Title: NITROSATED DERIVATIVES OF 2,5-DIHYDROXYBENZENE COMPOUNDS

Abstract: The present invention relates to nitrosated derivatives of 2,5-dihydroxybenzene compounds that are useful in the preparation of medicinal products for the treatment of different diseases. The diseases in question are, in particular: (a) cancer; (b) rosacea; (c) psoriasis; (d) fibrosis; (e) hemangiomatosis; (f) ocular diseases; (g) skin pigmentation and skin hyperpigmentation; (h) diseases associated with amyloidosis; (i) dermatitis; (j) actinic and seborrheic keratoses; (k) erectile dysfunction; (l) female sexual dysfunction; (m) arterial hypertension; (n) atherosclerosis; (o) inflammatory diseases in particular, arthritis, glomerulonephritis and asthma; (p) intestinal inflammatory diseases in particular, ulcerative colitis and Crohn's disease; (q) benign prostatic hyperplasia; (r) leishmaniasis; (s) angiogenesis associated with chronic temporal lobe epilepsy, (t) pain, (u) hyperlipidemia and (v) thrombosis.
NITROSATED DERIVATIVES OF 2,5-DIHYDROXYBENZENE COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to nitrosated derivatives of 2,5-dihydroxybenzene compounds that are useful in the preparation of medicinal products for the treatment of different diseases. The diseases in question are, in particular: (a) cancer; (b) rosacea; (c) psoriasis; (d) fibrosis; (e) hemangiomas; (f) ocular diseases; (g) skin pigmentation and skin hyperpigmentation; (h) diseases associated with amyloidosis; (i) dermatitis; (j) actinic and seborrheic keratosis; (k) erectile dysfunction; (l) female sexual dysfunction; (m) arterial hypertension; (n) atherosclerosis; (o) inflammatory diseases such as arthritis, glomerulonephritis and asthma; (p) intestinal inflammatory diseases such as ulcerative colitis and Crohn's disease; (q) benign prostatic hyperplasia; (r) leishmaniasis; (s) angiogenesis associated to chronic temporal lobe epilepsy, (t) pain, (u) hyperlipidemia and (v) thrombosis.

BACKGROUND OF THE INVENTION

In spite of recent advances in chemotherapy and radiation, cancer is one of the main causes of death at any age worldwide. In the United States alone there are almost three million new cancer cases diagnosed every year. The overall five-year survival is close to fifty per cent for all patients, and the prognosis is still particularly bad for those patients with advanced solid tumors.

Rosacea is a frequent ocular and facial disease usually affecting millions of people worldwide. It is a chronic and progressive vascular skin disorder, involving mainly the malar and nasal areas of the face. Rosacea is characterized by erythema, papules, pustules, telangiectasia, facial edema, ocular lesions and in its most advanced and severe form, tissue and sebaceous gland hyperplasia leading to rhinophyma. Rhinophyma, a florid overgrowth of the tip of the nose with hypervascularity and nodularity, is an uncommon progression of rosacea with an unknown cause. Ocular lesions, including mild conjunctivitis, burning and gritty
sensation, are common. Blepharitis, the most common ocular manifestation, is a non-ulcerative condition of the eyelid margins.

Psoriasis is a chronic disease affecting approximately 2-3% of the world population. It is characterized by epidermal cell hyperproliferation. Psoriasis symptoms include clearly defined erythematous spots covered by a characteristic crust, epidermal hyperproliferation, peeling and incomplete keratinocyte differentiation. Clinical psoriasis variants include erythrodermic, seborrheic, reverse and photosensitive psoriasis and psoriasis guttata, pustular variants and Reiter's disease. There is currently no cure for psoriasis.

Hemangioma is the most frequent childhood tumor. Apart from surgical treatment, which is sometimes difficult to perform due to the extension and location of the tumors, there are no effective treatments approved by health authorities for treating hemangiomas. Other vascular tumors, such as hemangioblastoma, are also difficult to treat.

Corneal and retinal neovascularization can cause visual difficulties and blindness. Diabetic retinopathy is the main cause of blindness after 20 years of age.

Erectile dysfunction is the persistent inability of men to reach or maintain sufficient penile erection for sexual activity. The prevalence of erectile dysfunction in Spain in men over the age of forty is 17.7%, although this figure exceeds 50% in studies conducted in other countries such as the United States. Although there are effective treatments for erectile dysfunction today, a considerable percentage of patients do not respond to conventional pharmacotherapy. In fact, the efficacy of the available pharmacological treatments decreases considerably in some groups of patients, such as diabetic patients or patients subjected to a radical prostatectomy, therefore a high number of patients could benefit from the development of new and more effective therapies.

Female sexual dysfunction includes a series of disorders affecting sexual desire, the excitement phase or orgasm. These alterations cause a deterioration of the sexual life of the affected woman. An inadequate increase of the genital blood flow during the excitement phase is one of the factors triggering female sexual dysfunction.
Imbalances in vascular tone regulation can cause arterial hypertension, a very prevalent disease causing severe health disorders because it favors the occurrence of cerebrovascular accidents and heart disease. Hypertension can be essential or secondary to other types of pathologies, such as kidney disease. The development of hypertension is due to a decrease of vasodilating ability and/or an increase in vasoconstriction.

Atherosclerosis is a vascular disease favored by hypertension in addition to other factors such as dyslipemia and can cause the obstruction of arteries, jeopardizing the blood supply to organs and tissues. Vascular smooth muscle proliferation phenomena and macrophage activation are also involved in the development of atheromatous plaques.

Inflammation is a complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue.

Arthritis is an often chronic illness, causing stiffness, pain and occasionally swelling of the joints (it includes osteoarthritis, rheumatoid arthritis, gouty arthritis, lupus-associated arthritis and the like).

Ulcerative colitis is a disease causing rectal and colon ulcers, causing bleeding and diarrhea.

Crohn's disease is a gastrointestinal tract disease. Although it can affect the entire gastrointestinal tract, it most frequently affects the ileum.

Glomerulonephritis includes a series of disorders characterized by the inflammation of the glomeruli, which can be primary or secondary to drug administration, to infections or to tumors. Glomerulonephritis causes high morbidity and mortality; it is a frequent cause of kidney failure and a cardiovascular risk factor. Treatments for glomerulonephritis are still unspecific, potentially dangerous and only partially effective.

Asthma is a chronic disease affecting the airways, causing them to constrict.

Asthma therapies today have limited efficacy and it is still one of the main causes of death during childhood.
Benign prostatic hyperplasia is a disease in which the prostate gland is enlarged and can cause problems associated with urination. Although there are pharmacological treatments for benign prostatic hyperplasia, they have limited efficacy and many patients end up needing surgery with resection of at least part of the gland.

Leishmaniasis, produced by the parasitation of species of the genus *Leishmania*, is the third most important disease among transmitted by vector-transmitted diseases. It is transmitted to mammals, including humans, by the bite of mosquitoes of the genus *Phlebotomus*. It is estimated that every year, there are 1.5 - 2 million cases of leishmaniasis worldwide, and that 350 million people are in risk of suffering from the disease. Leishmaniasis is associated to a wide variety of clinical symptoms that include, skin ulcerative lesions in the area of the bite (localized cutaneous leishmaniasis), multiple non-ulcerative nodules (diffuse cutaneous leishmaniasis), inflammation and destruction of mucosa (mucosal leishmaniasis) and disseminated visceral infection, potentially fatal (visceral leishmaniasis) (Murray et al. *Lancet*, 2005). The current treatment for leishmaniasis comprises pentavalent antimonial salts, mainly Pentostam (sodium stibogluconate) and Glucantime (N-methylglucamine antimoniate). These treatments are associated with important side effects affecting the kidney, the liver and the hearth (Oulette MJ et al, *Drug Resist Updated*, 2004). Therefore, there is a considerable clinical interest in finding new safe and efficient treatments for leishmaniasis.

Temporal lobe epilepsy is the most common variety of epilepsy. This kind of disease is resistant to antiepileptic treatment and it is associated with angiogenesis and the alteration of hematoencephalic barrier (Rigau V et al. *Brain*, 2007). The chronic alteration of the functionality of the hematoencephalic barrier has severe consequences such as neurovascular decoupling, inflammation and excitability.

Pain is an unpleasant emotional (subjective) and sensory (objective) experience associated with an injury. It is the most frequent reason for which patients consult a doctor.

Hyperlipidemia is defined as an elevated content of plasma lipids, based on the upper 5 to 10 percent of the distribution of plasma lipid levels within a
population. Hyperlipidemia includes hypercholesterolemia and hypertriglyceridemia, which are both important risk factors for atherosclerosis. The increases in cholesterol are associated mainly with a rise in low-density lipoproteins (LDL) and with increase incidence of premature ischemic heart disease. The increases in triglyceride are associated with a rise in very low-density lipoproteins (VLDL) and with premature atherosclerosis in some specific disorders. Primary hyperlipidemia is mainly due to genetic conditioning (familial hypercholesterolemia, familial hypertriglyceridemia and familial combined hyperlipidemia), while secondary hyperlipidemia is produced by dietary and life-style factors, obesity, uncontrolled diabetes, hypothyroidism, uremia, nephritic syndrome, obstructive liver disease or dysproteinemia, but may be also produced or aggravated by some drug therapies. Reduction of hyperlipidemia results in a decrease in progression of atherosclerosis. Therapeutical interventions resulting in fall of cholesterol levels have shown a favorable effect on incidence of the overall complications of ischemic heart disease.

Thrombosis is produced by the coagulation of blood within the circulatory system. Based on different pathogeny, thrombus structure and clinical significance, three types are distinguished: venous, arterial and that produced in cardiac cavities. Thrombi (generally constituted by erythrocytes, platelets and fibrin) generated on vascular walls can be detached or fragmented causing embolism. When thrombi come from venous system, they impact on pulmonary vascular tree, while thrombi developed in the left side of the heart or in the arteries cause systemic embolism. Thrombus is initiated when endothelial desquamation exists that exposes the subendothelial tissue (mainly collagen fibers) to the blood. In these conditions, platelets become activated and aggregate on the de-endothelialized area. Venous thrombus, when formed under stasis conditions is constituted by fibrin and erythrocytes with scarce presence of platelets (red thrombus). Arterial thrombus, formed under high flow conditions is mainly constituted by platelet aggregates linked by fibrin, although, when become occlusive, it also generates a stasis situation that allows the red thrombus formation. From a clinical point of view, thrombosis produces cardiovascular events that represent the first cause of mortality and morbidity in industrialized countries. Thus, the research and medical application of
molecules with the ability to inhibit or reduce thrombosis have high clinical relevance.

Therefore, and in spite of recent scientific progress and of the knowledge of the etiology of many of the diseases described in the present invention, there are still no really effective treatments against them.

SUMMARY OF THE INVENTION

The inventors have surprisingly found that nitrosated derivatives of 2,5-dihydroxybenzene compounds, i.e. 2,5-dihydroxybenzene compounds having at least one -ONO2 group as a substituent, as well as the pharmaceutically acceptable salts, isomers, solvates and prodrugs thereof, are useful in the preparation of medicinal products for the treatment and/or prophylaxis of diseases mediated by a deficiency of nitric oxide (NO). This medicinal activity is allegedly enhanced by the presence of at least an acetylated substitution as well as by the election of an appropriate substitution in position-1 of the benzene ring, which could be related to the inhibition of the fibroblast growth factor (FGF). In particular, they can be useful in the treatment and/or prophylaxis of diseases selected from cancer; rosacea; psoriasis; fibrosis; hemangiomas; ocular diseases; skin pigmentation and skin hyperpigmentation; diseases associated with amyloidosis; dermatitis; actinic and seborrheic keratosis; erectile dysfunction; female sexual dysfunction; arterial hypertension; atherosclerosis; inflammatory diseases such as arthritis, glomerulonephritis and asthma; intestinal inflammatory diseases such as ulcerative colitis and Crohn's disease; benign prostatic hyperplasia, leishmaniasis; angiogenesis associated to chronic temporal lobe epilepsy, pain, hyperlipidemia and thrombosis. There are evidences supporting the central role of nitric oxide in the treatment and the prevention of these diseases and thus the therapeutic activity of these nitrosated derivatives of 2,5-dihydroxybenzene compounds would be related to their capacity as nitric oxide donors, among other factors.

Therefore, a first aspect of the present invention relates to a compound of
Formula I (compounds of the invention), as well as to a salt, isomer, prodrug or solvate thereof.

A second aspect relates to a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, and a pharmaceutically acceptable carrier.

An additional aspect of the invention relates to a compound of Formula (I), or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof for its use as a medicinal product.

An additional aspect of the invention relates to the use of a compound of Formula (I), as well as a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof in the preparation of a medicinal product for the treatment and/or prophylaxis of any of the diseases selected from the group consisting of (a) cancer; (b) rosacea; (c) psoriasis; (d) fibrosis; (e) hemangiomas; (f) ocular diseases; (g) skin pigmentation and skin hyperpigmentation; (h) diseases associated with amyloidosis; (i) dermatitis; (j) actinic and seborrheic keratosis; (k) erectile dysfunction; (l) female sexual dysfunction; (m) arterial hypertension; (n) atherosclerosis; (o) inflammatory diseases such as arthritis, glomerulonephritis and asthma; (p) intestinal inflammatory diseases such as ulcerative colitis and Crohn's disease; (q) benign prostatic hyperplasia; (s) angiogenesis associated to chronic temporal lobe epilepsy; (t) pain; (u) hyperlipidemia and (v) thrombosis.

Another aspect of the invention is a pharmaceutical kit or set comprising one or more containers containing one or more compounds and/or compositions of the invention.

These and other aspects of the present invention will be explained in detail herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Inhibition by 2,5-dihydroxybenzenesulfonate and 2-hydroxy-5-(5-nitrooxy)pentanoyloxy)benzenesulfonate, respectively, of the mitogenesis induced by fibroblast growth factor-1 in quiescent cultures of Balb/c 3T3 fibroblasts.
Figure 2. Inhibition by 2,5-dihydroxybenzenesulfonate and 2-acetoxy-5-(5-(nitrooxy)pentanoyloxy)benzenesulfonate, respectively, of the mitogenesis induced by fibroblast growth factor-1 in quiescent cultures of Balb/c 3T3 fibroblasts.

Figure 3. Relaxant responses induced by potassium 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS) (1 nM to 100 µM) on rat aortic segments contracted with norepinephrine (0.1 µM). The lack of relaxant capacity of the parental molecule, potassium 2,5-dihydroxybenzene sulfonate (2,5-DHBS; 1 nM to 30 µM) is also shown for comparison. Data are expressed as mean±SEM of the percentage of maximum relaxation elicited by papaverine (0.1 mM). n indicates number of rats from which the aortae were collected for the study.

Figure 4. Relaxant responses induced by potassium 5-(5-(nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-2ABS) (1 nM to 100 µM) on rat aortic segments contracted with norepinephrine (0.1 µM). The lack of relaxant capacity of the parental molecule, calcium 2-acetyloxy-5-hydroxybenzene sulfonate (2A-5HBS; 1 nM to 30 µM) is also shown for comparison. Data are expressed as mean±SEM of the percentage of maximum relaxation elicited by papaverine (0.1 mM). n indicates number of rats from which the aortae were collected for the study.

Figure 5. Relaxant responses induced by calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS) (1 nM to 100 µM) on rat aortic segments contracted with norepinephrine (0.1 µM). The lack of relaxant capacity of the parental molecule, potassium 2,5-dihydroxybenzene sulfonate (2,5-DHBS; 1 nM to 30 µM) is also shown for comparison. Data are expressed as mean±SEM of the percentage of maximum relaxation elicited by papaverine (0.1 mM). n indicates number of rats from which the aortae were collected for the study. Since calcium salt yields two moles of anion 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate per mol of salt, indicated concentrations refer to the anion for allowing adequate comparison with potassium salt of 2,5-dihydroxybenzene sulfonate.
Figure 6. Potentiation produced by the type 5 phosphodiesterase (PDE5) inhibitor, tadalafil (50 nM), on the relaxations induced by 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS; 1 nM to 100 µM) (A), 5-(5-(nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-2ABS; 1 nM to 100 µM) (B) and calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS) (1 nM to 100 µM) (C) on rat aortic segments contracted with norepinephrine (0.1 µM). Data are expressed as mean±SEM of the percentage of maximum relaxation elicited by papaverine (0.1 mM). n indicates number of rats from which the aortae were collected for the study. For 2,5NO-BS, concentrations of the anion 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate are indicated.

Figure 7. Inhibition produced by the soluble guanylyl cyclase (sGC) inhibitor, IH-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ; 20 µM), on the relaxations induced by 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS; 1 nM to 100 µM) (A), 5-(5-(nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-2ABS; 1 nM to 100 µM) (B) and calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS) (1 nM to 100 µM) (C) on rat aortic segments contracted with norepinephrine (0.1 µM). Data are expressed as mean±SEM of the percentage of maximum relaxation elicited by papaverine (0.1 mM). n indicates number of rats from which the aortae were collected for the study. For 2,5NO-BS, concentrations of the anion 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate are indicated.

Figure 8. Mean arterial pressure (MAP) values before (basal) and after intravenous administration of potassium 2,5-dihydroxybenzene sulfonate (2,5-DHBS; 10 mg/kg) (A) and potassium 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS) at 3 mg/kg (B) and 10 mg/kg (C) doses to anesthetized rats. Data are expressed as mean±SEM of MAP values in mm Hg. n indicates number of rats used for the determinations. * indicates p < 0.05 vs basal values by paired t-test.
Figure 9. Mean arterial pressure (MAP) values before (basal) and after intravenous administration of calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS) at 3 mg/kg (A) and 10 mg/kg (B) doses to anesthetized rats. Data are expressed as mean±SEM of MAP values in mm Hg. n indicates number of rats used for the determinations. * indicates p < 0.05 vs basal values by paired t-test.

Figure 10. Mean arterial pressure (MAP) values before (basal) and after intravenous administration of calcium 2-acetyloxy-5-hydroxybenzene sulfonate (2A-5HBS; 10 mg/kg) (A) and potassium 5-(5-(nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-2ABS) at 3 mg/kg (B) and 10 mg/kg (C) doses to anesthetized rats. Data are expressed as mean±SEM of MAP values in mm Hg. n indicates number of rats used for the determinations. * indicates p < 0.05 vs basal values by paired t-test.

Figure 11. Heart rate (HR) values before (basal) and after intravenous administration of potassium 2,5-dihydroxybenzene sulfonate (2,5-DHBS; 10 mg/kg) (A) and potassium 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS) at 3 mg/kg (B) and 10 mg/kg (C) doses to anesthetized rats. Data are expressed as mean±SEM of HR values in beats per minute (bpm). n indicates number of rats used for the determinations.

Figure 12. Heart rate (HR) values before (basal) and after intravenous administration of calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS) at 3 mg/kg (A) and 10 mg/kg (B) doses to anesthetized rats. Data are expressed as mean±SEM of HR values in beats per minute (bpm). n indicates number of rats used for the determinations.

Figure 13. Heart rate (HR) values before (basal) and after intravenous administration of calcium 2-acetyloxy-5-hydroxybenzene sulfonate (2A-5HBS; 10 mg/kg) (A) and potassium 5-(5-(nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-2HBS) at 3 mg/kg (B) and 10 mg/kg (C) doses to anesthetized rats. Data are expressed as
mean±SEM of HR values in beats per minute (bpm). n indicates number of rats used for the determinations.

**Figure 14.** Effects of intravenously administered potassium 2,5-dihydroxybenzene sulfonate (2,5-DHBS; 10 mg/kg), potassium 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS; 3 and 10 mg/kg) and calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS; 3 and 10 mg/kg) on mean arterial pressure (MAP) in anesthetized rats. Data are expressed as mean±SEM of the percentage of change in MAP from baseline values. n indicates number of rats used for the determinations. * indicates p < 0.05, ** p < 0.01 vs 2,5-DHBS by means of a single-factor analysis of variance (ANOVA) followed by a Student-Newman-Keuls post-analysis.

**Figure 15.** Effects of intravenously administered calcium 2-acetyloxy-5-hydroxybenzene sulfonate (2A-5HBS; 10 mg/kg) and potassium 5-(5-(nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-2ABS; 3 and 10 mg/kg) on mean arterial pressure (MAP) in anesthetized rats. Data are expressed as mean±SEM of the percentage of change in MAP from baseline values. n indicates number of rats used for the determinations.

**Figure 16.** Effect of the treatment with potassium 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS) (25 to 200 µM) on the proliferation of rat glioma C6 cells. 5NO-2HBS was administered or not administered (control) after seeding the C6 cells in 24-well plates (10^4 per well) until they were fixed after 48 hours. The data are expressed as the mean±SEM of the percentage of the absorbance at 595 nm obtained in the control cultures, which is proportional to the number of cells stained with crystal violet. The data were obtained from 3 cultures for each treatment and control cultures.** indicates p < 0.01, *** indicates p < 0.001 with respect to the control by means of a single-factor analysis of variance (ANOVA) followed by a Student-Newman-Keuls post-analysis.
Figure 17. Effect of the treatment with potassium 5-(5-(nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-ABS) on the proliferation of rat glioma C6 cells. 5NO-2ABS was administered or not administered (control) after seeding the C6 cells in 24-well plates (10^4 per well) until they were fixed after 48 hours. The data are expressed as the mean±SEM of the percentage of the absorbance at 595 nm obtained in the control cultures, which is proportional to the number of cells stained with crystal violet. The data were obtained from 3 cultures for each treatment and control cultures. *** indicates p < 0.001 with respect to the control by means of a single-factor analysis of variance (ANOVA) followed by a Student-Newman-Keuls post-analysis.

Figure 18. Effect of of intravenously administered potassium 2,5-dihydroxybenzene sulfonate (2,5-DHBS; 10 mg/kg), potassium 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS; 10 mg/kg), potassium 5-(5-(nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-ABS) and calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS; 10 mg/kg) on bleeding time in anesthetized rats. The data are expressed as the mean±SEM in minutes. The numbers of rats used for determinations are in parenthesis. * indicates p < 0.05, *** indicates p < 0.001 with respect to basal by means of a single-factor analysis of variance (ANOVA) followed by a Student-Newman-Keuls post-analysis.

Figure 19. Effects of intravenous administration of vehicle (0.9% NaCl) (A) or calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS; 10 mg/kg) (B) on erectile responses elicited by cavernosal nerve electrical stimulation in anesthetized rats. Data are expressed as the mean±SEM of the area under the curve (AUC) of intracavernosal pressure (ICP) increase to cavernosal nerve stimulation (in mm Hg x s) normalized by mean arterial pressure (MAP) values, n indicates the number of animals used.

DETAILED DESCRIPTION OF THE INVENTION

As used throughout this description, it must be understood that the following
terms have the following meanings unless otherwise indicated.

The term "patient" relates to animals, preferably mammals, more preferably human beings, and includes men and women, and children and adults.

The expression "effective amount" relates to the amount of the compound and/or composition which is effective for achieving its desired purpose.

The terms "treat" or "treatment" relate to the use of the compounds or compositions of the present invention in a prophylactic manner to prevent the symptoms of the disease or disorder, or in a therapeutic manner to improve an existing condition.

The term "cancer" relates to a disease or disorder characterized by uncontrolled cell division and the ability of these cells to invade other tissues by the direct growth in adjacent tissue through invasion or by the implantation in distant sites through metastasis. Cancer relates to and includes skin cancer, cutaneous cancer, cancer of an organ, leukemia.

The term "cutaneous cancer" relates to and includes basal cell carcinoma, squamous cell carcinoma, melanomas, keratoacanthoma, Bowen's disease, warts, sarcomas, angiosarcoma such as Kaposi's angiosarcoma and the like.


The term "leukemia" relates to and includes blood cancers, such as for example acute lymphocytic leukemia, acute myelocytic leukemia, such as myeloblasts, promyeloblastic, myelomonocytic, erythrocytic leukemia and the like; chronic leukemia, such as chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia and the like; polycythemia vera, lymphoma (Hodgkin's disease and Non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease and the like.

The term "ocular diseases" relates to and includes a corneal or retinal neovascularization/angiogenesis, such as corneal neovascularization, or (diabetic and
non-diabetic) proliferative retinopathy.

The term "hemangioma" relates to a vascular tumor occurring during childhood.

The term "rosacea" relates to a chronic skin disease that causes redness and swelling, primarily on the face. Other areas that can be affected are the scalp, neck, ears, chest and back.

The term "psoriasis" relates to and includes diseases mediated by the immune system affecting the skin and joints. When it affects the skin, it normally appears in the form of raised, flaky red patches called plaques.

The term "fibrosis" relates to and includes the excessive formation or development of fibrous connective tissue in an organ or tissue as a reactive or repairing process, in opposition to the formation of fibrous tissue as a normal constituent of an organ or tissue. Fibrosis includes but is not limited to endomyocardial fibrosis, idiopathic pulmonary fibrosis, emphysema, pulmonary fibrosis (leading to chronic obstructive pulmonary disease), Peyronie's disease, scleroderma, diffuse parenchymal lung disease, cheloids, mediastinal fibrosis, progressive massive fibrosis, proliferative fibrosis, neoplastic fibrosis, renal interstitial fibrosis, hepatic fibrosis, organ fibrosis, surgical scars, burns and the like.

The term "corneal and retinal neovascularization" relates to the formation of new vessels invading the cornea or appearing in the retina and which can cause visual alterations and blindness, such as diabetic retinopathy or macular degeneration for example.

The term "diseases associated with amyloidosis" or "amyloid diseases" relates to and includes but is not limited to diseases associated with systemic, local, chronic and senile amyloidosis; the amyloid deposition is associated with Alzheimer's disease dementia, Lewy body dementia, to Down's syndrome, to the parkinsonism-dementia complex of Guam, to hereditary cerebral hemorrhage with amyloidosis-Dutch type and to other similar processes (in which the specific amyloid refers to the β-amyloid protein or AB); amyloidosis associated with chronic inflammation, for example osteomyelitis, tuberculosis, familial Mediterranean fever, hereditary cerebral hemorrhage, rheumatoid arthritis, Crohn's disease, ankylosing
spondylitis, Castleman's disease and the like (in which the specific amyloid refers to
AA-type amyloid or amyloidosis associated with inflammation); amyloidosis
associated with multiple myeloma, for example, to B-cell dyscrasia and the like, (in
which the specific amyloid refers to AL-type amyloid); amyloidosis associated with
type 2 diabetes (in which the specific amyloid is pancreatic islet amylin);
amyloidosis associated with prion disease, for example Creutzfeldt-Jakob disease,
Kuru, Gerstmann-Straussler-Scheinker disease, animal scrapie and the like (in which
the specific amyloid refers to PrP amyloid); amyloidosis associated with Down's
syndrome; amyloidosis associated with chronic hemodialysis, amyloidosis
associated with long-term hemodialysis, carpal tunnel syndrome and to other similar
processes, (in which the specific amyloid refers to B₂-microglobulin); senile cardiac
amyloidosis, familial amyloidotic polyneuropathy, and to similar processes (in which
the specific amyloid refers to transthyretin or prealbumin); amyloidosis associated
with endocrine tumors such as medullary thyroid carcinoma and to other similar
process (in which the specific amyloid refers to a procalcitonin variant).

The term "dermatitis" relates to and includes atopic dermatitis, contact
dermatitis and the like.

The term "atopic dermatitis" relates to a chronic disease affecting the skin.
Atopic dermatitis is due to a combination of genetic and environmental factors.

The term "contact dermatitis" relates to lesions occurring in the skin when
the latter comes into contact with an antigen or an irritant.

The term "actinic keratosis" refers to dry, squamous lesions with gritty texture
formed in the external layer of the skin after years of exposure to ultraviolet light,
such as solar rays.

The term "seborrheic keratosis" refers to non-cancerous growth of the external
layer of the skin.

The term "erectile dysfunction" relates to the total or partial inability of
having sexual relations due to the impossibility of reaching a suitably stiff erection.

The term "female sexual dysfunction" relates to the total or partial inability
for a woman to have sexual relations with a suitable degree of satisfaction due to the
lack of desire, the difficulty or impossibility of achieving suitable excitement
(objective or subjective) or the difficulty or impossibility of reaching an orgasm.

The term "arterial hypertension" relates to a situation in which the systolic, diastolic blood pressure or both are constantly or repeatedly above the normal ranges established according to the sex and age of the patient.

The term "atherosclerosis" relates to a disease affecting the arteries wherein vascular wall constrictions and irregularities are formed which hinder blood circulation and make the suitable perfusion of organs and tissues difficult.

By the term "inflammation disease" it is understood the biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.

The inflammatory process involves the interaction of immune cells with tissue cells, as well as the production and release of cytokines and growth factors by the different cell types. Examples of inflammatory diseases are arthritis, glomerulonephritis and asthma.

The term "arthritis" relates to a frequently chronic illness causing stiffness, pains and occasionally swelling of the joints and includes osteoarthritis, rheumatoid arthritis, polyarthritis, gouty arthritis, lupus-associated arthritis, psoriasis-associated arthritis and the like.

The term "glomerulonephritis" relates to a disease characterized by the inflammation of the glomeruli, which are the kidney filtration units, and can cause kidney dysfunction and failure.

The term "asthma" relates to a chronic disease affecting the airways and causing them to constrict.

A particular case of inflammatory disease is intestinal inflammatory disease which includes for example, ulcerative colitis and Crohn's disease.

The term "ulcerative colitis" relates to a disease causing rectal and colon ulcers, causing bleeding and diarrhea.

The term "Crohn's disease" relates to a gastrointestinal tract disease.

The term "benign prostatic hyperplasia" relates to the disease in which the prostate gland is enlarged and can cause problems associated with urination.

The term "leishmaniasis" relates to the parasitation by species of *Leishmania* genus in human and pets which causes a disease affecting the skin, mucosa or
viscera.

The term "angiogenesis associated to chronic temporal lobe epilepsy" relates to a complication of epilepsy which participates in the physiopathological process of the disease.

The term "pain" relates to an unpleasant emotional (subjective) and sensory (objective) experience associated with an injury.

The term "hyperlipidemia" relates to an elevated content of plasma lipids, based on the upper 5 to 10 percent of the distribution of plasma lipid levels within a population.

The term "thrombosis" relates to the coagulation of blood within the circulatory system.

The term "therapeutic agent" includes any therapeutic agent that can be used to treat or prevent the diseases described herein. "Therapeutic agents" include but are not limited to chemotherapeutic agents, steroids, retinoids, antimicrobial compounds, antioxidants, non-steroidal anti-inflammatory agents, NMDA receptor antagonists, endothelin antagonists, immunomodulating agents, vitamin D analogs, salicylic acid, cholinesterase inhibitors, tau protein phosphorylation inhibitors, nitric oxide donors, phosphodiesterase inhibitors and combinations of two or more thereof and the like. A therapeutic agent includes pharmaceutically acceptable salts thereof, prodrugs and pharmaceutical derivatives thereof.

The term "antimicrobial compound" relates to any compound altering the growth of bacteria, fungi or viruses whereinby the growth is prevented, modified, reduced, stabilized, inhibited or stopped. Antimicrobial compounds can be microbicides or microbiostatic agents and include but are not limited to antibiotics, semi-synthetic antibiotics, synthetic antibiotics, antifungal compounds, antiviral compounds and the like.

The term "antifungal compound" relates to any compound altering the growth of fungi whereinby the growth is prevented, modified, reduced, stabilized, inhibited or stopped.

The term "antiviral compound" relates to any compound altering the growth of viruses whereinby the growth is prevented, modified, altered, stabilized, inhibited
or stopped.

The term "antioxidant" relates to and includes any compound that can react and inactivate a free radical, including but not limited to free radical eliminators, iron chelating agents, small molecule antioxidants and antioxidant enzymes and the like.

The term "taxane" relates to any compound containing the central carbon frame represented by formula A:

![formula A]

The term "NSAIDs" relates to a non-steroidal anti-inflammatory compound or to a non-steroidal anti-inflammatory drug. NSAIDs inhibit cyclooxygenase, the enzyme responsible for the biosynthesis of prostaglandins and certain autacoid inhibitors, including inhibitors of several cyclooxygenase isozymes (including but not limited to cyclooxygenase 1 and 2), and inhibitors of both cyclooxygenase and lipoxygenase.

The term "topical" relates to the administration of a compound by means of the application on the body surface and includes but is not limited to transdermal administration and administration through the mucous membrane.

The term "transdermal" relates to the administration of a compound passing through the skin into the blood stream.

The expression "through the mucous membrane" relates to the administration of a compound passing through the mucous tissue into the blood stream.

The term "parenteral" relates to the administration of a compound by subcutaneous, intravenous, intramuscular, intracardiac, intradermal, intraperitoneal, intrathecal or intrasternal injection, and also includes local and systemic infusion techniques.

The expression "penetration enhancement" or "permeation enhancement"
relates to an increase in the permeability of the skin or mucous tissue for a pharmacologically active compound selected such that it increases the amount and/or the rate at which the compound penetrates the skin or mucous membranes or traverses the skin and mucous membranes.

"Excipients" or "carriers" relate to suitable carrier materials for the administration of a compound and include any of said materials known in the art such as for example, any liquid, gel, solvent, liquid diluent, solubilizer or the like, which is not toxic and does not interact with any component of the composition in a harmful manner.

The expression "sustained release" relates to the release of an active compound and/or composition such that the blood levels of the active compound are maintained in a desirable therapeutic interval for a time period. The sustained release formulation can be prepared using any conventional method known by persons skilled in the art to obtain the desired release characteristics.

The following terms have the indicated meaning in the definitions of the compounds described herein:

"Alkyl" relates to a linear or branched chain hydrocarbon radical formed by hydrogen and carbon atoms, which does not contain unsaturations, with one to twelve, preferably one to eight, more preferably one to six carbon atoms (lower alkyl) and which is joined to the rest the molecule by a single bond, for example, methyl, ethyl, w-propyl, /-propyl, w-butyl, /-butyl, w-pentyl, etc.

"Alkenyl" relates to a linear or branched chain hydrocarbon radical formed by hydrogen and carbon atoms, containing at least one unsaturation, with two to twelve, preferably two to eight, more preferably two to six carbon atoms and which is joined to the rest of the molecule by a single bond.

"Cycloalkyl" relates to a saturated carbocyclic ring having between three and eight, preferably three and six carbon atoms. It can have a bridged structure. Suitable cycloalkyl groups include but are not limited to cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

"Alkynyl" relates to a linear or branched chain hydrocarbon radical formed by hydrogen and carbon atoms, containing at least one conjugated or non-conjugated
carbon-carbon triple bonds, with two to twelve, preferably two to eight, more preferably two to six carbon atoms and which is joined to the rest of the molecule by a single bond, such as -CCH, -CH₂CCH, -CCCH₃, -CH₂CCCH₃.

"Aryl" relates to an aromatic hydrocarbon radical having from six to ten carbon atoms such as phenyl or naphthyl.

"Arylalkyl" relates to an aryl group joined to the rest of the molecule by an alkyl group. Examples of arylalkyl groups include benzyl, phenylethyl, 4-hydroxybenzyl, 3-fluorobenzyl, 2-fluorophenylethyl and the like.

"Alkylaryl" relates to an alkyl group joined to the rest of the molecule by an aryl group. Examples of alkylaryl groups include methylphenyl, ethylphenyl and the like.

"Heterocycle" relates to a stable ring having 3 to 15 members consisting of carbon atoms and between one and five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, preferably a ring having 4 to 8 members with one, two, three or four heteroatoms, more preferably a ring having 5 or 6 members with one, two or three heteroatoms. For the purposes of this invention, the heterocycle can be a monocyclic, bicyclic or tricyclic ring system, which can include fused ring systems; bridged structures; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical can optionally be oxidized; the nitrogen atom can optionally be quaternized; and the heterocyclyl radical can be partially or completely saturated or be aromatic. Examples of such heterocycles include but are not limited to azepines, benzimidazole, benzothiazole, furan, isothiazole, imidazole, indole, piperidine, pipерazine, purine, quinoline, thiadiazole, tetrahydrofuran. Unless otherwise indicated, the alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl and heterocycle radicals can optionally be substituted with one, two or three substituents such as halo, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, alkoxy, sulfoxyl, O-benzyl, O-benzoyl, carboxy, alkylcarboxy, arylcarboxy, alkylcarbonyl, arylcarbonyl, cyano, carbonyl, acyl, alkoxy carbonyl, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamine, imino, alkylsulfonyl, amidyl, carbamoyl, sulphonamido, nitro, nitrite, nitrate, thionitrate and carboxamido.

The term "alkoxycarbonyl" relates to compounds with the formula -C(=O)O-
, in which the C-end is joined to the molecule and the O-end is joined to a carbon atom to form an ester function. Said carbon atom can be part of an alkyl, alkenyl, cycloalkyl, alkynyl, aryl, aralkyl or heterocyclic group.

The term "alkylsulfonyl" relates to RsO-S(O)₂⁻, wherein R₅₀ is an alkyl group as defined herein.

The term "arylsulfonyl" relates to RsS-S(O)₂⁻, wherein R₅₅ is an aryl group as defined herein.

The term "alkylsulfmyl" relates to R₅₅O-S(O)⁻, wherein R₅₀ is an alkyl group as defined herein.

The term "arylsulfmyl" relates to R₅₅-S(O)⁻, wherein R₅₅ is an aryl group as defined herein.

The term "sulfonamido" relates to -S(O)₂⁻N(R₅₁(R₅₇)), wherein R₅₁ and R₅₇ are each independently a hydrogen atom, an alkyl group, an aryl group, heterocyclic group, as defined herein, or R₅₁ and R₅₇ together form a heterocyclic ring, a cycloalkyl group, or a bridged cycloalkyl group, as defined herein.

The term "alkylsulfonamido" relates to a sulfonamido group as defined herein, bonded to an alkyl group as defined herein.

The term "arylsulfonamido" relates to a sulfonamido group as defined herein, bonded to an aryl group as defined herein.

The term "alkylcarbonyl" relates to R₅₂-C(O)₂⁻, wherein R₅₂ is an alkyl group as defined herein.

The term "arylcarbonyl" relates to the radical R₅₅-C(O)⁻ radical, wherein R₅₅ is an aryl group as defined herein.

The term "carboxamido" relates to the -C(O)N(R₅₂)(R₅₈) radical, wherein R₅₂ and R₅₈ are each independently a hydrogen atom, an alkyl group, an aryl group, or a heterocyclic group, as defined herein, or R₅₂ and R₅₈ together from a heterocyclic ring, a cycloalkyl group, or a bridged cycloalkyl group, as defined herein.

The term "carboxylic ester" relates to -C(O)OR₅₉, wherein R₅₉ is an alkyl group, an aryl group or a heterocyclic group, as defined herein.

The term "alkoxyalkyl" relates to an alkoxy group as defined herein, bonded to an alkyl group as defined herein. Examples of alkoxyalkyl groups are
methoxymethyl, methoxyethyl, isopropoxymethyl and the like.

The term "amine" relates to any organic compound containing at least one basic nitrogen atom.

The term "organic cation" relates to a positively charged organic ion. Examples of organic cations include ammonium cations substituted with alkyl or unsubstituted ammonium cations, primary, secondary or tertiary amines, alkylamines, arylamines, cyclic amines, N,N'-dibenzylethlenediamine and the like.

The term "inorganic cation" relates to a positively charged metal ion. Examples of inorganic cations include Group I and II metal cations such as, for example, sodium, potassium, magnesium, calcium and the like.


A first aspect of the present invention relates to a nitrosated derivative of a 2,5-dihydroxybenzene compound, or compound of Formula I

\[
\begin{align*}
\text{Formula I} & \\
\text{wherein:} & \\
R_1 \text{ is selected from } -(\text{CH}_2)_aZ \text{ and } -\text{CH}=\text{CH}-(\text{CH}_2)_bZ; \text{ wherein:} & \\
Z \text{ is selected from } -\text{SO}_3\text{H}, -\text{SO}_3\text{X}^+, -\text{SO}_3\text{R}_3, -\text{PO}_3\text{H}, -\text{PO}_3\text{X}^+, -\text{PO}_3\text{R}_3, -\text{CO}_2\text{H}, -\text{CO}_2\text{X}^+ \text{ and } -\text{CO}_2\text{R}_3; \text{ wherein:} & \\
X^+ \text{ is an organic or inorganic cation and } R_3 \text{ is selected from an alkyl group,}
\end{align*}
\]
an aryl group, an arylalkyl group and an alkylaryl group;
a is an integer selected from 0, 1, 2, 3, 4, 5 and 6;
b is an integer selected from 0, 1, 2, 3, 4, 5 and 6;

R₉ and R₉' are independently selected from -OH, -OC(O)-RiO and -OR₂; with
the proviso that at least one of R₉ and R₉' is -OR₂ and wherein R₉ and R₉' can
have different values of R₂; wherein:
Rio is an alkyl group, an aryl group, an arylalkyl group or an alkylaryl group
and R₂ is selected from:

1. -Y'-(CR₄R₄')ₚ-ONO₂;
2. -YMCR₄R₄VT-(CR₄R₄VONO₂;

wherein T is located in an ortho, meta or para orientation;

(4)

(5) -Y^(CR₄R₄')ₚ-V-(CR₄R₄')q-(CH₂)q-ONO₂;
(6) -Y'-(CR₄R₄')p-T-(CR₄R₄')q-(CH₂)q-ONO₂;
(7) -Y'-(CR₄R₄')p-T-(C(Zi)-(CH₂)q-T-(CR₄R₄')q-(CH₂)q-ONO₂;
(8) -Y'-(CR₄R₄')p-T-(CH₂)q-V-(CR₄R₄')q-(CH₂)q-ONO₂;
(9) -Y'-(CR₄R₄')p-V-(CH₂)q-V-(CR₄R₄')q-(CH₂)q-ONO₂;
(10) -Y'-(CR₄R₄')p-(W)q-(CR₄R₄')q-(CH₂)q-ONO₂;
(11) \(-Y'(CH_2)q-(CH_2)q-V-(CR4R4')q-O-Q'(CR4R4')q-(CH2)-ONO_2;-\)
(12) \(-Y'(CR_4R_4')p-V-(CH_2)_q-(W)_q-(CR_4R_4')q-(CH_2)-ONO_2;-\)
(13) \(-Y'(CR_4R_4')q-O'-Q'(CR_4R_4')q-V-(CR_4R_4')q-(CH_2)-ONO_2;-\)
(14) \(-Y'-(CR_4R_4')o-Q'(CR_4R_4')o-(W)_q-(CR_4R_4')o-(CH_2)-ONO_2;\)
(15) \(-Y'-(CR_4R_4')p-T-(CR_4R_4')p-Q'(CR_4R_4')p-(CH_2)-ONO_2;\)
(16) \(-Y'(CR_4R_4')q-C(Z_1)-(CR_4R_4')q-(CH_2)-ONO_2;\)
(17) \(-Y'(CR_4R_4')p-Q'(CR_4R_4')p-(CH_2)-ONO_2;\)
(18) \(-Y'(CR_4R_4')q-P(O)MM';\)
(19) \(-Y'(CR_4R_4')o-Q'(CR_4R_4')o-(CH_2)-ONO_2;\)
(20) \(-Y'-(CR_4R_4')o-Q'(CR_4R_4')o-(CR_4R_4')o-(CH_2)-ONO_2;-\)
(21) \(-Y'(CR_4R_4')q-(W)_q-(CR_4R_4')q-O'-Q'(CR_4R_4')q-(CH_2)-ONO_2;-\)
(22) \(-Y'-(CR_4R_4')o-V-(CR_4R_4')o-Q'(CR_4R_4')o-(CH_2)-ONO_2;\)
(23) \(-Y'(CR_4R_4')p-(T)_o-(W)_q-(CR_4R_4')o-(CH_2)-ONO_2;\)
(24) \(-Y'(CR_4R_4')p-(W)_q-(T)_o-(CR_4R_4')p-(CH_2)-ONO_2;\)
(25) \(-Y'(CR_4R_4')q-C(Z_1)-V-(CR_4R_4')q-(CH_2)-ONO_2;\)
(26) \(-Y'-(CR_4R_4')o-C(R_4)(ONO_2)-(CR_4R_4')q-(T)_o-(W)_q-(T)_o-(CR_4R_4')o-R_5;\)
(27) \(-Y'-(CR_4R_4')o-V-(CR_4R_4')o-Q'(CR_4R_4')o-(CH_2)-ONO_2;\)
(28) \(-Y'-(CR_4R_4')q-C(Z_1)-Q'(CR_4R_4')o-(CH_2)-ONO_2;\)
(29) \(-Y'-(CR_4R_4')p-V-(CR_4R_4')p-(CH_2)-ONO_2;\)
(30) \(-Y'(CR_4R_4')o-V-(CH_2)_q-(T)_o-(CR_4R_4')q-(CH_2)-ONO_2;\)
(31) \(-Y'(CR_4R_4')p-(T)_o-Q'(T)_o-(CR_4R_4')q-(CH_2)-ONO_2;\)
(32) \(-Y'(CR_4R_4')q-C(Z_1)-(CR_4R_4')q-V-(CR_4R_4')q-O'(CR_4R_4')q-(CH_2)-ONO_2;\)
(33) \(-Y'(CR_4R_4')q-C(Z_1)-(CR_4R_4')q-(W)_q-(CR_4R_4')q-O'(CR_4R_4')q-(CH_2)-ONO_2;\)
(34) \(-Y'-(CR_4R_4')o-Q'(CR_4R_4')o-ONO_2;\) and
(35) \(-Y'(CR_4R_4')o-V-(CR_4R_4')o-Q'(CR_4R_4')o-ONO_2;\)

wherein:

R4 and R4' are independently selected in each case from hydrogen, a lower alkyl group, -OH, -CH2OH, -ONO2, -NO2 and -CH2ONO2; or R4 and R4' form together with the carbon atom to which they are joined a cycloalkyl
group or a heterocyclic ring;
V is selected from -C(O)-T-, -T-C(O)-, -T-C(O)-T and T-C(O)-C(O)-T;
W is a covalent bond or a carbonyl group;
T is independently selected in each case from O, (S(0)\(\_\))\(\_\)\(\_\) and NR,Rk;
wherein:
R, and R, are independently selected from hydrogen, an alkyl group, an aryl group, a heterocyclic ring, an alkylcarbonyl group, an arylcarbonyl group, an alkylsulfonyl group, an arylsulfonyl group, an alkylsulfanyl group, an arylsulfanyl group, a sulfonamido group, a N-alkylsulfonamido group, a N,N-diarylsulfonamido group, an N-alkyl-N-arylsulfonamido group, a carboxamido group and a hydroxy group;
p in each case is independently an integer selected from 1, 2, 3, 4, 5 and 6;
q in each case is independently an integer selected from 1, 2 and 3;
o and o' in each case are independently an integer selected from 0, 1 and 2;
Y' is -C=O or -C=S;
B is phenyl or (CH\(\_\))\(\_\);
Q' is selected from a cycloalkyl group, a heterocyclic ring and an aryl group;
Zi is selected from (=0), (=N-0R), (=N-NR\(\_\)\(\_\)) and (=CR\(\_\)\(\_\));
M and M' are independently selected in each case from -OH\(\_\)\(\_\)N\(\_\)\(\_\)+-(CR\(\_\)\(\_\)R\(\_\))\(\_\)q-
CH\(\_\)\(\_\)ONO\(\_\)\(\_\) and -T-(CR\(\_\)\(\_\)R\(\_\))\(\_\)o-CH\(\_\)\(\_\)ONO\(\_\)\(\_\);
R and R are independently selected in each case from a hydrogen radical, a hydroxy group, an alkyl group, an aryl group, an arylalkyl group, a carboxylic ester, an alkylcarbonyl group, an arylcarbonyl group, a carboxamido group, an alkoxycarbonyl group, an alkoxaryl group, a cycloalkyl group and a heterocyclic ring;
or a salt, isomer, prodrug or solvate thereof.

In a preferred embodiment, R has the following meanings in the structure of
Formula (I):
wherein T is ortho, meta or para:
(35) \( \text{ONO}_2 \)

(36) \( \text{NO}_2 \)

(37) \( \text{CO} \)

(38) \( \text{ONO}_2 \)

(39) \( \text{CO} \)

(40) \( \text{NO}_2 \)

(41) \( \text{CO} \)

(42) \( \text{NO}_2 \)

(43) \( \text{NO}_2 \)

(44) \( \text{NO}_2 \)
wherein:

- \( Y' \) is -C=O or -C=S;
- \( T' \) is selected from 0, S and NR\(_6\);
- \( X' \) is selected from O, (S(0)\(_0\))\(_0\)' and NR\(_6\);
- \( R_i \) is selected from hydrogen, an alkyl group and an aryl group;
R is a lower alkyl group or an aryl group;
Ri is independently selected in each case from hydrogen, a hydroxyl group, a lower alkyl group, an aryl group, -NO₂, -CH₂-ONO₂ and -CH₂-OH;
n' and m' in each case are independently an integer selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;
o and o' in each case are independently an integer selected from 0, 1 and 2;
or a salt, isomer, prodrug and solvate thereof.

In a preferred embodiment, in the compound of Formula (I) Ri is selected from -(CH₂)ₐZ and -CH=CH-(CH₂)ₐZ; wherein:
Z is selected from -SO₃H, -SO₃⁻X⁺, -SO₃R₃, -PO₃H, -PO₃⁻X⁺, -PO₃R₃, -CO₂H, -CO₂⁻X⁺ and -CO₂R₃; wherein:
X⁺ is an organic or inorganic cation, and Rᵢ is selected from a lower alkyl group, a phenyl group and a benzyl group;
a is O or 1; and
b is O or 1.

In another preferred embodiment, in the compound of Formula (I) R₉ and R₉' are independently selected from -OH, -OC(O)-RᵢO and -OR₂; with the proviso that at least one of R₉ and R₉' is -OR_2 and wherein R₉ and R₉' can have different values of R₂; wherein:
Rᵢ is a lower alkyl group and R₂ is selected from:
(1) -Y'-(CR₄R₄')ₚ-ONO₂;
(2) -YHCR₄R₄VT-(CR₄R₄VONO₂;
(3) where T is located in an ortho, meta or para orientation;
wherein:
Y' is -C=O;
R and R' are independently selected in each case from hydrogen, a lower alkyl group, -OH, -CH$_2$OH, -ONO$_2$, -NO$_2$ and -CH$_2$ONO$_2$; or R$_4$ and R$_4'$ form together with the carbon atom to which they are joined a cycloalkyl group or a heterocyclic ring;

T is independently selected from O and S;

p is an integer selected from 1, 2, 3, 4, 5 and 6; and

o is an integer selected from 0, 1 and 2;

or a salt, isomer, prodrug or solvate thereof.

In another preferred embodiment R$_i$ is selected from -(CH$_2$)$_a$Z and -CH=CH-(CH$_2$)$_b$Z; wherein:

Z is selected from -SO$_3$H, -SO$_3$X$^+$, -SO$_3$R$_3$, -CO$_2$H, -CO$_2$X$^+$ and -CO$_2$R$_3$; wherein:

X$^+$ is an organic or inorganic cation and R$_3$ is selected from a lower alkyl group, a phenyl group and a benzyl group;

a is O or 1;

b is O or 1; and

R$_9$ and R$_9'$ are independently selected from -OH, -OC(O)-RiO and OR$_2$; with the proviso that at least one of R$_9$ and R$_9'$ is -OR$_2$ and wherein R$_9$ and R$_9'$ can have different values of R$_2$; wherein:

Rio is a lower alkyl group and R$_2$ is selected from:

(1) -Y'-(CR$_4$R$_4'$)$_p$-ONO$_2$;

(2) -YHCR$_4$R$_4$VT-(CR$_4$R$_4$VONO$_2$; (3)

\[ \text{Y'}-(\text{CR}_4\text{R}_4')_o \text{---T---(CR}_4\text{R}_4')_p \text{---ONO}_2 \]

wherein T is located in an ortho, meta or para orientation;

wherein:

Y' is -C=O;
R₄ and R₄' are independently selected in each case from hydrogen, a lower alkyl group, -OH, -CH₂OH, -ONO₂, -NO₂ and -CH₂ONO₂; or R₄ and R₄' form together with the carbon atom to which they are joined a cycloalkyl group or a heterocyclic ring;

T is independently selected from O and S;
p is an integer selected from 1, 2, 3, 4, 5 and 6; and
o is an integer selected from o, 1 and 2;
or a salt, isomer, prodrug or solvate thereof.

In a more preferred embodiment, Ri is selected from -\((\text{CH}_2)ₙ\)Z and -CH=CH-(\text{CH}_2)ₙZ; wherein:

Z is selected from -SO₃H, -SO₃⁻X⁺, -SO₃R₃, -CO₂H, -CO₂⁻X⁺ and -CO₂R₃;

wherein:

X⁺ is an organic or inorganic cation and R₃ is a lower alkyl group;

a is O or 1;
b is O or 1; and

R₉ and R₉' are independently selected from -OH, -OC(O)-RiO and OR₂; with the proviso that at least one of R₉ and R₉' is -OR₂ and wherein R₉ and R₉' can have different values of R₂; wherein:

Rio is a lower alkyl group and R₂ is -Y'-(CR₄R₄')ₚ-ONO₂; wherein

Y' is -C=O;

R₄ and R₄' are independently selected in each case from hydrogen, a lower alkyl group, -OH, -CH₂OH, -ONO₂, -NO₂ and -CH₂ONO₂; or R₄ and R₄' form together with the carbon atom to which they are joined a cycloalkyl group or a heterocyclic ring;
p is an integer selected from 1, 2, 3, 4, 5, and 6.
or a salt, isomer, prodrug or solvate thereof.

In a still more preferred embodiment, in the compound of Formula (I):
Ri is selected from -\((\text{CH}_2)ₙ\)Z and -CH=CH-(\text{CH}_2)ₙZ; wherein:

Z is selected from -SO₃H, -SO₃⁻X⁺, -SO₃R₃, -CO₂H, -CO₂⁻X⁺ and -CO₂R₃;
wherein:

\( X^+ \) is an organic or inorganic cation and \( R_3 \) is a lower alkyl group;

a is 0 or 1;

b is 0 or 1; and

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\( R_g \) and \( R_g' \) are independently selected from \(-\text{OH}, -\text{OC(O)}\text{-RiO and OR}_2\); with the proviso that at least one of \( R_g \) and \( R_g' \) is \(-\text{OR}_2 \) and wherein \( R_g \) and \( R_g' \) can have different values of \( R_2 \); wherein:

\( R_9 \) is a lower alkyl group and \( R_2 \) is \(-\text{Y'}-(\text{CR}_4\text{R}_4')_p\text{-ONO}_2\); wherein

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\( Y' \) is \(-\text{C=O};\)

\( R_4 \) and \( R_4' \) are hydrogen;

p is an integer selected from 1, 2, 3, 4, 5, and 6.

or a salt, isomer, prodrug or solvate thereof.

In a still more preferred embodiment, in the compound of Formula (I):

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\( R_i \) is selected from \(-(\text{CH})_aZ \) and \(-\text{CH=CH-(CH}_2)_bZ \); wherein:

\( Z \) is selected from \(-\text{SO}_3\text{H}, -\text{SO}_3\text{X}^+ \) and \(-\text{SO}_3\text{R}_3 \); wherein:

\( X^+ \) is an organic or inorganic cation and \( R_3 \) is a lower alkyl group;

a is 0 or 1;

20

b is 0 or 1; and

\( R_g \) and \( R_g' \) are independently selected from \(-\text{OH}, -\text{OC(O)}\text{-RiO and OR}_2\); with the proviso that at least one of \( R_g \) and \( R_g' \) is \(-\text{OR}_2 \) and wherein \( R_g \) and \( R_g' \) can have different values of \( R_2 \); wherein:

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\( R_9 \) is a lower alkyl group and \( R_2 \) is \(-\text{Y'}-(\text{CR}_4\text{R}_4')_p\text{-ONO}_2\); wherein

\( Y' \) is \(-\text{C=O};\)

\( R_4 \) and \( R_4' \) are hydrogen;

p is an integer selected from 1, 2, 3, 4, 5, and 6.

or a salt, isomer, prodrug or solvate thereof.

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In a still more preferred embodiment, \( R_{i0} \) is methyl or ethyl.
In a particular embodiment of the invention R₃ is selected from methyl, ethyl, isopropyl and phenyl.

In other preferred embodiments of the invention, the compound of Formula (I) is in the form of acid or salt and Z is selected from -SO₃⁻X⁺, -SO₃H, -CO₂⁻X⁺ and -CO₂H.

In a preferred embodiment the cation X⁺ in the compounds of Formula (I) can be any physiologically acceptable cation known by persons skilled in the art, and includes but is not limited to those described in Heinrich Stahl, Camille G. Wermuth (Editors), "Handbook of Pharmaceutical Salts Properties, Selections and Use", Verlag Helvetica Chimica Acta, Zurich, Switzerland, Wiley-VCH, Weinheim, Germany, 2002; the entire descriptions of which are incorporated as a reference herein. Cation X⁺ is selected such that the total charge of the compounds of Formula (I) is neutral.

In a more preferred embodiment of the invention the inorganic cation is sodium, potassium, lithium, calcium or magnesium. More preferred inorganic cations are potassium and calcium. In another embodiment of the invention, the organic cation is [NH₄⁺Rₚ]⁺: wherein p in each case is independently selected from 0, 1, 2, 3 and 4; and R is a lower alkyl group. In another embodiment of the invention, the organic cation is a diethylamino group [H₂N⁺(C₂H₅)₂], piperazine or pyridine. A preferred inorganic cation is a diethylamino group.

In another embodiment of the invention the compounds of Formula (I) are the compounds of Formula (II) to the compounds of Formula (CVI);
(XXXIX)

(XL)

(XLI)

(XLII)
(LV)

(LVI)

(LVII)

(LVIII)
wherein:

\( n \) is 1 or 2; and

\( X_m \) is selected from hydrogen, an organic or inorganic cation \( X^+ \) and \( R_3 \) as
defined in Formula (I), with the proviso that when $X_m$ is hydrogen or $R_3$ then $n$ is 1.

Therefore, the compounds of Formula (II) to the compounds of Formula (CVI) may be in the form of acid, ester and salt. Nevertheless, compounds in the form of acid or salt are preferred, and then $X_m$ is selected from hydrogen and an organic or inorganic cation $X^+$. The compounds of the invention having one or more asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereoisomers, mixtures of enantiomers, mixtures of diastereoisomers, racemic mixtures of enantiomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. It must be understood that the scope of the invention foresees and includes all these isomers and mixtures thereof.

The compounds of Formula (I) can also be in the form of solvates, particularly in the form of hydrates. The preparation of the compounds of Formula (I) as well as the solvates thereof can be carried out by a person skilled in the art using conventional methods and reagents available on the market.

Although it was previously indicated in one of the preferred embodiments with respect to the definition of cation $X^+$, the scope of this invention includes any salt thereof, particularly any pharmaceutically acceptable salt of the compound. The term "pharmaceutically acceptable salts" includes the metal salts or the addition salts which can be used in dosage forms. For example, the pharmaceutically acceptable salts of the compounds provided herein can be acid addition salts, base addition salts or metal salts, and can be synthesized from parent compounds containing a basic or acid residue by means of conventional chemical processes. Such salts are generally prepared, for example, by reacting the free acid or base forms of these compounds with a stoichiometric amount of the suitable base or acid in water or in an organic solvent or in a mixture of both. Non-aqueous media are generally preferred, such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile. Examples of acid addition salts include mineral acid additions salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, organic acid addition salts such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and p-toluenesulfonate. Examples of alkali
addition salts include inorganic salts such as, for example, ammonium salts and organic alkaline salts such as, for example, diethylamine, ethylenediamine, ethanolamine, N,N-dialkyleneethanolamine, triethanolamine, glutamine and basic amino acid salts. Examples of metal salts include, for example, sodium, potassium, calcium, magnesium, aluminium and lithium salts.

The term "pharmaceutically acceptable" relates to molecular entities and compositions that are physiologically tolerable and do not normally cause an allergic reaction or a similar adverse reaction, such as gastric discomfort, dizziness and the like, when administered to humans. As used herein, the term "pharmaceutically acceptable" preferably means that it is approved by a regulatory agency of the federal or state government or listed in the US pharmacopoeia or another pharmacopoeia, generally recognized for its use in animals and more particularly in human beings.

It will be evident for persons skilled in the art that the scope of the present invention also comprises salts that are not pharmaceutically acceptable as possible means for obtaining pharmaceutically acceptable salts.

According to this invention, the term "solvate" must be understood to mean any form of the active compound according to the invention having another molecule (most likely a polar solvent) joined thereto by means of a non-covalent bond.

Examples of solvates include hydrates and alcoholates, preferably C1-C6 alcoholates, methanolate for example.

The pharmaceutically acceptable salts of 2,5-dihydroxybenzene compounds of Formula (I) can be obtained from organic or inorganic acids or bases by conventional methods by reacting the suitable acid or base with the compound.

The compounds of Formula (I), as well the compounds of Formulas (II) to (CVI) can be synthesized by a person having ordinary skill in the art using conventional methods. Nitrosation of the precursor compounds is thus carried out through one or more sites such as oxygen, sulfur and/or nitrogen using conventional methods known by a person having ordinary skill in the art. Said methods for carrying out the nitrosation of the precursor compounds are described in WO 00/061537, WO 94/03421, WO 94/04484, WO 94/12463, WO 95/09831, WO
95/19952, WO 95/30641, WO 97/27749, WO 98/09948, WO 98/19672, WO 98/21193, WO 00/51988, WO 00/61537, WO 01/00563, WO 01/04082, WO 01/10814, WO 01/12584, WO 01/45703, WO 00/61541, WO 00/61537, WO 02/11707, WO 02/30866, WO 06/066894, WO 06/079610, WO 06/008196 and in Oae et al, Org. Prep. Proc. Interno, 15(3): 165-198 (1983), the entire accesses of each of which are incorporated by reference. The methods for the nitrosation of the compounds described in these references can be applied by a person having ordinary skill in the art to produce any of the nitrosated cardiovascular compounds described and enclosed. The synthesis of the precursor compounds is also perfectly accessible for the person having ordinary skill in the art. Synthetic examples are provided hereinafter for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

An additional aspect of the invention relates to a pharmaceutical composition comprising at least one compound of the invention, a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof and a pharmaceutically stable carrier.

The term "carrier" relates to a diluent, adjuvant, excipient or vehicle whereinby the active ingredient is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of animal, plant, synthetic or petroleum origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like.

Aqueous saline solutions or water and aqueous dextrose and glycerol solutions, particularly for injectable solutions, in addition to buffers, isotonic agents or agents that can increase solubility, are preferably used as carriers. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin or "Tratado de Farmacia Galenica", C. Fauli i Trillo, Luzan 5, S.A. de Ediciones, 1993.

The pharmaceutical composition of the invention can be administered in the form of different preparations. Non-limiting examples of preparations for oral administration are tablets, capsules, syrups or suspensions for example; for ophthalmic administration, solutions, ointments and creams for example; and for parenteral administration, sterile aqueous and non-aqueous solutions for injections or sterile aqueous and non-aqueous suspensions for example. The pharmaceutical compositions of the invention can further include topical compositions, for example,
creams, liposome preparations, ointments or pastes, or transdermal preparations such as patches or strips. The pharmaceutical composition of the invention can also be prepared for vaginal or rectal administration, for example, rectal gel or suppositories.

The compounds of the invention can also be formulated for a delayed release. These prolonged action formulations can be administered by implantation (subcutaneously or intramuscularly for example) or by an intramuscular injection. Therefore, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (as an emulsion in an acceptable oil for example), or ion exchange resins, or as scarcely soluble derivatives, as a scarcely soluble salt for example.

The compositions comprise an effective amount of nitrosated 2,5-dihydroxybenzene compounds of Formula (I) between approximately 0.001 and approximately 30%.

In one embodiment, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered orally, buccally, by inhalation or parenterally in an amount of approximately 5 mg daily to approximately 10 g daily. In particular embodiments, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered orally, buccally, by inhalation or parenterally in an amount of approximately 10 mg daily to approximately 8 g daily. In more particular embodiments, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered orally, buccally, by inhalation or parenterally in an amount of approximately 25 mg daily to approximately 6 g daily. In a more particular embodiment, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered in an amount of approximately 50 mg daily to approximately 4 g daily.

In a still more particular embodiment, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered in an amount of approximately 75 mg daily to approximately 2 g daily. In another particular embodiment, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered in an amount of approximately 0.1 g daily to approximately 1 g daily. The particular amounts of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered in the form of a single dose once daily; or in multiple doses throughout the day; or as
an oral sustained release formulation. In one embodiment of the invention, approximately 10 g, 5 g, 2 g, 1 g, 0.5 g, 0.1 g, 75 mg, 50 mg or 10 mg of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) are administered orally, buccally, by inhalation or parenterally once daily (q.d). In another embodiment of the invention, approximately 10 g, 5 g, 2 g, 1 g, 0.5 g, 0.1 g, 75 mg, 50 mg or 10 mg of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) are administered orally, buccally, by inhalation or parenterally twice daily (b.i.d). In another embodiment of the invention, approximately 10 g, 5 g, 2 g, 1 g, 0.5 g, 0.1 g, 75 mg, 50 mg or 10 mg of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) are administered orally, buccally, by inhalation or parenterally three times daily (t.i.d.). In another embodiment of the invention, approximately 10 g, 5 g, 2 g, 1 g, 0.5 g, 0.1 g, 75 mg, 50 mg or 10 mg of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) are administered orally, buccally, by inhalation or parenterally four times daily.

In particular embodiments, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered topically in a formulation comprising an amount from approximately 0.001% to approximately 30% (w/w) of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I). In a more particular embodiment, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered topically in a formulation comprising an amount from approximately 0.01% to approximately 20% (w/w) of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I). In a still more particular embodiment, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered topically in a formulation comprising an amount from approximately 0.1% to approximately 15% (w/w) of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I). In a more particular embodiment, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered topically in a formulation comprising an amount from approximately 0.5% to approximately 10% (w/w) of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I). In another particular embodiment, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered topically in a formulation comprising an amount from approximately 1% to
approximately 5% (w/w) of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I). In a more particular embodiment, the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered topically in a formulation comprising an amount from approximately 2.5% to approximately 4% (w/w) of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I). The topical formulation comprising the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) can be administered in the form of a single dose once daily; or in multiple doses several times throughout the whole day. In one embodiment of the invention, the topical formulation comprising approximately 30%, 20%, 15%, 10%, 5%, 2.5%, 1%, 0.5%, 0.1% or 0.001% of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) is administered four times daily. In another embodiment of the invention, the topical formulation comprising approximately 30%, 20%, 15%, 10%, 5%, 2.5%, 1%, 0.5%, 0.1% or 0.001% of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) is administered three times daily (t.i.d). In another further embodiment of the invention, the topical formulation comprising approximately 30%, 20%, 15%, 10%, 5%, 2.5%, 1%, 0.5%, 0.1% or 0.001% of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) is administered twice daily (b.i.d). In another embodiment of the invention, the topical formulation comprising approximately 30%, 20%, 15%, 10%, 5%, 2.5%, 1%, 0.5%, 0.1% or 0.001% of the nitrosated 2,5-dihydroxybenzene compounds of Formula (I) is administered once daily (qd).

An effective administered amount of a compound used in the invention will generally depend on the relative efficacy of the chosen compound, the severity of the treated disorder, or the age, weight or method of administration. Nevertheless, the active compounds will normally be administered once or more times daily, for example 1, 2, 3, or 4 times daily, with a typical total daily dose ranging from 0.01 to 200 mg/kg/day.

The invention provides compositions comprising at least one nitrosated 2,5-dihydroxybenzene compound according to the invention and at least one other therapeutic agent, including but not limited to chemotherapeutic agents, steroids, retinoids, antimicrobial compounds, antioxidants, non-steroidal anti-inflammatory agents, NMDA receptor antagonists, endothelin antagonists, immunomodulating
agents, vitamin D analogs, salicylic acid, cholinesterase inhibitors, tau protein phosphorylation inhibitors, nitric oxide donors, phosphodiesterase inhibitors and combinations of two or more thereof. The invention also provides for said compositions in a pharmaceutically acceptable carrier.

The compounds used in the present invention can also be administered with other drugs to provide a combination therapy. The other drugs can form part of the same composition, or can be administered in the form of a separate composition for administration at the same time or at a different time.

Another embodiment of the invention provides the administration of sets or "kits" comprising at least one nitrosated 2,5-dihydroxybenzene compound and at least one therapeutic agent, including but not limited to chemotherapeutic agents, steroids, retinoids, antimicrobial compounds, antioxidants, non-steroidal anti-inflammatory agents, NMDA receptor antagonists, endothelin antagonists, immunomodulating agents, vitamin D analogs, salicylic acid, cholinesterase inhibitors, tau protein phosphorylation inhibitors, nitric oxide donors, phosphodiesterase inhibitors and combinations of two or more thereof. The nitrosated 2,5-dihydroxybenzene compound and the therapeutic agent can be separate components in the kit or can be in the form of a composition in one or more pharmaceutically acceptable carriers.

Suitable chemotherapeutic agents include but are not limited to alkylating agents such as, for example, cyclophosphamide, carmustine, daunorubicin, mechloretamine, chlorambucil, nimustine, melphalan and the like; anthracyclines, such as, for example, daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin and the like; taxane compounds, such as, for example, paclitaxel, docetaxel and the like; topoisomerase inhibitors such as, for example, etoposide, teniposide, tuliposide and the like; nucleotide analogs such as, for example, azacitidine, azathioprine, capecitabin, cytarabine, doxifluridine, 5-fluorouracil and its precursors, gemcitabine, mercaptopurine, methotrexate, thioguanine and the like; platinum-based agents such as, for example, carboplatin, cisplatin, oxaliplatin and the like; antineoplastic agents such as, for example, vincristine, leucovorin, lomustine, procarbazine and the like; hormone modulators
such as, for example, tamoxifen, finasteride, 5-α-reductase inhibitors and the like; vinca alkaloids such as, for example, vinblastine, vincristine, vinodesine, vinorelbine and the like. Suitable chemotherapeutic agents are described in more detail in the literature, such as in The Merck Index on CD-ROM, 13th Edition.

In some embodiments of the invention, the chemotherapeutic agents are 5-fluorouracil, tamoxifen, paclitaxel, cisplatin, carboplatin, carmustine, nimustine, leucovorin, gemcitabine, docetaxel, vincristine, vinblastine, vinorelbine, vindesine, irinotecan, vinca alkaloids or topoisomerase inhibitors.

Suitable steroids include but are not limited to budesonide, dexamethasone, corticosterone, prednisolone and the like. Suitable steroids are described in more detail in the literature, such as in The Merck Index on CD-ROM, 13th Edition.

In one embodiment of the invention, the steroids are dexamethasone, prednisolone and corticosteroids. Corticosteroids include but are not limited to both topical (in creams, ointments, unguents, or gels) and systemic, intra-articular and inhaled corticoids; topical corticoids such as, for example, triamcinolone acetate and the like; systemic corticoids such as, for example, prednisone, and the like.

Suitable retinoids include but are not limited to natural and synthetic analogs of vitamin A (retinol), vitamin A aldehyde (retinal), vitamin A acid (retinoic acid (RA)), including all the trans-, 9-cis- and 13-cis-retinoic acids), tretinoin, isotretinoin, alitretinoin, etretinate, acitretin, tazarotene, bexarotene and the like. Suitable retinoids are also described in document EP 0379367 A2, United States patent numbers 4,887,805; 4,888,342; 5,514,825; 5,698,700; 5,696,162; 5,688,957; 5,677,451; 5,677,323; 5,677,320; 5,675,033; 5,675,024; 5,672,710; 5,688,175; 5,663,367; 5,663,357; 5,663,347; 5,648,514; 5,648,503; 5,618,943; 5,618,931; 5,618,836; 5,605,915; 5,602,130; 5,648,563; 5,648,385; 5,618,839; 5,559,248; 5,616,712; 5,616,597; 5,602,135; 5,599,819; 5,556,996; 5,534,516; 5,516,904; 5,498,755; 5,470,999; 5,468,879; 5,455,265; 5,451,605; 5,343,173; 5,426,118; 5,414,007; 5,407,937; 5,399,586; 5,399,561; 5,391,753 and the like; the entire descriptions of which are incorporated herein as a reference.

In some embodiments of the invention, the retinoids are retinol, retinal, retinoic acid, tretinoin, isotretinoin or alitretinoin.
Suitable antimicrobial compounds include but are not limited to macrolides such as, for example, azithromycin, clarithromycin, dirithromycin, erythromycin, milbemycin, troleandomycin and the like; monobactams such as, for example, aztreonam and the like; tetracyclines such as, for example, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline and the like; aminoglycosides such as, for example, amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, streptomycin, tobramycin and the like; carbacephems such as, for example, loracarbef and the like; carbapenems such as, for example, ertapenem, imipenem, meropenem and the like; tetracyclines such as, for example, azithromycin, clarithromycin, dirithromycin, erythromycin, milbemycin, troleandomycin and the like; monobactams such as, for example, aztreonam and the like; tetracyclines such as, for example, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline and the like; aminoglycosides such as, for example, amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, streptomycin, tobramycin and the like; carbacephems such as, for example, loracarbef and the like; carbapenems such as, for example, ertapenem, imipenem, meropenem and the like; penicillins such as, for example, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, nafcillin, penicillin, pipercillin, ticarcillin and the like; polypeptides such as, for example, bacitracin, colistin, polymyxin B and the like; beta-lactamase inhibitors; cephalosporins such as, for example, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, cefadroxil, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefazolin, cephalaxin, cefepime and the like; quinolones such as, for example, ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacil, ofloxacin, trovafloxacin and the like; streptogramins; sulfonamides such as, for example, mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilamide, sulfasalazine, sulfisoxazole, trimethoprim, trimethoprim-sulfamethoxazole and the like; and the combination drugs such as, for example, sulfamethoxazole and trimethoprim and the like. Suitable antimicrobial compounds of the invention are more fully described in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, (1996); Merck Index on CD-ROM, 13th Edition; STN Express, file phar and file registry, the entire descriptions of which are incorporated herein as a reference.

In some embodiments of the invention, the antimicrobial compounds are tetracycline, erythromycin or clindamycin.

Suitable antioxidants include but are not limited to free radical eliminators, iron chelating agents, small molecule antioxidants and antioxidant enzymes and the
Suitable iron chelating agents include but are not limited to deferoxamine, deferiprone, dithiocarbamate, ethylenediaminetetraacetic acid and the like. Suitable small molecule antioxidants include but are not limited to hydralazine, glutathione, ascorbic acid (vitamin C), vitamin E, cysteine, N-acetyl-cysteine, β-carotene, ubiquinone, ubiquinol-10, tocopherols, coenzyme Q, superoxide dismutase mimetics such as, for example, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), DOXYL, PROXYL nitroxide compounds; 4-hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy (Tempol), M-40401, M-40403, M-40407, M-40419, M-40484, M-40587, M-40588 and the like. Suitable antioxidant enzymes include but are not limited to superoxide dismutase, catalase, glutathione peroxidase, NADPH oxidase inhibitors such as, for example, apocynin, aminoguanidine, ONO 1714, SI7834 (a benzo(b)pyran-4-one derivative) and the like; xanthine oxidase inhibitors such as, for example, allopurinol, oxypurinol, amflutizole, diethyldithiocarbamate, 2-styrylchromones, cristine, luteolin, kaempferol, quercetin, myricetin, isorhamnetin, benzophenones such as 2,2',4,4'-tetrahydroxybenzophenone, 3,4,5,2',3',4'-hexahydroxybenzophenone and 4,4'-dihydroxybenzophenone; benzothiazinone analogs such as 2-amino-4H-1,3-benzothiazin-4-one, 2-guanidine-4H-1,3-benzothiazin-4-one and rhodanine; N-hydroxyguanidine derivative such as PR5 (1-(3,4-dimethoxy-2-chlorobenzylideneamino)-3-hydroxyguanidine); 6-formylpterin and the like. The antioxidant enzymes can be released by gene therapy in the form of a viral vector and/or a non-viral vector. Suitable antioxidants are described in more detail in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and The Merck Index on CD-ROM, Thirteenth Edition; and in STN Express, file phar and file registry. In some embodiments, the antioxidants are ascorbic acid, vitamin E, apocynin, hydralazine compounds or superoxide dismutase mimetics.

Suitable anti-inflammatory drugs (NSAIDs) include but are not limited to acetaminophen, acemetacin, aceclofenac, alminoprofen, amfenac, bendazac, benoxaprofen, bromfenac, bucloxic acid, butibufen, carprofen, cinmetacin, clorpirac, diclofenaco, etodolac, felbinac, fenclozic acid, fenbufen, fenoprofen, fentiazac, flunoxaprofen, flurbiprofen, ibufenac, ibuprofen, indometacin, isofezolac, isoxepac,
indoprofen, ketoprofen, lonazolac, loxoprofen, metiazinic acid, mofezolac, miprofen, naproxen, oxaprozin, pirazolac, pirprofen, pranoprofen, protizinic acid, salicylamide, sulindac, suprofen, suxibuzone, tiaprofenic acid, tolmetin, xenbucin, ximoprofen, zaltoprofen, zomepirac, aspirin, acemetacin, bumadizone, carprofenac, clidanac, diflunisal, enfenamic acid, fendosal, flufenamic acid, flunixin, gentisic acid, ketorolac, meclofenamic acid, mefenamic acid, mesalamine, prodrugs thereof, and the like. Suitable NSAIDs are more fully described in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, pages 617-657; the Merck Index on CD-ROM, 13th Edition; and in US patent numbers 6,057,347 and 6,297,260 issued to NitroMed Inc., the entire descriptions of which are incorporated herein as a reference.

In some embodiments, the NSAIDs are acetaminophen, diclofenac, flurbiprofen, ibuprofen, indometacin, ketoprofen, naproxen or aspirin.

Suitable N-methyl-D-aspartate (NMDA) receptor antagonists include but are not limited to ketamine, dextromethorphan, memantine, amantadine, nitrous oxide, gacyclidine and the like.

In some embodiments, the NMDA receptor antagonist is dextromethorphan.

Suitable endothelin antagonists include but are not limited to atrasentan, bosentan, darusentan, enrasentan, sitaxsentan, sulfonamide, tezosentan, BMS 193884, BQ-123, SQ 28608 and the like. Suitable endothelin antagonists are described in more detail in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and The Merck Index on CD-ROM, Thirteenth Edition; and in STN Express, file phar and file registry.

Suitable immunomodulating agents include but are not limited to interferon α lib, autologous granulocyte-macrophage colony stimulating factor, APC 8015 (Provenge), anti-cancer vaccines, anti-sense oligonucleotides, bacille Calmette-Guerin (BCG) and the like.

Suitable vitamin D analogs include but are not limited to vitamin D3 analogs such as colecalciferol, calcidiol, calcitriol and the like.

Cholinesterase inhibitors include but are not limited to donepezil, tacine,
galantamine, rivastigmine, and the like.

Phosphodiesterase inhibitors include but are not limited to papaverine, zaprinast, sildenafil, tadalafil, vardenafil, avanafil, udenafil, rolipram, milrinone and the like.

Another aspect of the invention relates to a compound of the invention, a pharmaceutically acceptable salt, isomer or solvate thereof for its use as a medicinal product.

Another additional aspect of the present invention relates to a compound of the invention, a pharmaceutically acceptable salt, isomer or solvate thereof for its use in the treatment and/or prophylaxis of any of the diseases selected from the group consisting of (a) cancer (b) rosacea; (c) psoriasis; (d) fibrosis; (e) hemangiomas; (f) ocular diseases; (g) skin pigmentation and skin hyperpigmentation; (h) diseases associated with amyloidosis; (i) dermatitis; (j) actinic and seborrheic keratosis; (k) erectile dysfunction; (l) female sexual dysfunction; (m) arterial hypertension; (n) atherosclerosis; (o) inflammatory diseases such as arthritis, glomerulonephritis and asthma; (p) intestinal inflammatory diseases such as ulcerative colitis and Crohn's disease; (q) benign prostatic hyperplasia; (r) leishmaniasis; (s) angiogenesis associated to chronic temporal lobe epilepsy and (t) pain.

Another aspect of the invention relates to the use of a compound of the invention, a pharmaceutically acceptable salt, isomer or solvate thereof in the elaboration of a medicinal product.

Another additional aspect of the present invention relates to the use of a compound of the invention, a pharmaceutically acceptable salt, isomer or solvate thereof in the elaboration of a medicinal product for the treatment and/or prophylaxis of any of the diseases selected from the group consisting of (a) cancer (b) rosacea; (c) psoriasis; (d) fibrosis; (e) hemangiomas; (f) ocular diseases; (g) skin pigmentation and skin hyperpigmentation; (h) diseases associated with amyloidosis; (i) dermatitis; (j) actinic and seborrheic keratosis; (k) erectile dysfunction; (l) female sexual dysfunction; (m) arterial hypertension; (n) atherosclerosis; (o) inflammatory diseases such as arthritis, glomerulonephritis and asthma; (p) intestinal inflammatory diseases such as ulcerative colitis and Crohn's disease; (q) benign prostatic
hyperplasia; (r) leishmaniasis; (s) angiogenesis associated to chronic temporal lobe epilepsy and (t) pain.

In the context of this specification, the term "treatment and/or prophylaxis" means the administration of a compound or formulation according to the invention for preserving the health of a patient suffering or with the risk of suffering one of the diseases listed above. Said terms also include the administration of a compound or formulation according to the invention for preventing, improving or eliminating one or more symptoms associated with one of the diseases listed above.

In another embodiment, an effective amount of at least one nitrosated 2,5-dihydroxybenzene compound of Formula (I) and at least one therapeutic agent and combinations of two or more thereof, can be administered to the patient. The nitrosated 2,5-dihydroxybenzene compounds and/or the therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers. When administered separately, the nitrosated 2,5-dihydroxybenzene compound of Formula (I) can be administered approximately at the same time as part of the overall treatment regimen, i.e. as a combination therapy. The expression "approximately at the same time" includes administering the nitrosated 2,5-dihydroxybenzene compound simultaneously, sequentially, at the same time, at different times in the same day, on different days, as long as it is administered as part of an overall treatment regimen, i.e. a combination therapy or a therapeutic cocktail.

When administered alone, the compounds and compositions of the invention can be administered in combination with pharmaceutically acceptable carriers and in the dosages described herein. When the compounds and compositions of the invention are administered as a combination of at least one nitrosated 2,5-dihydroxybenzene compound of Formula (I), and/or at least one therapeutic agent, they can also be used in combination with one or more additional compounds which are known to be effective against the specific pathology set as a treatment target. The therapeutic agents and/or the different additional compounds can be administered
simultaneously with, after or before the administration of the nitrosated 2,5-
dihydroxybenzene compound.

The subject treated with the medicinal product of the invention is an animal, preferably a mammal, and more specifically a human being. The main purpose of the present invention is aimed at the treatment or prevention of the diseases described, mainly in humans. In a secondary manner, the present invention can be used for the treatment or prevention of said diseases in domestic animals or farm animals but is not limited to bovine, equine or porcine animals.

Another aspect of the invention is a pharmaceutical kit or set comprising one or more containers containing one or more compounds and/or compositions of the invention. A therapeutic agent or composition (for example chemotherapeutic agents, steroids, retinoids, antimicrobial compounds, antioxidants, non-steroidal anti-inflammatory agents, NMDA receptor antagonists, endothelin antagonists, immunomodulating agents, vitamin D analogs, salicylic acid, cholinesterase inhibitors, tau protein phosphorylation inhibitors, nitric oxide donors, phosphodiesterase inhibitors and combinations of two or more thereof) can be added, associated with such kit. The devices for administering these compositions would be in accordance with the provisions of the governmental agency regulating the manufacture, the use and the sale of pharmaceutical products or of biological products receiving approval by the agency for the manufacture, the use or the sale for human beings.

The following examples are given only as further illustration of the invention, they should not be taken as a definition of the limits of the invention.

Example 1: Preparation of compound V potassium salt (2-(hidroxy)-5-{(5-
nitrooxy)pentanoyl]oxy} benzene sulfonic acid potassium salt)
First step - Preparation of intermediate compound 1

A mixture of 4-nitrophenol (25 g), 5-bromo valeric acid (32.5 g), \( \text{N}-(\text{dimethylamino})\text{pyridine (DMAP, 3.5 g) in methylene dichloride (228 ml) was cooled to } 0 \degree C \), and then \( \text{EDCHCl} \) \( \text{(3-Dimethylaminopropyl)-N}^\text{\$} \text{-ethylcarbodiimide hydrochloride, 39.38 g) was added in portionwise. The mixture was stirred for 30 minutes at 0 \degree C. The temperature was slowly raised to rt and then it was stirred for an additional period of 8 hours. TLC showed completion of the reaction (3:7, EtOAc/Hexane). On completion of the reaction, it was charged 750 ml of water and the organic layer was separated. The organic layer was washed with 1N NaOH (110 ml) to remove the traces of nitrophenol and then it was washed with brine (200 ml), dried over anhydrous sodium sulphate, filtered and concentrated to yield compound 1 as a solid. Yield: 29 g (53.4%).

M.P: 53-55 \degree C; \( ^1\text{H} \text{NMR (CDCl}_3, 400 \text{MHz): } \delta 1.91 - 2.02 \ (4 \text{H, m}), 2.66 \ (2 \text{H, } t, J = 7.1 \text{ Hz}), 3.48 \ (2 \text{H, } t, 7.1 \text{ Hz}), 7.27 \ (2 \text{H, } d, J = 9.2 \text{ Hz}), 8.27 \ (2 \text{H, } d, J = 9.2 \text{ Hz).}

Second step - Preparation of intermediate compound 2 (5-nitrooxy valeric acid \( \text{A-nitrophenylester) }

5-bromovaleric acid 4-nitrophenylester (1) (6 g), obtained in the previous step, was dissolved in acetonitrile (60 ml) and silver nitrate (12 g) (to be handled under dark, under nitrogen atmosphere) was added. The mixture was heated at 60 \degree C for 30 hours. The reaction was monitored by TLC (2:8 EtOAc/Hexane), indicating a
trace amount of starting material. The reaction mass was cooled, evaporated and filtered using EtOAc. The filtrate was concentrated to obtain compound 2 as a yellow solid. (The reaction was carried under dark and nitrogen atmosphere). Yield: 5.2 g (92.8%).

M.P: 55-57 °C, 1H NMR (DMSO-400 MHz): δ 1.73 -1.80 (4H, m), 2.72 (2H, t, J = 7.0 Hz), 4.57 (2H, t, J = 7.0 Hz), 7.45 (2H, d, J = 8.8 Hz), 8.31 (2H, d, J = 8.8 Hz).

Third step - Preparation of compound V potassium salt (5NO-2HBS)

Hydroquinone (10 g) in 30 ml of n-heptane was cooled to 0 °C and then cone. H₂SO₄ (13.36 g) was added slowly dropwise. After completing the addition the reaction mixture was heated to 60 °C and it was stirred at this temperature for 1 h. The n-heptane was decanted then and the reaction mass was cooled to rt and 150 ml of water were added. Solid K₂CO₃ was slowly added to obtain pH 5-5.5, the reaction mixture was concentrated to reduce the aqueous layer volume to 2/3 and 200 ml of acetone were added. A white solid appeared then. The mixture was filtered and the filtrate was added to the 5-nitrooxy pentatonic acid-4-nitrophenyl ester 2 and DMAP. The reaction mixture was stirred at 25-30 °C for 8 h and it was monitored by TLC (3:7, EtOAc:Hexane). After completion of the reaction, the solvent was removed completely. 200 ml of methanol were added and the mixture was heated and stirred at 50 °C for 30 min. The solid obtained was filtered and dried to yield compound V potassium salt. Yield : 6.0 g.

M.P: 183 - 185 °C, 1H NMR (DMSO-400 MHz): δ 1.68 -1.78 (4H, m), 2.61 (2H, t, J = 6.0 Hz), 4.66 (2H, t, J = 6.0 Hz), 6.79 (IH, á, J = 8.8 Hz), 6.96 (IH, d, J = 8.8 Hz), 7.15 (IH, d, J = 2.8 Hz), 10.3 (IH, s). 13C NMR (DMSO-400 MHz): δ 20.5, 25.3, 32.6, 73.4, 116.9, 119.8, 124.3, 130.9, 141.8, 150.8, 171.8. MS: m/z 334 (M+K).

Example 2: Preparation of compound LXVII potassium salt

(2-(acetyloxy)-5-[(5-nitrooxy)pentanoyloxy] benzene sulfonic acid potassium salt)
Compound V potassium salt (6 g), obtained in the previous example, was dissolved in acetone (60 ml) and DMAP (0.1 g) was added. The mixture was cooled to 0 °C and acetic anhydride (8.6 ml) was charged through an addition funnel. The reaction mixture was stirred for 1 h at 0 °C to form a white solid. The temperature of the reaction mass was slowly raised to 25 °C and stirred for 5 h at this temperature. The reaction mixture was filtered and dried under vacuum to obtain compound LXVII potassium salt (5NO-2ABS) as a white solid. Yield: 4 g.

M.P: 212 - 213 °C, 1H NMR (DMSO-D6, 400 MHz): δ1.68 -1.80 (4H, m), 2.17 (3H, s), 2.66 (2H, t, J = 7.1 Hz), 4.57 (2H, t, J = 8.5 Hz), 7.06 (IH, d, J = 8.5 Hz), 7.09 (IH, d, J = 8.5 Hz), 7.41 (IH, d, J = 2.4 Hz). 13C NMR (DMSO-D6, 100 MHz): δ 20.5, 21.1, 25.3, 32.7, 73.4, 121.5, 123.0, 124.9, 140.7, 144.5, 147.0, 169.0, 171.6. MS: m/z 376.0 (M+K).

Example 3: Preparation of nitrosated 2,5-dihydroxybenzene compound VII (Bis-2, 5-{{(5-nitrooxy) pentanoyl}oxy}benzene sulfonyl acid calcium salt)
Calcium dobesilate (3g) was dissolved in 30 ml of ethanol and 5-nitrooxy-pentanoic acid 4-nitrophenyl ester (9.7 g) was added. Acetone (30 ml) was added to dissolve the reaction mixture. After obtaining clear solution, DMAP (0.42 g) was added to the reaction mixture and it was stirred for 1 h. A black green solution was obtained with a small amount of solid. The solid was filtered and the filtrate was stirred for 24 h at rt. The reaction was monitored by TLC and upon completion of reaction it was concentrated. Ethanol was added to the crude mass and it was stirred for 1 h. Compound VII (2,5NO-BS) is obtained as a white fluffy solid. Yield: 1.8 g. M.P: 145 - 147 °C. 1H NMR (DMSO-d6, 400 MHz): 61.68 -1.79 (4H, m), 2.55 (2H, t, J = 1.\ Hz), 2.66 (2H, t, J = 1.\ Hz), 4.54 - 4.58 (4H, m), 7.08 (IH, d, J = 8.8 Hz), 7.12 (IH, d, J = 8.8 Hz), 7.41 (IH, d, J = 2.5 Hz). MS: m/z 479.0 (M+K).

**Example 4: Preparation of compound VI calcium salt** (5-(hidroxy)-2-[[5-nitrooxy]pentanoyl]oxy) benzene sulfonic acid calcium salt)

First step - Preparation of intermediate compound 3 (Potassium salt of 5-[(tert-butoxycarbonyl)oxy]-2-hydroxy benzene sulfonic acid)

50 g of potassium dobesilate were dissolved in 500 ml of acetone and 125 ml of water. Boc-anhydride (47.75 g) was added dropwise to the reaction mixture at rt. Then DMAP (2.7 g) was added to it and it was stirred at rt for 20 h. The reaction was monitored by TLC and upon completion the reaction mixture was evaporated to dryness. 250 ml of MeOH were added and it was stirred for 30 min. Then it was filtered and washed with MeOH (100 ml). The solid obtained was dried to yield compound 3 as a solid. Yield: 28 g (39%).
B.P: 276 - 278 °C, \( \delta \) NMR (DMSO-\( \text{d}_6 \), 400 MHz): \( \delta \) 1.48 (9H, s), 6.79 (IH, d, \( J = 8.8 \) Hz), 7.02 (IH, d, \( J = 8.8 \) Hz), 7.17 (IH, d, \( J = 2.8 \) Hz), 10.3 (IH, s). MS: 288.8 (M\(^+\)-K).

**Second step - Preparation of intermediate compound 4**

Compound 3 (20 g), previously obtained, was dissolved in 200 ml of acetone and 50 ml of water. 5-nitrooxy valeric 4-nitro phenyl ester (25.97 g) and TEA (3.079 g) were added dropwise to the reaction mixture. It was stirred at rt for 18 h and monitored by TLC. The reaction mixture was evaporated under vacuum at 50 - 55 °C to get a crude mass. The compound 4 was purified by flash column chromatography (EtOAc : MeOH, 85 : 15). Yield: 16 g. MS: \( m/z \) 433.8 (M\(^+\)-K)

**Third step - Preparation of compound VI calcium salt (2NO-5HBS)**

Compound 4, previously obtained, (16 g) was stirred with 5N \( \text{H}_2\text{SO}_4 \) for 3 h. After 3 h, the reaction mixture was neutralized with \( \text{CaCO}_3 \) (40 g) and it was filtered. The filtrate was concentrated under vacuum at 55 - 60 °C to dryness. 90 ml of Acetone and 20 ml DM water were added and it was stirred for 10 min. Then, it was filtered and the filtrate was evaporated to yield compound VI. Yield: 8 g.

\( \delta \) NMR (DMSO-\( \text{d}_6 \), 400 MHz): \( \delta \) 1.65 (2H, m), 1.73 (2H, m), 3.03 (2H, m), 4.54 (2H, m), 6.67 (IH, d, \( J = 8.4 \) Hz), 6.76 (IH, d, \( J = 8.4 \) Hz), 7.15 (IH, d, \( J = 2.9 \) Hz). MS: 333.8 (M\(^+\)-K).

**Example 5: Inhibition of fibroblast growth factor-1 (FGF-I) induced mitogenesis**

Inhibition by 2,5-dihydroxybenzenesulfonate, 2-hydroxy-5-(5-(nitrooxy) pentanoyloxy) benzenesulfonate and 2-acetoxy-5-(5-(nitrooxy) pentanoyloxy) benzenesulfonate (Figures 1 and 2) of the mitogenesis induced by FGF-I in quiescent cultures of Balb/c 3T3 fibroblasts. The evaluated compounds were dissolved in 20 mM 4-(2-hydroxyethyl)-l-piperazineethanesulfonic acid and the pH of the solution adjusted at pH 7.2 with NaOH. Further dilutions of the inhibitors
required for preparing the appropriate solutions for the assays were carried out using the culture medium. The experiments were carried out as described in Fernandez-Tornero C et al. *J Biol Chem*, 2003.

5 **Example 6: Relaxation of isolated rat aorta** by nitrosated derivatives of 2,5-dihydroxybenzene sulfonate.

The following example shows the efficacy of potassium 5-(5-nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS), potassium 5-(5-nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-2ABS) and calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS) to relax pre-contracted rat aortic segments and supports the nitric oxide (NO) releasing capacity of these compounds.

Sprague-Dawley rats (300-400 g) were anesthetized with sodium pentobarbital (70 mg/kg, i.p.) and killed by bleeding. The thoracic aorta was carefully dissected, cleaned of excess fat and the connective tissue was placed in a Petri dish containing physiological salt solution (PSS) at 4 °C. The composition of PSS was (in mM): NaCl 119, KCl 4.6, CaCl$_2$ 1.5, MgCl$_2$ 1.2, NaHCO$_3$ 24.9, glucose 11, KH$_2$PO$_4$ 1.2 and EDTA 0.027. Aortae were divided into cylindrical segments of 4 to 5 mm in length. For the isometric tension recording, each vascular cylinder was set up in an organ bath as previously described by Angulo J et al. *(Hypertension, 28: 583-592, 1996)*. The organ chamber contained 5 ml of PSS at 37 °C and was continuously bubbled with 95% O$_2$/5% CO$_2$ mixture to maintain a pH of 7.4. Two horizontally arranged stainless steel pins were passed through the lumen of the vascular cylinder. One pin was fixed to the organ bath wall while the other one was connected vertically to a force transducer connected, in turn, to a data acquisition system (MacLab, AD Instruments, Castle Hill, Australia). The vascular segments were subjected to a tension of 1.5 g (optimal resting tension), which was readjusted every 15 min during a 90 min equilibration period.

The aortic segments were contracted with norepinephrine (NE; 0.3 µM) and, when a stable plateau was reached, exposed to acetylcholine (10 µM) to confirm the functional integrity of the endothelium. After a washout period, the vascular
segments were again contracted with NE (0.3 µM) and, when a stable plateau was reached, potassium 2,5-dihydroxybenzene sulfonate (2,5-DHBS), calcium 2-acetyloxy-5-hydroxybenzene sulfonate (2A-5HBS) or their respective nitrosated derivatives, 5NO-2HBS, 5NO-2ABS and 2,5NO-BS, at 1 nM to 100 µM concentrations, were added and the relaxation responses were determined. At the end of the experiments, papaverine (0.1 mM) was added to obtain maximal relaxation of aortic preparations.

Nitrosated derivatives, 5NO-2HBS, 5NO-2ABS and 2,5-NO-BS, but not their parental compounds, 2,5-DHBS and 2A-5HBS, caused concentration-dependent relaxation of aortic segments (Figures 3-5).

In other series of experiments, the isolated rat aortae were exposed to 5NO-2HBS, 5NO-2ABS and 2,5NO-BS (1 nM to 100 µM) and relaxant responses were determined. After an equilibration period, vascular segments were treated with the type 5 phosphodiesterase (PDE5) inhibitor, tadalafil (50 nM), or with the soluble guanylyl cyclase (sGC) inhibitor, 1H-[1,2,4]oxadiazolo[4,3-a] quinoxalin-1-one (ODQ) for 45 minutes and relaxant responses were again evaluated. Since PDE5 inhibition amplifies NO/cGMP mediated responses by preventing cGMP hydrolysis, the potentiation of 5NO-2HBS-, 5NO-2ABS- and 2,5NO-BS-induced vasodilation produced by tadalafil (Figure 6) suggests that relaxant capacity of 5NO-2HBS and 5NO-2ABS is mediated by the NO/cGMP pathway. This point is confirmed by the abolition of 5NO-2HBS-, 5NO-2ABS- and 2,5NO-BS-induced relaxation by inhibiting sGC, the enzyme responsible for synthesizing cGMP in response to NO (Figure 7), supporting the NO-releasing capacity of 5NO-2HBS, 5NO-2ABS and 2,5-NO-BS.

**Example 7:** Hypotensive effects of nitrosated derivatives of 2,5-dihydroxybenzene sulfonate.

The following example shows the efficacy of potassium 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS), potassium 5-(5-(nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-2ABS) and calcium
2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS) to lower blood pressure in vivo in anesthetized rats and supports the nitric oxide (NO) releasing capacity of these compounds.

Sprague-Dawley rats (250-400 g) were anesthetized with intraperitoneal injection of ketolar (50 mg/kg) and diazepam (4 mg/kg). Right carotid artery was catheterized for constant blood pressure and heart rate measurement by means of a pressure transducer connected to a PowerLab data acquisition system (ADInstruments) (Angulo J et al. Naunyn-Schiedadeberg's Arch Pharmacol, 358: 529-537, 1998). Left external jugular vein was catheterized for saline or drug infusion.

Once a stable blood pressure monitoring was achieved, intravenous injections of potassium 2,5-dihydroxybenzene sulfonate (2,5-DHBS; 10 mg/kg), calcium 2-acetyloxy-5-hydroxybenzene sulfonate (2A-5HBS; 10 mg/kg), 5NO-2HBS (3 and 10 mg/kg), 2,5NO-BS (3 and 10 mg/kg) or 5NO-2ABS (3 and 10 mg/kg) were administered and the effects on blood pressure were determined.

While 2,5-DHBS did not significantly influenced blood pressure, its nitrosated derivative 5NO-2HBS caused a significant drop in mean arterial pressure (MAP) at the two assayed doses (Figure 8). In the same way, the other nitrosated derivative of 2,5-DHBS, 2,5NO-BS, exerted a significant dose-dependent hypotensive effect at 3 and 10 mg/kg (Figure 9). The hypotensive effects of these compounds are compared in figure 13. The third nitrosated compound evaluated in this model, 5NO-2ABS, also caused a significant drop in MAP that was not mimicked by its parental compound, 2A-5HBS (Figures 10 and 15).

None of the molecules tested affected heart rate in anesthetized rats (Figures 11, 12 and 13).

Since the non-nitrosated compounds do not lower blood pressure, the hypotensive effects of the nitrosated derivatives shown in this example are likely mediated by the NO moiety of these molecules, supporting their in vivo capacity of releasing NO.

Example 8: Inhibition of glioma cell proliferation by 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate.
The following example shows the efficacy of potassium 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS) and potassium 5-(5-(nitrooxy)pentanoyloxy)-2-acetyloxybenzene sulfonate (5NO-2ABS) to reduce the proliferative capacity of glioma cells and supports the use of the compound in treating gliomas.

The cell line used was rat glioma C6 cells. The cells were cultured as previously described (Cuevas P et al. *Neurol Res*, 2005). The cells were cultured as adherent cells in Dulbecco's modified Eagle's medium, supplemented with 7.5% (v/v) of fetal bovine serum, 10 µg/ml of streptomycin and 10 units/ml of penicillin. The tumor cells were seeded in 24-well plates at a density of 10,000 cells/well, and were incubated at 37 °C in a humidified chamber with 5% CO₂. Once adhered, the cells were treated or not (controls) with 5NO-2HBS at 25, 50, 100 and 200 µM or 5NO-2ABS at 100, 200, 500 or 1000 µM and they were allowed to proliferate for 48 h. After this time, the glioma cell proliferation was evaluated by means of staining the fixed cells with crystal violet. The number of cells is proportional to the amount of retained dye, which was spectrophotometrically determined by measuring the absorbance at 595 nm once the dye was extracted from the cells.

Treatment with 5NO-2HBS inhibited rat glioma C6 cell proliferation in a concentration-dependent manner, an effect which was statistically significant at 25 µM concentration and above (Figure 16). Treatment with 5NO-2ABS inhibited rat glioma C6 cell proliferation in a concentration-dependent manner, an effect which was statistically significant at 1000 µM concentration (Figure 17).

**Example 9: Antithrombotic effects of nitrosated derivatives of 2,5-dihydroxybenzene sulfonate.**

The following example shows the efficacy of potassium 5-(5-(nitrooxy)pentanoyloxy)-2-hydroxybenzene sulfonate (5NO-2HBS) and calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS) to reduce thrombosis and support their use for clinical conditions that benefit from reduced platelet aggregation.
Sprague-Dawley rats were anesthetized with intraperitoneal injection of ketamine (50 mg/kg) and diazepam (4 mg/kg). Left external jugular vein was catheterized for saline or drug infusion. The tails of the rats were incised with disposable surgical blades. The bleeding of the incised tails was checked by blotting the blood with a filter paper every 30 s (Suzuki K et al. / Pharmacol Exp Ther, 309:607-615, 2004). Bleeding time was measured before and after intravenous administration of saline, potassium 2,5-dihydroxybenzene sulfonate (2,5-DHBS; 10 mg/kg), 5NO-2HBS (10 mg/kg) or 2,5NO-BS (10 mg/kg). Nitrosated compounds increased the bleeding time more efficiently than the parental molecule, 2,5-DHBS (Figure 18).

Example 10: Potentiating effects of nitrosated derivatives of 2,5-dihydroxybenzene sulfonate on erectile responses in rat.

The following example shows the efficacy of calcium 2,5-bis(5-(nitrooxy)pentanoyloxy)benzene sulfonate (2,5NO-BS) to potentiate erectile responses in anesthetized rats and support its use for treating erectile dysfunction.

Evaluation of erectile responses to cavernosal nerve electrical stimulation (CNES) was performed according to previously describe methods (Angulo et al. Br J Pharmacol, 139:854-862, 2003; Angulo J et al. / Sex Med, 2:111-122, 2005). Male Sprague-Dawley rats were anesthetized with ketamine (50 mg/kg) and diazepam (4 mg/kg). The surgical procedure consisted of dissection and isolation of the right cavernous nerve through an abdominal midline incision and exposure of penile crura through a transverse perineal incision. Intracavernosal pressure (ICP) measurements were accomplished by insertion into the right crus of a 23-gauge needle connected to a disposable pressure transducer (Abbott, Sligo, Ireland) and a data acquisition system (ADInstruments, Castle Hill, Australia). Left carotid artery and right external jugular vein were catheterized for constant blood pressure measurement and saline or drug infusion, respectively. Electrical stimulation was applied by a delicate platinum bipolar hook electrode connected to a stimulator and current amplifier (Cibertec, Madrid, Spain). Parameters of electrical stimulation consisted of pulses with a
duration of 1 ms and 1.5 mA of current intensity for 1 min. Frequency-response curves were performed by applying stimulation at 1, 3 and 10 Hz at 3 min intervals.

For evaluation of acute effects of 2,5NO-BS on erectile responses, a control stimulation at 1, 3 and 10 Hz was performed and, after an stabilization period, 2,5NO-BS (10 mg/kg) dissolved in saline (0.9% NaCl) or the vehicle alone were intravenously administered. The stimulation was repeated at 30 min after the administration of 2,5NO-BS or vehicle. Erectile responses were not affected by vehicle administration while were potentiated by administration of 2,5NO-BS (Figure 19).
CLAIMS

1. A compound of Formula (I):

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_9' \\
\text{R}_9 & \quad \text{T} \\
\text{R}_2 & \quad \text{ONO}_2
\end{align*}
\]

wherein:

- \text{R}_i is selected from \(-(\text{CH}_2)_a\)\text{Z} and \(-\text{CH}=\text{CH}(\text{CH}_2)_b\)\text{Z}; wherein:
  - \text{Z} is selected from \text{-SO}_3\text{H}, \text{-SO}_3\text{X}^+, \text{-SO}_3\text{R}_3, \text{-PO}_3\text{H}, \text{-PO}_3\text{X}^+, \text{-PO}_3\text{R}_3, \text{-CO}_2\text{H}, \text{-C0}_2\text{X}^+ and \text{-CO}_2\text{R}_3; wherein:
  - \text{X}^+ is an organic or inorganic cation and \text{R}_3 is selected from an alkyl group, an aryl group, an arylalkyl group and an alkylaryl group;
  - \text{a} is an integer selected from 0, 1, 2, 3, 4, 5 and 6;
  - \text{b} is an integer selected from 0, 1, 2, 3, 4, 5 and 6;

- \text{R}_9 and \text{R}_9' are independently selected from \text{-OH}, \text{-OC(O)-R}_i\text{O} and \text{-OR}_2; with the proviso that at least one of \text{R}_9 and \text{R}_9' is \text{-OR}_2 and wherein \text{R}_9 and \text{R}_9' can have different values of \text{R}_2; wherein:
  - \text{R}_i is an alkyl group, an aryl group, an arylalkyl group or an alkylaryl group and \text{R}_2 is selected from:

\[
\begin{align*}
\text{(I)} & \quad \text{-V-(CR}_4\text{R}_4\text{VONO}_2;} \\
\text{(2)} & \quad \text{-V-(CR}_4\text{R}_4')_p\text{-T-(CR}_4\text{R}_4')_p\text{-ONO}_2;}
\end{align*}
\]

\[
\begin{align*}
\text{(3)} & \quad \text{Y}^-(\text{CR}_4\text{R}_4')_o\text{-(CR}_4\text{R}_4')_p\text{ONO}_2
\end{align*}
\]

wherein \text{T} is located in an ortho, meta or para orientation;

25

(4)
(4')

5
(5) -Y'-(CR₄R'₄)q-V-B-T-(CR₄R'₄)p-ONO₂;
(6) -Y'-(CR₄R'₄)p-T-C(O)-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(7) -Y'-(CR₄R'₄)p-C(Zi)-(CH₂)q-V-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(8) -Y'-(CR₄R'₄)p-T-(CH₂)q-V-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(9) -Y'-(CR₄R'₄)p-V-(CH₂)q-V-(CR₄R'₄)q-(CH₂)₂-ONO₂;

10
(10) -Y'-(CR₄R'₄)q-(W)q-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(11) -Y'-(CH₂)q-(W)q-(CH₂)₂-V-(CR₄R'₄)q-O'-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(12) -Y'-(CR₄R'₄)q-V-(CH₂)q-(W)q-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(13) -Y'-(CR₄R'₄)q-O'-(CR₄R'₄)q-V-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(14) -Y'-(CR₄R'₄)o-O'-(CR₄R'₄)q-(W)q-(CR₄R'₄)q-(CH₂)₂-ONO₂;

15
(15) -Y'-(CR₄R'₄)q-T-(CR₄R'₄)q-Q'-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(16) -Y'-(CR₄R'₄)q-C(Zi)-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(17) -Y'-(CR₄R'₄)q-Q'-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(18) -Y'-(CR₄R'₄)q-P(O)MM';
(19) -Y'-(CR₄R'₄)q-O'-(CR₄R'₄)q-(CH₂)₂-ONO₂;

20
(20) -Y'-(CR₄R'₄)q-O'-(CR₄R'₄)q-(W)q-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(21) -Y'-(CR₄R'₄)q-(W)q-(CR₄R'₄)q-O'-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(22) -Y'(CR₄R'₄)q-V-(CR₄R'₄)q-Q'-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(23) -Y'(CR₄R'₄)q-(T)q-(W)q-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(24) -Y'(CR₄R'₄)q-(W)q-(T)q-(CR₄R'₄)q-(CH₂)₂-ONO₂;

25
(25) -Y'(CR₄R'₄)q-C(Zi)q-V-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(26) -Y'(CR₄R'₄)q-(CR₄R'₄)q-(W)q-(T)q-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(27) -Y'(CR₄R'₄)q-V-(CR₄R'₄)q-O'-(CR₄R'₄)q-(CH₂)₂-ONO₂;
(29) -Y'-(CR₄R₄')ₚ-(CH₂)⁻ONO₂;
(30) -V-(CR₄R₄')ₚ-(CH₂)⁻ONO₂;
(31) -V-(CR₄R₄')ₚ-(T)₀⁻Q'-(T)₀⁻(CR₄R₄')ₚ-(CH₂)⁻ONO₂;
(32) -V-(CR₄R₄')ₚ-(CH₂)⁻ONO₂;
(33) -V-(CR₄R₄')ₚ-(C(Z)₁-(CR₄R₄')ₚ-(W)₀⁻(CR₄R₄')₀⁻(CH₂)⁻ONO₂;
(34) -V-(CR₄R₄')₀⁻Q'-(CR₄R₄')₀⁻ONO₂; or
(35) -V-(CR₄R₄')₀⁻V-(CR₄R₄')₀⁻Q'-(CR₂R₂')₀⁻ONO₂;

wherein:

R₄ and R₂' are independently selected in each case from hydrogen, an alkyl group, -OH, -CH₂OH, -ONO₂, -NO₂ and -CH₂ONO₂; or R₄ and R₂' form together with the carbon atom to which they are joined a cycloalkyl group or a heterocyclic ring;

V is selected from -C(O)-T-, -T-C(O)-, -T-C(O)-T and T-C(O)-C(O)-T;
W is a covalent bond or a carbonyl group;
T is independently selected in each case from O, (S(0)₀), and NR,Rk;

wherein:

R₃ and R₆ are independently selected from hydrogen, an alkyl group, an aryl group, a heterocyclic ring, an alkylcarbonyl group, an alkylaryl group, an alkylsulfonyl group, an arylsulfonamido group, an arylsulfonyl group, an alkylsulfonyl group, an arylsulfonyl group, an alkylsulfonyl group, a sulfonamido group, an N-alkylsulfonylamido group, an N,N-diarylsulfonylamido group, an N-arylsulfonylamido, an N-alkyl-N-arylsulfonylamido group, a carboxamido group and a hydroxyl group;
p in each case is independently an integer selected from 1, 2, 3, 4, 5 and 6;
q in each case is independently an integer selected from 1, 2 and 3;
o and o' in each case are independently an integer selected from 0, 1 and 2;
V is -C=O or -C=S;

B is phenyl or (CH₂)₀;
Q’ is selected from a cycloalkyl group, a heterocyclic ring and an aryl group;
Zi is selected from (=0), (=N-OR), (=N-NR₅R'₅) and (=CR₅R'₅);
M and M' are independently selected in each case from -OH \( \equiv N^+ \) -(CR₄R₄)'₅-CH₂ONO₂ and -T-(CR₄R₄)₅ⁿ⁻CH₂ONO₂;
R₂ and R₂' are independently selected in each case from hydrogen, a hydroxyl group, an alkyl group, an aryl group, an alkylaryl group, a carboxylic ester, an alkylcarbonyl group, an arylcarbonyl group, a carboxamido group, an alkoxyalkyl group, a alkoxyaryl group, a cycloalkyl group and a heterocyclic ring.
or a salt, isomer, prodrug or solvate thereof.

2. The compound according to claim 1, wherein R₂ is selected from:

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<th>(1)</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
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<td><img src="image1.png" alt="Chemical Structure" /></td>
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wherein T is ortho, meta or para;

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<td><img src="image13.png" alt="Chemical Structure" /></td>
<td><img src="image14.png" alt="Chemical Structure" /></td>
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</table>
wherein:

5. \( Y' \) is -C=O or -C=S;

T' is selected from O, S and NR₆;

X₅ is selected from O, (S(O))ₐV and NR₆;

R₆ is selected from hydrogen, an alkyl group and an aryl group;

R₇ is a lower alkyl group or an aryl group;

R₈ is independently selected in each case from a hydrogen radical, a hydroxyl group, an alkyl group, an aryl group, -NO₂, -CH₂ONO₂ and -CH₂-OH;

n' and m' in each case are independently an integer selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

o and o' in each case are independently an integer selected from 0, 1 and 2;

or a salt, isomer, prodrug or solvate thereof.

3. The compound according to claim 1 or 2 wherein R₁ is selected from -(CH₂)ₐZ and -CH=CH-(CH₂)ₐZ; wherein:

Z is selected from -SO₃H, -SO₃⁺X⁺, -SO₃R₃, -PO₃H, -PO₃⁻X⁺, -PO₃R₃, -CO₂H, -CO₂⁻X⁺ and -CO₂R₃; wherein:

X⁺ is an organic or inorganic cation and R₃ is selected from a lower alkyl group, a phenyl group and a benzyl group;

a is 0 or 1; and

b is 0 or 1.

4. The compound according to anyone of claims 1 to 3 wherein:

R₉ and R-cr are independently selected from -OH, -OC(O)-R₁O and OR₂; with the proviso that at least one of R₉ and R-cr is -OR₂ and wherein R₉ and R₉' can
have different values of R₂; wherein:
R₁ is a lower alkyl group and R is selected from:
(1) -Y'-(CR₄R₄')ₚ-ONO₂;
(2) -YHCR₄VT-(CR₄R₄VONO₂;

wherein T is located in an ortho, meta or para orientation;
wherein:
Y' is -C=O;
R₄ and R₄' are independently selected in each case from hydrogen, a lower alkyl group, -OH, -CH₂OH, -ONO₂, -NO₂ and -CH₂ONO₂; or R₄ and R₄' form together with the carbon atom to which they are joined a cycloalkyl group or a heterocyclic ring;
T is independently selected from O and S;
p is an integer selected from 1, 2, 3, 4, 5 and 6; and
o is an integer selected from 0, 1 and 2;
or a salt, isomer, prodrug or solvate thereof.

5. The compound according to claim 1 wherein:
R₁ is selected from -(CH₂)ₐZ and -CH=CH-(CH₂)ₐZ; wherein:
Z is selected from -SO₃H, -SO₃X⁺, -SO₃R₃, -CO₂H, -CO₂⁻X⁺ and -CO₂R₃;
wherein:
X⁺ is an organic or inorganic cation and R₃ is selected from a lower alkyl group, a phenyl group and a benzyl group;
a is 0 or 1;
b is 0 or 1; and
Rᵩ and Rᵩ' are independently selected from -OH, -OC(O)-Rᵩ and ORᵩ; with the proviso that at least one of R₉ and Rᵩ is -OR₂ and wherein R₉ and Rᵩ can
have different values of $R_2$; wherein:

$R_1$ is a lower alkyl group and $R_2$ is selected from:

1. $\text{-Y}^\prime-(CR_4R_4')p\text{-ONO}_2$;
2. $\text{-YHCR}_4R_4\text{VT-(CR}_4R_4\text{VONO}_2$;
3. $\text{-Y}^\prime-(CR_4R_4')p\text{-ONO}_2$.

wherein $T$ is located in an ortho, meta or para orientation;

wherein:

$Y^\prime$ is -C=O;

$R_4$ and $R_4'$ are independently selected in each case from hydrogen, a lower alkyl group, -OH, -CH$_2$OH, -ONO$_2$, -NO$_2$ and -CH$_2$ONO$_2$; or $R_4$ and $R_4'$ form together with the carbon atom to which they are joined a cycloalkyl group or a heterocyclic ring;

$T$ is independently selected from O and S;

$p$ is an integer selected from 1, 2, 3, 4, 5 and 6; and

$o$ is an integer selected from 0, 1 and 2;

or a salt, isomer, prodrug or solvate thereof.

6. The compound according to claim 5 wherein:

$R_1$ is selected from $-(\text{CH}_2)_aZ$ and $-\text{CH}=\text{CH}-(\text{CH}_2)_bZ$; wherein:

$Z$ is selected from -SO$_2$H, -SO$_3$X$^+$, -SO$_3$R$_3$, -CO$_2$H, -CO$_2$X$^+$ and -CO$_2$R$_3$;

wherein:

$X^+$ is an organic or inorganic cation and $R_3$ is a lower alkyl group;

$a$ is 0 or 1;

$b$ is 0 or 1; and

$R_9$ and $R_9'$ are independently selected from -OH, -OC(O)-$R_1$Oand OR$_2$; with the proviso that at least one of $R_9$ and $R_{cr}$ is -OR$_2$ and wherein $R_9$ and $R_{cr}$ can have different values of $R_2$; wherein:

$R_{10}$ is a lower alkyl group and $R_2$ is $\text{-Y}^\prime-(CR_4R_4')p\text{-ONO}_2$; wherein
Y' is -C=O;
R and R' are independently selected in each case from a hydrogen radical, a lower alkyl group, -OH, -CH₂OH, -ONO₂, -NO₂ and -CH₂ONO₂; or R₄ and R₄' form together with the carbon atom to which they are joined a cycloalkyl group or a heterocyclic ring;
p is an integer selected from 1, 2, 3, 4, 5, and 6.
or a salt, isomer, prodrug or solvate thereof.

7. The compound according to claim 6 wherein:
R₁ is selected from -(CH₂)ₐZ and -CH=CH-(CH₂)ₐZ; wherein:
Z is selected from -SO₃H, -SO₃X⁺, -SO₃R₃, -CO₂H, -CO₂⁻X⁺ and -CO₂⁻R₃;
wherein:
X⁺ is an organic or inorganic cation and R₃ is a lower alkyl group;
a is O or 1;
b is O or 1; and
R₉ and R₉' are independently selected from -OH, -OC(O)-R₁O and OR₂; with the proviso that at least one of R₉ and R₉' is -OR₂ and wherein R₉ and R₉' can have different values of R₂; wherein:
R₁₀ is a lower alkyl group and R₂ is -Y'-(CR₄R₄')ₚ-ONO₂; wherein
Y' is -C=O;
R₄ and R₄' are hydrogen;
p is an integer selected from 1, 2, 3, 4, 5, and 6.
or a salt, isomer, prodrug or solvate thereof.

8. The compound according to claim 7 wherein:
R₁ is selected from -(CH₂)ₐZ and -CH=CH-(CH₂)ₐZ; wherein:
Z is selected from -SO₃H, -SO₃X⁺ and -SO₃R₃; wherein:
X⁺ is an organic or inorganic cation and R₃ is a lower alkyl group;
a is O or 1;
b is O or 1; and
R9 and Rcr are independently selected from -OH, -OC(O)-R1O and OR2; with the proviso that at least one of R9 and Rcr is -OR2 and wherein R9 and R9' can have different values of R2; wherein:

R1O is a lower alkyl group and R2 is -Y'(CR4R4')p-ONO2; wherein

Y' is -C=O;

R4 and R4' are hydrogen;

p is an integer selected from 1, 2, 3, 4, 5, and 6.

or a salt, isomer, prodrug or solvate thereof.

9. The compound according to anyone of claims 1 to 6 wherein Z is selected from -SO3-X+, -SO3H, -CO2-X+ and -CO2H.

10. The compound according to anyone of claims 1 to 5, having the formula:
(XVI)

(XVII)

(XVIII)

(XIX)
(XXIV)

(XXV)

(XXVI)

(XXVII)
(XXXII)

(XXXIII)

(XXXIV)

(XXXV)
LXVIII

LXIX

LXX

LXXI
LXXX

\[
\begin{align*}
\text{CH}_2\text{SO}_3^- & \quad \text{O} \quad \text{CH}_2\text{SO}_3^- \\
\text{AcO} & \quad \text{O} \quad \text{AcO} \\
\text{X}_m & \quad n
\end{align*}
\]

LXXXI

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{NO}_2 \\
\text{CH}_2\text{SO}_3^- & \quad \text{O} \quad \text{CH}_2\text{SO}_3^- \\
\text{X}_m & \quad n
\end{align*}
\]

LXXXII

\[
\begin{align*}
\text{CH}_2\text{SO}_3^- & \quad \text{O} \quad \text{CH}_2\text{SO}_3^- \\
\text{AcO} & \quad \text{O} \quad \text{AcO} \\
\text{X}_m & \quad n
\end{align*}
\]

LXXXIII

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{NO}_2 \\
\text{CH}_2\text{SO}_3^- & \quad \text{O} \quad \text{CH}_2\text{SO}_3^- \\
\text{X}_m & \quad n
\end{align*}
\]
XCVI

\[
\begin{array}{c}
\text{CH}=\text{CH}-\text{CO}_2^- \\
\text{O}_2\text{N} \quad \text{O}_2\text{N} \\
\text{AcO} \quad \text{O} \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}=\text{CH}-\text{CO}_2^- \\
\text{O}_2\text{N} \quad \text{O}_2\text{N} \\
\text{AcO} \quad \text{O} \\
\end{array}
\]

\[X_m \quad n\]

XCVII

\[
\begin{array}{c}
\text{CH}=\text{CH}-\text{CO}_2^- \\
\text{O}_2\text{N} \quad \text{O}_2\text{N} \\
\text{AcO} \quad \text{O} \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}=\text{CH}-\text{CO}_2^- \\
\text{O}_2\text{N} \quad \text{O}_2\text{N} \\
\text{AcO} \quad \text{O} \\
\end{array}
\]

\[X_m \quad n\]

XCVIII

\[
\begin{array}{c}
\text{CH}=\text{CH}-\text{CO}_2^- \\
\text{O}_2\text{N} \quad \text{O}_2\text{N} \\
\text{AcO} \quad \text{O} \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}=\text{CH}-\text{CO}_2^- \\
\text{O}_2\text{N} \quad \text{O}_2\text{N} \\
\text{AcO} \quad \text{O} \\
\end{array}
\]

\[X_m \quad n\]

XCIX

\[
\begin{array}{c}
\text{CH}=\text{CH}-\text{CO}_2^- \\
\text{O}_2\text{N} \quad \text{O}_2\text{N} \\
\text{AcO} \quad \text{O} \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}=\text{CH}-\text{CO}_2^- \\
\text{O}_2\text{N} \quad \text{O}_2\text{N} \\
\text{AcO} \quad \text{O} \\
\end{array}
\]

\[X_m \quad n\]

Page 5

Page 10
wherein:

n is 1 or 2; and

$X_m$ is selected from hydrogen, an organic or inorganic cation $X^+$ and $R_3$ as defined in claim 1, with the proviso that when $X_m$ is hydrogen or $R_3$ then n is 1.

11. The compound according to claim 10 wherein $X_m$ is selected from hydrogen and an organic or inorganic cation $X^+$.

12. A pharmaceutical composition comprising at least one compound according to anyone of the previous claims or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof and a pharmaceutically acceptable excipient, adjuvant or carrier.
13. The pharmaceutical composition according to claim 12 comprising at least one additional therapeutic agent.

14. The pharmaceutical composition according to claim 13, wherein the additional therapeutic agent is selected from: chemotherapeutic agents, steroids, retinoids, antimicrobial compounds, antioxidants, non-steroidal anti-inflammatory agents, NMDA receptor antagonists, endothelin antagonists, immunomodulating agents, vitamin D analogs, salicylic acid, cholinesterase inhibitors, tau protein phosphorylation inhibitors, nitric oxide donors, phosphodiesterase inhibitors and combinations of two or more thereof.

15. A compound as defined in anyone of claims 1 to 11 or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof for its use as a medicinal product.

16. A compound as defined in anyone of claims 1 to 11 or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof for the treatment and/or prophylaxis of any of the diseases selected from the group consisting of (a) cancer; (b) rosacea; (c) psoriasis; (d) fibrosis; (e) hemangiomas; (f) ocular diseases; (g) skin pigmentation and skin hyperpigmentation; (h) diseases associated with amyloidosis; (i) dermatitis; (j) actinic and seborrheic keratosis; (k) erectile dysfunction; (l) female sexual dysfunction; (m) arterial hypertension; (n) atherosclerosis; (o) inflammatory diseases in particular, arthritis, glomerulonephritis and asthma; (p) intestinal inflammatory diseases in particular, ulcerative colitis and Crohn's disease; (q) benign prostatic hyperplasia; (s) angiogenesis associated to chronic temporal lobe epilepsy; (t) pain; (u) hyperlipidemia and (v) thrombosis.

17. The use of a compound as defined in anyone of claims 1 to 11 or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof in the elaboration of a medicinal product.
18. The use of a compound as defined in anyone of claims 1 to 11 or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof in the elaboration of a medicinal product for its use in the treatment and/or prophylaxis of any of the diseases selected from the group consisting of (a) cancer; (b) rosacea; (c) psoriasis; (d) fibrosis; (e) hemangiomas; (f) ocular diseases; (g) skin pigmentation and skin hyperpigmentation; (h) diseases associated with amyloidosis; (i) dermatitis; (j) actinic and seborrheic keratosis; (k) erectile dysfunction; (l) female sexual dysfunction; (m) arterial hypertension; (n) atherosclerosis; (o) inflammatory diseases in particular, arthritis, glomerulonephritis and asthma; (p) intestinal inflammatory diseases in particular, ulcerative colitis and Crohn's disease; (q) benign prostatic hyperplasia; (s) angiogenesis associated to chronic temporal lobe epilepsy; (t) pain; (u) hyperlipidemia and (v) thrombosis.

19. A pharmaceutical kit or set comprising one or more containers containing one or more compounds according to anyone of claims 1 to 11 and/or compositions according to anyone of claims 12 to 14.
Figure 1

[Graph showing differential absorbance against [Inhibitor] (µM) with data points and annotations for 2-hydroxy-5-(5-nitrooxy)pentanoyloxybenzenesulfonate (C_{50} = 9 µM) and 2,5-dihydroxybenzenesulfonate (C_{50} = 4.6 µM).]
Figure 2

[Graph showing differential absorbance against [Inhibitor] (μM).]

- ● 2-acetoxy-5-(5-nitrooxy)pentanoyloxy)benzenesulfonate; $C_{50} = 58.2 \, \mu M$
- ○ 2,5-dihydroxybenzenesulfonate; $C_{50} = 20.8 \, \mu M$
Figure 3

rat aorta

% Contraction

log M [drugs]

2,5-DHBS
5NO-2HBS

n=4
Figure 4

rat aorta

% Contraction vs log M [drugs]

- 2A-5HBS
- 5NO-2ABS

n=4
Figure 5

rat aorta

% Contraction vs. log M [drugs]

2,5-DHBS

2,5NO-BS
Figure 8

(A) MAP (mm Hg) for basal and 2,5-DHBS at 10 mg/kg with n=6.

(B) MAP (mm Hg) for basal and 5NO-2HBS at 3 mg/kg with n=6.

(C) MAP (mm Hg) for basal and 5NO-2HBS at 10 mg/kg with n=6.
Figure 9

A

MAP (mm Hg)

basal  2,5NO-BS 3 mg/kg

B

MAP (mm Hg)

basal  2,5NO-BS 10 mg/kg

*
Figure 10

A

MAP (mm Hg)

basal 2A-5HBS 10 mg/kg

n=4

B

MAP (mm Hg)

basal 5NO-2ABS 3 mg/kg

n=4

C

MAP (mm Hg)

basal 5NO-2ABS 10 mg/kg

n=4
Figure 11

A

HR (bpm)

n=5

basal  2,5-DHBS  10 mg/kg

B

HR (bpm)

n=5

basal  5NO-2HBS  3 mg/kg

C

HR (bpm)

n=5

basal  5NO-2HBS  10 mg/kg
Figure 12

A

HR (bpm)

basal 2,5NO-BS 3 mg/kg

B

HR (bpm)

basal 2,5NO-BS 10 mg/kg
Figure 14

MAP (% of change)

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<tr>
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<th>2,5-DHBS</th>
<th>5NO-2HBS (mg/kg)</th>
<th>2,5NO-BS (mg/kg)</th>
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<tr>
<td>10 mg/kg</td>
<td>3</td>
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<td>3</td>
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* * * * *
Figure 15
Figure 16

C6 cells

absorbance at 595 nm

[5NO-2HBS] μM

* * *

*** *** ***
Figure 17

C6 cells

[5NO-2ABS] μM

absorbance at 595 nm

***
Figure 18

The graph shows the bleeding time (in minutes) for different conditions. The x-axis represents different treatments: basal, vehicle, 2,5-DHBS, 5NO-2HBS, and 2,5NO-BS. The y-axis represents the bleeding time from 0 to 25 minutes.

- Basal: (9) samples
- Vehicle: (1) sample
- 2,5-DHBS: (2) samples
- 5NO-2HBS: (2) samples
- 2,5NO-BS: (2) samples

Statistical significance is indicated: ***(p < 0.001)***