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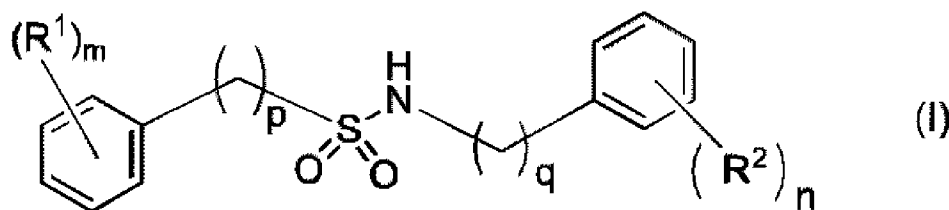
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(54) **Titre : COMPOSES POUR UNE UTILISATION DANS LE TRAITEMENT DE CONDITIONS ASSOCIEES A LA NADPH OXYDASE**  
 (54) **Title : COMPOUNDS FOR USE IN THE TREATMENT OF CONDITIONS ASSOCIATED WITH NADPH OXIDASE**



(57) **Abrégé/Abstract:**

A compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition or disorder associated with nicotinamide adenine dinucleotide phosphate oxidase.

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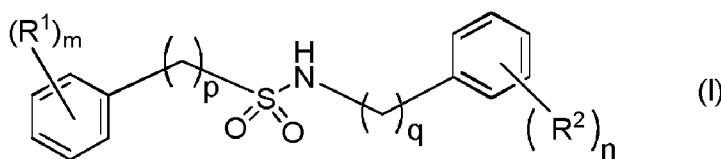
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(54) Title: COMPOUNDS FOR USE IN THE TREATMENT OF CONDITIONS ASSOCIATED WITH NADPH OXIDASE



(57) Abstract: A compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition or disorder associated with nicotinamide adenine dinucleotide phosphatase.

## COMPOUNDS FOR USE IN THE TREATMENT OF CONDITIONS ASSOCIATED WITH NADPH OXIDASE

### FIELD OF THE INVENTION

5 The present invention relates to sulfonamide derivatives for use in the treatment of conditions or disorders associated with nicotinamide adenine dinucleotide phosphate oxidase (Nox). More specifically, the present invention relates to sulfonamide derivatives as Nox inhibitors for use in the treatment of various diseases that are caused or driven by elevated Nox activity. In particular the invention relates to sulfonamide derivatives having selectivity for Nox4 for  
10 use in the treatment disorders associated with Nox4.

### BACKGROUND OF THE INVENTION

The definition of oxidative stress is an *in vivo* imbalance between the formation and elimination of reactive oxygen. Changes of the normal redox state in the cell or tissues can  
15 produce harmful radicals that may damage components of the cellular machinery, including DNA, proteins and lipids. If the cellular components are chemically altered that cause genetic changes, this has generally been considered to promote formation of cancer or other serious diseases.

20 *Sources of oxygen radicals* - Numerous *in vivo* generators of oxygen radicals ( $O_2^-$ ,  $H_2O_2$  and OH) that potentially can cause oxidative stress have been identified: complex I and III in the mitochondria and NAD(P)H oxidase, xanthine oxidase, cytochromes P450, metal ions (cobalt, vanadium, chromium, copper and iron) and some organic compounds that can redox cycle.

25 *General antioxidants* - There also are numerous endogenously cellular antioxidants such as superoxide dismutase (SOD), catalase, glutathione peroxidase, peroxiredoxins and sulfiredoxin. Vitamins provided by the food are also considered as an important part of the protection of the organism from harmful oxygen radicals, and recent discovery of important antioxidants present in many sources of food has increased the arsenal of antioxidants.

30

*Antioxidants as therapeutics* - It is very clear that some antioxidants can be helpful in preventing diseases and promote health. What is much less clear is what type of antioxidants can be used. Many of the antioxidants present in natural food are redox active. If these types of redox active substances are isolated and provided as complementary pharmaceuticals – this

may end up being more harmful than helpful. Clinical trials have shown that untargeted application of antioxidants, which broadly scavenge oxygen radicals, are not only ineffective but may even be harmful. This was illustrated in a study made with sixty-seven randomized trials with 232,550 participants including healthy and patients with various diseases

5 (Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Cochrane Database Syst Rev. 2008 Jul 16; (3):CD004183. Epub 2008 Jul 16).

Thus general antioxidants that are redox active may actually be adding to the cellular damage, by mediating a harmful redox cycle. Other general antioxidants will harmfully block normal cellular *in vivo* activity necessary to maintain bodily function.

*Source and role of reactive oxygen* - What has become increasingly clear is that what is causing excessive production and accumulation of reactive oxygen, in a number of pathological conditions, such as inflammation, type 2 diabetes, diabetes complications, polycystic ovary syndrome, stroke, detrimental neurological conditions and cancer, is not generally leaking oxygen radicals such as complex I or III in the mitochondria – rather it is up-regulated powerful producers of oxygen radicals – that are part of the normal cellular signal transduction system. Thus the definition of oxidative stress need not be oxygen radicals that will irreversibly alter DNA, protein or lipids, but instead increasingly interfere, if up regulated with “normal” signal transduction creating an imbalance on a cellular level that eventually may alter other tissues and whole bodily function. A typical example of this is the metabolic syndrome, connected to vascular disease, diabetes 2, stroke, nephropathy, neuropathy, heart failure and stroke with insulin resistance as the initiating factor (Reaven, “Role of insulin resistance in human disease”, Diabetes 37(12), 1988). Insulin resistance in itself is also part of normal bodily function as a tool to direct storage of energy selectively to a suitable receiving organ. However, when metabolic changes occur, such as in overfeeding, or other disturbances such as acromegaly with excess growth hormone production or malfunctioning leptin as in *ob/ob*-mice, this will induce a harmful condition with an uncontrolled insulin resistance that may cause organ failure connected to the metabolic syndrome. The common denominator to the uncontrolled insulin resistance is overproduction of local and systemic oxygen radicals (Houstis et al., Nature 440, 2006; Katakam et al., J cereb blood Flow Metab, 2012 Jan 11).

One of the most interesting candidates for this overproduction is a family of trans-membrane

proteins (enzymes), referred to as NAD(P)H oxidase (Nox). There are seven family members of Nox identified (Nox 1-5 and Duox 1-2) that very often are being recognized as a major or key source of reactive oxygen and that also play a major role in a number of cellular events as part of the normal cellular signal transduction system, including proliferation (Brar et al., Am J Physiol Lung Cell Mol Physiol, 282, 2002), growth (Brar et al., Am J Physiol Cell Physiol, 282, 2002), fibrosis (Grewal et al., Am J Physiol, 276, 1999), migration (Sundaresan et al., Science, 270, 1995), apoptosis (Lundqvist-Gustafsson et al., J Leukoc Biol, 65, 1999), differentiation (Steinbeck et al., J Cell Physiol, 176, 1998), cytoskeletal rearrangement (Wu et al., J Virol, 78, 2004) and contraction (Rueckschloss et al., Exp Gerontol, 45, 2010).

10

*NADPH oxidase and disease* - Some genetic conditions with decreased NADPH oxidase activity have been identified – defect Nox2 decreases immunologic response to kill and neutralize microbial attacks (Chronic granulomatous disease) – defect Nox3 in inner ear renders defective gravity perception and dual NAD(P)H oxidase Duox2 having deficient enzymatic activity in the thyroid gland gives rise to hypothyroidism.

15

There is however a much larger list of publications that also seems to grow exponentially, that witness of strong evidence that increased Nox activity is part of or even causative of a number of diseases (Lambeth JD, Review Article “*Nox enzymes, ROS, and chronic disease: An example of antagonistic pleiotropy*”, Free Radical Biology & Medicine 43, 2007; Takac I et al., “*The Nox Family of NADPH Oxidases: Friend or Foe of the Vascular System*”, Curr Hypertens Rep. 2011 Nov 10; Montezano AC, “*Novel Nox homologues in the vasculature: focusing on Nox4 and Nox5*”, Clin Sci London 2011; Bedard K et al., “*The Nox family of ROS-generating NADPH oxidases: physiology and pathophysiology*” Physiol Rev. 2007; Camici M et al., “*Obesity-related glomerulopathy and podocyte injury: a mini review*”, Front Biosci 2012; Nabeebaccus A et al., “*NADPH oxidases and cardiac remodeling*” Heart Fail Rev. 2011; Kuroda J et al., “*NADPH oxidase and cardiac failure*” J Cardiovasc Transl Res. 2010; Kuroda J et al., “*NADPH oxidase 4 is a major source of oxidative stress in the failing heart*” Proc Natl Acad Sci USA 2010; Maejima Y et al., “*Regulation of myocardial growth and death by NADPH oxidase*” J Mol Cell Cardiol. 2011; Barnes JL et al., “*Myofibroblast differentiation during fibrosis: role of NAD(P)H oxidases*” Kidney international, 2011; Alison Cave “*Selective targeting of NADPH oxidase for cardiovascular protection*” Current Opinion in Pharmacology 2009; Albert van der Vliet “*Nox enzymes in allergic airway inflammation*” Biochimica et Biophysica Acta 1810, 2011; Pendyala S et al., “*Redox*

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*regulation of Nox proteins*” Respiratory Physiology & Neurobiology 174, 2010; Nair D et al.,  
*“Intermittent Hypoxia-Induced Cognitive Deficits Are Mediated by NADPH oxidase Activity  
in a Murine Model of Sleep Apnea”* PLoS ONE, vol. 6, Issue 5, May 2011; Chia-Hung Hsieh  
et al., *“NADPH oxidase Subunit 4-Mediated Reactive Oxygen species Contribute to Cycling  
5 Hypoxia-Promoted Tumor Progression in Glioblastoma Multiforme”* PLoS ONE, vol 6, issue  
9, September 2011; Sedeek M et al., *“Molecular mechanisms of hypertension: role of nox  
family NADPH oxidase”* Current Opinion in Nephrology and Hypertension 2009; Augusto C  
et al., *“Novel Nox homologues in the vasculature: focusing on Nox4 and Nox5”* Clinical  
Science 2011; Briones AM et al., *“Differential regulation of Nox1, Nox2 and Nox4 in  
10 vascular smooth muscle cells from WKY and SHR”* Journal of the American Society of  
Hypertension 5:3, 2011).

It has been recently shown that the Nox enzymes and particularly Nox 4 and NAD(P)H-  
oxidase are highly involved in pulmonary fibrosis. The function of oxidative stress in fibrosis  
15 are well recognized (Kinnula VL, Fattman CL, Tan RJ, Oury TD (2005) Oxidative stress in  
pulmonary fibrosis: a possible role for redox modulatory therapy. Am J Respir Crit Care Med  
172:417–422), as there is a substantial and growing body of evidence indicating that oxidative  
stress plays an important role in the pathological development of lung fibrosis as well as  
fibrosis in multiple organ systems (Kuwano K, Nakashima N, Inoshima I, Hagimoto N, Fujita  
20 M, Yoshimi M, Maeyama T, Hamada N, Watanabe K, Hara N (2003) Oxidative stress in lung  
epithelial cells from patients with idiopathic interstitial pneumonias. Eur Respir J 21:232–  
240). Thus, Nox enzymes and particularly Nox4 appear to be involved also in lung infections,  
acute lung injury, pulmonary arterial hypertension, obstructive lung disorders, fibrotic lung  
disease, and lung cancer.

25

*NADPH oxidase isoenzymes, similarities, differences and function* - All the seven iso-  
enzymes of NADPH oxidase (identified) are similar in the way of having NADPH and FAD  
binding site and six trans-membrane domains and in that they include two heme complexes.

30 All the NADPH oxidase forms use the same basic mechanism to generate reactive oxygen,  
but the subcellular localizations and the modes of actions differ significantly.

The reactive oxygen species produced by the enzymatic Nox-family are either superoxide  $O_2^-$   
or hydrogen peroxide  $H_2O_2$ .

Nox1 and 2 are constitutively attached to p22phox and to activate the enzyme complex other components such as Rac, p47phox, p67phox are required for full Nox1 activity. Nox2 needs Rac, p40phox, p47phox and p67phox for full activation. Nox1 and 2 generate  $O_2^-$  when activated.

5

Nox3 also needs to assemble cytosolic proteins to be active (Cheng et al., J Biol Chem, 279(33), 2004).

10

Nox4 is also associated with p22phox, and is constitutively active in this form. Nox4 activity is, however, regulated through expression – not through assembly or ligand activation, which distinguishes this isoform from other isoforms (Serrander et al., Biochem J. 406, 2007). When induced, Nox4 is generally expressed at higher level than Nox1 and 2 (Ago et al., Circulation, 109, 2004). Nox4 seems to mainly generate  $H_2O_2$  instead of  $O_2^-$  as the other Nox-variants (Takac et al., J. Biol. Chem. 286, 2011). This makes this isoform unique because  $H_2O_2$  has the ability to cross membranes and thus to act at longer distance than  $O_2^-$  that has a very short half-life.

15

Nox5, Doux1 and Doux2 are activated by  $Ca^{2+}$  (De Deken, Wang et al., J.Biol Chem., 275(30), 2000).

20

*Nox4 and diseases* - The uniqueness of Nox4 in comparison to the other isoforms is also connected to uniqueness as a therapeutic target as it seems to be involved in a number of different diseases when overexpressed.

25

Nox4 is ubiquitously expressed in many cell-types although at a very low level until induced. It is mainly found in kidney, endothelial cells, adventitial fibroblasts, placenta, smooth muscle cells, osteoclasts and is the predominant Nox that is expressed in tumors (Chamseddine et al., Am J Physiol Heart Circ Physiol. 285, 2003; Ellmark et al., Cardiovasc Res. 65, 2005; Van Buul et al., Antioxid Redox Signal. 7, 2005; Kawahara et al., BMC Evol Biol. 7, 2007; Krause et al., Jpn J Infect is. 57(5), 2004; Griendling, Antioxid Redox Signal. 8(9), 2006). It was found that Nox4 was overexpressed in the majority of breast cancer cell-lines and primary breast tumors. Overexpression of Nox4 in already transformed breast tumor cells showed increased tumorigenicity, and Nox4 was here identified in the mitochondria. Nox4 was suggested as a target to treat breast cancer (Graham et al., Cancer Biol Ther 10(3), 2010).

30

Nox4 mediates oxidative stress and apoptosis caused by TNF- $\alpha$  in cerebral vascular endothelial cells (Basuroy et al., Am J Physiol Cell Physiol vol. 296, 2009). Its adverse effect following ischemic stroke is well demonstrated in animal models and human tissue.

Knockdown experiment, of Nox4, dramatically reduced the area of neuronal damage  
5 (Sedwick, PLoS Biology, vol.8 issue 9, 2010; Kleinschnitz et al., vol.8 issue 9, 2010).

Ischemic stroke accounts for approximately 80% of all cases of stroke and is the second leading cause of death in the world. It has been shown with KO mouse, that Nox4 is an effective therapeutic target in acute stroke. In a recent report (Kleinschnitz et al, *vide supra*)  
10 convincing data were published, showing that significant increase in Nox4 activity is the main cause of neuronal cell death that occurs in ischemic stroke. It was shown that upon ischemia, elevated Nox4 activity was induced in human as well as in mouse brain. A highly specific Nox4 inhibitor has the possibilities to be a safe drug. Total Knock-out of Nox4 demonstrates no obvious phenotypes in mice. The KO however dramatically improves neuronal cell  
15 survival, in induced ischemic stroke with more than 70% compared to wild type. Treatment of the stroke patient could also be performed without any risk for other types of strokes such as hemorrhagic stroke, thus the treatment could be started without the need for CAT scan.

Further, it was demonstrated through knockdown and overexpression studies in both  
20 microvascular and umbilical vein endothelial cells that increased Nox4 activity plays an important role in proliferation and migration of endothelial cells (Datla et al., Arterioscler Throm Vasc Biol. 27(11), 2007). Initially it was believed that Nox2 was responsible for the angiogenic defects in diabetes but the focus has shifted more towards Nox4 (Zhang et al., PNAS, 107, 2010; Garriodo-Urbani et al., Plos One 2011; Takac et al., Curr Hypertens Rep,  
25 14, 2012).

Nox4 play a key role in epithelial cell death during development of lung fibrosis (Camesecchi et al., Antiox Redox Signal. 1:15(3), 2011).

30 It was demonstrated that siRNA-mediated knockdown of Nox4 significantly reduces NADPH oxidase activity in purified mitochondria from mesangial cells and kidney cortex. The knockdown blocked glucose-induced mitochondrial superoxide generation. It was suggested that Nox4 acts as a central mediator to oxidative stress that may lead to mitochondrial dysfunction and cell injury in diabetes (Block et al., PNAS vol. 106, no. 34, 2009).



It was demonstrated that Nox4 was systemically up-regulated at diet-induced obesity in rats (Fan Jiang, Han K Lim, Margaret J Morris, Larissa Prior, Elena Velkoska, Xiao Wu & Gregory J Dusting (2011) Systemic upregulation of NADPH oxidase in diet-induced obesity in rats, *Redox Report*, 16:6, 223-229).

5 Nox4 has been strongly connected to the pathology in failing hearts. (Nabeebaccus A et al. "NADPH oxidases and cardiac remodeling" *Heart Fai Rev.* 2011; Kuroda J et al., "NADPH oxidase and cardiac failure *Cardiovasc Transl Res.* 2010; Kuroda J et al., "NADPH oxidase 4 is a major source of oxidative stress in the failing heart" *Proc Natl Acad Sci USA* 2010). A connection between increased mitochondrial Nox4 activity and dysfunction of "the aging heart" has been suggested (Tetsuro Ago et al, *AGING*, December 2010, vol.2 No 12).

10 Extracellular matrix accumulation contributes to the pathology of chronic kidney disease. The growth factor IGF-I activity is a major contributor to this process and Nox4 is a mediator in this process (New et al, *Am J Physiol Cell Physiol.* 302(1), 2012). The connection between chronic activation of the renin-angiotensin and the progression of kidney damage system is well established with Nox4 and Angiotensin II as collaborators in this process (Chen et al., *Mol Cell Biol.* 2012).

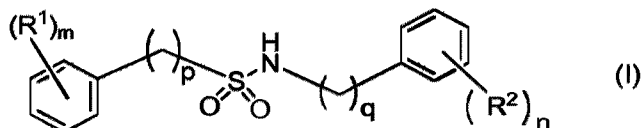
15 From the above, it thus appears that the Nox enzymes have several functions in the living body, and that they may also be involved in various disorders. Examples of such diseases and disorders are cardiovascular disorders, respiratory disorders, metabolism disorders, endocrine disorders, skin disorders, bone disorders, neuroinflammatory disorders, kidney diseases, reproduction disorders, diseases affecting the eye and/or the lens and/or conditions affecting the inner ear, inflammatory disorders, liver diseases,  
20 pain, cancers, allergic disorders, traumatism, septic, hemorrhagic and anaphylactic shock, diseases or disorders of the gastrointestinal system, angiogenesis, angiogenesis-dependent conditions. It also appears that especially Nox4 has been found to be involved in such disorders. Consequently, it is considered that compounds capable of inhibiting Nox, and in particular compounds capable of selectively inhibiting  
25 enzymes, and in particular Nox4.

#### SUMMARY OF THE INVENTION

According to one aspect, compounds are provided that are Nox inhibitors, for use in the treatment of diseases associated with, e.g. caused or driven by, elevated Nox activity, more specifically elevated Nox4 activity.

According to a further aspect, compounds are provided that are Nox inhibitors, more specifically Nox4 inhibitors, for use in the treatment of disorders, associated with elevated Nox activity, more specifically elevated Nox4 activity.

5 Thus, according to a first aspect, there is provided a compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein

p is an integer of from 0 to 2;

q is an integer of from 0 to 2;

10 m is an integer of from 1 to 3;

n is an integer of from 0 to 3;

each R<sup>1</sup> is independently selected from C1-C3 alkyl-X-;

each X is independently selected from a direct bond, O, and S;

each R<sup>2</sup> is independently selected from C1-C3 alkyl-Y-, and phenyl-(CH<sub>2</sub>)<sub>z</sub>-Y-;

15 each Y is independently selected from O and S; and

each z is independently selected from 0 and 1;

for use in the treatment of a condition or disorder associated with nicotinamide adenine

dinucleotide phosphate oxidase activity, e.g. selected from endocrine disorders,

cardiovascular disorders, respiratory disorders, metabolism disorders, skin disorders, bone

20 disorders, neuroinflammatory disorders, kidney diseases, reproduction disorders, diseases

affecting the eye and/or the lens and/or conditions affecting the inner ear, inflammatory

disorders, liver diseases, pain, cancers, allergic disorders, traumatism, septic, hemorrhagic

and anaphylactic shock, diseases or disorders of the gastrointestinal system, abnormal

angiogenesis and angiogenesis-dependent conditions.

25

According to a further aspect, a pharmaceutical composition is provided, comprising a

compound of formula (I) as defined herein above, or a pharmaceutically acceptable salt

thereof, and optionally a pharmaceutically acceptable excipient, for use in the treatment of

any of the above mentioned conditions.

30

Examples of such conditions and disorders e.g. are those mentioned herein above as related to

or mediated by Nox, in particular Nox4, for example conditions and disorders selected from

cardiovascular disorders, endocrine disorders, respiratory disorders, metabolism disorders, skin disorders, bone disorders, neuroinflammatory disorders, kidney diseases, reproduction disorders, endocrine disorders, diseases affecting the eye and/or the lens and/or conditions affecting the inner ear, inflammatory disorders, liver diseases, pain, cancers, allergic disorders, traumatism, septic, hemorrhagic and anaphylactic shock, diseases or disorders of the gastrointestinal system, angiogenesis, angiogenesis-dependent conditions, as well as lung infections, acute lung injury, pulmonary arterial hypertension, obstructive lung disorders, fibrosis, e.g. fibrotic lung disease, cerebrovascular accidents, and lung cancer.

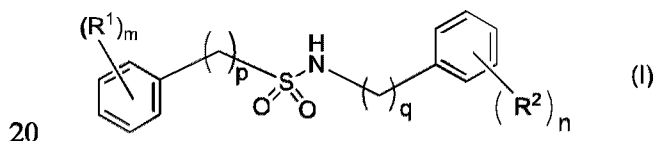
According to one aspect, a compound according to formula (I) as defined herein above is provided for inhibiting a nicotinamide adenine dinucleotide phosphate oxidase (Nox) in a mammal, in particular Nox4, for use in the treatment of a disorder associated with the expression of Nox, in particular Nox4.

According to one aspect, there is provided a method of inhibiting the activity of Nox, in particular Nox4, in a mammal in need thereof, by administering to said mammal a compound of formula (I) as defined herein above. The method is useful for the treatment of disorders associated with Nox activity, in particular Nox4 activity, as defined herein above.

According to a further aspect, the use of a compound as defined herein above is provided, for the manufacturing of a medicament for use in the treatment of disorders associated with Nox activity, in particular Nox4 activity, as defined herein above.

The present invention as claimed relates to:

- a compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein

m is an integer of from 1 to 3;

n is an integer of from 0 to 3;

p is an integer of from 0 to 2;

25 q is 2;

9a

each  $R^1$  is independently selected from C1-C3 alkyl-X-;

each X is independently selected from a direct bond, O, and S;

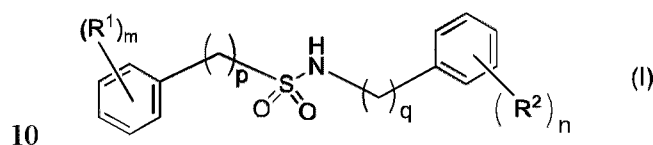
each  $R^2$  is independently selected from C1-C3 alkyl-Y-, and phenyl-(CH<sub>2</sub>)<sub>z</sub>-Y-;

each Y is independently selected from O and S; and

5 each z is independently selected from 0 and 1;

for use in the treatment of a condition or disorder associated with nicotinamide adenine dinucleotide phosphate oxidase activity, selected from diabetes, stroke, fibrosis, neuropatic pain and diabetes complications;

- use of a compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein

m is an integer of from 1 to 3;

n is an integer of from 0 to 3;

p is an integer of from 0 to 2;

15 q is 2;

each  $R^1$  is independently selected from C1-C3 alkyl-X-;

each X is independently selected from a direct bond, O, and S;

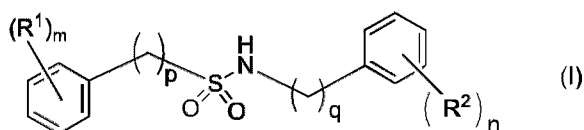
each  $R^2$  is independently selected from C1-C3 alkyl-Y-, and phenyl-(CH<sub>2</sub>)<sub>z</sub>-Y-;

each Y is independently selected from O and S; and

20 each z is independently selected from 0 and 1;

in the manufacture of a medicament for the treatment of a condition or disorder associated with nicotinamide adenine dinucleotide phosphate oxidase activity, selected from diabetes, stroke, fibrosis, neuropatic pain and diabetes complications; and

- use of a compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein

m is an integer of from 1 to 3;

5 n is an integer of from 0 to 3;

p is an integer of from 0 to 2;

q is 2;

each R<sup>1</sup> is independently selected from C1-C3 alkyl-X-;

each X is independently selected from a direct bond, O, and S;

10 each R<sup>2</sup> is independently selected from C1-C3 alkyl-Y-, and phenyl-(CH<sub>2</sub>)<sub>z</sub>-Y-;

each Y is independently selected from O and S; and

each z is independently selected from 0 and 1;

in the treatment of a condition or disorder associated with nicotinamide adenine dinucleotide phosphate oxidase activity, selected from diabetes, stroke, fibrosis, neuropatic pain and diabetes complications.

## 15 BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows dose-response curves for 4 different compounds of the invention in Nox4-transfected TRex-293 cells, at 11 concentrations obtained by serial dilution 1:3 of a 200 μM solution of tested compound: **A**) 2,4,6-trimethyl-N-phenethylbenzenesulfonamide, **B**) 4-methoxy-N-phenethylbenzenesulfonamide, **C**) N-(4-ethoxyphenyl)-3,4-dimethoxybenzene-sulfonamide and **D**) N-

20 (4-(benzyloxy)phenyl)-3,4-dimethoxybenzenesulfonamide.

FIGURE 2 is a graph showing isoluminol-dependent chemiluminescence as a measure of ROS production from Nox2 in **A**) PLB985 cells and **B**) PBMC cells, respectively, in the presence of a given concentration of 2,4,6-trimethyl-N-phenethylbenzenesulfonamide, in % compared to PMA (30 ng/ml) controls (=100%).

## DETAILED DESCRIPTION OF THE INVENTION

In general any term used herein shall be given its normal meaning as accepted within the field to which the present invention belongs. For the sake of clarity, however, some definitions will be given herein below, and shall apply throughout the specification and the appended claims,  
5 unless otherwise specified or apparent from the context.

The term "endocrine disorder" refers to disorders of the endocrine system and may be as well endocrine gland hyposecretion as hypersecretion, or tumors of endocrine glands. Diabetes and polycystic ovarian syndrome are examples of endocrine disorders.

10

The term "cardiovascular disorder or disease" comprises atherosclerosis, especially diseases or disorders associated with endothelial dysfunction including but not limited to hypertension, cardiovascular complications of Type I or Type II diabetes, intimal hyperplasia, coronary heart disease, cerebral, coronary or arterial vasospasm, endothelial dysfunction, heart failure  
15 including congestive heart failure, peripheral artery disease, restenosis, trauma caused by a stent, stroke, ischemic attack, vascular complications such as after organ transplantation, myocardial infarction, hypertension, formation of atherosclerotic plaques, platelet aggregation, angina pectoris, aneurysm, aortic dissection, ischemic heart disease, cardiac hypertrophy, pulmonary embolus, thrombotic events including deep vein thrombosis, injury  
20 caused after ischemia by restoration of blood flow or oxygen delivery as in organ transplantation, open heart surgery, angioplasty, hemorrhagic shock, angioplasty of ischemic organs including heart, brain, liver, kidney, retina and bowel.

25

The term "respiratory disorder or disease" comprises bronchial asthma, bronchitis, allergic rhinitis, adult respiratory syndrome, cystic fibrosis, lung viral infection (influenza), pulmonary hypertension, idiopathic pulmonary fibrosis and chronic obstructive pulmonary diseases (COPD).

30

The term "allergic disorder" includes hay fever and asthma.

The term "traumatism" includes polytraumatism.

The term "disease or disorder affecting the metabolism" includes obesity, metabolic syndrome and Type II diabetes.

The term "skin disease" or disorder" includes psoriasis, eczema, dermatitis, wound healing and scar formation.

5 The term "bone disorder" includes osteoporosis, osteoporosis, osteosclerosis, periodontitis, and hyperparathyroidism.

10 The term "demyelinating" is referring to a state or a disease of the CNS comprising the degradation of the myelin around the axons. In the context of the invention, the term demyelinating disease is intended to comprise conditions which comprise a process that demyelinate cells such as multiple sclerosis, progressive multifocal leukoencephalopathy (PML), myelopathies, any neuroinflammatory condition involving autoreactive leukocyte within the CNS, congenital metabolic disorder, a neuropathy with abnormal myelination, drug induced demyelination, radiation induced demyelination, a hereditary demyelinating condition, a prion induced demyelinating condition, encephalitis induced demyelination or a spinal cord injury. Preferably, the condition is multiple sclerosis.

20 The term "kidney disease or disorder" includes diabetic nephropathy, renal failure, glomerulonephritis, nephrotoxicity of aminoglycosides and platinum compounds and hyperactive bladder. In a particular embodiment, the term according to the invention includes chronic kidney diseases or disorders.

The term "reproduction disorder or disease" includes erectile dysfunction, fertility disorders, prostatic hypertrophy and benign prostatic hypertrophy.

25 The term "disease or disorder affecting the eye and/or the lens" includes cataract including diabetic cataract, re-opacification of the lens post cataract surgery, diabetic and other forms of retinopathy.

30 The term "conditions affecting the inner ear" includes presbycusis, tinnitus, Meniere's disease and other balance problems, utriculolithiasis, vestibular migraine, and noise induced hearing loss and drug induced hearing loss (ototoxicity).

The term "inflammatory disorder or disease" means inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, shock induced by trauma,

bronchial asthma, allergic rhinitis, rheumatoid arthritis, chronic rheumatoid arthritis, arteriosclerosis, intracerebral hemorrhage, cerebral infarction, heart failure, myocardial infarction, psoriasis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, myelitis, ankylosing spondylitis, Reuter syndrome, psoriatic arthritis, spondyloarthritis, juvenile arthritis or juvenile ankylosing spondylitis, reactive arthritis, infectious arthritis or arthritis after infection, gonococcal arthritis, syphilitic arthritis, Lyme disease, arthritis induced by "angiitis syndrome," polyarteritis nodosa, anaphylactic angiitis, Luegenec granulomatosis, rheumatoid polymyalgia, articular cell rheumatism, calcium crystal deposition arthritis, pseudogout, non-arthritic rheumatism, bursitis, tendosynovitis, epicondyle inflammation (tennis elbow), carpal tunnel syndrome, disorders by repetitive use (typing), mixed form of arthritis, neuropathic arthropathy, hemorrhagic arthritis, vascular peliosis, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis induced by specific diseases, blood pigmentation, sickle cell disease and other hemoglobin abnormality, hyperlipoproteinemia, dysgammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Bechet's disease, systemic autoimmune disease erythematosus, multiple sclerosis and Crohn's disease or diseases like relapsing polychondritis, chronic inflammatory bowel diseases (IBD) or the related diseases which require the administration to a mammal in a therapeutic effective dose of a compound expressed by Formula (I) in a sufficient dose to inhibit NADPH oxidase.

20

The term "liver diseases or disorders" include liver fibrosis, alcohol induced fibrosis, steatosis and non alcoholic steatohepatitis.

The term "arthritis" means acute rheumatic arthritis, chronic rheumatoid arthritis, chlamydial arthritis, chronic absorptive arthritis, anchylous arthritis, arthritis based on bowel disease, filarial arthritis, gonorrheal arthritis, gouty arthritis, hemophilic arthritis, hypertrophic arthritis, juvenile chronic arthritis, Lyme arthritis, neonatal foal arthritis, nodular arthritis, ochronotic arthritis, psoriatic arthritis or suppurative arthritis, or the related diseases which require the administration to a mammal in a therapeutic effective dose of a compound expressed by Formula (I) in a sufficient dose to inhibit NADPH oxidase.

30

The term "pain" includes hyperalgesia associated with inflammatory pain.



The term "cancer" means carcinoma (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endothelium sarcoma, lymphangiosarcoma, lymphangioendothelioma, periosteoma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, renal cancer, prostatic carcinoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatocellular carcinoma, cholangiocarcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, orchioncus, lung cancer, small-cell lung cancer, lung adenocarcinoma, bladder cancer or epithelial cancer) or the related diseases which require the administration to a mammal in a therapeutic effective dose of a compound expressed by the Formula (I) in a sufficient dose to inhibit NADPH oxidase.

15 The term "disease or disorders of the gastrointestinal system", includes gastric mucosa disorders ischemic bowel disease management, enteritis/colitis, cancer chemotherapy, or neutropenia.

The term "angiogenesis" includes sprouting angiogenesis, intussusceptive angiogenesis, vasculogenesis, arteriogenesis and lymphangiogenesis. Angiogenesis is the formation of new blood vessels from pre-existing capillaries or post-capillary venules and occurs in pathological conditions such as cancers, arthritis and inflammation. A large variety of tissues, or organs comprised of organized tissues, can support angiogenesis in disease conditions including skin, muscle, gut, connective tissue, joints, bones and the like tissue in which blood vessels can invade upon angiogenic stimuli. As used herein, the term "angiogenesis-dependent condition" is intended to mean a condition where the process of angiogenesis or vasculogenesis sustains or augments a pathological condition. Vasculogenesis results from the formation of new blood vessels arising from angioblasts which are endothelial cell precursors. Both processes result in new blood vessel formation and are included in the meaning of the term angiogenesis-dependent conditions. Similarly, the term "angiogenesis" as used herein is intended to include de novo formation of vessels such as those arising from vasculogenesis as well as those arising from branching and sprouting of existing vessels, capillaries and venules.

The term "angiogenesis inhibitory," means which is effective in the decrease in the extent, amount, or rate of neovascularization. Effecting a decrease in the extent, amount, or rate of endothelial cell proliferation or migration in the tissue is a specific example of inhibiting angiogenesis. Angiogenesis inhibitory activity is particularly useful in the treatment of any cancers as it targets tumor growth process and in the absence of neovascularization of tumor tissue, the tumor tissue does not obtain the required nutrients, slows in growth, ceases additional growth, regresses and ultimately becomes necrotic resulting in killing of the tumor. Further, an angiogenesis inhibitory activity is particularly useful in the treatment of any cancers as it is particularly effective against the formation of metastases because their formation also requires vascularization of a primary tumor so that the metastatic cancer cells can exit the primary tumor and their establishment in a secondary site requires neovascularization to support growth of the metastases.

As used herein, "treatment" and "treating" and the like generally mean obtaining a desired pharmacological and physiological effect. The effect may be prophylactic in terms of preventing or partially preventing a disease, symptom or condition thereof and/or may be therapeutic in terms of a partial or complete cure of a disease, condition, symptom or adverse effect attributed to the disease. The term "treatment" as used herein covers any treatment of a disease in a mammal, particularly a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; or relieving the disease, i.e., causing regression of the disease and/or its symptoms or conditions.

The term "subject" as used herein refers to mammals. For examples, mammals contemplated by the present invention include human, primates, domesticated animals such as cattle, sheep, pigs, horses and the like.

"An effective amount" or "therapeutically effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect).

The term "inhibitor" used in the context of the invention is defined as a molecule that inhibits completely or partially the activity of Nox, in particular Nox4, and/or inhibits or reduces the generation of reactive oxygen species (ROS).

- 5 "Pharmaceutically acceptable" means being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

The term C<sub>n</sub>, where n is an integer, specifies that a radical or moiety contains n carbon atoms.

10

The term C<sub>n</sub>-C<sub>m</sub>, where m and n are both integers, and m>n, refers to a radical or moiety containing at least n and at most m carbon atoms. Thus, the term C<sub>1</sub>-C<sub>6</sub> alkyl refers to an alkyl radical that may contain 1, 2, 3, 4, 5 or 6 carbon atoms.

- 15 A C<sub>1</sub>-C<sub>3</sub> alkyl according to the invention more particularly is a C<sub>1</sub>-C<sub>2</sub> alkyl, e.g. methyl.

In the compound of formula (I), m is 1, 2 or 3. In some embodiments, m is 1. In some other embodiments, m is 2. In still other embodiments, m is 3. In some other embodiments, m is 1 or 3. In still other embodiments, m is 2 or 3.

20

In formula (I), each moiety R<sup>1</sup> is independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl-X-, or from C<sub>1</sub>-C<sub>2</sub> alkyl-X-; e.g. CH<sub>3</sub>-X-.

- Each X is independently selected from a direct bond, O and S. In some embodiments, each X is selected from a direct bond and O. In some embodiments, each X is a direct bond. In some  
25 embodiments, each X is O or S, e.g. each X is O.

- In some particular embodiments, each R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>3</sub> alkyl and C<sub>1</sub>-C<sub>3</sub> alkoxy, such as methyl and methoxy. In some embodiments, each R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>3</sub> alkyl,  
30 such as methyl. In some other embodiments, each R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>3</sub> alkoxy, such as methoxy.

In a compound of formula (I), n is an integer of from 0 to 3, e.g. n is an integer of from 0 to 2. In some embodiments, n is 0 or 1. In some particular embodiments, n is 0. In some other embodiments, n is an integer of from 1 to 3, e.g. n is 1 or 2, in particular n is 1.

- 5 Each moiety  $R^2$  is independently selected from C1-C3 alkyl-Y-, and phenyl-(CH<sub>2</sub>)<sub>z</sub>-Y-. In some embodiments, each  $R^2$  is C1-C3 alkyl-Y-. In some embodiments, each  $R^2$  is and phenyl-(CH<sub>2</sub>)<sub>z</sub>-Y-.

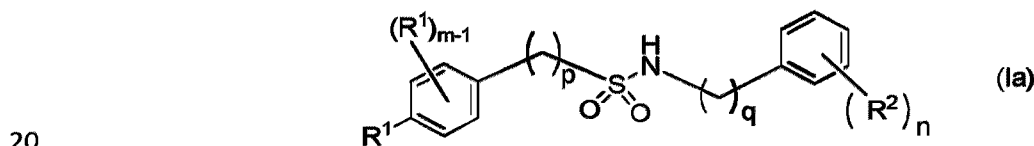
- 10 Any C1-C3 alkyl-Y- more particularly may be selected from C1-C2 alkyl-Y-; e.g. any C1-C3alkyl-Y- may be C<sub>2</sub>H<sub>5</sub>-Y-.

The moiety Y is independently selected from O and S, e.g. each Y is O.

- 15 In the moiety phenyl-(CH<sub>2</sub>)<sub>z</sub>-Y-, z is an integer selected from 0 and 1. In some embodiments, z is 0. In some other embodiments, z is 1.

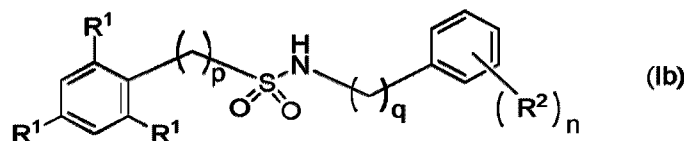
In some embodiments, n is 0, or n is 1 and  $R^2$  is ethoxy or benzyloxy.

In some embodiments, the compound of formula (I) may be represented by formula (Ia)



wherein m, n, p, q,  $R^1$  and  $R^2$  are as defined herein above. For example, in some embodiments of a compound of formula (Ia), p is 0. In some further embodiments of a compound of formula (Ia), p is 0 and q is 1 or 2, in particular q is 2.

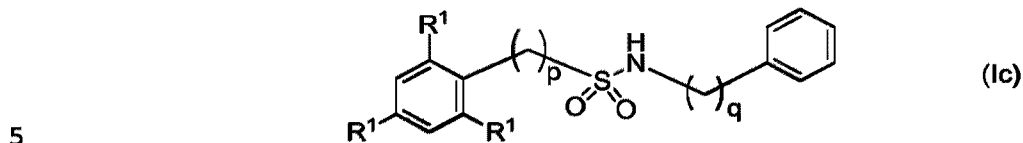
- 25 In some embodiments, the compound of formula (I) may be represented by formula (Ib)



wherein n, p, q,  $R^1$  and  $R^2$  are as defined herein above. For example, in some embodiments of a compound of formula (Ib), p is 0. In some embodiments of a compound of formula (Ib), q is

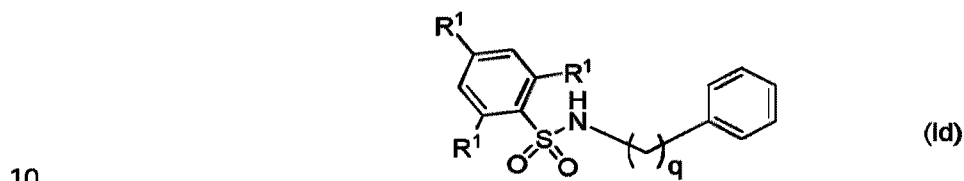
1 or 2, in particular q is 2. In some special embodiments of a compound of formula (Ib), p is 0 and q is 1 or 2, in particular q is 2.

In some embodiments, the compound of formula (I) may be represented by formula (Ic)



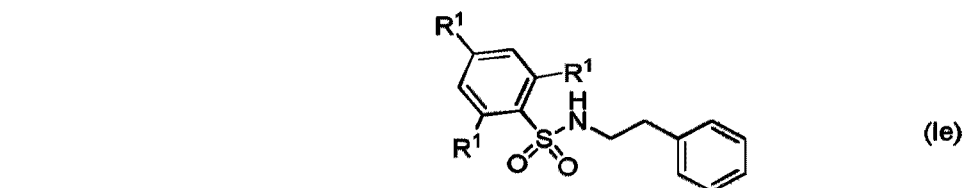
wherein p, q, and R<sup>1</sup> are as defined herein above. In some embodiments of a compound of formula (Ic), q is 1 or 2, in particular q is 2.

In some embodiments, the compound of formula (I) may be represented by formula (Id)



wherein q and R<sup>1</sup> are as defined herein above. For example, in some embodiments of a compound of formula (Id), q is 1 or 2.

In some particular embodiments, the compound of formula (I) may be represented by formula (Ie)

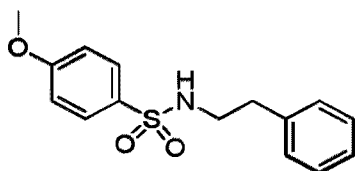


wherein each R<sup>1</sup> is as defined herein above.

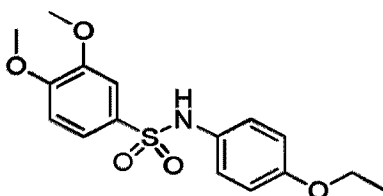
In some embodiments, the compound of formula (I) is selected from



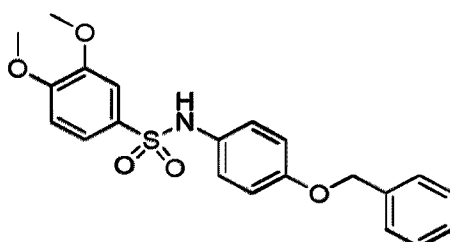
2,4,6-trimethyl-N-phenethylbenzenesulfonamide,



4-methoxy-N-phenethylbenzenesulfonamide,



N-(4-ethoxyphenyl)-3,4-dimethoxybenzenesulfonamide, and



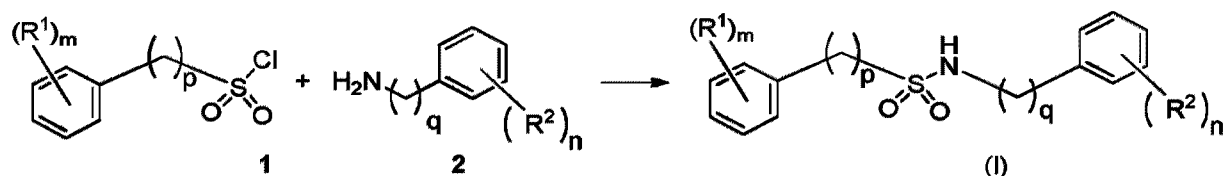
5

N-(4-(benzyloxy)phenyl)-3,4-dimethoxybenzenesulfonamide.

The compounds of formula (I) are commercially available or can be prepared by methods well known in the art, from readily available starting materials using general methods and procedures.

10

For example, a compound of formula (I) may be prepared by reacting a sulfonyl chloride **1** with an amine **2** in a suitable solvent medium, as illustrated in the following reaction scheme:



15

The compounds of the present invention are Nox inhibitors. More specifically, the compounds of the present invention are Nox4 inhibitors. The capacity of inhibiting predominantly one particular Nox isoform, i.e. Nox4, is considered to be an important advantage of the present compounds, in view of the fact that Nox isoforms not only are involved in diseases, as Nox4, but also have various important biological functions in the living body.

20

Depending on the process conditions the end products of formula (I) are obtained either in neutral or salt form. Both the free base and the free acid, as well as the salts of these end products are within the scope of the invention. Acid addition salts of the inventive compounds may in a manner known per se be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids. Alkali addition salts of the inventive compounds may in a manner known per se be transformed into the free acid by using acidic agents such as acid or by ion exchange. The free acid obtained may also form salts with organic or inorganic bases.

10 In the preparation of acid or base addition salts, preferably such acids or bases are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids, sulfuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybenzoic acid, embonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, halogenbenzenesulfonic acid, toluenesulfonic acid or naphthalenesulfonic acid. Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases such as alkoxides, alkyl amides, alkyl and aryl amines, and the like. Examples of bases useful in preparing salts of the present invention include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, and the like.

25 There may be several stereoisomers of the compounds of the invention, including enantiomers and diastereomers. Enantiomers can be present in their pure forms, or as racemic (equal) or unequal mixtures of two enantiomers. Diastereomers can be present in their pure forms, or as mixtures of diastereomers. Diastereomers also include geometric isomers, which can be present in their pure cis or trans forms or as mixtures of those.

30 According to a further aspect a pharmaceutical composition is provided herein, comprising a therapeutically effective amount of a compound of formula (I) as defined herein above, or pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable excipient.

Pharmaceutical formulations are usually prepared by mixing the active substance, i.e. a compound of the invention, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutical excipients. The formulations can be further prepared by known methods such as granulation, compression, microencapsulation, spray coating, etc. The formulations may be prepared by conventional methods in the dosage form of tablets, capsules, granules, powders, syrups, suspensions, suppositories or injections. Liquid formulations may be prepared by dissolving or suspending the active substance in water or other suitable vehicles. Tablets and granules may be coated in a conventional manner.

10 For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. These pharmaceutical preparations are a further object of the invention.

Usually the effective amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and preferably between 1 and 50% by weight in preparations for oral administration.

The dose level and frequency of dosage of the specific compound will vary depending on a variety of factors including the potency of the specific compound employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 100 mg per kilo of body weight, administered singly or multiply in doses, e.g. from about 0.01 mg to about 25 mg each. Normally, such a dosage is given orally but parenteral administration may also be chosen.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatine, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets.



Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch,  
5 amylopectin, cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or  
10 other suitable vehicle for gelatine rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl  
20 cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral, e.g. intravenous, administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a  
25 concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

The compounds of the present invention may also be used or administered in combination  
30 with one or more additional therapeutically active agents. The components may be in the same formulation or in separate formulations for administration simultaneously or sequentially.

Accordingly, in a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention for use according to the invention, as defined herein; and  
(B) another therapeutic agent; whereby (A) and (B) is formulated in admixture with a  
5 pharmaceutically acceptable excipient.

Such combination products provide for the administration of a compound of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the  
10 invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

Thus, there is further provided:

15 (1) a pharmaceutical formulation including a compound for use according to the invention, as hereinbefore defined, another therapeutic agent, and a pharmaceutically acceptable excipient, e.g. an adjuvant, diluent or carrier; and

(2) a kit of parts comprising, as components:

20 (a) a pharmaceutical formulation including a compound for use according to the invention, as defined herein, in admixture with a pharmaceutically acceptable excipient, e.g. an adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent in admixture with a pharmaceutically acceptable excipient, e.g. an adjuvant, diluent or carrier, which components

25 (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

The compounds of the present invention may also be used or administered in combination with other modes of treatment such as irradiation for the treatment of cancer.

30

According to one aspect, a compound according to formula (I) as defined herein above is provided for inhibiting a nicotineamide adenine dinucleotide phosphate oxidase (Nox) in a mammal, in particular Nox4, for use in the treatment of a disorder associated with the expression of Nox, in particular Nox4. The disorder may be selected from e.g. endocrine

disorders, cardiovascular disorders, respiratory disorders, metabolism disorders, skin disorders, bone disorders, neuroinflammatory disorders, kidney diseases, reproduction disorders, diseases affecting the eye and/or the lens and/or conditions affecting the inner ear, inflammatory disorders, liver diseases, pain, cancers, allergic disorders, traumatisms, septic, hemorrhagic and anaphylactic shock, diseases or disorders of the gastrointestinal system, abnormal angiogenesis and angiogenesis-dependent conditions. In some embodiments, the disorder is selected from diabetes, stroke, fibrosis, such as lung fibrosis, neuropathic pain and diabetes complications, such as neuropathy; e.g. the disorder is diabetes, or the disorder is stroke.

10

In some embodiments, the disorder is an endocrine disorder. In some embodiments, the disorder is a cardiovascular disorder. In some embodiments, the disorder is a respiratory disorder. In some embodiments, the disorder is a metabolism disorder. In some embodiments, the disorder is a skin disorder. In some embodiments, the disorder is a bone disorder. In some embodiments, the disorder is a neuroinflammatory disorder. In some embodiments, the disorder is a kidney disease. In some embodiments, the disorder is a reproduction disorder. In some embodiments, the disorder is a disease affecting the eye and/or the lens and/or conditions affecting the inner ear. In some embodiments, the disorder is an inflammatory disorder. In some embodiments, the disorder is a traumatism. In some embodiments, the disorder is a septic, hemorrhagic or anaphylactic shock. In some embodiments, the disorder is a disease or disorder of the gastrointestinal system. In some embodiments, the disorder is or involves abnormal angiogenesis. In some embodiments, the disorder is an angiogenesis-dependent condition.

15

20

According to one aspect, there is provided a method of inhibiting the activity of Nox, in particular Nox4, in a patient in need thereof, by administering to said patient a therapeutically effective amount of a compound of formula (I) as defined herein. The patient may be any mammal, but preferably is a human.

25

The patient to be treated may be one suffering from a condition or disorder associated with an elevated activity of Nox, in particular Nox4, or a patient at risk of developing such a condition or disorder.

30

## EXAMPLES

## Example 1

## Cell-based assays and analytical chemistry

## 1 CELL VIABILITY

## 5 1.1 Celltiter-Blue cell viability assay (Promega)

The assay is based on the ability of the cells to reduce resazurin to resorufin as a measure of viability. TReX™-293 Nox4 cells were cultured in a T-225 flask, collected by trypsination and re-suspended in cell medium. 20,000 cells in 90 µl were seeded to 96-well cell culture plates (black with transparent bottom). One background plate with 90 µl cell medium only  
10 was also prepared.

After 24 hours, 10 µl of compound, diluted to 10 times final concentration in 37° C cell medium, were added to cell and background plates. The compounds were tested in duplicate at a final concentration of 10 µM. Chlorpromazine, at a final concentration of 100 µM, was  
15 added as positive control. After 24 hours of treatment, 20 µl of CellTiter-Blue reagent were added and the plate was incubated for 120 min at 37° C. Resorufin fluorescence was read in Victor2V plate reader. All experimental values were corrected for background before analysis of the cell viability.

## 20 1.2 CytoTox 96® Non-radioactive Cytotoxicity Assay (Promega)

The assay is based on lactate dehydrogenase (LDH) activity in surrounding cell medium as a measure of membrane integrity. Membrane integrity can be affected by apoptosis, necrosis or chemicals. TReX™-293 Nox4 cells were cultured in a T-225 flask, collected by trypsination and re-suspended in HBSS to 100,000 cells per ml. 90 µl of cell suspension were added to  
25 each well of a V-bottom polypropylene 96-well plate. One background plate was prepared with HBSS only. Compounds were diluted in HBSS to 10 times final concentration and 10 µl was added per well. The compounds were tested in duplicate at a final concentration of 10 µM.

30 Plates were incubated 3 hours at 37° C. 45 minutes before end of incubation time, 10 µl of lysis solution (Triton® X-100) were added to total control wells to estimate total LDH content of cells. Spontaneous LDH leakage was determined with un-treated cells.

Cell plates were centrifuged 250 x g for 5 minutes and 50 µl of supernatant were transferred to 96-well Spectraplates. 50 µl of reconstituted substrate mix were added and plates were incubated for 30 minutes at room temperature. 50 µl of stop solution were added and plates were read in SpectraMax® at a wavelength of 490 nm. Compound specific background was subtracted and % cytotoxicity was calculated as:

$$[(\text{Experimental} - \text{Spontaneous}) / (\text{Total} - \text{Spontaneous})] * 100 \%$$

When tested in the two cell viability assays, none of the inventive compounds showed any significant cell toxicity effects.

## 2 DOSE-RESPONSE CURVES

Dose-response measurements with the Amplex® Red based assay were performed as follows: Compound serial dilution was carried out using the system based on the liquid handler Janus® (Perkin Elmer) and scheduling software Overlord (Process Analysis and Automation).

Starting with compound plates with 15 µl 10 mM compound stock solution in DMSO, 10 µl of DMSO were added to columns of compound plate (Flexdrop™). Serial dilution was performed by adding 5 µl compound solution to 10 µl DMSO (1:3) to 11 concentrations. To each well of the compound plate 90 µl of assay buffer were added. After mixing, 10 µl were transferred from each well of the compound plate to wells of an assay plate, followed by addition of 20 µl detection mix and 20 µl of a suspension of TReX™-293 Nox4 cells. The assay plate then was incubated for 40-60 min at room temperature.

Data was analysed using a custom calculation template in Activitybase XE (IDBS). Raw fluorescence data was transformed to %inhibition using the built-in formula:

$$\% \text{inhibition} = 100 - \frac{\text{RawData}_{\text{Compound}} - \text{RawData}_{\text{Low}}}{\text{RawData}_{\text{High}} - \text{RawData}_{\text{Low}}} \times 100$$

Dose-response curves were fitted using non-linear regression with four parameter logistic formula. In Figure 1, dose-response curves for compounds of the invention are shown.

### 3 *IDENTITY, PURITY AND STABILITY (IPS) ANALYSIS*

DMSO solutions were diluted to a final concentration of 100  $\mu$ M in PBS, pH 7.4. Two samples were prepared, one for immediate analysis and a second to be stored at 37° C for 24 h.

Analysis was performed on a reversed phase HPLC system with UV and ESI-MS detection.

- 5 Purity was defined as the relative area of the sample peak at 220 nm. Identity was determined by the presence of a molecular ion in the MS of the sample chromatogram. Stability was the ratio of the relative area of the sample peak after 24 hours to that of the 0 hour chromatogram. Purity and stability values were truncated to be reported in 10% increments (*i.e.* 96% is reported as 90%).

- 10 In the IPS analysis, tested compounds had positive identity, were 90%> pure or more and had a stability of 80% or more.

#### **Example 2**

##### **Activity of compounds of the invention vs Nox2**

- To evaluate the Nox4 specificity of compounds of the invention, a number of the compounds of the invention were tested for their potential inhibitory effect of on reactive oxygen species (ROS) production from Nox2.
- 15

### 1 *STUDY DESIGN*

- On PLB985 cells (a human acute myeloid leukemia cell line) and human peripheral blood mononuclear cells (PBMC), inhibition of ROS production from Nox2 after stimulation with phorbol 12-myristate 13-acetate (PMA) (30ng/ml) was evaluated using Isoluminol enhanced chemiluminescence. The inventive compounds and diphenyleneiodonium chloride (DPI) were titrated in a 3-fold dilution series ranging from 200 $\mu$ M to 0,0 1 $\mu$ M.
- 20

All samples were analyzed as duplicates.

### 2 *ANALYSIS ASSAY*

#### 2.1 *Isoluminol Assay*

- 25 Levels of ROS were measured using isoluminol-dependent chemiluminescence (Dahlgren, Claes & Karlsson-Bengtsson, Anna and Bylund, Johan. (2007). Measurement of Respiratory Burst Produced Generated by Professional Phagocytes. Methods in molecular biology (Clifton, N.J.). 412. 349-63.) Isoluminol is a hydrophobic dye unable to pass biological membranes. Hence,

extracellular ROS is measured using this method. Isoluminol is excited by ROS and the light emitted when excited molecules return to the ground state, relative to the amount of released ROS, is measured. This reaction is catalyzed and amplified by peroxidases. Naturally occurring peroxidases can achieve this, however secretions of such are limited and hence additional  
5 peroxidases, in the present case horseradish peroxidase fraction II, need to be added.

## 2.2 *Data collection and analysis*

Luminescence was detected using a FluoStar Optima (BMG Labtech) and white 96-well plates. Measurements were performed during 23 cycles à 67 seconds, at 37°C with shaking. From the 23 cycles an Area Under Curve (AUC) value was calculated. Results were evaluated as percentage  
10 change compared to PMA stimulated cells without addition of inhibitor.

Nonlinear regression and IC50 calculations were performed using Prism 5 for Mac OS X.

## 3 *MATERIALS AND METHODS*

### 3.1 *Human PBMC*

Human blood was purchased in one day-old buffy coats from Komponentlab, Sahlgrenska  
15 University hospital, Goteborg, Sweden.

#### 3.1.1 *PBMC isolation*

Erythrocytes were removed from whole blood by Dextran sedimentation. The erythrocyte free fraction was separated by density gradient centrifugation using Ficoll-Paque Plus (supplemented with 0.75 mg/ml NaCl) according to manufacturer's instructions. PBMCs were isolated from the  
20 interface between plasma and Ficoll-Paque Plus reagent. The PBMCs were washed in HBSS until contaminating platelets were removed. Cell count and viability were determined by trypan blue exclusion.

#### 3.1.2 *Cryopreservation of PBMC*

Cells were cryopreserved according to Kreher CR, Dittrich MT, Guerkov R, Boehm BO, Tary-Lehmann M. CD4+ and CD8+ cells in cryopreserved human PBMC maintain full functionality  
25 in cytokine ELISPOT assays. J Immuno Methods. 2003 Jul; 278(1-2): 79-93. Briefly, isolated cells were resuspended at  $20 \times 10^6$  cells/ml in room temperature freezing medium A (60% Fetal Bovine Serum, 40% RPMI 1640). An equal volume of room temperature freezing medium B

(20% DMSO, 80% Fetal Bovine Serum) was added drop wise.  $15 \times 10^6$  cells were aliquoted in cryo tubes and placed in a pre-chilled (4°C) Cryogenic Controlled-Rate Freezing Container in -80°C. After 24h, samples were transferred to -150°C freezer for indefinite storage.

### 3.1.3 *Thawing of PBMC*

- 5 Cells were thawed quickly in 37°C water bath, pipetted into room temperature HBSS and centrifuged (250 x g, 20°C, 5min). After washing (2x) in HBSS, cells were resuspended in HBSS at a concentration of  $2 \times 10^6$  cells/ml. Cell count and viability were determined by Trypan Blue exclusion.

One vial per assay plate was used, thawed and prepared just prior to analysis.

### 10 3.1.4 *Cell Count: Human PBMC*

Total Cell count (per vial):	9-9.75x10 <sup>6</sup> cells
Viability:	92-95%
Assay concentration viable cells:	2x10 <sup>6</sup> cells/ml

### 3.2 *PLB985*

- 15 PLB985 cells were cultured in RPMI 1640 supplemented with 10% Fetal Bovine Serum (FBS) and Penicillin/Streptomycin 100U/ml (= complete growth medium) at 37°C, 5% CO<sub>2</sub>. Cells were passaged approximately twice a week. For differentiation towards neutrophils, cells were spun down (250g, 5min, RT) and resuspended in complete growth medium supplemented with 1.25% DMSO for five days (Zhen L, King AA, Xiao Y, Chanock SJ, Orkin SH, Dinuer MC. Gene targeting of X chromosome-linked chronic granulomatous disease locus in a human myeloid leukemia cell line and rescue by expression of recombinant gp91phox. Proc Natl Acad Sci U S A. 1993 Nov 1; 90(21):9832-6. Tucker KA, Lilly MB, Heck L Jr, Rado TA. Characterization of a new human diploid myeloid leukemia cell line (PLB-985) with granulocytic and monocytic differentiating capacity. Blood. 1987 Aug;70(2):372-8. At the day of analysis, differentiated cells were pelleted (250g, 5min, RT), washed twice in HBSS and resuspended in HBSS at  $2 \times 10^6$  cells/ml. Cell count and viability were determined by Trypan Blue exclusion. Cells were stored in room temperature until use.
- 20
- 25



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28a

3.2.1 *Cell Count: PLB985*

**Total Cell count:** 94x10<sup>6</sup> cells  
**Viability:** 92%  
**Assay concentration viable cells:** 2x10<sup>6</sup> cells/ml

5 3.3 *Reagents*

Assay plates, white 96-well (Nunc 236108)

Dextran T500 (Pharmacosmos 5510 0500 4006)

DMSO (Sigma: D5879)

DPI

10 Fetal Bovine Serum (VWR: LONZ 14-801F )

Ficoll® Paque Plus (GE Healthcare 71-7167-00)

fMLF (Sigma: F3506)

HBSS (In house: 5.4mM KCl, 0.3mM Na<sub>2</sub>HPO<sub>4</sub> x 2H<sub>2</sub>O, 0.4mM KH<sub>2</sub>PO<sub>4</sub>, 4.2mM NaHCO<sub>3</sub>, 1.3mM CaCl<sub>2</sub> x 2H<sub>2</sub>O, 0.5mM MgCl<sub>2</sub> x 6H<sub>2</sub>O, 0.6mM MgSO<sub>4</sub> x 7H<sub>2</sub>O, 137mM NaCl, 5.6mM D-glucose)

5 HRP fraction II (Sigma P8250)

Isoluminol (4-Aminophthalhydrazide) (Sigma A8264)

PMA (Sigma P8139)

RPMI 1640 (VWR: LONZ12-702F/12 )

### 10 3.4 *Tested compounds*

100mM DMSO stock solutions of compounds of the invention were used for the tests.

### 3.5 *Isoluminol buffer*

The isoluminol buffer contains isoluminol (0,0175mg/ml) and HRP fraction II (1,75U/ml).

15 The buffer was prepared by diluting these ingredients at 4x working concentration in HBSS.

## 4 *PROCEDURES*

### 4.1 *Substance preparation*

20 The compounds to be tested were diluted in DMSO at 100x working concentration and titrated in a 3-fold dilution series from 200µM to 0.01µM as final concentrations.

DPI was diluted at 100x working concentration and dose titrated in the same dilution series as the test compounds. DPI was also used at a final concentration of 1µM as control on all plates. Dilution was then performed at 100x working concentration in DMSO.

25

PMA was diluted in isoluminol buffer at 4x working concentration.

### 4.2 *Isoluminol Assay*

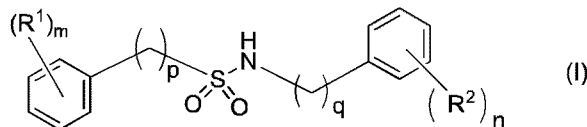
25µl of PMA diluted to 4x working concentration in isoluminol buffer were added to each well. To non-stimulated control wells only isoluminol buffer was added. Subsequently 24µl  
30 HBSS and 1µl of either the compound test solution or DPI solution were added to each well of the test plate (final DMSO concentration = 1.25%). Finally, 50µl of cell suspension (2x10<sup>6</sup> cells/ml) were added to each well, followed by immediate initiation of luminescence measurement.

5. *RESULTS*

The results for the compound 2,4,6-trimethyl-N-phenethylbenzenesulfonamide are represented as luminescence obtained in the presence of a given concentration of the tested substance in % compared to luminescence in the presence of PMA, cf. Figure 2.

CLAIMS:

1. A compound of formula (I)

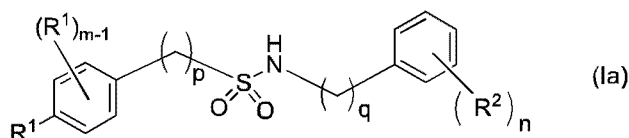


or a pharmaceutically acceptable salt thereof, wherein

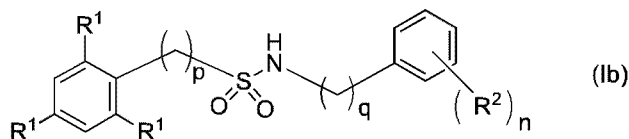
- 5 m is an integer of from 1 to 3;  
 n is an integer of from 0 to 3;  
 p is an integer of from 0 to 2;  
 q is 2;  
 each R<sup>1</sup> is independently selected from C1-C3 alkyl-X-;
- 10 each X is independently selected from a direct bond, O, and S;  
 each R<sup>2</sup> is independently selected from C1-C3 alkyl-Y-, and phenyl-(CH<sub>2</sub>)<sub>z</sub>-Y-;  
 each Y is independently selected from O and S; and  
 each z is independently selected from 0 and 1;
- for use in the treatment of a condition or disorder associated with nicotinamide adenine dinucleotide  
 15 phosphate oxidase activity, selected from diabetes, stroke, fibrosis, neuropatic pain and diabetes complications.
2. The compound or pharmaceutically acceptable salt thereof for use according to claim 1 wherein each X is independently selected from a direct bond and O.
3. The compound or pharmaceutically acceptable salt thereof for use according to claim 1 or  
 20 claim 2, wherein p is 0.
4. The compound or pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 3, wherein each Y is O.
5. The compound or pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 4, wherein n is 0 or 1.
- 25 6. The compound or pharmaceutically acceptable salt thereof for use according to claim 5, wherein n is 0.

7. The compound or pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 5, wherein each  $R^1$  is selected from methyl and methoxy, and each  $R^2$  is selected from ethoxy and benzyloxy.

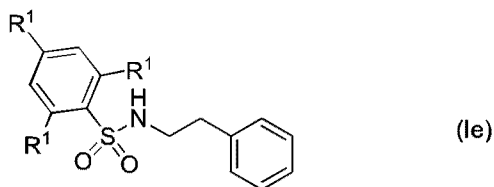
8. The compound or pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 7, wherein the compound is of formula (Ia)



9. The compound or pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 8, wherein the compound is of formula (Ib)



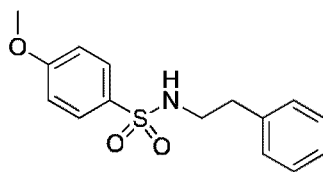
10. The compound or pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 9, wherein the compound is of formula (Ie)



11. The compound or pharmaceutically acceptable salt thereof for use according to claim 1, wherein the compound is selected from

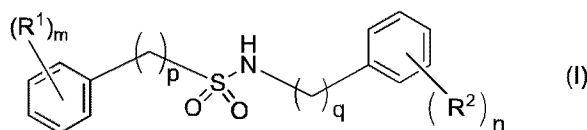


2,4,6-trimethyl-N-phenethylbenzenesulfonamide; and



4-methoxy-N-phenethylbenzenesulfonamide.

12. The compound or pharmaceutically acceptable salt thereof for use according to claim 11, wherein the compound is 2,4,6-trimethyl-N-phenethylbenzenesulfonamide.
13. The compound or pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 12, wherein the disorder is stroke.
- 5 14. The compound or pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 12, wherein the disorder is fibrosis.
15. The compound or pharmaceutically acceptable salt thereof for use according to claim 14, wherein the fibrosis is lung fibrosis.
16. The compound or pharmaceutically acceptable salt thereof for use according to any one of  
10 claims 1 to 12, wherein the disorder is the diabetes complication neuropathy.
17. The compound or pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 12, wherein the disorder is diabetes.
18. The compound or pharmaceutically acceptable salt thereof for use according to any one of  
15 claims 1 to 17, wherein the nicotinamide adenine dinucleotide phosphate oxidase is nicotinamide adenine dinucleotide phosphate oxidase 4.
19. Use of a compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein

- m is an integer of from 1 to 3;
- 20 n is an integer of from 0 to 3;
- p is an integer of from 0 to 2;
- q is 2;
- each R<sup>1</sup> is independently selected from C1-C3 alkyl-X-;
- each X is independently selected from a direct bond, O, and S;
- 25 each R<sup>2</sup> is independently selected from C1-C3 alkyl-Y-, and phenyl-(CH<sub>2</sub>)<sub>z</sub>-Y-;

each Y is independently selected from O and S; and

each z is independently selected from 0 and 1;

in the manufacture of a medicament for the treatment of a condition or disorder associated with nicotinamide adenine dinucleotide phosphate oxidase activity, selected from diabetes, stroke, fibrosis, neuropatic pain and diabetes complications.

20. The use according to claim 19, wherein each X is independently selected from a direct bond and O.

21. The use according to claim 19 or claim 20, wherein p is 0.

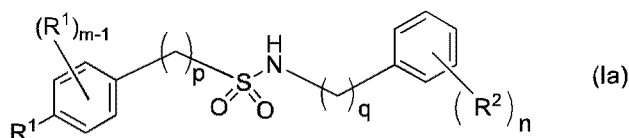
22. The use according to any one of claims 19 to 21, wherein each Y is O.

23. The use according to any one of claims 19 to 22, wherein n is 0 or 1.

24. The use according to claim 23, wherein n is 0.

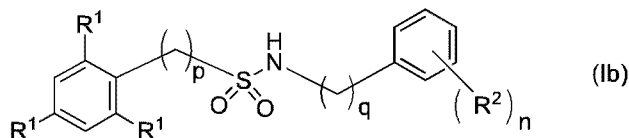
25. The use according to any one of the claims 19 to 23, wherein each R<sup>1</sup> is selected from methyl and methoxy, and each R<sup>2</sup> is selected from ethoxy and benzyloxy.

26. The use according to any one of claims 19 to 25, wherein the compound is of formula (Ia)

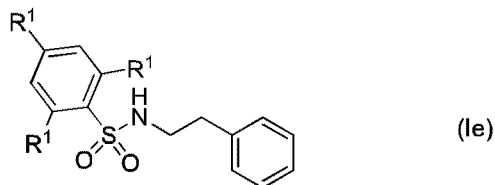


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27. The use according to any one of claims 19 to 26, wherein the compound is of formula (Ib)

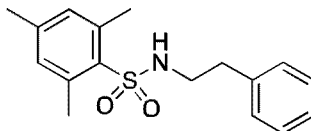


28. The use according to any one of claims 19 to 27, wherein the compound is of formula (Ic)

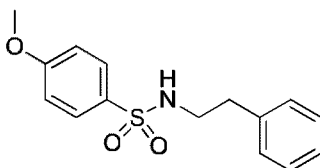


20

29. The use according to claim 19, wherein the compound is selected from



2,4,6-trimethyl-N-phenethylbenzenesulfonamide; and



5

4-methoxy-N-phenethylbenzenesulfonamide.

30. The use according to claim 29, wherein the compound is 2,4,6-trimethyl-N-phenethylbenzenesulfonamide.

31. The use according to any one of claims 19 to 30, wherein the disorder is stroke.

10 32. The use according to any one of claims 19 to 30, wherein the disorder is fibrosis.

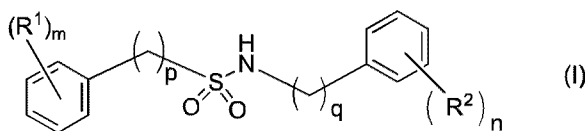
33. The use according to claim 32, wherein the fibrosis is lung fibrosis.

34. The use according to any one of claims 19 to 30, wherein the disorder is the diabetes complication neuropathy.

35. The use according to any one of claims 19 to 30, wherein the disorder is diabetes.

15 36. The use according to any one of claims 19 to 35, wherein the nicotinamide adenine dinucleotide phosphate oxidase is nicotinamide adenine dinucleotide phosphate oxidase 4.

37. Use of a compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein

20 m is an integer of from 1 to 3;

n is an integer of from 0 to 3;



p is an integer of from 0 to 2;

q is 2;

each R<sup>1</sup> is independently selected from C1-C3 alkyl-X-;

each X is independently selected from a direct bond, O, and S;

5 each R<sup>2</sup> is independently selected from C1-C3 alkyl-Y-, and phenyl-(CH<sub>2</sub>)<sub>z</sub>-Y-;

each Y is independently selected from O and S; and

each z is independently selected from 0 and 1;

10 in the treatment of a condition or disorder associated with nicotinamide adenine dinucleotide phosphate oxidase activity, selected from diabetes, stroke, fibrosis, neuropatic pain and diabetes complications.

38. The use according to claim 37, wherein each X is independently selected from a direct bond and O.

39. The use according to claim 37 or claim 38, wherein p is 0.

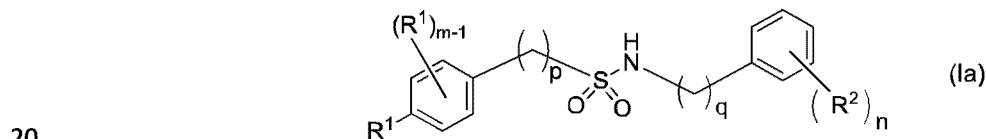
40. The use according to any one of claims 37 to 39, wherein each Y is O.

15 41. The use according to any one of claims 37 to 40, wherein n is 0 or 1.

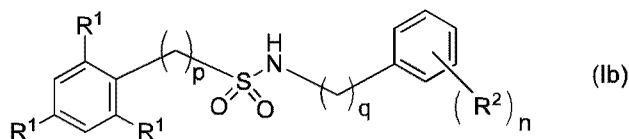
42. The use according to claim 41, wherein n is 0.

43. The use according to any one of claims 37 to 41, wherein each R<sup>1</sup> is selected from methyl and methoxy, and each R<sup>2</sup> is selected from ethoxy and benzyloxy.

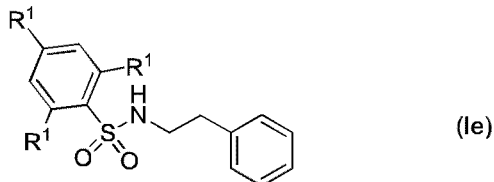
44. The use according to any one of claims 37 to 43, wherein the compound is of formula (Ia)



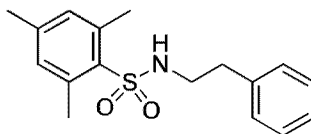
45. The use according to any one of claims 37 to 44, wherein the compound is of formula (Ib)



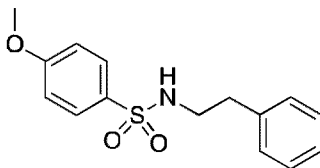
46. The use according to any one of claims 37 to 45, wherein the compound is of formula (Ie)



47. The use according to claim 37, wherein the compound is selected from



- 5 2,4,6-trimethyl-N-phenethylbenzenesulfonamide; and



4-methoxy-N-phenethylbenzenesulfonamide.

48. The use according to claim 47, wherein the compound is 2,4,6-trimethyl-N-phenethylbenzenesulfonamide.
- 10 49. The use according to any one of claims 27 to 48, wherein the disorder is stroke.
50. The use according to any one of claims 27 to 48, wherein the disorder is fibrosis.
51. The use according to claim 50, wherein the fibrosis is lung fibrosis.
52. The use according to any one of claims 27 to 48, wherein the disorder is the diabetes complication neuropathy.
- 15 53. The use according to any one of claims 27 to 48, wherein the disorder is diabetes.
54. The use according to any one of claims 37 to 53, wherein the nicotinamide adenine dinucleotide phosphate oxidase is nicotinamide adenine dinucleotide phosphate oxidase 4.

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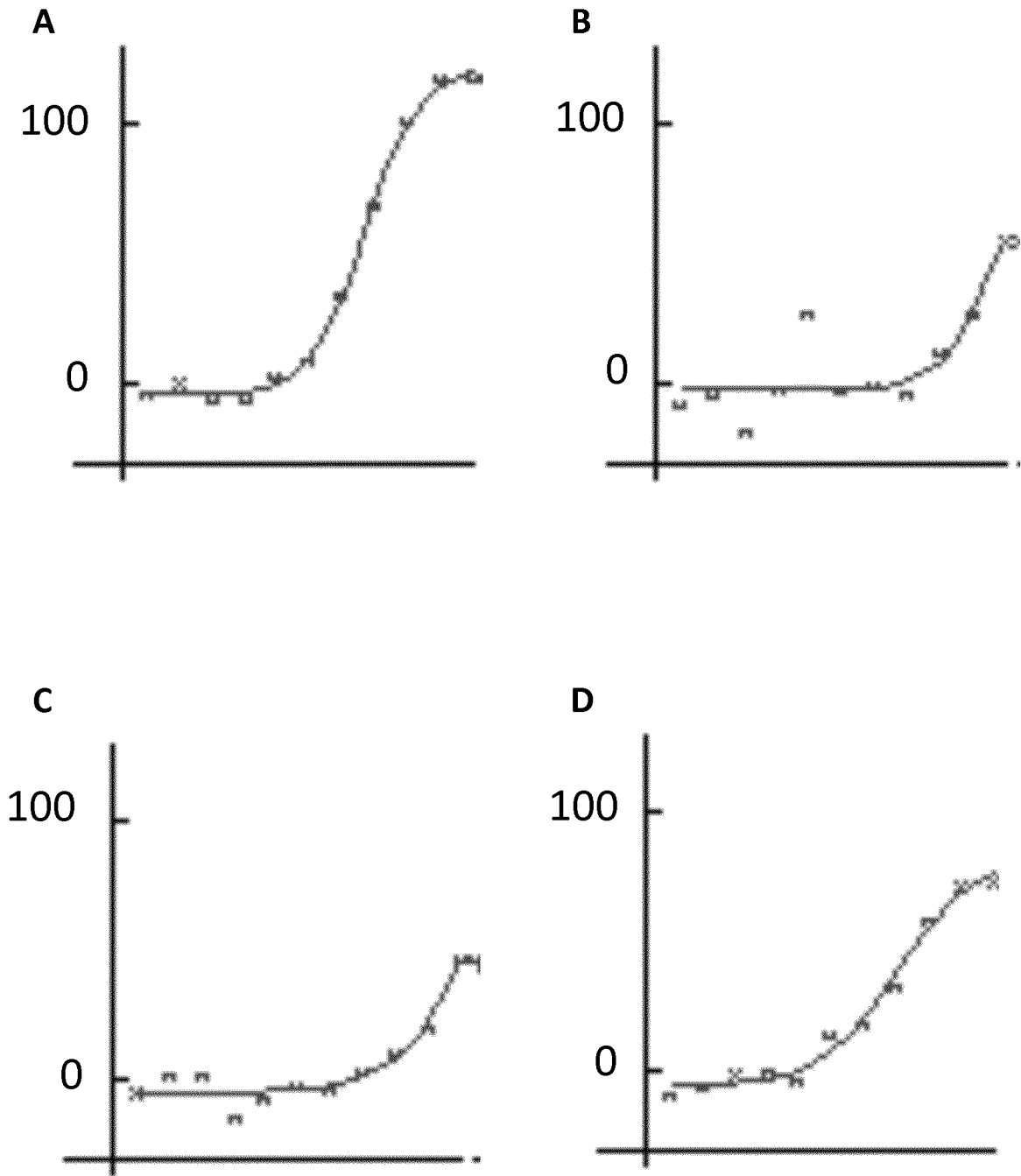
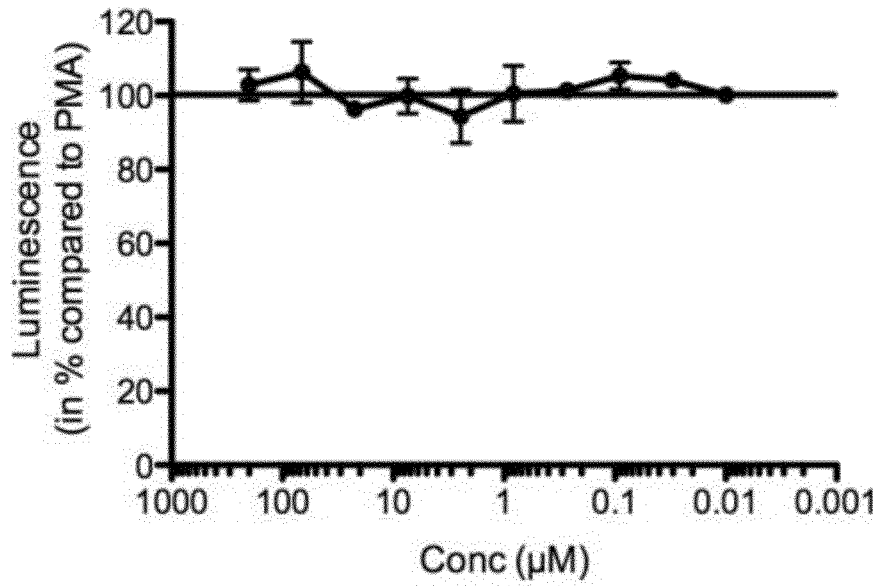


FIGURE 1

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A



B

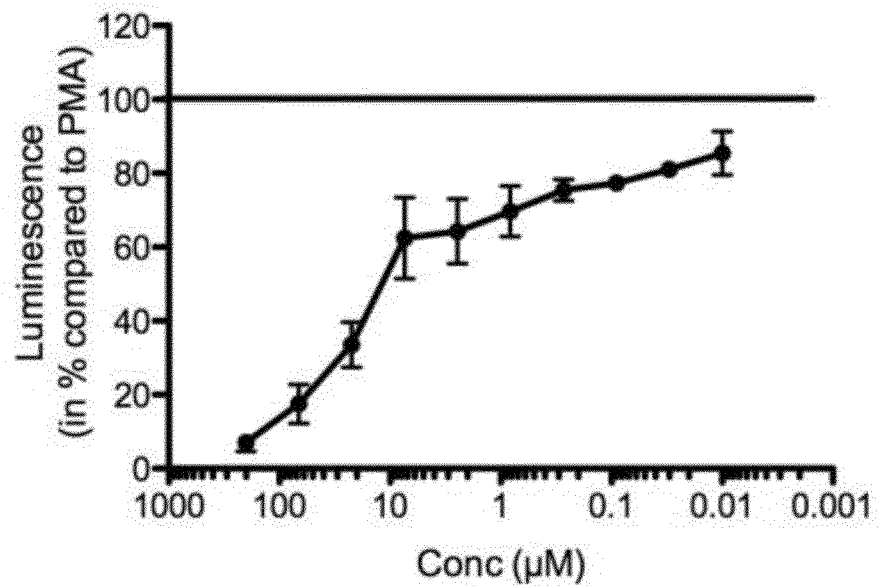


FIGURE 2

