(54) Title of the Invention: Glycomimetics
Abstract Title: Glycomimetics

(57) Glycomimetic compounds are disclosed for use in the treatment of vascular calcification and/or endothelial dysfunction, particularly small molecule mimetics of heparin/heparan sulfate, such as compounds according to at least one of formulae (A), (B), (C) or (D), or pharmaceutically acceptable derivatives thereof.
Figure 1

Scheme 1: (i) MeOH, H₂SO₄, reflux, 16 h; (ii) allylbromide, K₂CO₃, acetone, 0 – 25 °C; (iii) 4-Bromobutyl acetate, NaH, NBU₄, DMF, 0 – 25 °C; (iv) AD-mix-β, ¹BuOH, H₂O, MeSO₂NH₂, 0 °C, 12 h.

Figure 2

Scheme 2: (i) allylbromide, NaH, NBu₄, DMF, 25 °C, 16 h; (ii) AD-mix-α, ¹BuOH, H₂O, MeSO₂NH₂, 0 °C, 12 h; (iii) SO₃·NEt₃, DMF, 40 °C, 16 h.
Scheme 3: (i) KOH, EtOH, H₂O, 60 °C, 6 h; (ii) AD-mix-β, tBuOH, H₂O, MeSO₂NH₂, 0 °C, 12 h; (iii) SO₃·NEt₃, DMF, 40 °C, 16 h.

Scheme 4: (i) AD-mix-α, tBuOH, H₂O, MeSO₂NH₂, 0 °C, 12 h; (ii) SO₃·NEt₃, DMF, 40 °C, 16 h.
Figure 5

Scheme 5: (i) SO$_3$NE$_3$, DMF, 40 °C, 16 h.

Figure 6: Glycomimetic compounds C1-C4 prevent lipid-induced decrease in NO production from HUVECs. **P<0.001 vs control (CT), and #P<0.05, ###P<0.01 and ####P<0.001 vs PAL.
Figure 7: Effect of glycomimetic compounds C1-C4 on Akt, eNOS and NOX4 mRNA expression in lipid-induced endothelial cells. *P<0.05, **P<0.01, ***P<0.001 vs control (CT), and #P<0.05, ##P<0.01 and ###P<0.001 vs PAL.
Figure 8: Effect of glycomimetic compounds C1-C4 on Akt and eNOS phosphorylation in lipid-induced endothelial cells. *P<0.05 vs control (CT), and #P<0.05, ###P<0.01 and ####P<0.001 vs PAL.
Figure 9: Effect of glycomimetic compounds C1-C4 prevent lipid-induced oxidative stress. 
*P<0.05, **P<0.01, ***P<0.001 vs control (CT), and #P<0.05, ##P<0.01 and ###P<0.001 vs PAL.
Figure 10: Effect of glycomimetic compounds C1 and C4 on vascular relaxant responses induced by acetylcholine in intact aortic rings pre-contracted by U46619. *P<0.05, **P<0.01, ***P<0.001 vs control (CT), and #P<0.05, ##P<0.01 and ###P<0.001 vs PAL.
Figure 11

A
Figure 11: The effect of glycomimetic compounds C1-C4 on βGP-induced vascular calcification in HPSMCs.
Figure 12: Glycomimetic compounds C1-C4 prevent calcium deposition in βGP-induced HPSMCs. ***P<0.001.
Figure 13: Glycomimetic compounds C1-C4 decreased ALP activity at 4, 7 and 10 days in βGP-induced HPSMCs. ***P<0.001; **P<0.05; *P<0.01.
GLYCOMIMETICS

TECHNICAL FIELD

The present invention relates to medical treatments for vascular calcification and/or endothelial dysfunction, and particularly to the use of glycomimetic compounds or pharmaceutically acceptable derivatives thereof for the treatment of vascular calcification and/or endothelial dysfunction.

BACKGROUND ART

Vascular calcification and endothelial dysfunction

Vascular calcification (e.g. cardiovascular calcification) is a major clinical issue and elucidating an underlying problem is of vital importance to improving its prognosis and the eventual treatment of cardiovascular disease. Vascular calcification is a progressive condition which results in the build-up of calcium mineral deposits and plaques on the inner wall of arteries, which in turn reduces arterial contractility. This deterioration in the condition of the artery walls can lead to the onset of cardiovascular disease and a host of other complications in patients. Vascular calcification has been linked with the occurrence of endothelial dysfunction but the relationship between the two events is not yet fully understood.

Endothelial dysfunction is a systemic pathological state of the endothelium (i.e. the inner lining of blood vessels) and broadly involves an imbalance between vasodilating and vasoconstricting substances produced by the endothelium. Normal functions of endothelial cells include mediation of coagulation, platelet adhesion, immune function and control of volume and electrolyte content of the intravascular and extravascular spaces. Endothelial nitric oxide synthase (eNOS) is expressed in vascular endothelial cells, endomyocardial cells, atrial cells, vascular smooth muscle cells, respiratory endothelial cells, and the like. The production of eNOS in such cells serves to adjust vascular tone and maintain homeostasis of vascular endothelial cells by forming nitric oxide (NO). NO reduction is considered to be the hallmark of endothelial dysfunction, where a key feature of this dysfunction is the inability of endothelial cells to release vasodilators such as NO thus leading to a reduction in NO bioavailability. The biochemical mechanisms involved in the development of endothelial dysfunction are complex.

One such endothelial dysfunction related mechanism attracting interest at present is the disruption of the hepatocyte growth factor (HGF)/ receptor tyrosine kinase (c-Met) signaling pathway using NK4 or DAPT as inhibitors. Pathway studies have demonstrated that NK4 inhibits the direct interaction of HGF with c-Met, whereas, DAPT acts to inhibit Notch signaling
which is down-stream from the HGF/c-MET interaction. This mechanism has been linked with multiple biological effects on a wide variety of cells (Liu et al. Atherosclerosis 219 (2011) 440-447).

**Glycomimetic compounds**

Glycomimetic compounds are molecules that structurally and functionally mimic carbohydrates in the body, such as heparan sulfate, involved in important biological processes. These compounds, generally, have structures similar to carbohydrates but with some variation resulting in a modified biological activity. Therapeutically effective and commercially successful glycomimetic compounds include Tamiflu™ in the treatment of influenza virus and Acarbose for the treatment of type 2 diabetes.

Certain glycomimetics have been investigated for use in the treatment of type 1 and type 2 diabetes (WO 2011/109877A1, Parish et al.) as well as cancer progression (Raiber et al. Bioorganic & Medicinal Chemistry Letters 17 (2007) 6321-6325). Moreover, Raiber et al. have demonstrated that modulation of the interaction between HGF and c-MET using glycomimetic compounds may be useful in the context of cancer cells and thus cancer treatments, particularly with respect to tumor invasion and metastasis in cancers.

The present inventors have successfully identified small molecule glycomimetic compounds to satisfy an unmet need in the treatment of endothelial dysfunction and the prevention of vascular calcification.

This is surprising not least because, until now, there has been no link between the specific glycomimetic induced modulation of HGF/c-MET signaling and the treatment of endothelial dysfunction or vascular calcification.

**DISCLOSURE OF THE INVENTION**

In its broadest sense, the inventors propose the use of glycomimetics, particularly small molecule mimetics of heparin/heparan sulfate, for treating endothelial dysfunction and vascular calcification.

The inventors in particular propose glycomimetic compounds of formulae A-D or pharmaceutically acceptable derivatives thereof, as defined in the claims and further described in aspects and embodiments of the invention below, for the treatment of vascular calcification and/or endothelial dysfunction.
As indicated by the examples and figures described herein, the inventors have observed that the compounds of the invention show surprising activity in models of endothelial dysfunction and / or vascular calcification. Compounds of the invention in particular demonstrate a surprising ability to modulate specific biological pathways associated with these medical indications.

The present inventors have in particular observed that compounds of the invention show utility in treating endothelial dysfunction by exploiting a number of biochemical pathways, including (a) upregulation of the eNOS/Akt signalling pathway, (b) potentiation of the antioxidant defence system; and (c) regulation of NADPH oxidase activity and reactive oxygen species (ROS), thus underpinning a surprising utility of these compounds in the treatment of endothelial dysfunction.

The utility of compounds of the invention in treating vascular calcification is demonstrated by the effective blocking of ßGP-induced vascular calcification in human pelvic artery smooth muscle cells (HPSMCs), and by desirable effects in a calcium deposition assay (see examples and figures herein). Investigation of the mechanism of action of the compounds in line with Western blotting data indicated that the compounds exert these effects, *inter alia*, by effective inhibition of c-MET phosphorylation.

The inventors propose that compounds of the invention exhibit their surprising activity by virtue of modulating the interaction of HGF (hepatocyte growth factor) with glycoprotein co-receptor in the glycocalix of endothelial cells, which then has an effect on the downstream biochemical pathways associated with the HGF/c-MET pathway that relate specifically to endothelial dysfunction and / or vascular calcification. Previous treatments proposed for endothelial dysfunction and / or vascular calcification have instead focused on other mechanisms for modulating the HGF-binding properties, such as by providing variants of HGF, such as NK4 (see introduction section), to directly inhibit HGF – c-MET binding. Modulation of the interaction between HGF and glycoprotein co-receptor in the glycocalix has never before been proposed as a way in which to target and treat vascular calcification and / or endothelial
dysfunction. The present invention thus represents an important development in the field of treating vascular calcification and / or endothelial dysfunction.

Without wishing to be bound by theory, it is proposed that the activity of the compounds of the invention is at least in part achieved by mimicking the binding mode of native heparan sulfate to HGF. The inventors propose that the spatial orientation of the R\textsuperscript{1} carboxyl motif on the ring (or a corresponding bioisostere thereof) relative to the essential sulfate / sulfamide group pendant on the linear right hand side chain at R\textsuperscript{2} and / or R\textsuperscript{3} plays an important role in providing the desirable activity of the present compounds.

Accordingly, in an aspect, the invention provides a compound (i.e. a glycomimetic) according to formula (A), (B), (C) or (D):

![Chemical structures](A) (B) (C) (D)

or a pharmaceutically acceptable derivative thereof for use in the treatment of vascular calcification and / or endothelial dysfunction,

wherein:

![Ring symbol] is a 6-membered carbocyclic or heterocyclic ring;

![Ring symbol] is a 5-membered carbocyclic or heterocyclic ring;
J is H, halo, optionally substituted C_{1-10}alkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted C_{2-10}alkynyl, optionally substituted C_{2-10}heteroalkyl, optionally substituted C_{3-10}heterocycloalkyl, optionally substituted C_{2-10}heteroalkenyl, optionally substituted C_{3-10}heterocycloalkenyl, optionally substituted C_{2-10}heteroalkynyl, optionally substituted C_{6-14}aryl, optionally substituted C_{5-14}heteroaryl, or 

\[ \text{structure image} \]

Z is -O-, -N(R^A)-, -S-, or a C_{1-6}alkylene or C_{2-8}heteroalkylene linker group, wherein the C_{1-6}alkylene and C_{2-8}heteroalkylene linker groups are each independently optionally substituted with 1 to 3 substituents selected from halo, OH, C_{1-6}alkyl, C_{1-6}haloalkyl; -OSO_2H and -NH(SO_3H), and wherein R^6 is H or C_{1-6}alkyl;

Q is -O-, -N(R^B)-, -S-, or a C_{1-6}alkylene or C_{2-8}heteroalkylene linker group, wherein the C_{1-6}alkylene and C_{2-8}heteroalkylene linker groups are each independently optionally substituted with 1 to 3 substituents selected from halo, OH, C_{1-6}alkyl, C_{1-6}haloalkyl; -OSO_2H and -NH(SO_3H), and wherein R^B is H or C_{1-6}alkyl;

R^1 is -CO_2W or a bioisostere of a carboxyl group;

R^2 and R^3 are each independently H, -OR^7 or -NH(R^7), wherein each R^7 is independently selected from the group consisting of H, -SO_3Y, optionally substituted C_{1-10}alkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted C_{2-10}alkynyl, optionally substituted C_{2-10}heteroalkyl, optionally substituted C_{3-10}heterocycloalkyl, optionally substituted C_{2-10}heteroalkenyl, optionally substituted C_{3-10}heterocycloalkenyl, optionally substituted C_{2-10}heteroalkynyl, optionally substituted C_{6-14}aryl and optionally substituted C_{5-14}heteroaryl, wherein at least one of R^2 and R^3 is selected from -OSO_3Y and -NH(SO_3Y);

R^4 and R^5 are each independently H, -OR^8 or -NH(R^8), wherein each R^8 is independently selected from the group consisting of H, -SO_3Y, optionally substituted C_{1-10}alkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted C_{2-10}alkynyl, optionally substituted C_{2-10}heteroalkyl, optionally substituted C_{3-10}heterocycloalkyl, optionally substituted C_{2-10}heteroalkenyl, optionally substituted C_{3-10}heterocycloalkenyl, optionally substituted C_{2-10}heteroalkynyl, optionally substituted C_{6-14}aryl and optionally substituted C_{5-14}heteroaryl;
R\(^6\) is H, -CH\(_2\)OR\(^8\) or -CH\(_2\)NH(R\(^8\)), wherein R\(^8\) is independently selected from the group consisting of H, -SO\(_3\)Y, optionally substituted C\(_{1-10}\)alkyl, optionally substituted C\(_{3-10}\)cycloalkyl, optionally substituted C\(_{2-10}\)alkenyl, optionally substituted C\(_{3-10}\)cycloalkenyl, optionally substituted C\(_{2-10}\)alkynyl, optionally substituted C\(_{2-10}\)heteroalkyl, optionally substituted C\(_{3-10}\)heterocycloalkyl, optionally substituted C\(_{2-10}\)heteroalkenyl, optionally substituted C\(_{3-10}\)heterocycloalkenyl, optionally substituted C\(_{2-10}\)heteroalkynyl, optionally substituted C\(_{6-14}\)aryl and optionally substituted C\(_{5-14}\)heteroaryl;

s is an integer from 0 to 3;

t is an integer from 0 to 2;

each R\(^{10}\), when present, is independently selected from the group consisting of halo, C\(_{1-4}\)alkyl, C\(_{1-4}\)haloalkyl, -OSO\(_3\)Y and -NH(SO\(_3\)Y);

W is H, optionally substituted C\(_{1-10}\)alkyl, optionally substituted C\(_{3-10}\)cycloalkyl, optionally substituted C\(_{2-10}\)alkenyl, optionally substituted C\(_{3-10}\)cycloalkenyl, optionally substituted C\(_{2-10}\)alkynyl, optionally substituted C\(_{3-10}\)heteroalkyl, optionally substituted C\(_{2-10}\)heteroalkenyl, optionally substituted C\(_{3-10}\)heterocycloalkyl, optionally substituted C\(_{2-10}\)heterocycloalkenyl, optionally substituted C\(_{2-10}\)heteroalkynyl, optionally substituted C\(_{6-14}\)aryl or optionally substituted C\(_{5-14}\)heteroaryl; and

Y is H, optionally substituted C\(_{1-10}\)alkyl, optionally substituted C\(_{3-10}\)cycloalkyl, optionally substituted C\(_{2-10}\)alkenyl, optionally substituted C\(_{3-10}\)cycloalkenyl, optionally substituted C\(_{2-10}\)alkynyl, optionally substituted C\(_{3-10}\)heteroalkyl, optionally substituted C\(_{2-10}\)heteroalkenyl, optionally substituted C\(_{3-10}\)heterocycloalkyl, optionally substituted C\(_{2-10}\)heterocycloalkenyl, optionally substituted C\(_{2-10}\)heteroalkynyl, optionally substituted C\(_{6-14}\)aryl or optionally substituted C\(_{5-14}\)heteroaryl.

Thus, in an aspect, the invention provides the use of a compound (i.e. a glycomimetic) according to formula (A), (B), (C) or (D):

![Chemical Structures](A) and (B)
or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of vascular calcification and / or endothelial dysfunction,

wherein:

![6-membered carbocyclic or heterocyclic ring](image)

is a 6-membered carbocyclic or heterocyclic ring;

![5-membered carbocyclic or heterocyclic ring](image)

is a 5-membered carbocyclic or heterocyclic ring;

J is H, halo, optionally substituted C\textsubscript{1-10}alkyl, optionally substituted C\textsubscript{3-10}cycloalkyl, optionally substituted C\textsubscript{2-10}alkenyl, optionally substituted C\textsubscript{3-10}cycloalkenyl, optionally substituted C\textsubscript{2-10}alkynyl, optionally substituted C\textsubscript{2-10}heteroalkyl, optionally substituted C\textsubscript{3-10}heterocycloalkyl, optionally substituted C\textsubscript{2-10}heteroalkenyl, optionally substituted C\textsubscript{3-10}heterocycloalkenyl, optionally substituted C\textsubscript{5-14}heteroaryl, or C\textsubscript{6-14}aryl, optionally substituted C\textsubscript{5-14}heteroaryl, or \( \text{C}_{6-14} \text{aryl} \), optionally substituted C\textsubscript{5-14}heteroaryl, or \( \text{C}_{6-14} \text{aryl} \);

Z is -O-, -N(R\textsuperscript{A})-, -S-, or a C\textsubscript{1-6}alkylene or C\textsubscript{2-6}heteroalkylene linker group, wherein the C\textsubscript{1-6}alkylene and C\textsubscript{2-6}heteroalkylene linker groups are each independently optionally substituted with 1 to 3 substituents selected from halo, OH, C\textsubscript{1-6}alkyl, C\textsubscript{1-6}haloalkyl; -OSO\textsubscript{3}H and -NH(SO\textsubscript{3}H), and wherein R\textsuperscript{A} is H or C\textsubscript{1-6}alkyl;

Q is -O-, -N(R\textsuperscript{B})-, -S-, or a C\textsubscript{1-6}alkylene or C\textsubscript{2-6}heteroalkylene linker group, wherein the C\textsubscript{1-6}alkylene and C\textsubscript{2-6}heteroalkylene linker groups are each independently optionally substituted with 1 to 3 substituents selected from halo, OH, C\textsubscript{1-6}alkyl, C\textsubscript{1-6}haloalkyl; -OSO\textsubscript{3}H and -NH(SO\textsubscript{3}H), and wherein R\textsuperscript{B} is H or C\textsubscript{1-6}alkyl;

R\textsuperscript{1} is -CO\textsubscript{2}W or a bioisostere of a carboxyl group;
R² and R³ are each independently H, -OR⁷ or -NH(R⁷), wherein each R⁷ is independently selected from the group consisting of H, -SO₃Y, optionally substituted C₁₋₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₂₋₁₀heteroalkyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkenyl, optionally substituted C₂₋₁₀heteroalkynyl, optionally substituted C₆₋₁₄aryl and optionally substituted C₅₋₁₄heteroaryl, wherein at least one of R² and R³ is selected from -OSO₃Y and -NH(SO₃Y);

R⁴ and R⁵ are each independently H, -OR⁸ or -NH(R⁸), wherein each R⁸ is independently selected from the group consisting of H, -SO₃Y, optionally substituted C₁₋₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₂₋₁₀heteroalkyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkenyl, optionally substituted C₂₋₁₀heteroalkynyl, optionally substituted C₆₋₁₄aryl and optionally substituted C₅₋₁₄heteroaryl;

R⁶ is H, -CH₂OR⁶ or -CH₂NH(R⁹), wherein R⁹ is independently selected from the group consisting of H, -SO₃Y, optionally substituted C₁₋₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₂₋₁₀heteroalkyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkenyl, optionally substituted C₂₋₁₀heteroalkynyl, optionally substituted C₆₋₁₄aryl and optionally substituted C₅₋₁₄heteroaryl;

s is an integer from 0 to 3;

t is an integer from 0 to 2;

each R¹⁰, when present, is independently selected from the group consisting of halo, C₁₋₄alkyl, C₁₋₄haloalkyl, -OSO₃Y and -NH(SO₃Y);

W is H, optionally substituted C₁₋₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₂₋₁₀heteroalkyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkenyl, optionally substituted C₂₋₁₀heteroalkynyl, optionally substituted C₆₋₁₄aryl or optionally substituted C₅₋₁₄heteroaryl; and
Y is H, optionally substituted C\textsubscript{1-10}alkyl, optionally substituted C\textsubscript{3-10}cycloalkyl, optionally substituted C\textsubscript{2-10}alkenyl, optionally substituted C\textsubscript{3-10}cycloalkenyl, optionally substituted C\textsubscript{2-10}alkynyl, optionally substituted C\textsubscript{2-10}heteroalkyl, optionally substituted C\textsubscript{3-10}heterocycloalkyl, optionally substituted C\textsubscript{2-10}heteroalkenyl, optionally substituted C\textsubscript{3-10}heterocycloalkenyl, optionally substituted C\textsubscript{2-10}heteroalkynyl, optionally substituted C\textsubscript{6-14}aryl or optionally substituted C\textsubscript{5-14}heteroaryl.

In a further aspect, the invention provides a method of treating vascular calcification and/or endothelial dysfunction comprising administering a therapeutically effective amount of a compound (i.e. a glycomimetic) according to formula (A), (B), (C) or (D), or a pharmaceutically acceptable derivative thereof, to a patient (e.g. a patient in need thereof):

\[ \text{\textbullet} \]

wherein:

\[ \text{\textbullet} \]

is a 6-membered carbocyclic or heterocyclic ring;

\[ \text{\textbullet} \]

is a 5-membered carbocyclic or heterocyclic ring;

\[ \text{\textbullet} \]

J is H, halo, optionally substituted C\textsubscript{1-10}alkyl, optionally substituted C\textsubscript{2-10}cycloalkyl, optionally substituted C\textsubscript{2-10}alkenyl, optionally substituted C\textsubscript{3-10}cycloalkenyl, optionally substituted C\textsubscript{2-10}alkynyl, optionally substituted C\textsubscript{2-10}heteroalkyl, optionally substituted C\textsubscript{3-10}heterocycloalkyl, optionally substituted C\textsubscript{2-10}heteroalkenyl, optionally substituted C\textsubscript{3-10}heterocycloalkenyl, optionally substituted C\textsubscript{2-10}heteroalkynyl, optionally substituted C\textsubscript{6-14}aryl or optionally substituted C\textsubscript{5-14}heteroaryl.
C<sub>3-10</sub>heterocycloalkenyl, optionally substituted C<sub>2-10</sub>heteroalkynyl, optionally substituted C<sub>6-14</sub>aryl, optionally substituted C<sub>5-14</sub>heteroaryl, or 

\[ \text{Z is } -\text{O-}, -\text{N}(\text{R}^A)^-, -\text{S-}, \text{ or a } \text{C}_{1-6}\text{alkylene or } \text{C}_{2-6}\text{heteroalkylene linker group, wherein the } \text{C}_{1-6}\text{alkylene and } \text{C}_{2-6}\text{heteroalkylene linker groups are each independently optionally substituted with 1 to 3 substituents selected from halo, } \text{OH, } \text{C}_{1-6}\text{alkyl, } \text{C}_{1-6}\text{haloalkyl; -OSO}_3\text{H and -NH}\left(\text{SO}_3\text{H}\right), \text{ and wherein } \text{R}^A \text{ is } \text{H or } \text{C}_{1-6}\text{alkyl;}
\]

\[ \text{Q is } -\text{O-}, -\text{N}(\text{R}^B)^-, -\text{S-}, \text{ or a } \text{C}_{1-6}\text{alkylene or } \text{C}_{2-6}\text{heteroalkylene linker group, wherein the } \text{C}_{1-6}\text{alkylene and } \text{C}_{2-6}\text{heteroalkylene linker groups are each independently optionally substituted with 1 to 3 substituents selected from halo, } \text{OH, } \text{C}_{1-6}\text{alkyl, } \text{C}_{1-6}\text{haloalkyl; -OSO}_3\text{H and -NH}\left(\text{SO}_3\text{H}\right), \text{ and wherein } \text{R}^B \text{ is } \text{H or } \text{C}_{1-6}\text{alkyl;}
\]

\[ \text{R}^7 \text{ is } -\text{CO}_2\text{W or a bioisostere of a carboxyl group;}
\]

\[ \text{R}^2 \text{ and } \text{R}^3 \text{ are each independently } \text{H, -OR}^7 \text{ or -NH(} \text{R}^7 \text{), wherein each } \text{R}^7 \text{ is independently selected from the group consisting of } \text{H, -SO}_3\text{Y, optionally substituted } \text{C}_{1-10}\text{alkyl, optionally substituted } \text{C}_{3-10}\text{cycloalkyl, optionally substituted } \text{C}_{2-10}\text{alkenyl, optionally substituted } \text{C}_{3-10}\text{cycloalkenyl, optionally substituted } \text{C}_{2-10}\text{alkynyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkenyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkyl, optionally substituted } \text{C}_{2-10}\text{heteroalkenyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkenyl, optionally substituted } \text{C}_{2-10}\text{heteroalkynyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkenyl, optionally substituted } \text{C}_{2-10}\text{heteroalkynyl, optionally substituted } \text{C}_{6-14}\text{aryl and optionally substituted } \text{C}_{5-14}\text{heteroaryl, wherein at least one of } \text{R}^2 \text{ and } \text{R}^3 \text{ is selected from -OSO}_3\text{Y and -NH(} \text{SO}_3\text{Y);}
\]

\[ \text{R}^4 \text{ and } \text{R}^5 \text{ are each independently } \text{H, -OR}^8 \text{ or -NH(} \text{R}^8 \text{), wherein each } \text{R}^8 \text{ is independently selected from the group consisting of } \text{H, -SO}_3\text{Y, optionally substituted } \text{C}_{1-10}\text{alkyl, optionally substituted } \text{C}_{3-10}\text{cycloalkyl, optionally substituted } \text{C}_{2-10}\text{alkenyl, optionally substituted } \text{C}_{3-10}\text{cycloalkenyl, optionally substituted } \text{C}_{2-10}\text{alkynyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkenyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkyl, optionally substituted } \text{C}_{2-10}\text{heteroalkenyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkenyl, optionally substituted } \text{C}_{2-10}\text{heteroalkynyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkenyl, optionally substituted } \text{C}_{2-10}\text{heteroalkynyl, optionally substituted } \text{C}_{6-14}\text{aryl and optionally substituted } \text{C}_{5-14}\text{heteroaryl;}
\]

\[ \text{R}^8 \text{ is } \text{H, -CH}_2\text{OR}^9 \text{ or -CH}_2\text{NH(} \text{R}^9 \text{), wherein } \text{R}^9 \text{ is independently selected from the group consisting of } \text{H, -SO}_3\text{Y, optionally substituted } \text{C}_{1-10}\text{alkyl, optionally substituted } \text{C}_{2-10}\text{cycloalkyl, optionally substituted } \text{C}_{2-10}\text{alkenyl, optionally substituted } \text{C}_{3-10}\text{cycloalkenyl, optionally substituted } \text{C}_{2-10}\text{alkynyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkenyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkyl, optionally substituted } \text{C}_{2-10}\text{heteroalkenyl, optionally substituted } \text{C}_{3-10}\text{heterocycloalkenyl, optionally substituted } \text{C}_{2-10}\text{heteroalkynyl, optionally substituted }
\]
C_{3-10} \text{heterocycloalkenyl}, \text{ optionally substituted } C_{2-10} \text{heteroalkynyl}, \text{ optionally substituted } C_{5-14} \text{aryl} \text{ and optionally substituted } C_{5-14} \text{heteroaryl};

s \text{ is an integer from 0 to 3;}

t \text{ is an integer from 0 to 2;}

each R^{10}, \text{ when present, is independently selected from the group consisting of halo, } C_{1-4} \text{alkyl, } C_{1-4} \text{haloalkyl, } -\text{OSO}_3Y \text{ and } -\text{NH(}\text{SO}_3Y);\]

W \text{ is H, optionally substituted } C_{1-10} \text{alkyl, optionally substituted } C_{3-10} \text{cycloalkyl, option ally substituted } C_{2-10} \text{alkenyl, optionally substituted } C_{3-10} \text{cycloalkenyl, optionally substituted } C_{2-10} \text{alkynyl, optionally substituted } C_{2-10} \text{heteroalkyl, optionally substituted } C_{3-10} \text{heterocycloalkyl, optionally substituted } C_{2-10} \text{heteroalkenyl, optionally substituted } C_{2-10} \text{heteroalkynyl, optionally substituted } C_{6-14} \text{aryl or optionally substituted } C_{5-14} \text{heteroaryl}; \text{ and}

Y \text{ is H, optionally substituted } C_{1-10} \text{alkyl, optionally substituted } C_{3-10} \text{cycloalkyl, optionally substituted } C_{2-10} \text{alkenyl, optionally substituted } C_{3-10} \text{cycloalkenyl, optionally substituted } C_{2-10} \text{alkynyl, optionally substituted } C_{2-10} \text{heteroalkyl, optionally substituted } C_{3-10} \text{heterocycloalkyl, optionally substituted } C_{2-10} \text{heteroalkenyl, optionally substituted } C_{2-10} \text{heteroalkynyl, optionally substituted } C_{6-14} \text{aryl or optionally substituted } C_{5-14} \text{heteroaryl.}

\text{a) In embodiments of the above aspects, the compound or pharmaceutically acceptable derivative thereof provided may be according to formula (A) or (B):}

\begin{equation}
\begin{array}{c}
\begin{array}{c}
\text{(A)} \quad \text{(B)}
\end{array}
\end{array}
\end{equation}

\text{wherein } \text{, } R^1, R^3, R^{10}, J \text{ and } Z \text{ are as defined according to the above aspects.}
b) In embodiments of the above aspects or embodiment, the compound or pharmaceutically acceptable derivative may be according to formula (A):

\[
\begin{array}{c}
\text{J} \\
R_1 \\
\text{R}^{10}_s \\
\text{Z} \\
R^2 \\
\text{R}^3 \\
\end{array}
\]

(A);

wherein \( R^1 - R^3, R^{10}, J \) and \( Z \) are as defined above.

c) In embodiments of the above aspect and embodiments, \( \text{C} \) is a 6-membered aryl or heteroaryl ring.

d) In embodiments, formula (A) and (B) are according to formulae (A1) and (B1), respectively:

\[
\begin{array}{c}
\text{J} \\
E \\
\text{D} \\
\text{Z} \\
R^2 \\
R^3 \\
\end{array}
\]

(A1)

\[
\begin{array}{c}
\text{J} \\
E \\
\text{D} \\
\text{Z} \\
R^2 \\
R^3 \\
\end{array}
\]

(B1),

wherein \( C, D, E \) are each independently selected from the group consisting of \( \text{CH}, \text{CR}^{10} \) and \( \text{N} \); and

\( R^1 - R^3, R^{10}, J \) and \( Z \) are as defined above.

e) The compound or pharmaceutically acceptable derivative may for instance be a compound or pharmaceutically acceptable derivative according to formula (A1):

\[
\begin{array}{c}
\text{J} \\
E \\
\text{D} \\
\text{Z} \\
R^2 \\
\text{R}^3 \\
\end{array}
\]

(A1),
wherein groups $R^1-R^3$, C-E, J and Z are as defined in embodiment d) above.

f) In alternative embodiments of the above aspects and embodiments, may be a 6-membered saturated cycloalkyl or heterocycloalkyl ring.

g) The compound or pharmaceutically acceptable derivative according to the above aspects and embodiments may for instance be a compound or pharmaceutically acceptable derivative of any one of formulae (A) and (B), wherein formulae (A) and (B) are according to formulae (A2) and (B2), respectively:

\[
\begin{align*}
\text{(A2)} & \quad \text{C} \quad \text{D} \quad \text{E} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \\
\text{(B2)} & \quad \text{J} \quad \text{D} \quad \text{E} \quad \text{C} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3
\end{align*}
\]

wherein C, D and E are each independently selected from the group consisting of $\text{CH}_2$, $\text{CHR}^{10}$, NH and NR$^{10}$; and

$R^1-R^3$, $R^{10}$, J and Z are as defined above.

h) The compound or pharmaceutically acceptable derivative may in embodiments of the above aspects and embodiments be a compound or pharmaceutically acceptable derivative of formula (A2):

\[
\begin{align*}
\text{(A2)} & \quad \text{C} \quad \text{D} \quad \text{E} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3
\end{align*}
\]

wherein groups $R^1-R^3$, C-E, J and Z are as defined above in embodiment e).

i) In embodiments of the invention, Z is a C$_2$-heteroalkylene linker group optionally substituted with 1 to 3 substituents selected from halo, OH, C$_1$-alkyl, C$_1$-haloalkyl, -OSO$_3$H and -NH(SO$_3$H); optionally wherein Z is a C$_2$-heteroalkylene linker group.
j) In embodiments, the compound or pharmaceutically acceptable derivative of formula (A1) is a compound or pharmaceutically acceptable derivative of formula (A3):

wherein:

groups $R^1$-$R^3$, C-E, and J are as defined according to embodiment e);
A is NR$^A$, O or S, wherein $R^A$ is H or C$_{1-6}$alkyl; and
m is 1, 2, 3 or 4.

k) In some embodiments of the aspects of embodiments above, J is H, halo, optionally substituted C$_{1-10}$alkyl, optionally substituted C$_{3-10}$cycloalkyl, optionally substituted C$_{2-10}$heteroalkyl, optionally substituted C$_{3-10}$heterocycloalkyl, or C$_{3-10}$alkyl, wherein Q and $R^4$-$R^6$ are as defined above.

J may for instance be    wherein Q and $R^4$-$R^6$ are as defined above. In embodiments Q may be a C$_{2-6}$heteroalkylene linker group optionally substituted with 1 to 3 substituents selected from halo, OH, C$_{1-6}$alkyl, C$_{1-6}$haloalkyl; -OSO$_2$H and -NH(SO$_3$H)$_2$. In embodiments Q is unsubstituted, such as wherein Q is a C$_{2-6}$heteroalkylene linker group.

J may for instance be    , wherein
R\textsuperscript{4} - R\textsuperscript{6} are as defined in claim 1;
B is NR\textsuperscript{8}, O or S, wherein R\textsuperscript{8} is H or C\textsubscript{1-6}alkyl; and
n is 1, 2, 3, or 4.

I) In the present invention as described according to the above aspects of the invention, the
compound or pharmaceutically acceptable derivative may be a compound or pharmaceutically
acceptable derivative of formula (I):

\[
\begin{array}{c}
\text{R}^4 \\
\text{R}^5 \\
\text{R}^4 \\
\text{B} \quad \text{C} \quad \text{A} \\
\text{E} \\
\text{R}^2 \\
\text{R}^3
\end{array}
\]

wherein:
A is NR\textsuperscript{8}, O or S, wherein R\textsuperscript{8} is H or C\textsubscript{1-6}alkyl;
B is NR\textsuperscript{8}, O or S, wherein R\textsuperscript{8} is H or C\textsubscript{1-6}alkyl;
m is 1, 2, 3 or 4;
n is 1, 2, 3 or 4;
R\textsuperscript{1} is -CO\textsubscript{2}W or a bioisostere of a carboxyl group (e.g. -CO\textsubscript{2}W);
R\textsuperscript{2} and R\textsuperscript{3} are each independently H, -OR\textsuperscript{7} or -NH(R\textsuperscript{7}), wherein each R\textsuperscript{7} is independently
selected from the group consisting of H, -SO\textsubscript{3}Y, optionally substituted C\textsubscript{1-10}alkyl, optionally substituted C\textsubscript{1-10}cycloalkyl, optionally substituted C\textsubscript{2-10}alkenyl, optionally substituted C\textsubscript{2-10}cycloalkenyl, optionally substituted C\textsubscript{2-10}alkynyl, optionally substituted C\textsubscript{2-10}heteroalkyl, optionally substituted C\textsubscript{3-10}heterocycloalkyl, optionally substituted C\textsubscript{2-10}heteroalkenyl, optionally substituted C\textsubscript{3-10}heterocycloalkenyl, optionally substituted C\textsubscript{2-10}heteroalkynyl, optionally
substituted C\textsubscript{6-14}aryl and optionally substituted C\textsubscript{5-14}heteroaryl, wherein at least one of R\textsuperscript{2} and
R\textsuperscript{3} is selected from -OSO\textsubscript{3}Y and -NH(SO\textsubscript{3}Y);
R\textsuperscript{4} and R\textsuperscript{5} are each independently H, -OR\textsuperscript{8} or -NH(R\textsuperscript{8}), wherein each R\textsuperscript{8} is independently
selected from the group consisting of H, -SO\textsubscript{3}Y, optionally substituted C\textsubscript{1-10}alkyl, optionally substituted C\textsubscript{1-10}cycloalkyl, optionally substituted C\textsubscript{2-10}alkenyl, optionally substituted C\textsubscript{2-10}cycloalkenyl, optionally substituted C\textsubscript{2-10}alkynyl, optionally substituted C\textsubscript{2-10}heteroalkyl, optionally substituted C\textsubscript{3-10}heterocycloalkyl, optionally substituted C\textsubscript{2-10}heteroalkenyl, optionally substituted C\textsubscript{3-10}heterocycloalkenyl, optionally substituted C\textsubscript{2-10}heteroalkynyl, optionally
substituted C\textsubscript{6-14}aryl and optionally substituted C\textsubscript{5-14}heteroaryl, wherein at least one of R\textsuperscript{4} and
R\textsuperscript{5} is selected from -OSO\textsubscript{3}Y and -NH(SO\textsubscript{3}Y).
substituted C_{3,10}heterocy cloalkenyl, optionally substituted C_{2,10}heteroalkynyl, optionally substituted C_{5,14}aryl and optionally substituted C_{5,14}heteroaryl;

R^6 is H, -CH_2OR^6 or -CH_2NH(R^6), wherein R^6 is independently selected from the group consisting of H, -SO_3Y, optionally substituted C_{1,10}alkyl, optionally substituted C_{3,10}cycloalkyl, optionally substituted C_{2,10}alkenyl, optionally substituted C_{3,10}cycloalkenyl, optionally substituted C_{2,10}alkynyl, optionally substituted C_{2,10}heteroalkyl, optionally substituted C_{2,10}heterocycloalkyl, optionally substituted C_{2,10}heteroalkenyl, optionally substituted C_{2,10}heterocycloalkenyl, optionally substituted C_{2,10}heteroalkynyl, optionally substituted C_{6,14}aryl or optionally substituted C_{5,14}heteroaryl; and

W is H, optionally substituted C_{1,10}alkyl, optionally substituted C_{3,10}cycloalkyl, optionally substituted C_{2,10}alkenyl, optionally substituted C_{3,10}cycloalkenyl, optionally substituted C_{2,10}alkynyl, optionally substituted C_{2,10}heteroalkyl, optionally substituted C_{3,10}heterocycloalkyl, optionally substituted C_{2,10}heteroalkenyl, optionally substituted C_{3,10}heterocycloalkenyl, optionally substituted C_{2,10}heteroalkynyl, optionally substituted C_{6,14}aryl or optionally substituted C_{5,14}heteroaryl; and

Y is H, optionally substituted C_{1,10}alkyl, optionally substituted C_{3,10}cycloalkyl, optionally substituted C_{2,10}alkenyl, optionally substituted C_{3,10}cycloalkenyl, optionally substituted C_{2,10}alkynyl, optionally substituted C_{2,10}heteroalkyl, optionally substituted C_{3,10}heterocycloalkyl, optionally substituted C_{2,10}heteroalkenyl, optionally substituted C_{3,10}heterocycloalkenyl, optionally substituted C_{2,10}heteroalkynyl, optionally substituted C_{6,14}aryl or optionally substituted C_{5,14}heteroaryl;

C, D and E are each independently selected from the group consisting of CH, CR^{10} and N; and

each R^{10} is independently selected from the group consisting of halo, C_{1,4}alkyl, C_{1,4}haloalkyl, -OSO_3Y and -NH(SO_3Y). In this embodiment, each optionally substituted group may independently be substituted or unsubstituted. In a particular embodiment, each group is for instance unsubstituted.

m) In the aspects and embodiments above, R^1 may be -CO_2W, wherein W is defined above. W may be H, optionally substituted C_{1,10}alkyl, or optionally substituted C_{2,10}heteroalkyl. For instance W may be H or optionally substituted C_{1,10}alkyl, optionally wherein W is H or C_{1,6}alkyl, such as wherein W is H or methyl.
n) In the above aspects and embodiments, R² may in embodiments be -OR⁷ or -NH(R⁷), optionally wherein said R⁷ is -SO₂Y, such as wherein R³ is -OSO₂Y.

o) In the above aspects and embodiments, R³ may in embodiments be -OR⁷ or -NH(R⁷), optionally wherein said R⁷ is -SO₂Y, such as wherein R³ is -OSO₂Y.

R² and R³ may, for instance, be selected independently from -OSO₂Y and -NH(SO₂Y), such as wherein both R² and R³ are -OSO₂Y.

p) In embodiments of the invention, R⁴ may be H, -OR⁸ or -NH(R⁸), optionally wherein R⁸ is -SO₂Y, such as wherein R⁴ is -OSO₂Y. For instance, R⁴ may be H.

q) R⁵ may, in embodiments of the invention, be -OR⁸ or -NH(R⁸), optionally wherein R⁸ is -SO₂Y, such as wherein R⁵ is -OSO₂Y.

R⁴ and R⁵ may for instance be selected from -OSO₂Y and -NH(SO₂Y). For instance, R⁴ and R⁵ may be each independently selected from -OSO₂Y and -NH(SO₂Y), such as wherein both R⁴ and R⁵ are -OSO₂Y.

r) In embodiments, R⁶ may be H.

s) In embodiments of the above aspects and embodiments, each R⁷ may be independently selected from the group consisting of H, -SO₂Y and optionally substituted C₁₋₁₀alkyl. For instance, each R⁷ may be independently selected from the group consisting of H and -SO₂Y; such as wherein each R⁷ is -SO₂Y.

t) In embodiments of the above aspects and embodiments, each R⁸ may be independently selected from the group consisting of H, -SO₂Y and optionally substituted C₁₋₁₀alkyl. Each R⁸ may for instance be independently selected from the group consisting of H and -SO₂Y; such as wherein each R⁸ is -SO₂Y.

u) In aspects and embodiments described herein, where R⁹ is present, it may be selected from the group consisting of H, -SO₂Y and optionally substituted C₁₋₁₀alkyl. R⁹ may for instance be selected from the group consisting of H and -SO₂Y; such as wherein R⁹ is -SO₂Y.

v) Each R¹₀, where present, may be independently selected from the group consisting of halo, C₁₋₄alkyl, C₁₋₄haloalkyl and -OSO₂Y. Typically, each R¹₀, where present, is independently selected from CF, CCH₃, CF₃ and -OSO₂Y.

w) Typically, in aspects and embodiments of the invention s is 0. Typically, in aspects and embodiments of the invention t is 0. Both s and t may be 0.
x) In particular embodiments of the above aspects and embodiments, at least two, and optionally three, of \( R^2, R^3, R^4 \) and \( R^5 \) are \(-\text{OSO}_2Y\). For instance, in embodiments, each of \( R^2, R^3, R^4 \) and \( R^5 \) is \(-\text{OSO}_2Y \) and \( R^6 \) is \( H \). Alternatively, in embodiments, \( R^2, R^3 \) and \( R^5 \) are \(-\text{OSO}_2Y \), and \( R^4 \) and \( R^6 \) are each \( H \).

y) In the present invention, \( A \) may typically be \( O \) or \( S \), and in some embodiments \( O \).

z) In embodiments, \( B \) may be \( O \) or \( S \), typically \( O \). In typical embodiments, \( A \) and \( B \) are each \( O \).

aa) In embodiments wherein is a 6-membered aryl or heteroaryl ring, \( C \) may be selected from the group consisting of \( \text{CH} \) and \( \text{C}(\text{R}^{10}) \), wherein \( R^{10} \) is selected from the group consisting of halo, \( \text{C}_1\text{,}_4\text{alkyl} \) and \( \text{C}_1\text{,}_4\text{haloalkyl} \); optionally wherein \( R^{10} \) is halo, \( \text{CF} \) or \( \text{CCH}_3 \). Additionally or alternatively, in such embodiments, \( E \) may be selected from the group consisting of \( \text{CH} \) and \( \text{C}(\text{R}^{10}) \), wherein \( R^{10} \) is selected from the group consisting of halo, \( \text{C}_1\text{,}_4\text{alkyl} \) and \( \text{C}_1\text{,}_4\text{haloalkyl} \), such as wherein \( R^{10} \) is halo, \( \text{CF} \) or \( \text{CCH}_3 \). Additionally or alternatively to the definitions of \( C \) and \( / \) or \( E \) described above, \( D \) may be \( \text{CH} \) or \( \text{C}(\text{R}^{10}) \), wherein \( R^{10} \) is selected from the group consisting of halo, \( \text{C}_1\text{,}_4\text{alkyl} \) and \( -\text{OSO}_2Y \); such as wherein \( R^{10} \) is halo, \( \text{CF}, \text{CCH}_3 \), or \( -\text{OSO}_2Y \), e.g. \(-\text{OSO}_2Y \). In embodiments, \( C, D \) and \( E \) may for instance be independently selected from the group consisting of \( \text{CH} \) and \( \text{N} \), typically wherein \( C, D \) and \( E \) are each \( \text{CH} \).

bb) Where \( m \) is present in the formulae of the present invention, it may for instance be 1 or 2, such as 1. Similarly, \( n \) may be 1 or 2, e.g. 1. In embodiments, \( n \) is 2.

cc) In the present invention, \( Y \) may be independently selected from \( \text{H} \) and optionally substituted \( \text{C}_1\text{,}_10\text{alkyl} \); optionally wherein each \( Y \) is independently selected from \( \text{H} \) and \( \text{C}_1\text{,}_4\text{alkyl} \), such as wherein each \( Y \) is \( \text{H} \).

dd) In a particular embodiment, the compound of formula (I) or a pharmaceutically acceptable derivative thereof as described above may be wherein:

- \( A \) and \( B \) are selected independently from \( O \) or \( S \), such as wherein both \( A \) and \( B \) are \( O \);
- \( C, D \) and \( E \) are each \( \text{CH} \);
- \( m \) is 1 or 2;
- \( n \) is 1 or 2;
R¹ is \(-\text{CO}_2\)W;
R², R³, R⁴ and R⁵ are each independently selected from H and \(-\text{OSO}_3\)Y, wherein at least one, and optionally at least 2, of R², R³, R⁴ and R⁵ is \(-\text{SO}_3\)Y;
W is H or optionally substituted C₁₋₆alkyl; and
Y is H.

ee) In the present invention as described herein, formula (I) as described above may alternatively be according to formula (II):

![Diagram](image1)

wherein:
R¹ – R⁶, A, B, m, n are as defined above for embodiment 1) or any further embodiments thereof as described herein.

ff) In the present invention, formula (I) as described herein may be according to formula (III):

![Diagram](image2)

wherein:
R¹ – R⁶ and n are as defined above for embodiment 1) or any further embodiments thereof as described herein.

gg) In typical embodiments, formula (I) is according to formula (III):
wherein:

- $n$ is 1 or 2;
- $R^1$ is $-\text{CO}_2W$, wherein $W$ is H or optionally substituted $\text{C}_{1-6}$alkyl;
- $R^2$, $R^3$ and $R^5$ are each $-\text{OSO}_3\text{H}$; and
- $R^4$ is H or $-\text{OSO}_3\text{H}$.

hh) In embodiments, formula (I) as described herein (e.g. in embodiment l)) above, may be according to formula (IV):

wherein

- $R^1$, $R^4$ and $R^6$, $m$ and $n$ are as defined above for embodiment l) or any further embodiments thereof as described herein. Typically $R^1$ is $\text{CO}_2W$, $R^6$ is H and $R^4$ is H or $-\text{SO}_3\text{H}$

In a further aspect, the invention provides a compound according to any one of the following formulae, or a pharmaceutically acceptable derivative thereof, for use in the treatment of vascular calcification and / or endothelial dysfunction:
The invention also provides the use of a compound of the formulae listed above or pharmaceutically acceptable derivative thereof in a method for manufacturing a medicament for treating vascular calcification and/or endothelial dysfunction is also contemplated.

The invention also provides a method for the treatment of vascular calcification and/or endothelial dysfunction comprising administering a therapeutically effective amount of a compound (i.e., a glycomimetic) according any one of the formulae presented above, or a pharmaceutically acceptable derivative thereof, to a patient (e.g., a patient in need thereof):

The compound or pharmaceutically effective derivative thereof may for instance be selected from the group consisting of:
The compound or pharmaceutically effective derivative thereof may for instance be selected from the group consisting of:

1. 
\[
\begin{align*}
\text{HO}_3\text{SO} & \quad \text{OCOMe} \\
\text{SO}_3\text{H} & \quad \text{OSO}_3\text{H} \\
\text{OSO}_3\text{H} & \quad \text{O} \\
\text{OH} & \quad \text{OSO}_3\text{H} \\
\end{align*}
\]

2. 
\[
\begin{align*}
\text{HO}_3\text{SO} & \quad \text{OSO}_3\text{H} \\
\text{OSO}_3\text{H} & \quad \text{O} \\
\text{OH} & \quad \text{OSO}_3\text{H} \\
\text{OSO}_3\text{H} & \quad \text{O} \\
\end{align*}
\]

3. 
\[
\begin{align*}
\text{HO}_3\text{SO} & \quad \text{OCOMe} \\
\text{SO}_3\text{H} & \quad \text{OSO}_3\text{H} \\
\text{OSO}_3\text{H} & \quad \text{O} \\
\text{OH} & \quad \text{OSO}_3\text{H} \\
\end{align*}
\]

4. 
\[
\begin{align*}
\text{HO}_3\text{SO} & \quad \text{OSO}_3\text{H} \\
\text{OSO}_3\text{H} & \quad \text{O} \\
\text{OH} & \quad \text{OSO}_3\text{H} \\
\text{OSO}_3\text{H} & \quad \text{O} \\
\end{align*}
\]
In a further aspect, the invention provides a pharmaceutical composition comprising a compound or pharmaceutically acceptable derivative thereof according to any aspect or embodiment disclosed herein, and a pharmaceutically acceptable excipient. In an aspect, the invention thus provides a pharmaceutical composition comprising a compound or pharmaceutically acceptable derivative thereof according to any aspect or embodiment disclosed herein, and a pharmaceutically acceptable excipient for use in the treatment of vascular calcification and / or endothelial dysfunction. For avoidance of doubt, any specific embodiment of the compounds and pharmaceutically acceptable derivatives of the formulae of the invention described herein may be provided in the composition of the invention according to this aspect.

In a further aspect is provided the use of a compound or pharmaceutically acceptable derivative thereof as defined according to any aspect or embodiment disclosed herein, or a pharmaceutically acceptable composition as disclosed herein in the manufacture of a medicament for the treatment of vascular calcification and / or endothelial dysfunction. For avoidance of doubt, any specific embodiment of the compounds and pharmaceutically acceptable derivatives of the formulae of the invention described herein may be provided in the use according to this aspect.

In a further aspect is provided a method for the treatment of vascular calcification and / or endothelial dysfunction in a patient, comprising the step of administering a therapeutically effective amount of a compound or pharmaceutically acceptable derivative thereof as defined according to any aspect or embodiment disclosed herein, or a pharmaceutically acceptable composition as defined herein, to a patient, i.e. a patient in need thereof. For avoidance of doubt, any specific embodiment of the compounds and pharmaceutically acceptable
derivatives of the formulae of the invention described herein may be provided in the method according to this aspect.

In a further aspect of the invention is provided a method of modulating c-Met activity in an endothelial cell comprising contacting the cell with a compound or pharmaceutical derivative thereof as defined according to any aspect or embodiment thereof disclosed herein. Suitably, said method of modulating c-Met activity is not a method of treatment by therapy. Thus, typically, the method is not an in vivo method. For instance, such a method may be an in vitro or ex-vivo method. The endothelial cell is typically a mammalian endothelial cell, preferably a human endothelial cell. Where the method of modulating c-Met activity described above is a method of treatment by therapy, the method suitably comprises contacting the endothelial cell in a patient (suitably wherein a therapeutically effective amount of the compound or pharmaceutically acceptable derivative thereof has been administered to the patient). Typically, the patient is a patient that has been diagnosed with endothelial dysfunction and / or vascular calcification. In suitable embodiments, the patient may suitably be a patient that has not been diagnosed with cancer (particularly metastatic cancer) and / or diabetes. For instance, in suitable embodiments, the method is a method wherein the compound or pharmaceutically acceptable salt thereof has not been prescribed for treatment of cancer and / or diabetes.

Thus, the present invention also provides a method of treating a disease or condition mediated by c-Met in an endothelial cell.

In an aspect, the invention provides a compound as described herein, such as defined in the claims, or a pharmaceutically acceptable salt thereof, per se. The compound may for instance be provided in the form of a solid dosage form, e.g. a salt form, such as a metal salt form.

In the compounds for use, uses and methods described above, the patient may in embodiments suitably be a patient that has not been diagnosed with cancer (particularly metastatic cancer) and / or diabetes.

Further embodiments of the compounds of the present invention

General

Various embodiments of the compounds of formulae (A)-(D) and (I)-(IV) are described in this application. It should also be understood below that where an embodiment of a compound of any of these formulae is further defined (i.e. by reference to the respective substituent groups), the definition also applies to pharmaceutically acceptable derivatives of the respective
compounds. It is intended that features specified in each of these embodiments may be combined with other features specified in other embodiments to provide further embodiments of the invention. The skilled person will also appreciate that any chemically impossible compounds that would result from combining one or more of the embodiments below are not intended to be encompassed within the context of this invention.

**Formulae (A)-(D):**

In the invention, the compounds may be selected from formulae (A) to (D) and pharmaceutically acceptable derivatives thereof.

![Chemical structures](image)

wherein the respective substituent groups may be as defined in any of the aspects and embodiments described herein.

The compounds may be selected from formulae (A) and (B). Alternatively they may be selected from (C) and (D). The compounds are typically of formula (A), but may alternatively be selected from formula (B), (C) or (D).

**Six-membered rings:**

The group represented by \(\text{[structure]}\) is a 6-membered carbocyclic or heterocyclic ring. In typical embodiments, \(\text{[structure]}\) is a 6-membered carbocyclic ring. In alternative embodiments,
is a 6-membered heterocyclic ring. The carbocyclic and / or heterocyclic rings may be saturated or unsaturated. In typical embodiments, the carbocyclic and / or heterocyclic ring is unsaturated. For instance, in suitable embodiments, the carbocyclic and / or heterocyclic ring is aromatic, e.g. each may independently be a 6-membered aryl or heteroaryl ring.

Typically, \( \text{\textbullet} \) is a phenyl ring.

In the invention, the compounds may be selected from formulae (A1) and (B1):

\[
\begin{align*}
\text{J} & \quad \text{E} \quad \text{D} \quad \text{Z} \quad \text{R}^2 \quad \text{R}^3 \\
\text{R}^1
\end{align*}
\]

\[
\begin{align*}
\text{E} & \quad \text{D} \quad \text{Z} \quad \text{R}^2 \quad \text{R}^3 \\
\text{R}^1 \quad \text{J}
\end{align*}
\]

(A1) (B1),

wherein the respective substituent groups may be as defined in any of the aspects and embodiments described herein, e.g. embodiment d) or its sub-embodiments, above. Typically, compounds of the invention are of formula (A1):

\[
\begin{align*}
\text{J} & \quad \text{E} \quad \text{D} \quad \text{Z} \quad \text{R}^2 \quad \text{R}^3 \\
\text{R}^1
\end{align*}
\]

(A1),

wherein the respective substituent groups may be as defined in any of the aspects and embodiments described herein.
In the invention, where \[
\text{\begin{figure}
\includegraphics[width=0.5\textwidth]{cyclic}
\end{figure}}\]
is saturated, the compounds may be selected from formulae (A2) and (B2):

\[
\begin{align*}
\text{(A2):} & \quad \begin{array}{c}
J \quad C \quad R^1 \\
E \quad D \quad Z \quad R^2 \\
\end{array} \\
\text{(B2):} & \quad \begin{array}{c}
E \quad C \quad R^1 \\
J \quad D \quad Z \quad R^2 \\
\end{array}
\end{align*}
\]

wherein

C, D and E are each independently selected from the group consisting of CH\(_2\), CHR\(^{10}\), NH and NR\(^{10}\); and

R\(^{1}\)-R\(^{3}\), R\(^{10}\), J and Z are as defined elsewhere herein.

The compounds may for instance be according to formula (A2):

\[
\begin{align*}
\text{(A2):} & \quad \begin{array}{c}
J \quad C \quad R^1 \\
E \quad D \quad Z \quad R^2 \\
\end{array}
\end{align*}
\]

wherein groups R\(^{1}\)-R\(^{3}\), C-E, J and Z are as defined above.

__Five membered rings:\__

In formulae (A) to (D), the group represented by \[
\text{\begin{figure}
\includegraphics[width=0.2\textwidth]{cyclic}
\end{figure}}\] is a 5-membered carbocyclic or heterocyclic ring. In embodiments \[
\text{\begin{figure}
\includegraphics[width=0.2\textwidth]{cyclic}
\end{figure}}\] is a 5-membered carbocyclic ring. Alternatively, \[
\text{\begin{figure}
\includegraphics[width=0.2\textwidth]{cyclic}
\end{figure}}\] may be a 5-membered heterocyclic ring. The ring may be saturated or unsaturated.
The ring may be a saturated carbocyclic ring, e.g. cyclopentyl. Where \( \pentagon \) is a 5-membered heterocyclic ring, it may be heterocycloalkenyl or a heteroaryl ring. Suitable 5-membered aromatic rings include thiophene. For instance, in embodiments \( \pentagon \) is thienyl. For instance, formulae (C) and (D) may be selected from formulae (C1)-(C2) and (D1)-(D2), respectively:

![Chemical structures](image)

wherein the respective substituent groups are as defined according to any aspect or embodiment described herein.

**J group**

In compounds of the present invention, J may be H, halo, optionally substituted \( \text{C}_{1-10}\text{alkyl} \), optionally substituted \( \text{C}_{3-10}\text{cycloalkyl} \), optionally substituted \( \text{C}_{2-10}\text{alkenyl} \), optionally substituted \( \text{C}_{3-10}\text{cycloalkenyl} \), optionally substituted \( \text{C}_{2-10}\text{alkynyl} \), optionally substituted \( \text{C}_{2-10}\text{heteroalkyl} \), optionally substituted \( \text{C}_{3-10}\text{heterocycloalkyl} \), optionally substituted \( \text{C}_{2-10}\text{heteroalkenyl} \), optionally substituted \( \text{C}_{3-10}\text{heterocycloalkenyl} \), optionally substituted \( \text{C}_{2-10}\text{heteroalkynyl} \), optionally substituted \( \text{C}_{6-14}\text{aryl} \), optionally substituted \( \text{C}_{5-14}\text{heteroaryl} \), or \( R^4 \), wherein Q is as defined in the aspects or embodiments of the invention described above or below.
In embodiments, J may be H, halo, optionally substituted \( \text{C}_{1-10}\text{alkyl} \), optionally substituted \( \text{C}_{2-10}\text{alkenyl} \), optionally substituted \( \text{C}_{2-10}\text{alkynyl} \), optionally substituted \( \text{C}_{2-10}\text{heteroalkyl} \), optionally substituted \( \text{C}_{2-10}\text{heteroalkenyl} \), optionally substituted \( \text{C}_{2-10}\text{heteroalkynyl} \), or

\[
\begin{array}{c}
  R^4 \\
  \text{Q} \\
  R^6 \\
  R^5
\end{array}
\]

In some embodiments, J is H, halo, optionally substituted \( \text{C}_{1-10}\text{alkyl} \), optionally substituted \( \text{C}_{3-10}\text{cycloalkyl} \), optionally substituted \( \text{C}_{2-10}\text{heteroalkyl} \), optionally substituted \( \text{C}_{3-10}\text{heterocycloalkyl} \), or

\[
\begin{array}{c}
  R^4 \\
  \text{Q} \\
  R^6 \\
  R^5
\end{array}
\]

wherein Q and \( R^4-R^6 \) are as defined above or further below.

In some embodiments, J is optionally substituted \( \text{C}_{1-10}\text{alkyl} \), optionally substituted \( \text{C}_{2-10}\text{heteroalkyl} \), or

\[
\begin{array}{c}
  R^4 \\
  \text{Q} \\
  R^6 \\
  R^5
\end{array}
\]

wherein Q and \( R^4-R^6 \) are as defined above or further below. Typically, J is

\[
\begin{array}{c}
  R^4 \\
  \text{Q} \\
  R^6 \\
  R^5
\end{array}
\]

wherein Q and \( R^4-R^6 \) are as defined above or further below.

Preferably, J is

\[
\begin{array}{c}
  R^4 \\
  \text{Q} \\
  R^6 \\
  \text{n}
\end{array}
\]

wherein

\( R^4-R^6 \) are as defined herein above or below according to any aspect or embodiment thereof;

\( B \) is \( \text{NR}^8 \), \( \text{O} \) or \( \text{S} \), wherein \( R^8 \) is \( \text{H} \) or \( \text{C}_{1-6}\text{alkyl} \); and

\( n \) is 1, 2, 3, or 4, preferably 1 or 2, such as 1. Alternatively n may be 2.
**Z group**

In the present invention, Z may be -O-, -N(R^4)-, -S-, or a C\textsubscript{1-6}alkylene or C\textsubscript{2-6}heteroalkylene linker group, wherein the C\textsubscript{1-6}alkylene and C\textsubscript{2-6}heteroalkylene linker groups are each independently optionally substituted with 1 to 3 substituents selected from halo, OH, C\textsubscript{1-6}alkyl, C\textsubscript{1-6}haloalkyl; -OSO\textsubscript{2}H and -NH(SO\textsubscript{2}H), and wherein R\textsuperscript{8} is H or C\textsubscript{1-6}alkyl.

In embodiments, Z is a C\textsubscript{1-6}alkylene linker group optionally substituted with 1 to 3 substituents selected from halo, OH, C\textsubscript{1-6}alkyl, C\textsubscript{1-6}haloalkyl, -OSO\textsubscript{2}H and -NH(SO\textsubscript{2}H). In suitable embodiments, Z is a C\textsubscript{2-6}heteroalkylene linker group optionally substituted with 1 to 3 substituents selected from -OSO\textsubscript{2}H and -NH(SO\textsubscript{2}H). Z may for instance be an unsubstituted C\textsubscript{2-6}alkylene linker group, such as a methylene or ethylene group.

In embodiments, Z is a C\textsubscript{2-6}heteroalkylene linker group optionally substituted with 1 to 3 substituents selected from halo, OH, C\textsubscript{1-6}alkyl, C\textsubscript{1-6}haloalkyl, -OSO\textsubscript{2}H and -NH(SO\textsubscript{2}H); optionally wherein Z is a C\textsubscript{2-6}heteroalkylene linker group. In suitable embodiments, Z is a C\textsubscript{2-6}heteroalkylene linker group optionally substituted with 1 to 3 substituents selected from -OSO\textsubscript{2}H and -NH(SO\textsubscript{2}H). Typically, Z is an unsubstituted C\textsubscript{2-6}heteroalkylene linker group, such as where the heteroatom is O, e.g., -O-CH\textsubscript{2}-. 

**Q group**

In the present invention, Q may be -O-, -N(R^8)-, -S-, or a C\textsubscript{1-6}alkylene or C\textsubscript{2-6}heteroalkylene linker group, wherein the C\textsubscript{1-6}alkylene and C\textsubscript{2-6}heteroalkylene linker groups are each independently optionally substituted with 1 to 3 substituents selected from halo, OH, C\textsubscript{1-6}alkyl, C\textsubscript{1-6}haloalkyl; -OSO\textsubscript{2}H and -NH(SO\textsubscript{2}H), and wherein R\textsuperscript{8} is H or C\textsubscript{1-6}alkyl.

In embodiments, Q is a C\textsubscript{1-6}alkylene linker group optionally substituted with 1 to 3 substituents selected from halo, OH, C\textsubscript{1-6}alkyl, C\textsubscript{1-6}haloalkyl, -OSO\textsubscript{2}H and -NH(SO\textsubscript{2}H). In suitable embodiments, Q is a C\textsubscript{2-6}heteroalkylene linker group optionally substituted with 1 to 3 substituents selected from -OSO\textsubscript{2}H and -NH(SO\textsubscript{2}H). Q may for instance be an unsubstituted C\textsubscript{2-6}alkylene linker group, such as a methylene or ethylene group.

In embodiments, Q is a C\textsubscript{2-6}heteroalkylene linker group optionally substituted with 1 to 3 substituents selected from halo, OH, C\textsubscript{1-6}alkyl, C\textsubscript{1-6}haloalkyl, -OSO\textsubscript{2}H and -NH(SO\textsubscript{2}H). In suitable embodiments, Q is a C\textsubscript{2-6}heteroalkylene linker group optionally substituted with 1 to 3
substituents selected from -OSO$_3$H and -NH(SO$_3$H). Typically, Q is an unsubstituted C$_2$-heteroalkylene linker group, such as wherein the heteroatom is O, e.g. –O-CH$_2$–.

**A and B groups**

In embodiments of the present invention as recited in the respective formulae herein, A and/or B groups may be present. For instance, A and B groups are present in compounds of formula (I) or (II) as defined herein.

In compounds as defined herein, A may be NR$^\text{A}$, O or S, wherein R$^\text{A}$ is H or C$_1$-alkyl. A may suitably be O or S. Alternatively, A may be NR$^\text{A}$ wherein R$^\text{A}$ is H or C$_1$-alkyl. R$^\text{A}$ may for instance be H in such embodiments. Typically, A is O.

In compounds as defined herein, B may be NR$^\text{B}$, O or S, wherein R$^\text{B}$ is H or C$_1$-alkyl. B may suitably be O or S. Alternatively, B may be NR$^\text{B}$ wherein R$^\text{B}$ is H or C$_1$-alkyl. R$^\text{B}$ may for instance be H in such embodiments. Typically, B is O.

Typically, A may be O and B may be O. In embodiments, A may be O and B may be selected from NH, O and S. In another embodiment B may be O and A may be selected from NH, O and S.

**m and n groups**

In compounds of the present invention, m may be 1, 2, 3 or 4, such as 1 or 2.

Typically m may be 1, however, in some embodiments m may be 2.

In compounds of the present invention, n may be 1, 2, 3 or 4, such as 1 or 2.

Typically n may be 2, however in some embodiments n may be 1.

Typically m+n may be 3 or 4, typically 3, such as when m is 2 and n is 1. In other embodiments, m+n may be 3 when m is 1 and n is 2. In embodiments, m+n may be 4.

In compounds of the present invention, m and n may each independently be 1 or 2.

**C, D and E groups**

In compounds of the invention, C, D and E may be present.

In embodiments of the invention, where is aromatic (e.g. compounds of formula A1, B1 and embodiments thereof), C, D and E may each be independently selected from the group consisting of CH, CR$^{10}$ and N, such as selected from CH and CR$^{10}$, wherein R$^{10}$ may be as defined herein above or below.
In embodiments, C is CH or CR\(^{10}\). Alternatively C may be N. Typically C is CH. Where CR\(^{10}\) is present at C, R\(^{10}\) may suitably be halo, C\(_{1,4}\)alkyl or C\(_{1,4}\)haloalkyl, such as halo, CF or CCH\(_3\).

In embodiments, D is CH or CR\(^{10}\). Alternatively D may be N. Typically D is CH. Where CR\(^{10}\) is present at D, R\(^{10}\) may suitably be halo, C\(_{1,4}\)alkyl, C\(_{1,4}\)haloalkyl or -OSO\(_3\)Y; optionally wherein R\(^{10}\) is halo, CF, CCH\(_3\), or -OSO\(_3\)Y, such as -OSO\(_3\)Y, e.g. -OSO\(_3\)H.

In embodiments, E is CH or CR\(^{10}\). Alternatively E may be N. Typically E is CH. Where CR\(^{10}\) is present at E, R\(^{10}\) may suitably be halo, C\(_{1,4}\)alkyl or C\(_{1,4}\)haloalkyl, such as halo, CF or CCH\(_3\).

C, D and E may each independently be selected from CH and N. In embodiments C, D and E may be N. In other embodiments C and E may be CH and D may be N. In typical embodiments C, D and E are each CH.

In embodiments of the invention, where \(\text{O}_2\text{H}\) is not aromatic (e.g. compounds of formula A2, B2 and embodiments thereof), e.g. saturated, C, D and E may each be independently selected from the group consisting of CH\(_2\), CHR\(^{10}\), NR\(^{10}\), and NH, wherein R\(^{10}\) may be as defined herein above or below, such as selected from CH\(_2\) or CHR\(^{10}\). In such embodiments, C may be CH\(_2\) or CHR\(^{10}\). Alternatively C may be NH or NR\(^{10}\), e.g. NH. Typically, in such embodiments, C is CH\(_2\). Where R\(^{10}\) is present, e.g. at position C as in the case of CHR\(^{10}\), R\(^{10}\) may suitably be halo, C\(_{1,4}\)alkyl or C\(_{1,4}\)haloalkyl, such as halo, CF or CCH\(_3\). In embodiments, D is CH\(_2\) or CHR\(^{10}\). Alternatively D may be NH or NR\(^{10}\), e.g. NH. Typically, in such embodiments, D is CH\(_2\). Where R\(^{10}\) is present at D, e.g. as in the case of CHR\(^{10}\), R\(^{10}\) may suitably be halo, C\(_{1,4}\)alkyl, C\(_{1,4}\)haloalkyl or -OSO\(_3\)Y; optionally wherein R\(^{10}\) is halo, CF, CCH\(_3\), or -OSO\(_3\)Y, such as -OSO\(_3\)Y, e.g. -OSO\(_3\)H. In such embodiments, E may be CH\(_2\) or CHR\(^{10}\). Alternatively E may be NH or NR\(^{10}\), e.g. NH. Typically, in such embodiments, E is CH\(_2\). Where R\(^{10}\) is present, e.g. at position E as in the case of CHR\(^{10}\), R\(^{10}\) may suitably be halo, C\(_{1,4}\)alkyl or C\(_{1,4}\)haloalkyl, such as halo, CF or CCH\(_3\).

C, D and E may each independently be selected from CH\(_2\) and NH. In embodiments C, D and E may be NH. In other embodiments C and E may be CH\(_2\) and D may be NH. In typical embodiments C, D and E are each CH\(_2\).

**Group R\(^{1}\)**

R\(^{1}\) may be -CO\(_2\)W or a bioisostere of a carboxyl group. Typically, R\(^{1}\) is -CO\(_2\)W. Suitable bioisosteres may, for instance be, heterocyclic bioisosteres, e.g. tetrazole. Others may be acyclic bioisosteres, e.g. amides, thioamides, ureas.
W may be as defined herein above or below. W may be H, optionally substituted C_{1-10}alkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{3-10}cycloalkeny1, optionally substituted C_{2-10}alkynyl, optionally substituted C_{2-10}heteroalkyl, optionally substituted C_{3-10}heterocycloalkyl, optionally substituted C_{2-10}heteroalkenyl, optionally substituted C_{3-10}heterocycloalkeny1, optionally substituted C_{2-10}heteroalkynyl, optionally substituted C_{6-14}ary1 or optionally substituted C_{5-14}heteroary1.

Suitably, W is H, or optionally substituted C_{1-10}alkyl, C_{3-10}cycloalkyl, C_{2-10}heteroalkyl, C_{3-10}heterocycloalkyl, C_{6-14}ary1 or C_{5-14}heteroary1. In some embodiments, W is H, or optionally substituted C_{1-10}alkyl or C_{3-10}cycloalkyl. In other embodiments, W is H, or optionally substituted C_{1-6}alkyl, e.g. C_{1-6}alkyl.

In embodiments, W is H, optionally substituted C_{1-10}alkyl, or optionally substituted C_{2-10}heteroalkyl. For instance, W may be H or optionally substituted C_{1-10}alkyl, such as wherein W is H or C_{1-6}alkyl. In yet further embodiments, W may preferably be H or methyl. W may be H. W may be methyl.

Typically, where W is not H, it is not substituted. In embodiments, where the W group is not H and is substituted, the substituent(s) may be selected from the substituent groups described generally below, or may for instance be halo, e.g. fluoro.

**R^2, R^3, R^4 and R^5 groups**

In the compounds of the invention, R^2 and R^3 are each independently H, -OR^7 or -NH(R^7), wherein each R^7 is independently selected from the group consisting of H, -SO_3Y, optionally substituted C_{1-10}alkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{3-10}cycloalkeny1, optionally substituted C_{2-10}alkynyl, optionally substituted C_{2-10}heteroalkyl, optionally substituted C_{3-10}heterocycloalkyl, optionally substituted C_{2-10}heteroalkenyl, optionally substituted C_{3-10}heterocycloalkeny1, optionally substituted C_{2-10}heteroalkynyl, optionally substituted C_{6-14}ary1 and optionally substituted C_{5-14}heteroary1, wherein at least one of R^2 and R^3 is selected from -OSO_3Y and -NH(SO_3Y). Y may be as defined herein above or further below. Typically, in such instances, Y is H.

In this regard, it is an essential feature of the invention that at least R^2 or R^3 is selected from -OSO_3Y and -NH(SO_3Y). Preferably, both R^2 and R^3 are selected from -OSO_3Y and -NH(SO_3Y), particularly -OSO_3Y, e.g. -SO_3H. Thus, when R^2 and R^3 are described independently below, the skilled person will understand that at least one of R^2 and R^3 must be selected from -OSO_3Y and -NH(SO_3Y).
R² may thus, in embodiments, be -NH(R⁷) or -OR⁷, preferably –OR⁷. Alternatively, R² may be H. In embodiments, R² is -OR⁷ or -NH(R⁷) wherein said R⁷ is -SO₃Y, e.g. wherein R² is -OSO₃Y.

R³ may thus, in embodiments, be -NH(R⁷) or -OR⁷, preferably –OR⁷. Alternatively, R³ may be H. In embodiments, R³ is -OR⁷ or -NH(R⁷) wherein said R⁷ is -SO₃Y, e.g. wherein R³ is -OSO₃Y.

For instance, R² and R³ may be selected independently from -OSO₃Y and -NH(SO₃Y), such as wherein both R² and R³ are -OSO₃Y (preferably wherein Y is H).

In the compounds of the invention, R⁴ and R⁵ may each be independently H, -OR⁸ or -NH(R⁸), wherein each R⁸ is independently selected from the group consisting of H, -SO₃Y, optionally substituted C₁₋₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₂₋₁₀heteroalkyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₂₋₁₀heterocycloalkenyl, optionally substituted C₅₋₁₄aryl and optionally substituted C₅₋₁₄heteroaryl. Y is as defined herein above or below.

R⁴ may thus, in embodiments, be -OR⁸ or -NH(R⁸), preferably –OR⁸. Alternatively, R⁴ may be H. In embodiments, R⁴ is -OR⁸ or -NH(R⁸) wherein said R⁸ is -SO₃Y, e.g. wherein R⁴ is -OSO₃Y.

R⁵ may thus, in embodiments, be -OR⁸ or -NH(R⁸), preferably –OR⁸. Alternatively, R⁵ may be H. In embodiments, R⁵ is -OR⁸ or -NH(R⁸) wherein said R⁸ is -SO₃Y, e.g. wherein R⁵ is -OSO₃Y. R⁴ and R⁵ may for instance each be independently selected from H, or -SO₃Y.

In embodiments, at least one of R⁴ and R⁵ is selected from -OSO₃Y and -NH(SO₃Y), such as wherein R⁴ and R⁵ are each independently selected from -OSO₃Y and -NH(SO₃Y), e.g. wherein both R⁴ and R⁵ are -OSO₃Y.

In embodiments, at least two, and optionally three, of R², R³, R⁴ and R⁵ are -OSO₃Y. In some embodiments, R², R³ and R⁵ may be -SO₃Y whereas R⁴ may be H, wherein Y may be optionally substituted C₁₋₁₀alkyl, C₃₋₁₀cycloalkyl, C₂₋₁₀heteroalkyl or C₃₋₁₀heterocycloalkyl. In some embodiments, each of R², R³, R⁴ and R⁵ is -OSO₃Y.

In some embodiments, R² ≠ R³. Similarly, in some embodiments, R⁴ ≠ R⁵. In further embodiments, R² ≠ R³ and R⁴ ≠ R⁵. In preferred embodiments, R²=R³. In some embodiments, R⁴ ≠ H.
**R^6 groups**

R^6 is H, -CH₂OR⁹ or -CH₂NH(R⁹), wherein R⁹ is independently selected from the group consisting of H, -SO₃Y, optionally substituted C₁₋₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₂₋₁₀heteroalkyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₂₋₁₀heterocycloalkenyl, optionally substituted C₂₋₁₀heteroalkynyl, optionally substituted C₆₋₁₄aryl and optionally substituted C₅₋₁₄heteroaryl.

R^6 may thus in embodiments be -CH₂OR⁹ or -CH₂NH(R⁹), preferably -CH₂OR⁹. Alternatively, R^6 is typically H.

In embodiments, each of R^6, R³, R⁴ and R⁵ is -OSO₃Y and R⁶ is H. Alternatively, R², R³ and R⁵ may be -OSO₃Y, and R⁴ and R⁶ may each be H.

**R⁷ groups**

R⁷ groups may be present at R² and / or R⁴. Where present, each R⁷ group is, in embodiments of the invention, independently selected from the group consisting of H, -SO₃Y, optionally substituted C₁₋₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₂₋₁₀heteroalkyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkenyl, optionally substituted C₂₋₁₀heteroalkynyl, optionally substituted C₆₋₁₄aryl and optionally substituted C₅₋₁₄heteroaryl.

In embodiments, each R⁷ is independently selected from the group consisting of H, -SO₃Y, optionally substituted C₁₋₁₀alkyl, optionally substituted C₂₋₁₀heteroalkyl, optionally substituted C₆₋₁₄aryl and optionally substituted C₅₋₁₄heteroaryl. Each R⁷ may for instance be independently selected from the group consisting of H, -SO₃Y and optionally substituted C₁₋₁₀alkyl, such as wherein each R⁷ is independently selected from the group consisting of H and -SO₃Y, e.g. wherein each R⁷ is -SO₃Y.

The optional substituents of R⁷ groups may be as described in the general substituents section below. In embodiments, optional R⁷ substituents may for instance be selected from OH, NH₂, halo, C₁₋₄alkyl, C₁₋₄haloalkyl. The optionally substituted C₁₋₁₀alkyl may be unsubstituted, e.g. C₁₋₆alkyl.
**R^8 groups**

In the compounds of formula (A) to (D), or pharmaceutically acceptable derivatives thereof, each R^8 may be independently selected from the group consisting of H, -SO_2Y, optionally substituted C_{1-10}alkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted C_{2-10}alkynyl, optionally substituted C_{2-10}heteroalkyl, optionally substituted C_{3-10}heterocycloalkyl, optionally substituted C_{2-10}heteroalkenyl, optionally substituted C_{3-10}heterocycloalkenyl, optionally substituted C_{2-10}heteroalkynyl, optionally substituted C_{6-14}aryl and optionally substituted C_{5-14}heteroaryl.

In embodiments, each R^8 is independently selected from the group consisting of H, -SO_2Y, optionally substituted C_{1-10}alkyl, optionally substituted C_{2-10}heteroalkyl, optionally substituted C_{6-14}aryl and optionally substituted C_{5-14}heteroaryl. Each R^8 may for instance be independently selected from the group consisting of H, -SO_2Y and optionally substituted C_{1-10}alkyl, such as wherein each R^8 is independently selected from the group consisting of H and -SO_2Y, e.g. wherein each R^8 is -SO_2Y. The optionally substituted C_{1-10}alkyl may be unsubstituted, e.g. C_{1-6}alkyl.

**R^9 groups**

In the compounds of formula (A) to (D), or pharmaceutically acceptable derivatives thereof, each R^9 may be independently selected from the group consisting of H, -SO_2Y, optionally substituted C_{1-10}alkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{3-10}cycloalkenyl, optionally substituted C_{2-10}alkynyl, optionally substituted C_{2-10}heteroalkyl, optionally substituted C_{3-10}heterocycloalkyl, optionally substituted C_{2-10}heteroalkenyl, optionally substituted C_{3-10}heterocycloalkenyl, optionally substituted C_{2-10}heteroalkynyl, optionally substituted C_{6-14}aryl and optionally substituted C_{5-14}heteroaryl.

In embodiments, each R^9 is independently selected from the group consisting of H, -SO_2Y, optionally substituted C_{1-10}alkyl, optionally substituted C_{2-10}heteroalkyl, optionally substituted C_{6-14}aryl and optionally substituted C_{5-14}heteroaryl. Each R^9 may for instance be independently selected from the group consisting of H, -SO_2Y and optionally substituted C_{1-10}alkyl, such as wherein each R^9 is independently selected from the group consisting of H and -SO_2Y, e.g. wherein each R^9 is -SO_2Y. The optionally substituted C_{1-10}alkyl may be unsubstituted, e.g. C_{1-6}alkyl.

**R^10 groups**

In embodiments of the above aspects or embodiments thereof, each R^{10}, where present, may be independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}haloalkyl, -OSO_2Y
and –NH(SO$_3$Y). Each R$^{10}$, where present, may, for instance, be independently selected from the group consisting of halo, C$_{1-4}$alkyl, C$_{1-4}$haloalkyl and -OSO$_3$Y. Each R10 may be halo, e.g. F, Cl, Br or I. Each R$^{10}$ may be C$_{1-4}$haloalkyl, e.g. CF or CF$_3$. Suitably, R$^{10}$ may be –SO$_3$Y, wherein Y is as described herein above or below, e.g. -SO$_3$H. Each R$^{10}$, where present, may be independently selected from CF, CCH$_3$, CF$_3$ and –OSO$_3$Y, e.g. -SO$_3$H. Typically, where an R$^{10}$ group is present, only 1 R$^{10}$ group is present, e.g. wherein s is 1 or t is 1. Typically R$^{10}$ is not present. Thus, these embodiments for R$^{10}$ may apply to any embodiment of C, D and or E recited herein above, or below, e.g. as claimed.

**s and t groups**

s may be an integer selected from 0-3. Typically s is 0. s may, however be 1. s may be 2. s may alternatively be 3.

Similarly, t may be an integer selected from 0-2. Typically t is 0. t may, however be 1. Alternatively, t may be 2.

**Y group**

Group Y may be H, optionally substituted C$_{1-10}$alkyl, optionally substituted C$_{3-10}$cycloalkyl, optionally substituted C$_{2-10}$alkenyl, optionally substituted C$_{3-10}$cycloalkenyl, optionally substituted C$_{2-10}$alkynyl, optionally substituted C$_{2-10}$heteroalkyl, optionally substituted C$_{3-10}$heterocycloalkyl, optionally substituted C$_{2-10}$heteroalkenyl, optionally substituted C$_{3-10}$heterocycloalkenyl, optionally substituted C$_{2-10}$heteroalkynyl, optionally substituted C$_{6-14}$aryl or optionally substituted C$_{5-14}$heteroaryl. In embodiments, Y may be optionally substituted C$_{1-10}$alkyl, C$_{3-10}$cycloalkyl, C$_{2-10}$heteroalkyl or C$_{3-10}$heterocycloalkyl. In some embodiments, Y may be C$_{1-10}$alkyl or C$_{3-10}$cycloalkyl. In further embodiments, Y may be C$_{2-10}$heteroalkyl or C$_{3-10}$heterocycloalkyl. In yet further embodiments, Y may be C$_{6-14}$aryl or C$_{5-14}$heteroaryl. More particularly, Y may be H or C$_{1-6}$alkyl. Even more particularly, Y may be H or C$_{1-10}$alkyl, particularly C$_{1-4}$alkyl, for example, methyl.

In typical embodiments, Y is independently selected from H and optionally substituted C$_{1-10}$alkyl; optionally wherein each Y is independently selected from H and C$_{1-6}$alkyl, such as wherein each Y is H.

**Stereochemistry**

In some embodiments, the stereochemistry of the centre to which R$^2$ is bonded is S. In other embodiments, the stereochemistry of the centre to which R$^2$ is bonded is R. Similarly, in embodiments, the stereochemistry of the centre to which R$^4$ is bonded is S. In other embodiments, the stereochemistry of the centre to which R$^4$ is bonded is R.
In some embodiments, the stereochemistry of the centres to which $R^2$ and $R^4$ are bonded are both $R$. In other embodiments, the stereochemistry of the centres to which $R^2$ and $R^4$ are bonded are both $S$. In further embodiments the stereochemistry of the centre to which $R^2$ is bonded is $R$ whereas the stereochemistry of the centre to which $R^4$ is bonded is $S$. In yet further embodiments the stereochemistry of the centre to which $R^2$ is bonded is $S$ whereas the stereochemistry of the centre to which $R^4$ is bonded is $R$.

Where \( \text{C} \) is not aromatic, further stereocentres may be present in the ring where the respective $J$, $Z$ and optionally $R^{10}$ groups are bonded to the ring. All enantiomeric and diastereomeric embodiments are intended to encompassed by the present invention. Individual enantiomers / diastereomers are included within the scope of the invention. Mixtures of isomers, e.g. racemic mixtures and / or diastereomeric mixtures may also be provided.

**Substituents**

Optionally substituted groups of the compounds of the invention (e.g. alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, alkylene, alkenylene, heteroalkyl, heterocycloalkyl, heteroalkenyl, heterocycloalkenyl, heteroalkynyl, heteroalkylene, heteroalkenylene, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroaryalkyl or heteroarylheteroalkyl groups, etc.) may be substituted or unsubstituted, for instance unsubstituted. Typically, substitution involves the notional replacement of a hydrogen atom with a substituent group, or two hydrogen atoms in the case of substitution by $=O$.

Where substituents are present, there may, for instance, be from 1 to 6 substituents, depending on the available substituent positions of the group. Typically there will be from 1 to 3 substituents, in embodiments 1 or 2 substituents, such as only 1 substituent.

In such embodiments, the optional substituent(s) is/are independently halogen, $C_{1-6}$haloalkyl (e.g. trihalomethyl, trihaloethyl), $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-N^+(C_{1-6}alkyl)_2O^-$, $-CO_2H$, $-CO_2C_{1-6}alkyl$, $-SO_2H$, $-OSO_3H$, $-OSO_2C_{1-6}alkyl$, $-NHSO_3H$, $-NHSO_3C_{1-6}alkyl$, $-N(C_{1-6}alkyl)SO_3H$, $-N(C_{1-6}alkyl)SO_3C_{1-6}alkyl$, $-SO_2C_{1-6}alkyl$, $-SO_2C_{1-6}alkyl$, $-SO_2C_{1-6}alkyl$, $-SO_2C_{1-6}alkyl$, $-OC(=O)OC_{1-6}alkyl$, $-C(=O)H$, $-C(=O)C_{1-6}alkyl$, $-OC(=O)C_{1-6}alkyl$, $=O$, $-N(C_{1-6}alkyl)_2$, $-C(=O)NH_2$, $-C(=O)N(C_{1-6}alkyl)_2$, $-N(C_{1-6}alkyl)C(=O)O(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)C(=O)N(C_{1-6}alkyl)_2$, $-OC(=O)N(C_{1-6}alkyl)_2$, $-N(C_{1-6}alkyl)C(=O)C_{1-6}alkyl$, $-C(=S)N(C_{1-6}alkyl)_2$, $-N(C_{1-6}alkyl)C(=S)C_{1-6}alkyl$, $-SO_2N(C_{1-6}alkyl)_2$, $-N(C_{1-6}alkyl)SO_2C_{1-6}alkyl$, $-N(C_{1-6}alkyl)C(=S)N(C_{1-6}alkyl)_2$, $-N(C_{1-6}alkyl)SO_2N(C_{1-6}alkyl)_2$, $-C_{1-6}alkyl$, $-C_{2-6}$heteroalkyl, $-C_{3-6}$cycloalkyl, $-C_{3-6}$heterocycloalkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$heteroalkenyl, $-C_{3-6}$cycloalkenyl, $-C_{3-6}$heterocycloalkenyl, $-C_{2-6}$alkynyl, $-C_{2-6}$heteroalkynyl.
\(-\text{Z}^\nu\text{-C}_{1,6}\text{alkyl}, \ -\text{Z}^\nu\text{-C}_3\text{cycloalkyl}, \ -\text{Z}^\nu\text{-C}_2,6\text{alkenyl}, \ -\text{Z}^\nu\text{-C}_3\text{cycloalkenyl or } \ -\text{Z}^\nu\text{-C}_{2,6}\text{alkynyl},\) wherein

\(\text{Z}^\nu\) is independently O, S, NH or N(C\(_1,6\)alkyl).

In another embodiment, the optional substituent(s) is/are independently halogen, trihalomethyl, trihaloethyl, -OSO\(_3\)H, -OSO\(_3\)C\(_1,6\)alkyl, -NHSO\(_3\)H, -NHSO\(_3\)C\(_1,6\)alkyl, -N(C\(_1,6\)alkyl)SO\(_3\)H, -N(C\(_1,6\)alkyl)SO\(_3\)C\(_1,6\)alkyl, -OH, -NH\(_2\), -NO\(_2\), -CN, -N\(^+(\text{C}_{1,6}\text{alkyl})_2\)O\(^-\), -CO\(_2\)H, -SOC\(_1,6\)alkyl, -SO\(_2\)C\(_1,6\)alkyl, -C(=O)C\(_1,6\)alkyl, =O, -N(C\(_1,6\)alkyl)\(_2\), -C(=O)NH\(_2\), -C\(_1,6\)alkyl, -C\(_3,6\)cycloalkyl, -C\(_3,6\)heterocycloalkyl, -Z\(^\nu\)C\(_1,6\)alkyl or -Z\(^\nu\)C\(_3,6\)cycloalkyl, wherein Z\(^\nu\) is defined above.

In another embodiment, the optional substituent(s) is/are independently halogen, trihalomethyl, -OH, -CO\(_2\)H, -SO\(_3\)H, -OSO\(_3\)H, -NHSO\(_3\)C\(_1,6\)alkyl, -SOC\(_1,6\)alkyl, -SO\(_2\)C\(_1,6\)alkyl, -C(=O)C\(_1,6\)alkyl, =O, -C\(_1,6\)alkyl, -C\(_3,6\)cycloalkyl, -C\(_3,6\)heterocycloalkyl, -Z\(^\nu\)C\(_1,6\)alkyl or -Z\(^\nu\)C\(_3,6\)cycloalkyl, wherein Z\(^\nu\) is defined above.

In another embodiment, the optional substituent(s) is/are independently halogen, -OH, -CO\(_2\)H or -SO\(_3\)H.

In another embodiment, the optional substituent(s) is/are independently -CO\(_2\)H, -OSO\(_3\)H, e.g. -OSO\(_3\)H.

**Specific compounds**

The invention provides the following specific compounds:

Methyl 5-(2,3-bis(sulfooxy)propoxy)-2-(2,3-bis(sulfooxy)propoxy)benzoate;

2-(2,3-Bis(sulfooxy)propoxy)-5-(2,3-bis(sulfooxy)propoxy)benzoic acid; and

Methyl 5-(2,3-bis(sulfooxy)propoxy)-2-(4-(sulfooxy)butoxy)benzoate;

and pharmaceutically acceptable derivatives thereof.

In embodiments, the invention provides the following specific compounds:

Methyl 5-{((\(R\)))-2,3-bis(sulfooxy)propoxy)-2-{((\(S\))-2,3-bis(sulfooxy)propoxy)benzoate;  
Methyl 5-{((\(R\))-2,3-bis(sulfooxy)propoxy)-2-{((\(R\))-2,3-bis(sulfooxy)propoxy)benzoate;  
Methyl 5-{((\(S\))-2,3-bis(sulfooxy)propoxy)-2-{((\(R\))-2,3-bis(sulfooxy)propoxy)benzoate;  
Methyl 5-{((\(S\))-2,3-bis(sulfooxy)propoxy)-2-{((\(R\))-2,3-bis(sulfooxy)propoxy)benzoate;
2-((R)-2,3-Bis(sulfooxy)propoxy)-5-((S)-2,3-bis(sulfooxy)propoxy)benzoic acid;
2-((R)-2,3-Bis(sulfooxy)propoxy)-5-((R)-2,3-bis(sulfooxy)propoxy)benzoic acid;
2-((S)-2,3-Bis(sulfooxy)propoxy)-5-((S)-2,3-bis(sulfooxy)propoxy)benzoic acid;
2-((S)-2,3-Bis(sulfooxy)propoxy)-5-((R)-2,3-bis(sulfooxy)propoxy)benzoic acid;
Methyl (R)-5-(2,3-bis(sulfooxy)propoxy)-2-(4-(sulfooxy)butoxy)benzoate; and
Methyl (S)-5-(2,3-bis(sulfooxy)propoxy)-2-(4-(sulfooxy)butoxy)benzoate;
and pharmaceutically acceptable derivatives thereof.

In embodiments, the invention provides the following specific compounds:
Methyl 5-((R)-2,3-bis(sulfooxy)propoxy)-2-((S)-2,3-bis(sulfooxy)propoxy)benzoate;
2-((R)-2,3-Bis(sulfooxy)propoxy)-5-((S)-2,3-bis(sulfooxy)propoxy)benzoic acid;
Methyl (R)-5-(2,3-bis(sulfooxy)propoxy)-2-(4-(sulfooxy)butoxy)benzoate; and
Methyl (S)-5-(2,3-bis(sulfooxy)propoxy)-2-(4-(sulfooxy)butoxy)benzoate;
and pharmaceutically acceptable derivatives thereof.

**Chemical Groups**

**Halo**

The term “halogen” (or “halo”) includes fluorine, chlorine, bromine and iodine.

**Alkyl, alkyne, alkenyl, alkynyl, cycloalkyl etc.**

The terms “alkyl”, “alkylene”, “alkenyl” or “alkynyl” are used herein to refer to both straight and branched chain acyclic forms. Cyclic analogues thereof are referred to as cycloalkyl, etc.

The term “alkyl” includes monovalent, straight or branched, saturated, acyclic hydrocarbyl groups. In embodiments, alkyl is C_{1-10}alkyl, in another embodiment C_{1-6}alkyl, in another embodiment C_{1-4}alkyl, such as methyl, ethyl, n-propyl, i-propyl or t-butyl groups.

The term “cycloalkyl” includes monovalent, saturated, cyclic hydrocarbyl groups. In one embodiment cycloalkyl is C_{3-10}cycloalkyl, in another embodiment C_{3-6}cycloalkyl such as cyclopentyl and cyclohexyl.

The term “alkoxy” means alkyl-O-.

The term “alkylamino” means alkyl-NH-. 
The term “alkylthio” means alkyl-S(O)\textsubscript{t}, wherein t is defined below.

The term “haloalkyl” refers to an alkyl group wherein at least one H is replaced by a halo group. In embodiments, haloalkyl refers to substitution by from 1-3 halo groups, e.g. 1. Examples include trihalomethyl, trihaloethyl, e.g. trifluoromethyl, etc.

The term “alkenyl” includes monovalent, straight or branched, unsaturated, acyclic hydrocarbyl groups having at least one carbon-carbon double bond and, in one embodiment, no carbon-carbon triple bonds. In one embodiment alkenyl is C\textsubscript{2-10}alkenyl, in another embodiment C\textsubscript{2-6}alkenyl, in another embodiment C\textsubscript{2-4}alkenyl.

The term “cycloalkenyl” includes monovalent, partially unsaturated, cyclic hydrocarbyl groups having at least one carbon-carbon double bond and, in one embodiment, no carbon-carbon triple bonds. In embodiments, cycloalkenyl is C\textsubscript{3-10}cycloalkenyl, in another embodiment C\textsubscript{5-10}cycloalkenyl, e.g. cyclohexenyl or benzocyclohexyl.

The term “alkynyl” includes monovalent, straight or branched, unsaturated, acyclic hydrocarbyl groups having at least one carbon-carbon triple bond and, in one embodiment, no carbon-carbon double bonds. In one embodiment, alkynyl is C\textsubscript{2-10}alkynyl, in another embodiment C\textsubscript{2-6}alkynyl, in another embodiment C\textsubscript{2-4}alkynyl.

The term “alkylene” includes divalent, straight or branched, saturated, acyclic hydrocarbyl groups. In one embodiment alkyene is C\textsubscript{1-10}alkylene, in another embodiment C\textsubscript{1-6}alkylene, in another embodiment C\textsubscript{1-4}alkylene, such as methylene, ethylene, n-propylene, i-propylene or t-butylene groups.

The term “alkylene” includes divalent, straight or branched, unsaturated, acyclic hydrocarbyl groups having at least one carbon-carbon double bond and, in one embodiment, no carbon-carbon triple bonds. In one embodiment alkenylene is C\textsubscript{2-10}alkenylene, in another embodiment C\textsubscript{2-6}alkenylene, in another embodiment C\textsubscript{2-4}alkenylene.

**Heteroalkyl, etc.**

The term “heteroalkyl” includes alkyl groups in which up to three carbon atoms, in one embodiment up to two carbon atoms, in another embodiment one carbon atom, are each replaced independently by O, S(O)\textsubscript{t} or N, provided at least one of the alkyl carbon atoms remains. The heteroalkyl group may be C-linked or hetero-linked, i.e. it may be linked to the remainder of the molecule through a carbon atom or through O, S(O)\textsubscript{t} or N, wherein t is defined below.

The term “heterocycloalkyl” includes cycloalkyl groups in which up to three carbon atoms, in one embodiment up to two carbon atoms, in another embodiment one carbon atom, are each
replaced independently by O, S(O)₂, or N, provided at least one of the cycloalkyl carbon atoms remains. Examples of heterocycloalkyl groups include oxiranyl, thiaranyl, aziridinyl, oxetanyl, thiatripyridinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, 1,4-dioxanyl, 1,4-oxathianyl, morpholinyl, 1,4-dithianyl, piperazinyl, 1,4-azathianyl, oxepanyl, thiepanyl, azepanyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazaepanyl, 1,4-dithiepanyl, 1,4-thieazepanyl and 1,4-diazepanyl. The heterocycloalkyl group may be C-linked or N-linked, i.e. it may be linked to the remainder of the molecule through a carbon atom or through a nitrogen atom.

The term “heteroalkenyl” includes alkenyl groups in which up to three carbon atoms, in one embodiment up to two carbon atoms, in another embodiment one carbon atom, are each replaced independently by O, S(O)₂, or N, provided at least one of the alkenyl carbon atoms remains. The heteroalkenyl group may be C-linked or hetero-linked, i.e. it may be linked to the remainder of the molecule through a carbon atom or through O, S(O)₂ or N.

The term “heterocycloalkenyl” includes cycloalkenyl groups in which up to three carbon atoms, in one embodiment up to two carbon atoms, in another embodiment one carbon atom, are each replaced independently by O, S(O)₂, or N, provided at least one of the cycloalkenyl carbon atoms remains. Examples of heterocycloalkenyl groups include 3,4-dihydro-2H-pyranyl, 5-6-dihydro-2H-pyranyl, 2H-pyranyl, 1,2,3,4-tetrahydropyridinyl and 1,2,5,6-tetrahydropyridinyl. The heterocycloalkenyl group may be C-linked or N-linked, i.e. it may be linked to the remainder of the molecule through a carbon atom or through a nitrogen atom.

The term “heteroalkynyl” includes alkynyl groups in which up to three carbon atoms, in one embodiment up to two carbon atoms, in another embodiment one carbon atom, are each replaced independently by O, S(O)₂, or N, provided at least one of the alkynyl carbon atoms remains. The heteroalkynyl group may be C-linked or hetero-linked, i.e. it may be linked to the remainder of the molecule through a carbon atom or through O, S(O)₂ or N.

The term “heteroalkylene” includes alkenylene groups in which up to three carbon atoms, in one embodiment up to two carbon atoms, in another embodiment one carbon atom, are each replaced independently by O, S(O)₂, or N, provided at least one of the alkenylene carbon atoms remains.

The term “heteroalkenylene” includes alkynylene groups in which up to three carbon atoms, in one embodiment up to two carbon atoms, in another embodiment one carbon atom, are each replaced independently by O, S(O)₂, or N, provided at least one of the alkenylene carbon atoms remains.
**Aryl**

The term “aryl” includes monovalent, aromatic, cyclic hydrocarbyl groups, such as phenyl or naphthyl (e.g. 1-naphthyl or 2-naphthyl). In general, the aryl groups may be monocyclic or polycyclic fused ring aromatic groups. Preferred aryl groups are \( \text{C}_6-\text{C}_{14}\)aryl.

Other examples of aryl groups are monovalent derivatives of aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, chrysene, coronene, fluoranthene, fluorene, as-indacene, s-indacene, indene, naphthalene, ovalene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene and rubicene.

The term “arylalkyl” means alkyl substituted with an aryl group, e.g. benzyl.

**Heteroaryl**

The term “heteroaryl” includes aryl groups in which one or more carbon atoms are each replaced by heteroatoms independently selected from O, S, N and NR\(^N\), where R\(^N\) is defined below (and in one embodiment is H or alkyl (e.g. C\(_{1-6}\)alkyl)).

In general, the heteroaryl groups may be monocyclic or polycyclic (e.g. bicyclic) fused ring heteroaromatic groups. Typically, heteroaryl groups contain 5-14 ring members (preferably 5-10 members) wherein 1, 2, 3 or 4 ring members are independently selected from O, S, N and NR\(^N\). In one embodiment, a heteroaryl group may be 5, 6, 9 or 10 membered, e.g. 5-membered monocyclic, 6-membered monocyclic, 9-membered fused-ring bicyclic or 10-membered fused-ring bicyclic.

Monocyclic heteroaromatic groups include heteroaromatic groups containing 5-6 ring members wherein 1, 2, 3 or 4 ring members are independently selected from O, S, N or NR\(^N\).

In one embodiment, 5-membered monocyclic heteroaryl groups contain 1 ring member which is an -NR\(^N\)- group, an -O- atom or an -S- atom and, optionally, 1-3 ring members (e.g. 1 or 2 ring members) which are =N- atoms (where the remainder of the 5 ring members are carbon atoms).

Examples of 5-membered monocyclic heteroaryl groups are pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1,2,3 triazolyl, 1,2,4 triazolyl, 1,2,3 oxadiazolyl, 1,2,4 oxadiazolyl, 1,2,5 oxadiazolyl, 1,3,4 oxadiazolyl, 1,3,4 thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5 triazinyl, 1,2,4 triazinyl, 1,2,3 triazinyl and tetrazolyl.

Examples of 6-membered monocyclic heteroaryl groups are pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl.
In one embodiment, 6-membered monocyclic heteroaryl groups contain 1 or 2 ring members which are =N- atoms (where the remainder of the 6 ring members are carbon atoms). Bicyclic heteroaromatic groups include fused-ring heteroaromatic groups containing 9-14 ring members wherein 1, 2, 3, 4 or more ring members are independently selected from O, S, N or NR^N.

In one embodiment, 9-membered bicyclic heteroaryl groups contain 1 ring member which is an -NR^N- group, an −O- atom or an −S- atom and, optionally, 1-3 ring members (e.g. 1 or 2 ring members) which are =N- atoms (where the remainder of the 9 ring members are carbon atoms).


In one embodiment, 10-membered bicyclic heteroaryl groups contain 1-3 ring members which are =N- atoms (where the remainder of the 10 ring members are carbon atoms).

Examples of 10-membered fused-ring bicyclic heteroaryl groups are quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, 1,5-naphthyridinyl, 2,6-naphthyridinyl, 2,7-naphthyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[4,3-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrido[2,3-d]pyrimidinyl, pyrido[3,4-b]pyrazinyl, pyrimido[5,4-d]pyrimidinyl, pyrazino[2,3-b]pyrazinyl and pyrimido[4,5-d]pyrimidinyl.

The term “heteroarylalkyl” means alkyl substituted with a heteroaryl group.

**General**

Unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, e.g. aryalkyl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

Where reference is made to a carbon atom of an alkyl group or other group being replaced by O, S(O)ₙ or N, what is intended is that:

\[
\begin{array}{c}
\text{CH} \\
\hline
\end{array}
\quad \text{is replaced by} \quad \begin{array}{c}
\text{N} \\
\hline
\end{array}
\]
-CH= is replaced by -N=;
≡C-H is replaced by ≡N; or
-CH₂- is replaced by -O-, -S(O)₂- or -NR₉-.

By way of clarification, in relation to the above mentioned heteroatom containing groups (such as heteroalkyl etc.), where a numerical of carbon atoms is given, for instance C₃₋₆heteroalkyl, what is intended is a group based on C₃₋₆alkyl in which one of more of the 3-6 chain carbon atoms is replaced by O, S(O)₂ or N. Accordingly, a C₃₋₆heteroalkyl group, for example, will contain less than 3-6 chain carbon atoms.

Where mentioned above, R¹ is H, alkyl, cycloalkyl, aryl, heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, -S(O)₂-alkyl, -S(O)₂-aryl or -S(O)₂-heteroaryl. R¹ may, in particular, be H, alkyl (e.g. C₁₋₆alkyl) or cycloalkyl (e.g. C₃₋₆cycloalkyl).

Where mentioned above, t is independently 0, 1 or 2, for example 2. Typically, t is 0.

Where a group has at least 2 positions which may be substituted, the group may be substituted by both ends of an alkylene or heteroalkylene chain to form a cyclic moiety.

Compounds of the invention and and derivatives thereof

As used herein, unless it is detailed otherwise, the terms “compounds of the invention” and “compound of formula (A), (B), (C), (D), (I), etc. include pharmaceutically acceptable derivatives thereof, polymorphs, isomers and isotopically labelled variants thereof. It is thus intended that this applies to all other formulae describing compounds according to the present invention as described herein and their pharmaceutically acceptable derivatives and embodiments thereof disclosed herein.

Pharmaceutically acceptable derivatives

The term “pharmaceutically acceptable derivative” herein includes any pharmaceutically acceptable salt, solvate (e.g. hydrate) or prodrug. In an embodiment, the pharmaceutically acceptable derivative is a pharmaceutically acceptable salt, solvate (e.g. hydrate) of the compound, i.e. compound of formula (I), typically a pharmaceutically acceptable salt thereof. In other words, the term “pharmaceutically acceptable salt” may thus optionally replace the term “pharmaceutically acceptable derivative” as recited anywhere herein.

Pharmaceutically acceptable salts

The term “pharmaceutically acceptable salt” includes a salt prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic or organic acids and bases.
Compounds of the invention that contain basic, e.g. amino, groups are capable of forming pharmaceutically acceptable salts with acids. In one embodiment, pharmaceutically acceptable acid addition salts of the compounds of the invention include, but are not limited to, those of inorganic acids such as hydrohalic acids (e.g. hydrochloric, hydrobromic and hydroiodic acid), sulfuric acid, nitric acid and phosphoric acids. In one embodiment, pharmaceutically acceptable acid addition salts of the compounds of the invention include, but are not limited to, those of organic acids such as aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which include: aliphatic monocarboxylic acids such as formic acid, acetic acid, propionic acid or butyric acid; aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid; dicarboxylic acids such as maleic acid or succinic acid; aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, phenylacetic acid, diphenylacetic acid or triphenylacetic acid; aromatic hydroxyl acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid; and sulfonic acids such as methanesulfonic acid, ethanesulfonic acid or benzenesulfonic acid. Other pharmaceutically acceptable acid addition salts of the compounds of the invention include, but are not limited to, those of glycolic acid, glucuronic acid, furoic acid, glutamic acid, anthranilic acid, salicylic acid, mandelic acid, embonic (pamoic) acid, pantothenic acid, stearic acid, sulfanilic acid, alginic acid and galacturonic acid. Wherein the compound of the invention comprises a plurality of basic groups, multiple centres may be protonated to provide multiple salts, e.g. di- or tri-salts of compounds of the invention. For example, a hydrohalic acid salt of a compound of the invention as described herein may be a monohydrohalide, dihydrohalide or trihydrohalide, etc. In one embodiment, the salts include, but are not limited to those resulting from addition of any of the acids disclosed above. In one embodiment of the compound of the invention, two basic groups form acid addition salts. In a further embodiment, the two addition salt counterions are the same species, e.g. dihydrochloride, dihydrosulphide etc. Typically, the pharmaceutically acceptable salt is may be a hydrochloride salt, such as a dihydrochloride salt.

Compounds of the invention which contain acidic, e.g. carboxyl and / or -SO₃H groups are capable of forming pharmaceutically acceptable salts with bases. In embodiments, pharmaceutically acceptable basic salts of the compounds of the invention include, but are not limited to, metal salts such as alkali metal or alkaline earth metal salts (e.g. sodium, potassium, magnesium or calcium salts) and zinc or aluminium salts. In one embodiment, pharmaceutically acceptable basic salts of the compounds of the invention include, but are not limited to, salts formed with ammonia or pharmaceutically acceptable organic amines or
heterocyclic bases such as ethanolamines (e.g. diethanolamine), benzylamines, N-methylglucamine, amino acids (e.g. lysine) or pyridine.

Hemisalts of acids and bases may also be formed, e.g. hemisulphate salts.

Pharmaceutically acceptable salts of compounds of the invention may be prepared by methods well-known in the art. Thus, in typical embodiments of the aspects and embodiments of the invention, the pharmaceutically acceptable derivative thereof is a base addition salt, such as a metal salt (e.g. a sodium salt), or a salt formed using ammonia, a pharmaceutically acceptable organic amine or a heterocyclic base.


**Prodrugs**

The invention includes prodrugs of the compounds of the invention. Prodrugs are derivatives of compounds of the invention (which may have little or no pharmacological activity themselves), which can, when administered *in vivo*, be converted into compounds of the invention.

Prodrugs can, for example, be produced by replacing functionalities present in the compounds of the invention with appropriate moieties which are metabolized *in vivo* to form a compound of the invention. The design of prodrugs is well-known in the art, as discussed in Bundgaard, *Design of Prodrugs 1985* (Elsevier), *The Practice of Medicinal Chemistry 2003*, 2nd Ed, 561-585 and Leinweber, *Drug Metab. Res. 1987, 18*: 379.

Examples of prodrugs of compounds of the invention are esters and amides of the compounds of the invention. For example, where the compound of the invention contains a carboxylic acid group (-COOH) and / or sulfonic acid group (-OSO₂H) the hydrogen atom of the acid group may be replaced in order to form an ester (e.g. the hydrogen atom may be replaced by C₁₋₈alkyl). Where the compound of the invention contains an alcohol group (-OH), the hydrogen atom of the alcohol group may be replaced in order to form an ester (e.g. the hydrogen atom may be replaced by -C(O)C₁₋₈alkyl. Where the compound of the invention contains a primary or secondary amino group, one or more hydrogen atoms of the amino group may be replaced in order to form an amide (e.g. one or more hydrogen atoms may be replaced by -C(O)C₁₋₈alkyl).
**Amorphous & crystalline forms**

The compounds of the invention may exist in solid states from amorphous through to crystalline forms. All such solid forms are included within the invention, including solvated (e.g. hydrated) and non-solvated forms, as described below.

**Solvates & hydrates**

The compounds of the invention may exist in both unsolvated and solvated solid forms. The term “solvate” includes molecular complexes comprising a compound of the invention and one or more pharmaceutically acceptable solvent molecules such as water or C_{1-6} alcohols, e.g. ethanol. The term “hydrate” means a “solvate” where the solvent is water.

**Isomeric forms**

Compounds of the invention may exist in one or more geometrical, optical, enantiomeric, diastereomeric and tautomeric forms, including, but not limited to, cis- and trans-forms, E- and Z-forms, R-, S- and meso-forms, keto- and enol-forms. All such isomeric forms are included within the invention. The isomeric forms may be in isomerically pure or enriched form, as well as in mixtures of isomers (e.g. racemic or diastereomeric mixtures).

Accordingly, the invention provides, for use in the methods and treatments described herein:

- stereoisomeric mixtures of compounds of the invention;
- a diastereomERICally enriched or diastereomERICally pure isomer of a compound of the invention; or
- an enantiomERICally enriched or enantiomERICally pure isomer of a compound of the invention.

Where appropriate, isomers can be separated from their mixtures by the application or adaptation of known methods (e.g. chromatographic techniques - such as chiral chromatography - , resolution techniques and recrystallization techniques). Where appropriate, isomers can be prepared by the application or adaptation of known methods (e.g. asymmetric synthesis).

**Isotopic labelling**

The invention includes pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.
Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as \(^2\)H and \(^3\)H, carbon, such as \(^1\)C, \(^13\)C and \(^14\)C, chlorine, such as \(^36\)Cl, fluorine, such as \(^18\)F, iodine, such as \(^123\)I and \(^125\)I, nitrogen, such as \(^14\)N and \(^15\)N, oxygen, such as \(^18\)O, \(^17\)O and \(^18\)O, phosphorus, such as \(^32\)P, and sulphur, such as \(^35\)S. Certain isotopically-labelled compounds of the invention, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes \(^3\)H and \(^14\)C are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with positron emitting isotopes, such as \(^11\)C, \(^18\)F, \(^15\)O and \(^13\)N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labelled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

Typically, where the present disclosure refers to a pharmaceutically acceptable derivative of a compound, e.g. a compound of the invention, the derivative may suitably be a pharmaceutically acceptable salt.

**Treatment of Diseases and Conditions**

The compounds of the present invention have advantageously been found to be useful in the treatment of vascular calcification and endothelial dysfunction. Individual enantiomers / diastereomers are proposed for the uses, methods and treatments disclosed herein. Mixtures of isomers, e.g. racemic mixtures and / or diastereomeric mixtures may also be provided, as discussed above under “stereoisomers”.

As described above the inventors propose the use of glycomimetics, particularly small molecule mimetics of heparin/heparan sulfate, for treating endothelial dysfunction and vascular calcification. The inventors in particular propose glycomimetic compounds of formulae A-D (e.g. formulae (I), (II) or (III)) or pharmaceutically acceptable derivatives thereof, as defined in the claims and further described in aspects and embodiments of the invention herein and below, for the treatment of vascular calcification and/or endothelial dysfunction.

In a further aspect, the invention provides a pharmaceutical composition comprising a compound or pharmaceutically acceptable derivative thereof according to any aspect or
embodiment disclosed herein, and a pharmaceutically acceptable excipient. For instance, the invention provides a pharmaceutical composition comprising a compound or pharmaceutically acceptable derivative thereof according to any aspect or embodiment disclosed herein, and a pharmaceutically acceptable excipient for use in the treatment of vascular calcification and/or endothelial dysfunction. For avoidance of doubt, any specific embodiment of the compounds and pharmaceutically acceptable derivatives of the formulae of the invention described herein may be provided in the composition of the invention according to this aspect.

In a further aspect is provided the use of a compound or pharmaceutically acceptable derivative thereof as defined according to any aspect or embodiment disclosed herein, or a pharmaceutically acceptable composition as disclosed herein (e.g. above), in the manufacture of a medicament for the treatment of vascular calcification and/or endothelial dysfunction. For avoidance of doubt, any specific embodiment of the compounds and pharmaceutically acceptable derivatives of the formulae of the invention described herein may be provided in the use according to this aspect.

In a further aspect is provided a method for the treatment of vascular calcification and/or endothelial dysfunction in a patient, comprising the step of administering a therapeutically effective amount of a compound or pharmaceutically acceptable derivative thereof as defined according to any aspect or embodiment disclosed herein, or a pharmaceutically acceptable composition as defined herein, to a patient, i.e. a patient in need thereof. For avoidance of doubt, any specific embodiment of the compounds and pharmaceutically acceptable derivatives of the formulae of the invention described herein may be provided in the method according to this aspect.

The invention further provides a method of modulating c-Met activity in an endothelial cell comprising contacting the cell with a compound or pharmaceutical derivative thereof as defined according to any aspect or embodiment thereof disclosed herein. Suitably, said method of modulating c-Met activity is not a method of treatment by therapy. Thus, typically, the method is not an in vivo method. For instance, such a method may be an in vitro or ex-vivo method. The endothelial cell is typically a mammalian endothelial cell, preferably a human endothelial cell. Where the method of modulating c-Met activity described above is a method of treatment by therapy, the method suitably comprises contacting the endothelial cell in a patient (suitably wherein a therapeutically effective amount of the compound or pharmaceutically acceptable derivative thereof has been administered to the patient).

Typically, the patient is a patient that has been diagnosed with endothelial dysfunction and/or vascular calcification. In suitable embodiments, the patient (i.e. the patient that is receiving, or
whom has been identified to be in need of, the treatment) may suitably be a patient that has not been diagnosed with cancer (e.g. metastatic cancer) and / or diabetes. For instance, in suitable embodiments, the treatment, method or use described above is a treatment, method or use wherein the compound or pharmaceutically acceptable salt thereof has not been prescribed for treatment of cancer and / or diabetes, i.e. wherein the treatment does not comprise prescribing and / or administering a compound of the invention or pharmaceutically acceptable derivative thereof as described herein for treatment of cancer and / or diabetes.

Thus, the present invention also provides a method of treating a disease or condition mediated by c-Met in an endothelial cell, the method comprising the step of administering a therapeutically effective amount of a compound or pharmaceutically acceptable derivative thereof as defined according to any aspect or embodiment disclosed herein, or a pharmaceutically acceptable composition as defined herein, to a patient, i.e. a patient in need thereof. In this regard, the invention also provides a compound of any one of formulae (A)-(D), (I), (II), (III), etc. as defined according to the above aspects and embodiments thereof, or a pharmaceutically acceptable derivative thereof, for use in the treatment of a disease or condition mediated by c-Met in an endothelial cell. Thus, the use of a compound of any one of formulae (A)-(D), (I), (II), (III), etc. as defined according to the above aspects and embodiments thereof, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment of a disease or condition mediated by c-Met in an endothelial cell, is also provided by the present invention. Suitable diseases mediated by c-Met in a endothelial cell include endothelial dysfunction and / or vascular calcification.

The invention further provides a method of modulating c-Met activity in an endothelial cell comprising contacting the cell with a compound or pharmaceutical derivative thereof as defined according to any aspect or embodiment thereof disclosed herein. Suitably, said method of modulating c-Met activity is not a method of treatment by therapy. Thus, typically, the method is not an in vivo method. For instance, such a method may be an in vitro or ex-vivo method. The endothelial cell is typically a mammalian endothelial cell, preferably a human endothelial cell. Where the method of modulating c-Met activity described above is a method of treatment by therapy, the method suitably comprises contacting the endothelial cell in a patient (suitably wherein a therapeutically effective amount of the compound or pharmaceutically acceptable derivative thereof has been administered to the patient). Typically, the patient is a patient that has been diagnosed with endothelial dysfunction and / or vascular calcification.
In accordance with the above method, the invention thus further provides a compound of any one of formulae (A)-(D), (I), (II), (III), etc. as defined according to the above aspects and embodiments thereof, or a pharmaceutically acceptable derivative thereof, for use in a method of modulating c-Met activity in an endothelial cell. Thus, the use of a compound of any one of formulae (A)-(D), (I), (II), (III), etc. as defined according to the above aspects and embodiments thereof, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for a method of modulating c-Met activity in an endothelial cell is also provided by the present invention. Suitable diseases mediated by c-Met in an endothelial cell include endothelial dysfunction and/or vascular calcification. The endothelial cell is typically a mammalian endothelial cell, preferably a human endothelial cell. The method, use or treatment suitably comprises contacting the endothelial cell in a patient (suitably wherein a therapeutically effective amount of the compound or pharmaceutically acceptable derivative thereof has been administered to the patient). Typically, the patient is a patient that has been diagnosed with endothelial dysfunction and/or vascular calcification.

In the compounds for use, uses and methods described above, the patient may in embodiments suitably be a patient that has not been diagnosed with cancer (particularly metastatic cancer) and/or diabetes.

The invention also provides a crystal of HGF bonded to a compound or pharmaceutically acceptable derivative thereof of any of formulae (A) to (D) or embodiments thereof. Such crystals can be used for X-ray diffraction studies of c-Met receptor binding in endothelial cells, e.g. to provide atomic structural information in order to aid rational design of further c-Met receptor modulators.

The treatments/uses/methods discussed above involve treatment of endothelial dysfunction and/or vascular calcification. Suitably, the treatment may be treatment of endothelial dysfunction. In embodiments, the treatment may be treatment of vascular calcification. In embodiments the treatment is for endothelial dysfunction and vascular calcification in a patient. Vascular calcification as referred to above may, in embodiments, be vascular calcification caused by endothelial dysfunction. In alternative embodiments, the vascular calcification is not vascular calcification caused by endothelial dysfunction.

In embodiments, in the compounds for use, the uses, or the methods of treatment defined herein, the treatment of endothelial dysfunction and/or vascular calcification may be a treatment of vascular disease. The vascular disease may for instance be selected from, or be incident in a patient diagnosed with, one or more of the following:
a) cardiovascular diseases, such as angina pectoris, coronary arteriosclerosis (chronic ischemic heart disease, asymptomatic ischemic heart disease and arteriosclerotic cardiovascular disease); heart failure, congestive heart failure, painless ischemic heart disease, myocardial ischemia, myocardial infarction and diseases that arise from thrombotic states in which the coagulation cascade is activated;

b) peripheral vascular diseases, including peripheral arterial disease, such as chronic arterial occlusion including arteriosclerosis, arteriosclerosis obliterans and thromboangiitis obliterans (Buerger's disease), macroangiopathy, microangiopathy, thrombophlebitis, phlebemphraxis, Raynaud's disease, Raynaud's syndrome, CREST syndrome, vascular claudication, disturbance of peripheral circulation function, peripheral circulation disorder, erectile dysfunction, male impotence, female sexual dysfunction, retinopathy, maculopathy, occlusion of the retinal artery, obstruction of central artery of retina, occlusion of retinal vein, neovascular maculopathy, edema, vasculitis, frostbite (cold injury), chilblain, gangrene, hypertension, pulmonary hypertension, portal hypertension, diabetic nephropathy, renal failure, vasospasm, acrocyanosis, ateriovenous fistula, arteriovenous malformations, chronic venous insufficiency, deep vein thrombosis, erythromelalgia, fibromuscular dysplasia, Klippel-Trenauney syndrome, lymphedema, lipedemia, varicose veins and vascular birthmark; and

c) cerebrovascular diseases, such as, migraine, cerebral ischemia, cerebral infarction, cerebral vasospasm and thrombotic stroke.

For instance, the disease or condition mediated by c-Met may be a vascular disease selected from pulmonary hypertension and portal hypertension. In particular, the pulmonary hypertension may be pulmonary arterial hypertension.

**Therapeutic definitions**

As used herein, “treatment” includes curative and prophylactic treatment. As used herein, a “patient” means an animal, preferably a mammal, preferably a human, in need of treatment.

The amount of the compound of the invention administered should be a therapeutically effective amount where the compound or derivative is used for the treatment of a disease or condition and a prophylactically effective amount where the compound or derivative is used for the prevention of a disease or condition.

The term “therapeutically effective amount” used herein refers to the amount of compound needed to treat or ameliorate a targeted disease or condition. The term “prophylactically effective amount” used herein refers to the amount of compound needed to prevent a targeted
disease or condition. The exact dosage will generally be dependent on the patient's status at
the time of administration. Factors that may be taken into consideration when determining
dosage include the severity of the disease state in the patient, the general health of the
patient, the age, weight, gender, diet, time, frequency and route of administration, drug
combinations, reaction sensitivities and the patient's tolerance or response to therapy. The
precise amount can be determined by routine experimentation, but may ultimately lie with the
judgement of the clinician. An effective dose may in instances be from 0.01 mg/kg/day (mass
of drug compared to mass of patient) to 1000 mg/kg/day, e.g. 1 mg/kg/day to 100 mg/kg/day.
Compositions may be administered individually to a patient or may be administered in
combination with other agents, drugs or hormones.

Administration & Formulation

General

For pharmaceutical use, the compounds of the invention may be administered as a
medicament by enteral or parenteral routes, including intravenous, intramuscular,
subcutaneous, transdermal, airway (aerosol), oral, intranasal, rectal, vaginal, urethral and
topical (including buccal and sublingual) administration. The compounds of the invention
should be assessed for their biopharmaceutical properties, such as solubility and solution
stability (across pH), permeability, etc., in order to select the most appropriate dosage form
and route of administration for treatment of the proposed indication.

The compounds of the invention may be administered as crystalline or amorphous products.
The compounds of the invention may be administered alone or in combination with one or
more other compounds of the invention or in combination with one or more other drugs (or as
any combination thereof). Generally, they will be administered as a formulation in association
with one or more pharmaceutically acceptable excipients. The term “excipient” includes any
ingredient other than the compound(s) of the invention which may impart either a functional
(e.g. drug release rate controlling) and/or a non-functional (e.g. processing aid or diluent)
characteristic to the formulations. The choice of excipient will to a large extent depend on
factors such as the particular mode of administration, the effect of the excipient on solubility
and stability and the nature of the dosage form.

Typical pharmaceutically acceptable excipients include:

- diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
- lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or
  polyethylene glycol;
• binders, *e.g.* magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone;

• disintegrants, *e.g.* starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

• absorbants, colorants, flavours and/or sweeteners.


Accordingly, in an embodiment, the present invention provides a pharmaceutical composition comprising a compound of the present invention, *e.g.* a compound of formula (I) or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable excipient.

**Oral administration**

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual, or sublingual administration by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid plugs, solid microparticulates, semi-solid and liquid (including multiple phases or dispersed systems) such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids (*e.g.* aqueous solutions), emulsions or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches.

Formulations suitable for oral administration may also be designed to deliver the compounds the invention in an immediate release manner or in a rate-sustaining manner, wherein the release profile can be delayed, pulsed, controlled, sustained, or delayed and sustained or modified in such a manner which optimises the therapeutic efficacy of the said compounds. Means to deliver compounds in a rate-sustaining manner are known in the art and include slow release polymers that can be formulated with the said compounds to control their release.

Examples of rate-sustaining polymers include degradable and non-degradable polymers that can be used to release the said compounds by diffusion or a combination of diffusion and polymer erosion. Examples of rate-sustaining polymers include hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, sodium carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, xanthum gum, polymethacrylates, polyethylene oxide and polyethylene glycol.
Liquid (including multiple phases and dispersed systems) formulations include emulsions, suspensions, solutions, syrups and elixirs. Such formulations may be presented as fillers in soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, *Expert Opinion in Therapeutic Patents* 2001, 11(6): 981-986.


*Parenteral administration*

The compounds of the invention can be administered parenterally.

The compounds of the invention may be administered directly into the blood stream, into subcutaneous tissue, into muscle, or into an internal organ. Suitable means for administration include intravenous, intraarterial, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial and subcutaneous. Suitable devices for administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous or oily solutions. Where the solution is aqueous, excipients such as sugars (including but not restricted to glucose, mannitol, sorbitol, etc.) salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water (WFI).

Parenteral formulations may include implants derived from degradable polymers such as polyesters (*i.e.* polylactic acid, polylactide, polylactide-co-glycolide, polycapro-lactone, polyhydroxybutyrate), polyorthoesters and polyanhydrides. These formulations may be administered via surgical incision into the subcutaneous tissue, muscular tissue or directly into specific organs.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.
The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of co-solvents and/or solubility-enhancing agents such as surfactants, micelle structures and cyclodextrins.

Inhalation & intranasal administration

The compounds of the invention can be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler, as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, or as nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as L-leucine, mannitol or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(lactic-co-glycolic acid) (PLGA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.
Transdermal administration

Suitable formulations for transdermal application include a therapeutically effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Combination Therapy

The compounds of the invention may be administered alone or may be administered in combination with another compound of the invention or another therapeutic agent (i.e. a different agent to the compound of the invention). Preferably, the compound of the invention and the other therapeutic agent are administered in a therapeutically effective amount.

The compound of the present invention may be administered either simultaneously with, or before or after, the other therapeutic agent. The compound of the present invention may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition.

In one embodiment, the invention provides a product comprising a compound of the invention and another therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy, i.e. in treating endothelial dysfunction and/or vascular calcification. In one embodiment, the therapy is the treatment of a disease or condition mediated by endothelial dysfunction and/or vascular calcification. Products provided as a combined preparation include a composition comprising the compound of the invention and the other therapeutic agent together in the same pharmaceutical composition, or the compound of the invention and the other therapeutic agent in separate form, e.g. in the form of a kit.

In an embodiment, the invention thus provides a pharmaceutical composition comprising a compound of the invention and another therapeutic agent. Optionally, the pharmaceutical composition may comprise a pharmaceutically acceptable excipient, as described above in “Administration and formulation”.

In one embodiment, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention. In one embodiment, the kit comprises means for separately retaining said compositions, such as
a container, divided bottle or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

The kit of the invention may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the invention may typically comprise directions for administration.

In the combination therapies of the invention, the compound of the invention and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the invention and the other therapeutic may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (e.g. in the case of a kit comprising the compound of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, e.g. during sequential administration of the compound of the invention and the other therapeutic agent.

It will be understood that the compounds, compositions and combinations discussed above may be used in the treatments and uses herein described with respect to treating vascular calcification and/or endothelial dysfunction, such as described in the claims.

**General**

The term “comprising” encompasses “including” as well as “consisting” e.g. a composition “comprising” X may consist essentially of X or may consist exclusively of X, or may include something additional e.g. X + Y.

The word “substantially” does not exclude “completely” e.g. a composition which is “substantially free” from Y may be completely free from Y. Where necessary, the word “substantially” may be omitted from the definition of the invention.

The term “about” in relation to a numerical value x is optional and means, for example, x±10 %.

**BRIEF DESCRIPTION OF FIGURES**

Figure 1 includes scheme 1, describing the synthesis of compounds 2 to 5.

Figure 2 includes scheme 2, describing the synthesis of compounds 6 to 8.

Figure 3 includes scheme 3, describing the synthesis of compounds 9 to 11.
Figure 4 includes scheme 4, describing the synthesis of compounds 12 to 13.

Figure 5 includes scheme 5, describing the synthesis of compound 14.

Figure 6 illustrates representative assay data showing the effect of compounds 8 (C1), 11 (C2), 13 (C3) and 14 (C4) on lipid induced NO levels in endothelial cells at 3 h (the left hand line graph shows data corresponding to PAL (bottom line), control (top line), PAL + C2 (line second from top), as well as PAL + C1, PAL + C3 and PAL + C4 (lines clustered next to bottom)) and at 12 h (the left hand line graph shows data corresponding to PAL (bottom line), control (top line), PAL + C2 (line second from top), PAL + C4 (second from bottom), as well as PAL + C3 and PAL + C4 (lines clustered third from bottom)). ***P<0.001 vs control (CT), and #P<0.05, ##P<0.01 and ###P<0.001 vs PAL.

Figure 7 illustrates representative assay data showing the effect of compounds 8 (C1), 11 (C2), 13 (C3) and 14 (C4) on lipid induced Akt, eNOS and NOX4 mRNA expression in endothelial cells relative to PAL. *P<0.05, **P<0.01, ***P<0.001 vs control (CT), and #P<0.05, ##P<0.01 and ###P<0.001 vs PAL.

Figure 8 illustrates representative assay data showing the effect of compounds 8 (C1), 11 (C2), 13 (C3) and 14 (C4) on lipid induced Akt and eNOS phosphorylation in endothelial cells relative to PAL. *P<0.05 vs control (CT), and #P<0.05, ##P<0.01 and ###P<0.001 vs PAL.

Figure 9 illustrates representative assay data showing the effect of compounds 8 (C1), 11 (C2), 13 (C3) and 14 (C4) on lipid induced oxidative stress in endothelial cells relative to PAL. *P<0.05, **P<0.01, ***P<0.001 vs control (CT), and #P<0.05, ##P<0.01 and ###P<0.001 vs PAL.

Figures 10A-D illustrate representative assay data showing the effect of compounds 8 (C1), 11 (C2), 13 (C3) and 14 (C4) on vascular relaxant responses induced by acetylcholine in mouse-descending aorta samples pre-contracted by U46619. Data corresponding to reference compounds are also provided in Figure 10E. *P<0.05, **P<0.01, ***P<0.001 vs control (CT), and #P<0.05, ##P<0.01 and ###P<0.001 vs PAL.

Figure 11 illustrates representative assay data showing the effect of compounds 8 (C1), 11 (C2), 13 (C3) and 14 (C4) on βGP-induced vascular calcification in HPSMCs.

Figure 12 illustrates representative assay data showing the effect of compounds 8 (C1), 11 (C2), 13 (C3) and 14 (C4) on calcium deposition in βGP-induced HPSMCs relative to osteogenic media. ***P<0.001.
Figure 13 illustrates representative assay data showing the effect of compounds 8 (C1), 11 (C2), 13 (C3) and 14 (C4) on ALP activity in βGP-induced HPSMCs. In the line graph, the bottom line at the point of the maximum represents data for Ost + C4, the line second from bottom at the same position represents data for Ost + C1, the hashed line shows data for Ost + C2, the line above the hashed line shows data for Ost + C3 and the upper line shows data for Ost alone. ***P<0.001; **P<0.05; *P<0.01.

METHODS AND EXAMPLES

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. If not mentioned otherwise, all evaporations are performed under reduced pressure, between about 50 mmHg and 100 mmHg. The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis, melting point (m.p.) and spectroscopic characteristics, e.g. MS, IR and NMR. Abbreviations used are those conventional in the art.

Preparation of compounds

In general, compounds 2 -14 may be prepared according to reaction schemes 1 to 5 (see Figures 1 to 5). Suitable reaction conditions are described below and can also be found disclosed in Raiber et al (referenced above). The skilled person will appreciate that further compounds of the invention are accessible via these general methods be modification of the starting materials and / or substituent groups included in these general methods.

Compound 1 - 2,5-Dihydroxybenzoic acid. This starting material was purchased from Apollo Scientific, Stockport, UK.

Compound 2 - Methyl 2,5-dihydroxybenzoate. Compound 1 (2,5-Dihydroxybenzoic acid) (5.00 g, 32.5 mmol) was dissolved in methanol (33 mL) and concentrated sulphuric acid (5 mL) added drop wise. The reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The residue was treated with saturated aqueous NaHCO₃ until pH 7 was reached. The product was extracted with ethyl acetate (50 mL x 3) and the combined organic layer was washed with brine (20 mL), dried (MgSO₄), filtered and the filtrate was evaporated to afford the product as a light brown powder (5.13 g, 94%). \(^1\text{H NMR (CDCl}_3\) \(\delta 10.35 (s, 1H), 7.29 (d, J = 3.2 \text{ Hz}, 1H), 7.02 (dd, J = 8.7, 3.2 \text{ Hz}, 1H), 6.89 (d, 8.7 \text{ Hz}, 1H), 4.69 (s, 1H), 3.95 (s, 1H); \(^{13}\text{C NMR (CDCl}_3\) \(\delta 170.1, 155.8,\)
147.6, 124.0, 118.5, 114.7, 112.1, 52.4; HRMS (ESI): [M-H]^+ calcd. for C₈H₇O₄ 167.0344, found 167.0359.

**Compound 3 - Methyl 5-(allyloxy)-2-hydroxybenzoate.** Compound 2 (0.50 g, 2.9 mmol) in anhydrous acetone (15 mL) was added at 0 °C to a flask containing potassium carbonate (0.80 g, 5.8 mmol) in anhydrous acetone (2.5 mL). After stirring for 1 h at 0 °C, allyl bromide (0.28 mL, 4.0 mmol) and tetrabutyl ammonium iodide (0.21 g, 0.58 mmol) were added and the reaction mixture was stirred for 15 h at 25 °C. Acetone was evaporated and the mixture was dissolved in ethyl acetate (20 mL) followed by successively washing with water (3 x 10 mL), brine (10 mL), drying over magnesium sulfate and concentration in vacuo. The crude compound was purified by silica gel flash column chromatography (cyclohexane : ethyl acetate; 8 : 2) to give a white powder (0.67 g, 47%). ¹H NMR (CDCl₃) δ 10.39 (s, 1H), 7.32 (d, J = 3.2 Hz, 1H), 7.11 (dd, J = 9.2, 3.2 Hz, 1H), 6.92 (d, J = 9.2 Hz, 1H), 6.10-6.00 (m, 1H), 5.45-5.38 (m, 1H), 5.32-5.27 (m, 1H), 4.52-4.48 (m, 2H), 3.95 (s, 3H); ¹³C NMR (CDCl₃) δ 170.2, 156.1, 150.8, 133.1, 124.6, 118.4, 117.7, 113.1, 111.7, 69.5, 52.3; HRMS (ESI): [M+NH₄]^+ calcd. for C₁₂H₁₈NO₄ 240.1230, found 240.1229.

**Compound 4 - Methyl 2-(4-acetoxybutoxy)-5-(allyloxy)benzoate.** To a solution of sodium hydride (60% dispersion in oil) (144 mg, 3.6 mmol) in anhydrous DMF (3 mL) was added at 0 °C, Compound 3 (0.37 g, 1.8 mmol) in anhydrous DMF (3 mL). After stirring for 1 h at 0 °C, tetrabutyl ammonium iodide (266 mg, 0.72 mmol) and 4-bromobutyl acetate (2.7 mL, 2.0 mmol) were added and the reaction mixture was stirred for a further 12 h at 25 °C. The reaction was stopped with the addition of saturated aqueous ammonium chloride (5 mL). Ethyl acetate (10mL) was added and the organic layer was washed with water (5 x 15 mL), brine (15 mL) and dried over magnesium sulfate. Purification by silica gel flash column chromatography (cyclohexane : ethyl acetate; 8 : 2) afforded 4 as colourless oil (87 mg, 15%). ¹H NMR (CDCl₃) δ 7.35 (d, J = 3.2 Hz, 1H), 7.03 (dd, J = 8.7, 3.2 Hz, 1H), 6.90 (d, J = 8.7 Hz, 1H), 6.10-5.99 (m, 1H), 5.45-5.38 (m, 1H), 5.32-5.27 (m, 1H), 4.54-4.50 (m, 2H), 4.15 (t, J = 6.0 Hz, 2H), 4.02 (t, J = 6 Hz, 2H), 3.89 (s, 3H), 2.06 (s, 3H), 1.90-1.85 (m, 4H); HRMS (ESI): [M+H]^+ calcd. for C₁₇H₂₃O₆ 323.1489, found 323.1486.

**Compound 5 - Methyl (R)-5-(2,3-dihydroxypropoxy)-2-(4-hydroxybutoxy)benzoate.** AD mix-β (441 mg) was dissolved in a mixture of t-BuOH/ water (2.4 mL / 2.4 mL) and cooled to 0 °C. Compound 4 (51.0 mg, 0.16 mmol) and methanesulfonamide (16 mg, 0.17 mmol) were added and the reaction mixture was stirred for 12 h at 0 °C. The reaction was quenched with
sodium sulfite (0.38 g) and the solvent was removed *in vacuo*. Ethanol (1 mL) was added to the crude product and the mixture was heated at reflux during 1 h. The salt was filtered off and purification by silica gel flash column chromatography (DCM/ methanol, 9:1) afforded 5 as colourless oil (10 mg, 3%). ¹H NMR (CD₂OD) δ 7.30 (d, J = 3.2 Hz, 1H), 7.12 (dd, J = 9.0, 3.2 Hz, 1H), 7.03 (d, J = 9.0 Hz, 1H), 4.04-4.00 (m, 1H), 3.96-3.91 (m, 2H), 3.86 (s, 3H), 3.67-3.60 (m, 4H), 1.88-1.81 (m, 2H), 1.77-1.69 (m, 2H).

**Compound 6 - Methyl 2,5-bis(allyloxy)benzoate.** Compound 2 (1.00 g, 5.98 mmol) in anhydrous DMF (30 mL) was added to a flask containing sodium hydride (60% dispersion in oil) (0.57 g, 23.7 mmol) in anhydrous DMF (5 mL) at 0 °C. After 1 h at 0 °C, allyl bromide (1.5 mL, 17 mmol) and tetrabutyl ammonium iodide (0.44 g, 1.2 mmol) were added and the reaction mixture was stirred for 16 h at 25 °C. The reaction was quenched with saturated aqueous ammonium chloride (10 mL). Dilution with ethyl acetate (30 mL) was followed by successively washing with water (5 x 60 mL), brine (30 mL), drying over magnesium sulfate and concentration *in vacuo*. The crude compound was purified by silica gel flash column chromatography (DCM : ethyl acetate; 8:2) to afford 6 as yellow coloured oil (1.45 g, 98%). ¹H NMR (CDCl₃) δ 7.39-7.35 (m, 1H), 7.02 (dd, J = 9.2, 3.2 Hz, 1H), 6.90 (d, J = 9.2 Hz, 1H), 6.10-5.98 (m, 2H), 5.51-5.37 (m, 2H), 5.30-5.25 (m, 2H), 4.58-4.54 (m, 2H), 4.52-4.49 (m, 2H), 3.89 (s, 3H).

**Compound 7 – Methyl 2-((R)-2,3-dihydroxypropoxy)-5-((S)-2,3-dihydroxypropoxy)benzoate.** AD mix-α (3.33 g) was dissolved in a mixture of t-BuOH/ water (12 mL/ 12 mL) and cooled to 0 °C. Compound 6 (0.30 g, 1.2 mmol) and methanesulfonamide (110 mg, 1.2 mmol) were added and the reaction mixture was stirred for 12 h at 0 °C. The reaction was quenched with sodium sulfite (3.0 g) and the solvent was removed *in vacuo*. Methanol (9 mL) was added to the crude product and the mixture was heated at reflux for 1 h. The salt was filtered off and column chromatography (DCM/ methanol, 7:3) of the filtrate gave 7 as colourless oil (40 mg, 11%). ¹H NMR (CD₂OD) δ 7.35 (d, J = 3.2 Hz, 1H), 7.15 (dd, J =9.0, 3.2 Hz, 1H), 7.08 (d, J =9.0 Hz, 1H), 4.11-3.90 (m, 5H), 3.87 (s, 3H), 3.75-3.48 (m, 5H); HRMS (ESI): [M+H]+ calcd. for C₁₄H₂₁O₉ 317.1236, found 317.1218.

**Compound 8 - Methyl 5-((R)-2,3-bis(sulfooxy)propoxy)-2-((S)-2,3-bis(sulfooxy)propoxy)benzoate.** Compound 7 (40 mg, 0.13 mmol) was dissolved in DMF (0.5 mL). Sulfur trioxide-trimethylamine complex (70 mg, 0.50 mmol) was added and the
reaction mixture was stirred for 16 h at 40 °C. The solvent was removed in vacuo and the crude product was purified by silica gel flash column chromatography (DCM : Methanol; 7:3 to 0:10) to afford 8 as yellow crystals (60 mg, 76%). \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 7.34-7.32 (m, 1H), 7.16-7.12 (m, 1H), 7.11-7.07 (m, 1H), 4.20-4.02 (m, 10H), 3.89 (s, 3H); HRMS (ESI): [M-2H]-/2 calcd. for C\(_{16}\)H\(_{18}\)S\(_2\)O\(_{20}\)/2 316.9715, found 316.9680.

**Compound 9 - 2,5-Bis(allyloxy)benzoic acid.** To a flask containing potassium hydroxide (334 mg, 6.0 mmol) in water/ethanol (0.8 mL / 0.8 mL) was added compound 7 (0.74 g, 3.0 mmol) and the mixture stirred for 6 h at 60 °C. The reaction was quenched with a solution of 2 M hydrochloric acid (1.0 mL). Solvents were removed in vacuo and the crude product was used directly in the next step. \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 7.22-7.20 (m, 1H), 6.99-6.96 (m, 2H), 6.12-5.99 (m, 2H), 5.47-5.36 (m, 2H), 5.26-5.21 (m, 2H), 4.60-4.56 (m, 2H), 4.52-4.48 (m, 2H); HRMS (ESI): [M+Na]+ calcd. for C\(_{14}\)H\(_{16}\)NaO\(_4\) 271.0946, found 271.0936.

**Compound 10 - 5-((R)-2,3-Dihydroxypropoxy)-2-((S)-2,3-dihydroxypropoxy)benzoic acid.** AD mix-\(\beta\) (1.28 g) was dissolved in a mixture of t-BuOH/water (16 mL / 16 mL) and cooled to 0 °C. Compound 9 (106 mg, 0.45 mmol) and methanesulfonamide (44 mg, 0.46 mmol) were added and the reaction mixture was stirred for 12 h at 0 °C. The reaction was quenched with sodium sulfate (1.2 g) and the solvent was removed in vacuo. Methanol (2 mL) was added to the crude product and the mixture was heated at reflux for 1 h. The salt was filtered off and silica gel flash column chromatography (DCM : Methanol; 10 : 1 to 7 : 3) afforded 10 as colourless oil (120 mg, 88%). \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 7.30-7.28 (m, 1H), 7.05-7.03 (m, 2H), 4.17-4.12 (m, 1H), 4.07-4.01 (m, 1H), 3.98-3.92 (m, 4H), 3.71-3.62 (m, 4H).

**Compound 11 - 2-((R)-2,3-Bis(sulfooxy)propoxy)-5-((S)-2,3-bis(sulfooxy)propoxy)benzoic acid.** Compound 10 (54 mg, 0.18 mmol) was dissolved in DMF (1.3 mL). Sulfur-trioxide-trimethylamine complex (149 mg, 1.08 mmol) was added and the reaction mixture was stirred for 16 h at 40 °C. The solvent was removed in vacuo and the crude product was purified by silica gel flash column chromatography (methanol) to afford 11 as a yellow oil (58 mg, 51%). \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 7.43-7.40 (m, 1H), 7.20-7.12 (m, 2H), 4.38-3.88 (m, 10H); HRMS (ESI): [M-2H]-/2 calcd. for C\(_{15}\)H\(_{16}\)S\(_4\)O\(_{20}\)/2 309.9564, found 309.9566.

**Compound 12 - Methyl (S)-5-(2,3-dihydroxypropoxy)-2-(4-hydroxybutoxy)benzoate.** AD mix-\(\alpha\) (312 mg) was dissolved in a mixture of t-BuOH/ water (1.7 mL/1.7 mL) and cooled to 0 °C. Compound 4 (36.0 mg, 0.11 mmol) and methanesulfonamide (13 mg, 0.13 mmol) were
added and the reaction mixture was stirred for 12 h at 0 °C. The reaction was quenched with sodium sulfite (0.28 g) and the solvent was removed in vacuo. Ethanol (1 mL) was added to the crude product and the mixture was heated at reflux during 1 h. The salt was filtered off and purification by silica gel flash column chromatography (DCM/ methanol, 9:1) afforded 12 as colourless oil (30 mg, 10%). \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 7.30 (d, \(J = 3.2\) Hz, 1H), 7.12 (dd, \(J = 9.0, 3.2\) Hz, 1H), 7.03 (d, \(J = 9.0\) Hz, 1H), 4.04-4.00 (m, 1H), 3.96-3.91 (m, 2H), 3.86 (s, 3H), 3.67-3.60 (m, 4H), 1.88-1.81 (m, 2H), 1.77-1.69 (m, 2H).

**Compound 13 - Methyl (R)-5-(2,3-bis(sulfooxy)propoxy)-2-(4-sulfooxy)butoxy)benzoate.**

Compound 12 (15.0 mg, 0.05 mmol) was dissolved in anhydrous DMF (0.5 mL). Sulfur-trioxide-trimethylamine complex (30.0 mg, 0.22 mmol) was added and the reaction mixture was stirred for 16 h at 40 °C. The solvent was removed in vacuo and the crude mixture was purified by silica gel flash column chromatography (methanol) to afford 13 as a yellow oil (24 mg, 88%). \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 7.31-7.29 (m, 1H), 7.18-7.12 (m, 1H), 7.08-7.03 (m, 1H), 4.35-4.11 (m, 4H), 4.10-4.01 (m, 5H), 3.87 (s, 3H), 1.90-1.85 (m, 4H). HRMS (ESI): [M-H]\(^+\) calcd. for C\(_{15}\)H\(_{21}\)O\(_{16}\)S\(_3\) 552.9992, found 553.0062.

**Compound 14 - Methyl (S)-5-(2,3-bis(sulfooxy)propoxy)-2-(4-sulfooxy)butoxy)benzoate.**

Compound 5 (10.0 mg, 0.032 mmol) was dissolved in anhydrous DMF (0.4 mL). Sulfur-trioxide-trimethylamine complex (20.0 mg, 0.14 mmol) was added and the reaction mixture was stirred for 16 h at 40 °C. The solvent was removed in vacuo and the crude mixture was purified by silica gel flash column chromatography (methanol) to afford 14 as a rose coloured oil (26 mg, 98%). \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 7.31-7.28 (m, 1H), 7.18-7.13 (m, 1H), 7.09-7.05 (m, 1H), 4.33-4.10 (m, 4H), 4.10-4.01 (m, 5H), 3.86 (s, 3H), 1.90-1.85 (m, 4H). HRMS (ESI): [M-H]\(^+\) calcd. for C\(_{15}\)H\(_{21}\)O\(_{16}\)S\(_3\) 552.9992, found 553.0065.

The identification of compounds 2-14 was performed using proton nuclear magnetic resonance (\(^1\)H NMR) spectroscopy. In addition, the chemical purities were also assessed by melting point determination, thin layer chromatography, and mass spectrometry.

All analytical data were consistent with the assigned structures with over 95% purity for the four derivatives.
BIOLOGICAL ASSAYS

1. **Endothelial Protection**

The protective effects of selected glycomimetic compounds were investigated against lipid-induced endothelial dysfunction. Lipid induced endothelial dysfunction is an early event involved in the development of atherosclerosis and ultimately vascular calcification. The effects of compounds \(8, 11, 13\) and \(14\) (referred to as C1, C2, C3 and C4, respectively in the biological data described herein) on endothelial dysfunction induced by palmitic acid in cultured endothelial cells (\textit{in vitro}) and isolated vessels (\textit{ex vivo}) were investigated. Palmitic acid is a major component of dietary saturated fat and forms 20% of the total serum free fatty acids (FFA). Palmitic acid is often used to induce endothelial dysfunction (Maloney E, Sweet IR, Hockenbery DM, Pham M, Rizzo NO, Tateya S, Handa P, Schwartz MW, Kim F. Activation of NF-kappaB by palmitate in endothelial cells: a key role for NADPH oxidase-derived superoxide in response to TLR4 activation. \textit{Arterioscler Thromb Vasc Biol} 2009 Sep 29(9):1370-5).

**Cultured endothelial cells (in vitro assay)**

Lipid-containing media was prepared by conjugation of sodium palmitate (Sigma-Aldrich No. P9767) with bovine serum albumin solution (BSA) using a method modified from that described previously (see Chavez JA, Summers SA. Characterizing the effects of saturated fatty acids on insulin signaling and ceramide and diacylglycerol accumulation in 3T3-L1 adipocytes and C2C12 myotubes. \textit{Arch Biochem Biophys} 2003;419(2):101-109). In particular, sodium palmitate was dissolved in ethanol whilst heating at 60°C in a water bath until completely dissolved. The sodium palmitate solution was then diluted in M119 media (Sigma Aldrich: Cat no; M4530) containing 2% (wt/vol) fatty acid-free BSA and left to stir for 1 h in a 37°C incubator to provide a lipid-containing media.

Human umbilical vein endothelial cells (HUVECs) were then:

A. incubated in the lipid-containing media (having a concentration of 100 \(\mu\)M sodium palmitate) in the absence of test compounds (illustrated in Figure 6 as PAL);
B. incubated in the lipid-containing media (having a concentration of 100 μM sodium palmitate) in the presence of test compounds C1 to C4 (at a concentration of 1 μM in dimethylsulfoxide (DMSO)) (illustrated in Figure 6 as PAL + C1-C4) for 3 h; or
C. pre-incubated with the test compounds C1 to C4 (at a concentration of 1 μM in DMSO) in serum free medium for 12 h followed by 3 h incubation in serum free M119 containing 2% (wt/vol) fatty acid-free BSA (illustrated in Figure 6 as CT).

As illustrated in Figure 6, the test compounds 8, 11, 13 and 14 (i.e. C1-C4, respectively) protected HUVECs against palmitate-induced oxidative stress and reduced A23187-stimulated nitric oxide (NO) production using test conditions B and C defined above. Moreover, palmitate significantly (P<0.001) reduced the Ca^{2+} ionophore A23187-stimulated NO production (shown in top-left graph of Figure 6) and quantified using the area under the curve. Co-incubation of HUVECs with glycomimetics and palmitate for 3 h markedly restored the A23187-stimulated NO production.

Pre-incubation of HUVECs with test compounds 8, 11, 13 and 14 (i.e. C1-C4, respectively), at a concentration of 1 μM, increased mRNA expression of Akt and eNOS, while decreasing the expression of NOX4, as illustrated by Figure 7. It is shown that palmitate treatment for 3 h as well as 24 h produced a marked decrease in both Akt and eNOS mRNA expression and an increase in NOX4 mRNA expression. HUVECs treated with glycomimetics C1 to C4 for 24 h in the presence of palmitate showed a significant increase in gene expression of Akt and eNOS, while treatment of dysfunctional HUVECs (treated with palmitate) with C1-C4 for 24 h significantly reduced gene expression of NOX4.

In addition, test compounds C1-C4 increased phosphorylation of Akt and eNOS illustrated by Figure 8, decreased ROS-induced lipid peroxidation and potentiated the activity of superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA) as illustrated by Figure 9. All test compounds C1-C4 significantly decreased the activity of NADPH oxidase as shown in Figure 9. In particular, in the presence of palmitate, treatment of HUVECs with compounds C1-C4 diminished palmitate induced ROS production. In addition, treatment of the palmitate-induced HUVECs with compounds C1-C4 for 24 h markedly diminished MDA content. Furthermore, treatment with palmitate significantly decreased the activity of SOD and CAT.
HUVECs treated with C1-C4 for 24 h in the presence of palmitate noticeably enhanced activity of the antioxidant enzymes SOD and CAT.

The inventors have also demonstrated similar effects of C1-C4 on the activity of NADPH oxidase activity in whole blood vessel assays. The data illustrated by Figure 8 supports the mRNA expression data shown in Figure 7. That is, palmitate treatment for 3 h as well as 24 h produced a marked decrease in both Akt and eNOS protein expression and an increase in NOX4 protein expression. HUVECs treated with glycomimetics C1 to C4 for 24 h in the presence of palmitate showed a significant increase in protein expression of Akt and eNOS, while treatment of dysfunctional HUVECs (treated with palmitate) with C1-C4 for 24 h significantly reduced protein expression of NOX4.

Nitric oxide (NO) and reactive oxygen species (ROS) production was measured using DAF-2 and H2DCF-DA, respectively. Colorimetric assays were used to determine lipid peroxidation and activity of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT). Expression of Akt, eNOS and NOX4 was assessed using RT-PCR and western blotting. The activity of NADPH oxidase was quantified by using a lucigenin-enhanced chemiluminescence method. Also, the dose-response effect of the test compounds was studied using 1, 10 and 100 µM of each compound.

The biological assays mentioned above and illustrated in Figures 6 to 9 were performed according to the methods and materials provided below.

**Assay of NO release**

NO released by HUVECS was quantified using the NO-sensitive fluorescent probe diaminofluorescein-2 (DAF-2) as described previously (Quintela AM, Jimenez R, Piqueras L, Gomez-Guzman M, Haro J, Zarzuelo MJ, Cogolludo A, Sanz MJ, Toral M, Romero M, Perez-Vizcaíno F, Duarte J. PPARβ/δ activation restores the high glucose-induced impairment of insulin signalling in endothelial cells. *Br J Pharmacol. 2014 Jun;171(12):3089-102*). After incubation according to conditions A-C described above, HUVEC cells were washed with phosphate buffered saline (PBS) and then pre-incubated with L-arginine (100 µM in PBS) for 5 min at 37°C. In some experiments, L-NAME (100 µM in PBS) was added 20 min before the addition of L-arginine. Cells were then incubated with DAF-2 (0.1 µM) for 2 min and then the
calcium ionophore calimycin (A23187, 1 μM in PBS) was added for 30 min. The fluorescence intensity (arbitrary units, AU) was measured using microplate reader (BioTek) and autofluorescence was subtracted from each value.

**Assay of intracellular ROS production**

Confluent HUVECs in 96-well plates, incubated according to conditions A to C described above, were further incubated with 10 μM of the fluorescent probe 2'-7'-dichlorodihydrofluorescein diacetate (CM-H2DCFDA, Sigma-Aldrich) whilst protected from light for 30 min at 37 °C. The cells were then washed with PBS and the fluorescent intensity was measured at excitation 490 nm and emission 540 nm using microplate reader (BioTek).

**Assay NADPH oxidase activity**

NADPH-enhanced superoxide (O$_2^-$) release in homogenates from cultured HUVECs was quantified by lucigenin-enhanced chemiluminescence, as previously described (Sanchez M, Lodi F, Vera R, Villar IC, Cogolludo A, Jimenez R, Moreno L, Romero M, Tamargo J, Perez-Vizcaino F, Duarte J. Quercetin and isorhamnetin prevent endothelial dysfunction, superoxide production, and overexpression of p47phox induced by angiotensin II in rat aorta. J Nutr. 2007 Apr;137(4):910-5.). Following incubation, according to the conditions A to C described above, HUVECs were homogenized in buffer (of the following composition (mmol/L): HEPES, 10 (pH 8); KCl, 10; EDTA, 1; EGTA, 1; dithiothreitol, 1; aprotinin, 0.006; leupeptin, 0.009; Na-p-tosyl-l-lysine chloromethyl ketone, 0.011; NaF, 5; Na$_2$MoO$_4$, 10; NaVO$_4$ and phenylmethanesulfonyl fluoride, 0.5 and centrifuged) to provide a HUVEC homogenate suspension. NADPH (100 μM) was then added to the buffer containing 50 μg protein of the HUVECS homogenate suspension in a total volume of 500 μl and lucigenin (5 μM in DMSO) was injected automatically. NADPH oxidase activity was calculated by subtracting the basal values from those in the presence of NADPH. The data is expressed as RLU/min/μg protein.

**Measurement of lipid peroxidation**

Malondialdehyde (MDA), an index for determining the extent of lipid peroxidation, was measured using OxiSelect TBARS assay kit (Cell Biolabs, San Diego, CA, USA) according to the manufacturer’s instructions. Following incubation of HUVECs with palmitate and/or EMPs, according to conditions A to C specified above, the cells were washed and homogenized before the addition of sodium dodecyl sulfate (SDS) lysis solution to the HUVECs samples or
MDA standards. Samples and standards were then incubated with thiobarbituric acid for 45 min at 95°C. Samples were brought to room temperature and centrifuged at 1000 x g for 15 min. Supernatants were removed to 96-well plate and absorbance was measured spectrophotometrically at 532 nm using microplate reader (BioTek), and the results were expressed as nmol MDA/mg protein.

Determination of Superoxide dismutase (SOD) and catalase (CAT) activity

SOD and CAT activity were determined in HUVECs homogenate using Cayman’s assay kits (Ann Arbor, MI, USA).

The SOD assay utilizes a tetrazolium salt for the detection of superoxide radicals generated by xanthine oxidase and hypoxanthine. In a 96-well plate, samples from the HUVECs incubated according to conditions A to C specified above, and standards were mixed with a tetrazolium salt solution and xanthine oxidase (supplied by the manufacturer in the SOD assay kit (Sigma-Aldrich cat no # 19160), covered and incubated for 30 min at room temperature with continuous shaking. The absorbance of samples and standards was read at 440 nm. One unit of SOD was defined as the amount of enzyme needed to exhibit 50% dismutation of the superoxide radicals.

The CAT assay method is based on the reaction of CAT with methanol in the presence of an optimal concentration of hydrogen peroxide (H₂O₂) to form formaldehyde. The formaldehyde formed reacts with 4-amino-hydrazino-5-mercaptopo-1,2,4-triazole forming a purple colored heterocycle upon oxidation. Samples were prepared and assayed with a catalase assay kit from Sigma Aldrich Cat no # CAT100 in a similar manner to the SOD assay in a 96 well plate containing samples, standards and mixed with 4-amino-hydrazino-5-mercaptopo-1,2,4-triazole (chromogen) and xanthine oxidase. Absorbance of the chromogen was measured at 540 nm using a plate reader. One CAT unit was defined as the amount of enzyme that causes the formation of 1.0 nmol of formaldehyde per min at 25 °C.

RNA isolation and reverse transcriptase-polymerase chain reaction (RT-PCR) analysis

Total RNA was extracted from HUVECs using Trizol reagent (Invitrogen). RNA samples were quantified at 260 nm. RNA samples with A260/A280 ratios ≥ 1.7 were selected. The first strand cDNAs were synthesized from 2 µg total RNA, using SuperScript II reverse
transcriptase and oligo deoxynucleotidylate primers (Sigma Aldrich). Reverse transcription was performed with Surecycler 8800 thermocycler (Agilent Technologies), and the reverse transcription products were amplified amplified by SYBR Green master mix (Bioline, UK) in a total volume of 20 µl using the primer set described in Table 1. Real-time PCR reaction involving 10 min at 95°C followed by 40 cycles of 30 sec at 95°C, 60 sec at annealing temperature of respective primer set, and 30 sec at 72°C steps was used to carry out the reaction. To evaluate the specificity and quality of PCR amplifications, melt curve analysis and agarose gel electrophoresis based quality check were performed. The cycle threshold values were analyzed using the $2^{-\Delta\Delta Ct}$ method. The housekeeping gene GAPDH was used for normalizing gene expression.

**Table 1: Primer sequences used for qRT-PCR**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sequence (5'-&gt;3')</th>
<th>Accession number</th>
<th>Tm</th>
</tr>
</thead>
</table>
| AKT  | F: AATGGACAGAAGCTATCCAGGC  
       | R: TGATGGGTGTAGAGGCATCC | NM_005465 | 61.8 | 61.3 |
| NOX4 | F: CAGATGTTGGGGCTAGGATTG  
       | R: GAGTGTTCGGCACATGGTA  | NM_001143836 | 60.2 | 61.9 |
| GAPDH| F: GGAGCGAGATCCCTCCAAAAT  
       | R: GGCTGTGTGCACATTCCTCATGG | NM_001256799 | 61.6 | 60.9 |
| eNOS | F: GCATCACCTATGACACCCTC  
       | R: CATGTACCAGCCACTGAAGG | XM_006716002.2 | 62.6 | 63.1 |

**Western blotting analysis:**

HUVECs were harvested and lysed in Radio-Immunoprecipitation Assay (RIPA) buffer supplemented with proteinase inhibitors for total protein extraction. Protein concentration of each sample was determined by the Bicinchoninic Acid (BCA) Protein Assay kit (Pierce Biotechnology). Equal amounts of protein (30 µg) were denatured and separated by sodium dodecyl sulphate (SDS)-polyacrylamide gel electrophoresis. Proteins were transferred to polyvinylidene fluoride (PVDF) membranes, blocked for 1 h in Tris-Buffered Saline Tween-20 (TBST) with 5% nonfat milk, and probed with primary rabbit polyclonal anti-phospho-eNOS
(Cell Signaling), rabbit anti-eNOS, rabbit anti-phospho-protein kinase B (Akt), rabbit anti-Akt (all three from Santa Cruz Biotechnology) and mouse anti-β-actin (Sigma), with gentle agitation overnight at 4°C. The membranes were washed with Tris-buffered saline and tween 20 (TBST) and incubated with the corresponding secondary peroxidase conjugated antibodies for 1 h at room temperature. The membranes were then visualized with an ECL system (Amersham Pharmacia Biotech, Amersham, UK) and densitometric analysis was performed using ImageJ.

**Isolated vessels (ex vivo assay)**

Vascular reactivity studies were performed using mouse descending aorta samples. Mouse thoracic aortic (MTA) rings were dissected in sterile phosphate buffered saline (PBS) cleared of periadventitial tissue and cut transversely into 2.0 mm rings. The MTA rings were then incubated for 24 h in serum-free dulbecco’s modified eagle’s medium (DMEM) supplemented with 10% FBS, 100 U/mL penicillin and 100 µg/mL streptomycin. The MTA rings were then incubated for 24 h in serum free DMEM containing 2% fatty acid-free BSA (control) or sodium palmitate (100 µM) conjugated with BSA using the modified Chavez method described above, in either the presence or absence of the test compounds C1-C4 (1 and 10 µM in DMSO). MTA rings were then handled carefully to avoid damage to the inner surface and transferred to a chamber filled with fresh Krebs solution and mounted in a myograph (model 610M, Danish Myo Technology, Aarhus, Denmark) for isometric tension measurement (Toral M, Gomez-Guzman M, Jimenez R, Romero M, Sanchez M, Utrilla MP, Garrido-Mesa N, Rodriguez-Cabezas ME, Olivares M, Galvez J, Duarte J. The probiotic Lactobacillus coryniformis CECT5711 reduces the vascular pro-oxidant and pro-inflammatory status in obese mice. *Clin Sci (Lond)*. 2014 Jul;127(1):33-45.). Concentration-relaxation response curves to acetylcholine (10⁻⁹ M-10⁻⁵ M) were performed on intact MTA rings precontracted by U46619 (10⁻⁶ M in DMSO) in control or on L-NAME (100 µM in PBS) treated MTA rings. To examine whether ROS are involved in endothelial dysfunction induced by palmitate within mouse descending aorta samples, responses to acetylcholine were studied. These studies were performed after incubation with the mitochondrial antioxidant mitoQ (0.1 µM) or the NADPH oxidase inhibitor apocynin (10 µM) incubated for 60 min before the addition of U46619 (10⁻⁶ M in DMSO). Relaxant responses to acetylcholine were expressed as a percentage or precontraction.
Incubation of mouse descending aorta samples, with the palmitate, inhibited the endothelium-dependent relaxation to acetylcholine. The tested glycomimetic compounds C1-C4 restored the aortic relaxation to acetylcholine in a dose-dependent manner. The relaxant response induced by acetylcholine was almost fully inhibited by the eNOS inhibitor L-NAME in all experimental groups. Both, mitoQ and apocynin significantly improved the impaired aortic relaxation to acetylcholine induced by palmitate as illustrated by Figure 10. Aortas treated with palmitate produced a significant decline in endothelium-dependent vasodilatation. In contrast, all of compounds C1-C4 significantly improved the palmitate-reduced endothelium-dependent vasodilatation. The relaxant response induced by Ach was almost fully inhibited by the eNOS inhibitor L-NAME in all experimental groups. In conclusion, small molecule glycomimetics prevented palmitate impaired endothelium-dependent relaxation to acetylcholine ex vivo and ROS production in situ.

2. Calcification Inhibition

The preventive effect of glycomimetics compounds C1-C4 on vascular calcification using samples from patients with cardiovascular disease was investigated. β-glycerophosphate (βGP) has been reported to accelerate calcification in cultured bovine vascular smooth muscle cells (Shioi A, Nishizawa Y, Jono S, Koyama H, Hosoi M, Morii H. Beta-glycerophosphate accelerates calcification in cultured bovine vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 1995 Nov;15(11):2003-9). Due to these calcification effects it is commonly utilized in well-established in vitro vascular calcification models which are used for function and mechanistic studies. The in vitro effects of the synthesized compounds on βGP-induced vascular calcification in human pelvic artery smooth muscle cells (HPSMCs) were investigated. By taking advantage of hepatocyte growth factor receptor (HGFR/c-Met) inhibitor, the results of this investigation indicated that glycomimetics compounds C1-C4 exerted their effects through inhibiting c-Met phosphorylation in these vascular smooth muscle cells.

After reaching confluence, the HPSMCs were incubated in DMEM containing 10% fetal bovine serum (FBS), 0.8 mM CaCl₂, 5 mM βGP. Starting from the first day induction, 10 μM of each test compound was added and the media changed every 3 days. HPSMCs cultured in 6-well plates for 21 days were used for calcification staining using alizarin red S, calcium deposition quantification and western blotting.
By day 21, all tested compounds were able to effectively block βGP-induced vascular calcification in HPSMCs as demonstrated by alizarin red S staining as illustrated by Figure 11 and calcium deposition assay as illustrated by Figure 12. All compounds C1-C4 significantly attenuated vascular calcification as indicated by the alizarin red S staining. As shown in Figure 11, A1-A2 represents control HPSMCs, B1-B2 represents HPSMCs incubated with osteogenic media, C1-C2 represents HPSMCs treated with C1, D1-D2 represents HPSMCs treated with C2, E1-E2 represents HPSMCs treated with C3, F1-F2 represents HPSMCs treated with C4 and G represents absorbance of stain eluted with 10% formic acid. This illustrates that compounds C1-C4 are effective in attenuating calcium deposition, reducing mineral deposition and prevent βGP-induced vascular calcification.

Another set of cells were cultured in 12-well plates and used for assaying alkaline phosphatase (ALP) activity at days 0, 4, 7 and 10. In another experimental set, treated HPSMCs were harvested on day 7 for gene expression analysis using RT-PCR. All compounds C1-C4 significantly decreased ALP activity at all tested time points as illustrated by Figure 13. By taking into account that vascular calcification is not a simple process due to an elevated calcium phosphate product, but rather involves an active transdifferentiation into osteoblast-like cells (Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, Jahnen-Dechent W, Weissberg PL, Shanahan CM. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. J Am Soc Nephrol 2004 Nov;15(11):2857-67.), the effect of compounds C1-C4 on the expression levels of specific genes in osteoblastic and osteogenic cells were investigated. Moreover, since ALP activity is an early marker of vascular calcification and this data demonstrates a reduction in activity thus supporting the conclusion of attenuated mineralisation of the cells.

**Conclusions**

In accordance with the data disclosed herein, it has been demonstrated that compounds of the present invention show surprising efficacy in assays of endothelial dysfunction and vascular calcification and thus show surprising utility in treating such conditions.
It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention, such as identified in the claims.
CLAIMS:

1. A compound according to formula (A), (B), (C) or (D):

\[
\begin{align*}
&\text{(A)} &\text{(B)} \\
&J &J \\
&(R^{10}_s) & (R^{10}_s) \\
&Z &Z \\
&R_1 &R_1 \\
&R_2 &R_2 \\
&R_3 &R_3 \\
\end{align*}
\]

\[
\begin{align*}
&\text{(C)} &\text{(D)} \\
&J &J \\
&(R^{10}_t) & (R^{10}_t) \\
&Z &Z \\
&R_1 &R_1 \\
&R_2 &R_2 \\
&R_3 &R_3 \\
\end{align*}
\]

or a pharmaceutically acceptable derivative thereof for use in the treatment of vascular calcification and/or endothelial dysfunction,

wherein:

- is a 6-membered carbocyclic or heterocyclic ring;
- is a 5-membered carbocyclic or heterocyclic ring;

J is H, halo, optionally substituted C\text{1-10}alkyl, optionally substituted C\text{3-10}cycloalkyl, optionally substituted C\text{2-10}alkenyl, optionally substituted C\text{3-10}cycloalkenyl, optionally substituted C\text{2-10}alkynyl, optionally substituted C\text{2-10}heteroalkyl, optionally substituted C\text{3-10}heterocycloalkyl, optionally substituted C\text{2-10}heteroalkenyl, optionally substituted C\text{3-10}heterocycloalkenyl, optionally substituted C\text{6-14}aryl, optionally substituted C\text{5-14}heteroaryl, or

Z is -O-, -N(R\text{A})-, -S-, or a C\text{1-6}alkylene or C\text{2-6}heteroalkylene linker group, wherein the C\text{1-6}alkylene and C\text{2-6}heteroalkylene linker groups are each independently
optionally substituted with 1 to 3 substituents selected from halo, OH, C_{1-6}alkyl, C_{1-6}haloalkyl; -OSO_2H and -NH(SO_2H), and wherein R^6 is H or C_{1-6}alkyl;

Q is -O-, -N(R^B), -S-, or a C_{1-6}alkylene or C_{2-6}heteroalkylene linker group, wherein the C_{1-6}alkylene and C_{2-6}heteroalkylene linker groups are each independently optionally substituted with 1 to 3 substituents selected from halo, OH, C_{1-6}alkyl, C_{1-6}haloalkyl; -OSO_2H and -NH(SO_2H), and wherein R^B is H or C_{1-6}alkyl;

R^1 is -CO_2W or a bioisostere of a carboxyl group;

R^2 and R^3 are each independently H, -OR^7 or -NH(R^7), wherein each R^7 is independently selected from the group consisting of H, -SO_3Y, optionally substituted C_{1-10}alkyl, optionally substituted C_3-10cycloalkyl, optionally substituted C_2-10alkenyl, optionally substituted C_3-10cycloalkenyl, optionally substituted C_2-10alkynyl, optionally substituted C_2-10heteroalkyl, optionally substituted C_3-10heterocycloalkyl, optionally substituted C_2-10heteroalkenyl, optionally substituted C_2-10heteroalkynyl, optionally substituted C_6-14aryl and optionally substituted C_5-14heteroaryl, wherein at least one of R^2 and R^3 is selected from -OSO_3Y and -NH(SO_3Y);

R^4 and R^5 are each independently selected from the group consisting of H, -SO_3Y, optionally substituted C_{1-10}alkyl, optionally substituted C_3-10cycloalkyl, optionally substituted C_2-10alkenyl, optionally substituted C_3-10cycloalkenyl, optionally substituted C_2-10alkynyl, optionally substituted C_2-10heteroalkyl, optionally substituted C_3-10heterocycloalkyl, optionally substituted C_2-10heteroalkenyl, optionally substituted C_2-10heteroalkynyl, optionally substituted C_6-14aryl and optionally substituted C_5-14heteroaryl;

R^6 is H, -CH_2OR^9 or -CH_2NH(R^9), wherein R^9 is independently selected from the group consisting of H, -SO_3Y, optionally substituted C_{1-10}alkyl, optionally substituted C_3-10cycloalkyl, optionally substituted C_2-10alkenyl, optionally substituted C_3-10cycloalkenyl, optionally substituted C_2-10alkynyl, optionally substituted C_2-10heteroalkyl, optionally substituted C_3-10heterocycloalkyl, optionally substituted C_2-10heteroalkenyl, optionally substituted C_2-10heteroalkynyl, optionally substituted C_6-14aryl and optionally substituted C_5-14heteroaryl;

s is an integer from 0 to 3;

t is an integer from 0 to 2;

each R^{10}, when present, is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}haloalkyl, -OSO_3Y and -NH(SO_3Y);
W is H, optionally substituted C\textsubscript{1-10}alkyl, optionally substituted C\textsubscript{3-10}cycloalkyl, optionally substituted C\textsubscript{2-10}alkenyl, optionally substituted C\textsubscript{3-10}cycloalkenyl, optionally substituted C\textsubscript{2-10}alkynyl, optionally substituted C\textsubscript{3-10}heteroalkyl, optionally substituted C\textsubscript{3-10}heterocycloalkyl, optionally substituted C\textsubscript{2-10}heteroalkenyl, optionally substituted C\textsubscript{3-10}heterocycloalkenyl, optionally substituted C\textsubscript{2-10}heteroalkynyl, optionally substituted C\textsubscript{6-14}aryl or optionally substituted C\textsubscript{5-14}heteroaryl; and

Y is H, optionally substituted C\textsubscript{1-10}alkyl, optionally substituted C\textsubscript{3-10}cycloalkyl, optionally substituted C\textsubscript{2-10}alkenyl, optionally substituted C\textsubscript{3-10}cycloalkenyl, optionally substituted C\textsubscript{2-10}alkynyl, optionally substituted C\textsubscript{3-10}heteroalkyl, optionally substituted C\textsubscript{3-10}heterocycloalkyl, optionally substituted C\textsubscript{2-10}heteroalkenyl, optionally substituted C\textsubscript{3-10}heterocycloalkenyl, optionally substituted C\textsubscript{2-10}heteroalkynyl, optionally substituted C\textsubscript{6-14}aryl or optionally substituted C\textsubscript{5-14}heteroaryl.

2. The compound or a pharmaceutically acceptable derivative for use according to claim 1 wherein the compound is according to formula (A) or (B):

\[
\begin{align*}
R^1 & \quad (R^{10})_S \\
J & \quad Z \quad R^2 \quad R^3
\end{align*}
\]

(A)

\[
\begin{align*}
R^1 & \quad (R^{10})_S \\
J & \quad Z \quad R^2 \quad R^3
\end{align*}
\]

\[
\begin{align*}
\text{wherein } & \quad R^1-R^3, \quad R^{10}, \quad J \quad \text{and} \quad Z \quad \text{are as defined according to claim 1}.
\end{align*}
\]

3. The compound or pharmaceutically acceptable derivative for use according to claim 2, wherein the compound is according to formula (A):

\[
\begin{align*}
R^1 & \quad (R^{10})_S \\
J & \quad Z \quad R^2 \quad R^3
\end{align*}
\]

(A)
wherein the dashed ring, R₁-R₃, R₁⁰, J and Z are as defined according to claim 1.

4. The compound or pharmaceutically acceptable derivative for use according to any previous claim, wherein the dashed ring is a 6-membered aryl or heteroaryl ring.

5. The compound or pharmaceutically acceptable derivative for use according to claim 1, 2 or 4, wherein formula (A) and (B) are according to formulae (A1) and (B1), respectively:

\[
\begin{align*}
\text{R}^1 & \quad \text{E} & \quad \text{D} & \quad \text{Z} & \quad \text{R}^2 & \quad \text{R}^3 \\
\text{C} & \quad \text{R}^1 & \quad \text{E} & \quad \text{D} & \quad \text{Z} & \quad \text{R}^2 & \quad \text{R}^3 \\
\text{J} & \quad \text{R}^1 & \quad \text{E} & \quad \text{D} & \quad \text{Z} & \quad \text{R}^2 & \quad \text{R}^3
\end{align*}
\]

wherein C, D and E are each independently selected from the group consisting of CH, CR₁⁰ and N; and R₁-R₃, R₁⁰, J and Z are as defined according to claim 1.

6. The compound or pharmaceutically acceptable derivative for use according to any previous claim, wherein the compound is according to formula (A1):

\[
\begin{align*}
\text{R}^1 & \quad \text{E} & \quad \text{D} & \quad \text{Z} & \quad \text{R}^2 & \quad \text{R}^3 \\
\text{C} & \quad \text{R}^1 & \quad \text{E} & \quad \text{D} & \quad \text{Z} & \quad \text{R}^2 & \quad \text{R}^3
\end{align*}
\]

wherein groups R₁-R₃, C-E, J and Z are as defined according to claim 5.
7. The compound or pharmaceutically acceptable derivative for use according to any one of claims 1 to 3, wherein \( \text{[Diagram]} \) is a 6-membered saturated cycloalkyl or heterocycloalkyl ring.

8. The compound or pharmaceutically acceptable derivative for use according to any one of claims 1 to 3 and 7, wherein formulae (A) and (B) are according to formulae (A2) and (B2), respectively:

\[
\begin{align*}
\text{(A2):} & \quad \text{wherein C, D and E are each independently selected from the group consisting of } \text{CH}_2, \text{CHR}^1, \text{NH} \text{ and } \text{NR}^1; \text{ and} \\
\text{R}^1-\text{R}^3, \text{R}^1, \text{J and Z are as defined according to claim 1.}
\end{align*}
\]

9. The compound or pharmaceutically acceptable derivative for use according to any one of claims 1 to 3, 7 and 8, wherein the compound is according to formula (A2):

\[
\begin{align*}
\text{(A2):} & \quad \text{wherein groups R}^1-\text{R}^3, \text{C-E, J and Z are as defined according to claim 8.}
\end{align*}
\]

10. The compound or pharmaceutically acceptable derivative for use according to any one of claims 1 to 9, wherein Z is a \( \text{C}_{2-6} \text{heteroalkylene linker group optionally substituted with 1 to 3 substituents selected from halo, OH, C}_{1-6} \text{alkyl, C}_{1-6} \text{haloalkyl, } \text{-OSO}_3\text{H and } \text{-NH(SO}_3\text{H); optionally wherein Z is a } \text{C}_{2-6} \text{heteroalkylene linker group, e.g. an } \text{-O-C}_{1-2} \text{alkylene group.} \)
11. The compound or pharmaceutically acceptable derivative for use according to claim 6, wherein formula (A1) is according to formula (A3):

![Chemical Structure](A3)

wherein:
- groups $R^1$-$R^3$, C-E, and J are as defined according to claim 5;
- $A$ is NR$^A$, O or S, wherein R$^A$ is H or C$_{1-6}$alkyl; and
- $m$ is 1, 2, 3 or 4.

12. The compound or pharmaceutically acceptable derivative for use according to any previous claim, wherein J is H, halo, optionally substituted C$_{1-10}$alkyl, optionally substituted C$_{3-10}$cycloalkyl, optionally substituted C$_{2-10}$heteroalkyl, optionally substituted C$_{2-10}$heterocycloalkyl, or wherein Q and R$^4$-$R^6$ are as defined in claim 1.

13. The compound or pharmaceutically acceptable derivative for use according to claim 12,

![Chemical Structure](Q)

wherein J is optionally wherein Q and R$^4$-$R^6$ are as defined in claim 1; optionally wherein Q is a C$_{2-6}$heteroalkylene linker group optionally substituted with 1 to 3 substituents selected from halo, OH, C$_{1-6}$alkyl, C$_{1-6}$haloalkyl; -OSO$_3$H and -NH(SO$_3$H); optionally wherein Q is a C$_{2-6}$heteroalkylene linker group, e.g. -O-C$_{1-2}$alkylene.
14. The compound or pharmaceutically acceptable derivative for use according to claim 13,

\[ \text{wherein } J = \ldots \], wherein

- \( R^4 \) and \( R^6 \) are as defined in claim 1;
- \( B = N{R^8}, O \) or \( S \), wherein \( R^8 \) is \( H \) or \( C_{1-6} \)alkyl; and
- \( n \) is 1, 2, 3, or 4.

15. The compound or pharmaceutically acceptable derivative for use according to claim 14, wherein the compound is according to formula (I):

\[ \text{(I)} \]

wherein:

- \( A = N{R^A}, O \) or \( S \), wherein \( R^A \) is \( H \) or \( C_{1-6} \)alkyl;
- \( B = N{R^B}, O \) or \( S \), wherein \( R^B \) is \( H \) or \( C_{1-6} \)alkyl;
- \( m \) is 1, 2, 3 or 4;
- \( n \) is 1, 2, 3 or 4;
- \( R^1 \) is \(-\text{CO}_2\text{W}\) or a bioisostere of a carboxyl group;
- \( R^2 \) and \( R^3 \) are each independently \( H \), \(-\text{OR}^7\) or \(-\text{NH}(\text{R}^7)\), wherein each \( R^7 \) is independently selected from the group consisting of \( H \), \(-\text{SO}_2\text{Y}\), optionally substituted \( C_{1-10} \)alkyl, optionally substituted \( C_{3-10} \)cycloalkyl, optionally substituted \( C_{2-10} \)alkenyl, optionally substituted \( C_{3-10} \)cycloalkenyl, optionally substituted \( C_{2-10} \)alkynyl, optionally substituted \( C_{2-10} \)heteroalkyl, optionally substituted \( C_{3-10} \)heterocycloalkyl, optionally substituted \( C_{2-10} \)heteroalkenyl, optionally substituted \( C_{3-10} \)heterocycloalkenyl, optionally substituted \( C_{2-10} \)heteroalkynyl, optionally substituted \( C_{6-14} \)aryl and optionally substituted \( C_{5-14} \)heteroaryl, wherein at least one of \( R^2 \) and \( R^3 \) is selected from \(-\text{SO}_3\text{Y}\) and \(-\text{NH}(\text{SO}_2\text{Y})\).
R⁴ and R⁵ are each independently H, -OR⁶ or -NH(R⁶), wherein each R⁶ is independently selected from the group consisting of H, -SO₂Y, optionally substituted C₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₂₋₁₀heteroalkyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkenyl, optionally substituted C₂₋₁₀heteroalkynyl, optionally substituted C₅₋₁₄aryl and optionally substituted C₅₋₁₄heteroaryl;

R⁷ is H, -CH₂OR⁶ or -CH₂NH(R⁶), wherein R⁶ is independently selected from the group consisting of H, -SO₂Y, optionally substituted C₁₋₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₃₋₁₀heteroalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkenyl, optionally substituted C₂₋₁₀heteroalkynyl, optionally substituted C₆₋₁₄aryl and optionally substituted C₅₋₁₄heteroaryl;

W is H, optionally substituted C₁₋₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₃₋₁₀heteroalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkenyl, optionally substituted C₂₋₁₀heteroalkynyl, optionally substituted C₆₋₁₄aryl or optionally substituted C₅₋₁₄heteroaryl; and

Y is H, optionally substituted C₁₋₁₀alkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₃₋₁₀cycloalkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₃₋₁₀heteroalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkyl, optionally substituted C₂₋₁₀heteroalkenyl, optionally substituted C₃₋₁₀heterocycloalkenyl, optionally substituted C₂₋₁₀heteroalkynyl, optionally substituted C₆₋₁₄aryl or optionally substituted C₅₋₁₄heteroaryl;

C, D and E are each independently selected from the group consisting of CH, CR¹⁰ and N; and

each R¹⁰ is independently selected from the group consisting of halo, C₁₋₄alkyl, C₁₋₄haloalkyl, -OSO₂Y and -NH(SO₂Y).

16. The compound or pharmaceutically acceptable derivative for use according to any one of claims 1 to 15, wherein R¹ is -CO₂W, wherein W is defined according to claim 1.
17. The compound or pharmaceutically acceptable derivative for use according to any
previous claim, wherein W is H, optionally substituted C\textsubscript{1-10}alkyl, or optionally
substituted C\textsubscript{2-10}heteroalkyl; optionally wherein W is H or optionally substituted C\textsubscript{1-10}alkyl; optionally wherein W is H or C\textsubscript{1-8}alkyl, such as wherein W is H or methyl.

18. The compound or pharmaceutically acceptable derivative for use according to any one
of claims 1 to 17, wherein R\textsuperscript{2} is -OR\textsuperscript{7} or -NH(R\textsuperscript{7}), optionally wherein said R\textsuperscript{7} is -SO\textsubscript{3}Y, such as wherein R\textsuperscript{2} is -OSO\textsubscript{3}Y.

19. The compound or pharmaceutically acceptable derivative for use according to any one
of claims 1 to 18, wherein R\textsuperscript{3} is -OR\textsuperscript{7} or -NH(R\textsuperscript{7}), optionally wherein said R\textsuperscript{7} is -SO\textsubscript{3}Y, such as wherein R\textsuperscript{3} is -OSO\textsubscript{3}Y.

20. The compound or pharmaceutically acceptable derivative for use according to any one
of claims 1 to 19, wherein R\textsuperscript{2} and R\textsuperscript{3} are selected independently from -OSO\textsubscript{3}Y and
-NH(SO\textsubscript{3}Y), such as wherein both R\textsuperscript{2} and R\textsuperscript{3} are -OSO\textsubscript{3}Y.

21. The compound or pharmaceutically acceptable derivative according to any one of
claims 1 to 20, for use according to claim 1, wherein R\textsuperscript{4} is H, -OR\textsuperscript{8} or -NH(R\textsuperscript{8});
optionally wherein R\textsuperscript{4} is -OR\textsuperscript{8} or -NH(R\textsuperscript{8}); and optionally wherein R\textsuperscript{8} is -SO\textsubscript{3}Y, such as
wherein R\textsuperscript{4} is -OSO\textsubscript{3}Y.

22. The compound or pharmaceutically acceptable derivative for use according to any one
of claims 1 to 20, wherein R\textsuperscript{4} is H.

23. The compound or pharmaceutically acceptable derivative for use according to any one
of claims 1 to 22, wherein R\textsuperscript{5} is -OR\textsuperscript{8} or -NH(R\textsuperscript{8}), optionally wherein R\textsuperscript{8} is -SO\textsubscript{3}Y, such as
wherein R\textsuperscript{5} is -OSO\textsubscript{3}Y.

24. The compound or pharmaceutically acceptable derivative for use according to any one
of claims 1 to 23, wherein at least one of R\textsuperscript{4} and R\textsuperscript{5} is selected from -OSO\textsubscript{3}Y and
-NH(SO\textsubscript{3}Y), optionally wherein R\textsuperscript{4} and R\textsuperscript{5} are each independently selected from
-OSO\textsubscript{3}Y and -NH(SO\textsubscript{3}Y), such as wherein both R\textsuperscript{4} and R\textsuperscript{5} are -OSO\textsubscript{3}Y.

25. The compound or pharmaceutically acceptable derivative for use according to any one
of claims 1 to 24, wherein R\textsuperscript{6} is H.

26. The compound or pharmaceutically acceptable derivative for use according to any one
of claims 1 to 25, wherein each R\textsuperscript{7} is independently selected from the group consisting
of H, -SO\textsubscript{3}Y and optionally substituted C\textsubscript{1-10}alkyl; optionally wherein each R\textsuperscript{7} is
independently selected from the group consisting of H and -SO_3Y; such as wherein each R^7 is -SO_3Y.

27. The compound or pharmaceutically acceptable derivative for use according to any one of claims 1 to 26, wherein each R^9 is independently selected from the group consisting of H, -SO_3Y and optionally substituted C_{1-10}alkyl; optionally wherein each R^8 is independently selected from the group consisting of H and -SO_3Y; such as wherein each R^8 is -SO_3Y.

28. The compound or pharmaceutically acceptable derivative for use according to any one of claims 1 to 24, 26 and 27, wherein R^9 is selected from the group consisting of H, -SO_3Y and optionally substituted C_{1-10}alkyl; optionally wherein R^9 is selected from the group consisting of H and -SO_3Y; such as wherein R^9 is -SO_3Y.

29. The compound or pharmaceutically acceptable derivative for use according to any one of claims 1 to 28, wherein each R^{10}, where present, is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}haloalkyl and -OSO_3Y; optionally wherein each R^{10}, where present, is independently selected from CF, C(CH_3)_2, CF_3 and -OSO_3Y.

30. The compound or pharmaceutically acceptable derivative for use according to any one of claims 1 to 28, wherein s is 0.

31. The compound or pharmaceutically acceptable derivative thereof according to any one of claims 1 to 30 wherein at least two, and optionally three, of R^2, R^3, R^4 and R^5 are -OSO_3Y, optionally wherein each of R^2, R^3, R^4 and R^5 is -OSO_3Y and R^8 is H.

32. The compound or pharmaceutically acceptable derivative thereof for use according to any one of claims 1 to 30, wherein R^2, R^3 and R^5 are -OSO_3Y, and R^4 and R^6 are each H.

33. The compound or pharmaceutically acceptable derivative for use according to any one of claims 11 to 32, wherein A is O or S, optionally O.

34. The compound or pharmaceutically acceptable derivative for use according to any one of claims 14 to 33, wherein B is O or S, optionally O, such as wherein A and B are each O.

35. The compound or pharmaceutically acceptable derivative for use according to any one of claims 5, 6 and 10 to 34, wherein C is selected from the group consisting of CH and
C(R^{10}), wherein R^{10} is selected from the group consisting of halo, C_{1-4}alkyl and C_{1-4}haloalkyl; optionally wherein R^{10} is halo, CF or CCH$_3$.

36. The compound or pharmaceutically acceptable derivative for use according to any one of claims 5, 6 and 10 to 35, wherein E is selected from the group consisting of CH and C(R^{10}), wherein R^{10} is selected from the group consisting of halo, C_{1-4}alkyl and C_{1-4}haloalkyl; optionally wherein R^{10} is halo, CF or CCH$_3$.

37. The compound or pharmaceutically acceptable derivative for use according to any one of claims 5, 6 and 10 to 36, wherein D is CH or C(R^{10}), wherein R^{10} is selected from the group consisting of halo, C_{1-4}alkyl and -OSO$_3$Y; optionally wherein R^{10} is halo, CF, CCH$_3$, or -OSO$_3$Y, such as -OSO$_3$Y.

38. The compound or pharmaceutically acceptable derivative for use according to any one of claims 5, 6 and 10 to 34, wherein C, D and E are each independently selected from the group consisting of CH and N, optionally wherein C, D and E are each CH.

39. The compound or pharmaceutically acceptable derivative for use according to any one of claims 11 to 38, wherein m is 1 or 2, optionally wherein m is 1.

40. The compound or pharmaceutically acceptable derivative for use according to any one of claims 14 to 39, wherein n is 1 or 2.

41. The compound or pharmaceutically acceptable derivative for use according to any one of claims 1 to 40, wherein each Y is independently selected from H and optionally substituted C_{1-10}alkyl; optionally wherein each Y is independently selected from H and C_{1-6}alkyl, such as wherein each Y is H.

42. The compound of formula (I) or a pharmaceutically acceptable derivative thereof for use according to claim 15, wherein:

A and B are selected independently from O or S, optionally wherein both A and B are O;

C, D and E are each CH;

m is 1 or 2;

n is 1 or 2;

R$^1$ is -CO$_2$W;
R², R³, R⁴ and R⁵ are each independently selected from H and -OSO₂Y, wherein at least one, and optionally at least 2, of R², R³, R⁴ and R⁵ is -SO₂Y;

W is H or optionally substituted C₁₆alkyl; and

Y is H.

43. The compound or pharmaceutically acceptable derivative thereof for use according to claim 42 wherein formula (I) is according to formula (III):

   \[
   \text{\text{R}}^5 \text{R}^4 \text{O} \text{R}^1 \text{O} \text{R}^3 \text{R}^2 \text{R}^3 \text{R}^1
   \]

   (III),

   wherein:

   n is 1 or 2;

   R¹ is -CO₂W, wherein W is H or optionally substituted C₁₆alkyl;

   R², R³ and R⁵ are each -OSO₂H or -NHSO₃H; and

   R⁴ is H or -OSO₂H or -NHSO₃H.

44. A compound according to any one of the following formulae, or a pharmaceutically acceptable derivative thereof, for use in the treatment of vascular calcification and / or endothelial dysfunction:

\[
\text{HO}_3\text{SO} \text{O} \text{OMe} \text{O} \text{Me} \text{OSO}_3\text{H} \text{OSO}_3\text{H} \text{OSO}_3\text{H} \text{OSO}_3\text{H}
\]

; 

\[
\text{HO}_3\text{SO} \text{O} \text{OSO}_3\text{H} \text{O} \text{OMe} \text{OSO}_3\text{H} \text{OSO}_3\text{H} \text{OSO}_3\text{H} \text{OSO}_3\text{H}
\]

;
A compound according to any one of the following formulae, or a pharmaceutically acceptable derivative thereof, for use in the treatment of vascular calcification and/or endothelial dysfunction:
46. A compound selected from any one of the following formulae, or a pharmaceutically acceptable derivative thereof, for use in the treatment of vascular calcification and/or endothelial dysfunction:
47. A compound or pharmaceutically acceptable derivative thereof for use according to any previous claim, wherein the pharmaceutically acceptable derivative thereof is a pharmaceutically acceptable salt; optionally wherein the pharmaceutically acceptable salt is a base addition salt, such as a metal salt (e.g. a sodium salt), or a salt formed using ammonia, a pharmaceutically acceptable organic amine or a heterocyclic base.

48. A pharmaceutical composition comprising a compound or pharmaceutically acceptable derivative thereof defined according to any previous claim and a pharmaceutically acceptable excipient, for use in the treatment of vascular calcification and / or endothelial dysfunction.

49. Use of a compound or pharmaceutically acceptable derivative thereof as defined according to any one of claims 1 to 47, or a pharmaceutically acceptable composition according to claim 48 in the manufacture of a medicament for the treatment of vascular calcification and / or endothelial dysfunction.

50. A method for the treatment of vascular calcification and / or endothelial dysfunction in a patient, comprising the step of administering a therapeutically effective amount of a compound or pharmaceutically acceptable derivative thereof as defined according to any one of claims 1 to 47, or a pharmaceutically acceptable composition according to claim 48 to a patient.

51. A method of modulating c-Met activity in an endothelial cell comprising contacting the cell with a compound or pharmaceutical derivative thereof as defined according to any one of claims 1 to 47, optionally wherein the endothelial cell is a human endothelial cell.

52. The method of claim 51, wherein the method is not a method of treatment by therapy, optionally wherein the method is an in vitro or ex-vivo method.
Application No: GB1515850.4  Examiner: Dr Bill Thomson
Claims searched: 1-52  Date of search: 31 May 2016

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

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Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC

Worldwide search of patent documents classified in the following areas of the IPC

The following online and other databases have been used in the preparation of this search report

CAS-ONLINE, EPODOC & WPI

International Classification:

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