

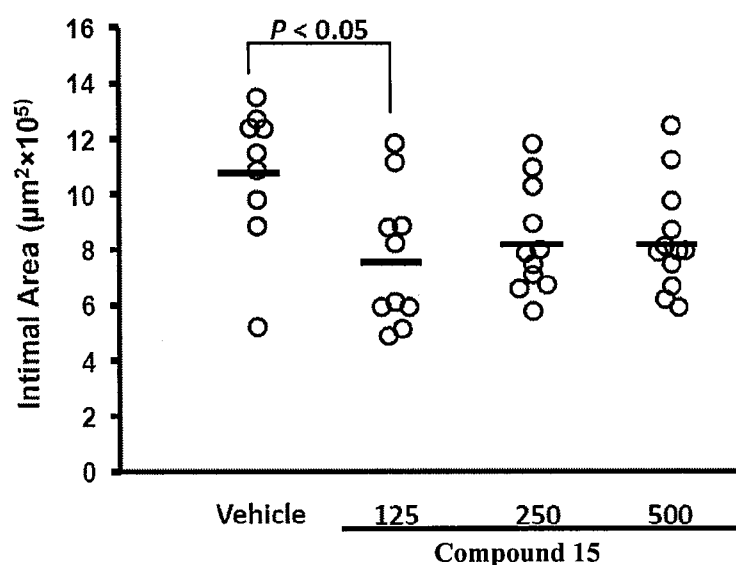


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[Continued on next page]

(54) Title: SELECTIVE MMP INHIBITORS

FIGURE 1A



(57) Abstract: Described are methods for treating diseases by use of agents that selectively inhibit human metalloproteinases (MMP), such as MMP-9 and MMP-2, while optionally sparing MMP-1. Prevention of atherosclerotic plaque development and rupture and/or carotid arterial plaque development and rupture, by MMP inhibition can reduce the adverse consequences of plaque development and rupture including thromboembolism, stroke, myocardial infarction and acute coronary syndromes.

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SELECTIVE MMP INHIBITORS**BACKGROUND OF THE INVENTION****Field of the Invention**

[0001] The present invention is in the field of methods for treating and preventing atherosclerotic plaque development and rupture (e.g., carotid arterial plaque development and rupture) and resultant thromboembolism, stroke, myocardial infarction, and acute coronary syndromes through administration of the compounds disclosed herein.

Summary of the Related Art

[0002] Atherosclerosis is a chronic inflammatory response in the walls of arterial blood vessels, caused largely by the accumulation of macrophage white blood cells and promoted by low-density lipoproteins without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL). Artery walls can thicken as a result of the accumulation of multiple plaques within the arteries, formed from fatty materials such as cholesterol.

[0003] The precipitating event of myocardial infarction (MI) and acute coronary syndromes (ACS) is the hemorrhage into and rupture of an unstable atherosclerotic plaque. One of the proposed mechanisms for plaque rupture is MMP-induced tissue breakdown. Atherosclerotic plaques are separated into two broad categories: stable and unstable (*i.e.*, vulnerable). Unstable plaques are rich in macrophages and foam cells and the extracellular matrix separating the lesion from the arterial lumen is usually weak and prone to rupture. Ruptures of the fibrous cap expose thrombogenic material such as collagen to the circulation and eventually induce thrombus formation in the lumen. Upon formation, intraluminal thrombi can occlude arteries (*i.e.*, coronary occlusion) or detach and move into the circulation and eventually occlude smaller downstream branches causing thromboembolism (*i.e.*, stroke).

SUMMARY OF THE INVENTION

[0004] The proteolytic effects of MMPs in atherosclerotic plaques may contribute to the tissue breakdown and result in plaque development rupture and activation of the thrombotic cascade that leads to coronary artery occlusion. Current therapies have focused on preventing the thrombotic events that occur after plaque rupture by the use of drugs such as aspirin and other antithrombotic agents. Herein, a novel approach to the prevention of

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myocardial infarction (MI) and acute coronary syndromes (ACS) is described herein which utilizes the selective inhibition of the proteolytic MMP enzymes within atherosclerotic plaque to prevent plaque development and rupture and reduce the risk of myocardial damage from the resulting occlusion of the coronary artery.

[0005] Selective inhibition of the proteolytic MMP enzymes can lead to stabilization of plaque and be a useful treatment of atherosclerosis. For example, elevated levels of MMP-9 have been observed in patients with evidence of spontaneous embolization (see Loftus *et al.*, *Eur. J. Endovasc. Surg.* 2001, 21, 17.) Expression of MMP-9 murine atherosclerotic models elicited elastin degradation and induced significant plaque disruption. (see, Gough *et al.*, *J. Clin. Invest.* 2006, 116, 59). And, in studies of carotid artery atherosclerotic disease, MMP-2 and MMP-9 have been strongly correlated with plaque instability. (see Heo *et al.*, *J. Clin. Neurol.* 2011, 7, 69). In addition, a causal connection has been drawn between increased vascular MMP activity and intraplaque hemorrhage (see Hu *et al.*, *Circulation* 2010, 121, 1637). For example, MMP-1 has been expected to promote plaque rupture. (see Schwartz *et al.*; *Arterioscler. Thromb. Vasc. Biol.* 2007, 27, 705).

[0006] Herein, it has been discovered that MMP inhibition by an optionally MMP-1 sparing MMP antagonist is particularly useful for plaque stabilization. Advantageously, such an approach can limit the need for antithrombotic drugs and their resultant toxicity.

[0007] Accordingly, the present invention generally provides methods of atherosclerotic plaque stabilization through inhibition of matrix metalloproteinases via administration of the compounds disclosed herein, which are selective MMP antagonists (e.g., selective for MMP-2 and/or MMP-9) and/or MMP-1 sparing. Prevention of atherosclerotic plaque development and rupture (e.g., carotid arterial plaque development and rupture) by MMP inhibition can reduce the adverse consequences of plaque development and rupture, including thromboembolism, stroke, myocardial infarction, and acute coronary syndromes. Consequently, the present invention also relates to methods for treating diseases resulting from atherosclerotic plaque development and rupture (e.g., carotid arterial plaque development and rupture) by use of agents that selectively inhibit human metalloproteinases, such as MMP-9 and/or MMP-2, while optionally sparing MMP-1. In certain examples, the methods use agents that selectively inhibit MMP-9 and/or MMP-2, while sparing MMP-1.

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[0008] The invention also comprises a method of inhibiting atherosclerotic lesion formation and growth as well as reducing aortic intimal lipid accumulation in mammals comprising administering an effective amount of a compound of the invention to a mammal.

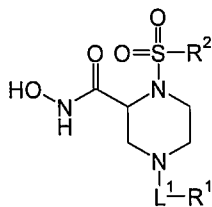
[0009] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting. All patents, applications, and publications recited herein are hereby incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figures 1A-1D display the results of *in vivo* experiments demonstrating that the selective MMP inhibitor compound 15 decreases aortic root atherosclerosis in uPA- overexpressing (SR-uPA^{+/0}) mice. SR-uPA^{+/0} mice were treated for 10 weeks with either vehicle or with compound 15 at one of three doses. Fig. 1A displays mean intimal area of aortic root lesions. Fig. 1B displays circumference of the aortic root at the level of the internal elastic lamina (IEL). Fig. 1C displays the mean percentage of aortic root intimal lesions staining positively for oil red O. Fig. 1D displays the mean percentage of aortic root intimal lesions staining positively for the macrophage marker Mac-2. Data points are individual mice; bars are group means.

DETAILED DESCRIPTION OF THE INVENTION

[0011] In a first aspect, the methods of the invention use a compound of structural formula I:



I

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein

L¹ is -C(O)-, -S(O)₂-, or -(CH₂)_n-;

R¹ is -H, -OR¹¹, -(CH₂)_nR¹¹, -C(O)R¹¹, or -NR¹²R¹³;

R¹¹, R¹², and R¹³ independently are

a) R⁵⁰;

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- b) saturated or mono- or poly- unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one or two R⁵⁰ substituents;
- c) C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, or -C(O)H, each of which is optionally substituted with one, two or three substituents independently selected from R⁵⁰ and saturated or mono- or poly- unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two or three R⁵⁰ substituents;
- or R¹² and R¹³ together with the N to which they are covalently bound, a C₅-C₆ heterocycle optionally containing a second annular heteroatom and optionally substituted with one or two R⁵⁰ substituents;

R² is -R²¹-L²-R²²;

R²¹ is saturated or mono- or poly- unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R⁵⁰ substituents;

L² is -O-, -C(O)-, -CH₂-, -NH-, -S(O₂)- or a direct bond;

R²² is saturated or mono- or poly- unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R⁵⁰ substituents; and

R⁵⁰ is R⁵¹-L³-(CH₂)_n;

L³ is -O-, -NH-, -S(O)₀₋₂-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -C₆H₄-, or a direct bond;

R⁵¹ is -H, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, halo, -CF₃, -OCF₃, -OH, -NH₂, mono-C₁-C₆alkyl amino, di-C₁-C₆alkyl amino, -SH, -CO₂H, -CN, -NO₂, -SO₃H, or a saturated or mono- or poly- unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three substituents;

wherein n is 0, 1, 2, or 3;

provided that an O or S is not singly bonded to another O or S in a chain of atoms.

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[0012] In one example of compounds of structural formula **I**, L^1 is $-C(O)-$ or $-S(O)_2-$.

[0013] In another example of compounds of structural formula **I**, L^1 is $-C(O)-$ and R^1 is $-OR^{11}$ or $-(CH_2)_nR^{11}$, $-OC_1-C_6alkyl$ -mono- C_1-C_6alkyl amino, $-OC_1-C_6alkyl$ -di- C_1-C_6alkyl amino, $-OC_1-C_6alkyl$ -N-heterocyclyl, $-C_1-C_6alkyl$ -mono- C_1-C_6alkyl amino, $-C_1-C_6alkyl$ -di- C_1-C_6alkyl amino, or $-C_1-C_6alkyl$ -N-heterocyclyl. In a more specific example, R^1 is C_1-C_6 -alkoxy- C_1-C_6 -alkoxy; and in a still more specific example R^1 is methoxyethoxy.

[0014] In another example of compounds of structural formula **I**, L^1 is $-S(O)_2-$, and R^1 is $-NR^{12}R^{13}$, $-(CH_2)_nR^{11}$, $-C_1-C_6alkyl$ -mono- C_1-C_6alkyl amino, $-C_1-C_6alkyl$ -di- C_1-C_6alkyl amino, or $-C_1-C_6alkyl$ -N-heterocyclyl.

[0015] In another example of compounds of structural formula **I** or any of the preceding embodiments thereof, L^2 is $-O-$.

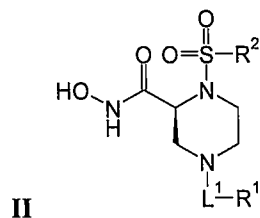
[0016] In another example of compounds of structural formula **I** or any of the preceding embodiments thereof, R^2 is phenoxyphenyl wherein each phenyl is optionally substituted with one or two R^{50} substituents. In a more specific example, the R^{50} substituents are halo.

[0017] In another example of compounds of structural formula **I** or any of the preceding embodiments thereof, the saturated or mono- or poly- unsaturated C_5-C_{14} -mono- or fused poly- cyclic hydrocarbonyl containing one or two annular heteroatoms per ring is selected from the group consisting of morpholinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, furyl, thienyl, pyranyl, isobenzofuranyl, chromenyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolinyl, carbazolyl, acrydyl, and furazanyl, optionally substituted with one or two R^{50} substituents.

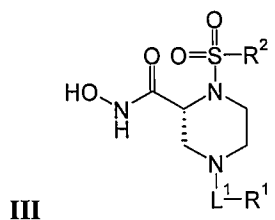
[0018] In another example of compounds of structural formula **I** or any of the preceding embodiments thereof, R^{12} and R^{13} , together with the N to which they are covalently bound, form a heterocycle selected from the group consisting of morpholinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolinyl, carbazolyl, acrydyl, and furazanyl, optionally substituted with one or two R^{50} substituents.

[0019] In another example, the compound of structural formula **I** or any of the preceding embodiments thereof, has the absolute stereochemistry of structural formula **II**:

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[0020] In another example, the compound of structural formula **I** or any of the preceding embodiments thereof, have the absolute stereochemistry of structural formula **III**:



[0021] In another example, the compounds of structural formula **I**, **II**, or **III**, or any of the preceding embodiments thereof, wherein $-L^1-R^1$ is selected from Table 1;

Table 1

$-R^{14}$		

- 7 -

wherein each R^{14} is independently selected from $-H$, $-(CH_2)_{1-3}CO_2H$, alkyl, alkoxy, alkenyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

and R^2 is selected from Table 2;

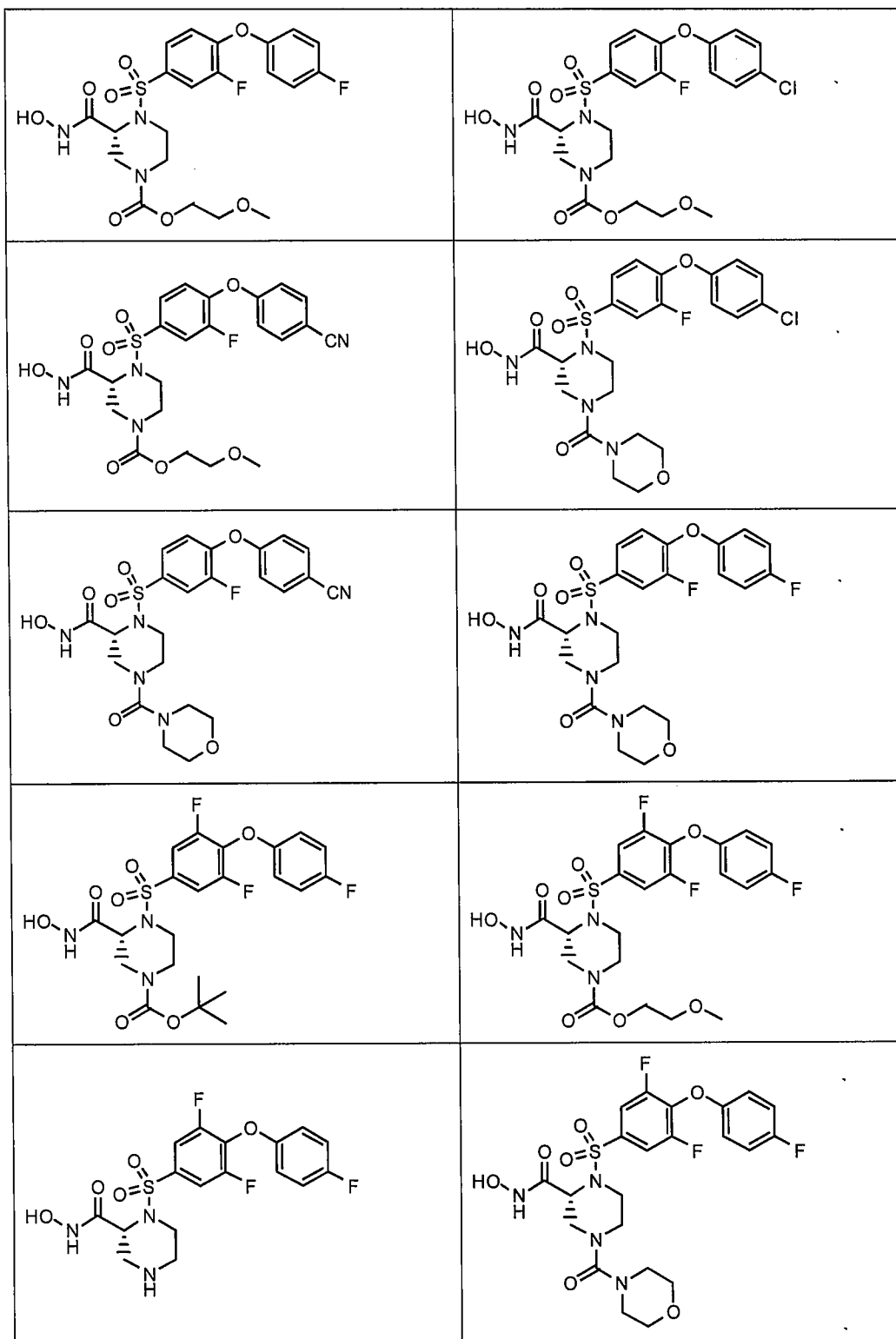
Table 2

- 8 -

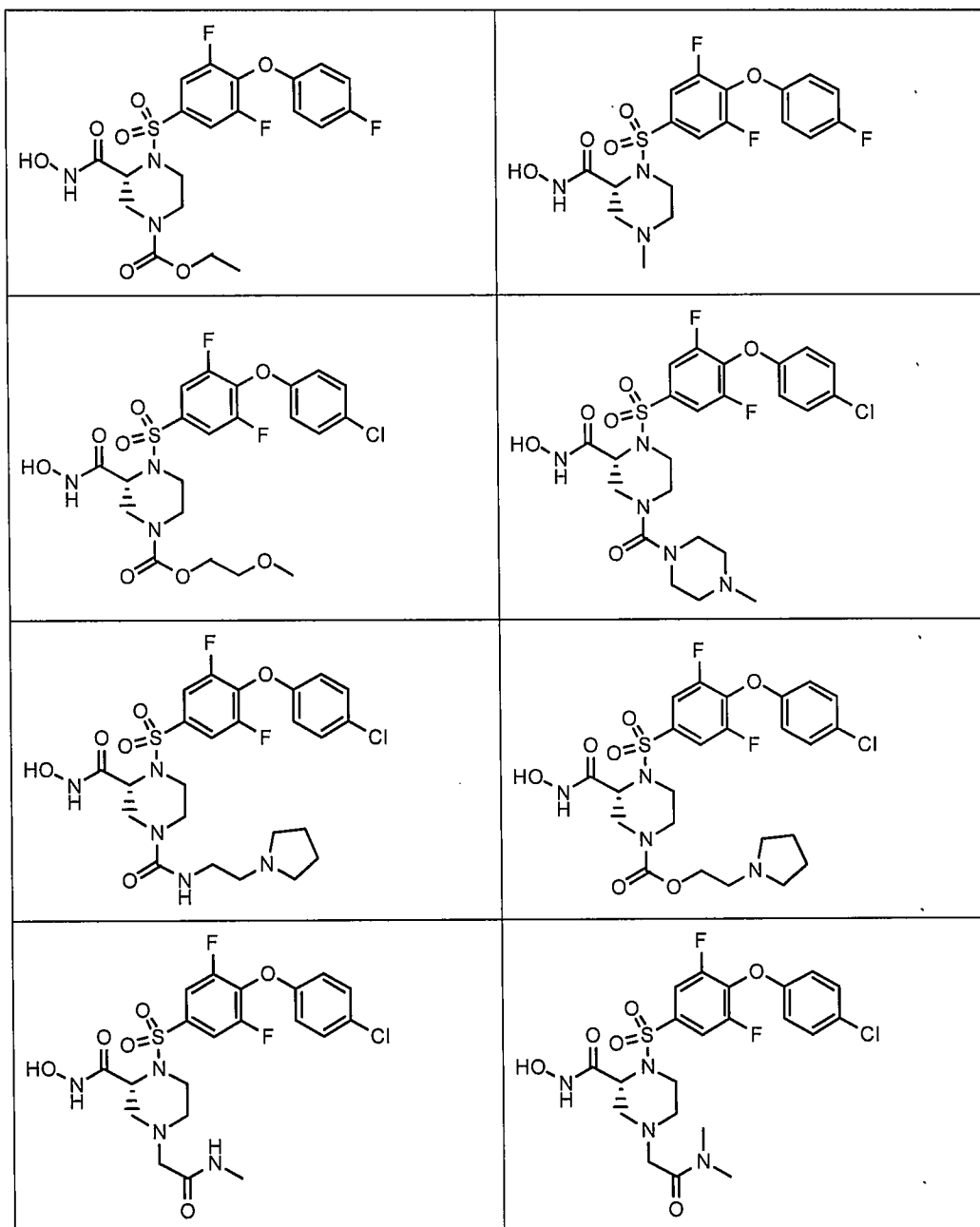
[0022] In another example the compounds of structural formula I is selected from Table 3:

Table 3

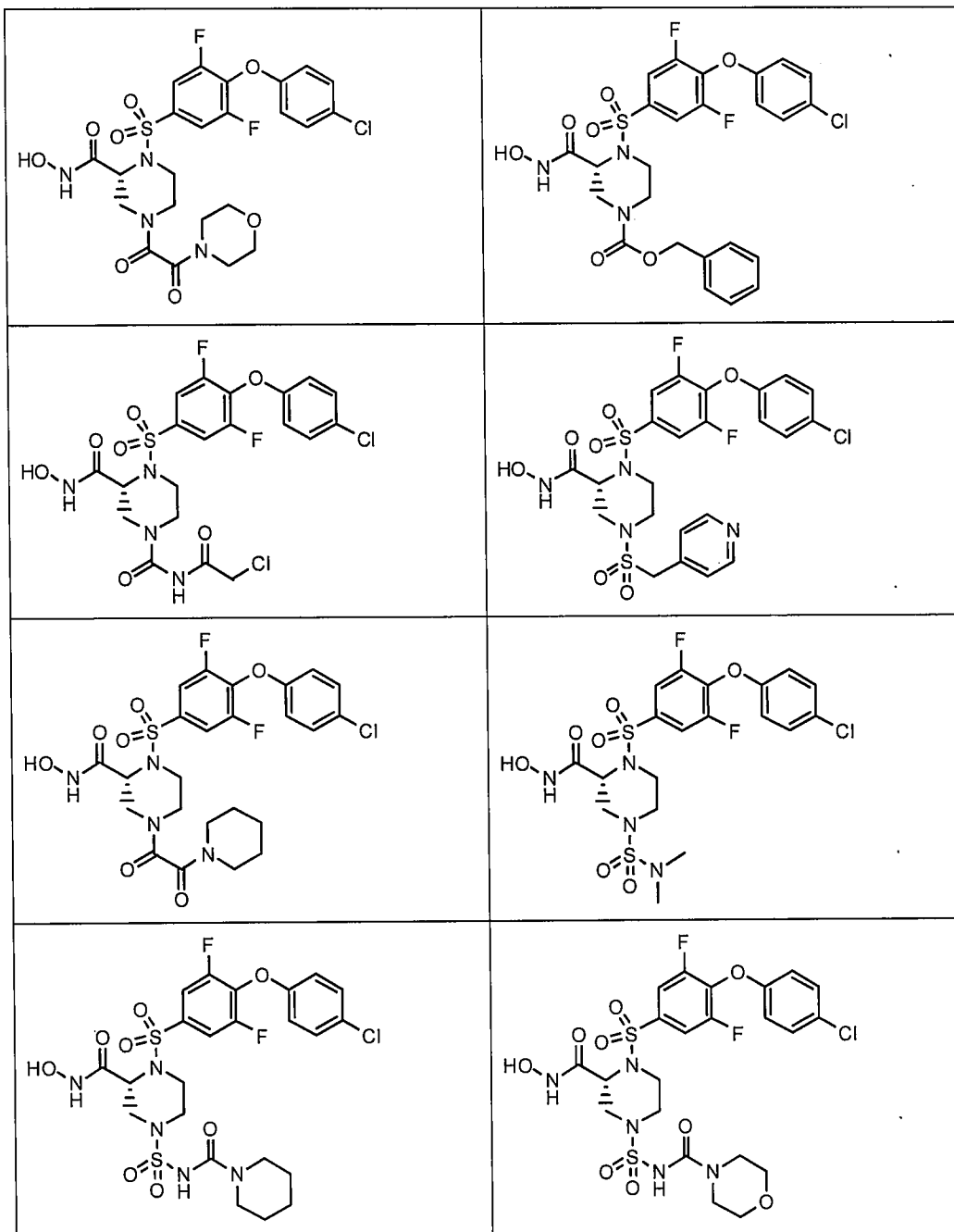
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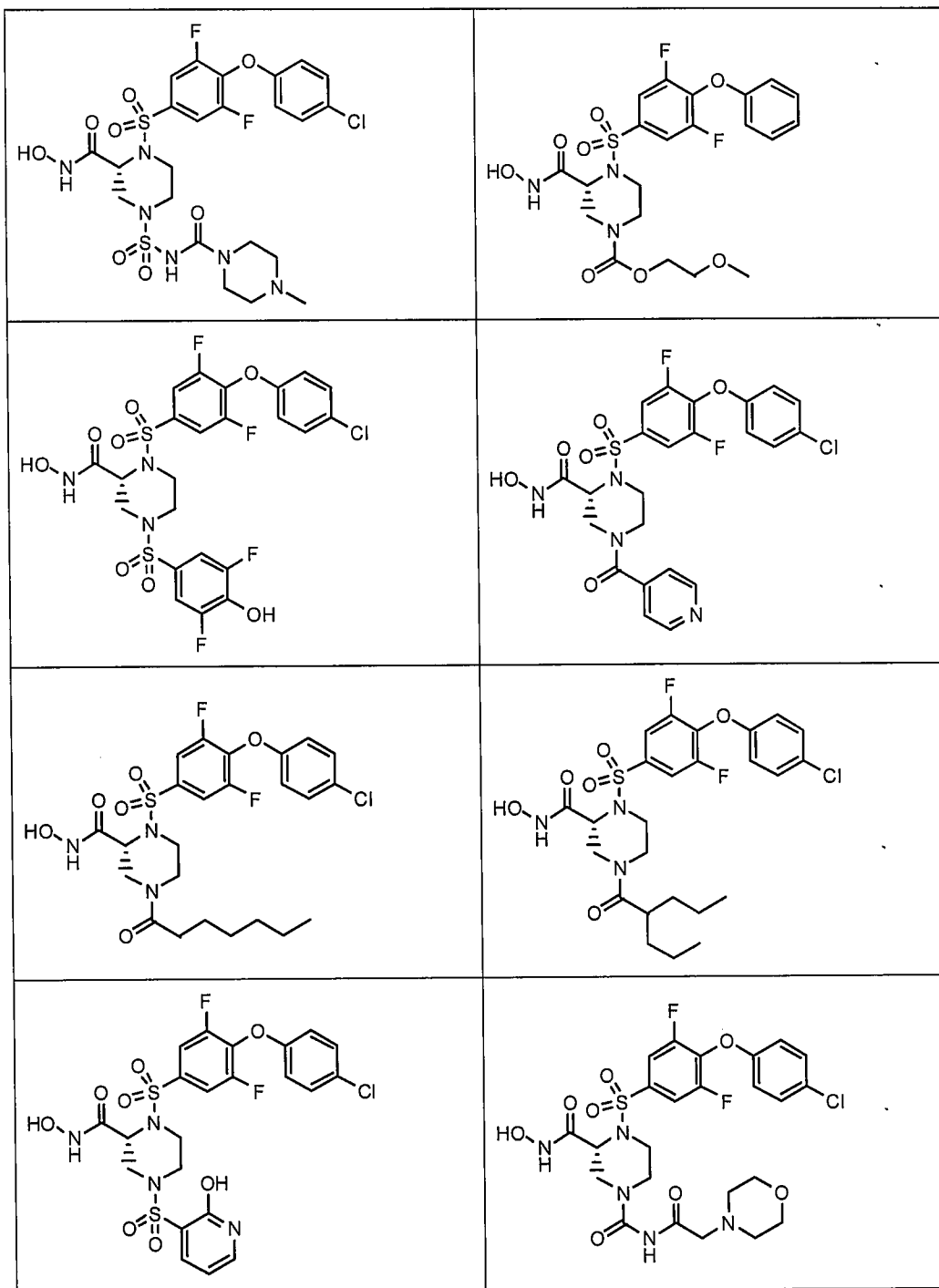
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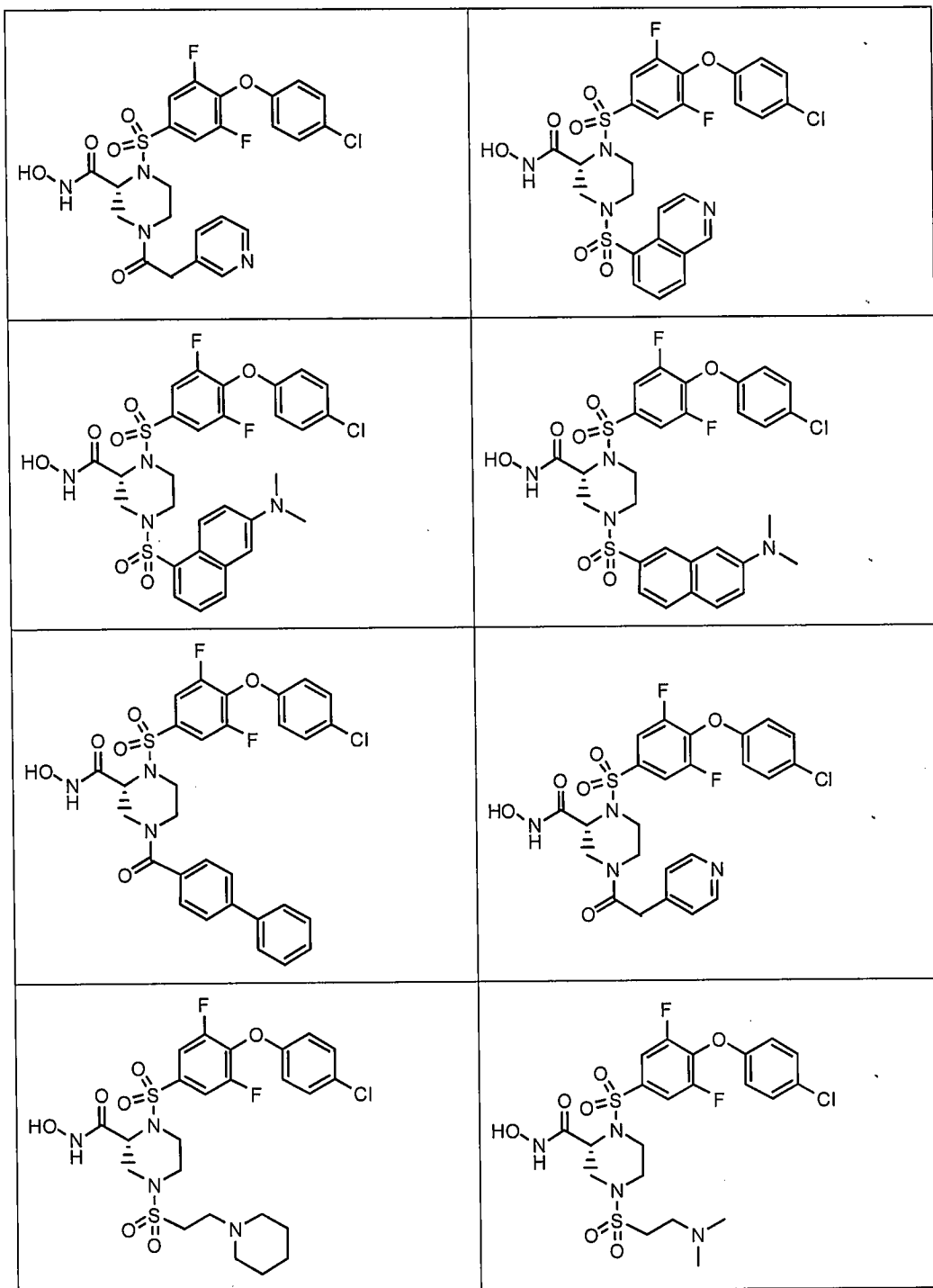
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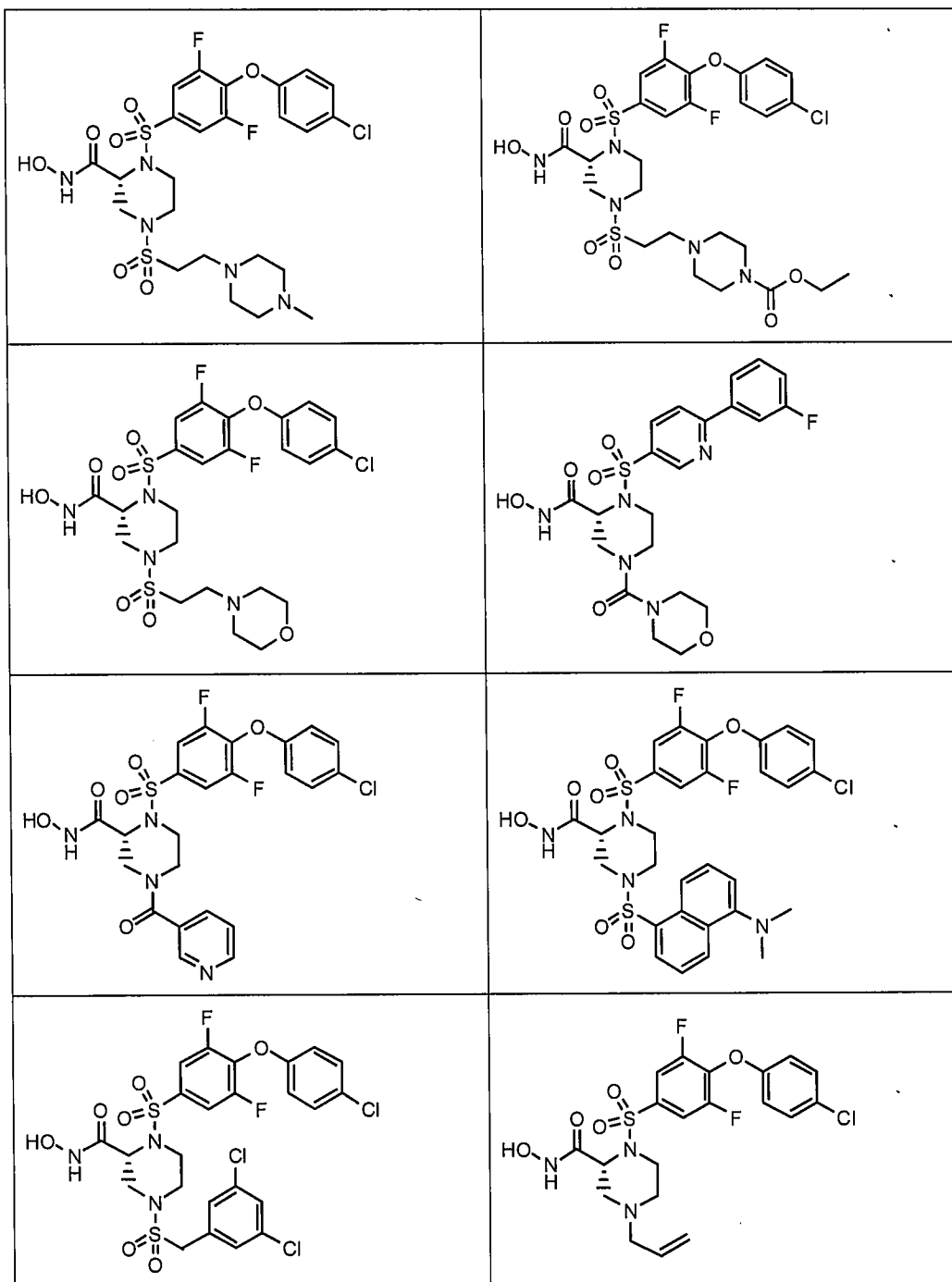
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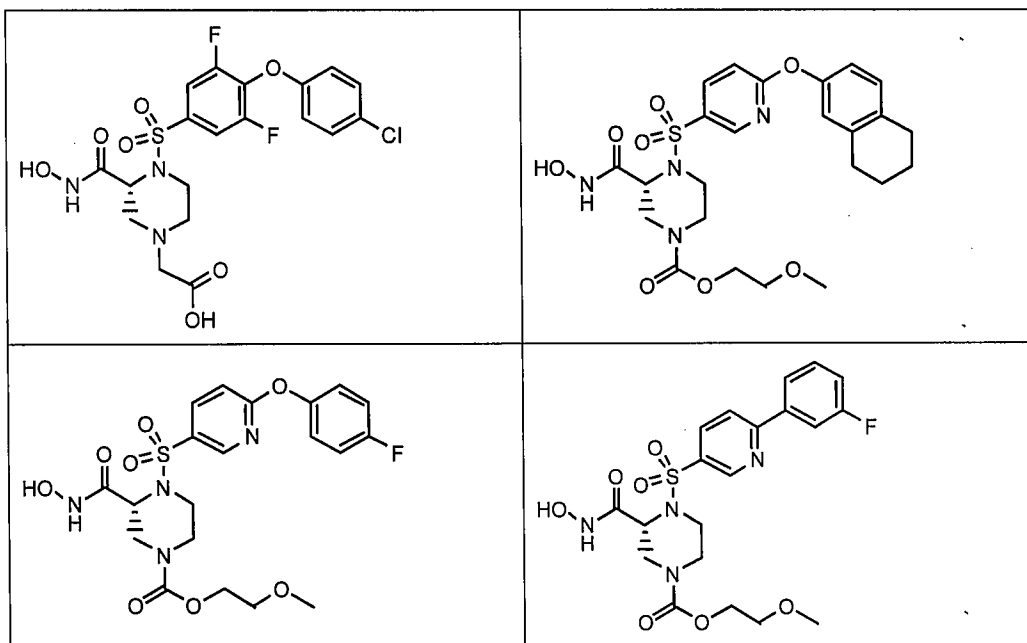
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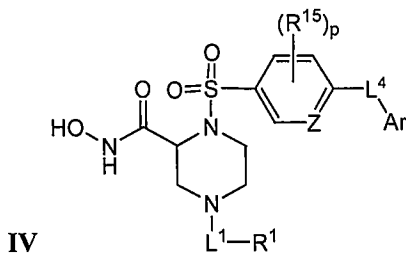
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[0023] In a second aspect, the invention comprises methods for treating atherosclerosis using compounds according to formula IV,



and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein,

Z is $-\text{C}(\text{R}^{15})=$, $-\text{C}(\text{H})=$, or $-\text{N}=$;

Ar is aryl or heteroaryl, each optionally substituted;

R^{15} is fluoro;

p is 0, 1, 2, or 3;

L^1 is $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, or $-(\text{CH}_2)_n-$;

L^4 is nothing or $-\text{O}-$;

R^1 is $-\text{H}$, $-\text{OR}^{11}$, $-(\text{CH}_2)_n\text{R}^{11}$, $-\text{C}(\text{O})\text{R}^{11}$, or $-\text{NR}^{12}\text{R}^{13}$;

R^{11} , R^{12} , and R^{13} independently are

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- a) R^{50} ;
- b) saturated or mono- or poly- unsaturated C_5 - C_{14} -mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one or two R^{50} substituents;
- c) C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, or $-C(O)H$, each of which is optionally substituted with one, two or three substituents independently selected from R^{50} and saturated or mono- or poly- unsaturated C_5 - C_{14} -mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two or three R^{50} substituents;
- or R^{12} and R^{13} together with the N to which they are covalently bound, a C_5 - C_6 heterocycle optionally containing a second annular heteroatom and optionally substituted with one or two R^{50} substituents; and

R^{50} is R^{51} - L^3 -(CH_2) $_n$;

L^3 is $-O-$, $-NH-$, $-S(O)_{0-2}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)-$, $-NHC(O)-$, $-C_6H_4-$, or a direct bond;

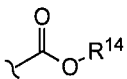
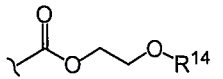
R^{51} is $-H$, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, halo, $-CF_3$, $-OCF_3$, $-OH$, $-NH_2$, mono- C_1 - C_6 alkyl amino, di- C_1 - C_6 alkyl amino, $-SH$, $-CO_2H$, $-CN$, $-NO_2$, $-SO_3H$, or a saturated or mono- or poly- unsaturated C_5 - C_{14} -mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three substituents;

wherein n is 0, 1, 2, or 3;

provided that an O or S is not singly bonded to another O or S in a chain of atoms.

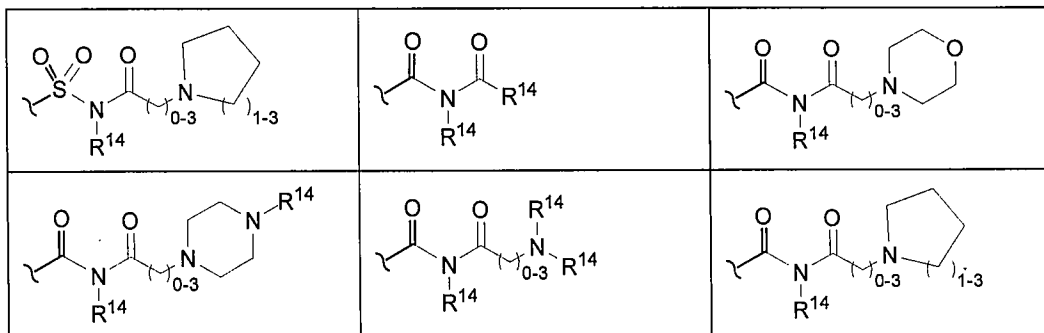
[0024] In one example of the compound of structural formula IV, $-L^1-R^1$ is selected from Table 4,

Table 4

$-R^{14}$		
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wherein each R^{14} is independently selected from $-H$, $-(CH_2)_{1-3}CO_2H$, alkyl, alkoxy, alkenyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl.

[0025] In another example of the compound of structural formula **IV**, Z is $-C(R^{15})=$ or $-C(H)=$; L^4 is $-O-$; and p is at least one, such are referred to as compounds of formula **IVa**.

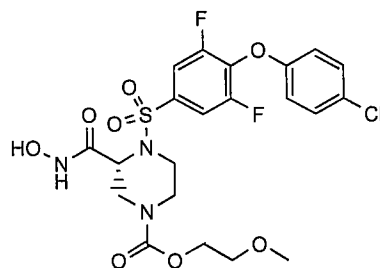
[0026] In example of the compounds of structural formula **IV** or **IVa**, Ar is selected from the group consisting of phenyl, biphenyl, naphthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.

[0027] In another example of the compound of structural formula **IV** or **IVa**, Ar is phenyl, optionally substituted, with at least one halogen.

[0028] In another example of the compound of structural formula **IV** or **IVa**, and any of the preceding embodiments thereof, p is at least two.

[0029] In another example of the compound of structural formula **IV** or **IVa**, and any of the preceding embodiments thereof, $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_2OR^{14}$.

[0030] In another example the compound of structural formula **IV** has the structure:



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[0031] In another example of the compound of structural formula **IV**, Z is $-N=$; and L^4 is $-O-$, such are referred to as compounds of formula **IVb**.

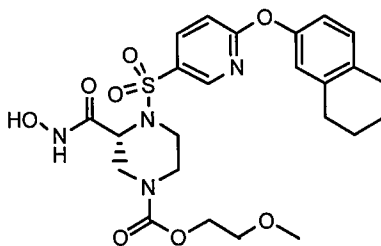
[0032] In an example of the compound of structural formula **IVb**, Ar is selected from the group consisting of phenyl, biphenyl, naphthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.

[0033] In another example of the compound of structural formula **IVb**, Ar is optionally substituted tetrahydro-naphthalene.

[0034] In another example of the compound of structural formula **IVb** and any of the preceding embodiments thereof, $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_{2-3}OR^{14}$.

[0035] In another example of the compound of structural formula **IVb** and any of the preceding embodiments thereof, p is zero.

[0036] In another example the compound of structural formula **IVb** has the structure:



[0037] In another example of the compound of the compound of structural formula **IV**, Z is $-N=$; and L^4 is nothing such are referred to as compounds of formula **IVc**.

[0038] In an example of the compound of structural formula **IVc**, Ar is selected from the group consisting of phenyl, biphenyl, naphthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.

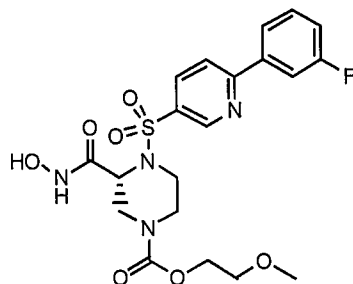
[0039] In another example of the compound of structural formula **IVc** and any of the preceding embodiments thereof, p is zero.

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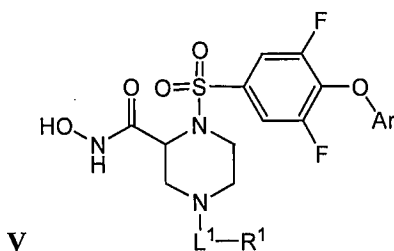
[0040] In another example of the compound of structural formula **IVc** and any of the preceding embodiments thereof, Ar is optionally substituted phenyl.

[0041] In another example of the compound of structural formula **IVc** and any of the preceding embodiments thereof, $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_{2-3}OR^{14}$.

[0042] In another example, the compound of structural formula **IVc** has the structure:



[0043] In another example, the compound of structural formula **IV** is of formula **V**,

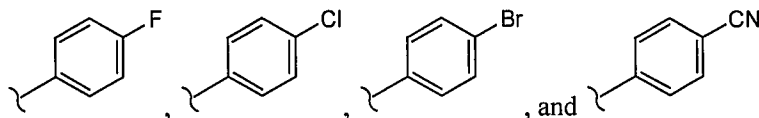


[0044] In another example of the compound of structural formula **V**, Ar is selected from the group consisting of phenyl, biphenyl, naphthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.

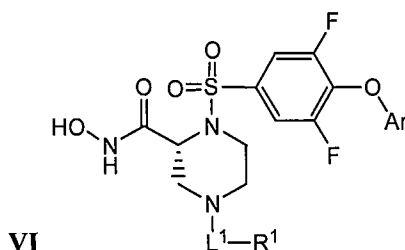
[0045] In another example of the compound of structural formula **V** and any of the preceding embodiments thereof, Ar is phenyl, optionally substituted, with at least one halogen.

[0046] In another example of the compound of structural formula **V** and any of the preceding embodiments thereof, Ar is selected from,

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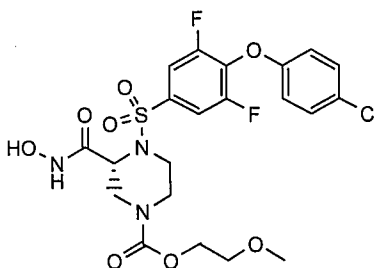


[0047] In another example, the compound of structural formula **V** has the absolute stereochemistry is according to formula **VI**,



[0048] In another example of the compound of structural formula **VI**, $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_{2-3}OR^{14}$.

[0049] In another example the compound of structural formula **VI** has the structure:



[0050] In a third aspect, the invention comprises a method for treating atherosclerosis comprising administering to a patient in need of such treatment, a therapeutically effective amount of a pharmaceutical composition comprising a compound as described in any of the embodiments described in the preceding paragraphs of the first or second aspects of the invention, optionally with a pharmaceutically acceptable carrier.

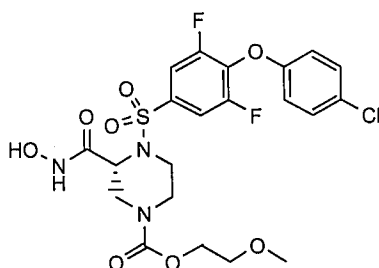
[0051] In a fourth aspect, the invention comprises method for treating, preventing, or reducing the risk of carotid, aortic, or other arterial plaque development and rupture, atherosclerosis, thromboembolism, stroke, acute coronary syndromes, and/or myocardial infarction in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of a compound described in any of the embodiments of the first and second aspects of the invention, optionally with a pharmaceutically acceptable carrier.

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[0052] In a fifth aspect, the invention comprises a method of inhibiting atherosclerotic lesion formation and growth as well as reducing aortic intimal lipid accumulation in a patient comprising administering to the patient a therapeutically effective amount of a compound described in any of the embodiments of the first and second aspects of the invention, optionally with a pharmaceutically acceptable carrier.

[0053] "Patient" as used herein refers to a mammal, including a human.

[0054] The invention also comprises all the foregoing methods in which the compound is a pharmaceutically acceptable salt. In a particular embodiment of the methods disclosed herein is the use of the Mg^{2+} salt of any of the genera and specific compounds disclosed herein. In another particular embodiment, the compound is the Mg^{2+} salt of the compound



DEFINITIONS

[0055] The following paragraphs provide definitions of the various chemical moieties that make up the compounds of the invention and are intended to apply uniformly throughout the specification and claims unless expressly stated otherwise.

[0056] The term alkyl refers inclusively to a univalent C_1 to C_{20} (unless explicitly stated otherwise) saturated straight, branched, cyclic, and combinations thereof alkane moiety and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. In certain instances, specific cycloalkyls are defined (*e.g.* C_3 - C_8 cycloalkyl) to differentiate them from generically described alkyls (that, again, are intended to construe inclusion of cycloalkyls). Thus "alkyl" includes, *e.g.*, C_3 - C_8 cycloalkyl. The term "alkyl" also includes, *e.g.*, C_3 - C_8 cycloalkyl C_1 - C_6 alkyl, which is a C_1 - C_6 alkyl having a C_3 - C_8 cycloalkyl terminus. Alkyl's can be optionally substituted with any appropriate group, including but not limited to one or more moieties selected from halo, hydroxyl, amino, arylalkyl, heteroarylalkyl, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either

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unprotected, or protected as necessary, as known to those skilled in the art or as taught, for example, in Greene, *et al.*, "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991.

[0057] The term alkoxy refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is "polyalkoxy" or -O- (optionally substituted alkylene)-(optionally substituted alkoxy), and includes groups such as -OCH₂CH₂OCH₃, and glycol ethers such as polyethyleneglycol and -O(CH₂CH₂O)_xCH₃, where x is an integer of between about 2 and about 20, in another example, between about 2 and about 10, and in a further example between about 2 and about 5. Another exemplary substituted alkoxy group is hydroxyalkoxy or -OCH₂(CH₂)_yOH, where y is for example an integer of between about 1 and about 10, in another example y is an integer of between about 1 and about 4.

[0058] The term alkenyl refers to a univalent C₂-C₆ straight, branched, or in the case of C₅₋₈, cyclic hydrocarbon with at least one double bond.

[0059] The term aryl refers to a univalent phenyl, biphenyl, naphthyl, and the like. The aryl group can be optionally substituted with any suitable group, including but not limited to one or more moieties selected from halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, *et al.*, "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991). As well, substitution on an aryl can include fused rings such as in tetrahydronaphthalene, chromen-2-one, dibenzofuran, and the like. In such cases, e.g. tetrahydronaphthalene, the aryl portion of the tetrahydronaphthalene is attached to the portion of a molecule described as having an aryl group.

[0060] The term heteroatom means O, S, P, or N.

[0061] The term heterocycle refers to a cyclic alkyl, alkenyl, or aryl moiety as defined above wherein one or more ring carbon atoms is replaced with a heteroatom.

[0062] The term heteroaryl specifically refers to an aryl that includes at least one of sulfur, oxygen, and nitrogen in the aromatic ring. Non-limiting examples are pyrrolyl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl.

[0063] The term halo refers to chloro, fluoro, iodo, or bromo.

[0064] As used herein, the term pharmaceutically acceptable salts or complexes refers to salts or complexes that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR^+ + Z^-$, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenyl-acetate).

[0065] The term pharmaceutically active derivative refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the compounds disclosed herein.

[0066] In some examples, as will be appreciated by those skilled in the art, two adjacent carbon containing groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be substituted with one or more substitution groups "R". It should additionally be noted that for cycloalkyl (i.e. saturated ring structures), each positional carbon may contain two substitution groups, *e.g.* R and R'.

[0067] Some of the compounds used in the present invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclic ring systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, i.e., amino, imino, hydroxy or oxo, respectively.

[0068] Compounds used in the present invention are generally named using ACD/Name (available from Advanced Chemistry Development, Inc. of Toronto, Canada). This software derives names from chemical structures according to systematic application of the

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nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

[0069] The compounds used in the present invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

[0070] The compounds used in the present invention and their pharmaceutically acceptable salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0071] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When desired, the R- and S-isomers may be resolved by methods known to one skilled in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0072] “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said

event or circumstance occurs and instances in which it does not. It will be understood by one skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible. "Optionally substituted" refers to all subsequent modifiers in a term, for example in the term "optionally substituted C₁₋₈alkylaryl," optional substitution may occur on both the "C₁₋₈alkyl" portion and the "aryl" portion of the molecule.

[0073] "Substituted" alkyl, aryl, and heterocyclyl, for example, refer respectively to alkyl, aryl, and heterocyclyl, wherein one or more (for example up to about 5, in another example, up to about 3) hydrogen atoms are replaced by a substituent independently selected from, but not limited to: halogen, cyano, nitro, oxo, alkyl, haloalkyl (e.g., fluoroalkyl, trifluoromethyl), alkylenedioxy (e.g. methylenedioxy), cycloalkyl, cycloalkylalkyl, heterocyclalkyl, heterocyclyl, aryl (e.g., phenyl), arylalkyl (e.g., benzyl), heteroaryl, heteroarylalkyl, -OR⁰ (e.g., aryloxy or arylalkyloxy, such as, phenoxy or benzyloxy), -SR⁰, -N(R⁰)₂, -C(O)R⁰, -C(O)OR⁰, -C(O)N(R⁰)₂, -C(=NR⁰)N(R⁰)₂, -OC(O)R⁰, -OC(O)OR⁰, -OC(O)N(R⁰)₂ (e.g. benzyloxycarbonylamino (CBZ-amino), -N(R⁰)C(O)R⁰, -N(R⁰)C(O)OR⁰, -N(R⁰)C(O)N(R⁰)₂, -S(O)R⁰, -S(O)₂R⁰, -OS(O)₂R⁰, or -N(R⁰)S(O)₂R⁰, wherein each R⁰ is independently hydrogen, C₁₋₆alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclalkyl, arylalkyl, or heteroarylalkyl. In certain examples, each R⁰ is independently hydrogen or C₁₋₆alkyl, or arylalkyl (e.g., benzyl). In certain other examples, each R⁰ is independently hydrogen or C₁₋₆alkyl.

[0074] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about 1 and about 6 carbons) wherein the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about 1 and about 6 carbons). Amides and esters of the compounds of the present invention may be prepared

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according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[0075] In addition, the compounds can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0076] As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

[0077] As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

[0078] In certain embodiments, a therapeutically effective amount can be an amount suitable for

[0079] (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

[0080] (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder; or

[0081] (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

[0082] As used here, the terms "treatment" and "treating" means (i) ameliorating the referenced disease state, for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the

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disease, condition or disorder (*i.e.*, reversing or improving the pathology and/or symptomatology) such as decreasing the severity of disease; or (ii) eliciting the referenced biological effect.

[0083] Examples of diseases and disorders in which may be treated by use of agents that inhibit human metalloproteinase (MMP), such as MMP-9 and/or MMP-2 while optionally sparing MMP-1. And include, but are not limited to, atherosclerosis. Specifically the prevention of atherosclerotic plaque development and rupture (*e.g.*, carotid arterial plaque development and rupture) by MMP inhibition will reduce the adverse consequences of plaque development and rupture including thromboembolism, stroke, myocardial infarction, and acute coronary syndromes. Acute coronary syndrome (ACS) is usually one of three diseases involving the coronary arteries: ST elevation myocardial infarction, non ST elevation myocardial infarction, or unstable angina.

[0084] The therapeutic dosage of the compounds can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound described herein in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds described herein can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

Examples

[0085] The compounds useful in the methods of the invention can be prepared as described in U.S. Patent No. 7,629,341, which is hereby incorporated by reference in its entirety. The compounds herein can be tested for plaque stabilization and/or disruption

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according to models known to those skilled in the art; for example, the *apoE*^{-/-} murine atherosclerotic model described in Gough et al., J. Clin. Invest. 2006, 116, 59.

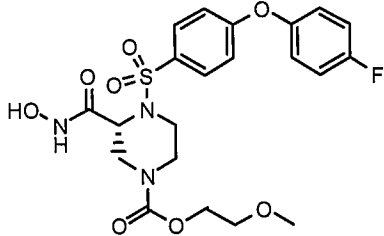
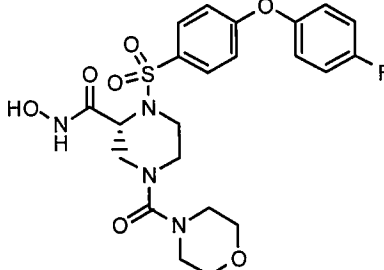
Example 1: Enzyme Assays

[0086] Table 5 below shows structure activity relationship data for selected compounds for use in the present invention when tested *in vitro* with various metalloproteases.

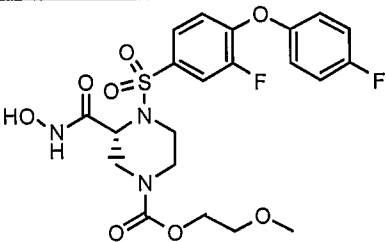
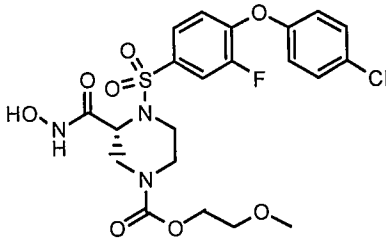
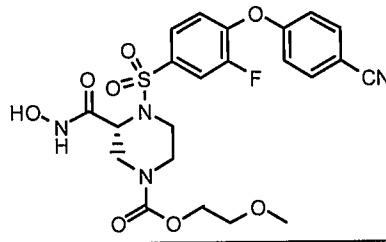
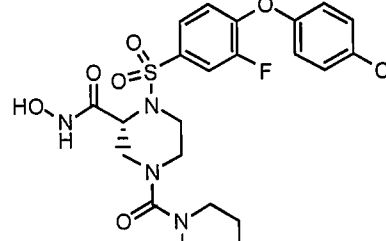
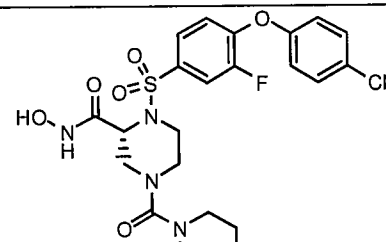
Inhibition is indicated as IC₅₀ with the following key: A = IC₅₀ less than 50 nM, B = IC₅₀ greater than 50 nM, but less than 1000 nM, C = IC₅₀ greater than 1000 nM, but less than 20,000 nM, and D = IC₅₀ greater than 20,000 nM. Blank cells indicate lack of data only.

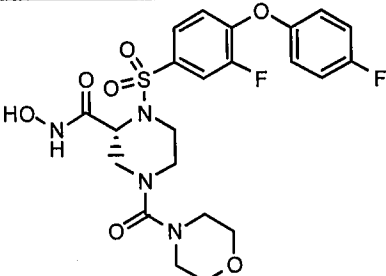
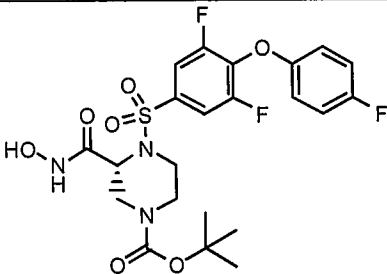
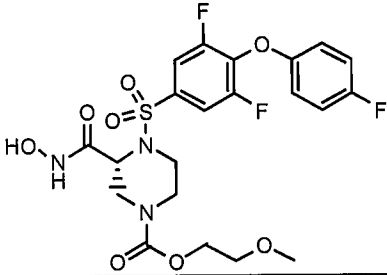
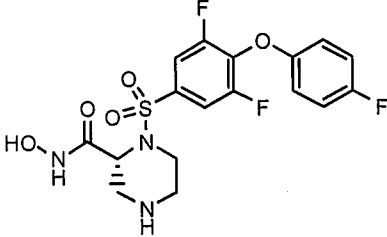
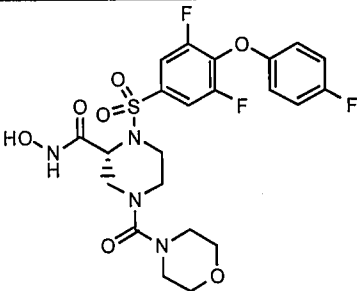
The abbreviations in Table 5 are defined as follows: MMP-1 stands for Fibroblast collagenase; MMP-2 stands for 72 kDa gelatinase (gelatinase A); and MMP-9 stands for 92 kDa gelatinase (gelatinase B).

Table 5

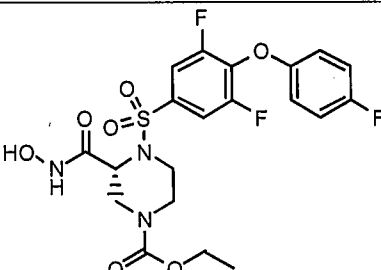
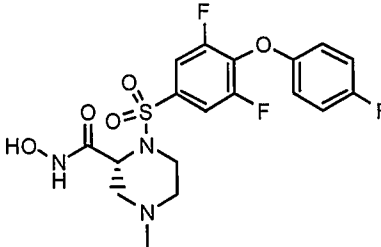
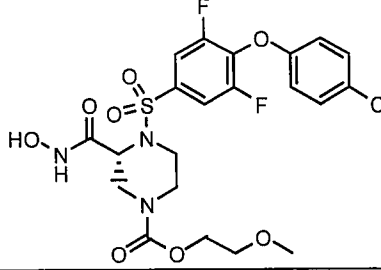
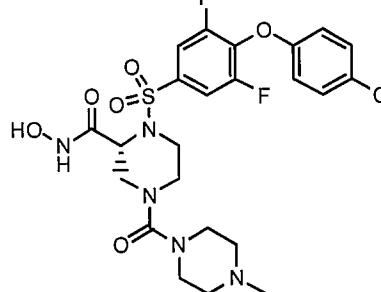
ENTRY	STRUCTURE	MMP-1 IC ₅₀	MMP-2 IC ₅₀	MMP-9 IC ₅₀
1		A	A	
2		A	A	

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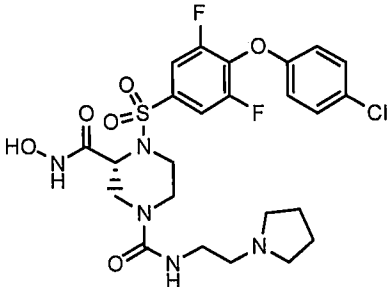
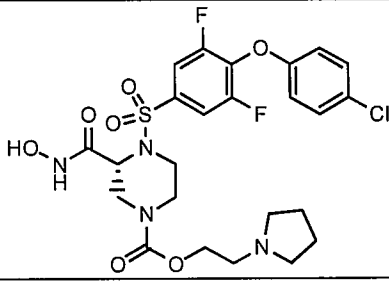
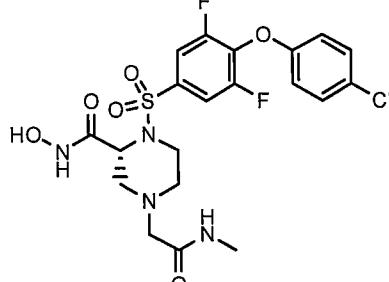
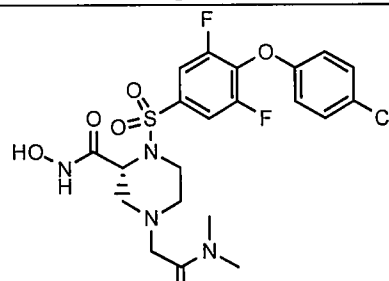
ENTRY	STRUCTURE	MMP-1 IC ₅₀	MMP-2 IC ₅₀	MMP-9 IC ₅₀
3		B	A	
4		B	A	
5		B	A	
6		B	A	
7		B	A	

ENTRY	STRUCTURE	MMP-1 IC ₅₀	MMP-2 IC ₅₀	MMP-9 IC ₅₀
8		B	A	
9		C	A	
10		C	A	
11		D	B	
12		C	A	

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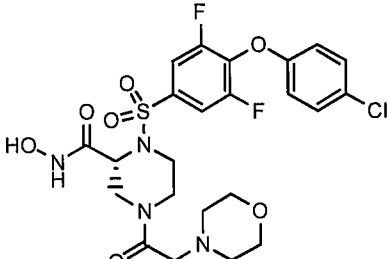
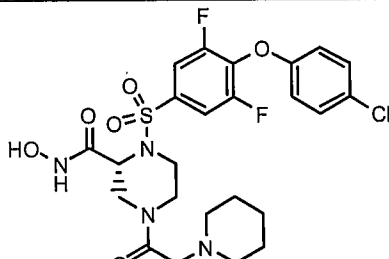
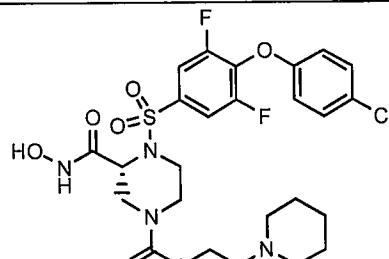
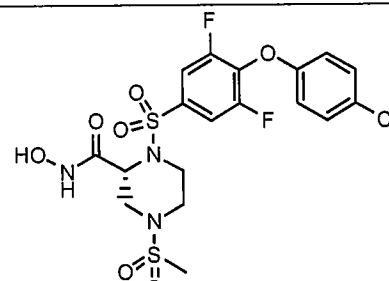
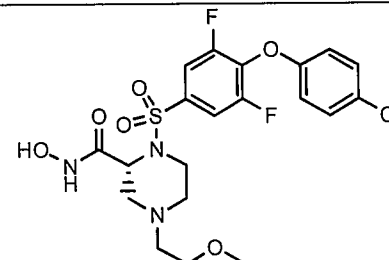
ENTRY	STRUCTURE	MMP-1 IC ₅₀	MMP-2 IC ₅₀	MMP-9 IC ₅₀
13		C	A	
14		D	A	
15		C	A	A
16		D	A	

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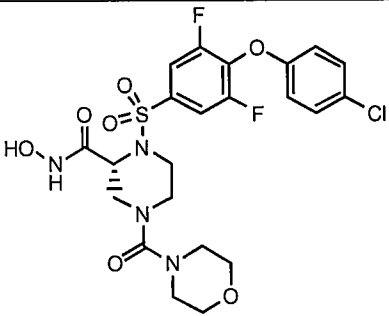
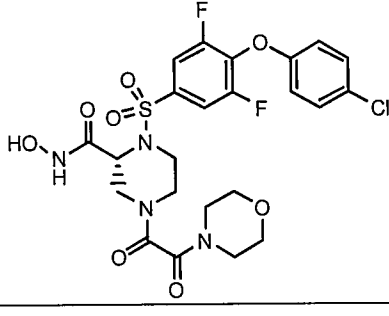
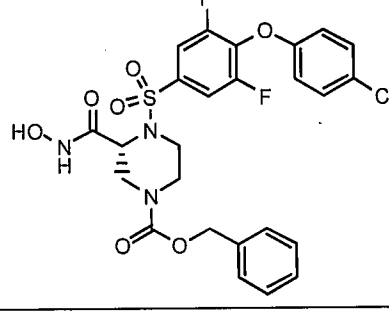
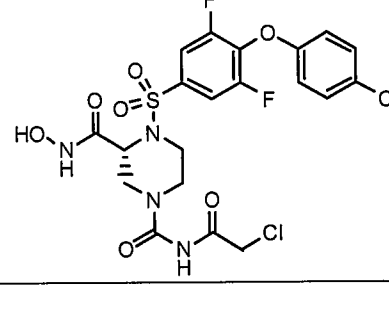
ENTRY	STRUCTURE	MMP-1 IC ₅₀	MMP-2 IC ₅₀	MMP-9 IC ₅₀
17		C	A	
18		D	A	
19		D	A	
20		D	A	

[illegible]

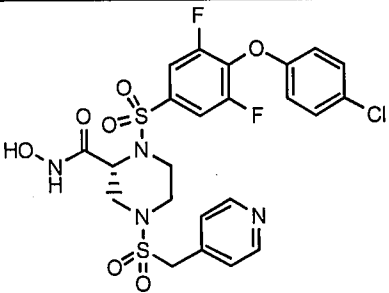
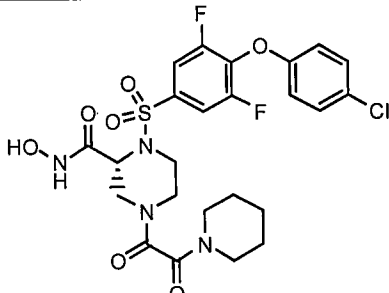
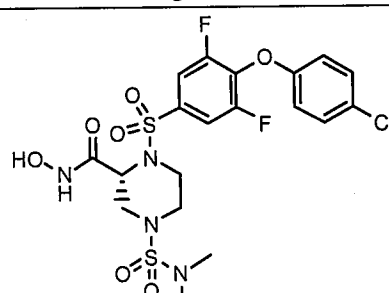
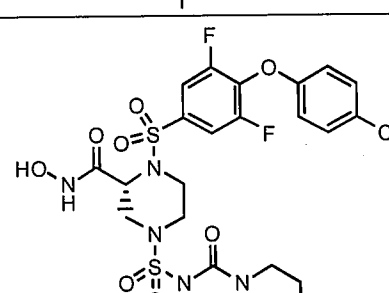
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26		D	A	
27		C	A	
28		B	A	
29		C	A	

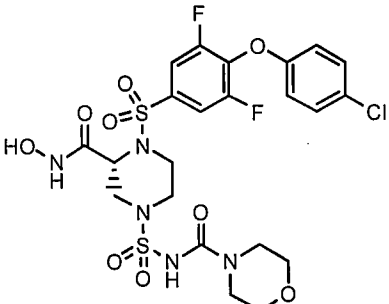
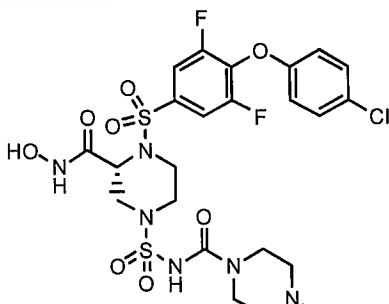
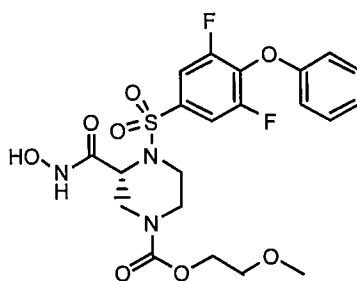
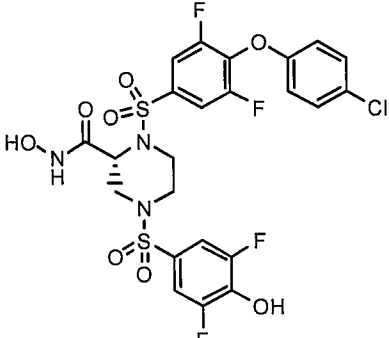
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31		C	A	
32		C	A	
33		C	A	

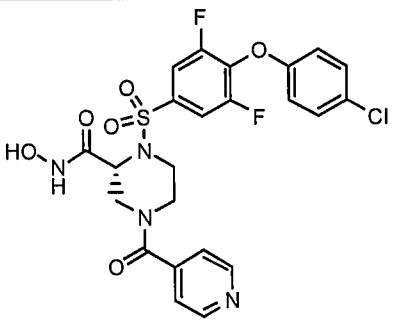
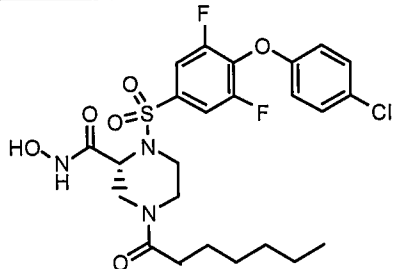
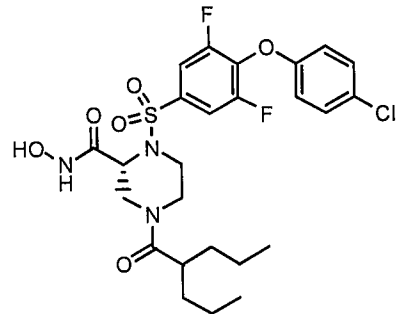
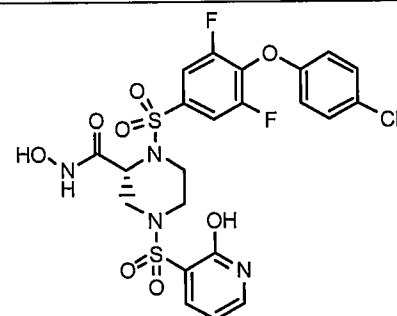
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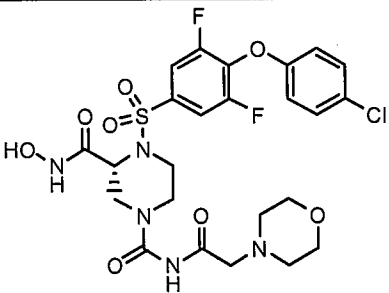
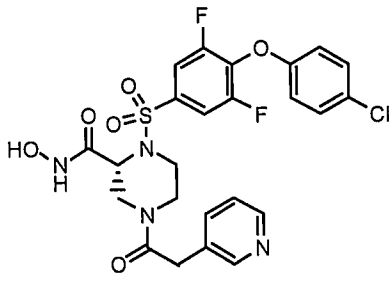
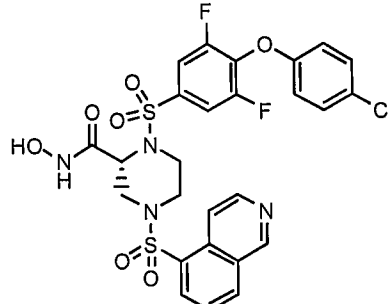
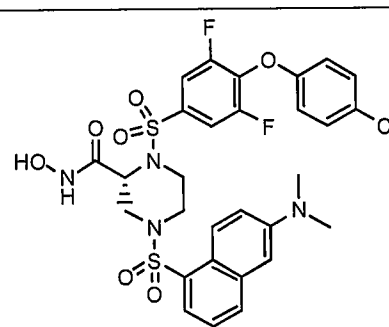
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34		C	A	
35		C	A	
36		C	A	
37		C	A	

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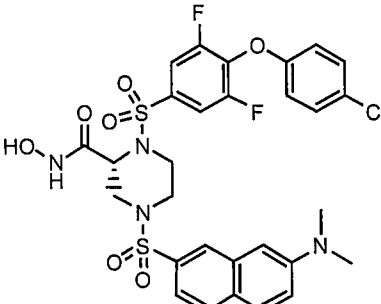
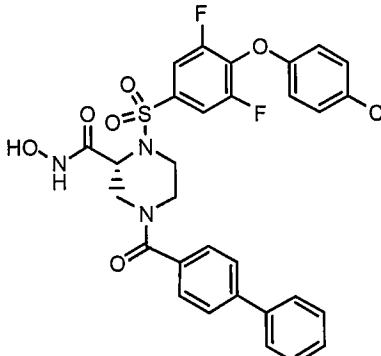
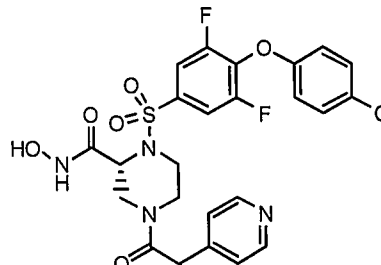
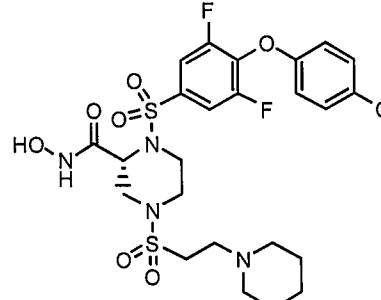
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38		C	A	
39		B	A	
40		C	A	
41		C	A	

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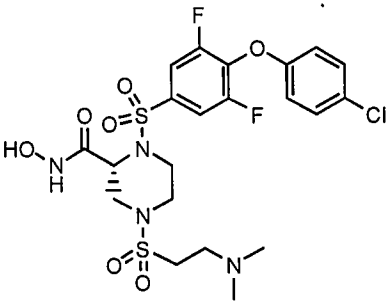
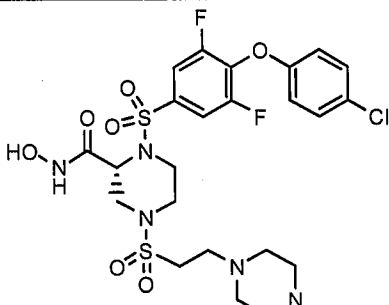
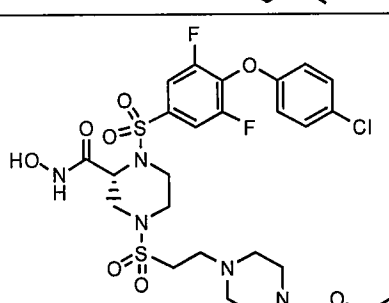
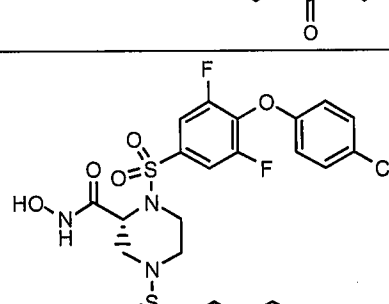
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42		C	A	
43		D	A	
44		D	A	
45		C	A	

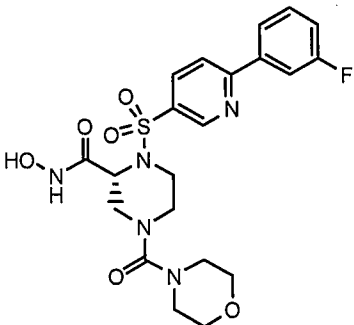
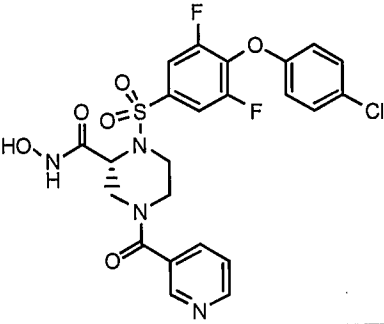
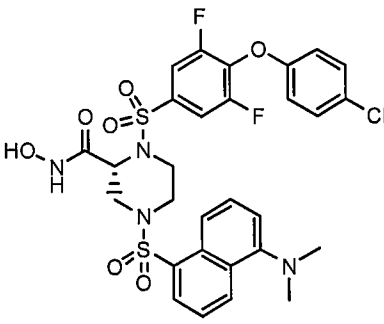
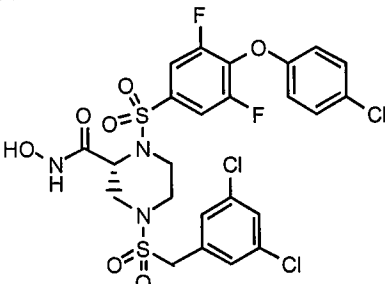
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46		C	A	
47		D	A	
48		D	A	
49		D	A	

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ENTRY	STRUCTURE	MMP-1 IC ₅₀	MMP-2 IC ₅₀	MMP-9 IC ₅₀
50		D	D	
51		C	B	
52		C	A	
53		B	A	

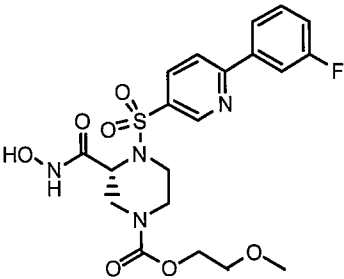
- 43 -

ENTRY	STRUCTURE	MMP-1 IC ₅₀	MMP-2 IC ₅₀	MMP-9 IC ₅₀
54		B	A	
55		C	A	
56		C	A	
57		D	B	

ENTRY	STRUCTURE	MMP-1 IC ₅₀	MMP-2 IC ₅₀	MMP-9 IC ₅₀
58		B	A	
59		C	A	
60		D	A	
61		D	C	

ENTRY	STRUCTURE	MMP-1 IC ₅₀	MMP-2 IC ₅₀	MMP-9 IC ₅₀
62		D	A	
63		D	B	
64		B	A	
65		A	A	

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ENTRY	STRUCTURE	MMP-1 IC ₅₀	MMP-2 IC ₅₀	MMP-9 IC ₅₀
66		B	A	

Example 2: Compound 15 Significantly Reduces Atherosclerosis in the SR-uPA^{+/-} mouse model of atherosclerosis

[0087] Female *Apoe*^{-/-} mice were studied and were transgenic for a murine uPA gene. SR-uPA^{+/-} mice were bred with nontransgenic *Apoe*^{-/-} mice to yield SR-uPA^{+/-} and non-transgenic SR-uPA^{0/0} littermate controls. The SR-uPA mice are known to have accelerated atherosclerosis, coronary artery occlusions, aortic root dilation, and sudden premature death that are driven by increased uPA enzymatic activity.^{1,5} They also have elevated MMP activity in their aortae,⁴ which may play a role in accelerating atherosclerosis and in promoting aortic root dilation and plaque rupture. The mice were fed a high-fat diet (HFD: 21% fat, 0.15% cholesterol by weight) beginning at 5 – 6 wk of age and continuing for 10 wk. Mice received one of three doses of compound 15 (125, 250, or 500 mg/kg or the vehicle alone by gavage daily. After 10 wk on HFD the Aortas were removed and examined.

[0088] Total cholesterol was measured in blood obtained from the retro-orbital plexus (Spectrum cholesterol assay, Abbott). Complete blood counts were performed by an outside laboratory (Phoenix Central Laboratory). Total MMP activity in aortic CM was measured with the Omni MMP activity assay.⁴

[0089] Data are mean ± SD or median (25% – 75% range). In experiments testing multiple doses of compound 15, we used ANOVA followed by the Holm-Sidak post-hoc correction for multiple comparisons to test whether each of the treatment groups differed significantly from the control group. When conditions of normality and equal variance were

not met we used Kruskal-Wallis ANOVA. Categorical data (presence or absence of aortic pathology) were analyzed by Chi Square or Fisher exact test. All tests were carried out with the SigmaStat program (Systat Software).

[0090] The experiments described above demonstrate that that systemic inhibition of MMP activity with the limited-spectrum MMP inhibitor compound 15 reduces atherosclerosis in SR-uPA^{+/-0} mouse model of atherosclerosis (mice with a urokinase transgene driven by the scavenger receptor A promoter). Treatment with all 3 doses of compound 15 reduced aortic root intimal lesion area (22 – 29%; $P < 0.05$ only for the lowest dose; Figure 1A). All 3 doses of compound 15 also yielded non-significant trends towards reduced aortic root circumference/dilatation (5 – 10%; $P > 0.05$ for all 3; Figure 1B). Moreover, all 3 doses of compound 15 significantly reduced total aortic root lesion ORO (oil red O)-positive area (a measure of atherosclerosis extent) (36 – 42%; $P < 0.05$ for all doses compared to vehicle; Figure 1C) but did not significantly affect the percentage of lesion ORO-positivity (Table 6). All 3 compound 15 doses also nominally reduced total aortic root lesion macrophage-positive area, with the highest dose having a significant effect (33% reduction; $P < 0.05$; Figure 1D). The percentage of macrophage positivity in aortic root lesions was not significantly affected by any of the compound 15 doses (Table 6). Of note none of the 3 doses of compound 15 significantly affected either total peripheral blood monocyte counts, percentages of circulating monocytes, or total plasma cholesterol (Table 6) showing that the changes in lesion size and content did not merely reflect systemic changes in monocyte or cholesterol levels. Total MMP activity in aortic CM was modestly decreased (4 – 13%) in all 3 groups of compound 15-treated versus vehicle-fed mice but these differences were not statistically significant (Table 6).

[0091] Thus these findings demonstrate that compound 15 reduces the volume of atherosclerotic lesions and intimal lipid accumulation in aortas of susceptible mice.

Table 6 Comparison of mice treated with compound and with vehicle-treated transgenic (SR-uPA^{+/0}) mice. Values are mean $\pm$ SD except for % Sudanophilic lesions of thoracic aortic lumen surface area, which are median and (25%–75%) range. n indicates mice in each group.

	Vehicle (n)	Compound 15		
		(125 mg/kg) (n)	(250mg/kg) (n)	(500mg/kg) (n)
Aortic root Oil Red O area (% of intimal area)	15.0 $\pm$ 4.6 (9)	12.0 $\pm$ 3.7 (10)	13.0 $\pm$ 3.1 (11)	12.0 $\pm$ 4.1 (12)
Aortic root Mac-2 area (% of intimal area)	22.0 $\pm$ 7.3 (9)	22.0 $\pm$ 8.7 (10)	20.0 $\pm$ 6.3 (11)	16.0 $\pm$ 5.9 (12)
Thoracic aortic lumen surface area (mm ²)	36.0 $\pm$ 1.8 (9)	37.0 $\pm$ 4.0 (10)	37.0 $\pm$ 3.4 (11)	35.0 $\pm$ 1.7 (11)
Sudanophilic lesions (% of thoracic aortic)	3.5 (2.9-3.9) (9)	3.7 (2.04.1) (10)	3.3 (2.6-3.5) (11)	3.3 (2.06.7) (11)
MMP activity (ARFU/min)	28.0 $\pm$ 7.2 (8)	25.0 $\pm$ 7.4 (9)	27.0 $\pm$ 6.6 (10)	24.0 $\pm$ 6.9 (7)
Peripheral blood monocytes (per NI)	100 $\pm$ 140 (5)	140 $\pm$ 53 (5)	290 $\pm$ 240 (5)	230 $\pm$ 150 (5)
Peripheral blood monocytes (% total)	2.2 $\pm$ 2.2 (9)	4.2 $\pm$ 1.3 (10)	4.6 $\pm$ 3.6 (11)	4.0 $\pm$ 2.6 (12)
Plasma cholesterol (mg/dL)	1400 $\pm$ 210 (9)	1600 $\pm$ 280 (10)	1400 $\pm$ 340 (11)	1300 $\pm$ 300 (12)

References

- [0092] 1. Cozen AE, Moriwaki H, Kremen M, DeYoung MB, Dichek HL, Slezicki KI, Young SG, Veniant M, Dichek DA. Macrophage-targeted overexpression of urokinase causes accelerated atherosclerosis, coronary artery occlusions, and premature death. *Circulation*. 2004;109:2129–2135.
- [0093] 2. Farris SD, Hu JH, Krishnan R, Emery I, Chu T, Du L, Kremen M, Dichek HL, Gold E, Ramsey SA, Dichek DA. Mechanisms of Urokinase Plasminogen Activator (uPA)-mediated Atherosclerosis: Role of the uPA Receptor and S100A8/A9 proteins. *J Biol Chem*. 2011;286:22665–22677.
- [0094] 3. Williams JM, Zhang J, North P, Lacy S, Yakes M, Dahly-Vernon A, Roman RJ. Evaluation of metalloprotease inhibitors on hypertension and diabetic nephropathy. *Am J Physiol Renal Physiol*; 300:F983-998.

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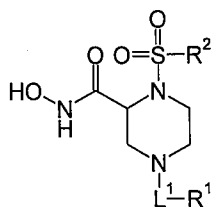
[0095] 4. Hu JH, Du L, Chu T, Otsuka G, Dronadula N, Jaffe M, Gill SE, Parks WC, Dichek DA. Overexpression of urokinase by plaque macrophages causes histologic features of plaque rupture and increases vascular MMP activity in aged apo E-Null mice. *Circulation*. 2010;121:1637–1644.

[0096] 5. Kremen M, Krishnan R, Emery I, Hu JH, Slezicki K, Wu A, Qian K, Du L, Plawman A, Stempien-Otero A, Dichek DA. Plasminogen mediates the atherogenic effects of macrophage-expressed urokinase and accelerates atherosclerosis in apoE-knockout mice. *Proc Natl Acad Sci U.S.A.* 2008;105:17109–17114.

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We claim:

1. A method for treating, preventing, or reducing the risk of carotid, aortic, or other arterial plaque development and rupture, atherosclerosis, thromboembolism, stroke, acute coronary syndromes, and/or myocardial infarction in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of a compound of structural formula I:



I

or pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein

L¹ is -C(O)-, -S(O)₂-, or -(CH₂)_n-;

R¹ is -H, -OR¹¹, -(CH₂)_nR¹¹, -C(O)R¹¹, or -NR¹²R¹³;

R¹¹, R¹², and R¹³ independently are

- a) R⁵⁰;
- b) saturated or mono- or poly- unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one or two R⁵⁰ substituents;
- c) C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, or -C(O)H, each of which is optionally substituted with one, two or three substituents independently selected from R⁵⁰ and saturated or mono- or poly- unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two or three R⁵⁰ substituents;

or R¹² and R¹³ together with the N to which they are covalently bound, a C₅-C₆ heterocycle optionally containing a second annular heteroatom and optionally substituted with one or two R⁵⁰ substituents;

R² is -R²¹-L²-R²²;

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R^{21} is saturated or mono- or poly- unsaturated C_5 - C_{14} -mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R^{50} substituents;

L^2 is -O-, -C(O)-, -CH₂-, -NH-, -S(O₂)- or a direct bond;

R^{22} is saturated or mono- or poly- unsaturated C_5 - C_{14} -mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R^{50} substituents; and

R^{50} is R^{51} - L^3 -(CH₂)_n;

L^3 is -O-, -NH-, -S(O)₀₋₂-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -C₆H₄-, or a direct bond;

R^{51} is -H, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, halo, -CF₃, -OCF₃, -OH, -NH₂, mono- C_1 - C_6 alkyl amino, di- C_1 - C_6 alkyl amino, -SH, -CO₂H, -CN, -NO₂, -SO₃H, or a saturated or mono- or poly- unsaturated C_5 - C_{14} -mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three substituents;

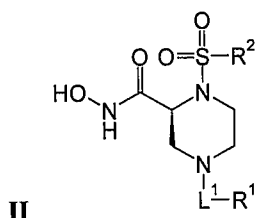
wherein n is 0, 1, 2, or 3;

provided that an O or S is not singly bonded to another O or S in a chain of atoms.

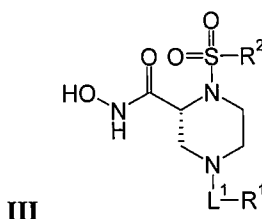
2. The method according to claim 1, wherein L^1 is -C(O)- or -S(O)₂-.
3. The method according to claim 2, wherein L^1 is -C(O)- and R^1 is -OR¹¹ or -(CH₂)_nR¹¹, -OC₁-C₆alkyl-mono- C_1 -C₆alkyl amino, -OC₁-C₆alkyl-di- C_1 -C₆alkyl amino, -OC₁-C₆alkyl-N-heterocyclyl, -C₁-C₆alkyl-mono- C_1 -C₆alkyl amino, -C₁-C₆alkyl-di- C_1 -C₆alkyl amino, or -C₁-C₆alkyl-N-heterocyclyl.
4. The method according to claim 2, wherein, R^1 is C_1 - C_6 -alkoxy- C_1 - C_6 -alkoxy.
5. The method according to claim 2, wherein R^1 is methoxyethoxy.
6. The method according to claim 3, wherein L^1 is -S(O)₂-, and R^1 is -NR¹²R¹³, -(CH₂)_nR¹¹, -C₁-C₆alkyl-mono- C_1 -C₆alkyl amino, -C₁-C₆alkyl-di- C_1 -C₆alkyl amino, or -C₁-C₆alkyl-N-heterocyclyl.
7. The method according to claim 3, wherein L^2 is -O-.

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8. The method according to claim 7, wherein, R^2 is phenoxyphenyl wherein each phenyl is optionally substituted with one or two R^{50} substituents.
9. The method according to claim 8, wherein the saturated or mono- or poly-unsaturated C_5 - C_{14} -mono- or fused poly- cyclic hydrocarbonyl containing one or two annular heteroatoms per ring is selected from the group consisting of morpholinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, furyl, thienyl, pyranyl, isobenzofuranyl, chromenyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolinyl, carbazolyl, acrydinyl, and furazanyl, optionally substituted with one or two R^{50} substituents.
10. The method according to claim 8, wherein R^{12} and R^{13} , together with the N to which they are covalently bound, form a heterocycle selected from the group consisting of morpholinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolinyl, carbazolyl, acrydinyl, and furazanyl, optionally substituted with one or two R^{50} substituents.
11. The method according to claim 1, wherein the compound comprises the absolute stereochemistry of structural formula II:



12. The method according to claim 1, wherein the compound comprises the absolute stereochemistry of structural formula III:



13. The method according to claim 1, wherein $-L^1-R^1$ is selected from:

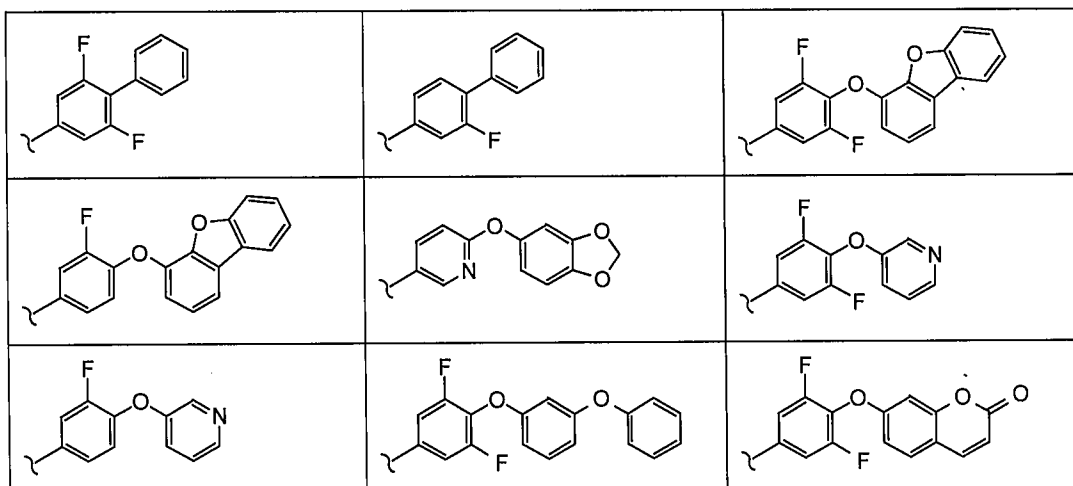
$-R^{14}$		

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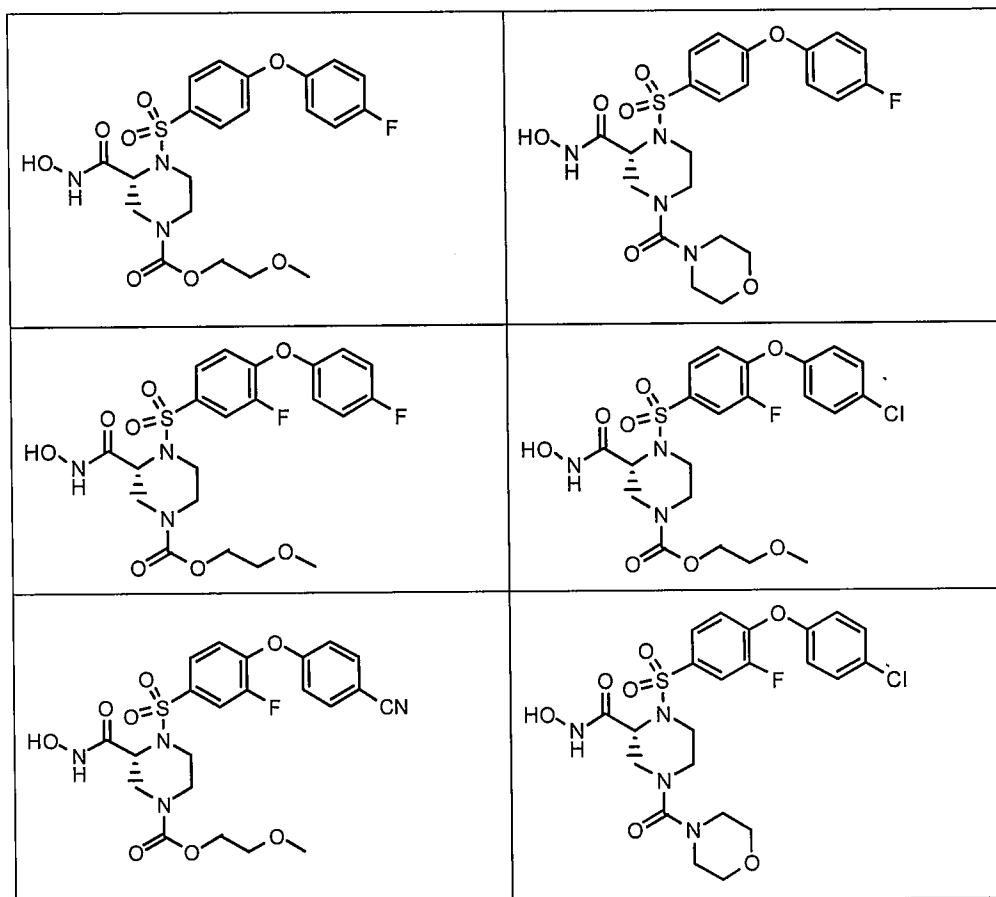
wherein each R^{14} is independently selected from $-H$, $-(CH_2)_{1-3}CO_2H$, alkyl, alkoxy, alkenyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; and

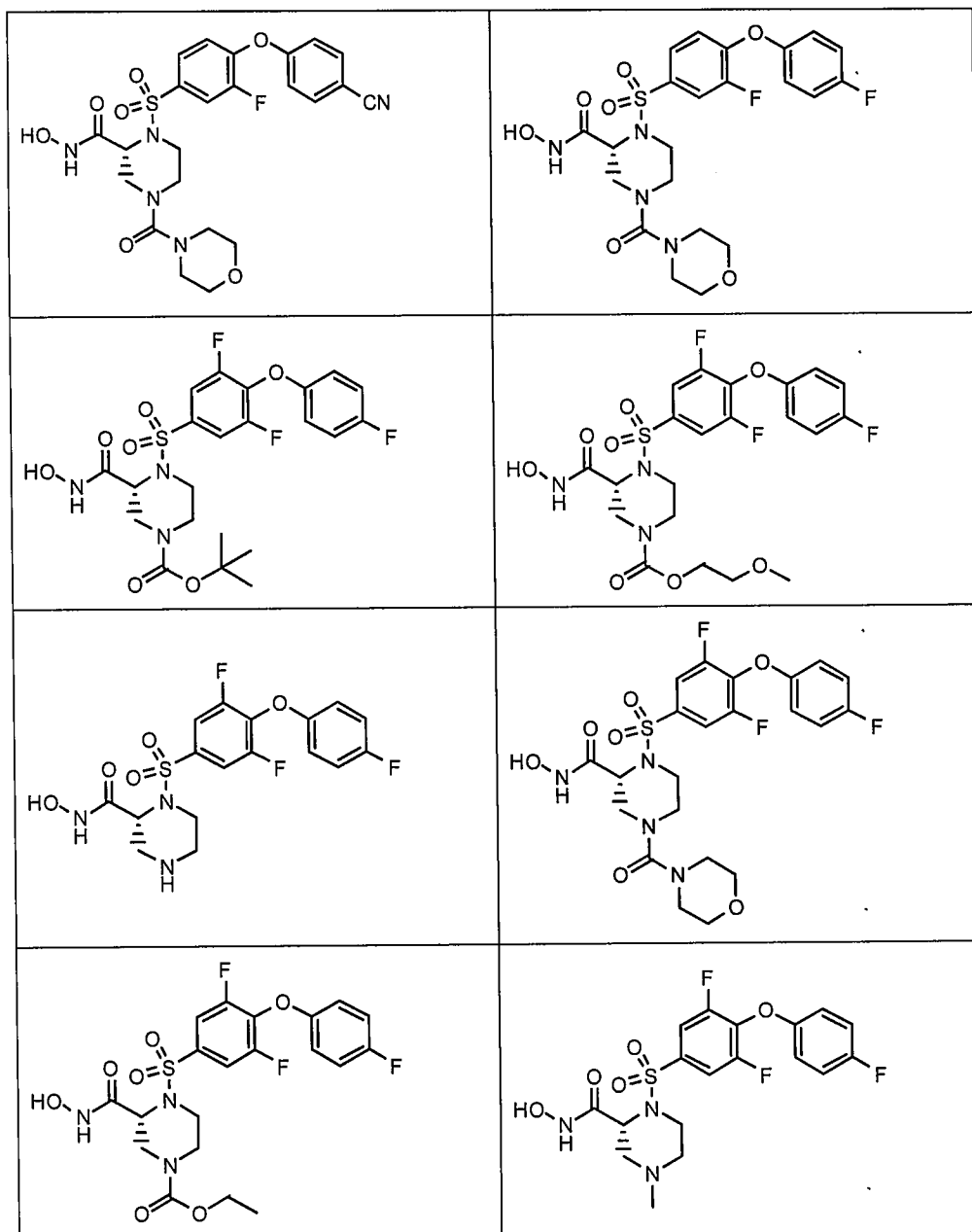
R^2 is selected from:

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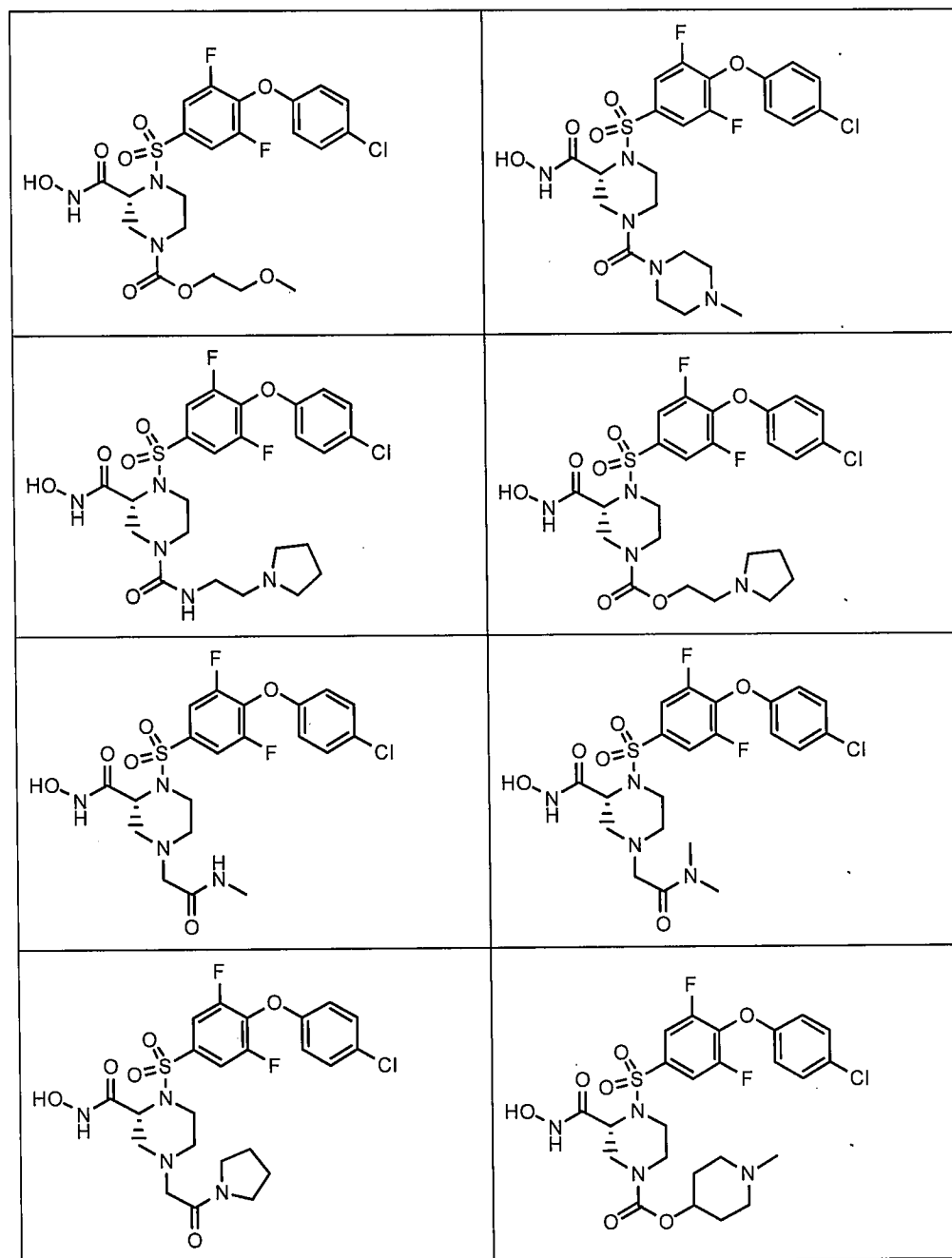


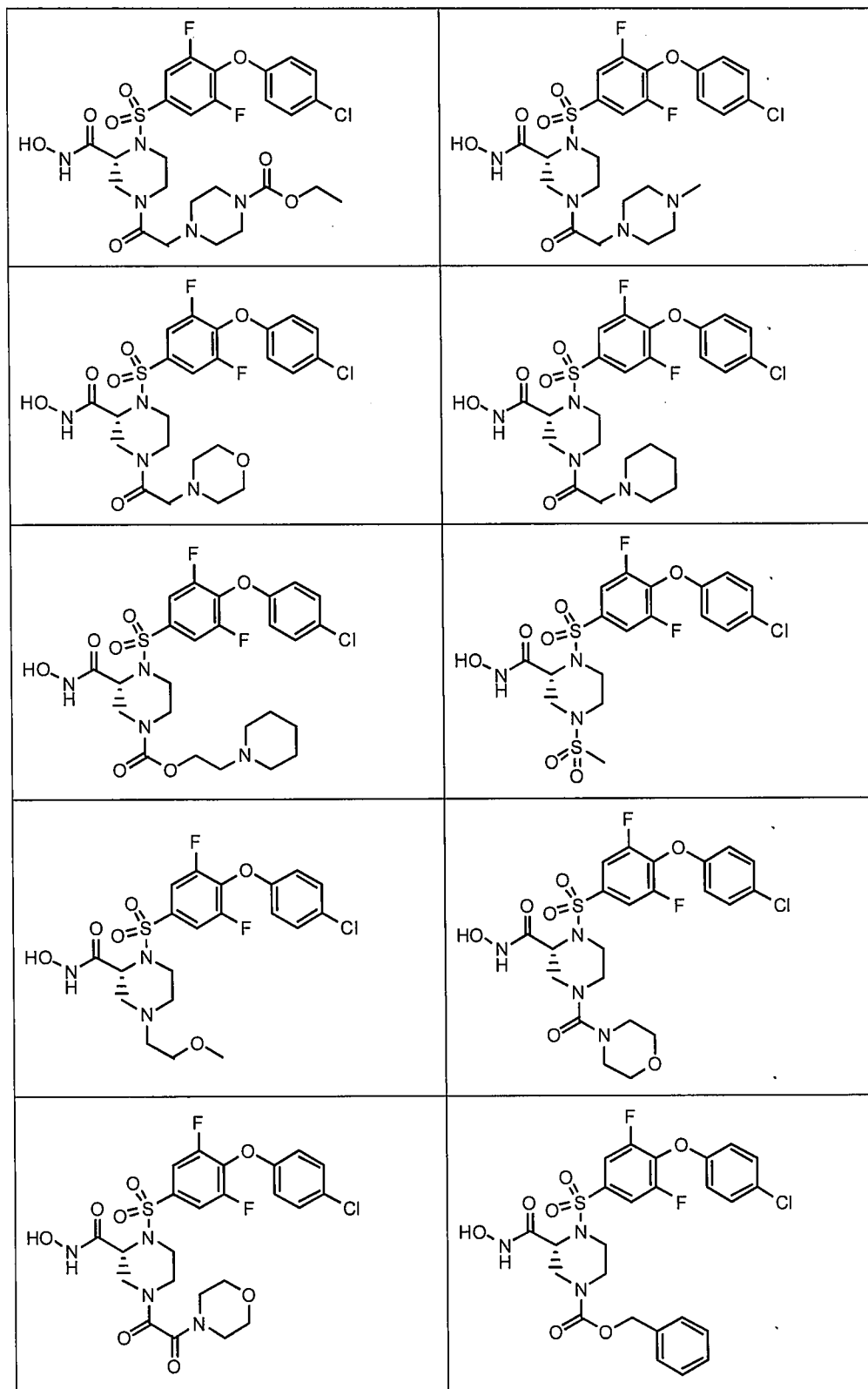
14. The method according to claim 1, wherein the compound is selected from:

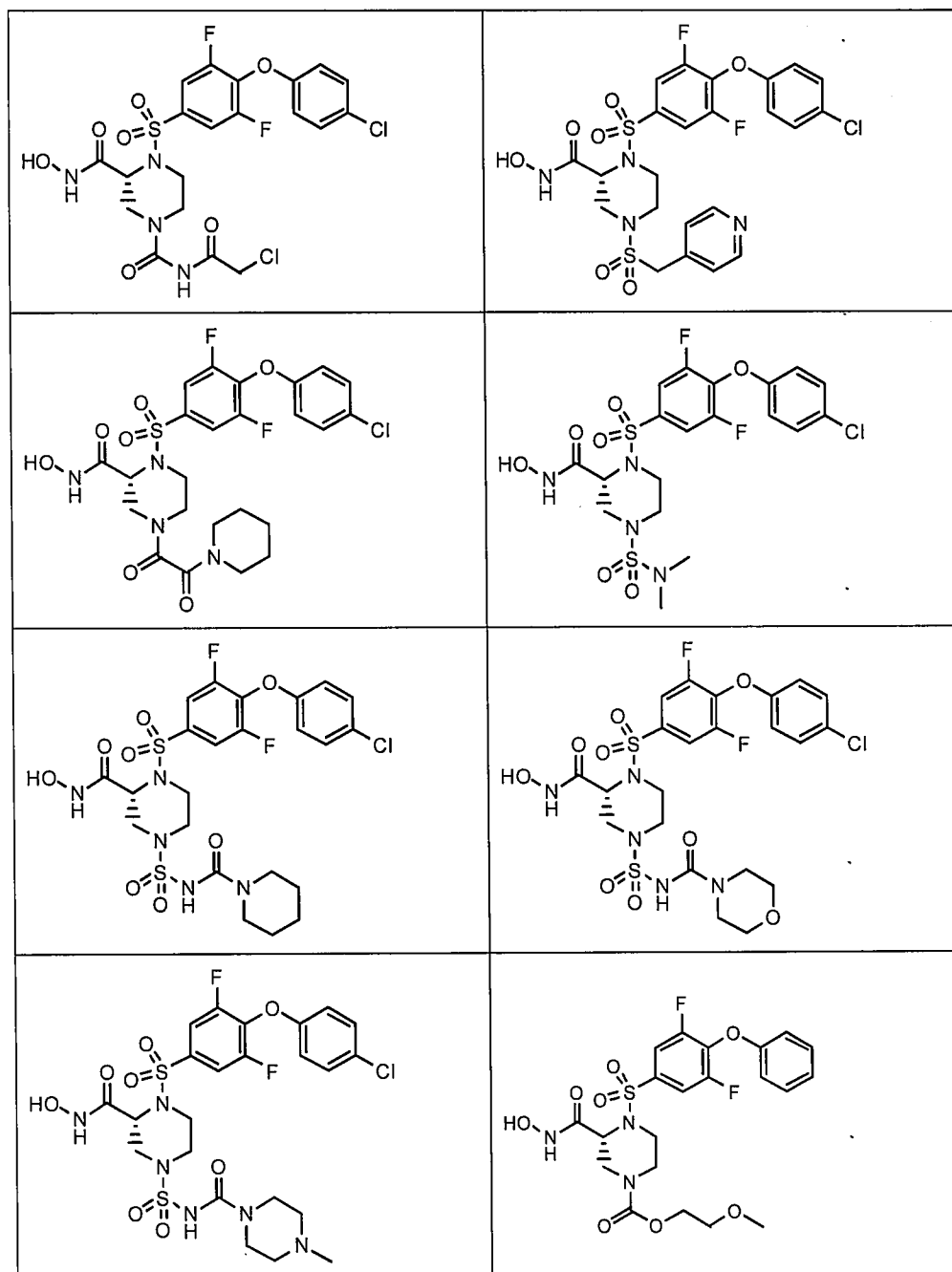




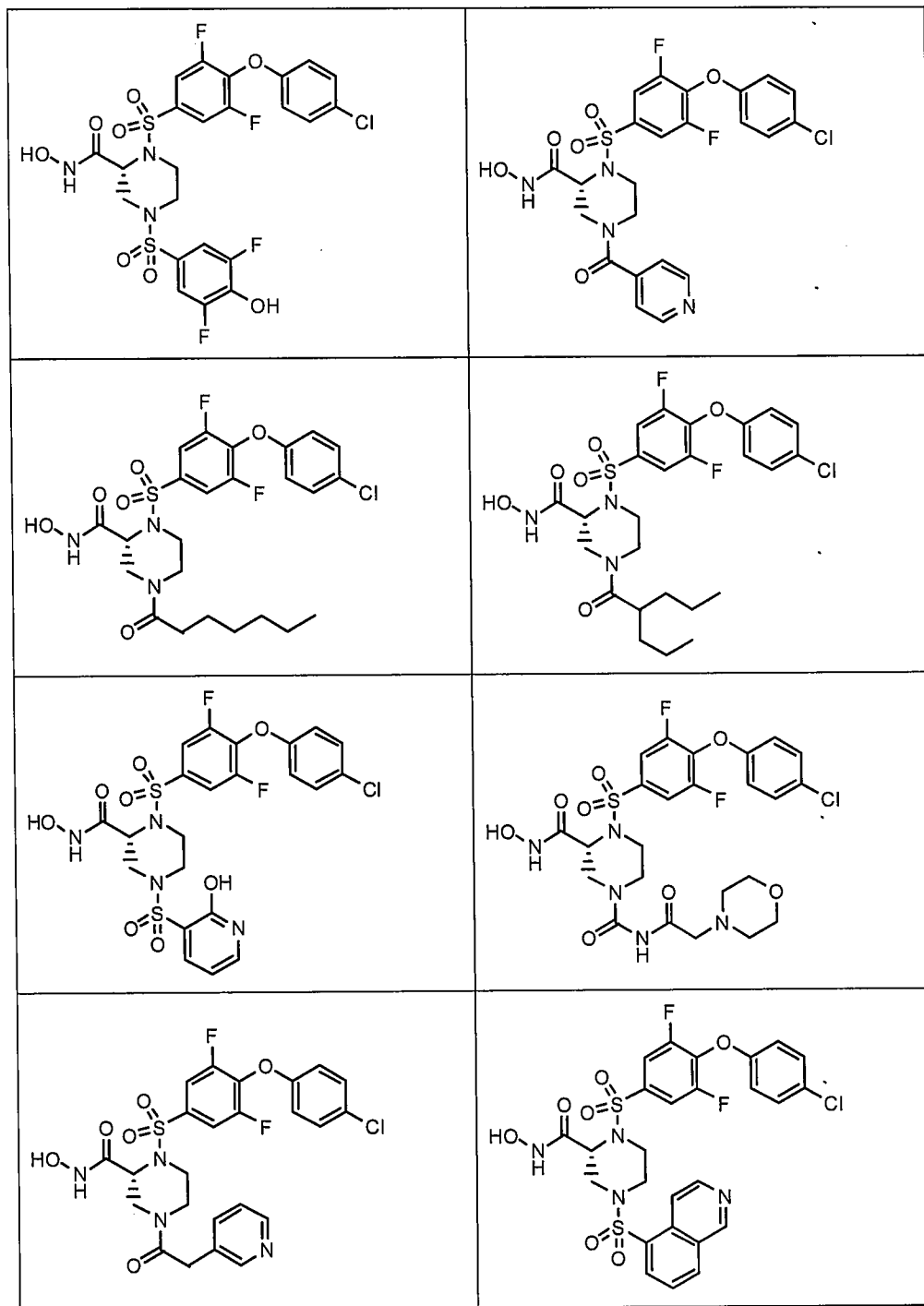
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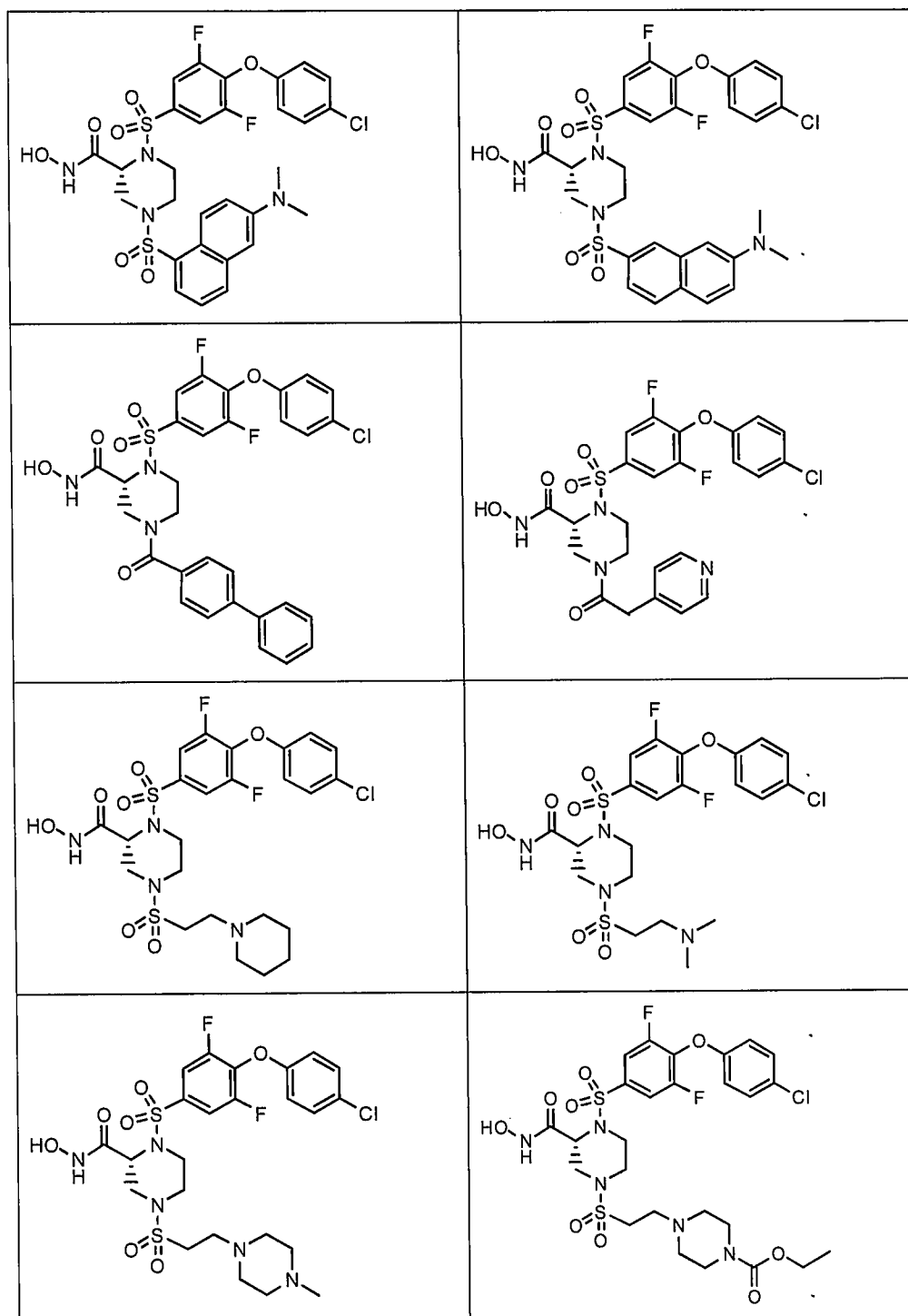


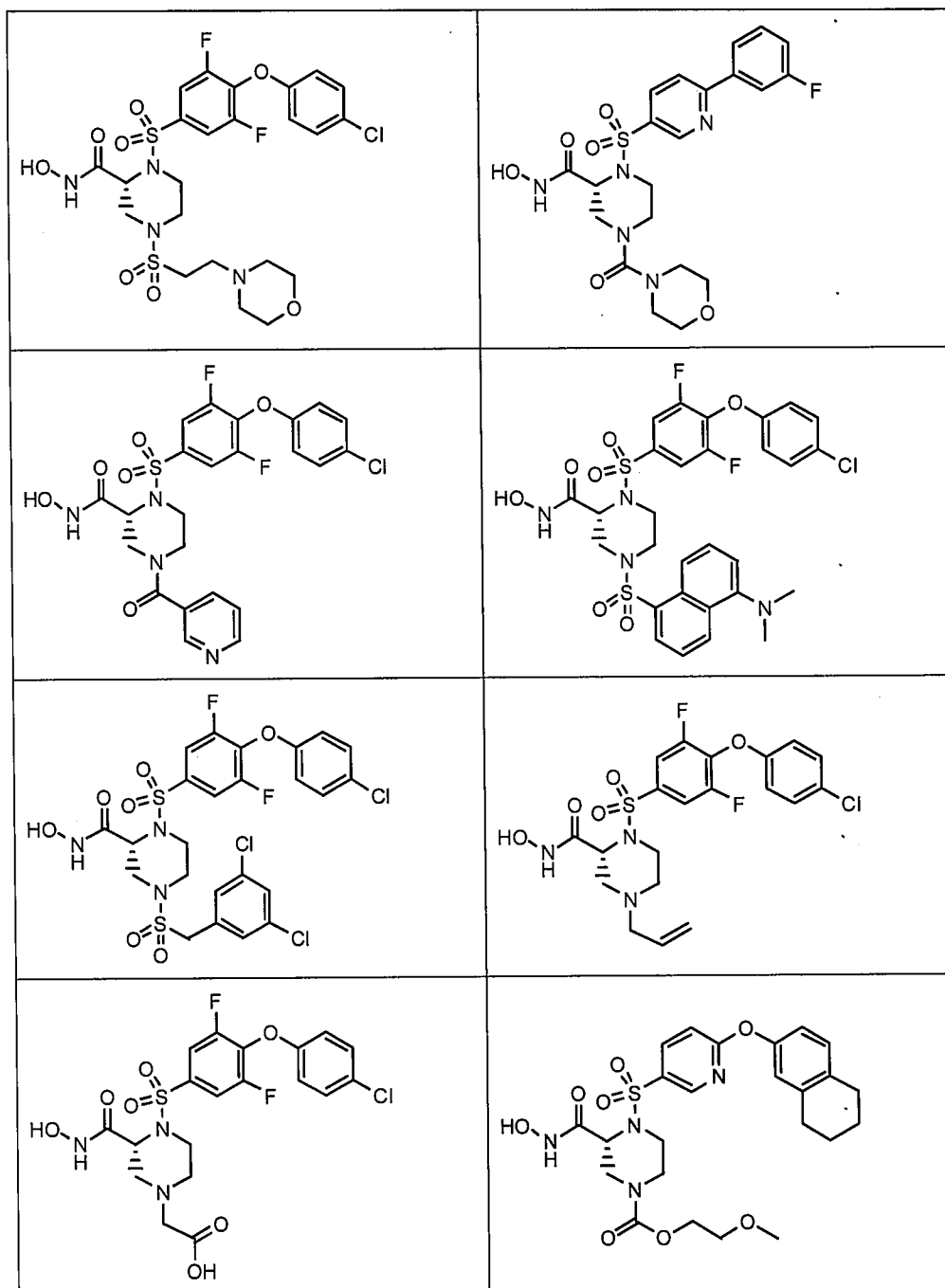




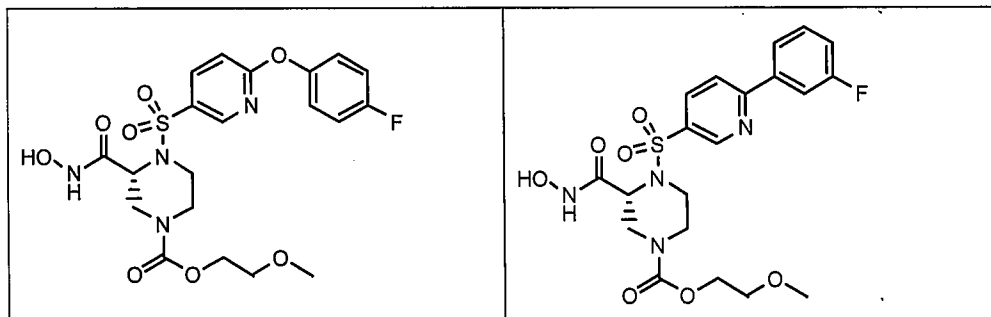
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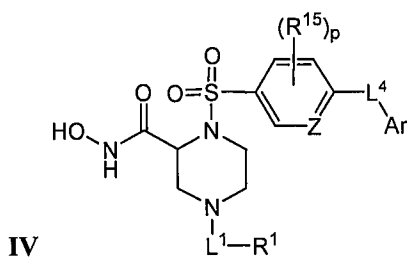




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15. A method for treating, preventing, or reducing the risk of carotid, aortic, or other arterial plaque development and rupture, atherosclerosis, acute coronary syndromes, thromboembolism, stroke, and/or myocardial infarction in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of a compound according to formula **IV**,



and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein,

Z is $-\text{C}(\text{R}^{15})=$, $-\text{C}(\text{H})=$, or $-\text{N}=$;

Ar is aryl or heteroaryl, each optionally substituted;

R^{15} is fluoro;

p is 0, 1, 2, or 3;

L^1 is $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, or $-(\text{CH}_2)_n-$;

L^4 is nothing or $-\text{O}-$;

R^1 is $-\text{H}$, $-\text{OR}^{11}$, $-(\text{CH}_2)_n\text{R}^{11}$, $-\text{C}(\text{O})\text{R}^{11}$, or $-\text{NR}^{12}\text{R}^{13}$;

R^{11} , R^{12} , and R^{13} independently are

- a) R^{50} ;
- b) saturated or mono- or poly- unsaturated C_5 - C_{14} -mono- or fused poly-cyclic hydrocarbyl, optionally containing one or two annular

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heteroatoms per ring and optionally substituted with one or two R^{50} substituents;

- c) C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, or $-C(O)H$, each of which is optionally substituted with one, two or three substituents independently selected from R^{50} and saturated or mono- or poly-unsaturated C_5 - C_{14} -mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two or three R^{50} substituents;

or R^{12} and R^{13} together with the N to which they are covalently bound, a C_5 - C_6 heterocycle optionally containing a second annular heteroatom and optionally substituted with one or two R^{50} substituents; and

R^{50} is R^{51} - L^3 -(CH_2) $_n$;

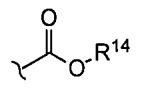
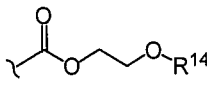
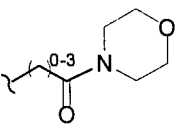
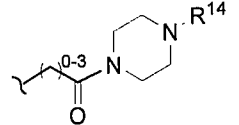
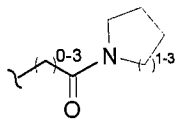
L^3 is $-O-$, $-NH-$, $-S(O)_{0-2}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)-$, $-NHC(O)-$, $-C_6H_4-$, or a direct bond;

R^{51} is $-H$, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, halo, $-CF_3$, $-OCF_3$, $-OH$, $-NH_2$, mono- C_1 - C_6 alkyl amino, di- C_1 - C_6 alkyl amino, $-SH$, $-CO_2H$, $-CN$, $-NO_2$, $-SO_3H$, or a saturated or mono- or poly- unsaturated C_5 - C_{14} -mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three substituents;

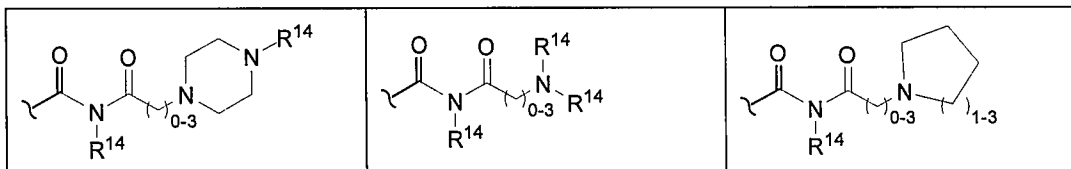
wherein n is 0, 1, 2, or 3;

provided that an O or S is not singly bonded to another O or S in a chain of atoms.

16. The method according to claim 15, wherein $-L^1-R^1$ is selected from:

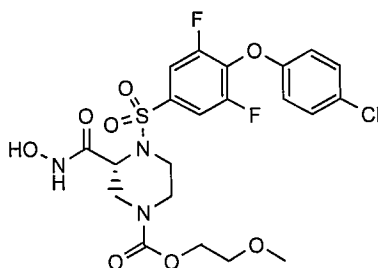
$-R^{14}$		
		

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wherein each R^{14} is independently selected from $-H$, $-(CH_2)_{1-3}CO_2H$, alkyl, alkoxy, alkenyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl.

17. The method according to claim 16, wherein Z is $-C(R^{15})=$ or $-C(H)=$; L^4 is $-O-$; and p is at least one.
18. The method according to claim 17, wherein Ar is selected from the group consisting of phenyl, biphenyl, naphthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.
19. The method according to claim 18, wherein Ar is phenyl, optionally substituted, with at least one halogen.
20. The method according to claim 19, wherein p is at least two.
21. The method according to claim 20, wherein $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_2OR^{14}$.
22. The method according to claim 21, wherein the compound is

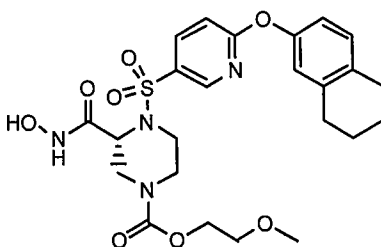


23. The method according to claim 16, wherein Z is $-N=$; and L^4 is $-O-$.
24. The method according to claim 23, wherein Ar is selected from the group consisting of phenyl, biphenyl, naphthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl,

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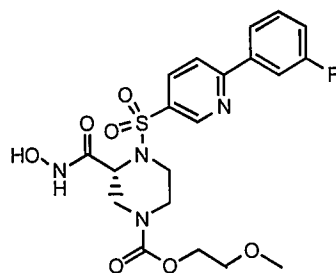
pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.

25. The method according to claim 24, wherein Ar is optionally substituted tetrahydronaphthalene.
26. The method according to claim 25, wherein $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_{2-3}OR^{14}$.
27. The method according to claim 26, wherein p is zero.
28. The method according to claim 27, wherein the compound is

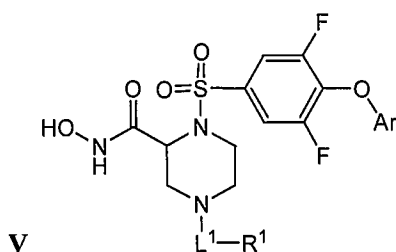


29. The method according to claim 16, wherein Z is $-N=$; and L^4 is nothing.
30. The method according to claim 29, wherein Ar is selected from the group consisting of phenyl, biphenyl, naphthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.
31. The method according to claim 30, wherein p is zero.
32. The method according to claim 31, wherein Ar is optionally substituted phenyl.
33. The method according to claim 32, wherein $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_{2-3}OR^{14}$.
34. The method according to claim 33, wherein the compound is

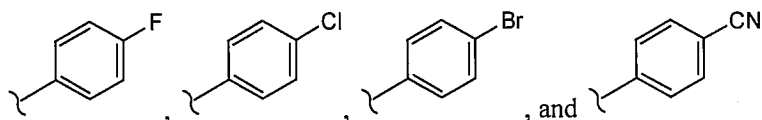
- 68 -



35. The method according to claim 16, wherein the compound is according to formula V,

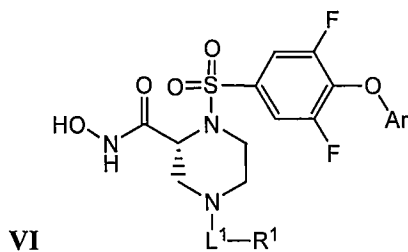


36. The method according to claim 35, wherein Ar is selected from the group consisting of phenyl, biphenyl, naphthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.
37. The method according to claim 36, wherein Ar is phenyl, optionally substituted, with at least one halogen.
38. The method according to claim 36, wherein Ar is selected from,

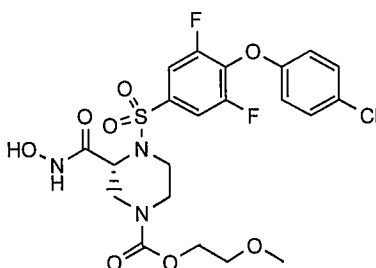


39. The method according to claim 37, wherein the absolute stereochemistry is according to formula VI,

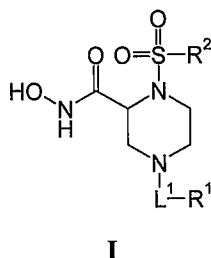
- 69 -



40. The method according to claim 39, wherein $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_{2-3}OR^{14}$.
41. The method according to claim 40, wherein the compound is



42. A method of inhibiting atherosclerotic lesion formation and growth or reducing aortic intimal lipid accumulation in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of a compound of structural formula I:



and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein

L^1 is $-C(O)-$, $-S(O)_2-$, or $-(CH_2)_n-$;

R^1 is $-H$, $-OR^{11}$, $-(CH_2)_nR^{11}$, $-C(O)R^{11}$, or $-NR^{12}R^{13}$;

R^{11} , R^{12} , and R^{13} independently are

- a) R^{50} ;
- b) saturated or mono- or poly- unsaturated C_5 - C_{14} -mono- or fused poly-cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one or two R^{50} substituents;

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- c) C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, or -C(O)H, each of which is optionally substituted with one, two or three substituents independently selected from R⁵⁰ and saturated or mono- or poly-unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two or three R⁵⁰ substituents;

or R¹² and R¹³ together with the N to which they are covalently bound, a C₅-C₆ heterocycle optionally containing a second annular heteroatom and optionally substituted with one or two R⁵⁰ substituents;

R² is -R²¹-L²-R²²;

R²¹ is saturated or mono- or poly- unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R⁵⁰ substituents;

L² is -O-, -C(O)-, -CH₂-, -NH-, -S(O₂)- or a direct bond;

R²² is saturated or mono- or poly- unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R⁵⁰ substituents; and

R⁵⁰ is R⁵¹-L³-(CH₂)_n;

L³ is -O-, -NH-, -S(O)₀₋₂-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -C₆H₄-, or a direct bond;

R⁵¹ is -H, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, halo, -CF₃, -OCF₃, -OH, -NH₂, mono-C₁-C₆alkyl amino, di-C₁-C₆alkyl amino, -SH, -CO₂H, -CN, -NO₂, -SO₃H, or a saturated or mono- or poly- unsaturated C₅-C₁₄-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three substituents;

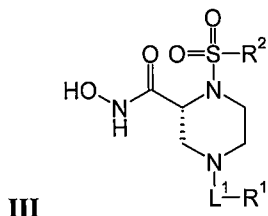
wherein n is 0, 1, 2, or 3;

provided that an O or S is not singly bonded to another O or S in a chain of atoms.

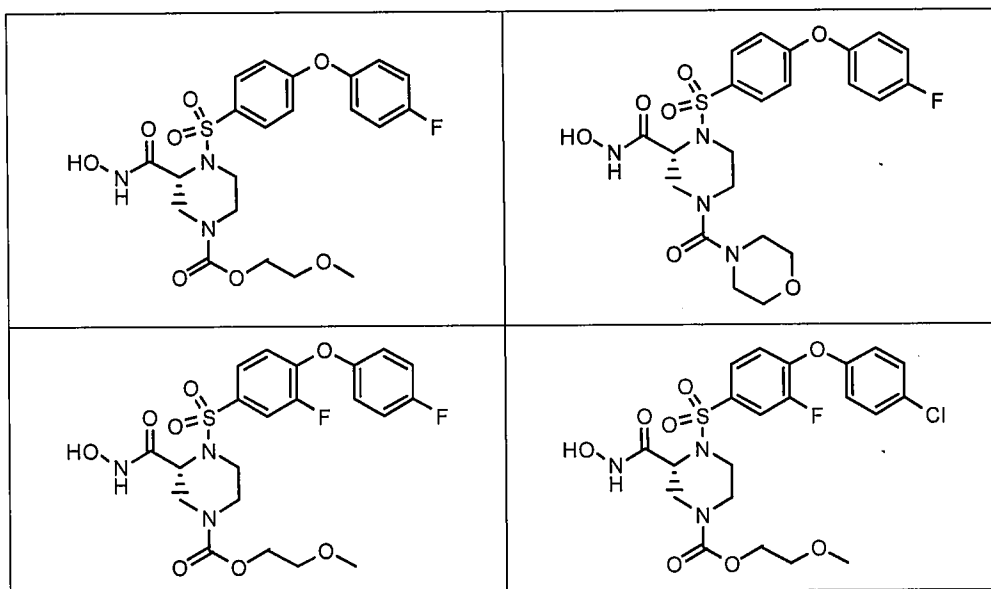
43. The method according to claim 42, wherein L¹ is -C(O)- or -S(O)₂-.

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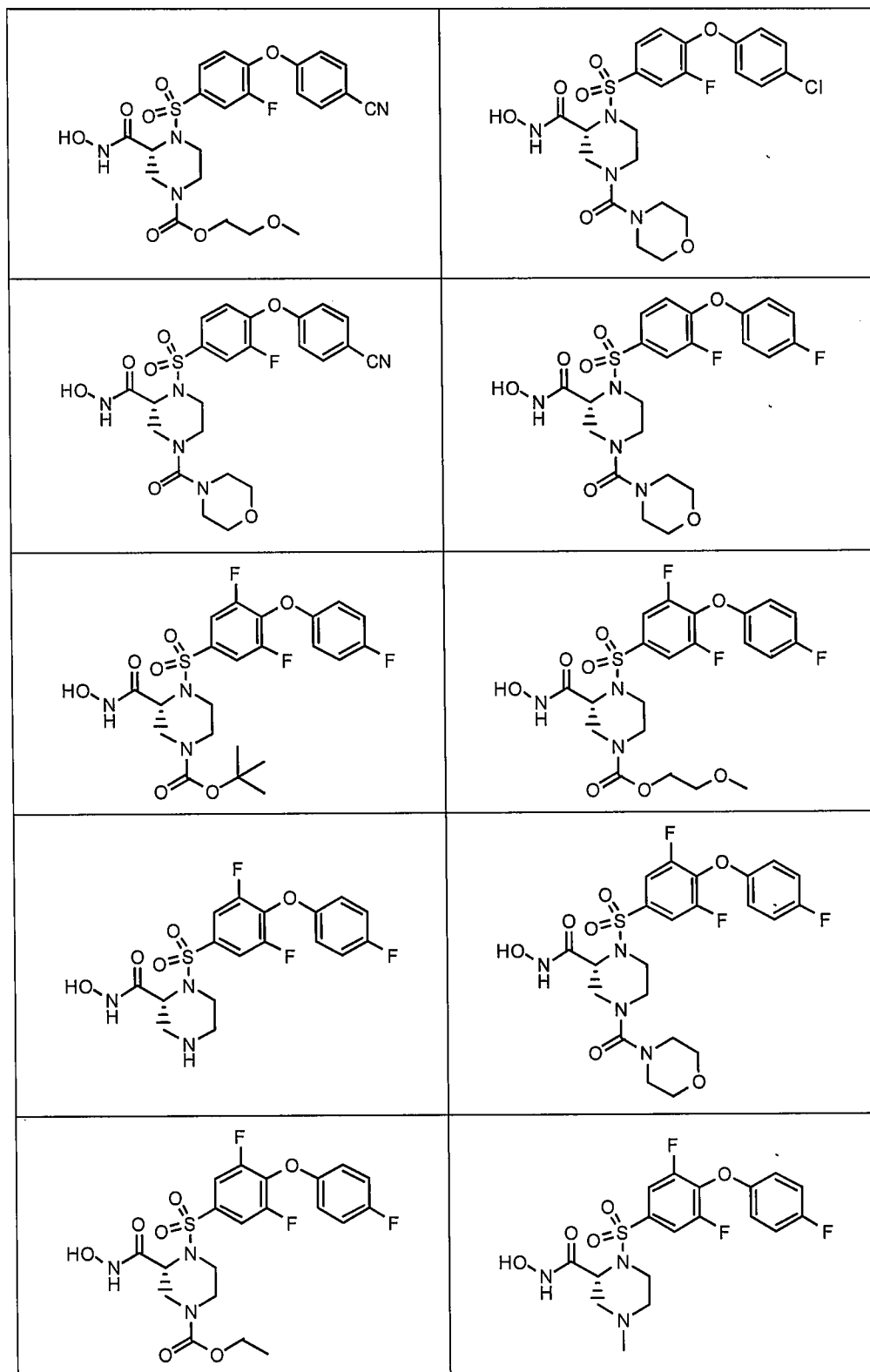
44. The method according to claim 43, wherein L^1 is $-C(O)-$ and R^1 is $-OR^{11}$ or $-(CH_2)_nR^{11}$, $-OC_1-C_6$ alkyl-mono- C_1-C_6 alkyl amino, $-OC_1-C_6$ alkyl-di- C_1-C_6 alkyl amino, $-OC_1-C_6$ alkyl-N-heterocyclyl, $-C_1-C_6$ alkyl-mono- C_1-C_6 alkyl amino, $-C_1-C_6$ alkyl-di- C_1-C_6 alkyl amino, or $-C_1-C_6$ alkyl-N-heterocyclyl.
45. The method according to claim 43, wherein, R^1 is C_1-C_6 -alkoxy- C_1-C_6 -alkoxy.
46. The method according to claim 43, wherein R^1 is methoxyethoxy.
47. The method according to claim 42 or 44, wherein, R^2 is phenoxyphenyl wherein each phenyl is optionally substituted with one or two R^{50} substituents.
48. The method according to claim 47, wherein the compound comprises the absolute stereochemistry of structural formula **III**:



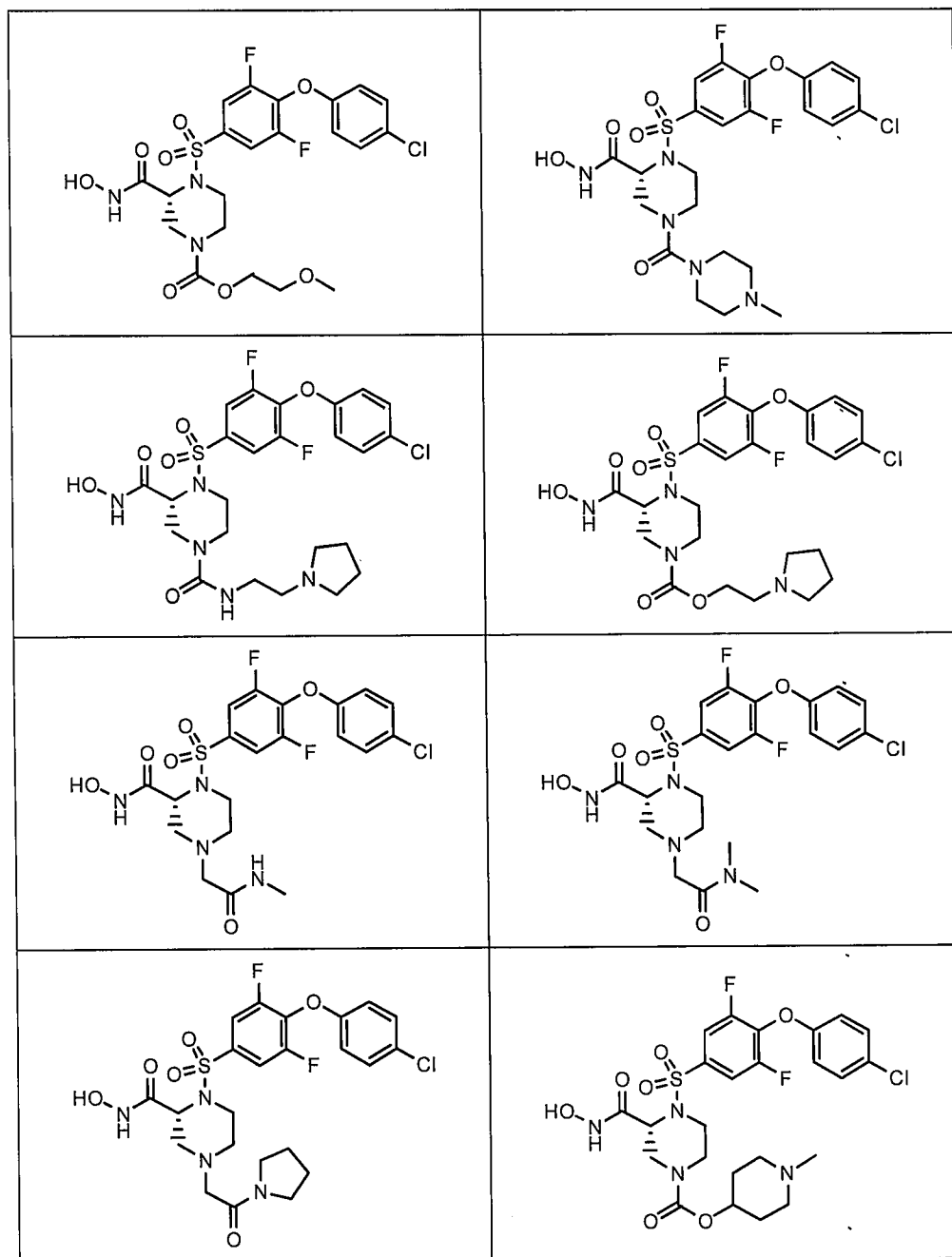
49. The method according to claim 42, where in the compound is selected from:

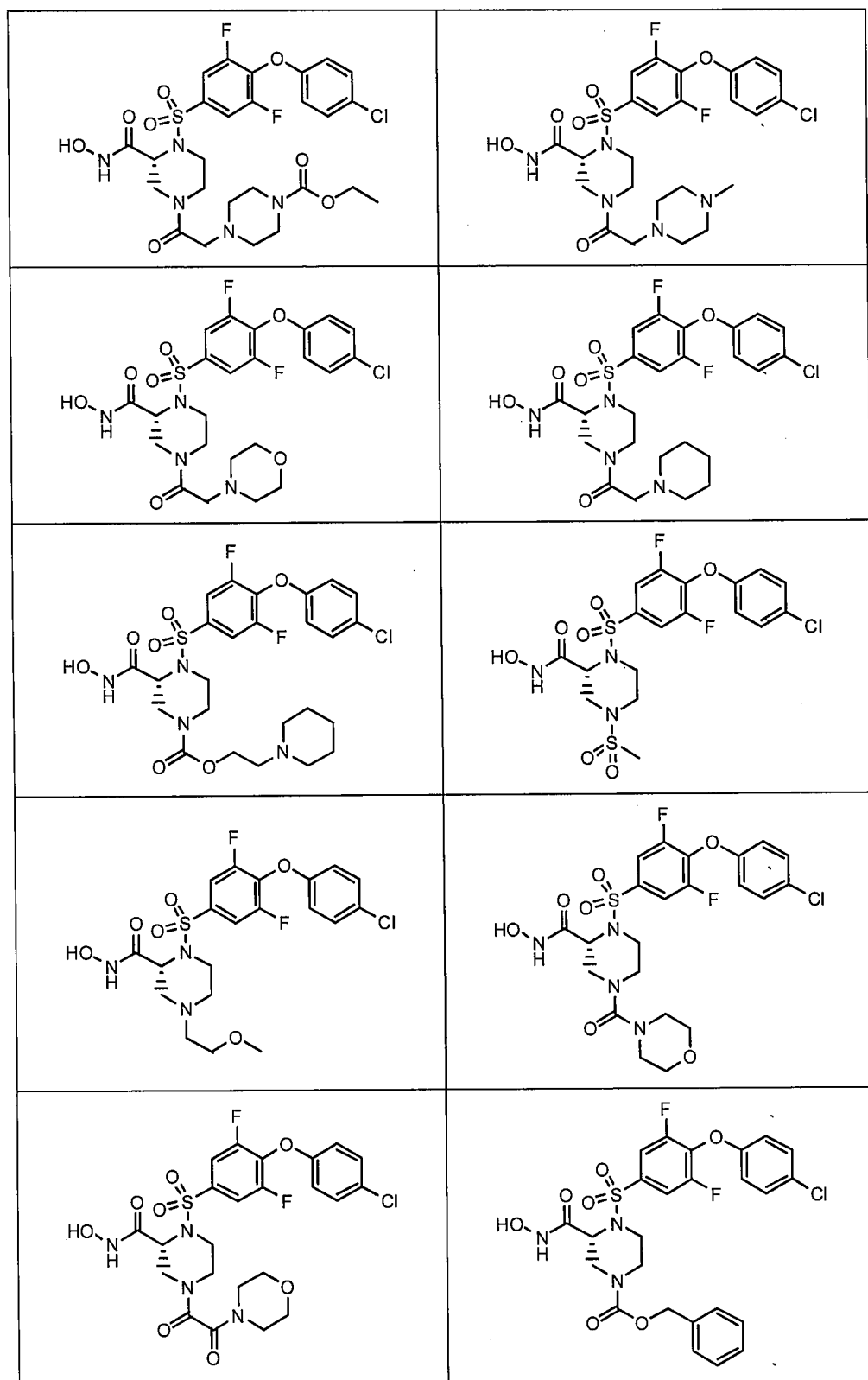


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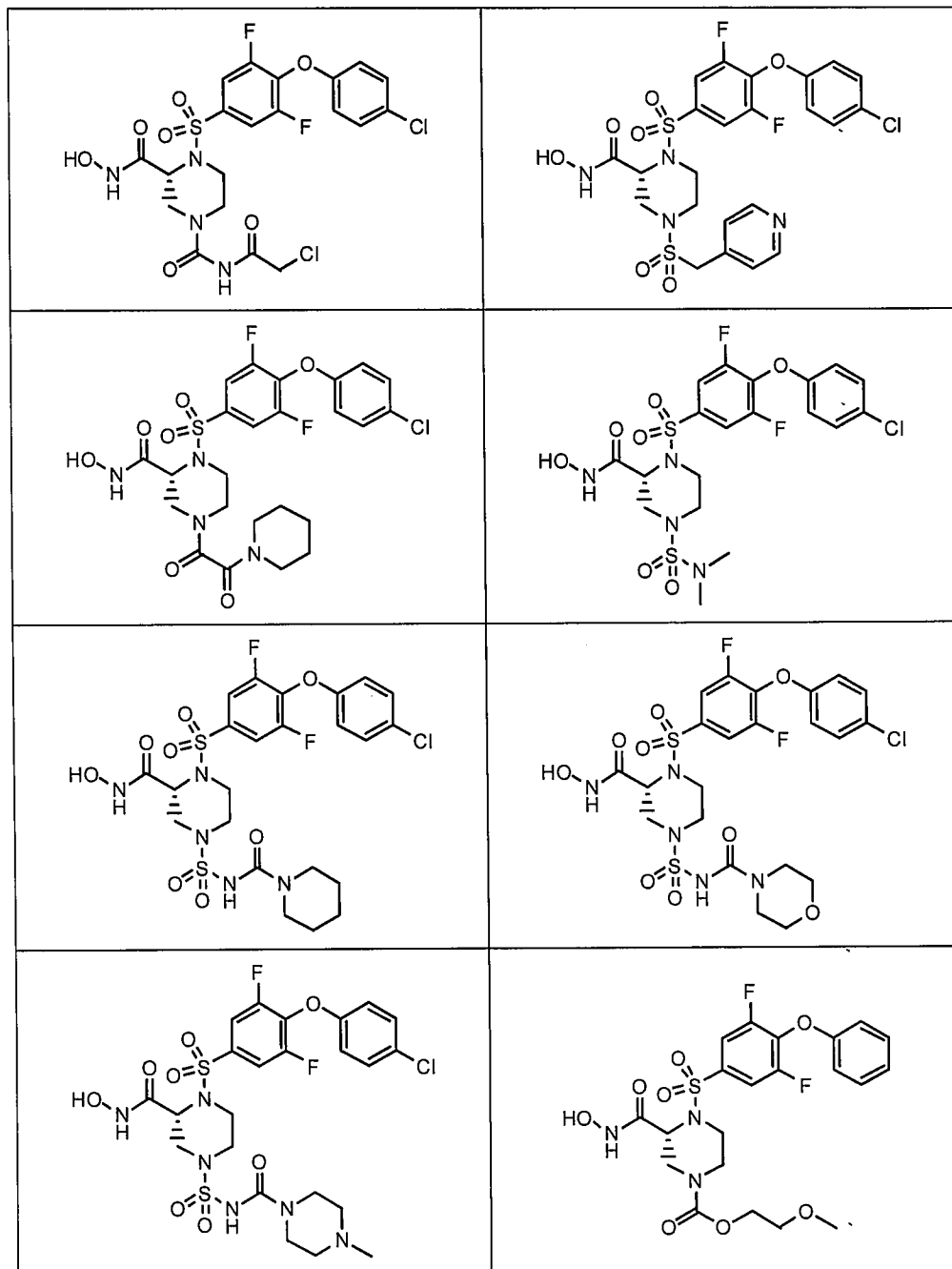


- 73 -

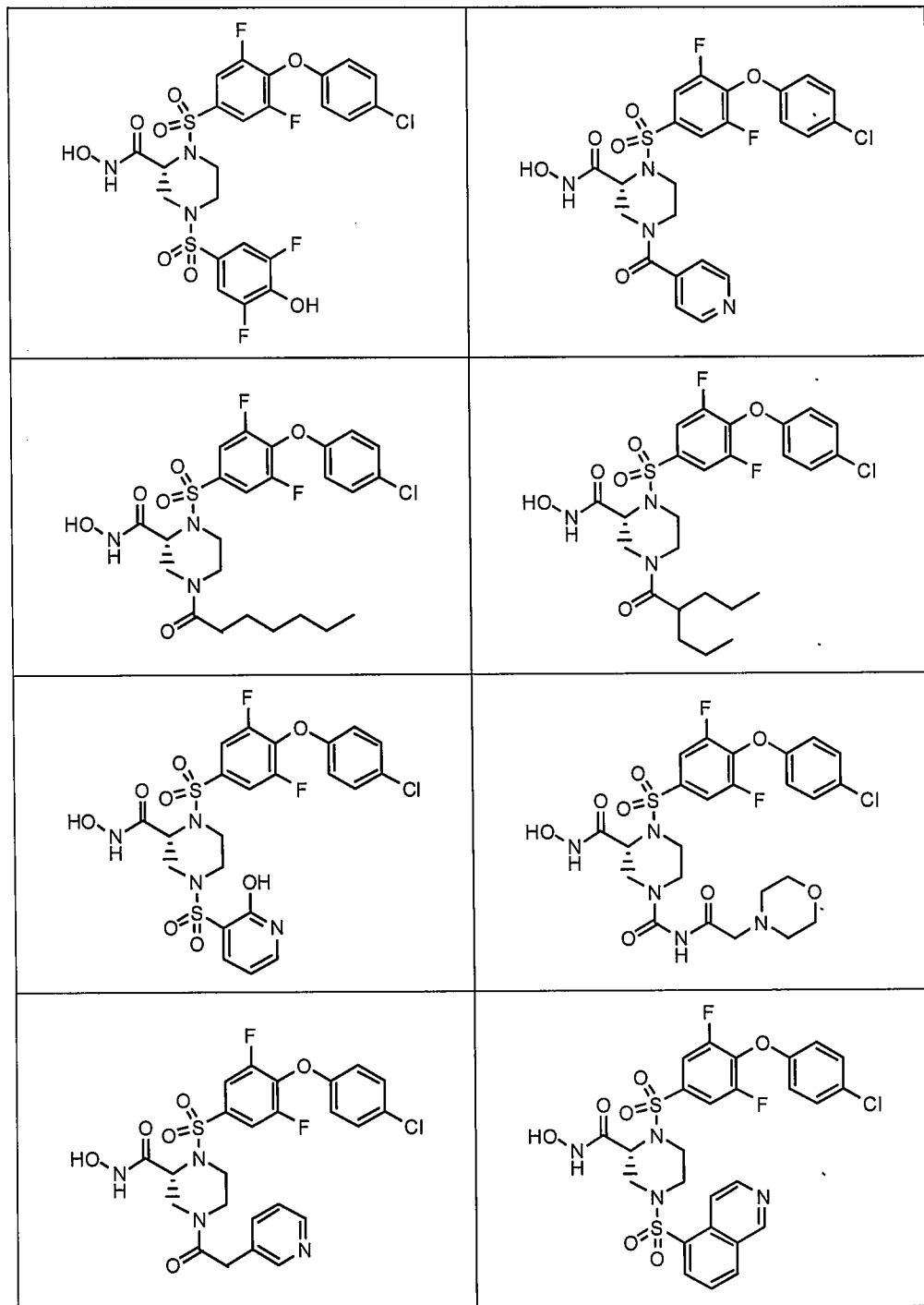




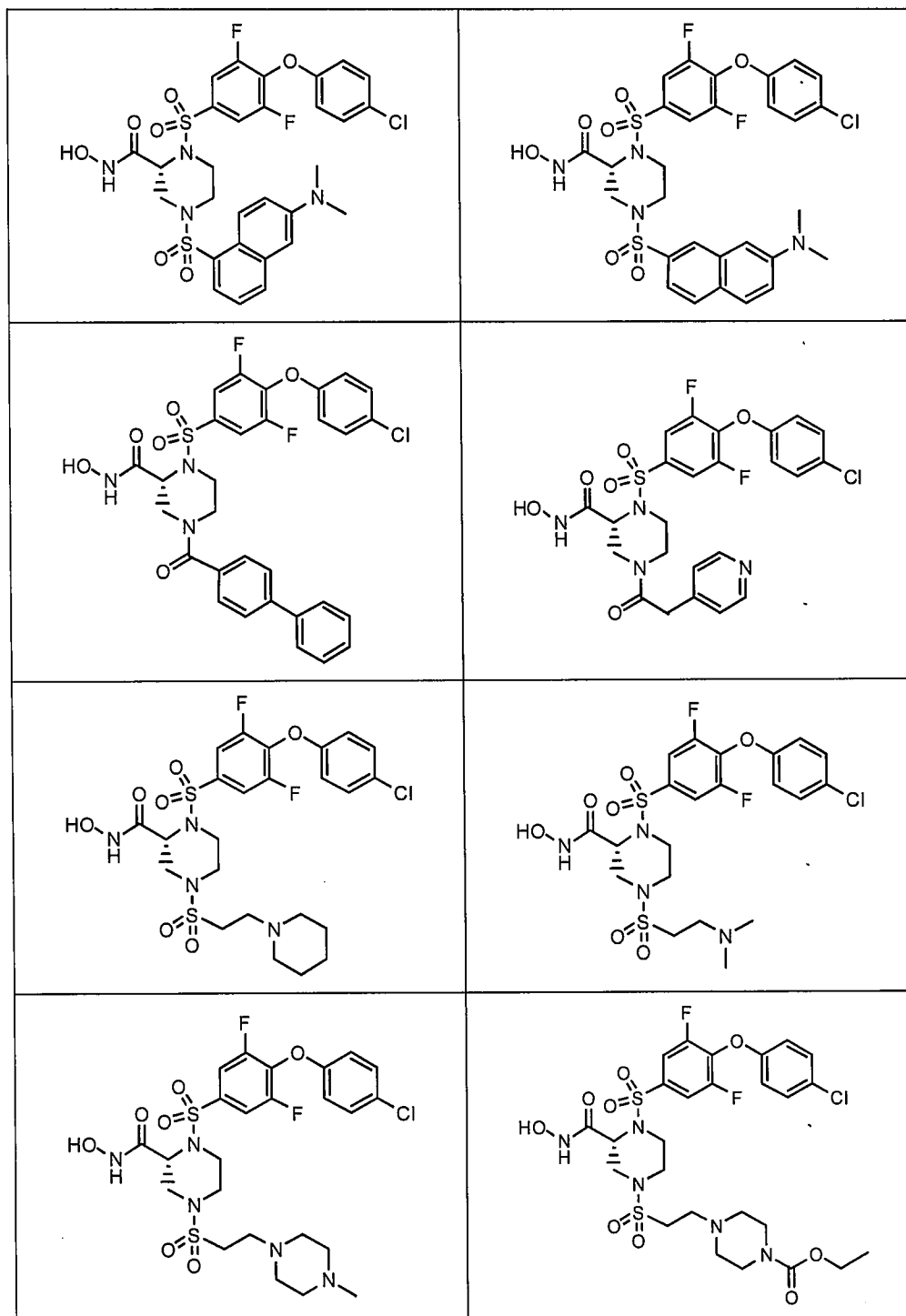
- 75 -



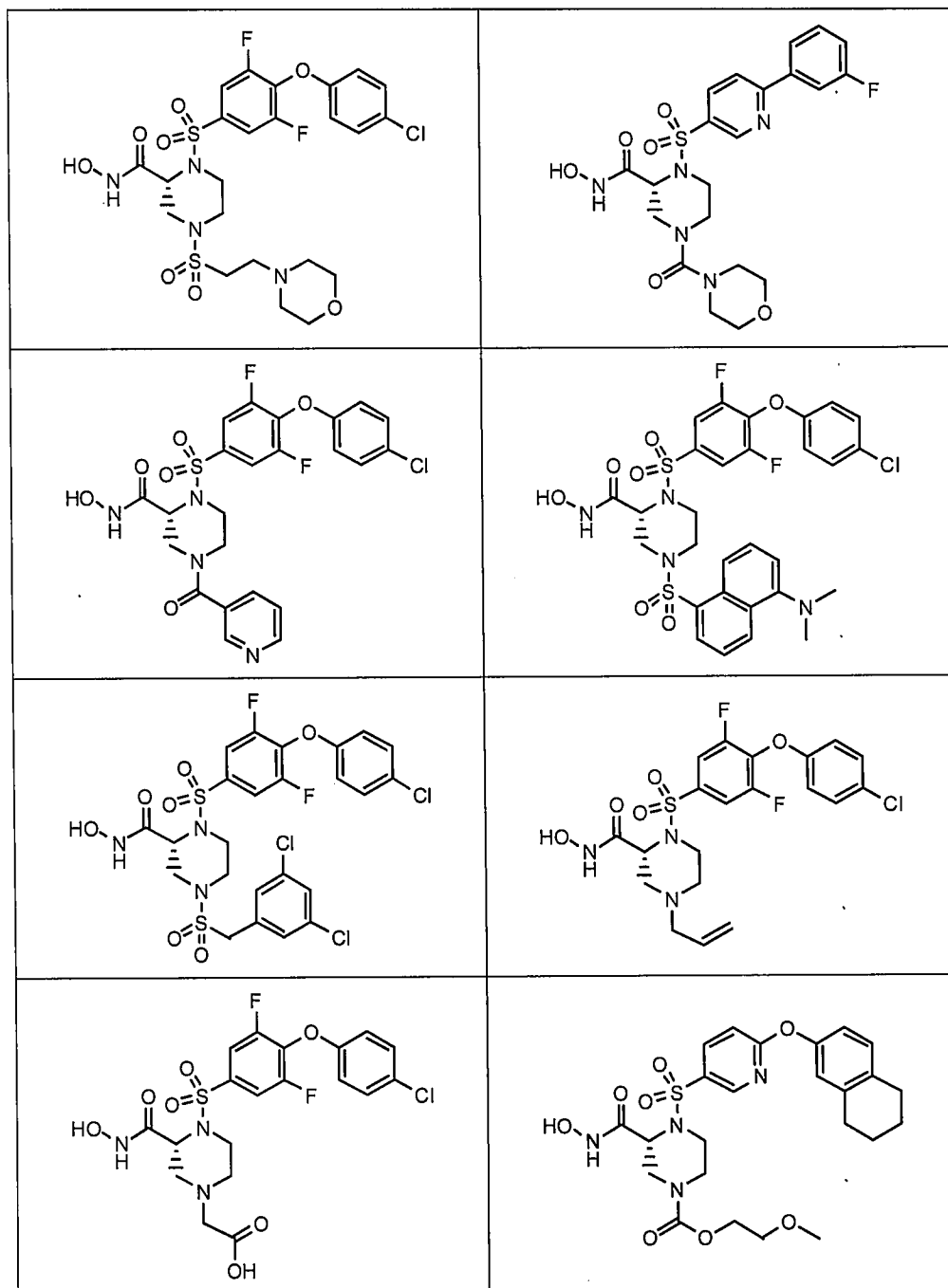
- 76 -



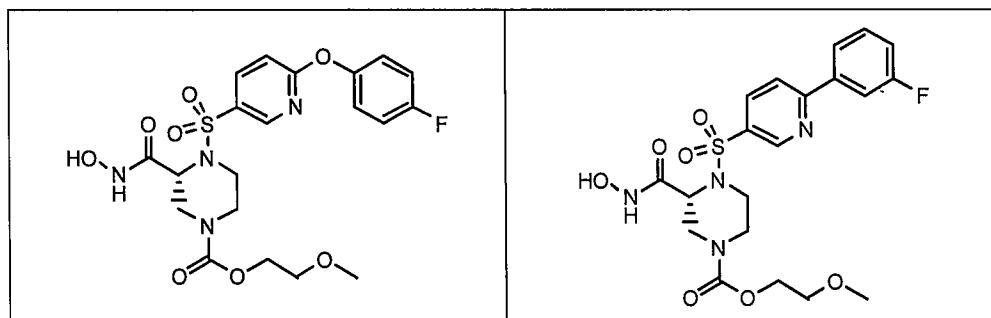
- 77 -



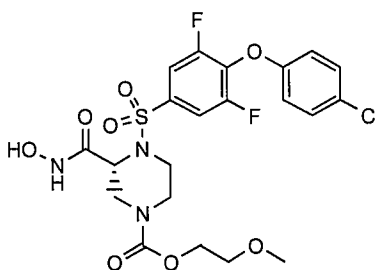
- 78 -



- 79 -



50. The method according to claim 42, wherein the compound is



51. The method according to claim 22, 41, or 50, wherein the compound is in the form of an Mg^{2+} salt.

FIGURE 1A

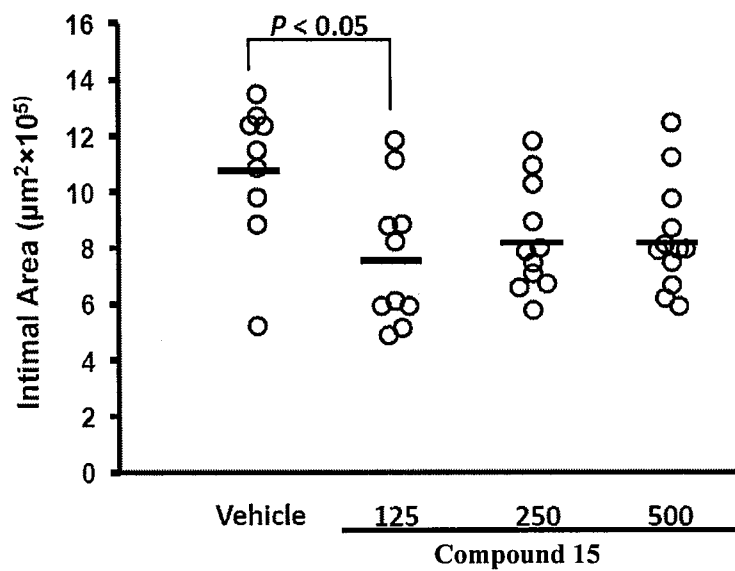


FIGURE 1B

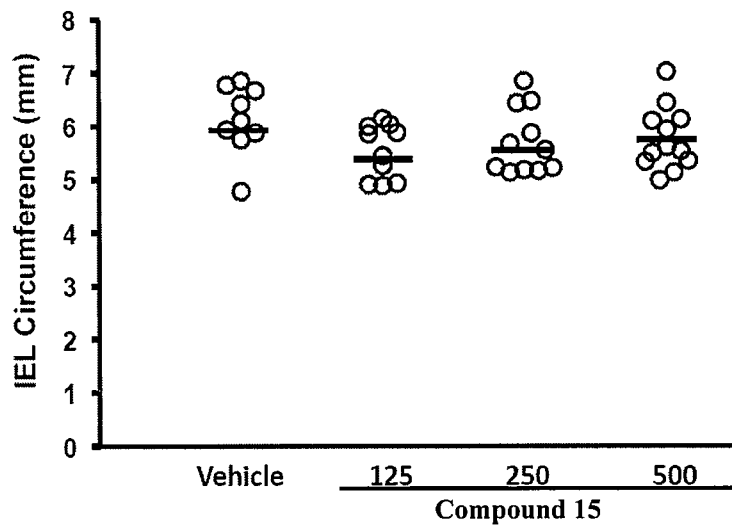


FIGURE 1C

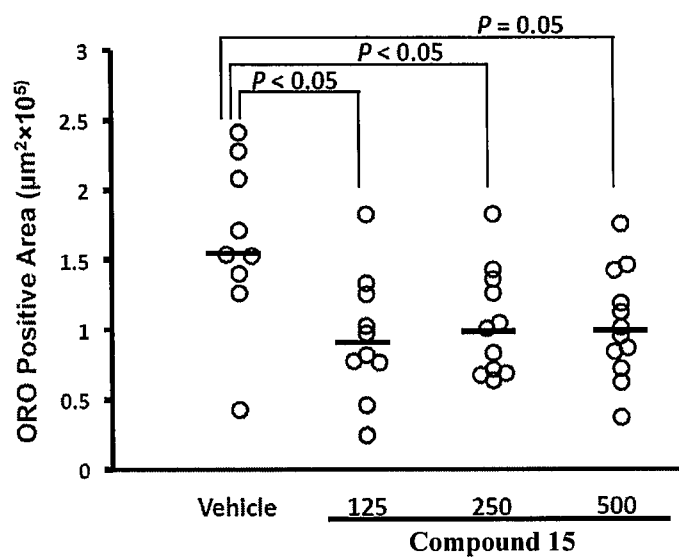
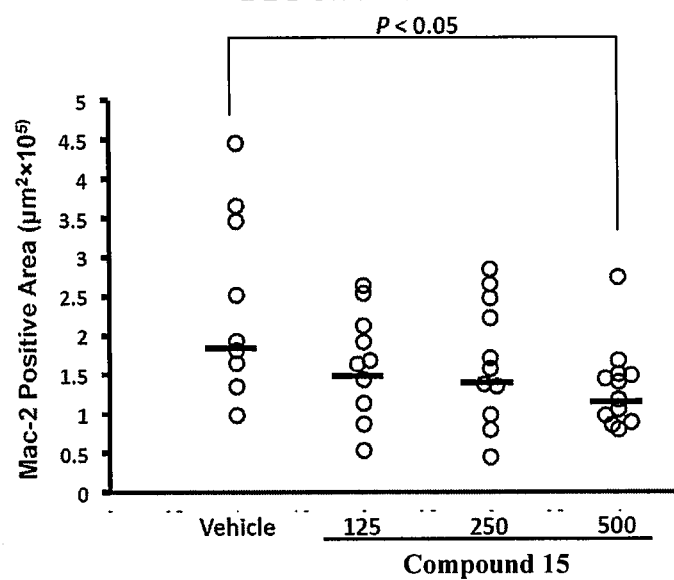


FIGURE 1D



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/054368

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/18 A61K31/166 A61K31/496
ADD.

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)

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 practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/199820 A1 (BANNEN LYNNE C [US] ET AL BANNEN LYNNE CANNE [US] ET AL) 7 September 2006 (2006-09-07)	1-51
Y	paragraphs [0002], [0013], [0015] - [0041] tables 1-5 paragraphs [0044] - [0087] -/-	1-51



Further documents are listed in the continuation of Box C.



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 application or patent but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

17 October 2013

Date of mailing of the international search report

30/10/2013

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Hörtner, Michael

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2013/054368

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
L	& Anonymous: "XL-784", Thomson Reuters Integrity, 3 February 2004 (2004-02-03), page 1, XP055084176, Internet Retrieved from the Internet: URL:https://integrity.thomson-pharma.com/i ntegrity/xmlxsl/pk_prod_list.prod_list_gra ph_pr?p_origen=PROD&p_session_id=10517404& p_graph_value_type=THER [retrieved on 2013-10-16] the whole document -----	
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Y	paragraphs [0002] - [0097] paragraphs [0160], [0170] claims 1-15 -----	1-51
Y	US 2011/082114 A1 (WOOD ALASTAIR J J [US]) 7 April 2011 (2011-04-07) claims 1-19	1-51
Y	M. KUZUYA ET AL: "Effect of MMP-2 Deficiency on Atherosclerotic Lesion Formation in ApoE-Deficient Mice", ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, vol. 26, no. 5, 1 May 2006 (2006-05-01), pages 1120-1125, XP055084128, ISSN: 1079-5642, DOI: 10.1161/01.ATV.0000218496.60097.e0 abstract page 1124, left-hand column, last paragraph - right-hand column, paragraph 1 -----	1-51
Y	M DONNERS ET AL: "ADAM10: a novel metalloprotease interacting with the VEGF(R) pathway, expressed in human atherosclerosis and associated with plaque neovascularization", 29TH CONGRESS OF THE EUROPEAN-SOCIETY-OF-CARDIOLOGY, vol. 28, 1 September 2007 (2007-09-01), page 746, XP055084037, abstract ----- -/--	1-51

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2013/054368

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	M. M. P. C. DONNERS ET AL: "A Disintegrin and Metalloprotease 10 Is a Novel Mediator of Vascular Endothelial Growth Factor-Induced Endothelial Cell Function in Angiogenesis and Is Associated With Atherosclerosis", ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, vol. 30, no. 11, 1 November 2010 (2010-11-01), pages 2188-2195, XP055084094, ISSN: 1079-5642, DOI: 10.1161/ATVBAHA.110.213124 abstract page 2189, left-hand column, paragraph 3 page 2195, right-hand column, paragraph 1 -----	1-51
Y	US 2005/227997 A1 (NOE MARK C [US] ET AL) 13 October 2005 (2005-10-13) paragraphs [0096] - [0103] paragraphs [0108], [0115] table 2 -----	1-51
A	CHENG M ET AL: "DESIGN AND SYNTHESIS OF PIPERAZINE-BASED MATRIX METALLOPROTEINASE INHIBITORS", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, vol. 43, no. 3, 1 January 2000 (2000-01-01), pages 369-380, XP000919159, ISSN: 0022-2623, DOI: 10.1021/JM990366Q abstract Scheme 1 tables 1-4 -----	1-51

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2013/054368

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 2436676 A1	04-04-2012
		ES 2425013 T3	10-10-2013
		JP 4718172 B2	06-07-2011
		JP 2005533789 A	10-11-2005
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		US 2010105953 A1	29-04-2010
		US 2012071653 A1	22-03-2012
		US 2013144056 A1	06-06-2013
		WO 03106381 A2	24-12-2003
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		JP 2013506684 A	28-02-2013
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		WO 2011041545 A1	07-04-2011
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