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(54) Title: CAPTOPRIL DERIVATIVES

(57) Abstract: Captopril nitroderivatives having improved pharmacological activity and enhanced tolerability are described. They can be employed for the treatment or prophylaxis of cardiovascular, inflammatory and renal diseases.



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"CAPTOPRIL DERIVATIVES"

The present invention relates to new captopril derivatives,
5 pharmaceutical compositions containing them and their use
for the treatment of cardiovascular, inflammatory, renal
diseases and ocular hypertension.

Captopril (1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline)
is the first ACE (Angiotensin Converting Enzyme) inhibitor
10 to be marketed. It is the only ACE inhibitor approved for
use in the United States that contains a sulfhydryl moiety.
ACE inhibitors are antihypertensive drugs that act as
vasodilators and reduce peripheral resistance. They inhibit
angiotensin converting enzyme (ACE), which is involved in
15 the conversion of angiotensin I to angiotensin II.
Angiotensin II stimulates the synthesis and secretion of
aldosterone and raises blood pressure via a potent direct
vasoconstrictor effect. ACE is identical to bradykininase
(kininase II) an enzyme that inactivates bradykinin and ACE
20 inhibitors may reduce the degradation of bradykinin, a
potent vasodilator.

Captopril is used in the management of hypertension, in
heart failure, following myocardial infarction and in
diabetic nephropathy (Martindale, Thirty-third edition, pp.
25 823, 854).

Given orally, captopril is rapidly adsorbed and has a
bioavailability of about 75%; it produces a maximum effect
within 1 to 2 hours and most of the drug is eliminated in
urine (Goodman & Gilman's, Tenth edition, McGraw-Hill, p.
30 821).

Now, it has been reported that captopril has side-effects
such as for example hypotension, cough, hyperkalemia, acute

renal failure, skin rash, proteinuria, angioedema, dysgeusia and neutropenia.

U.S. Pat. No. 6,242,432 discloses derivatives of formula A-
(X₁-NO₂)_{t₀} having an antithrombotic activity, wherein A is
5 the residue of ACE inhibitors or Beta-Adrenergic Blockers,
particularly enalapril or timolol, X₁ is a bivalent
connecting bridge and t₀ is 1 or 2.

U.S. Pat. No. 6,218,417 discloses nitric salts of ACE
inhibitors having platelet anti-aggregating activity and
10 antihypertension activity having reduced bronchial side
effects.

U.S. Pat. No. 6,462,044 discloses a pharmaceutical
composition comprising the phosphodiesterase inhibitor and
an S-nitrosothiol such as S-nitroso-captopril.

15 U.S. Pat. No. 6,433,182 discloses a method of treating a
sexual dysfunction in a female individual in need thereof
comprising administering to the female individual an amount
of an α -adrenergic receptor antagonist and an S-
nitrosothiol such as S-nitroso-captopril.

20 U.S. Pat. No. 5,648,393 describes a method for the
treatment or prevention of impotence in a human male in
need thereof, comprising treating or preventing impotence
in a human male in need thereof by administering a corpus
cavernosum nonvascular smooth muscle relaxing amount of an
25 S-nitrosothiol such as S-nitroso-captopril.

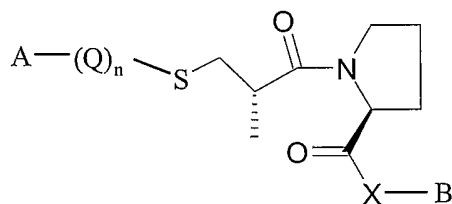
U.S. Pat. No. 5,852,047 discloses pharmaceutical product
comprising a salicylate of an esterifiable ACE inhibitor,
especially captopril-S-aspirinate; U.S. Pat. No. 4,331,673
describes pyridinium salts of captopril.

30 WO 90/02118 discloses S-protected derivatives of captopril
and its analogues and methods for their preparation.

It was an object of the present invention to provide new
captopril derivatives having better effectiveness and

tolerability, that are free from the above mentioned side effects and thus could be employed for the treatment or prophylaxis of cardiovascular, inflammatory, renal diseases and ocular hypertension.

- 5 In particular, it has been recognized that the captopril derivatives of the present invention can be employed for treating or preventing acute coronary syndromes, stroke, pulmonary and ocular hypertension, hypertension, diabetic nephropathy and peripheral vascular diseases.
- 10 Object of the present invention are therefore captopril nitro-derivatives and/or pharmaceutically acceptable salts or stereoisomers thereof of general formula (I):



(I)

wherein:

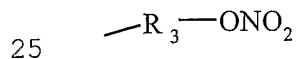
Q = -CO-, -OCO-, -CONH-, -COCH(R)NH- wherein R is H, straight or branched (C₁-C₆)-alkyl, -(CH₂)₂SCH₃ or benzyl;

20 with the proviso that -S- is bound to -CO;

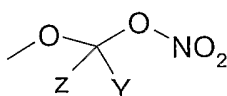
n is an integer equal to 0 or 1;

A = H, W (wherein W is C₁-C₆-alkyl, phenyl or benzyl) or is chosen from the following groups:

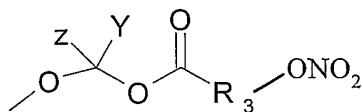
1a)



1b)

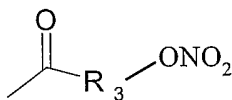


1c)

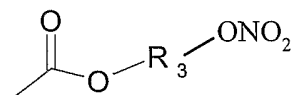


wherein z and Y are the same or different, and are H or straight or branched (C₁-C₄)-alkyl; with the proviso that when A is selected from the groups 1b and 1c, Q = -CO-;

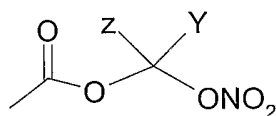
5 1d₁)



1d₂)



10 1d₃)



wherein z and Y are as above defined;

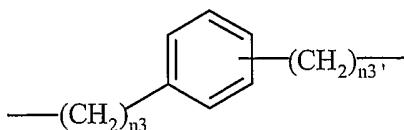
with the proviso that when A is selected from the groups 1d₁-1d₃, Q = -COCH(R)NH- wherein R is as above defined;

15 R₃ is a bivalent radical having the following meanings:

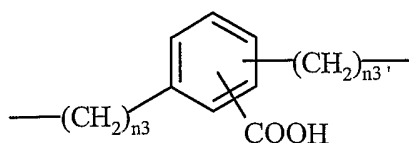
a) a straight or whenever possible branched C₁-C₂₀ alkylene, optionally substituted with at least an halogen atom, preferably having from 1 to 5 carbon atoms and or an optionally substituted cycloalkylene having from 5 to 7

20 carbon atoms;

b)



c)



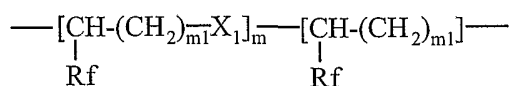
wherein:

n_3 is an integer from 0 to 20, preferably from 0 to 5;

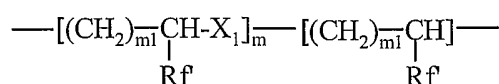
n_3' is an integer from 1 to 20, preferably from 1 to 5;

5 wherein the $-\text{ONO}_2$ group is bound to a $-\text{CH}_2$ group;

d)

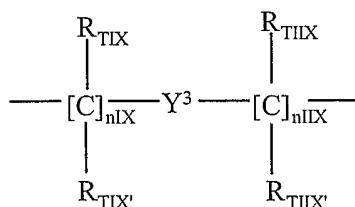


d1)



10 wherein X_1 is $-\text{O}-$ or $-\text{S}-$, m is an integer from 1 to 6, preferably from 1 to 4, m_1 is an integer from 1 to 10, preferably from 1 to 5, Rf is a hydrogen atom or CH_3 , Rf' is CH_3 ;

e)



15

wherein:

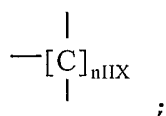
n_{IX} is an integer from 0 to 10, preferably from 0 to 3;

n_{IIX} is an integer from 1 to 10, preferably from 1 to 3;

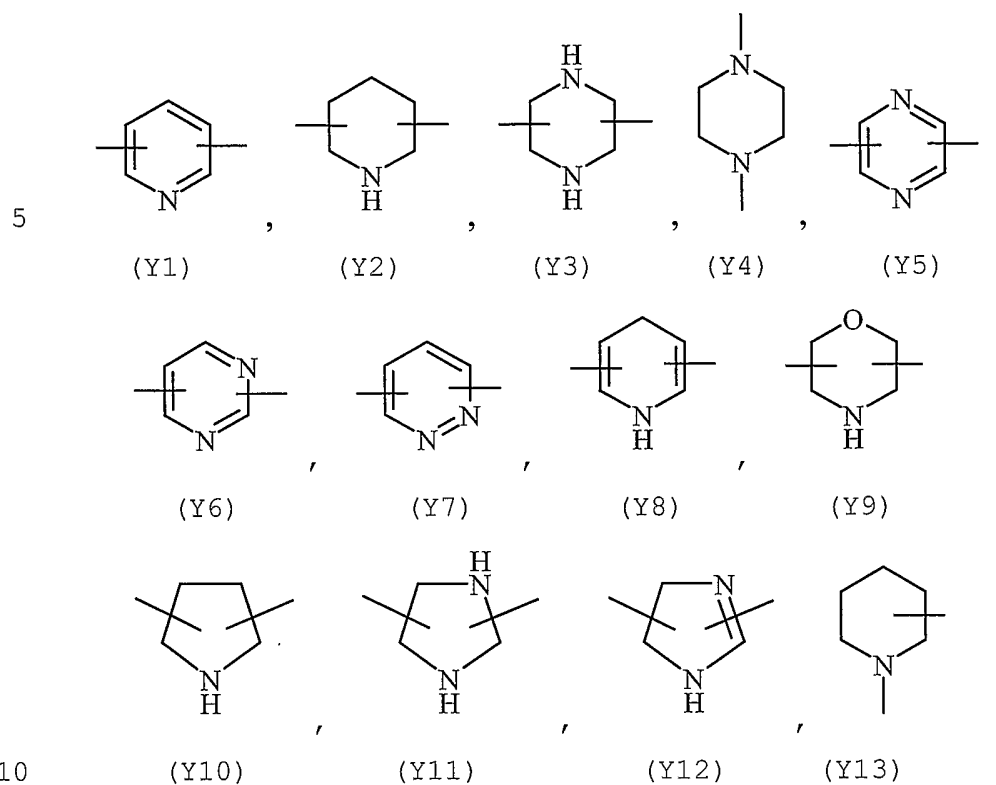
R_{TIX} , $\text{R}_{\text{TIX}'}$, R_{TIIIX} , $\text{R}_{\text{TIIIX}'}$, are the same or different, and are H

20 or straight or branched $(\text{C}_1\text{--}\text{C}_4)$ -alkyl, preferably R_{TIX} , $\text{R}_{\text{TIX}'}$, R_{TIIIX} , $\text{R}_{\text{TIIIX}'}$ are H;

and wherein the $-\text{ONO}_2$ group is bound to



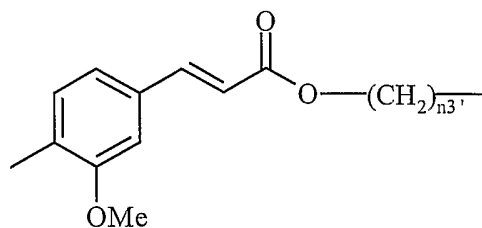
Y^3 è an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, and selected for example from



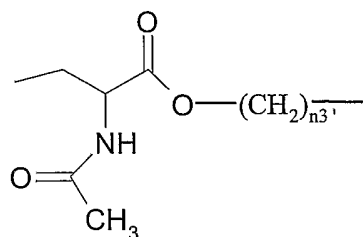
X = -NH-, -O-, -S-;

B = H, $-R_{3a}-ONO_2$ wherein R_{3a} has the same meaning of R_3 as above defined or is chosen from the following groups:

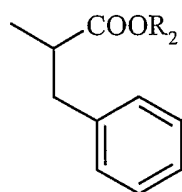
15 f)



g)



wherein $n3'$ is as above defined; and wherein the $-ONO_2$ group is bound to the group $-(CH_2)_{n3'}$;
or B is the group of formula (IA):



5

(IA)

wherein R_2 is H, a straight or branched (C_1-C_6) -alkyl or $-R_{3b}-ONO_2$ wherein R_{3b} has the same meaning of R_3 as above defined in a);

10 Provided that:

i) when R_{3a} is the group as defined in f) and g) then A is W;

ii) when R_{3a} is the group as defined in g) then X is -S-;

iii) when B is the group of formula (IA) then X is -NH-;

15 iv) at least one of the groups A or B contains a $-ONO_2$ group. The term " (C_1-C_6) -alkyl" as used herein refers to branched or straight chain alkyl groups comprising one to six carbon atoms, including methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl and the like. The term " C_1-C_{20}
20 alkylene" as used herein refers to branched or straight chain C_1-C_{20} hydrocarbon, preferably having from 2 to 5 carbon atoms such as ethylene, propylene, butylene, pentylene.

The term "halogen atom" as used herein refers to chloro,
25 bromo or fluoro atoms.

The term "cycloalkylene" as used herein refers to ring having from 5 to 7 carbon atoms including, but not limited to, cyclopentylene, cyclohexylene optionally substituted with side chains such as straight or branched (C₁-C₁₀)-alkyl, preferably CH₃.

The term "heterocyclic" as used herein refers to saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, such as for example pyridine, pyrazine, pyrimidine, pyrrolidine, morpholine, imidazole and the like.

As already said, the invention includes also the pharmaceutically acceptable salts of the compounds of formula (I).

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.

Another aspect of the present invention provides the use of the compounds of formula (I) in combination with at least a compounds used to treat cardiovascular disease selected from the group consisting of: beta adrenergic blockers, calcium channel blockers, angiotensin II receptor antagonists, antithrombotics, HMGCoA reductase inhibitors, aspirin or nitrooxyderivatives of aspirin, nitrosated beta blockers, nitrosated or nitrosilated calcium channel blockers.

The present invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the compounds and or compositions of the present invention and one or more of the compounds used to treat cardiovascular disease reported above.

Suitable beta adrenergic blockers, calcium channel blockers, angiotensin II receptor antagonists, antithrombotics, are described in the literature such as The Merck Index (13th edition).

- 5 Suitable nitrosated beta adrenergic blockers and nitrooxyderivatives of aspirin are disclosed respectively in WO 98/21193 and WO97/16405.

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

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acid.

- 15 Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acid.

Salts with nitric acid are preferred.

The compounds of the invention which have one or more asymmetric carbon atoms can exist as the optically pure
20 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).

- 25 Preferred compounds are those of formula (I) wherein:

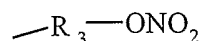
Q = -CO-, -OCO-, -CONH-, -COCH(R)NH- wherein R is H or CH₃; with the proviso that -S- is bound to -CO;

n is an integer equal to 0 or 1;

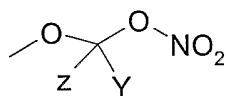
A = H, W (wherein W is C₁-C₆-alkyl preferably CH₃) or is

- 30 chosen from the following groups:

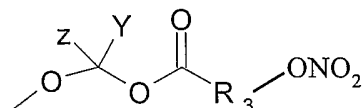
1a)



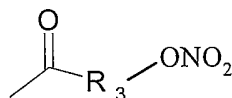
1b)



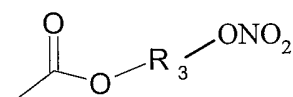
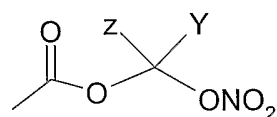
1c)



wherein z and Y are the same or different, and are H or
 5 CH₃; with the proviso that when A is selected from the
 groups 1b and 1c, Q = -CO-;

1d₁)1d₂)

10

1d₃)

15

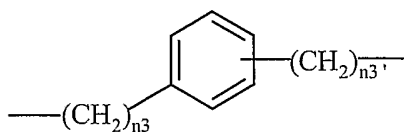
wherein z and Y are as above defined;

with the proviso that when A is selected from groups 1d₁-
 1d₃, Q = -COCH(R)NH- wherein R is as above defined;

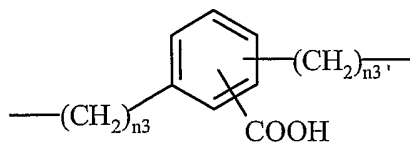
R₃ is a bivalent radical having the following meanings:

20 a) straight C₁-C₆ alkylene, preferably C₃-C₅ alkylene;

b)



c)

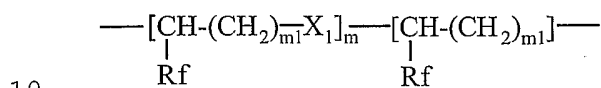


wherein:

5 n_3 is an integer from 0 to 5 and $n_{3'}$ is an integer from 1 to 5;

wherein the $-\text{ONO}_2$ group is bound to a $-\text{CH}_2$ group;

d)



wherein X_1 is $-\text{O}-$, m is an integer from 1 to 4, preferably 1, m_1 is an integer from 1 to 5, preferably 1, Rf is a hydrogen atom or CH_3 ;

e)



wherein:

n_{IX} is an integer from 0 to 3 and n_{IIX} is an integer from 1 to 3;

R_{TIX} , $\text{R}_{\text{TIX}'}$, R_{TII} , $\text{R}_{\text{TII}'}$ are the same and are H;

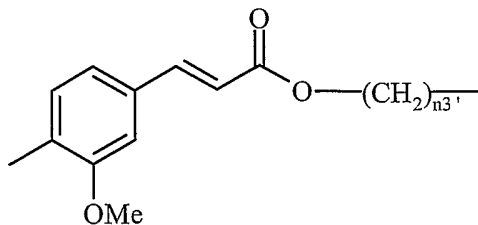
20 and wherein the $-\text{ONO}_2$ group is bound to a $-\text{CH}_2$ group;

Y^3 is a heterocyclic saturated, unsaturated or aromatic, containing one or more atoms of nitrogen and selected from Y1-Y6 as defined in claim 1;

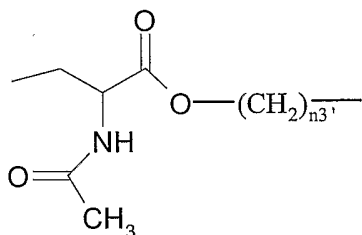
$\text{X} = -\text{NH}-$, $-\text{O}-$, $-\text{S}-$;

25 $\text{B} = \text{H}$, $-\text{R}_{3a}-\text{ONO}_2$ wherein R_{3a} has the same meaning of R_3 as above defined or is chosen from the following groups:

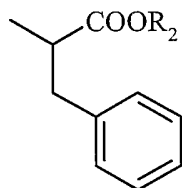
f)



g)



- 5 wherein $n_{3'}$ is as above defined, preferably 4; wherein the $-\text{ONO}_2$ group is bound to the group $-(\text{CH}_2)_{n_{3'}}$; or B is the group of formula (IA):

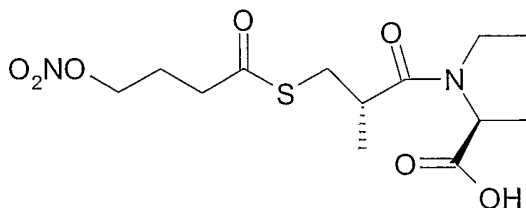


(IA)

- 10 wherein R_2 is H, a straight or branched $(\text{C}_1\text{-C}_6)$ -alkyl or $-\text{R}_{3b}\text{-ONO}_2$ wherein R_{3b} has the same meaning of R_3 as above defined in a);

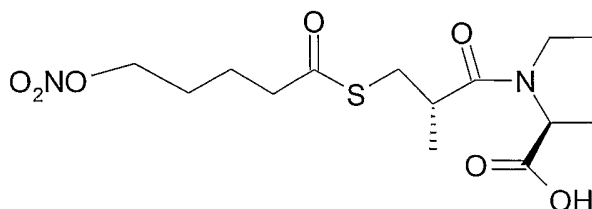
Preferred compounds of formula (I) according to the present invention are the following:

- 15 (1) A compound of formula (I) wherein $Q = -\text{CO}-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -\text{O}-$ and B is H:



(1)

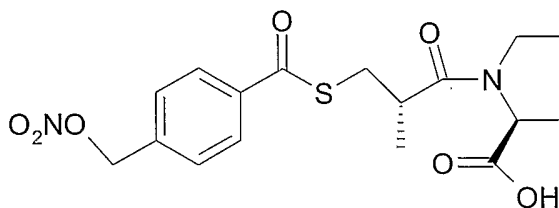
(2) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is H:



5

(2)

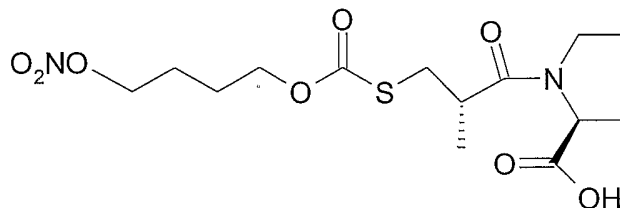
(3) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1, $X = -O-$ and B is H:



(3)

(4) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is H:

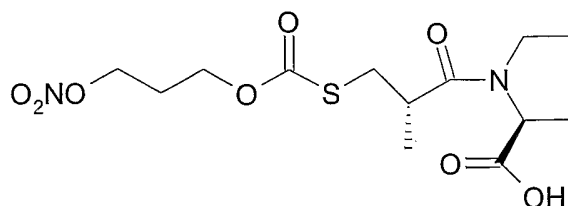
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(4)

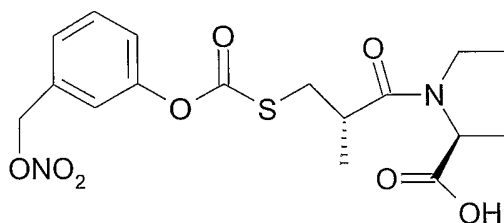
(5) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is H:

20



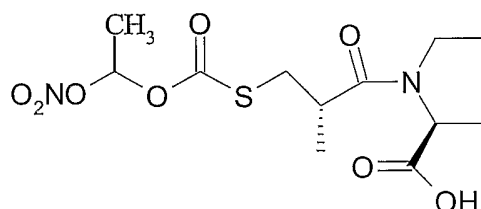
(5)

(6) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and $n_{3'}$ is an integer equal to 1, $X = -O-$ and B is H:



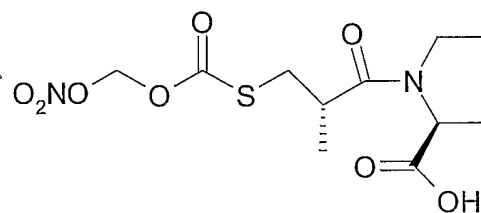
(6)

(7) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z is H and Y is CH_3 , $X = -O-$ and B is H:



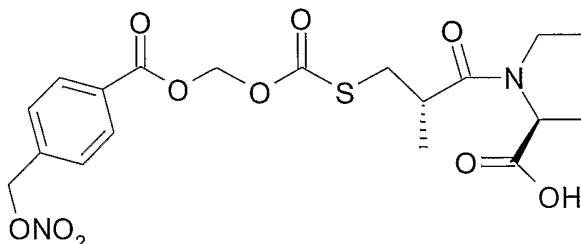
(7)

(8) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z and Y are H, $X = -O-$ and B is H:



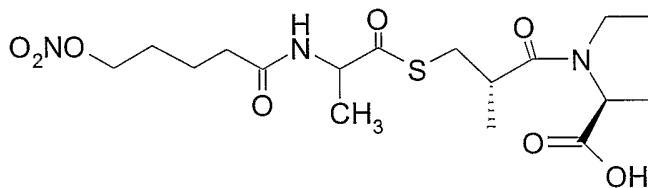
(8)

(9) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1c) wherein z and Y are H, R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1, $X = -O-$ and B is H:



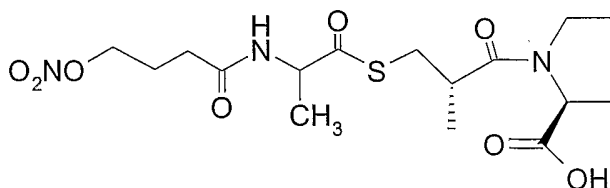
(9)

(10) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and B is H:



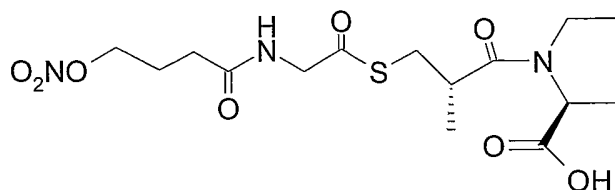
(10)

(11) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and B is H:



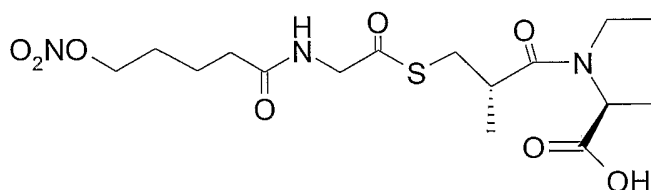
(11)

(12) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and B is H:



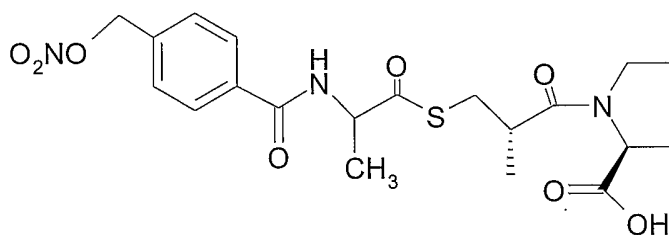
(12)

(13) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁)
 5 wherein R_3 is a straight C₄ alkylene, $X = -O-$ and B is H:



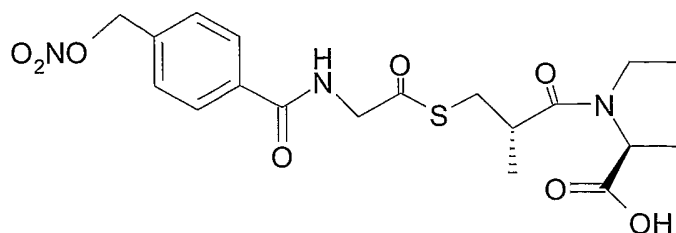
(13)

(14) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁)
 10 wherein R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1, $X = -O-$ and B is H:



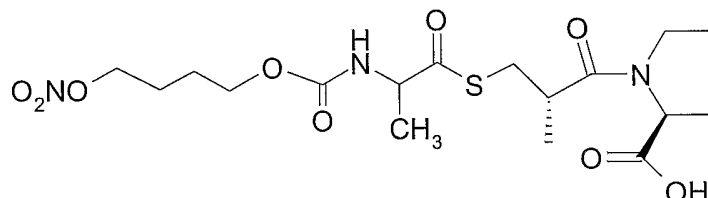
(14)

15 (15) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1, $X = -O-$ and B is H:



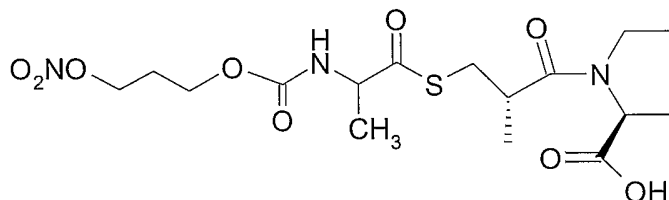
(15)

(16) A compound of formula (I) wherein Q = -COCH(R)NH-
with R = CH₃, n = 1, A is the group as defined in 1d₂)
5 wherein R₃ is a straight C₄ alkylene, X = -O- and B is H:



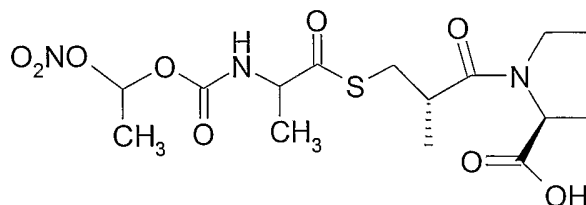
(16)

(17) A compound of formula (I) wherein Q = -COCH(R)NH-
with R = CH₃, n = 1, A is the group as defined in 1d₂)
10 wherein R₃ is a straight C₃ alkylene, X = -O- and B is H:



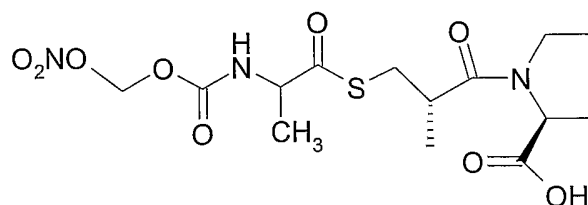
(17)

(18) A compound of formula (I) wherein Q = -COCH(R)NH-
with R = CH₃, n = 1, A is the group as defined in 1d₃)
15 wherein z is H and Y is CH₃, X = -O- and B is H:



(18)

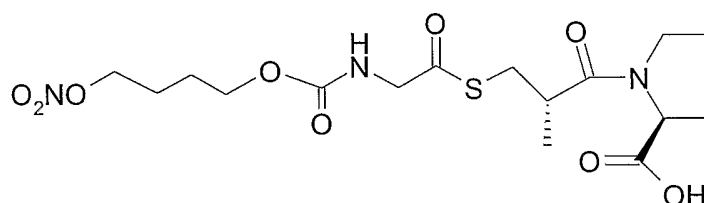
(19) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₃) wherein z and Y are H, $X = -O-$ and B is H:



5

(19)

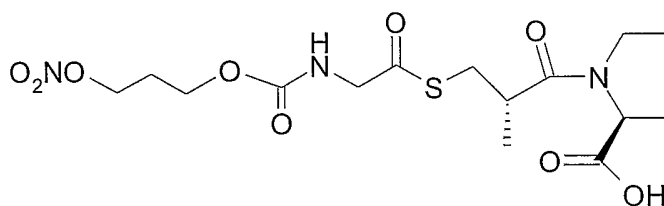
(20) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₂) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and B is H:



10

(20)

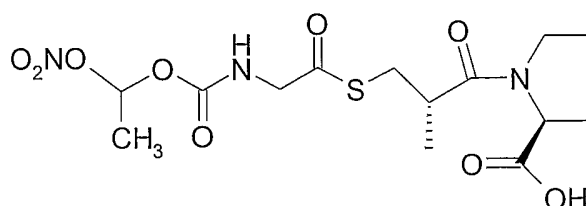
(21) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₂) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and B is H:



15

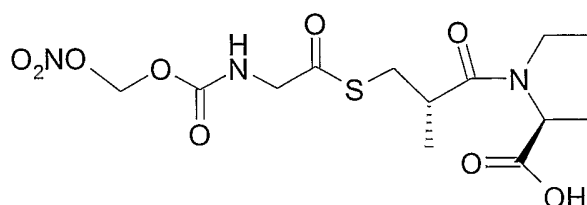
(21)

(22) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₃) wherein z is H and Y is CH₃, $X = -O-$ and B is H:



(22)

(23) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₃) wherein z and Y are H, X = -O- and B is H:

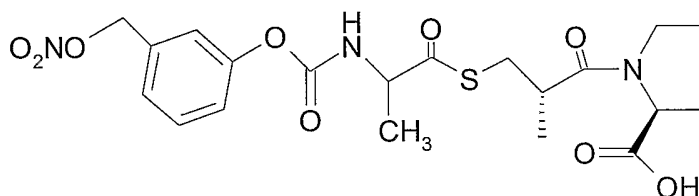


5

(23)

(24) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₂) wherein R₃ is the group as defined in b) wherein n₃ is an integer equal to 0 and n₃' is an integer equal to 1, X = -O- and B is H:

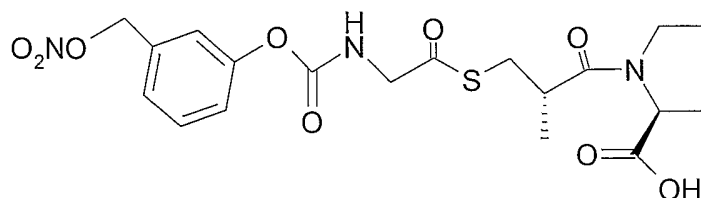
10



(24)

(25) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₂) wherein R₃ is the group as defined in b) wherein n₃ is an integer equal to 0 and n₃' is an integer equal to 1, X = -O- and B is H:

15

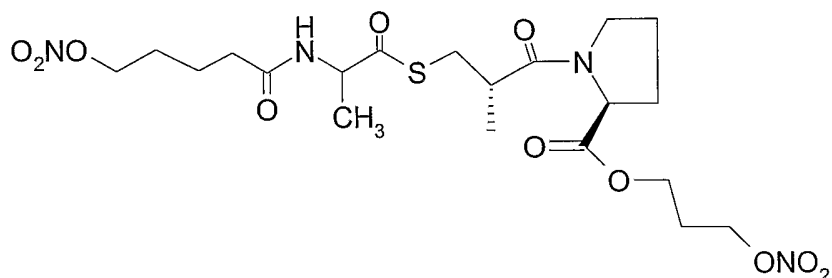


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(25)

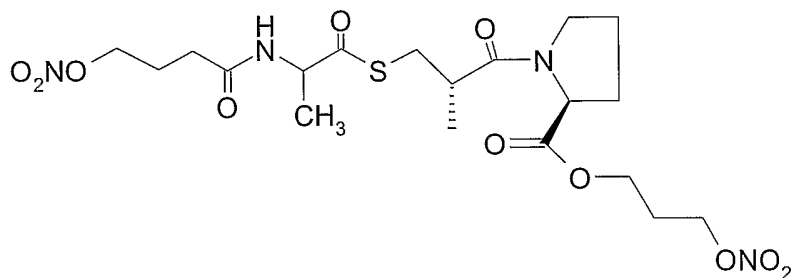
(26) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁)

wherein R_3 is a straight C_4 alkylene, $X = -O-$ and $B = -R_{3a}-$
 ONO_2 wherein R_{3a} is a straight C_3 alkylene:



(26)

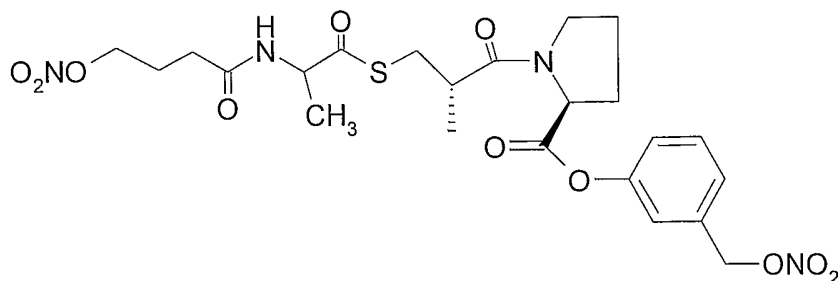
- 5 (27) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in $1d_1$ wherein R_3 is a straight C_3 alkylene, $X = -O-$ and $B = -R_{3a}-$
 ONO_2 wherein R_{3a} is a straight C_3 alkylene:



10

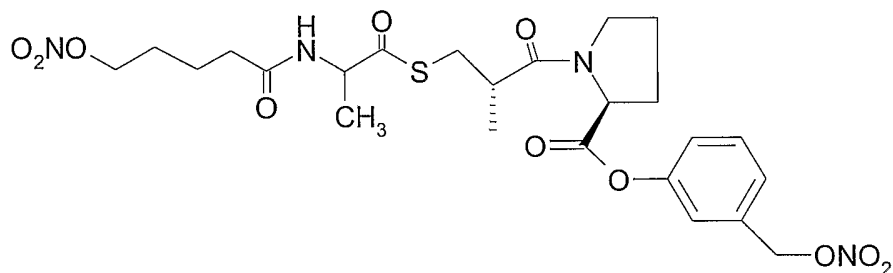
(27)

- (28) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in $1d_1$ wherein R_3 is a straight C_3 alkylene, $X = -O-$ and $B = -R_{3a}-$
 ONO_2 wherein R_{3a} is the group as defined in b) wherein n_3
 15 is an integer equal to 0 and $n_{3'}$ is an integer equal to 1:



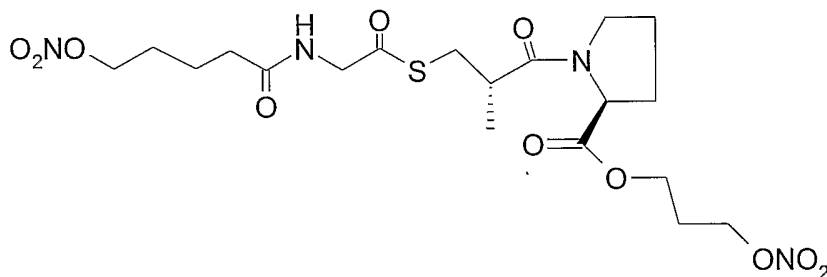
(28)

(29) A compound of formula (I) wherein Q = -COCH(R)NH-
 with R = CH₃, n = 1, A is the group as defined in 1d₁)
 wherein R₃ is a straight C₄ alkylene, X = -O- and B = -R_{3a}-
 ONO₂ wherein R_{3a} is the group as defined in b) wherein n₃
 5 is an integer equal to 0 and n_{3'} is an integer equal to 1:



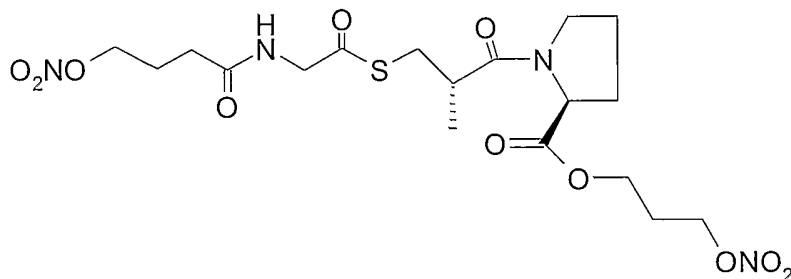
(29)

(30) A compound of formula (I) wherein Q = -COCH(R)NH-
 with R = H, n = 1, A is the group as defined in 1d₁)
 10 wherein R₃ is a straight C₄ alkylene, X = -O- and B = -R_{3a}-
 ONO₂ wherein R_{3a} is a straight C₃ alkylene:



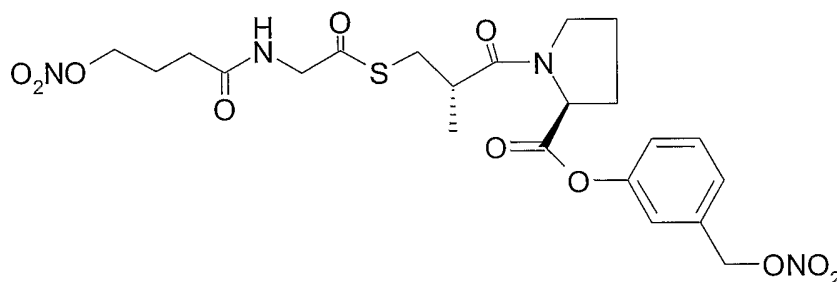
(30)

(31) A compound of formula (I) wherein Q = -COCH(R)NH-
 15 with R = H, n = 1, A is the group as defined in 1d₁)
 wherein R₃ is a straight C₃ alkylene, X = -O- and B = -R_{3a}-
 ONO₂ wherein R_{3a} is a straight C₃ alkylene:



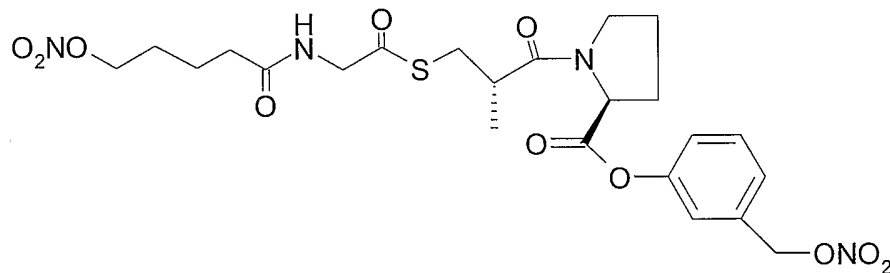
(31)

(32) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and $B = -R_{3a}-$
 5 ONO_2 wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and $n_{3'}$ is an integer equal to 1:



(32)

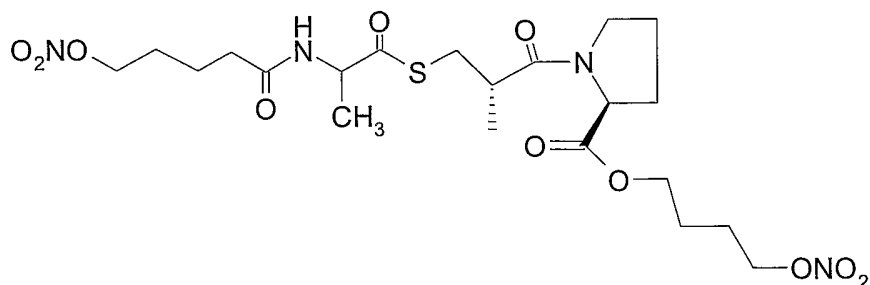
(33) A compound of formula (I) wherein $Q = -COCH(R)NH-$
 10 with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and $B = -R_{3a}-$
 ONO_2 wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and $n_{3'}$ is an integer equal to 1:



15

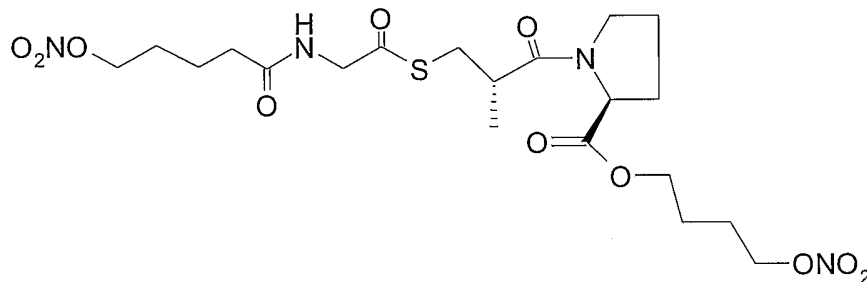
(33)

(34) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and $B = -R_{3a}-$
 ONO_2 wherein R_{3a} is a straight C₄ alkylene:



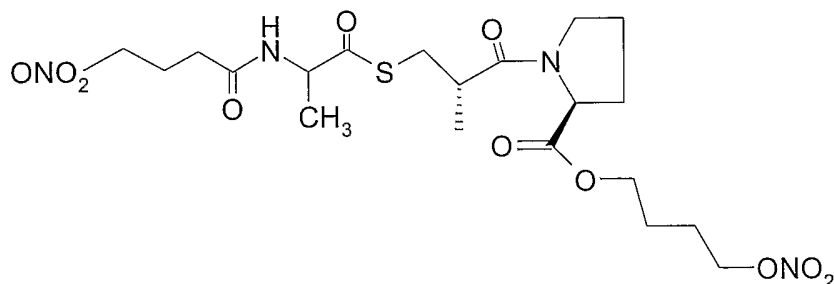
(34)

(35) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁)
 5 wherein R_3 is a straight C₄ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₄ alkylene:



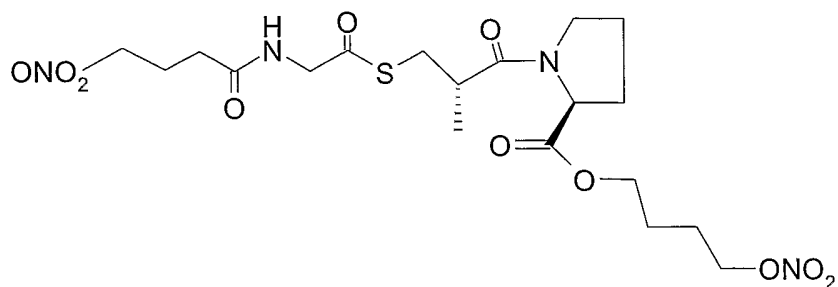
(35)

(36) A compound of formula (I) wherein $Q = -COCH(R)NH-$
 10 with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁)
 wherein R_3 is a straight C₃ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₄ alkylene:



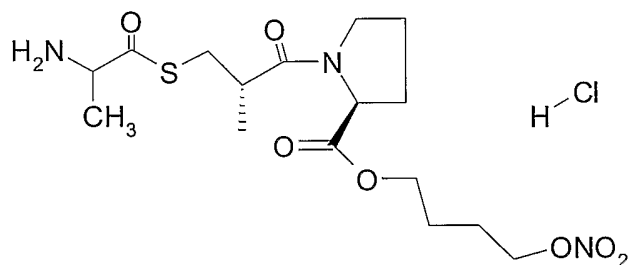
(36)

(37) A compound of formula (I) wherein $Q = -COCH(R)NH-$
 15 with $R = H$, $n = 1$, A is the group as defined in 1d₁)
 wherein R_3 is a straight C₃ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₄ alkylene:



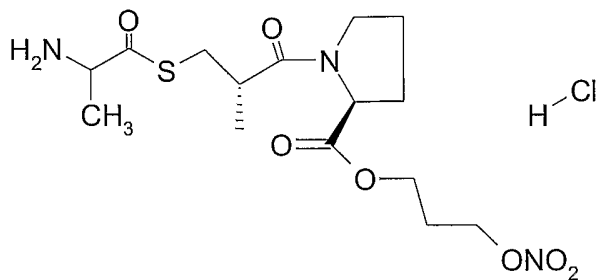
(37)

(38) A compound of formula (I) wherein Q = -COCH(R)NH-
 with R = CH₃, n = 1, A is H, X = -O- and B = -R_{3a}-ONO₂
 5 wherein R_{3a} is a straight C₄ alkylene:



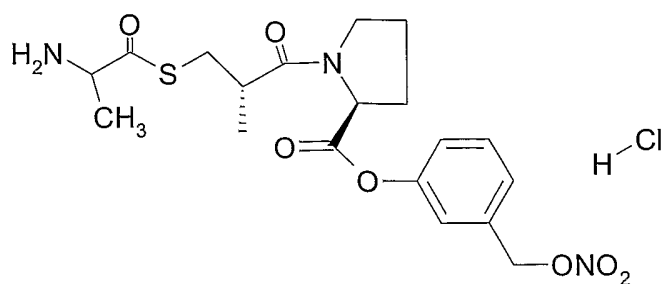
(38)

(39) A compound of formula (I) wherein Q = -COCH(R)NH-
 with R = CH₃, n = 1, A is H, X = -O- and B = -R_{3a}-ONO₂
 10 wherein R_{3a} is a straight C₃ alkylene:



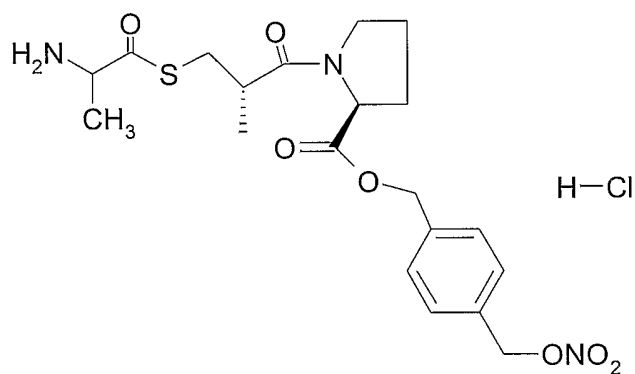
(39)

(40) A compound of formula (I) wherein Q = -COCH(R)NH-
 with R = CH₃, n = 1, A is H, X = -O- and B = -R_{3a}-ONO₂
 15 wherein R_{3a} is the group as defined in b) wherein n₃ is an
 integer equal to 0 and n_{3'} is an integer equal to 1:



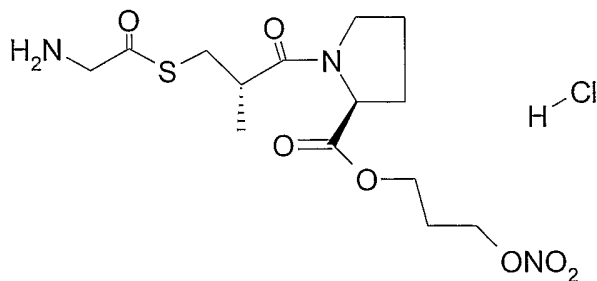
(40)

(41) A compound of formula (I) wherein Q = -COCH(R)NH-
 with R = CH₃, n = 1, A is H, X = -O- and B = -R_{3a}-ONO₂
 5 wherein R_{3a} is the group as defined in b) wherein n₃ and
 n₃' are an integer equal to 1:



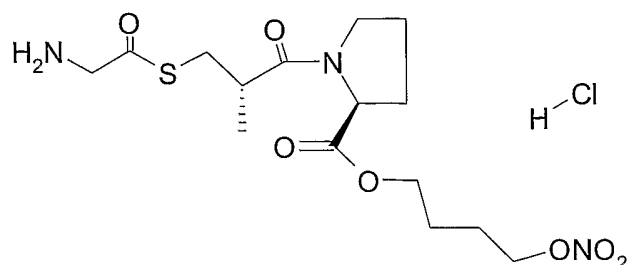
(41)

10 (42) A compound of formula (I) wherein Q = -COCH(R)NH-
 wherein R and A are H, n = 1, X = -O- and B = -R_{3a}-ONO₂
 wherein R_{3a} is a straight C₃ alkylene:



(42)

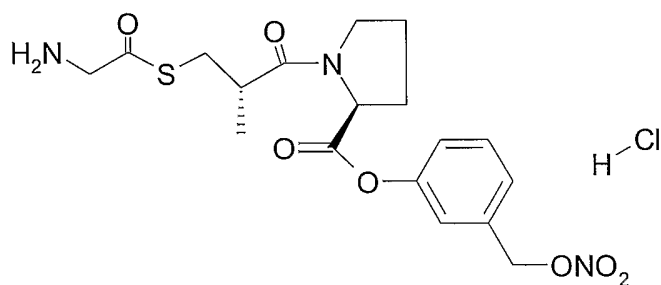
(43) A compound of formula (I) wherein $Q = -COCH(R)NH-$ wherein R and A are H, $n = 1$, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene:



5

(43)

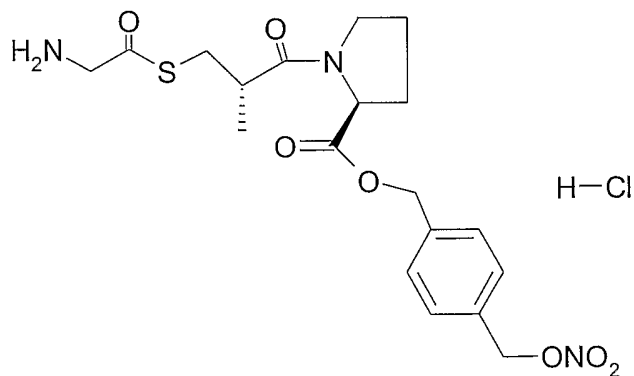
(44) A compound of formula (I) wherein $Q = -COCH(R)NH-$ wherein R and A are H, $n = 1$, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1:



10

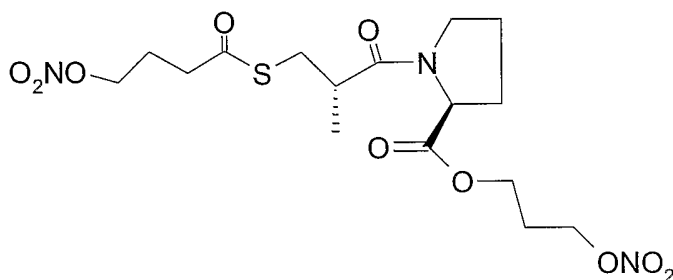
(44)

(45) A compound of formula (I) wherein $Q = -COCH(R)NH-$ wherein R and A are H, $n = 1$, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 and n_3' are an integer equal to 1:



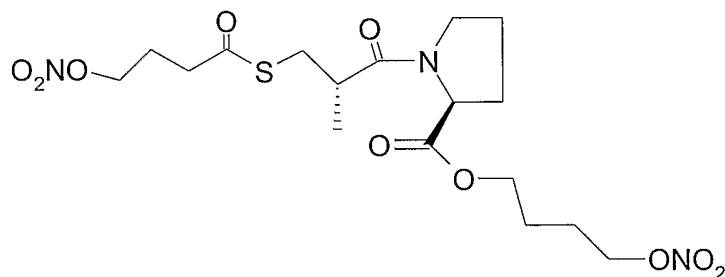
(45)

(46) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein
 5 R_{3a} is a straight C_3 alkylene:



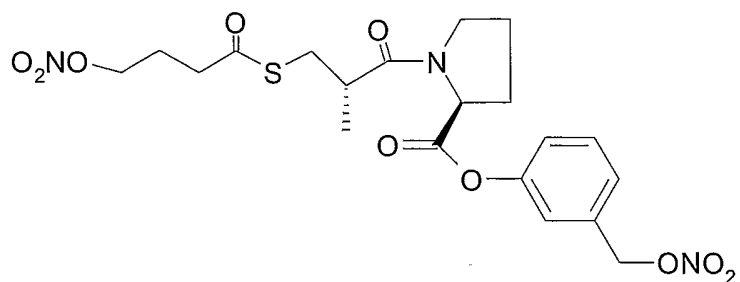
(46)

(47) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein
 10 R_{3a} is a straight C_4 alkylene:



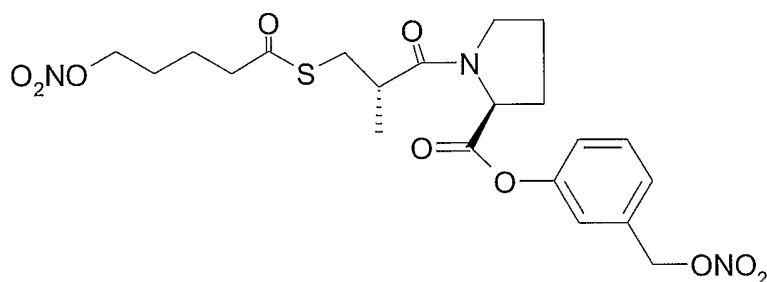
(47)

(48) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein
 15 R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and $n_{3'}$ is an integer equal to 1:



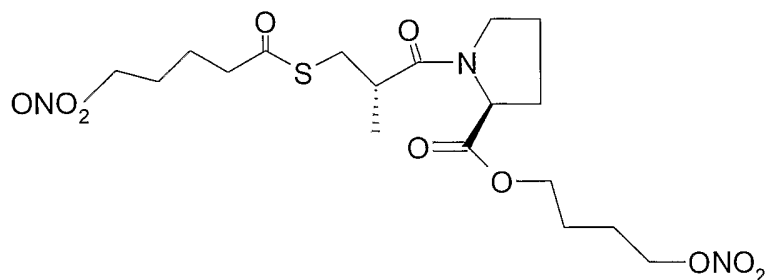
(48)

(49) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1:



(49)

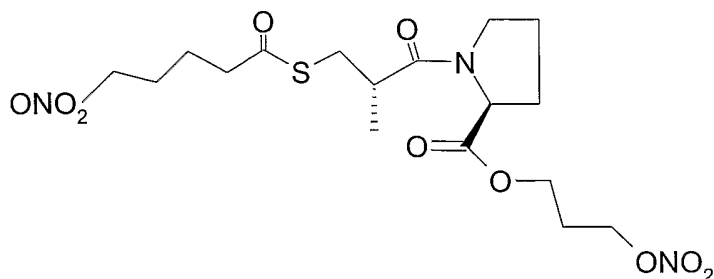
(50) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene:



(50)

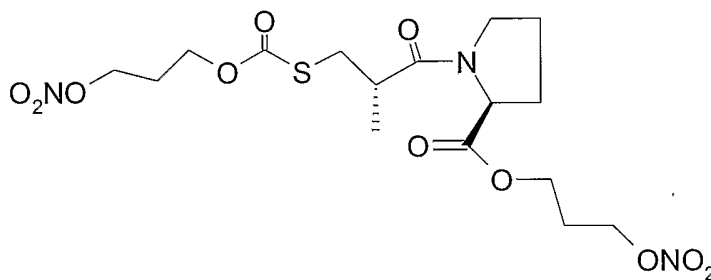
(51) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a

straight C₄ alkylene, X = -O- and B is = -R_{3a}-ONO₂ wherein R_{3a} is a straight C₃ alkylene:



(51)

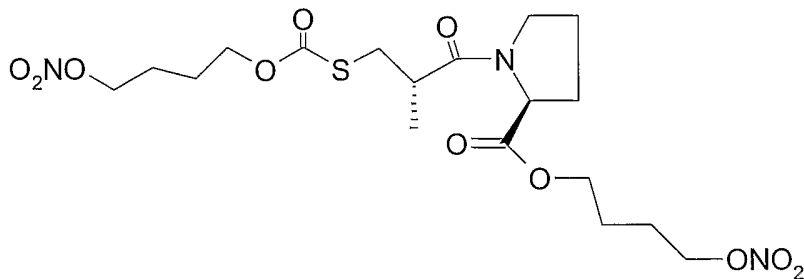
- 5 (52) A compound of formula (I) wherein Q = -OCO-, n = 1, A is the group as defined in 1a) wherein R₃ is a straight C₃ alkylene, X = -O- and B is = -R_{3a}-ONO₂ wherein R_{3a} is a straight C₃ alkylene:



(52)

10

- (53) A compound of formula (I) wherein Q = -OCO-, n = 1, A is the group as defined in 1a) wherein R₃ is a straight C₄ alkylene, X = -O- and B is = -R_{3a}-ONO₂ wherein R_{3a} is a straight C₄ alkylene:

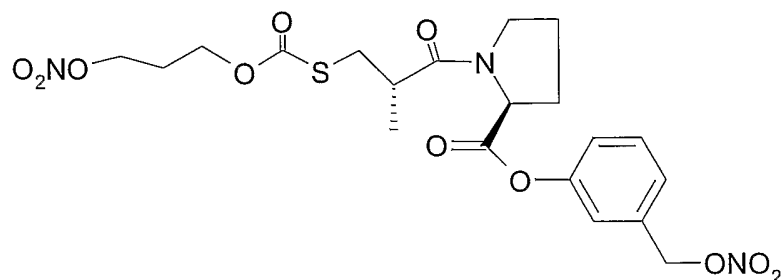


(53)

15

- (54) A compound of formula (I) wherein Q = -OCO-, n = 1, A is the group as defined in 1a) wherein R₃ is a

straight C₃ alkylene, X = -O- and B is = -R_{3a}-ONO₂ wherein R_{3a} is the group as defined in b) wherein n₃ is an integer equal to 0 and n_{3'} is an integer equal to 1:

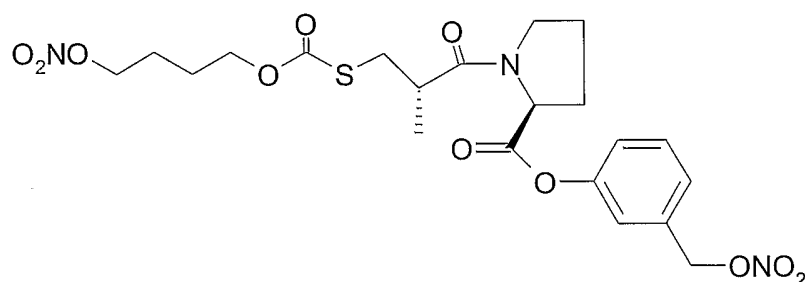


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(54)

(55) A compound of formula (I) wherein Q = -OCO-, n = 1, A is the group as defined in 1a) wherein R₃ is a straight C₄ alkylene, X = -O- and B is = -R_{3a}-ONO₂ wherein R_{3a} is the group as defined in b) wherein n₃ is an integer equal to 0 and n_{3'} is an integer equal to 1:

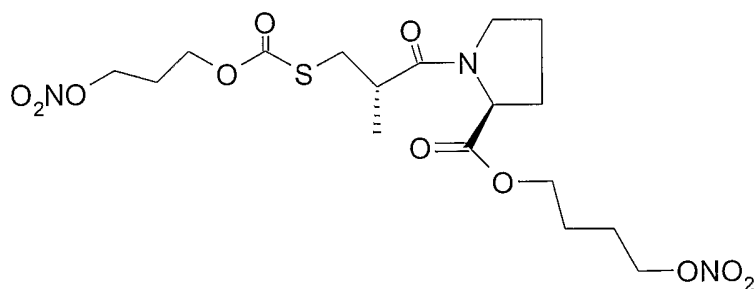
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(55)

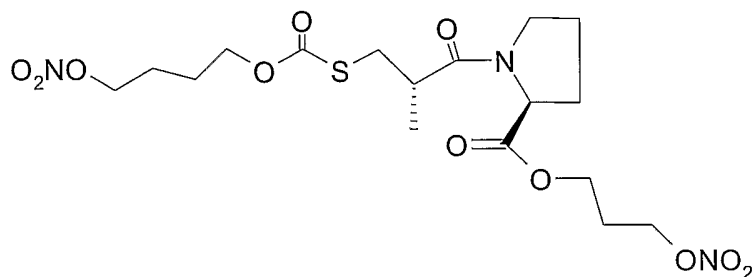
(56) A compound of formula (I) wherein Q = -OCO-, n = 1, A is the group as defined in 1a) wherein R₃ is a straight C₃ alkylene, X = -O- and B is = -R_{3a}-ONO₂ wherein R_{3a} is a straight C₄ alkylene:

15



(56)

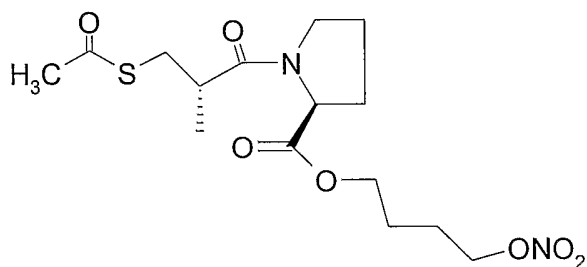
(57) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene:



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(57)

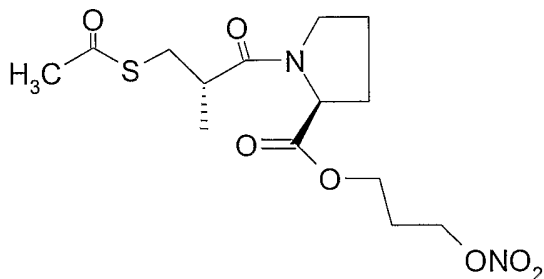
(58) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A = W wherein W is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene;



10

(58)

(59) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A = W wherein W is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene:

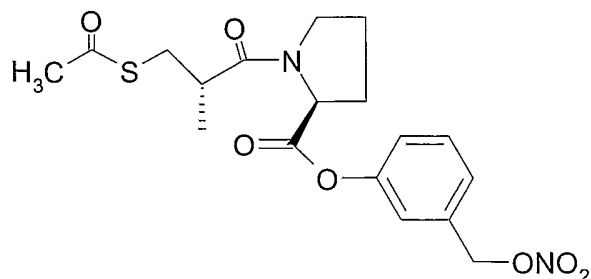


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(59)

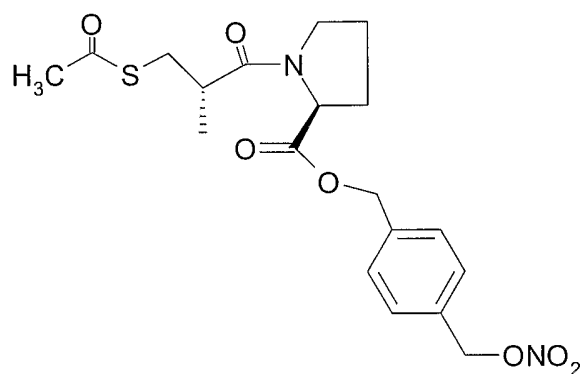
(60) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A = W wherein W is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$

wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and $n_{3'}$ is an integer equal to 1:



(60)

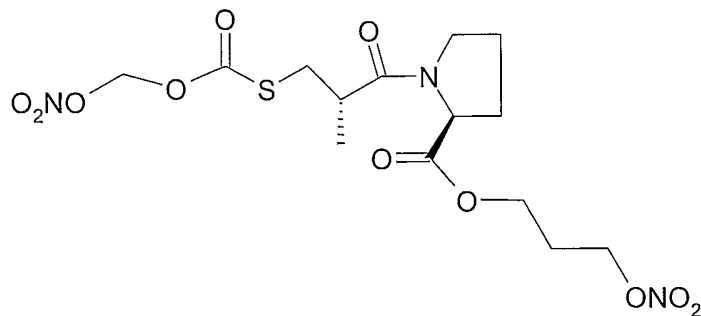
- 5 (61) A compound of formula (I) wherein $Q = -\text{CO}-$, $n = 1$, $A = W$ wherein W is CH_3 , $X = -\text{O}-$ and B is $= -R_{3a}-\text{ONO}_2$ wherein R_{3a} is the group as defined in b) wherein n_3 and $n_{3'}$ are an integer equal to 1:



(61)

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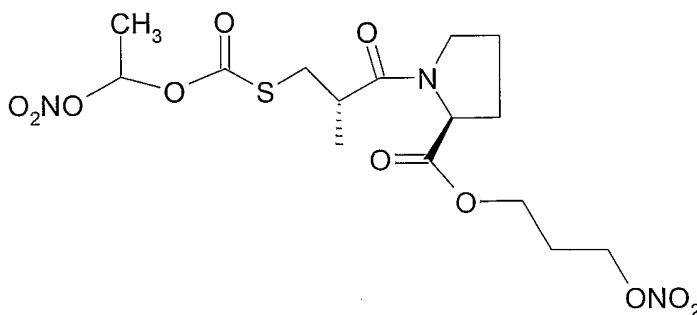
- (62) A compound of formula (I) wherein $Q = -\text{CO}-$, $n = 1$, A is the group as defined in 1b) wherein z and Y are H , $X = -\text{O}-$ and B is $= -R_{3a}-\text{ONO}_2$ wherein R_{3a} is a straight C_3 alkylene:



(62)

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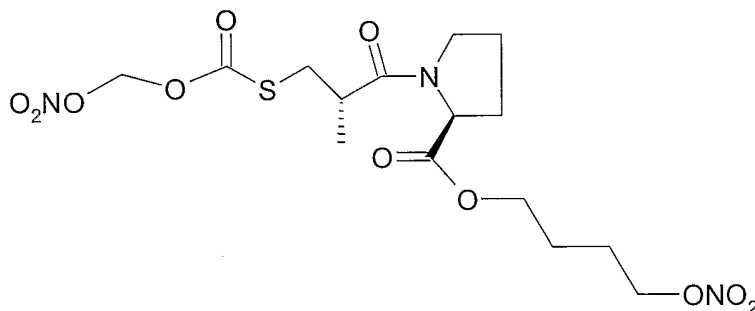
(63) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z is H and Y is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene:



5

(63)

(64) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z and Y are H, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene:

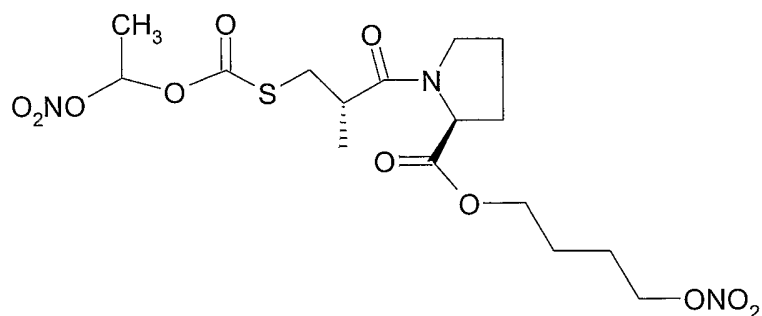


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(64)

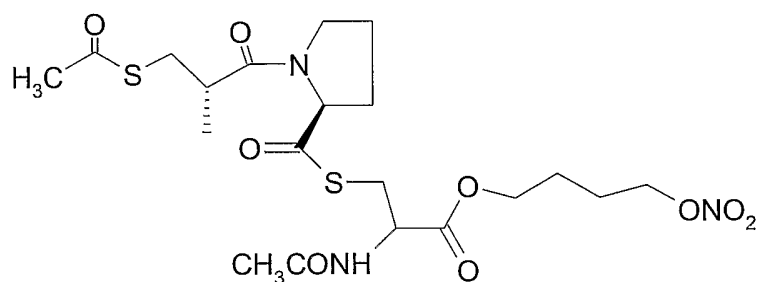
(65) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z is H and Y is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene:

15



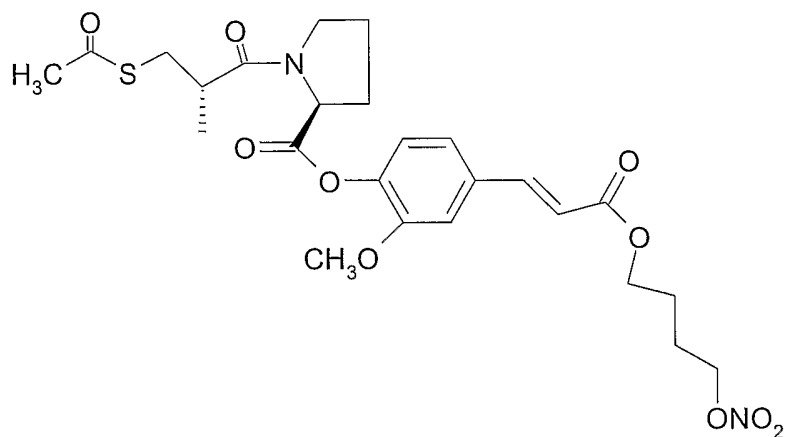
(65)

(66) A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -S- and B is = -R_{3a}-ONO₂ wherein R_{3a} is the group as defined in g) wherein n₃' is an integer equal to 4:



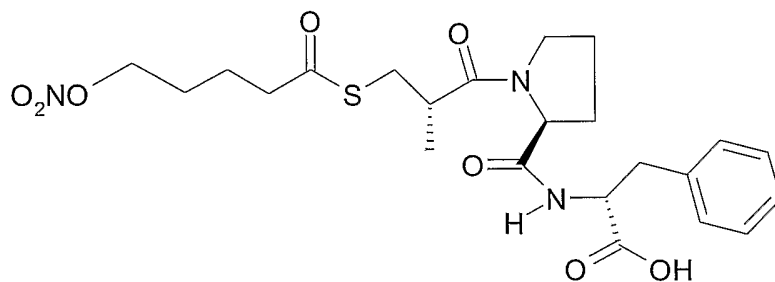
(66)

(67) A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -O- and B is = -R_{3a}-ONO₂ wherein R_{3a} is the group as defined in f) wherein n₃' is an integer equal to 4:



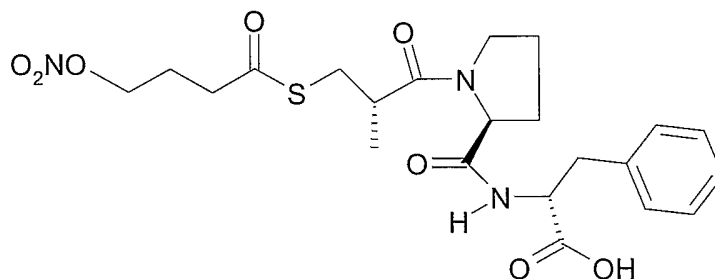
(67)

(68) A compound of formula (I) wherein Q = -CO-, n = 1, A is the group as defined in 1a) wherein R₃ is a straight C₄ alkylene, X = -NH- and B is the group of
 5 formula (IA) wherein R₂ is H:



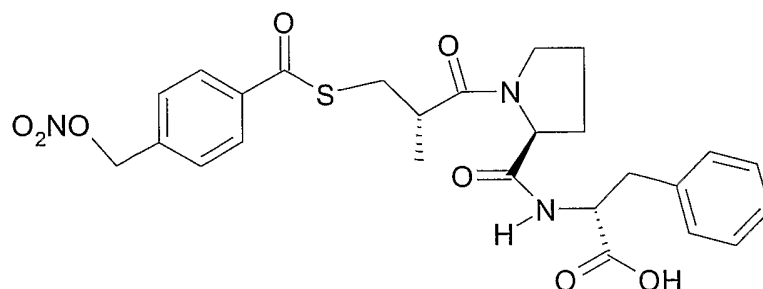
(68)

(69) A compound of formula (I) wherein Q = -CO-, n = 1, A is the group as defined in 1a) wherein R₃ is a straight C₃ alkylene, X = -NH- and B is the group of
 10 formula (IA) wherein R₂ is H:



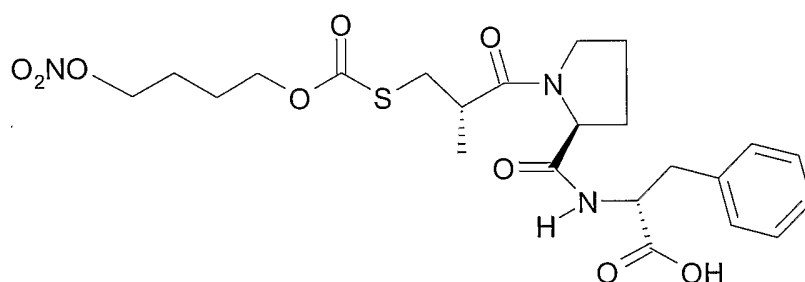
(69)

(70) A compound of formula (I) wherein Q = -CO-, n = 1, A is the group as defined in 1a) wherein R₃ is the group as defined in b) wherein n₃ is an integer equal to 0 and n₃' is an integer equal to 1, X = -NH- and B is the group of
 15 formula (IA) wherein R₂ is H:



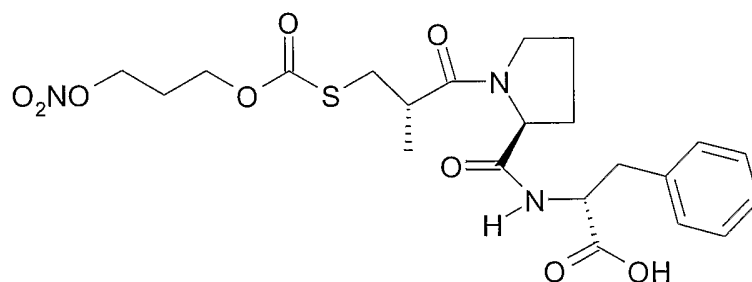
(70)

(71) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -NH-$ and B is the group of formula (IA) wherein R_2 is H:



(71)

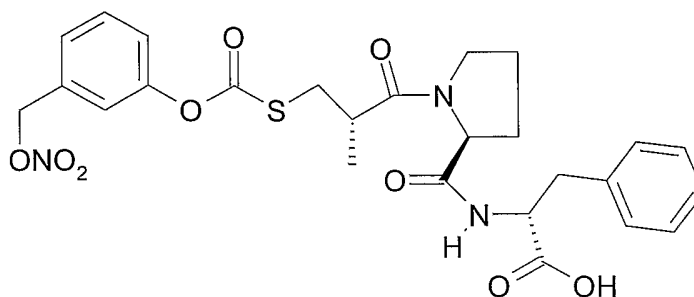
(72) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -NH-$ and B is the group of formula (IA) wherein R_2 is H:



(72)

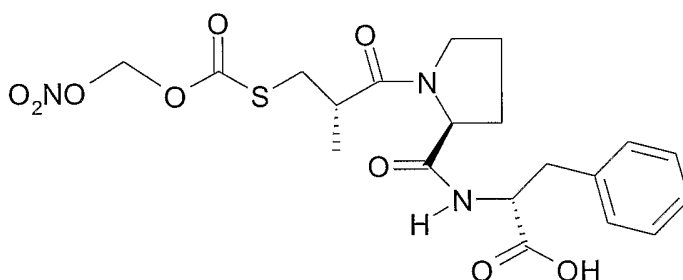
(73) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and

$n3'$ is an integer equal to 1, $X = -NH-$ and B is the group of formula (IA) wherein R_2 is H:



(73)

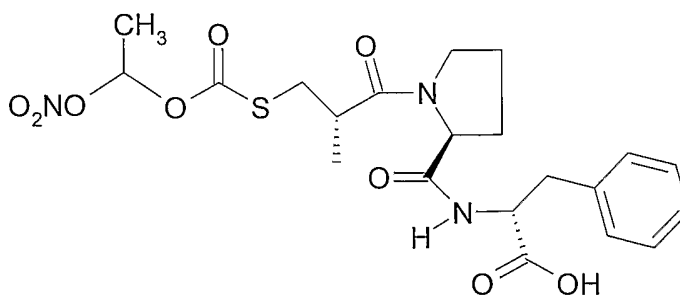
5 (74) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z and Y are H, $X = -NH-$ and B is the group of formula (IA) wherein R_2 is H:



(74)

10

(75) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z is H and Y is CH_3 , $X = -NH-$ and B is the group of formula (IA) wherein R_2 is H:

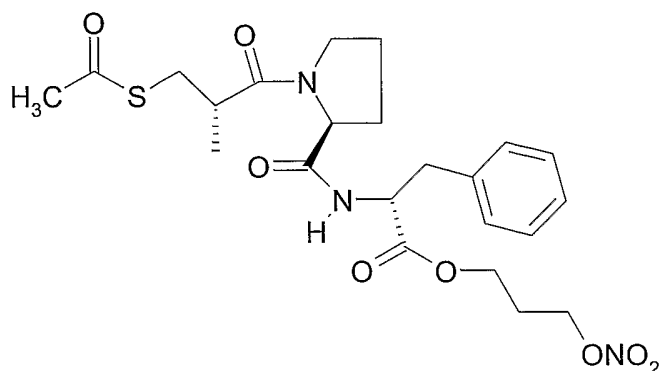


(75)

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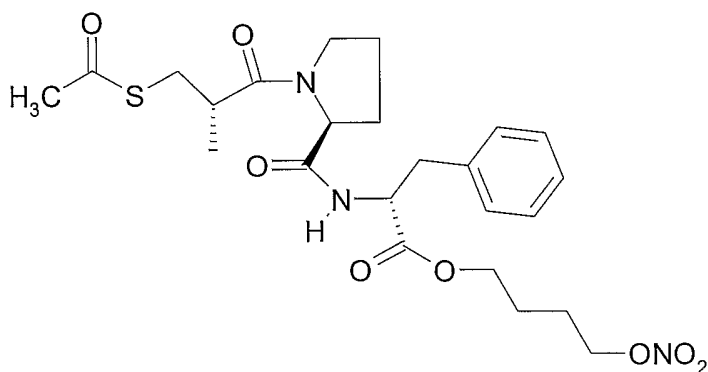
(76) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A = W wherein W is CH_3 , $X = -NH-$ and B is the group of

formula (IA) where $R_2 = -R_{3b}-ONO_2$ wherein R_{3b} is a straight C_3 alkylene:



(76)

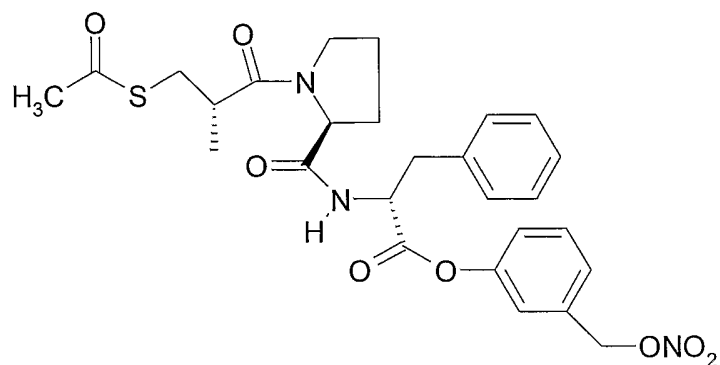
5 (77) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, $A = W$ wherein W is CH_3 , $X = -NH-$ and B is the group of formula (IA) where $R_2 = -R_{3b}-ONO_2$ wherein R_{3b} is a straight C_4 alkylene:



(77)

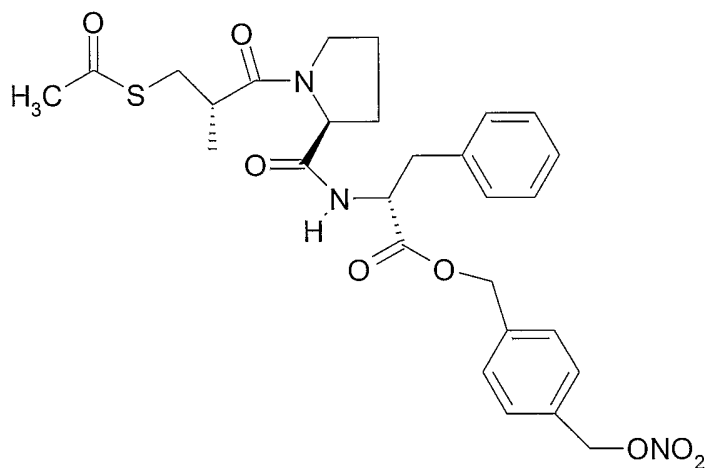
10

(78) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, $A = W$ wherein W is CH_3 , $X = -NH-$ and B is the group of formula (IA) where $R_2 = -R_{3b}-ONO_2$ wherein R_{3b} is the group as defined in b) wherein n_3 is an integer equal to 0 and
 15 $n_{3'}$ is an integer equal to 1:



(78)

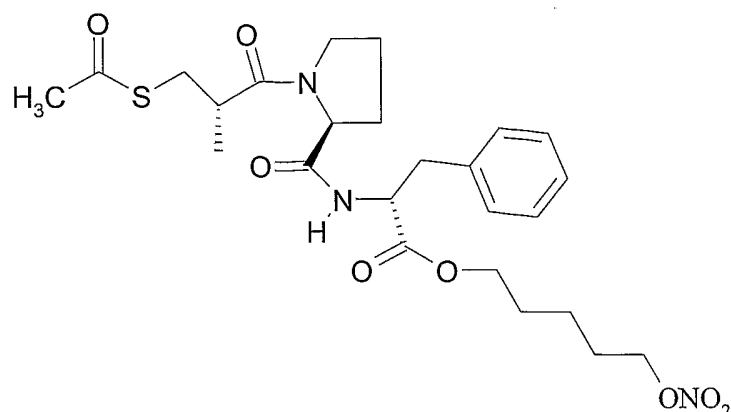
(79) A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -NH- and B is the group of formula (IA) where R₂ = -R_{3b}-ONO₂ wherein R_{3b} is the group as defined in b) wherein n₃ and n_{3'} are an integer equal to 1:



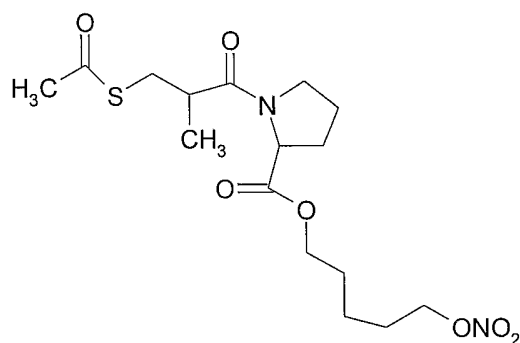
(79)

10

(80). A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -NH- and B is the group of formula (IA) where R₂ = -R_{3b}-ONO₂ wherein R_{3b} is a straight C₅ alkylene:



(81). A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -O- and B is = -R_{3a}-ONO₂ wherein R_{3a} is a straight C₅ alkylene;



5

In a further aspect, the present invention provides pharmaceutical compositions which comprise a compound of the general formula (I) reported above in combination with a pharmaceutical acceptable carrier. The daily dose of active ingredient administered to a host can be a single dose or it can be an effective amount divided into several smaller doses that are to be administered throughout the day. Usually, total daily dose may be in amounts from 1 to 2000 mg, preferably from 10 to 1000 mg, in particular from 50 to 500 mg. The dosage regimen and administration frequency for treating the mentioned diseases with the compound of the invention and/or with the pharmaceutical compositions of the present invention will be selected in accordance with a variety of factors, including for example

age, body weight, sex and medical condition of the patient as well as severity of the disease, route of administration, pharmacological considerations and eventual concomitant therapy with other drugs. In some instances, 5 dosage levels below or above the aforesaid range and/or more frequent may be adequate, and this logically will be within the judgment of the physician and will depend on the disease state.

The compounds of the invention may be administered orally, 10 parenterally, rectally or topically, by inhalation spray or aerosol, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles as desired. Topical administration may also involve the use of transdermal 15 administration such as transdermal patches or iontophoresis devices. The term "parenteral" as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Injectable preparations, for example, sterile injectable 20 aqueous or oleaginous suspensions may be formulated according to known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or 25 solvent. Among the acceptable vehicles and solvents are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed 30 including synthetic mono- or diglycerides, in addition fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the active ingredient with a suitable non-irritating excipient, such as cocoa butter and polyethylene glycols.

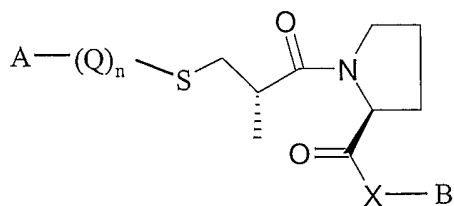
- 5 Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as in normal
10 practice, additional substances other than inert diluents, e.g. lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.
- 15 Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents,
20 emulsifying and suspending agents, and sweetening, flavoring and the like.

The compounds of the present invention can be synthesized as follows.

25 Experimentals: synthesis procedure

The compound of general formula (I) as above defined, or a pharmaceutically acceptable salt, can be obtained by a process comprising:

- i) reacting a compound of formula (II):



(II)

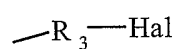
wherein:

Q and n are as above defined;

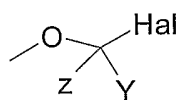
5 A = H, W wherein W is as above defined, aminic protecting group or

is chosen from the following groups:

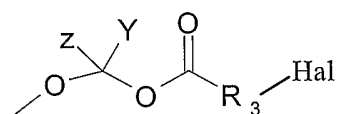
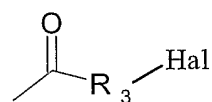
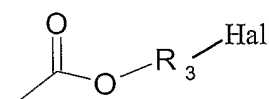
1a)



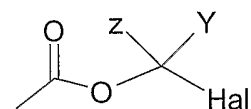
10 1b)



1c)

15 1d₁)1d₂)

20

1d₃)

25 wherein R₃, z and Y are as above defined;

X is as above defined;

B = H, carboxylic protecting group, $-R_{3a}-\text{Hal}$ wherein R_{3a} is as above defined or

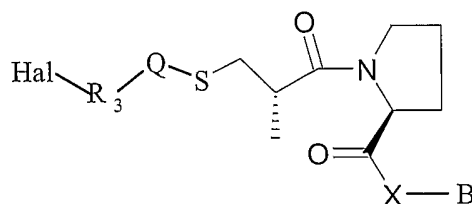
B is the group of formula (IA) as above defined, wherein R_2 is H, a straight or branched (C_1-C_6) -alkyl or $-R_{3b}-\text{Hal}$ wherein R_{3b} is as above defined; and Hal is an halogen preferably Cl, Br, and I,

with AgNO_3 in a suitable organic solvent such as acetonitrile or tetrahydrofuran (THF) under nitrogen at temperatures range between $20^\circ-80^\circ\text{C}$ and

ii) optionally acid hydrolysing the carboxylic protecting group or the aminic protecting group such as tert-butyloxycarbonyl ester (t-Boc), as well known in the art, for example as described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980 and

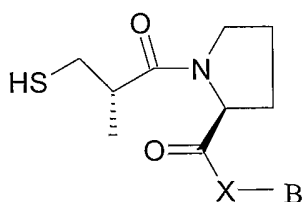
iii) if desired, converting the resulting compound of general formula (I) into a pharmaceutically acceptable salt thereof.

- The compound of formula (II) wherein $Q = -\text{CO}-$ or $-\text{OCO}-$, $n = 1$, $A = 1a$, $X = -\text{O}-$ or $-\text{NH}-$ and $B = \text{H}$, a carboxylic protecting group or the group (IA) wherein R_2 is a carboxylic protecting group, having the following formula:



25

can be obtained reacting a compound of formula (III):



(III)

with a compound of formula (IV):

5 Hal-R₃-Q-Hal (IV)

wherein Hal, R₃ and Q are as above defined;

The reaction is generally carried out in presence of a base in an aprotic polar/non-polar solvent such as THF or CH₂Cl₂ at temperatures range between 0°-65°C or in a double phase
 10 system H₂O/Et₂O at temperatures range between 20°- 40°C, or when Q = -CO- and X = -O- with the corresponding acid Hal-R₃-COOH in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or N,N'-carbonyldiimidazol (CDI) in solvent such as DMF, THF, chloroform at a
 15 temperature in the range from -5°C to 50°C.

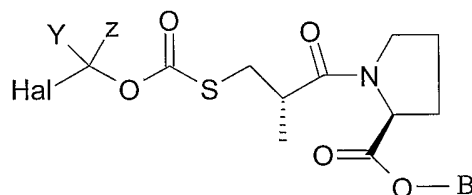
The compound of formula (III) wherein X = -O- and B is H is Captopril and it is commercially available; the compound of formula (III) wherein X = -O- and B is a carboxylic protecting group, preferably ter-butyl, can be obtained
 20 from Captopril according to well known reactions as described in U.S. Pat. No. 4,105,776; the compound of formula (III) wherein X = -NH- and B is the group (IA) wherein R₂ is a carboxylic protecting group can be obtained as described in U.S. Pat. No. 4,248,883.

25 The compounds of formula (IV) wherein Q = -CO- are commercially available or can be obtained from the corresponding acids by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P^{III} or P^V in solvents inert such as toluene, chloroform, DMF, etc.

The corresponding acids are commercially available compounds.

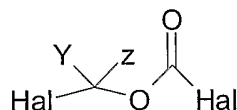
The compounds of formula (IV) wherein $Q = -OCO-$ are commercially available or can be obtained from the
5 corresponding alcohols by reaction with triphosgene in presence of an organic base.

- The compound of formula (II) wherein $Q = -CO-$, $n = 1$, $A = 1b$), $X = -O-$ and $B = H$ or a carboxylic protecting group, having the following formula:



10

can be obtained reacting a compound of formula (III) as above defined with a compound of formula (V):



15

(V)

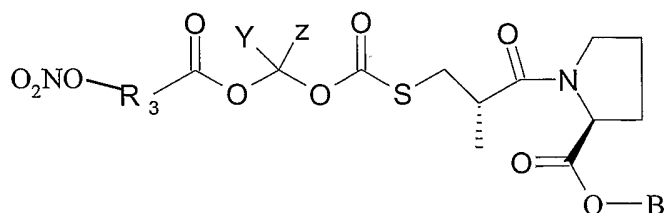
wherein Hal, Y and z are as above defined;

when Y and z are H or CH_3 , then the compounds of formula (V) are commercially available;

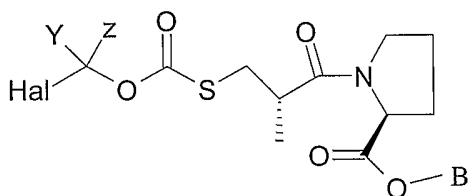
The reaction is generally carried out in presence of a base
20 in an aprotic polar solvent such as THF or dioxane at room temperature.

Alternatively, the compound of general formula (I) wherein $Q = -CO-$, $n = 1$, $A = 1c$), $X = -O-$ and $B = H$ or a carboxylic protecting group, having the following formula:

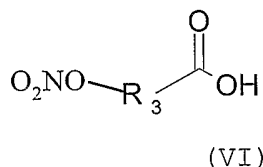
25



can be obtained by reacting a compound of formula (II) wherein $Q = -CO-$, $n = 1$, $A = 1b$), $X = -O-$ and $B = H$ or a
 5 carboxylic protecting group, as above described, having the following formula:

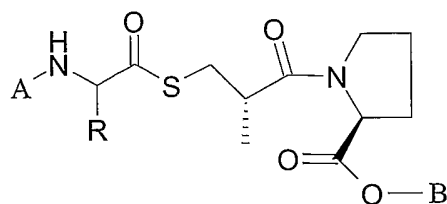


wherein Hal, Y and z are as above defined;
 10 with a compound of formula (VI):

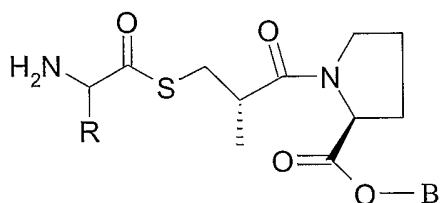


wherein R_3 is as above defined;

15 The reaction is generally carried out in presence of a base in an aprotic polar solvent such as THF at room temperature, or using the preformed Cs salt of the acid. The compounds of formula (VI) can be obtained from the corresponding alcohols by reaction with nitric acid and
 20 acetic anhydride in a temperature range from -50°C to 0°C .
 - The compound of formula (II) wherein $Q = -COCH(R)NH-$, $n = 1$, $A = 1d_{1-3}$), $X = -O-$ and $B = H$ or a carboxylic protecting group, having the following formula:



can be obtained by reacting a compound of formula (VII):



5

(VII)

with a compound of formula (IV) as above defined wherein Q
= -CO-, when A = 1d₁;

or

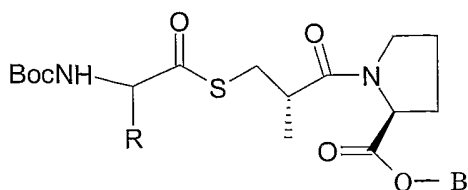
10 with a compound of formula (IV) as above defined wherein Q
= -OCO-, when A = 1d₂;

or

with a compound of formula (V) as above defined, when A =
1d₃;

15 The reaction is generally carried out in presence of an
organic or inorganic base in a dioxane/H₂O solution or in
an organic solvent such as CH₂Cl₂ at temperatures range
between 0°- 40°C.

The compound of formula (VII) can be obtained hydrolysing a
20 compound of formula (VIII) as known in the literature, for
example as described in T. W. Greene "Protective groups in
organic synthesis", Harvard University Press, 1980:



(VIII)

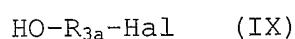
The compounds of formula (VIII) can be obtained reacting a compound of formula (III), as above defined, with an N-BOC aminoacid and carbonyldiimidazole in THF at temperatures range between 0°- 40°C.

The reaction is generally carried out in a monophasic or biphasic system in presence of an organic or inorganic base.

10 - The compound of formula (II) wherein Q is as above defined, $n = 1$, $A = H, W, 1a$), $X = -O-$ and B is $-R_{3a}-Hal$ can be obtained by esterifying a compound of formula (II) wherein:

Q is as above defined, $n = 1$, $A = H, W, 1a$), $X = -O-$ and B is H

15 with a compound of formula (IX):



wherein Hal and R_{3a} are as above defined;

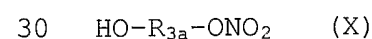
The reaction is generally carried out in presence of condensing agent such as DCC, in solvent such as $CHCl_3/EtOAc$.

The compounds of formula (IX) are commercially available.

Alternatively the compound of general formula (I) wherein Q = $-CO-$ or $-COCH(R)NH-$, $A = W$ or H , $n = 1$, $X = -O-$ and B is $-R_{3a}-Hal$ can be obtained by esterifying a compound of formula (II) wherein:

Q = $-CO-$ or $-COCH(R)NH-$, $A = W$ or H , $n = 1$, $X = -O-$ and B is H

with a compound of formula (X):



wherein R and R_{3a} are as above defined;

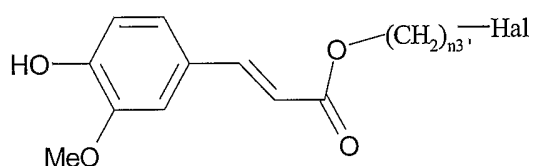
The reaction is generally carried out in presence of condensing agent as above reported.

The compounds of formula (X) can be obtained reacting a
5 compound of formula (IX) with AgNO₃ in a suitable organic solvent such as acetonitrile or THF under nitrogen at temperatures range between 20°-80°C.

- The compound of formula (II) wherein Q = -CO-, n = 1, A = W, X = -O- or -S- and B is -R_{3a}-Hal with R_{3a} = f) or g) can
10 be obtained by esterifying a compound of formula (II) wherein:

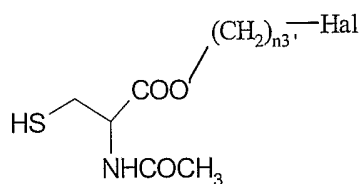
Q = -CO-, n = 1, A = W, X = -O- and B is H

with a compound of formula (XI) when R_{3a} = f):



15 (XI)

or with a compound of formula (XII) when R_{3a} = g):



(XII)

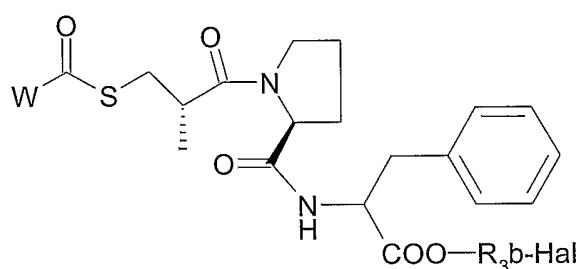
20 wherein n_{3'}, R_{3a}, W, f) and g) are as above defined;

The reaction is generally carried out in presence of condensing agent such as DCC or CDI, in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C.

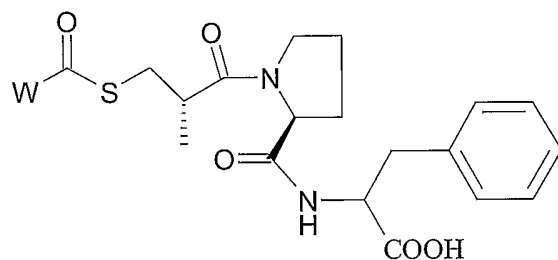
25 The compounds of formula (XI) and (XII) wherein n_{3'} is an integer equal to 4, can be obtained from the corresponding acids by reaction with triphenylphosphine in the presence

of an halogenating agent such as CBr_4 in THF at room temperature.

- The compound of formula (II) wherein $Q = -\text{CO}-$, $n = 1$, $A = W$, $X = -\text{NH}-$ and $B = (\text{IA})$ with $R_2 = -R_{3b}-\text{Hal}$, having the
5 following formula:



can be obtained by reacting a compound of formula (XIII):



10

(XIII)

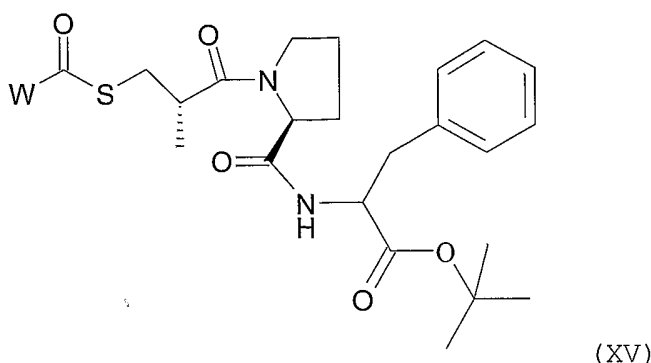
with a compound of formula (XIV):

$\text{HO}-R_{3b}-\text{Hal}$ (XIV)

wherein Hal , W , (IA) and R_{3b} are as above defined;

15 The reaction is generally carried out in presence of condensing agent such as DCC, in solvent such as CHCl_3 .

The compounds of formula (XIII) can be obtained by known methods from the compounds of formula (XV) by acid hydrolysis, as described in U.S. Pat. No. 4,248,883



When in formula (XIII) W is CH₃, the compound is known as Alacepril.

The compounds of formula (XIV) are commercially available.

- 5 The following examples are offered to further illustrate, but not to limit, the claimed invention.

Example 1

10 Synthesis of 1-[(2S)-3-(4-Nitrooxymethylbenzoyl) mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 3)

α-chloro-toluic acid (9.0 g, 0.0528 Mol) and carbonyldiimidazole (10.3 g, 0.0634 Mol) were dissolved in THF (100ml) and stirred overnight at room temperature. Then TEA was added (7.4 ml, 0.0528 Mol) and to this reaction mixture a solution of captopril (11.5 g, 0.0528 Mol) in THF (20ml) was added dropwise and the reaction was stirred overnight at room temperature. The mixture was then partitioned between KHSO₄ 10% and EtOAc (120 ml). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 60 ml). The combined organic phases were washed with water (3 x 60 ml), dried over sodium sulphate and evaporated under reduced pressure affording 14.1 g of 1-[(2S)-3-(4-chloromethylbenzoyl)mercapto-2-methyl-1-oxopropyl]-L-proline as a white solid used for the next step without further purification.

25

1-[(2S)-3-(4-chloromethylbenzoyl)mercapto-2-methyl-1-oxopropyl]-L-proline (13.94 g, 0.0378 Mol) was dissolved in acetonitrile (150 ml) under nitrogen in the dark. Silver nitrate (12.83 g, 0.0756 Mol) was added and the mixture was heated to 60° C for 6 h. After cooling silver salts were filtered off and the mixture was diluted with CH₂Cl₂ (150 ml) and washed with water (3 x 100 ml), then with brine (3 x 100 ml). The organic layer was then evaporated under reduced pressure affording the title compound (8.90 g, 60%) as a dense pale yellow oil.

¹H-NMR: (CDCl₃) (2 rotamers) 8.24 (d, 2H), 7.54 (d, 2H), 5.52 (s, 2H), 4.63 (m, 1H), 3.59 (m, 2H), 3.13 (m, 1H), 2.96 (m, 2H), 2.51 (m, 1H), 2.09 (m, 1H), 1.87 (m, 2H), 1.28 (d, 3H).

C₁₇H₂₀N₂O₇S : required % (found%) C 51.51 (51.41) H 5.09 (5.15) N 7.07 (7.05).

Examples 1a, 1b.

With the same procedure as described in Example 1, but starting utilizing the appropriate 'a-logeno substituted-carboxylic acid the following compounds can be obtained:

Ex. 1a). 1-[(2S)-3-(4-Nitrooxybutanoyl)mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 1) (oil, 48%).

¹H-NMR: (CDCl₃) (2 rotamers)), 4.63 (bd, 1H), 4.49 (t, 2H), 3.59 (m, 2H), 3.13 (m, 1H), 2.96 (m, 2H), 2.51 (m, 1H), 2.10 (m, 3H), 1.87 (m, 4H), 1.27 (d, 3H).

C₁₃H₂₀N₂O₇S : required % (found%) C 44.82 (44.75) H 5.79 (5.90) N 8.04 (7.95).

Ex. 1.b). 1-[(2S)-3-(4-Nitrooxypentanoyl)mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 2) (oil, 50%).

¹H-NMR: (CDCl₃) (2 rotamers)), 4.63 (m, 1H), 4.49 (t, 2H), 3.59 (m, 2H), 3.13 (m, 1H), 2.95 (m, 2H), 2.51 (m, 1H), 2.10 (m, 3H), 1.87 (m, 6H), 1.28 (d, 3H).

Example 2

5 **Synthesis of 1-[(2S)-3-(4-Nitrooxybutoxycarbonyl) mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 4)**

Captopril (3.50 g, 0.0161 Mol) and *N,N*-diisopropyl ethylamine (6.80 ml, 0.039 Mol) were dissolved in H₂O/CH₃CN
10 (80 ml, 1:1) and the mixture was cooled to 0°C. Then 4-chlorobutylchloroformate (2.70 ml, 0.0198 Mol) was added and the reaction was slowly warmed to room temperature and stirred for 4 h. The mixture was then partitioned between HCl (4%, 100 ml) and EtOAc (100 ml). The organic layer was
15 separated and the aqueous phase was extracted with EtOAc (2 x 100 ml). The combined organic phases were washed with brine (3 x 60 ml), dried over sodium sulphate and evaporated under reduced pressure affording **1-[(2S)-3-(4-chlorobutoxycarbonyl)mercapto-2-methyl-1-oxopropyl]-L-**
20 **proline** (5.90 g) as a colourless oil that was used without further purification.

1-[(2S)-3-(4-chlorobutoxycarbonyl)mercapto-2-methyl-1-oxopropyl]-L-proline (5.80 g, 0.0157 Mol) was dissolved in CH₃CN (100 ml) and NaI (23.9 g, 0.160 Mol) was added to the
25 solution. The mixture was refluxed for 7 h, then concentrated and diluted with CH₂Cl₂. The solid formed was filtered off and the organic phase was washed with H₂O (3 x 50 ml), dried over sodium sulphate and evaporated under reduced pressure affording **1-[(2S)-3-(4-iodobutoxycarbonyl)mercapto-2-methyl-1-oxopropyl]-L-proline** (7.10 g) as an
30 oil that was used without further purification.

1-[(2S)-3-(4-iodobutoxycarbonyl)mercapto-2-methyl-1-oxopropyl]-L-proline (7.0 g, 0.0152 Mol) was dissolved in

CH₃CN (40 ml) under nitrogen, in the dark, and AgNO₃ (8.44 g, 0.497 Mol) was added. The mixture was heated at 40-50°C for 2 hours. The salts were filtered off, the solution was diluted with CH₂Cl₂ and the organic phase was washed with H₂O (2 x 50 ml) and brine (50 ml), dried over sodium sulphate and evaporated under reduced pressure affording the title compound as a pure yellow oil (5.13 g, 89 %).

¹H-NMR: (CDCl₃) (2 rotamers) 4.65 (m, 1H), 4.50 (t, 2H), 4.28 (t, 2H), 3.61 (m, 2H), 3.12 (m, 1H), 2.96 (m, 2H), 2,50 (m, 1H), 2.14 (m, 3H), 1.83 (m, 4H), 1.28 (d, 3H).

Examples 2a, 2b,

With the same procedure as described in Example 2, but starting utilizing the appropriate 'a-ogeno-substituted-chloroformate the following compounds can be obtained:

Ex. 2a). 1-[(2S)-3-(4-Nitrooxypropoxycarbonyl)mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 5) (oil 75%).

¹H-NMR: (CDCl₃) (2 rotamers) 4.65 (m, 1H), 4.50 (t, 2H), 4.28 (t, 2H), 3.61 (m, 2H), 3.12 (m, 1H), 2.96 (m, 2H), 2,50 (m, 1H), 2.14 (m, 3H), 1.83 (m, 2H), 1.28 (d, 3H).

Ex. 2b). 1-[(2S)-3-(3-Nitrooxymethylbenzoyl)mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 6) (foam 75%).

¹H-NMR: (CDCl₃) (2 rotamers) 7.47-7.13 (4H, m), 5.44 (2H, s), 4.65 (m, 1H), 3.61 (m, 2H), 3.12 (m, 1H), 2.96 (m, 2H), 2,50 (m, 1H), 2.14 (m, 1H), 1.83 (m, 2H), 1.28 (d, 3H).

Example 3

Synthesis of 1-[(2S)-3-(Nitrooxymethoxycarbonyl)mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 8)

Captopril (2.48 g, 0.0114 Mol) and *N,N*-diisopropylethylamine (4.50 ml, 0.0258 Mol) were dissolved in

dioxane/H₂O (30 ml, 1:1). The mixture was cooled to 0°C and 1-chloromethyl chloroformate (1.20 ml, 0.0147 Mol) was added. The reaction was stirred at 0°C for 4 h, then partitioned between HCl (4 %, 30 ml) and CH₂Cl₂ (30 ml). The aqueous phase was extracted with CH₂Cl₂ (2 x 30 ml) and the combined organic phases were washed with HCl (4 %, 30 ml) and brine (3 x 30 ml), dried over sodium sulphate and evaporated under reduced pressure affording **1-[(2S)-3-(chloromethoxycarbonyl)mercapto-2-methyl-1-oxopropyl]-L-proline** as a clear oil (2.60 g) that was used without further purification.

1-[(2S)-3-(chloromethoxycarbonyl)mercapto-2-methyl-1-oxopropyl]-L-proline (2.59 g, 0.0084 Mol) was dissolved in dry CH₃CN (18 ml) under nitrogen, in the dark, and AgNO₃ (3.20 g, 0.019 Mol) was added. The mixture was heated at 40-50°C for 5 h and the salts were filtered off. It was then diluted with CH₂Cl₂ and the organic phase was washed with H₂O (2 x 50 ml) and brine (3 x 100 ml), dried over sodium sulphate and evaporated under reduced pressure affording the title compound as a pure light yellow foam (2.26 g, 84 %).

¹H-NMR: (CDCl₃) (2 rotamers) 6.1 (dd, 2H), 4.51 (m, 1H), 3.64 (m, 2H), 3.17 (m, 1H), 2.99 (m, 2H), 2.35 (m, 1H), 2.08 (m, 3H), 1.29 (d, 3H).

25 **Example 3a**

With the same procedure as described in Example 3, but starting from 1-chloroethylchloroformate, **1-[(2S)-3-(1-Nitrooxyethoxycarbonyl)mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 7)** was obtained as an oil (35%).

¹H-NMR: (CDCl₃) (2 rotamers) 6.5 (q, 1H), 4.51 (m, 1H), 3.64 (m, 2H), 3.17 (m, 1H), 2.99 (m, 2H), 2.35 (m, 1H), 2.08 (m, 3H), 1.98 (d, 3H), 1.29 (d, 3H).

Example 4**Synthesis of L-alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline 3-nitrooxypropyl ester hydrochloride (corresponding to compound 39)**

5 N-Boc alanine (10 g, 0.0528 Mol) and carbonyldiimidazole (10.3 g, 0.0634 Mol) were dissolved in THF (100ml) and stirred overnight at room temperature. Then TEA was added (7.4 ml, 0.0528 Mol) and to this reaction mixture a solution of captopril (11.5 g, 0.0528 Mol) in THF
10 (20ml) was added dropwise and the reaction was stirred overnight at room temperature. The mixture was then partitioned between KHSO₄ 10% and EtOAc (120 ml). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 60 ml). The combined organic
15 phases were washed with water (3 x 60 ml), dried over sodium sulphate and evaporated under reduced pressure affording 16 g of **L-N-Boc-alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline** as a white solid.

¹H-NMR (CDCl₃): (2 rotamers) 5.05 (bd, 1H), 4.90 (bd, 1H),
20 4.60 (m, 1H), 4.45 (m, 1H), 4.30 (m, 1H), 3.55 (m, 2H), 3.1 and 2.9 (m, 3H), 2.5 (m, 1H), 2.05 (m, 3H), 1.47 (s, 9H), 1.4 (d, 3H), 1.25 (d, 3H).

To a cold (0° C) solution of L-N-Boc-alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline (9.6 g, 0.0236 Mol),
25 bromopropanol (1.71 ml, 0.0196 Mol) and DMAP (0.24 g, 0.00196 Mol) in CHCl₃ (100ml) a solution of DCC (4.87 g, 0.0236 Mol) in CHCl₃ (20 ml) was added dropwise and the reaction was slowly warmed to room temperature and stirred overnight. Then the solvent was evaporated under reduced
30 pressure and the mixture was dissolved in EtOAc. The precipitated DCU was filtered off. The solution was evaporated and the residue was dissolved in EtOAc/n-Hexane 1:1 (100 ml) and again the precipitated DCU was filtered

off. The solution was evaporated and the residue was purified by flash chromatography (Hexane: EtOAc 6.5: 3.5) to afford 7 g of **L-N-boc alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline 3-bromopropyl ester** as a white foam.

¹H-NMR: (CDCl₃) (2 rotamers) 5.05 (bd, 1H), 4.4 (m, 1H), 4.25 and 4.2 (m, 3H), 3.55 (t, 2H), 3.4 (t, 2H), 3.0 and 2.9 (m, 2H), 2.75 (m, 1H), 2.15 (m, 3H), 1.95 (m, 3H), 1.4 (s, 9H), 1.3 (d, 3H), 1.2 (d, 3H).

L-N-boc-alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline 3-bromopropyl ester (7.0 g, 0.0132 Mol) was dissolved in dry CH₃CN (100 ml) under nitrogen, in the dark, and AgNO₃ (6.7 g, 0.0396 Mol) was added. The mixture was heated at 60°C for 8 h. Then the salts were filtered off and the residue was diluted with CH₂Cl₂ and the organic phase was washed with H₂O (2 x 50 ml) and brine (3 x 100 ml), dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by flash chromatography (n-hexane/EtOAc 1:1) affording 3 g of **L-N-boc-alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline 3-nitrooxypropyl ester** as a white solid.

¹H-NMR (CDCl₃): (2 rotamers) 4.9 (bd, 1H), 4.56 (t, 2H), 4.47 (m, 1H), 4.35 and 4.25 (m, 3H), 3.63 (t, 2H), 3.05 and 2.97 (m, 2H), 2.85 (m, 1H), 2.23 and 2.18 (m, 6H), 1.47 (s, 9H), 1.37 (d, 3H), 1.25 (d, 3H).

In a cold (0°C) solution of L-N-boc-alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline 3-nitrooxypropyl ester (3.0 g, 0.0058 Mol) in EtOAc (30 ml) a gaseous HCl stream was passed. After 1 hour the solution was evaporated and the residue was crystallized from EtOAc/diethyl ether affording the title compound (2.5 g 95%) as a white solid.

¹H-NMR (CDCl₃): (2 rotamers) 8.69 (bs, 3H), 4.6 and 4.5 (m, 3H), 4.35 (ds, 1H), 4.19 (t, 2H), 3.55 (bm, 2H), 3.15 (m,

2H), 2.85 (m, 1H), 2.2 and 2.0 (m, 6H), 1.7 (d, 3H), 1.25 (d, 3H).

Examples 4a, 4b, 4c.

Ex. 4a). With the same procedure as described in
5 Example 4 but utilizing 4-bromopropanol **L-Alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline 4-nitrooxybutyl ester hydrochloride** (corresponding to compound 38) was obtained as a white solid (80%);

Ex. 4b). With the same procedure as described in
10 Example 4 but utilizing 3-bromomethylphenol **L-Alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline 3-nitrooxymethylphenyl ester hydrochloride** (corresponding to compound 40) was obtained as a white solid (80%);

Ex. 4c). With the same procedure as described in
15 Example 4 but utilizing 4-bromomethylbenzylalcohol **L-Alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline 4-nitrooxymethylbenzyl ester hydrochloride** (corresponding to compound 41) was obtained as a white solid (78%).

20 **Example 5**

Synthesis of 1-[3-(4-Nitrooxybutoxycarbonyl)-L-alanyl-(2S)-mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 16)

In a cold (0°C) solution of L-N-Boc-alanyl-(2S)-3-
25 mercapto-2-methylpropanoyl-L-proline (12 g, 0.015 Mol), (obtained as described in first step of **Example 4**) in EtOAc (50 ml) a gaseous HCl stream was passed. After 1 h the solution was evaporated and the residue was crystallized from EtOAc/diethyl ether affording **L-alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline hydrochloride** (8.0 g
30 90%) as a white solid.

L-alanyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline hydrochloride (4.6 g, 0.0161 Mol) and N,N-diisopropyl

ethylamine (6.80 ml, 0.039 Mol) were dissolved in H₂O/CH₃CN (80 ml, 1:1) and the mixture was cooled to 0°C. Then 4-chlorobutylchloroformate (2.70 ml, 0.0198 Mol) was added and the reaction was slowly warmed to room temperature and stirred for 4 h. The mixture was then partitioned between HCl (4 %, 100 ml) and EtOAc (100 ml). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 100 ml). The combined organic phases were washed with brine (3 x 60 ml), dried over sodium sulphate and evaporated under reduced pressure affording **1-[(4-chlorobutoxycarbonyl)-L-alanyl-(2S)-3-mercapto-2-methyl-1-oxopropyl]-L-proline** (5.17 g) as a foam that was used without further purification.

1-[(4-chlorobutoxycarbonyl)-L-alanyl-(2S)-3-mercapto-2-methyl-1-oxopropyl]-L-proline (3.15 g, 0.0078 Mol) was dissolved in CH₃CN (100 ml) and NaI (11.7 g, 0.078 Mol) was added to the solution. The mixture was refluxed for 7 h, then concentrated and diluted with CH₂Cl₂. The solid formed was filtered off and the organic phase was washed with H₂O (3 x 50 ml), dried over sodium sulphate and evaporated under reduced pressure affording **1-[(4-iodobutoxycarbonyl)-L-alanyl-(2S)-3-mercapto-2-methyl-1-oxopropyl]-L-proline** (4.03 g) as a foam that was used without further purification.

1-[(4-iodobutoxycarbonyl)-L-alanyl-(2S)-3-mercapto-2-methyl-1-oxopropyl]-L-proline (4.0 g, 0.0078 Mol) was dissolved in CH₃CN (40 ml) under nitrogen, in the dark, and AgNO₃ (2.6 g, 0.0156 Mol) was added. The mixture was heated at 40-50 °C for 2 h. The salts were filtered off, the solution was diluted with CH₂Cl₂ and the organic phase was washed with H₂O (2 x 50 ml) and brine (50 ml), dried over sodium sulphate and evaporated under reduced pressure

affording the title compound as a pure yellow oil (3.6 g, 90 %).

Examples 5a, 5b, 5c, 5d.

With the same procedure as described in Example 5, but starting utilizing the appropriate α -halogeno substituted-chloroformate the following compounds can be obtained:

Ex. 5a). 1-[3-(4-Nitrooxypropoxycarbonyl)-L-alanyl-(2S)-mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 17);

10 **Ex. 5b).** 1-[3-(Nitrooxymethylphenoxy carbonyl)-L-alanyl-(2S)-mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 24).

Examples. 5c) 5d).

Using chloromethylchloroformate or 1-chloroethylchloroformate but directing nitrating the intermediate compounds (as described in **Example 3**) the following compounds can be obtained:

Ex. 5c) 1-[3-(Nitrooxymethoxycarbonyl)-L-alanyl-(2S)-mercapto to-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 19) (oil, 60%);

Ex. 5d). 1-[3-(1-Nitrooxyethoxycarbonyl)-L-alanyl-(2S)-mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 18) (oil, 65%).

25 **Example 6**

Synthesis of 1-[3-(4-Nitrooxymethylbenzoyl)-L-alanyl-(2S)-mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 14)

30 α -chloro-toluic acid (9.0 g, 0.0528 Mol) and carbonyldiimidazole (10.3 g, 0.0634 Mol) were dissolved in THF (100ml) and stirred overnight at room temperature. Then TEA was added (7.4 ml. 0.0528 Mol) and to this reaction mixture a solution of L-alanyl-(2S)-3-mercapto-2-

methylpropanoyl-L-proline hydrochloride (15.2 g, 0.0528 Mol) (obtained as described in first step **Example 5**) in THF (30 ml) was added dropwise and the reaction was stirred overnight at room temperature. The mixture was then
5 partitioned between KHSO₄ 10% and EtOAc (120 ml). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 60 ml). The combined organic phases were washed with water (3 x 60 ml), dried over sodium sulphate and evaporated under reduced pressure
10 affording 17.6 g. of **1-[3-(4-chloromethylbenzoyl)-L-alanyl-(2S)-mercapto-2-methyl-1-oxopropyl]-L-proline** as a white solid used for the next step without further purification.

1-[3-(4-chloromethylbenzoyl)-L-alanyl-(2S)-mercapto-2-methyl-1-oxopropyl]-L-proline (16.6 g, 0.0378 Mol) was
15 dissolved in acetonitrile (150 ml) under nitrogen in the dark. Silver nitrate (12.83 g, 0.0756 Mol) was added and the mixture was heated to 60° C for 6 h. After cooling silver salts were filtered off and the mixture was diluted with CH₂Cl₂ (150 ml) and washed with water (3 x 100 ml),
20 then with brine (3 x 100 ml). The organic layer was then evaporated under reduced pressure affording the title compound (10.6 g, 60%) as a pale yellow foam.

Examples 6a, 6b,

With the same procedure as described in Example 6, but
25 starting utilizing the appropriate 'α-alogeno substituted-carboxylic acid the following compounds can be obtained:

Ex. 6a). 1-[3-(4-nitrooxypentanoyl)-L-alanyl-(2S)-mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 10);

30 **Ex. 6b).** 1-[3-(4-nitrooxybutanoyl)-L-alanyl-(2S)-mercapto-2-methyl-1-oxopropyl]-L-proline (corresponding to compound 11).

Example 7

With the same procedure described in **Example 4**, N-Boc-glycine (9.25 g) (instead of N-Boc-alanine) was connected to captopril affording **N-Boc-glycyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline** (14.5 g). By acid hydrolysis as described in **Example 5**, **glycyl-(2S)-3-mercapto-2-methylpropanoyl-L-proline hydrochloride** (7.5 g) can be obtained. From it and the appropriate α -halogeno substituted-chloroformate or α -bromo substituted-carboxylic acid the compounds **12, 13, 15, 20, 21, 22, 23, 25** can be obtained.

Example 8

Synthesis of 1-[3-(Acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline 3-nitrooxypropyl ester (corresponding to compound 59)

A solution of DCC (2.37 g, 0.0115 Mol) in chloroform (20 ml) was dropped into a cold solution (0° C) of N-[3-(acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline hydrate (3.0 g, 0.0115 Mol), 3-bromopropanol (0.84 ml, 0.0096 Mol) and DMAP (0.142 g, 0.0011 mol) in chloroform (60 ml). The cold bath was removed and the mixture was stirred overnight. Then the solvent was evaporated under reduced pressure and the mixture was dissolved in EtOAc. The precipitated DCU was filtered off and the residue was purified by flash chromatography (Hexane: EtOAc 7:3) to afford **1-[3-(acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline 3-bromopropyl ester** (3.30 g) as a colourless oil.

1-[3-(acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline 3-bromopropyl ester (3.0 g, 0.0079 Mol) was dissolved in acetonitrile (50 ml) under nitrogen in the dark. Silver nitrate (4.03 g, 0.0237 Mol) was added and the mixture was heated to 60° C for 6 h. After cooling silver salts were

filtered off and the mixture was diluted with CH₂Cl₂ (100 ml) and washed with water (3 x 100 ml) then with brine (3 x 60 ml). The organic layer was then evaporated under reduced pressure and the residue was purified by flash chromatography (Hexane: EtOAc 6 : 4) to afford the title compound (1.70 g, 48%) as a colourless oil.

¹H-NMR (CDCl₃): (2 rotamers) 4.57 (t, 2H), 4.48 (m, 1H), 4.25 (2H, m), 3.62 (2H, t), 3.10 (1H, dd), 2.98 (1H, dd), 2.82 and 2.55 (1H, m), 2.34 and 2.31 (s, 3H), 2.3-1.9 (6 H, m) 1.24 and 1.19 (3H, d).

Examples 8a, 8b.

Ex. 8a). With the same procedure described in Example 8 but utilizing 4-bromopropanol 1-[(2S)-3-(Acetylthio)-2-methyl-1-oxopropyl]-L-proline 4-nitrooxybutylester (corresponding to compound 58) was obtained as a colourless oil (50%).

¹H-NMR (CDCl₃): (2 rotamers) 4.58 (t, 2H), 4.48 (m, 1H), 4.25 (2H, m), 3.62 (2H, t), 3.10 (1H, dd), 2.98 (1H, dd), 2.82 and 2.55 (1H, m), 2.34 and 2.31 (s, 3H), 2.3-1.8 (8 H, m) 1.24 and 1.19 (3H, d).

Ex. 8b). With the same procedure described in Example 8 but utilizing 3-bromomethylphenol 1-[3-(acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline 3-nitrooxymethylphenyl ester (corresponding to compound 60) was obtained as a dense pale yellow oil (55%).

¹H-NMR (CDCl₃): (2 rotamers) 7.5-7.1 (4H, m), 5.46 and 5.43 (2H, s), 4.75-4.6 (1H, m), 3.7 (2H, m), 3.10 (1H, dd), 2.98 (1H, dd), 2.85 (1H, m), 2.48-2.0 (4H, m), 1.23 (3H, d).

30 Example 9

Synthesis of 1-[(2S)-3-(Acetylthio)-2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine 3-nitrooxymethyl phenyl ester

(i.e. Alacepril 3-nitrooxymethyl phenyl ester)
(corresponding to compound 78)

N-[3-(acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline hydrate (1.00 g, 0.039 Mol), 4-dimethylaminopyridine (0.095 g, 0.008 Mol), L-Phenylalanine tert-butyl ester (1.00 g, 0.039 Mol) and triethylamine (1.60 ml, 0.12 Mol) were dissolved in CHCl₃ (15.0 ml). The solution was cooled to 0°C and N'-(3-Dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (0.890 mg, 0.046 Mol) was added. The reaction was stirred at room temperature for 6 h then it was diluted with CH₂Cl₂ (15 ml) and extracted with HCl 4 %, (3 x 20 ml), NaHCO₃ 5 %, (3 x 20 ml), washed with brine (3 x 20 ml), dried over Na₂SO₄ and evaporated under reduced pressure to afford 1-[(2S)-3-(Acetylthio)-2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine tert-butyl ester (1.19 g, 66 %) as pale yellow oil.

¹H-NMR (CDCl₃): 7.15 (m, 5H), 4.63 (m, 2H), 3.46 (m, 2H), 2.99 (m, 4H), 2.73 (m, 1H), 2.28 (s, 3H), 1.88 (m, 3H), 1.37 (s, 9H), 1.08 (d, 3H)

1-[(2S)-3-(Acetylthio)-2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine tert-butyl ester (1.19 g, 0.025 Mol) was dissolved in a solution of trifluoroacetic acid : CH₂Cl₂ (1:2, 30 ml) and the reaction was stirred at room temperature for 1 hour. Then it was evaporated under reduced pressure affording 1-[(2S)-3-(acetylthio)-2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine as a clear oil (1.00 g, 100 %) that was used in the subsequent reaction without any further purification.

¹H-NMR (CDCl₃): 7.23 (m, 5H), 7.05 (d, 1H), 4.91 (m, 1H), 4.55 (m, 1H), 3.62 (m, 2H), 3.15 (m, 3H), 2.92 (m, 2H), 2.38 (s, 3H), 2.07 (m, 4H), 1.88 (m, 3H), 1.17 (d, 3H).

1-[(2S)-3-(acetylthio)-2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine (1.00 g, 0.025 Mol), 1-hydroxy-3-

bromomethylbenzene (0.463 g, 0.025 Mol) and 4-dimethylaminopyridine (0.060 g, 0.005 Mol) were dissolved in CHCl₃ (10 ml) and the solution was cooled to 0°C. Dicyclohexylcarbodiimide (0.70 g, 0.033 Mol) was then added
5 and the solution was slowly warmed to room temperature and stirred for 5 h. The crude material was concentrated and purified by flash chromatography eluting with EtOAc/n-Hexane 1:1, affording 1-[(2S)-3-(Acetylthio)-2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine 3-bromomethyl phenyl
10 ester (i.e. Alacepril 3-bromomethyl phenyl ester) (1.00 g) as a white powder.

¹H-NMR (CDCl₃): 7.30 (m, 7H), 6.98 (m, 2H), 4.98 (m, 1H), 4.66 (m, 1H), 4.45 (s, 2H), 3.45 (m, 3H), 3.28 (m, 2H), 3.09 (m, 1H), 3.07 (m, 1H), 2.78 (m, 1H), 2.34 (s, 3H),
15 2.00 (m, 4H), 1.01 (d, 3H).

1-[(2S)-3-(Acetylthio)-2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine 3-bromomethyl phenyl ester (1.00 g, 0.017 Mol) was dissolved in CH₃CN (10 ml) and AgNO₃ (0.73 g, 0.043 Mol) was added in the dark, under nitrogen. The
20 mixture was heated at 40-50°C for 6 h. The salts were filtered off, the solution was diluted with CH₂Cl₂ and the organic phase was washed with H₂O (2 x 50 ml) and brine (50 ml), dried over Na₂SO₄ and concentrated. The crude material was purified by flash chromatography eluting with EtOAc/n-
25 Hexane (1:1), affording the title compound as a dense oil (380 mg, 40%).

¹H-NMR (CDCl₃): 7.30 (m, 7H), 6.98 (m, 2H), 5.55 (s, 2H), 4.98 (m, 1H), 4.66 (m, 1H), 3.45 (m, 3H), 3.28 (m, 2H), 3.09 (m, 1H), 3.07 (m, 1H), 2.78 (m, 1H), 2.34 (s, 3H),
30 2.00 (m, 4H), 1.01 (d, 3H).

Examples 9a, 9b, 9c.

Ex. 9a). With the same procedure described in Example 9 but starting from 3-bromo propanol 1-[(2S)-3-(Acetylthio)-

2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine 3-nitrooxypropyl ester (corresponding to compound 76) was obtained;

Ex. 9b). With the same procedure described in Example 9 but starting from 4-bromobutanol 1-[(2S)-3-(Acetylthio)-2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine 4-nitrooxybutyl ester (corresponding to compound 77) was obtained as a white solid;

Ex. 9c). With the same procedure described in Example 9 but starting from 4-bromomethylbenzyl alcohol 1-[(2S)-3-(Acetylthio)-2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine 4-nitrooxymethylbenzyl ester (corresponding to compound 79) was obtained as a white solid.

15 Pharmacological experiments

Example 10

Evaluation of the vasorelaxing activity of the compounds according to the invention and the native ACE inhibitor 20 captopril.

The tested compounds are the following:

- 1-[3-(Acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline 3-nitrooxy propyl ester, (compound of Ex.8)
- 1-[3-(acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline 3-nitrooxymethylphenyl ester, (compound of Ex. 8b)
- 1-[(2S)-3-(Nitrooxymethoxycarbonyl) mercapto-2-methyl-1-oxopropyl]-L-proline, (compound of Ex. 3)
- 1-[(2S)-3-(4-Nitrooxybutoxycarbonyl) mercapto-2-methyl-1-oxopropyl]-L-proline, (compound of Ex. 2)

- 1-[(2S)-3-(Acetylthio)-2-methyl-1-oxopropyl]-L-prolyl-L-phenylalanine 3-nitrooxymethyl phenyl ester, (compound Ex. of 9)
- captopril.

5 The ability of the captopril nitroderivatives of the invention to induce vasorelaxation was tested *in vitro* in isolated rabbit thoracic aorta preparations (Wanstall J.C. et al., Br. J. Pharmacol., 134:463-472, 2001). Male New Zealand rabbits were anaesthetized with thiopental-Na (50
10 mg/kg, iv), sacrificed by exsanguinations and then the thorax was opened and the aorta dissected. Single ring preparations (4 mm in length) of thoracic aorta were set up in physiological salt solution (PSS) at 37°C in small organ chambers (5 ml). The composition of PSS was (mM): NaCl 130,
15 NaHCO₃ 14.9, KH₂PO₄ 1.2, MgSO₄ 1.2, HEPES 10, CaCl₂, ascorbic acid 170 and glucose 1.1 (95% O₂ /5% CO₂ ; pH 7.4). Each ring was mounted under 2 g passive tension. Isometric tension was recorded with a Grass transducer (Grass FT03) attached to a BIOPAC MP150 System. Preparations were
20 allowed to equilibrate for 1 h, then contracted submaximally with noradrenaline (NA, 1 µM) and, when the contraction was stable, acetylcholine (ACh, 10 µM) was added. A relaxant response to ACh indicated the presence of a functional endothelium. Vessel that were unable to
25 contract to NA or showed no relaxation to ACh were discarded. When a stable precontraction was reached, a cumulative concentration-response curve for each of the tested compounds was obtained in the presence of a functional endothelium. Time intervals between different
30 concentrations were based on the time needed to reach a full response. Each arterial ring was exposed to only one combination of inhibitor and the tested compounds.

Moreover, the effect of the soluble guanylyl cyclase inhibitor ODQ (1-H-(1,2,4)-oxadiazol(4,3-a)quinoxalin-1-one) on the dilator responses elicited by the compounds was examined preincubating the aortic rings with ODQ (10 μ M) for 20 min.

Results are expressed as IC_{50} value, which is the concentration of the tested compound producing 50% of the maximum relaxation, and as E_{max} value which is the maximum efficacy at a concentration of 100 μ M of the tested compound.

During the experimental period, the plateau obtained with NA was stable without significant spontaneous loss of contraction in the aortic rings. Under these experimental conditions, the native ACE inhibitor, captopril, did not produce relaxation at any of the concentration tested, the curve being not different from that built up in presence of vehicle alone.

Furthermore, in experiments performed in presence of ODQ (10 μ M), the vasorelaxant responses to all the tested compounds were inhibited.

Table 1

Vasorelaxing activity of the compounds according to the invention and of captopril		
Compound	E _{max}	IC ₅₀ (μM)
Captopril	0	0
Compound of Ex. 8b	92.4 ± 4.15	4.01 ± 1.18
Compound of Ex. 8	77.9 ± 3.21	26.1 ± 3.91
Compound of Ex. 3	97.9 ± 1.51	6.7 ± 0.84
Compound of Ex. 2	96.9 ± 1.87	6.0 ± 0.87
Compound of Ex. 9	96.8 ± 0.65	3.2 ± 0.65

5 Example 11

Evaluation of antihypertensive activity and of the ACE activity of the compounds according to the invention versus captopril in a genetic model of hypertension (SHR rats).

10 The tested compounds are the following:

- 1-[3-(Acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline 3-nitrooxy propyl ester, (compound Ex.8)

- 1-[3-(acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline 3-nitrooxymethylphenyl ester, (compound in Ex. 8b)
- captopril

SHR rats were treated orally in a single dose of 30 mg/Kg. After 2 hours the animal were anaesthetized with tiopental-Na; a fluid catheter was inserted in a right carotid artery and connected to a transducer for the homodynamic measurements. 4 hours after the treatment the arterial pressure (MAP, mmHg) was measured. Results are reported in table 2.

As shown in Table 2, the nitroderivatives of the invention 1-[3-(Acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline 3-nitrooxy propyl ester (compound Ex.8) and 1-[3-(acetylthio)-(2S)-methyl-1-oxopropyl]-L-proline 3-nitrooxy methylphenyl ester (compound Ex.8b), were able to reduce blood pressure by 35% and by 43% respectively vs the control at 4 hrs after treatment.

At the end of the experiments the blood was collected from the right carotid. The heparinized blood samples were centrifuged at 1000g for 20 min at 4°C. The plasma was stored at -20°C until the ACE activity measurements.

The ACE activity was determined by a spectrophotometric method (Sigma) based on the enzymatic reaction catalysed by ACE, where the FAPGG was hydrolysed to FAP.

FAPGG hydrolysis produced a decrease in the absorbance at 340 nm, a marker of ACE activity in the sample. Results, reported in table 3, were expressed as U/L in heparinized plasma.

As shown in Table 3, the compounds of the invention inhibited ACE activity in a better extent than captopril.

Table 2

Arterial pressure (MAP, mmHg) monitored at the 4 th hours after the treatment.			
vehicle	Captopril	Comp. of Ex. 8	Comp. of Ex. 8b
202	145	132	116

5

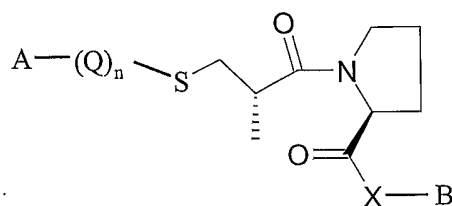
Table 3

ACE activity (U/L)			
vehicle	Captopril	Comp. of Ex. 8	Comp. of Ex. 8b
85	66	59	53

CLAIMS

1. A compound of general formula (I) and/or a pharmaceutically acceptable salt or stereoisomer thereof

5



(I)

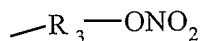
wherein:

Q = -CO-, -OCO-, -CONH-, -COCH(R)NH- wherein R is H,
10 straight or branched (C₁-C₆)-alkyl, -(CH₂)₂SCH₃ or benzyl;
with the proviso that -S- is bound to -CO;

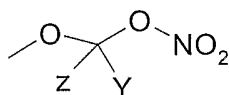
n is an integer equal to 0 or 1;

A = H, W (wherein W is C₁-C₆-alkyl, phenyl or benzyl) or is
chosen from the following groups:

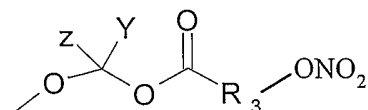
15 1a)



1b)

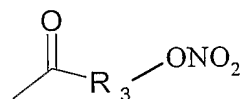


1c)

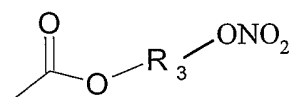
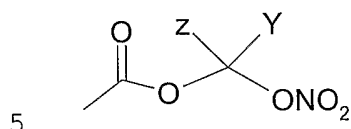


20

wherein z and Y are the same or different, and are H or
straight or branched (C₁-C₄)-alkyl; with the proviso that
when A is selected from the groups 1b and 1c, Q = -CO-;

1d₁)

25

1d₂)1d₃)

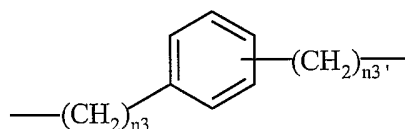
wherein z and Y are as above defined;

with the proviso that when A is selected from the groups 1d₁-1d₃, Q = -COCH(R)NH- wherein R is as above defined;

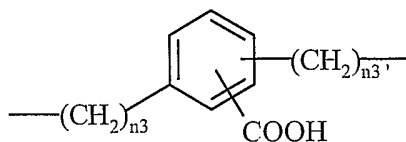
R₃ is a bivalent radical having the following meanings:

- 10 a) straight or whenever possible branched C₁-C₂₀ alkylene, optionally substituted with at least an alogen atom, preferably having from 1 to 5 carbon atoms, or an optionally substituted cycloalkylene having from 5 to 7 carbon atoms;

- 15 b)



- c)



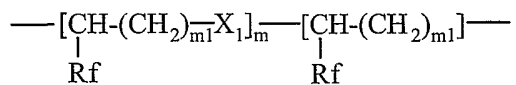
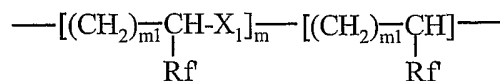
- 20 wherein:

n₃ is an integer from 0 to 20, preferably from 0 to 5;

n₃' is an integer from 1 to 20, preferably from 1 to 5;

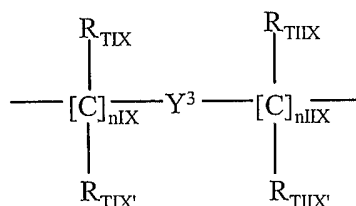
wherein the -ONO₂ group is bound to a -CH₂ group;

- d)

d₁)

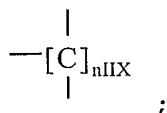
- wherein X₁ is -O- or -S-, m is an integer from 1 to 6,
 5 preferably from 1 to 4, m₁ is an integer from 1 to 10,
 preferably from 1 to 5, Rf is a hydrogen atom or CH₃, Rf'
 is CH₃;
 wherein m is an integer from 1 to 6, preferably from 1 to
 4, Rf is a hydrogen atom or CH₃;

10 e)

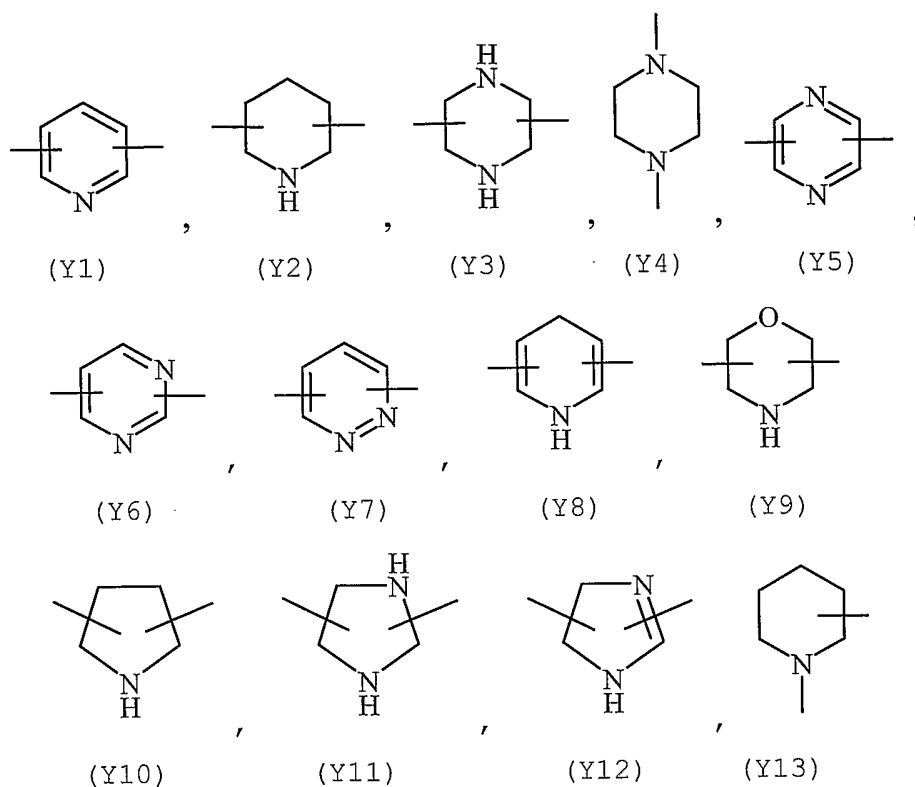


wherein:

- nIX is an integer from 0 to 10, preferably from 0 to 3;
 nIIX is an integer from 1 to 10, preferably from 1 to 3;
 15 R_{TIX}, R_{TIX'}, R_{TIIX}, R_{TIIX'}, are the same or different, and are H
 or straight or branched (C₁-C₄)-alkyl, preferably R_{TIX}, R_{TIX'},
 R_{TIIX}, R_{TIIX'} are H;
 and wherein the -ONO₂ group is bound to



- 20 Y³ è an heterocyclic saturated, unsaturated or aromatic 5
 or 6 members ring, containing one or more heteroatoms
 selected from nitrogen, oxygen, sulphur, and selected
 for example from

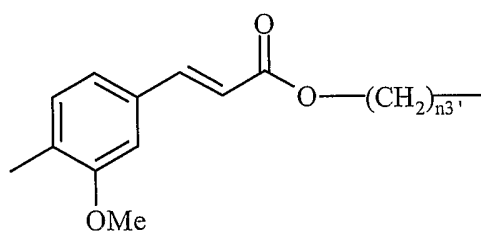


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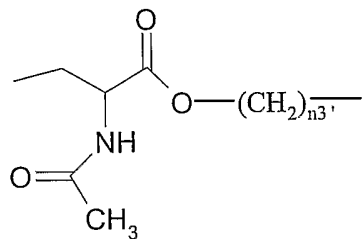
X = -NH-, -O-, -S-;

B = H , -R_{3a}-ONO₂ wherein R_{3a} has the same meaning of R₃ as
 10 above defined or is chosen from the following groups:

f)

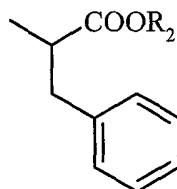


g)



wherein $n_{3'}$ is as above defined; wherein the $-\text{ONO}_2$ group is bound to the group $-(\text{CH}_2)_{n_{3'}}$;

or B is the group of formula (IA):



5 (IA)

wherein R_2 is H, a straight or branched $(\text{C}_1\text{-C}_6)$ -alkyl or $-\text{R}_{3b}\text{-ONO}_2$, R_{3b} has the same meaning of R_3 as above defined in a);

Provided that:

- 10 i) when R_{3a} is the group as defined in f) and g) then A is W;
- ii) when R_{3a} is the group as defined in g) then X is $-\text{S}-$;
- iii) when B is the group of formula (IA) then X is $-\text{NH}-$;
- 15 iv) at least one of the groups A or B contains a $-\text{ONO}_2$ group.

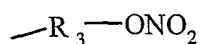
2. A compound of general formula (I) and/or a pharmaceutically acceptable salt or stereoisomer thereof according to claim 1 wherein:

- 20 Q = $-\text{CO}-$, $-\text{OCO}-$, $-\text{CONH}-$, $-\text{COCH}(\text{R})\text{NH}-$ wherein R is H or CH_3 ; with the proviso that $-\text{S}-$ is bound to $-\text{CO}$;

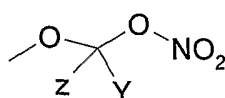
n is an integer equal to 0 or 1;

A = H, W (wherein W is $\text{C}_1\text{-C}_6$ -alkyl preferably CH_3) or is chosen from the following groups:

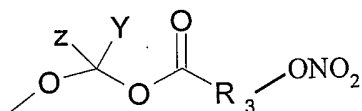
- 25 1a)



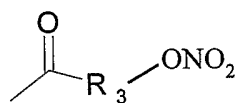
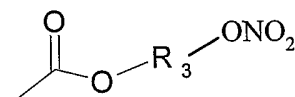
- 1b)



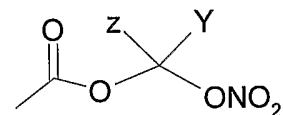
1c)



wherein z and Y are the same or different, and are H or CH₃; with the proviso that when A is selected from the groups 1b and 1c, Q = -CO-;

1d₁)1d₂)

10

1d₃)

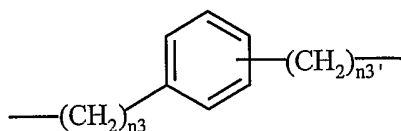
wherein z and Y are as above defined;
with the proviso that when A is selected from groups 1d₁-1d₃, Q = -COCH(R)NH- where R is as above defined;

R₃ is a bivalent radical having the following meanings:

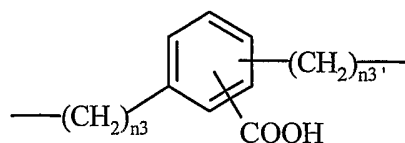
a) straight C₁-C₆ alkylene, preferably C₃-C₅ alkylene;

20

b)



c)

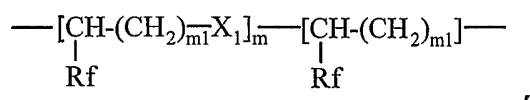


wherein:

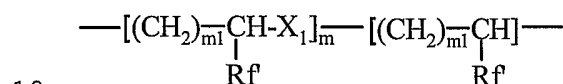
n_3 is an integer from 0 to 5 and $n_{3'}$ is an integer from 1 to 5;

5 wherein the $-\text{ONO}_2$ group is bound to a $-\text{CH}_2$ group;

d)



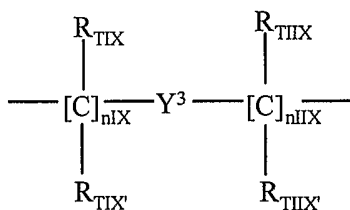
d₁)



10

wherein X_1 is $-\text{O}-$ or $-\text{S}-$, m is an integer from 1 to 6, preferably from 1 to 4, m_1 is an integer from 1 to 10, preferably from 1 to 5, Rf is a hydrogen atom or CH_3 , Rf' is CH_3 ;

15 e)



wherein:

n_{IX} is an integer from 0 to 3 and n_{IIX} is an integer from 1 to 3;

20 R_{TIX} , $\text{R}_{\text{TIX}'}$, R_{TII} , $\text{R}_{\text{TII}'}$ are the same and are H;

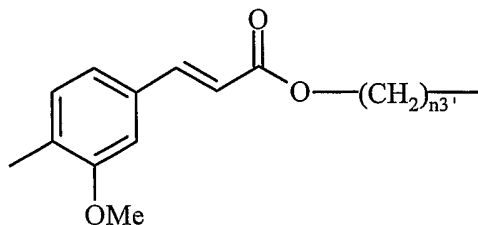
wherein the $-\text{ONO}_2$ group is bound to a $-\text{CH}_2$ group;

Y^3 is a heterocyclic saturated, unsaturated or aromatic, containing one or more atoms of nitrogen and selected from Y1-Y6 as defined in claim 1.

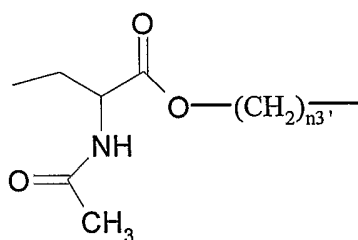
25 $\text{X} = -\text{NH}-$, $-\text{O}-$, $-\text{S}-$;

B = H, $-R_{3a}-ONO_2$ wherein R_{3a} has the same meaning of R_3 as above defined or is chosen from the following groups:

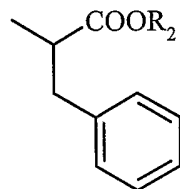
f)



5 g)



wherein $n_{3'}$ is as above defined, preferably 4; wherein the $-ONO_2$ group is bound to the group $-(CH_2)_{n_{3'}}$; or B is the group of formula (IA):



10

(IA)

wherein R_2 is H, a straight or branched (C_1-C_6) -alkyl or $-R_{3b}-ONO_2$, R_{3b} has the same meaning of R_3 as above defined in a).

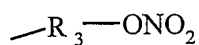
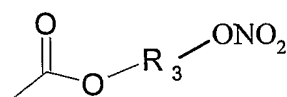
15

3. A compound of general formula (I) and/or a pharmaceutically acceptable salt or stereoisomer thereof according to claim 1 wherein:

Q = $-CO-$, $-OCO-$, $-CONH-$, $-COCH(R)NH-$ wherein R is H or
20 CH_3 ; with the proviso that $-S-$ is bound to $-CO$;
n is 1;

A is chosen from the following groups:

1a)

1d₂)

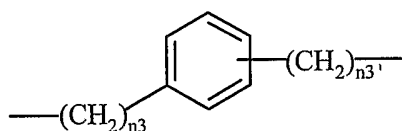
5

with the proviso that when A is selected from group 1d₂, Q
= -COCH(R)NH- where R is as above defined;

R₃ is a bivalent radical having the following meanings:

a) straight or branched C₁-C₆ alkylene;

10 b)



wherein:

n₃ is 0 or 1 and n_{3'} is 1;

15 wherein the -ONO₂ group is bound to a -CH₂ group;

X = -O-;

B = H.

4. A compound of general formula (I) and/or a
20 pharmaceutically acceptable salt or stereoisomer thereof
according to claim 1 wherein:

Q = -CO-;

n is 1;

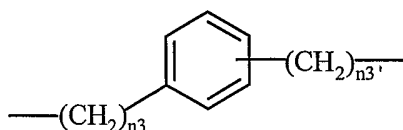
A is CH₃;

25 X = -O-;

B is -R_{3a}-ONO₂ wherein R_{3a} have the following meanings:

a) straight C₁-C₆ alkylene;

b)



wherein:

n_3 is 0 or 1 and $n_{3'}$ is 1;

5 wherein the $-\text{ONO}_2$ group is bound to a $-\text{CH}_2$ group;

5. A compound of general formula (I) and/or a pharmaceutically acceptable salt or stereoisomer thereof according to claim 1 wherein:

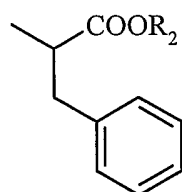
10 Q = $-\text{CO}-$;

n is 1;

A is CH_3 ;

X = $-\text{NH}-$;

B is the group of formula (IA):



15

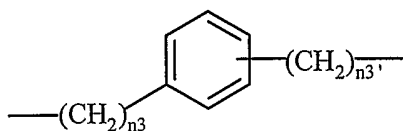
(IA)

wherein R_2 is $-\text{R}_{3b}-\text{ONO}_2$,

wherein R_{3b} have the following meanings:

a) straight C_1 - C_6 alkylene;

20 b)



wherein:

n_3 is 0 or 1 and $n_{3'}$ are 1;

25 wherein the $-\text{ONO}_2$ group is bound to a $-\text{CH}_2-$ group.

6. A compound according to claim 1, selected from the group consisting of:

- (1) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is H;
5
- (2) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is H;
- (3) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A
10 is the group as defined in 1a) wherein R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1, $X = -O-$ and B is H;
- (4) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4
15 alkylene, $X = -O-$ and B is H;
- (5) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is H;
- (6) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A
20 is the group as defined in 1a) wherein R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1, $X = -O-$ and B is H;
- (7) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z is H and Y is CH_3 ,
25 $X = -O-$ and B is H;
- (8) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z and Y are H, $X = -O-$ and B is H;
- (9) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A
30 is the group as defined in 1c) wherein z and Y are H, R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1, $X = -O-$ and B is H;

- (10) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and B is H;
- (11) A compound of formula (I) wherein $Q = -COCH(R)NH-$ 5 with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and B is H;
- (12) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and B is H;
- 10 - (13) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and B is H;
- (14) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) 15 wherein R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1, $X = -O-$ and B is H;
- (15) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) 20 wherein R_3 is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1, $X = -O-$ and B is H;
- (16) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₂) 25 wherein R_3 is a straight C₄ alkylene, $X = -O-$ and B is H;
- (17) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₂) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and B is H;
- (18) A compound of formula (I) wherein $Q = -COCH(R)NH-$ 30 with $R = CH_3$, $n = 1$, A is the group as defined in 1d₃) wherein z is H and Y is CH₃, $X = -O-$ and B is H;

- (19) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₃) wherein z and Y are H, $X = -O-$ and B is H;
- (20) A compound of formula (I) wherein $Q = -COCH(R)NH-$
5 with $R = H$, $n = 1$, A is the group as defined in 1d₂) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and B is H;
- (21) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₂) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and B is H;
- 10 - (22) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₃) wherein z is H and Y is CH₃, $X = -O-$ and B is H;
- (23) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₃)
15 wherein z and Y are H, $X = -O-$ and B is H;
- (24) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₂) wherein R_3 is the group as defined in b) wherein n₃ is an integer equal to 0 and n₃' is an integer equal to 1, $X = -$
20 $O-$ and B is H;
- (25) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₂) wherein R_3 is the group as defined in b) wherein n₃ is an integer equal to 0 and n₃' is an integer equal to 1, $X = -$
25 $O-$ and B is H;
- (26) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₃ alkylene;
- 30 - (27) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₃ alkylene;

- (28) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1;
- (29) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1;
- (30) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₃ alkylene;
- (31) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₃ alkylene;
- (32) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1;
- (33) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1;
- (34) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₄ alkylene;

- (35) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₄ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₄ alkylene;
- 5 - (36) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₄ alkylene;
- (37) A compound of formula (I) wherein $Q = -COCH(R)NH-$
10 with $R = H$, $n = 1$, A is the group as defined in 1d₁) wherein R_3 is a straight C₃ alkylene, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₄ alkylene;
- (38) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is H, $X = -O-$ and $B = -R_{3a}-ONO_2$
15 wherein R_{3a} is a straight C₄ alkylene;
- (39) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is H, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₃ alkylene;
- (40) A compound of formula (I) wherein $Q = -COCH(R)NH-$
20 with $R = CH_3$, $n = 1$, A is H, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and $n_{3'}$ is an integer equal to 1;
- (41) A compound of formula (I) wherein $Q = -COCH(R)NH-$ with $R = CH_3$, $n = 1$, A is H, $X = -O-$ and $B = -R_{3a}-ONO_2$
25 wherein R_{3a} is the group as defined in b) wherein n_3 and $n_{3'}$ are an integer equal to 1;
- (42) A compound of formula (I) wherein $Q = -COCH(R)NH-$ wherein R and A are H, $n = 1$, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₃ alkylene;
- 30 - (43) A compound of formula (I) wherein $Q = -COCH(R)NH-$ wherein R and A are H, $n = 1$, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is a straight C₄ alkylene;

- (44) A compound of formula (I) wherein $Q = -COCH(R)NH-$ wherein R and A are H, $n = 1$, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1;
- 5 - (45) A compound of formula (I) wherein $Q = -COCH(R)NH-$ wherein R and A are H, $n = 1$, $X = -O-$ and $B = -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 and n_3' are an integer equal to 1;
- (46) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene;
- 10 - (47) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene;
- 15 - (48) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1;
- 20 - (49) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1;
- 25 - (50) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene;
- 30 - (51) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4

- alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene;
- (52) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene;
- 5 C_3 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene;
- (53) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene;
- 10 straight C_4 alkylene;
- (54) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1;
- 15 and n_3' is an integer equal to 1;
- (55) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1;
- 20 and n_3' is an integer equal to 1;
- (56) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_3 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene;
- 25 straight C_4 alkylene;
- (57) A compound of formula (I) wherein $Q = -OCO-$, $n = 1$, A is the group as defined in 1a) wherein R_3 is a straight C_4 alkylene, $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene;
- 30 straight C_3 alkylene;
- (58) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, $A = W$ wherein W is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene;

- (59) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, $A = W$ wherein W is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene;
- (60) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, $A = W$ wherein W is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 is an integer equal to 0 and n_3' is an integer equal to 1;
- (61) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, $A = W$ wherein W is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in b) wherein n_3 and n_3' are an integer equal to 1;
- (62) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z and Y are H , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene;
- (63) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z is H and Y is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_3 alkylene;
- (64) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z and Y are H , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene;
- (65) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, A is the group as defined in 1b) wherein z is H and Y is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is a straight C_4 alkylene;
- (66) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, $A = W$ wherein W is CH_3 , $X = -S-$ and B is $= -R_{3a}-ONO_2$ wherein R_{3a} is the group as defined in g) wherein n_3' is an integer equal to 4;
- (67) A compound of formula (I) wherein $Q = -CO-$, $n = 1$, $A = W$ wherein W is CH_3 , $X = -O-$ and B is $= -R_{3a}-ONO_2$ wherein

R_{3a} is the group as defined in f) wherein n₃' is an integer equal to 4;

- (68) A compound of formula (I) wherein Q = -CO-, n = 1, A is the group as defined in 1a) wherein R₃ is a straight C₄ alkylene, X = -NH- and B is the group of formula (IA) wherein R₂ is H;

- (69) A compound of formula (I) wherein Q = -CO-, n = 1, A is the group as defined in 1a) wherein R₃ is a straight C₃ alkylene, X = -NH- and B is the group of formula (IA) wherein R₂ is H;

- (70) A compound of formula (I) wherein Q = -CO-, n = 1, A is the group as defined in 1a) wherein R₃ is the group as defined in b) wherein n₃ is an integer equal to 0 and n₃' is an integer equal to 1, X = -NH- and B is the group of formula (IA) wherein R₂ is H;

- (71) A compound of formula (I) wherein Q = -OCO-, n = 1, A is the group as defined in 1a) wherein R₃ is a straight C₄ alkylene, X = -NH- and B is the group of formula (IA) wherein R₂ is H;

- (72) A compound of formula (I) wherein Q = -OCO-, n = 1, A is the group as defined in 1a) wherein R₃ is a straight C₃ alkylene, X = -NH- and B is the group of formula (IA) wherein R₂ is H;

- (73) A compound of formula (I) wherein Q = -OCO-, n = 1, A is the group as defined in 1a) wherein R₃ is the group as defined in b) wherein n₃ is an integer equal to 0 and n₃' is an integer equal to 1, X = -NH- and B is the group of formula (IA) wherein R₂ is H;

- (74) A compound of formula (I) wherein Q = -CO-, n = 1, A is the group as defined in 1b) wherein z and Y are H, X = -NH- and B is the group of formula (IA) wherein R₂ is H;

- (75) A compound of formula (I) wherein Q = -CO-, n = 1, A is the group as defined in 1b) wherein z is H and Y is CH₃,

X = -NH- and B is the group of formula (IA) wherein R₂ is H;

- (76) A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -NH- and B is the group of formula (IA) where R₂ = -R_{3b}-ONO₂ wherein R_{3b} is a straight C₃ alkylene;

- (77) A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -NH- and B is the group of formula (IA) where R₂ = -R_{3b}-ONO₂ wherein R_{3b} is a straight C₄ alkylene;

- (78) A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -NH- and B is the group of formula (IA) where R₂ = -R_{3b}-ONO₂ wherein R_{3b} is the group as defined in b) wherein n₃ is an integer equal to 0 and n_{3'} is an integer equal to 1;

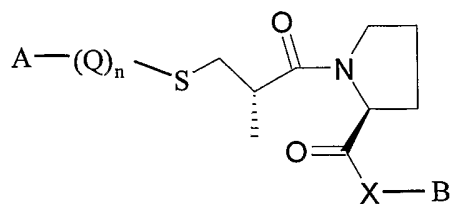
- (79) A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -NH- and B is the group of formula (IA) where R₂ = -R_{3b}-ONO₂ wherein R_{3b} is the group as defined in b) wherein n₃ and n_{3'} are an integer equal to 1;

- (80). A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -NH- and B is the group of formula (IA) where R₂ = -R_{3b}-ONO₂ wherein R_{3b} is a straight C₅ alkylene;

- (81). A compound of formula (I) wherein Q = -CO-, n = 1, A = W wherein W is CH₃, X = -O- and B is = -R_{3a}-ONO₂ wherein R_{3a} is a straight C₅ alkylene;

7. A process for preparing a compound of general formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, which process comprises:

i) reacting a compound of formula (II):



(II)

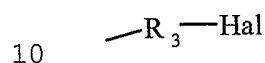
wherein:

5 Q and n are as defined in claim 1;

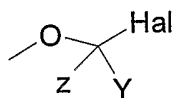
A = H, W wherein W is as defined in claim 1, an aminic protecting group or

is chosen from the following groups:

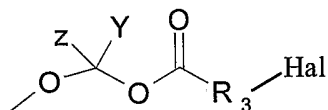
1a)



1b)

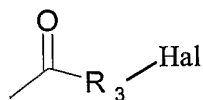


1c)



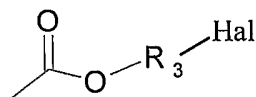
15

1d₁)

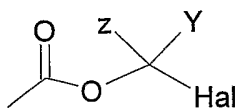


1d₂)

20



1d₃)



wherein R_3 , z and Y are as defined in claim 1;

X is as defined in claim 1;

5 $B = H$, carboxylic protecting group, $-R_{3a}-Hal$ wherein R_{3a} is as defined in claim 1 or

B is the group of formula (IA) as defined in claim 1, wherein R_2 is H , a straight or branched (C_1-C_6) -alkyl or $-R_{3b}-Hal$ wherein R_{3b} is as defined in claim 1; and Hal is an

10 halogen preferably Cl , Br , and I ,

with $AgNO_3$ in a suitable organic solvent such as acetonitrile or tetrahydrofuran (THF) under nitrogen at temperatures range between $20^\circ-80^\circ C$ and

15 ii) optionally acid hydrolysing the carboxylic or aminic protecting group and

iii) if desired, converting the resulting compound of general formula (I) into a pharmaceutically acceptable salt thereof.

20 **8.** Use of a compound of general formula (I) and/or a salt or stereoisomer thereof according to claim 1, as therapeutic agent.

25 **9.** Use of a compound of general formula (I) and/or a salt or stereoisomer thereof according to claim 1, for preparing a drug that can be employed in the treatment or prophylaxis of cardiovascular, inflammatory and renal diseases.

30 **10.** Use of a compound of general formula (I) and/or a salt or stereoisomer thereof according to claim 1, for preparing a drug that can be employed for treating acute coronary syndromes, stroke, pulmonary hypertension, hypertension,

ocular hypertension, diabetic nephropathy, peripheral vascular diseases.

11. A pharmaceutical composition comprising a
5 pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of general formula (I) and/or a salt or stereoisomer thereof according to claim 1.

12. A composition according to claim 12 in a suitable form
10 for the oral, parenteral, rectal, topic and transdermic administration, by inhalation spray or aerosol or iontophoresis devices.

13. Liquid or solid pharmaceutical composition for oral,
15 parenteral, rectal, topic and transdermic administration or inhalation in the form of tablets, capsules and pills eventually con enteric coating, powders, granules, gels, emulsions, solutions, suspensions, syrups, elixir, injectable forms, suppositories, in transdermal patches or
20 liposomes, containing a compound of formula (I) according to claim 1 and/or a salt or stereoisomer thereof and a pharmaceutically acceptable carrier.

14. Pharmaceutical composition comprising a compound of
25 formula I as defined in claim 1, a compound used to treat cardiovascular disease and a pharmaceutical acceptable excipient.

15. Pharmaceutical composition according to claim 14
30 wherein the compound used to treat cardiovascular disease is selected from the group consisting of beta adrenergic blockers, calcium channel blockers, angiotensin II receptor antagonists, antithrombotics, HMGCoA reductase inhibitors,

aspirin or nitrooxyderivatives of aspirin, nitrosated beta blockers, nitrosated or nitrosilated calcium channel blockers.

- 5 **16.** A pharmaceutical kit for simultaneous, successively or previously administration of a composition according to claim 11 and a compound used to treat cardiovascular disease.

10

INTERNATIONAL SEARCH REPORT

PCT/EP2004/050899

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D207/16 A61K31/401

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)

IPC 7 C07D

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, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 08, 30 June 1999 (1999-06-30) & JP 11 071279 A (SANKYO CO LTD), 16 March 1999 (1999-03-16) Examples of Table I, starting with 1-55. abstract	1-8, 11-13
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Y	WO 95/20571 A (CAL INT LTD ; BYRNE WILLIAM (IE); RYNNE ANDREW (IE)) 3 August 1995 (1995-08-03) cited in the application the whole document	1-16
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *Z* document member of the same patent family

Date of the actual completion of the international search

16 September 2004

Date of mailing of the international search report

23/09/2004

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 99/00361 A (NICOX SA ; DEL SOLDATO PIERO (IT)) 7 January 1999 (1999-01-07) cited in the application the whole document -----	1-16
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