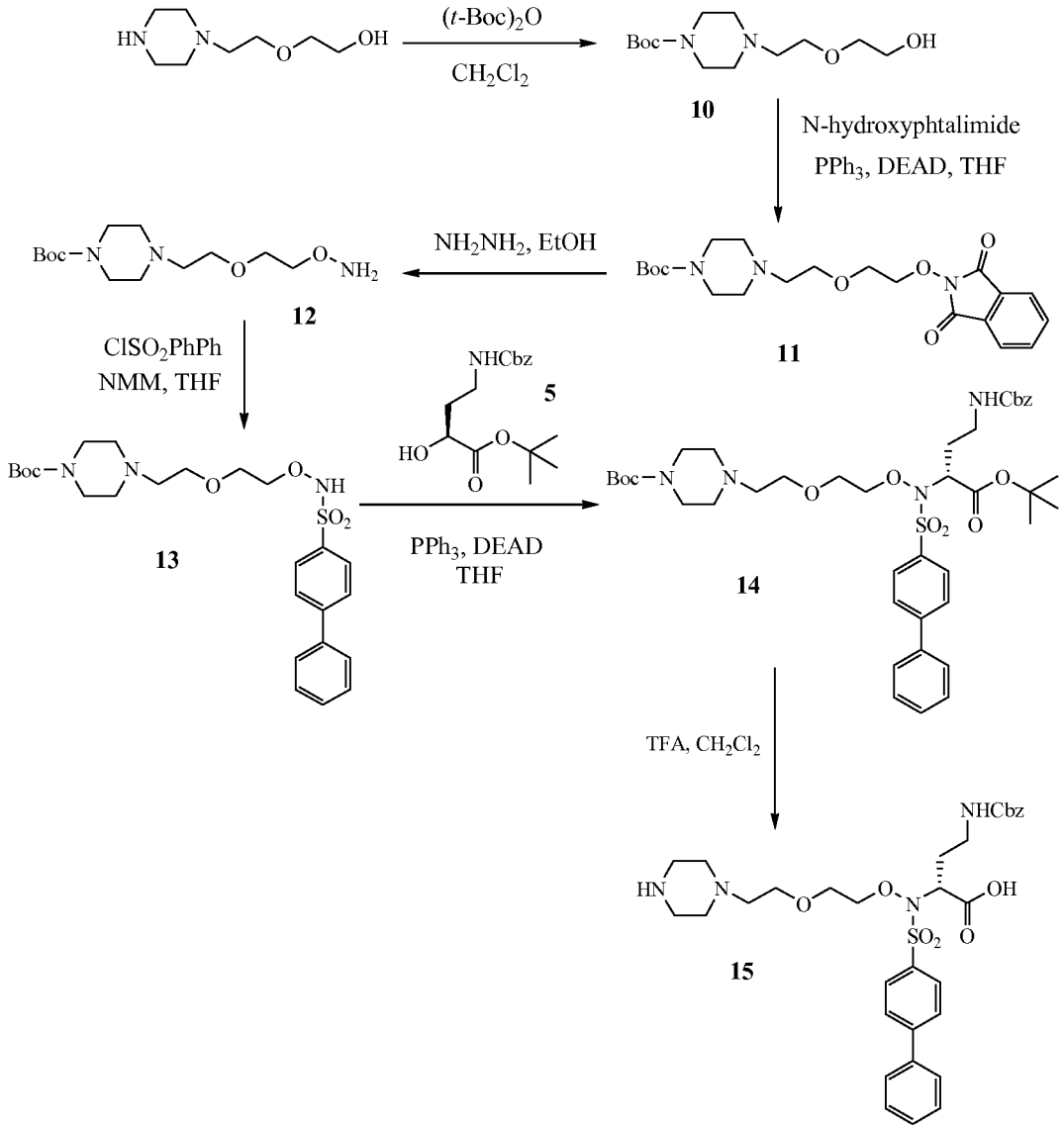


Commercially available biphenyl-4-sulfonyl chloride was coupled with *O*-benzylhydroxylamine hydrochloride upon treatment with *N*-methylmorpholine (see Rossello, A. et al.; *Bioorg. Med. Chem.* 2004, 12, 2441) to give sulphonamide **4**. A

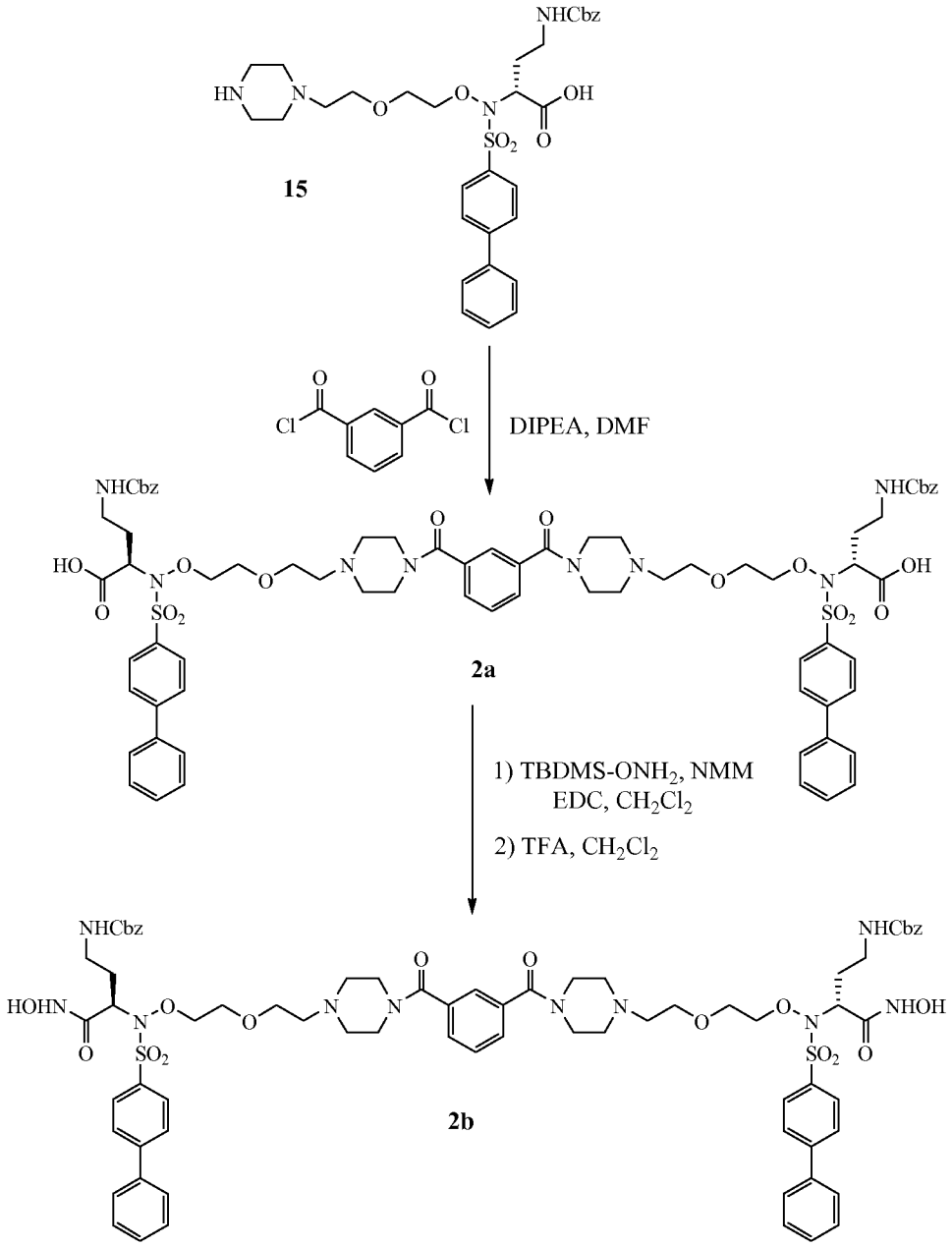
Mitsunobu condensation reaction of sulphonamide **4** with α-hydroxy-*tert*-butyl-ester **5** (see Rossello, A.et al.; *Bioorg. Med. Chem. Lett,* 2005, *15*, 1321), gave *tert*-butyl ester **6**. The dimeric *tert*-butyl ester **9** was obtained by Pd-catalyzed hydrogenation of **6** followed by acylation with acyl chloride **8.** The latter was synthesized as reported in Rossello, A. et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2311-2314. Acid cleavage of **9** yielded carboxylate **1a** which was subsequently converted into *tert*-butyl *O*-silylate. Hydroxamic acid **1b** was then obtained by treatment of the *tert*-butyl *O*-silylate with trifluoroacetic acid.

Additional compounds of formula (I) of the invention **(2a,b)** were also prepared according to the following schemes 8 and 9.

Scheme 8


(t-Boc)2O
CH2Cl2
10
N-hydroxyphtalimide
PPh3, DEAD, THF
11
NH2NH2, EtOH
12
ClSO2PhPh
NMM, THF
13
5
PPh3, DEAD
THF
14
TFA, CH2Cl2
15

Scheme 9

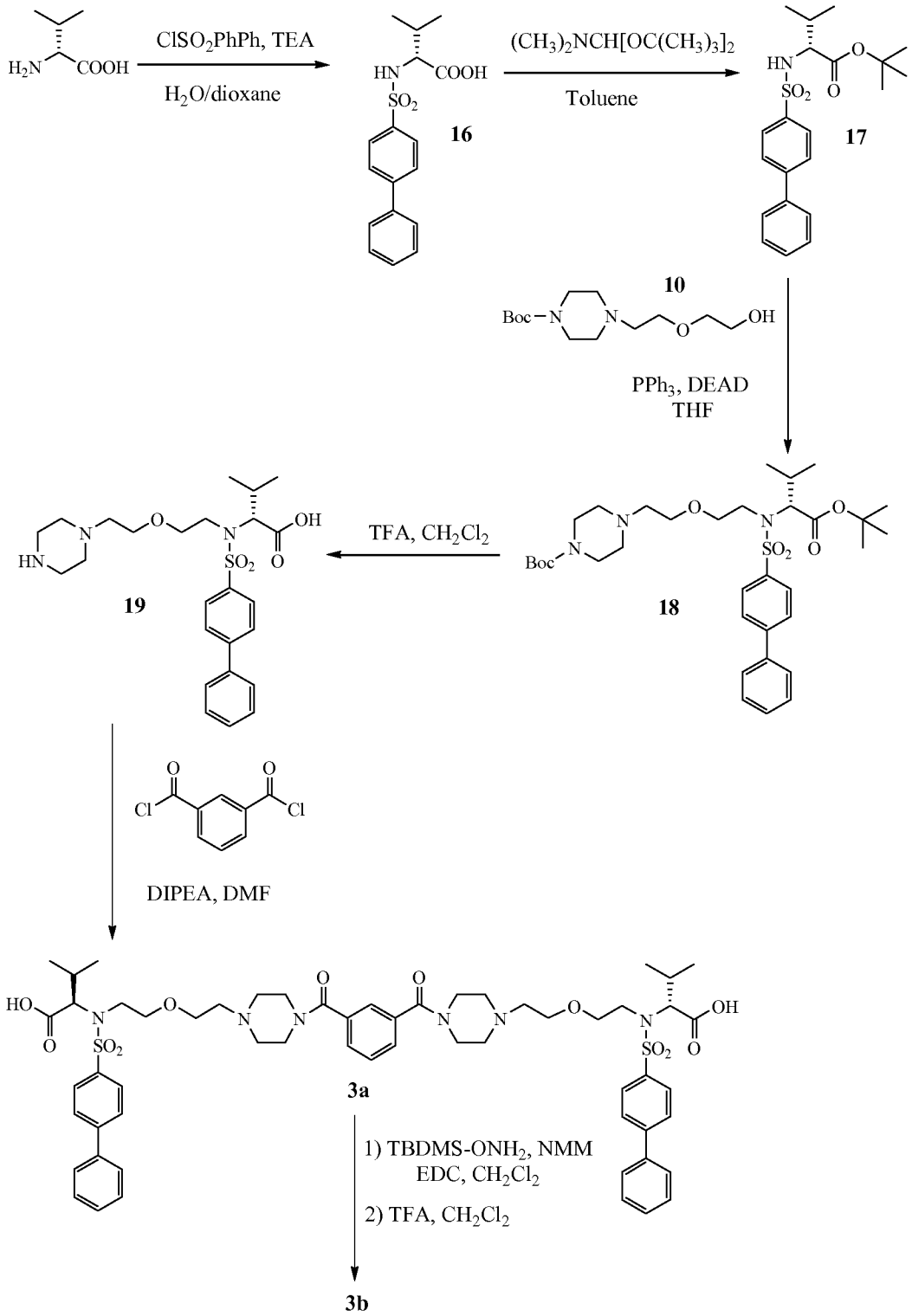


N-protection of commercial 1-[2-(2-hydroxyethoxy)ethyl]piperazine upon reaction with di-*tert*-butyldicarbonate gave piperazine derivative (**10**). Mitsunobu reaction with *N*-hydroxyphthalimide provided (**11**) which was converted to (**12**) by hydrazinolysis with hydrazine hydrate in ethanol. Commercially available biphenyl-4-sulfonyl chloride was coupled with (**12**) upon treatment with *N*-methylmorpholine to give sulphonamide (**13**). A Mitsunobu condensation reaction of sulphonamide (**13**) with α-hydroxy-*tert*-butyl-ester (**5**) (described above), gave *tert*-butyl ester (**14**). Acid cleavage of **14** yielded

carboxylate **(15)** which was acylated by reaction with isophthaloyl chloride. The dimeric acid **(2a)** was converted into *tert*-butyl *O*-silylate and subsequently hydrolyzed to hydroxamic acid **(2b)** by treatment with trifluoroacetic acid.

Additional compounds of formula (I) of the invention **(3a, 3b)** were also prepared according to the following scheme 10.

Scheme 10


ClSO2PhPh, TEA
H2O/dioxane
(CH3)2NCH[OC(CH3)3]2
Toluene
16
17
10
PPh3, DEAD
THF
TFA, CH2Cl2
18
19
DIPEA, DMF
3a
1) TBDMS-ONH2, NMM
EDC, CH2Cl2
2) TFA, CH2Cl2
3b

Dimeric inhibitors of formula (**3a**, **b)** were prepared by the method outlined in Scheme 10. D-valine was acylated by reaction with biphenyl-4-sulfonyl chloride in the presence of triethylamine to give (**16**). The latter was protected as *tert*-butyl ester by reaction with *N*,*N*-dimethylformamide di-*tert*-butyl acetal and then condensed with alcohol (**10)** (described above) by Mitsunobu reaction. Acid cleavage of (**18)** yielded carboxylate (**19)** which was acylated by reaction with isophthaloyl chloride to give (**3a)**. The dimeric acid (**3a)** was converted into *tert*-butyl *O*-silylate and subsequently hydrolyzed to hydroxamic acid (**3b)** by treatment with trifluoroacetic acid.

Example 1

Preparation of intermediate of formula (II): compound (1a): (R)-benzyl 3-(N-(benzyloxy)biphenyl-4-ylsulfonamido)-4-(hydroxyamino)-4-oxobutylcarbamate

Preparation of compound (6)

A solution of (*S*)-(+)-Z-4-amino-2-hydroxybutyric acid **(5)** (5 g, 19.74 mmol) in toluene (38 mL) containing N,N-dimethylformamide di-tert-butyl acetal (18.92 mL, 78.96 mmol) was heated to 95°C for 3 h. The solvent was then evaporated and the crude product was purified by flash chromatography on silica gel (n-hexane/EtOAc = 7:4) to give **(6)** (3.4 g, 55.7 % yields) as yellow solid.

Mp 42-44°C; $[\alpha]^{20}_{D}$= - 5.9° (c= 10.1 mg/ml, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δ**:** 1.47 (s, 9H); 1.76-1.85 (m, 1H); 1.94-2.09 (m, 1H); 2.74 (br s, 1H); 3.36 (dd, *J*= 6.04 Hz, *J*= 11.99 Hz, 2H); 4.10 (dd, *J*= 4.02 Hz, *J*= 8.05 Hz, 1H); 5.09 (s, 2H); 5.21 (br s, 1H); 7.31-7.37 (m, 5H)

Anal. Calcd. for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.22; H, 7.48; N, 4.53.

Preparation of compound (7)

A solution of biphenyl-4-sulfonyl chloride **(56)** (3.17 g, 12.53 mmol) in anhydrous THF (32 mL) was added dropwise to a stirred and cooled (0°C) solution of O-benzylhydroxylamine hydrochloride **(53)** (2 g, 12.53 mmol) and N-methylmorpholine (2.75 mL, 25.06 mmol) in anhydrous THF (32 mL). After 30 min. under these conditions, the reaction mixture was stirred at rt for 3 days, then was diluted with AcOEt and washed with H_2O giving, after work-up, sulfonamide **(7)** (3.62 g, 85%) as a white solid.

Mp= 130-132°C;

^{1}H-NMR ($CDCl_3$) δ: 5.01 (s, 2H); 7.01 (s, 1H); 7.35 (m, 5H); 7.44-7.51 (m, 3H); 7.57-7.62 (m, 2H); 7.70-7.75 (m, 2H); 7.97-8.01 (m, 2H).

Preparation of compound (11)

Diisopropyl azodicarboxylate (DIAD) (1.28 mL, 6.52 mmol) was added dropwise to a solution containing the secondary alcohol **(6)** (0.8 g, 2.61 mmol), the sulfonamide **(7)** (1.3 g, 3.91 mmol) and triphenylphosphine (2.05 g, 7.83 mmol) in anhydrous THF (45 mL) under nitrogen atmosphere at 0°C. The resulting solution was stirred for 5 h at rt and evaporated under reduced pressure to afford a crude product, which was purified by flash chromatography on silica gel (n-hexane/EtOAc = 3:1) to yield compound **(11)** (0.95 g, 58% yield) as pure yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (s, 9H); 1.90-2.04 (m, 2H); 3.16-3.40 (m, 2H); 4.16 (t, *J*= 7.1Hz, 1H); 4.93-5.00 (m, 1H); 5.07-5.19 (m, 4H); 7.33-7.37 (m, 10H); 7.41-7.59 (m, 5H); 7.66-7.70 (m, 2H); 7.92-7.97 (m, 2H).

^{13}C-NMR ($CDCl_3$) δ: 22.09; 27.87; 37.59; 62.75; 66.76; 80.87; 82.56; 127.43; 127.67; 128.16; 128.56; 128.72; 128.92; 129.14; 129.89; 129.94; 133.89; 134;80; 139.17; 146.84; 156.27.

Preparation of compound (35)

Trifluoroacetic acid (0.9 mL, 57.00 mmol) was added dropwise to a stirred solution of tert-butyl ester **(11)** (136 mg, 0.21 mmol) in freshly distilled CH_2Cl_2 (1.0 mL), cooled to 0°C. The solution was stirred for 5 h at 0°C and the solvent was removed in vacuo to give compound **(35)** (128 mg, 100 % yield) as oil.

^{1}H-NMR ($CDCl_3$) δ: 1.60-1.70 (m, 1H); 1.88-2.08 (m, 1H); 3.19 (m, 2H); 4.30 (t, *J*=6.9Hz, 1H); 5.02-5.17 (m, 4H); 7.28-7.34 (m, 10H); 7.40-7.51 (m, 3H); 7.55-7.59 (m, 2H); 7.65-7.70 (m, 2H); 7.91-7.95 (m, 2H).

Preparation of compound (37)

To a solution of carboxylic acid **(35)** (117 mg, 0.2 mmol) and O-(tert-butyldimethyl-silyl)hydroxylamine (44 mg, 0.3 mmol) in freshly distilled CH_2Cl_2 (3.6 mL) cooled to 0°C, was added 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (EDCI) portionwise (57.5 mg, 0.3 mmol). After stirring at rt for 20 h, the mixture was washed with H_2O and the organic phase was dried and evaporated in vacuo. The residue

was purified by flash chromatography on silica gel (n-hexane/EtOAc = 2.5:1) to yield compound **(37)** (28 mg, 20 % yield) as yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.13 (s, 6H); 0.90 (s, 9H); 1.90-2.11 (m, 2H); 2.80-3.40 (m, 2H); 4.13-4.22 (m, 1H); 5.02-5.27 (m, 4H); 7.31-7.46 (m, 13H); 7.53-7.58 (m, 2H); 7.64-7.68 (m, 2H); 7.84-7.88 (m, 2H).

Preparation of the title compound (1a)

Trifluoroacetic acid (0.15 mL, 1.85 mmol) was added dropwise to a stirred solution of compound **(37)** (23 mg, 0.03 mmol) in freshly distilled CH_2Cl_2 (1 mL), cooled to 0°C. The solution was stirred for 5 h at 0°C and the solvent was removed in vacuo to give a crude product that was recrystallized from Et_2O and n-hexane to give **(1a)** (10 mg, 53 % yield) as solid.

^{1}H-NMR ($CDCl_3$) δ: 1.99 (m, 2H); 3.00-3.35 (m, 2H); 4.29 (m, 1H); 5.08-5.26 (m, 4H); 7.34-7.45 (m, 13H); 7.53-7.58 (m, 2H); 7.66-7.70 (m, 2H); 7.87-7.91 (m, 2H).

Example 2

Preparation of intermediate of formula (II): compound (1b): (R)-*N*-(4-(hydroxyamino)-3-(*N*-isopropoxybiphenyl-4-ylsulfonamido)-4-oxobutyl)benzamide

Preparation of compound (8)

N-isopropoxy-1,1'-biphenyl-4-sulfonamide was prepared as previously described by Rossello, A.et al. (*Bioorg. Med. Chem.* 2004, *12*, 2441).

Preparation of compound (12)

Tert-butyl ester **(12)** was prepared from sulfonamide derivative **(8)** (1.08g, 3.72 mmol) and alcohol **(6)** (0.76 g, 2.48 mmol) following the procedure previously described for the preparation of compound **(11)**, as set forth in Example 1. The crude reaction mixture was purified by flash chromatography (n-hexane/AcOEt = 5:1), to give **(12)** (1.14 g, 79 % yield) as a yellow oil.

$[\alpha]^{20}_D$= + 55° (c= 9.1 mg/L, $CHCl_3$);

^{1}H-NMR ($CDCl_3$) δ**:** 1.22-1.25 (m, 15H); 2.04 (m, 2H); 3.22-3.37 (m, 2H); 4.12 (dd, *J*= 7.14 Hz, *J*= 14.29 Hz, 1H); 4.43 (septet, *J*= 6.2 Hz, 1H); 5.08 (s, 2H); 7.34 (m, 5H); 7.42-7.53 (m, 3H); 7.55-7.61 (m, 2H); 7.7-7.74 (m, 2H); 7.94-7.98 (m, 2H).

Preparation of compound (15)

A solution of compound **(12)** (0.74 g, 1.27 mmol) in MeOH (80 mL) was stirred under hydrogen atmosphere in the presence of 10% Pd-C (0.20 g) and glacial acetic acid (80

mL) for 17 h at room temperature. The resulting mixture was filtered on celite and the filtrate was evaporated under reduced pressure to give **(15)** (0.60 g, 93 % yield) as a brownish oil.

^{1}H-NMR (CDCl3) δ: 1.10 (brs, 9H); 1.20 (t, *J*=4.4Hz, 6H); 2.16-2.30 (m, 2H); 3.16 (m, 2H); 4.34-4.46 (m, 2H); 7.40-7.51 (m, 3H); 7.56-7.59 (m, 2H); 7.71-7.75 (m, 2H); 8.00-8.04 (m, 2H).

^{13}C-NMR (CDCl3) δ: 21.15; 21.22; 27.72; 36.70; 62.97; 80.03; 82.49; 127.03; 127.45; 127.59; 127.76; 128.67; 129.14; 130.49; 133.60; 139.30; 146.89.

Preparation of compound (17)

A solution of compound **(15)** (0.30 g, 0.59 mmol) in dry DMF (6 mL) was treated with benzoyl chloride (0.08 mL, 0.70 mmol) and i-Pr_2NEt (0.20 mL, 1.18 mmol). The reaction mixture was stirred at rt for 17 h, then was diluted with ethyl acetate, washed with H_2O, dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography (n-hexane/AcOEt = 2.5:1), to give **(17)** (112 mg, 34 % yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ**:** 1.13 (brs, 9H); 1.23 (d, *J*=5.1Hz, 3H); 1.26 (d, *J*=4.4Hz, 3H); 2.10-2.21 (m, 2H); 3.34-3.50 (m, 1H); 3.80-3.92 (m, 1H); 4.23 (t, *J*=7.1Hz, 1H); 4.45 (septet, 1H); 7.39-7.59 (m, 10H); 7.69-7.73 (m, 2H); 7.93-7.98 (m, 2H).

Preparation of compound (23)

Carboxylic acid **(23)** (89 mg**,** 100 % yield) was prepared from ester derivative **(17)** (0.10 g, 0.18 mmol) following the procedure previously described for the preparation of compound **(35)**, as per Example 1.

^{1}H-NMR ($CDCl_3$) δ**:** 1.20 (t, *J*=5.1Hz, 6H); 1.80-2.28 (m, 2H); 3.40-3.55 (m, 1H); 3.60-3.82 (m, 1H); 4.30-4.50 (m, 2H); 6.56 (brs, 1H); 7.43-7.58 (m, 10H); 7.66-7.69 (m, 2H); 7.91-7.94 (m, 2H).

Preparation of compound (29)

Following an analogous procedure to that used for the preparation of compound **(37)**, in Example 1, carboxylic acid **(23)** (90 mg, 0.18 mmol) was coupled with O-(tert-butyldimethyl-silyl)hydroxylamine. Silica gel column chromatography (n-hexane/AcOEt = 2:1) yielded the desired product (30 mg, 27 % yield).

^{1}H-NMR ($CDCl_3$) δ**:** 0.16 (s, 6H); 0.93 (s, 9H); 1.22 (d, *J*=6.2Hz, 3H); 1.28 (d, *J*=6.2Hz, 3H); 2.02-2.16 (m, 2H); 3.20 (m, 1H); 3.43 (m, 1H); 4.06-4.20 (m, 1H); 4.46

(septet, 1H); 6.76 (brs, 1H); 7.35-7.65 (m, 10H); 7.73-7.77 (m, 2H); 7.87-7.91 (m, 2H); 9.01 (brs, 1H).

Preparation of the title compound(1b)

Following a procedure analogous to that used for the preparation of compound **(1a)**, in Example 1, tert-butyl O-silylate **(29)** (30 mg, 0.05 mmol) was treated with TFA to give the desired hydroxamic acid (15 mg, 60.5 % yield) after recrystallization from Et_2O.

^{1}H-NMR ($CDCl_3$) δ: 1.24 (t, *J*=6.5Hz, 6H); 1.44-1.69 (m, 1H); 2.05-2.21 (m, 1H); 3.10-3.50 (m, 2H); 4.20-4.50 (m, 2H); 7.10 (brs, 1H); 7.30-7.55 (m, 10H); 7.59-7.63 (m, 2H); 7.86-7.90 (m, 2H).

Example 3

Preparation of intermediate of formula (II): compound (1c): (R)-N-hydroxy-2-(N-isopropoxybiphenyl-4-ylsulfonamido)-4-(methylsulfonamido)butanamide

Preparation of compound (18)

A solution of compound **(15)** prepared according to Example 2 (0.30 g, 0.60 mmol), in dry THF (3 mL), was treated with methanesulfonyl chloride (0.05 mL, 0.60 mmol) and N-methylmorpholine (0.13 mL, 1.2 mmol). The reaction mixture was stirred at room temperature overnight, then was diluted with AcOEt, washed with H_2O, dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography (n-hexane/AcOEt = 3:2), to give **(18)** (100 mg, 32 % yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.14 (brs, 9H); 1.20-1.26 (m, 6H); 2.04 (brs, 2H); 2.95 (s, 3H); 3.29 (brs, 2H); 4.25 (t, *J*=7.1Hz, 1H); 4.42 (septet, 1H); 7.43-7.54 (m, 3H); 7.58-7.62 (m, 2H); 7.74-7.78 (m, 2H); 7.96-8.00 (m, 2H).

Preparation of compound (24)

Following a procedure analogous to that used for the preparation of compound **(35)**, in Example 1, ester derivative **(18)** (100 mg, 0.19 mmol) was treated with TFA to give the desired carboxylic acid **(24)** (73 mg, 79 % yield), after recrystallization from Et_2O and n-hexane.

^{1}H-NMR ($CDCl_3$) δ: 1.22 (d, *J*=6.2Hz, 6H); 2.06-2.17 (m, 2H); 2.91 (s, 3H); 3.21 (brs, 2H); 4.34-4.44 (m, 2H); 7.42-7.53 (m, 3H); 7.61-7.66 (m, 2H); 7.74-7.78 (m, 2H); 7.95-7.99 (m, 2H).

Preparation of compound (30)

Following a procedure analogous to that used for the preparation of compound **(37)**, in Example 1, carboxylic acid **(24)** (70 mg, 0.15 mmol) was coupled with O-(tert-butyldimethylsilyl)hydroxylamine. Silica gel column chromatography (n-hexane/AcOEt = 1:1) yielded the desired product (32 mg, 33 % yield).

^{1}H-NMR ($CDCl_3$) δ: 0.15 (s, 6H); 0.93 (s, 9H); 1.20 (d, *J*=6.2Hz, 3H); 1.25 (d, *J*=5.8Hz, 3H); 2.00-2.15 (m, 2H); 2.83 (s, 3H); 2.89-2.99 (m, 2H); 4.23-4.29 (m, 1H); 4.40 (septet, 1H); 7.42-7.52 (m, 3H); 7.61-7.66 (m, 2H); 7.79-7.83 (m, 2H); 7.96-8.00 (m, 2H); 8.64 (brs, 1H).

Preparation of the title compound (1c)

Following a procedure analogous to that used for the preparation of the compound **(1a)**, in Example 1, tert-butyl *O*-silylate **(30)** (30 mg, 0.05 mmol) was treated with TFA to give the desired hydroxamic acid (15 mg, 60 % yield), after recrystallization from Et_2O and n-hexane.

^{1}H-NMR ($CDCl_3$) δ: 1.24 (t, *J*=6.4Hz, 6H); 2.01-2.18 (m, 2H); 2.88 (s, 3H); 3.00-3.20 (m, 2H); 4.40-4.48 (m, 2H); 4.88 (brs, 1H); 7.42-7.53 (m, 3H); 7.62-7.66 (m, 2H); 7.78-7.83 (m, 2H); 7.95-7.99 (m, 2H).

Example 4

Preparation of intermediate of formula (II): compound (1d): (R)-4-acetamido-*N*-hydroxy-2-(*N*-isopropoxybiphenyl-4-ylsulfonamido)butanamide

Preparation of compound (19)

Following a procedure analogous to that used for the preparation of compound **(17)**, in Example 2, ester derivative **(15)** (0.30 g, 0.59 mmol) was acylated with acetyl chloride. Silica gel column chromatography (n-hexane/AcOEt = 1:1) yielded the desired product **(19)** (60 mg, 22 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.19-1.24 (m, 15H); 1.90-2.01 (m, 5H); 3.13-3.23 (m, 1H); 3.53 (m, 1H); 4.12 (m, 1H); 4.40 (septet, 1H); 6.11 (brs, 1H); 7.41-7.52 (m, 3H); 7.57-7.61 (m, 2H); 7.72-7.76 (m, 2H); 7.94-7.98 (m, 2H).

^{13}C-NMR ($CDCl_3$) δ: 21.17; 23.48; 27.76; 36.17; 63.59; 79.80; 82.25; 127.39; 127.52; 128.72; 129.16; 130.14; 133.80; 139.19; 146.84; 170.22.

Preparation of compound (25)

Following a procedure analogous to that used for the preparation of compound **(35)**, in Example 1, ester derivative **(19)** (60 mg, 0.12 mmol) was treated with TFA to give the desired carboxylic acid **(25)** (60 mg, 100 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.16 (d, *J*=2.01, 3H); 1.19 (d, *J*=2.01, 3H); 1.92-2.10 (m, 5H); 3.15-3.60 (m, 2H); 4.20-4.39 (m, 2H); 6.73 (brs, 1H); 7.42-7.52 (m, 3H); 7.59-7.63 (m, 2H); 7.73-7.77 (m, 2H); 7.93-7.97 (m, 2H); 10.24 (brs, 1H).

Preparation of compound (31)

Following a procedure analogous to that used for the preparation of compound **(37)**, in Example 1, carboxylic acid **(25)** (60 mg, 0.14 mmol) was coupled with O-(tert-butyldimethylsilyl)hydroxylamine. Silica gel column chromatography (n-hexane/AcOEt = 1:2) yielded the desired product (12 mg, 16 % yield).

^{1}H-NMR ($CDCl_3$) δ: 0.15 (s, 6H); 0.93 (s, 9H); 1.21 (d, *J*=6.2Hz, 3H); 1.25 (d, *J*=6.2Hz, 3H); 1.90-2.05 (m, 5H); 2.80-3.26 (m, 2H); 4.06-4.16 (m, 1H); 4.44 (septet, 1H); 5.95 (brs, 1H); 7.42-7.53 (m, 3H); 7.58-7.65 (m, 2H); 7.76-7.80 (m, 2H); 7.92-7.96 (m, 2H); 8.90 (brs, 1H).

Preparation of the title compound (1d)

Following a procedure analogous to that used for the preparation of compound **(1a)**, in Example 1, tert-butyl *O*-silylate **(31)** (12 mg, 0.02 mmol) was treated with TFA to give the desired hydroxamic acid (11 mg, 90 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.23 (d, *J*=6.7, 6H); 1.90-2.08 (m, 5H); 3.04-3.35 (m, 2H); 4.22 (m, 1H); 4.40 (septet, 1H); 6.73 (brs, 1H); 7.42-7.52 (m, 3H); 7.59-7.63 (m, 2H); 7.76-7.80 (m, 2H); 7.92-7.96 (m, 2H).

Example 5

Preparation of intermediate of formula (II): compound (1e): (R)-*N*-hydroxy-2-(*N*-isopropoxybiphenyl-4-ylsulfonamido)-4-(2-phenylacetamido)butanamide

Preparation of compound (20)

Following a procedure analogous to that used for the preparation of compound **(17)**, in Example 2, ester derivative **(15)** (0.30 g, 0.59 mmol) was acylated with phenylacetyl chloride. Silica gel column chromatography (n-hexane/AcOEt = 2:1) yielded the desired product (55 mg, 16 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.22 (m, 15H); 1.81-2.05 (m, 2H); 3.00-3.21 (m, 1H); 3.50-3.60 (m, 3H); 3.96 (t, *J*=7.5Hz, 1H); 4.38 (septet, 1H); 7.28-7.37 (m, 5H); 7.43-7.54 (m, 3H); 7.57-7.62 (m, 2H); 7.68-7.73 (m, 2H); 7.80-7.84 (m, 2H).

Preparation of compound (26)

Following a procedure analogous to that used for the preparation of compound **(35),** in Example 1, ester derivative **(20)** (55 mg, 0.09 mmol) was treated with TFA to give the desired carboxylic acid **(26)** (53 mg, 100 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.14 (d, *J*=3.4, 3H); 1.17 (d, *J*=3.4, 3H); 1.93-2.10 (m, 2H); 3.14 (m, 1H); 3.47 (m, 1H); 3.61 (s, 2H); 4.13 (t, *J*=7.3Hz, 1H); 4.33 (septet, 1H); 5.32 (brs, 1H); 6.14 (brs, 1H); 7.22-7.26 (m, 1H); 7.30-7.37 (m, 4H); 7.42-7.53 (m, 3H); 7.58-7.63 (m, 2H); 7.67-7.73 (m, 2H); 7.82-7.86 (m, 2H).

Preparation of compound (32)

Following a procedure analogous to that used for the preparation of compound **(37)**, in Example 1, carboxylic acid **(26)** (53 mg, 0.10 mmol) was coupled with O-(tert-butyldimethylsilyl)hydroxylamine to give compound **(32)** (54 mg, 80 % yield).

Preparation of the title compound (1e)

Following a procedure analogous to that used for the preparation of compound **(1a)**, in Example 1, tert-butyl *O*-silylate **(32)** (54 mg, 0.08 mmol) was treated with TFA to give the desired hydroxamic acid (30 mg, 68 % yield), after recrystallization from Et_2O and n-hexane.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.32 (m, 6H); 1.83-2.22 (m, 2H); 3.10-3.28 (m, 2H); 3.48 (s, 2H); 4.11 (m, 1H); 4.39 (septet, 1H); 6.23 (brs, 1H); 7.16-7.36 (m, 5H); 7.43-7.47 (m, 3H); 7.57-7.61 (m, 2H); 7.67-7.72 (m, 2H); 7.86-7.90 (m, 2H).

Example 6

Preparation of intermediate of formula (II): compound (1f): (R)-4-acetamido-*N*-hydroxy-2-(*N*-isopropoxy-4'-methoxybiphenyl-4-ylsulfonamido)butanamide

Preparation of compound (9)

A solution of the commercially available 4'-methoxy-biphenyl-4-yl sulfonyl chloride (1 g, 3.53 mmol) in anhydrous THF (8 mL) was added dropwise to a stirred and cooled (0°C) solution of O-isopropylhydroxylamine hydrochloride (0.4 g, 3.53 mmol) and N-methylmorpholine (0.77 mL, 7.06 mmol) in anhydrous THF (8 mL). After 30 min under these conditions, the reaction mixture was stirred at room temperature for 3 days, then

was diluted with AcOEt and washed with H_2O giving, after work-up, sulfonamide **(9)** (0.94 g, 83 % yield) as a white solid.

Mp= 162-163°C;

^{1}H-NMR ($CDCl_3$) δ: 1.20 (d, *J*=6.2 Hz, 6H); 3.86 (s, 3H); 4.28 (septet, *J*=6.0 Hz, 1H); 6.80 (s, 1H); 6.97-7.04 (m, 2H); 7.53-7.60 (m, 2H); 7.68-7.72 (m, 2H); 7.93-7.97 (m, 2H).

Preparation of compound (13)

Tert-butyl ester **(13)** was prepared from sulfonamide **(9)** (482 mg, 1.5 mmol) and alcohol **(6)** (310 mg, 1.0 mmol) following the procedure previously described for the preparation of compound **(11)**, in Example 1. The crude reaction mixture was purified by flash chromatography (n-hexane/AcOEt = 5:2), to give **(13)** (455 mg, 74 % yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ**:** 1.21-1.32 (m, 15H); 1.90-2.10 (m, 2H); 3.10-3.50 (m, 2H); 3.86 (s, 3H); 4.06-4.16 (m, 1H); 4.43 (septet, *J*= 6.2 Hz, 1H); 5.08 (s, 2H); 6.97-7.02 (m, 2H); 7.34 (m, 5H); 7.51-7.56 (m, 2H); 7.65-7.70 (m, 2H); 7.90-7.94 (m, 2H).

Preparation of compound (16)

Following a procedure analogous to that used for the preparation of compound **(15)**, ester **(13)** (450 mg, 0.73 mmol) was hydrogenated in the presence of 10% Pd-C to give **(16)** (428 mg, 100 % yield).

^{1}H-NMR (CDCl3) δ: 1.15-1.27 (m, 15H); 2.04-2.10 (m, 2H); 3.06 (m, 2H); 3.86 (s, 3H); 4.27 (m, 1H); 4.41 (septet, *J*= 6.2 Hz, 1H); 6.98-7.02 (m, 2H); 7.52-7.56 (m, 2H); 7.68-7.72 (m, 2H); 7.95-7.99 (m, 2H).

Preparation of compound (21)

Following a procedure analogous to that used for the preparation of compound **(17)**, in Example 2, ester **(16)** (215 mg, 0.40 mmol) was acylated with acetyl chloride. Silica gel column chromatography (n-hexane/AcOEt = 2:3) yielded the desired product (86 mg, 42 % yield).

^{1}H-NMR ($CDCl_3$) δ**:** 1.19-1.25 (m, 15H); 1.90-2.04 (m, 5H); 3.13-3.50 (m, 2H); 3.87 (s, 3H); 4.12 (m, 1H); 4.41 (septet, 1H); 6.99-7.03 (m, 2H); 7.53-7.57 (m, 2H); 7.69-7.73 (m, 2H); 7.91-7.95 (m, 2H).

Preparation of compound (27)

Following a procedure analogous to that used for the preparation of compound **(35)**, in Example 1, ester **(21)** (81 mg, 0.15 mmol) was treated with TFA to give the desired carboxylic acid **(27)** (50 mg, 67 % yield), after recrystallization from Et_2O and n-hexane.

^{1}H-NMR ($CDCl_3$) δ**:** 1.15-1.22 (m, 6H); 1.88-2.05 (m, 5H); 3.19-3.35 (m, 2H); 3.84 (s, 3H); 4.24 (t, 1H); 4.37 (septet, 1H); 6.30 (brs, 1H); 6.96-7.00 (m, 2H); 7.53-7.58 (m, 2H); 7.67-7.71 (m, 2H); 7.89-7.94 (m, 2H).

Preparation of compound (33)

Following a procedure analogous to that used for the preparation of compound **(37)**, in Example 1, carboxylic acid **(27)** (50 mg, 0.10 mmol) was coupled with O-(tert-butyldimethylsilyl)hydroxylamine. Silica gel column chromatography (n-hexane/AcOEt = 1:2) yielded the desired product (45 mg, 71 % yield).

^{1}H-NMR ($CDCl_3$) δ**:** 0.15 (s, 6H); 0.92 (s, 9H); 1.23-1.27 (m, 6H); 1.91-2.00 (m, 5H); 3.00-3.20 (m, 2H); 3.87 (s, 3H); 4.06-4.13 (m, 1H); 4.43 (septet, 1H); 5.89 (brs, 1H); 6.98-7.03 (m, 2H); 7.56-7.60 (m, 2H); 7.72-7.76 (m, 2H); 7.88-7.93 (m, 2H); 8.80 (brs, 1H).

Preparation of the title compound (1f)

Following a procedure analogous to that used for the preparation of compound **(1a)**, tert-butyl O-silylate **(33)** (43 mg, 0.07 mmol) was treated with TFA to give the desired hydroxamic acid (31 mg, 90 % yield), after recrystallization from Et_2O and n-hexane. Mp= 83-85°C;

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.26 (m, 6H); 1.94-2.04 (m, 5H); 3.02-3.40 (m, 2H); 3.86 (s, 3H); 4.22 (m, 1H); 4.45 (septet, 1H); 6.09 (brs, 1H); 6.98-7.02 (m, 2H); 7.55-7.59 (m, 2H); 7.71-7.75 (m, 2H); 7.89-7.94 (m, 2H).

Example 7

Preparation of intermediate of formula (II): compound (1g): (R)-*N*-hydroxy-2-(*N*-isopropoxy-4'-methoxybiphenyl-4-ylsulfonamido)-4-(2-phenylacetamido) butanamide

Preparation of compound (22)

Following a procedure analogous to that used for the preparation of compound **(17)**, in Example 2, ester **(16)** (200 mg, 0.37 mmol) was acylated with phenylacetyl chloride.

Silica gel column chromatography (n-hexane/AcOEt = 3:2) yielded the desired product (53 mg, 24 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.16-1.25 (m, 15H); 1.90-2.05 (m, 2H); 3.12 (m, 2H); 3.57 (s, 2H); 3.87 (s, 3H); 3.94 (t, *J*=7.5Hz, 1H); 4.37 (septet, 1H); 6.98-7.04 (m, 2H); 7.31-7.37 (m, 5H); 7.52-7.57 (m, 2H); 7.64-7.68 (m, 2H); 7.77-7.81 (m, 2H).

Preparation of compound (28)

Following a procedure analogous to that used for the preparation of compound **(35)**, in Example 1, ester **(22)** (48 mg, 0.08 mmol) was treated with TFA to give the desired carboxylic acid **(28)** (46 mg, 100 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.15 (d, *J*=1.8Hz, 3H); 1.18 (d, *J*=1.8Hz, 3H); 1.93-2.10 (m, 2H); 3.10 (m, 2H); 3.56 (s, 2H); 3.86 (s, 3H); 4.15 (m, 1H); 4.37 (septet, 1H); 6.98-7.02 (m, 2H); 7.30-7.39 (m, 5H); 7.54-7.58 (m, 2H); 7.63-7.67 (m, 2H); 7.80-7.84 (m, 2H).

Preparation of compound (34)

Following a procedure analogous to that used for the preparation of compound **(37)**, in Example 1, carboxylic acid **(28)** (42 mg, 0.07 mmol) was coupled with O-(tert-butyldimethylsilyl)hydroxylamine. Silica gel column chromatography (n-hexane/AcOEt = 2:1) yielded the desired product (17 mg, 32 % yield).

^{1}H-NMR ($CDCl_3$) δ: 0.15 (s, 6H); 0.92 (s, 9H); 1.17-1.25 (m, 6H); 1.91-1.95 (m, 2H); 3.00-3.20 (m, 2H); 3.50 (s, 2H); 3.87 (s, 3H); 4.01-4.06 (m, 1H); 4.39 (septet, 1H); 5.75 (brs, 1H); 6.98-7.02 (m, 2H); 7.21-7.34 (m, 5H); 7.54-7.59 (m, 2H); 7.67-7.71 (m, 2H); 7.82-7.87 (m, 2H).

Preparation of the title compound (1g)

Following a procedure analogous to that used for the preparation of compound **(1a)**, tert-butyl O-silylate **(34)** (15 mg, 0.02 mmol) was treated with TFA to give the desired hydroxamic acid (10 mg, 77 % yield), after recrystallization from Et_2O and n-hexane.

^{1}H-NMR ($CDCl_3$) δ: 1.19-1.22 (m, 6H); 1.94-1.98 (m, 2H); 3.00-3.20 (m, 2H); 3.51 (s, 2H); 3.86 (s, 3H); 4.10-4.16 (m, 1H); 4.41 (septet, 1H); 5.89 (brs, 1H); 6.97-7.01 (m, 2H); 7.21-7.32 (m, 5H); 7.53-7.57 (m, 2H); 7.65-7.69 (m, 2H); 7.83-7.87 (m, 2H).

Example 8

Preparation of intermediate of formula (II): compound (1h): (R)-benzyl 4-(hydroxyamino)-4-oxo-3-(*N*-(2-(2-(piperazin-1-yl)ethoxy)ethoxy)biphenyl-4-ylsulfonamido)butylcarbamate

Preparation of compound (61)

To a solution of 1-[2-(2-hydroxyethoxy)ethyl]piperazine **(60)** (5.0 g, 28.7 mmol) in CH_2Cl_2 (20 mL) wad added dropwise a solution of di-tert-butyldicarbonate (6.9 g, 31.5 mmol) in CH_2Cl_2 (20 mL) at 0° C. After stirring at room temperature for 12 h, the solution was diluted with Et_2O, washed with a saturated solution of $NaHCO_3$, with brine, dried (Na_2SO_4) and concentrated to yield the Boc-protected derivative **(61)** (7.2 g, 92 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.43 (s, 9H); 2.45 (t, *J*= 4.9Hz, 4H); 2.57 (t, *J*= 5.3Hz, 2H); 3.44(t, *J*= 5.1Hz, 4H); 3.56-3.67 (m, 6H); 4.17 (t, *J*= 5.6Hz, 1H).

^{13}C-NMR ($CDCl_3$) δ : 28.47; 43.46; 53.16; 57.97; 61.86; 67.69; 72.44; 79.69; 155.00

Preparation of compound (62)

Diethyl azodicarboxylate (DEAD) (2.15 mL, 13.65 mmol) was added dropwise to a solution containing alcohol **(61)** (2.50 g, 9.10 mmol), N-hydroxyphthalimide (1.48 g, 9.10 mmol) and triphenylphosphine (3.58 g, 13.6 mmol) in anhydrous THF (100 mL), under nitrogen atmosphere. The resulting solution was stirred overnight at rt and evaporated under reduced pressure to afford a crude product, which was purified by flash chromatography on silica gel (n-hexane/AcOEt = 4:1) to yield **(62)** (4.30 g, 98% yield) as a pure yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 9H); 2.38 (t, *J*= 4.9Hz, 4H); 2.50 (t, *J*= 5.6Hz, 2H); 3.39 (t, *J*= 5.3Hz, 4H); 3.64 (t, *J*= 5.6Hz, 2H); 3.82 (t, *J*= 4.2Hz, 2H); 4.37 (t, *J*= 4.3Hz, 2H); 7.72-7.86 (m, 4H).

Preparation of compound (55)

Hydrazine hydrate (1.73 mL, 35.87 mmol) was added to a solution of compound **(62)** (4.30 g, 10.25 mmol) in ethanol (210 mL). After stirring at room temperature for 14 h the mixture was filtered and the filtrate concentrated. The residue was diluted with AcOEt, the precipitate was removed by filtration and the filtrate was evaporated to yield the desired O-alkylhydroxylamine **(55)** (2.15 g, 72.6 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9H); 2.45 (t, *J*= 4.9Hz, 4H); 2.61 (t, *J*= 5.8Hz, 2H); 3.43 (t, *J*= 5.1Hz, 4H); 3.58-3.65 (m, 4H); 3.80-3.85 (m, 2H).

Preparation of compound (10)

Following a procedure analogous to that used for the preparation of compound **(7)**, in Example 1, O-alkylhydroxylamine **(55)** (2.85 g, 9.86 mmol) was reacted with biphenyl-

4-sulfonyl chloride **(56)**. Silica gel column chromatography (AcOEt) yielded the desired sulfonamide (3.05 g, 61 % yield).

^{1}H-NMR ($CDCl_3$) δ : 1.44 (s, 9H); 2.44 (t, *J*= 4.9Hz, 4H); 2.58 (t, *J*= 5.6Hz, 2H); 3.43 (t, *J*= 5.3Hz, 4H); 3.61 (t, *J*= 5.5Hz, 2H); 3.67-3.71 (m, 2H); 4.10-4.15 (m, 2H); 7.41-7.53 (m, 3H); 7.58-7.63 (m, 2H); 7.71-7.75 (m, 2H); 7.97-8.01 (m, 2H).

Preparation of compound (14)

Tert-butyl ester **(14)** was prepared from sulfonamide **(10)** (1.18 g, 2.33 mmol) and alcohol **(6)** following the procedure previously described for the preparation of compound **(11)**, in Example 1. The crude reaction mixture was purified by flash chromatography (n-hexane/AcOEt = 1:5), to give the desired product (1.39 g, 75 % yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 9H); 1.43 (s, 9H); 1.74-1.98 (m, 2H); 2.42 (m, 4H); 2.58 (t, *J*= 5.3Hz, 2H); 3.12-3.26 (m, 2H); 3.40 (m, 4H); 3.56-3.65 (m, 4H); 4.09-4.41 (m, 3H); 5.05 (s, 2H); 5.22 (br s, 1H); 7.32 (m, 5H); 7.40-7.74 (m, 7H); 7.96-8.00 (m, 2H).

Preparation of compound (36)

Following a procedure analogous to that used for the preparation of compound **(35)**, in Example 1, ester **(14)** (1.39 g, 1.74 mmol) was treated with TFA to give the desired carboxylic acid **(36)** (1.30 g, 86 % yield), after recrystallization from Et_2O.

^{1}H-NMR ($CDCl_3$) δ: 1.80-2.05 (m, 2H); 3.19-3.29 (m, 6H); 3.40 (m, 4H); 3.62 (m, 10H); 4.15 (m, 2H); 4.29 (t, *J*= 6.5Hz, 1H); 5.01 (s, 2H); 5.35 (brs, 1H); 7.29 (m, 5H); 7.43-7.52 (m, 3H); 7.57-7.63 (m, 2H); 7.70-7.74 (m, 2H); 7.90-7.94 (m, 2H).

Preparation of the title compound (1h)

Following a procedure analogous to that used for the preparation of compound **(37),** in Example 1, carboxylic acid **(36)** (0.14 g, 0.16 mmol) was coupled with O-(tert-butyldimethylsilyl)hydroxylamine. Silica gel column chromatography ($CHCl_3$/MeOH = 9:1) yielded the desired hydroxamic acid (13 mg, 12 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.80-2.00 (m, 2H); 2.47-3.17 (m, 16H); 4.13 (m, 3H); 4.92 (s, 2H); 6.25 (brs, 1H); 7.18 (m, 5H); 7.38-7.64 (m, 7H); 7.96 (m, 2H).

Example 9

Preparation of intermediate of formula (II): compound (2): (R)-4-(1,3-dioxoisoindolin-2-yl)-*N*-hydroxy-2-(*N*-isopropoxy-4'-methoxybiphenyl-4-ylsulfonamido)butanamide

Preparation of compound (40)

Following a procedure analogous to that used for the preparation of compound **(6)**, in Example 1, (S)-α-hydroxy-1,3-dioxo-2-isoindolinebutyric acid **(39)** (1.0 g, 4.0 mmol) was treated with N,N-dimethylformamide di-tert-butyl acetal. Silica gel column chromatography (n-hexane/AcOEt = 3:2) yielded the desired ester (530 mg, 43 % yield), as a white solid.

Mp=122-123°C;

^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H); 1.87-2.23 (m, 2H); 3.02 (d, *J*= 5.3Hz, 1H); 3.86 (t, *J*= 7.3Hz, 2H); 4.07-4.16 (m, 1H); 7.69-7.75 (m, 2H); 7.80-7.87 (m, 2H).

Preparation of compound (43)

Tert-butyl ester **(43)** was prepared from sulfonamide **(9)** (400 mg, 1.24 mmol) and alcohol **(40)** (250 mg, 0.82 mmol) following the procedure previously described for the preparation of compound **(11).** The crude reaction mixture was purified by flash chromatography (n-hexane/AcOEt = 2:1), to give the desired product (217 mg, 43 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.24-1.29 (m, 15H); 2.10-2.30 (m, 2H); 3.51-3.74 (m, 2H); 3.87 (s, 3H); 4.06-4.23 (m, 1H); 4.46 (septet, 1H); 6.98-7.03 (m, 2H); 7.52-7.88 (m, 10H).

Preparation of compound (46)

Following a procedure analogous to that used for compound **(35)**, ester **(43)** (205 mg, 0.33 mmol) was treated with TFA to give the desired carboxylic acid **(46)** (135 mg, 74 % yield), after recrystallization from Et_2O.

Mp=185-187°C;

^{1}H-NMR ($CDCl_3$) δ: 1.21 (d, *J*= 6.2Hz, 3H); 1.27 (d, *J*= 6.2Hz, 3H); 2.10-2.28 (m, 2H); 3.61 (m, 2H); 3.87 (s, 3H); 4.33 (m, 1H); 4.46 (septet, 1H); 6.98-7.02 (m, 2H); 7.50-7.54 (m, 4H); 7.65-7.85 (m, 6H).

Preparation of compound (48)

Following a procedure analogous to that used for the preparation of compound **(37)**, carboxylic acid **(46)** (130 mg, 0.23 mmol) was coupled with O-(tert-butyldimethyl-silyl)hydroxylamine. Silica gel column chromatography (n-hexane/AcOEt = 3:2) yielded the desired product (110 mg, 70 % yield).

^{1}H-NMR ($CDCl_3$) δ: 0.26 (s, 6H); 1.00 (s, 9H); 1.23 (d, *J*= 6.2Hz, 3H); 1.30 (d, *J*= 6.2Hz, 3H); 2.15-2.30 (m, 2H); 3.30-3.60 (m, 2H); 3.89 (s, 3H); 4.03 (m, 1H); 4.43

(septet, 1H); 6.98-7.02 (m, 2H); 7.16 (m, 2H); 7.36-7.41 (m, 2H); 7.61 (m, 4H); 7.68-7.72 (m, 2H); 8.72 (brs, 1H).

Preparation of compound (2)

Following a procedure analogous to that used for the preparation of compound **(1a)**, tert-butyl O-silylate **(48)** (100 mg, 0.14 mmol) was treated with TFA to give the desired hydroxamic acid (61 mg, 77%), after recrystallization from Et_2O and n-hexane.

Mp= 75-76°C;

^{1}H-NMR ($CDCl_3$) δ: 1.23 (d, *J*= 6.2Hz, 3H); 1.30 (d, *J*= 6.2Hz, 3H); 2.12-2.32 (m, 2H); 3.40-3.53 (m, 2H); 3.88 (s, 3H); 4.02-4.20 (m, 1H); 4.46 (septet, 1H); 6.98-7.02 (m, 2H); 7.29-7.39 (m, 2H); 7.42-7.46 (m, 2H); 7.63 (m, 4H); 7.72-7.76 (m, 2H).

Example 10

Preparation of intermediate of formula (II): compound (3) (R)-4-(1,3-dioxoisoindolin-2-yl)-*N*-hydroxy-2-(*N*-isopropoxy-4-phenoxyphenylsulfonamido) butanamide

Preparation of compound (41)

Following a procedure analogous to that used for the preparation of compound **(7)**, O-isopropylhydroxylamine **(54)** (415 mg, 3.72 mmol) was reacted with 4-phenoxybenzenesulfonyl chloride **(58)** to give the desired sulfonamide **(41)** (989 mg, 86 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.19 (d, *J*= 6.2Hz, 6H); 4.25 (septet, *J*= 6.2Hz, 1H); 6.71 (s, 1H); 7.03-7.10 (m, 4H); 7.19-7.27 (m, 1H); 7.38-7.46 (m, 2H); 7.83-7.88 (m, 2H).

Preparation of compound (44)

Tert-butyl ester **(44)** was prepared from sulfonamide **(41)** (378 mg, 1.23 mmol) and alcohol **(40)** following the procedure previously described for compound **(11)**. The crude reaction mixture was purified by flash chromatography (n-hexane/AcOEt = 7:2), to give the desired product (253 mg, 51 % yiedl).

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.45 (m, 15H); 1.99-2.38 (m, 2H); 3.56-3.74 (m, 2H); 4.06-4.15 (m, 1H); 4.43 (septet, *J*= 6.2Hz, 1H); 6.94-6.98 (m, 2H); 7.09-7.12 (m, 2H); 7.21-7.28 (m, 2H); 7.39-7.47 (m, 2H); 7.67-7.83 (m, 5H).

Preparation of compound (47)

Following a procedure analogous to that used for the preparation of compound **(35)**, ester **(44)** (250 mg, 0.42 mmol) was treated with TFA to give the desired carboxylic acid **(47)** (164 mg, 71%), after recrystallization from Et_2O and n-hexane.

^{1}H-NMR ($CDCl_3$) δ: 1.20 (d, *J*= 6.2Hz, 3H); 1.25 (d, *J*= 6.2Hz, 3H); 2.10-2.30 (m, 2H); 3.55-3.75 (m, 2H); 4.25-4.35 (m, 1H); 4.44 (septet, *J*= 6.2Hz, 1H); 6.88-6.92 (m, 2H); 7.09-7.13 (m, 2H); 7.21-7.28 (m, 2H); 7.39-7.47 (m, 2H); 7.69-7.84 (m, 5H).

Preparation of compound (49)

Following a procedure analogous to that used for the preparation of compound **(37)**, carboxylic acid **(47)** (160 mg, 0.30 mmol) was coupled with O-(tert-butyldimethyl-silyl)hydroxylamine to give the desired product (178 mg, 87 % yield).

^{1}H-NMR ($CDCl_3$) δ: 0.26 (s, 6H); 1.00 (s, 9H); 1.21 (d, *J*= 6.2Hz, 3H); 1.26 (d, *J*= 6.2Hz, 3H); 2.10-2.31 (m, 2H); 3.40-3.65 (m, 2H); 3.90-4.10 (m, 1H); 4.40 (septet, *J*= 6.2Hz, 1H); 6.59 (brs, 1H); 7.08-7.13 (m, 2H); 7.22-7.30 (m, 2H); 7.41-7.49 (m, 2H); 7.58-7.62 (m, 2H); 7.69-7.83 (m, 5H).

Preparation of the title compound (3)

Following a procedure analogous to that used for the preparation of compound **(1a)**, tert-butyl *O*-silylate **(49)** (170 mg, 0.25 mmol) was treated with TFA to give the desired hydroxamic acid **(3)** (97 mg, 68 % yield), after recrystallization from Et_2O and n-hexane.

^{1}H-NMR ($CDCl_3$) δ: 1.22 (d, *J*= 6.2Hz, 3H); 1.26 (d, *J*= 6.2Hz, 3H); 2.07-2.28 (m, 2H); 3.43-3.65 (m, 2H); 4.05-4.20 (m, 1H); 4.44 (septet, *J*= 6.2Hz, 1H); 6.70-6.83 (m, 2H); 7.09-7.13 (m, 2H); 7.22-7.29 (m, 2H); 7.40-7.48 (m, 2H); 7.64-7.83 (m, 5H).

Example 11

Preparation of intermediate of formula (II): compound (4) (R)-4-(1,3-dioxoisoindolin-2-yl)-2-(4'-ethoxy-*N*-isopropoxybiphenyl-4-ylsulfonamido)-*N*-hydroxybutanamide

Preparation of compound (42)

Following a procedure analogous to that used for the preparation of compound **(7)**, O-isopropylhydroxylamine **(54)** (436 mg, 3.91 mmol) was reacted with 4-bromobenzenesulfonyl chloride **(59)** to give the desired sulfonamide **(42)** (870 mg, 75%).

^{1}H-NMR ($CDCl_3$) δ: 1.18 (d, *J*= 6.2Hz, 6H); 4.25 (septet, *J*= 6.2Hz, 1H); 6.80 (s, 1H); 7.66-7.70 (m, 2H); 7.75-7.80 (m, 2H).

Preparation of compound (45)

Tert-butyl ester **(45)** was prepared from sulfonamide **(42)** (864 mg, 2.94 mmol) and alcohol **(40)** following the procedure previously described for the preparation of compound **(11)**. The crude reaction mixture was purified by flash chromatography (n-hexane/AcOEt = 5:1), to give the desired product (720 mg, 63 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.19-1.40 (m, 15H); 2.05-2.20 (m, 2H); 3.55-3.80 (m, 2H); 4.02-4.20 (m, 1H); 4.43 (septet, *J*= 6.2Hz, 1H); 7.60-7.76 (m, 6H); 7.80-7.87 (m, 2H).

Preparation of compound (50)

A mixture of ester **(45)** (200 mg, 0.34 mmol), 4-ethoxyphenylboronic acid (96 mg, 0.58 mmol), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) and K_3PO_4 (166 mg, 0.78 mmol) in 4.5 mL dioxane/H_2O 5:1 was heated to 85°C under nitrogen. After 2h, the reaction mixture was diluted with sat. solution of $NaHCO_3$, extracted with ACOEt and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the crude product was purified by flash chromatography on silica gel (n-hexane/AcOEt = 4:1) to give **(50)** (193 mg, 88 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.39 (m, 15H); 1.45 (t, *J*= 6.9Hz, 3H); 2.04-2.35 (m, 2H); 3.50-3.80 (m, 2H); 4.05-4.15 (m, 3H); 4.46 (septet, *J*= 6.2Hz, 1H); 6.97-7.01 (m, 2H); 7.51-7.88 (m, 10H).

Preparation of compound (51)

Following a procedure analogous to that used for the preparation of compound **(35)**, ester **(50)** (193 mg, 0.30 mmol) was treated with TFA to give the desired carboxylic acid **(51)** (150 mg, 87%), after recrystallization from Et_2O and n-hexane.

^{1}H-NMR ($CDCl_3$) δ: 1.21 (d, *J*= 6.2Hz, 3H); 1.24 (d, *J*= 6.2Hz, 3H); 1.46 (t, *J*= 6.9Hz, 3H); 2.10-2.30 (m, 2H); 3.50-3.75 (m, 2H); 4.10 (q, *J*= 6.9Hz, 2H); 4.22-4.50 (m, 2H); 6.97-7.01 (m, 2H); 7.48-7.53 (m, 4H); 7.65-7.85 (m, 6H).

Preparation of compound (52)

Following a procedure analogous to that used for the preparation of compound **(37)**, carboxylic acid **(51)** (140 mg, 0.25 mmol) was coupled with O-(tert-butyldimethyl-silyl)hydroxylamine. Silica gel column chromatography (n-hexane/AcOEt = 2:1) yielded the desired product (120 mg, 71 % yield).

^{1}H-NMR ($CDCl_3$) δ: 0.26 (s, 6H); 1.00 (s, 9H); 1.23 (d, *J*= 6.2Hz, 3H); 1.30 (d, *J*= 6.2Hz, 3H); 1.47 (t, *J*= 6.9Hz, 3H); 2.10-2.30 (m, 2H); 3.30-3.60 (m, 2H); 3.90-4.05 (m, 1H); 4.11 (q, *J*= 6.9Hz, 2H); 4.43 (septet, *J*= 6.2Hz, 1H); 6.99-7.01 (m, 2H); 7.10-7.22 (m, 2H); 7.35-7.39 (m, 2H); 7.60-7.71 (m, 6H); 8.70 (brs, 1H).

Preparation of the title compound (4) Following a procedure analogous to that used for the preparation of compound **(1a)**, tert-butyl *O*-silylate **(52)** (120 mg, 0.17 mmol) was treated with TFA to give the desired hydroxamic acid **(4)** (83 mg, 82%), after recrystallization from Et_2O and n-hexane.

^{1}H-NMR ($CDCl_3$) δ: 1.24 (d, *J*= 6.2Hz, 3H); 1.30 (d, *J*= 6.2Hz, 3H); 1.46 (t, *J*= 6.9Hz, 3H); 2.10-2.35 (m, 2H); 3.40-3.60 (m, 2H); 4.05-4.16 (m, 3H); 4.46 (septet, *J*= 6.2Hz, 1H); 6.96-7.01 (m, 2H); 7.31-7.44 (m, 4H); 7.63-7.75 (m, 6H).

Example 12

Preparation of intermediate of formula (II): compound (64): benzyl 3-(N-isopropoxybiphenyl-4-ylsulfonamido)propylcarbamate

Carbamate **(64)** was prepared from sulfonamide **(8)** (400 mg, 1.37 mmol) and commercial alcohol **(63)** following the procedure previously described for the preparation of compound **(11)**. The crude reaction mixture was purified by flash chromatography (n-hexane/AcOEt = 3:1), to give the desired product (400 mg, 87 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.23-1.27 (m, 8H); 1.76-1.89 (m, 2H); 3.30 (q, *J*= 62Hz, 2H); 4.54 (septet, *J*= 6.2Hz, 1H); 5.08 (s, 2H); 7.34 (m, 5H); 7.41-7.53 (m, 3H); 7.59-7.63 (m, 2H); 7.72-7.76 (m, 2H); 7.88-7.93 (m, 2H)

Example 13

Preparation of intermediate of formula (II): compound (1i)

Preparation of compound (65)

To a solution of compound **(55)** of example 8 (1.76 g; 6 mmol) in THF (15 ml) at 0°C was added N-methylmorpholine (0.66 ml, 6 mmol) and a solution of 4'-methoxy[1,1'-biphenyl]-4-sulfonyl chloride (1.69 g, 6 mmol) in THF (15 ml). The reaction mixture was stirred at room temperature for 3 days, then concentrated. The residue was taken up with ethyl acetate, washed with water and the organic phase was concentrated to obtain an orange oil. The crude product was purified by flash chromatography (EtOAc) to give compound **(65)** as a yellow oil in 75% yield.

1H-NMR ($CDCl_3$, 200 MHz):7.95 (d, 2H); 7.68 (d, 2H); 7.55 (d, 2H); 7.0 (d, 2H); 4.12 (m, 2H); 3.86 (s, 3H); 3.67 (m, 4H); 3.6 (m, 4H); 3.42 (t, *J*= 5.3Hz, 4H); 2.56 (t, *J*= 5.6Hz, 2H); 2.42 (t, *J*= 4.95Hz, 4H); 1.44 (s, 9H).

Preparation of compound (66)

DEAD (0.153 ml, 0.97 mmol) was added dropwise, at 0°C, to a solution of sulfonamide **(65)** (458.8 mg; 0.97 mmol), compound **(6)** of example 1 (300 mg, 0.97 mmol) and triphenylphosphine (255 mg; 0.97 mmol) in dry THF (16 ml).

The mixture was stirred at room temperature overnight then concentrated and purified by flash chromatography (hexane/ethyl acetate 1/5) to give compound **(66)** as an oil in 70 % yield.

1H-NMR ($CDCl_3$, 200 MHz): 7.95 (d, *J*= 8.6Hz, 2H); 7.57 (m, 4H); 7.26 (s, 5H); 7.0 (d, *J*= 8.8Hz, 2H); 5.18 (m, 1H); 5.06 (s, 2H); 4.33 (m, 1H); 4.14 (m, 2H); 3.87 (s, 3H); 3.62 (m, 4H); 3.39 (m, 4H); 3.21 (m, 2H); 2.56 (t, *J*= 5.4Hz, 2H); 2.4 (m, 4H); 1.92 (m, 2H); 1.44 (s, 9H), 1.34 (s, 9H).

Preparation of compound (1i)

To a solution of *tert*-Butyl ester **(66)** (800 mg, 0.966 mmol) in dry CH_2Cl_2 (12 ml), TFA (7.4 ml, 96.6 mmol) was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 1h and then 4h at room temperature. The solvent and TFA were removed in vacuo to give carboxylic acid **(1i),** as di-trifluoroacetate salt, as a white foam in 79% yield.

1H-NMR ($CDCl_3$, 200 MHz): 9.45 (bs, $^{+}NH_2$, ^{+}NH); 8.0 (d, *J*= 7.8Hz, 2H); 7.68 (m, 4H); 7.4 (s, 5H); 7.1 (d, *J*= 8.2Hz, 2H); 5.6 (s, 1H); 5.13 (s, 2H); 4.27 (m, 3H); 3.97 (s, 3H); 3.78 (m,10H); 3.44 (m, 4H); 1.98 (m, 2H).

Example 14

Preparation of intermediate of formula (II): compound (1j)

To a solution of acid **(1i)** (150 mg, 0.167 mmol) in dry CH_2Cl_2 (4 ml) was added *O*-(*tert*-Butyldimethylsilyl)hydroxylamine (79 mg, 0.534 mmol) and EDCI (96 mg, 0.501 mmol). The reaction mixture was stirred at room temperature for 5h then concentrated and the residue was dissolved in EtOAc and washed with water. The organic phase was dried (Na_2SO_4) and evaporated in vacuo. Thus obtained white solid (140 mg) was dissolved in dry CH_2Cl_2 (3 ml) and treated with TFA (0.8 ml). The reaction mixture was stirred at 0°C for 1h then allowed to reach room temperature and stirred for 4h. The

solution was concentrated to obtain a brown oil that was triturated with a mixture of CH_2Cl_2/Et_2O to give a brown solid hydroxamic acid **(1j)**, as di-trifluoroacetate, in 50% yield.

1H-NMR ($CDCl_3$, 200MHz): 7.86 (d, *J*= 7.2Hz, 2H); 7.56 (m, 4H); 7.24 (s, 5H); 6.94 (d, *J*= 8.2Hz, 2H); 5.73 (s, 1H); 5.1 (s, 2H); 4.1 (m, 4H); 3.82 (s, 3H); 3.53 (m, 8H); 3.25 (m, 4H); 2.05 (m, 2H).

Example 15

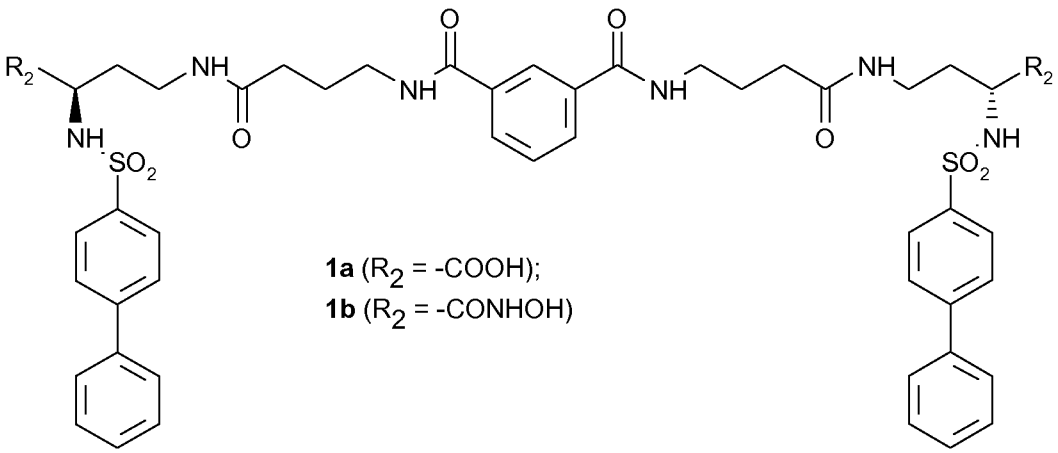
Preparation of intermediate of formula (II): compound (1k)

To a solution of **(1j)** (40 mg, 0.04 mmol) in dry DMSO (1 ml) was added 2,5-dioxipyrrolidine-1-yl propionate (10 mg, 0.534 mmol) and TEA (10 drops, pH=8). The reaction mixture was stirred at room temperature for 24 h then were added 10 ml of Et_2O. The reaction was stopped and the solution cooled to -15°C then left to reach 0°C. The ethyl ether layer was decanted and the residual yellow oil concentrated in vacuo. The pure compound **(1k)** was obtained after chromatography (CH_2Cl_2/MeOH) as a colorless oil in 24% yield.

1H-NMR ($CDCl_3$, 200 MHz): 7.88 (d, *J*= 8.2Hz, 2H); 7.6 (m, 4H); 7.26 (s, 5H); 6.96 (d, *J*= 8.8Hz, 2H); 5.09 (s, 2H); 4.34 (m, 3H); 3.87 (s, 3H); 3.62 (m, 6H); 3.45 (m, 4H); 2.59 (m, 2H); 2.46 (m, 4H); 2.28 (q, *J*= 7.5Hz, 2H); 1.68 (m, 2H); 1.11 (t, *J*= 7.5Hz, 3H).

Example 16

Compounds of formula (I) – see compounds (1a) and (1b) of scheme 7



1a (R_2 = -COOH);
1b (R_2 = -CONHOH)

Preparation of compound (4)

A solution of biphenyl-4-sulfonyl chloride (3.17 g, 12.53 mmol) in anhydrous THF (32 mL) was added dropwise to a stirred and cooled (0°C) solution of O-benzylhydroxylamine hydrochloride (2 g, 12.53 mmol) and N-methylmorpholine (2.75 mL, 25.06 mmol) in anhydrous THF (32 mL). After 30 min. under these conditions, the reaction mixture was stirred at rt for 3 days, then was diluted with AcOEt and washed with H_2O giving, after work-up, sulfonamide (**4**) (3.62 g, 85%) as a white solid.

Mp= 130-132°C;

^{1}H-NMR ($CDCl_3$) δ: 5.01 (s, 2H); 7.01 (s, 1H); 7.35 (m, 5H); 7.44-7.51 (m, 3H); 7.57-7.62 (m, 2H); 7.70-7.75 (m, 2H); 7.97-8.01 (m, 2H).

Preparation of compound (6)

Diisopropyl azodicarboxylate (DIAD) (1.28 mL, 6.52 mmol) was added dropwise to a solution containing the secondary alcohol (**5**) (0.8 g, 2.61 mmol), the sulfonamide (**4**) (1.3 g, 3.91 mmol) and triphenylphosphine (2.05 g, 7.83 mmol) in anhydrous THF (45 mL) under nitrogen atmosphere at 0°C. The resulting solution was stirred for 5 h at rt and evaporated under reduced pressure to afford a crude product, which was purified by flash chromatography on silica gel (n-hexane/EtOAc = 3:1) to yield compound (**6**) (0.95 g, 58% yield) as pure yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (s, 9H); 1.90-2.04 (m, 2H); 3.16-3.40 (m, 2H); 4.16 (t, *J*= 7.1Hz, 1H); 4.93-5.00 (m, 1H); 5.07-5.19 (m, 4H); 7.33-7.37 (m, 10H); 7.41-7.59 (m, 5H); 7.66-7.70 (m, 2H); 7.92-7.97 (m, 2H).

^{13}C-NMR ($CDCl_3$) δ: 22.09; 27.87; 37.59; 62.75; 66.76; 80.87; 82.56; 127.43; 127.67; 128.16; 128.56; 128.72; 128.92; 129.14; 129.89; 129.94; 133.89; 134;80; 139.17; 146.84; 156.27.

Preparation of compound (7)

A solution of compound (**6**) (0.8 g, 1.27 mmol) in MeOH (90 mL) was stirred under hydrogen atmosphere in the presence of 10% Pd-C (0.40 g) and glacial acetic acid (90 mL) for 17 h at room temperature. The resulting mixture was filtered on celite and the filtrate was evaporated under reduced pressure to give (**7**) (0.56 g, 98 % yield) as a clear oil.

^{1}H-NMR (CDCl3) δ: 1.18 (s, 9H); 3.10-3.30 (m, 2H); 3.93 (br s, 1H); 5.0 (br s, 1H); 7.39-7.57 (m, 5H); 7.65-7.69 (m, 2H); 7.90-7.94 (m, 2H); 8.51 (br s, 1H).

EI-MS, m/z: 91 (100); 152 (25); 217 (23); 260 (52); 391 (M, 5).

Preparation of compound (9)

A solution of compound (**7**) (0.40 g, 0.88 mmol) in dry DMF (6 mL) was treated with acyl chloride (**8**) (164 mg, 0.44 mmol) and i-Pr_2NEt (0.30 mL, 1.76 mmol). The reaction mixture was stirred at rt for 17 h, then was diluted with ethyl acetate, washed with H_2O, dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography (n-hexane/AcOEt = 1:2), to give (**9**) (120 mg, 25 % yield) as a clear oil.

^{1}H-NMR ($CDCl_3$) δ: 1.14 (s, 18H); 2.09-2.31 (m, 8H); 2.58 (t, J= 7.8Hz, 4H); 3.38-3.53 (m, 2H); 3.77-3.87 (m, 4H); 3.96 (t, J= 7.1Hz, 4H); 5.42 (d, J= 9.3Hz, 2H); 7.40-7.59 (m, 10H); 7.67-7.72 (m, 4H); 7.92-7.96 (m, 4H); 8.11-8.15 (m, 4H).

Preparation of compound (1a)

Trifluoroacetic acid (0.48 mL, 6.27 mmol) was added dropwise to a stirred solution of tert-butyl ester (**9**) (120 mg, 0.11 mmol) in freshly distilled CH_2Cl_2 (1.0 mL), cooled to 0°C. The solution was stirred for 5 h at 0°C and the solvent was removed in vacuo to give compound (**1a**) (109 mg, 100 % yield) as a solid.

^{1}H-NMR ($CDCl_3$) δ: 2.07-2.19 (m, 8H); 2.57 (t, J= 7.8Hz, 4H); 3.45-3.54 (m, 2H); 3.62-3.80 (m, 2H); 3.94 (t, J= 6.9Hz, 4H); 3.99-4.10 (m, 2H); 5.42 (d, J= 8.0Hz, 2H); 7.15 (t, J= 5.8Hz, 2H); 7.40-7.58 (m, 10H); 7.65-7.69 (m, 4H); 7.83-7.95 (m, 8H).

Preparation of the title compound (1b)

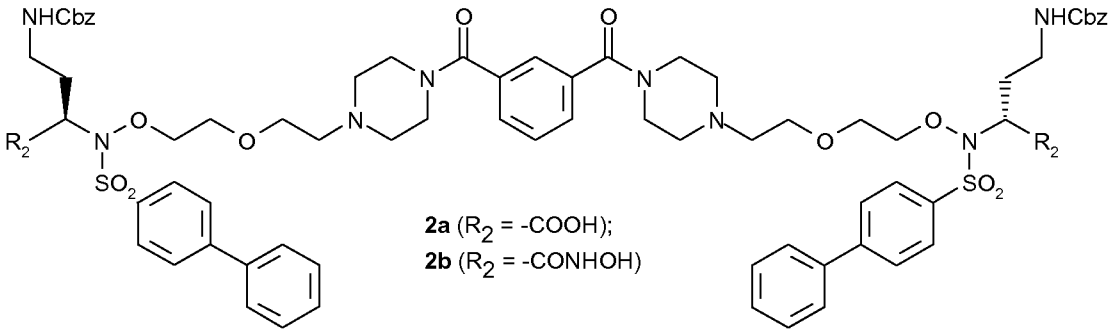
To a solution of carboxylic acid (**1a**) (80 mg, 0.08 mmol) and *O*-(tert-butyldimethyl-silyl)hydroxylamine (36 mg, 0.24 mmol) in freshly distilled CH_2Cl_2 (3.0 mL) cooled to 0°C, was added 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (EDC) portionwise (47.2 mg, 0.24 mmol). After stirring at r.t. for 20 h, the mixture was washed with H_2O and the organic phase was dried and evaporated in vacuo. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH = 15:1) to yield the *tert*-butyl *O*-silylate derivative(14 mg, 14 % yield) as yellow oil.

Trifluoroacetic acid (0.10 mL, 1.3 mmol) was added dropwise to a stirred solution of the *tert*-butyl *O*-silylate derivative (14 mg, 0.01 mmol) in freshly distilled CH_2Cl_2 (1 mL), cooled to 0°C. The solution was stirred for 5 h at 0°C and the solvent was removed in vacuo to give a crude product that was recrystallized from Et_2O and CH_2Cl_2 to give **(1b)** (10 mg, 91 % yield) as solid.

^{1}H-NMR $(CD_3)_2CO$ δ: 1.91-2.06 (m, 8H); 2.56 (t, J= 7.7Hz, 4H); 3.34-3.50 (m, 4H); 3.92 (t, J= 7.1Hz, 4H); 3.95-4.10 (m, 2H); 7.03 (br s, 2H); 7.45-7.50 (m, 7H); 7.66-8.08 (m, 15H).

Example 17

Compounds of formula (I) – see compounds (2a) and (2b) of scheme 9



Preparation of compound (10) of scheme 8

To a solution of 1-[2-(2-hydroxyethoxy)ethyl]piperazine (5.0 g, 28.7 mmol) in CH_2Cl_2 (20 mL) wad added dropwise a solution of di-tert-butyldicarbonate (6.9 g, 31.5 mmol) in CH_2Cl_2 (20 mL) at 0°C. After stirring at room temperature for 12 h, the solution was diluted with Et_2O, washed with a saturated solution of $NaHCO_3$, with brine, dried (Na_2SO_4) and concentrated to yield the Boc-protected derivative **(10)** (7.2 g, 92 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.43 (s, 9H); 2.45 (t, *J*= 4.9Hz, 4H); 2.57 (t, *J*= 5.3Hz, 2H); 3.44(t, *J*= 5.1Hz, 4H); 3.56-3.67 (m, 6H); 4.17 (t, *J*= 5.6Hz, 1H).

^{13}C-NMR ($CDCl_3$) δ : 28.47; 43.46; 53.16; 57.97; 61.86; 67.69; 72.44; 79.69; 155.00

Preparation of compound (11)

Diethyl azodicarboxylate (DEAD) (2.15 mL, 13.65 mmol) was added dropwise to a solution containing alcohol **(10)** (2.50 g, 9.10 mmol), N-hydroxyphthalimide (1.48 g, 9.10 mmol) and triphenylphosphine (3.58 g, 13.6 mmol) in anhydrous THF (100 mL), under nitrogen atmosphere. The resulting solution was stirred overnight at rt and evaporated under reduced pressure to afford a crude product, which was purified by flash chromatography on silica gel (n-hexane/AcOEt = 4:1) to yield **(11)** (4.30 g, 98% yield) as a pure yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 9H); 2.38 (t, *J*= 4.9Hz, 4H); 2.50 (t, *J*= 5.6Hz, 2H); 3.39 (t, *J*= 5.3Hz, 4H); 3.64 (t, *J*= 5.6Hz, 2H); 3.82 (t, *J*= 4.2Hz, 2H); 4.37 (t, *J*= 4.3Hz, 2H); 7.72-7.86 (m, 4H).

Preparation of compound (12)

Hydrazine hydrate (1.73 mL, 35.87 mmol) was added to a solution of compound **(11)** (4.30 g, 10.25 mmol) in ethanol (210 mL). After stirring at room temperature for 14 h the mixture was filtered and the filtrate concentrated. The residue was diluted with AcOEt, the precipitate was removed by filtration and the filtrate was evaporated to yield the desired compound **(12)** (2.15 g, 72.6 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9H); 2.45 (t, *J*= 4.9Hz, 4H); 2.61 (t, *J*= 5.8Hz, 2H); 3.43 (t, *J*= 5.1Hz, 4H); 3.58-3.65 (m, 4H); 3.80-3.85 (m, 2H).

Preparation of compound (13)

Following a procedure analogous to that used for the preparation of compound **(4)**, in Example 16, compound **(12)** (2.85 g, 9.86 mmol) was reacted with biphenyl-4-sulfonyl chloride. Silica gel column chromatography (AcOEt) yielded the desired sulfonamide **(13)** (3.05 g, 61 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 9H); 2.44 (t, *J*= 4.94 Hz, 4H); 2.58 (t, *J*= 5.6 Hz, 2H); 3.43 (t, *J*= 5.3 Hz, 4H); 3.61 (t, *J*= 5.5 Hz, 2H); 3.67-3.71 (m, 2H); 4.10-4.15 (m, 2H); 7.41-7.53 (m, 3H); 7.58-7.63 (m, 2H); 7.71-7.75 (m, 2H); 7.97-8.01 (m, 2H).

Preparation of compound (14)

Tert-butyl ester (**14**) was prepared from sulfonamide **(13)** (1.18 g, 2.33 mmol) and alcohol **(5)** following the procedure previously described for the preparation of compound **(6)**, in Example 16. The crude reaction mixture was purified by flash chromatography (n-hexane/AcOEt = 1:5), to give the desired product (**14**) (1.39 g, 75 % yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 9H); 1.43 (s, 9H); 1.74-1.98 (m, 2H); 2.42 (m, 4H); 2.58 (t, *J*= 5.3Hz, 2H); 3.12-3.26 (m, 2H); 3.40 (m, 4H); 3.56-3.65 (m, 4H); 4.09-4.41 (m, 3H); 5.05 (s, 2H); 5.22 (br s, 1H); 7.32 (m, 5H); 7.40-7.74 (m, 7H); 7.96-8.00 (m, 2H).

Preparation of compound (15)

Following a procedure analogous to that used for the preparation of compound **(1a)**, in Example 16, ester **(14)** (1.39 g, 1.74 mmol) was treated with TFA to give the desired carboxylic acid **(15)** (1.30 g, 86 % yield), after recrystallization from Et_2O.

^{1}H-NMR ($CDCl_3$) δ: 1.80-2.05 (m, 2H); 3.19-3.29 (m, 6H); 3.40 (m, 4H); 3.62 (m, 10H); 4.15 (m, 2H); 4.29 (t, *J*= 6.5Hz, 1H); 5.01 (s, 2H); 5.35 (brs, 1H); 7.29 (m, 5H); 7.43-7.52 (m, 3H); 7.57-7.63 (m, 2H); 7.70-7.74 (m, 2H); 7.90-7.94 (m, 2H).

Preparation of compound (2a)

Following a procedure analogous to that used for the preparation of compound **(9)**, in Example 16, **(15)** (1.30 g, 1.5 mmol) was reacted with isophthaloyl chloride to give the desired carboxylic acid (**2a**) as a white solid (0.23 g, 22 % yield) after purification by reverse phase chromatography (H_2O/MeOH= 4.5:5.5).

^{1}H-NMR ($CDCl_3$) δ: 2.04-2.17 (m, 4H); 2.81 (m, 12H); 3.23 (m, 4H); 3.62-3.91 (m, 16H); 4.13-4.36 (m, 6H); 5.03 (s, 4H); 5.34 (br s, 2H); 7.28 (m, 10H); 7.41-7.50 (m, 10H); 7.56-7.61 (m, 4H); 7.68-7.73 (m, 4H); 7.91-7.95 (m, 4H).

Preparation of the title compound (2b)

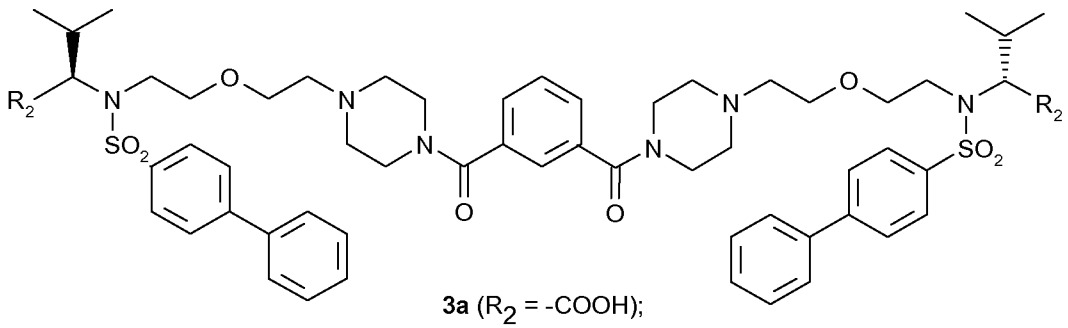
Following a procedure analogous to that used for the preparation of compound **(1b)**, in Example 16, the dimeric hydroxamic acid (**2b)** was obtained from carboxylic acid **2a** (0.20 g, 0.14 mmol) by reaction with *O*-(tert-butyldimethyl-silyl)hydroxylamine followed by hydrolysis with TFA.

The crude was recrystallized from Et_2O to give (**2b)** as a solid (13 mg, 65 % yield).

^{1}H-NMR ($CDCl_3$) δ: 1.90-2.05 (m, 4H); 2.88-3.90 (m, 32H); 4.06-4.20 (m, 6H); 4.94 (s, 4H); 5.80 (br s, 2H); 7.24 (m, 10H); 7.41 (m, 10H); 7.54 (m, 4H); 7.69 (m, 4H); 7.86-7.89 (m, 4H); 10.60 (br s, 2H).

Example 18

Compounds of formula (I) – see compounds (3a) and (3b) of scheme 10



3a (R_2 = -COOH);
3b (R_2 = -CONHOH)

Preparation of compound (16)

To a solution of D-valine (5.0 g, 42.68 mmol) and TEA (8.92 ml, 64.02 mmol) in H_2O/diossano 1:1 (66.7 ml) was added biphenyl-4-sulfonyl chloride (11.86g, 46.95 mmol). After stirring at r.t. for 20 h, the mixture was diluted with CH_2Cl_2, washed with HCl 1N and the organic phase was dried and evaporated in vacuo. After recrystallization from *n*-hexane, the desired carboxylic acid (**16**) was obtained as a white solid (7.72 g, 54.2 % yield).

^{1}H-NMR ($CDCl_3$) δ: 0.83 (d, *J*= 6.7 Hz, 3H); 0.95 (d, *J*= 6.7 Hz, 3H); 2.00-2.16 (m, 1H); 2.46 (br s, 1H); 3.76-3.83 (dd, *J*= 4.4 Hz, *J*= 9.8 Hz, 1H); 5.15 (d, *J*= 9.8 Hz, 1H); 7.42-7.70 (m, 7H); 7.84-7.88 (m, 2H).

Preparation of compound (17)

A solution of **(16)** (3.47 g, 10.4 mmol) in toluene (20.0 ml) containing N,N-dimethylformamide di-tert-butyl acetal (10.0 ml, 41.6 mmol) was heated to 95°C for 3 h. The solvent was then evaporated and the crude product was purified by flash chromatography on silica gel (n-hexane/EtOAc = 4:1) to give **(17)** (1.7 g, 42 % yields) as a pink solid.

Mp= 119-121°C;

^{1}H-NMR ($CDCl_3$) δ: 0.86 (d, *J*= 6.7 Hz, 3H); 1.02 (d, *J*= 6.7 Hz, 3H); 1.19 (s, 9H); 1.98-2.14 (m, 1H); 3.63-3.70 (dd, *J*= 4.6 Hz, *J*= 10.0 Hz, 1H); 5.15 (d, *J*= 9.8 Hz, 1H); 7.41-7.58 (m, 5H); 7.66-7.70 (m, 2H); 7.88-7.92 (m, 2H).

Preparation of compound (18)

Tert-butyl ester (**18**) was prepared from sulfonamide **(17)** (0.80 g, 2.05 mmol) and alcohol **(10)** (0.56 g, 2.05 mmol) following the procedure previously described for the preparation of compound **(6)**, in Example 16. The crude reaction mixture was purified by flash chromatography (n-hexane/AcOEt = 1:1), to give the desired product (**18**) (0.85 g, 64 % yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.94 (d, *J*= 6.6 Hz, 3H); 1.03 (d, *J*= 6.6 Hz, 3H); 1.23 (s, 9H); 1.45 (s, 9H); 1.99-2.14 (m, 1H); 2.43 (t, *J*= 4.9 Hz, 4H); 2.56 (t, *J*= 5.8 Hz, 2H);3.43 (t, *J*= 5.1 Hz, 4H); 3.53-3.77 (m, 6H); 3.97 (d, *J*= 10.4 Hz, 1H); 7.40-7.59 (m, 5H); 7.65-7.69 (m, 2H); 7.89-7.93 (m, 2H).

Preparation of compound (19)

Following a procedure analogous to that used for the preparation of compound **(1a)**, in Example 16, ester **(18)** (0.85g, 1.32 mmol) was treated with TFA to give the desired carboxylic acid **(19)** (100 % yield), as brown oil.

^{1}H-NMR ($CDCl_3$) δ: 0.61 (d, *J*= 6.4 Hz, 3H); 0.94 (d, *J*= 6.41 Hz, 3H); 1.98-2.07 (m, 1H); 3.32-3.94 (m, 17H); 7.43-7.63 (m, 5H); 7.73-7.77 (m, 2H); 7.84-7.88 (m, 2H); 9.00 (br s, 2H); 10.33 (br s, 1H)

Preparation of compound (3a)

Following a procedure analogous to that used for the preparation of compound **(9)**, in Example 16, **19** (2.10 g, 2.92 mmol) was reacted with isophthaloyl chloride to give the desired carboxylic acid (**3a**) as a yellow solid (0.14 g, 10 % yield) after purification by reverse phase chromatography (H_2O/MeOH= 1:1).

Mp= 128-130°C;

^{1}H-NMR (CD_3OD) δ: 0.90 (d, *J*= 6.6 Hz, 6H); 0.99 (d, *J*= 6.4 Hz, 6H); 2.06-2.20 (m, 1H); 2.80-3.15 (m, 12H); 3.39-3.75 (m, 20H); 4.00 (d, *J*= 10.8 Hz, 2H); 7.38-8.15 (m, 22H).

Preparation of the title compound (3b)

Following a procedure analogous to that used for the preparation of compound **(1b)**, in Example 16, the dimeric hydroxamic acid (**3b)** was obtained from carboxylic acid (**3a)** (0.12 g, 0.109 mmol) by reaction with *O*-(tert-butyldimethyl-silyl)hydroxylamine followed by hydrolysis with TFA.

The crude product was purified by reverse phase chromatography (CH_3CN) to give (**3b)** as a solid (3 mg, 10 % yield).

^{1}H-NMR (DMSO-d_6) δ: 0.83-0.90 (m, 12H); 2.07 (m, 2H); 3.16-4.06 (m, 32H); 4.12 (d, *J*= 5.5 Hz, 2H); 7.45-7.94 (m, 22H); 9.60 (br s, 2H); 10.20 (br s, 2H); 11.35 (s, 2H).

Example 19

MMP inhibition assays

Recombinant human pro-MMP-2 was supplied by Prof. Gillian Murphy (Department of Oncology, University of Cambridge, UK), while pro-MMP-13 and pro-MMP-14 were purchased from Calbiochem. Proenzymes were activated immediately prior to use with p-aminophenylmercuric acetate (APMA: 2 mM for 1 h at 37°C for pro-MMP-2 and 1 mM for 30 min at 37°C for pro-MMP-13). Pro-MMP-14 was activated with trypsin 5 μg/ml for 15 min at 37°C followed by soybean trypsin inhibitor (SBTI) 23 μg/ml. For

assay measurements, the inhibitor stock solutions (DMSO, 100 mM) were further diluted, at seven different concentrations (0.01 nM - 100 μM) for each MMP in the fluorimetric assay buffer (FAB: Tris 50 mM, pH = 7.5, NaCl 150 mM, $CaCl_2$ 10 mM, Brij 35 0.05 % and DMSO 1%). Activated enzyme (final concentration 2.9 nM for MMP-2, 1 nM for MMP-14, 0.33 nM for MMP-13) and inhibitor solutions were incubated in the assay buffer for 4 h at 25°C. After the addition of 200 μM solution of the fluorogenic substrate Mca-Lys-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2 (Bachem) (see, for a reference, Neumann, U.; Kubota, H.; Frei, K.; Ganu, V.; Leppert, D. *Anal. Biochem.* 2004, *328*, 166) for all of the enzymes in DMSO (final concentration 2 μM), the hydrolysis was monitored every 15 sec. for 20 min recording the increase in fluorescence (λ_{ex} = 325 nm, λ_{em} = 395 nm) using a Molecular Device SpectraMax Gemini XS plate reader.

The assays were performed in triplicate, in a total volume of 200 μl per well, in 96-well microtitre plates (Corning, black, NBS). Control wells lack inhibitor. The MMP inhibition activity was expressed in relative fluorescent units (RFU). Percent of inhibition was calculated from control reactions without the inhibitor. IC_{50} was determined using the formula: $V_i/V_o = 1/(1 + [I]/ IC_{50})$, where V_i is the initial velocity of substrate cleavage in the presence of the inhibitor at concentration [I] and V_o is the initial velocity in the absence of the inhibitor. Results were analyzed using SoftMax Pro software and GraFit software.

Table 1

Compound	IC_{50} MMP-2 (nM)	IC_{50} MMP-13 (nM)	IC_{50} MMP-14 (nM)
Reference Compound (R,R)-2b	19.8	14.7	116
1b – example 16	3.7	2.4	31
2b – example 17	3.6	1.93	---

As clearly indicated in the above table 1, the compounds of formula (I) of the invention resulted to be endowed with a significant inhibitory activity against MMP-2, MMP-13 and MMP-14 and may be thus useful, in therapy, for the treatment of degenerative disorders involving those same enzymes.

Surprisingly, based on this highly sensible method for assessing the inhibitory activity against the tested enzymes, the compounds of the invention resulted to be endowed with an inhibitory activity markedly higher than that exerted by the structurally closest Reference Compound (R,R)-2b of the prior art.

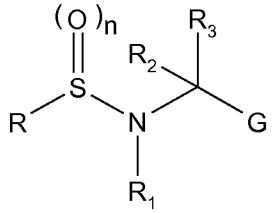
Remarkably, apart from being particularly active in the inhibition of the above metalloproteases MMP-2, MMP-13 and MMP-14, each considered alone, the fact that the compounds of the invention are effective in the inhibition of all of these enzymes is particularly advantageous, in therapy, where it is known that they all play a role in the degenerative processes.

CLAIMS

1) A compound of formula (I)

(M)-L-(M') (I)

wherein M and M', the same or different from each other, represent the residues of the metalloproteases inhibitors of formula (II)



(II)

wherein:

R is a group of formula –Ar–X–Ar' (III) wherein Ar is an arylene, heteroarylene, aryl or heteroaryl group and Ar', the same or different and independently from Ar, is an aryl or heteroaryl group or H; the said Ar and Ar' being optionally substituted by one or more groups selected from:

(i) straight or branched alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, amino, aminoalkyl, alkylamino, aminoacyl, acylamino, carboxy or perfluorinated alkyl, each of which having from 1 to 4 carbon atoms in the alkyl chain;

(ii) straight or branched C_2-C_6 alkenyl or alkynyl group;

(iii) halogen or a cyano (–CN) group;

X is a single bond or it is a divalent linker selected from a straight or branched C_1-C_4 alkylene chain, –O–, –S–, –S(O)$_2$–, –CO–, –NR'–, –NR'CO– or –CONR'–, wherein R' is H or a straight or branched C_1-C_4 alkyl group;

R_1 is hydrogen, hydroxy or a group –Ra or –ORa wherein Ra is selected from straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl groups; or Ra is a group of formula (IV)

$$–(CH_2)_p–Z–(CH_2)_r–W \qquad (IV)$$

wherein p is zero or an integer from 1 to 4; Z is a single bond or a divalent linker selected from –O–, –NR'–, –NR'CO– or –CONR'–, wherein R' is as above defined; r is zero or an integer from 1 to 4; and W is phenyl or a 5 or 6 membered heterocycle, each of which being optionally substituted by one or more groups selected from –NH_2,

–COR', –CONHR', –COOR' or –SO_2NHR' wherein R' is as above defined, by aryl or heteroaryl or by one or more of the above groups from (i) to (ii);

R_2 and **R_3** are, the same or different and each independently, hydrogen, a straight or branched C_1-C_4 alkyl group optionally substituted by hydroxyl or C_1-C_4 alkoxy groups, or a zinc binding group selected from –COOH, –COORb, –CONHOH, –CONHORb, –CONRbOH, –$CONHS(O)_2$Rb, –$CONH_2$, –CONHRb or –$P(O)(OH)_2$, wherein Rb is a straight or branched alkyl, arylalkyl or heteroarylalkyl group having from 1 to 4 carbon atoms in the alkyl chain; or any of the above R_2 or R_3 groups is linked to R_1 so as to form a 5 to 7 membered heterocyclic ring, optionally substituted by one or more oxo groups (=O);

G is a group selected from straight or branched C_1-C_6 alkyl, aryl, heteroaryl or arylalkyl or it is a group –$(CH_2)_m$-$N(R_4)(R_5)$;

R_4 is H or a group selected from –CORc, –COORc, –$S(O)_2$Rc, –CONHRc or –$S(O)_2$NHRc, wherein Rc is a group selected from C_3-C_6 cycloalkyl, straight or branched alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylaryl, alkylheteroaryl, a 5 or 6 membered heterocyclyl, alkylheterocyclyl or heterocycloalkyl having from 1 to 4 carbon atoms in the alkyl chain;

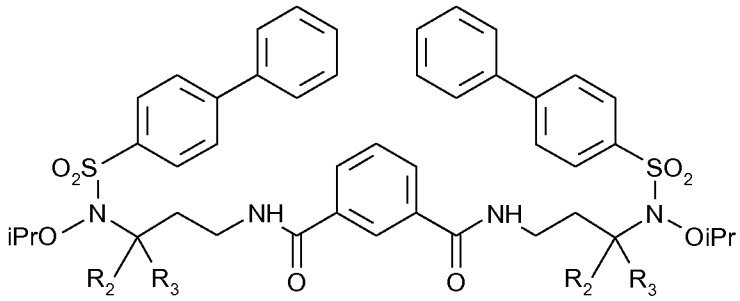
R_5 is H or, together with the N atom to which they are bonded, R_4 and R_5 form an optionally benzocondensed 4 to 6 membered heterocycle, optionally substituted by a group Ra as above defined and/or by one or more oxo (=O) groups;

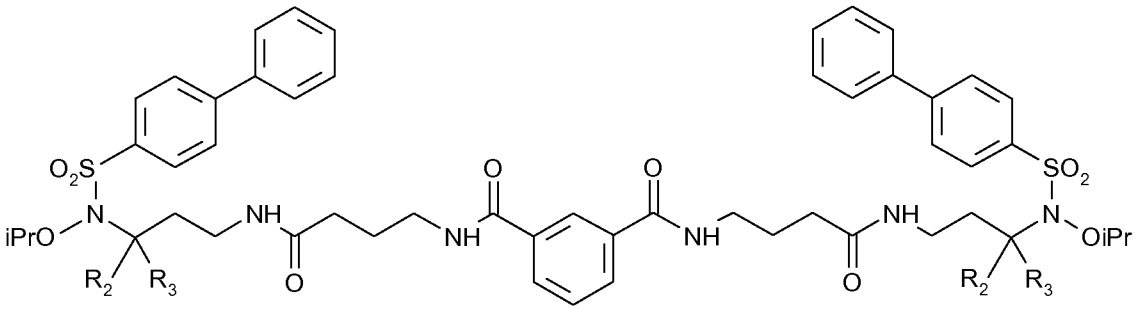
n is 1 or 2;

m is an integer from 1 to 6;

L is a bond or a linker connecting moieties M and M' comprising a hydrocarbon chain with from 1 to 20 carbon atoms, optionally interrupted by one or more groups selected from arylene, heteroarylene, cycloalkylene, heterocycloalkylene, –O–, –S–, –$S(O)_2$–, –CO–, –OCO–, –COO–, –NR'–, –NR'CO– or –CONR'–, wherein R' is as above defined, the said chain being optionally substituted by oxo (=O), amino, hydroxy or carboxy groups;

with the proviso that when the compounds of formula (I) are:

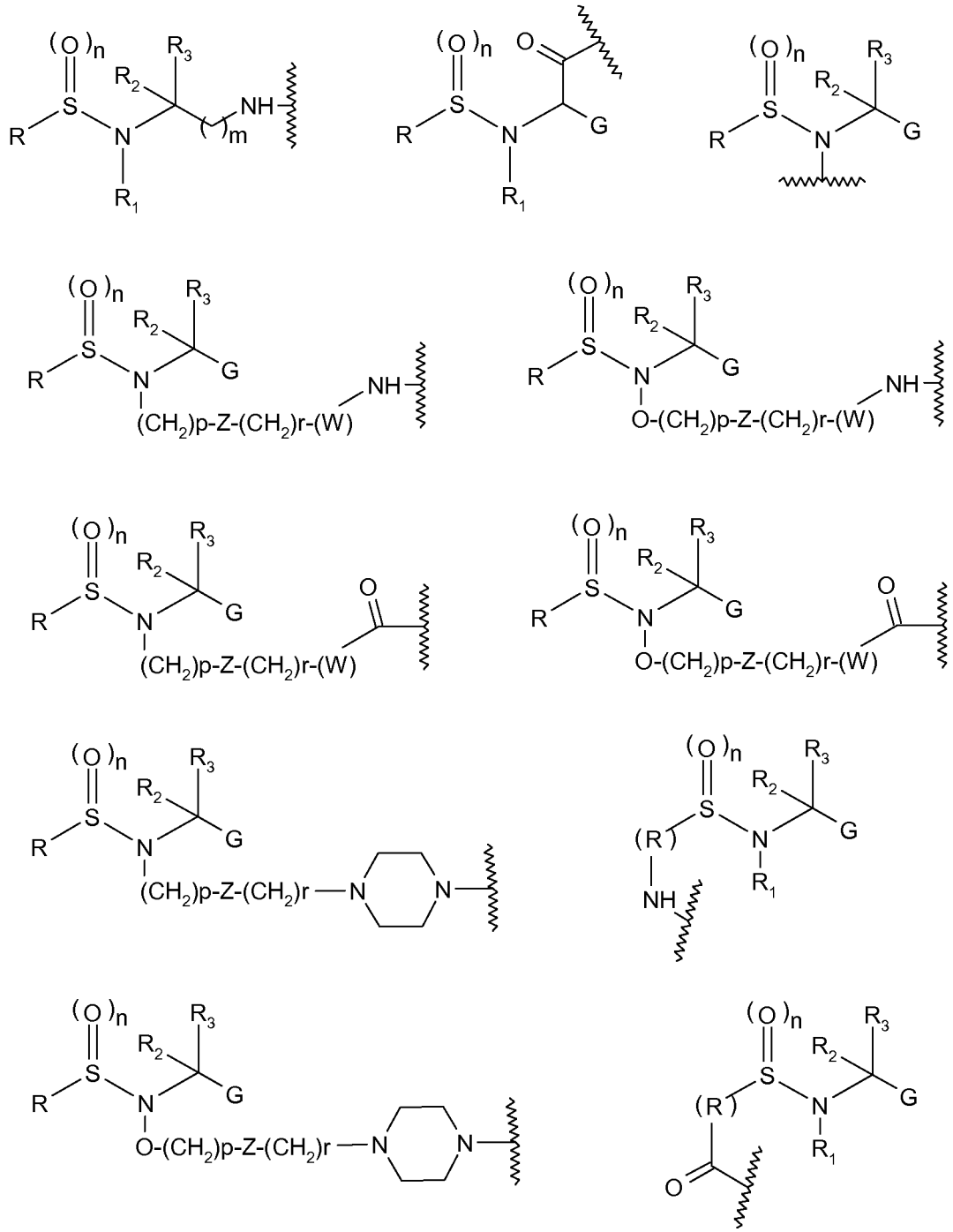




where M and M' are the same, and one of R_2 or R_3 is hydrogen, then the other of R_2 or R_3 is not –COOH, –COO^{t}Bu or –CONHOH;

and the pharmaceutically acceptable salts thereof.

2) A compound of formula (I) according to claim 1 wherein M and M', the same or different from each other, are selected from:



wherein R, n, R_1, R_2, R_3, m, G, p, Z, r and W are as defined in claim 1, the line (~~~~) represents the point of attachment with the rest of the molecule.

3) A compound of formula (I) according to claim 1 or 2 wherein the residues M and M' are the same.

4) A compound of formula (I) according to claim 1 or 2 wherein R is a group of formula (III) wherein Ar represents an optionally substituted phenylene group, X represents a single bond or a divalent linker selected from –O–, –S– or –NH– and Ar' represents H or an optionally substituted phenyl group.

5) A compound of formula (I) according to claim 4 wherein R is a group of formula (III) wherein Ar represents a phenylene group, X represents a single bond or –O– and Ar' represents H or a phenyl group, the phenylene and phenyl groups being optionally further substituted.

6) A compound of formula (I) according to claim 5 wherein R is a group selected from biphenyl-4-yl, 4-bromophenyl, 4-(4'-methoxyphenyl)-phenyl, 4-(4'-ethoxyphenyl)-phenyl, 4-phenoxy-phenyl, 4-(4'methoxyphenoxy)-phenyl and 4-(4'ethoxyphenoxy)-phenyl.

7) A compound of formula (I) according to claim 1 or 2 wherein R_1 is hydrogen or a group –Ra or –ORa, wherein Ra is an alkyl or alkenyl group, or it is a group of formula (IV) wherein p is 1 or 2, Z is a single bond or a divalent group selected from –O– or –NH–, r is 0, 1 or 2, and W is an optionally substituted phenyl or heterocyclic group.

8) A compound of formula (I) according to claim 7 wherein R_1 is selected from hydrogen, isopropoxy, benzyloxy, 4-phenyl-benzyloxy, allyloxy, 2-[2(piperazinyl-1-yl)ethoxy]ethoxy, 2-[2(piperazinyl-1-yl)ethoxy]ethyl or 2-[2(4(ethylcarbonyl) piperazinyl-1-yl)ethoxy]ethoxy.

9) A compound of formula (I) according to claim 1 or 2 wherein R_2 and R_3 are selected, each independently, from H, straight or branched C_1-C_4 alkyl, –COOH, –COORb, –CONHOH or –CONHORb, wherein Rb is a straight or branched alkyl, arylalkyl or heteroarylalkyl group having from 1 to 4 carbon atoms in the alkyl chain.

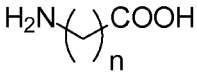
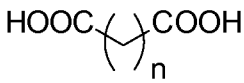
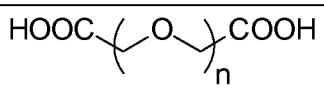
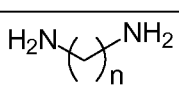
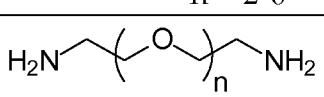
10) A compound of formula (I) according to claim 9 wherein one of R_2 or R_3 is hydrogen and the remaining one of R_2 or R_3 is –COOH or –CONHOH.

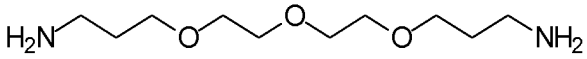
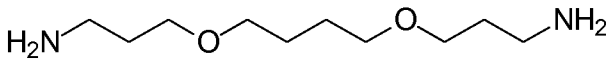
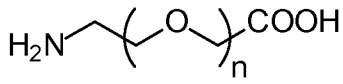
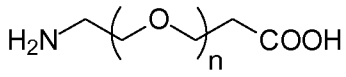
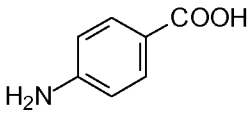
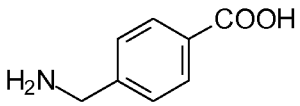
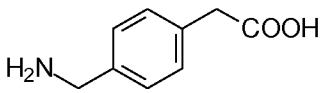
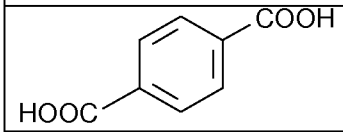
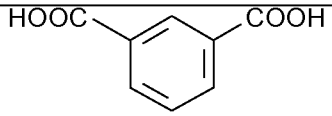
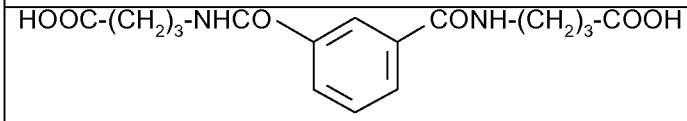
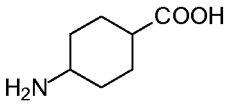
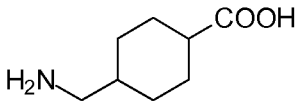
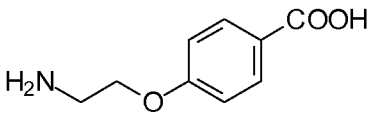
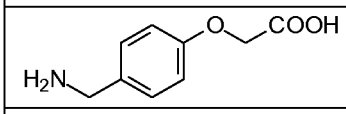
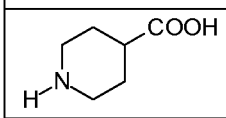
11) A compound of formula (I) according to claim 1 or 2 wherein G is a straight or branched C_1-C_6 alkyl or it is a group of formula $–(CH_2)_m$-$N(R_4)(R_5)$ wherein m, R_4 and R_5 are as defined in claim 1.

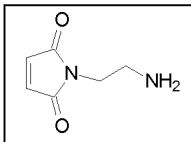
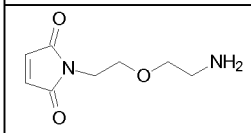
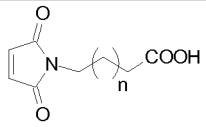
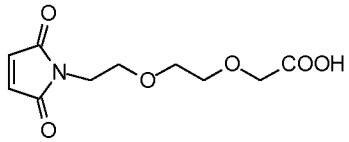
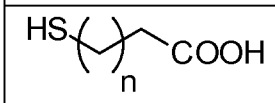
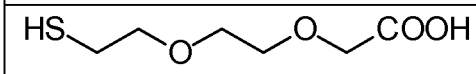
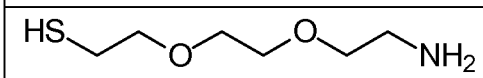
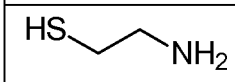
12) A compound of formula (I) according to claim 11 wherein G is isopropyl or a group of formula $–(CH_2)_m$-$N(R_4)(R_5)$ wherein m is 2, R_4 and R_5 are both H, or R_4 is selected from –CORc, –COORc or $–S(O)_2Rc$, wherein Rc is aryl, straight or branched alkyl or arylalkyl with from 1 to 4 carbon atoms in the alkyl chain and R_5 is H.

13) A compound of formula (I) according to claim 1 or 2 wherein L is a linker connecting moieties M and M' comprising a hydrocarbon chain with from 1 to 20 carbon atoms, optionally interrupted by one or more groups selected from arylene, heteroarylene, cycloalkylene, heterocycloalkylene, -CO-, -OCO-, -NR'-, -NR'CO-, -CONR'-, wherein R' is a defined in claim 1, the said chain being optionally substituted by oxo (=O), amino, hydroxy or carboxy groups.

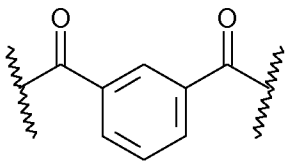
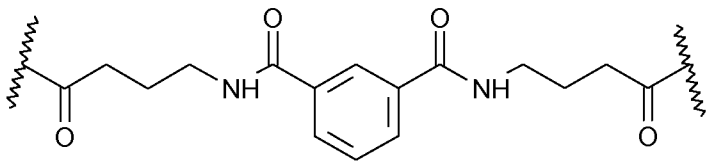
14) A compound of formula (I) according to claim 13 wherein the linker L is represented by the compounds selected from the group consisting of:

 n = 1-6,
 n = 1-4
 n = 1-3
 n = 2-6
 n = 1-5



 n = 1-4
 n = 1-6














 n = 0-3

 n = 0-1




15) A compound of formula (I) according to anyone of previous claims wherein L is a linker selected from:

wherein the lines (~~~~) represent the points of attachment with the rest of the molecule.

16) A pharmaceutical composition comprising an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in anyone of

claims from 1 to 15, together with optional excipents, diluents or carriers for pharmaceutical use.

17) A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in anyone of claims from 1 to 15, for use as a medicament.

18) Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in anyone of claims from 1 to 15, in the preparation of a medicament for the treatment of degenerative disorders.

19) Use according to claim 18 wherein the degenerative disorder is associated with an unpaired regulation of matrix metalloproteases.

20) Use according to claim 19 wherein the degenerative disorder is associated with an overexpression of matrix metalloproteases selected from the group consisting of MMP-2, MMP-13 and MMP-14.

21) Use according to anyone of claims from 18 to 20 wherein the degenerative disorder comprises pathologies leading to an altered tissutal morphology with uncontrolled cell proliferation.

22) Use according to claim 21 wherein the degenerative disorder is selected from the group consisting of tumours; arthritis and connective tissue disorders; neurodegenerative disorders such as multiple sclerosis, Alzheimer's disease, stroke and ALS (Amyotrophic Lateral Sclerosis); cardiovascular disorders such as atherosclerosis, aneurism, heart failure, dilated cardiomyopathy; pulmonary diseases such as emphysema or cystic fibrosis; gastric ulcers; sepsis and autoimmune disorders.

23) A method for the treatment of degenerative disorders in mammals which method comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in anyone of claims from 1 to 15, or a composition as defined in claim 16.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/059339

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D295/205 C07C311/00 A61K31/496 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 2009	15/10/2009

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

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Form PCT/ISA/210 (second sheet) (April 2005)

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International application No
PCT/EP2009/059339

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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