Title: NITROXYDERIVATIVES OF CARVEDILOL AND OTHER BETA BLOCKERS AS ANTIHYPERTENSIVE DRUGS

Abstract: The present invention relates to β-adrenergic blockers nitroxyderivatives of general formula (I): A-(Y-ONO₂)ₙ, wherein s is an integer equal to 1 or 2; A is selected from the following β-adrenergic blockers residues of formula (II), wherein R₁ is selected from the group consisting of: formula (IIa), formula (IIb), formula (IIc) or other residues defined in claim 1; R₂ is selected from the group consisting of: -CH(CH₃)₂, -(CH₂)₃ or formula (IIIa), formula (IIib), Z is H or is a group capable of binding Y as defined in claim 1, Z₁ is H or a -CO- capable of binding Y; the other substituents are defined in claim 1; and enantiomers and diastereoisomers and pharmaceutically acceptable salts thereof, pharmaceutical compositions containing them and their use for the treatment of hypertension, cardiovascular diseases, glaucoma, migraine headache and vascular diseases.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
The present invention relates to β-adrenergic blockers derivatives. More particularly, the present invention relates to β-adrenergic blockers nitrooxyderivatives, pharmaceutical compositions containing them and their use for the treatment of hypertension, cardiovascular diseases, glaucoma, migraine headache, vascular diseases and elevated intraocular pressure.

β-adrenergic blockers (β-blockers) are widely used in the treatment of hypertension and cardiovascular diseases including angina pectoris, arrhythmias, acute myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure. They work to block the effects of catecholamines at receptor sites in the heart, but they differ somewhat in their ability to block receptors in the blood vessels and lungs. Selective β-blockers have their major actions on the heart, some others are weak stimulators of the β-receptor while still blocking the major actions of catecholamines, some block both the β₁ and β₂ receptors in the heart and those in the blood vessels and have no stimulatory activity and some block other catecholamine receptors that can lead to further vascular effects on blood vessels.

Several side effects are associated with this class of drugs such as muscle fatigue, sleep disturbances, decreased heart rate, hypotension, cold extremities, bronchospasm in asthmatic patients, hypoglycemia, increased in plasma lipids. Moreover, abrupt withdrawal after long-term treatment with β-blockers has to be avoided, because an increased sensitivity to β-adrenergic system develops.

U.S. Pat. No. 6,242,432 discloses derivatives of formula A-{X₁-NO₂}ₚ, having an antithrombotic activity, wherein A is the residue of a β-adrenergic blocker, X₁ is a bivalent connecting bridge and p₁ is any of 1 or 2. The invention is limited to particular residues of β-adrenergic blockers.

U.S. Pat. No 5,502,237 and U.S. Pat. No 5,639,904 disclose derivatives of formula R₁-Ar-O-CH₂-CH(OH)-CH₂-NH-CH(CH₃)₂ used for the treatment of cardiovascular affections, wherein R₁ is a chain having at least one nitroxy group as substituent.

U.S. Pat. No. 4,801,596 discloses aminopropanol derivatives of formula

\[ \text{R} \downarrow \text{N-CH₂-CH(OH)-CH₂-NH-R} \]

\[ \text{R} \downarrow \text{N-CH₂-CH(OH)-CH₂-NH-R} \]
that can be used for prophylaxis and/or treatment of heart and circulatory diseases, wherein R₃ is an alkyl or a nitroxyalkyl radical containing 3 to 8 carbon atoms.

It was an object of the present invention to provide new β-adrenergic blockers nitrooxyderivatives having a significantly improved overall pharmacological profile as compared to native β-blockers that are able not only to eliminate or at least reduce the side effects associated with their parent compounds, but also having an improved pharmacological activity and tolerability.

It has been so surprisingly found that the β-adrenergic blockers nitrooxyderivatives of the present invention have a better pharmacological activity and organ protection properties, enhanced effects as anti-inflammatory, and on renal functions. In addition, they are effective in other pathologies including atherosclerosis, diabetes, peripheral vascular diseases (PVD) and elevated intraocular pressure.

In particular, it has been recognized that the β-adrenergic blockers nitrooxyderivatives of the present invention, differently from the above mentioned compounds of the prior art, exhibit an improved activity on the cardiovascular system and enhanced tolerability and can be employed for treating or preventing hypertension, cardiovascular diseases, glaucoma, migraine headache, vascular diseases and elevated intraocular pressure.

Object of the present invention are β-adrenergic blockers nitrooxyderivatives of general formula (I):

\[ A-(Y-\text{ONO}_2)_s \]

and enantiomers and diastereoisomers and pharmaceutically acceptable salts thereof, wherein s is an integer equal to 1 or 2;

A is selected from the following β-adrenergic blocker residues of formula (II):

\[ Z \]
\[ O \]
\[ R_1 \]
\[ N \]
\[ Z_1 \]
\[ R_2 \]

(II)

wherein

R₁ is selected from the group consisting of:
R₂ is selected from the group consisting of: -CH(CH₃)₂, -C(CH₃)₃ or
when the radical $R_1$ has chosen from the formulae (IIa), (IIc), (IId), (IIg), (IIh), (III), (IIIm), $R_2$

is $\text{-CH(CH}_3\text{)}_2\text{;}$

when the radical $R_1$ has chosen from the formulae (IIe), (IIf) or (IIin), $R_2$ is $\text{-C(CH}_3\text{)}_3\text{;}$

when $R_1$ is the radical (IIb), $R_2$ is (IIIa);

when $R_1$ is the radical (III), $R_2$ is (IIlb);

$Z$ is H or is a group capable of binding $Y$ selected from the group consisting of:

$-\text{C(O)}\cdot, -\text{C(O)O- or}$

wherein $R'$ and $R''$ are the same or different, and are H or straight or branched $C_1$-$C_4$ alkyl;

$Z_1$ is H or a $-\text{C(O)}\cdot$ capable of binding $Y$;

with the proviso that when $s$ of formula (I) is 1, $Z$ or $Z_1$ is H;

preferably when $s$ of formula (I) is 2, $Z$ and $Z_1$ are $-\text{C(O)}\cdot$;

$Y$ is a bivalent radical having the following meanings:

a)

- straight or branched $C_1$-$C_{20}$ alkylene, preferably $C_1$-$C_{10}$ alkylene, more preferably $C_2$-$C_8$

alkylene, being optionally substituted with one or more of the substituents selected from

the group consisting of: halogen atoms, hydroxy, $-\text{ONO}_2$ or T, wherein T is $-\text{OC(O)(C}_1$-$

$C_{10}$alkyl)-$\text{ONO}_2$, $-\text{O(C}_1$-$C_{10}$alkyl)-$\text{ONO}_2$;

b)

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally

substituted with side chains $T_1$, wherein $T_1$ is straight or branched alkyl with from 1 to 10

carbon atoms, $T_1$ is preferably $\text{CH}_3$;

c)
wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0 or 1,

\( n_1 \) is an integer from 1 to 20, preferably from 1 to 10, more preferably \( n_1 \) is 1;

\( n_2, n_3, n_4 \) and \( n_5 \) are integers equal or different from one another, equal to 0 or 1;

\( R^5 \) and \( R^6 \) are independently selected from H or CH₃;

\( Y^1 \) is \(-CH_2-\) or \(-(CH_2)_{na}-CH=CH-\) wherein \( na \) is an integer from 0 to 20, preferably \( na \) is equal to 0;

\( X_i \) is \(-WC(O)-\) or \(-C(O)W-\), wherein \( W \) is oxygen, sulfur or NH, preferably \( W \) is oxygen;

d)

\[
\begin{align*}
\text{R}^5 & \quad \text{R}^6 \\
\text{C}^A_{n5} & \quad \text{C}^B_{n7} \\
\text{R}^6 & \quad \text{R}^5 \\
\text{X}_1 & \quad \text{CH}_2_{n1} \\
\end{align*}
\]

wherein:

\( n_1 \) is an integer from 1 to 20, preferably from 1 to 10;

\( X_i \) is \(-WC(O)-\) or \(-C(O)W-\), wherein \( W \) is oxygen, sulfur or NH, preferably \( W \) is sulfur or NH;

\( n_6 \) is an integer from 1 to 20, preferably from 1 to 5, more preferably \( n_6 \) is 1,

\( n_7 \) is an integer from 0 to 20, preferably from 0 to 5, more preferably \( n_7 \) is 1,

\( R^5, R^6, R^7 \) and \( R^8 \) are independently selected from the group consisting of: H, CH₃, OH, NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;

when the bond between the \( C^A \) and \( C^B \) carbons is a double bond \( R^5 \) and \( R^6 \) or \( R^7 \) and \( R^8 \) are absent;

with the proviso that when \( Y \) is selected from the bivalent radicals mentioned under c)-d), the \(-ONO₂\) group is linked to the \(-(CH_2)_{n1-}\) group;

e)

\[
\begin{align*}
\text{R}^{11} & \quad \text{R}^{11} \\
\text{CH} & \quad \text{CH} & \quad \text{CH} & \quad \text{CH} \\
\text{CH}_2_{n10a}X_2 & \quad \text{CH}_2_{n10X_2} & \quad \text{CH}_2_{n11} & \quad \text{CH}_2_{n12} \\
\text{R}^{11a} & \quad \text{R}^{11a} & \quad \text{R}^{11a} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^{11a} & \quad \text{R}^{11a} \\
\text{(CH}_2_{n10a-}CH & \quad \text{(CH}_2_{n10-}CH & \quad \text{CH}_2_{n11} & \quad \text{(CH}_2_{n12-}CH \\
\text{R}^{11a} & \quad \text{R}^{11a} & \quad \text{R}^{11a} \\
\end{align*}
\]
wherein \( X_2 \) is O or S,
n10a, n10 and n12 are integer independently selected from 0 to 20,
n10a is preferably selected from 0 to 10, more preferably n10a is 0 or 1,
n10 and n12 are preferably selected from 1 to 10, more preferably n10 and n12 are 1 or 2
n11 is an integer from 0 to 6, preferably from 0 to 4, more preferably n11 is 0 or 1,
\( R^{11} \) is H, CH₃ or nitrooxy group, preferably \( R^{11} \) is H or a nitrooxy group and
\( R^{11a} \) is CH₃ or nitrooxy group;
f).

\[
\begin{align*}
&\begin{array}{c}
\text{R}^9 \quad \text{R}^8 \\
\text{[C]}_{n8} \quad \text{Y}^2 \\
\text{R}^{10} \quad \text{R}^7
\end{array}
\end{align*}
\]

(VIII)

wherein
n8 is an integer from 0 to 10;
n9 is an integer from 1 to 10;
\( R^9, R^{10}, R^8, R^7 \) are same or different, and are H or straight or branched C₁-C₄ alkyl,
preferably \( R^9, R^{10}, R^8, R^7 \) are H;
wherein the \(-\text{ONO}_2\) group is linked to

\[
\begin{align*}
&\begin{array}{c}
\text{[C]} \\
n_9
\end{array}
\end{align*}
\]

wherein n9 is as defined above;

\( Y^2 \) is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing
one or more heteroatoms selected from nitrogen, oxygen, sulfur,
and is selected from the group consisting of

\[
\begin{align*}
\text{(Y1)} & \quad \text{(Y2)} & \quad \text{(Y3)} & \quad \text{(Y4)} & \quad \text{(Y5)}
\end{align*}
\]
One embodiment provides compounds of formula (I) wherein:

s is 2,

A is selected from the following β-adrenergic blocker residues of formula (II):

wherein

R₁ is selected from the group consisting of:

- (IIa)
- (IIb)
- (IIc)
- (IId)
- (IIe)
- (IIIf)
R₂ is selected from the group consisting of: -CH(CH₃)₂, -C(CH₃)₃ or -CH₂(CH₂)₂;
when the radical R₁ has chosen from the formulae (IIa), (IIc), (IId), (IIg), (IIh), (III), (IIIm), R₂ is -CH(CH₃)₂;
when the radical R₁ has chosen from the formulae (IIe), (IIf) or (IIIn), R₂ is -C(CH₃)₃;
when R₁ is the radical (IIb), R₂ is (IIla);
when R₁ is the radical (III), R₂ is (IIlb);
Z is a group capable of binding Y selected from the group consisting of: -C(O)-, -C(O)O- or
wherein R' and R'' are the same or different, and are H or straight or branched C₁-C₄ alkyl; Z₁ is H or a -C(O)- capable of binding Y, preferably Z and Z₁ are -C(O)-; Y is a bivalent radical having the following meaning:

5 a) - straight or branched C₁-C₂₀ alkylene, preferably C₁-C₁₀ alkylene, more preferably C₃-C₆ alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, -ONO₂ or T, wherein T is -OC(O)(C₁-C₁₀alkyl)-ONO₂, -O(C₁-C₁₀alkyl)-ONO₂;

10 b) - cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T₁, wherein T₁ is straight or branched alkyl with from 1 to 10 carbon atoms, T₁ is preferably CH₃;

c) 

\[
\begin{align*}
\text{(IV)} & \\
\end{align*}
\] 

wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0 or 1,

20 n₁ is an integer from 1 to 20, preferably from 1 to 10, more preferably n₁ is 1;

n₂, n₃, n₄ and n₅ are integers equal or different from one another, equal to 0 or 1;

R³ and R⁴ are independently selected from H or CH₃;

Y¹ is -CH₂⁻ or -(CH₂)ₙₐ-CH=CH⁻ wherein nₐ is an integer from 0 to 20, preferably nₐ is equal to 0;

25 X₁ is -WC(O)- or -C(O)W⁻, wherein W is oxygen, sulfur or NH, preferably W is oxygen; d)
wherein:
n1 is an integer from 1 to 20, preferably from 1 to 10;
\(X_1\) is \(-\text{WC(O)}-\) or \(-\text{C(O)}W-\), wherein W is oxygen, sulfur or NH, preferably W is sulfur or NH;
n6 is an integer from 1 to 20, preferably from 1 to 5, more preferably n6 is 1,
n7 is an integer from 0 to 20, preferably from 0 to 5, more preferably n7 is 1,
R<sup>5</sup> and R<sup>5</sup>' R<sup>6</sup> and R<sup>6</sup>' are independently selected from the group consisting of: H, CH₃, OH, NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;
when the bond between the C<sup>A</sup> and C<sup>B</sup> carbons is a double bond R<sup>5</sup> and R<sup>6</sup> or R<sup>6</sup>' and R<sup>5</sup>' are absent;
with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the \(-\text{ONO}_2\) group is linked to the \(-(\text{CH}_2)_n\) group;
e)

\[ \text{[Diagram showing molecular structure with n10a, n10 and n12]} \]

wherein \(X_2\) is O or S,
n10a, n10 and n12 are integer independently selected from 0 to 20,
n10a is preferably selected from 0 to 10, more preferably n10a is 0 or 1;
n10 and n12 are preferably selected from 1 to 10, more preferably n10 and n12 are 1 or 2;
n11 is an integer from 0 to 6, preferably from 0 to 4, more preferably n11 is 0 or 1;
R<sup>11</sup> is H, CH₃ or nitrooxy group, preferably R<sup>11</sup> is H or nitroxy;
f)

\[ \text{[Diagram showing molecular structure with n8, n9, n10, n11 and n12]} \]
wherein
n8 is an integer from 0 to 10;
n9 is an integer from 1 to 10;
R^8, R'^10, R^6, R'^7 are same or different, and are H or straight or branched C_1-C_4 alkyl,
preferably R^8, R'^10, R^6, R'^7 are H;
wherein the –ONO₂ group is linked to
\[
\text{[C] } _{n9}
\]
wherein n9 is as defined above;
Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing
one or more heteroatoms selected from nitrogen, oxygen, sulfur,
and is selected from the group consisting of

\begin{align*}
\text{(Y1)} & \quad \text{(Y2)} & \quad \text{(Y3)} & \quad \text{(Y4)} & \quad \text{(Y5)} \\
\text{(Y6)} & \quad \text{(Y7)} & \quad \text{(Y8)} & \quad \text{(Y9)} & \quad \text{(Y10)} \\
\text{(Y11)} & \quad \text{(Y12)} & \quad \text{(Y13)} & & \\
\end{align*}

Another embodiment provides compounds of formula (I) wherein:
s is 1,
A is selected from the following β-adrenergic blocker residues of formula (II):

\begin{align*}
\text{[C] } _{n9}
\end{align*}
wherein

\[ R_1 \text{ is selected from the group consisting of:} \]

\[ (\text{IIa}) \]

\[ (\text{IIb}) \]

\[ (\text{IIc}) \]

\[ (\text{IIId}) \]

\[ (\text{IIe}) \]

\[ (\text{IIf}) \]

\[ (\text{IIg}) \]

\[ (\text{IIh}) \]

\[ (\text{III}) \]

\[ (\text{III}) \]
R₂ is selected from the group consisting of: -CH(CH₃)₂, -C(CH₃)₃ or

when the radical R₁ has chosen from the formulae (IIa), (IIc), (IId), (IIg), (IIh), (III), (IIm), R₂ is -CH(CH₃)₂;
when the radical R₁ has chosen from the formulae (IIe), (III) or (IIn), R₂ is -C(CH₃)₃;
when R₁ is the radical (IIb), R₂ is (IIla);
when R₁ is the radical (III), R₂ is (IIIb);
Z is H and Z₁ a -C(O)- capable of binding Y;
Y is a bivalent radical having the following meaning:
a) - straight or branched C₁-C₂₀ alkyene, preferably C₁-C₁₀ alkyene, more preferably C₃-C₆
alkyene, being optionally substituted with one or more of the substituents selected from
the group consisting of: halogen atoms, hydroxy, -ONO₂ or T, wherein T is -OC(O)(C₁-
C₁₀alkyl)-ONO₂, -O(C₁-C₁₀alkyl)-ONO₂;
b) - cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally
substituted with side chains T₁, wherein T₁ is straight or branched alkyl with from 1 to 10
carbon atoms, T₁ is preferably CH₃;
c)
wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0 or 1, and n1 is an integer from 1 to 20, preferably from 1 to 10, more preferably n1 is 1;
n2, n3, n4 and n5 are integers equal or different from one another, equal to 0 or 1;
R³ and R⁴ are independently selected from H or CH₃;
Y¹ is \(-\text{CH}_2-\) or \(-(\text{CH}_2)_{n_a}\text{-CH}=\text{CH}-\) wherein na is an integer from 0 to 20, preferably na is equal to 0;
X₁ is \(-\text{WC(O)}-\) or \(-\text{C(O)W}-\), wherein W is oxygen, sulfur or NH, preferably W is oxygen;

\[\begin{align*}
\text{R⁶} & \quad \text{R⁵} \\
(\text{C}^A)_{n₆} \quad (\text{C}^B)_{n₇} \quad (\text{X₁}) \quad (\text{CH}_2)_{n₁}\end{align*}\]

(V)

wherein:

n1 is an integer from 1 to 20, preferably from 1 to 10;
X₁ is \(-\text{WC(O)}-\) or \(-\text{C(O)W}-\), wherein W is oxygen, sulfur or NH, preferably W is sulfur or NH;
n6 is an integer from 1 to 20, preferably from 1 to 5, more preferably n6 is 1,
n7 is an integer from 0 to 20, preferably from 0 to 5, more preferably n7 is 1,
R⁶ and R⁵, R⁶ and R⁵ are independently selected from the group consisting of: H, CH₃, OH, NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;
when the bond between the C² and C² carbons is a double bond R⁵ and R⁶ or R⁵ and R⁶ are absent;
with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the \(-\text{ONO}_2\) group is linked to a \(-(\text{CH}_2)_{n_{₁₁}}\) group;

\[\begin{align*}
\text{R}^{11} & \quad \text{R}^{11} \\
\text{R}^{11} & \quad \text{R}^{11} \\
\text{R}^{11} & \quad \text{R}^{11}\end{align*}\]

(VI)

\[\begin{align*}
\text{R}^{11a} & \quad \text{R}^{11a} \\
\text{R}^{11a} & \quad \text{R}^{11a} \\
\text{R}^{11a} & \quad \text{R}^{11a}\end{align*}\]

(VII)
wherein $X_2$ is O or S;
n10a, n10 and n12 are integer independently selected from 0 to 20,
n10a is preferably selected from 0 to 10, more preferably n10a is 0 or 1;
n10 and n12 are preferably selected from 1 to 10, more preferably n10 and n12 are 1 or 2;
n11 is an integer from 0 to 6, preferably from 0 to 4, more preferably n11 is 0 or 1;
$R^{11}$ is H, CH$_3$ or nitrooxy group, preferably $R^{11}$ is H or nitroxy;
$R^{11a}$ is CH$_3$ or nitrooxy group;
f)

$\overset{R^9}{\text{[C]}}_{n8} \overset{Y^2}{\text{[C]}}_{n9} \overset{R^8}{\text{[C]}}_{n9} \overset{R^7}{\text{[C]}}_{n9}$

(VIII)

wherein
n8 is an integer from 0 to 10;
n9 is an integer from 1 to 10;
$R^9$, $R^{10}$, $R^8$, $R^7$ are same or different, and are H or straight or branched C$_1$-C$_4$ alkyl,
preferably $R^9$, $R^{10}$, $R^8$, $R^7$ are H;
wherein the $-\text{ONO}_2$ group is linked to

$\overset{\text{[C]}}{\text{[C]}}_{n9}$

wherein n9 is as defined above;
$Y^2$ is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing
one or more heteroatoms selected from nitrogen, oxygen, sulfur,
and is selected from the group consisting of

![Diagram](Y1)  ![Diagram](Y2)  ![Diagram](Y3)  ![Diagram](Y4)  ![Diagram](Y5)
Another embodiment provides compounds of formula (I) wherein s is 1, A is selected from the following β-adrenergic blocker residues of formula (II):

wherein

R₁ is selected from the group consisting of:
R₂ is selected from the group consisting of: -CH(CH₃)₂, -C(CH₃)₃ or

when the radical R₁ has chosen from the formulae (IIa), (IIc), (IId), (Ilg), (IIh), (III), (IIIm), R₂ is -CH(CH₃)₂;
when the radical R₁ has chosen from the formulae (IIe), (IIf) or (IIIn), R₂ is -C(CH₃)₃;
when R₁ is the radical (IIL), R₂ is (IIIb);
Z₁ is H;
Z is a group capable of binding Y selected from the group consisting of:
-C(O)-, -C(O)O- or
wherein $R'$ and $R''$ are the same or different, and are H or straight or branched $C_1$-$C_4$ alkyl; 
$Y$ is a bivalent radical having the following meaning:
c)

\[
\begin{array}{c}
\text{(IV)}
\end{array}
\]

wherein:
$n$ is an integer from 0 to 20, preferably $n$ is an integer from 0 to 10, more preferably $n$ is 0 or 1,
n1 is an integer from 1 to 20, preferably from 1 to 10, more preferably $n1$ is 1;
n2, n3, n4 and n5 are integers equal or different from one another, equal to 0 or 1;
$R^3$ and $R^4$ are independently selected from H or CH$_3$;
$Y^1$ is --CH$_2$- or --(CH$_2$)$_{na}$-CH=CH- wherein na is an integer from 0 to 20, preferably na is equal to 0;

\[
\begin{array}{c}
\text{(VI)}
\end{array}
\]

$X_1$ is --WC(O)-- or --C(O)W--, wherein W is oxygen, sulfur or NH, preferably W is oxygen;
e)

\[
\begin{array}{c}
\text{(VII)}
\end{array}
\]

wherein:
$X_2$ is O or S,
n10a is 0 or 1,
n11 is 0 or 1,
n10 and n12 are 1 or 2;
$R^{11}$ is H, CH$_3$ or nitrooxy group;
$R^{11a}$ is CH$_3$ or nitrooxy group;
f)

\[
\begin{align*}
\text{[C]}_n & \text{R}^9 \quad \text{Y}^2 \quad \text{[C]}_n & \text{R}^8 \\
\text{R}^{10} & \quad & \text{R}^7 & \\
\end{align*}
\]

(VIII)

wherein

- n8 is an integer from 0 to 10;
- n9 is an integer from 1 to 10;
- R^9, R^{10}, R^8, R^7 are same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^8, R^{10}, R^8, R^7 are H;
- wherein the −ONO_2 group is linked to

\[
\begin{align*}
\text{[C]}_n & \\
\end{align*}
\]

wherein n9 is as defined above;

- Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur,
- and is selected from the group consisting of

- (Y1)
- (Y2)
- (Y3)
- (Y4)
- (Y5)
- (Y6)
- (Y7)
- (Y8)
- (Y9)
- (Y10)
- (Y11)
- (Y12)
- (Y13)
Another embodiment provides compounds of formula (I) wherein
s is an integer equal to 1 or 2
A is the β-adrenergic blocker residue of formula (II):

![Chemical structure](image)

(II)

wherein

R₁ is (IIlb)

![Chemical structure](image)

(IIlb)

R₂ is (IIla)

![Chemical structure](image)

(IIla)

Z is H or is a group capable of binding Y selected from the group consisting of:
-C(O)-, -C(O)O- or

![Chemical structure](image)

wherein \( R' \) and \( R'' \) are the same or different, and are H or straight or branched \( C₁-C₄ \) alkyl;
Z₁ is H or a -C(O)- capable of binding Y;
with the proviso that when \( s \) of formula (I) is 1, \( Z \) or \( Z₁ \) is H;
preferably when \( s \) of formula (I) is 2, \( Z \) and \( Z₁ \) are -C(O)-;
Y is a bivalent radical having the following meaning:
a) - straight or branched \( C₁-C₂₀ \) alkylene, preferably \( C₁-C₁₀ \) alkylene, more preferably \( C₃-C₆ \) alkylene, being optionally substituted with one or more of the substituents selected from
the group consisting of: halogen atoms, hydroxy, \(-\text{ONO}_2\) or \(T\), wherein \(T\) is \(-\text{OC(O)(C}_1-\text{C}_{10}\text{alkyl})\text{-ONO}_2\), \(-\text{O(C}_1-\text{C}_{10}\text{alkyl})\text{-ONO}_2\);

b)

cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains \(T_1\), wherein \(T_1\) is straight or branched alkyl with from 1 to 10 carbon atoms, \(T_1\) is preferably \(\text{CH}_3\);

c)

\[
\text{(IV)}
\]

wherein:

\(n\) is an integer from 0 to 20, preferably \(n\) is an integer from 0 to 10, more preferably \(n\) is 0 or 1,

\(n_1\) is an integer from 1 to 20, preferably from 1 to 10, more preferably \(n_1\) is 1,

\(n_2, n_3, n_4\) and \(n_5\) are integers equal or different from one another, equal to 0 or 1,

\(R^3\) and \(R^4\) are independently selected from \(\text{H}\) or \(\text{CH}_3\);

\(Y^1\) is \(-\text{CH}_2-\) or \(-\text{(CH}_2\text{)}_m\text{-CH=CH}\) wherein \(m\) is an integer from 0 to 20, preferably \(m\) is equal to 0;

\(X_1\) is \(-\text{WC(O)- or -C(O)W}\), wherein \(W\) is oxygen, sulfur or \(\text{NH}\), preferably \(W\) is oxygen;

d)

\[
\text{(V)}
\]

wherein:

\(n_1\) is an integer from 1 to 20, preferably from 1 to 10;

\(X_1\) is \(-\text{WC(O)- or -C(O)W}\), wherein \(W\) is oxygen, sulfur or \(\text{NH}\), preferably \(W\) is sulfur or \(\text{NH}\);

\(n_6\) is an integer from 1 to 20, preferably from 1 to 5, more preferably \(n_6\) is 1,

\(n_7\) is an integer from 0 to 20, preferably from 0 to 5, more preferably \(n_7\) is 1,

\(R^5\) and \(R^6\), \(R^5\) and \(R^6\) are independently selected from the group consisting of: \(\text{H, CH}_3, \text{OH, NH}_2, \text{NHCOCH}_3, \text{COOH, CH}_2\text{SH and C(CH}_3)_2\text{SH}\).
when the bond between the C^A and C^B carbons is a double bond R^8 and R^{8' or} R^{8''} and R^{8'''} are absent;
with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the –ONO₂ group is linked to a –(CH₂)ₙ₁ group;

5 e) 

\[
\begin{align*}
\text{(VI)} & \quad \text{CH} - (\text{CH}_2)_{n10a} X_2 - [\text{CH} - (\text{CH}_2)_{n10b} X_2]_{n11} - \text{CH} - (\text{CH}_2)_{n12} \\
\end{align*}
\]

\[
\begin{align*}
\text{(VII)} & \quad (\text{CH}_2)_{n10a} \text{CH} - X_2 - [(\text{CH}_2)_{n10b} \text{CH} - X_2]_{n11} - (\text{CH}_2)_{n12} \text{CH} \\
\end{align*}
\]

wherein X_2 is O or S, n10a, n10 and n12 are integer independently selected from 0 to 20, 
n10a is preferably selected from 0 to 10, more preferably n10a is 0 or 1; 
n10 and n12 are preferably selected from 1 to 10, more preferably n10 and n12 are 1 or 2, 
n11 is an integer from 0 to 6, preferably from 0 to 4, more preferably n11 is 0 or 1; 
R^{11} is H, CH₃ or nitroxy group, preferably R^{11} is H or a nitroxy group,

15 R^{11a} is CH₃ or nitroxy group;

f) 

\[
\begin{align*}
\text{[C]_{n8}} & \quad Y^2 \quad [\text{C}]_{n9} \\
\end{align*}
\]

(VIII)

wherein

20 n8 is an integer from 0 to 10; 
n9 is an integer from 1 to 10; 
R^9, R^{10}, R^8, R^7 are same or different, and are H or straight or branched C₁-C₄ alkyl, 
preferably R^9, R^{10}, R^8, R^7 are H;

wherein the –ONO₂ group is linked to

\[
\begin{align*}
[\text{C}]_{n9} \\
\end{align*}
\]

wherein n9 is as defined above;
Y\textsuperscript{2} is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur, and is selected from the group consisting of

\begin{align*}
\text{(Y1)} & \quad \text{(Y2)} & \quad \text{(Y3)} & \quad \text{(Y4)} & \quad \text{(Y5)} \\
\text{(Y6)} & \quad \text{(Y7)} & \quad \text{(Y8)} & \quad \text{(Y9)} & \quad \text{(Y10)} \\
\text{(Y11)} & \quad \text{(Y12)} & \quad \text{(Y13)}
\end{align*}

Preferred compounds are those of formula (I) wherein:

s is 2,
A is a β-adrenergic blocker residues of formula (II) as above defined
Z and Z\textsubscript{1} are \(-(CO)\)-
Y is a bivalent radical having the following meanings:
a) straight C\textsubscript{1}-C\textsubscript{10} alkylene, preferably C\textsubscript{3}-C\textsubscript{6} alkylene;
c)

\begin{align*}
\text{(IV)}
\end{align*}

wherein the -ONO\textsubscript{2} group is bound to \((CH\textsubscript{2})\textsubscript{n1}\);
n, n2, n3, n4, n5 are equal to 0, n1 is 1 and the \(-(CH\textsubscript{2})\textsubscript{n1}\) group is bound to the phenyl ring through the [C]\textsubscript{2} or [C]\textsubscript{3} or [C]\textsubscript{4};
or n, n2, n5 are 1, n3 and n4 are equal to 0, and
n1 is an integer from 1 to 10,
Y is -(CH₂)ₙ₅CH=CH- wherein n₅ is 0, X₁ is -WC(O)- wherein W is oxygen and the
WC(O) group is bound to the phenyl ring through the [C]₆, R⁴ is CH₃ and the (OR⁴) group
is bound to the phenyl ring through the [C]₅;
d)

(V)

wherein
n₁ is an integer from 1 to 10,
n₆ and n₇ are 1,
X₁ is -WC(O)- wherein W is sulfur,
R⁵, R⁶ and R⁶ are H, R⁶ is NHCOCH₃ and
the -ONO₂ is bound to the -(CH₂)ₙ₁ group;
e)

(VI)

wherein
X₂ is O or S, and n₁₁ is 0,
n₁₀a is an integer from 0 to 10,
n₁₂ is an integer from 1 to 10,
R¹¹ is H or a nitrooxy group
and the -ONO₂ group is bound to (CH₂)ₙ₁₂;
Another group of preferred compounds comprises compounds of formula (I)

25

wherein
s is 1,
A is a β-adrenergic blocker residues of formula (II) as above defined,
Z is H,
Z₁ is -(CO)-
30 Y is a bivalent radical having the following meanings:
a) straight C₁-C₁₀ alkylene, preferably C₃-C₆ alkylene;
c) 

\[
\begin{align*}
&\text{(IV)} \\
&\text{wherein the } -\text{ONO}_2 \text{ group is bound to } (\text{CH}_2)_{n1}; \\
&n, n2, n3, n4, n5 \text{ are equal to } 0, n1 \text{ is } 1 \text{ and the } -(\text{CH}_2)_{n1-} \text{ group is bound to the phenyl ring through the } [\text{C}]_2 \text{ or } [\text{C}]_3 \text{ or } [\text{C}]_4; \\
or n, n2, n5 \text{ are } 1, n3 \text{ and } n4 \text{ are equal to } 0, \text{ and } n1 \text{ is an integer from } 1 \text{ to } 10, Y^1 \text{ is } -(\text{CH}_2)_{n1-}\text{CH} = \text{CH}- \text{ wherein } n \text{ is } 0, X_1 \text{ is } -\text{WC(O)}- \text{ wherein } W \text{ is oxygen and the WC(O) group is bound to the phenyl ring through the } [\text{C}]_4, R^4 \text{ is } \text{CH}_3 \text{ and the } (\text{OR}^4) \text{ group is bound to the phenyl ring through the } [\text{C}]_3; \\
d) 
\]

\[
\begin{align*}
&\text{(V)} \\
&\text{wherein} \\
&n1 \text{ is an integer from } 1 \text{ to } 10; \\
&X_1 \text{ is } -\text{WC(O)}- \text{ wherein } W \text{ is sulfur;} \\
n6 \text{ is } 1 \\
n7 \text{ is } 1, \\
R^6, R^6' \text{ and } R^6'' \text{ are } H, R^6 \text{ is, } \text{NHCOCH}_3 \text{ and} \\
&\text{the } -\text{ONO}_2 \text{ is bound to the } -(\text{CH}_2)_{n1-} \text{ group;} \\
e) 
\]

\[
\begin{align*}
&\text{(VI)} \\
&\text{wherein} \\
&X_2 \text{ is } O \text{ or } S, \text{ and } n11 \text{ is } 0, \\
n10a \text{ is an integer from } 0 \text{ to } 10, \\
n12 \text{ is an integer from } 1 \text{ to } 10,
\end{align*}
\]
R is H or a nitrooxy group
and the -ONO₂ group is bound to (CH₂)ₙ₁;

Another group of preferred compounds comprises compounds of formula (I) wherein

5  s is 1,
 A is a β-adrenergic blocker residues of formula (II) as above defined,
 Z₁ is H,
 Z is -(CO)- or -C(O)O- and
 Y is a bivalent radical having the following meanings:
10  c)

wherein the -ONO₂ group is bound to (CH₂)ₙ₁;
n, n₂, n₃, n₄, n₅ are equal to 0,
15  n₁ is 1 and the -(CH₂)ₙ₁- group is bound to the phenyl ring through the [C]₂ or [C]₃ or [C]₄;
or in formula (IV)
n, n₂, n₅ are 1,
n₃ and n₄ are equal to 0,
n₁ is an integer from 1 to 10,
20  Y is -(CH₂)ₙₐ-CH=CH- wherein na is 0, X₆ is -(WCONNECT)(O)- wherein W is oxygen and the
 W(CO) group is bound to the phenyl ring through the [C]₄, R₄ is CH₃ and the (OR₅) group
 is bound to the phenyl ring through the [C]₃;

Another groups of preferred compounds comprises compounds of formula (I) wherein:
 s is 1,
25  A is the β-adrenergic blocker residues of formula (II) wherein
 R₁ is

(IIIb)
R₂ is

\[
\begin{array}{c}
\text{O} - \text{CH₂}^- \\
\text{OMe}
\end{array}
\]

(lIIa)

Z₁ is H and Z is –(CO)- or –C(O)O- and

Y is a bivalent radical having the following meanings:

a) straight C₁-C₁₀ alkylene, preferably C₃-C₆ alkylene;

c) \[
\begin{array}{c}
\text{R}^4 \quad \text{R}^3 \\
\text{R}^1 \quad \text{R}^2 \\
\end{array}
\]

(lV)

wherein the -ONO₂ group is bound to (CH₂)ₙ₁;

n, n₂, n₃, n₄, n₅ are equal to 0, n₁ is 1 and the -(CH₂)ₙ₁- group is bound to the phenyl ring through the [C]₂ or [C]₃ or [C]₄;

or in formula (lV)

n, n₂, n₅ are 1, n₃ and n₄ are equal to 0,

n₁ is an integer from 1 to 10,

Y¹ is –(CH₉)ₙ₄-CH=CH₂- wherein na is 0,

X₁ is –WC(O)- wherein W is oxygen and the WC(O) group is bound to the phenyl ring through the [C]₄, R⁴ is CH₃ and the (OR⁴) group is bound to the phenyl ring through the [C]₅;

d)

\[
\begin{array}{c}
\text{R}^6 \quad \text{R}^5 \\
\text{R}^8 \quad \text{R}^8 \\
\end{array}
\]

(lV)

wherein

n₁ is an integer from 1 to 10,

n₆ and n₇ are 1,

X₁ is –WC(O)- wherein W is sulfur,

R⁶, R⁵ and R⁸ are H, R⁶ is NHCOCH₃ and
the -ONO₂ is bound to the -(CH₂)ₙ₁⁻ group;

e)  

\[
\begin{align*}
\text{CH} & \text{-(CH}_2\text{)}_{n_{10a}}\text{X}_2 \text{-[CH-(CH}_2\text{)}_{n_{10b}}\text{X}_{2n_{11}}\text{CH-(CH}_2\text{)}_{n_{12}} \text{R}_{11}^1
\end{align*}
\]

(VI)

wherein

X₂ is O or S, and n₁ is 0,
n₁₀a is an integer from 0 to 10,
n₁₂ is an integer from 1 to 10,
R¹¹ is H or a nitroxy group

and the -ONO₂ group is bound to (CH₂)ₙ₁₂.

Most preferred compounds of formula (I) according to the present invention are the following:

1. \[
\begin{align*}
\text{ONO}_2 \text{O} & \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO}
\end{align*}
\]

2. \[
\begin{align*}
\text{ONO}_2 \text{O} & \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO}
\end{align*}
\]

3. \[
\begin{align*}
\text{ONO}_2 \text{O} & \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO}
\end{align*}
\]

4. \[
\begin{align*}
\text{ONO}_2 \text{O} & \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO}
\end{align*}
\]

5. \[
\begin{align*}
\text{ONO}_2 \text{O} & \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO}
\end{align*}
\]

6. \[
\begin{align*}
\text{ONO}_2 \text{O} & \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO}
\end{align*}
\]

7. \[
\begin{align*}
\text{ONO}_2 \text{O} & \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO}
\end{align*}
\]

8. \[
\begin{align*}
\text{ONO}_2 \text{O} & \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO}
\end{align*}
\]

9. \[
\begin{align*}
\text{ONO}_2 \text{O} & \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO} \\
\text{ON}_{\text{O}_2} & \text{O} \text{N} \text{MeO} \text{O} \text{O} \text{O} \text{O} \text{MeO}
\end{align*}
\]
Examples of "straight or branched C₃-C₂₀ alkyene" include, but are not limited to, methylene, ethylene, propylene, isopropylene, n-butylene, pentylene, n-hexylene and the like.

As stated above, the invention includes also the pharmaceutically acceptable salts of the compounds of formula (I) and stereoisomers thereof.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, triethylamine, dibenzylamine, piperidine and other acceptable organic amines.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in an organic solvent such as acetonitrile, tetrahydrofuran with the corresponding organic or inorganic acids.

Examples of pharmaceutical acceptable organic acids are: oxalic, tartaric, maleic, succinic, citric acids. Examples of pharmaceutical acceptable inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids. Salts with nitric acid are preferred.

The compounds of the invention which have one or more asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures.

Within the object of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

The compounds and compositions of the present invention can be administered by any available and effective delivery system including but not limited to, orally, buccally, parenterally, by inhalation spray, by topical application, by injection, transdermally, or rectally (e.g. by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Parenteral includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion technique.

Solid dosage forms for oral administration can include for example capsule, tablets, pills, powders, granules and gel. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage form can also comprise, as normal practice, additional substance other than inert diluent, e.g., lubricating agent such as magnesium stearate.

Injectable preparations, for example sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents.
The composition of this invention can further include conventional excipients, i.e., pharmaceutical acceptable organic or inorganic substances which do not deleteriously react with the active compounds.

The doses of β-adrenergic blockers nitrooxyderivatives can be determined by standard clinique technique and are in the same ranges or less than as described for commercially available compounds as reported in the: Physician’s Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 58th Ed., 2004; The pharmacological basis of therapeutics, Goodman and Gilman, J. G. Hardman, L. e. Limbird, 20th Ed.

EXPERIMENTAL

Synthesis procedure

Compounds of the invention can be synthesized as shown in Schemes 1 to 6. Compounds of general formula (I) A-(Y-ONO₂)s, defined in Scheme 1-3 as compounds of formula D, wherein s is 1, Y is as above defined and A is a β-adrenergic blocker residue of formula (II), wherein Z is –C(O)- and Z₁ is H, the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof, can be prepared as outlined in Schemes 1-3.

Scheme 1

![Chemical diagram]

Compounds of formula (I) wherein R₁, R₂, Z and Y are as above defined, P₁ is an amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) and X₃ is an halogen atom.
preferably Cl, Br and I, are converted to compounds of formula (L) wherein R₁, R₂, P₁, Z
and Y are as above defined, by reaction with AgNO₃ in a suitable organic solvent such as
acetanilide, tetrahydrofuran, a silver nitrate molar excess is preferably used and the
reaction is carried out, in the dark, at a temperature from room temperature to the boiling
temperature of the solvent. The compounds of formula (L) are converted to the
compounds of formula (D) by deprotecting the amine group (strong acid, such as HCl in
dioxane or trifluoroacetic acid, is used to remove a t-butyl carbamate). Other preferred
methods for removing the amine protecting groups are those described in T. W. Greene

The compounds of formula (H) wherein R₁, R₂, Z, P₁ and Y are as above defined, are
converted to the esters of formula (I) wherein R₁, R₂, Y, Z, X₃ and P₁ are as above defined,
by reaction with an appropriate acid (Q1) of formula X₃-Y-COOH wherein Y and X₃ are as
above defined. The reaction is generally carried out in an inert organic solvent such as
N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated
aliphatic hydrocarbon at a temperature from 0°C to 50°C in presence of a dehydrating
agent such as dicyclohexylcarbodiimide DCC or 1-ethyl-3-(3-dimethylaminopropyl)
carboamidimide hydrochloride (EDAC HCl) with a catalyst, such as 4-N,N-
dimethylaminopyridine (DMAP).

The compounds of formula (H) wherein R₁, R₂ and P₁ are as above defined, can be
obtained by deprotecting the hydroxyl group of the compounds of formula (G) wherein
R₁, R₂ are as above defined and P is a hydroxylic protecting group such as silyl ethers,
such as trimethylsilyl or tert-butyl-dimethylsilyl and those described in T. W. Greene
"Protective groups in organic synthesis", Harvard University Press, 1980. Fluoride ion is
the preferred method for removing silyl ether protecting group.

The compounds of formula (G) wherein R₁, R₂, P and P₁ are as above defined, can be
obtained by reacting the compounds of formula (F) wherein R₁, R₂ and P are as above
defined with a suitable amine protecting group (P₁) as above described.

The alcohol group of the compounds of formula (A) wherein R₁, R₂ are as above defined,
is protected to afford the compounds of formula (F) wherein R₁, R₂ are as above defined
Preferred protecting group for the alcohol moiety are silyl ethers, such as trimethylsilyl or
tert-butyl-dimethylsilyl.
The compounds (A) wherein R₁, R₂ are as above defined are commercially available, the
acids of formula X₃-Y-COOH wherein X₃ is as above defined, are commercially available.

Scheme 2
Compounds of formula (B) wherein \( R_1, R_2, Z, Y \) are as above defined and \( X_3 \) is an halogen atom, such as Cl, Br and I, are converted to compounds of formula (D) wherein \( R_1, R_2, Z \) and \( Y \) are as above defined, by reaction with \( \text{AgNO}_3 \) in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

The compounds of formula (B) wherein \( R_1, R_2, Z, Y \) and \( X_3 \) are as above defined can be obtained by reaction of the compounds of formula (A) with an appropriate acyl chloride (Q) of formula \( X_3\text{-Y-C(O)Cl} \), wherein \( X_3 \) is chosen among chlorine, bromine, and \( Y \) is as above defined. The esterification is carried out in an inert organic solvent such as \( N,N'\text{-dimethylformamide, tetrahydrofuran, benzene, toluene, chloroform} \) in presence of a base as triethylamine, pyridine at a temperature from room temperature and 50°C. The reaction is completed within a time range from 30 minutes to 24 hours.

Alternatively the compounds of formula (B) can be obtained by reaction of compounds of formula (A) with an acid (Q1) of formula \( X_3\text{-Y-C(O)OH} \) in the presence of a dehydrating agent as \( \text{dicyclohexylcarbodiimide (DCC)} \) or \( N'\text{-\{3-dimethylaminopropyl\}-N-ethylcarbodiimide hydrochloride (EDAC)} \) and a catalyst, such as \( N,N\text{-dimethylaminopyridine} \). The reaction is carried out in an inert organic solvent such as \( N,N'\text{-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon} \) at a temperature from 0°C and 50°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (Q1), where \( X_3 \) is an halogen atom are commercially available or can be obtained from the corresponding commercially available hydroxy acid by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of \( \text{P}^{III} \) or \( \text{P}^{V} \) in solvents inert such as toluene, chloroform, DMF, etc.

The compounds (A) wherein \( R_1, R_2 \) are as above defined are commercially available

**Scheme 3**
Alternatively the compounds of formula (D) can be obtained as described below. The compounds of formula are converted to the compounds (D) by reaction of hydroxy group with a nitrooxy derivative, containing activated acylating group, of formula Cl(O)C-Y-ONO₂.

The nitrooxy compounds can be obtained from the corresponding alcohols of formula Cl(O)C-Y-OH by reaction with nitric acid and acetic anhydride in a temperature range from −50°C to 0°C or from the corresponding halogen derivatives of formula Cl(O)C-Y-Hal by reaction with silver nitrate in the presence of an inert solvent such as acetonitrile, tetrahydrofurane. A silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, a temperature from the boiling temperature and room temperature. The reaction is completed within a time range from 30 minutes to 3 days.

The compounds of general formula (I) A-(Y-ONO₂)s, defined in Scheme 4 as compounds of formula (D1), wherein s is 1, Y is as above defined and A is a β-adrenergic blocker residue of formula (II), wherein Z is -C(O)O- and Z₁ is H, the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof, can be prepared as outlined in Scheme 4.

**Scheme 4**

The compounds of formula (B1) wherein R₁, R₂, Y are as above defined and X₃ is a halogen atom, such as Cl, Br and I, are converted to compounds of formula (D1) wherein R₁, R₂, and Y are as above defined, by reaction with AgNO₃ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.
The compounds of formula (A) wherein \(R_1\) and \(R_2\) are as above defined are converted to the compounds (B1) by reaction with an appropriate compound (Q2) having formula \(X_3\)-Y-OC(O)Cl wherein \(X_3\) is Cl, Br or I, and Y is as defined above. The reaction is generally carried out in presence of a base in an aprotic polar or non-polar solvent such as THF or CH\(_2\)Cl\(_2\) at temperature range between 0°-65°C or in a double phase system H\(_2\)O/Et\(_2\)O at temperature range between 20°-40°C.

The compounds of formula (Q2) are commercially available or can be obtained from the corresponding alcohols by reaction with triphosgene in presence of an organic base.

The compounds of general formula (I) A-(Y-ONO\(_2\))\(_s\), defined in Scheme 5 as compounds of formula (D), wherein \(s\) is 1, Y is as above defined and A is a \(\beta\)-adrenergic blocker residue of formula (II), wherein Z is H or straight or branched C\(_1\)-C\(_4\) alkyl and Z\(_{1}\) is H, the enantiomers, diastereoisomer and a pharmaceutically acceptable salts thereof, may be prepared as outlined in Scheme 5:

**Scheme 5**

\[
\begin{align*}
\text{(H)} & \quad \xrightarrow{\text{R}} \quad \text{(M)} & \quad \xrightarrow{\text{R}} \quad \text{(L)} \\
\text{(D)}
\end{align*}
\]

The compounds of formula (I) wherein \(R_1\), \(R_2\), Z and Y are as above defined, \(P_1\) is an amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) and \(X_3\) is an halogen atom such as Cl, Br and I, are converted to compounds of formula (L) wherein \(R_1\), \(R_2\), \(P_1\), Z and Y are as above defined, by reaction with AgNO\(_3\) in a suitable organic solvent such as acetonitrile, tetrahydrofuran, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent. The compounds of formula (L) are converted to the compounds of formula (D) by deprotecting the amine group (strong acid, such as HCl in
dioxane or trifluoroacetic acid, is used to remove a t-butyl carbamate). Other preferred methods for removing the amine protecting groups are those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980.

The compounds of formula (i) wherein \( R_1, R_2, Y, X_3, Z \) and \( P \) are as above defined, can be obtained by reacting the compounds of formula (M) wherein \( R_1, R_2, P, R', R'' \) and \( X_3 \) are as above defined, with an acid (Q1) of formula \( X_3-Y-COOH \) wherein \( X_3 \) is an halogen atom and \( Y \) is as above defined. The reaction is carried out in an inert organic solvent such as \( N,N' \)-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature range from 0°C to 50°C in the presence of a dehydrating agent such as dicyclohexylcarbodiimide DCC or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC HCl) with a catalyst, such as 4-N,N,N-dimethylaminopyridine (DMAP).

The reaction is complete within a time ranges from 30 minutes to 24 hours.

The compounds of formula (M) wherein \( R_1, R_2, P, R', R'' \) and \( X_3 \) are as above defined, can be obtained by reacting the compounds of formula (H) with a compound (S) of formula \( X_3-C(R')(R'')-O\left(OC\right)X_3 \) wherein \( X_3 \) is an halogen atom. The reaction is carried out in presence of an organic or inorganic base in a polar solvent as DMF, THF, acetonitrile at a temperature in the range from -5°C to 60°C or in a double phase system according to methods well known in the literature.

The amine group of the compounds (A) is protected to afford the compounds of formula (H) wherein \( P \) is a suitable amine protecting group such as tert-butyloxycarbonyl ester (t-Boc). The compounds (S) are commercially available.

The compounds of general formula (I) \( A-(Y-ONO_2), \) defined in Scheme 6 as compounds of formula (E), wherein \( s \) is 2, \( Y \) is as above defined and \( A \) is a \( \beta \)-adrenergic blocker residue of formula (II), wherein \( Z_1 \) and \( Z \) are \(-C(O),\) the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof, can be synthesized as shown in Scheme 6.

**Scheme 6**

![Scheme 6](image)

Compounds of formula (C) wherein \( R_1, R_2, Z, Z_1 \) and \( Y \) are as above defined and \( X_3 \) is an halogen atom, such as CI, Br and I, are converted to compounds of formula (E) wherein
R₁, R₂, Z and Y are as above defined, by reaction with AgNO₃ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

The compounds of formula (C) wherein R₁, R₂, Z, Z₁, Y and X₃ are as above defined can be obtained by reaction of the compounds of formula (A) with an appropriate acyl halide (Q) of formula X₃-Y-C(O)Cl, wherein X₃ is chosen among chlorine, bromine, and Y is as above defined. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, chloroform in presence of a base as triethylamine, pyridine at a temperature from room temperature and 50°C. The reaction is completed within a time range from 30 minutes to 24 hours.

Alternatively the compounds of formula (C) can be obtained by reaction of the compounds of formula (A) with an acid (Q₁) of formula X₃-Y-COOH in the presence of a dehydrating agent such as dicyclohexylcarbodiimide (DCC) or N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDAC) and a catalytic amount of N,N-dimethylamino pyridine. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from 0°C and 50°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (Q₁), where X₃ is an halogen atom are commercially available or can be obtained from the corresponding commercially available hydroxy acid by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P³⁺ or P⁵⁻ in solvents inert such as toluene, chloroform, DMF, etc.

The compounds (A) wherein R₁, R₂ are as above defined are commercially available.

The compounds of formula (E) can also be obtained as described below. The compounds of formula A are converted to the compounds (E) by reaction with a nitrooxy derivative of formula Cl(O)C-Y-ONO₂ containing an activated acylating group. The nitrooxycompounds can be obtained from the corresponding alcohols of formula Cl(O)C-Y-OH by reaction with nitric acid and acetic anhydride in a temperature range from -50°C to 0°C or from the corresponding halogen derivatives of formula Cl(O)C-Y-Hal by reaction with silver nitrate in the presence of an inert solvent such as acetonitrile, tetrahydrofurane. A silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, a temperature from the boiling temperature and room temperature. The reaction is completed within a time range from 30 minutes to 3 days.

Examples
The following non-limiting examples further describe and enable one of ordinary skilled in the art to make and use the present invention.

Example 1

4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxo)ethyl] amino]-2-propanoate of formula (8).

![Chemical Structure](image)

**1a.** 4-(Chloromethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxo)ethyl] amino]-2-propanoate

To a solution of carvedilol (2g, 5mmol) in chloroform (50ml) 4-chloromethyl benzoic acid (0.9g, 5.5mmol), EDAC (1.15g, 6mmol) and N,N-dimethylaminoprydine (catalytic amount) were added. The reaction was stirred at room temperature for 24 hours. The solution was treated with water and the organic layer was dried over sodium sulphate. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 6/4 (Rf=0.2). The title product 0.27g was obtained as a white powder.

**1b.** 4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxo) ethyl] amino]-2-propanoate

A solution of the product of Example 1a (0.27g, 0.48mmol) and silver nitrate (0.16g, 0.96mmol) in acetonitrile (30ml) was stirred at 60°C, in the dark, for 36 hours. The precipitated (silver salts) was filtered off and the solvent was evaporated under vacuum. The residue was treated with chloroform and water. The organic layer was dried over sodium sulphate. The solvent was evaporated and the residue was purified by flash chromatography eluting with ethyl acetate/n-hexane 6/4. The title product 0.03g was obtained as a white powder.

^1H-NMR (DMSO) δ (ppm): 11.31 (1H,s); 8.15 (2H,m); 7.8-7.5 (2H,m); 7.43 (1H,d); 7.30 (2H,m); 7.15-6.85 (7H,m); 6.77 (1Hd); 6.03 (1H,m); 5.65 (2H,s); 4.55 (2H,m); 4.33 (2H,m); 4.0-3.7 (5H,m); 3.51 (2H,m).

Example 2
4-(Nitrooxymethyl)benzoic acid 1- (9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][ (4-nitrooxymethyl)benzoyl] amino]-2-propanoate of formula (11).

(11)

2a. 4-(Chloromethyl)benzoic acid 1- (9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][ (4-chloromethyl)benzoyl] amino]-2-propanoate

To a solution of carvedilol (2g, 5mmol) in chloroform (50ml) 4-chloromethyl benzoic acid (0.9g, 5.5mmol), EDAC (1.15g, 6mmol) and N,N-dimethylaminopyridine (catalytic amount) were added. The reaction was stirred for 24 hours at room temperature. The solution was treated with water and the organic layer was dried over sodium sulfate and filtered. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 1/1 (Rf=0.42). The title product (0.06g) was obtained as a white powder.

2b. 4-(Nitrooxymethyl)benzoic acid 1- (9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][ (4-nitrooxymethyl)benzoyl] amino]-2-propanoate

A solution of the product of example 2a (0.06g, 0.08mmol) and silver nitrate (0.06g, 0.32mmol) in acetonitrile (20ml) was stirred at 60°C, in the dark, for 36 hours. The precipitated (silver salts) was removed by filtration. The filtrate was concentrated and the residue was treated with chloroform and water. The combined organic layer extracts were dried over sodium sulfate and filtered. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 6/4. The title product 0.015g was obtained as a powder.

$^1$H-NMR (DMSO) δ (ppm): 1.24(1H,s); 8.1 (3H,m); 7.7-7.2 (8H,m); 7.2-6.7 (8H,m); 6.05 (1H,m); 5.6-5.8 (4H,d); 4.55 (1H,m); 4.30 (2H,m); 4.15 (3H,m); 3.71 (5H,s).

Example 3
1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][ (4-nitrooxymethyl)benzoyl] amino]-2-propanol of formula (15)
3a. 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][[(4-chloromethyl)benzoyl]amino]-2-propanol

To a solution of carvedilol (2g, 5mmol) in chloroform (50ml) 4-chloromethyl benzoic acid (0.9g, 5.5mmol), EDAC (1.15g, 6mmol) and N,N-dimethylaminopyridine (catalytic amount) were added. The reaction was stirred for 24 hours at room temperature. The solution was treated with water and the organic layer was dried over sodium sulfate and filtered. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 6/4 (Rf=0.42). The title product 1.05g was obtained as a white powder.

3b. 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][[(4-nitrooxymethyl)benzoyl]amino]-2-propanol

A solution of the product of example 3a (1.0g, 1.78mmol) and silver nitrate (0.6g, 3.6 mmol) in acetonitrile (100ml) was stirred at 65°C, in the dark, for 32 hours. The precipitated (silver salts) was removed by filtration. The filtrate was concentrated and the residue was treated with methylene chloride and water. The combined organic layer extracts were dried over sodium sulphate. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 1/1. The title product 0.4g was obtained as yellow powder.

$^1$H-NMR (DMSO) δ (ppm): 11.24 (1H, s); 8.40-6.50 (15H, m); 5.61 (2H, m); 5.51 (1H, m); 5.36 (1H, m); 4.40-3.90 (4H, m); 3.74-3.71 (7H, m).

Example 4

25 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][[(3-nitrooxypropanoyl)amino]-2-propanol of formula (112)
The compound was synthesized under the analogous procedure described in example 3 starting from carvedilol and 3-bromopropanoic acid.

$^1$H-NMR (DMSO) $\delta$ (ppm): 11.24 (1H, s); 8.25 (1H, dd); 7.46 (1H, dd); 7.29 (2H, m); 7.08 (2H, m); 6.90 (4H, m); 6.70 (1H, dd); 5.50 (1H, d); 4.80 (2H, m); 4.35 (1H, m); 4.20-3.6 (9H, m); 3.6-2.8 (4H, m).

Example 5

1-(9H-carbazol-4-yloxy)-3-[(2-(2-methoxyphenoxy)ethyl][6-nitrooxyhexanoyl]amino]-2-propanol of formula (113)

The compound was synthesized under the analogous procedure described in example 3 starting from carvedilol and 6-bromohexanoic acid.

$^1$H-NMR (DMSO) $\delta$ (ppm): 11.24 (1H, s); 8.25 (1H, dd); 7.46 (1H, dd); 7.29 (2H, m); 7.08 (2H, m); 6.90 (4H, m); 6.70 (1H, dd); 5.40 (1H, d); 4.50 -3.50 (13H, m); 2.6-2.3 (2H, m); 1.70-0.50 (6H, m).

Example 6

6-(nitrooxy)hexanoic acid 1-(9H-carbazol-4-yloxy)-3-[(2-(2-methoxyphenoxy) ethyl][6-nitrooxyhexanoyl] amino]-2-propanol of formula (111)
The compound was synthesized under the analogous procedure described in example 2 starting from carvedilol and 6-bromohexanoic acid.

$^1$H-NMR (DMSO) $\delta$ (ppm): 11.24 (1H, s); 8.15 (1H, dd); 7.46 (1H, dd); 7.29 (2H, m); 7.08 (2H, m); 6.90 (4H, m); 6.70 (1H, dd); 5.65 (1H, m); 4.6-4.20 (6H, m); 4.2-3.5 (9H, m); 2.50 (2H, m); 2.29 (2H, m); 1.70-0.60 (12H, m).

Example 7

6-(nitrooxy)hexanoic acid 1-(9H-carbazol-4-yl)oxy)-3-[[2-(methoxyphenoxy) ethyl]amino]-2-propanol hydrochloride of formula (110)

The compound was synthesized under the analogous procedure described in example 1 starting from carvedilol and 6-bromohexanoic acid.

$^1$H-NMR (DMSO) $\delta$ (ppm): 11.30(1H, s); 8.15 (1H, dd); 7.44 (1H, dd); 7.32 (2H, m); 7.10-6.90 (6H, m); 6.70 (1H, dd); 5.65 (1H, m); 4.50-4.20 (7H, m); 3.90-3.40 (7H, m); 2.40 (2H, m); 1.60-1.10 (6H, m).

Example 8

Measurements of cGMP in rat PC12 cell line.
cGMP contributes to the function and interaction of several vascular cell types and its dysfunction is involved in major cardiovascular diseases such as hypertension, diabetic complications, atherosclerosis, and tissue infarction. Therefore the extent of cGMP formation elicited by the compounds of the inventions was evaluated in the rat pheochromocytoma (PC12) cell line.

**Tested compounds**

1) Carvedilol (parent drug)
2) 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl] amino]-2-propanol (compound of example 3);
3) 4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl] amino]-2-propanoate (compound of example 1);
4) 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(3-nitrooxypropanoyl)amino]-2-propanol (compound of example 4);
5) 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(6-nitrooxhexanoyl)amino]-2-propanol (compound of example 5).

**Method**

Cells were maintained at 37°C in DMEM medium enriched with 10% horse serum and 5% foetal bovine serum under 5% CO₂ atmosphere. At the time of experiments the cells were washed once with Hank’s Balanced Salt Solution (HBSS) supplemented with 0.05% ascorbic acid and preincubated in the same buffer for 10 min in a floating water bath. After the preincubation step, cells were exposed for additional 45 min to either control conditions or increasing concentrations of test compounds ranging from 0.1 to 25 μM, in the presence of the phosphodiesterase inhibitor, IBMX (100 μM) and the NO-independent activator of soluble guanylyl cyclase, YC-1 (20 μM). The reaction was terminated by the removal of the incubating buffer and consecutive addition of 100 μl of absolute ethanol. The organic extracts were then evaporated to dryness and the residues dissolved in aqueous buffer for quantitative determination of intracellular cGMP levels using the cGMP enzyme immunoassay kit.

The obtained results reported in Table 1 are expressed as EC₅₀ (μM) and efficacy Emax (% of vehicle). As shown in the table the nitroderivatives of carvedilol induced a consistent increase of intracellular cGMP formation in PC12 cell line. Conversely, this effect was not induced by the parent compound.

<p>| Table 1: Effects of the nitroxyderivatives of carvedilol and the carvedilol on cGMP accumulation in PC12 cells |</p>
<table>
<thead>
<tr>
<th>Compound</th>
<th>EC$_{50}$ (μM)</th>
<th>E$_{max}$ (% of vehicle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>Not effective</td>
<td>Not effective</td>
</tr>
<tr>
<td>Compound of example 3</td>
<td>1.8</td>
<td>565</td>
</tr>
<tr>
<td>Compound of example 1</td>
<td>2.3</td>
<td>480</td>
</tr>
<tr>
<td>Compound of example 4</td>
<td>1.7</td>
<td>395</td>
</tr>
<tr>
<td>Compound of example 5</td>
<td>0.6</td>
<td>322</td>
</tr>
</tbody>
</table>
1. A compound of general formula A-(Y-ONO₂)s (I) and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof, wherein 

s is an integer equal to 1 or 2;

A is selected from the following β-adrenergic blockers residues of formula (II):

wherein

R₁ is selected from the group consisting of:
$R_2$ is selected from the group consisting of: $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$ or

[(IIIa)]

[(IIIb)]

when the radical $R_1$ has chosen from the formulae (IIa), (IIc), (IIId), (IIIg), (IIIh), (IIIi), (IIIm), $R_2$ is $-\text{CH}(\text{CH}_3)_2$;

when the radical $R_1$ has chosen from the formulae (IIe), (IIIf) or (IIIn), $R_2$ is $-\text{C}(\text{CH}_3)_3$;

when $R_1$ is the radical (IIb), $R_2$ is (IIIa);

when $R_1$ is the radical (III), $R_2$ is (IIIb);

$Z$ is $\text{H}$ or is a group capable of binding $Y$ selected from the group consisting of:

$-\text{C}(\text{O})$-, $-\text{C}(\text{O})\text{O}$- or

$\begin{array}{c}
\text{O} \\
\text{R'} \\
\text{R''} \\
\text{O}
\end{array}$

wherein $R'$ and $R''$ are the same or different, and are $\text{H}$ or straight or branched $C_1$-$C_4$ alkyl;

$Z_1$ is $\text{H}$ or a $-\text{C}(\text{O})$- group capable of binding $Y$;

with the proviso that when $s$ of formula (I) is 1, $Z$ or $Z_1$ is $\text{H}$;

$Y$ is a bivalent radical having the following meaning:
a) straight or branched C₁-C₂₀ alkylene being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, -ONO₂ or T, wherein T is -OC(O)(C₁-C₁₀alkyl)-ONO₂, -O(C₁-C₁₀alkyl)-ONO₂;

b) cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T₁, wherein T₁ is straight or branched alkyl with from 1 to 10 carbon atoms;

c)

\[
\begin{array}{c}
\text{(IV)} \\
\end{array}
\]

wherein:
n is an integer from 0 to 20,
n₁ is an integer from 1 to 20;
n₂, n₃, n₄ and n₅ are integers equal or different from each other, equal to 0 or 1,

R³ and R⁴ are independently selected from H or CH₃,

Y¹ is -CH₂- or -(CH₂)ₙ₋₁CH=CH- wherein n is an integer from 0 to 20;

X₁ is -WC(O)- or -C(O)W-, wherein W is oxygen, sulfur or NH;

d)

\[
\begin{array}{c}
\text{(V)} \\
\end{array}
\]

wherein:
n₁, n₁ is an integer from 1 to 20

X₁ is -WC(O)- or -C(O)W-, wherein W is oxygen, sulfur or NH;
n₆ is an integer from 1 to 20,
n₇ is an integer from 0 to 20,

R⁶, R⁶', R⁷, R⁷' and R⁸ are independently selected from the group consisting of: H, CH₃, OH, NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;
when the bond between the C^a and C^b carbons is a double bond R^5 and R^6 or R^6 and R^5 are absent;
when Y is selected from the bivalent radicals mentioned under c)-d), the –ONO₂ group is linked to the –(CH₂)_{n₁} group;

\[ \text{(VI)} \]

\[ \text{(VII)} \]

wherein
X₂ is O or S,
n₁₀a, n₁₀ and n₁₂ are integer independently selected from 0 to 20,
n₁₁ is an integer from 0 to 6;
R^{1₁} is H, CH₃ or nitrooxy group;
R^{1₁}a is CH₃ or nitrooxy group;

\[ \text{(VIII)} \]

wherein:
n₈ is an integer from 0 to 10;
n₉ is an integer from 1 to 10;
R^9, R^{1₀}, R^8, R^7 are the same or different, and are H or straight or branched C₁-C₄ alkyl;
wherein the –ONO₂ group is linked to

\[ \text{[C]}_{n₉} \]

wherein n₉ is as defined above;
Y² is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur,
and is selected from the group consisting of:

(Y1)   (Y2)   (Y3)   (Y4)   (Y5)

(Y6)   (Y7)   (Y8)   (Y9)   (Y10)

(Y11)   (Y12)   (Y13)

2. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 1 wherein s is 2 and Z and Z₁ are -C(O)-.

3. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 2 wherein Y is a straight or branched C₁-C₂₀ alkylene being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, -ONO₂ or T, wherein T is -OC(O)(C₁-C₁₀ alkyl)-ONO₂, -O(C₁-C₁₀ alkyl)-ONO₂.

4. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 3 wherein Y is a straight or branched C₁-C₁₀ alkylene.

5. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 2 wherein Y is
wherein
n is an integer from 0 to 20,
n1 is an integer from 1 to 20;
n2, n3, n4 and n5 are integers equal or different from each other, equal to 0 or 1;
R³ and R⁴ are independently selected from H or CH₃;
Y¹ is –CH₂– or –(CH₂)ₙ₄–CH=CH– wherein n₄ is an integer from 0 to 20;
X₁ is –WC(O)– or –C(O)W– wherein W is oxygen, sulfur or NH.

6. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 5 wherein
n₂, n₃, n₄, n₅ are equal to 0,
n₁ is 1,
n is an integer from 0 to 10,
Y¹ is CH₂.

7. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 5 wherein
n, n₂, n₅ are 1,
n₃ and n₄ are equal to 0, and
n₁ is an integer from 1 to 10,
Y¹ is –(CH₂)ₙ₄–CH=CH– wherein n₄ is 0,
X₁ is –WC(O)– wherein W is oxygen and X₁ is bound to the phenyl ring through the [C]₄,
R⁴ is CH₃ and the group (OR⁴) is bound to the phenyl ring through the [C]₃.

8. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 2 wherein
Y is

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9. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 8 wherein

\[ Y = \text{(structure VI)} \]

wherein

- \( X_2 \) is O or S,
- \( n_{10a}, n_{10} \) and \( n_{12} \) are integers independently selected from 0 to 20,
- \( n_{11} \) is an integer from 0 to 6,
- \( R^{11} \) is H, CH₃ or a nitrooxy group,
- \( R^{11a} \) is CH₃ or a nitrooxy group.

10. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 2 wherein

\[ Y = \text{(structure V)} \]

wherein:

- \( X_2 \) is O or S,
- \( n_5 \) is an integer from 0 to 10,
- \( n_{11} \) are 0,
- \( n_{12} \) is an integer from 1 to 10,
- \( R^{11} \) is H or a nitrooxy group;
- wherein the \(-\text{ONO}_2\) group is bound to the \(-(\text{CH}_2)_{n_{12}}\) group.
n1 is an integer from 1 to 20;
X₁ is \(-\text{WC(O)}\) or a \(-\text{C(O)W}\), wherein W is oxygen, sulfur or NH.
n6 is an integer from 1 to 20,
n7 is an integer from 0 to 20,
R⁵, R⁶, R⁷ and R⁸ are independently selected from the group consisting of: H, CH₃, 
OH, NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;
when the bond between the C⁴ and C⁵ carbons is a double bond R⁶ and R⁷ or R⁸ and 
R⁹ are absent.

11. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable 
salts thereof according to claim 10 wherein
n1 is an integer from 1 to 10,
n6 and n7 are 1;
X₁ is \(-\text{WC(O)}\) wherein W is sulfur;
R⁵, R⁶ and R⁷ are H,
R⁸ is NHCOCH₃,
with the proviso that the \(-\text{ONO}_₂\) group is bound to the \(-(\text{CH}_2)_{n1}\) group.

12. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable 
salts thereof according to claim 1 wherein
s is equal to 1
A is selected from the following β-adrenergic blockers residues of formula (II):

\[
\begin{align*}
\text{(II)}
\end{align*}
\]

wherein
R₁ is selected from the group consisting of:

\[
\text{(IIa)}
\]

\[
\text{(IIc)}
\]
R₂ is selected from the group consisting of: -CH(CH₃)₂, -C(CH₃)₃ or
when the radical $R_1$ has chosen from the formulae (IIa), (IIc), (IId), (IIg), (IIh), (III), (IIm), $R_2$ is $\text{-CH(CH}_3\text{)}_2$;

when the radical $R_1$ has chosen from the formulae (Ile), (IIf) or (IIln), $R_2$ is $\text{-C(CH}_3\text{)}_3$;

when $R_1$ is the radical (III), $R_2$ is (IIIb);

$Z$ is a group capable of binding $Y$ selected from the group consisting of:

$\text{-C(O)}-$, $\text{-C(O)O-}$ or

$\text{O} \quad \text{R''} \quad \text{R'} \quad \text{O}$

wherein $R'$ and $R''$ are the same or different, and are H or straight or branched $\text{C}_1$-$\text{C}_4$ alkyl;

$Z_1$ is H and

$Y$ is a bivalent radical having the following meanings:

c)

$$
\text{--(Y')}_n \quad \text{(COOH)}_{n4} \quad \text{(X)}_{n5} \quad \text{(CH}_2\text{)}_{n1} \\
\text{(OR)}_{n3} \quad \text{(OR')}_n2
$$

wherein:

15 $n$ is an integer from 0 to 20,

$n_1$ is an integer from 1 to 20;

$n_2$, $n_3$, $n_4$ and $n_5$ are integers equal or different from each other, equal to 0 or 1,

$R^3$ and $R^4$ are independently selected from H or $\text{CH}_3$, $\text{Y'}$ is $\text{-CH}_2$-$\text{or}$ $\text{-C(H}_2\text{)}_{na}$-$\text{CH=CH}$. wherein $na$ is an integer from 0 to 20;

20 $X_1$ is $\text{-WC(O)-}$ or $\text{-C(O)W-}$, wherein W is oxygen, sulfur or NH;

e)

$$
\text{--CH--(CH}_2\text{)}_{n10a} \text{X}_2 \quad \text{[CH--(CH}_2\text{)}_{n10} \text{X}_2 \quad \text{n11} \quad \text{CH--(CH}_2\text{)}_{n12} \\
\text{R}^{11} \quad \text{R}^{11} \quad \text{R}^{11}
$$

$$
\text{--(CH}_2\text{)}_{n10a} \text{CH--X}_2 \quad \text{[CH--(CH}_2\text{)}_{n10} \text{CH--X}_2 \quad \text{n11} \quad \text{(CH}_2\text{)}_{n12} \text{CH} \\
\text{R}^{11a} \quad \text{R}^{11a} \quad \text{R}^{11a}
$$

wherein

25 $X_2$ is O or S,
n10a is 0 or 1,
n11 is 0 or 1,
n10 and n12 is 1 or 2,
R°° is H, CH₃ or nitrooxy group;
5  R°°a is CH₃ or nitrooxy group;
f)

\[
\begin{align*}
\text{[C]}_{n\text{g}} \quad & \quad Y^2 \quad & \quad \text{[C]}_{n\text{g}} \\
R^{10} \quad & \quad & \quad R^7 \\
\end{align*}
\]

(VIII)

wherein:
10  n8 is an integer from 0 to 10;
n9 is an integer from 1 to 10;
R⁹, R¹⁰, R⁸, R⁷ are the same or different, and are H or straight or branched C₁-C₄ alkyl;
wherein the –ONO₂ group is linked to

\[
\begin{align*}
\text{[C]}_{n\text{g}} \\
\end{align*}
\]

wherein n9 is as defined above;
Y² is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing
one or more heteroatoms selected from nitrogen, oxygen, sulfur,
and is selected from the group consisting of:

\[
\begin{align*}
\text{(Y1)} & \quad \text{(Y2)} & \quad \text{(Y3)} & \quad \text{(Y4)} & \quad \text{(Y5)} \\
\text{(Y6)} & \quad \text{(Y7)} & \quad \text{(Y8)} & \quad \text{(Y9)} & \quad \text{(Y10)}
\end{align*}
\]
13. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 12 wherein Z is –C(O)–.

14. A compound and enantiomers and diastereoisomers and pharmaceutically acceptable salts thereof according to claims 12 and 13 wherein

\[
\begin{align*}
\text{Y} &= \text{(COOH)}_{n4} \\
&\quad \text{–(X)}_{n5} \text{–(CH)}_{n1} \\
&\quad \text{(OR)}_{n2} \\
&\quad \text{(OR)}_{n3} \\
&\quad \text{–(Y)}_{n} \\
\end{align*}
\]

wherein

\[
\begin{align*}
n &\text{ is an integer from 0 to 20, and } n1 \text{ is an integer from 1 to 20;}
\end{align*}
\]

n2, n3, n4 and n5 are integers equal or different from one another, equal to 0 or 1;

\[
\begin{align*}
R^3 \text{ and } R^4 &\text{ are independently selected from H or CH}_3; \\
Y^1 &\text{ is –CH}_2– \text{ or } –(\text{CH}_2)_{nA}–\text{CH}=\text{CH}– \text{ wherein } nA \text{ is an integer from 0 to 20;}
\end{align*}
\]

X1 is –WC(O)– or –C(O)W–, wherein W is oxygen, sulfur or NH.

15. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 14 wherein

\[
\begin{align*}
n &\text{ is an integer from 0 to 10,}
\end{align*}
\]

16. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 14 wherein

\[
\begin{align*}
n, n2, n5 &\text{ are 1,} \\
n3 \text{ and } n4 &\text{ are equal to 0,}
\end{align*}
\]

\[
\begin{align*}
n &\text{ is an integer from 0 to 10,}
\end{align*}
\]

Y1 is CH2.
n1 is an integer from 1 to 10,
$Y^1$ is $-(CH_2)_{na}-CH=CH-$ wherein na is 0,
$X_1$ is $-WC(O)-$ wherein W is oxygen and $X_1$ is bound to the phenyl ring through the $[C]_4$,
$R^4$ is CH$_3$ and the (OR$^4$) group is bound to the phenyl ring through the $[C]_3$.

17. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 12 and 13 wherein
$Y$ is
$$
\begin{array}{c}
\text{CH} \quad (CH_2)_{n10a} \quad \text{X}_2 \quad [CH \quad (CH_2)_{n10} \quad \text{X}_2_{n11} \quad \text{CH} \quad (CH_2)_{n12} ]
\end{array}
$$

(VI)

wherein
$X_2$ is O or S,
n10a and n11 are 0,
n12 is 1,
$R^{11}$ is H;
wherein the $-\text{ONO}_2$ group is bound to the $-(CH_2)_{n12}$ group.

18. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 12 wherein Z is $-\text{C(O)}\text{O}-$.

19. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 12 and 18 wherein
$Y$ is
$$
\begin{array}{c}
\text{(COOH)}_{n4} \\
\text{(Y)}_n \\
\text{(OR$^3$)}_{n3} \\
\text{(OR$^4$)}_{n2} \\
\text{(CH$_2$)$_{n1}$} \\
\text{(X$_1$)$_{n5}$} \\
\end{array}
$$

(IV)

wherein
n is an integer from 0 to 20, and n1 is an integer from 1 to 20;
n2, n3, n4 and n5 are integers equal or different from one another, equal to 0 or 1;
$R^3$ and $R^4$ are independently selected from H or CH$_3$;
$Y^1$ is $-\text{CH}_2-$ or $-(CH_2)_{na}-CH=CH-$ wherein na is an integer from 0 to 20;
X is \(-\text{WC(O)}-\) or \(-\text{C(O)W}-\), wherein W is oxygen, sulfur or NH.

20. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 19 wherein

\[ n_2, n_3, n_4, n_5 \text{ are equal to } 0, \]
\[ n_1 \text{ is } 1, \]
\[ n \text{ is an integer from } 0 \text{ to } 10, \]
\[ \text{Y}^1 \text{ is CH}_2. \]

21. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 12 and 18 wherein

\[ \text{Y} \text{ is} \]

\[
\begin{array}{c}
\text{CH}-(\text{CH}_2)_{n_{10a}}X_2\text{CH}-(\text{CH}_2)_{n_{10}}X_{2n_{11}}\text{CH}-(\text{CH}_2)_{n_{12}}
\end{array}
\]

\[ R^{11} \]

(VI)

\[ \text{wherein} \]
\[ X_2 \text{ is O or S}, \]
\[ n_{10a} \text{ and } n_{11} \text{ are } 0, \]
\[ n_{12} \text{ is } 1, \]
\[ R^{11} \text{ is H}; \]
\[ \text{wherein the } -\text{ONO}_2 \text{ group is bound to the } -\text{(CH}_2)_{n_{12}}^\text{group}. \]

22. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 12 wherein \( Z \) is

\[
\begin{array}{c}
\text{O} \quad \text{O}
\end{array}
\]

\[ R'' \quad R' \]

25

23. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 12 and 22 wherein

\[ \text{Y} \text{ is} \]

\[
\begin{array}{c}
\text{COOH}_{n_4} \quad \text{(CH}_2)_{n_1}
\end{array}
\]

\[ (X_{1n}) \quad (\text{OR})_{n_2} \]

\[ (\text{OR})_{n_3} \]

\[ (\text{Y}^1)_n \]
wherein
n is an integer from 0 to 20,
n1 is an integer from 1 to 20;
n2, n3, n4 and n5 are equal to 0;
Y is $-\text{CH}_2$;

24. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 23 wherein n is 0 and n1 is 1.

25. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 12 and 22 wherein
Y is

\[
\text{R}^{11} \quad \text{R}^{11} \quad \text{R}^{11}
\]

wherein
X2 is O or S,
n10a and n11 are 0,
n12 is 1,
R11 is H;
wherein the $-\text{ONO}_2$ group is bound to the $-(\text{CH}_2)_n\text{CH}_2$ group.

26. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 1 wherein s is 1, Z is H and Z1 are $-\text{C}(\text{O})$.

27. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 26 wherein
Y is a straight or branched C1-C20 alkylene being optionally substituted with one or more of the substituents selected from the group consisting of halogen atoms, hydroxy, $-\text{ONO}_2$ or T, wherein T is $-\text{OC}(\text{O})(\text{C}_1\text{C}_{10}\text{alkyl})\text{-ONO}_2$, $-\text{O}(\text{C}_1\text{C}_{10}\text{alkyl})\text{-ONO}_2$.

28. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 27 wherein Y is a straight or branched C1-C10 alkylene.
29. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 26 wherein
\[ Y \text{ is } \]

\[
\begin{align*}
\text{I (IV)} \\
\text{wherein }
\end{align*}
\]

\[ n \text{ is an integer from 0 to 20,} \\
n1 \text{ is an integer from 1 to 20;} \\
n2, n3, n4 \text{ and } n5 \text{ are integers equal or different from each other, equal to 0 or 1;} \\
R^2 \text{ and } R^4 \text{ are independently selected from } H \text{ or } CH_3; \\
Y' \text{ is } -CH_2- \text{ or } -(CH_2)_{na}CH=CH- \text{ wherein } na \text{ is an integer from 0 to 20; } \\
X_1 \text{ is } -W(C(O)- or } -C(O)W-, \text{ wherein } W \text{ is oxygen, sulfur or NH.}
\]

30. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 29 wherein
\[ n2, n3, n4, n5 \text{ are equal to 0,} \\
n1 \text{ is 1,} \\
n \text{ is an integer from 0 to 10,} \\
Y' \text{ is } CH_2.
\]

31. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 29 wherein
\[ n, n2, n5 \text{ are 1,} \\
n3 \text{ and } n4 \text{ are equal to 0,} \\
n1 \text{ is an integer from 1 to 10,} \\
Y' \text{ is } -(CH_2)_{na}CH=CH- \text{ wherein } na \text{ is 0,} \\
X_1 \text{ is } -W(C(O)- \text{ wherein } W \text{ is oxygen and } X_1 \text{ is bound to the phenyl ring through the } [C]_4; \\
R^4 \text{ is } CH_3 \text{ and the group } (OR^4) \text{ is bound to the phenyl ring through the } [C]_3.
\]

32. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 26 wherein
\[ \]
Y is

\[
\begin{align*}
&\text{(VI)} \\
&\text{(VII)}
\end{align*}
\]

wherein

X₂ is O or S,
n₁₀a, n₁₀ and n₁₂ are integers independently selected from 0 to 20;
n₁₁ is an integer from 0 to 6;
R¹¹ is H, CH₃ or a nitrooxy group;
R¹¹a is CH₃ or a nitrooxy group.

33. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 32 wherein

Y is

\[
\begin{align*}
&\text{(VI)}
\end{align*}
\]

wherein

X₂ is O or S,
n₁₀a is 0 or 1,
n₁₁ is 0 or 1,
n₁₀ and n₁₂ are 1 or 2,
R¹¹ is H or nitrooxy;
wherein the –ONO₂ group is bound to the –(CH₂)ₙ₁₂ group.

34. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 26 wherein

Y is
wherein:

n1 is an integer from 1 to 20;

X₁ is -WC(O)- or a -C(O)W-, wherein W is oxygen, sulfur or NH.

n6 is an integer from 1 to 20,
n7 is an integer from 0 to 20,
R₅ and R⁵, R⁶ and R⁶' are independently selected from the group consisting of: H, CH₃, OH, NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;

when the bond between the C⁴ and C⁸ carbons is a double bond R⁵ and R⁶ or R⁵' and R⁶' are absent.

35. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 34 wherein

n1 is an integer from 1 to 10,
n6 and n7 are 1;
X₁ is -WC(O)- wherein W is sulfur;
R⁵, R⁵' and R⁶' are H,
R⁸ is NHCOCH₃;

with the proviso that the -ONO₂ group is bound to the -(CH₂)ₙ₁-.

36. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 1 wherein
s is an integer equal to 1 or 2;

A is the β-adrenergic blocker residue of formula (II):

wherein

R₁ is
R₂ is

(Z is H or is a group capable of binding Y selected from the group consisting of:
- \(-\text{C(O)}\cdot\), \(-\text{C(O)O}\cdot\) or
- \(\begin{array}{c}
\text{O} \\
\text{R'} \quad \text{O} \\
\text{R''}
\end{array}\)

wherein \(\text{R'}\) and \(\text{R''}\) are the same or different, and are \(\text{H}\) or straight or branched \(\text{C}_1-\text{C}_4\) alkyl;
\(Z₁\) is \(\text{H}\) or a \(-\text{C(O)}\cdot\) group capable of binding \(Y\);
with the proviso that when \(s\) of formula (I) is 1, \(Z\) or \(Z₁\) is \(\text{H}\);
\(Y\) is a bivalent radical having the following meaning:
a)
- straight or branched \(\text{C}_1-\text{C}_{20}\) alkylene being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, \(-\text{ONO}_2\) or \(T\), wherein \(T\) is \(-\text{OC(O)(C}_1-\text{C}_{10}\text{alkyl)}-\text{ONO}_2\), \(-\text{O(C}_1-\text{C}_{10}\text{alkyl)}-\text{ONO}_2\);
b)
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains \(T₁\), wherein \(T₁\) is straight or branched alkyl with from 1 to 10 carbon atoms;
c)
wherein:
n is an integer from 0 to 20,
n1 is an integer from 1 to 20;
n2, n3, n4 and n5 are integers equal or different from each other, equal to 0 or 1,
5
R³ and R⁴ are independently selected from H or CH₃,
Y¹ is –CH₂– or –(CH₂)ₙa–CH=CH– wherein na is an integer from 0 to 20;
X₁ is –WC(O)– or –C(O)W–, wherein W is oxygen, sulfur or NH;
d)

\[
\begin{align*}
  & \text{R}^{5} \quad \text{R}^{6} \\
  & \text{C}^{A}_{\text{n6}} \quad \text{C}^{B}_{\text{n7}} \quad \text{X}_{1} \quad \text{R}^{5'} \\
  & \text{R}^{6'} \quad \text{R}^{6} \\
\end{align*}
\]

wherein:
n1, n1 is an integer from 1 to 20
X₁ is –WC(O)– or –C(O)W–, wherein W is oxygen, sulfur or NH;
n6 is an integer from 1 to 20,
15
n7 is an integer from 0 to 20,
R₆, R₅, R₆ and R₅ are independently selected from the group consisting of: H, CH₃, OH, NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;
when the bond between the C⁴ and C⁵ carbons is a double bond R⁵ and R₆ or R₆ and R₅ are absent;
when Y is selected from the bivalent radicals mentioned under c)-d), the –ONO₂ group is linked to the –(CH₂)ₙ1– group;
e)

\[
\begin{align*}
  & \text{CH} – \text{-(CH₂)ₙₐ₁} \text{X₂} – \text{[CH} – \text{(CH₂)ₙ₁ₐ} \text{X₁₂} – \text{CH} – \text{(CH₂)ₙ₁₂} \text{]} \\
  & \text{R}^{11} \quad \text{R}^{11} \quad \text{R}^{11} \\
\end{align*}
\]

\[
\begin{align*}
  & \text{-(CH₂)ₙ₁ₐ} \text{CH} – \text{X₁₂} – \text{[CH} – \text{(CH₂)ₙ₁₀} \text{CH} – \text{X₂₁₁} – \text{(CH₂)ₙ₁₂} \text{CH} – \text{]} \\
  & \text{R}^{11a} \quad \text{R}^{11a} \quad \text{R}^{11a} \\
\end{align*}
\]

wherein

X₂ is O or S,
n₁₀ₐ, n₁₀ and n₁₂ are integer independently selected from 0 to 20,
n11 is an integer from 0 to 6;
R^{11} is H, CH₃ or nitrooxy group;
R^{11a} is CH₃ or nitrooxy group;
f)

\[
\begin{array}{c}
\text{[C]}_{n8} \quad Y^2 \quad \text{[C]}_{n9} \\
\text{R}^{10} \quad \text{R}^7
\end{array}
\]

(VIII)

wherein:
n8 is an integer from 0 to 10;
n9 is an integer from 1 to 10;
R^8, R^{10}, R^8, R^7 are the same or different, and are H or straight or branched C₁-C₄ alkyl;
wherein the –ONO₂ group is linked to

\[
\text{[C]}_{n9}
\]

wherein n9 is as defined above;
Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing
one or more heteroatoms selected from nitrogen, oxygen, sulfur,
and is selected from the group consisting of:

\[
\begin{array}{cccc}
\text{(Y1)} & \text{(Y2)} & \text{(Y3)} & \text{(Y4)} \\
\text{(Y5)} & \text{(Y6)} & \text{(Y7)} & \text{(Y8)} \\
\text{(Y9)} & \text{(Y10)} & & 
\end{array}
\]
37. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim and 36 wherein s is 2 and Z and Z₁ are –C(O)-.

38. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 37 wherein
Y is a straight or branched C₁₋₂₀ alkylene being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, –ONO₂ or T, wherein T is –OC(O)(C₁₋₁₀alkyl)-ONO₂, –O(C₁₋₁₀alkyl)-ONO₂.

39. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 38 wherein Y is a straight or branched C₃₋₈ alkylene.

40. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 37 wherein
Y is

\[ \text{(IV)} \]

wherein
n is an integer from 0 to 20;
n₁ is an integer from 1 to 20;
n₂, n₃, n₄ and n₅ are integers equal or different from each other, equal to 0 or 1;
R³ and R⁴ are independently selected from H or CH₃;
Y' is –CH₂– or –(CH₂)ₙₐ–CH=CH– wherein nₐ is an integer from 0 to 20;
Xₗ is –WC(O)– or –C(O)W–, wherein W is oxygen, sulfur or NH.
41. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 40 wherein
n2, n3, n4, n5 are equal to 0,
n1 is 1,
n is an integer from 0 to 10,
Y² is CH₂.

42. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 40 wherein
n, n2, n5 are 1,
n3 and n4 are equal to 0, and
n1 is an integer from 1 to 10,
Y¹ is –(CH₂)na=CH=CH- wherein na is 0,
X₁ is –WC(O)- wherein W is oxygen and X₁ is bound to the phenyl ring through the
[C]₄,
R¹ is CH₃ and the group (OR⁴) is bound to the phenyl ring through the [C]₃.

43. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 37 wherein
Y is

(VI)

(VII)

wherein
X₂ is O or S,
n₁₀ₐ, n₁₀ and n₁₂ are integers independently selected from 0 to 20;
n₁₁ is an integer from 0 to 6;
R¹¹ is H, CH₃ or a nitrooxy group;
R¹¹a is CH₃ or a nitrooxy group.
44. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 43 wherein

\[
Y = \begin{array}{c}
\text{CH} \quad \text{(CH}_2\text{)}_{n10a} \quad X_2 \quad \text{[CH} \quad \text{(CH}_2\text{)}_{n16} \quad X_2 \quad \text{CH} \quad \text{(CH}_2\text{)}_{n12} \\
R^{11} \quad R^{11} \quad R^{11}
\end{array}
\]

(VI)

wherein

\[X_2 \text{ is O or S},\]
\[n_{10a} \text{ is an integer from 0 to 10},\]
\[n_{11} \text{ are 0},\]
\[n_{12} \text{ is an integer from 1 to 10},\]
\[R^{11} \text{ is H or a nitrooxy group};\]

wherein the \(-\text{ONO}_2\) group is bound to the \(-\text{(CH}_2\text{)}_{n12}\) group.

45. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 37 wherein

\[
Y = \begin{array}{c}
\text{(C}^A\text{)}_{n6} \quad \text{(C}^B\text{)}_{n7} \quad \text{(X}_i\text{)} \quad \text{(CH}_2\text{)}_{n1} \\
R^S \quad R^S \quad R^S \quad R^S \quad R^S \quad R^S
\end{array}
\]

(V)

wherein:

\[n_{1} \text{ is an integer from 1 to 20};\]
\[X_i \text{ is } -\text{WC(O)}- \text{ or a } -\text{C(O)}\text{W}-, \text{ wherein W is oxygen, sulfur or NH.}\]
\[n_{6} \text{ is an integer from 1 to 20},\]
\[n_{7} \text{ is an integer from 0 to 20},\]
\[R^S, R^{S'}, R^S \text{ and } R^{S'} \text{ are independently selected from the group consisting of: } H, \text{CH}_3, \text{OH, NH}_2, \text{NCOCH}_3, \text{COOH, CH}_2\text{SH and C(CH}_3\text{)}_2\text{SH};\]

when the bond between the \(C^A\) and \(C^B\) carbons is a double bond \(R^S\) and \(R^{S'}\) are absent.

46. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 45 wherein

\[n_{1} \text{ is an integer from 1 to 10},\]
n6 and n7 are 1;
X₁ is –WC(O)– wherein W is sulfur;
R₅, R⁶ and R⁷ are H,
R₈ is NHCOCH₃;
with the proviso that the –ONO₂ group is bound to the –(CH₂)ₙ₁– group.

47. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 36 wherein s is 1, Z is H and Z₁ is –C(O)-.

48. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 47 wherein
Y is a straight or branched C₁-C₂₀ alkylene being optionally substituted with one or more of the substituents selected from the group consisting of halogen atoms, hydroxy, –ONO₂ or T, wherein T is –OC(O)(C₁-C₁₀alkyl)-ONO₂, –O(C₁-C₁₀alkyl)-ONO₂.

49. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 48 wherein Y is a straight or branched C₁-C₁₀ alkylene.

50. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 47 wherein
Y is

\[ \text{(IV)} \]

\begin{align*}
\text{wherein}
\text{n is an integer from 0 to 20,}
\text{n₁ is an integer from 1 to 20;}
\text{n₂, n₃, n₄ and n₅ are integers equal or different from each other, equal to 0 or 1;}
\text{R₃ and R₄ are independently selected from H or CH₃;}
\text{Y₁ is –CH₂- or –(CH₂)ₙₐ-CH=CH- wherein nₐ is an integer from 0 to 20;}
\text{X₁ is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH.}
\end{align*}
51. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 50 wherein
n2, n3, n4, n5 are equal to 0,
n1 is 1,
n is an integer from 0 to 10,
Y' is CH₂.

52. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 50 wherein
n, n2, n5 are 1, n3 and n4 are equal to 0,
n1 is an integer from 1 to 10,
Y' is -(CH₂)ₙα-CH=CH- wherein na is 0,
X₁ is -W(C=O)- wherein W is oxygen and X₁ is bound to the phenyl ring through the [C]₂,
R₄ is CH₃ and the group (OR₄) is bound to the phenyl ring through the [C]₃.

53. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 47 wherein
Y is

\[\text{CH}-(\text{CH}_2)_{n10a}\text{X}_2-[\text{CH}-(\text{CH}_2)_{n10}\text{X}_2\text{R}_{111}]-\text{CH}-(\text{CH}_2)_{n12} \]

\[\text{R}^{11} \quad \text{R}^{11} \quad \text{R}^{11} \]

(VI)

\[\text{(CH}_2)_{n10a}\text{CH}-\text{X}_2-[\text{(CH}_2)_{n10}\text{CH}-\text{X}_2\text{R}_{11a}]-\text{(CH}_2)_{n12}\text{CH}^{-} \]

\[\text{R}^{11a} \quad \text{R}^{11a} \quad \text{R}^{11a} \]

(VII)

wherein
X₂ is O or S,
n₁₀a, n₁₀ and n₁₂ are integers independently selected from 0 to 20;
n₁₁ is an integer from 0 to 6;
R₁₁ is H, CH₃ or a nitrooxy group;
R₁₁a is CH₃ or a nitrooxy group.

54. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 53 wherein
Y is

\[
\text{--CH--(CH}_2\text{)}_{n_{10a}}\text{X}_2\text{--}[\text{--CH--(CH}_2\text{)}_{n_{10}}\text{X}_2\text{]}_{n_{11}}\text{CH--(CH}_2\text{)}_{n_{12}}
\]

\[R^{11}\quad R^{11}\quad R^{11}\]

(VI)

wherein

5

\(X_2\) is O or S,
\(n_{10a}\) and \(n_{11}\) are 0,
\(n_{12}\) is 1,
\(R^{11}\) is H;

wherein the \(-\text{ONO}_2\) group is bound to the \(-(\text{CH}_2)_{n_{12}}\) group.

10

55. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 47 wherein

Y is

\[
\text{\text{--\left(\text{C}^A\right)}_{n_6}\text{--\left(\text{C}^B\right)}_{n_7}\text{--\left(X_1\right)}\text{--(CH}_2\text{)}_{n_1}}
\]

\[R^6\quad R^5\quad R^6\quad R^5\]

(V)

wherein:

n_1 is an integer from 1 to 20;
\(X_1\) is \(-\text{WC(O)}\)- or a \(-\text{C(O)}\text{W}\)-, wherein W is oxygen, sulfur or NH.
n_6 is an integer from 1 to 20,
n_7 is an integer from 0 to 20,
\(R^5\) and \(R^6\), \(R^6\) and \(R^9\) are independently selected from the group consisting of: H, \(\text{CH}_3\), \(\text{OH}\), \(\text{NH}_2\), \(\text{NHCOCH}_3\), \(\text{COOH}\), \(\text{CH}_2\text{SH}\) and \(\text{C(\text{CH}_3)_2\text{SH}}\);

when the bond between the \(\text{C}^A\) and \(\text{C}^B\) carbons is a double bond \(R^5\) and \(R^6\) or \(R^6\) and \(R^9\) are absent.

25

56. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 55 wherein

n_1 is an integer from 1 to 10,
n_6 and n_7 are 1;

30

\(X_1\) is \(-\text{WC(O)}\)- wherein W is sulfur;
\(R^5\), \(R^5\) and \(R^9\) are H,
R⁵ is NHCOCH₃;  
with the proviso that the –ONO₂ group is bound to the –(CH₂)ₙ₁–.

57. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 36 wherein s is 1, Z₁ is H and Z = –C(O)–.

58. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 57 wherein  
Y is a straight or branched C₁₋C₂₀ alkylene being optionally substituted with one or more of the substituents selected from the group consisting of halogen atoms, hydroxy, –ONO₂ or T, wherein T is –OC(O)(C₁₋C₁₀alkyl)-ONO₂, –O(C₁₋C₁₀alkyl)-ONO₂.

59. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 58 wherein Y is a straight or branched C₃₋C₆ alkylene.

60. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 57 wherein  
Y is

```
      5
     /\
    /  \
   /    \
  6-----4
     |  |
     |  |
     |  |
  (COOH)ₙ₄

        3
       /\
      /  \
     /    \
    2-----3
         |
         |
         |
  (OR³)ₙ₃
```

(IV)

wherein  
n₃ is an integer from 0 to 20,  
n₁ is an integer from 1 to 20;  
n₂, n₃, n₄ and n₅ are integers equal or different from each other, equal to 0 or 1;  
R³ and R⁴ are independently selected from H or CH₃;  
Y¹ is –CH₂– or –(CH₂)ₙ₄–CH=CH– wherein n₄ is an integer from 0 to 20;  
X₁ is –WC(O)– or –C(O)W–, wherein W is oxygen, sulfur or NH.

61. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 60 wherein  
n₂, n₃, n₄, n₅ are equal to 0,  
n₁ is 1,
n is an integer from 0 to 10,
Y¹ is CH₂.

62. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable
salts thereof according to claim 60 wherein
n, n₂, n₅ are 1, n₃ and n₄ are equal to 0,
n₁ is an integer from 1 to 10,
Y¹ is –(CH₂)n₄–CH=CH– wherein n₄ is 0,
X₁ is –W(C)O– wherein W is oxygen and X₁ is bound to the phenyl ring through the
[Cl]₄,
R² is CH₃ and the group (OR⁴) is bound to the phenyl ring through the [Cl]₃.

63. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable
salts thereof according to claim 57 wherein
Y is

\[
\begin{align*}
\text{(VII)} & \\
\text{(VI)} & \\
\end{align*}
\]

wherein
X₂ is O or S,
n₁₀a, n₁₀ and n₁₂ are integers independently selected from 0 to 20;
n₁₁ is an integer from 0 to 6;
R¹¹ is H, CH₃ or a nitrooxy group;
R¹¹a is CH₃ or a nitrooxy group.

64. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable
salts thereof according to claim 63 wherein
Y is

\[
\begin{align*}
\text{(VI)} & \\
\text{(VII)} & \\
\end{align*}
\]
wherein
X₂ is O or S,
n₁₀a and n₁₁ are 0,
n₁₂ is 1,
R⁽¹¹⁾ is H;
wherein the –ONO₂ group is bound to the -(CH₂)ₙ₁₂- group.

65. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable
salts thereof according to claim 57 wherein
Y is
\[
\begin{align*}
&\text{R}^6 \\
&\text{C}^A_{n₈} \\
&\text{C}^B_{n₇}(X₁) \\
&\text{R}^6' \\
&\text{R}^5 \\
&\text{C}^A_{n₈} \\
&\text{C}^B_{n₇}(X₁) \\
&\text{R}^6' \\
&\text{R}^5'
\end{align*}
\]

(V)

wherein:
n₁ is an integer from 1 to 20;
X₁ is –WC(O)- or a –C(O)W-, wherein W is oxygen, sulfur or NH.
n₈ is an integer from 1 to 20,
n₇ is an integer from 0 to 20,
R₅ and R₅', R₅ and R₅' are independently selected from the group consisting of: H, CH₃, OH, NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;
when the bond between the C⁴ and C⁷ carbons is a double bond R₅ and R₅' or R₆ and R₆' are absent.

66. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable
salts thereof according to claim 65 wherein
n₁ is an integer from 1 to 10,
n₈ and n₇ are 1;
X₁ is –WC(O)- wherein W is sulfur;
R₅, R₅' and R₅' are H,
R₈ is NHCOCH₃;
with the proviso that the –ONO₂ group is bound to the -(CH₂)ₙ₁₂-.
67. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 36 wherein s is 1, Z₁ is H and Z = C(=O)O–.

68. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 67 wherein

Y is a straight or branched C₁₋C₂₀ alkylene being optionally substituted with one or more of the substituents selected from the group consisting of halogen atoms, hydroxy, –ONO₂ or T, wherein T is –OC(O)(C₁₋C₁₀alkyl)-ONO₂, –O(C₁₋C₁₀alkyl)-ONO₂.

69. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 68 wherein Y is a straight or branched C₃₋C₆ alkylene.

70. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 67 wherein

Y is

[Diagram: Structure (IV)]

wherein

n is an integer from 0 to 20,
n₁ is an integer from 1 to 20;
n₂, n₃, n₄ and n₅ are integers equal or different from each other, equal to 0 or 1;
R³ and R⁴ are independently selected from H or CH₃;
Y¹ is –CH₂– or –(CH₂)ₙa–CH=CH– wherein na is an integer from 0 to 20;
X₁ is –WC(O)– or –C(O)W–, wherein W is oxygen, sulfur or NH.

71. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 70 wherein

n₂, n₃, n₄, n₅ are equal to 0,
n₁ is 1,
n is an integer from 0 to 10,
Y¹ is CH₂.
72. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 70 wherein
n, n2, n5 are 1, n3 and n4 are equal to 0,
n1 is an integer from 1 to 10,
Y is \(-\text{(CH}_2\text{)}_{\text{n}a}\text{-CH=CH-}\) wherein na is 0,
X1 is \(-\text{WC(O)-}\) wherein W is oxygen and X1 is bound to the phenyl ring through the [C]4,
R4 is CH3 and the group (OR4) is bound to the phenyl ring through the [C]3.

73. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 67 wherein
Y is
\[\begin{array}{c}
\text{CH} - (\text{CH}_2\text{)}_{\text{n}10a}\text{X}_2 - [\text{CH} - (\text{CH}_2\text{)}_{\text{n}10}\text{X}_2\text{n}11\text{CH} - (\text{CH}_2\text{)}_{\text{n}12}] \\
\text{R}^{11} \quad \text{R}^{11} \quad \text{R}^{11}
\end{array}\]

(VI)
\[\begin{array}{c}
(\text{CH}_2\text{)}_{\text{n}10a}\text{CH}\text{X}_2 - [(\text{CH}_2\text{)}_{\text{n}10}\text{CH}\text{X}_2\text{n}11(\text{CH}_2\text{)}_{\text{n}12}\text{CH} \text{R}^{11a}\text{R}^{11a}\text{R}^{11a}
\end{array}\]

(VII)

wherein
X2 is O or S,
n10a, n10 and n12 are integers independently selected from 0 to 20;
n11 is an integer from 0 to 6;
R11 is H, CH3 or a nitrooxy group;
R11a is CH3 or a nitrooxy group.

74. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 73 wherein
Y is
\[\begin{array}{c}
\text{CH} - (\text{CH}_2\text{)}_{\text{n}10a}\text{X}_2 - [\text{CH} - (\text{CH}_2\text{)}_{\text{n}10}\text{X}_2\text{n}11\text{CH} - (\text{CH}_2\text{)}_{\text{n}12}] \\
\text{R}^{11} \quad \text{R}^{11} \quad \text{R}^{11}
\end{array}\]

(VI)

wherein
X2 is O or S,
n10a is 0 or 1,
n11 is 0 or 1,
n12 is 1 or 2,
R\textsuperscript{11} is H;

wherein the –ONO\textsubscript{2} group is bound to the –\text{(CH\textsubscript{2})\textsubscript{n12}– group.

75. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 67 wherein

\[ R^6 \quad \text{C}^A \quad \text{C}^B \quad (X_1) \quad \text{CH}_2 \quad \text{R}^5 \]

\[ \text{R}^{\prime 6} \quad \text{R}^{\prime 5} \]

\[ (V) \]

wherein:
n1 is an integer from 1 to 20;
X\textsubscript{1} is –WC(O)– or a –C(O)W–, wherein W is oxygen, sulfur or NH.
n6 is an integer from 1 to 20,
n7 is an integer from 0 to 20,
R\textsuperscript{6} and R\textsuperscript{6} \textsuperscript{′} R\textsuperscript{6} \textsuperscript{′} and R\textsuperscript{6} \textsuperscript{′} \textsuperscript{′} are independently selected from the group consisting of: H, CH\textsubscript{3}, OH, NH\textsubscript{2}, NHCOCH\textsubscript{3}, COOH, CH\textsubscript{2}SH and C(CH\textsubscript{3})\textsubscript{2}SH;
when the bond between the C\textsuperscript{A} and C\textsuperscript{B} carbons is a double bond R\textsuperscript{5} and R\textsuperscript{5} \textsuperscript{′} or R\textsuperscript{5} \textsuperscript{′} \textsuperscript{′} and
R\textsuperscript{5} \textsuperscript{′} \textsuperscript{′} \textsuperscript{′} are absent.

76. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 75 wherein

n1 is an integer from 1 to 10,
n6 and n7 are 1;
X\textsubscript{1} is –WC(O)– wherein W is sulfur;
R\textsuperscript{5} \textsuperscript{′}, R\textsuperscript{5} \textsuperscript{′} \textsuperscript{′} and R\textsuperscript{5} \textsuperscript{′} \textsuperscript{′} \textsuperscript{′} are H,
R\textsuperscript{5} \textsuperscript{′} is NHCOCH\textsubscript{3};
with the proviso that the –ONO\textsubscript{2} group is bound to the –\text{(CH\textsubscript{2})\textsubscript{n1}– group.

77. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 36 wherein s is 1, Z\textsubscript{i} is H and Z is
78. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 77 wherein

\[ Y = \text{特定的结构式} \]

wherein

- \( n \) is an integer from 0 to 20,
- \( n_1 \) is an integer from 1 to 20;
- \( n_2, n_3, n_4 \) and \( n_5 \) are equal to 0;
- \( Y^1 \) is \(-\text{CH}_2\,-\).

79. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 78 wherein \( n = 0 \) and \( n_1 = 1 \).

80. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 77 wherein

\[ Y = \text{特定的结构式} \]

wherein

- \( X_2 \) is O or S,
- \( n_{10a} \) and \( n_{11} \) are 0,
- \( n_{12} \) is 1,
- \( R^{11} \) is H;

wherein the \(-\text{ONO}_2\) group is bound to the \(-(\text{CH}_2)_{n_{12}}\) group.
81. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to any of claims 36 and 57 to 67 wherein the compounds are:

82. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to any of claims 12 to 17 wherein the compounds are:
83. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to any of claims 36 and 67 to 76 wherein the compounds are:

(21) \[ \text{Structure} \]

(22) \[ \text{Structure} \]

(23) \[ \text{Structure} \]

(24) \[ \text{Structure} \]

(25) \[ \text{Structure} \]

84. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to any of claims 36 to 46 wherein the compounds are:

(2) \[ \text{Structure} \]

(5) \[ \text{Structure} \]

(10) \[ \text{Structure} \]

(26) \[ \text{Structure} \]
85. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to any of claims 2 to 11 wherein the compounds are:

(33)
86. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to any of claims 36 and 47 to 55 wherein the compounds are:
87. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to any of claims 26 to 35 wherein the compounds are:
88. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts according to claims 36 and 47, that is 4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yl)oxy)-3-[[2-(2-methoxyphenoxy) ethyl]amino]-2-propanoate.

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89. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts according to claims 36 and 57, that is 4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxyl)-2-(2-methoxyphenoxo)ethyl][6-nitrooxymethyl]benzoyl]amino-2-propanoate.

90. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts according to claims 36 and 47, that is 1-(9H-carbazol-4-yloxyl)-3-(2-methoxyphenoxo)ethyl][6-nitrooxymethyl]benzoyl] amino-2-propanol.

91. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts according to claims 36 and 47, that is 6-(Nitrooxy)hexanoic acid 1-(9H-carbazol-4-yloxyl)-3-(2-methoxyphenoxo)ethyl][6-nitrooxyhexanoyl]amino-2-propanol hydrochloride.

92. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts according to claims 36 and 47, that is 6-(Nitrooxy)hexanoic acid 1-(9H-carbazol-4-yloxyl)-3-(2-methoxyphenoxo)ethyl][6-nitrooxyhexanoyl] amino-2-propanol.

93. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts according to claims 36 and 47, that is 1-(9H-carbazol-4-yloxyl)-3-(2-methoxyphenoxo)ethyl][6-nitrooxyhexanoyl]amino-2-propanol.

94. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts according to claims 36 and 47, that is 1-(9H-carbazol-4-yloxyl)-3-(2-methoxyphenoxo)ethyl][3-nitrooxypropanoyl]amino-2-propanol.

95. A compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof as defined in any of claims 1 to 94 for use as medicament.

96. Use of a compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof as defined in any of claims 1 to 94 for preparing a drug that can be employed in the treatment or prophylaxis of hypertension, cardiovascular and vascular diseases.

97. Use of a compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof as defined in any of claims 1 to 94 for
preparing a drug that can be employed in the treatment of glaucoma and elevated intraocular pressure.

98. A pharmaceutical composition comprising a compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof as defined in any of claims 1 to 94 and at least pharmaceutical acceptable carrier.
**INTERNATIONAL SEARCH REPORT**

A. CLASSIFICATION OF SUBJECT MATTER

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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)

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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, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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Date of the actual completion of the international search

17 March 2005

Date of mailing of the international search report

31/03/2005

Name and mailing address of the ISA

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Cortés, J

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