(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2012 (12.07.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/093383 A1

(51) International Patent Classification:
A61P 29/00 (2006.01) *A61K 31/445* (2006.01)
A61K 31/40 (2006.01) *A61K 31/55* (2006.01)

(21) International Application Number:
PCT/IL2011/000879

(22) International Filing Date:
15 November 2011 (15.11.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/429,588 4 January 2011 (04.01.2011) US

(71) Applicant *(for all designated States except US)*: **RADIKAL THERAPEUTICS INC.** [US/US]; 8 Solviva Road, PO Box 1626, West Tisbury, Massachusetts 02575 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **SALZMAN, Andrew Lurie** [IL/US]; 8 Solviva Road, PO Box 1626, West Tisbury, Massachusetts 02575 (US).

(74) Agent: **BEN-AMI & ASSOCIATES**; P.O. Box 94, 76100 Rehovot (IL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

WO 2012/093383 A1

(54) Title: COMPOSITIONS AND METHODS FOR TREATMENT OF SEPSIS AND RELATED CONDITIONS

(57) Abstract: The invention provides compositions and methods for treatment of sepsis and conditions associated therewith using piperidine, pyrrolidine, or azepane derivatives comprising one to four nitric oxide (NO) donor groups and a reactive oxygen species (ROS) degradation catalyst.

COMPOSITIONS AND METHODS FOR TREATMENT OF SEPSIS AND RELATED CONDITIONS

TECHNICAL FIELD

[0001] The present invention relates to use of compounds comprising a nitric oxide (NO) donor and a reactive oxygen species (ROS) degradation catalyst in pharmaceutical compositions and methods for treatment of sepsis and conditions associated therewith.

BACKGROUND ART

[0002] Sepsis is driven by widespread tissue injury mediated by alterations in the biosynthesis of the free radicals nitric oxide (NO) and superoxide anion (O_2^-) (Traber *et al.*, 2007). The imbalance of these two free radical species produces major changes in the distribution of extracellular water, disrupts epithelial and endothelial tight junctions, impairs endothelial function and vascular smooth muscle tone, chokes off microcirculatory blood flow (Trzeciak *et al.*, 2008), triggers pulmonary arterial hypertension, and raises endothelial permeability (Maybauer *et al.*, 2009). Despite aggressive support, sepsis may progress to a state of circulatory collapse, with widespread tissue dysfunction and multiple organ failure prior to death.

[0003] Although NO is produced during sepsis via the inducible NO synthase (iNOS) isoform, paradoxically NO is deficient within the microcirculation, resulting in ischemia of critical tissues. NO deficiency results both from its consumption by O_2^- and its diminished synthesis by the endothelial NO synthase (ecNOS) isoform secondary to depletion of its precursor (L-arginine) and synthetic co-factor (tetrahydrobiopterin; BH4) (Luiking and Deutz, 2007; Luiking *et al.*, 2004). O_2^- is correspondingly elevated due to its excessive production by uncoupled mitochondria and the enzymes NADPH oxidase, xanthine oxidase (XO), and uncoupled ecNOS. The imbalance of NO and O_2^- directly impairs the ability of the arteriolar microcirculation to dilate, producing a biological cascade of ischemia,

tissue dysfunction, hemodynamic collapse, and multiple organ failure. A successful treatment of sepsis may require the *simultaneous* replenishment of NO and removal of O_2^-.

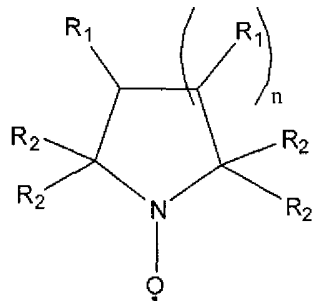
[0004] US Patent Nos. 6,448,267, 6,455,542 and 6,759,430, herewith incorporated by reference in their entirety as if fully described herein, disclose, *inter alia*, piperidine, pyrrolidine and azepane derivatives comprising an NO donor and a superoxide scavenger, capable of acting as sources of NO and as ROS degradation catalysts, their preparation, and their use in the treatment of various conditions associated with oxidative stress or endothelial dysfunction such as diabetes mellitus and cardiovascular diseases.

SUMMARY OF INVENTION

[0005] It has now been found, in accordance with the present invention, that administration of certain 1-pyrrolidinyloxy derivatives, more particular 3-nitrato methyl-2,2,5,5-tetramethylpyrrolidinyloxy, in a murine endotoxin shock model, one hour after the injection of *E. coli* lipopolysaccharide (LPS), provides protection in a dose-dependent manner. More particularly, whereas the mortality for animals exposed to a lethal dose of LPS was 100%, no mortality at all has been observed for the group treated with the highest dose (80 mg/kg/day) of 3-nitratomethyl-2,2,5,5-tetramethylpyrrolidinyloxy. Moreover, said radical was dose-dependently protective against injury to the kidney, liver, and pancreas.

[0006] As further found, administration of said radical (80 mg/kg/day) in an ovine *Pseudomonas aeruginosa* (PSA)-septic shock model, 1 hour post-injury and then continuously for 24 hours, atttenuates pulmonary hypertension, peak pulmonary airway pressure, and pulmonary shunt of the treated animal, and significantly inhibits the development of sepsis-related coagulopathy.

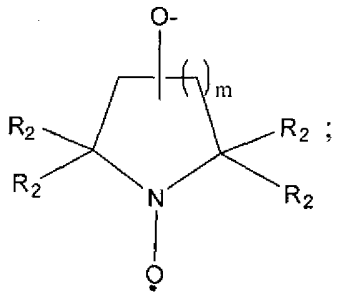
[0007] In one aspect, the present invention thus relates to a method for treatment of sepsis and conditions associated therewith in an individual in need thereof, comprising administering to said individual a therapeutically effective amount of a compound of the general formula I:

I 

or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof,

wherein

R_1 each independently is selected from H, -OH, -COR_3, -$COOR_3$, -$OCOOR_3$, -$OCON(R_3)_2$, -$(C_1$-$C_{16})$alkylene-$COOR_3$, -CN, -NO_2, -SH, -SR_3, -$(C_1$-$C_{16})$alkyl, -O-$(C_1$-$C_{16})$alkyl, -$N(R_3)_2$, -$CON(R_3)_2$, -SO_2R_3, -$S(=O)R_3$, or an NO-donor group of the formula -X_1-X_2-X_3, wherein X_1 is absent or selected from -O-, -S- or -NH-; X_2 is absent or is $(C_1$-$C_{20})$alkylene optionally substituted by one or more -ONO_2 groups and optionally further substituted by a moiety of the general formula D:

D 

and X_3 is -NO or -ONO_2, provided that at least one R_1 group is an NO-donor group;

R_2 each independently is selected from $(C_1$-$C_{16})$alkyl, $(C_2$-$C_{16})$alkenyl, or $(C_2$-$C_{16})$alkynyl;

R_3 each independently is selected from H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_{10})$cycloalkyl, 4-12-membered heterocyclyl, or $(C_6$-$C_{14})$aryl, each of which other than H may optionally be substituted with -OH, -COR_4, -$COOR_4$, -$OCOOR_4$, -$OCON(R_4)_2$, -$(C_1$-$C_8)$alkylene-$COOR_4$, -CN, -NO_2, -SH, -SR_4, -$(C_1$-$C_8)$alkyl, -O-$(C_1$-$C_8)$alkyl, -$N(R_4)_2$, -$CON(R_4)_2$, -SO_2R_4, or -$S(=O)R_4$;

R_4 each independently is selected from H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_{10})$cycloalkyl, 4-12-membered heterocyclyl, or $(C_6$-$C_{14})$aryl; and

n and m each independently is an integer of 1 to 3.

[0008] In another aspect, the present invention provides a pharmaceutical composition for treatment of sepsis and conditions associated therewith comprising a compound of the general formula I as defined above, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

[0009] In a further aspect, the present invention provides a compound of the general formula I as defined above, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, for use in treatment of sepsis and conditions associated therewith.

[0010] In yet another aspect, the present invention relates to use of a compound of the general formula I as defined above, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, for the preparation of a pharmaceutical composition for treatment of sepsis and conditions associated therewith.

BRIEF DESCRIPTION OF DRAWINGS

[0011] **Fig. 1** shows the percent survival of Balb/c mice exposed to a lethal dose of *E. coli* lipopolysaccharide (LPS; 10 mg/kg IP), after treatment with compound **1a** (R-100; 0, 20, 40, or 80 mg/kg/day, BID IP), with the initial dose given 1 hr after LPS injection. As shown, mortality was 100% for the control group (LPS+vehicle) *vs.* 0% for the highest dose group (80 mg/kg/day) of compound **1a** treatment ($p<0.001$). The doses (mg/kg) noted in the legend represent the quantity administered via an intraperitoneal route of administration every 12 hrs (** means $p<0.01$; *** means $p<0.001$).

[0012] **Fig. 2** shows histological analysis of the ileum of mice 16 hrs after administration of LPS (10 mg/kg IP; upper panels), indicating massive confluent infiltration by neutrophils, macrophages, and plasma cells; and the effect of compound **1a** (R-100; 80 mg/kg/day, BID IP) administered 1 hr and 13 hrs after

LPS administration (left lower panel) as compared to control (Sham; right lower panel).

[0013] **Fig. 3** shows that mice treated with LPS (10 mg/kg IP) showed a marked reduction in mean arterial pressure when compared to the control untreated group (Sham+Vehicle); and administration of compound **1a** (R-100; 10 mg/kg, IP) 1 hr and 6 hrs after LPS administration significantly increased blood pressure when compared with the LPS-treated controls.

[0014] **Figs. 4A-4H** show the effect of compound **1a** (R-100; 80 mg/kg/day, IV) on the PaO_2/FiO_2 ratio (**4A**), the peak airway pressure (**4B**), pause airway pressure (**4C**), pulmonary artery pressure (**4D**), activated clotting time (**4E**), fluid balance after 24 hours (**4F**), mean arterial pressure (**4G**) and systemic vascular resistance index (**4H**) in an ovine *Pseudomonas aeruginosa*-septic shock model. Measurements were taken at baseline and every 3 hrs during the 24 hrs study period. Data are expressed as mean±SEM. Statistical analysis: two-way ANOVA and Bonferroni post hoc comparison. $p<0.05$ was considered as statistically significant.

DETAILED DESCRIPTION OF THE INVENTION

[0015] In one aspect, the present invention provides a method for treatment of sepsis and conditions associated therewith, by administration of piperidine, pyrrolidine, or azepane derivatives of the general formula I as defined above, comprising one to four NO donor groups and a reactive oxygen species (ROS) degradation catalyst, i.e., a superoxide scavenger.

[0016] The term "alkyl" as used herein typically means a straight or branched saturated hydrocarbon radical having 1-16 carbon atoms and includes, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 2,2-dimethylpropyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, and the like. Preferred are (C_1-C_6)alkyl groups, more preferably (C_1-C_4)alkyl groups, most preferably methyl and ethyl. The terms "alkenyl" and "alkynyl" typically mean straight and branched hydrocarbon radicals having 2-16 carbon atoms and 1 double or triple bond,

respectively, and include ethenyl, propenyl, 3-buten-1-yl, 2-ethenylbutyl, 3-octen-1-yl, 3-nonenyl, 3-decenyl, and the like, and propynyl, 2-butyn-1-yl, 3-pentyn-1-yl, 3-hexynyl, 3-octynyl, 4-decynyl, and the like. C_2-C_6 alkenyl and alkynyl radicals are preferred, more preferably C_2-C_4 alkenyl and alkynyl.

[0017] The term "alkylene" typically means a divalent straight or branched hydrocarbon radical having 1-20 carbon atoms and includes, e.g., methylene, ethylene, propylene, butylene, 2-methylpropylene, pentylene, 2-methylbutylene, hexylene, 2-methylpentylene, 3-methylpentylene, 2,3-dimethylbutylene, heptylene, octylene and the like. Preferred are (C_1-C_8)alkylene, more preferably (C_1-C_4)alkylene, most preferably (C_1-C_2)alkylene.

[0018] The term "cycloalkyl" as used herein means a cyclic or bicyclic hydrocarbyl group having 3-12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, bicyclo[3.2.1]octyl, bicyclo[2.2.1]heptyl, and the like. Preferred are (C_5-C_{10})cycloalkyls, more preferably (C_5-C_7)cycloalkyls.

[0019] The term "aryl" denotes an aromatic carbocyclic group having 6-14 carbon atoms consisting of a single ring or multiple rings either condensed or linked by a covalent bond such as, but not limited to, phenyl, naphthyl, phenanthryl, and biphenyl.

[0020] The term "heterocyclic ring" denotes a mono- or poly-cyclic non-aromatic ring of 4-12 atoms containing at least one carbon atom and one to three heteroatoms selected from sulfur, oxygen or nitrogen, which may be saturated or unsaturated, i.e., containing at least one unsaturated bond. Preferred are 5- or 6-membered heterocyclic rings. The term "heterocyclyl" as used herein refers to any univalent radical derived from a heterocyclic ring as defined herein by removal of hydrogen from any ring atom. Examples of such radicals include, without limitation, piperidino, 4-morpholinyl, or pyrrolidinyl.

[0021] The term "NO-donor group" as defined herein refers to any group of the formula -X_1-X_2-X_3, wherein X_1 may be absent or is selected from -O-, -S- or -NH-; X_2 may be absent or is (C_1-C_{20})alkylene optionally substituted by one or more -

ONO_2 groups and optionally further substituted by a moiety of the general formula D as defined above; and X_3 is -NO or $-ONO_2$. Preferred NO-donor groups are those in which X_1 is absent or is -O-; X_2 is absent or is -(C_1-C_6)alkylene, preferably -(C_1-C_4)alkylene, more preferably methylene; and X_3 is -NO or $-ONO_2$, preferably $-ONO_2$, and said alkylene is optionally substituted as defined hereinabove. According to the method of the present invention, the compound of the general formula I may comprise one NO-donor group or more than one identical or different NO-donor groups.

[0022] In certain embodiments, the compound used according to the method of the present invention is a compound of the general formula I, wherein R_1 each independently is selected from H, $-COOR_3$, $-CON(R_3)_2$, or an NO-donor group; and R_3 is H.

[0023] In certain embodiments, the compound used according to the method of the present invention is a compound of the general formula I, wherein R_2 each independently is (C_1-C_8)alkyl, preferably (C_1-C_4)alkyl, more preferably (C_1-C_2)alkyl, most preferably methyl. Preferred embodiments are those in which all the R_2 groups in the formula I are identical.

[0024] In certain embodiments, the compound used according to the method of the present invention is a compound of the general formula I, wherein in said NO-donor group, X_1 is absent or -O-; X_2 is absent or (C_1-C_{20})alkylene, preferably -(C_1-C_6)alkylene, more preferably -(C_1-C_4)alkylene, most preferably methylene; X_3 is -NO or $-ONO_2$, preferably $-ONO_2$; and said alkylene is optionally substituted by one or more $-ONO_2$ groups and optionally further substituted by a moiety of the general formula D as defined above.

[0025] In certain embodiments, the compound used according to the method of the present invention is a compound of the general formula I, wherein n is 1, 2 or 3, preferably 1 or 2.

[0026] In certain embodiments, the compound used according to the method of the present invention has the general formula I, wherein n is 1, i.e., a 1-pyrrolidinyloxy derivative of the formula Ia (see **Table 1**). In particular embodiments, the

compound used according to this method has the general formula Ia, wherein either the carbon atom at position 3 of the pyrrolidine ring or the carbon atom at position 4 of the pyrrolidine ring, or both, are each linked to an NO-donor group.

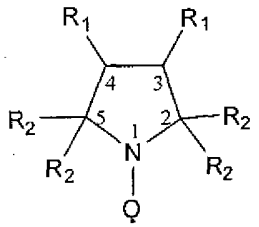
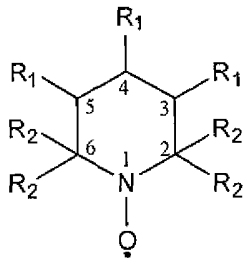
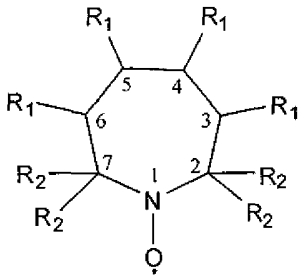
[0027] In other certain embodiments, the compound used according to the method of the present invention has the general formula I, wherein n is 2, i.e., a 1-piperidinyloxy derivative of the formula Ib (see **Table 1**). In particular embodiments, the compound used according to this method has the general formula Ib, wherein one, two or three of the carbon atoms at positions 3 to 5 of the piperidine ring are each linked to an NO-donor group. In more particular embodiments, (i) the carbon atom at position 3 of the piperidine ring and optionally one or more of the carbon atoms at positions 4 or 5 of the piperidine ring are each linked to an NO-donor group; (ii) the carbon atom at position 4 of the piperidine ring and optionally one or more of the carbon atoms at positions 3 or 5 of the piperidine ring are each linked to an NO-donor group; or (iii) the carbon atom at position 5 of the piperidine ring and optionally one or more of the carbon atoms at positions 3 or 4 of the piperidine ring are each linked to an NO-donor group.

[0028] In further certain embodiments, the compound used according to the method of the present invention has the general formula I, wherein n is 3, i.e., a 1-azepanyloxy derivative of the formula Ic (see **Table 1**). In particular embodiments, the compound used according to this method has the general formula Ic, wherein one, two, three or four of the carbon atoms at positions 3 to 6 of the azepane ring are each linked to an NO-donor group. In more particular embodiments, (i) the carbon atom at position 3 of the azepane ring and optionally one or more of the carbon atoms at positions 4 to 6 of the azepane ring are each linked to an NO-donor group; (ii) the carbon atom at position 4 of the azepane ring and optionally one or more of the carbon atoms at positions 3, 5 or 6 of the azepane ring are each linked to an NO-donor group; (iii) the carbon atom at position 5 of the azepane ring and optionally one or more of the carbon atoms at positions 3, 4 or 6 of the azepane ring are each linked to an NO-donor group; or (iv) the carbon atom at position 6 of the

azepane ring and optionally one or more of the carbon atoms at positions 3 to 5 of the azepane ring are each linked to an NO-donor group.

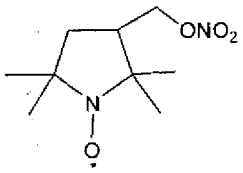
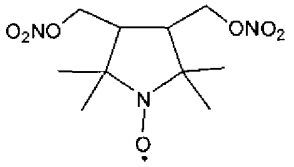
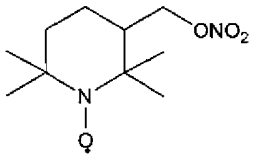
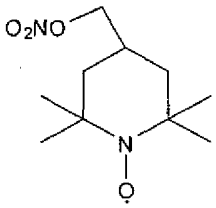
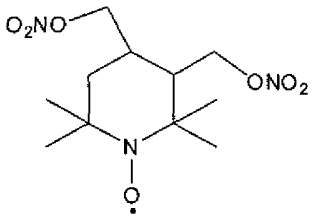
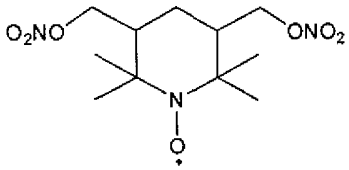
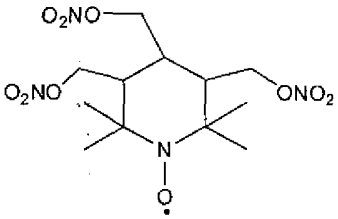
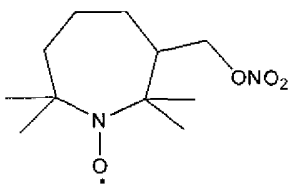
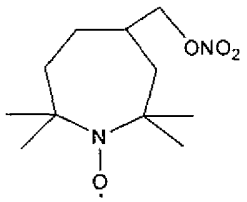
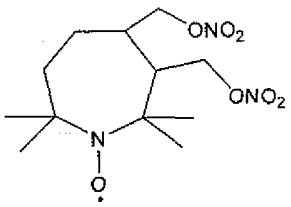
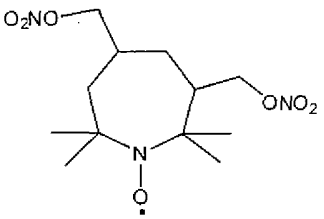
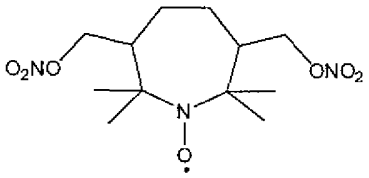
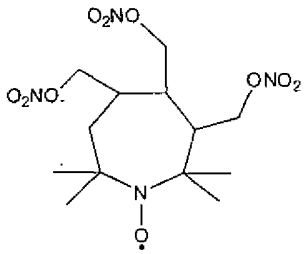
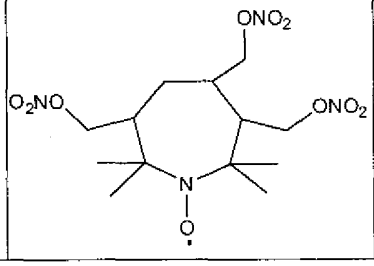
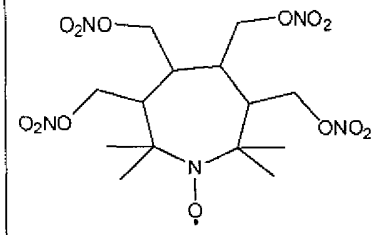
[0029] In particular embodiments, the compound used according to the method of the invention is a 1-pyrrolidinyloxy derivative of the formula Ia, 1-piperidinyloxy derivative of the formula Ib, or 1-azepanyloxy derivative of the formula Ic, and each one of the NO-donor groups in said compound independently is of the formula -(C_1-C_6)alkylene-ONO_2, preferably -(C_1-C_4)alkylene-ONO_2, more preferably -CH_2-ONO_2, or -O-(C_1-C_6)alkylene-ONO_2, wherein said alkylene is optionally substituted by one or more -ONO_2 groups, or is -ONO_2.

Table 1: Structures Ia, Ib and Ic, indicating 1-pyrrolidinyloxy, 1-piperidinyloxy and 1-azepanyloxy derivatives, respectively

Ia	Ib	Ic
		

[0030] Specific compounds of the general formulas Ia, Ib and Ic described herein, in which each one of the R_1 groups independently is either H or the NO-donor group -CH_2-ONO_2 or -ONO_2, are herein identified compounds **1a/b-15a/b** in bold (compound **1a** is also identified R-100), and their full chemical structures are depicted in **Table 2**. Other specific compounds of the general formulas Ia and Ib described herein, in which one R_1 group is the NO-donor group -CH_2-ONO_2 or -ONO_2, and another R_1 group is not H, are herein identified compounds **16a/b-17a/b** in bold, and their full chemical structures are depicted in **Table 3**. A further specific compound of the general formula Ib described herein, in which one R_1 group is the NO-donor group -O-CH_2-$CH(ONO_2)CH_2$-ONO_2, and the other R_1 groups are H, is herein identified compound **18** in bold, and its full chemical structure is depicted in **Table 3**.

Table 2: Compounds of the general formulas Ia, Ib and Ic, identified **1a-15a***

1a	**2a**	**3a**
		
4a	**5a**	**6a**
		
7a	**8a**	**9a**
		
10a	**11a**	**12a**
		
13a	**14a**	**15a**
		

* The compounds corresponding to **1a-15a**, in which each one of the $-CH_2-ONO_2$ groups is replaced by the $-ONO_2$ group, are identified compounds **1b-15b**

[0031] In specific embodiments, the compound used according to the method of the invention is the compound of formula Ia, i.e., a compound of the general formula I in which n is 1, wherein R_2 each is methyl; and (i) the R_1 group linked to

the carbon atom at position 3 of the pyrrolidine ring is the NO-donor group -CH_2-ONO_2 or ONO_2; and the R_1 group linked to the carbon atom at position 4 of the pyrrolidine ring is H, i.e., 3-nitratomethyl-2,2,5,5-tetramethylpyrrolidinyloxy (compound **1a**; R-100) or 3-nitrato-2,2,5,5-tetramethylpyrrolidinyloxy (compound **1b**), respectively; or (ii) each one of the R_1 groups linked to the carbon atoms at positions 3 and 4 of the pyrrolidine ring is the NO-donor group -CH_2-ONO_2 or ONO_2, i.e., 3,4-dinitrato methyl-2,2,5,5-tetramethylpyrrolidinyloxy (compound **2a**) or 3,4-dinitrato-2,2,5,5-tetramethylpyrrolidinyloxy (compound **2b**), respectively.

[0032] In other specific embodiments, the compound used according to the method of the invention is the compound of formula Ib, i.e., a compound of the general formula I wherein n is 2, wherein R_2 each is methyl; and (i) the R_1 group linked to the carbon atom at position 3 of the piperidine ring is the NO-donor group -CH_2-ONO_2 or ONO_2; and each one of the R_1 groups linked to the carbon atoms at positions 4 and 5 of the piperidine ring is H, i.e., 3-nitratomethyl-2,2,6,6-tetramethylpiperidinyloxy (3-nitratomethyl-TEMPO; compound **3a**) or 3-nitrato-2,2,6,6-tetramethylpiperidinyloxy (3-nitrato-TEMPO; compound **3b**), respectively; (ii) the R_1 group linked to the carbon atom at position 4 of the piperidine ring is the NO-donor group -CH_2-ONO_2 or ONO_2; and each one of the R_1 groups linked to the carbon atoms at positions 3 and 5 of the piperidine ring is H, i.e., 4-nitratomethyl-2,2,6,6-tetramethylpiperidinyloxy (4-nitratomethyl-TEMPO; compound **4a**) or 4-nitrato-2,2,6,6-tetramethylpiperidinyloxy (3-nitrato-TEMPO; compound **4b**), respectively; (iii) each one of the R_1 groups linked to the carbon atoms at positions 3 and 4 of the piperidine ring is the NO-donor group -CH_2-ONO_2 or ONO_2; and the R_1 group linked to the carbon atom at position 5 of the piperidine ring is H, i.e., 3,4-dinitratomethyl-2,2,6,6-tetramethylpiperidinyloxy (3,4-dinitratomethyl-TEMPO; compound **5a**) or 3,4-dinitrato-2,2,6,6-tetramethylpiperidinyloxy (3,4-dinitrato-TEMPO; compound **5b**), respectively; (iv) each one of the R_1 groups linked to the carbon atoms at positions 3 and 5 of the piperidine ring is the NO-donor group -CH_2-ONO_2 or ONO_2; and the R_1 group linked to the carbon atom at position 4 of the piperidine ring is H, i.e., 3,5-dinitratomethyl-2,2,6,6-tetramethylpiperidinyloxy

(3,5-dinitratomethyl-TEMPO; compound **6a**) or 3,5-dinitrato-2,2,6,6-tetramethyl piperidinyloxy (3,5-dinitrato-TEMPO; compound **6b**), respectively; or (v) each one of the R_1 groups linked to the carbon atoms at positions 3 to 5 of the piperidine ring is the NO-donor group $-CH_2-ONO_2$ or ONO_2, i.e., 3,4,5-trinitratomethyl-2,2,6,6-tetramethylpiperidinyloxy (3,4,5-trinitratomethyl-TEMPO; compound **7a**) or 3,4,5-trinitrato-2,2,6,6-tetramethylpiperidinyloxy (3,4,5-trinitrato-TEMPO; compound **7b**), respectively.

[0033] In further specific embodiments, the compound used according to the method of the invention is the compound of formula Ic, i.e., a compound of the general formula I wherein n is 3, wherein R_2 each is methyl; and (i) the R_1 group linked to the carbon atom at position 3 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or ONO_2; and each one of the R_1 groups linked to the carbon atoms at positions 4 to 6 of the azepane ring is H, i.e., 3-nitratomethyl-2,2,7,7-tetramethylazepanyloxy (compound **8a**) or 3-nitrato-2,2,7,7-tetramethylazepanyloxy (compound **8b**), respectively; (ii) the R_1 group linked to the carbon atom at position 4 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or ONO_2; and each one of the R_1 groups linked to the carbon atoms at position 3, 5 and 6 of the azepane ring is H, i.e., 4-nitratomethyl-2,2,7,7-tetramethylazepanyloxy (compound **9a**) or 4-nitrato-2,2,7,7-tetramethylazepanyloxy (compound **9b**), respectively; (iii) each one of the R_1 groups linked to the carbon atoms at positions 3 and 4 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or ONO_2; and each one of the R_1 groups linked to the carbon atoms at positions 5 and 6 of the azepane ring is H, i.e., 3,4-dinitratomethyl-2,2,7,7-tetramethylazepanyloxy (compound **10a**) or 3,4-dinitrato-2,2,7,7-tetra methylazepanyloxy (compound **10b**), respectively; (iv) each one of the R_1 groups linked to the carbon atoms at positions 3 and 5 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or ONO_2; and each one of the R_1 groups linked to the carbon atoms at positions 4 and 6 of the azepane ring is H, i.e., 3,5-dinitratomethyl-2,2,7,7-tetramethylazepanyloxy (compound **11a**) or 3,5-dinitrato-2,2,7,7-tetramethyl azepanyloxy (compound **11b**), respectively; (v) each one of the R_1 groups linked to the carbon atoms at positions 3 and 6 of the azepane ring is the NO-donor group -

CH_2-ONO_2 or ONO_2; and each one of the R_1 groups linked to the carbon atoms at positions 4 and 5 of the azepane ring is H, i.e., 3,6-dinitratomethyl-2,2,7,7-tetramethylazepanyloxy (compound **12a**) or 3,6-dinitrato-2,2,7,7-tetramethyl azepanyloxy (compound **12b**), respectively; (vi) each one of the R_1 groups linked to the carbon atoms at positions 3 to 5 of the azepane ring is the NO-donor group -CH_2-ONO_2 or ONO_2; and the R_1 group linked to the carbon atom at position 6 of the azepane ring is H, i.e., 3,4,5-trinitratomethyl-2,2,7,7-tetramethylazepanyloxy (compound **13a**) or 3,4,5-trinitrato-2,2,7,7-tetramethylazepanyloxy (compound **13b**), respectively; (vii) each of the R_1 groups linked to the carbon atoms at positions 3, 4 and 6 of the azepane ring is the NO-donor group -CH_2-ONO_2 or ONO_2; and the R_1 group linked to the carbon atom at position 5 of the azepane ring is H, i.e., 3,4,6-trinitratomethyl-2,2,7,7-tetramethylazepanyloxy (compound **14a**) or 3,4,6-trinitrato-2,2,7,7-tetramethylazepanyloxy (compound **14b**), respectively); or (viii) each of the R_1 groups linked to the carbon atoms at positions 3 to 6 of the azepane ring is the NO-donor group -CH_2-ONO_2 or ONO_2, i.e., 3,4,5,6-tetranitratomethyl-2,2,7,7-tetramethylazepanyloxy (compound **15a**) or 3,4,5,6-tetranitrato-2,2,7,7-tetramethylazepanyloxy (compound **15b**), respectively.

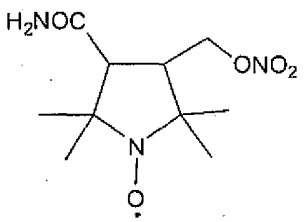
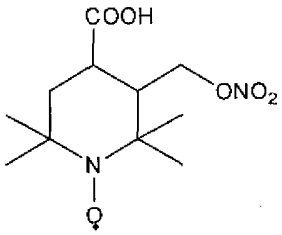
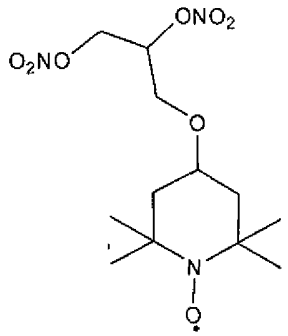
[0034] In still other specific embodiments, the compound used according to the method of the invention is the compound of formula Ia, wherein R_2 each is methyl; the R_1 group linked to the carbon atom at position 3 of the pyrrolidine ring is the NO-donor group -CH_2-ONO_2 or -ONO_2; and the R_1 group linked to the carbon atom at position 4 of the pyrrolidine ring is -$CONH_2$, i.e., 3-nitratomethyl-4-carbamoyl-2,2,5,5-tetramethylpyrrolidinyloxy (compound **16a**) or 3-nitrato-4-carbamoyl-2,2,5,5-tetramethylpyrrolidinyloxy (compound **16b**), respectively.

[0035] In yet other specific embodiments, the compound used according to the method of the invention is the compound of formula Ib, wherein R_2 each is methyl; the R_1 group linked to the carbon atom at position 3 of the piperidine ring is the NO-donor group -CH_2-ONO_2 or -ONO_2; the R_1 group linked to the carbon atom at position 4 of the piperidine ring is -COOH; and the R_1 group linked to the carbon atoms at position 5 of the piperidine ring is H, i.e., 3-nitratomethyl-4-carboxy-

2,2,6,6-tetramethylpiperidinyloxy (3-nitratomethyl-4-carboxy-TEMPO; compound **17a**) or 3-nitrato-4-carboxy-2,2,6,6-tetramethylpiperidinyloxy (3-nitrato-4-carboxy-TEMPO; compound **17b**), respectively.

[0036] In still a further specific embodiment, the compound used according to the method of the invention is the compound of formula Ib, wherein R_2 each is methyl; the R_1 group linked to the carbon atom at position 4 of the piperidine ring is the NO-donor group -O-CH_2-$CH(ONO_2)CH_2$-ONO_2; and each one of the R_1 groups linked to the carbon atom at position 3 and 5 of the piperidine ring is H, i.e., 4-(2,3-dinitratopropyloxy)-2,2,6,6-tetramethylpiperidinyloxy (4-(2,3-dinitratopropyloxy)-TEMPO; compound **18**).

Table 3: Compounds of the general formulas Ia and Ib, identified **16a-17a*** **and 18**

16a	17a	18
		

* The compounds corresponding to **16a** and **17a**, in which each one of the -CH_2-ONO_2 groups is replaced by the -ONO_2 group, are identified compounds **16b** and **17b**

[0037] In other particular embodiments, the compound used according to the method of the present invention is a 1-pyrrolidinyloxy derivative of the formula Ia, 1-piperidinyloxy derivative of the formula Ib, or 1-azepanyloxy derivative of the formula Ic; wherein at least one of the NO-donor groups in said compound is of the formula -O-(C_1-C_6)alkylene-ONO_2; and said alkylene is substituted by a moiety of the general formula D as defined above, and is optionally further substituted by one or more -ONO_2 groups. The general formula D, in which oxygen atom is linked to the carbon atom at position 3 or 4 of the ring, represents a 3-hydroxy-pyrrolidinoxy, 3- or 4-hydroxy-piperidinyloxy, or 3- or 4-hydroxy-azepanyloxy derivative. Conceptually, the compound used in this case is thus a dimer- or higher multimer-

like compound, in which two or more identical or different entities, each independently being selected from 1-pyrrolidinyloxy, 1-piperidinyloxy or 1-azepanyloxy derivatives, are linked via alkylene bridges substituted by one or more $-ONO_2$ groups, wherein each alkylene bridge links two entities only.

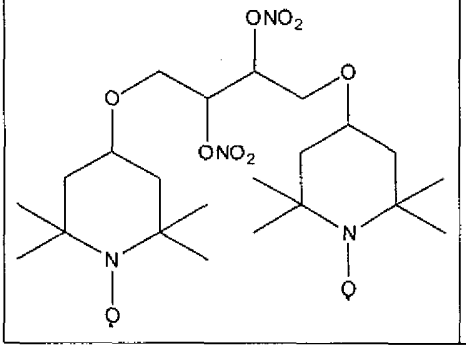
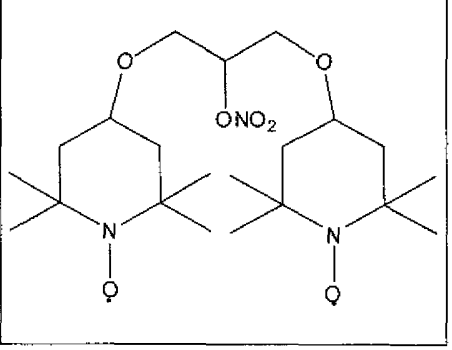
[0038] Preferred dimer- or higher multimer-like compounds to be used according to the method of the invention are those in which (i) a 1-pyrrolidinyloxy derivative of the general formula Ia is linked via one or two NO-donor groups thereof to one or two identical or different moieties of a 3-hydroxy-pyrrolidinoxy, i.e., one or two moieties of the general formula D in which m is 1; (ii) a 1-piperidinyloxy derivative of the general formula Ib is linked via one, two or three NO-donor groups thereof to one, two or three identical or different moieties of a 3-, or 4-hydroxy-piperidinyloxy, i.e., one to three moieties of the general formula D in which m is 2; or (iii) a 1-azepanyloxy derivative of the general formula Ic is linked via one, two, three or four NO-donor groups thereof to one, two, three or four identical or different moieties of a 3-, or 4-hydroxy-azepanyloxy, i.e., one to four moieties of the general formula D in which m is 3.

[0039] Specific compounds of the general formula Ib described herein, having a dimer-like structure, are herein identified compounds **19-20** in bold, and their full chemical structures are depicted in **Table 4**.

[0040] In specific embodiments, the compound used according to the method of the invention is the dimer-like compound of formula Ib, wherein each one of R_1 linked to the carbon atoms at positions 3 and 5 of the piperidine ring is H; and (i) R_1 linked to the carbon atom at position 4 of the piperidine ring is the NO-donor group $-O-CH_2-CH_2-CH(CH_3)-ONO_2$, wherein the 1,3 butane diyl is substituted at position 2 with $-ONO_2$ group and at position 4 with a moiety of the general formula D, wherein m is 2, and the oxygen atom is linked to the carbon atom at position 4 of the piperidine ring in the formula D; and R_2 each is methyl, i.e., 1,4-di-(4-oxo-TEMPO)-2,3-dinitratobutane (compound **19**); or (ii) R_1 linked to the carbon atom at position 4 of the piperidine ring is the NO-donor group $-O-CH_2-CH(CH_3)-ONO_2$, wherein the 1,2 propane diyl is substituted at position 3 with a moiety of the general

formula D, wherein m is 2, and the oxygen atom is linked to the carbon atom at position 4 of the piperidine ring in the formula D; and R_2 each is methyl, i.e., 1,3-di-(4-oxo-TEMPO)-2-nitratopropane (compound **20**).

Table 4: Compounds of the general formula Ib, identified **19-20**

19	**20**
	

[0041] The compounds used according to the method of the present invention may be synthesized according to any technology or procedure known in the art, e.g., as described in detail in US 6,448,267, 6,455,542 and 6,759,430.

[0042] The compounds of the general formula I may have one or more asymmetric centers, and may accordingly exist both as enantiomers, i.e., optical isomers (R, S, or racemate, wherein a certain enantiomer may have an optical purity of 90%, 95%, 99% or more) and as diastereoisomers. Specifically, those chiral centers may be, e.g., in each one of the carbon atoms of the 1-pyrrolidinyloxy derivative, 1-piperidinyloxy derivative; and 1-azepanyloxy derivative of the general formulas Ia, Ib and Ic, respectively. It should be understood that according to the method of the present invention, treatment of sepsis and conditions associated therewith can be carried out by administration of all such enantiomers, isomers and mixtures thereof, as well as pharmaceutically acceptable salts and solvates thereof.

[0043] Optically active forms of the compounds of the general formula I may be prepared using any method known in the art, e.g., by resolution of the racemic form by recrystallization techniques; by chiral synthesis; by extraction with chiral solvents; or by chromatographic separation using a chiral stationary phase. A non-limiting example of a method for obtaining optically active materials is transport

across chiral membranes, i.e., a technique whereby a racemate is placed in contact with a thin membrane barrier, the concentration or pressure differential causes preferential transport across the membrane barrier, and separation occurs as a result of the non-racemic chiral nature of the membrane that allows only one enantiomer of the racemate to pass through. Chiral chromatography, including simulated moving bed chromatography, can also be used. A wide variety of chiral stationary phases are commercially available.

[0044] While reducing the present invention into practice, it has been found that an aqueous solution of a compound of the general formula I having a concentration several times greater than that with commonly used co-solvents can be obtained by stirring said compound in water with an hydroxyalkyl-cyclodextrin such as hydroxyalkyl-β-cyclodextrin, in particular 2-hydroxyalkyl-β-cyclodextrin (HPCD), in ratios typically between 1:10 and 1:20 w/w, depending on the degree of substitution of the cyclodextrin with the hydroxypropyl side chain. Moreover, an aqueous solution containing substantially higher concentration of said compound with HPCD can be achieved by stirring HPCD in distilled water with said compound; filtering and freeze drying the filtrate; and re-dissolving the resulting freeze dried solid, i.e., the lyophilizate, in a volume of water that is less than that originally used to prepare the solution prior to lyophilization.

[0045] Sepsis is a serious, life-threatening medical condition characterized by an overwhelming systemic infection resulting in vasolidation leading to hypotension, i.e., to septic shock, which may consequently lead to an inadequate tissue perfusion that is insufficient to meet cellular metabolic needs and is also known as hypoperfusional state. Sepsis can particularly be caused by Gram negative bacteria such as, without being limited to, *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia* species, *Salmonella* species, *Shigella* species, *Enterobacter* species, *Citrobacter* species, *Proteus* species, and *Klebsiella* species; Gram-positive cocci such as, without limiting, *Pneumococcal* species, *Enterococcal* species, *Staphylococcal* species, *and Streptococcal* species; certain fungi and yeast,

Rickettsial species, Plasmodial species, *Clostridial* species, and viruses; as well as Gram-positive bacterial toxins.

[0046] The term "treatment" as used herein with respect to sepsis and conditions associated therewith refers to administration of a compound of the general formula I as defined above, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, after the onset of symptoms of sepsis, regardless of the cause for that medical condition. According to the present invention, administration of said compound for treatment of sepsis and conditions associated therewith is aimed at inhibiting, i.e., limiting or reducing, medical conditions resulting from the systemic infection, most particularly pulmonary hypertension, pulmonary shunt, and loss of pulmonary compliance. In particular cases, administration of said compound is further aimed at inhibiting development of sepsis-related coagulopathy. Of special importance, said compound does not reduce peripheral arterial blood pressure or peripheral vascular resistance in the septic condition. The term "therapeutically effective amount" as used herein refer to the quantity of the compound of the general formula I as defined above, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, that is useful to treat prevent or treat sepsis and conditions associated therewith.

[0047] As shown in the Examples section hereinafter, administration of R-100 in a murine endotoxin shock model, one hour after the injection of a lethal dose of *E. coli* lipopolysaccharide (LPS), provided protection in a dose-dependent manner, wherein no mortality at all has been observed at the group treated with the highest dose (80 mg/kg/day) of that compound *vs.* 100% mortality at the group of untreated animals. Furthermore, R-100 was dose-dependently protective against injury to the kidney, liver, and pancreas, as indicated by the levels of certain parameters, more particular, creatinine, aspartate transminase (AST), alanine transaminase (ALT), bilirubin, amylase, lipase, and alkaline phosphatase, measured in the serum of the animals about 16 hours after LPS administration. In histological analysis of the ileum of untreated animals, massive confluent infiltration by neutrophils,

macrophages, and plasma cells was observed; however, this injury was entirely abrogated by post-LPS administration of R-100 to the point of achieving an appearance comparable to that demonstrated in the sham animals. It should be noted that whereas mice treated with LPS showed a marked reduction in mean arterial pressure when compared to the control untreated group, administration of R-100 1 hour and 6 hours after LPS treatment significantly increased blood pressure when compared with the LPS-treated controls.

[0048] As further shown in the Examples section, intravenous administration of R-100, formulated as an aqueous solution in HPCD (R-100:HPCD 1:13 w/w) and diluted in 500 ml of 5% Dextrose, in a an ovine *Pseudomonas aeruginosa* (PSA)-septic shock model, 1 hour post-injury and then continuously for 24 hours, stabilized the pulmonary function of the treated sheep, wherein all the treated sheep showed significant improvement in PaO_2/FiO_2 ratio at 24 hours and peak ventilatory pressures; a markedly reduced increase in the pulmonary artery pressure; and a lower total fluid balance 24 hours post-injury compared to the control group. No difference in the peripheral blood pressure (MAP) was shown between the R-100-treated group and the control group. As further found, R-100 administration significantly inhibited the development of sepsis-related coagulopathy.

[0049] In certain embodiments, the sepsis treated according to the method of the present invention is caused by microorganisms or products thereof. In particular embodiments, the sepsis is caused by Gram negative bacteria, e.g., *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia* species, *Salmonella* species, *Shigella* species, *Enterobacter* species, *Citrobacter* species, *Proteus* species, and *Klebsiella* species; Gram-positive cocci, e.g., *Pneumococcal* species, *Staphylococcal* species, *Enterococcal* species, and *Streptococcal* species; certain fungi and yeast, Rickettsial species Plasmodial species, *Clostridial* species or viruses; or Gram-positive bacterial toxins, including toxic shock syndrome toxins. In certain particular embodiments, the method of the invention is aimed at inhibiting development of sepsis-related coagulopathy.

[0050] In another aspect, the present invention provides a pharmaceutical composition for treatment of sepsis and conditions associated therewith comprising a compound of the general formula I as defined above, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. In particular embodiments, the pharmaceutical composition of the invention comprises a compound selected from compounds **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**, **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **12a**, **12b**, **13a**, **13b**, **14a**, **14b**, **15a**, **15b**, **16a**, **16b**, **17a**, **17b**, **18**, **19** or **20**, preferably compound **1a**, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof.

[0051] The pharmaceutical compositions of the present invention can be provided in a variety of formulations, e.g., in a pharmaceutically acceptable form and/or in a salt form, as well as in a variety of dosages.

[0052] In one embodiment, the pharmaceutical composition of the present invention comprises a non-toxic pharmaceutically acceptable salt of a compound of the general formula I. Suitable pharmaceutically acceptable salts include acid addition salts such as, without being limited to, those formed with hydrochloric acid, fumaric acid, *p*-toluenesulfonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl, or aralkyl moiety. Furthermore, where the compounds of the general formula I carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g., sodium or potassium salts, and alkaline earth metal salts, e.g., calcium or magnesium salts.

[0053] The pharmaceutically acceptable salts of the present invention may be formed by conventional means, e.g., by reacting the free base form of the product, i.e., the compound of the general formula I, with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying, or by

exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

[0054] The present invention encompasses solvates of the compounds of the general formula I as well as salts thereof, e.g., hydrates.

[0055] The pharmaceutical compositions provided by the present invention may be prepared by conventional techniques, e.g., as described in Remington: The Science and Practice of Pharmacy, 19th Ed., 1995. The compositions can be prepared, e.g., by uniformly and intimately bringing the active ingredient, i.e., the compound of the general formula I, into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into the desired formulation. The compositions may be in liquid, solid or semisolid form and may further include pharmaceutically acceptable fillers, carriers, diluents or adjuvants, and other inert ingredients and excipients. In one embodiment, the pharmaceutical composition of the present invention is formulated as nanoparticles.

[0056] The compositions can be formulated for any suitable route of administration, but they are preferably formulated for parenteral administration, e.g., intravenous, intraarterial, intramuscular, intraperitoneal, intrathecal, intrapleural, subcutaneous, intratracheal or administration, as well as for inhalation. The dosage will depend on the state of the patient, and will be determined as deemed appropriate by the practitioner.

[0057] The pharmaceutical composition of the invention may be in the form of a sterile injectable aqueous or oleagenous suspension, which may be formulated according to the known art using suitable dispersing, wetting or suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Acceptable vehicles and solvents that may be employed include, without limiting, water, Ringer's solution and isotonic sodium chloride solution.

[0058] Pharmaceutical compositions according to the present invention, when formulated for inhalation, may be administered utilizing any suitable device known

in the art, such as metered dose inhalers, liquid nebulizers, dry powder inhalers, sprayers, thermal vaporizers, electrohydrodynamic aerosolizers, and the like.

[0059] Pharmaceutical compositions according to the present invention, when formulated for administration route other than parenteral administration, may be in a form suitable for oral use, e.g., as tablets, troches, lozenges, aqueous, or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and may further comprise one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be, e.g., inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, or sodium phosphate; granulating and disintegrating agents, e.g., corn starch or alginic acid; binding agents, e.g., starch, gelatin or acacia; and lubricating agents, e.g., magnesium stearate, stearic acid, or talc. The tablets may be either uncoated or coated utilizing known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated using the techniques described in the US Patent Nos. 4,256,108, 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for control release. The pharmaceutical composition of the invention may also be in the form of oil-in-water emulsion.

[0060] The pharmaceutical compositions of the invention may be formulated for controlled release of the active agent. Such compositions may be formulated as controlled-release matrix, e.g., as controlled-release matrix tablets in which the release of a soluble active agent is controlled by having the active diffuse through a gel formed after the swelling of a hydrophilic polymer brought into contact with dissolving liquid (*in vitro*) or gastro-intestinal fluid (*in vivo*). Many polymers have

been described as capable of forming such gel, e.g., derivatives of cellulose, in particular the cellulose ethers such as hydroxypropyl cellulose, hydroxymethyl cellulose, methylcellulose or methyl hydroxypropyl cellulose, and among the different commercial grades of these ethers are those showing fairly high viscosity. In other configurations, the compositions comprise the active agent formulated for controlled release in microencapsulated dosage form, in which small droplets of the active agent are surrounded by a coating or a membrane to form particles in the range of a few micrometers to a few millimeters.

[0061] Another contemplated formulation is depot systems, based on biodegradable polymers, wherein as the polymer degrades, the active ingredient is slowly released. The most common class of biodegradable polymers is the hydrolytically labile polyesters prepared from lactic acid, glycolic acid, or combinations of these two molecules. Polymers prepared from these individual monomers include poly (D,L-lactide) (PLA), poly (glycolide) (PGA), and the copolymer poly (D,L-lactide-co-glycolide) (PLG).

[0062] In a further aspect, the present invention provides a compound of the general formula I as defined above, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, for use in treatment of sepsis and conditions associated therewith.

[0063] In yet another aspect, the present invention relates to use of a compound of the general formula I as defined above, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, for the preparation of a pharmaceutical composition for treatment of sepsis and conditions associated therewith.

[0064] The invention will now be illustrated by the following non-limiting Examples.

EXAMPLES

Example 1. R-100 is effective in a murine model of sepsis

[0065] Balb/c mice (8 weeks old; 25 gram; *n*=10 per group) exposed to a lethal dose of *E. coli* lipopolysaccharide (LPS; 10 mg/kg IP) were treated with compound **1a** (R-100; 0, 20, 40, or 80 mg/kg/day, BID IP), with the initial dose given 1 hr after LPS injection. As shown in **Fig. 1**, whereas the mortality for the animal treated with LPS only (the control group) was 100%, all the animals treated with the highest dose of R-100 survived.

[0066] In a satellite study, tissues and sera were collected at 16 hrs, i.e., 15 hours after the first administration and 3 hrs after the second administration of R-100, for analysis, and the level of certain parameters associated with kidney, pancreas, and liver functioning were measured. These parameters were creatinine, aspartate transminase (AST), alanine transaminase (ALT), bilirubin, amylase, lipase, and alkaline phosphatase (ALP). As noted in **Table 5** below, R-100 dose-dependently protected the kidney, pancreas, and liver from LPS-mediated injury. Histological analysis was notable for massive confluent infiltration by neutrophils, macrophages, and plasma cells in the murine ileum, as shown in **Fig. 2** (upper panels). This injury was entirely abrogated by post-LPS administration of R-100 to the point of achieving an appearance comparable to that demonstrated in the sham animals, as shown in **Fig. 2** (lower panels).

Table 5: R-100 protects the kidney, pancreas and liver from LPS-mediated injury

Parameter (U/ml)	Sham	Sham+**R-100**	LPS*	LPS+**R-100** (20 mg/kg)**	LPS+**R-100** (40 mg/kg)**	LPS+**R-100** (80 mg/kg)**
Creatinine	0.21±0.01	0.22±0.01	0.95±0.03	0.73±0.03	0.48±0.02	0.26±0.01
AST	51±2	48±1	251±6	187±3	123±2	63±6
ALT	15±1	15±1	52±1	42±1	33±2	25±1
Bilirubin	0.26±0.02	0.27±0.02	1.11±0.06	0.75±0.07	0.50±0.03	0.33±0.02
Amylase	135±33	1393±18	3711±55	4007±120	2300±65	1477±13
Lipase	23.0±1.4	21.2±0.9	60.7±1.3	51.7±3.6	40.2±1.1	28.86±1.0
ALP	59±2	59±2	174±10	155±3	139±3	71±2

Data are expressed as mean±SE; * $p<0.05$ *vs.* Sham; ** $p<0.05$ *vs.* LPS

Example 2. R-100 in LPS-treated mice improves the fall in blood pressure

[0067] Mice were exposed to a lethal dose of *E. coli* lipopolysaccharide (LPS; 10 mg/kg IP). Immediately after LPS injection, mice were anaesthetized with an intraperitoneal injection of ketamine:xylazine (100:2.5 mg/kg) and placed on a heating pad. A tracheotomy was performed to facilitate respiration. The animal's temperature was monitored using a rectal probe, and the body temperature was kept constant at 37±2°C throughout the study with the heating pad. The right carotid artery was cannulated with polyethylene tubing connected to a pressure transducer for continuously monitoring arterial blood pressure using the MacLab data acquisition and analysis software. Changes in blood pressure were expressed as percentages of control values.

[0068] All experimental animals in each LPS-treated group survived after exposure to LPS for 18 hrs. As shown in **Fig. 3**, mice treated with LPS showed a marked reduction in mean arterial pressure when compared to the control untreated group. As further shown, when compound **1a** (R-100) at the dose of 10 mg/kg (IP) was administered 1 and 6 hrs after LPS treatment, there was a significant increase in blood pressure when compared with the LPS-treated controls.

Example 3. R-100 improves pulmonary function in sheep suffering from *Pseudomonas aeruginosa*-induced septic pneumonia

[0069] In the present study, a model of sheep suffering from *Pseudomonas aeruginosa* (PSA)-induced septic pneumonia and consequent pulmonary dysfunction was used. Female Merino sheep were operatively instrumented for chronic study with Swan-Ganz®, i.e., pulmonary artery, and femoral artery catheters, and were randomly allocated to vehicle control (n=6) or treatment group (n=5). Smoke inhalation injury (48 breaths of cotton smoke) was induced and $2.4x10^{11}$ colony-forming units (CFU) of PSA were instilled in the lung via bronchoscope under general anesthesia. The animal in the treatment group were intravenously (IV) administered with a total of 80 mg/kg of R-100, formulated as an aqueous solution in hydroxypropyl-β-cyclodextrin (HPCD) (R-100:HPCD 1:13

w/w) and diluted in 500 ml of 5% dextrose, wherein a bolus (30 min) of 10 mg/kg was started 1 hr post-injury and followed by the continuous infusion of the remaining 70 mg/kg for 24 hrs. Ringer's lactate solution was titrated IV to maintain hematocrit (hct) at baseline±3%. The control group received the same amount of HPCD diluted in the same amount of dextrose. Measurements were taken at baseline and every 3 hrs during the 24 hrs study period. Data are expressed as mean±SEM. Statistical analysis: two-way ANOVA and Bonferroni post hoc comparison. A p-value $p<0.05$ was considered as statistically significant.

[0070] As shown in **Figs 4A-4H**, all R-100 treated sheep showed significant improvement in PaO_2/FiO_2 (partial pressure of oxygen in arterial blood/percentage of oxygen in air inhaled) ratio at 24 hrs (**4A**) and peak ventilatory pressures (significant at 24 hrs) (**4B**); a markedly reduced increase in the pulmonary artery pressure (significant at 24 hrs) (**4C-4D**); and a lower total fluid balance 24 hrs post-injury compared to the control group (**4F**), indicating that R-100 infusion reduces pulmonary damage, improves pulmonary compliance, decreases pulmonary shunt, and prevents fluid imbalance in ovine PSA septic shock. As further shown in **Fig. 4E**, R-100 significantly inhibited the development of sepsis-related coagulopathy. In line with the results shown in Example 2, mean peripheral arterial pressure was not lowered by treatment with R-100. That is, R-100 did not reduce peripheral blood pressure (MAP) (**4G**) or systemic vascular resistance (**4H**) compared to the control group in this model as well.

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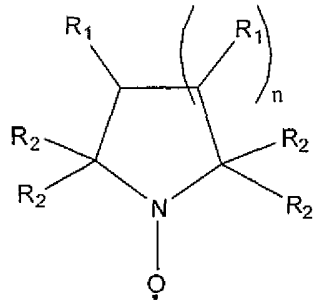
CLAIMS

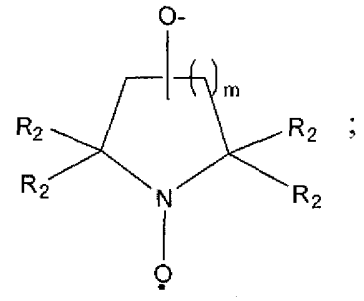
1. A method for treatment of sepsis and conditions associated therewith in an individual in need thereof, comprising administering to said individual a therapeutically effective amount of a compound of the general formula I:

I 

or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof,

wherein

R_1 each independently is selected from H, -OH, -COR_3, -$COOR_3$, -$OCOOR_3$, -$OCON(R_3)_2$, -$(C_1$-$C_{16})$alkylene-$COOR_3$, -CN, -NO_2, -SH, -SR_3, -$(C_1$-$C_{16})$alkyl, -O-$(C_1$-$C_{16})$alkyl, -$N(R_3)_2$, -$CON(R_3)_2$, -SO_2R_3, -$S(=O)R_3$, or an NO-donor group of the formula -X_1-X_2-X_3, wherein X_1 is absent or selected from -O-, -S- or -NH-; X_2 is absent or is $(C_1$-$C_{20})$alkylene optionally substituted by one or more -ONO_2 groups and optionally further substituted by a moiety of the general formula D:

D  ;

and X_3 is -NO or -ONO_2, provided that at least one R_1 group is an NO-donor group;

R_2 each independently is selected from $(C_1$-$C_{16})$alkyl, $(C_2$-$C_{16})$alkenyl, or $(C_2$-$C_{16})$alkynyl;

R_3 each independently is selected from H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_{10})$cycloalkyl, 4-12-membered heterocyclyl, or $(C_6$-$C_{14})$aryl, each of which other than H may

optionally be substituted with -OH, -COR_4, -$COOR_4$, -$OCOOR_4$, -$OCON(R_4)_2$, -$(C_1$-$C_8)$alkylene-$COOR_4$, -CN, -NO_2, -SH, -SR_4, -$(C_1$-$C_8)$alkyl, -O-$(C_1$-$C_8)$alkyl, -$N(R_4)_2$, -$CON(R_4)_2$, -SO_2R_4, or -S(=O)R_4;

R_4 each independently is selected from H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_{10})$cycloalkyl, 4-12-membered heterocyclyl, or $(C_6$-$C_{14})$aryl; and

n and m each independently is an integer of 1 to 3.

2. The method of claim 1, wherein R_1 each independently is selected from H, -$COOR_3$, -$CON(R_3)_2$, or an NO-donor group; and R_3 is H.

3. The method of claim 1, wherein R_2 each independently is $(C_1$-$C_8)$alkyl, preferably $(C_1$-$C_4)$alkyl, more preferably $(C_1$-$C_2)$alkyl, most preferably methyl.

4. The method of claim 3, wherein R_2 are identical.

5. The method of claim 1, wherein in said NO-donor group, X_1 is absent or -O-; X_2 is absent or $(C_1$-$C_{20})$alkylene, preferably $(C_1$-$C_6)$alkylene, more preferably $(C_1$-$C_3)$alkylene, most preferably methylene; X_3 is -NO or -ONO_2, preferably -ONO_2; and said alkylene is optionally substituted by one or more -ONO_2 groups and optionally further substituted by a moiety of the general formula D.

6. The method of any one of claims 1 to 5, wherein (i) n is 1; and one or two of the carbon atoms at positions 3 or 4 of the pyrrolidine ring are linked to an NO-donor group; (ii) n is 2; and one or more of the carbon atoms at positions 3 to 5 of the piperidine ring are linked to an NO-donor group; or (iii) n is 3; and one or more of the carbon atoms at positions 3 to 6 of the azepane ring are linked to an NO-donor group.

7. The method of claim 6, wherein said compound comprises more than one identical or different NO-donor groups.

8. The method of claim 6, wherein each one of said NO-donor groups independently is of the formula -$(C_1$-$C_6)$alkylene-ONO_2, preferably -$(C_1$-

C_3)alkylene-ONO_2, more preferably -CH_2-ONO_2, or -O-(C_1-C_6)alkylene-ONO_2, wherein said alkylene is optionally substituted by one or more -ONO_2 groups; or is -ONO_2.

9. The method of claim 8, wherein n is 1; R_2 each is methyl; and
   (i) R_1 linked to the carbon atom at position 3 of the pyrrolidine ring is the NO-donor group -CH_2-ONO_2 or -ONO_2; and R_1 linked to the carbon atom at position 4 of the pyrrolidine ring is H (herein identified compounds **1a** and **1b**, respectively); or
   (ii) each one of R_1 linked to the carbon atoms at positions 3 and 4 of the pyrrolidine ring is the NO-donor group -CH_2-ONO_2 or -ONO_2 (herein identified compounds **2a** and **2b**, respectively).

10. The method of claim 8, wherein n is 2; R_2 each is methyl; and
   (i) R_1 linked to the carbon atom at position 3 of the piperidine ring is the NO-donor group -CH_2-ONO_2 or -ONO_2; and each one of R_1 linked to the carbon atoms at positions 4 and 5 of the piperidine ring is H (herein identified compounds **3a** and **3b**, respectively);
   (ii) R_1 linked to the carbon atom at position 4 of the piperidine ring is the NO-donor group -CH_2-ONO_2 or -ONO_2; and each one of R_1 linked to the carbon atoms at positions 3 and 5 of the piperidine ring is H (herein identified compounds **4a** and **4b**, respectively);
   (iii) each one of R_1 linked to the carbon atoms at positions 3 and 4 of the piperidine ring is the NO-donor group -CH_2-ONO_2 or -ONO_2; and R_1 linked to the carbon atom at position 5 of the piperidine ring is H (herein identified compounds **5a** and **5b**, respectively);
   (iv) each one of R_1 linked to the carbon atoms at positions 3 and 5 of the piperidine ring is the NO-donor group -CH_2-ONO_2 or -ONO_2; and R_1 linked to the carbon atom at position 4 of the piperidine ring is H (herein identified compounds **6a** and **6b**, respectively);

(v) each one of R_1 linked to the carbon atoms at positions 3 to 5 of the piperidine ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$ (herein identified compounds **7a** and **7b**, respectively).

11. The method of claim 8, wherein n is 3; R_2 each is methyl; and

(i) R_1 linked to the carbon atom at position 3 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$; and each one of R_1 linked to the carbon atoms at positions 4 to 6 of the azepane ring is H (herein identified compounds **8a** and **8b**, respectively);

(ii) R_1 linked to the carbon atom at position 4 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$; and each one of R_1 linked to the carbon atoms at position 3, 5 and 6 of the azepane ring is H (herein identified compounds **9a** and **9b**, respectively);

(iii) each one of R_1 linked to the carbon atoms at positions 3 and 4 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$; and each one of R_1 linked to the carbon atoms at positions 5 and 6 of the azepane ring is H (herein identified compounds **10a** and **10b**, respectively);

(iv) each one of R_1 linked to the carbon atoms at positions 3 and 5 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$; and each one of R_1 linked to the carbon atoms at positions 4 and 6 of the azepane ring is H (herein identified compounds **11a** and **11b**, respectively);

(v) each one of R_1 linked to the carbon atoms at positions 3 and 6 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$; and each one of R_1 linked to the carbon atoms at positions 4 and 5 of the azepane ring is H (herein identified compounds **12a** and **12b**, respectively);

(vi) each one of R_1 linked to the carbon atoms at positions 3 to 5 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$; and R_1 linked to the carbon atom at position 6 of the azepane ring is H (herein identified compounds **13a** and **13b**, respectively);

(vii) each of R_1 linked to the carbon atoms at positions 3, 4 and 6 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$; and R_1

linked to the carbon atom at position 5 of the azepane ring is H (herein identified compounds **14a** and **14b**, respectively); or

(viii) each of R_1 linked to the carbon atoms at positions 3 to 6 of the azepane ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$ (herein identified compounds **15a** and **15b**, respectively).

12. The method of claim 8, wherein n is 1; R_2 each is methyl; R_1 linked to the carbon atom at position 3 of the pyrrolidine ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$; and R_1 linked to the carbon atom at position 4 of the pyrrolidine ring is $-CONH_2$ (herein identified compounds **16a** and **16b**, respectively).

13. The method of claim 8, wherein n is 2; R_2 each is methyl; R_1 linked to the carbon atom at position 3 of the piperidine ring is the NO-donor group $-CH_2-ONO_2$ or $-ONO_2$; R_1 linked to the carbon atom at position 4 of the piperidine ring is -COOH; and R_1 linked to the carbon atoms at position 5 of the piperidine ring is H (herein identified compounds **17a** and **17b**, respectively).

14. The method of claim 8, wherein n is 2; R_2 each is methyl; R_1 linked to the carbon atom at position 4 of the piperidine ring is the NO-donor group $-O-CH_2-CH(ONO_2)CH_2-ONO_2$; and each one of R_1 linked to the carbon atoms at positions 3 and 5 of the piperidine ring is H (herein identified compound **18**).

15. The method of claim 6, wherein each one of said NO-donor groups independently is of the formula $-O-(C_1-C_6)$alkylene$-ONO_2$, wherein said alkylene is substituted by a moiety of the general formula D and optionally further substituted by one or more $-ONO_2$ groups.

16. The method of claim 15, wherein n is 2; each one of R_1 linked to the carbon atoms at positions 3 and 5 of the piperidine ring is H; and (i) R_1 linked to the carbon atom at position 4 of the piperidine ring is the NO-donor group $-O-CH_2-CH_2-CH(CH_3)-ONO_2$, wherein the 1,3 butane diyl is substituted at position 2 with the $-ONO_2$ group and at position 4 with a moiety of the general formula D, wherein m is

2, and the oxygen atom is linked to the carbon atom at position 4 of the piperidine ring in the formula D; and R_2 each is methyl (herein identified compound **19**); or (ii) R_1 linked to the carbon atom at position 4 of the piperidine ring is the NO-donor group -O-CH_2-$CH(CH_3)$-ONO_2, wherein the 1,2 propane diyl is substituted at position 3 with a moiety of the general formula D, wherein m is 2, and the oxygen atom is linked to the carbon atom at position 4 of the piperidine ring in the formula D; and R_2 each is methyl (herein identified compound **20**).

17. The method of claim 9, wherein compound **1a**, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, is administered.

18. The method of any one of claims 1 to 17, wherein said sepsis is caused by Gram negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia* species, *Salmonella* species, *Shigella* species, *Enterobacter* species, *Citrobacter* species, *Proteus* species, and *Klebsiella* species; Gram-positive cocci such as *Pneumococcal* species, *Staphylococcal* species, *Enterococcal* species, and *Streptococcal* species; fungi and yeast; Rickettsial species Plasmodial species, *Clostridial* species; viruses, or Gram-positive bacterial toxins, including toxic shock syndrome toxins.

19. The method of claim 18, for inhibiting development of sepsis-related coagulopathy.

20. A pharmaceutical composition for treatment of sepsis and conditions associated therewith comprising a compound of the general formula I, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

21. The pharmaceutical composition of claim 20, wherein said compound is selected from compounds **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**, **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **12a**, **12b**, **13a**, **13b**, **14a**, **14b**, **15a**, **15b**, **16a**, **16b**,

17a, **18b**, **18**, **19** or **20**, preferably compound **1a**, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof.

22. The pharmaceutical composition of claim 21, for intravenous, intramuscular, intraperitoneal, intrathecal, intrapleural, subcutaneous, intratracheal, or inhalational administration.

23. A compound of the general formula I, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, for use in treatment of sepsis and conditions associated therewith.

24. Use of a compound of the general formula I, or an enantiomer, diastereomer, racemate, or pharmaceutically acceptable salt or solvate thereof, for the preparation of a pharmaceutical composition for treatment of sepsis and conditions associated therewith.

Fig. 1

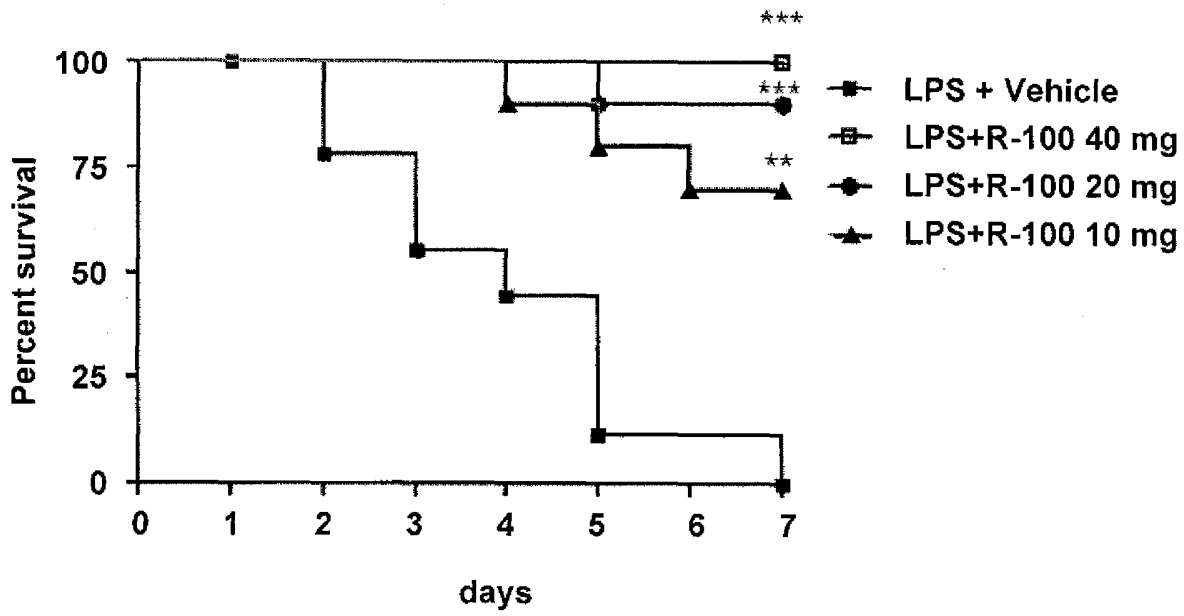

***
***
**
100
75
50
25
0
Percent survival
0
1
2
3
4
5
6
7
days
LPS + Vehicle
LPS+R-100 40 mg
LPS+R-100 20 mg
LPS+R-100 10 mg

Fig. 2

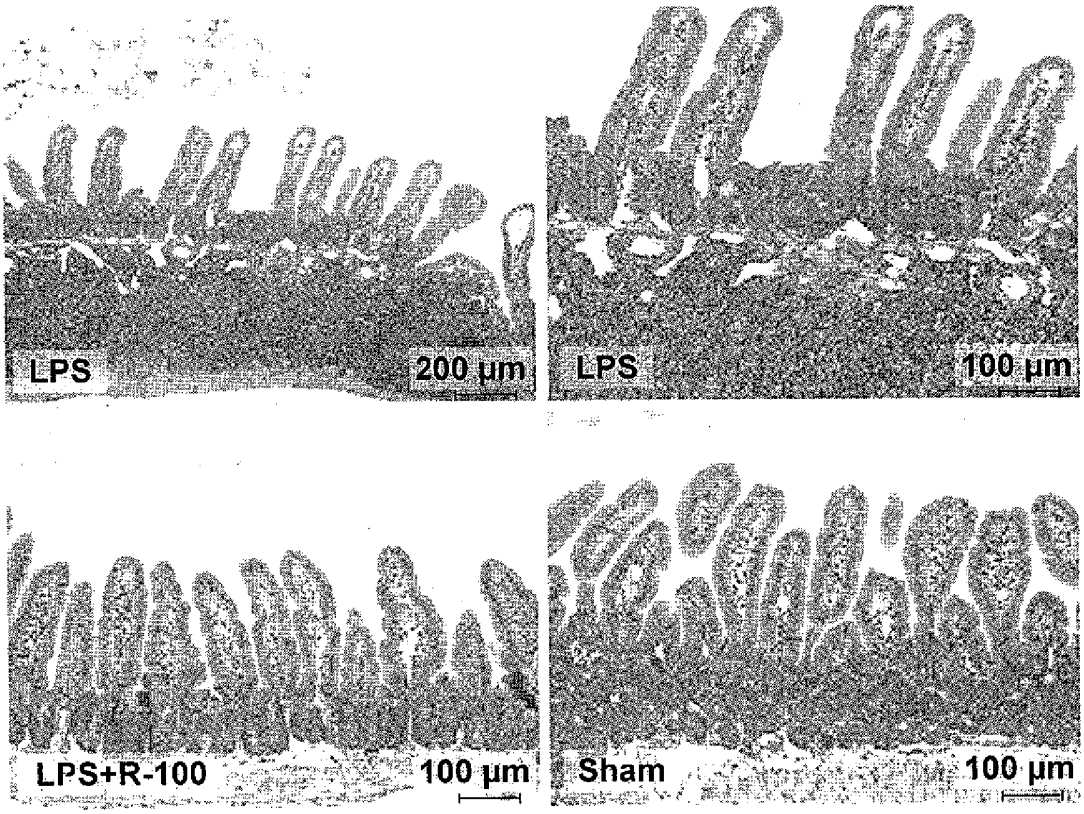


Fig. 3

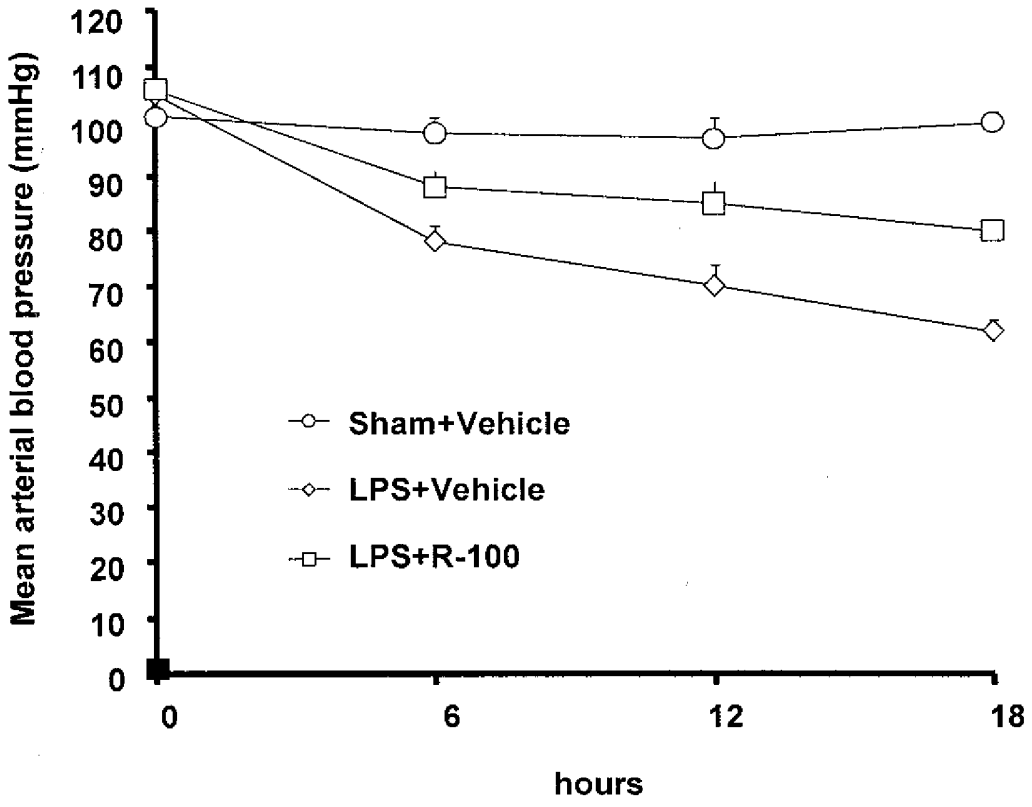

Mean arterial blood pressure (mmHg)
120
110
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
hours
Sham+Vehicle
LPS+Vehicle
LPS+R-100

Fig. 4A

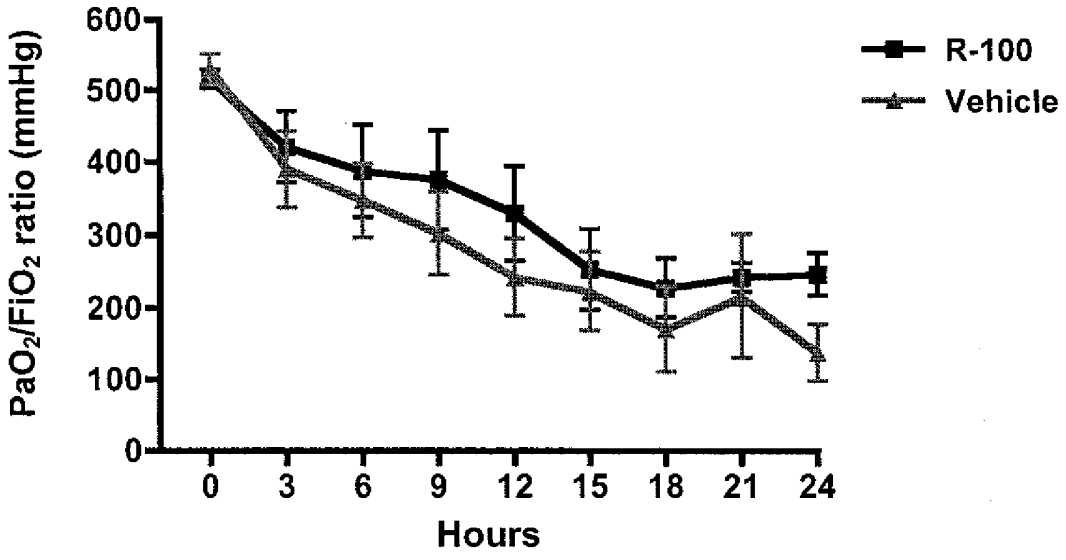

600
500
400
300
200
100
0
PaO2/FiO2 ratio (mmHg)
0 3 6 9 12 15 18 21 24
Hours
R-100
Vehicle

Fig. 4B

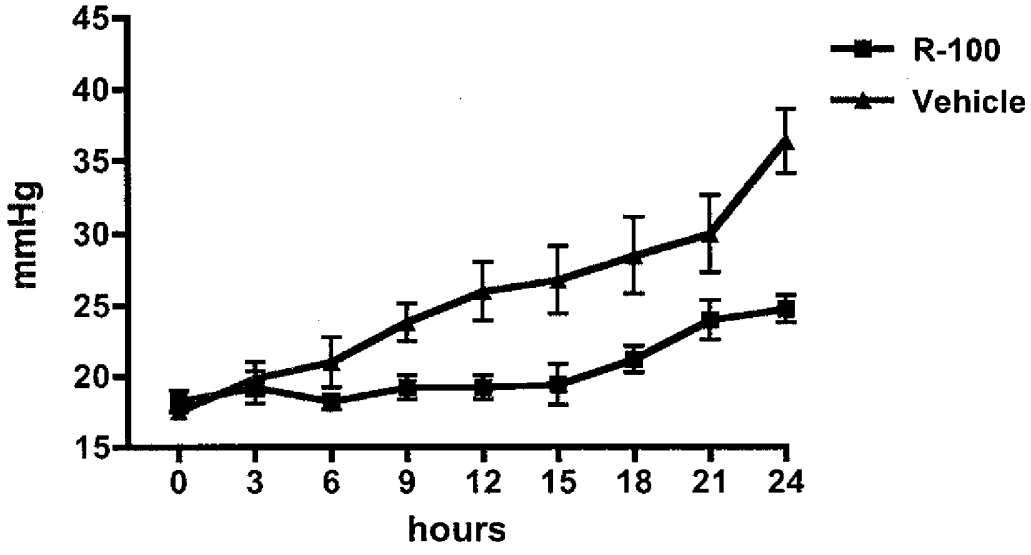

45
40
35
30
25
20
15
mmHg
0 3 6 9 12 15 18 21 24
hours
R-100
Vehicle

Fig. 4C

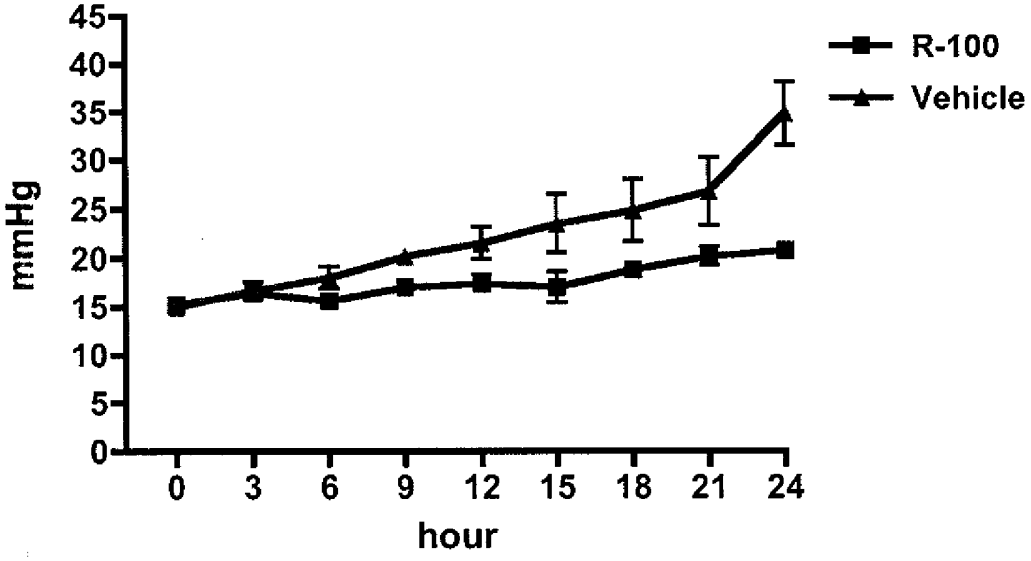

45
40
35
30
25
20
15
10
5
0
mmHg
0
3
6
9
12
15
18
21
24
hour
R-100
Vehicle

Fig. 4D

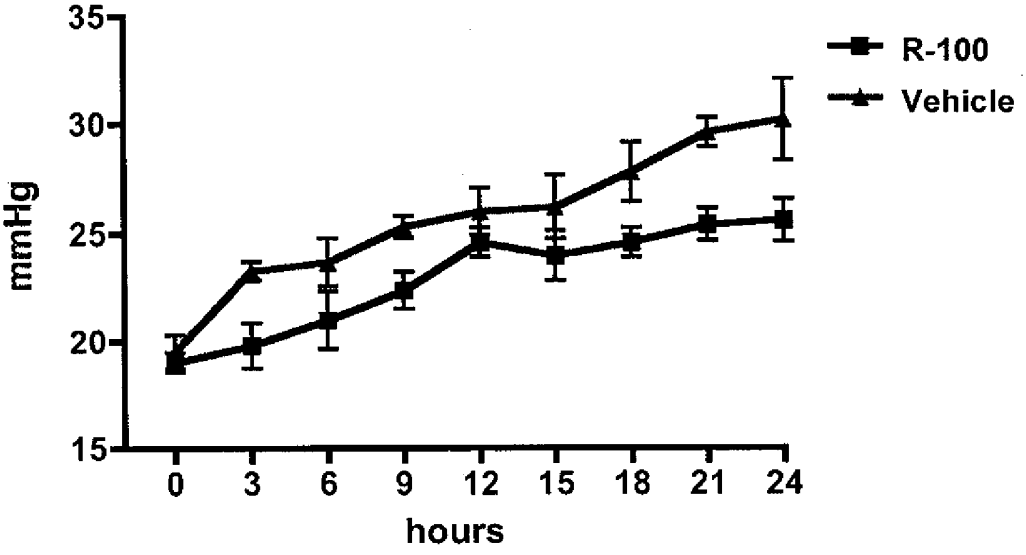

35
30
25
20
15
mmHg
0
3
6
9
12
15
18
21
24
hours
R-100
Vehicle

Fig. 4E

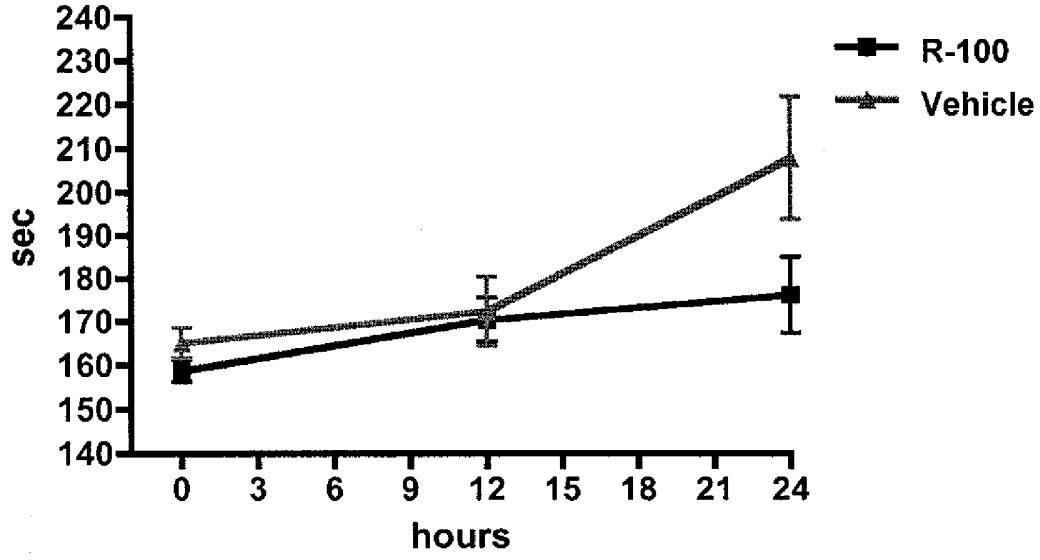

240
230
220
210
200
190
180
170
160
150
140
sec
0
3
6
9
12
15
18
21
24
hours
R-100
Vehicle

Fig. 4F

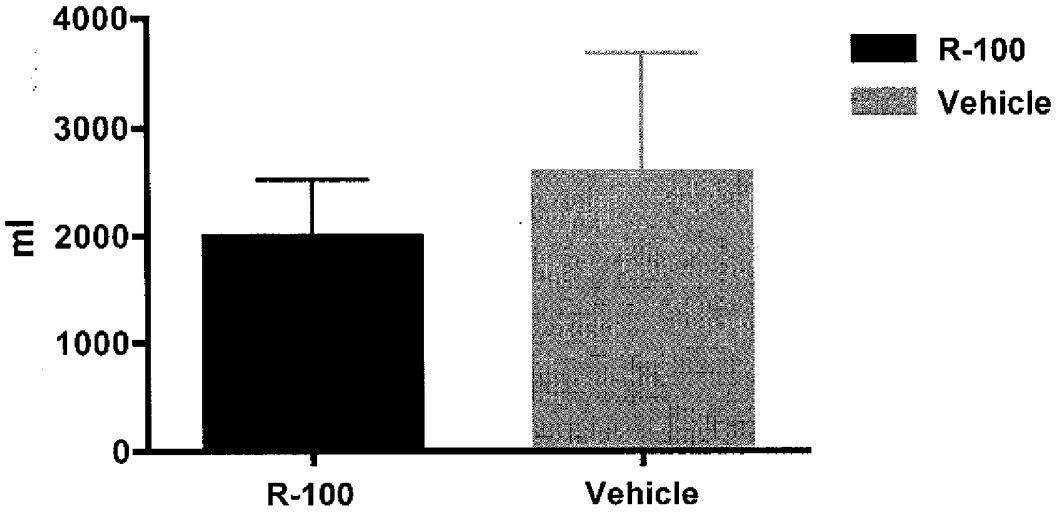

4000
3000
2000
1000
0
ml
R-100
Vehicle
R-100
Vehicle

Fig. 4G

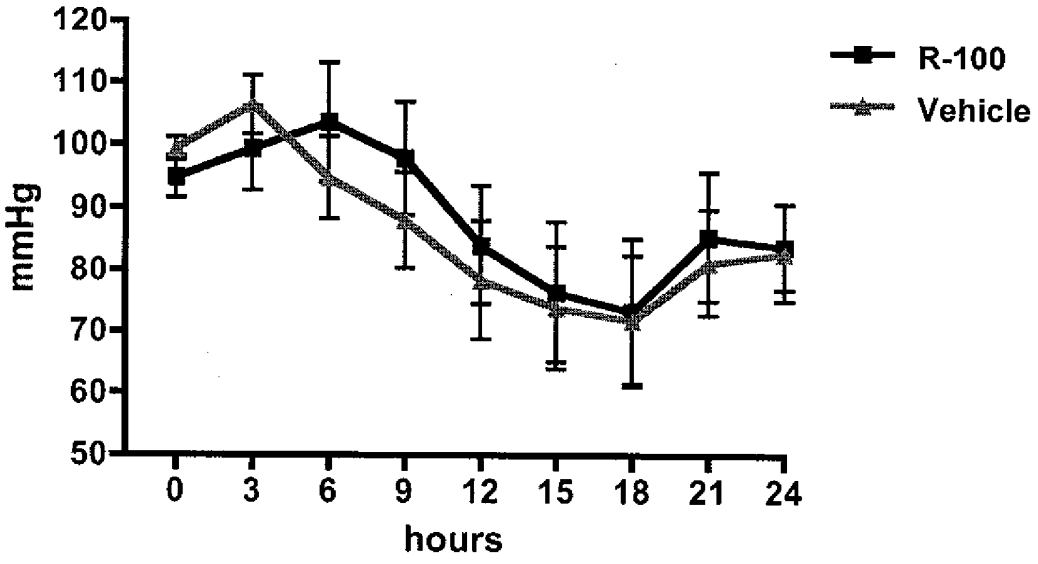
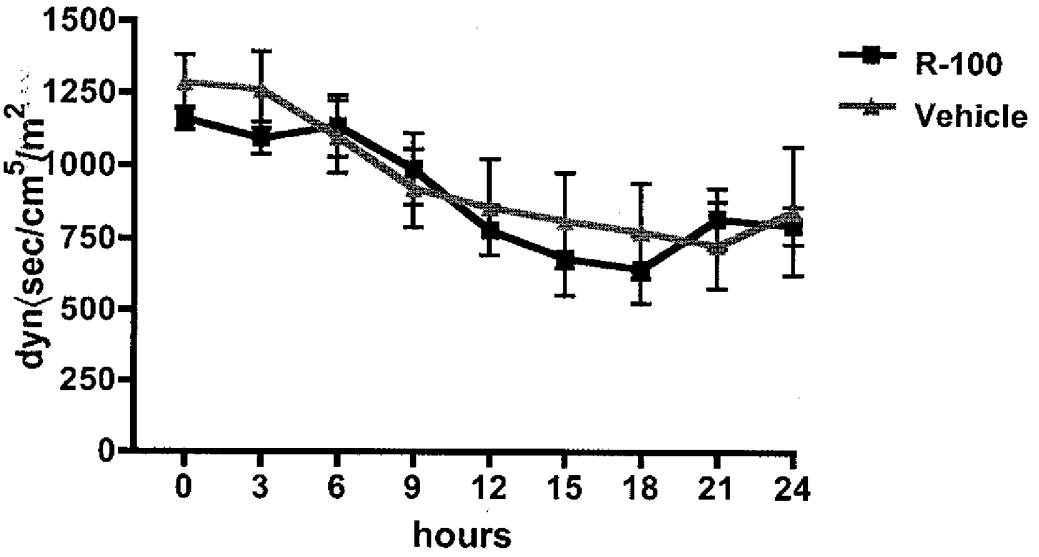

120
110
100
90
80
70
60
50
mmHg
0
3
6
9
12
15
18
21
24
hours
R-100
Vehicle

Fig. 4H


1500
1250
1000
750
500
250
0
dyn(sec/cm5/m2
0
3
6
9
12
15
18
21
24
hours
R-100
Vehicle

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2011/000879

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P29/00 A61K31/40 A61K31/445 A61K31/55
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/069429 A1 (ANGGARD ERIK EMIL [GB] ET AL) 10 April 2003 (2003-04-10) See the claimed and exemplified compounds, in particular compounds having RN: 232611-63-1, 232611-64-2, 232611-65-3, 232611-66-4, 232611-67-5, 232611-68-6, 232611-69-7, 232611-70-0 and their use in the treatment of conditions associated with oxidative stree, including septic shock (paragraph 43) -----	1-16, 20-24
Y	WO 03/088961 A1 (YISSUM RES DEV CO [IL]; HAJ-YEHIA ABDULLAH IBRAHIM [IL]) 30 October 2003 (2003-10-30) See claimed compounds 4, and in particular compound 4. as nitrogen oxide donors. See claims 18, 29, 32: use for the treatment of inflammatory disorders ----- -/--	1-24

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2012	03/02/2012

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2011/000879

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/087212 A2 (AGA AB [SE]; CHEN LUNI [SE]; DA JIPING [SE]; HEDENSTIERNA GOERAN [SE]) 14 October 2004 (2004-10-14) See claims 1, 6: nitric oxide donors in the treatment of spesis. See nitric oxide donors of passage bridging pages 11 and 12	1-24
Y	WO 2005/105065 A2 (RENOPHARM LTD [IL]; ASSAF PETER [IL]) 10 November 2005 (2005-11-10) See claims and compounds of table 1 (page 71 ff), and in particular page 80, compound Pet-75: nitric oxide donor compounds and their use for the treatment of inflammatory conditions	1-24
Y	US 2010/197702 A1 (HELLBERG MARK R [US] ET AL) 5 August 2010 (2010-08-05) Relevant compounds for the treatment of ocular conditions	1-24
Y,P	WO 2011/092690 A1 (YISSUM RES DEV CO [IL]; RADIKAL THERAPEUTICS INC [US]; SALZMAN ANDREW) 4 August 2011 (2011-08-04) See the claims and the examples: the relevant compounds, as NO donors, and their use in the treatment of pulmonary hypertension	1-24
Y	XIZHONG CUI ET AL: "Neuronal nitric oxide synthase deficiency decreases survival in bacterial peritonitis and sepsis", INTENSIVE CARE MEDICINE, SPRINGER, BERLIN, DE, vol. 33, no. 11, 8 August 2007 (2007-08-08), pages 1993-2003, XP019558954, ISSN: 1432-1238, DOI: 10.1007/S00134-007-0814-9 See abstract and discussion: deficiency and inhibition of NOS1 is important for survival, bacterial clearance, and regulation of cytokine response during infection and sepsis	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IL2011/000879

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		WO 2005105765 A1	10-11-2005
US 2010197702 A1	05-08-2010	NONE	
WO 2011092690 A1	04-08-2011	NONE	