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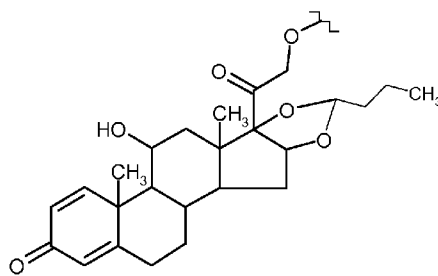
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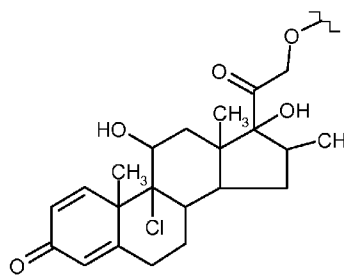
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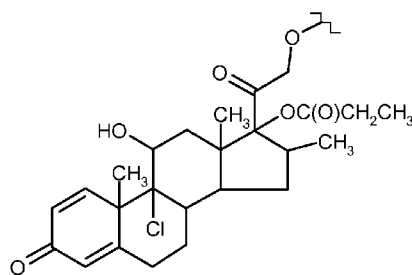
(54) Title: NITRIC OXIDE RELEASING STEROIDS



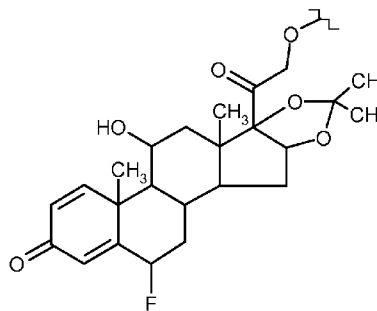
(II)



(III)



(IV)



(V)

(57) Abstract: The invention relates to nitrooxyderivative of corticosteroids of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof wherein R is a corticosteroid residue selected from: The compounds are useful in the treatment of respiratory diseases.

**NITRIC OXIDE RELEASING STEROIDS**

The present invention relates to use of nitric oxide releasing steroidal compounds having an improved pharmacological activity and low side effects in the treatment of respiratory diseases, and to a process for their preparation. The present invention also relates to nitric oxide releasing steroidal compounds and to pharmaceutical formulations containing them.

Respiratory diseases comprise asthma, COPD (chronic obstructive pulmonary diseases), ARDS (Acute Respiratory Distress Syndrome), allergic rhinitis, respiratory tract diseases associated with inflammation.

At present, the most drugs used in the treatment of respiratory diseases are steroids. However the currently available steroids have unsatisfactory site selectivity, for example all inhaled steroids are absorbed systemically from the lungs, and thus cause serious adverse effects by long-term administration.

Therefore, there is a demand for development of a new class of compounds for use in the treatment of respiratory diseases which exerts a powerful effect and low systemic effect.

**BACKGROUND OF THE INVENTION**

In the prior art nitrooxy derivatives of steroids, which are usable also as cardiovascular agents for the coronary insufficiency or angina pectoris therapy, are described.

For example, German patent DE 2,222,491 describes the preparation of pregnane derivatives having in position 21 the -CH<sub>2</sub>-O-NO<sub>2</sub> group. In said patent it is stated that said derivatives have a cardiotropic activity. This activity represents a drawback for said compounds, since they modify the cardiac frequency.

USP 3,494,941 describes steroid derivatives from 3-hydroxy-extrane or from extr-4 en-3 one, used as vasodilators in the

treatment of cardiac affections such as coronary insufficiency and angina pectoris. In the structure of said compounds a ONO<sub>2</sub> group is at the free end of the alkylene chain which is linked by an ether bond to the steroid in position 17. According to  
5 said patent it is possible to have nitrate groups also in the positions 3 and 16 of the steroidal structure. The same drawbacks mentioned above as regards the effects on the cardiac frequency can be repeated for the compounds of this patent.

USP 3,183,252 describes derivatives of 16-nitrate-alkylpregnanes wherein the alkyl group is linked to the pregnane  
10 structure by a carbon-carbon bond. The compounds according to said patent can be used as vasodilators. The same drawbacks reported for the above prior art can be repeated.

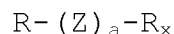
WO 98/15568 and WO 03/064443 in the name of the Applicant  
15 describe nitrate esters of steroidal compounds, wherein between the steroidal structure and the nitrooxy group a bivalent linking group is inserted. Said compounds show a good efficacy and/or good tolerability with respect to the corresponding precursors.

Patent application WO 00/61604 in the name of the Applicant  
20 describes nitrooxy derivatives of steroidal compounds with various linking groups having at one end a nitrooxy group, and covalently linked with the other end to a steroidal compound. In said application the uses concern the compounds usable in  
25 the treatment of patients in oxidative stress. Said compounds contain in the molecule also a bivalent linking group which must be capable to prevent the free radicals production and is selected on the basis of the tests reported therein.

The Applicant has surprisingly and unexpectedly found a  
30 class of nitric oxide releasing compounds with a better efficacy, bioavailability and/or a prolonged release of NO in comparison with the compounds known in prior art. In general the compounds of the present invention have a better

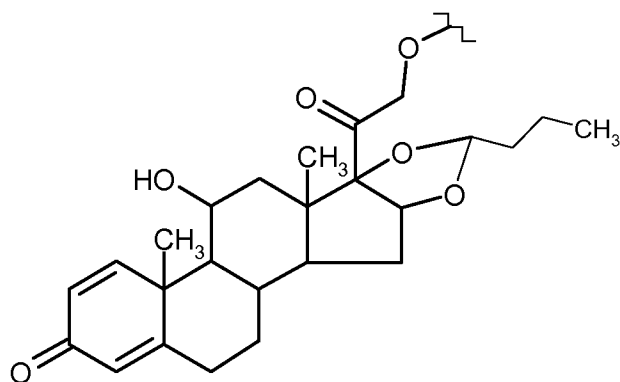
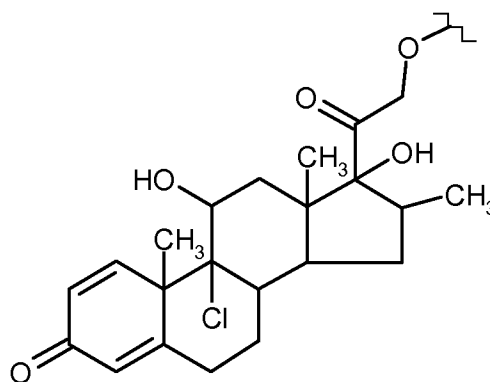
drugability in comparison to the corresponding compounds of the prior art.

An object of the present invention is to provide nitric oxide releasing compounds of general formula (I)

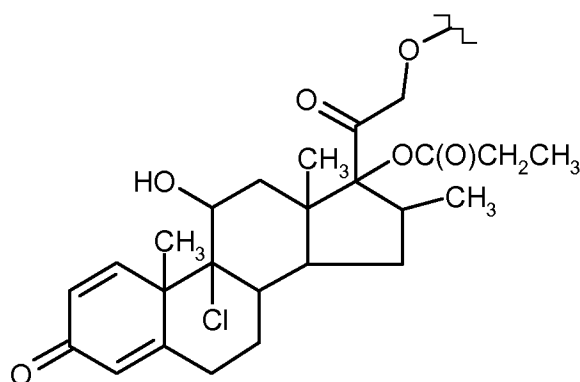


(I)

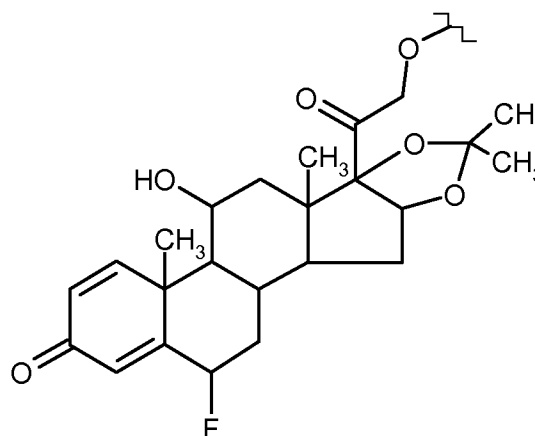
and pharmaceutically acceptable salts or stereoisomers thereof for use in the treatment of respiratory diseases, wherein in formula (I) R is a corticosteroid residue selected from:


$$(II)$$


(III)



(IV)



(V)

a is 0 or 1,

15 Z is a group capable of binding  $R_X$  and is selected from  $-C(O)-$ ,  
or  $-CH(R')-O-$  wherein  $R'$  is selected from H or a straight or  
branched  $C_1-C_4$  alkyl, preferably  $R'$  is H or  $-CH_3$ ;

R<sub>x</sub> is a radical selected from the following meanings:

A)

20 (a1)  $-\text{HN}-\text{CH}(\text{R}^1)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

- (a2)  $-\text{C}(\text{O})-\text{CH}(\text{R}^1)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$   
 (a3)  $-\text{HN}-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{COOR}^{3a}$   
 (a4)  $-\text{C}(\text{O})-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NHR}^{4a}$   
 (a5)  $-\text{R}^{1b}-\text{CH}(\text{NHR}^{4a})-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$   
 5 (a6)  $-\text{R}^{1b}-\text{CH}(\text{COOR}^{3a})\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$   
 (a7)  $-\text{HN}-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$   
 (a8)  $-\text{C}(\text{O})-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$   
 (a9)  $-\text{R}^{1b}-\text{CH}(\text{NH}-\text{T}'-\text{Y}'-\text{ONO}_2)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$   
 (a10)  $-\text{R}^{1b}-\text{CH}(\text{C}(\text{O})-\text{T}-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

10 wherein:

$\text{R}^1$  is selected from:

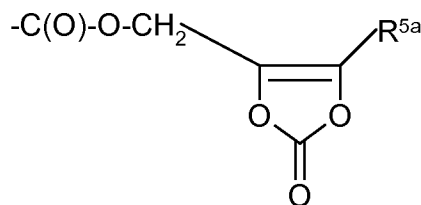
A1) H,  $-\text{CH}_3$ , isopropyl, isobutyl, sec-butyl, tert-butyl, methylthio- $(\text{CH}_2)_2-$ , phenyl, benzyl,  $\text{C}_6\text{H}_5-\text{CH}_2-\text{CH}_2-$ , 2-monosubstituted benzyl, or 3-monosubstituted benzyl or  
 15 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from  $-\text{F}$ ,  $-\text{Cl}$ , I,  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $-\text{CH}_3$ , CN,  $\text{C}_6\text{H}_5\text{CO}-$ ;

2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, 2-pyrrolidyl, 3-triptyophanyl- $\text{CH}_2-$ , 3-benzothienyl- $\text{CH}_2-$ ,  
 20 4-imidazolyl- $\text{CH}_2-$ , 9-anthranyl- $\text{CH}_2-$ , cyclohexyl, cyclohexyl- $\text{CH}_2-$ , cyclohexyl- $(\text{CH}_2)_2-$ , cyclopentyl- $\text{CH}_2-$ ,  $(\text{C}_6\text{H}_5)_2\text{CH}-$ , 4-B(OH) $_2$ -benzyl, 4-quinolyl- $\text{CH}_2-$ , 3-quinolyl- $\text{CH}_2-$ , 2-quinolyl- $\text{CH}_2-$ , 2-quinoxalyl- $\text{CH}_2-$ , 2-furyl- $\text{CH}_2-$ , 1-naphtyl- $\text{CH}_2-$ , 2-naphtyl- $\text{CH}_2-$ ,  
 25 , 2-pyridyl- $\text{CH}_2-$ , 3-pyridyl- $\text{CH}_2-$ , 4-pyridyl- $\text{CH}_2-$ , 2-thienyl- $\text{CH}_2-$ , 3-thienyl- $\text{CH}_2-$ ,  $\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{CH}_2-$ ,  $\text{CH}_2=\text{CH}-\text{CH}_2-$ ,  $\text{CH}\equiv\text{CH}-\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}-\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}-(\text{CH}_2)_2-$ ,  $\text{NH}_2(=\text{NH})\text{NH}-(\text{CH}_2)_3-$ ,  $\text{P}(=\text{O})(\text{OCH}_3)_2$ ,  $\text{I}-\text{CH}_2-$ , preferably  $\text{R}^1$  is H,  $-\text{CH}_3$ , isopropyl, benzyl;

30 A2)  $-\text{CH}_2-\text{SH}$ ,  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_2)-(3,5\text{-diiodo})-(4-\text{OH})]$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_3)-(3\text{-nitro})-(4-\text{OH})]$ , preferably  $\text{R}^1$  is  $-\text{CH}_2-\text{OH}$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ;

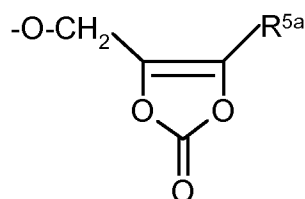
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A3)  $-\text{CH}_2-\text{NHR}''$ ,  $-(\text{CH}_2)_2-\text{NHR}''$ ,  $-(\text{CH}_2)_3-\text{NHR}''$ ,  $-(\text{CH}_2)_4-\text{NHR}''$ ,  
 wherein  $\text{R}''$  is  $\text{H}$ ,  $-\text{C}(\text{O})\text{CH}_3$  or



wherein  $\text{R}^{5a}$  is  $\text{H}$  or a linear or branched  $\text{C}_1$ - $\text{C}_{10}$  alkyl chain,  
 preferably  $\text{R}^{5a}$  is  $\text{H}$  or a linear ( $\text{C}_1$ - $\text{C}_5$ ) alkyl, preferably  $\text{R}^1$  is  
 $-(\text{CH}_2)_4-\text{NHR}''$ , wherein  $\text{R}''$  is as above defined,

A4)  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''$  wherein  $\text{R}'''$   
 is  $-\text{OR}^{5a}$  or



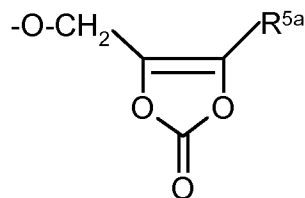
wherein  $\text{R}^{5a}$  is as above defined, preferably  $\text{R}^1$  is  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  
 wherein  $\text{R}'''$  is as above defined,  
 $\text{R}^{1a}$  is selected from:

A5)  $-\text{CH}_2-\text{S}-$ ,  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{O}-$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ ,  
 $-\text{CH}_2-[(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)-(4-\text{O})-]$ ,  
 $-\text{CH}_2-[(3\text{-nitro})-(\text{C}_6\text{H}_3)-(4-\text{O})-]$ , preferably  $\text{R}^{1a}$  is  $-\text{CH}_2-\text{O}-$ ;

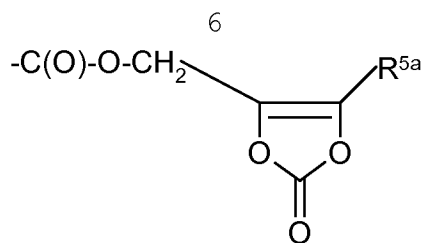
A6)  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,  $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ ,  
 preferably  $\text{R}^{1a}$  is  $-(\text{CH}_2)_4-\text{NH}-$  or  $-\text{CH}_2-\text{NH}-$ ,

A7)  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ , preferably  $\text{R}^{1a}$   
 is  $-\text{CH}_2-\text{C}(\text{O})-$ ;

$\text{R}^{3a}$  is selected from  $\text{H}$ ,  $-\text{R}^{5a}$  or



wherein  $\text{R}^{5a}$  is as above defined,  
 $\text{R}^{4a}$  is selected from  $\text{H}$  or  $-\text{C}(\text{O})\text{CH}_3$  or



wherein  $R^{5a}$  is as above defined,

$R^{1b}$  is selected from

A8)  $-S-CH_2-$ ,  $-O-CH(CH_3)-$ ,  $-O-CH_2-$ ,  $[-(4-O)-(C_6H_4)]-CH_2-$ ,

5  $[-(4-O)-(3,5-diiodo)-(C_6H_2)]-CH_2-$ ,

$[-(4-O)-(3-nitro)-(C_6H_3)]-CH_2-$ , preferably  $R^{1b}$  is  $-O-CH_2-$  or  $[-(4-O)-(C_6H_4)]-CH_2-$ ;

A9)  $-HN-CH_2-$ ,  $-HN-(CH_2)_2-$ ,  $-HN-(CH_2)_3-$ ,  $-HN-(CH_2)_4-$ , preferably  $R^{1b}$  is  $-HN-(CH_2)_4-$  or  $-HN-CH_2-$ ;

10 A10)  $-C(O)-CH_2-$ ,  $-C(O)-(CH_2)_2-$ ,  $-C(O)-(CH_2)_4-$ , preferably  $R^{1b}$  is  $-C(O)-CH_2-$ ;

T is selected from  $-O-$ ,  $-S-$ ,  $-NR'-$ ,  $-O-CH(R')-O-C(O)-$  or  $-O-CH(R')-O-C(O)O-$  wherein  $R'$  is as above defined;

T' is  $-C(O)-$ ,  $-C(O)-X''-$  wherein  $X''$  is  $-O-$  or  $-S-$ , or T' is

15  $-C(O)-NR'-$  wherein  $R'$  is as above defined;

T'' is independently selected from  $-C(O)-$ ,  $-C(O)-X''-$ ,  $-C(O)-NR'-$ ,  $-O-$ ,  $-S-$ ,  $-NR'-$ ,  $-O-CH(R')-O-C(O)-$ ,  $-O-CH(R')-O-C(O)O-$ , wherein  $X''$  and  $R'$  are as above defined,

with the proviso that T'' is  $-C(O)-$ ,  $-C(O)-X''-$  or  $-C(O)-NR'-$

20 when T'' is linked to  $-NH-$ ,  $-O-$ , or  $-S-$ , or T'' is  $-O-$ ,  $-S-$ ,  $-NR'-$ ,  $-O-CH(R')-O-C(O)-$ ,  $-O-CH(R')-O-C(O)O-$  when T'' is linked to  $-C(O)-$ ,

Y and Y' are as below defined;

or  $R_x$  is selected from:

25 B)

(b1)  $-HN-CH(R^2)-CH_2-C(O)-(T-Y-ONO_2)$

(b2)  $-C(O)-CH_2-CH(R^2)-NH-(T'-Y-ONO_2)$

(b3)  $-HN-CH(R^{2a}-T''-Y'-ONO_2)-CH_2COOR^{3a}$

(b4)  $-C(O)-CH_2-CH(R^{2a}-T''-Y'-ONO_2)-NHR^{4a}$

30 (b5)  $-R^{2b}-CH(NHR^{4a})-CH_2C(O)-(T-Y-ONO_2)$

(b6)  $-R^{2b}-CH(CH_2COOR^{3a})NH-(T'-Y-ONO_2)$

(b7)  $-\text{HN}-\text{CH}(\text{R}^{2a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{CH}_2-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

(b8)  $-\text{C}(\text{O})-\text{CH}_2-\text{CH}(\text{R}^{2a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

(b9)  $-\text{R}^{2b}-\text{CH}(\text{NH}-\text{T}'-\text{Y}'-\text{ONO}_2)-\text{CH}_2\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

(b10)  $-\text{R}^{2b}-\text{CH}(\text{CH}_2\text{C}(\text{O})-\text{T}-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

5 wherein

$\text{R}^2$  is selected from:

B1) H,  $-\text{CH}_3$ ,  $\text{CF}_3$ , isopropyl, isobutyl, sec-butyl, methylthio- $(\text{CH}_2)_2-$ , phenyl, benzyl, 3-triptophanyl- $\text{CH}_2-$ ,  $\text{NH}_2-\text{C}(\text{O})-\text{CH}_2-$ ,  $\text{NH}_2-\text{C}(\text{O})-(\text{CH}_2)_2-$ ,  $\text{NH}_2(=\text{NH})\text{NH}-(\text{CH}_2)_3-$ , tBuO- $\text{CH}(\text{CH}_3)-$ ,  
10 , benzyl-O- $\text{CH}_2-$ , 4-terbutoxy-benzyl, 4-phenylbenzyl, preferably  $\text{R}^2$  is H,  $-\text{CH}_3$ , isopropyl, benzyl,

B2)  $-\text{CH}_2-\text{SH}$ ,  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ,  
 $-\text{CH}_2-[(\text{C}_6\text{H}_2)-(3,5\text{-diiodo})-(4-\text{OH})]$ ,  
 $-\text{CH}_2-[(\text{C}_6\text{H}_3)-(3\text{-nitro})-(4-\text{OH})]$ ;

15 B3)  $-\text{CH}_2-\text{NHR}''$ ,  $-(\text{CH}_2)_2-\text{NHR}''$ ,  $-(\text{CH}_2)_3-\text{NHR}''$ ,  $-(\text{CH}_2)_4-\text{NHR}''$ , wherein  $\text{R}''$  is as above defined, preferably  $\text{R}^2$  is  $-(\text{CH}_2)_4-\text{NHR}''$ ;

B4)  $-\text{CH}_2-\text{C}(\text{O})-\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-\text{R}'''$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-\text{R}'''$  wherein  $\text{R}'''$  is as above defined, preferably  $\text{R}^2$  is  $-\text{CH}_2-\text{C}(\text{O})-\text{R}'''$ ;  
 $\text{R}^{2a}$  is selected from:

20 B5)  $-\text{CH}_2-\text{S}-$ ,  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{O}-$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ ,  
 $-\text{CH}_2-[(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)-(4-\text{O})-]$ ,  
 $-\text{CH}_2-[(3\text{-nitro})-(\text{C}_6\text{H}_3)-(4-\text{O})-]$ , preferably  $\text{R}^{2a}$  is  $-\text{CH}_2-\text{O}-$ ;

B6)  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,  $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ , preferably  $\text{R}^{2a}$  is  $-(\text{CH}_2)_4-\text{NH}-$  or  $-\text{CH}_2-\text{NH}-$ ;

25 B7)  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ , preferably  $\text{R}^{2a}$  is  $-\text{CH}_2-\text{C}(\text{O})-$ ;

$\text{R}^{2b}$  is selected from

B8)  $-\text{S}-\text{CH}_2-$ ,  $-\text{O}-\text{CH}(\text{CH}_3)-$ ,  $-\text{O}-\text{CH}_2-$ ,  $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ,  
 $[-(4-\text{O})-(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)]-\text{CH}_2-$ ,  $[-(4-\text{O})-(3\text{-nitro})-(\text{C}_6\text{H}_3)]-\text{CH}_2-$ ,  
30 , preferably  $\text{R}^{2b}$  is  $-\text{O}-\text{CH}_2-$  or  $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ;

B9)  $-\text{HN}-\text{CH}_2-$ ,  $-\text{HN}-(\text{CH}_2)_2-$ ,  $-\text{HN}-(\text{CH}_2)_3-$ ,  $-\text{HN}-(\text{CH}_2)_4-$ , preferably  $\text{R}^{2b}$  is  $-\text{HN}-(\text{CH}_2)_4-$  or  $-\text{HN}-\text{CH}_2-$ ;

B10)  $-\text{C}(\text{O})-\text{CH}_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_4-$ , preferably  $\text{R}^{2b}$  is  $-\text{C}(\text{O})-\text{CH}_2-$ ;



$R^{3a}$  and  $R^{4a}$  are as above defined;

$T$ ,  $T'$  and  $T''$  are as above defined and  $Y$  and  $Y'$  are as below defined;

or  $R_x$  is selected from:

5 C)

(c1)  $-\text{HN}-(\text{CH}_2)_b-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$ ;

(c2)  $-\text{C}(\text{O})-(\text{CH}_2)_b-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$ ;

wherein  $b$  is an integer from 3 to 6,

$T$  and  $T'$  are as above defined and  $Y$  and  $Y'$  are as below defined;

10 D)

(d1)  $-\text{HN}-\text{CH}(\text{R}^{12})-\text{CH}_2-\text{O}-(\text{T}'''-\text{Y}-\text{ONO}_2)$

(d2)  $-\text{O}-\text{CH}_2-\text{CH}(\text{R}^{12})-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

(d3)  $-\text{HN}-\text{CH}(\text{R}^{12a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{CH}_2\text{OH}$

(d4)  $-\text{O}-\text{CH}_2-\text{CH}(\text{R}^{12a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NHR}^{4a}$

15 (d5)  $-\text{R}^{12b}-\text{CH}(\text{NHR}^{4a})-\text{CH}_2-\text{O}-(\text{T}'''-\text{Y}-\text{ONO}_2)$

(d6)  $-\text{R}^{12b}-\text{CH}(\text{CH}_2\text{OH})-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

(d7)  $-\text{HN}-\text{CH}(\text{R}^{12a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{CH}_2-\text{O}-(\text{T}'''-\text{Y}-\text{ONO}_2)$

(d8)  $-\text{O}-\text{CH}_2-\text{CH}(\text{R}^{12a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

(d9)  $-\text{R}^{12b}-\text{CH}(\text{NH}-\text{T}'-\text{Y}'-\text{ONO}_2)-\text{CH}_2-\text{O}-(\text{T}'''-\text{Y}-\text{ONO}_2)$

20 (d10)  $-\text{R}^{12b}-\text{CH}(\text{CH}_2-\text{O}-\text{T}'''-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

wherein

$\text{T}'''$  is independently selected from  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{X}''-$  wherein  $\text{X}''$  is  $-\text{O}-$  or  $-\text{S}-$ , or  $-\text{C}(\text{O})-\text{NR}'-$  wherein  $\text{R}'$  is as above defined;

$T'$  and  $T''$  are as above defined,

25  $Y$  and  $Y'$  are as below defined;

$\text{R}^{12}$  is selected from:

D1)  $\text{H}$ ,  $-\text{CH}_3$ , isopropyl, isobutyl, sec-butyl, methylthio- $(\text{CH}_2)_2-$ , benzyl, 3-triptophanyl- $\text{CH}_2-$ , 4-imidazolyl- $\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}-\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}-(\text{CH}_2)_2-$ ,  $\text{NH}_2(=\text{NH})\text{NH}-(\text{CH}_2)_3-$ , preferably  $\text{R}^{12}$  is  $\text{H}$ ;

D2)  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ,  $-\text{CH}_2-[(\text{C}_6\text{H}_3)-(3,5\text{-diiodo})-(4-\text{OH})]$ ,  $-\text{CH}_2-[(\text{C}_6\text{H}_3)-(3\text{-nitro})-(4-\text{OH})]$ , preferably  $\text{R}^{12}$  is  $-\text{CH}_2-\text{OH}$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ;

D3)  $-\text{CH}_2-\text{NHR}''$ ,  $-(\text{CH}_2)_2-\text{NHR}''$ ,  $-(\text{CH}_2)_3-\text{NHR}''$ ,  $-(\text{CH}_2)_4-\text{NHR}''$ , wherein  $\text{R}''$  is as above defined, preferably  $\text{R}^{12}$  is  $-(\text{CH}_2)_4-\text{NHR}''$ ;

D4)  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''$  wherein  $\text{R}'''$  is as above defined, preferably  $\text{R}^{12}$  is  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ;

5  $\text{R}^{12a}$  is selected from

D5)  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{O}-$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ ,  $-\text{CH}_2-[3,5\text{-diiodo}-(\text{C}_6\text{H}_2)-(4-\text{O})-]$ ,  $-\text{CH}_2-[3\text{-nitro}-(\text{C}_6\text{H}_3)-4-\text{O}-]$ , preferably  $\text{R}^{12a}$  is  $\text{CH}_2-\text{O}-$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ ,

D6)  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,  $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ , preferably  
10  $\text{R}^{12a}$  is  $-(\text{CH}_2)_4-\text{NH}-$  or  $-\text{CH}_2-\text{NH}-$ ,

D7)  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ , preferably  $\text{R}^{12a}$  is  $-\text{CH}_2-\text{C}(\text{O})-$ ,

$\text{R}^{12b}$  is selected from

D8)  $-\text{O}-\text{CH}_2-$ ,  $-\text{O}-\text{CH}(\text{CH}_3)-$ ,  $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ,  
15  $[-(4-\text{O})-(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)]-\text{CH}_2-$ ,  $[-(4-\text{O})-(3\text{-nitro})-(\text{C}_6\text{H}_3)]-\text{CH}_2-$ ,  
preferably  $\text{R}^{12b}$  is  $-\text{O}-\text{CH}_2-$  or  $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ;

D9)  $-\text{HN}-\text{CH}_2-$ ,  $-\text{HN}-(\text{CH}_2)_2-$ ,  $-\text{HN}-(\text{CH}_2)_3-$ ,  $-\text{HN}-(\text{CH}_2)_4-$ , preferably  $\text{R}^{12b}$  is  $-\text{HN}-(\text{CH}_2)_4-$  or  $-\text{HN}-\text{CH}_2-$ ;

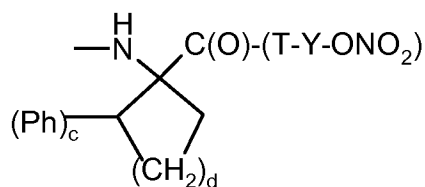
D10)  $-\text{C}(\text{O})-\text{CH}_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_4-$ , preferably  $\text{R}^{12b}$   
20 is  $-\text{C}(\text{O})-\text{CH}_2-$ ;

$\text{R}^{4a}$  is as above defined;

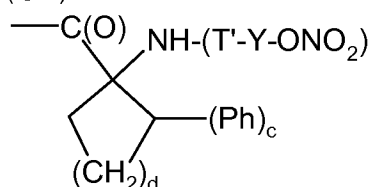
or  $\text{R}_x$  is selected from:

E)

(e1)



(e2)

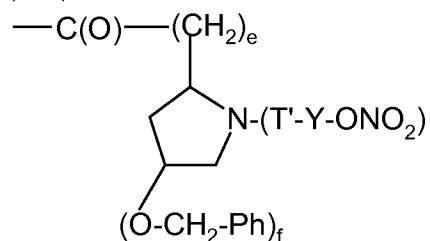


wherein  $c$  is equal to 0 or 1,  $d$  is an integer from 0 to 3 with the proviso that  $c$  is 0 or 1 when  $d$  is 0 and  $c$  is 0 when  $d$  is

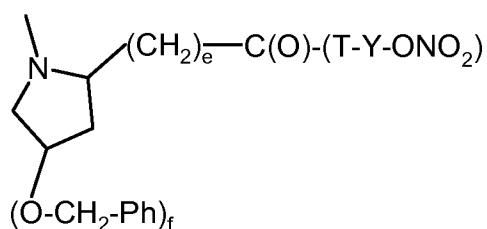
1, 2 or 3, T and T' are as above defined and Y is as below defined;

F)

(f1)



(f2)



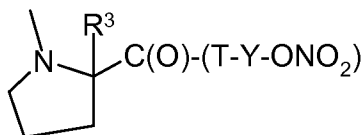
(XI)

wherein e and f are equal to 0 or 1, with the proviso that f is 0 when e is 0 and f is 0 or 1 when e is 1,

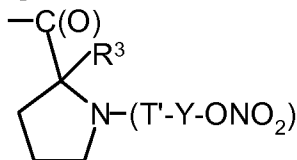
T and T' are as above defined and Y is as below reported;

G)

(g1)



(g2)

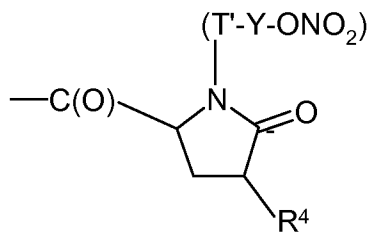


wherein R<sup>3</sup> is H, CH<sub>3</sub>, propyl, (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CH-, 1-naphtyl-CH<sub>2</sub>-, benzyl, allyl, 2-bromobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-fluorobenzyl, 4-bromobenzyl, 4-methylbenzyl, preferably R<sup>3</sup> is

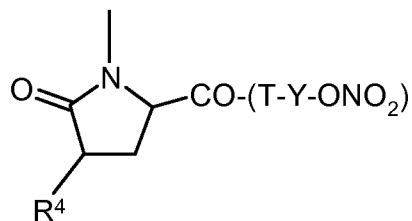
H, T and T' are as above defined and Y is as below defined;

H)

(h1)



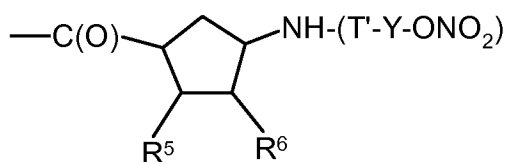
(h2)



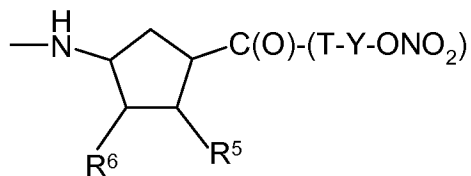
wherein  $R^4$  is H, benzyl, 4-bromobenzyl, 2-bromobenzyl, T and T' are as above defined and Y is as below defined;

I)

(i1)



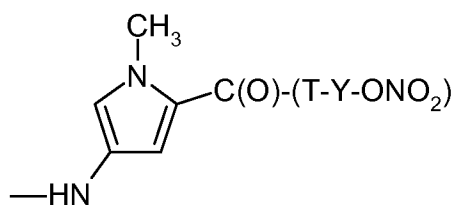
(i2)



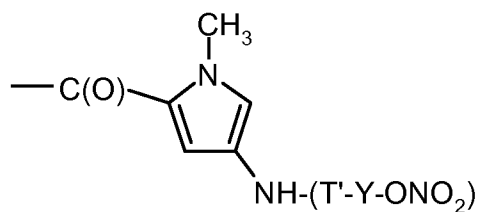
wherein  $R^5$  is H,  $R^6$  is H, or  $R^5$  and  $R^6$  when taken together are a double bond, T and T' are as above defined and Y is as below reported;

L)

(l1)



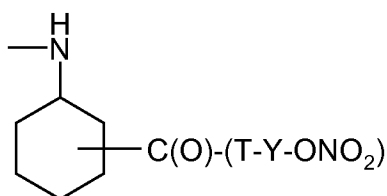
(l2)



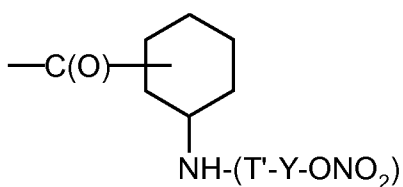
wherein T and T' are as above defined and Y is as below reported;

M)

5 (m1)



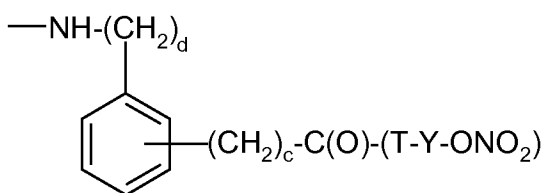
(m2)



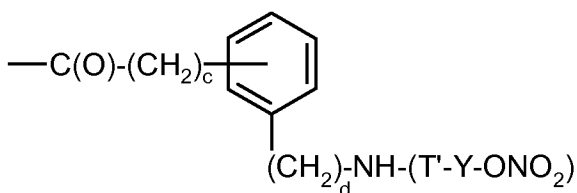
wherein T and T' are as above defined and Y is as below reported;

N)

(n1)



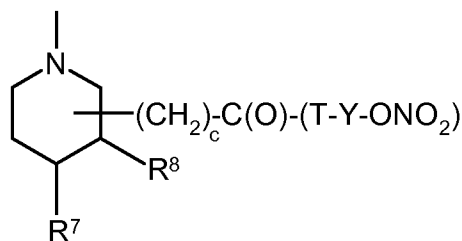
(n2)



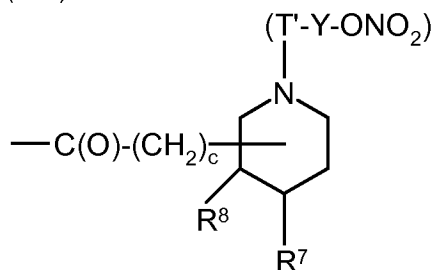
wherein c is as above defined, d is equal to 0 or 1, T and T' are as above defined and Y is as below reported;

O)

(o1)



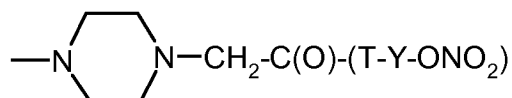
(o2)



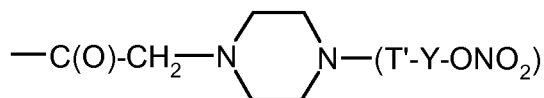
wherein  $R^7$  is H,  $R^8$  is H, or  $R^7$  and  $R^8$  when taken together are a  
 5 double bond,  $c$  is as above defined,  $T$  and  $T'$  are as above  
 defined and  $Y$  is as below reported;

P)

(p1)



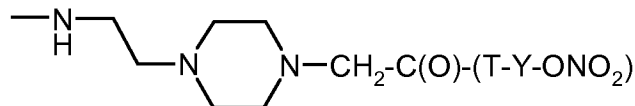
10 (p2)



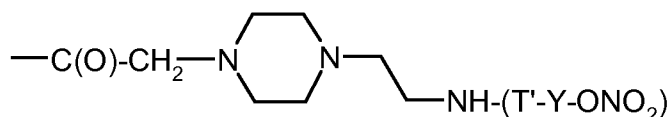
wherein  $T$  and  $T'$  are as above defined and  $Y$  is as below  
 reported;

Q)

15 (q1)



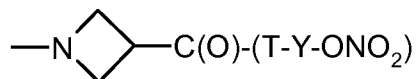
(q2)



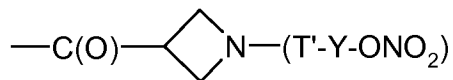
wherein  $T$  and  $T'$  are as above defined and  $Y$  is as below  
 20 reported;

R)

(r1)



(r2)

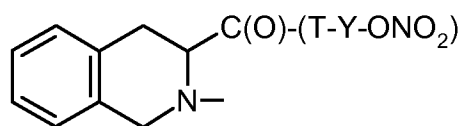


5

wherein T and T' are as above defined and Y is as below reported;

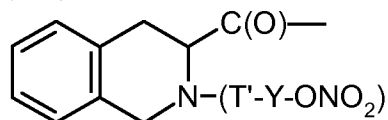
S)

(s1)



10

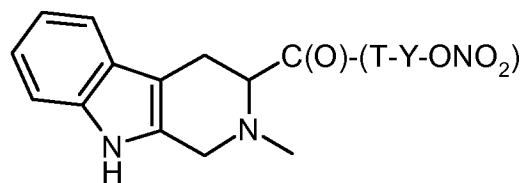
(s2)



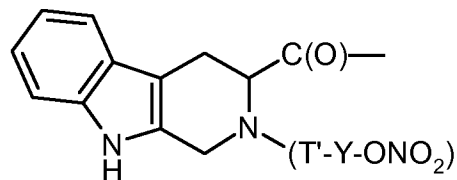
wherein T and T' are as above defined and Y is as below reported;

15 T)

(t1)



(t2)

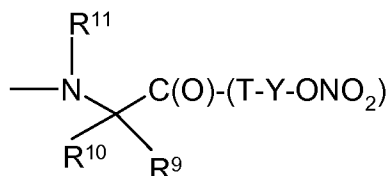


20

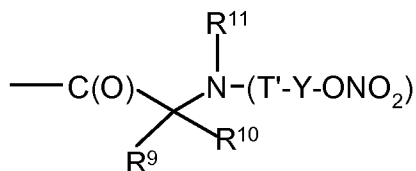
wherein T and T' are as above defined and Y is as below reported;

U)

(u1)



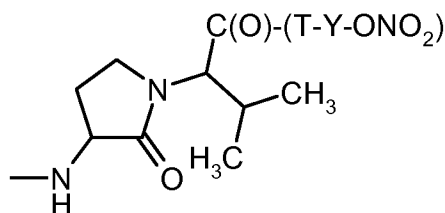
(u2)



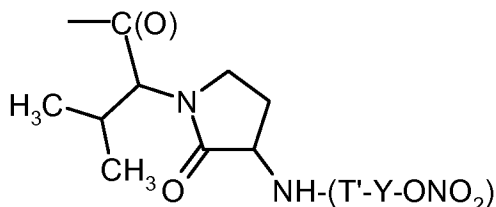
wherein  $R^9$  and  $R^{10}$  are H,  $\text{CH}_3$ ,  $R^{11}$  is  $\text{CH}_3$  or 4-piperidinyl with the proviso that  $R^9$  and  $R^{10}$  are H when  $R^{11}$  is 4-piperidinyl and  $R^9$  and  $R^{10}$  are  $\text{CH}_3$  when  $R^{11}$  is  $\text{CH}_3$ , T and T' are as above defined and Y is as below reported;

V)

(v1)



(v2)



wherein T and T' are as above defined and Y is as below reported;

with the proviso that in the formula (I):

a is 0 or a is 1 and Z is  $-\text{CH(R}^{\prime}\text{)}-\text{O}-$  wherein  $R^{\prime}$  is as above defined, when  $R_x$  is:

- (a2), (a4) or (a8);

- (a5), (a6), (a9) or (a10) and  $R^{1b}$  is selected from the group A10);

- (b2), (b4) or (b8);

- (b5), (b6), (b9) or (b10) and  $R^{2b}$  is selected from the group B10);



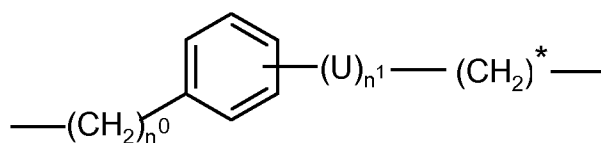
- (c2);
  - (d5), (d6), (d9) or (d10) and  $R^{12b}$  is selected from the group D10);
  - (e2), (f1), (g2), (h1), (i1), (l2), (m2), (n2), (o2), (p2),  
 5 (q2), (r2), (s2), (t1) or (u2);
- a is 1 and Z is -C(O)-, when  $R_x$  is:
- (a1), (a3) or (a7);
  - (a5), (a6), (a9) or (a10) and  $R^{1b}$  is selected from the groups A8) and A9);
  - 10 - (b1), (b3) or (b7);
  - (b5), (b6), (b9) or (b10) and  $R^{2b}$  is selected from the groups B8) or B9);
  - (c1);
  - (d1), (d2), (d3), (d4), (d7) or (d8);
  - 15 - (d5), (d6), (d9) or (d10) and  $R^{12b}$  is selected from the groups D8) or D9);
  - (e1), (f2), (g1), (h2), (i2), (l1), (m1), (n1), (o1), (p1), (q1), (r1), (s1), (t2) or (u1).

Y and Y' are bivalent radicals each independently selected from  
 20 the following meanings:

a)

- straight or branched  $C_1$ - $C_{20}$  alkylene, preferably a straight or branched  $C_1$ - $C_{10}$  alkylene,
- straight or branched  $C_1$ - $C_{20}$  alkylene substituted with one or  
 25 more of the substituents selected from the group consisting of:  
 halogen atoms, hydroxy, -ONO<sub>2</sub> or T<sub>2</sub>, wherein T<sub>2</sub> is -OC(O)( $C_1$ - $C_{10}$  alkyl)-ONO<sub>2</sub> or -O( $C_1$ - $C_{10}$  alkyl)-ONO<sub>2</sub>, preferably Y or Y' is a  
 straight or branched  $C_1$ - $C_{10}$  alkylene substituted with a -ONO<sub>2</sub> group;
- 30 - cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with one or more  
 straight or branched  $C_1$ - $C_{10}$  alkyl chains, preferably the ring  
 being optionally substituted with CH<sub>3</sub>;

b)



b)

wherein

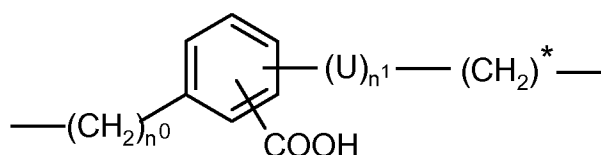
5  $n^0$  is an integer from 0 to 20, preferably  $n^0$  is 0 or 1;

$n^1$  is 0 or 1, preferably  $n^1$  is 1;

U is a linear or branched  $\text{C}_1\text{--C}_{20}$  alkylene optionally substituted with a  $\text{--ONO}_2$  group, preferably U is a linear  $\text{C}_1\text{--C}_{10}$  alkylene or U is a linear or branched  $\text{C}_1\text{--C}_{10}$  alkylene substituted with a  $\text{--ONO}_2$  group;

10

c)



c)

wherein

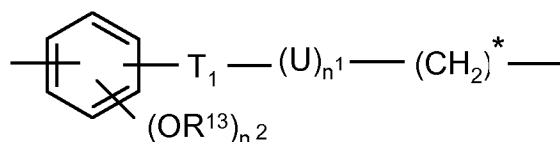
15  $n^0$  is an integer from 0 to 20, preferably  $n^0$  is 0 or 1;

$n^1$  is 0 or 1, preferably  $n^1$  is 1;

U is a linear or branched  $\text{C}_1\text{--C}_{20}$  alkylene optionally substituted with a  $\text{--ONO}_2$  group, preferably U is a linear  $\text{C}_1\text{--C}_{10}$  alkylene or U is a linear or branched  $\text{C}_1\text{--C}_{10}$  alkylene substituted with a  $\text{--ONO}_2$  group;

20

d)



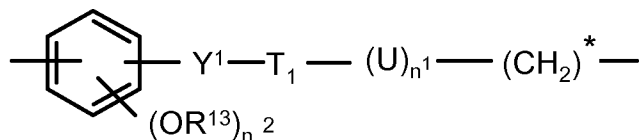
d)

wherein:

25  $n^2$  is an integer from 0 to 2,  $\text{R}^{13}$  is H or  $\text{CH}_3$ ,  $\text{T}_1$  is  $\text{--O--C(O)--}$  or  $\text{--C(O)O--}$ ;

$n^1$  and U are as above defined;

e)



e)

5  $n^2$  is an integer from 0 to 2, preferably  $n^2$  is 1;

$\text{R}^{13}$  is H or  $\text{CH}_3$ , preferably  $\text{R}^{13}$  is  $\text{CH}_3$ ;

$\text{Y}^1$  is  $-\text{CH}_2-\text{CH}_2-$  or  $-\text{CH}=\text{CH}-(\text{CH}_2)_{n^{2'}}-$ , wherein  $n^{2'}$  is 0 or 1, preferably  $\text{Y}^1$  is  $-\text{CH}=\text{CH}-(\text{CH}_2)_{n^{2'}}-$  and  $n^{2'}$  is 0;

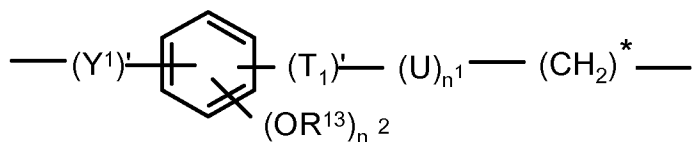
$\text{T}_1 = -\text{O}-\text{C}(\text{O})-$  or  $-\text{C}(\text{O})\text{O}-$ , preferably  $\text{T}_1$  is  $-\text{C}(\text{O})\text{O}-$ ;

10  $n^1$  is 0 or 1, preferably  $n^1$  is 1;

U is a linear or branched  $\text{C}_1\text{--C}_{20}$  alkylene optionally substituted with a  $-\text{ONO}_2$  group, preferably U is a linear  $\text{C}_1\text{--C}_{10}$  alkylene or U is a linear or branched  $\text{C}_1\text{--C}_{10}$  alkylene substituted with a  $-\text{ONO}_2$  group;

15 more preferably  $n^2$  is 1,  $\text{R}^{13}$  is  $\text{CH}_3$ ,  $\text{Y}^1$  is  $-\text{CH}=\text{CH}-(\text{CH}_2)_{n^{2'}}-$  and  $n^{2'}$  is 0,  $\text{T}_1$  is  $-\text{C}(\text{O})\text{O}-$  and U is a linear  $\text{C}_1\text{--C}_{10}$  alkylene;

e')



e')

20 wherein:

$n^2$  is an integer from 0 to 2, preferably  $n^2$  is 1;

$\text{R}^{13}$  is H or  $\text{CH}_3$ , preferably  $\text{R}^{13}$  is  $\text{CH}_3$ ;

$\text{Y}^1$  is  $-\text{CH}_2-\text{CH}_2-$  or  $-(\text{CH}_2)_{n^{2'}}-\text{CH}=\text{CH}-$ , wherein  $n^{2'}$  is 0 or 1, preferably  $\text{Y}^1$  is  $-(\text{CH}_2)_{n^{2'}}-\text{CH}=\text{CH}-$  and  $n^{2'}$  is 0;

25  $\text{T}_1 = -\text{O}-\text{C}(\text{O})-$ ;

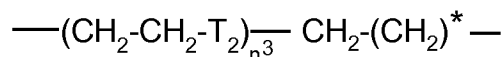
$n^1$  is 0 or 1, preferably  $n^1$  is 1;

U is a linear or branched  $\text{C}_1\text{--C}_{20}$  alkylene optionally substituted with a  $-\text{ONO}_2$  group, preferably U is a linear  $\text{C}_1\text{--C}_{10}$  alkylene or U

is a linear or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

more preferably n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>, Y<sup>1</sup> is -CH=CH-(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>- and n<sup>2'</sup> is 0, T<sub>1</sub> is -OC(O)- and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene;

5 f)



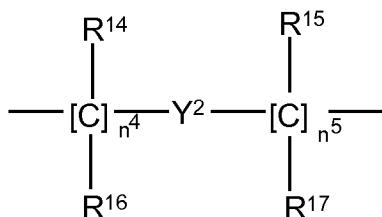
f)

wherein T<sub>2</sub> is -O- or -S-, -NH-, preferably T<sub>2</sub> is -O-, n<sup>3</sup> is an integer from 1 to 6, preferably n<sup>3</sup> is 1;

10 when Y and Y' are selected from b), c), d), e), e') or f), the -ONO<sub>2</sub> group of -(T-Y-ONO<sub>2</sub>), -(T'-Y-ONO<sub>2</sub>), -(T''-Y'-ONO<sub>2</sub>), -(T'-Y'-ONO<sub>2</sub>), -(T'''-Y-ONO<sub>2</sub>) and -(T'''-Y'-ONO<sub>2</sub>) is linked to the -(CH<sub>2</sub>)<sup>\*</sup>- group;

g)

15



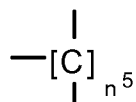
wherein:

n<sup>4</sup> is an integer from 0 to 10, preferably n<sup>4</sup> is 0 or 1;

n<sup>5</sup> is an integer from 1 to 10, preferably n<sup>5</sup> is 1;

20 R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> are the same or different, and are H or straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, preferably R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H;

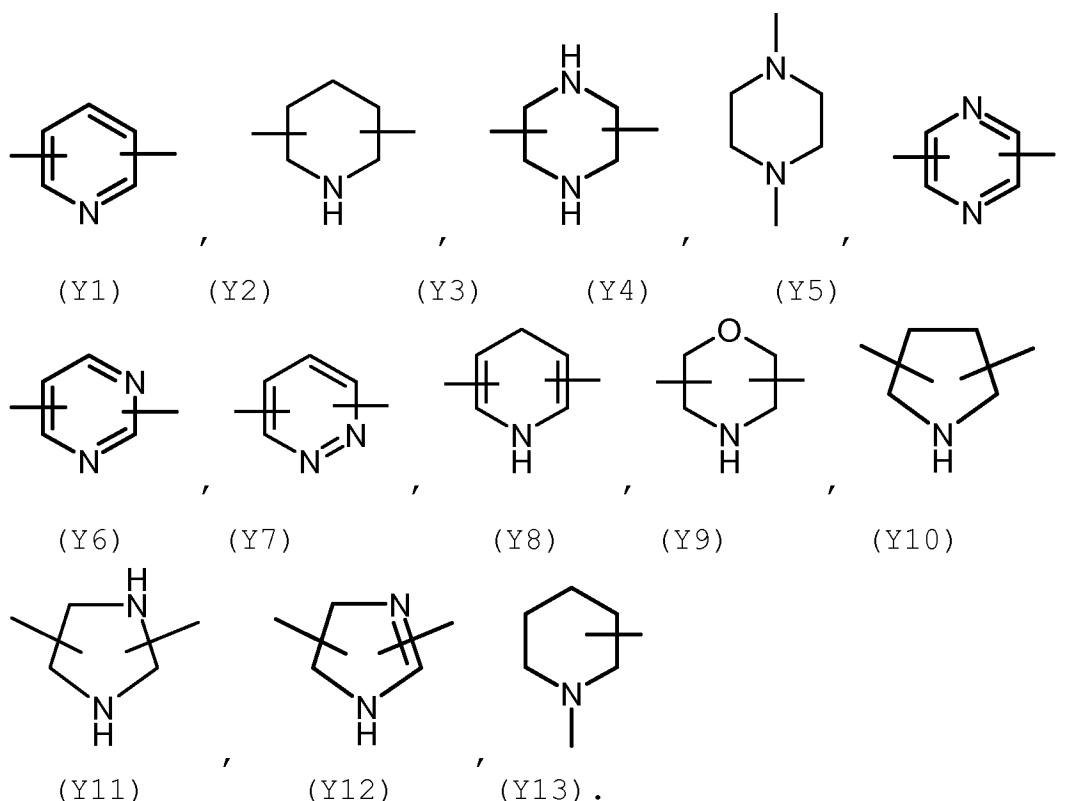
wherein the -ONO<sub>2</sub> group is linked to



25 wherein n<sup>5</sup> is as defined above;

Y<sup>2</sup> is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur,

and is selected from the group consisting of:



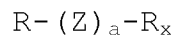
The term "C<sub>1</sub>-C<sub>10</sub> alkyl" as used herein refers to branched or straight alkyl groups including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, hexyl, octyl and the like.

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 (C<sub>1</sub>-C<sub>10</sub>)-alkyl, preferably CH<sub>3</sub>.

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.

Respiratory diseases comprises asthma, COPD (chronic obstructive pulmonary diseases), ARDS (Acute Respiratory Distress Syndrome), allergic rhinitis, respiratory tract diseases associated with inflammation.

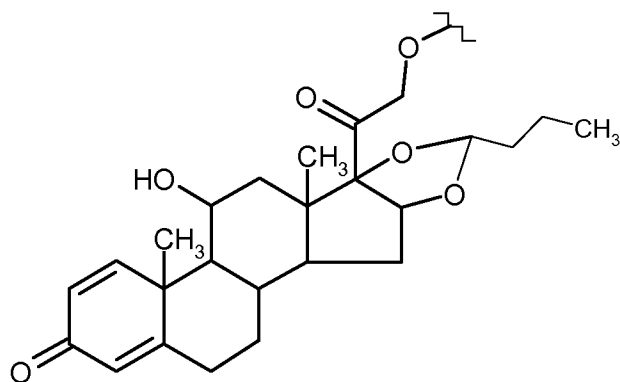
An embodiment of the invention relates to nitric oxide releasing compounds of general formula (I)



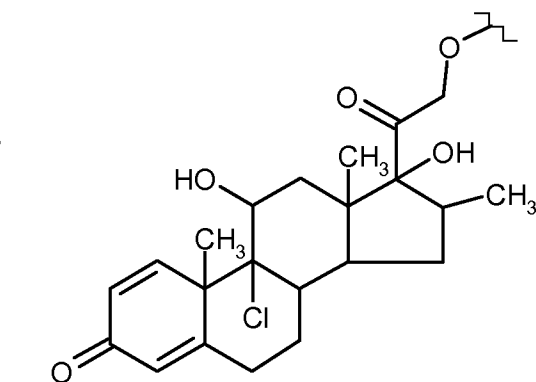
(I)

5 and pharmaceutically acceptable salts or stereoisomers thereof  
for use in the treatment of respiratory diseases wherein in  
formula (I)

the corticosteroid residue R is selected from:

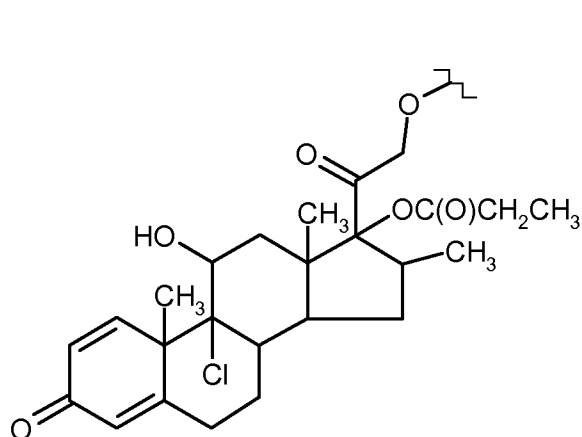


(II)

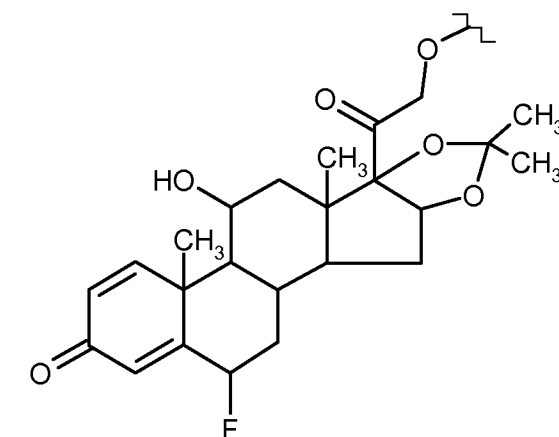


(III)

10



(IV)



(V)

a is 0 and

$R_x$  is selected from:

15 (a2)  $-C(O)-CH(R^1)-NH-(T'-Y-ONO_2)$

wherein

R<sup>1</sup> of the group A1) is selected from H, isobutyl, benzyl,

C<sub>6</sub>H<sub>5</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4- monosubstituted benzyl wherein the substituent of

the benzyl is selected from -F, -Cl, I, -NO<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>3</sub>, CN, C<sub>6</sub>H<sub>5</sub>CO-;

R<sup>1</sup> of the group A2) is selected from -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)OH- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-OH)], or

5 R<sup>1</sup> of the group A3) is selected from -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'', wherein R'' is H, or -C(O)CH<sub>3</sub>;

R<sup>1</sup> of the group A4) is selected from -CH<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>4</sub>-C(O)R''' wherein R''' is OR<sup>5a</sup> wherein R<sup>5a</sup> is H or a linear (C<sub>1</sub>-C<sub>5</sub>) alkyl;

10 T' is -C(O)-, -C(O)-X'' wherein X'' is -S- or -O-, preferably T' is -C(O)-;

Y is as below defined;

or R<sub>x</sub> is

(a4) -C(O)-CH(R<sup>1a</sup>-T''-Y'-ONO<sub>2</sub>)-NHR<sup>4a</sup>

15 wherein R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-, or

R<sup>1a</sup> of the group A7) is selected from -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-, 20 - (CH<sub>2</sub>)<sub>4</sub>-C(O)-,

R<sup>4a</sup> is H or -C(O)CH<sub>3</sub>,

T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from the group A5) or A6), preferably T'' is -C(O)-;

T'' is -O-, -S-, -NR'- or -O-CH(R')-O-C(O)- wherein R' is H or 25 -CH<sub>3</sub>, when R<sup>1a</sup> is selected from the group A7),

Y' is as below defined;

or R<sub>x</sub> is selected from:

(a5) -R<sup>1b</sup>-CH(NHR<sup>4a</sup>)-C(O)-(T-Y-ONO<sub>2</sub>)

(a6) -R<sup>1b</sup>-CH(COOR<sup>3a</sup>)NH-(T'-Y-ONO<sub>2</sub>)

30 (a9) -R<sup>1b</sup>-CH(NH-T'-Y'-ONO<sub>2</sub>)-C(O)-(T-Y-ONO<sub>2</sub>) or

(a10) -R<sup>1b</sup>-CH(C(O)-T-Y'-ONO<sub>2</sub>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

R<sup>1b</sup> of the group A10) is selected from -C(O)-CH<sub>2</sub>-, -C(O)-(CH<sub>2</sub>)<sub>2</sub>-, -C(O)-(CH<sub>2</sub>)<sub>4</sub>-,

$R^{3a}$  is H or a (C<sub>1</sub>-C<sub>5</sub>) alkyl,

$R^{4a}$  is H or -C(O)CH<sub>3</sub>,

T is -O-, -S-, -NR'- or -O-CH(R')-O-C(O)- wherein R' is H or -CH<sub>3</sub>, preferably T is -O-,

5 T' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, preferably T' is -C(O)-,

Y and Y' are as below defined;

or R<sub>x</sub> is

(a8) -C(O)-CH(R<sup>1a</sup>-T''-Y'-ONO<sub>2</sub>)-NH-(T'-Y-ONO<sub>2</sub>)

10 wherein

R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)-O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-, or

15 R<sup>1a</sup> of the group A7) is selected from -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>4</sub>-C(O)-,

T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from the group A5) or A6), preferably T'' is -C(O)-,

20 T'' is -O-, -S-, -NR'- or -O-CH(R')-O-C(O)- wherein R' is H or -CH<sub>3</sub>, when R<sup>1a</sup> is selected from the group A7);

T' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, preferably T' is -C(O)-,

Y and Y' are as below defined,

or R<sub>x</sub> is

25 (b2) -C(O)-CH<sub>2</sub>-CH(R<sup>2</sup>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

R<sup>2</sup> of the group B1) is selected from H, CH<sub>3</sub>, isobutyl, isopropyl, benzyl;

30 T' is -C(O)-, -C(O)-X'' wherein X'' is -S- or -O-, preferably T' is -C(O)-;

Y and Y' are each independently selected from

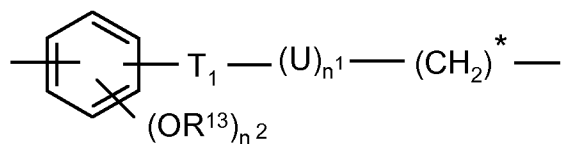
a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,



- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

d)



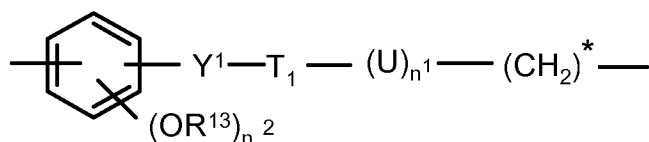
5 d)

wherein:

n<sup>2</sup> is an integer from 0 to 2, R<sup>13</sup> is H or CH<sub>3</sub>, T<sub>1</sub> is -O-C(O)- or -C(O)O-;

n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or  
10 branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

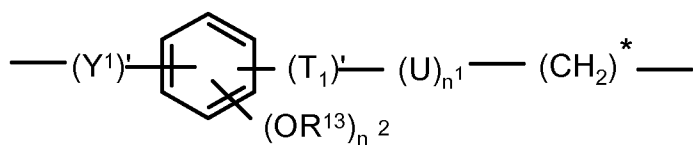
e)



e)

n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>, Y<sup>1</sup> is -CH=CH-(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>- and n<sup>2'</sup> is 0, T<sub>1</sub> is  
15 -C(O)O- and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene;

e')



e')

wherein:

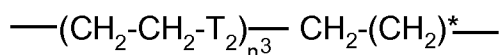
20 n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>;

Y<sup>1</sup> is -(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>-CH=CH- and n<sup>2'</sup> is 0;

T<sub>1</sub> = -O-C(O)-;

n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or  
branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

25 f)

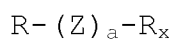


f)

wherein T<sub>2</sub> is -O- or -S-, -NH-, preferably T<sub>2</sub> is -O-, n<sup>3</sup> is 1 or 2;

when Y and Y' are selected from d), e), e') or f), the  $-\text{ONO}_2$  group of  $-(\text{T}-\text{Y}-\text{ONO}_2)$ ,  $-(\text{T}'-\text{Y}-\text{ONO}_2)$ ,  $-(\text{T}''-\text{Y}'-\text{ONO}_2)$ ,  $-(\text{T}'-\text{Y}'-\text{ONO}_2)$ ,  $-(\text{T}'''-\text{Y}-\text{ONO}_2)$  and  $-(\text{T}'''-\text{Y}'-\text{ONO}_2)$  is linked to the  $-(\text{CH}_2)^*$ -group.

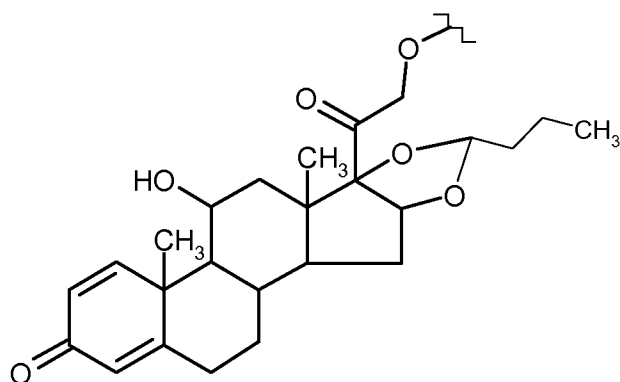
Another embodiment of the invention relates to nitric oxide releasing compounds of general formula (I)



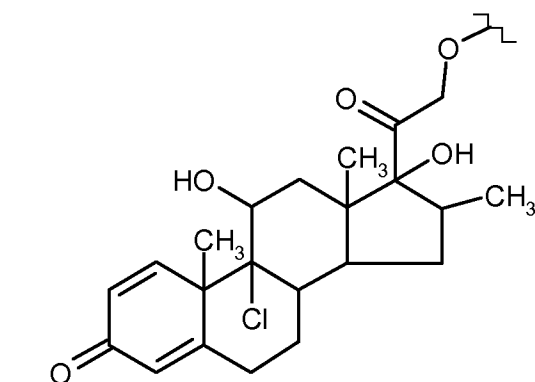
(I)

and pharmaceutically acceptable salts or stereoisomers thereof  
for use in the treatment of respiratory diseases wherein in  
formula (I)

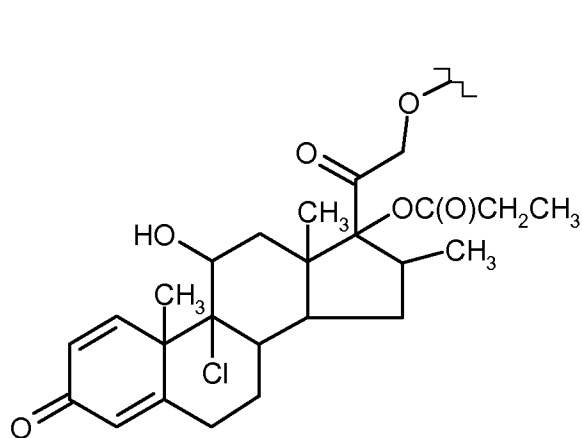
the corticosteroid residue R is selected from:



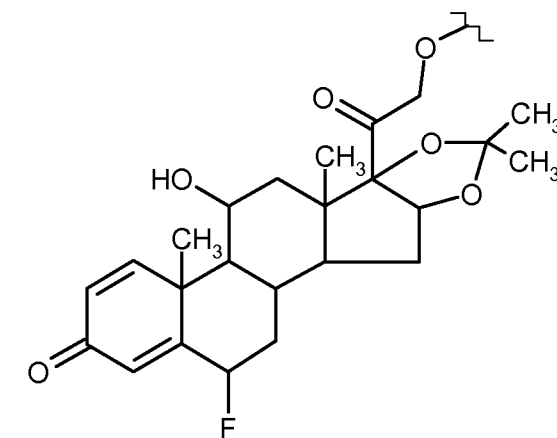
(II)



(III)



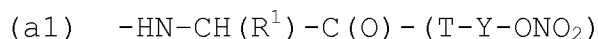
(IV)



(V)

a is 1 and Z is  $-C(0)-$ ;

R<sub>x</sub> is



wherein

R<sup>1</sup> of the group A1) is selected from H, isobutyl, benzyl, C<sub>6</sub>H<sub>5</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from -F, -Cl, I, -NO<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>3</sub>, CN, C<sub>6</sub>H<sub>5</sub>CO- or

R<sup>1</sup> of the group A2) is selected from:

10  $\text{-CH}_2\text{-OH}$ ,  $\text{-CH(CH}_3\text{)-OH-}$  or  $\text{-CH}_2\text{[(C}_6\text{H}_4\text{)-(4-OH)]}$ , or

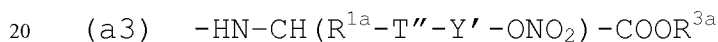
R<sup>1</sup> of the group A3) is selected from  $\text{-CH}_2\text{-NHR''}$ ,  $\text{-(CH}_2\text{)}_2\text{-NHR''}$ ,  $\text{-(CH}_2\text{)}_3\text{-NHR''}$ ,  $\text{-(CH}_2\text{)}_4\text{-NHR''}$ , wherein R'' is H, or -C(O)CH<sub>3</sub>,

R<sup>1</sup> of the group A4) is  $\text{-CH}_2\text{-C(O)R'''}$ ,  $\text{-(CH}_2\text{)}_2\text{-C(O)R'''}$ ,  $\text{-(CH}_2\text{)}_4\text{-C(O)R'''}$  wherein R''' is OR<sup>5a</sup> wherein R<sup>5a</sup> is H or a linear (C<sub>1</sub>-C<sub>5</sub>) alkyl;

T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, preferably T is -O-,

Y is as below defined;

or R<sub>x</sub> is



wherein

R<sup>1a</sup> of the group A5) is selected from  $\text{-CH}_2\text{-O-}$ ,  $\text{-CH(CH}_3\text{)O-}$  or  $\text{-CH}_2\text{[(C}_6\text{H}_4\text{)-(4-O)-]}$ , or

R<sup>1a</sup> of the group A6) is selected from  $\text{-CH}_2\text{-NH-}$ ,  $\text{-(CH}_2\text{)}_2\text{-NH-}$ ,  $\text{-(CH}_2\text{)}_3\text{-NH-}$ ,  $\text{-(CH}_2\text{)}_4\text{-NH-}$ , or

R<sup>1a</sup> of the group A7) is  $\text{-CH}_2\text{-C(O)-}$ ,  $\text{-(CH}_2\text{)}_2\text{-C(O)-}$ ,  $\text{-(CH}_2\text{)}_4\text{-C(O)-}$ , R<sup>3a</sup> is H or a (C<sub>1</sub>-C<sub>5</sub>) alkyl,

T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from the group A5) or A6), preferably T'' is -C(O)-;

30 T'' is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, when R<sup>1a</sup> is selected from the group A7);

Y' is as below defined;

or R<sub>x</sub> is selected from.

(a5)  $-R^{1b}-CH(NHR^{4a})-C(O)-(T-Y-ONO_2)$

(a6)  $-R^{1b}-CH(COOR^{3a})NH-(T'-Y-ONO_2)$

(a9)  $-R^{1b}-CH(NH-T'-Y'-ONO_2)-C(O)-(T-Y-ONO_2)$  or

(a10)  $-R^{1b}-CH(C(O)-T-Y'-ONO_2)-NH-(T'-Y-ONO_2)$

5 wherein

$R^{1b}$  of the group A8) is selected from  $-O-CH(CH_3)-$ ,  $-O-CH_2-$ ,  $[-4-O-(C_6H_4)]-CH_2-$ , or

$R^{1b}$  of the group A9) is selected from  $-HN-CH_2-$ ,  $-HN-(CH_2)_2-$ ,  $-HN-(CH_2)_3-$ ,  $-HN-(CH_2)_4-$ ,

10  $R^{3a}$  is H or a  $(C_1-C_5)$  alkyl,

$R^{4a}$  is H or  $-C(O)CH_3$ ,

T is  $-O-$ ,  $-S-$ ,  $-NR'-$ ,  $-O-CH(R')-O-C(O)-$  wherein  $R'$  is H or a straight or branched  $C_1-C_4$  alkyl, preferably T is  $-O-$ ,

15  $T'$  is  $-C(O)-$  or  $-C(O)-X''$  wherein  $X''$  is  $-S-$  or  $-O-$ , preferably  $T'$  is  $-C(O)-$ ,

Y and  $Y'$  are as below defined;

or  $R_x$  is

(a7)  $-HN-CH(R^{1a}-T''-Y'-ONO_2)-C(O)-(T-Y-ONO_2)$

wherein

20  $R^{1a}$  of the group A5) is selected from  $-CH_2-O-$ ,  $-CH(CH_3)-O-$  or  $-CH_2[(C_6H_4)-(4-O)-]$ , or

$R^{1a}$  of the group A6) is selected from  $-CH_2-NH-$ ,  $-(CH_2)_2-NH-$ ,  $-(CH_2)_3-NH-$ ,  $-(CH_2)_4-NH-$ , or

$R^{1a}$  of the group A7) is  $-CH_2-C(O)-$ ,  $-(CH_2)_2-C(O)-$ ,  $-(CH_2)_4-C(O)-$ ;

25  $T''$  is  $-C(O)-$  or  $-C(O)-X''$ , wherein  $X''$  is  $-S-$  or  $-O-$ , when  $R^{1a}$  is selected from A5) or A6), preferably  $T''$  is  $-C(O)-$

$T''$  is  $-O-$ ,  $-S-$ ,  $-NR'-$ ,  $-O-CH(R')-O-C(O)-$ , wherein  $R'$  is H or a straight or branched  $C_1-C_4$  alkyl, when  $R^{1a}$  is selected from A7), preferably  $T''$  is  $-O-$ ,

30 T is  $-O-$ ,  $-S-$ ,  $-NR'-$ ,  $-O-CH(R')-O-C(O)-$  wherein  $R'$  is H or a straight or branched  $C_1-C_4$  alkyl, preferably T is  $-O-$ ;

Y and  $Y'$  are as below defined;

or  $R_x$  is

(b1)  $-HN-CH(R^2)-CH_2-C(O)-(T-Y-ONO_2)$

wherein

$R^2$  of the group B1) is selected from H,  $CH_3$ , isobutyl, isopropyl, benzyl;

$R^2$  of the group B2) is selected from  $-CH_2-OH$ ,  $-CH(CH_3)-OH$ - or

5  $-CH_2[(C_6H_4)(4-OH)]$ , or

$R^2$  of the group B3) is selected from  $-CH_2-NHR''$ ,  $-(CH_2)_2-NHR''$ ,  $-(CH_2)_3-NHR''$ ,  $-(CH_2)_4-NHR''$ , wherein  $R''$  is H, or  $-C(O)CH_3$ ,

$R^2$  of the group B4) is  $-CH_2-C(O)R'''$ ,  $-(CH_2)_2-C(O)R'''$ ,

10  $-(CH_2)_4-C(O)R'''$  wherein  $R'''$  is  $OR^{5a}$  wherein  $R^{5a}$  is H or a linear  $(C_1-C_5)$  alkyl;

T is  $-O-$ ,  $-S-$ ,  $-NR'-$ ,  $-O-CH(R')-O-C(O)-$  wherein  $R'$  is H or a straight or branched  $C_1-C_4$  alkyl, preferably T is  $-O-$ ,

Y is as below defined;

or  $R_x$  is selected from

15 (d1)  $-HN-CH(R^{12})-CH_2-O-(T'''-Y-ONO_2)$  or

(d2)  $-O-CH_2-CH(R^{12})-NH-(T'-Y-ONO_2)$

wherein

$R^{12}$  of the group D1) is selected from H,  $CH_3$ , isobutyl, isopropyl, benzyl, or

20  $R^{12}$  of the group D2) is selected from  $-CH_2-OH$ ,  $-CH(CH_3)OH$ - or  $-CH_2[(C_6H_4)-(4-OH)]$ , or

$R^{12}$  of the group D3) is selected from  $-CH_2-NHR''$ ,  $-(CH_2)_2-NHR''$ ,  $-(CH_2)_3-NHR''$ ,  $-(CH_2)_4-NHR''$  wherein  $R''$  is H, or

25  $R^{12}$  of the group D4) is  $-CH_2-C(O)R'''$ ,  $-(CH_2)_2-C(O)R'''$ ,  $-(CH_2)_4-C(O)R'''$  wherein  $R'''$  is  $OR^{5a}$  wherein  $R^{5a}$  is H or a linear  $(C_1-C_5)$  alkyl;

$T'$  and  $T'''$  are each independently selected from  $-C(O)-$  or  $-C(O)-X''$  wherein  $X''$  is  $-S-$  or  $-O-$ , preferably  $T'$  and  $T'''$  are  $-C(O)-$ ,

30 Y is as below defined;

or  $R_x$  is selected from:

(d3)  $-HN-CH(R^{12a}-T''-Y'-ONO_2)-CH_2OH$

(d4)  $-O-CH_2-CH(R^{12a}-T''-Y'-ONO_2)-NHR^{4a}$

(d7)  $-HN-CH(R^{12a}-T''-Y'-ONO_2)-CH_2-O-(T'''-Y-ONO_2)$  or

(d8)  $-O-CH_2-CH(R^{12a}-T''-Y'-ONO_2)-NH-(T'-Y-ONO_2)$

wherein

$R^{12a}$  of the group D5) is selected from  $-CH_2-O-$ ,  $-CH(CH_3)-O-$  or  $-CH_2[(C_6H_4)-(4-O)-]$ , or

5  $R^{12a}$  of the group D6) is selected from  $-CH_2-NH-$ ,  $-(CH_2)_2-NH-$ ,  $-(CH_2)_3-NH-$ ,  $-(CH_2)_4-NH-$ , or

$R^{12a}$  of the group D7) is  $-CH_2-C(O)-$ ,  $-(CH_2)_2-C(O)-$ ,  $-(CH_2)_4-C(O)-$ ;  $R^{4a}$  is H or  $-C(O)CH_3$ ,

10  $T''$  is selected from  $-C(O)-$  or  $-C(O)-X''$ , wherein  $X''$  is  $-S-$  or  $-O-$ , when  $R^{12a}$  is selected from D5) or D6), preferably  $T'$  and  $T'''$  are  $-C(O)-$ ,

$T''$  is  $-O-$ ,  $-S-$ ,  $-NR'-$ ,  $-O-CH(R')-O-C(O)-$ , wherein  $R'$  is H or a straight or branched  $C_1-C_4$  alkyl, when  $R^{12a}$  is selected from D7), preferably  $T$  is  $-O-$ ,

15  $T'''$  is selected from  $-C(O)-$  or  $-C(O)-X''$  wherein  $X''$  is  $-S-$  or  $-O-$ , preferably  $T'''$  is  $-C(O)-$ ,

$Y$  and  $Y'$  are as below defined;

or  $R_x$  is selected from:

(d5)  $-R^{12b}-CH(NHR^{4a})-CH_2-O-(T'''-Y-ONO_2)$

20 (d6)  $-R^{12b}-CH(CH_2OH)-NH-(T'-Y-ONO_2)$

(d9)  $-R^{12b}-CH(NH-T'-Y'-ONO_2)-CH_2-O-(T'''-Y-ONO_2)$  or

(d10)  $-R^{12b}-CH(CH_2-O-T'''-Y'-ONO_2)-NH-(T'-Y-ONO_2)$

wherein

25  $R^{12b}$  of the group D8) is selected from  $-O-CH(CH_3)-$ ,  $-O-CH_2-$ ,  $[-4-O-(C_6H_4)]-CH_2-$ , or

$R^{12b}$  of the group D9) is selected from  $-HN-CH_2-$ ,  $-HN-(CH_2)_2-$ ,  $-HN-(CH_2)_3-$ ,  $-HN-(CH_2)_4-$ ;

$R^{4a}$  is H or  $-C(O)-CH_3$ ,

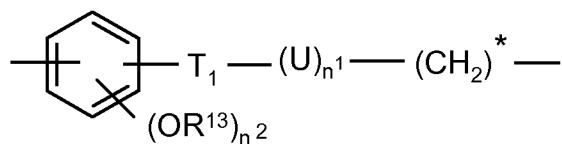
30  $T'$  and  $T'''$  are each independently selected from  $-C(O)-$ ,  $-C(O)-X''$ , wherein  $X''$  is  $-S-$  or  $-O-$ , preferably  $T'$  and  $T'''$  are  $-C(O)-$ ,  $Y$  and  $Y'$  are each independently selected from

a)

- a straight or branched  $C_1-C_{10}$  alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

d)



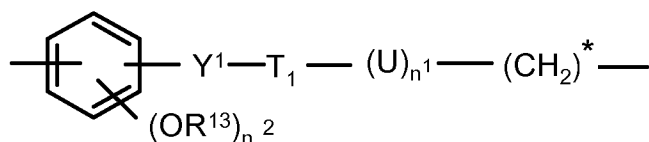
5 d)

wherein:

n<sup>2</sup> is an integer from 0 to 2, R<sup>13</sup> is H or CH<sub>3</sub>, T<sub>1</sub> is -O-C(O)- or -C(O)O-,

n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or  
10 branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

e)

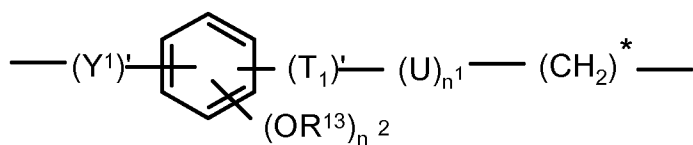


e)

n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>, Y<sup>1</sup> is -CH=CH-(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>- and n<sup>2'</sup> is 0,

15 T<sub>1</sub> is -C(O)O- and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene;

e')



e'

wherein:

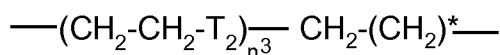
20 n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>,

Y<sup>1</sup> is -(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>-CH=CH- and n<sup>2'</sup> is 0,

T<sub>1</sub> = -O-C(O)-,

n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or  
branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

25 f)

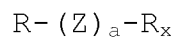


f)

wherein  $T_2$  is -O- or -S-, -NH-, preferably  $T_2$  is -O-,  $n^3$  is 1 or 2,

when Y and Y' are selected from d), e), e') or f), the -ONO<sub>2</sub> group of -(T-Y-ONO<sub>2</sub>), -(T'-Y-ONO<sub>2</sub>), -(T''-Y'-ONO<sub>2</sub>), -(T'-Y'-ONO<sub>2</sub>),  
 5 -(T'''-Y-ONO<sub>2</sub>) and -(T'''-Y'-ONO<sub>2</sub>) is linked to the -(CH<sub>2</sub>)\*-group.

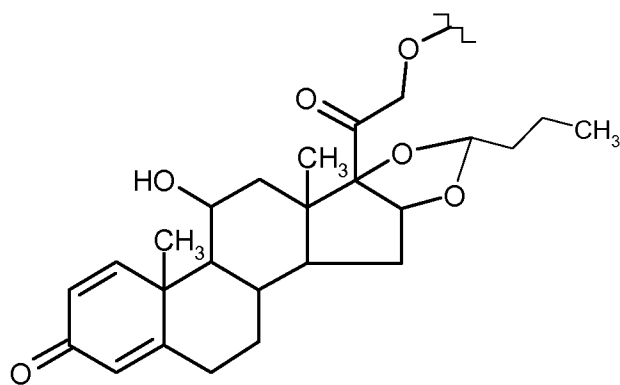
Another embodiment of the present invention is to provide nitric oxide releasing compounds of general formula (I)



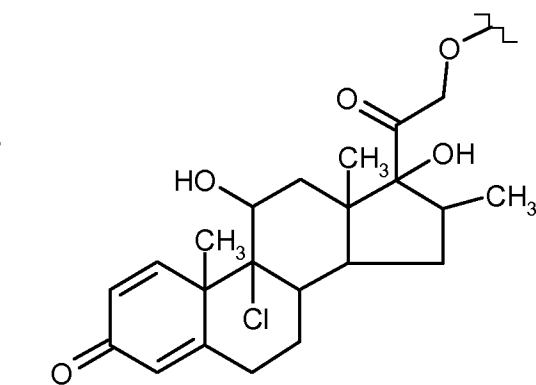
(I)

and pharmaceutically acceptable salts or stereoisomers thereof for use in the treatment of respiratory diseases, wherein in formula (I)

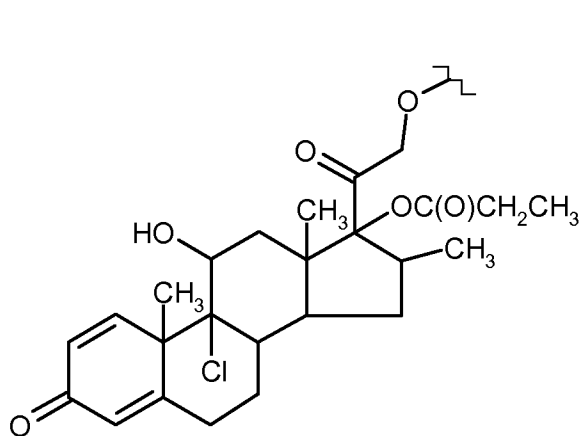
the corticosteroid residue R is selected from:



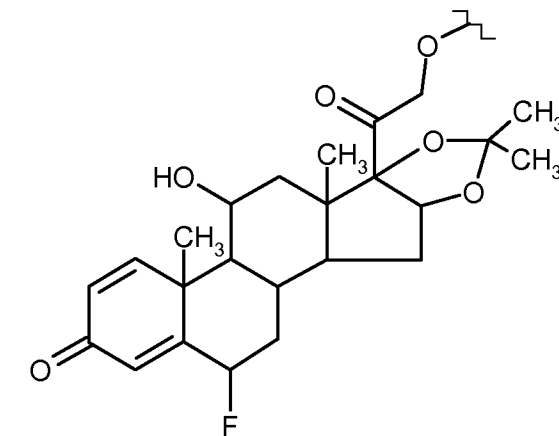
(II)



(III)



(IV)



(V)



R<sub>x</sub> is

(a2)  $-C(O)-CH(R^1)-NH-(T'-Y-ONO_2)$

wherein

R<sup>1</sup> of of the group A1) is H

5 T' is  $-C(O)-$ ;

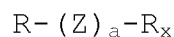
Y is selected from

a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

10 - a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a  $-ONO_2$  group;

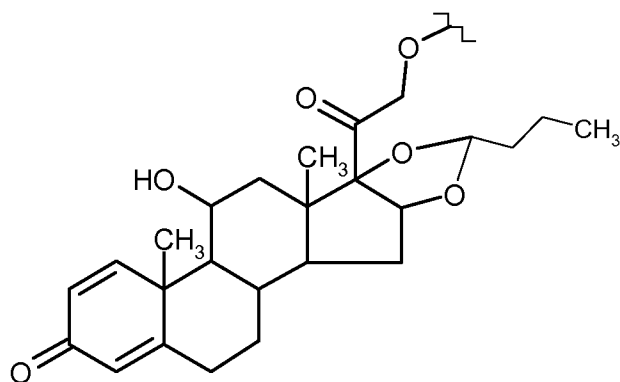
Another embodiment relates to nitric oxide releasing compounds of general formula (I)



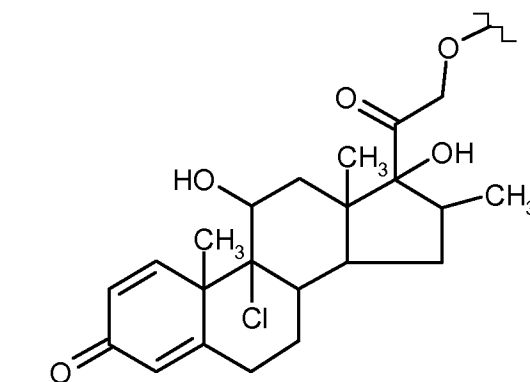
(I)

15 and pharmaceutically acceptable salts or stereoisomers thereof for use in the treatment of respiratory diseases, wherein in formula (I)

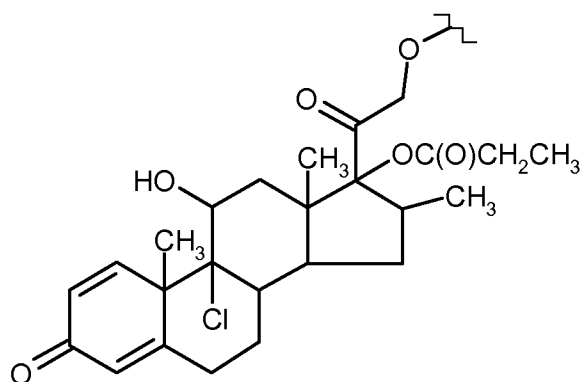
the corticosteroid residue R is selected from:



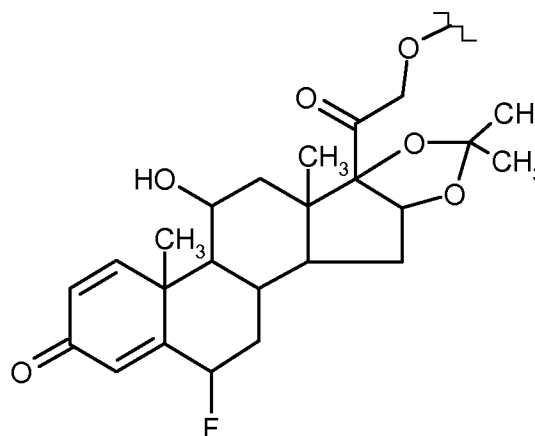
(II)



(III)



(IV)



(V)

a is 0,

R<sub>x</sub> is selected from

5 R<sub>x</sub> is selected from

(a5) -R<sup>1b</sup>-CH(NHR<sup>4a</sup>)-C(O)-(T-Y-ONO<sub>2</sub>)

(a6) -R<sup>1b</sup>-CH(COOR<sup>3a</sup>)NH-(T'-Y-ONO<sub>2</sub>) or

(a9) -R<sup>1b</sup>-CH(NH-T'-Y'-ONO<sub>2</sub>)-C(O)-(T-Y-ONO<sub>2</sub>)

wherein

10 R<sup>1b</sup> of the group A10) is -C(O)-CH<sub>2</sub>-,

R<sup>3a</sup> is H or a (C<sub>1</sub>-C<sub>5</sub>) alkyl,

R<sup>4a</sup> is H or -C(O)CH<sub>3</sub>,

T is selected from -O-, -S-, -NR'- wherein R' is as above defined,

15 T' is -C(O)- and

Y and Y' are each independently selected from

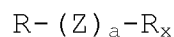
a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group.

20

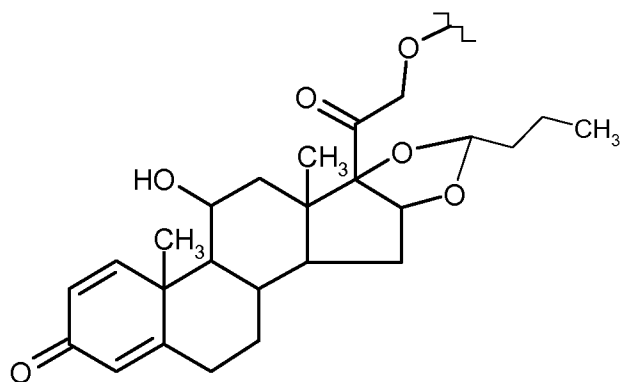
Another embodiment relates to nitric oxide releasing compounds of general formula (I)



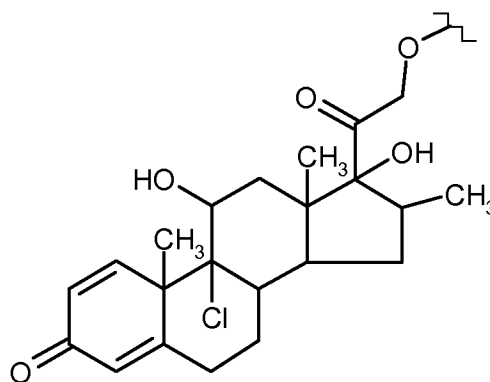
(I)

25 and pharmaceutically acceptable salts or stereoisomers thereof for use in the treatment of respiratory diseases, wherein in formula (I)

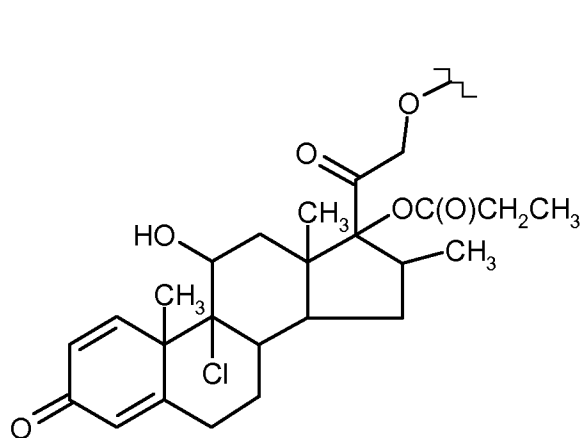
the corticosteroid residue R is selected from:



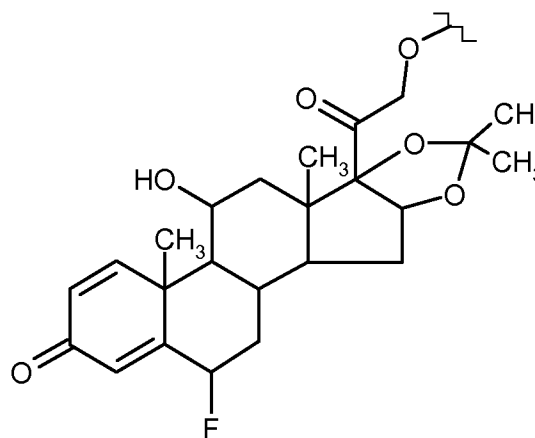
(II)



(III)



(IV)



(V)

a is 1 and Z is  $-C(O)-$ ,

$R_x$  is

(a5)  $-R^{1b}-CH(NHR^{4a})-C(O)-(T-Y-ONO_2)$  or

(a9)  $-R^{1b}-CH(NH-T'-Y'-ONO_2)-C(O)-(T-Y-ONO_2)$

wherein  $R^{1b}$  of A10) is  $-O-CH_2-$  or  $[-4-O-(C_6H_4)]-CH_2-$ ,

$R^{4a}$  is H or  $-C(O)CH_3$ ,

T is selected from  $-O-$ ,  $-S-$ ,  $-NR'-$  wherein  $R'$  is as above defined,

$T'$  is  $-C(O)-$  and

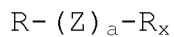
Y and  $Y'$  are each independently selected from

a)

- a straight or branched  $C_1-C_{10}$  alkylene,

- a straight or branched  $C_1-C_{10}$  alkylene substituted with a  $-ONO_2$  group.

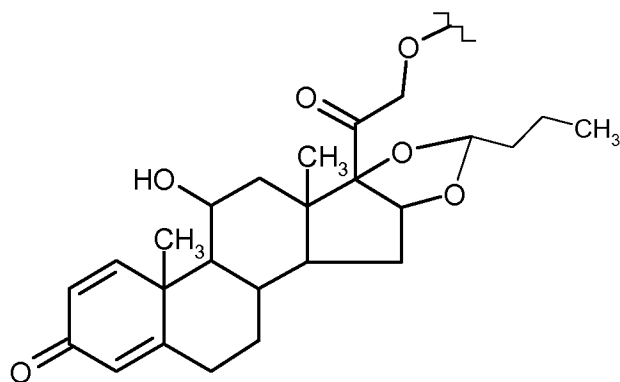
Another embodiment of the invention relates to nitric oxide releasing compounds of general formula (I)



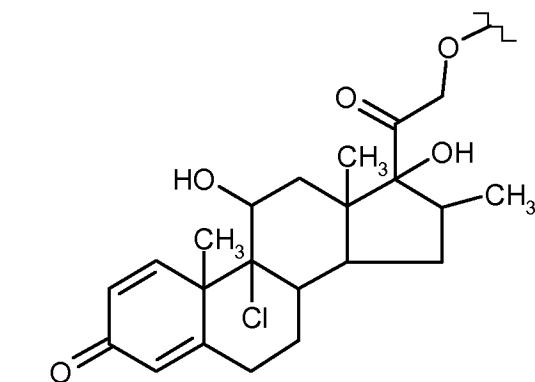
(I)

5 and pharmaceutically acceptable salts or stereoisomers thereof  
for use in the treatment of respiratory diseases, wherein in  
formula (I)

the corticosteroid residue R is selected from:

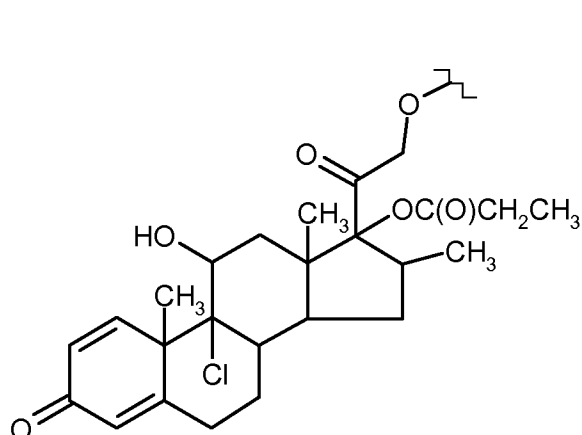


(II)

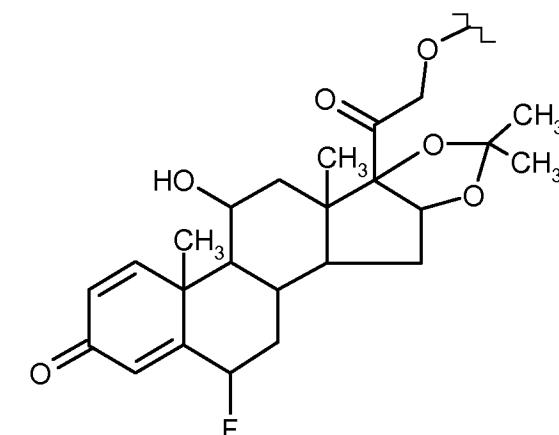


(III)

10



(IV)



(V)

a is 0,

 $R_X$  is

15 (b2)  $-C(O)-CH_2-CH(R^2)-NH-(T'-Y-ONO_2)$

wherein

$R^2$  of the group B1) is  $H$ ,

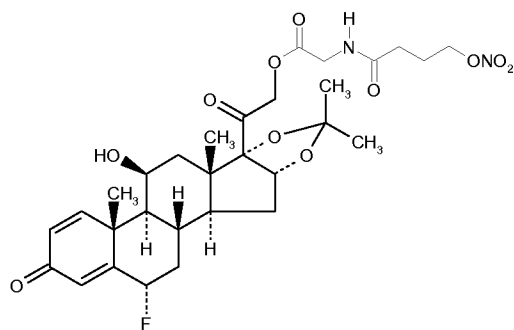
T' is  $-C(O)-$ ;

$Y$  and  $Y'$  are each independently selected from

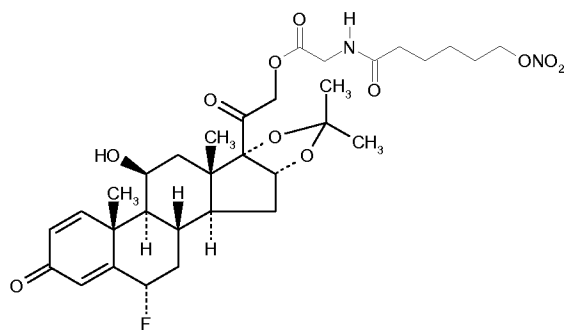
20 a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,
- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group.

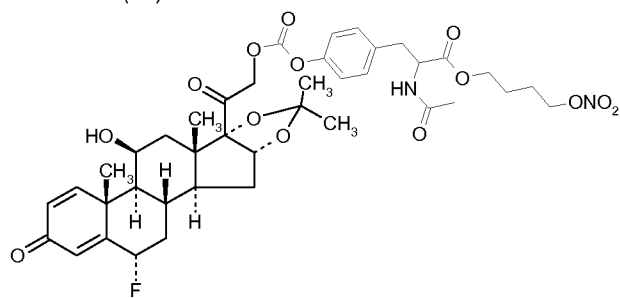
The most preferred nitric oxide releasing compounds of general formula (I) for the use in the treatment of respiratory diseases are:



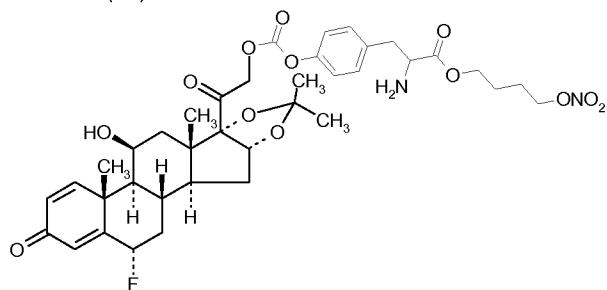
(1)



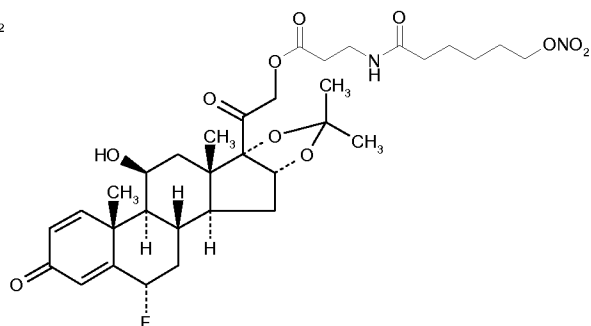
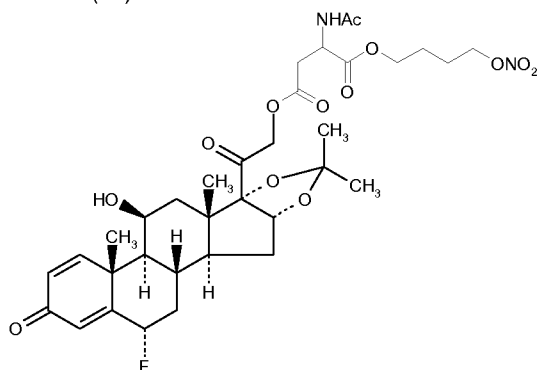
(2)



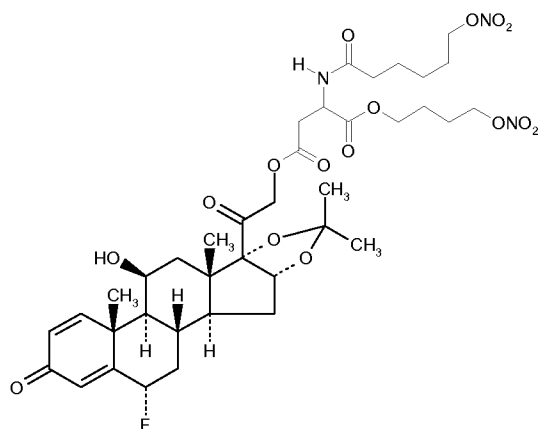
(3)



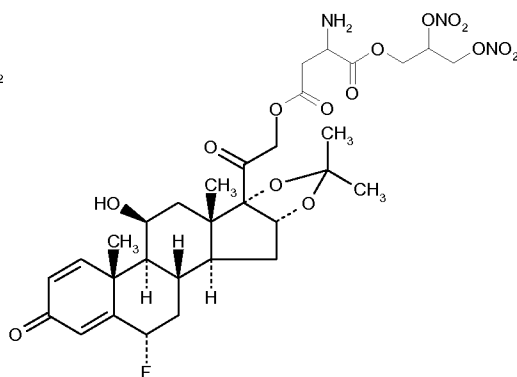
(4)



(5)

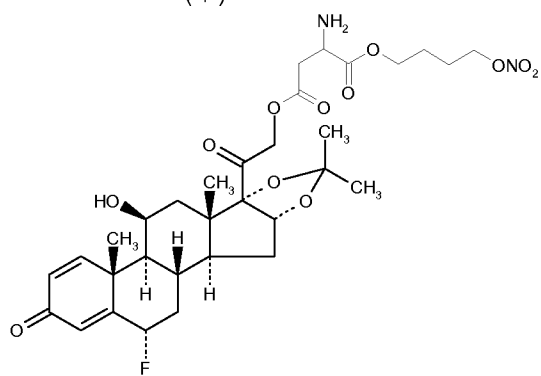


(6)

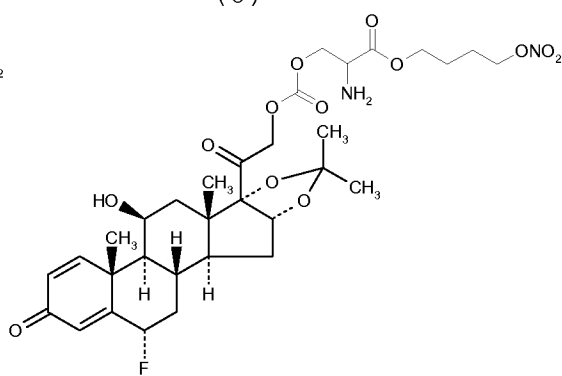


5

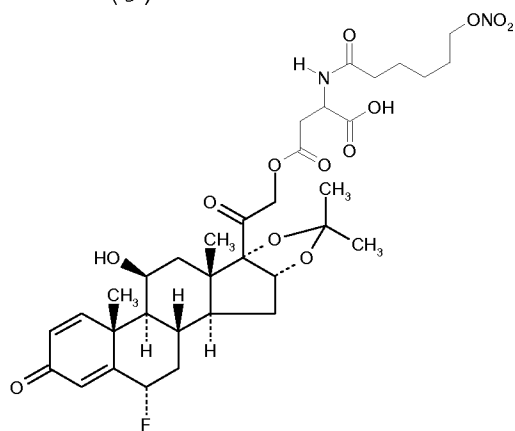
(7)



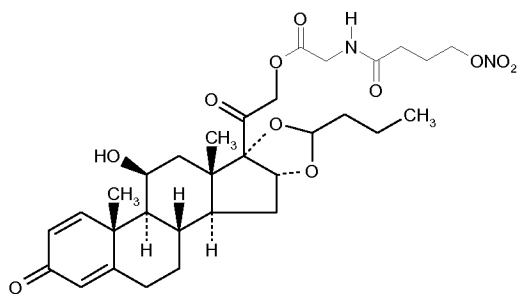
(8)



(9)



(10)



10

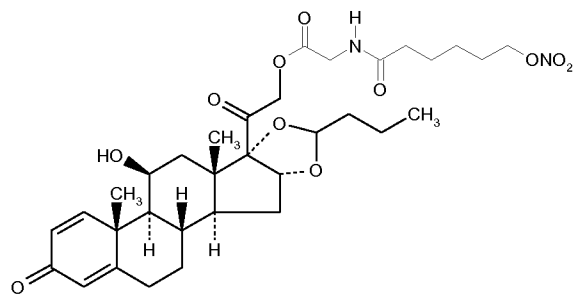
(11)



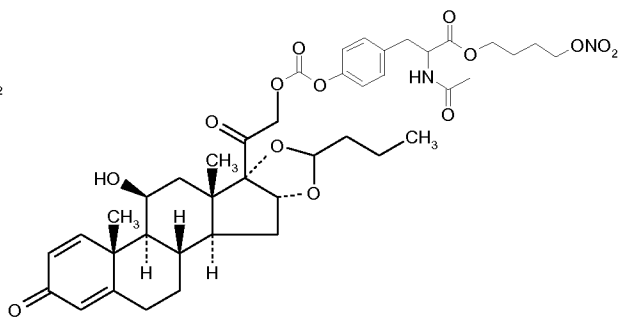
(12)



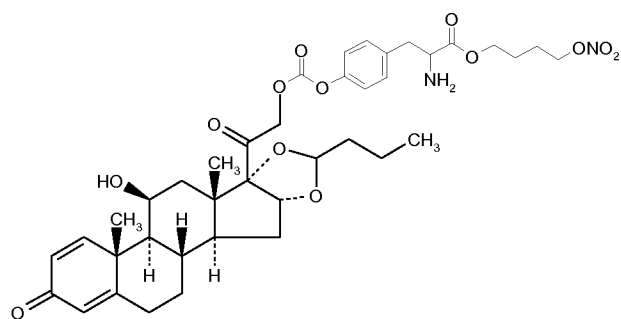
38



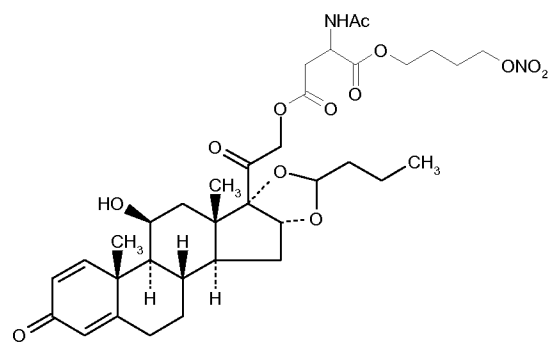
(13)



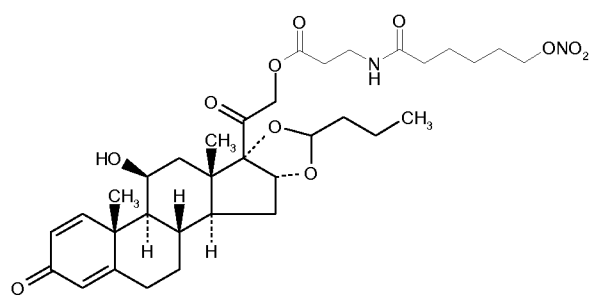
(14)



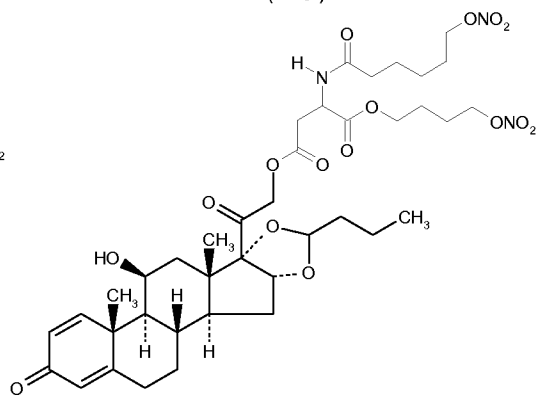
(15)



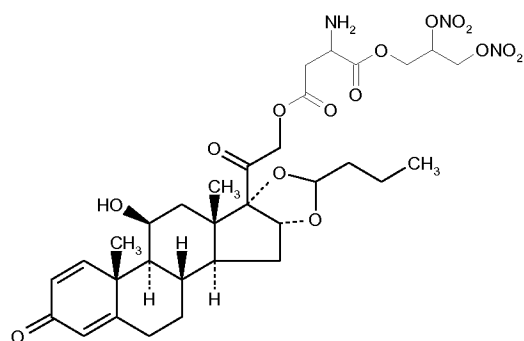
(16)



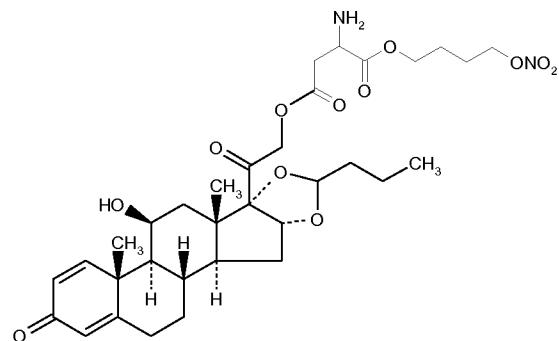
(17)



(18)



(19)

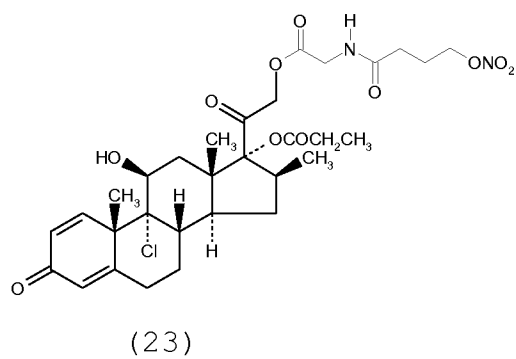
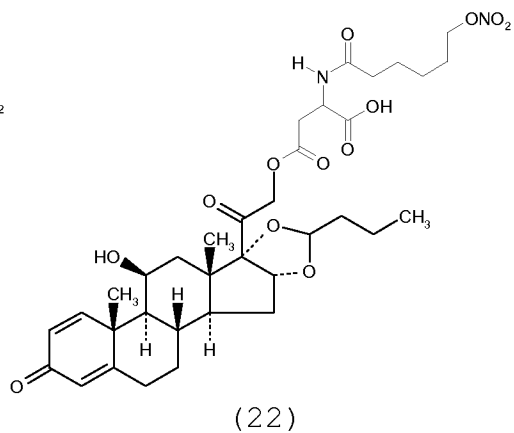
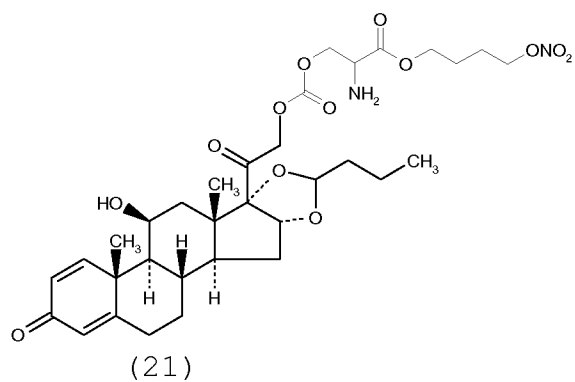


(20)

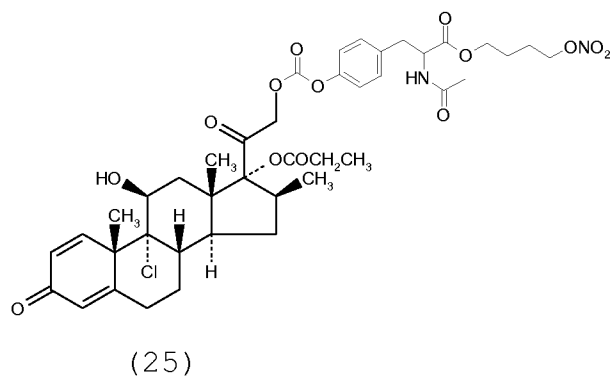
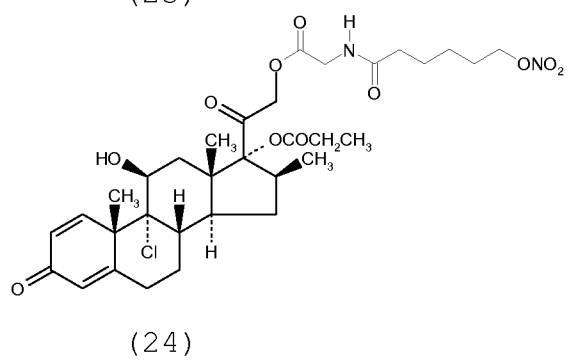
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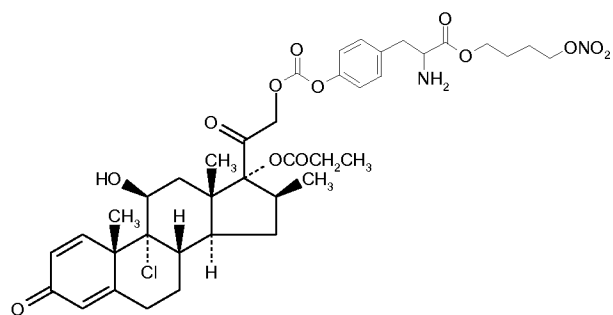


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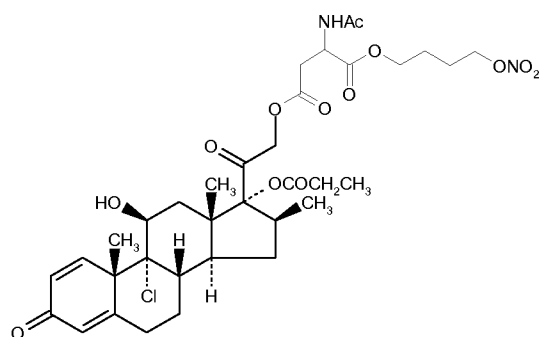


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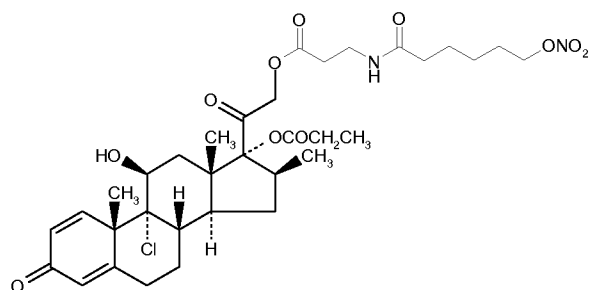




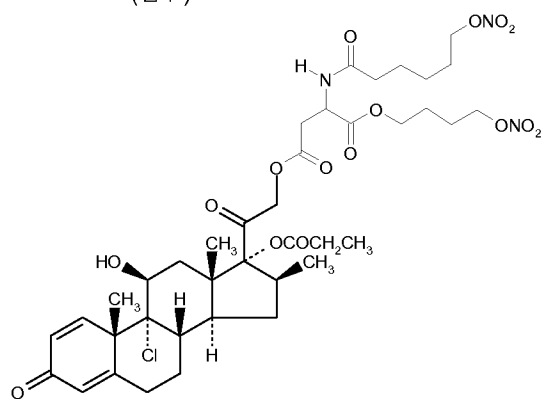
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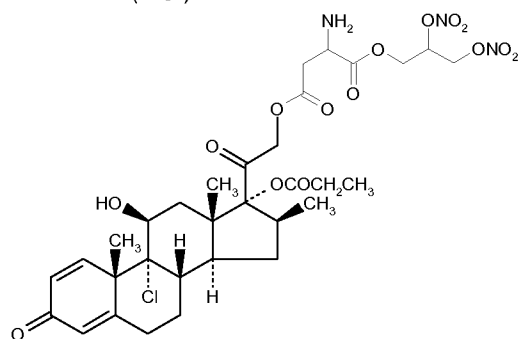
(27)



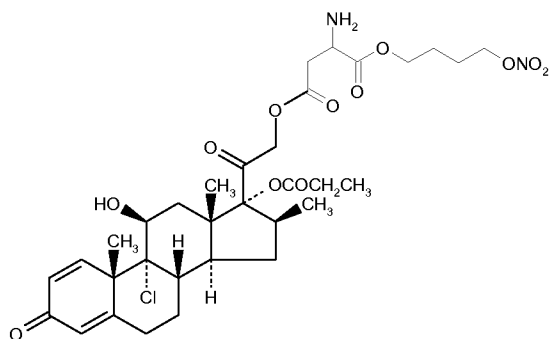
(28)



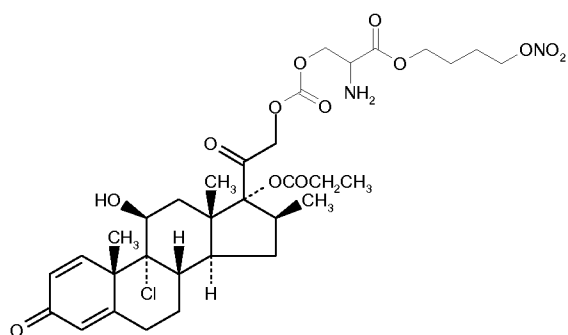
(29)



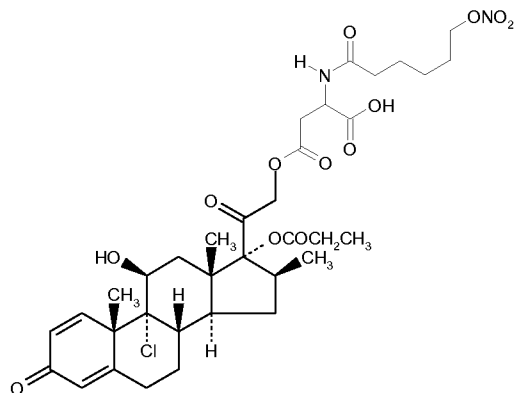
(30)



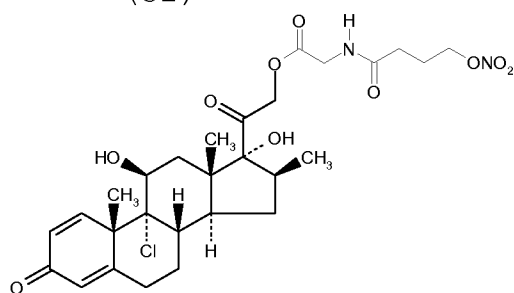
(31)



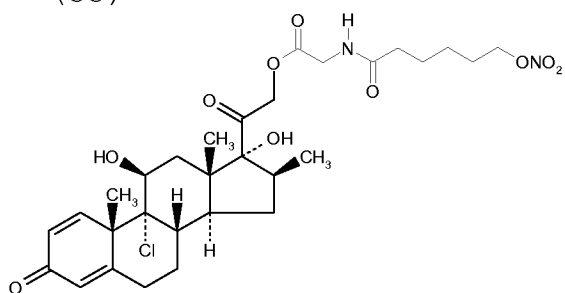
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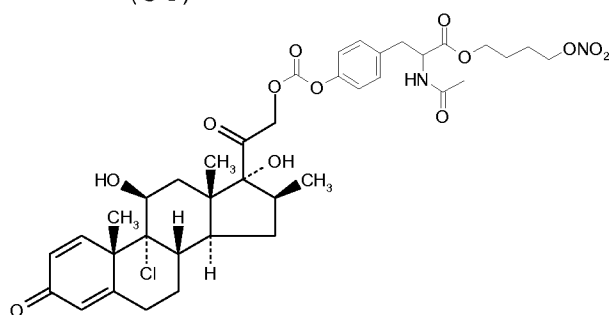
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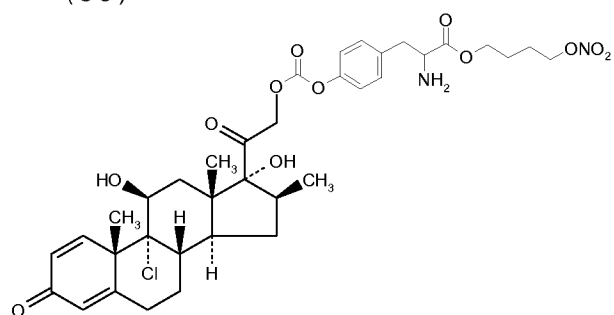
(34)



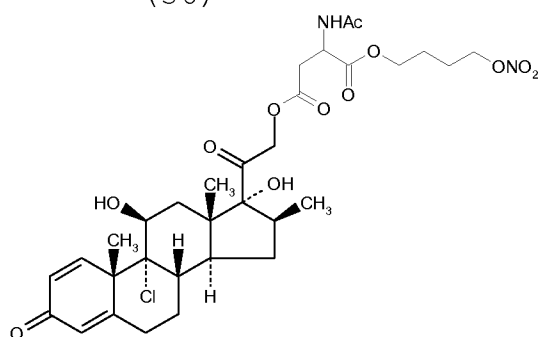
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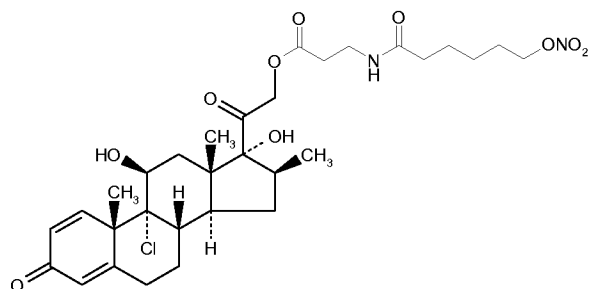
(36)



(37)

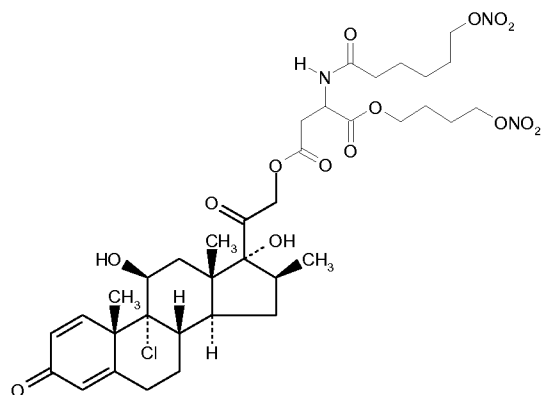


(38)

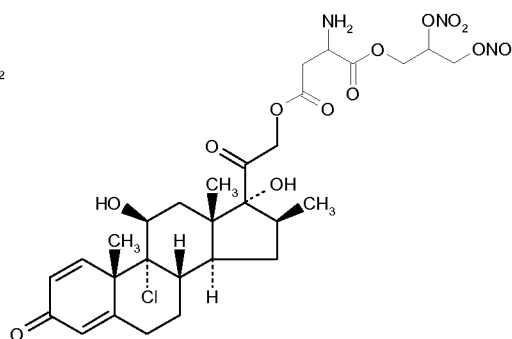


(39)

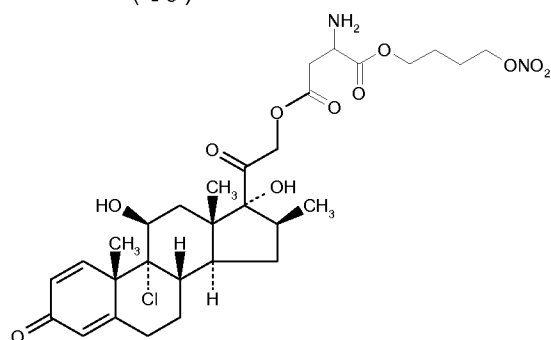
42



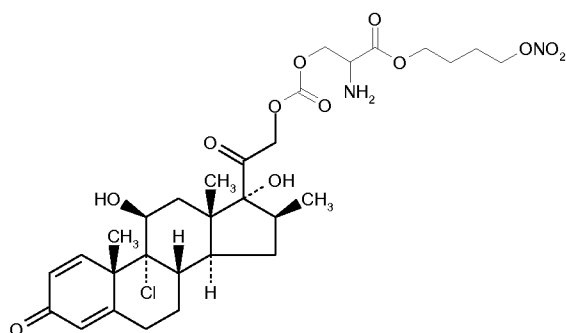
(40)



(41)

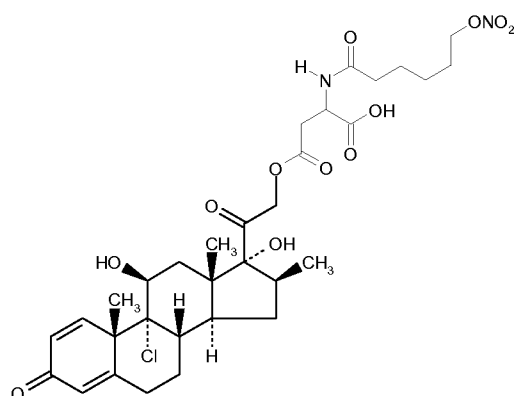


(42)



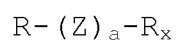
(43)

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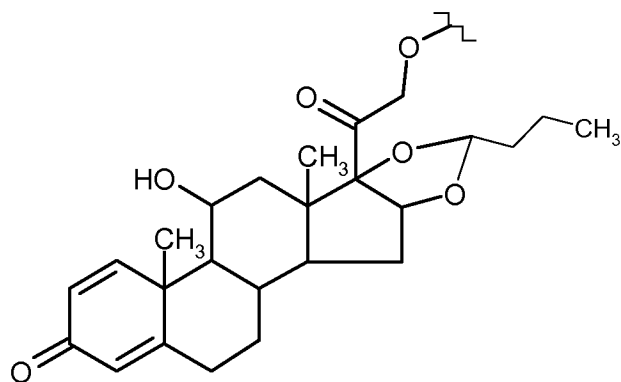
(44)

Another object of the present invention provides nitric  
 10 oxide releasing compounds of general formula (I) and  
 pharmaceutically acceptable salts or stereoisomers thereof

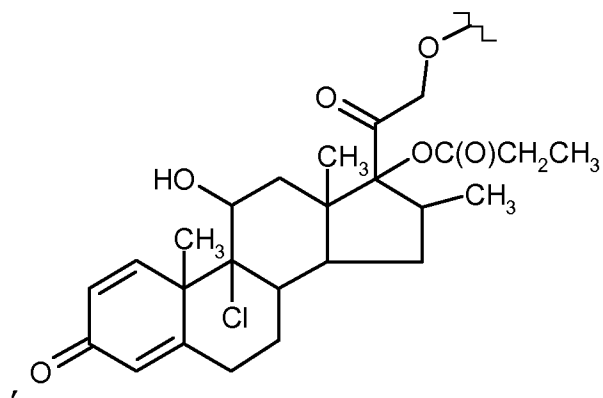


(I)

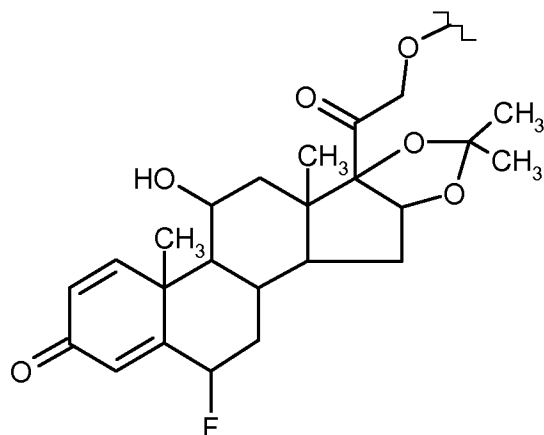
wherein R is a corticosteroid residue selected from:



(II)



(IV)



(V)

5 a is 0 or 1,

Z is a group capable of binding  $R_x$  and is selected from  $-C(O)-$ ,  
or  $-CH(R')-O-$  wherein  $R'$  is selected from H or a straight or  
branched  $C_1-C_4$  alkyl, preferably  $R'$  is H or  $-CH_3$ ;

$R_x$  is a radical selected from the following meanings:

10 A)

(a1)  $-HN-CH(R^1)-C(O)-(T-Y-ONO_2)$

(a2)  $-C(O)-CH(R^1)-NH-(T'-Y-ONO_2)$

(a3)  $-HN-CH(R^{1a}-T''-Y'-ONO_2)-COOR^{3a}$

(a4)  $-C(O)-CH(R^{1a}-T''-Y'-ONO_2)-NHR^{4a}$

15 (a5)  $-R^{1b}-CH(NHR^{4a})-C(O)-(T-Y-ONO_2)$

(a6)  $-R^{1b}-CH(COOR^{3a})NH-(T'-Y-ONO_2)$

(a7)  $-HN-CH(R^{1a}-T''-Y'-ONO_2)-C(O)-(T-Y-ONO_2)$

(a8)  $-C(O)-CH(R^{1a}-T''-Y'-ONO_2)-NH-(T'-Y-ONO_2)$

(a9)  $-R^{1b}-CH(NH-T'-Y'-ONO_2)-C(O)-(T-Y-ONO_2)$

20 (a10)  $-R^{1b}-CH(C(O)-T-Y'-ONO_2)-NH-(T'-Y-ONO_2)$

wherein:

R<sup>1</sup> is selected from:

A1) H, -CH<sub>3</sub>, isopropyl, isobutyl, sec-butyl, tert-butyl, methylthio-(CH<sub>2</sub>)<sub>2</sub>-, phenyl, benzyl, C<sub>6</sub>H<sub>5</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,

2-monosubstituted benzyl, or 3-monosubstituted benzyl or  
4-monosubstituted benzyl wherein the substituent of the  
benzyl is selected from -F, -Cl, I, -NO<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>3</sub>, CN,  
C<sub>6</sub>H<sub>5</sub>CO-;

2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl,  
2-pyrrolidyl, 3-triptyophanyl-CH<sub>2</sub>-, 3-benzothienyl-CH<sub>2</sub>-,

4-imidazolyl-CH<sub>2</sub>-, 9-anthranyl-CH<sub>2</sub>-, cyclohexyl,  
cyclohexyl-CH<sub>2</sub>-, cyclohexyl-(CH<sub>2</sub>)<sub>2</sub>-, cyclopentyl-CH<sub>2</sub>-,  
(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CH-, 4-B(OH)<sub>2</sub>-benzyl, 4-quinolyl-CH<sub>2</sub>-, 3-quinolyl-CH<sub>2</sub>-,  
2-quinolyl-CH<sub>2</sub>-,

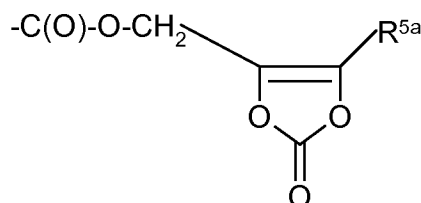
2-quinoxalyl-CH<sub>2</sub>-, 2-furyl-CH<sub>2</sub>-, 1-naphtyl-CH<sub>2</sub>-, 2-naphtyl-CH<sub>2</sub>-,  
2-pyridyl-CH<sub>2</sub>-, 3-pyridyl-CH<sub>2</sub>-, 4-pyridyl-CH<sub>2</sub>-,

2-thienyl-CH<sub>2</sub>-, 3-thienyl-CH<sub>2</sub>-, C<sub>6</sub>H<sub>4</sub>-CH=CH-CH<sub>2</sub>-, CH<sub>2</sub>=CH-CH<sub>2</sub>-,  
CH≡CH-CH<sub>2</sub>-, NH<sub>2</sub>-CO-CH<sub>2</sub>-, NH<sub>2</sub>-CO-(CH<sub>2</sub>)<sub>2</sub>-, NH<sub>2</sub>(=NH)NH-(CH<sub>2</sub>)<sub>3</sub>-,  
P(=O)(OCH<sub>3</sub>)<sub>2</sub>, I-CH<sub>2</sub>-, preferably R<sup>1</sup> is H, -CH<sub>3</sub>, isopropyl,

benzyl;

A2) -CH<sub>2</sub>-SH, -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)-OH, -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-OH)],  
-CH<sub>2</sub>[(C<sub>6</sub>H<sub>2</sub>)-(3,5-diiodo)-(4-OH)],  
-CH<sub>2</sub>[(C<sub>6</sub>H<sub>3</sub>)-(3-nitro)-(4-OH)], preferably R<sup>1</sup> is -CH<sub>2</sub>-OH or  
-CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-OH)];

A3) -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'',  
wherein R'' is H, -C(O)CH<sub>3</sub> or

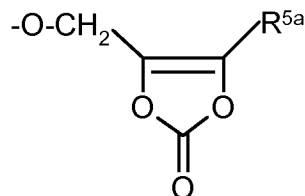


wherein R<sup>5a</sup> is H or a linear or branched C<sub>1</sub>-C<sub>10</sub> alkyl chain,  
preferably R<sup>5a</sup> is H or a linear (C<sub>1</sub>-C<sub>5</sub>) alkyl, preferably R<sup>1</sup> is

-(CH<sub>2</sub>)<sub>4</sub>-NHR'', wherein R'' is as above defined,

45

A4)  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''$  wherein  $\text{R}'''$  is  $-\text{OR}^{5a}$  or



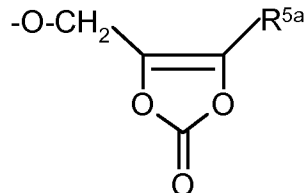
wherein  $\text{R}^{5a}$  is as above defined, preferably  $\text{R}^1$  is  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  
 5 wherein  $\text{R}'''$  is as above defined,  
 $\text{R}^{1a}$  is selected from:

A5)  $-\text{CH}_2-\text{S}-$ ,  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{O}-$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ ,  
 $-\text{CH}_2-[(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)-(4-\text{O})-]$ ,  
 $-\text{CH}_2-[(3\text{-nitro})-(\text{C}_6\text{H}_3)-(4-\text{O})-]$ , preferably  $\text{R}^{1a}$  is  $-\text{CH}_2-\text{O}-$ ;

10 A6)  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,  $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ ,  
 preferably  $\text{R}^{1a}$  is  $-(\text{CH}_2)_4-\text{NH}-$  or  $-\text{CH}_2-\text{NH}-$ ,

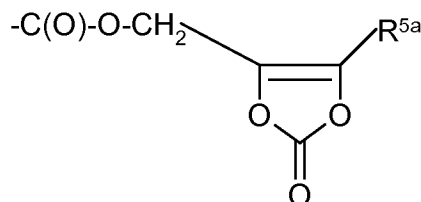
A7)  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ , preferably  $\text{R}^{1a}$  is  $-\text{CH}_2-\text{C}(\text{O})-$ ;

$\text{R}^{3a}$  is selected from H,  $-\text{R}^{5a}$  or



15 wherein  $\text{R}^{5a}$  is as above defined,

$\text{R}^{4a}$  is selected from H or  $-\text{C}(\text{O})\text{CH}_3$  or



wherein  $\text{R}^{5a}$  is as above defined,

20  $\text{R}^{1b}$  is selected from

A8)  $-\text{S}-\text{CH}_2-$ ,  $-\text{O}-\text{CH}(\text{CH}_3)-$ ,  $-\text{O}-\text{CH}_2-$ ,  $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ,  
 $[-(4-\text{O})-(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)]-\text{CH}_2-$ ,  
 $[-(4-\text{O})-(3\text{-nitro})-(\text{C}_6\text{H}_3)]-\text{CH}_2-$ , preferably  $\text{R}^{1b}$  is  $-\text{O}-\text{CH}_2-$  or  
 $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ;

A9)  $-\text{HN}-\text{CH}_2-$ ,  $-\text{HN}-(\text{CH}_2)_2-$ ,  $-\text{HN}-(\text{CH}_2)_3-$ ,  $-\text{HN}-(\text{CH}_2)_4-$ , preferably  $\text{R}^{1b}$  is  $-\text{HN}-(\text{CH}_2)_4-$  or  $-\text{HN}-\text{CH}_2-$ ;

A10)  $-\text{C}(\text{O})-\text{CH}_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_4-$ , preferably  $\text{R}^{1b}$  is  $-\text{C}(\text{O})-\text{CH}_2-$ ;

5 T is selected from  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$  or  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})\text{O}-$  wherein  $\text{R}'$  is as above defined;  
 $\text{T}'$  is  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{X}''-$  wherein  $\text{X}''$  is  $-\text{O}-$  or  $-\text{S}-$ , or  $\text{T}'$  is  $-\text{C}(\text{O})-\text{NR}'-$  wherein  $\text{R}'$  is as above defined;  
 $\text{T}''$  is independently selected from  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{X}''-$ ,  
 10  $-\text{C}(\text{O})-\text{NR}'-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$ ,  
 $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})\text{O}-$ , wherein  $\text{X}''$  and  $\text{R}'$  are as above defined,  
 with the proviso that  $\text{T}''$  is  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{X}''-$  or  $-\text{C}(\text{O})-\text{NR}'-$   
 when  $\text{T}''$  is linked to  $-\text{NH}-$ ,  $-\text{O}-$ , or  $-\text{S}-$ , or  
 $\text{T}''$  is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})\text{O}-$   
 15 when  $\text{T}''$  is linked to  $-\text{C}(\text{O})-$ ,  
 $\text{Y}$  and  $\text{Y}'$  are as below defined;  
 or  $\text{R}_x$  is selected from:

B)

- (b1)  $-\text{HN}-\text{CH}(\text{R}^2)-\text{CH}_2-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$
- 20 (b2)  $-\text{C}(\text{O})-\text{CH}_2-\text{CH}(\text{R}^2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$
- (b3)  $-\text{HN}-\text{CH}(\text{R}^{2a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{CH}_2\text{COOR}^{3a}$
- (b4)  $-\text{C}(\text{O})-\text{CH}_2-\text{CH}(\text{R}^{2a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NHR}^{4a}$
- (b5)  $-\text{R}^{2b}-\text{CH}(\text{NHR}^{4a})-\text{CH}_2-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$
- (b6)  $-\text{R}^{2b}-\text{CH}(\text{CH}_2\text{COOR}^{3a})\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$
- 25 (b7)  $-\text{HN}-\text{CH}(\text{R}^{2a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{CH}_2-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$
- (b8)  $-\text{C}(\text{O})-\text{CH}_2-\text{CH}(\text{R}^{2a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$
- (b9)  $-\text{R}^{2b}-\text{CH}(\text{NH}-\text{T}'-\text{Y}'-\text{ONO}_2)-\text{CH}_2\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$
- (b10)  $-\text{R}^{2b}-\text{CH}(\text{CH}_2\text{C}(\text{O})-\text{T}-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

wherein

30  $\text{R}^2$  is selected from:

B1)  $\text{H}$ ,  $-\text{CH}_3$ ,  $\text{CF}_3$ , isopropyl, isobutyl, sec-butyl, methylthio- $(\text{CH}_2)_2-$ , phenyl, benzyl, 3-triptophanyl- $\text{CH}_2-$ ,

$\text{NH}_2\text{-C(O)-CH}_2\text{-}$ ,  $\text{NH}_2\text{-C(O)-(CH}_2)_2\text{-}$ ,  $\text{NH}_2\text{(=NH)NH-(CH}_2)_3\text{-}$ ,  $\text{tBuO-CH(CH}_3)\text{-}$ ,  
 ,  $\text{benzyl-O-CH}_2\text{-}$ , 4-terbutoxy-benzyl, 4-phenylbenzyl, preferably  
 $\text{R}^2$  is H,  $\text{-CH}_3$ , isopropyl, benzyl,

B2)  $\text{-CH}_2\text{-SH}$ ,  $\text{-CH}_2\text{-OH}$ ,  $\text{-CH(CH}_3)\text{-OH}$ ,  $\text{-CH}_2\text{[(C}_6\text{H}_4)\text{-(4-OH)]}$ ,

5  $\text{-CH}_2\text{[(C}_6\text{H}_2)\text{-(3,5-diiodo)-(4-OH)]}$ ,

$\text{-CH}_2\text{[(C}_6\text{H}_3)\text{-(3-nitro)-(4-OH)]}$ ;

B3)  $\text{-CH}_2\text{-NHR''}$ ,  $\text{-(CH}_2)_2\text{-NHR''}$ ,  $\text{-(CH}_2)_3\text{-NHR''}$ ,  $\text{-(CH}_2)_4\text{-NHR''}$ , wherein  
 $\text{R''}$  is as above defined, preferably  $\text{R}^2$  is  $\text{-(CH}_2)_4\text{-NHR''}$ ;

B4)  $\text{-CH}_2\text{-C(O)-R'''}$ ,  $\text{-(CH}_2)_2\text{-C(O)-R'''}$ ,  $\text{-(CH}_2)_4\text{-C(O)-R'''}$  wherein

10  $\text{R'''}$  is as above defined, preferably  $\text{R}^2$  is  $\text{-CH}_2\text{-C(O)-R''}'$ ;

$\text{R}^{2a}$  is selected from:

B5)  $\text{-CH}_2\text{-S-}$ ,  $\text{-CH}_2\text{-O-}$ ,  $\text{-CH(CH}_3)\text{-O-}$  or  $\text{-CH}_2\text{[(C}_6\text{H}_4)\text{-(4-O)-]}$ ,

$\text{-CH}_2\text{[(3,5-diiodo)-(C}_6\text{H}_2)\text{-(4-O)-]}$ ,

$\text{-CH}_2\text{[(3-nitro)-(C}_6\text{H}_3)\text{-(4-O)-]}$ , preferably  $\text{R}^{2a}$  is  $\text{-CH}_2\text{-O-}$ ;

15 B6)  $\text{-CH}_2\text{-NH-}$ ,  $\text{-(CH}_2)_2\text{-NH-}$ ,  $\text{-(CH}_2)_3\text{-NH-}$ ,  $\text{-(CH}_2)_4\text{-NH-}$ , preferably  
 $\text{R}^{2a}$  is  $\text{-(CH}_2)_4\text{-NH-}$  or  $\text{-CH}_2\text{-NH-}$ ;

B7)  $\text{-CH}_2\text{-C(O)-}$ ,  $\text{-(CH}_2)_2\text{-C(O)-}$ ,  $\text{-(CH}_2)_4\text{-C(O)-}$ , preferably  $\text{R}^{2a}$  is  
 $\text{-CH}_2\text{-C(O)-}$ ;

$\text{R}^{2b}$  is selected from

20 B8)  $\text{-S-CH}_2\text{-}$ ,  $\text{-O-CH(CH}_3)\text{-}$ ,  $\text{-O-CH}_2\text{-}$ ,  $\text{[-(4-O)-(C}_6\text{H}_4)]\text{-CH}_2\text{-}$ ,

$\text{[-(4-O)-(3,5-diiodo)-(C}_6\text{H}_2)]\text{-CH}_2\text{-}$ ,  $\text{[-(4-O)-(3-nitro)-(C}_6\text{H}_3)]\text{-CH}_2\text{-}$ ,  
 , preferably  $\text{R}^{2b}$  is  $\text{-O-CH}_2\text{-}$  or  $\text{[-(4-O)-(C}_6\text{H}_4)]\text{-CH}_2\text{-}$ ;

B9)  $\text{-HN-CH}_2\text{-}$ ,  $\text{-HN-(CH}_2)_2\text{-}$ ,  $\text{-HN-(CH}_2)_3\text{-}$ ,  $\text{-HN-(CH}_2)_4\text{-}$ , preferably  
 $\text{R}^{2b}$  is  $\text{-HN-(CH}_2)_4\text{-}$  or  $\text{-HN-CH}_2\text{-}$ ;

25 B10)  $\text{-C(O)-CH}_2\text{-}$ ,  $\text{-C(O)-(CH}_2)_2\text{-}$ ,  $\text{-C(O)-(CH}_2)_4\text{-}$ , preferably  $\text{R}^{2b}$  is  
 $\text{-C(O)-CH}_2\text{-}$ ;

$\text{R}^{3a}$  and  $\text{R}^{4a}$  are as above defined;

$\text{T}$ ,  $\text{T'}$  and  $\text{T''}$  are as above defined and  $\text{Y}$  and  $\text{Y'}$  are as below  
 defined;

30 or  $\text{R}_x$  is selected from:

C)

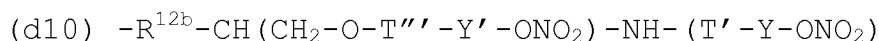
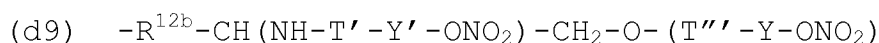
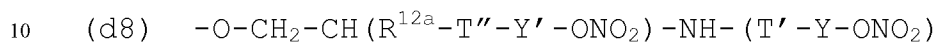
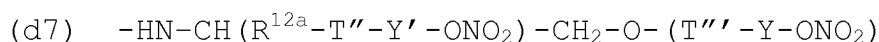
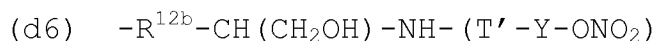
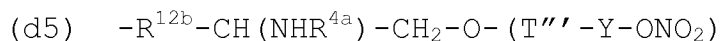
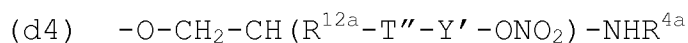
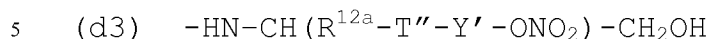
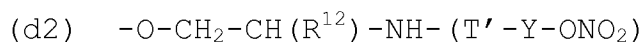
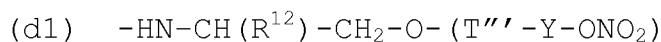
(c1)  $\text{-HN-(CH}_2)_b\text{-C(O)-(T-Y-ONO}_2\text{)}$ ;

(c2)  $\text{-C(O)-(CH}_2)_b\text{-NH-(T'-Y-ONO}_2\text{)}$ ;

wherein  $b$  is an integer from 3 to 6,



T and T' are as above defined and Y and Y' are as below defined;  
D)



wherein

T''' is independently selected from  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{X}''$ - wherein X''  
15 is  $-\text{O}-$  or  $-\text{S}-$ , or  $-\text{C}(\text{O})-\text{NR}'$ - wherein R' is as above defined;

T' and T'' are as above defined,

Y and Y' are as below defined;

R<sup>12</sup> is selected from:

D1) H,  $-\text{CH}_3$ , isopropyl, isobutyl, sec-butyl,  
20 methylthio- $(\text{CH}_2)_2-$ , benzyl, 3-triptyophanyl- $\text{CH}_2-$ ,  
4-imidazolyl- $\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}-\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}-(\text{CH}_2)_2-$ ,  $\text{NH}_2(=\text{NH})\text{NH}-(\text{CH}_2)_3-$ ,  
preferably R<sup>12</sup> is H;

D2)  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ,  
 $-\text{CH}_2-[(\text{C}_6\text{H}_3)-(3,5\text{-diiodo})-(4-\text{OH})]$ ,  
25  $-\text{CH}_2-[(\text{C}_6\text{H}_3)-(3\text{-nitro})-(4-\text{OH})]$ , preferably R<sup>12</sup> is  $-\text{CH}_2-\text{OH}$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ;

D3)  $-\text{CH}_2-\text{NHR}''$ ,  $-(\text{CH}_2)_2-\text{NHR}''$ ,  $-(\text{CH}_2)_3-\text{NHR}''$ ,  $-(\text{CH}_2)_4-\text{NHR}''$ , wherein  
R'' is as above defined, preferably R<sup>12</sup> is  $-(\text{CH}_2)_4-\text{NHR}''$ ;

D4)  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''$  wherein R'''  
30 is as above defined, preferably R<sup>12</sup> is  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ;

R<sup>12a</sup> is selected from

D5)  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{O}-$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ ,  $-\text{CH}_2-[3,5\text{-diiodo}-(\text{C}_6\text{H}_2)-(4-\text{O})-]$ ,  $-\text{CH}_2-[3\text{-nitro}-(\text{C}_6\text{H}_3)-4-\text{O}-]$ , preferably R<sup>12a</sup>  
is  $\text{CH}_2-\text{O}-$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ ,

D6)  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,  $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ , preferably  $\text{R}^{12a}$  is  $-(\text{CH}_2)_4-\text{NH}-$  or  $-\text{CH}_2-\text{NH}-$ ,

D7)  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ , preferably  $\text{R}^{12a}$  is  $-\text{CH}_2-\text{C}(\text{O})-$ ,

5  $\text{R}^{12b}$  is selected from

D8)  $-\text{O}-\text{CH}_2-$ ,  $-\text{O}-\text{CH}(\text{CH}_3)-$ ,  $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ,  
 $[-(4-\text{O})-(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)]-\text{CH}_2-$ ,  $[-(4-\text{O})-(3\text{-nitro})-(\text{C}_6\text{H}_3)]-\text{CH}_2-$ ,  
 preferably  $\text{R}^{12b}$  is  $-\text{O}-\text{CH}_2-$  or  $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ;

D9)  $-\text{HN}-\text{CH}_2-$ ,  $-\text{HN}-(\text{CH}_2)_2-$ ,  $-\text{HN}-(\text{CH}_2)_3-$ ,  $-\text{HN}-(\text{CH}_2)_4-$ , preferably  
 10  $\text{R}^{12b}$  is  $-\text{HN}-(\text{CH}_2)_4-$  or  $-\text{HN}-\text{CH}_2-$ ;

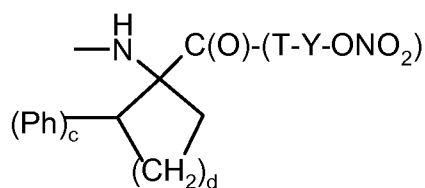
D10)  $-\text{C}(\text{O})-\text{CH}_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_4-$ , preferably  $\text{R}^{12b}$   
 is  $-\text{C}(\text{O})-\text{CH}_2-$ ;

$\text{R}^{4a}$  is as above defined;

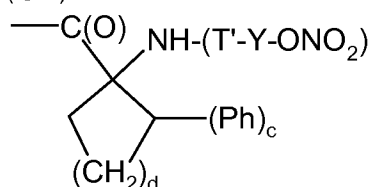
or  $\text{R}_x$  is selected from:

15 E)

(e1)



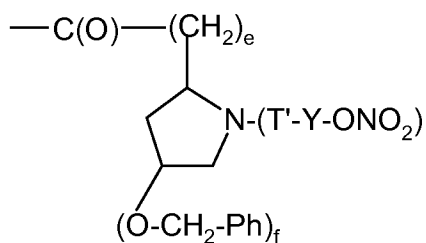
(e2)



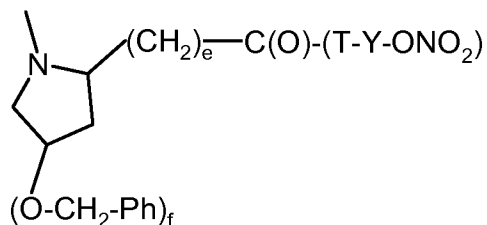
20 wherein  $c$  is equal to 0 or 1,  $d$  is an integer from 0 to 3 with  
 the proviso that  $c$  is 0 or 1 when  $d$  is 0 and  $c$  is 0 when  $d$  is  
 1, 2 or 3,  $T$  and  $T'$  are as above defined and  $Y$  is as below  
 defined;

F)

25 (f1)



(f2)

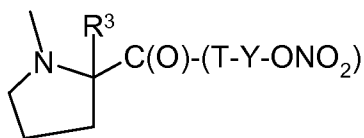


(XI)

5 wherein e and f are equal to 0 or 1, with the proviso that f is 0 when e is 0 and f is 0 or 1 when e is 1, T and T' are as above defined and Y is as below reported;

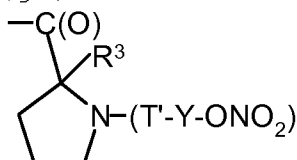
G)

(g1)



10

(g2)

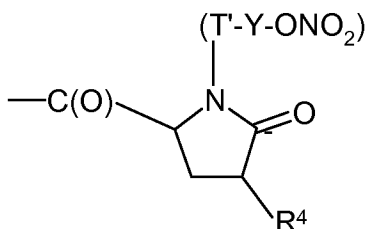


wherein R<sup>3</sup> is H, CH<sub>3</sub>, propyl, (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CH-, 1-naphtyl-CH<sub>2</sub>-, benzyl, allyl, 2-bromobenzyl, 2-chlorobenzyl, 3-chlorobenzyl,

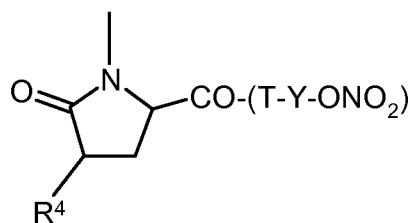
15 4-fluorobenzyl, 4-bromobenzyl, 4-methylbenzyl, preferably R<sup>3</sup> is H, T and T' are as above defined and Y is as below defined;

H)

(h1)



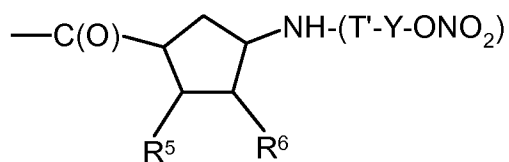
(h2)



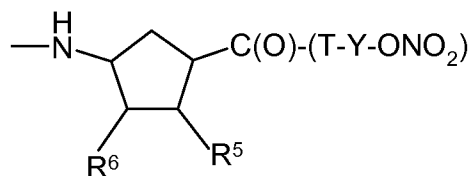
wherein  $R^4$  is H, benzyl, 4-bromobenzyl, 2-bromobenzyl, T and T' are as above defined and Y is as below defined;

5 I)

(i1)



(i2)

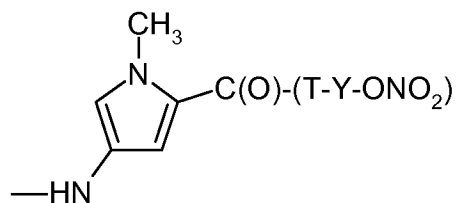


10

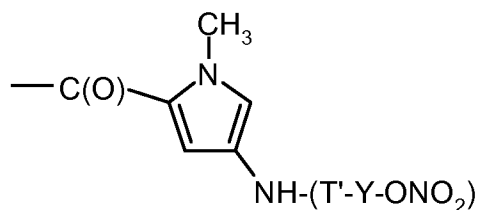
wherein  $R^5$  is H,  $R^6$  is H, or  $R^5$  and  $R^6$  when taken together are a double bond, T and T' are as above defined and Y is as below reported;

L)

15 (l1)



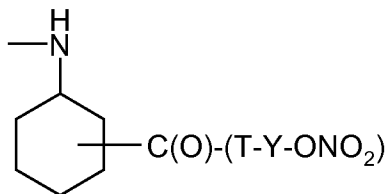
(l2)



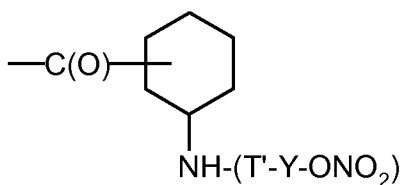
wherein T and T' are as above defined and Y is as below reported;

M)

(m1)



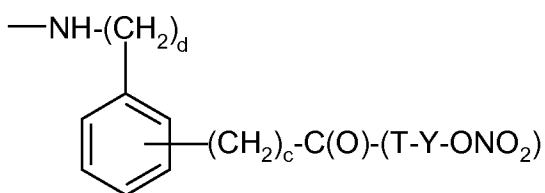
(m2)



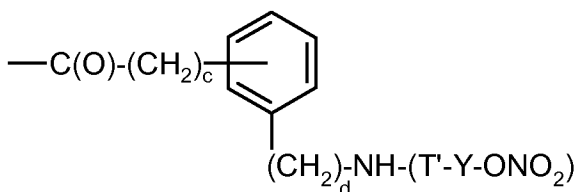
wherein T and T' are as above defined and Y is as below reported;

N)

(n1)



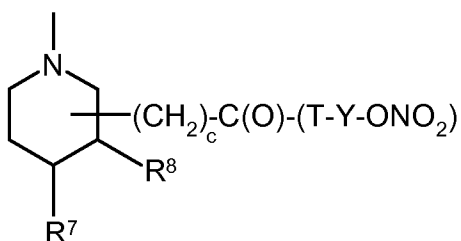
(n2)



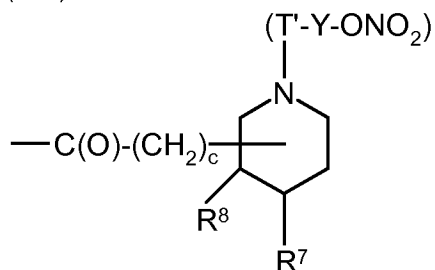
wherein c is as above defined, d is equal to 0 or 1, T and T' are as above defined and Y is as below reported;

O)

(o1)



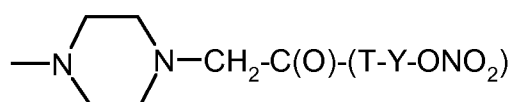
(o2)



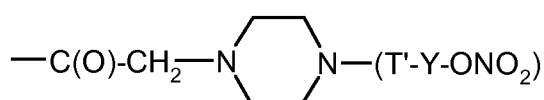
wherein  $R^7$  is H,  $R^8$  is H, or  $R^7$  and  $R^8$  when taken together are a double bond,  $c$  is as above defined,  $T$  and  $T'$  are as above defined and  $Y$  is as below reported;

P)

(p1)



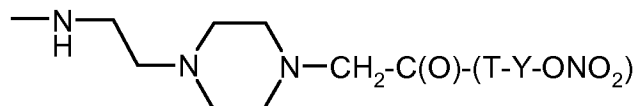
(p2)



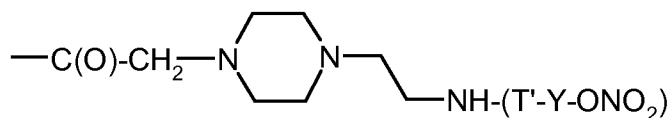
wherein  $T$  and  $T'$  are as above defined and  $Y$  is as below reported;

Q)

(q1)



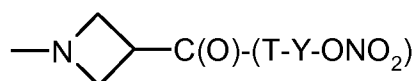
(q2)



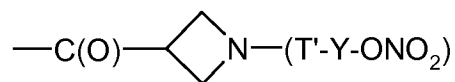
wherein  $T$  and  $T'$  are as above defined and  $Y$  is as below reported;

R)

(r1)



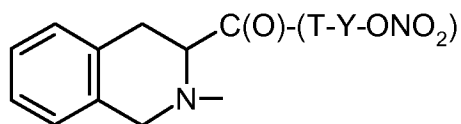
(r2)



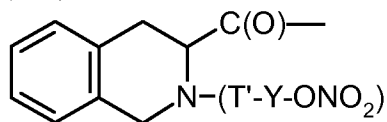
wherein T and T' are as above defined and Y is as below reported;

S)

5 (s1)



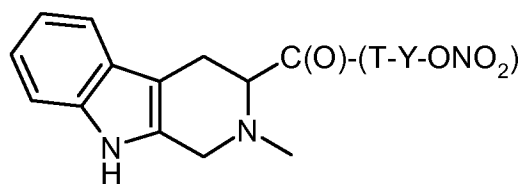
(s2)



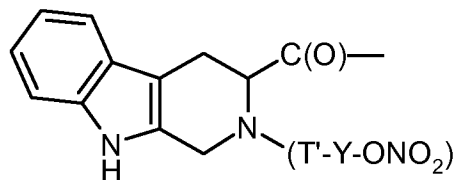
wherein T and T' are as above defined and Y is as below reported;

T)

(t1)



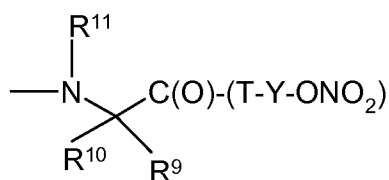
(t2)



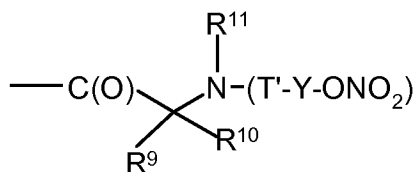
wherein T and T' are as above defined and Y is as below reported;

U)

(u1)



(u2)

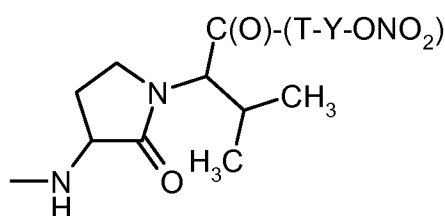


wherein  $\text{R}^9$  and  $\text{R}^{10}$  are H,  $\text{CH}_3$ ,  $\text{R}^{11}$  is  $\text{CH}_3$  or 4-piperidinyl with the proviso that  $\text{R}^9$  and  $\text{R}^{10}$  are H when  $\text{R}^{11}$  is 4-piperidinyl and  $\text{R}^9$  and  $\text{R}^{10}$  are  $\text{CH}_3$  when  $\text{R}^{11}$  is  $\text{CH}_3$ , T and T' are as above defined and Y

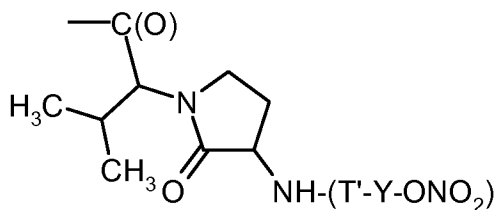
is as below reported;

V)

(v1)



(v2)



wherein T and T' are as above defined and Y is as below reported;

with the proviso that in the formula (I):

a is 0 or a is 1 and Z is  $-\text{CH(R')}-\text{O}-$  wherein  $\text{R}'$  is as above defined, when  $\text{R}_x$  is:

- (a2), (a4) or (a8);

- (a5), (a6), (a9) or (a10) and  $\text{R}^{1b}$  is selected from the group A10);

- (b2), (b4) or (b8);

- (b5), (b6), (b9) or (b10) and  $\text{R}^{2b}$  is selected from the group B10);

- (c2);

- (d5), (d6), (d9) or (d10) and  $\text{R}^{12b}$  is selected from the group D10);



- (e2), (f1), (g2), (h1), (i1), (l2), (m2), (n2), (o2), (p2), (q2), (r2), (s2), (t1) or (u2);

a is 1 and Z is -C(O)-, when R<sub>x</sub> is:

- (a1), (a3) or (a7);

5 - (a5), (a6), (a9) or (a10) and R<sup>1b</sup> is selected from the groups A8) and A9);

- (b1), (b3) or (b7);

- (b5), (b6), (b9) or (b10) and R<sup>2b</sup> is selected from the groups B8) or B9);

10 - (c1);

- (d1), (d2), (d3), (d4), (d7) or (d8);

- (d5), (d6), (d9) or (d10) and R<sup>12b</sup> is selected from the groups D8) or D9);

15 - (e1), (f2), (g1), (h2), (i2), (l1), (m1), (n1), (o1), (p1), (q1), (r1), (s1), (t2) or (u1).

Y and Y' are bivalent radicals each independently selected from the following meanings:

a)

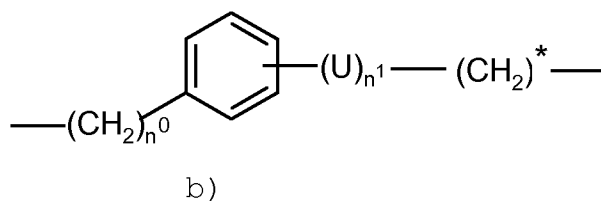
20 - straight or branched C<sub>1</sub>-C<sub>20</sub> alkylene, preferably a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- straight or branched C<sub>1</sub>-C<sub>20</sub> alkylene substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, -ONO<sub>2</sub> or T<sub>2</sub>, wherein T<sub>2</sub> is -OC(O)(C<sub>1</sub>-C<sub>10</sub> alkyl)-ONO<sub>2</sub> or -O(C<sub>1</sub>-C<sub>10</sub> alkyl)-ONO<sub>2</sub>, preferably Y or Y' is a

25 straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

30 - cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with one or more straight or branched C<sub>1</sub>-C<sub>10</sub> alkyl chains, preferably the ring being optionally substituted with CH<sub>3</sub>;

b)



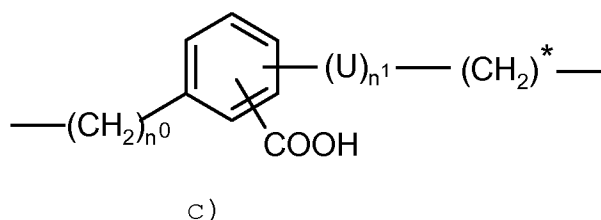
wherein

$n^0$  is an integer from 0 to 20, preferably  $n^0$  is 0 or 1;

5  $n^1$  is 0 or 1, preferably  $n^1$  is 1;

U is a linear or branched  $C_1$ - $C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group, preferably U is a linear  $C_1$ - $C_{10}$  alkylene or U is a linear or branched  $C_1$ - $C_{10}$  alkylene substituted with a  $-ONO_2$  group;

10 c)



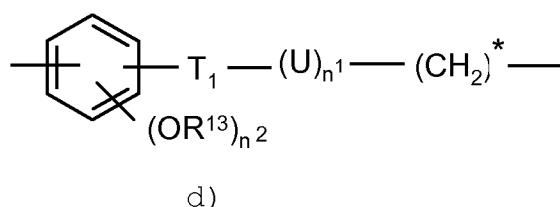
wherein

$n^0$  is an integer from 0 to 20, preferably  $n^0$  is 0 or 1;

15  $n^1$  is 0 or 1, preferably  $n^1$  is 1;

U is a linear or branched  $C_1$ - $C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group, preferably U is a linear  $C_1$ - $C_{10}$  alkylene or U is a linear or branched  $C_1$ - $C_{10}$  alkylene substituted with a  $-ONO_2$  group;

20 d)

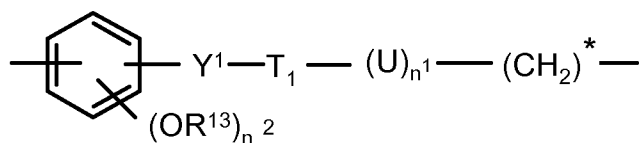


wherein:

$n^2$  is an integer from 0 to 2,  $R^{13}$  is H or  $CH_3$ ,  $T_1$  is  $-O-C(O)-$  or  $-C(O)O-$ ;

$n^1$  and U are as above defined;

e)



e)

$n^2$  is an integer from 0 to 2, preferably  $n^2$  is 1;

5  $R^{13}$  is H or  $CH_3$ , preferably  $R^{13}$  is  $CH_3$ ;

$Y^1$  is  $-CH_2-CH_2-$  or  $-CH=CH-(CH_2)_{n^{2'}}-$ , wherein  $n^{2'}$  is 0 or 1, preferably  $Y^1$  is  $-CH=CH-(CH_2)_{n^{2'}}-$  and  $n^{2'}$  is 0;

$T_1 = -O-C(O)-$  or  $-C(O)O-$ , preferably  $T_1$  is  $-C(O)O-$ ;

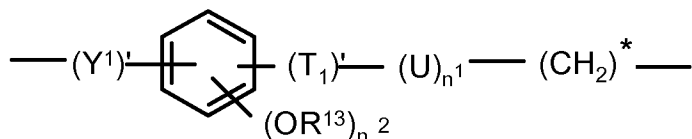
$n^1$  is 0 or 1, preferably  $n^1$  is 1;

10 U is a linear or branched  $C_1-C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group, preferably U is a linear  $C_1-C_{10}$  alkylene or U is a linear or branched  $C_1-C_{10}$  alkylene substituted with a  $-ONO_2$  group;

more preferably  $n^2$  is 1,  $R^{13}$  is  $CH_3$ ,  $Y^1$  is  $-CH=CH-(CH_2)_{n^{2'}}-$  and  $n^{2'}$

15 is 0,  $T_1$  is  $-C(O)O-$  and U is a linear  $C_1-C_{10}$  alkylene;

e')



e')

wherein:

20  $n^2$  is an integer from 0 to 2, preferably  $n^2$  is 1;

$R^{13}$  is H or  $CH_3$ , preferably  $R^{13}$  is  $CH_3$ ;

$Y^1$  is  $-CH_2-CH_2-$  or  $-(CH_2)_{n^{2'}}-CH=CH-$ , wherein  $n^{2'}$  is 0 or 1, preferably  $Y^1$  is  $-(CH_2)_{n^{2'}}-CH=CH-$  and  $n^{2'}$  is 0;

$T_1 = -O-C(O)-$ ;

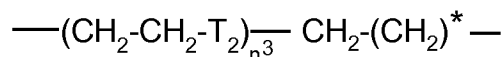
25  $n^1$  is 0 or 1, preferably  $n^1$  is 1;

U is a linear or branched  $C_1-C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group, preferably U is a linear  $C_1-C_{10}$  alkylene or U

is a linear or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

more preferably n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>, Y<sup>1</sup> is -CH=CH-(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>- and n<sup>2'</sup> is 0, T<sub>1</sub> is -OC(O)- and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene;

5 f)



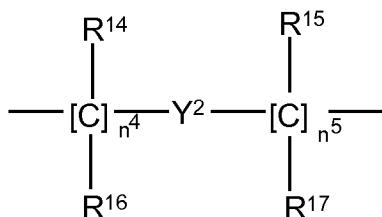
f)

wherein T<sub>2</sub> is -O- or -S-, -NH-, preferably T<sub>2</sub> is -O-, n<sup>3</sup> is an integer from 1 to 6, preferably n<sup>3</sup> is 1;

10 when Y and Y' are selected from b), c), d), e), e') or f), the -ONO<sub>2</sub> group of -(T-Y-ONO<sub>2</sub>), -(T'-Y-ONO<sub>2</sub>), -(T''-Y'-ONO<sub>2</sub>), -(T'-Y'-ONO<sub>2</sub>), -(T'''-Y-ONO<sub>2</sub>) and -(T'''-Y'-ONO<sub>2</sub>) is linked to the -(CH<sub>2</sub>)<sup>\*</sup>- group;

g)

15



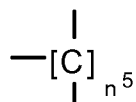
wherein:

n<sup>4</sup> is an integer from 0 to 10, preferably n<sup>4</sup> is 0 or 1;

n<sup>5</sup> is an integer from 1 to 10, preferably n<sup>5</sup> is 1;

20 R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> are the same or different, and are H or straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, preferably R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H;

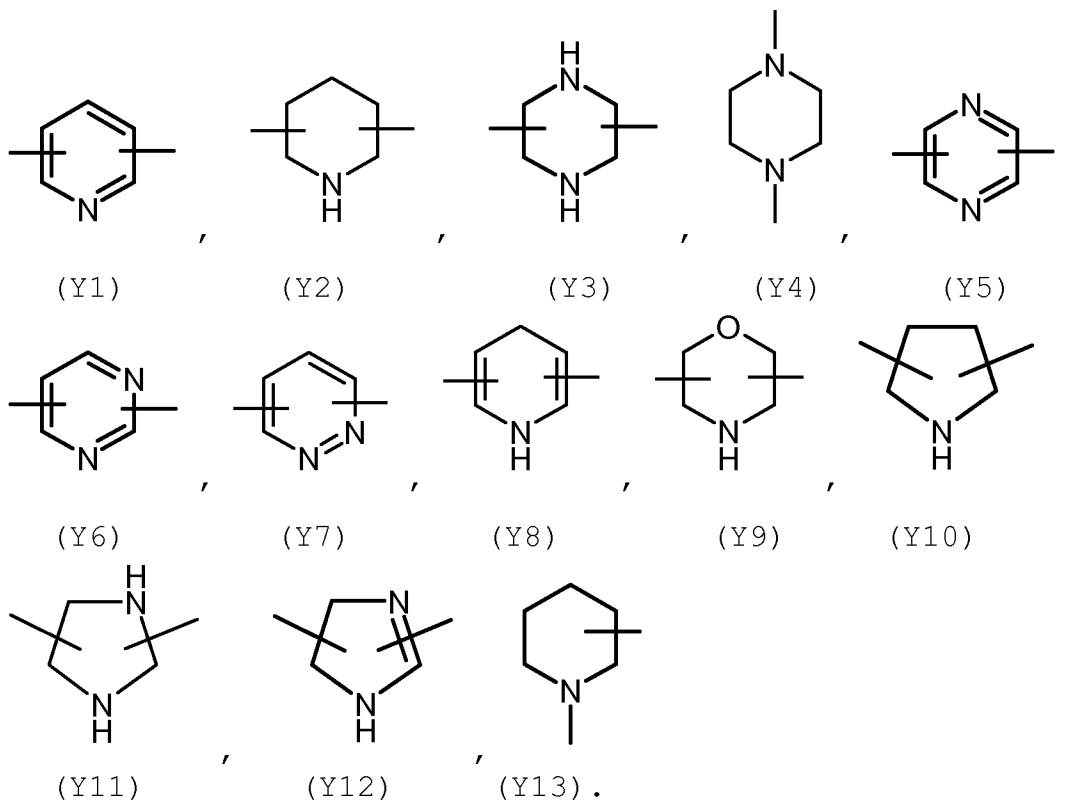
wherein the -ONO<sub>2</sub> group is linked to



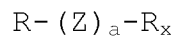
25 wherein n<sup>5</sup> is as defined above;

Y<sup>2</sup> is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur,

and is selected from the group consisting of:

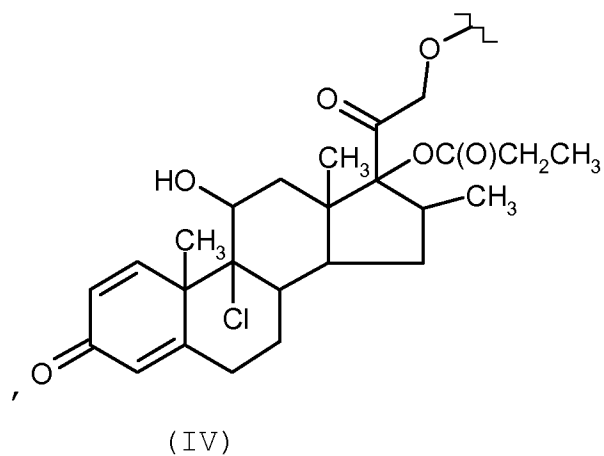
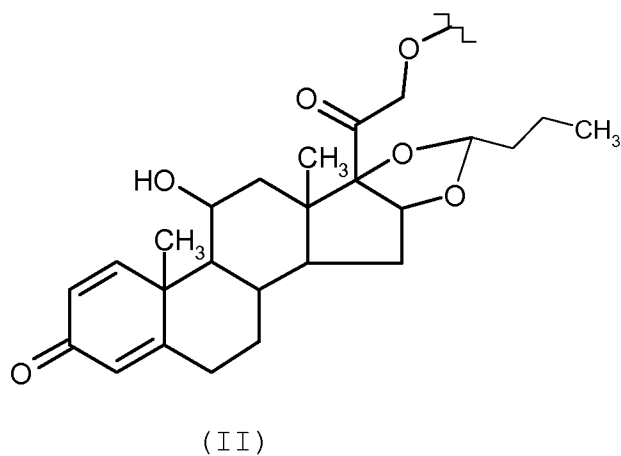


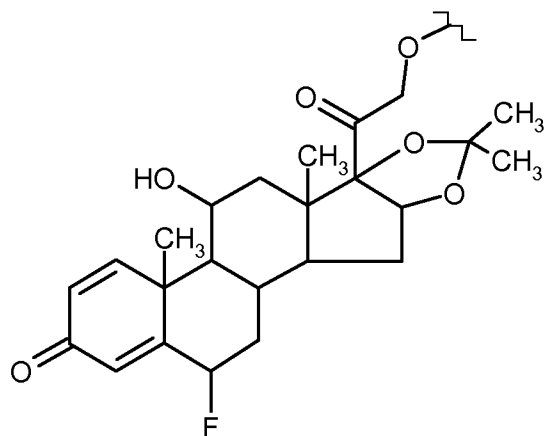
Another object of the present invention provides nitric oxide releasing compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof



(I)

wherein R is a corticosteroid residue selected from:





(V)

a is 0 and

R<sub>x</sub> is selected from:

- 5 (a2) -C(O)-CH(R<sup>1</sup>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

R<sup>1</sup> of the group A1) is selected from H, isobutyl, benzyl,

C<sub>6</sub>H<sub>5</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, 2-monosubstituted benzyl, or 3-monosubstituted  
 10 benzyl or 4-monosubstituted benzyl wherein the substituent of  
 the benzyl is selected from -F, -Cl, I, -NO<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>3</sub>, CN,  
 C<sub>6</sub>H<sub>5</sub>CO-;

R<sup>1</sup> of the group A2) is selected from -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)OH- or  
 -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-OH)], or

- 15 R<sup>1</sup> of the group A3) is selected from -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'',  
 -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'', wherein R'' is H, or -C(O)CH<sub>3</sub>;

R<sup>1</sup> of the group A4) is selected from -CH<sub>2</sub>-C(O)R''',  
 -(CH<sub>2</sub>)<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>4</sub>-C(O)R''' wherein R''' is OR<sup>5a</sup> wherein R<sup>5a</sup>  
 is H or a linear (C<sub>1</sub>-C<sub>5</sub>) alkyl;

- 20 T' is -C(O)-, -C(O)-X'' wherein X'' is -S- or -O-, preferably T'  
 is -C(O)-;

Y is as below defined;

or R<sub>x</sub> is

- (a4) -C(O)-CH(R<sup>1a</sup>-T''-Y'-ONO<sub>2</sub>)-NHR<sup>4a</sup>

- 25 wherein R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)O-  
 or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-,

$-(\text{CH}_2)_3\text{-NH-}$ ,  $-(\text{CH}_2)_4\text{-NH-}$ , or

$\text{R}^{1a}$  of the group A7) is selected from  $-\text{CH}_2\text{-C(O)-}$ ,  $-(\text{CH}_2)_2\text{-C(O)-}$ ,  
 $-(\text{CH}_2)_4\text{-C(O)-}$ ,

$\text{R}^{4a}$  is H or  $-\text{C(O)CH}_3$ ,

5  $\text{T}''$  is  $-\text{C(O)-}$  or  $-\text{C(O)-X}''$  wherein  $\text{X}''$  is  $-\text{S-}$  or  $-\text{O-}$ , when  $\text{R}^{1a}$  is selected from the group A5) or A6), preferably  $\text{T}''$  is  $-\text{C(O)-}$ ;  
 $\text{T}''$  is  $-\text{O-}$ ,  $-\text{S-}$ ,  $-\text{NR}'-$  or  $-\text{O-CH(R')-O-C(O)-}$  wherein  $\text{R}'$  is H or  $-\text{CH}_3$ , when  $\text{R}^{1a}$  is selected from the group A7),  
 $\text{Y}'$  is as below defined;

10 or  $\text{R}_x$  is selected from:

(a5)  $-\text{R}^{1b}\text{-CH(NHR}^{4a})\text{-C(O)- (T-Y-ONO}_2\text{)}$

(a6)  $-\text{R}^{1b}\text{-CH(COOR}^{3a})\text{NH- (T'-Y-ONO}_2\text{)}$

(a9)  $-\text{R}^{1b}\text{-CH(NH-T'-Y'-ONO}_2\text{)-C(O)- (T-Y-ONO}_2\text{)}$  or

(a10)  $-\text{R}^{1b}\text{-CH(C(O)-T-Y'-ONO}_2\text{)-NH- (T'-Y-ONO}_2\text{)}$

15 wherein

$\text{R}^{1b}$  of the group A10) is selected from  $-\text{C(O)-CH}_2-$ ,  $-\text{C(O)- (CH}_2\text{)}_2-$ ,  
 $-\text{C(O)- (CH}_2\text{)}_4-$ ,

$\text{R}^{3a}$  is H or a  $(\text{C}_1\text{-C}_5)$  alkyl,

20  $\text{R}^{4a}$  is H or  $-\text{C(O)CH}_3$ ,

$\text{T}$  is  $-\text{O-}$ ,  $-\text{S-}$ ,  $-\text{NR}'-$  or  $-\text{O-CH(R')-O-C(O)-}$  wherein  $\text{R}'$  is H or  $-\text{CH}_3$ , preferably  $\text{T}$  is  $-\text{O-}$ ,

$\text{T}'$  is  $-\text{C(O)-}$  or  $-\text{C(O)-X}''$  wherein  $\text{X}''$  is  $-\text{S-}$  or  $-\text{O-}$ , preferably  $\text{T}'$  is  $-\text{C(O)-}$ ,

25  $\text{Y}$  and  $\text{Y}'$  are as below defined;

or  $\text{R}_x$  is

(a8)  $-\text{C(O)-CH(R}^{1a}\text{-T''-Y'-ONO}_2\text{)-NH- (T'-Y-ONO}_2\text{)}$

wherein

$\text{R}^{1a}$  of the group A5) is selected from  $-\text{CH}_2\text{-O-}$ ,  $-\text{CH(CH}_3\text{)-O-}$  or

30  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4\text{-O})-]$ , or

$\text{R}^{1a}$  of the group A6) is selected from  $-\text{CH}_2\text{-NH-}$ ,  $-(\text{CH}_2)_2\text{-NH-}$ ,  
 $-(\text{CH}_2)_3\text{-NH-}$ ,  $-(\text{CH}_2)_4\text{-NH-}$ , or

$\text{R}^{1a}$  of the group A7) is selected from  $-\text{CH}_2\text{-C(O)-}$ ,  $-(\text{CH}_2)_2\text{-C(O)-}$ ,  
 $-(\text{CH}_2)_4\text{-C(O)-}$ ,

T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from the group A5) or A6), preferably T'' is -C(O)-, T'' is -O-, -S-, -NR'- or -O-CH(R')-O-C(O)- wherein R' is H or -CH<sub>3</sub>, when R<sup>1a</sup> is selected from the group A7);

5 T' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, preferably T' is -C(O)-,

Y and Y' are as below defined,

or R<sub>x</sub> is



10 wherein

R<sup>2</sup> of the group B1) is selected from H, CH<sub>3</sub>, isobutyl, isopropyl, benzyl;

T' is -C(O)-, -C(O)-X'' wherein X'' is -S- or -O-, preferably T' is -C(O)-;

15 Y and Y' are each independently selected from

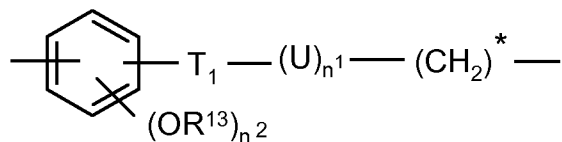
a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub>

20 group;

d)



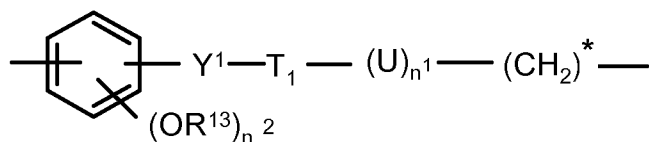
d)

wherein:

25 n<sup>2</sup> is an integer from 0 to 2, R<sup>13</sup> is H or CH<sub>3</sub>, T<sub>1</sub> is -O-C(O)- or -C(O)O-;

n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

e)

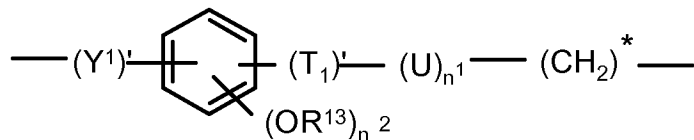




e)

$n^2$  is 1,  $R^{13}$  is  $CH_3$ ,  $Y^1$  is  $-CH=CH-(CH_2)_{n^{2'}}-$  and  $n^{2'}$  is 0,  $T_1$  is  $-C(O)O-$  and U is a linear  $C_1$ - $C_{10}$  alkylene;

e')



e')

wherein:

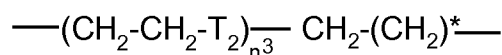
$n^2$  is 1,  $R^{13}$  is  $CH_3$ ;

$Y^1$  is  $-(CH_2)_{n^{2'}}-CH=CH-$  and  $n^{2'}$  is 0;

$T_1 = -O-C(O)-$ ;

$n^1$  is 1 and U is a linear  $C_1$ - $C_{10}$  alkylene or U is a linear or branched  $C_1$ - $C_{10}$  alkylene substituted with a  $-ONO_2$  group;

f)

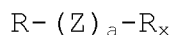


f)

wherein  $T_2$  is  $-O-$  or  $-S-$ ,  $-NH-$ , preferably  $T_2$  is  $-O-$ ,  $n^3$  is 1 or 2;

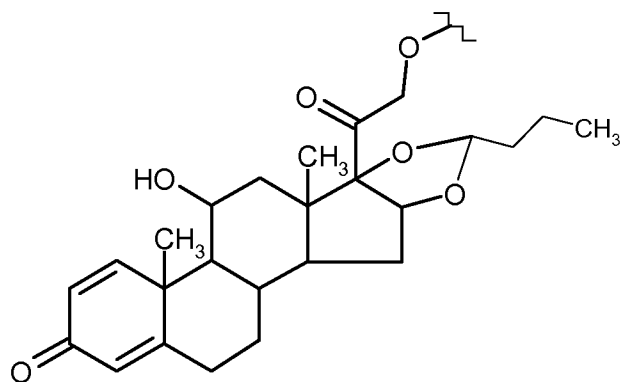
when Y and Y' are selected from d), e), e') or f), the  $-ONO_2$  group of  $-(T-Y-ONO_2)$ ,  $-(T'-Y-ONO_2)$ ,  $-(T''-Y'-ONO_2)$ ,  $-(T'-Y'-ONO_2)$ ,  $-(T'''-Y-ONO_2)$  and  $-(T'''-Y'-ONO_2)$  is linked to the  $-(CH_2)^*$ -group.

Another object of the present invention provides nitric oxide releasing compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof

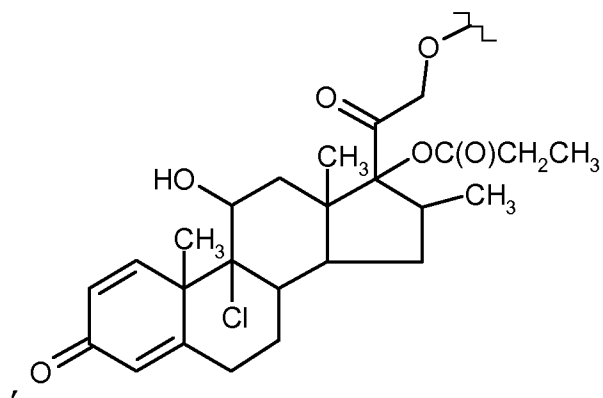


(I)

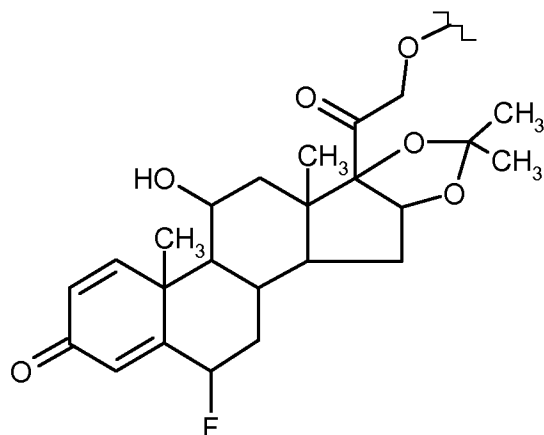
wherein R is a corticosteroid residue selected from:



(II)



(IV)



(V)

5 a is 1 and Z is  $-\text{C}(\text{O})-$ ;

$\text{R}_x$  is

(a1)  $-\text{HN}-\text{CH}(\text{R}^1)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

wherein

$\text{R}^1$  of the group A1) is selected from H, isobutyl, benzyl,  $\text{C}_6\text{H}_5-$   
 10  $\text{CH}_2-\text{CH}_2-$ , 2-monosubstituted benzyl, or 3-monosubstituted benzyl  
 or 4- monosubstituted benzyl wherein the substituent of the  
 benzyl is selected from  $-\text{F}$ ,  $-\text{Cl}$ , I,  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $-\text{CH}_3$ , CN,  $\text{C}_6\text{H}_5\text{CO}-$   
 or

$\text{R}^1$  of of the group A2) is selected from:

15  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}-$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ , or

$\text{R}^1$  of the group A3) is selected from  $-\text{CH}_2-\text{NHR}''$ ,  $-(\text{CH}_2)_2-\text{NHR}''$ ,  
 $-(\text{CH}_2)_3-\text{NHR}''$ ,  $-(\text{CH}_2)_4-\text{NHR}''$ , wherein  $\text{R}''$  is H, or  $-\text{C}(\text{O})\text{CH}_3$ ,

$\text{R}^1$  of the group A4) is  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''$ ,

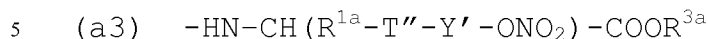
$-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''$  wherein  $\text{R}'''$  is  $\text{OR}^{5a}$  wherein  $\text{R}^{5a}$  is H or a linear

20  $(\text{C}_1-\text{C}_5)$  alkyl;

T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, preferably T is -O-,

Y is as below defined;

or R<sub>x</sub> is



wherein

R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-,

10 -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-, or

R<sup>1a</sup> of the group A7) is -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>4</sub>-C(O)-,

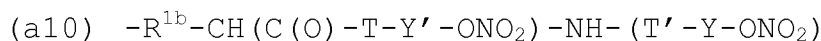
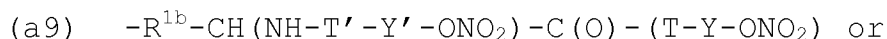
R<sup>3a</sup> is H or a (C<sub>1</sub>-C<sub>5</sub>) alkyl,

T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from the group A5) or A6), preferably T'' is -C(O)-;

15 T'' is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, when R<sup>1a</sup> is selected from the group A7);

Y' is as below defined;

or R<sub>x</sub> is selected from.



wherein

25 R<sup>1b</sup> of the group A8) is selected from -O-CH(CH<sub>3</sub>)-, -O-CH<sub>2</sub>-, [-4-O)-(C<sub>6</sub>H<sub>4</sub>)]-CH<sub>2</sub>-, or

R<sup>1b</sup> of the group A9) is selected from -HN-CH<sub>2</sub>-, -HN-(CH<sub>2</sub>)<sub>2</sub>-, -HN-(CH<sub>2</sub>)<sub>3</sub>-, -HN-(CH<sub>2</sub>)<sub>4</sub>-,

R<sup>3a</sup> is H or a (C<sub>1</sub>-C<sub>5</sub>) alkyl,

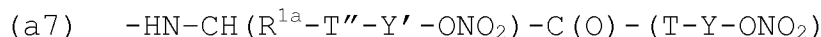
30 R<sup>4a</sup> is H or -C(O)CH<sub>3</sub>,

T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, preferably T is -O-,

T' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, preferably T' is -C(O)-,

Y and Y' are as below defined;

or R<sub>x</sub> is



wherein

5 R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)-O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-, or

R<sup>1a</sup> of the group A7) is -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>4</sub>-C(O)-;

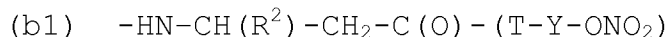
10 T'' is -C(O)- or -C(O)-X'', wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from A5) or A6), preferably T'' is -C(O)-

T'' is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)-, wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, when R<sup>1a</sup> is selected from A7), preferably T'' is -O-,

15 T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, preferably T is -O-;

Y and Y' are as below defined;

or R<sub>x</sub> is



20 wherein

R<sup>2</sup> of the group B1) is selected from H, CH<sub>3</sub>, isobutyl, isopropyl, benzyl;

R<sup>2</sup> of the group B2) is selected from -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)-OH- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)(4-OH)], or

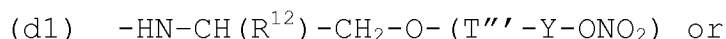
25 R<sup>2</sup> of the group B3) is selected from -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'', wherein R'' is H, or -C(O)CH<sub>3</sub>,

R<sup>2</sup> of the group B4) is -CH<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>4</sub>-C(O)R''' wherein R''' is OR<sup>5a</sup> wherein R<sup>5a</sup> is H or a linear (C<sub>1</sub>-C<sub>5</sub>) alkyl;

30 T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, preferably T is -O-,

Y is as below defined;

or R<sub>x</sub> is selected from



(d2)  $-O-CH_2-CH(R^{12})-NH-(T'-Y-ONO_2)$

wherein

$R^{12}$  of the group D1) is selected from H,  $CH_3$ , isobutyl, isopropyl, benzyl, or

5  $R^{12}$  of the group D2) is selected from  $-CH_2-OH$ ,  $-CH(CH_3)OH$ - or  $-CH_2[(C_6H_4)-(4-OH)]$ , or

$R^{12}$  of the group D3) is selected from  $-CH_2-NHR''$ ,  $-(CH_2)_2-NHR''$ ,  $-(CH_2)_3-NHR''$ ,  $-(CH_2)_4-NHR''$  wherein  $R''$  is H, or

10  $R^{12}$  of the group D4) is  $-CH_2-C(O)R'''$ ,  $-(CH_2)_2-C(O)R'''$ ,  $-(CH_2)_4-C(O)R'''$  wherein  $R'''$  is  $OR^{5a}$  wherein  $R^{5a}$  is H or a linear  $(C_1-C_5)$  alkyl;

$T'$  and  $T'''$  are each independently selected from  $-C(O)-$  or  $-C(O)-X''$  wherein  $X''$  is  $-S-$  or  $-O-$ , preferably  $T'$  and  $T'''$  are  $-C(O)-$ ,

15 Y is as below defined;

or  $R_x$  is selected from:

(d3)  $-HN-CH(R^{12a}-T''-Y'-ONO_2)-CH_2OH$

(d4)  $-O-CH_2-CH(R^{12a}-T''-Y'-ONO_2)-NHR^{4a}$

(d7)  $-HN-CH(R^{12a}-T''-Y'-ONO_2)-CH_2-O-(T'''-Y-ONO_2)$  or

20 (d8)  $-O-CH_2-CH(R^{12a}-T''-Y'-ONO_2)-NH-(T'-Y-ONO_2)$

wherein

$R^{12a}$  of the group D5) is selected from  $-CH_2-O-$ ,  $-CH(CH_3)-O-$  or  $-CH_2[(C_6H_4)-(4-O)-]$ , or

25  $R^{12a}$  of the group D6) is selected from  $-CH_2-NH-$ ,  $-(CH_2)_2-NH-$ ,  $-(CH_2)_3-NH-$ ,  $-(CH_2)_4-NH-$ , or

$R^{12a}$  of the group D7) is  $-CH_2-C(O)-$ ,  $-(CH_2)_2-C(O)-$ ,  $-(CH_2)_4-C(O)-$ ;  $R^{4a}$  is H or  $-C(O)CH_3$ ,

30  $T''$  is selected from  $-C(O)-$  or  $-C(O)-X''$ , wherein  $X''$  is  $-S-$  or  $-O-$ , when  $R^{12a}$  is selected from D5) or D6), preferably  $T'$  and  $T'''$  are  $-C(O)-$ ,

$T''$  is  $-O-$ ,  $-S-$ ,  $-NR'-$ ,  $-O-CH(R')-O-C(O)-$ , wherein  $R'$  is H or a straight or branched  $C_1-C_4$  alkyl, when  $R^{12a}$  is selected from D7),  
 , preferably  $T$  is  $-O-$ ,

T''' is selected from -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, preferably T''' is -C(O)-,

Y and Y' are as below defined;

or R<sub>x</sub> is selected from:

- 5 (d5) -R<sup>12b</sup>-CH(NHR<sup>4a</sup>)-CH<sub>2</sub>-O-(T'''-Y-ONO<sub>2</sub>)  
 (d6) -R<sup>12b</sup>-CH(CH<sub>2</sub>OH)-NH-(T'-Y-ONO<sub>2</sub>)  
 (d9) -R<sup>12b</sup>-CH(NH-T'-Y'-ONO<sub>2</sub>)-CH<sub>2</sub>-O-(T'''-Y-ONO<sub>2</sub>) or  
 (d10) -R<sup>12b</sup>-CH(CH<sub>2</sub>-O-T'''-Y'-ONO<sub>2</sub>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

- 10 R<sup>12b</sup> of the group D8) is selected from -O-CH(CH<sub>3</sub>)-, -O-CH<sub>2</sub>-,  
 [-4-O-(C<sub>6</sub>H<sub>4</sub>)]-CH<sub>2</sub>-, or

R<sup>12b</sup> of the group D9) is selected from -HN-CH<sub>2</sub>-, -HN-(CH<sub>2</sub>)<sub>2</sub>-,  
 -HN-(CH<sub>2</sub>)<sub>3</sub>-, -HN-(CH<sub>2</sub>)<sub>4</sub>-;

R<sup>4a</sup> is H or -C(O)-CH<sub>3</sub>,

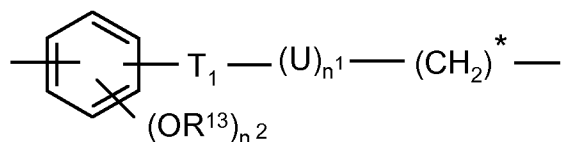
- 15 T' and T''' are each independently selected from -C(O)-, -C(O)-X'', wherein X'' is -S- or -O-, preferably T' and T''' are -C(O)-,  
 Y and Y' are each independently selected from

a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- 20 - a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

d)



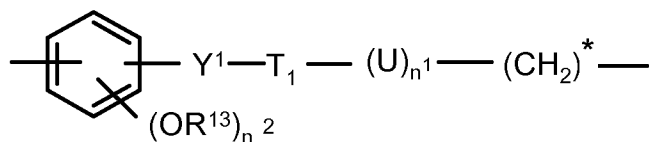
d)

- 25 wherein:

n<sup>2</sup> is an integer from 0 to 2, R<sup>13</sup> is H or CH<sub>3</sub>, T<sub>1</sub> is -O-C(O)- or -C(O)O-,

n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

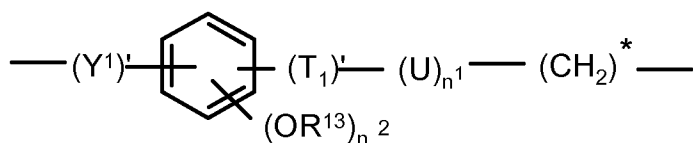
- 30 e)



e)

n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>, Y<sup>1</sup> is -CH=CH-(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>- and n<sup>2'</sup> is 0,  
T<sub>1</sub> is -C(O)O- and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene;

5 e')



e')

wherein:

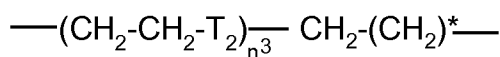
n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>,

10 Y<sup>1</sup> is -(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>-CH=CH- and n<sup>2'</sup> is 0,

T<sub>1</sub> = -O-C(O)-,

n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or  
branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

f)



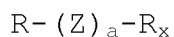
15

f)

wherein T<sub>2</sub> is -O- or -S-, -NH-, preferably T<sub>2</sub> is -O-, n<sup>3</sup> is 1 or  
2,

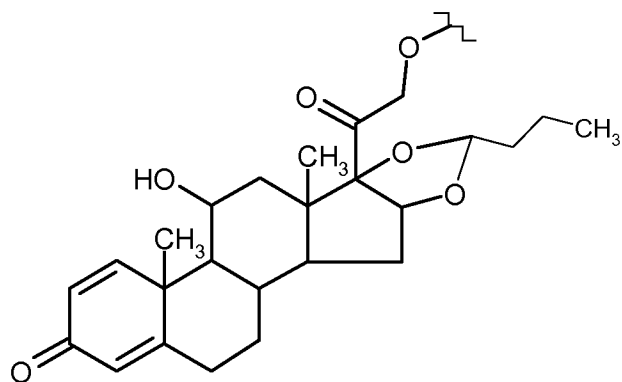
when Y and Y' are selected from d), e), e') or f), the -ONO<sub>2</sub>  
20 group of -(T-Y-ONO<sub>2</sub>), -(T'-Y-ONO<sub>2</sub>), -(T''-Y'-ONO<sub>2</sub>), -(T'-Y'-ONO<sub>2</sub>),  
-(T'''-Y-ONO<sub>2</sub>) and -(T'''-Y'-ONO<sub>2</sub>) is linked to the -(CH<sub>2</sub>)\*-  
group.

Another object of the present invention provides nitric  
oxide releasing compounds of general formula (I) and  
25 pharmaceutically acceptable salts or stereoisomers thereof

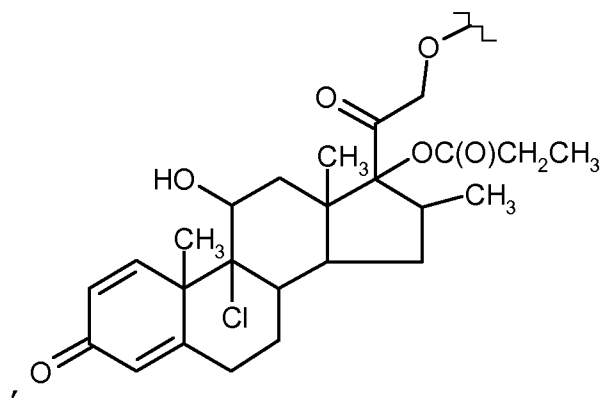


(I)

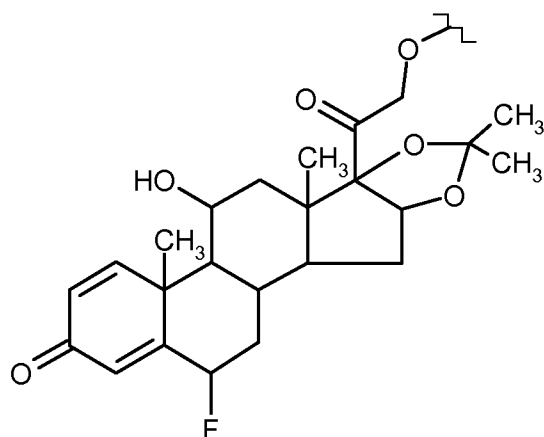
wherein R is a corticosteroid residue selected from:



(II)



(IV)



(V)

5 a is 0,

R<sub>x</sub> is

(a2) -C(O)-CH(R<sup>1</sup>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

R<sup>1</sup> of the group A1) is H

10 T' is -C(O)-;

Y is selected from

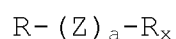
a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub>

15 group;

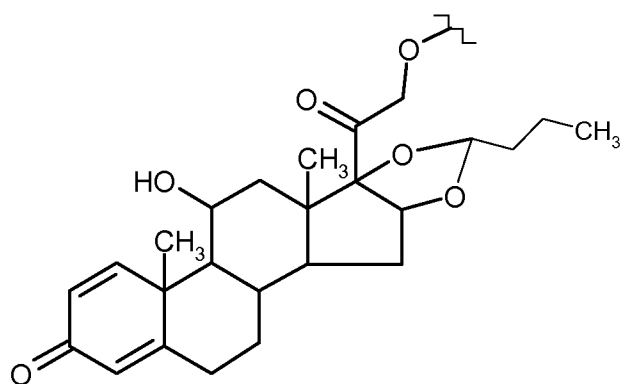
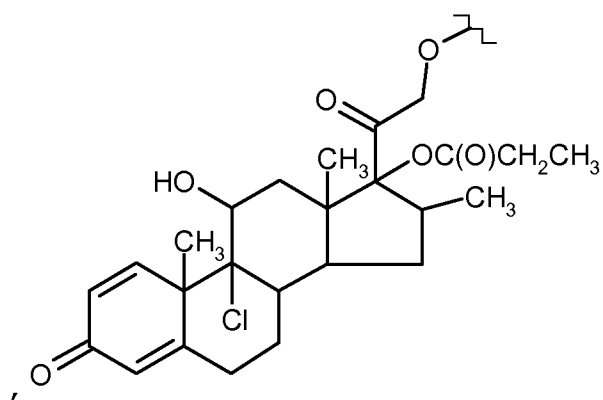
Another object of the present invention provides nitric oxide releasing compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof



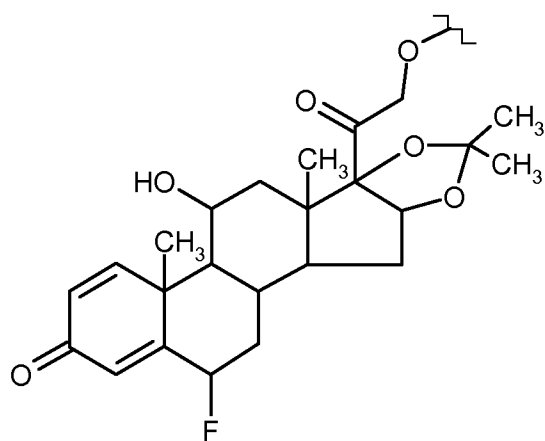
(I)



wherein R is a corticosteroid residue selected from:


$$(II)$$


(IV)



(V)

a is 0,

$R_x$  is selected from

$R_X$  is selected from

$$(a5) \quad -R^{1b}-CH(NHR^{4a})-C(O)-(T-Y-ONO_2)$$
$$(a6) \quad -R^{1b}-CH(COOR^{3a})NH-(T'-Y-ONO_2) \quad \text{or}$$
$$(a9) \quad -R^{1b}-CH(NH-T'-Y'-ONO_2)-C(O)-(T-Y-ONO_2)$$

wherein

R<sup>1b</sup> of the group A10) is -C(O)-CH<sub>2</sub>-,

R<sup>3a</sup> is H or a (C<sub>1</sub>-C<sub>5</sub>) alkyl,

$R^{4a}$  is H or  $-C(O)CH_3$ ,

T is selected from -O-, -S-, -NR'- wherein R' is as above defined,

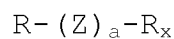
T' is  $-C(O)-$  and

Y and Y' are each independently selected from

a)

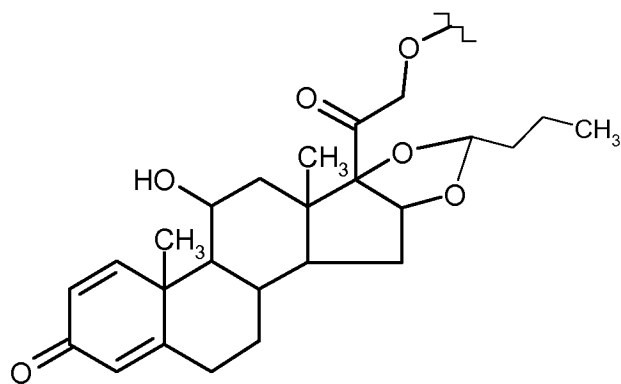
- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,
- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group.

Another object of the present invention provides nitric  
oxide releasing compounds of general formula (I) and  
pharmaceutically acceptable salts or stereoisomers thereof

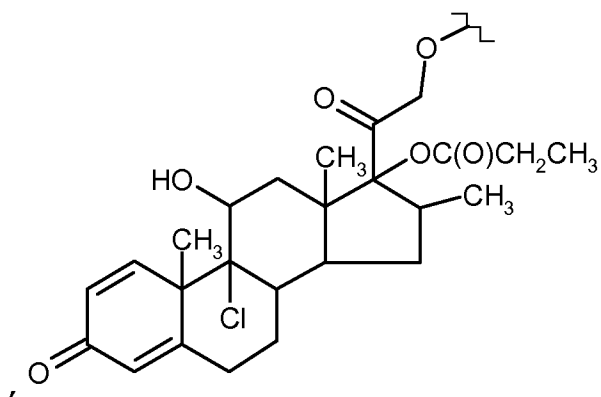


(I)

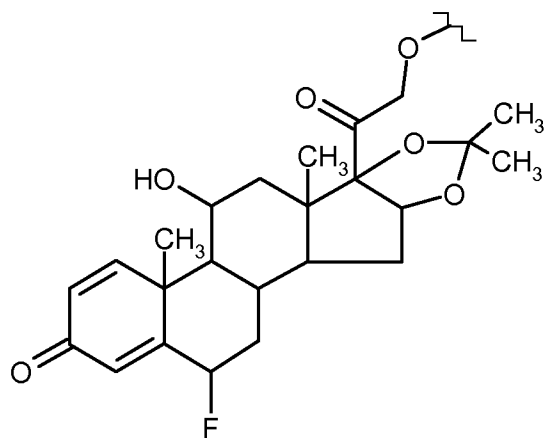
wherein R is a corticosteroid residue selected from:



(II)



(IV)



(V)

a is 1 and Z is -C(O)-,

R<sub>x</sub> is

(a5) -R<sup>1b</sup>-CH(NHR<sup>4a</sup>)-C(O)-(T-Y-ONO<sub>2</sub>) or

(a9) -R<sup>1b</sup>-CH(NH-T'-Y'-ONO<sub>2</sub>)-C(O)-(T-Y-ONO<sub>2</sub>)

wherein R<sup>1b</sup> of A10) is -O-CH<sub>2</sub>- or [-4-O-(C<sub>6</sub>H<sub>4</sub>)]-CH<sub>2</sub>-,

R<sup>4a</sup> is H or -C(O)CH<sub>3</sub>,

T is selected from -O-, -S-, -NR'- wherein R' is as above defined,

T' is -C(O)- and

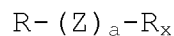
Y and Y' are each independently selected from

5 a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

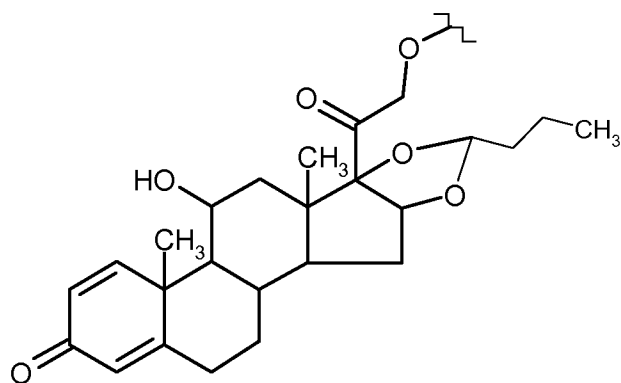
- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group.

Another object of the present invention provides nitric  
10 oxide releasing compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof

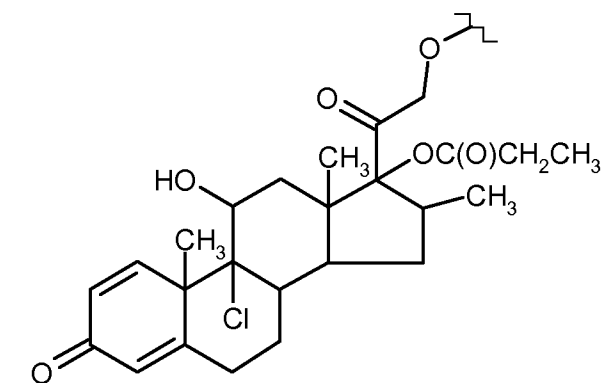


(I)

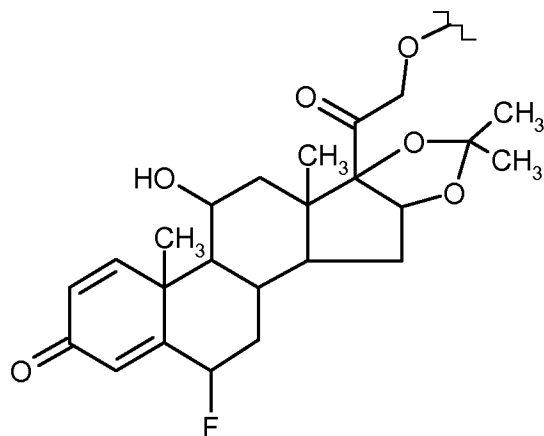
wherein R is a corticosteroid residue selected from:



(II)



(IV)



(V)

a is 0,

20 R<sub>x</sub> is

(b2)  $-C(O)-CH_2-CH(R^2)-NH-(T'-Y-ONO_2)$

wherein

$R^2$  of the group B1) is H,

$T'$  is  $-C(O)-$ ;

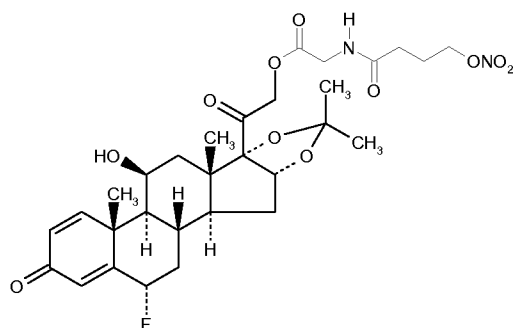
5 Y and  $Y'$  are each independently selected from

a)

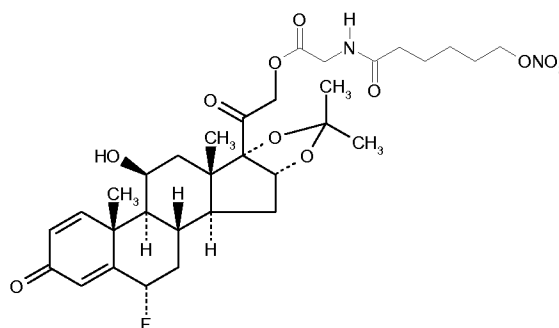
- a straight or branched  $C_1-C_{10}$  alkylene,

- a straight or branched  $C_1-C_{10}$  alkylene substituted with a  $-ONO_2$  group.

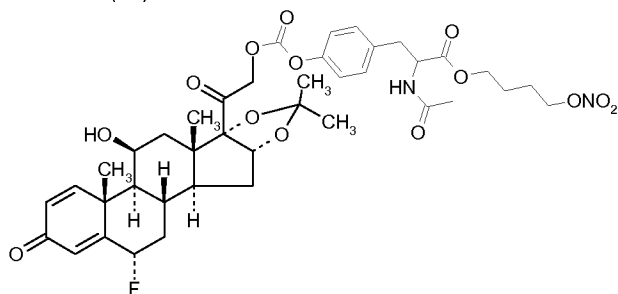
10 The most preferred nitric oxide releasing compounds of general formula (I) are:



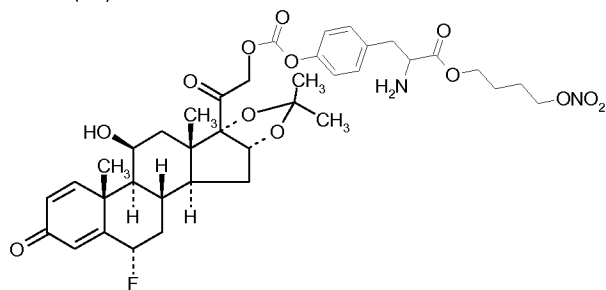
(1)



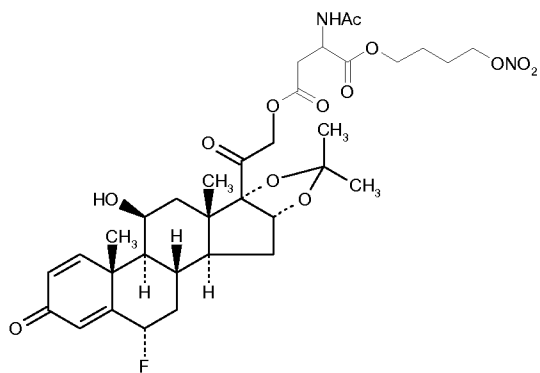
(2)



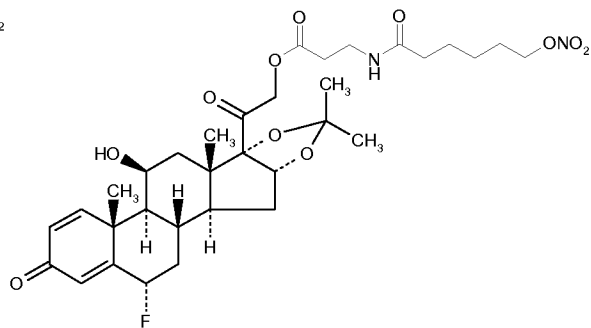
(3)



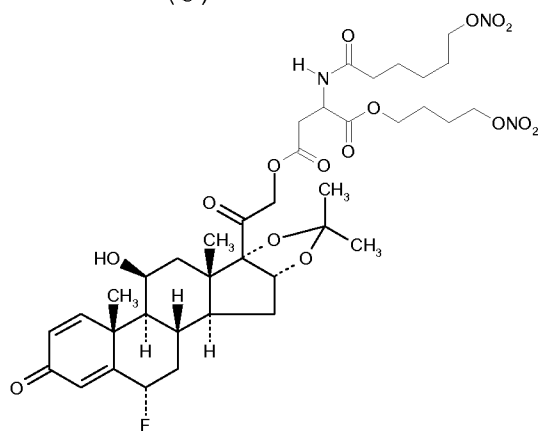
(4)



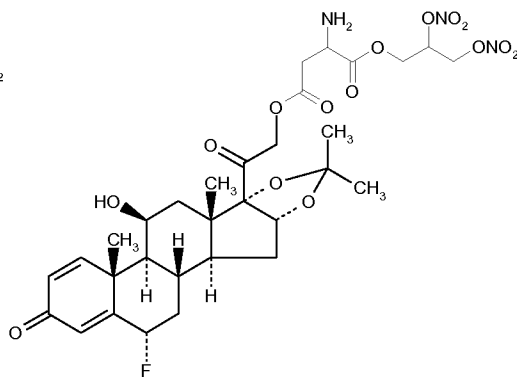
(5)



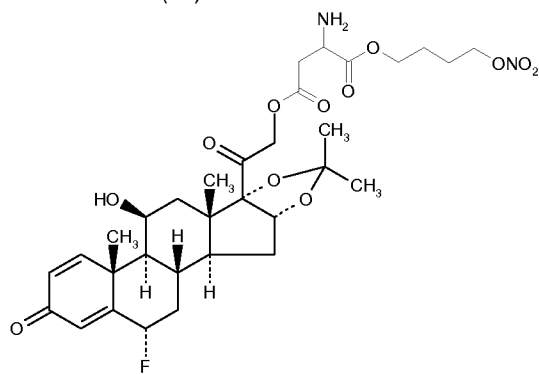
(6)



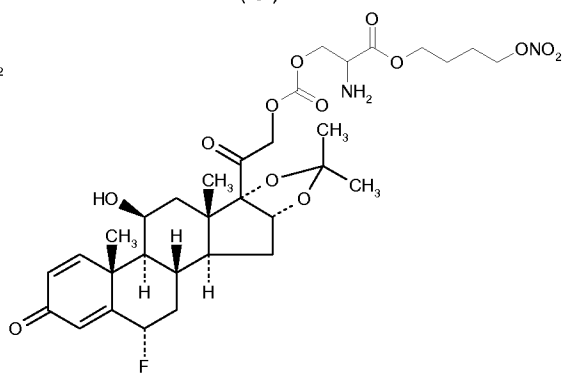
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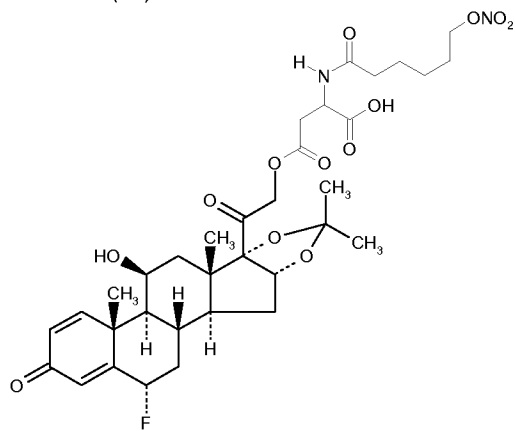
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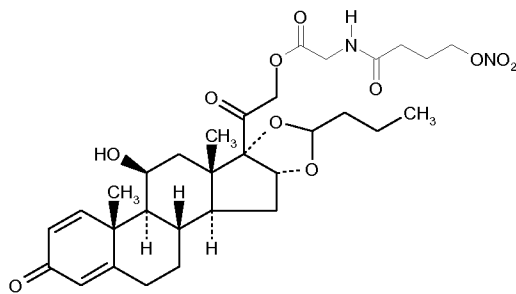
(9)



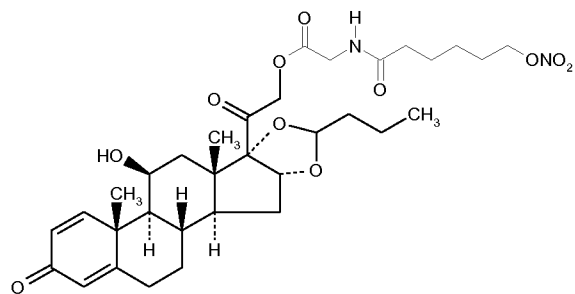
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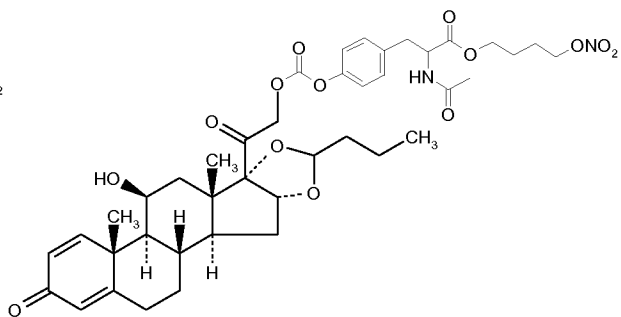
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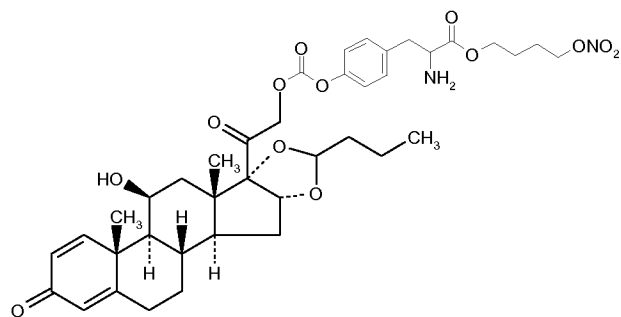
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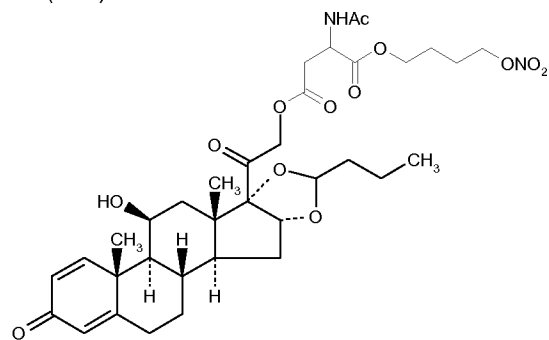
(13)



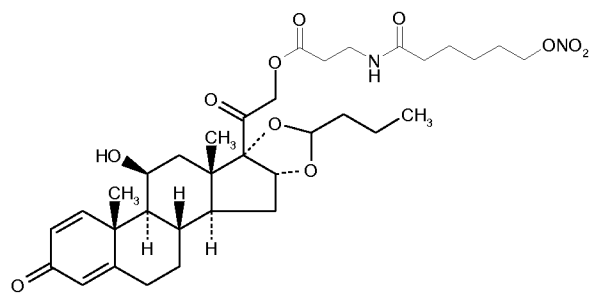
(14)



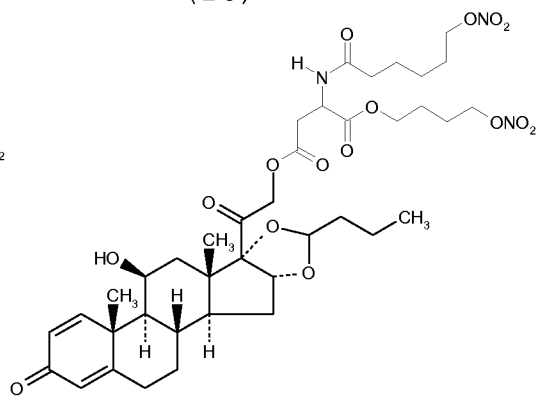
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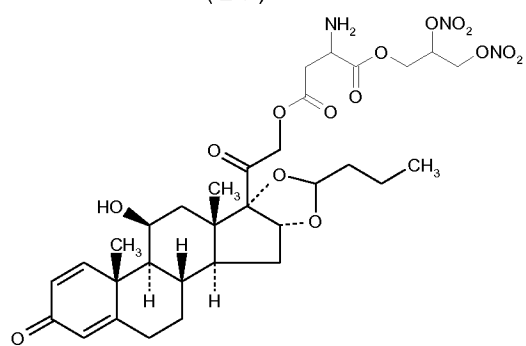
(16)



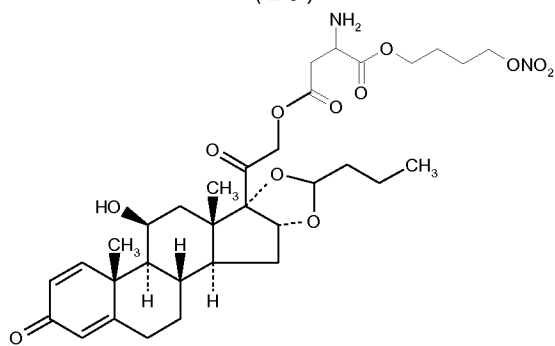
(17)



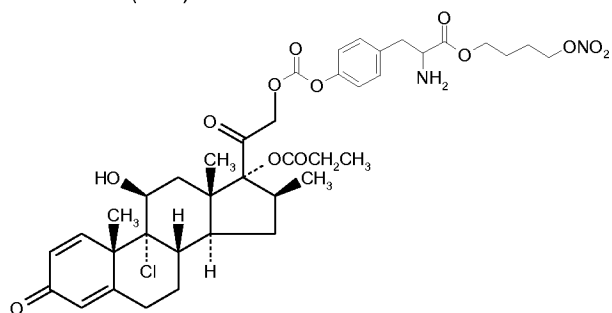
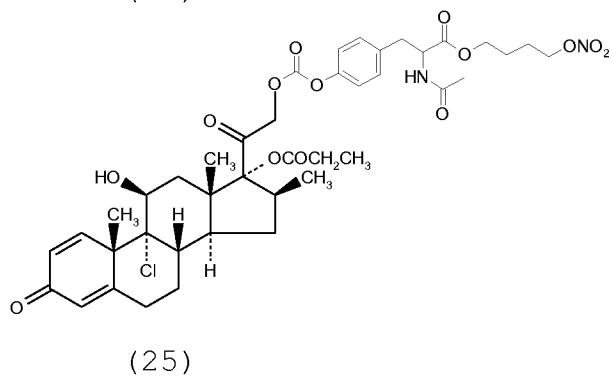
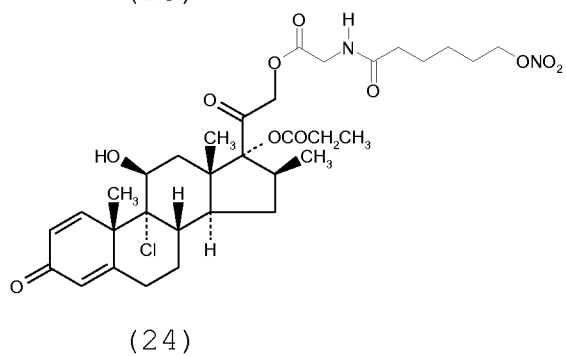
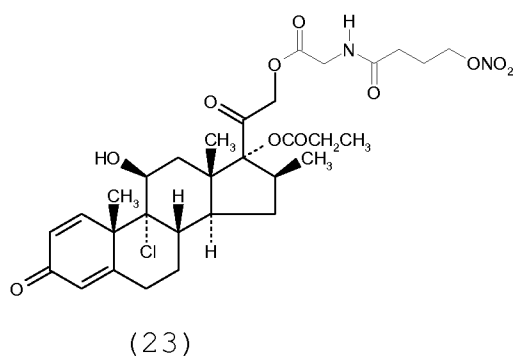
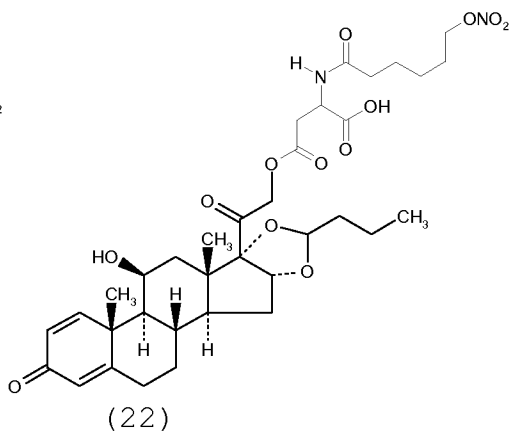
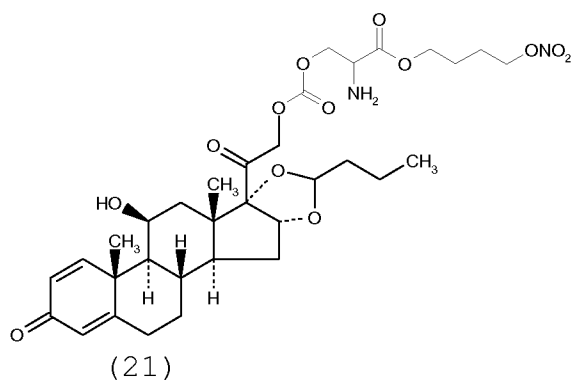
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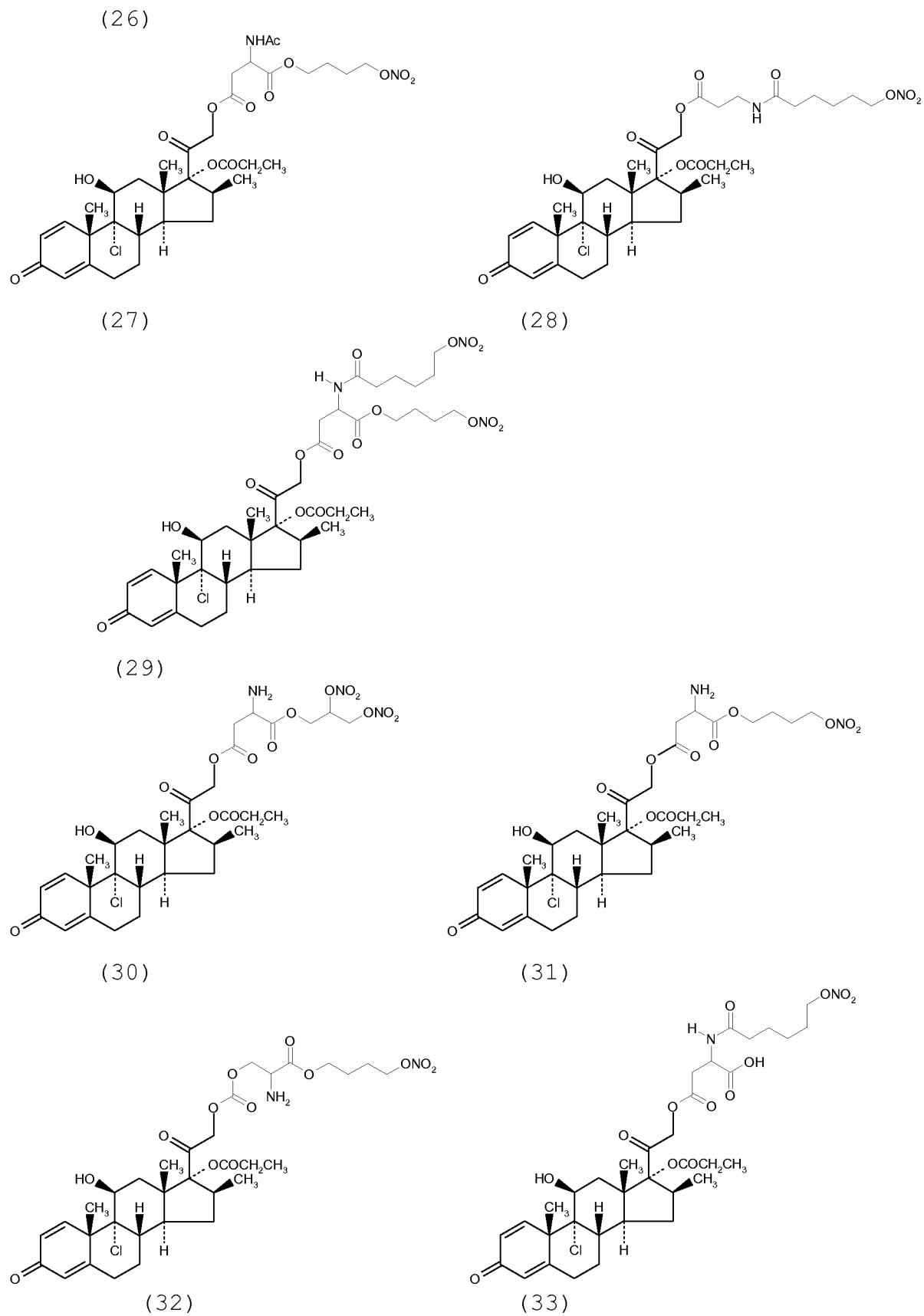


(19)



(20)







Another object of the invention is a composition comprising a compound of formula (I) above reported and at least one bronchodilator or a pharmaceutical acceptable salt or solvate thereof.

5 Bronchodilators that can be used in the composition of the invention include: anticholinergic bronchodilators which includes tiotropium and ipratropium,  $\beta_2$ -agonists which include salbutamol, bitolterol mesylate, formoterol, isoproterenol, levalbuterol, metaproterenol, salmeterol, terbutaline and  
10 fenoterol. In addition to  $\beta_2$ -agonists and anticholinergics, other bronchodilator that may be used in the composition of the present invention are ephedrine and xanthines. Representative xanthines include theophylline, aminophylline and oxtriphyline.

In another embodiment, the compound of formula (I) and at  
15 least one bronchodilator are administered simultaneously wherein the two components may be administered by the same or different administration pathways.

In another embodiment, the compound of formula (I) and at least one bronchodilator are administered sequentially wherein  
20 the compound of formula (I) may be administered before or after the bronchodilator and the two components may be administered by the same or different administration pathways.

In another embodiment the invention provides the use of a composition comprising a compound of formula (I) above reported  
25 and at least one bronchodilator or a pharmaceutical acceptable salt or solvate thereof in the treatment of respiratory diseases which comprise asthma, COPD (chronic obstructive pulmonary diseases), ARDS (Acute Respiratory Distress Syndrome), allergic rhinitis and respiratory tract diseases  
30 associated with inflammation.

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

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

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

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

The compounds of the invention which have one or more  
15 asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures. Within the object of the invention are  
20 also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

The compounds of the present invention are formulated in the corresponding pharmaceutical compositions, also with belated release, for parenteral, oral and topic use, such as for  
25 example inhalatory, suppository, transdermal, according to the well known techniques in the art, together with the usual excipients; see for example the publication "Remington's Pharmaceutical Sciences" 15<sup>th</sup> Ed.

The amount on a molar basis of the active principle in said  
30 compositions is generally the same, or lower than that of the corresponding precursor drug.

The daily administrable doses are those of the precursor drugs, or optionally lower. The precursor daily doses can be

found in the publications of the field, such for example in the "Physician's Desk reference".

### Synthesis procedure

5 **1)** The compounds of general formula (I) as above defined wherein a is equal to 0, the radical  $R_x$  is selected from (a2), (a4), (a8), (b2), (b4), (b8), (c2), (e2), (f1), (g2), (h1), (i1), (l2), (m2), (n2), (o2), (p2), (q2), (r2), (s2), (t2), (u2), (v2), can be obtained:

10 **1-i)** by reacting a compound of formula (II<sub>1</sub>)



wherein R is as defined above, with a compound of formula (Ia)

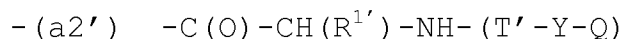


wherein W is -OH, Cl, O-R<sub>a</sub> wherein R<sub>a</sub> is pentafluorophenyl, 4-nitrophenyl or -(N-succimidyl), X<sub>1</sub> is as below defined, to obtain the compounds of formula (II<sub>2</sub>)



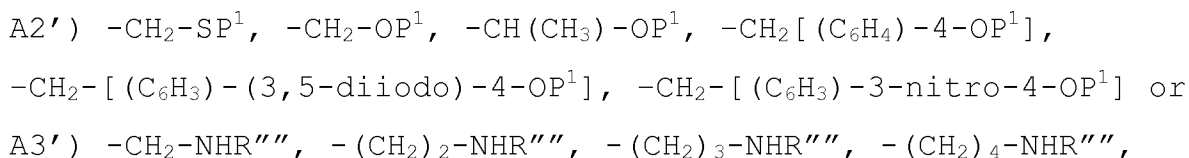
wherein X<sub>1</sub> is as below defined,

X<sub>1</sub> is a radical having the following meaning:

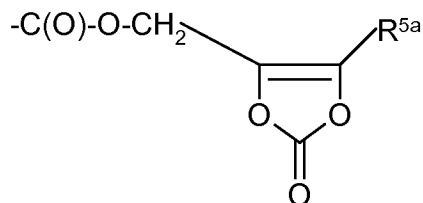


25 wherein R<sup>1'</sup> is selected from

A1) as defined above or



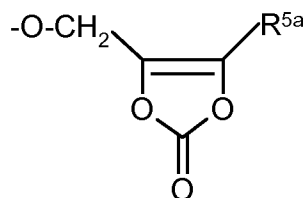
30 wherein R''' is P<sup>3</sup> or -C(O)CH<sub>3</sub> or



wherein  $\text{R}^{5a}$  is as defined above;

A4')  $\text{-CH}_2\text{-C(O)R}^{''''}$ ,  $\text{-(CH}_2)_2\text{-C(O)R}^{''''}$ ,  $\text{-(CH}_2)_4\text{-C(O)R}^{''''}$

wherein  $\text{R}^{''''}$  is  $\text{P}^2$ ,  $\text{-OR}^{5a}$  or

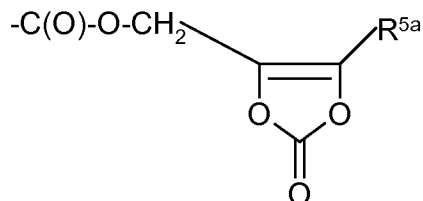


wherein  $\text{R}^{5a}$  is as above defined;

-(a4')  $\text{-C(O)-CH(R}^{1a}\text{-T''-Y'-Q)-NHR}^{4a'}$

-(a8')  $\text{-C(O)-CH(R}^{1a}\text{-T''-Y'-Q)-NH-(T'-Y-Q)}$

wherein  $\text{R}^{1a}$  is as defined above and  $\text{R}^{4a'}$  is  $\text{P}^3$  or  $\text{-C(O)-CH}_3$  or



-(b2')  $\text{-C(O)-CH}_2\text{-CH(R}^{2'}\text{)-NH-(T'-Y-Q)}$

wherein  $\text{R}^{2'}$  is selected from

B1) as defined above or

B2')  $\text{-CH(CH}_3\text{)-OP}^1$ ,  $\text{-CH}_2\text{-[(C}_6\text{H}_4\text{)-4-OP}^1\text{]}$ ;

B3')  $\text{-CH}_2\text{-NHR}^{''''}$ ,  $\text{-(CH}_2)_2\text{-NHR}^{''''}$ ,  $\text{-(CH}_2)_3\text{-NHR}^{''''}$ ,  $\text{-(CH}_2)_4\text{-NHR}^{''''}$ ,

wherein  $\text{R}^{''''}$  is as above defined;

B4')  $\text{-CH}_2\text{-C(O)-R}^{''''}$ ,  $\text{-(CH}_2)_2\text{-C(O)-R}^{''''}$ ,  $\text{-(CH}_2)_4\text{-C(O)-R}^{''''}$  wherein  $\text{R}^{''''}$  is as above defined;

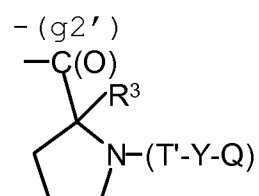
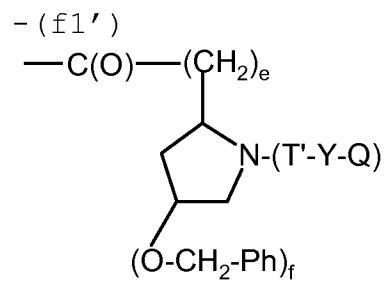
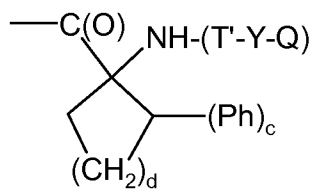
-(b4')  $\text{-C(O)-CH}_2\text{-CH(R}^{2a}\text{-T''-Y'-Q)-NHR}^{4a'}$

-(b8')  $\text{-C(O)-CH}_2\text{-CH(R}^{2a}\text{-T''-Y'-Q)-NH-(T'-Y-Q)}$

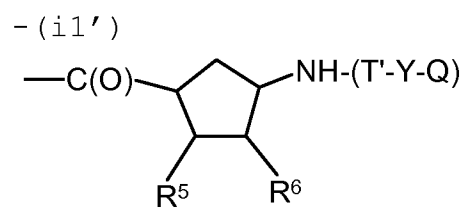
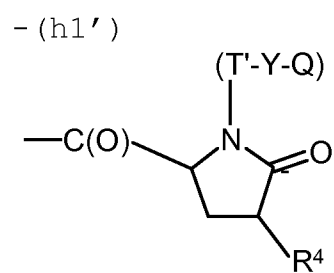
wherein  $\text{R}^{2a}$  and  $\text{R}^{4a'}$  are as defined above;

-(c2')  $\text{-C(O)-(CH}_2)_b\text{-NH-(T'-Y-Q)}$ ;

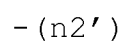
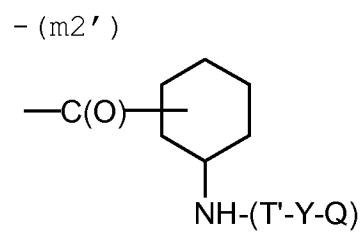
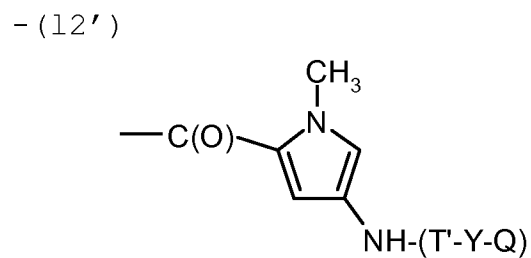
-(e2')

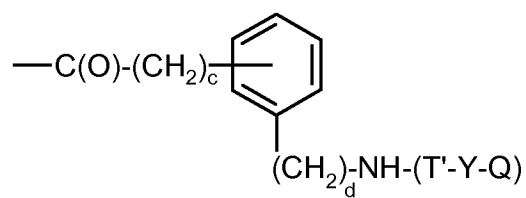


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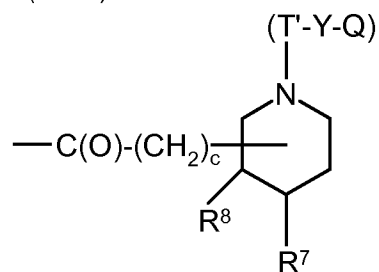


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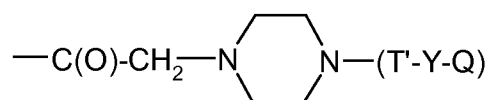




- (o2')

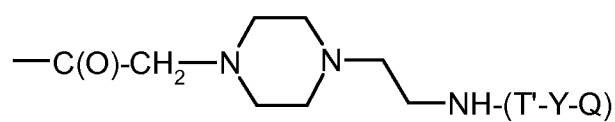


- (p2')

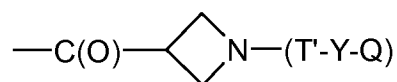


5

- (q2')

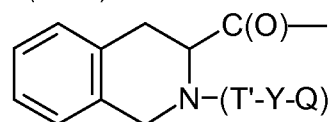


- (r2')

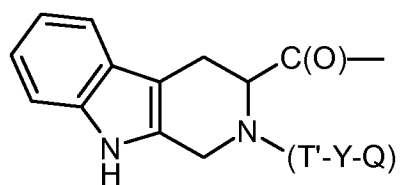


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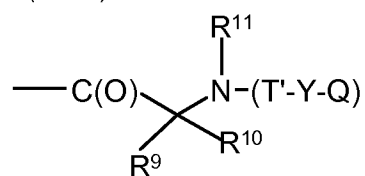
- (s2')



- (t2')

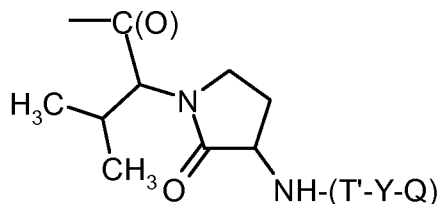


- (u2')



15

- (v2')



wherein  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ , b, c, d, e and f are as above defined;

- 5 wherein  $P^1$  is a hydroxyl or thiol protecting group such as silyl ethers, such as trimethylsilyl, tert-butyl-dimethylsilyl or trityl and those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980,  $P^2$  is a carboxylic protecting group such as tert-butyl ester and those  
10 described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980,  $P^3$  is a amino protecting group such as Boc, Fmoc or those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980,

- 15 T, T', T'', Y and Y' are as above defined,

Q is independently  $-ONO_2$  or  $Z_2$  wherein  $Z_2$  is selected from the group consisting of: a chlorine atom, a bromine atom, a iodine atom, a mesyl group or a tosyl group, and

- 1-ii) when Q is  $Z_2$ , by converting the compound obtained in the  
20 step 1-i) into nitro derivative by reaction with a nitrate source such as silver nitrate, lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate, calcium nitrate, iron nitrate, zinc nitrate or tetraalkylammonium nitrate (wherein alkyl is  $C_1$ - $C_{10}$  alkyl) in a suitable organic solvent such as  
25 acetonitrile, tetrahydrofuran, methyl ethyl ketone, ethyl acetate, DMF, the reaction is carried out, in the dark, at a temperature from room temperature to the boiling temperature of the solvent. Preferred nitrate source is silver nitrate and

1-iii) optionally deprotecting the compounds obtained in step 1-i) or 1-ii) as described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980, 2<sup>nd</sup> edition. Fluoride ion is the preferred method for removing silyl ether protecting group. Trifluoroacetic acid or anhydrous inorganic acid are the preferred method for removing Boc protecting group, anhydrous organic or inorganic acid is the preferred method for removing trityl protecting group. Organic base such as piperidine is the preferred method for removing Fmoc protecting group. Aqueous or anhydrous organic or inorganic acid is the preferred method for removing t-butyl ester protecting group.

1-i-1) The reaction of a compound of formula (Ia) wherein W = -OH and X<sub>1</sub> is as above defined, with a compound of formula (II<sub>1</sub>) may be carried out in presence of a condensing agent as dicyclohexylcarbodiimide (DCC), N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDAC) N,N'-carbonyldiimidazole (CDI), in the presence or not of a base as for example as N,N-dimethylamino pyridine (DMAP).

The reaction is carried out in an inert organic dry solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C to 50°C. The reaction is completed within a time range from 30 minutes to 36 hours.

1-i-2) The reaction of a compound of formula (Ia) wherein W = -O-R<sub>a</sub> wherein R<sub>a</sub> and X<sub>1</sub> are as above defined, with a compound of formula (II<sub>1</sub>) may be carried out in presence of a catalyst, such as N,N-dimethylamino pyridine (DMAP) or in the presence of DMAP and a Lewis acid such as Sc(OTf)<sub>3</sub> or Bi(OTf)<sub>3</sub>.

The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a



temperature from -20°C to 40°C. The reaction is completed within a time range from 30 minutes to 36 hours.

1-i-3) The reaction of a compound of formula (Ia) wherein W = -Cl, and X<sub>1</sub> is as above defined, with a compound of formula (II<sub>1</sub>) may be carried out in presence of an organic base such as N,N-dimethylamino pyridine (DMAP), triethylamine, pyridine. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C to 40°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (II<sub>1</sub>) are commercially available.

**1a)** The compounds of formula (Ia) wherein W is -OH, and X<sub>1</sub> is the radical selected from (a2'), (a4'), (b2'), (b4'), (c2'), (e2'), (f1'), (g2'), (h1'), (i1'), (l2'), (m2'), (n2'), (o2'), (p2'), (q2'), (r2'), (s2'), (t2'), (u2'), (v2'), wherein R<sup>1'</sup> is selected from A1), A2'), A3') or A4'), R<sup>1a</sup> is selected from A5) or A6), R<sup>2a</sup> is selected from B5) or B6) and R<sup>2'</sup> is selected from B1), B2'), B3') or B4'), wherein T' and T'' are C(O) and Y, Y' and R<sup>4a'</sup> are as above defined, can be obtained

**1a-i)** by reacting a compound of formula (IIIa)



(IIIa)

wherein P<sup>2</sup> is as above defined, X<sub>2</sub> is a radical having the following meaning

-(a2'') -C(O)-CH(R<sup>1'</sup>)-NH<sub>2</sub>

-(a4'') -C(O)-CH(R<sup>1a</sup>-H)-NHR<sup>4a'</sup>

wherein R<sup>1'</sup> is selected from A1), A2'), A3'), A4'), R<sup>1a</sup> is selected from A5) or A6) and R<sup>4a'</sup> is as defined above

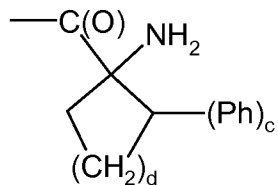
-(b2'') -C(O)-CH<sub>2</sub>-CH(R<sup>2'</sup>)-NH<sub>2</sub>,

-(b4'')  $-\text{C}(\text{O})-\text{CH}_2-\text{CH}(\text{R}^{2a}-\text{H})-\text{NHR}^{4a'}$

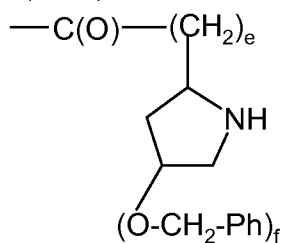
wherein  $\text{R}^{2'}$  is selected from B1), B2'), B3'), B4'),  $\text{R}^{2a}$  is selected from B5) or B6) and  $\text{R}^{4a'}$  is as defined above,

-(c2'')  $-\text{C}(\text{O})-(\text{CH}_2)_b-\text{NH}_2$ ,

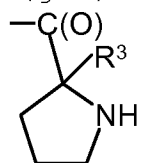
5 -(e2'')



-(f1'')

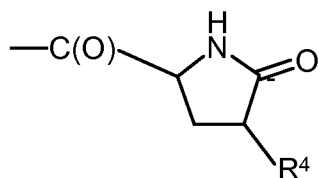


-(g2'')

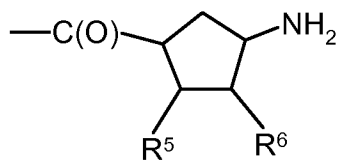


10

-(h1'')

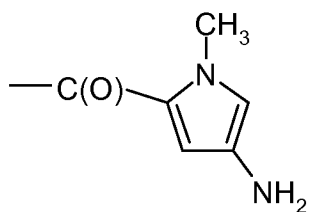


-(i1'')

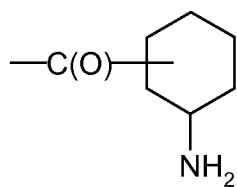


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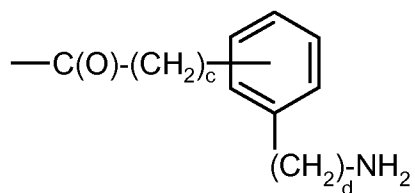
-(l2'')



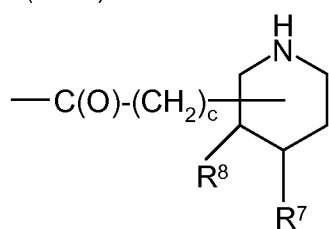
-(m2'')



— (n2'')

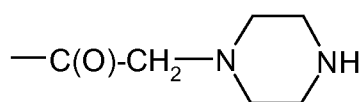


— (o2'')

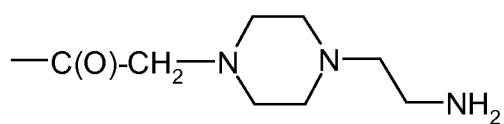


5

— (p2'')

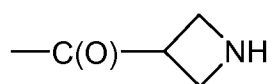


— (q2'')

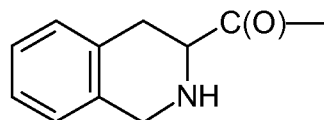


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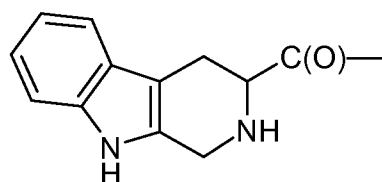
— (r2'')



— (s2'')

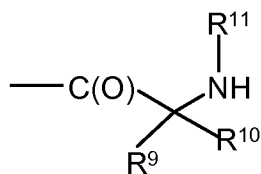


— (t2'')

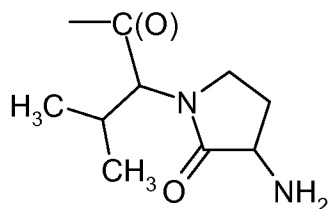


15

— (u2'')

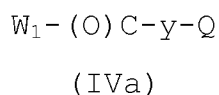


-(v2'')



wherein  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $b$ ,  $c$ ,  $d$ ,  $e$  and  $f$  are  
 5 as above defined;

with a compound of formula (IVa)



wherein  $W_1$  is OH or  $O-R_a$  and  $R_a$  and  $Q$  are as above defined,  $y$  is  
 10 the radical  $Y$  when  $X_2$  is selected from (a2'), (b2'), (c2'),  
 (e2'), (f1'), (g2'), (h1'), (i1'), (l2'), (m2'), (n2'), (o2'),  
 (p2'), (q2'), (r2'), (s2'), (t2'), (u2'), (v2'), and  $y$  is the  
 radical  $Y'$  when  $X_2$  is selected from (a4') or (b4'), wherein  $Y$   
 and  $Y'$  are as defined above, and

15 1a-ii) when  $Q$  is  $Z_2$ , by converting the compound obtained in the  
 step 1a-i) into nitro derivative by reaction with a nitrate  
 source as above described and

1a-iii) optionally deprotecting the compounds obtained in step  
 1a-i) or 1a-ii) as above described.

20 The reaction of a compound of formula (IIIa) wherein  $P^2$  and  $X_2$   
 are as above defined, with a compound of formula (IVa) wherein  
 $W_1$  is OH,  $y$ ,  $Q$  are as above defined, may be carried out as  
 described in 1-i-1) or in presence of other known condensing  
 reagents such as  $O$ -(7-azabenzotriazol-1-yl)- $N,N,N',N'$ -

25 tetramethyluronium hexafluorophosphate (HATU).

The reaction of a compound of formula (IIIa) wherein  $P^2$  and  $X_2$   
 are as above defined, with a compound of formula (IVa) wherein

W<sub>1</sub> is O-R<sub>a</sub>, y, Q are as above defined, may be carried as described in 1-i-2).

The compounds of formula (IIIa) are commercially available or  
5 can be obtained as known in the literature.

The compounds of formula (IVa) wherein W<sub>1</sub> is OH, y and Q are as above defined, can be obtained from the corresponding alcohols of formula HOOC-y-OH (IVb) by reaction with nitric acid and  
10 acetic anhydride in a temperature range from -50°C to 0°C or from the corresponding derivatives of formula HOOC-y-Z<sub>2</sub> (IVc) wherein Z<sub>2</sub> is as above defined, by reaction with a nitrate source as above described. Alternatively the reaction with AgNO<sub>3</sub> can be performed under microwave irradiation in solvents such  
15 acetonitrile or THF at temperatures in the range between 100 and 180°C for time range from 1 to 60 min.

The compounds of formula (IVb) are commercially available.

20 The compounds of formula (IVc) are commercially available or can be obtained as known in the literature.

The compounds of formula (IVa) wherein W<sub>1</sub> is O-R<sub>a</sub>, y, Q are as above defined, can be obtained from the corresponding acids of  
25 formula (IVa) wherein W<sub>1</sub> is OH as known in the literature.

The compounds of formula (Ia) wherein W= Cl or O-R<sub>a</sub>, X<sub>1</sub> is selected from (a2'), (a4'), (b2'), (b4'), (c2'), (e2'), (f1'), (g2'), (h1'), (i1'), (l2'), (m2'), (n2'), (o2'), (p2'), (q2'),  
30 (r2'), (s2'), (t2'), (u2'), (v2'), wherein R<sup>1'</sup> is selected from A1), A2'), A3') or A4'), R<sup>1a</sup> is selected from A5) or A6), R<sup>2a</sup> is selected from B5) or B6) and R<sup>2'</sup> is selected from B1), B2'),

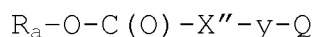
B3') or B4'), and wherein Y, Y' and Q are as above defined and T' and T'' are C(O), can be obtained from the corresponding acids (Ia) wherein W is -OH as known in the literature.

- 5 **1b)** The compounds of formula (Ia) wherein W is -OH, X<sub>1</sub> is the radical selected from (a2'), (a4'), (b2'), (b4') (c2'), (e2'), (f1'), (g2'), (h1'), (i1'), (l2'), (m2'), (n2'), (o2'), (p2'), (q2'), (r2'), (s2'), (t2'), (u2'), (v2'), wherein R<sup>1'</sup> is selected from A1), A2'), A3') or A4'), R<sup>1a</sup> is selected from A5)  
 10 or A6), R<sup>2a</sup> is selected from B5) or B6) and R<sup>2'</sup> is selected from B1), B2'), B3') or B4'), Y and Y' are as above defined, T' and T'' are C(O)-X'', wherein X'' is -O- or -S-can be obtained  
**1b-i)** by reacting a compound of formula (IIIa)



15 (IIIa)

wherein P<sup>2</sup> and X<sub>2</sub> are as defined above, with a compound of formula (IVd)



(IVd)

- 20 wherein R<sub>a</sub>, X'' and Q are as above defined, y is the radical Y when X<sub>2</sub> is selected from (a2'), (b2'), (c2'), (e2'), (f1'), (g2'), (h1'), (i1'), (l2'), (m2'), (n2'), (o2'), (p2'), (q2'), (r2'), (s2'), (t2'), (u2'), (v2'), and y is the radical Y' when X<sub>2</sub> is selected from (a4') or (b4'), wherein Y and Y' are as  
 25 above defined, and

1b-ii) when Q is Z<sub>2</sub>, by converting the compound obtained in the step 1b-i) into nitro derivative by reaction with a nitrate source as above described and

- 1b-iii) optionally deprotecting the compounds obtained in step  
 30 1b-i) or 1b-ii) as above described.

The reaction of a compound of formula (IIIa) wherein P<sup>2</sup> and X<sub>2</sub> are as above defined, with a compound of formula (IVd) wherein

R<sub>a</sub>, X'', y and Q are as above defined, may be carried out as described in 1-i-2)

The compounds of formula (IVd) wherein R<sub>a</sub>, X'', y, Q are as above defined, can be obtained from the compounds of formula HX''-y-Q (IVe) wherein X'', y, Q are as above defined, as known in literature.

The compounds of formula (IVe) are commercially available or are known in literature.

The compounds of formula (Ia) wherein W is -Cl or O-R<sub>a</sub>, X<sub>1</sub> is selected from (a2'), (a4'), (b2'), (b4'), (c2'), (e2'), (f1'), (g2'), (h1'), (i1'), (l2'), (m2'), (n2'), (o2'), (p2'), (q2'), (r2'), (s2'), (t2'), (u2'), (v2'), wherein R<sup>1'</sup> is selected from A1), A2'), A3'), A4'), R<sup>1a</sup> is selected from A5) or A6), R<sup>2a</sup> is selected from B5) or B6) and R<sup>2'</sup> is selected from B1), B2'), B3'), B4'), Y, Y' and Q are as above defined, T' and T'' are C(O)-X'' wherein X'' is O or S, can be obtained from the corresponding acids (Ia) wherein W is -OH as known in the literature.

**1c)** The compounds of formula (Ia) wherein W is -OH and X<sub>1</sub> is a radical selected from (a8') or (b8'), wherein R<sup>1a</sup> is selected from A5) or A6), R<sup>2a</sup> is selected from B5) or B6), Q is as above defined, T' and T'' are C(O), Y and Y' are the same and are as above defined, can be obtained

**1c-i)** by reacting a compound of formula (IIIb),

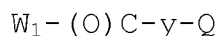


(IIIb)

wherein P<sup>2</sup> is as above defined, X<sub>3</sub> is the radical of formula - (a8'') -C(O)-CH(R<sup>1a</sup>-H)-NH<sub>2</sub>

-(b8'') -C(O)-CH<sub>2</sub>-CH(R<sup>2a</sup>-H)-NH<sub>2</sub>

wherein R<sup>1a</sup> is selected from A5) or A6), R<sup>2a</sup> is selected from B5) or B6), with a compound of formula (IVa)



(IVa)

wherein W<sub>1</sub> and Q are as above defined, wherein y is the radical Y or Y', wherein Y and Y' are as above defined, and

1c-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 1c-i) into nitro derivative by reaction with a nitrate

source as above described and

1c-iii) optionally deprotecting the compounds obtained in step 1c-i) or 1c-ii) as above described.

The reaction of a compound of formula (IIIb) wherein P<sup>2</sup> and X<sub>3</sub> are as above defined, with a compound of formula (IVa) wherein W<sub>1</sub> is OH, y and Q are as above defined, may be carried out as described in 1a-i) using a ratio (IIIb)/(IVa) 1:2.

The reaction of a compound of formula (IIIb) wherein P<sup>2</sup> and X<sub>3</sub> are as above defined, with a compound of formula (IVa) wherein W<sub>1</sub> is OR<sub>a</sub>, y and Q are as above defined, may be carried out as described in 1-i-2) using a ratio (IIIb)/(IVa) 1:2.

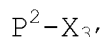
The compounds of formula (IIIb) are commercially available or can be obtained as known in the literature.

The compounds of formula (Ia) wherein W is -Cl or O-R<sub>a</sub>, X<sub>1</sub> is the radical selected from (a8') or (b8') wherein R<sup>1a</sup> is selected from A5) or A6), R<sup>2a</sup> is selected from B5) or B6) and wherein Y, Y' and Q are as above defined and T' and T'' are C(O), can be obtained from the corresponding acids (Ia) wherein W is -OH as known in the literature.



**1d)** The compounds of formula (Ia) wherein W is -OH,  $X_1$  is the radical selected from (a8') or (b8'), wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6), Q, Y and Y' are as above defined, T' is C(O) or C(O)-X'' wherein X'' is as above defined, T'' is C(O), can be obtained

**1d-i)** by reacting a compound of formula (Ib)



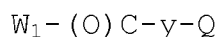
(Ib)

wherein  $P^2$  is as above defined,  $X_3$  is the radical of formula

- (a8''') -C(O)-CH( $R^{1a}$ -H)-NH-(T'-Y-Q)

- (b8''') -C(O)-CH<sub>2</sub>-CH( $R^{2a}$ -H)-NH-(T'-Y-Q)

wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6), with a compound of formula (IVa)



(IVa)

wherein  $W_1$  and Q are as above defined, wherein y is the radical Y', wherein Y' is as above defined, and

1d-ii) when Q is  $Z_2$ , by converting the compounds obtained in the step 1d-i) into nitro derivative by reaction with a nitrate

source as above described and

1d-iii) optionally deprotecting the compounds obtained in step 1d-i) or 1d-ii) as above described.

The reaction of a compound of formula (Ib) wherein  $P^2$  and  $X_3$  are as above defined, with a compound of formula (IVa) wherein  $W_1$  is OH, y and Q are as above defined, may be carried out as described in 1a-i).

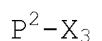
The reaction of a compound of formula (Ib) wherein  $P^2$  and  $X_3$  are as above defined, with a compound of formula (IVa) wherein  $W_1$  is  $OR_a$ , y and Q are as above defined may be carried out as described in 1-i-2).

The compounds of formula (Ib) wherein  $T'$  is  $C(O)$ ,  $P^2$  and  $X_3$  are as above defined, are obtained as described in 1a).

The compounds of formula (Ib) wherein  $T'$  is  $C(O)-X''$ ,  $P^2$  and  $X_3$  are as above defined, are obtained as described in 1b).

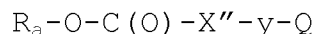
The compounds of formula (Ia) wherein  $W$  is  $-Cl$  or  $O-R_a$ ,  $X_1$  is the radical selected from (a8') or (b8') wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6) and wherein  $Q$ ,  $Y$  and  $Y'$  are as above defined,  $T'$  is  $C(O)$  or  $C(O)-X''$  wherein  $X''$  is as above defined,  $T''$  is  $C(O)$ , can be obtained from the corresponding acids (Ia) wherein  $W$  is  $-OH$  as known in literature.

**1e)** The compounds of formula (Ia) wherein  $W$  is  $-OH$ ,  $X_1$  is the radical selected from (a8') or (b8'), wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6),  $Q$  is as above defined,  $Y$  and  $Y'$  are the same and are as above defined,  $T'$  and  $T''$  are  $C(O)-X''$  wherein  $X''$  is as above defined, can be obtained **1e-i)** by reacting a compound of formula (IIIb)



(IIIb)

wherein  $P^2$  and  $X_3$  are as above defined, with a compound of formula (IVd)



(IVd)

wherein  $R_a$  and  $Q$  are as above defined, wherein  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

1e-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 1e-i) into nitro derivative by reaction with a nitrate source as above described and

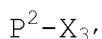
1e-iii) optionally deprotecting the compounds obtained in step 1e-i) or 1e-ii) as above described.

The reaction of a compound of formula (IIIb) wherein  $P^2$  and  $X_3$  are as above defined, with a compound of formula (IVd) wherein  $R_a$ ,  $y$  and  $Q$  are as above defined, may be carried out as described in 1-i-2) using a ratio (IIIb)/(IVd) 1:2.

The compounds of formula (Ia) wherein  $W$  is  $-Cl$  or  $O-R_a$ ,  $X_1$  is the radical selected from (a8') or (b8') wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6) and wherein  $Y$  and  $Y'$ ,  $Q$  is as above defined and  $T'$  and  $T''$  are  $C(O)-X''$  wherein  $X''$  is as above defined, can be obtained from the corresponding acids (Ia) wherein  $W$  is  $-OH$  as known in literature.

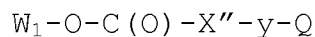
**1f)** The compounds of formula (Ia) wherein  $W$  is  $-OH$ ,  $X_1$  is selected from (a8') or (b8'), wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6),  $Q$ ,  $Y$  and  $Y'$  are as above defined,  $T'$  is  $C(O)$  or  $C(O)-X''$  wherein  $X''$  is as above defined,  $T''$  is  $C(O)-X''$ , can be obtained

**1f-i)** by reacting a compound of formula (Ib)



(Ib)

wherein  $X_3$  and  $P^2$  are as above defined, with a compound of formula (IVd)



(IVd)

wherein  $W_1$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

1f-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 1f-i) into nitro derivative by reaction with a nitrate source as above described and

1f-iii) optionally deprotecting the compounds obtained in step 1f-i) or 1f-ii) as above described.

The reaction of a compound of formula (Ib) wherein  $P^2$  and  $X_{3'}$  are as above defined, with a compound of formula (IVd) wherein  $W_1$  is OH, y and Q are as above defined, may be carried out as described in 1a-i).

The reaction of a compound of formula (Ib) wherein  $P^2$  and  $X_{3'}$  are as above defined, with a compound of formula (IVd) wherein  $W_1$  is  $OR_a$ , y and Q are as above defined may be carried out as described in 1-i-2).

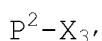
The compounds of formula (Ib) wherein  $T'$  is  $C(O)$ ,  $P^2$  and  $X_{3'}$  are as above defined, are obtained as described in 1a).

The compounds of formula (Ib) wherein  $T'$  is  $C(O)-X''$ ,  $P^2$  and  $X_{3'}$  are as above defined, are obtained as described in 1b).

The compounds of formula (Ia) wherein W is  $-Cl$  or  $O-R_a$ ,  $X_1$  is a radical selected from (a8') or (b8') wherein  $R^{1a}$  is A5) or A6),  $R^{2a}$  is B5) or B6) and wherein Q, Y and  $Y'$  are as above defined,  $T'$  is  $C(O)$  or  $C(O)-X''$  and  $T''$  is  $C(O)-X$ , wherein  $X''$  is as above defined, can be obtained from the corresponding acids (Ia) wherein W is  $-OH$  as known in literature.

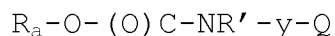
**1g)** The compounds of formula (Ia) wherein W is  $-OH$ ,  $X_1$  is a radical is selected from (a8') or (b8'), wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6), Q, Y and  $Y'$  are as above defined,  $T'$  is  $C(O)$  or  $C(O)-X''$  wherein  $X''$  is as above defined,  $T''$  is  $C(O)-NR'$  wherein  $R'$  is above defined, can be obtained

**1g-i)** by reacting a compound of formula (Ib)



(Ib)

wherein  $P^2$  and  $X_{3'}$  are as above defined, with a compound of formula



(IVf)

wherein  $R_a$ ,  $R'$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

1g-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 1g-i) into nitro derivative by reaction with a nitrate

source as above described and

1g-iii) optionally deprotecting the compounds obtained in step 1g-i) or 1g-ii) as above described.

The reaction of a compound of formula (Ib) wherein  $P^2$  and  $X_{3'}$  are as above defined, with a compound of formula (IVf) wherein  $R_a$ ,  $R'$ ,  $y$ ,  $Q$  are as above defined, may be carried out as described in 1-i-2).

The compounds of formula (Ib) wherein  $T'$  is  $C(O)$ , wherein  $P^2$  and  $X_{3'}$  are as above defined, are obtained as described in 1a-i), 1a-ii).

The compounds of formula (Ib) wherein  $T'$  is  $C(O)-X''$ , wherein  $P^2$  and  $X_{3'}$  are as above defined, are obtained as described in 1b-i), 1b-ii).

The compounds of formula (IVf) wherein  $R'$ ,  $y$  and  $Q$  are as above defined, can be obtained from the compounds of formula  $HR'N-y-Q$  (IVg) by reaction with a chloroformate as known in the literature.

The compounds of formula (IVg) wherein  $y$  is as above defined and  $Q$  is  $Z_2$  are commercially available, the compounds of formula (IVg) wherein  $y$  is as above defined and  $Q$  is  $-ONO_2$  may be

obtained from the compounds of formula  $P^3-R'N-y-ONO_2$  (IVh) wherein  $P^3$  is as above defined by deprotection of amino group as known in literature. The compounds of formula (IVh) wherein  $P^3$  and  $y$  are as above defined may be obtained from the alcohol  $P^3-R'N-y-OH$  (IVi) by reacting with tetraalkylammonium nitrate as already described for analogous compounds. The compounds of formula (IVi) are commercially available or known in literature. Alternatively the compounds of formula (IVh) wherein  $P^3$  and  $y$  are as above defined may be obtained from the corresponding compounds of formula  $P^3-R'N-y-Z_2$  (IVl) wherein  $P^3$ ,  $y$  and  $Z_2$  are as above defined, by reaction with a nitrate source as above described.

The compounds of formula (Ia) wherein  $W$  is  $-Cl$  or  $O-R_a$ ,  $X_1$  is a radical selected from (a8') or (b8') wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6) and wherein  $Y$ ,  $Y'$  and  $Q$  are as above defined and  $T'$  is  $C(O)$  or  $C(O)-X''$ ,  $T''$  is  $C(O)-NR'-$ , wherein  $X''$  and  $R'$  are as above defined, can be obtained from the corresponding acids (Ia) wherein  $W$  is  $-OH$  as known in literature.

**1h)** The compounds of formula (Ia) wherein  $W$  is  $-OH$ ,  $X_1$  is a radical selected from (a8') or (b8'), wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7),  $Q$ ,  $Y$  and  $Y'$  are as above defined,  $T'$  is  $C(O)$  or  $C(O)-X''$ ,  $T''$  is  $X''$  wherein  $X''$  is above defined, can be obtained

**1h-i)** by reacting a compound of formula (Ie),



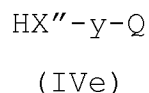
(Ie)

wherein  $P^2$  is defined above,  $X_5$  is the radical of formula

-(a8''')  $-C(O)-CH(R^{1a}-OH)-NH-(T'-Y-Q)$

-(b8''')  $-C(O)-CH_2-CH(R^{2a}-OH)-NH-(T'-Y-Q)$

wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7), with a compound of formula (IVe)



- 5 wherein  $X''$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and
- 1h-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 1h-i) into nitro derivative by reaction with a nitrate source as above described and
- 10 1h-iii) optionally deprotecting the compounds obtained in step 1h-i) or 1h-ii) as above described.

The reaction of a compound of formula (Ie) wherein  $P^2$  and  $X_5$  are as above defined, with a compound of formula (IVe) wherein  $y$ ,  $X''$  and  $Q$  are as above defined, may be carried out as described

15 in 1-i-1).

The compounds of formula (Ie) wherein  $T'$  is  $C(O)$ , wherein  $P^2$  and  $X_5$  are as above defined, are obtained as described in 1a-i), 1a-ii).

20 The compounds of formula (Ie) wherein  $T'$  is  $C(O)\text{-}X''$ , wherein  $P^2$  and  $X_5$  are as above defined, are obtained as described in 1b-i), 1b-ii).

25 The compounds of formula (Ia) wherein  $W$  is  $\text{-Cl}$  or  $\text{O-R}_a$ ,  $X_1$  is a radical selected from (a8') or (b8') wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7) and wherein  $Y$ ,  $Y'$  and  $Q$  are as above defined,  $T'$  is  $C(O)$  or  $C(O)\text{-}X''$ , and  $T''$  is  $X''$  wherein  $X''$  is as above defined, can be obtained from the corresponding

30 acids (Ia) wherein  $W$  is  $\text{-OH}$  as known in literature.

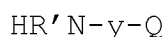
**1i)** The compounds of formula (Ia) wherein W is -OH,  $X_1$  is a radical selected from (a8') or (b8'), wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7), Q, Y and Y' are as above defined, T' is C(O) or C(O)-X'' wherein X'' is as above defined, T'' is -NR' wherein R' is above defined, can be obtained

**1i-i)** by reacting a compound of formula (Ie),



(Ie)

wherein  $P^2$  and  $X_5$  are defined above, with a compound of formula (IVg)



(IVg)

wherein R' and Q are as above defined, y is the radical Y', wherein Y' is as above defined, and

1i-ii) when Q is  $Z_2$ , by converting the compounds obtained in the step 1i-i) into nitro derivative by reaction with a nitrate source such as above described and

1i-iii) optionally deprotecting the compounds obtained in step 1i-i) or 1i-ii) as above described.

The reaction of a compound of formula (Ie) wherein  $P^2$  and  $X_5$  are as above defined, with a compound of formula (IVg) wherein R', y and Q are as above defined, may be carried out as described in 1a-i).

The compounds of formula (Ia) wherein W is -Cl or O- $R_a$ ,  $X_1$  is the radical selected from (a8') or (b8') wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7) and wherein Y, Y' and Q are as above defined, T' is C(O) or C(O)-X'' wherein X'' is as above defined, and T'' is -NR' wherein R' is as above defined can be obtained from the corresponding acids (Ia) wherein W is -OH as known in literature



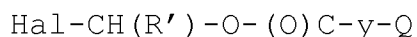
**11)** The compounds of formula (Ia) wherein W is -OH,  $X_1$  is a radical selected from (a8') or (b8'), wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7), Q, Y and Y' are as above defined, T' is C(O) or C(O)-X'' wherein X'' is as above defined,  
 5 T'' is -O-CH(R')-O-C(O)-, wherein R' is as above defined, can be obtained

**11-i)** by reacting a compound of formula (Ie),



(Ie)

10 wherein is  $P^2$  and  $X_5$  are defined above, with a compound of formula (IVm)



(IVm)

wherein R' and Q are as above defined, Hal is an halogen atom,  
 15 y is the radical Y', wherein Y' is as above defined, and  
 11-ii) when Q is  $Z_2$ , by converting the compounds obtained in the step 11-i) into nitro derivative by reaction with a nitrate source such as above described and  
 11-iii) optionally deprotecting the compounds obtained in step  
 20 11-i) or 11-ii) as above described.

The reaction of a compound of formula (Ie) wherein  $P^5$  and  $X_5$  are as above defined, with a compound of formula (IVm) wherein y, Q, R' are as above defined may be carried out in the presence of a inorganic or organic base in an aprotic polar/non-polar  
 25 solvent such as DMF, THF or  $\text{CH}_2\text{Cl}_2$  at temperature in the range between 0° and 100°C or in a double phase system  $\text{H}_2\text{O}/\text{Et}_2\text{O}$  temperature in the range between 20° and 40°C.

The compounds of formula (IVm) wherein y, Q, R' are as above  
 30 defined, Hal is an halogen atom may be obtained by reacting a compound  $\text{R}'-\text{CH}_2-\text{CHO}$ , commercially available, with a compound of formula  $\text{Hal}-(\text{O})\text{C}-\text{y}-\text{Q}$  (IVn), wherein y and Q are as above

defined, Hal is a chlorine atom and  $\text{ZnCl}_2$  as known in literature.

The compounds of formula (IVn) may be obtained as known in literature.

5

The compounds of formula (Ia) wherein W is -Cl or O- $\text{R}_a$ , ,  $\text{X}_1$  is a radical selected from (a8') or (b8') wherein  $\text{R}^{1a}$  is selected from A7),  $\text{R}^{2a}$  is selected from B7) and wherein Y, Y', and Q are as above defined, T' is C(O) or C(O)-X'' wherein X'' is as above defined, and T'' is -O-CH(R')-O-C(O)- wherein R' is as above defined can be obtained from the corresponding acids (Ia) wherein W is -OH as known in literature.

10

15 **1m)** The compounds of formula (Ia) wherein W is -OH,  $\text{X}_1$  is a radical selected from (a8') or (b8'), wherein  $\text{R}^{1a}$  is selected from A7),  $\text{R}^{2a}$  is selected from B7), Q, Y and Y' are as above defined, T' is C(O) or C(O)-X'' wherein X'' is as above defined, T'' is -O-CH(R')-O-C(O)O-, wherein R' is as above defined, can be obtained

20

**1m-i)** by reacting a compound of formula (Ie),

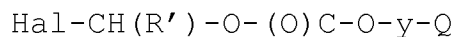


(Ie)

wherein  $\text{P}^2$  and  $\text{X}_5$  are defined above, with a compound of

25

formula (IVo)



(IVo)

wherein R' and Q are as above defined, y is the radical Y', wherein Y' is as above defined, Hal is an halogen atom, and

30

**1m-ii)** when Q is  $\text{Z}_2$ , by converting the compounds obtained in the step 1m-i) into nitro derivative by reaction with a nitrate source such as above described and

1m-iii) optionally deprotecting the compounds obtained in step 1m-i) or 1m-ii) as above described.

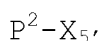
The reaction of a compound of formula (Ie) wherein  $P^2$  and  $X_5$  are as above defined, with a compound of formula (IVo) wherein y, R', Q, Hal are as above defined may be carried out as described in 1m-i).

The compounds of formula (IVo) wherein y, R', Q are as above defined, may be obtained by reacting the compounds of formula Hal-(R')CH-OC(O)Hal, wherein Hal is as above defined, commercially available, with a compound of formula HO-y-Q (IVe) wherein y, Q are as above defined, in the presence of a inorganic or organic base in an aprotic polar or in an aprotic non-polar solvent such as DMF, THF or  $CH_2Cl_2$  at temperatures range between 0° to 65°C.

The compounds of formula (Ia) wherein W is -Cl or O- $R_a$ ,  $X_1$  is a radical selected from (a8') or (b8') wherein  $R^{1a}$  selected from A7),  $R^{2a}$  selected from B7) and wherein Y, Y' and Q are as above defined, T' is C(O) or C(O)- $X''$  wherein  $X''$  is as above defined, and T'' is -O-CH(R')-O-C(O)O-, may be obtained from the corresponding acids (Ia) wherein W is -OH as known in literature.

**1n)** The compounds of formula (Ia) wherein W is -OH,  $X_1$  is a radical selected from (a4') or (b4'), wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7), Y', Q and  $R^{4a'}$  are as above defined and T'' is  $X''$  wherein  $X''$  is as above defined, can be obtained

**1n-i)** by reacting a compound of formula (IIIc)



(IIIc)

wherein  $P^2$  is defined above,  $X_5$  is

-(a4'')  $-C(O)-CH(R^{1a}-OH)-NHR^{4a'}$

-(b4'')  $-C(O)-CH_2-CH(R^{2a}-OH)-NHR^{4a'}$

5 wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7),

with a compound of formula (IVe)

$$HX''-y-Q$$

(IVe)

wherein  $X''$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ ,

10 wherein  $Y'$  is as above defined, and

1n-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 1n-i) into nitro derivative by reaction with a nitrate source as above described and

1n-iii) optionally deprotecting the compounds obtained in step  
15 1n-i) or 1n-ii) as above described.

The reaction of a compound of formula (IIIc) wherein  $X_5$  and  $P^2$  are as above defined, with a compound of formula (IVe) wherein  $X''$ ,  $y$ ,  $Q$  are as above defined may be carried out as described in 1-i-1).

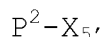
20

The compounds of formula (IIIc) wherein  $X_5$  and  $P^2$  are as above defined, are commercially available or can be obtained as known in the literature.

25 The compounds of formula (Ia) wherein  $W$  is  $-Cl$  or  $O-R_a$ ,  $X_1$  is a radical selected from (a4') or (b4'), wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7),  $Y'$  and  $Q$  are as above defined,  $T''$  is  $X''$ , wherein  $X''$  is as above defined, can be obtained from the corresponding acids (Ia) wherein  $W$  is  $-OH$  as  
30 known in literature.

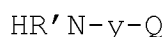
**1o)** The compounds of formula (Ia) wherein W is -OH,  $X_1$  is a radical selected from (a4') or (b4'), wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7),  $Y'$ , Q and  $R^{4a'}$  are as above defined and  $T''$  is -NR' wherein R' is as above defined, can be  
5 obtained

**1o-i)** by reacting a compound of formula (IIIc)



(IIIc)

wherein  $P^2$  and  $X_5$  are as above defined, with a compound of  
10 formula (IVg)



(IVg)

wherein R' and Q are as above defined, y is the radical  $Y'$ , and  
1o-ii) when Q is  $Z_2$ , by converting the compounds obtained in the  
15 step 1o-i) into nitro derivative by reaction with a nitrate  
source as above described and

1o-iii) optionally deprotecting the compounds obtained in step  
1o-i) or 1o-ii) as above described.

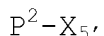
The reaction of a compound of formula (IIIc) wherein  $X_5$  and  $P^2$   
20 are as above defined, with a compound of formula (IVg) wherein  
R', y and Q are as above defined may be carried out as  
described in 1a-i).

The compounds of formula (Ia) wherein W is -Cl or -OR<sub>a</sub>,  $X_1$  is a  
25 radical selected from (a4') or (b4'), wherein  $R^{1a}$  is selected  
from A7),  $R^{2a}$  is selected from B7) and wherein  $Y'$  and Q are as  
above defined and  $T''$  is -NR' wherein R' is as above defined,  
can be obtained from the corresponding acids (Ia) wherein W = -  
OH as known in literature.

**1p)** The compounds of formula (Ia) wherein W is -OH,  $X_1$  is a  
radical selected from (a4') or (b4'), wherein  $R^{1a}$  is selected

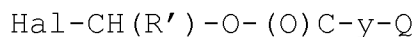
from A7),  $R^{2a}$  is selected from B7),  $Y'$ ,  $Q$  and  $R^{4a'}$  are as above defined and  $T''$  is  $-O-CH(R')-O-C(O)$ , wherein  $R'$  is as above defined, can be obtained

**1p-i)** by reacting a compound of formula (IIIc)



(IIIc)

wherein  $P^2$  and  $X_{5'}$  are as above defined, with a compound of formula (IVm)



(IVm)

wherein  $R'$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined,  $Hal$  is an halogen atom and **1p-ii)** when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step **1p-i)** into nitro derivative by reaction with a nitrate source as above described and

**1p-iii)** optionally deprotecting the compounds obtained in step **1p-i)** or **1p-ii)** as above described.

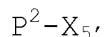
The reaction of a compound of formula (IIIc) wherein  $P^2$  and  $X_{5'}$  are as above defined, with a compound of formula (IVm) wherein  $R'$ ,  $y$ ,  $Q$ ,  $Hal$  are as above defined, may be carried out as described in 11-1).

The compounds of formula (Ia) wherein  $W$  is  $-Cl$  or  $OR_a$ ,  $X_1$  is a radical selected from (a4') or (b4'), wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7) and wherein  $Y$  and  $Q$  are as above defined and  $T''$  is the group  $-O-CH(R')-O-C(O)$ , wherein  $R'$  is as above defined, can be obtained from the corresponding acids (Ia) wherein  $W = -OH$  as known in literature.

**1q)** The compounds of formula (Ia) wherein  $W$  is  $-OH$ ,  $X_1$  is a radical selected from (a4') or (b4'), wherein  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7),  $Y'$ ,  $Q$  and  $R^{4a'}$  are as above

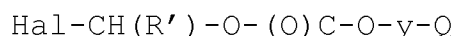
defined and T'' is -O-CH(R')-O-C(O)-O-, wherein R' is as above defined, can be obtained

**1q-i)** by reacting a compound of formula (IIIc)



(IIIc)

wherein P<sup>2</sup> and X<sub>5'</sub> are as above defined, with a compound of formula (IVo)



(IVo)

wherein R' and Q are as above defined, y is the radical Y', wherein Y' is as above defined, Hal is an halogen atom and 1q-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 1q-i) into nitro derivative by reaction with a nitrate source as above described and

1q-iii) optionally deprotecting the compounds obtained in step 1q-i) or 1q-ii) as above described.

The reaction of a compound of formula (IIIc) wherein P<sup>2</sup> and X<sub>5'</sub> are as above defined, with a compound of formula (IVo) wherein R', y, Q, Hal are as above defined, may be carried out as

described in 11-1).

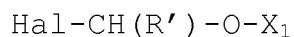
The compounds of formula (Ia) wherein W is -Cl or OR<sub>a</sub>, X<sub>1</sub> is a radical selected from (a4') or (b4'), wherein R<sup>1a</sup> is selected from A7), R<sup>2a</sup> is selected from B7) and wherein Y and Q, are as above defined and T'' is the group -O-CH(R')-O-C(O)-O-, wherein R' is as above defined, can be obtained from the corresponding acids (Ia) wherein W = -OH as known in literature.

**2)** The compounds of general formula (I) as above defined

wherein a is equal to 1, the radical R<sub>x</sub> is selected from (a2), (a4), (a8), (b2), (b4), (b8), (c2), (e2), (f1), (g2), (h1), (i1), (l2), (m2), (n2), (o2), (p2), (q2), (r2), (s2), (t2),

(u2), (v2), Z is -CH(R')-O- wherein R' is selected from H or straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, can be obtained:

**2-i)** by reacting a compound of formula (II<sub>1</sub>) as above defined with a compound of formula (If)



(If)

wherein Hal is an halogen atom, R' and X<sub>1</sub> are as above defined and

2-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 2-i) into nitro derivative by reaction with a nitrate source as above described and

2-iii) optionally deprotecting the compounds obtained in step 2-i) or 2-ii) as above described.

The reaction of a compound of formula (If) wherein X<sub>1</sub> and R' are as above defined, with a compound of formula (II<sub>1</sub>) may be carried out as described in 11-i).

The compounds of formula (If) are obtained by reacting a compound R'-CHO, wherein R' is as above defined with compounds of formula (Ia)

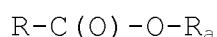


(Ia)

wherein W is a chlorine atom, X<sub>1</sub> is as above defined, and ZnCl<sub>2</sub> as known in literature.

**3)** The compounds of general formula (I) as above defined wherein a is equal to 1, the radical R<sub>x</sub> is selected from (a1), (a3), (a7), (b1), (b3), (b7), (c1), (e1), (f2), (g1), (h2), (i2), (l1), (m1), (n1), (o1), (p1), (q1), (r1), (s1), (t1), (u1), (v1), Z is C(O), can be obtained

**3-i)** by reacting a compound of formula (II<sub>3</sub>)





(II<sub>3</sub>)

wherein R and R<sub>a</sub> are as above defined, with a compound of formula (Ig)

H-X<sub>2</sub>

5

(Ig)

wherein X<sub>2</sub> is a radical having the following meanings:

-(a1') -HN-CH(R<sup>1'</sup>)-C(O)-(T-Y-Q)

-(a3') -HN-CH(R<sup>1a</sup>-T''-Y'-Q)-COOR<sup>3a'</sup>

-(a7') -HN-CH(R<sup>1a</sup>-T''-Y'-Q)-C(O)-(T-Y-Q)

10

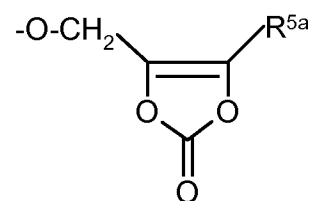
-(b1') -HN-CH(R<sup>2'</sup>)-CH<sub>2</sub>C(O)-(T-Y-Q)

-(b3') -HN-CH(R<sup>2a</sup>-T''-Y'-Q)-CH<sub>2</sub>COOR<sup>3a'</sup>

-(b7') -HN-CH(R<sup>2a</sup>-T''-Y'-Q)-CH<sub>2</sub>-C(O)-(T-Y-Q)

wherein R<sup>1'</sup>, R<sup>1a</sup>, R<sup>2'</sup>, R<sup>2a</sup> are as above defined

R<sup>3a'</sup> is selected from P<sup>2</sup>, -OR<sup>5a</sup> or

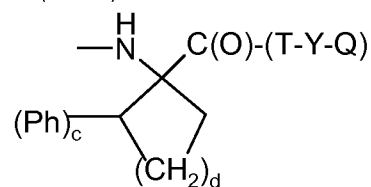


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wherein R<sup>5a</sup> is as above defined;

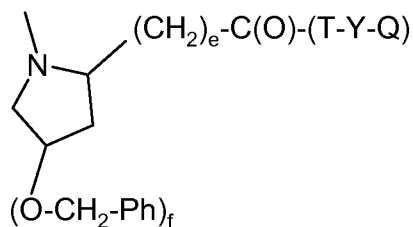
-(c1') -HN-(CH<sub>2</sub>)<sub>b</sub>-C(O)-(T-Y-Q);

-(e1')

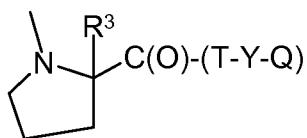


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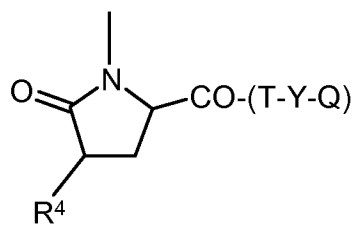
-(f2')



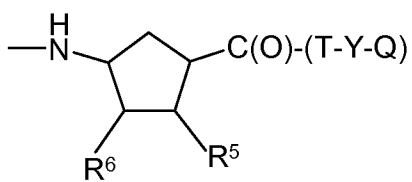
-(g1')



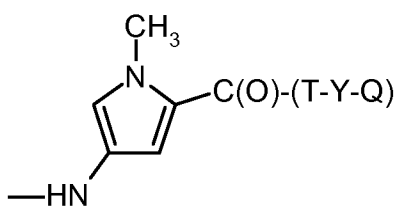
- (h2')



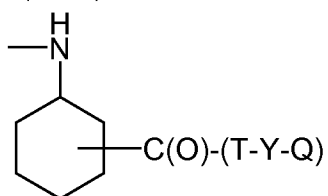
- (i2')



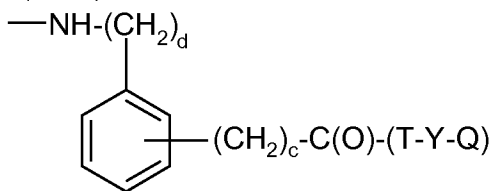
- (l1')



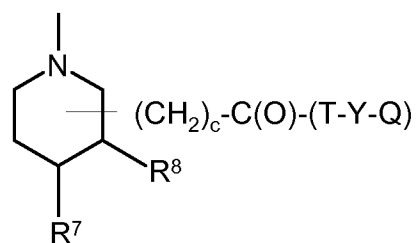
- (m1')



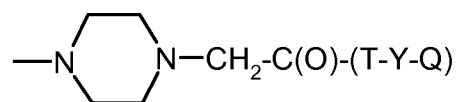
- (n1')



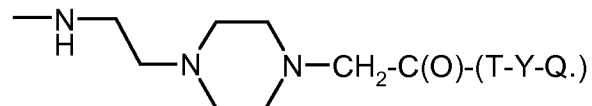
- (o1')



-(p1')

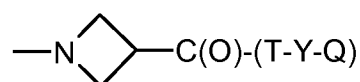


-(q1')

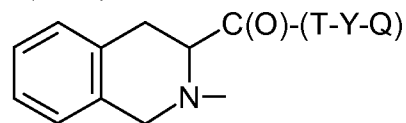


5

-(r1')

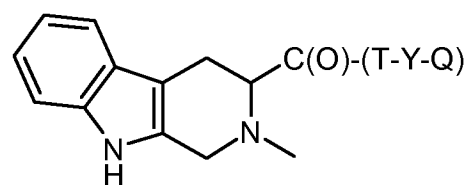


-(s1')

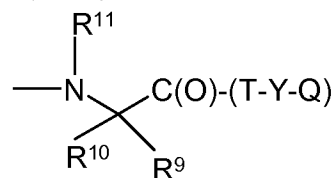


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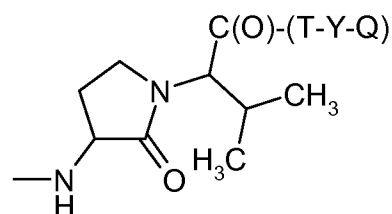
-(t1')



-(u1')



-(v1')



15

wherein T, T'', Y and Y' are as above defined,

3-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 3-i) into nitro derivative by reaction with a nitrate source such as above described and

3-iii) optionally deprotecting the compounds obtained in step 3-i) or 3-ii) as above described.

The reaction of a compound of formula (II<sub>3</sub>), wherein R and R<sub>a</sub> are as above defined, with a compound of formula (Ig) wherein X<sub>1</sub> is as above defined, may be carried out as described in 1-i-2).

The compounds of formula (II<sub>3</sub>) wherein R and R<sub>a</sub> are as above defined, are obtained from the compounds of formula (II<sub>1</sub>) by reaction with the compounds of formula Cl-C(O)-O-R<sub>a</sub> wherein R<sub>a</sub> is as above defined, as known in literature.

**3a)** The compounds of formula (Ig) wherein X<sub>2</sub> is selected from (a1'), (a3'), (b1'), (b3'), (c1'), (e1'), (f2'), (g1'), (h2'), (i2'), (l1'), (m1'), (n1'), (o1'), (p1'), (q1'), (r1'), (s1'), (t1'), (u1'), (v1'), wherein R<sup>1'</sup> is selected from A1), A2'), A3') or A4'), R<sup>1a</sup> is selected from A7), R<sup>2a</sup> is selected from B7) and R<sup>2'</sup> is selected from B1), B2'), B3') or B4'), Y and Y' are as above defined, T and T'' are X'' wherein X'' is as above defined may be obtained

**3a-i)** by reacting a compound of formula (IIIe),



(IIIe)

wherein P<sup>3</sup> is as above defined, X<sub>6</sub> is a radical having the following meanings:

-(a1'') -HN-CH(R<sup>1'</sup>)-C(O)-OH

-(a3'') -HN-CH(R<sup>1a</sup>-OH)-COOR<sup>3a'</sup>

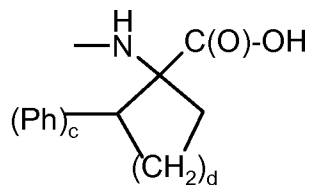
-(b1'') -HN-CH(R<sup>2'</sup>)-CH<sub>2</sub>C(O)-OH

-(b3'') -HN-CH(R<sup>2a</sup>-OH)-CH<sub>2</sub>COOR<sup>3a'</sup>

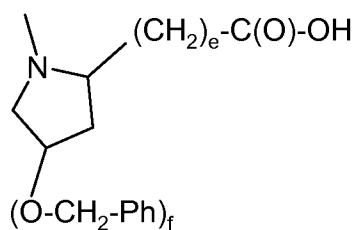
wherein  $R^{1'}$  is selected from A1), A2'), A3') or A4'),  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7) and  $R^{2'}$  is selected from B1), B2'), B3') or B4'), and  $R^{3a'}$  is defined above

-(c1'')  $\text{-HN-(CH}_2\text{)}_b\text{-C(O)-OH}$ ;

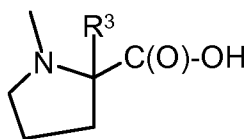
5 -(e1'')



-(f2'')

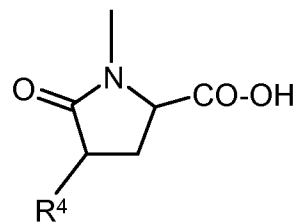


-(g1'')

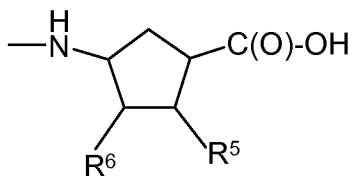


10

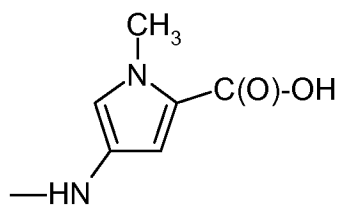
-(h2'')



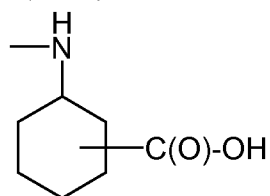
-(i2'')



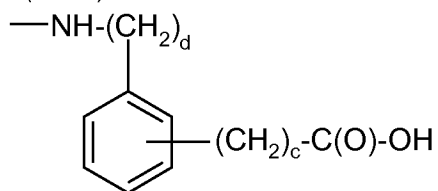
15 -(l1'')



- (m1'')

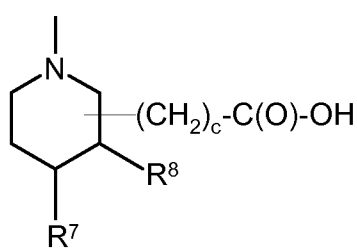


- (n1'')

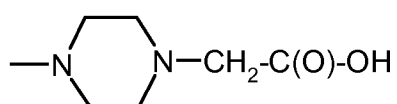


5

- (o1'')

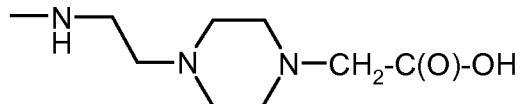


- (p1'')

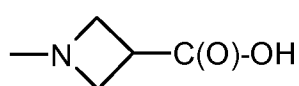


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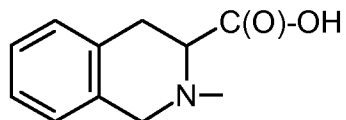
- (q1'')



- (r1'')

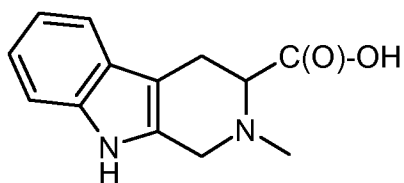


- (s1'')

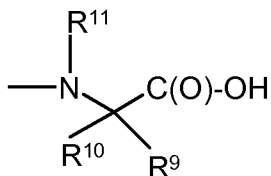


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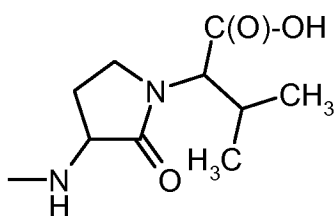
- (t1'')



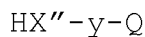
- (u1'')



5 - (v1'')



with a compound of formula (IVe)



10

(IVe)

wherein Q and X'' are as above defined y is the radical Y when X<sub>6</sub> is selected from (a1'), (b1'), (c1'), (e1'), (f2'), (g1'), (h2'), (i2'), (l1'), (m1'), (n1'), (o1'), (p1'), (q1'), (r1'), (s1'), (t1'), (u1') and (v1'), y is the radical Y' when X<sub>6</sub> is selected from (a3') and (b3'), wherein Y and Y' are as defined above, and

3a-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 3a-i) into nitro derivative by reaction with a nitrate source as above described and

20 3a-iii) optionally deprotecting the compounds obtained in step 3a-i) or 3a-ii) as above described.

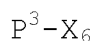
The reaction of a compound of formula (IIIe) wherein P<sup>3</sup> and X<sub>6</sub> are as above defined, with a compound of formula (IVe), wherein

y, Q and X'' are as above defined, may be carried out as described in 1-i-1).

The compounds of formula (IIIe) are commercially available or  
5 can be obtained as known in the literature.

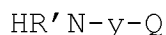
**3b)** The compounds of formula (Ig) wherein X<sub>2</sub> is selected from (a1'), (a3'), (b1'), (b3'), (c1'), (e1'), (f2'), (g1'), (h2'), (i2'), (l1'), (m1'), (n1'), (o1'), (p1'), (q1'), (r1'), (s1'),  
10 (t1'), (u1'), (v1'), wherein R<sup>1'</sup> is selected from A1), A2'), A3') or A4'), R<sup>1a</sup> is selected from A7), R<sup>2a</sup> is selected from B7) and R<sup>2'</sup> is selected from B1), B2'), B3') or B4'), and R<sup>3a'</sup>, Y and Y' are as above defined, T and T'' are -NR' wherein R' is as above defined may be obtained

**3b-i)** by reacting a compound of formula (IIIe),



(IIIe)

wherein P<sup>3</sup> and X<sub>6</sub> are as above defined, with a compound of formula



(IVg)

wherein R' and Q are as above defined, y is the radical Y when X<sub>6</sub> is selected from (a1'), (b1'), (c1'), (e1'), (f2'), (g1'), (h2'), (i2'), (l1'), (m1'), (n1'), (o1'), (p1'), (q1'), (r1'),  
25 (s1'), (t1'), (u1') and (v1'), y is the radical Y' when X<sub>6</sub> is selected from (a3') and (b3'), wherein Y and Y' are as defined above, and

3b-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the  
30 step 3b-i) into nitro derivative by reaction with a nitrate source as above described and

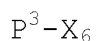


3b-iii) optionally deprotecting the compounds obtained in step 3b-i) or 3b-ii) as above described.

The reaction of a compound of formula (IIIe) wherein  $P^3$  and  $X_6$  are as above defined, with a compound of formula (IVg) wherein  
 5  $R'$ ,  $y$ ,  $Q$  are as above defined, may be carried out 1a-i).

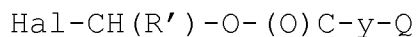
**3c)** The compounds of formula (Ig) wherein  $X_2$  is selected from (a1'), (a3'), (b1'), (b3'), (c1'), (e1'), (f2'), (g1'), (h2'), (i2'), (l1'), (m1'), (n1'), (o1'), (p1'), (q1'), (r1'), (s1'),  
 10 (t1'), (u1'), (v1'), wherein  $R^{1'}$  is selected from A1), A2'), A3'), A4'),  $R^{1a}$  is selected from A7),  $R^{2a}$  is selected from B7) and  $R^{2'}$  is selected from B1), B2'), B3'), B4'), and  $R^{3a'}$ ,  $Y$  and  $Y'$  are as above defined,  $T$  and  $T''$  are  $-O-CH(R')-O-C(O)-$ , wherein  $R'$  is as above defined, may be obtained

15 **3c-i)** by reacting a compound of formula (IIIe)



(IIIe)

wherein  $P^3$ ,  $X_6$  are as above defined with compounds of formula (IVm)



(IVm)

wherein  $R'$  and  $Q$  are as above defined,  $Hal$  is an halogen atom,  $y$  is the radical  $Y$  when  $X_6$  is selected from (a1'), (b1'), (c1'), (e1'), (f2'), (g1'), (h2'), (i2'), (l1'), (m1'), (n1'), (o1'),  
 25 (p1'), (q1'), (r1'), (s1'), (t1'), (u1') and (v1'),  $y$  is the radical  $Y'$  when  $X_6$  is selected from (a3') and (b3'), wherein  $Y$  and  $Y'$  are as defined above, and

3c-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 3c-i) into nitro derivative by reaction with a nitrate  
 30 source as above described and

3c-iii) optionally deprotecting the compounds obtained in step 3c-i) or 3c-ii) as above described.

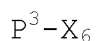
The reaction of a compound of formula (IIIe) wherein  $P^3$  and  $X_6$  are as above defined, with a compound of formula (IVm) wherein  $y$ ,  $Q$ ,  $R'$  are as above defined, may be carried out as described in 11-i)

5

**3d)** The compounds of formula (Ig) wherein  $X_2$  is selected from ( $a1'$ ), ( $a3'$ ), ( $b1'$ ), ( $b3'$ ), ( $c1'$ ), ( $e1'$ ), ( $f2'$ ), ( $g1'$ ), ( $h2'$ ), ( $i2'$ ), ( $l1'$ ), ( $m1'$ ), ( $n1'$ ), ( $o1'$ ), ( $p1'$ ), ( $q1'$ ), ( $r1'$ ), ( $s1'$ ), ( $t1'$ ), ( $u1'$ ), ( $v1'$ ), wherein  $R^{1'}$  is selected from  $A1$ ),  $A2'$ ),  $A3'$ ) or  $A4'$ ),  $R^{1a}$  is selected from  $A7$ ),  $R^{2a}$  is selected from  $B7$ ) and  $R^{2'}$  is selected from  $B1$ ),  $B2'$ ),  $B3'$ ) or  $B4'$ ), and  $R^{3a'}$ ,  $Y$  and  $Y'$  are as above defined,  $T$  and  $T''$  are  $-O-CH(R')-O-C(O)O-$  wherein  $R'$  is as above defined may be obtained

10

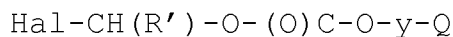
15 **3d-i)** by reacting a compound of formula (IIIe)



(IIIe)

wherein  $P^3$  and  $X_6$  are as above defined, with compounds of formula (IVo)

20



(IVo)

wherein  $R'$  and  $Q$  are as above defined,  $Hal$  is an halogen atom  $y$  is the radical  $Y$  when  $X_6$  is selected from ( $a1'$ ), ( $b1'$ ), ( $c1'$ ), ( $e1'$ ), ( $f2'$ ), ( $g1'$ ), ( $h2'$ ), ( $i2'$ ), ( $l1'$ ), ( $m1'$ ), ( $n1'$ ), ( $o1'$ ), ( $p1'$ ), ( $q1'$ ), ( $r1'$ ), ( $s1'$ ), ( $t1'$ ), ( $u1'$ ) and ( $v1'$ ),  $y$  is the radical  $Y'$  when  $X_6$  is selected from ( $a3'$ ) and ( $b3'$ ), wherein  $Y$  and  $Y'$  are as defined above, and

25

3d-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 3d-i) into nitro derivative by reaction with a nitrate

30

source as above described and

3d-iii) optionally deprotecting the compounds obtained in step 3d-i) or 3d-ii) as above described.

The reaction of a compound of formula (IIIe) wherein  $P^3$  and  $X_6$  are as above defined, with a compound of formula (IVo) wherein  $y$ ,  $Q$ ,  $R'$  are as above defined, may be carried out as described in 11-i).

5

**3e)** The compounds of formula (Ig) wherein  $X_2$  is selected from (a7') or (b7') wherein  $R^{1a}$  is selected from A5) or A6),  $R^{1b}$  is selected from B5) or B6)  $T''$  is  $-C(O)-$ ,  $T$  is  $-X''$ ,  $-NR'$ ,  $-O-CH(R')-O-C(O)-$  or  $-O-CH(R')-O-C(O)O-$  wherein  $X''$  and  $R'$ ,  $Y$  and  $Y'$  are as above defined, may be obtained

10

**3e-i)** by reacting a compound of formula (Ih)



(Ih)

wherein  $P^3$  is as above defined and  $X_7$  is the radical having the following meaning

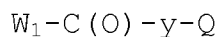
15

-(a7'')  $-HN-CH(R^{1a}-H)-C(O)-(T-Y-Q)$

-(b7'')  $-HN-CH(R^{2a}-H)-CH_2-C(O)-(T-Y-Q)$

wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6), with compounds of formula (IVa)

20



(IVa)

wherein  $W_1$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

3e-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 3e-i) into nitro derivative by reaction with a nitrate source as above described and

25

3e-iii) optionally deprotecting the compounds obtained in step 3e-i) or 3e-ii) as above described.

The reaction of a compound of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, with a compound of formula (IVa) wherein  $y$ ,  $Q$ ,  $W_1$  are as above defined may be carried out as described in 1-i-1), 1-i-2), 1-i-3) and 1a-i).

30

The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, T is  $-X''$  are obtained as described in 3a).

- 5 The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, T is  $-NR'$  are obtained as described in 3b).

The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, T is  $-O-CH(R')-O-C(O)-$  are obtained as described in  
10 3c).

The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, T is  $-O-CH(R')-O-C(O)O-$  are obtained as described in  
15 3d).

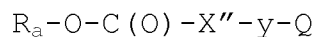
**3f)** The compounds of formula (Ig) wherein  $X_2$  is selected from (a7') or (b7') wherein  $R^{1a}$  is selected from A5) or A6),  $R^{1b}$  is selected from B5) or B6) T'' is  $-C(O)-X''$ , T is  $-X''$ ,  $-NR'$ ,  $-O-CH(R')-O-C(O)-$  or  $-O-CH(R')-O-C(O)O-$  wherein  $X''$  and  $R'$ , Y and  
20 Y' are as above defined, may be obtained

**3f-i)** by reacting a compound of formula (Ih)



(Ih)

wherein  $P^3$  and  $X_7$  are as above defined with compounds of formula  
25 (IVd)



(IVd)

wherein  $R_a$ ,  $X''$  and Q are as above defined, y is the radical Y', wherein Y' is as above defined, and

30 3f-ii) when Q is  $Z_2$ , by converting the compounds obtained in the step 3f-i) into nitro derivative by reaction with a nitrate source as above described and

3f-iii) optionally deprotecting the compounds obtained in step 3e-i) or 3f-ii) as above described.

The reaction of a compound of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, with a compound of formula (IVd) wherein  $y$ ,  $Q$ ,  $R_a$  are as above defined, may be carried out as described in 1-i-2).

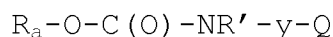
**3g)** The compounds of formula (Ig) wherein  $X_2$  is selected from (a7') or (b7') wherein  $R^{1a}$  is selected from A5) or A6),  $R^{1b}$  is selected from B5) or B6),  $T''$  is  $-C(O)-NR'$ ,  $T$  is  $X''$ ,  $NR'$ ,  $-O-CH(R')-O-C(O)-$  or  $-O-CH(R')-O-C(O)O-$  wherein  $X''$  and  $R'$ ,  $Y$  and  $Y'$  are as above defined, may be obtained

**3g-i)** by reacting a compound of formula (Ih)



(Ih)

wherein  $P^3$  and  $X_7$  are as above defined, with compounds of formula (IVf)



(IVf)

wherein  $R_a$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

3g-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 3g-i) into nitro derivative by reaction with a nitrate source as above described and

3g-iii) optionally deprotecting the compounds obtained in step 3g-i) or 3g-ii) as above described.

The reaction of a compound of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, with a compound of formula (IVf) wherein  $y$ ,  $Q$ ,  $R_a$  and  $R'$  are as above defined may be carried out as described in 1-i-2).

The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, T is  $-X''$  are obtained as described in 3a).

The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, T is  $-NR'$  are obtained as described in 3b).

The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, T is  $-O-CH(R')-O-C(O)-$  are obtained as described in 3c).

10

The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, T is  $-O-CH(R')-O-C(O)O-$  are obtained as described in 3d).

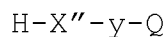
15 **3h)** The compounds of formula (Ig) wherein  $X_2$  is selected from (a7') or (b7') wherein  $R^{1a}$  is selected from A7),  $R^{1b}$  is selected from B7), T'' is  $-X''$ , T is  $-X''$ ,  $-NR'$ ,  $-O-CH(R')-O-C(O)-$  or  $-O-CH(R')-O-C(O)O-$  wherein  $X''$  and  $R'$ , Y and Y' are as above defined, may be obtained

20 **3h-i)** by reacting a compound of formula (Ih)



(Ih)

wherein  $P^3$  is as above defined and  $X_7$  is as above defined wherein  $R^{1a}$  is selected from A7),  $R^{1b}$  is selected from B7), with  
25 compounds of formula (IVe)



(IVe)

wherein  $X''$  and Q are as above defined, y is the radical Y', wherein Y' is as above defined, and

30 **3h-ii)** when Q is  $Z_2$ , by converting the compounds obtained in the step 3h-i) into nitro derivative by reaction with a nitrate source as above described and

3h-iii) optionally deprotecting the compounds obtained in step 3h-i) or 3h-ii) as above described.

The reaction of a compound of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, with a compound of formula (IVe) wherein  $y$ ,  $Q$ ,  $X''$  are as above defined, may be carried out as described in 1-i-1), 1-i-2) and 1a-1).

The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined,  $T$  is  $-X''$  are obtained as described in 3a).

The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined,  $T$  is  $-NR'$  are obtained as described in 3b).

The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined,  $T$  is  $-O-CH(R')-O-C(O)-$  are obtained as described in 3c).

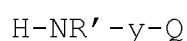
The compounds of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined,  $T$  is  $-O-CH(R')-O-C(O)O-$  are obtained as described in 3d).

**3i)** The compounds of formula (Ig) wherein  $X_2$  is selected from (a7') or (b7') wherein  $R^{1a}$  is selected from A7),  $R^{1b}$  is selected from B7),  $T''$  is  $NR'$ ,  $T$  is  $-X''$ ,  $-NR'$ ,  $-O-CH(R')-O-C(O)-$  or  $-O-CH(R')-O-C(O)O-$  wherein  $X''$  and  $R'$ ,  $Y$  and  $Y'$  are as above defined, may be obtained

**3i-i)** by reacting a compound of formula (Ih)



wherein  $P^3$  and  $X_7$  are as above defined, with compounds of formula (IVg)



(IVg)

wherein R' and Q are as above defined, y is the radical Y',  
 wherein Y' is as above defined, and

5 3i-ii) when Q is Z<sub>2</sub>, by converting the compound obtained in the  
 step 3i-i) into nitro derivative by reaction with a nitrate  
 source as above described and

3i-iii) optionally deprotecting the compounds obtained in step  
 3i-i) or 3i-ii) as above described.

10 The reaction of a compound of formula (Ih) wherein P<sup>3</sup> and X<sub>87</sub> are  
 as above defined, with a compound of formula (IVg) wherein y,  
 Q, R' are as above defined, may be carried out as described in  
 1a-i).

15 **31)** The compounds of formula (Ig) wherein X<sub>2</sub> is selected from  
 (a7') or (b7') wherein R<sup>1a</sup> is selected from A7), R<sup>1b</sup> is selected  
 from B7), T'' is -O-CH(R')-O-C(O)-, T is X'', NR', -O-CH(R')-O-  
 C(O)- or -O-CH(R')-O-C(O)O- wherein X'' and R', Y and Y' are as  
 above defined, may be obtained

20 **31-i)** by reacting a compound of formula (Ih)



(Ih)

wherein P<sup>3</sup> and X<sub>8</sub> are as above defined with compounds of formula  
 (IVm)

25 Hal-CH(R')-O-(O)C-y-Q

(IVm)

wherein R' and Q are as above defined, y is the radical Y',  
 wherein Y' is as above defined, Hal is an halogen atom and

30 31-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the  
 step 31-i) into nitro derivative by reaction with a nitrate  
 source as above described and



3l-iii) optionally deprotecting the compounds obtained in step 3l-i) or 3l-ii) as above described.

The reaction of a compound of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, with a compound of formula (IVm) wherein y, Q, R' are as above defined, may be carried out as described in 11-i).

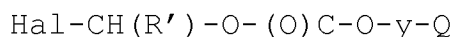
**3m)** The compounds of formula (Ig) wherein  $X_2$  is selected from (a7') or (b7') wherein  $R^{1a}$  is selected from A7),  $R^{1b}$  is selected from B7),  $T''$  is  $-O-CH(R')-O-C(O)O-$ , T is  $X''$ ,  $NR'$ ,  $-O-CH(R')-O-C(O)-$  or  $-O-CH(R')-O-C(O)O-$  wherein  $X''$  and  $R'$ , Y and  $Y'$  are as above defined, may be obtained

**3m-i)** by reacting a compound of formula (Ih)



(Ih)

wherein  $P^3$  and  $X_8$  are as above defined with a compound of formula (IVo)



(IVo)

wherein  $R'$  and Q are as above defined, y is the radical  $Y'$ , wherein  $Y'$  is as above defined, Hal is an halogen atom and 3m-ii) when Q is  $Z_2$ , by converting the compounds obtained in the step 3m-i) into nitro derivative by reaction with a nitrate source as above described and

3m-iii) optionally deprotecting the compounds obtained in step 3l-i) or 3m-ii) as above described.

The reaction of a compound of formula (Ih) wherein  $P^3$  and  $X_7$  are as above defined, with a compound of formula (IVo) wherein y, Q, R' are as above defined, may be carried out as described in 11-i).

**3n)** The compounds of formula (Ig) wherein  $X_2$  is selected from (a3') or (b3'), wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6),  $Y'$  is as above defined,  $T''$  is  $C(O)$  may be obtained

5 **3n-i)** by reacting a compound of formula (IIIIf),



(IIIIf)

wherein  $P^3$  is as above defined,  $X_9$  is a radical having the following meaning

- 10 - (a3'')  $-HN-CH(R^{1a}-H)-COOR^{3a'}$   
 - (b3'')  $-HN-CH(R^{2a}-H)-CH_2COOR^{3a'}$

wherein  $R^{1a}$  is selected from A5 or A6) and  $R^{2a}$  is selected from B5) or B6), wherein  $R^{3a'}$  is as above defined, with a compound of formula (IVa)



wherein  $W_1$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

- 3n-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the  
 20 step 3n-i) into nitro derivative by reaction with a nitrate source as above described and  
 3n-iii) optionally deprotecting the compounds obtained in step 3n-i) or 3n-ii) as above described.

The reaction of a compound of formula (IIIIf) wherein  $P^3$  and  $X_9$  are as above defined, with a compound of formula (IVa) wherein  
 25  $W_1$ ,  $y$ ,  $Q$  are as above defined, may be carried out as described in 1-i-1), 1-i-2), 1a-1).

The compounds of formula (IIIIf) wherein  $P^3$  and  $X_9$  are as above  
 30 defined, are commercially available or obtained as known in literature.

**3o)** The compounds of formula (Ig) wherein  $X_2$  is selected from (a3') or (b3'), wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6),  $Y'$  is as above defined,  $T''$  is  $C(O)-X''$  wherein  $X''$  is as above defined, can be obtained

5 **3o-i)** by reacting a compound of formula (IIIIf)



(IIIIf)

wherein  $P^3$  and  $X_9$  are as above defined with a compound of formula (IVd)



(IVd)

wherein  $R_a$ ,  $X''$ ,  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

3o-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the  
15 step 3o-i) into nitro derivative by reaction with a nitrate source as above described and

3o-iii) optionally deprotecting the compounds obtained in step 3o-i) or 3o-ii) as above described.

The reaction of a compound of formula (IIIIf) wherein  $P^3$  and  $X_9$   
20 are as above defined, with a compound of formula (IVd) wherein  $R_a$ ,  $X''$ ,  $y$ ,  $Q$  are as above defined, may be carried out as described in 1-i-2).

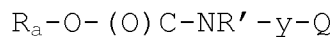
**3p)** The compounds of formula (Ig) wherein  $X_2$  is selected from  
25 (a3') or (b3'), wherein  $R^{1a}$  is selected from A5) or A6),  $R^{2a}$  is selected from B5) or B6),  $Y'$  is as above defined,  $T''$  is  $C(O)-NR'$  wherein  $R'$  is as above defined, can be obtained

**3p-i)** by reacting a compound of formula (IIIIf),



(IIIIf)

wherein  $P^3$  and  $X_9$  are as above defined, with a compound of  
30 formula (IVf)



(IVf)

wherein  $R_a$ ,  $R'$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

5 3p-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 3p-i) into nitro derivative by reaction with a nitrate source as above described and

3p-iii) optionally deprotecting the compounds obtained in step 3p-i) or 3p-ii) as above described.

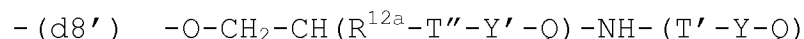
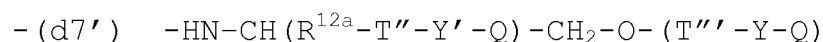
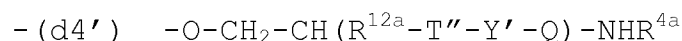
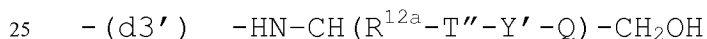
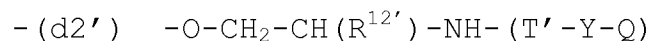
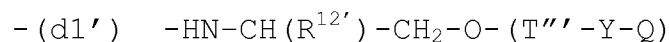
10 The reaction of a compound of formula (IIIIf) wherein  $P^3$  and  $X_9$  are as above defined, with a compound of formula (IVf) wherein  $R_a$ ,  $R'$ ,  $y$ ,  $Q$  are as above defined, may be carried out as described in 1-i-2).

15 **4)** The compounds of general formula (I) as above defined wherein  $a$  is equal to 1, the radical  $R_x$  is selected from (d1), (d2), (d3), (d4), (d7) or (d8),  $Z$  is  $C(O)$ , can be obtained **4-i)** by reacting a compound of formula (II<sub>3</sub>) as above defined wherein  $R_a$  is as above defined, with a compound of formula (Im)



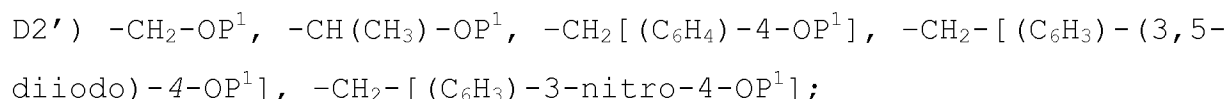
(Im)

wherein  $X_{12}$  is the radical  $R_x$  having the following meaning



wherein  $R^{12'}$  is

30 D1),



D3')  $-\text{CH}_2-\text{NHR}''''$ ,  $-(\text{CH}_2)_2-\text{NHR}''''$ ,  $-(\text{CH}_2)_3-\text{NHR}''''$ ,  $-(\text{CH}_2)_4-\text{NHR}''''$ ,  
 wherein  $\text{R}''''$  is as above defined;

D4')  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''''$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''''$ , wherein  
 $\text{R}'''''$  is as above defined;

5 wherein  $\text{R}^{12a}$  is as above defined;

and

4-ii) when Q is  $\text{Z}_2$ , by converting the compounds obtained in the  
 step 4-i) into nitro derivative by reaction with a nitrate  
 source as above described and

10 4-iii) optionally deprotecting the compounds obtained in step  
 4-i) or 4-ii) as above described.

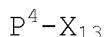
The reaction of a compound of formula (II<sub>3</sub>) wherein R and  $\text{R}_a$  are  
 as above defined, with a compound of formula (Im) wherein  $\text{X}_{12}$  is  
 as above defined, may be carried out as described in 1-i-2).

15

**4a)** The compounds of formula (Im) wherein  $\text{X}_{12}$  is selected from  
 (d1'), (d2'), (d3') or (d4') wherein  $\text{R}^{12'}$  is selected from D1),  
 D2'), D3') or D4') and  $\text{R}^{12a}$  is selected from D5) or D6), Y and  
 $\text{Y}'$  are as above defined,  $\text{T}'$  and  $\text{T}''$  and  $\text{T}'''$  are C(O) can be

20 obtained

4a-i) by reacting a compound of formula (IIIi),



(IIIi)

wherein  $\text{P}^4$  is  $\text{P}^3$  or  $\text{P}^1$  as above defined and  $\text{X}_{13}$  is a radical

25 having the following meaning

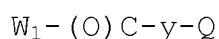
$-(\text{d1}'') \quad -\text{HN}-\text{CH}(\text{R}^{12'})-\text{CH}_2-\text{OH}$

$-(\text{d2}'') \quad -\text{O}-\text{CH}_2-\text{CH}(\text{R}^{12'})-\text{NH}_2$

$-(\text{d3}'') \quad -\text{HN}-\text{CH}(\text{R}^{12a}-\text{H})-\text{CH}_2\text{OP}^1$

$-(\text{d4}'') \quad -\text{O}-\text{CH}_2-\text{CH}(\text{R}^{12a}-\text{H})-\text{NHR}^{4a'}$

30 wherein  $\text{R}^{12'}$  is D1), D2'), D3') or D4'),  $\text{R}^{12a}$  is D5) or D6),  $\text{R}^{4a'}$   
 and  $\text{P}^1$  are as above defined, with a compound of formula (IVa)



(IVa)

wherein Q and W<sub>1</sub> are as above defined, y is the radical Y when X<sub>13</sub> is selected from (d1') or (d2'), y is the radical Y' when X<sub>13</sub> is selected from (d3') or (d4'), wherein Y and Y' are as above defined, and

4a-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 4a-i) into nitro derivative by reaction with a nitrate source as above described and

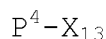
4a-iii) optionally deprotecting the compounds obtained in step 4a-i) or 4a-ii) as above described.

The reaction of a compound of formula (IIIi) wherein X<sub>13</sub> and P<sup>4</sup> are as above defined, with a compound of formula (IVa) wherein W<sub>1</sub>, y and Q are as above defined, may be carried out as described in 1-i-1) and 1-i-2).

The compounds of formula (IIIi) wherein X<sub>13</sub> and P<sup>4</sup> are as above described, are commercially available or known in literature.

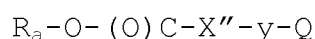
**4b)** The compounds of formula (Im) wherein X<sub>12</sub> is selected from (d1'), (d2'), (d3') or (d4') wherein R<sup>12'</sup> is selected from D1), D2'), D3') or D4') and R<sup>12a</sup> is selected from D5) or D6), Y and Y' are as above defined, T' and T'' and T''' are C(O)-X'', wherein X'' is as above defined, can be obtained

4b-i) by reacting a compound of formula (IIIi),



(IIIi)

wherein P<sup>4</sup> and X<sub>13</sub> are defined above, with a compound of formula (IVd)



(IVd)

wherein Q, R<sub>a</sub> and X'' are as above defined, y is the radical Y when X<sub>13</sub> is selected from (d1') or (d2'), y is the radical Y'

when  $X_{13}$  is selected from (d3') or (d4'), wherein Y and Y' are as above defined, and

4b-ii) when Q is  $Z_2$ , by converting the compounds obtained in the step 4b-i) into nitro derivative by reaction with a nitrate

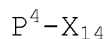
source as above described and

4b-iii) optionally deprotecting the compounds obtained in step 4b-i) or 4b-ii) as above described.

The reaction of a compound of formula (IIIi) wherein  $X_{13}$  and  $P^4$  are as above defined, with a compound of formula (IVd) wherein y, Q,  $R_a$  and  $X''$  are as above defined, may be carried out as described in 1-i-2).

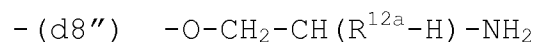
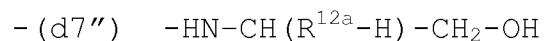
**4c)** The compounds of formula (Im) wherein  $X_{12}$  is selected from (d7') or (d8') wherein  $R^{12a}$  is selected from D5) or D6), Y' and Y are as above defined, T' and T'' and T''' are C(O), can be obtained

**4c-i)** by reacting a compound of formula (IIIl),

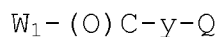


(IIIl)

wherein  $P^4$  is  $P^1$  or  $P^3$ ,  $X_{14}$  is the radical having the following meaning



wherein  $R^{12a}$  is selected from D5) or D6), with a compound of formula (IVa)



(IVa)

wherein  $W_1$  and Q are as above defined, y is the radical Y', wherein Y' is as above defined, and

4c-ii) when Q is  $Z_2$ , by converting the compounds obtained in the step 4c-i) into nitro derivative by reaction with a nitrate source as above described and

4c-iii) optionally deprotecting the compounds obtained in step 4c-i) or 4c-ii) as above described.

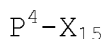
The reaction of a compound of formula (IIIl) wherein  $P^4$  and  $X_{14}$  are as above defined, with a compound of formula (IVa) wherein  $W_1$  is OH, y and Q are as above defined, may be carried out as described in 1-i-1) using a ratio (IIIl)/(IVa) 1:2.

The reaction of a compound of formula (IIIl) wherein  $P^4$  and  $X_{14}$  are as above defined, with a compound of formula (IVa) wherein  $W_1$  is  $OR_a$ , y and Q are as above defined, may be carried out as described in 1-i-2) using a ratio (IIIl)/(IVa) 1:2.

The compounds of formula (IIIl) wherein  $P^4$  and  $X_{14}$  are as above described, are commercially available or known in literature.

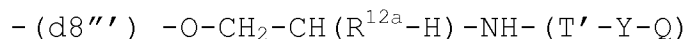
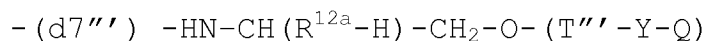
**4d)** The compounds of formula (Im) wherein  $X_{12}$  is selected from (d7') or (d8') wherein  $R^{12a}$  is selected from D5) or D6), Q, Y and Y' are as above defined, T', T''' and T'' are C(O), can be obtained

**4d-i)** by reacting a compound of formula (In)

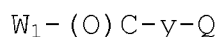


(In)

wherein  $P^4$  is defined above and  $X_{15}$  is the radical having the following meaning



wherein  $R^{12a}$  is selected from D5) or D6), Y, Q, T' and T''' are as above defined, with a compound of formula (IVa)



(IVa)

wherein  $W_1$ , y and Q' are as above defined, y is the radical Y', wherein Y' is as above defined, and



4d-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 4d-i) into nitro derivative by reaction with a nitrate source as above described and

4d-iii) optionally deprotecting the compounds obtained in step 4d-i) or 4d-ii) as above described.

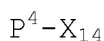
The reaction of a compound of formula (In) wherein P<sup>4</sup> and X<sub>15</sub> are as above defined, with a compound of formula (IVa) wherein W<sub>1</sub> is OH, y and Q are as above defined, may be carried out as described in 1-i-1).

The reaction of a compound of formula (In) wherein P<sup>4</sup> and X<sub>15</sub> are as above defined, with a compound of formula (IVa) wherein W<sub>1</sub> is OR<sub>a</sub>, y and Q are as above defined, may be carried out as described in 1-i-2).

The compounds of formula (In) wherein P<sup>4</sup> and X<sub>15</sub> are as above defined, T' and T''' are -C(O)- can be obtained as described in 4a).

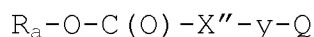
**4e)** The compounds of formula (Im) wherein X<sub>12</sub> is selected from (d7') or (d8') wherein R<sup>12a</sup> is selected from D5) or D6), Y and Y' are the same and are as above defined, T', T'' and T''' are C(O)-X'' wherein X'' is as above defined, can be obtained

**4e-i)** by reacting a compound of formula (IIII),



(IIII)

wherein P<sup>4</sup> and X<sub>14</sub> are as above defined, with a compound of formula (IVd)



(IVd)

wherein R<sub>a</sub>, X'' and Q are as above defined, y is the radical Y', wherein Y' is as above defined, and

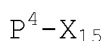
4e-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 4e-i) into nitro derivative by reaction with a nitrate source as above described and

4e-iii) optionally deprotecting the compounds obtained in step 4e-i) or 4e-ii) as above described.

The reaction of a compound of formula (IIIl) wherein P<sup>4</sup> and X<sub>14</sub> are as above defined, with a compound of formula (IVd) wherein R<sub>a</sub>, X'', y and Q are as above defined, may be carried out as described in 1-i-2) using a ratio (IIIl)/(IVd) 1:2.

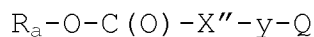
**4f)** The compounds of formula (Im) wherein X<sub>12</sub> is selected from (d7') or (d8') wherein R<sup>12a</sup> is selected from D5) or D6), Q, Y and Y' are as above defined, T'' is C(O)-X'', T' and T''' are C(O) or C(O)-X'', wherein X'' is as above defined, can be obtained

**4f-i)** by reacting a compound of formula (In)



(In)

wherein P<sup>4</sup> and X<sub>15</sub> are as above defined, with a compound of formula (IVd)



(IVd)

wherein R<sub>a</sub>, X'' and Q are as above defined, y is the radical Y', wherein Y' is as above defined, and

4f-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 4f-i) into nitro derivative by reaction with a nitrate source as above described and

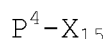
4f-iii) optionally deprotecting the compounds obtained in step 4f-i) or 4f-ii) as above described.

The reaction of a compound of formula (In) wherein P<sup>4</sup> and X<sub>15</sub> are as above defined, with a compound of formula (IVd) wherein R<sub>a</sub>, X'', y and Q are as above defined, may be carried out as described in 1-i-2).

The compounds of formula (In) wherein T' or T''' are C(O), P<sup>4</sup> and X<sub>15</sub> are as above defined are obtained as described in 4a-i), 4a-ii).

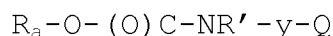
The compounds of formula (In) wherein T' or T''' are C(O)-X'', wherein P<sup>4</sup> and X<sub>15</sub> are as above defined are obtained as described in 4b-i), 4b-ii).

**4g)** The compounds of formula (Im) wherein X<sub>12</sub> is selected from (d7') or (d8') wherein R<sup>12a</sup> is selected from D5) or D6), Q, Y and Y' are as above defined, T'' is C(O)-NR'-, T' and T''' are C(O) or C(O)-X'', wherein X'' is as above defined, can be obtained **4g-i)** by reacting a compound of formula (In)



(In)

wherein P<sup>4</sup> and X<sub>15</sub> are as above defined, with a compound of formula



(IVf)

wherein R<sub>a</sub>, R' and Q are as above defined, y is the radical Y', wherein Y' is as above defined, and

4g-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 4g-i) into nitro derivative by reaction with a nitrate source as above described and

4g-iii) optionally deprotecting the compounds obtained in step 4g-i) or 4g-ii) as above described.

The reaction of a compound of formula (In) P<sup>4</sup> and X<sub>15</sub> are as above defined, with a compound of formula (IVf) wherein R<sub>a</sub>, R', y, Q are as above defined, may be carried out as described in 1-i-2).

The compounds of formula (In) wherein T' or T''' are C(O), wherein P<sup>4</sup> and X<sub>15</sub> are as above defined, are obtained as described in 4a-i), 4a-ii).

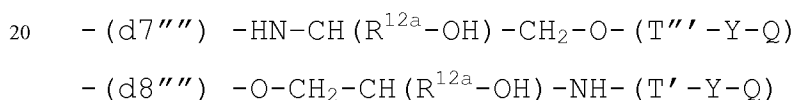
- 5 The compounds of formula (In) wherein T' or T''' are C(O)-X'', wherein P<sup>4</sup> and X<sub>15</sub> are as above defined, are obtained as described in 4b-i), 4b-ii).

**4h)** The compounds of formula (Im) wherein X<sub>12</sub> is selected from (d7') or (d8') wherein R<sup>12a</sup> is selected from D7), Q, Y and Y' are as above defined, T'' is X'', wherein X'' is as above defined, T' and T''' are C(O) or C(O)-X'', wherein X'' is as above defined, can be obtained

**4h-i)** by reacting a compound of formula (Ir),



wherein P<sup>4</sup> is defined above and X<sub>16</sub> is the radical having the following meaning



wherein R<sup>12a</sup> is selected from D7), with a compound of formula (IVe)



wherein Y', X'' and Q are as above defined, y is the radical Y', wherein Y' is as above defined, and

4h-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 4h-i) into nitro derivative by reaction with a nitrate

30 source as above described and

4h-iii) optionally deprotecting the compounds obtained in step 4h-i) or 4h-ii) as above described.

The reaction of a compound of formula (Ir) wherein  $P^4$  and  $X_{16}$  are as above defined with a compound of formula (IVe) wherein  $y$ ,  $X''$  and  $Q$  are as above defined, may be carried out as described in 1-i-1).

5

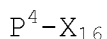
The compounds of formula (Ir) wherein  $T'$  or  $T'''$  are  $C(O)$ ,  $P^4$  and  $X_{16}$  are as above defined are obtained as described in 4a-i), 4a-ii).

10 The compounds of formula (Ir) wherein  $T'$  or  $T'''$  are  $C(O)-X''$ ,  $P^4$  and  $X_{16}$  are as above defined, are obtained as described in 4b-i), 4b-ii).

**4i)** The compounds of formula (Im) wherein  $X_{12}$  is selected from  
 15 (d7') or (d8') wherein  $R^{12a}$  is selected from D7),  $Q$ ,  $Y$  and  $Y'$  are as above defined,  $T''$  is  $-NR'$  wherein  $R'$  is as above defined,  $T'$  and  $T'''$  are  $C(O)$  or  $C(O)-X''$ , wherein  $X''$  is as above defined, can be obtained

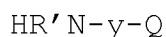
**4i-i)** by reacting a compound of formula (Ir),

20



(Ir)

wherein  $P^4$  and  $X_{16}$  are as above defined and  $R^{12a}$  is selected from D7), with a compound of formula



25

(IVg)

wherein  $R'$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

4i-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 4i-i) into nitro derivative by reaction with a nitrate

30 source such as above described and

4i-iii) optionally deprotecting the compounds obtained in step 4i-i) or 4i-ii) as above described.

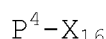
The reaction of a compound of formula (Ir)  $P^4$  and  $X_{16}$  are as above defined, with a compound of formula (IVg) wherein  $R'$ ,  $y$ ,  $Q$  are as above defined, may be carried out as described in 1-i-1).

5

**41)** The compounds of formula (Im) wherein  $X_{12}$  is selected from (d7') or (d8') wherein  $R^{12a}$  is selected from D7),  $Q$ ,  $Y$  and  $Y'$  are as above defined,  $T''$  is  $-O-CH(R')-O-C(O)-$ , wherein  $R'$  is as above defined,  $T'$  and  $T'''$  are  $C(O)$  or  $C(O)-X''$ , wherein  $X''$  is as above defined, can be obtained

10

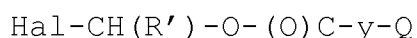
**41-i)** by reacting a compound of formula (Ir),



(Ir)

wherein  $P^4$  and  $X_{16}$  are as above defined and  $R^{12a}$  is selected from D7), with a compound of formula (IVm)

15



(IVm)

wherein  $R'$  and  $Q$  are as above defined,  $Hal$  is an halogen atom,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

20

41-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 41-i) into nitro derivative by reaction with a nitrate source such as above described and

41-iii) optionally deprotecting the compounds obtained in step 41-i) or 41-ii) as above described.

25

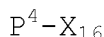
The reaction of a compound of formula (Ir) wherein  $P^4$  and  $X_{16}$  are as above defined, with a compound of formula (IVm) wherein  $y$ ,  $Q$ ,  $R'$  are as above defined, may be carried out as described in 11-i).

30

**4m)** The compounds of formula (Im) wherein  $X_{12}$  is selected from (d7') or (d8') wherein  $R^{12a}$  is selected from D7),  $Q$ ,  $Y$  and  $Y'$  are as above defined,  $T''$  is  $-O-CH(R')-O-C(O)-O-$ , wherein  $R'$  is as

above defined, T' and T''' are C(O) or C(O)-X'', wherein X'' is as above defined, can be obtained

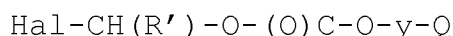
**4m-i)** by reacting a compound of formula (Ir),



5

(Ir)

wherein P<sup>4</sup> and X<sub>16</sub> are as above defined and R<sup>12a</sup> is selected from D7), with a compound of formula (IVo)



(IVo)

10 wherein R and Q' are as above defined, Hal is an halogen atom, y is the radical Y', wherein Y' is as above defined, and 4m-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 4m-i) into nitro derivative by reaction with a nitrate source as above described and

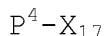
15 4m-iii) optionally deprotecting the compounds obtained in step 4m-i) or 4m-ii) as above described.

The reaction of a compound of formula (Ir) wherein P<sup>4</sup> and X<sub>16</sub> are as above defined, with a compound of formula (IVo) wherein y, R', Q, Hal are as above defined, may be carried out as

20 described in 11-i).

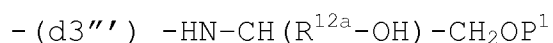
**4n)** The compounds of formula (Im) wherein X<sub>12</sub> is selected from (d3') or (d4') wherein R<sup>12a</sup> is selected from D7), Y' is as above defined, T'' is X'', wherein X'' is defined above, can be obtained

25 **4n-i)** by reacting a compound of formula (IIIm),



(IIIm)

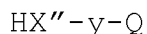
wherein P<sup>4</sup> is defined above and X<sub>17</sub> is the radical



30  $-(\text{d4}')-\text{O}-\text{CH}_2-\text{CH}(\text{R}^{12a}-\text{OH})-\text{NHR}^{4a'}$

wherein R<sup>12a</sup> is selected from D7), wherein P<sup>1</sup> and R<sup>4a'</sup> are as above defined, with a compound of formula (IVe)

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(IVe)

wherein  $X''$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ ,  
 wherein  $Y'$  is as above defined, and

5 4n-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the  
 step 4n-i) into nitro derivative by reaction with a nitrate  
 source as above described and

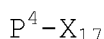
4n-iii) optionally deprotecting the compounds obtained in step  
 4n-i) or 4n-ii) as above described.

10 The reaction of a compound of formula (IIIIm) wherein  $P^4$  and  $X_{17}$   
 are as above defined with a compound of formula (IVe) wherein  
 $y$ ,  $X''$  and  $Q$  are as above defined, may be carried out as  
 described in 1-i-1).

15 The compounds of formula (IIIIm), wherein  $P^4$  and  $X_{17}$  are as above  
 defined, are commercially available or obtained as known in  
 literature.

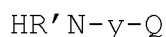
**4o)** The compounds of formula (Im) wherein  $X_{12}$  is selected from  
 20 (d3') or (d4') wherein  $R^{12a}$  is selected from D7),  $Y'$  is as above  
 defined,  $T''$  is  $-NR'$  wherein  $R'$  is as above defined, can be  
 obtained

**4o-i)** by reacting a compound of formula (IIIIm),



25 (IIIIm)

wherein  $P^4$  and  $X_{17}$  are as defined above, wherein  $R^{12a}$  is selected  
 from D7), with a compound of formula



(IVg)

30 wherein  $R'$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ ,  
 wherein  $Y'$  is as above defined, and



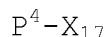
4o-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 4o-i) into nitro derivative by reaction with a nitrate source such as above described and

4o-iii) optionally deprotecting the compounds obtained in step 4o-i) or 4o-ii) as above described.

The reaction of a compound of formula (III<sub>m</sub>) wherein P<sup>4</sup> and X<sub>17</sub> are as above defined, with a compound of formula (IV<sub>g</sub>) wherein R', y, Q are as above defined, may be carried out as described in 1a-i).

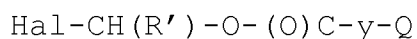
**4p)** The compounds of formula (I<sub>m</sub>) wherein X<sub>12</sub> is selected from (d3') or (d4') wherein R<sup>12a</sup> is selected from D7), Y' is as above defined, T'' is -O-CH(R')-O-C(O)- wherein R' is as above defined, can be obtained

**4p-i)** by reacting a compound of formula (III<sub>m</sub>),



(III<sub>m</sub>)

wherein P<sup>4</sup> and X<sub>17</sub> are as defined above, wherein R<sup>12a</sup> is selected from D7), with a compound of formula (IV<sub>m</sub>)



(IV<sub>m</sub>)

wherein R' and Q are as above defined, Hal is a halogen atom, y is the radical Y', wherein Y' is as above defined, and

4p-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 4p-i) into nitro derivative by reaction with a nitrate source such as above described and

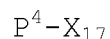
4p-iii) optionally deprotecting the compounds obtained in step 4p-i) or 4p-ii) as above described.

The reaction of a compound of formula (III<sub>m</sub>) wherein P<sup>4</sup> and X<sub>17</sub> are as above defined, with a compound of formula (IV<sub>m</sub>) wherein

R', y, Q are as above defined, may be carried out as described in 11-i).

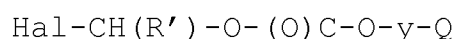
**4q)** The compounds of formula (Im) wherein X<sub>12</sub> is selected from (d3') or (d4') wherein R<sup>12a</sup> is selected from D7), Y' is as above defined, T'' is -O-CH(R')-O-C(O)-O- wherein R' is as above defined, can be obtained

**4q-i)** by reacting a compound of formula (IIIIm),



(IIIIm)

wherein P<sup>4</sup> and X<sub>17</sub> are as defined above, wherein R<sup>12a</sup> is selected from D7), with a compound of formula (IVo)



(IVo)

wherein R' and Q are as above defined, Hal is an halogen atom, y is the radical Y', wherein Y' is as above defined, and 4q-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 4q-i) into nitro derivative by reaction with a nitrate source as above described and

4q-iii) optionally deprotecting the compounds obtained in step 4q-i) or 4q-ii) as above described.

The reaction of a compound of formula (IIIIm) wherein P<sup>4</sup> and X<sub>17</sub> are as above defined, with a compound of formula (IVo) wherein y, R', Q, Hal are as above defined, may be carried out as described in 11-i).

**5)** The compounds of general formula (I) as above defined wherein a is equal to 0, R<sub>x</sub> is a radical selected from (d5), (d6), (d9) or (d10), wherein R<sup>12b</sup> is selected from D10) can be obtained

**5-i)** by reacting a compound of formula (II<sub>1</sub>) as above defined with a compound of formula (Is)

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W-X<sub>18</sub>

(Is)

wherein W is as above defined, X<sub>18</sub> is the radical having the following meanings

- 5 - (d5') -R<sup>12b</sup>-CH(NHR<sup>4a</sup>)-CH<sub>2</sub>-O-(T'''-Y-Q)  
 - (d6') -R<sup>12b</sup>-CH(CH<sub>2</sub>OH)-NH-(T'-Y-Q)  
 - (d9') -R<sup>12b</sup>-CH(NH-T'''-Y'-Q)-CH<sub>2</sub>-O-(T'-Y-Q)  
 - (d10') -R<sup>12b</sup>-CH(CH<sub>2</sub>-O-T'''-Y'-Q)-NH-(T'-Y-Q)

wherein R<sup>12b</sup> is selected from D10), T', T''', Y, Y' and Q are as  
 10 above defined and

5-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 5-i) into nitro derivative by reaction with a nitrate source as above described and

5-iii) optionally deprotecting the compounds obtained in step  
 15 5-i) or 5-ii) as above described.

The reaction of a compound of formula (II<sub>3</sub>) as above defined, with a compound of formula (Is) wherein W and X<sub>18</sub> are as above defined may be carried out as described in 1).

20 **5a)** The compounds of formula (Is) wherein X<sub>18</sub> is a radical of formula (d5') or (d6'), wherein R<sup>12b</sup> is selected from D10), T' and T''' are C(O) can be obtained

**5a-i)** by reacting a compound of formula (III<sub>n</sub>),

P<sup>2</sup>-X<sub>19</sub>

25 (III<sub>n</sub>)

wherein P<sup>2</sup> is as above defined, X<sub>19</sub> is the radical having the following meanings

- (d5'') -R<sup>12b</sup>-CH(NHP<sup>3</sup>)-CH<sub>2</sub>-OH  
 - (d6'') -R<sup>12b</sup>-CH(CH<sub>2</sub>OP<sup>1</sup>)-NH<sub>2</sub>

30 wherein P<sup>1</sup> and P<sup>3</sup> are as above defined and R<sup>12b</sup> is selected from D10), with a compound of formula (IVa)

W<sub>1</sub>-C(O)-Y-Q

(IVa)

wherein  $W_1$ ,  $y$ ,  $Q$  are as above defined,  $y$  is the radical  $Y$ ,  
 wherein  $Y$  is as above defined, and

5 5a-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the  
 step 5a-i) into nitro derivative by reaction with a nitrate  
 source as above described and

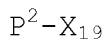
5a-iii) optionally deprotecting the compounds obtained in step  
 5a-i) or 5a-ii) as above described.

The reaction of a compound of formula (IIIIn) wherein  $P^2$  and  $X_{19}$   
 10 are as above defined, with a compound of formula (IVa)  $W_1$ ,  $y$ ,  
 and  $Q$  are as above defined may be carried out as described in  
 1-i-1), 1-i-2), 1-i-3) and 1a-1).

The compounds of formula (IIIIn), wherein  $P^2$  and  $X_{19}$  are as above  
 15 defined, are commercially available or obtained as known in  
 literature.

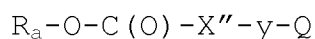
**5b)** The compounds of formula (Is) wherein  $X_{18}$  is a radical of  
 formula (d5') or (d6'), wherein  $R^{12b}$  is selected from D10),  $T'$   
 20 and  $T'''$  are  $C(O)-X''$ , wherein  $X''$  is defined above, can be  
 obtained

**5b-i)** by reacting a compound of formula (IIIIn),



(IIIIn)

25 wherein  $P^2$  and  $X_{19}$  are as above defined, with a compound of  
 formula (IVd)



(IVd)

wherein  $R_a$  and  $Q$ ,  $X''$  are as above defined,  $y$  is the radical  $Y$ ,  
 30 wherein  $Y$  is as above defined, and

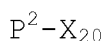
5b-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 5b-i) into nitro derivative by reaction with a nitrate source as above described and

5b-iii) optionally deprotecting the compounds obtained in step 5b-i) or 5b-ii) as above described.

The reaction of a compound of formula (III<sub>n</sub>) wherein P<sup>2</sup> and X<sub>19</sub> are as above defined, with a compound of formula (IV<sub>d</sub>) R<sub>a</sub>, y, Q, X'' are as above defined may be carried out as described in 1-i-2).

**5c)** The compounds of formula (I<sub>s</sub>) wherein X<sub>18</sub> is a radical of formula (d9'), wherein R<sup>12b</sup> is selected from D10), Y and Y' are as defined above, T' is C(O)- and T''' is C(O) or C(O)-X'', wherein X'' is defined above, can be obtained

**5c-i)** by reacting a compound of formula (It),

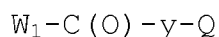


(It)

wherein P<sup>2</sup> is as above defined and X<sub>20</sub> is the radical having the following meanings

-(d9'') -R<sup>12b</sup>-CH(NH<sub>2</sub>)-CH<sub>2</sub>-O-(T'''-Y-Q)

wherein R<sup>12b</sup> is selected from D10), T''', Y and Q are as above defined, with a compound of formula (IV<sub>a</sub>)



(IV<sub>a</sub>)

wherein W<sub>1</sub> and Q are as above defined, y is the radical Y', wherein Y' is as above defined, and

5c-ii) when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 5c-i) into nitro derivative by reaction with a nitrate source as above described and

5c-iii) optionally deprotecting the compounds obtained in step 5c-i) or 5c-ii) as above described.

The reaction of a compound of formula (It) wherein P<sup>2</sup> and X<sub>20</sub>

are as above defined, with a compound of formula (IVa) wherein  $W_1$ ,  $y$ ,  $Q$  are as above defined, may be carried out as described in 1-i-1), 1-i-2), 1-i-3) and 1a-1).

5 **5d)** The compounds of formula (Is) wherein  $X_{18}$  is a radical of formula (d9'), wherein  $R^{12b}$  is selected from D10),  $T'$  is  $C(O)-X''$  and  $T'''$  is  $C(O)-$  or  $C(O)-X''$ , wherein  $X''$  is defined above, can be obtained

**5d-i)** by reacting a compound of formula (It),



wherein  $P^2$  and  $X_{20}$  are as above defined, with a compound of formula (IVd)



wherein  $R_a$  and  $Q$ ,  $X''$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

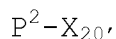
5d-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 5d-i) into nitro derivative by reaction with a nitrate  
20 source as above described and  
5d-iii) optionally deprotecting the compounds obtained in step 5d-i) or 5d-ii) as above described.

The reaction of a compound of formula (It) wherein  $P^2$  and  $X_{20}$  are as above defined, with a compound of formula (IVd)  $R_a$ ,  $y$ ,  $Q$ ,  
25  $X''$  are as above defined may be carried out as described in 1-i-2).

**5e)** The compounds of formula (Is) wherein  $X_{18}$  is the radical of formula (d10'), wherein  $R^{12b}$  is selected from D10),  $Y$  and  $Y'$  are  
30 as defined above,  $T'''$  is  $C(O)-$  and  $T'$  is  $C(O)$  or  $C(O)-X''$ , wherein  $X''$  is defined above, can be obtained

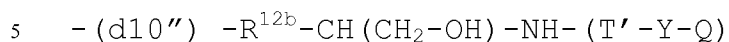
**5e-i)** by reacting a compound of formula (It),

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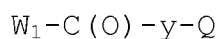


(It')

wherein  $P^2$  is as above defined and  $X_{20}$  is the radical having the following meaning



wherein  $R^{12b}$  is selected from D10),  $T'$ ,  $Y$  and  $Q$  are as above defined, with a compound of formula (IVa)



(IVa)

10 wherein  $W_1$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

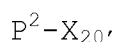
5e-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 5e-i) into nitro derivative by reaction with a nitrate source as above described and

15 5e-iii) optionally deprotecting the compounds obtained in step 5e-i) or 5e-ii) as above described.

The reaction of a compound of formula (It') wherein  $P^2$  and  $X_{20}$  are as above defined, with a compound of formula (IVa) wherein  $W_1$ ,  $y$ ,  $Q$  are as above defined, may be carried out as described  
20 in 1-i-1), 1-i-2), 1-i-3) and 1a-1).

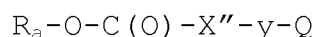
**5f)** The compounds of formula (Is) wherein  $X_{18}$  is the radical of formula (d10'), wherein  $R^{12b}$  is selected from D10),  $T'''$  is  $C(O)-X''$  and  $T'$  is  $C(O)-$  or  $C(O)-X''$ , wherein  $X''$  is defined above, can  
25 be obtained

**5f-i)** by reacting a compound of formula (It'),



(It')

wherein  $P^2$  and  $X_{20}$  are as above defined, with a compound of  
30 formula (IVd)



(IVd)

wherein  $R_a$  and  $Q$ ,  $X''$  are as above defined,  $y$  is the radical  $Y'$ ,  
 wherein  $Y'$  is as above defined, and

5f-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the  
 step 5f-i) into nitro derivative by reaction with a nitrate

source as above described and

5f-iii) optionally deprotecting the compounds obtained in step  
 5f-i) or 5f-ii) as above described.

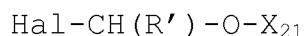
The reaction of a compound of formula (It') wherein  $P^2$  and  $X_{20}$ ,  
 are as above defined, with a compound of formula (IVd)  $R_a$ ,  $y$ ,  $Q$ ,  
 10  $X''$  are as above defined may be carried out as described in 1-i-  
 2).

**6)** The compounds of general formula (I) as above defined

wherein  $a$  is equal to 1,  $R_x$  is a radical selected from (d5),

15 (d6), (d9) or (d10), wherein  $R^{12b}$  is selected from D10),  $Z$  is -  
 $CH(R')-O-$ , wherein  $R'$  is defined above, can be obtained

**6-i)** by reacting a compound of formula (II<sub>1</sub>) as above defined  
 with a compound of formula (Iu)



(Iu)

wherein Hal is an halogen atom,  $R'$  is as above defined and  $X_{21}$   
 is a radical selected from (d5'), (d6'), (d9') or (d10'),  
 wherein  $R^{12b}$  is selected from D10), and

6-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the  
 step 6-i) into nitro derivative by reaction with a nitrate  
 source as above described and

6-iii) optionally deprotecting the compounds obtained in step  
 6-i) or 6-ii) as above described.

The reaction of a compound of formula (Iu) wherein Hal,  $X_{21}$  and  
 30  $R'$  are as above defined, with a compound of formula (II<sub>1</sub>) as  
 above defined may be carried out as described in 11-i).

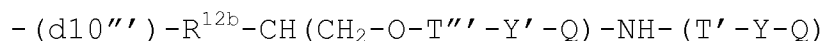
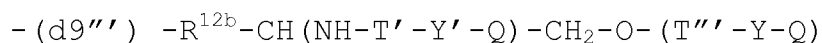


The compounds of formula (Iu) are obtained by reacting a compound  $R'-CHO$ , wherein  $R'$  is as above defined with compounds of formula (IIIo)



(IIIo)

wherein  $W$  is a chlorine atom,  $X_{22}$  is the radical having the following meanings



wherein  $R^{12b}$ ,  $P^3$ ,  $P^1$ ,  $T'$ ,  $T'''$ ,  $Y'$ ,  $Y$  and  $Q$  are as above defined, and  $ZnCl_2$  as known in literature.

The compounds of formula (IIIo), wherein  $W$  and  $X_{22}$  are as above defined, may be carried out as described in 5).

**7)** The compounds of general formula (I) as above defined wherein  $a$  is equal to 1,  $R_x$  is a radical selected from (d5), (d6), (d9) or (d10), wherein  $R^{12b}$  is selected from D8) or D9),  $Z$  is  $-C(O)-$ , can be obtained

**7-i)** by reacting a compound of formula (II<sub>3</sub>) as above defined wherein  $R_a$  is as above defined with a compound of formula (Iv)



(Iv)

wherein  $X_{23}$  is a radical selected from (d5'), (d6'), (d9') or (d10'), wherein  $R^{12b}$  is selected from D8) or D9), and

7-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 7-i) into nitro derivative by reaction with a nitrate source as above described and

7-iii) optionally deprotecting the compounds obtained in step 7-i) or 7-ii) as above described.

The reaction of a compound of formula (Iv) wherein  $X_{23}$  and is as above defined, with a compound of formula (II<sub>3</sub>) as above defined may be carried out as described in 11-i).

5 **8)** The compounds of general formula (I) as above defined wherein a is equal to 0,  $R_x$  is a radical selected from (a5), (a6), (a9) or (a10), (b5), (b6), (b9) or (b10) wherein  $R^{1b}$  is selected from A10) and  $R^{2b}$  is selected from B10), can be obtained

10 **8-i)** by reacting a compound of formula (II<sub>1</sub>) as above defined with a compound of formula (Iz)



(Iz)

wherein W is as above defined,  $X_{24}$  is the radical  $R_x$  having the  
15 following meanings

- (a5')  $-R^{1b}-CH(NHR^{4a})-C(O)-(T-Y-Q)$
- (a6')  $-R^{1b}-CH(COOR^{3a})NH-(T'-Y-Q)$
- (a9')  $-R^{1b}-CH(NH-T'-Y'-Q)-C(O)-(T-Y-Q)$
- (a10')  $-R^{1b}-CH(C(O)-T'-Y'-Q)-NH-(T-Y-Q)$
- 20 - (b5')  $-R^{2b}-CH(NHR^{4a})-CH_2C(O)-(T-Y-Q)$
- (b6')  $-R^{2b}-CH(CH_2COOR^{3a})NH-(T'-Y-Q)$
- (b9')  $-R^{2b}-CH(NH-T'-Y'-Q)-CH_2C(O)-(T-Y-Q)$
- (b10')  $-R^{2b}-CH(CH_2C(O)-T'-Y'-Q)-NH-(T-Y-Q)$

wherein  $R^{1b}$  is selected from A10),  $R^{2b}$  is selected from B10), T,  
25 T', Y and Q are as above defined and

8-ii) when Q is  $Z_2$ , by converting the compounds obtained in the step 8-i) into nitro derivative by reaction with a nitrate source as above described and

8-iii) optionally deprotecting the compounds obtained in step  
30 8-i) or 8-ii) as above described.

The reaction of a compound of formula (II<sub>1</sub>) as above defined

wherein R is as above defined, with a compound of formula (Iv) wherein W and X<sub>24</sub> are as above defined may be carried out as described in 1).

- 5 **8a)** The compounds of formula (Iz) wherein X<sub>24</sub> is a radical of formula (a5'), (a6'), (b5') or (b6'), wherein R<sup>1b</sup> is selected from A10) and R<sup>2b</sup> is selected from B10), T and T' are C(O) can be obtained

**8a-i)** by reacting a compound of formula (IIIq),

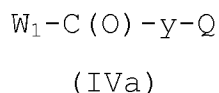


wherein P<sup>2</sup> is as above defined, X<sub>25</sub> is the radical having the following meanings

- 15 
$$\begin{array}{l} \text{-(a5'')} \quad \text{-R}^{1b}\text{-CH(NHP}^3\text{)-C(O)-OH} \\ \text{-(a6'')} \quad \text{-R}^{1b}\text{-CH(COOP}^2\text{)-NH}_2 \\ \text{-(b5'')} \quad \text{-R}^{2b}\text{-CH(NH P}^3\text{)-CH}_2\text{C(O)-OH} \\ \text{-(b6'')} \quad \text{-R}^{2b}\text{-CH(CH}_2\text{COO P}^2\text{)NH}_2 \end{array}$$

wherein P<sup>2</sup> and P<sup>3</sup> are as above defined and R<sup>1b</sup> is selected from A10), R<sup>2b</sup> is selected from B10), with a compound of formula

20 (IVa)



wherein W<sub>1</sub> and Q are as above defined, y is the radical Y, wherein Y is as above defined, and

- 25 **8a-ii)** when Q is Z<sub>2</sub>, by converting the compounds obtained in the step 8a-i) into nitro derivative by reaction with a nitrate source as above described and  
**8a-iii)** optionally deprotecting the compounds obtained in step 8a-i) or 8a-ii) as above described.

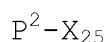
- 30 The reaction of a compound of formula (IIIq) wherein P<sup>2</sup> and X<sub>25</sub> are as above defined, with a compound of formula (IVa) W<sub>1</sub>, Y,

and Q are as above defined may be carried out as described in 1-i-1), 1-i-2), 1-i-3) and 1a-1).

The compounds of formula (IIIq), wherein  $P^2$  and  $X_{25}$  are as above  
5 defined, are commercially available or obtained as known in literature.

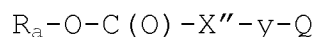
**8b)** The compounds of formula (Iz) wherein  $X_{24}$  is the radical of formula (a5'), (a6'), (b5') or (b6'), wherein  $R^{1b}$  is selected  
10 from A10) and  $R^{2b}$  is selected from B10), T and T' are C(O)-X'', wherein X'' is defined above, can be obtained

**8b-i)** by reacting a compound of formula (IIIq),



(IIIq)

15 wherein  $P^2$  and  $X_{25}$  are as above defined, with a compound of formula (IVd)



(IVd)

wherein  $R_a$ , Q and X'' are as above defined, y is the radical Y,

20 wherein Y is as above defined, and

8b-ii) when Q is  $Z_2$ , by converting the compounds obtained in the step 8b-i) into nitro derivative by reaction with a nitrate source as above described and

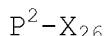
8b-iii) optionally deprotecting the compounds obtained in step  
25 8b-i) or 8b-ii) as above described.

The reaction of a compound of formula (IIIq) wherein  $P^2$  and  $X_{25}$  are as above defined, with a compound of formula (IVd)  $R_a$ , y, Q, X'' are as above defined may be carried out as described in 1-i-2).

**8c)** The compounds of formula (Iz) wherein  $X_{24}$  is the radical of formula (a9') or (b9') wherein  $R^{1b}$  is selected from A10), and  $R^{2b}$

is selected from B10) Y and Y' are as defined above, T is C(O)- or C(O)-X'', wherein X'' is defined above and T' is C(O) can be obtained

**8c-i)** by reacting a compound of formula (Iy),



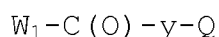
(Iy)

wherein  $P^2$  is as above defined and  $X_{26}$  is the radical having the following meanings

-(a9'')  $-R^{1b}-CH(NH_2)-C(O)-(T-Y-Q)$

-(b9'')  $-R^{2b}-CH(NH_2)-CH_2C(O)-(T-Y-Q)$

wherein  $R^{1b}$  is selected from A10) and  $R^{2b}$  is selected from B10), with a compound of formula (IVa)



(IVa)

wherein  $W_1$  and Q are as above defined, y is the radical Y', wherein Y' is as above defined, and

8c-ii) when Q is  $Z_2$ , by converting the compounds obtained in the step 8c-i) into nitro derivative by reaction with a nitrate source as above described and

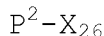
8c-iii) optionally deprotecting the compounds obtained in step 8c-i) or 8c-ii) as above described.

The reaction of a compound of formula (Iy) wherein  $P^2$  and  $X_{26}$  are as above defined, with a compound of formula (IVa) wherein  $W_1$ , y, Q are as above defined, may be carried out as described in 1-i-1), 1-i-2), 1-i-3) and 1a-1).

**8d)** The compounds of formula (Iz) wherein  $X_{24}$  is the radical of formula (a9') or (b9') wherein  $R^{1b}$  is selected from A10),  $R^{2b}$  is selected from B10), Y and Y' are as defined above, T is C(O)- or C(O)-X'', wherein X'' is defined above and T' is C(O)-X'' can be obtained

**8d-i)** by reacting a compound of formula (Iy),

157



(Iy)

wherein  $P^2$  and  $X_{26}$  are as above defined, with a compound of formula (IVd)



wherein  $R_a$  and  $X''$  are as above defined,  $y$  is the radical  $Y'$ , wherein  $Y'$  is as above defined, and

8d-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 8d-i) into nitro derivative by reaction with a nitrate source as above described and

8d-iii) optionally deprotecting the compounds obtained in step 8d-i) or 8d-ii) as above described.

The reaction of a compound of formula (Iy) wherein  $P^2$  and  $X_{20}$  are as above defined, with a compound of formula (IVd)  $R_a$ ,  $y$ ,  $Q$ ,  $X''$  are as above defined may be carried out as described in 1-i-2).

**8e)** The compounds of formula (Iz) wherein  $X_{24}$  is the radical of formula (a10') or (b10') wherein  $R^{1b}$  is selected from A10), and  $R^{2b}$  is selected from B10)  $Y$  and  $Y'$  are as defined above,  $T$  is  $C(O)-$  or  $C(O)-X''$ , wherein  $X''$  is defined above and  $T'$  is  $C(O)$  can be obtained

**8e-i)** by reacting a compound of formula (Iy'),

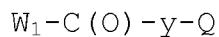


wherein  $P^2$  is as above defined and  $X_{26}$  is the radical having the following meanings

-(a10'')  $-R^{1b}-CH(C(O)-OH)-NH-(T-Y-Q)$

-(b10'')  $-R^{2b}-CH(CH_2C(O)-OH)-NH-(T-Y-Q)$

wherein  $R^{1b}$  is selected from selected from A10) and  $R^{2b}$  is B10), with a compound of formula (IVa)



(IVa)

wherein  $W_1$  and  $Q$  are as above defined,  $y$  is the radical  $Y'$ ,  
 wherein  $Y'$  is as above defined, and

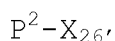
5 8e-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the  
 step 8e-i) into nitro derivative by reaction with a nitrate  
 source as above described and

8e-iii) optionally deprotecting the compounds obtained in step  
 8e-i) or 8e-ii) as above described.

10 The reaction of a compound of formula  $(Iy')$  wherein  $P^2$  and  
 $X_{26}'$  are as above defined, with a compound of formula (IVa)  
 wherein  $W_1$ ,  $y$ ,  $Q$  are as above defined, may be carried out as  
 described in 1-i-1), 1-i-2), 1-i-3) and 1a-1).

15 **8f)** The compounds of formula  $(Iz)$  wherein  $X_{24}$  is the radical of  
 formula  $(a10')$  or  $(b10')$  wherein  $R^{1b}$  is selected from  $A10)$ , and  
 $R^{2b}$  is selected from  $B10)$ ,  $Y$  and  $Y'$  are as defined above,  $T$  is  
 $C(O)-$  or  $C(O)-X''$ , wherein  $X''$  is defined above and  $T'$  is  $C(O)-X''$   
 can be obtained

20 **8f-i)** by reacting a compound of formula  $(Iy')$ ,



(Iy')

wherein  $P^2$  and  $X_{26}'$  are as above defined, with a compound of  
 formula (IVd)



(IVd)

wherein  $R_a$  and  $X''$  are as above defined,  $y$  is the radical  $Y'$ ,  
 wherein  $Y'$  is as above defined, and

8f-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the  
 step 8f-i) into nitro derivative by reaction with a nitrate  
 30 source as above described and

8f-iii) optionally deprotecting the compounds obtained in step 8f-i) or 8f-ii) as above described.

The reaction of a compound of formula (Iy') wherein  $P^2$  and  $X_{26}$  are as above defined, with a compound of formula (IVd)  $R_a$ ,  $y$ ,  $Q$ ,  $X''$  are as above defined may be carried out as described in 1-i-2).

**9)** The compounds of general formula (I) as above defined wherein  $a$  is equal to 1,  $R_x$  is a radical selected from (a5), (a6), (a9) or (a10), (b5), (b6), (b9) or (b10) wherein  $R^{1b}$  is selected from A8) or A9),  $R^{2b}$  is selected from B8) or B9),  $Z$  is  $-C(O)-$ , can be obtained

**9-i)** by reacting a compound of formula (II<sub>3</sub>) as above defined with a compound of formula (Ix)



wherein  $X_{27}$  is the radical selected from (a5'), (a6'), (a9'), (a10'), (b5'), (b6'), (b9') or (b10'), wherein  $R^{1b}$  is selected from A8) or A9),  $R^{2b}$  is selected from B8) or B9), and

9-ii) when  $Q$  is  $Z_2$ , by converting the compounds obtained in the step 9-i) into nitro derivative by reaction with a nitrate source as above described and

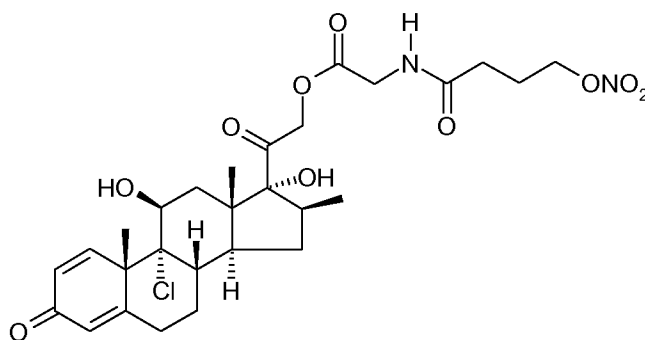
9-iii) optionally deprotecting the compounds obtained in step 9-i) or 9-ii) as above described.

The reaction of a compound of formula (Ix) wherein  $X_{27}$  and is as above defined, with a compound of formula (II<sub>3</sub>) may be carried out as described in 11-i).

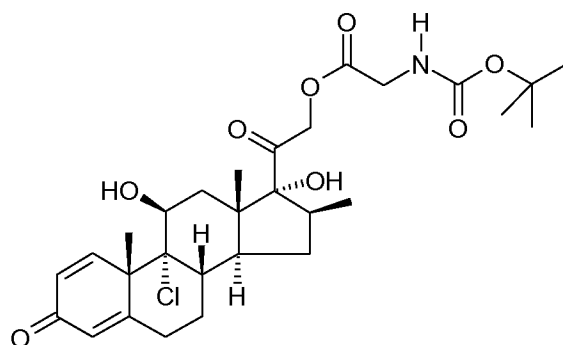
### Example 1

Synthesis of (11 $\beta$ ,16 $\beta$ )-9-Chloro-11,17-dihydroxy-16-methyl-21-[1-oxo-((2-(4-(nitrooxy)butyloxy-carbonylamino)acetyl)]-pregna-1,4-diene-3,20-dione.



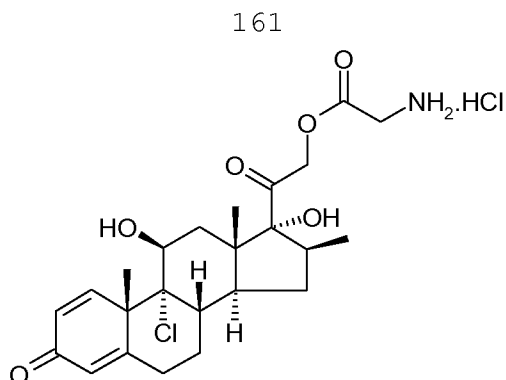


(11 $\beta$ ,16 $\beta$ )-9-Chloro-11,17-dihydroxy-16-methyl-21-[1-oxo-2-((tert-  
 5 butylcarbonylamino)acetyl)]-pregna-1,4-diene-3,20-dione



To a solution of beclomethasone (0.6 g, 1.46 mmol) in acetone  
 10 (35 ml), N-Boc-glycine (0.334 g, 1.90 mmol) and DMAP (cat.  
 amount) were added. The reaction was cooled at 0°C and EDAC  
 (0.365 g, 1.90 mmol) was added. The reaction was stirred at  
 room temperature for 2 hours. The solvent was evaporated under  
 vacuum. The residue was treated with water (50 ml) and  
 15 methylene chloride (50x3 ml), the organic layers were dried  
 over sodium sulfate and concentrated under reduced pressure.  
 The residue was purified by flash chromatography, eluent n-  
 hexane/ethyl acetate 6/4. The product (0.8 g) was obtained.

20 (11 $\beta$ ,16 $\beta$ )-9-Chloro-11,17-dihydroxy-16-methyl-21-[1-oxo-2-  
 ((carbonylamino)acetyl)]-pregna-1,4-diene-3,20-dione  
 hydrochloride



A solution of compound A (0.8 g, 0.41 mmol) in methylene chloride (70 ml) was stirred at room temperature. HCl gas was  
 5 bubble in the solution for 1 hour. The solvent was evaporated under reduced pressure. The product was used in the next step without any purification.

(11 $\beta$ ,16 $\beta$ )-9-Chloro-11,17-dihydroxy-16-methyl-21-[1-oxo-(2-((4-  
 10 (nitrooxy)butyoxycarbonylamino)acetyl)]-pregna-1,4-diene-3,20-dione

To a solution of B) (0.75 g, 1.46 mmol) in methylene chloride (40 ml), 4-nitrooxybutyric acid pentafluorophenyl ester (0.41 g, 1.46 mmol), DMAP (cat. amount) and triethylamine (0.3 ml,  
 15 2.19 mmol) were added. The reaction was stirred at room temperature for 24 hours. The solution was treated with a 5% solution of H<sub>3</sub>PO<sub>4</sub> (50 ml). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, (Biotage System,  
 20 column FLASH 40+M™ KP-Sil ) eluent : gradient n-hexane/ethyl acetate 1/1 (130 ml), to ethyl acetate 100% during 130 ml, ethyl acetate 100% (130 ml). The product (0.62 g) was obtained as white powder.

<sup>1</sup>H-NMR: (DMSO),  $\delta$ : 8.42 (1H, t); 7.30 (1H, d); 6.22 (1H, dd);  
 25 5.98 (1H, s); 5.46 (1H, d); 5.42 (2H, s); 5.05 (1H, d); 4.84 (1H, d); 4.5 (2H, t); 4.34 (1H, sb); 3.97 (2H, d); 2.71-2.57

(2H, m); 2.5-2.2 (6H, m); 2.0-1.7 (5H, m); 1.65-1.35 (5H, m);  
1.25-0.97 (4H, m); 0.8 (3H, s).

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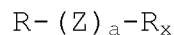
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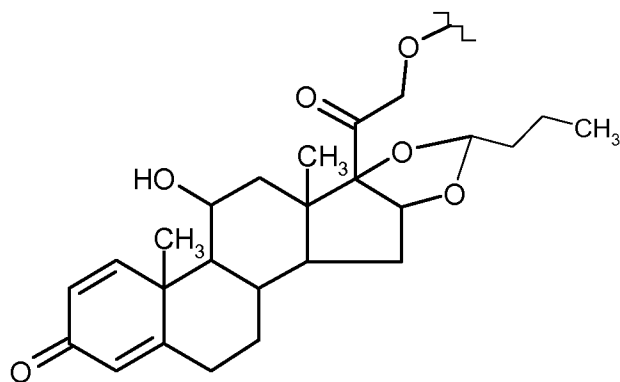
## CLAIMS

1. Nitric oxide releasing compounds of general formula (I)

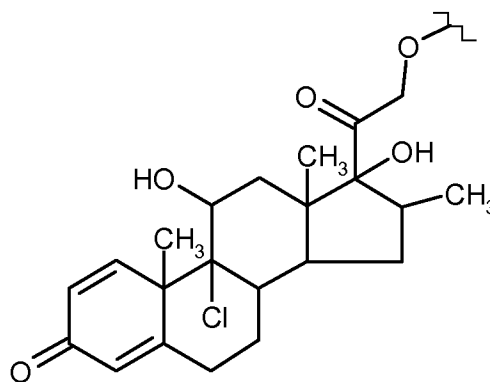


(I)

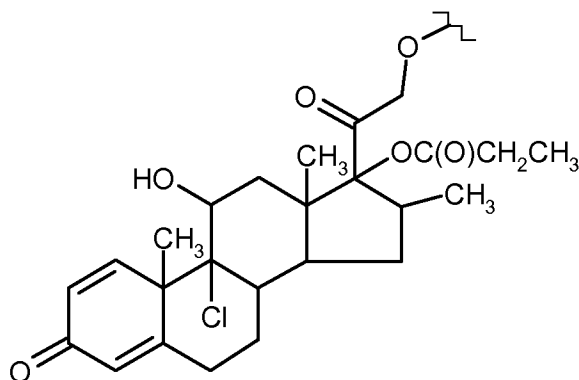
5 and pharmaceutically acceptable salts or stereoisomers thereof for use in the treatment of respiratory diseases, wherein in formula (I) R is a corticosteroid residue selected from:



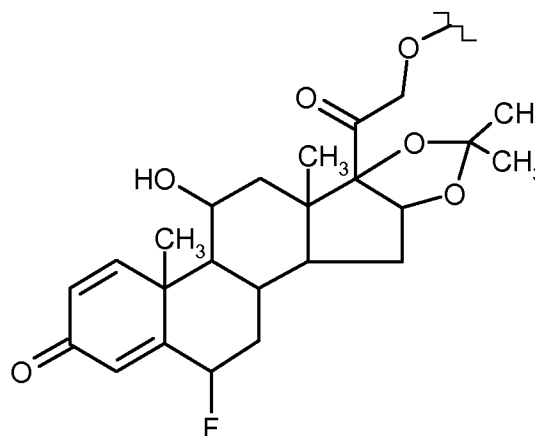
(II)



(III)



(IV)



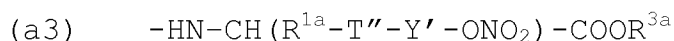
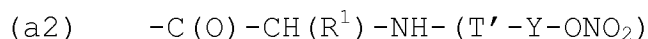
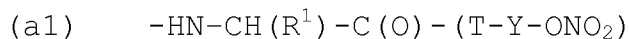
(V)

a is 0 or 1,

Z is a group capable of binding  $R_x$  and is selected from  $-C(O)-$ ,  
or  $-CH(R')-O-$  wherein  $R'$  is selected from H or a straight or  
15 branched  $C_1-C_4$  alkyl, preferably  $R'$  is H or  $-CH_3$ ;

$R_x$  is a radical selected from the following meanings:

A)



- (a4)  $-\text{C}(\text{O})-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NHR}^{4a}$   
 (a5)  $-\text{R}^{1b}-\text{CH}(\text{NHR}^{4a})-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$   
 (a6)  $-\text{R}^{1b}-\text{CH}(\text{COOR}^{3a})\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$   
 (a7)  $-\text{HN}-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$   
 5 (a8)  $-\text{C}(\text{O})-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$   
 (a9)  $-\text{R}^{1b}-\text{CH}(\text{NH}-\text{T}'-\text{Y}'-\text{ONO}_2)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$   
 (a10)  $-\text{R}^{1b}-\text{CH}(\text{C}(\text{O})-\text{T}-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

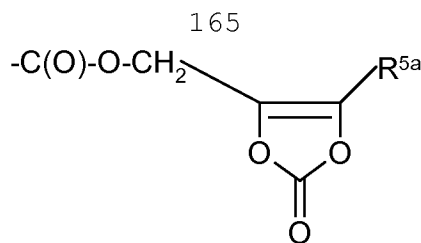
wherein:

$\text{R}^1$  is selected from:

- 10 A1) H,  $-\text{CH}_3$ , isopropyl, isobutyl, sec-butyl, tert-butyl, methylthio- $(\text{CH}_2)_2-$ , phenyl, benzyl,  $\text{C}_6\text{H}_5-\text{CH}_2-\text{CH}_2-$ , 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from  $-\text{F}$ ,  $-\text{Cl}$ , I,  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $-\text{CH}_3$ , CN,  
 15  $\text{C}_6\text{H}_5\text{CO}-$ , 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, 2-pyrrolidyl, 3-triptyophanyl- $\text{CH}_2-$ , 3-benzothienyl- $\text{CH}_2-$ , 4-imidazolyl- $\text{CH}_2-$ , 9-anthranyl- $\text{CH}_2-$ , cyclohexyl, cyclohexyl- $\text{CH}_2-$ , cyclohexyl- $(\text{CH}_2)_2-$ , cyclopentyl- $\text{CH}_2-$ ,  $(\text{C}_6\text{H}_5)_2\text{CH}-$ ,  
 20 4-B(OH) $_2$ -benzyl, 4-quinolyl- $\text{CH}_2-$ , 3-quinolyl- $\text{CH}_2-$ , 2-quinolyl- $\text{CH}_2-$ , 2-quinoxalyl- $\text{CH}_2-$ , 2-furyl- $\text{CH}_2-$ , 1-naphtyl- $\text{CH}_2-$ , 2-naphtyl- $\text{CH}_2-$ , 2-pyridyl- $\text{CH}_2-$ , 3-pyridyl- $\text{CH}_2-$ , 4-pyridyl- $\text{CH}_2-$ , 2-thienyl- $\text{CH}_2-$ , 3-thienyl- $\text{CH}_2-$ ,  $\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{CH}_2-$ ,  $\text{CH}_2=\text{CH}-\text{CH}_2-$ ,  
 25  $\text{CH}\equiv\text{CH}-\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}-\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}-(\text{CH}_2)_2-$ ,  $\text{NH}_2(=\text{NH})\text{NH}-(\text{CH}_2)_3-$ ,  $\text{P}(=\text{O})(\text{OCH}_3)_2$ ;

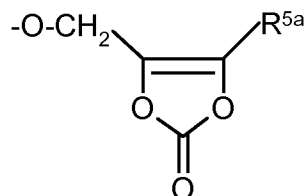
A2)  $-\text{CH}_2-\text{SH}$ ,  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ,  
 $-\text{CH}_2[(\text{C}_6\text{H}_2)-(3,5\text{-diiodo})-(4-\text{OH})]$ ,  
 $-\text{CH}_2[(\text{C}_6\text{H}_3)-(3\text{-nitro})-(4-\text{OH})]$ ,

- 30 A3)  $-\text{CH}_2-\text{NHR}''$ ,  $-(\text{CH}_2)_2-\text{NHR}''$ ,  $-(\text{CH}_2)_3-\text{NHR}''$ ,  $-(\text{CH}_2)_4-\text{NHR}''$ ,  
 wherein  $\text{R}''$  is H,  $-\text{C}(\text{O})\text{CH}_3$  or



wherein  $R^{5a}$  is H or a linear or branched  $C_1$ - $C_{10}$  alkyl chain,

A4)  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''$  wherein  $\text{R}'''$  is  $-\text{OR}^{5a}$  or



5

wherein  $R^{5a}$  is as above defined;

$R^{1a}$  is selected from,

A5)  $-\text{CH}_2-\text{S}-$ ,  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{O}-$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ ,

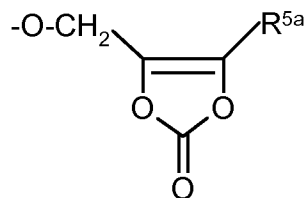
$-\text{CH}_2-[(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)-(4-\text{O})-]$ ,

10  $-\text{CH}_2-[(3\text{-nitro})-(\text{C}_6\text{H}_3)-(4-\text{O})-]$ ,

A6)  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,  $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ ,

A7)  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ ;

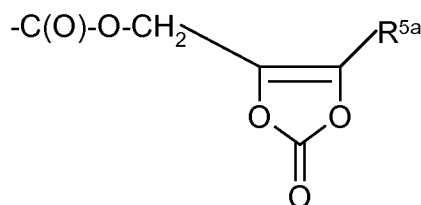
$R^{3a}$  is selected from H,  $-\text{R}^{5a}$  or



15

wherein  $R^{5a}$  is as above defined,

$R^{4a}$  is selected from H or  $-\text{C}(\text{O})\text{CH}_3$  or



wherein  $R^{5a}$  is as above defined,

$R^{1b}$  is selected from

20 A8)  $-\text{S}-\text{CH}_2-$ ,  $-\text{O}-\text{CH}(\text{CH}_3)-$ ,  $-\text{O}-\text{CH}_2-$ ,  $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ,

$[-(4-\text{O})-(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)]-\text{CH}_2-$ ,

$[-(4-\text{O})-(3\text{-nitro})-(\text{C}_6\text{H}_3)]-\text{CH}_2-$ ,

A9)  $-\text{HN}-\text{CH}_2-$ ,  $-\text{HN}-(\text{CH}_2)_2-$ ,  $-\text{HN}-(\text{CH}_2)_3-$ ,  $-\text{HN}-(\text{CH}_2)_4-$ ,

A10)  $-\text{C}(\text{O})-\text{CH}_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_4-$ ,

T is selected from  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$  or  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})\text{O}-$  wherein  $\text{R}'$  is as above defined,

5 T' is  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{X}''-$  wherein  $\text{X}''$  is  $-\text{O}-$  or  $-\text{S}-$ , or T' is  $-\text{C}(\text{O})-\text{NR}'-$  wherein  $\text{R}'$  is as above defined,

T'' is independently selected from  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{X}''-$ ,

$-\text{C}(\text{O})-\text{NR}'-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$ ,

$-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})\text{O}-$ , wherein  $\text{X}''$  and  $\text{R}'$  are as above defined,

10 with the proviso that T'' is  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{X}''-$  or  $-\text{C}(\text{O})-\text{NR}'-$  when T'' is linked to  $-\text{NH}-$ ,  $-\text{O}-$ , or  $-\text{S}-$ , or

T'' is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})\text{O}-$  when T'' is linked to  $-\text{C}(\text{O})-$ ,

Y and Y' are as below defined;

15 or  $\text{R}_x$  is selected from:

B)

(b1)  $-\text{HN}-\text{CH}(\text{R}^2)-\text{CH}_2-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

(b2)  $-\text{C}(\text{O})-\text{CH}_2-\text{CH}(\text{R}^2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

(b3)  $-\text{HN}-\text{CH}(\text{R}^{2a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{CH}_2\text{COOR}^{3a}$

20 (b4)  $-\text{C}(\text{O})-\text{CH}_2-\text{CH}(\text{R}^{2a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NHR}^{4a}$

(b5)  $-\text{R}^{2b}-\text{CH}(\text{NHR}^{4a})-\text{CH}_2-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

(b6)  $-\text{R}^{2b}-\text{CH}(\text{CH}_2\text{COOR}^{3a})\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

(b7)  $-\text{HN}-\text{CH}(\text{R}^{2a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{CH}_2-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

(b8)  $-\text{C}(\text{O})-\text{CH}_2-\text{CH}(\text{R}^{2a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

25 (b9)  $-\text{R}^{2b}-\text{CH}(\text{NH}-\text{T}'-\text{Y}'-\text{ONO}_2)-\text{CH}_2\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

(b10)  $-\text{R}^{2b}-\text{CH}(\text{CH}_2\text{C}(\text{O})-\text{T}-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

wherein

$\text{R}^2$  is selected from

30 B1) H,  $-\text{CH}_3$ ,  $\text{CF}_3$ , isopropyl, isobutyl, sec-butyl, methylthio-  
( $\text{CH}_2$ )<sub>2</sub>-, phenyl, benzyl, 3-triptophanyl- $\text{CH}_2-$ ,  $\text{NH}_2-\text{C}(\text{O})-\text{CH}_2-$ ,

$\text{NH}_2-\text{C}(\text{O})-(\text{CH}_2)_2-$ ,  $\text{NH}_2(=\text{NH})\text{NH}-(\text{CH}_2)_3-$ ,  $\text{tBuO}-\text{CH}(\text{CH}_3)-$ ,

benzyl- $\text{O}-\text{CH}_2-$ ,

4-terbutoxy-benzyl, 4-phenylbenzyl,

B2)  $-\text{CH}_2-\text{SH}$ ,  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ,

-CH<sub>2</sub>-[(C<sub>6</sub>H<sub>2</sub>)-(3,5-diiodo)-(4-OH)],

-CH<sub>2</sub>-[(C<sub>6</sub>H<sub>3</sub>)-(3-nitro)-(4-OH)],

B3) -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'', wherein R'' is as above defined,

5 B4) -CH<sub>2</sub>-C(O)-R''', -(CH<sub>2</sub>)<sub>2</sub>-C(O)-R''', -(CH<sub>2</sub>)<sub>4</sub>-C(O)-R''' wherein R''' is as above defined, preferably R<sup>2</sup> is -CH<sub>2</sub>-C(O)-R''';

R<sup>2a</sup> is selected from:

B5) -CH<sub>2</sub>-S-, -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)-O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-],  
-CH<sub>2</sub>-[(3,5-diiodo)-(C<sub>6</sub>H<sub>2</sub>)-(4-O)-],

10 -CH<sub>2</sub>-[(3-nitro)-(C<sub>6</sub>H<sub>3</sub>)-(4-O)-],

B6) -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-,

B7) -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>4</sub>-C(O)-,

R<sup>2b</sup> is selected from.

B8) -S-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)-, -O-CH<sub>2</sub>-, [-(4-O)-(C<sub>6</sub>H<sub>4</sub>)]-CH<sub>2</sub>-,

15 [-(4-O)-(3,5-diiodo)-(C<sub>6</sub>H<sub>2</sub>)]-CH<sub>2</sub>-, [-(4-O)-(3-nitro)-(C<sub>6</sub>H<sub>3</sub>)]-CH<sub>2</sub>-,

B9) -HN-CH<sub>2</sub>-, -HN-(CH<sub>2</sub>)<sub>2</sub>-, -HN-(CH<sub>2</sub>)<sub>3</sub>-, -HN-(CH<sub>2</sub>)<sub>4</sub>-,

B10) -C(O)-CH<sub>2</sub>-, -C(O)-(CH<sub>2</sub>)<sub>2</sub>-, -C(O)-(CH<sub>2</sub>)<sub>4</sub>-,

R<sup>3a</sup> and R<sup>4a</sup> are as above defined,

T, T' and T'' are as above defined and Y and Y' are as below  
20 defined;

or R<sub>x</sub> is selected from:

C)

(c1) -HN-(CH<sub>2</sub>)<sub>b</sub>-C(O)-(T-Y-ONO<sub>2</sub>) or

(c2) -C(O)-(CH<sub>2</sub>)<sub>b</sub>-NH-(T'-Y-ONO<sub>2</sub>),

25 wherein b is an integer from 3 to 6,

T and T' are as above defined and Y and Y' are as below defined;

or R<sub>x</sub> is selected from:

D)

(d1) -HN-CH(R<sup>12</sup>)-CH<sub>2</sub>-O-(T'''-Y-ONO<sub>2</sub>)

30 (d2) -O-CH<sub>2</sub>-CH(R<sup>12</sup>)-NH-(T'-Y-ONO<sub>2</sub>)

(d3) -HN-CH(R<sup>12a</sup>-T''-Y'-ONO<sub>2</sub>)-CH<sub>2</sub>OH

(d4) -O-CH<sub>2</sub>-CH(R<sup>12a</sup>-T''-Y'-ONO<sub>2</sub>)-NHR<sup>4a</sup>



(d5)  $-R^{12b}-CH(NHR^{4a})-CH_2-O-(T'''-Y-ONO_2)$

(d6)  $-R^{12b}-CH(CH_2OH)-NH-(T'-Y-ONO_2)$

(d7)  $-HN-CH(R^{12a}-T''-Y'-ONO_2)-CH_2-O-(T'''-Y-ONO_2)$

(d8)  $-O-CH_2-CH(R^{12a}-T''-Y'-ONO_2)-NH-(T'-Y-ONO_2)$

5 (d9)  $-R^{12b}-CH(NH-T'-Y'-ONO_2)-CH_2-O-(T'''-Y-ONO_2)$  or

(d10)  $-R^{12b}-CH(CH_2-O-T'''-Y'-ONO_2)-NH-(T'-Y-ONO_2)$

wherein

$T'''$  is independently selected from  $-C(O)-$ ,  $-C(O)X''-$  wherein  $X''$  is  $-O-$  or  $-S-$ , or  $-C(O)-NR'-$  wherein  $R'$  is as above defined,

10  $T'$  and  $T''$  are as above defined,

$Y$  and  $Y'$  are as below defined,

$R^{12}$  is selected from:

D1)  $H$ ,  $-CH_3$ , isopropyl, isobutyl, sec-butyl, methylthio-  
( $CH_2$ )<sub>2</sub>-, benzyl, 3-triptophanyl- $CH_2-$ , 4-imidazolyl- $CH_2-$ ,

15  $NH_2-CO-CH_2-$ ,  $NH_2-CO-(CH_2)_2-$ ,  $NH_2(=NH)NH-(CH_2)_3-$ ;

D2)  $-CH_2-OH$ ,  $-CH(CH_3)-OH$ ,  $-CH_2[(C_6H_4)-(4-OH)]$ ,  
 $-CH_2-[(C_6H_3)-(3,5-diiodo)-(4-OH)]$ ,  
 $-CH_2-[(C_6H_3)-(3-nitro)-(4-OH)]$ ,

D3)  $-CH_2-NHR''$ ,  $-(CH_2)_2-NHR''$ ,  $-(CH_2)_3-NHR''$ ,  $-(CH_2)_4-NHR''$ , wherein  
20  $R''$  is as above defined, preferably  $R^{12}$  is  $-(CH_2)_4-NHR''$ ;

D4)  $-CH_2-C(O)R'''$ ,  $-(CH_2)_2-C(O)R'''$ ,  $-(CH_2)_4-C(O)R'''$  wherein  $R'''$  is as above defined,

$R^{12a}$  is selected from:

D5)  $-CH_2-O-$ ,  $-CH(CH_3)-O-$  or  $-CH_2[(C_6H_4)-(4-O)-]$ ,  
25  $-CH_2-[3,5-diiodo-(C_6H_2)-(4-O)-]$ ,  $-CH_2-[3-nitro-(C_6H_3)-4-O-]$ ,

D6)  $-CH_2-NH-$ ,  $-(CH_2)_2-NH-$ ,  $-(CH_2)_3-NH-$ ,  $-(CH_2)_4-NH-$ ,

D7)  $-CH_2-C(O)-$ ,  $-(CH_2)_2-C(O)-$ ,  $-(CH_2)_4-C(O)-$ ,

$R^{12b}$  is selected from:

D8)  $-O-CH_2-$ ,  $-O-CH(CH_3)-$ ,  $[-(4-O)-(C_6H_4)]-CH_2-$ ,  
30  $[-(4-O)-(3,5-diiodo)-(C_6H_2)]-CH_2-$ ,  $[-(4-O)-(3-nitro)-(C_6H_3)]-CH_2-$ ,

D9)  $-HN-CH_2-$ ,  $-HN-(CH_2)_2-$ ,  $-HN-(CH_2)_3-$ ,  $-HN-(CH_2)_4-$ ,

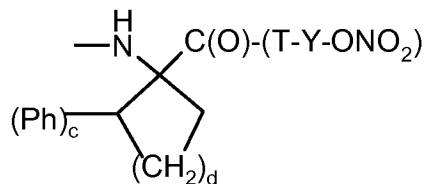
D10)  $-C(O)-CH_2-$ ,  $-C(O)-(CH_2)_2-$ ,  $-C(O)-(CH_2)_4-$ ,

$R^{4a}$  is as above defined;

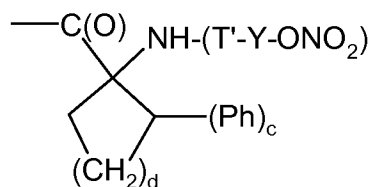
or  $R_x$  is selected from:

E)

(e1)



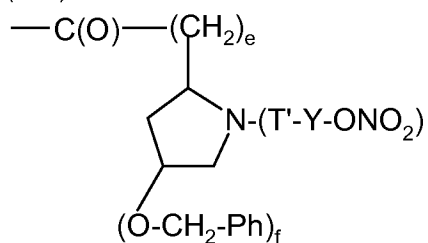
(e2)



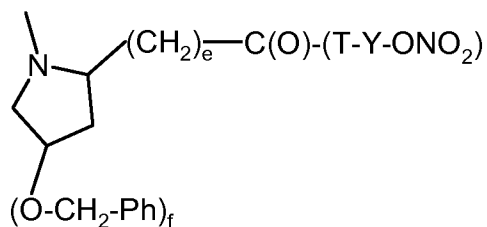
wherein  $c$  is equal to 0 or 1,  $d$  is an integer from 0 to 3 with the proviso that  $c$  is 0 or 1 when  $d$  is 0 and  $c$  is 0 when  $d$  is 1, 2 or 3,  $T$  and  $T'$  are as above defined and  $Y$  is as below defined;

F)

(f1)



(f2)



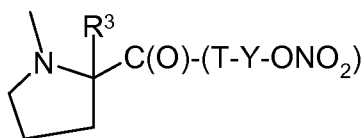
(XI)

wherein  $e$  and  $f$  are equal to 0 or 1, with the proviso that  $f$  is 0 when  $e$  is 0 and  $f$  is 0 or 1 when  $e$  is 1,

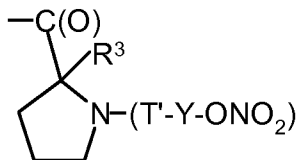
$T$  and  $T'$  are as above defined and  $Y$  is as below reported;

G)

(g1)



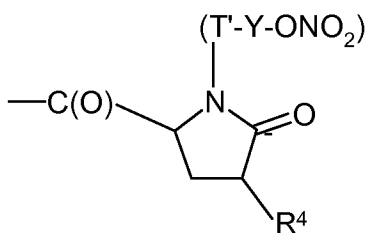
(g2)



wherein  $R^3$  is H,  $CH_3$ , propyl,  $(C_6H_5)_2CH-$ , 1-naphtyl- $CH_2-$ , benzyl,  
 5 allyl, 2-bromobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-  
 fluorobenzyl, 4-bromobenzyl, 4-methylbenzyl, T and T' are as  
 above defined and Y is as below defined;

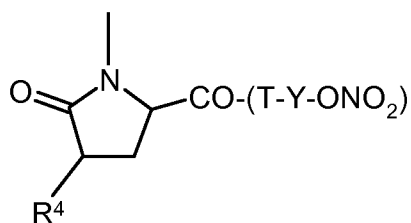
H)

(h1)



10

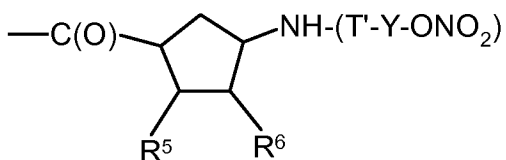
(h2)



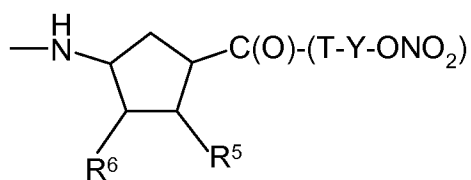
wherein  $R^4$  is H, benzyl, 4-bromobenzyl, 2-bromobenzyl, T and T'  
 are as above defined and Y is as below defined;

15 I)

(i1)



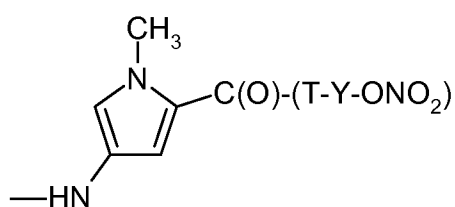
(i2)



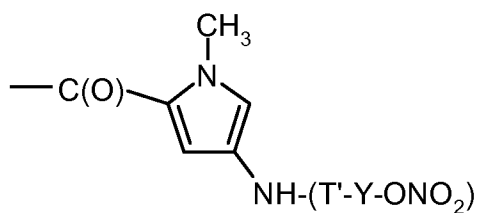
wherein  $R^5$  is H,  $R^6$  is H, or  $R^5$  and  $R^6$  when taken together are a double bond, T and T' are as above defined and Y is as below reported;

L)

(11)



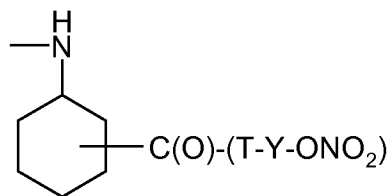
(12)



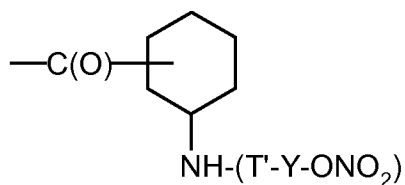
wherein T and T' are as above defined and Y is as below reported;

M)

(m1)



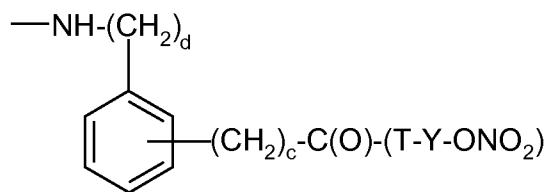
(m2)



wherein T and T' are as above defined and Y is as below reported;

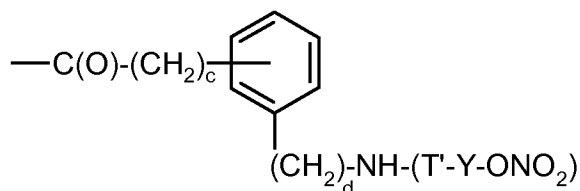
N)

(n1)



5

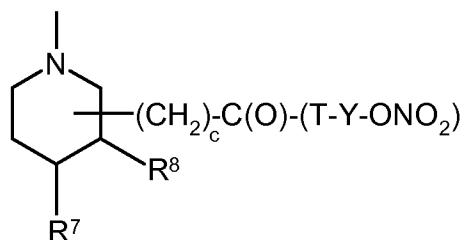
(n2)



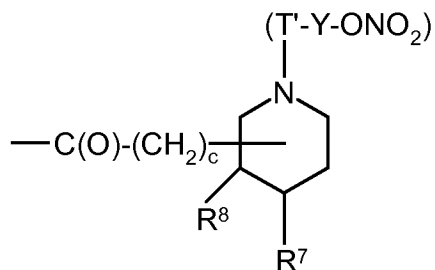
wherein c is as above defined, d is equal to 0 or 1, T and T' are as above defined and Y is as below reported;

10 O)

(o1)



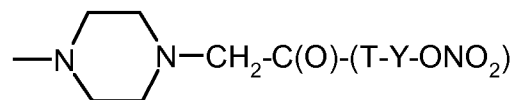
(o2)



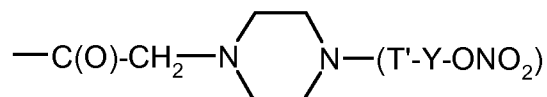
15 wherein R<sup>7</sup> is H, R<sup>8</sup> is H, or R<sup>7</sup> and R<sup>8</sup> when taken together are a double bond, c is as above defined, T and T' are as above defined and Y is as below reported;

P)

(p1)



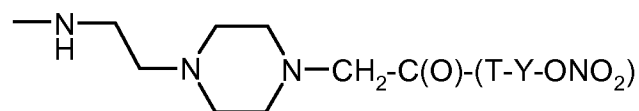
(p2)



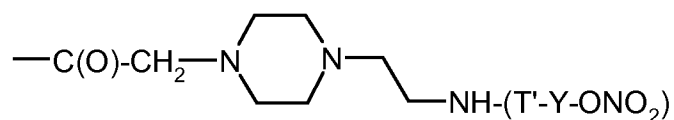
wherein T and T' are as above defined and Y is as below  
reported;

Q)

(q1)



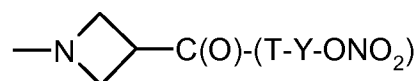
(q2)



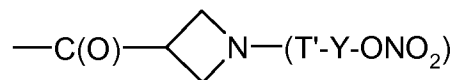
wherein T and T' are as above defined and Y is as below  
reported;

R)

(r1)



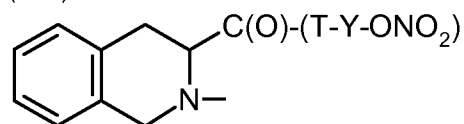
(r2)



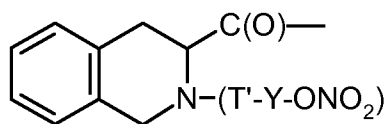
wherein T and T' are as above defined and Y is as below  
reported;

S)

(s1)



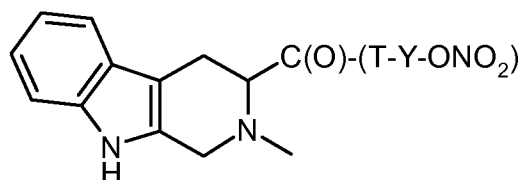
(s2)



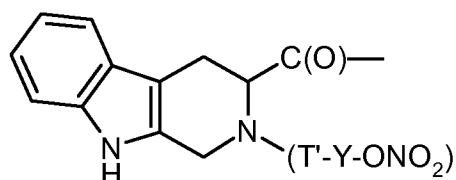
wherein T and T' are as above defined and Y is as below reported;

T)

5 (t1)



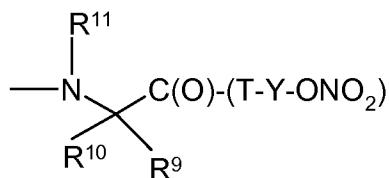
(t2)



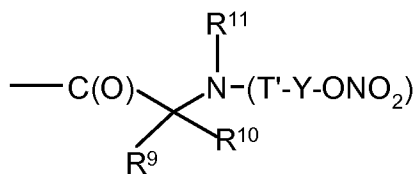
wherein T and T' are as above defined and Y is as below reported;

U)

(u1)



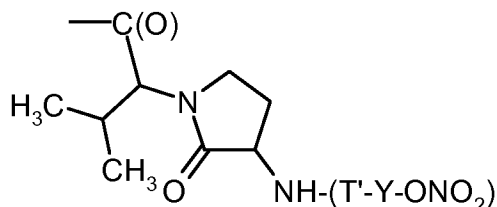
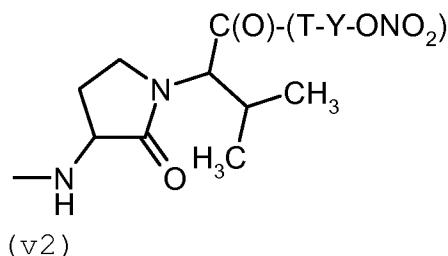
(u2)



wherein R<sup>9</sup> and R<sup>10</sup> are H, CH<sub>3</sub>, R<sup>11</sup> is CH<sub>3</sub> or 4-piperidinyl with the proviso that R<sup>9</sup> and R<sup>10</sup> are H when R<sup>11</sup> is 4-piperidinyl and R<sup>9</sup> and R<sup>10</sup> are CH<sub>3</sub> when R<sup>11</sup> is CH<sub>3</sub>, T and T' are as above defined and Y is as below reported;

V)

(v1)



wherein T and T' are as above defined and Y is as below  
 5 reported;

with the proviso that in the formula (I):

a is 0 or a is 1 and Z is -CH(R')-O- wherein R' is as above  
 defined, when R<sub>x</sub> is:

- (a2), (a4) or (a8);

10 - (a5), (a6), (a9) or (a10) and R<sup>1b</sup> is selected from the group  
 A10);

- (b2), (b4) or (b8);

- (b5), (b6), (b9) or (b10) and R<sup>2b</sup> is selected from the group  
 B10);

15 - (c2);

- (d5), (d6), (d9) or (d10) and R<sup>12b</sup> is selected from the group  
 D10);

- (e2), (f1), (g2), (h1), (i1), (l2), (m2), (n2), (o2), (p2),  
 (q2), (r2), (s2), (t1) or (u2);

20 a is 1 and Z is -C(O)-, when R<sub>x</sub> is:

- (a1), (a3) or (a7);

- (a5), (a6), (a9) or (a10) and R<sup>1b</sup> is selected from the groups  
 A8) and A9);

- (b1), (b3) or (b7);

25 - (b5), (b6), (b9) or (b10) and R<sup>2b</sup> is selected from the groups  
 B8) or B9);

- (c1);



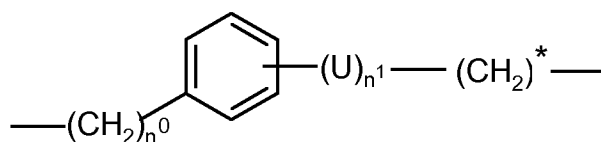
- (d1), (d2), (d3), (d4), (d7) or (d8);
- (d5), (d6), (d9) or (d10) and  $R^{12b}$  is selected from the groups D8) or D9);
- (e1), (f2), (g1), (h2), (i2), (l1), (m1), (n1), (o1), (p1), (q1), (r1), (s1), (t2) or (u1).

Y and Y' are bivalent radicals each independently selected from the following meanings:

a)

- straight or branched  $C_1$ - $C_{20}$  alkylene,
- straight or branched  $C_1$ - $C_{20}$  alkylene substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy,  $-ONO_2$  or  $T_2$ , wherein  $T_2$  is  $-OC(O)(C_1-C_{10} \text{ alkyl})-ONO_2$  or  $-O(C_1-C_{10} \text{ alkyl})-ONO_2$ ;
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with one or more straight or branched  $C_1$ - $C_{10}$  alkyl chains;

b)



b)

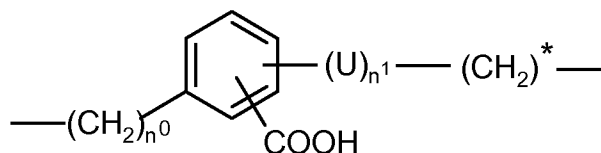
wherein

$n^0$  is an integer from 0 to 20;

$n^1$  is 0 or 1;

U is a linear or branched  $C_1$ - $C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group;

c)



c)

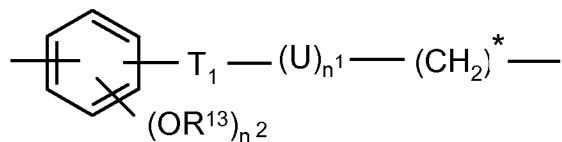
wherein

$n^0$  is an integer from 0 to 20;

$n^1$  is 0 or 1;

U is a linear or branched  $C_1$ - $C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group;

d)

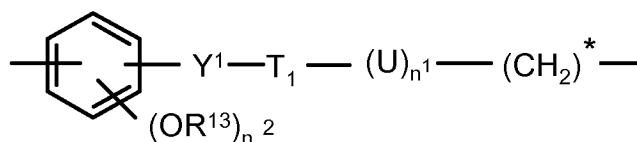


wherein:

$n^2$  is an integer from 0 to 2,  $R^{13}$  is H or  $CH_3$ ,  $T_1$  is  $-O-C(O)-$  or  $-C(O)O-$ ;

$n^1$  and U are as above defined;

e)



$n^2$  is an integer from 0 to 2,

$R^{13}$  is H or  $CH_3$ ,

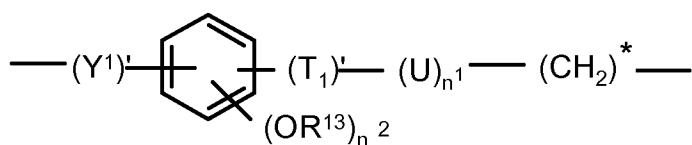
$Y^1$  is  $-CH_2-CH_2-$  or  $-CH=CH-(CH_2)_{n^{2'}}-$ , wherein  $n^{2'}$  is 0 or 1,

$T_1 = -O-C(O)-$  or  $-C(O)O-$ ,

$n^1$  is 0 or 1, preferably  $n^1$  is 1,

U is a linear or branched  $C_1$ - $C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group;

e')



wherein:

$n^2$  is an integer from 0 to 2,

$R^{13}$  is H or  $CH_3$ ,

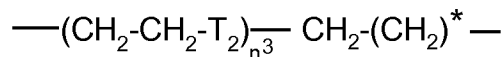
$Y^1$  is  $-CH_2-CH_2-$  or  $-(CH_2)_{n^{2'}}-CH=CH-$ , wherein  $n^{2'}$  is 0 or 1,

$(T_1)' = -O-C(O)-$ ;

$n^1$  is 0 or 1,

U is a linear or branched  $C_1$ - $C_{20}$  alkylene optionally substituted with a  $-\text{ONO}_2$  group;

f)

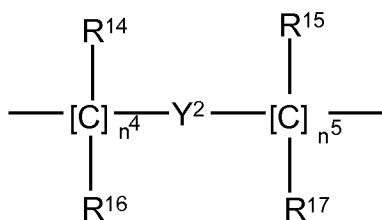


f)

wherein  $T_2$  is  $-\text{O}-$  or  $-\text{S}-$ ,  $-\text{NH}-$ , preferably  $T_2$  is  $-\text{O}-$ ,  $n^3$  is an integer from 1 to 6;

when Y and Y' are selected from b), c), d), e), e') or f), the  $-\text{ONO}_2$  group of  $-(\text{T}-\text{Y}-\text{ONO}_2)$ ,  $-(\text{T}'-\text{Y}-\text{ONO}_2)$ ,  $-(\text{T}''-\text{Y}'-\text{ONO}_2)$ ,  $-(\text{T}'-\text{Y}'-\text{ONO}_2)$ ,  $-(\text{T}'''-\text{Y}-\text{ONO}_2)$  and  $-(\text{T}'''-\text{Y}'-\text{ONO}_2)$  is linked to the  $-(\text{CH}_2)^*$ -group;

g)



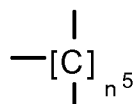
wherein:

$n^4$  is an integer from 0 to 10,

$n^5$  is an integer from 1 to 10,

$\text{R}^{14}$ ,  $\text{R}^{15}$ ,  $\text{R}^{16}$ ,  $\text{R}^{17}$  are the same or different, and are H or straight or branched  $C_1$ - $C_4$  alkyl,

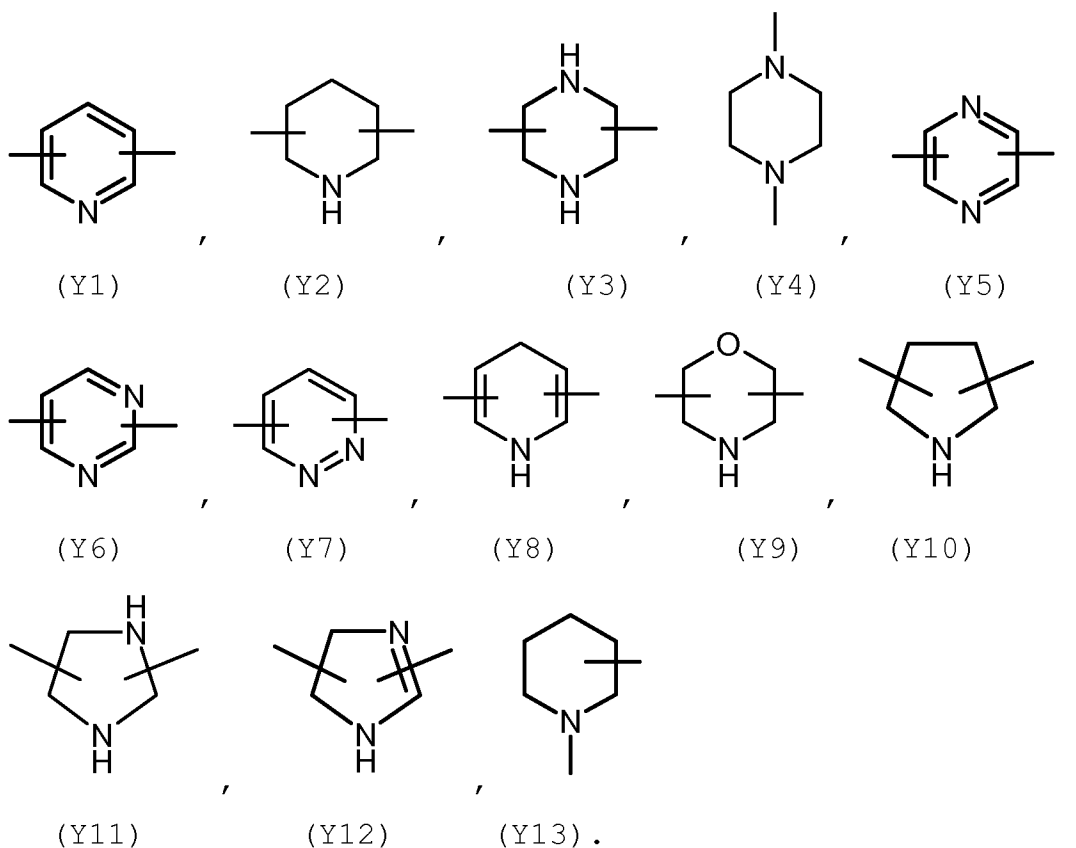
wherein the  $-\text{ONO}_2$  group is linked to



wherein  $n^5$  is as defined above;

$\text{Y}^2$  is a heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur,

and is selected from the group consisting of:



2. The nitric oxide releasing compounds according to claim 1 wherein

a is 1 and Z is  $-\text{C}(\text{O})-$ ;

$\text{R}_x$  is

(a1)  $-\text{HN}-\text{CH}(\text{R}^1)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

wherein

$\text{R}^1$  of the group A1) is selected from H, isobutyl, benzyl,

$\text{C}_6\text{H}_5-\text{CH}_2-\text{CH}_2-$ , 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from  $-\text{F}$ ,  $-\text{Cl}$ , I,  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $-\text{CH}_3$ , CN,  $\text{C}_6\text{H}_5\text{CO}-$

or

$\text{R}^1$  of the group A2) is selected from  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}-$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ , or

$\text{R}^1$  of the group A3) is selected from  $-\text{CH}_2-\text{NHR}''$ ,  $-(\text{CH}_2)_2-\text{NHR}''$ ,  $-(\text{CH}_2)_3-\text{NHR}''$ ,  $-(\text{CH}_2)_4-\text{NHR}''$ , wherein  $\text{R}''$  is H, or  $-\text{C}(\text{O})\text{CH}_3$ ,

$\text{R}^1$  of the group A4) is  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''$ ,

$-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''$  wherein  $\text{R}'''$  is  $\text{OR}^{5a}$  wherein  $\text{R}^{5a}$  is H or a linear  $(\text{C}_1-\text{C}_5)$  alkyl,

T is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$  wherein  $\text{R}'$  is H or a straight or branched  $\text{C}_1-\text{C}_4$  alkyl,

5 Y is as below defined;

or  $\text{R}_x$  is

(a3)  $-\text{HN}-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{COOR}^{3a}$

wherein

$\text{R}^{1a}$  of the group A5) is selected from  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)\text{O}-$  or

10  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ , or

$\text{R}^{1a}$  of the group A6) is selected from  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,  $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ , or

$\text{R}^{1a}$  of the group A7) is  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ ,  $\text{R}^{3a}$  is H or a  $(\text{C}_1-\text{C}_5)$  alkyl,

15  $\text{T}''$  is  $-\text{C}(\text{O})-$  or  $-\text{C}(\text{O})-\text{X}''$  wherein  $\text{X}''$  is  $-\text{S}-$  or  $-\text{O}-$ , when  $\text{R}^{1a}$  is selected from the group A5) or A6),

$\text{T}''$  is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$  wherein  $\text{R}'$  is H or a straight or branched  $\text{C}_1-\text{C}_4$  alkyl, when  $\text{R}^{1a}$  is selected from the group A7),

20  $\text{Y}'$  is as below defined;

or  $\text{R}_x$  is selected from:

(a5)  $-\text{R}^{1b}-\text{CH}(\text{NHR}^{4a})-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

(a6)  $-\text{R}^{1b}-\text{CH}(\text{COOR}^{3a})\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

(a9)  $-\text{R}^{1b}-\text{CH}(\text{NH}-\text{T}'-\text{Y}'-\text{ONO}_2)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$  or

25 (a10)  $-\text{R}^{1b}-\text{CH}(\text{C}(\text{O})-\text{T}-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

wherein

$\text{R}^{1b}$  of the group A8) is selected from  $-\text{O}-\text{CH}(\text{CH}_3)-$ ,  $-\text{O}-\text{CH}_2-$ ,  $[-4-\text{O}-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ , or

$\text{R}^{1b}$  of the group A9) is selected from  $-\text{HN}-\text{CH}_2-$ ,  $-\text{HN}-(\text{CH}_2)_2-$ ,

30  $-\text{HN}-(\text{CH}_2)_3-$ ,  $-\text{HN}-(\text{CH}_2)_4-$ ,

$\text{R}^{1b}$  of the group A10) is  $-\text{O}-\text{CH}_2-$  or  $[-4-\text{O}-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ,

$\text{R}^{3a}$  is H or a  $(\text{C}_1-\text{C}_5)$  alkyl,

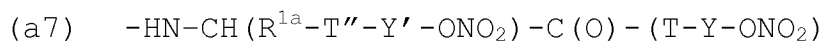
$\text{R}^{4a}$  is H or  $-\text{C}(\text{O})\text{CH}_3$ ,

T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl,

T' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-,

Y and Y' are as below defined;

5 or R<sub>x</sub> is



wherein

R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)-O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

10 R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-, or

R<sup>1a</sup> of the group A7) is -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>4</sub>-C(O)-,

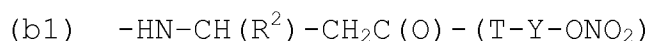
T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from A5) or A6);

15 T'' is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, when R<sup>1a</sup> is selected from A7),

T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl,

Y and Y' are as below defined;

20 or R<sub>x</sub> is



wherein

R<sup>2</sup> of the group B1) is selected from H, CH<sub>3</sub>, isobutyl, isopropyl, benzyl,

25 R<sup>2</sup> of the group B2) is selected from -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)-OH- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)(4-OH)], or

R<sup>2</sup> of the group B3) is selected from -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'', wherein R'' is H, or -C(O)CH<sub>3</sub>,

R<sup>2</sup> of the group B4) is -CH<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>2</sub>-C(O)R''',

30 -(CH<sub>2</sub>)<sub>4</sub>-C(O)R''' wherein R''' is OR<sup>5a</sup> wherein R<sup>5a</sup> is H or a linear (C<sub>1</sub>-C<sub>5</sub>) alkyl,

T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl,

Y is as below defined;

or  $R_x$  is selected from

(d1)  $-\text{HN}-\text{CH}(\text{R}^{12})-\text{CH}_2-\text{O}-(\text{T}'''-\text{Y}-\text{ONO}_2)$  or

(d2)  $-\text{O}-\text{CH}_2-\text{CH}(\text{R}^{12})-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

wherein

5  $\text{R}^{12}$  of the group D1) is selected from H,  $\text{CH}_3$ , isobutyl, isopropyl, benzyl, or

$\text{R}^{12}$  of the group D2) is selected from  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)\text{OH}-$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ , or

$\text{R}^{12}$  of the group D3) is selected from  $-\text{CH}_2-\text{NHR}''$ ,  $-(\text{CH}_2)_2-\text{NHR}''$ ,  
10  $-(\text{CH}_2)_3-\text{NHR}''$ ,  $-(\text{CH}_2)_4-\text{NHR}''$  wherein  $\text{R}''$  is H, or  
 $\text{R}^{12}$  of the group D4) is  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''$ ,  
 $-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''$  wherein  $\text{R}'''$  is  $\text{OR}^{5a}$  wherein  $\text{R}^{5a}$  is H or a linear  
( $\text{C}_1-\text{C}_5$ ) alkyl,

$\text{T}'$  and  $\text{T}'''$  are each independently selected from  $-\text{C}(\text{O})-$  or  
15  $-\text{C}(\text{O})-\text{X}''$  wherein  $\text{X}''$  is  $-\text{S}-$  or  $-\text{O}-$ ,

$\text{Y}$  is as below defined;

or  $R_x$  is selected from:

(d3)  $-\text{HN}-\text{CH}(\text{R}^{12a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{CH}_2\text{OH}$

(d4)  $-\text{O}-\text{CH}_2-\text{CH}(\text{R}^{12a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NHR}^{4a}$

20 (d7)  $-\text{HN}-\text{CH}(\text{R}^{12a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{CH}_2-\text{O}-(\text{T}'''-\text{Y}-\text{ONO}_2)$  or

(d8)  $-\text{O}-\text{CH}_2-\text{CH}(\text{R}^{12a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

wherein

$\text{R}^{12a}$  of the group D5) is selected from  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{O}-$  or  
 $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ , or

25  $\text{R}^{12a}$  of the group D6) is selected from  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,  
 $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ , or

$\text{R}^{12a}$  of the group D7) is  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ ,  
 $\text{R}^{4a}$  is H or  $-\text{C}(\text{O})\text{CH}_3$ ,

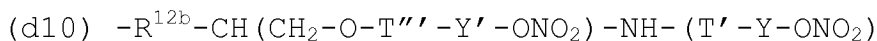
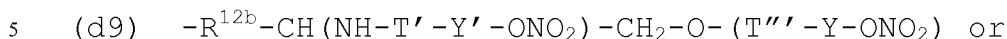
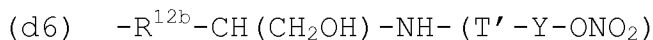
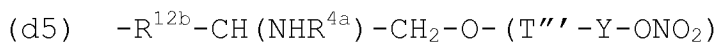
$\text{T}''$  is selected from  $-\text{C}(\text{O})-$  or  $-\text{C}(\text{O})-\text{X}''$  wherein  $\text{X}''$  is  $-\text{S}-$  or  $-\text{O}-$   
30 when  $\text{R}^{12a}$  is selected from D5) or D6),

$\text{T}''$  is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$  wherein  $\text{R}'$  is H or a  
straight or branched  $\text{C}_1-\text{C}_4$  alkyl when  $\text{R}^{12a}$  is selected from D7),

$\text{T}'''$  is selected from  $-\text{C}(\text{O})-$  or  $-\text{C}(\text{O})-\text{X}''$  wherein  $\text{X}''$  is  $-\text{S}-$  or  
 $-\text{O}-$ ,

Y and Y' are as below defined;

or R<sub>x</sub> is selected from:



wherein

R<sup>12b</sup> of the group D8) is selected from -O-CH(CH<sub>3</sub>)-, -O-CH<sub>2</sub>-,  
[-4-O-(C<sub>6</sub>H<sub>4</sub>)]-CH<sub>2</sub>-, or

10 R<sup>12b</sup> of the group D9) is selected from -HN-CH<sub>2</sub>-, -HN-(CH<sub>2</sub>)<sub>2</sub>-,  
-HN-(CH<sub>2</sub>)<sub>3</sub>-, -HN-(CH<sub>2</sub>)<sub>4</sub>-,

R<sup>4a</sup> is H or -C(O)-CH<sub>3</sub>,

T' and T''' are each independently selected from -C(O)-,  
-C(O)-X'', wherein X'' is -S- or -O-,

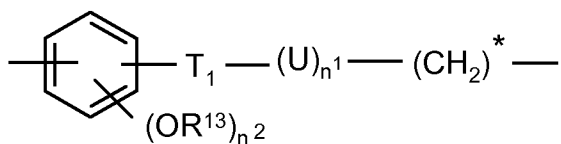
15 Y and Y' are each independently selected from

a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

20 d)



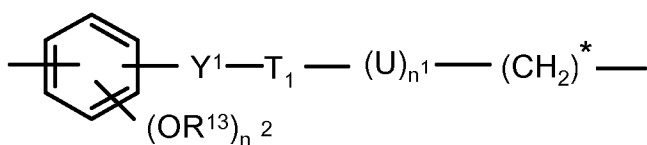
d)

wherein:

n<sup>2</sup> is an integer from 0 to 2, R<sup>13</sup> is H or CH<sub>3</sub>, T<sub>1</sub> is -O-C(O)- or  
25 -C(O)O-,

n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or  
branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

e)

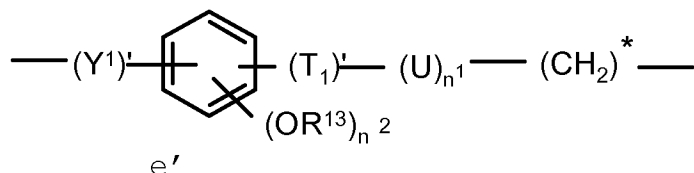


30 e)

n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>, Y<sup>1</sup> is -CH=CH-(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>- and n<sup>2'</sup> is 0,



T<sub>1</sub> is -C(O)O- and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene;  
e')



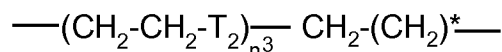
5 wherein:

n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>,

Y<sup>1</sup> is -(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>-CH=CH- and n<sup>2'</sup> is 0,

(T<sub>1</sub>)' = -O-C(O)-,

n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or  
10 branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;  
f)



f)

wherein T<sub>2</sub> is -O- or -S-, -NH- and n<sup>3</sup> is 1 or 2,

15 when Y and Y' are selected from d), e), e') or f), the -ONO<sub>2</sub>  
group of -(T-Y-ONO<sub>2</sub>), -(T'-Y-ONO<sub>2</sub>), -(T''-Y'-ONO<sub>2</sub>), -(T'-Y'-ONO<sub>2</sub>),  
-(T'''-Y-ONO<sub>2</sub>) and -(T'''-Y'-ONO<sub>2</sub>) is linked to the -(CH<sub>2</sub>)\*-  
group.

20 **3.** The nitric oxide releasing compounds according to claim 2  
wherein

R<sub>x</sub> is

(a5) -R<sup>1b</sup>-CH(NHR<sup>4a</sup>)-C(O)-(T-Y-ONO<sub>2</sub>) or

(a9) -R<sup>1b</sup>-CH(NH-T'-Y'-ONO<sub>2</sub>)-C(O)-(T-Y-ONO<sub>2</sub>)

25 R<sup>1b</sup> of the group A10) is -O-CH<sub>2</sub>- or [-(4-O)-(C<sub>6</sub>H<sub>4</sub>)]-CH<sub>2</sub>-,

R<sup>4a</sup> is H or -C(O)CH<sub>3</sub>,

T is selected from -O-, -S-, -NR'- wherein R' is as above  
defined,

T' is -C(O)- and

30 Y and Y' are each independently selected from

a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group.

4. The nitric oxide releasing compounds according to claim 1 wherein a is 0 and

R<sub>x</sub> is

(a2) -C(O)-CH(R<sup>1</sup>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

R<sup>1</sup> of the group A1) is selected from H, isobutyl, benzyl,

10 C<sub>6</sub>H<sub>5</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from -F, -Cl, I, -NO<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>3</sub>, CN, C<sub>6</sub>H<sub>5</sub>CO-,

R<sup>1</sup> of the group A2) is selected from -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)OH- or

15 -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-OH)], or

R<sup>1</sup> of the group A3) is selected from -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'', wherein R'' is H, or -C(O)CH<sub>3</sub>,

R<sup>1</sup> of the group A4) is selected from -CH<sub>2</sub>-C(O)R''',

-(CH<sub>2</sub>)<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>4</sub>-C(O)R''' wherein R''' is OR<sup>5a</sup> wherein R<sup>5a</sup>

20 is H or a linear (C<sub>1</sub>-C<sub>5</sub>) alkyl,

T' is -C(O)-, -C(O)-X'' wherein X'' is -S- or -O-,

Y is as below defined;

or R<sub>x</sub> is

(a4) -C(O)-CH(R<sup>1a</sup>-T''-Y'-ONO<sub>2</sub>)-NHR<sup>4a</sup>

25 wherein R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-, or

R<sup>1a</sup> of the group A7) is selected from -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-,

30 -(CH<sub>2</sub>)<sub>4</sub>-C(O)-;

R<sup>4a</sup> is H or -C(O)CH<sub>3</sub>,

T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O- when R<sup>1a</sup> is selected from the group A5) or A6),

T'' is -O-, -S-, -NR'- or -O-CH(R')-O-C(O)- wherein R' is H or

-CH<sub>3</sub> when R<sup>1a</sup> is selected from the group A7),

Y' is as below defined;

or R<sub>x</sub> is selected from:

(a5) -R<sup>1b</sup>-CH(NHR<sup>4a</sup>)-C(O)-(T-Y-ONO<sub>2</sub>)

5 (a6) -R<sup>1b</sup>-CH(COOR<sup>3a</sup>)NH-(T'-Y-ONO<sub>2</sub>)

(a9) -R<sup>1b</sup>-CH(NH-T'-Y'-ONO<sub>2</sub>)-C(O)-(T-Y-ONO<sub>2</sub>) or

(a10) -R<sup>1b</sup>-CH(C(O)-T-Y'-ONO<sub>2</sub>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

R<sup>1b</sup> of the group A10) is selected from -C(O)-CH<sub>2</sub>-, -C(O)-(CH<sub>2</sub>)<sub>2</sub>-,

10 -C(O)-(CH<sub>2</sub>)<sub>4</sub>-,

R<sup>3a</sup> is H or a (C<sub>1</sub>-C<sub>5</sub>) alkyl,

R<sup>4a</sup> is H or -C(O)CH<sub>3</sub>,

T is -O-, -S-, -NR'- or -O-CH(R')-O-C(O)- wherein R' is H or -CH<sub>3</sub>,

15 T' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-,

Y and Y' are as below defined;

or R<sub>x</sub> is

(a8) -C(O)-CH(R<sup>1a</sup>-T''-Y'-ONO<sub>2</sub>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

20 R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)-O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-, or

25 R<sup>1a</sup> of the group A7) is selected from -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>4</sub>-C(O)-,

T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from the group A5) or A6),

T'' is -O-, -S-, -NR'- or -O-CH(R')-O-C(O)- wherein R' is H or -CH<sub>3</sub>, when R<sup>1a</sup> is selected from the group A7),

30 T' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-,

Y and Y' are as below defined;

or R<sub>x</sub> is

(b2) -C(O)-CH<sub>2</sub>-CH(R<sup>2</sup>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

$R^2$  of the group B1) is selected from H,  $CH_3$ , isobutyl, isopropyl, benzyl,

$T'$  is  $-C(O)-$ ,  $-C(O)-X''$  wherein  $X''$  is  $-S-$  or  $-O-$ ,

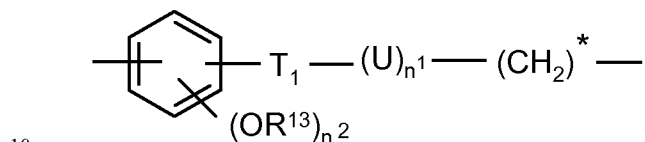
Y and  $Y'$  are each independently selected from

5 a)

- a straight or branched  $C_1-C_{10}$  alkylene,

- a straight or branched  $C_1-C_{10}$  alkylene substituted with a  $-ONO_2$  group;

d)



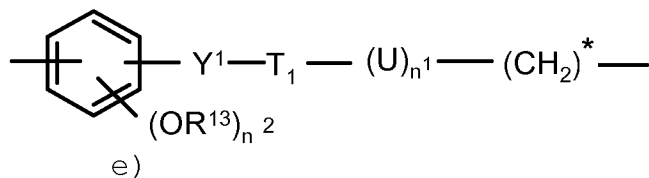
d)

wherein:

$n^2$  is an integer from 0 to 2,  $R^{13}$  is H or  $CH_3$ ,  $T_1$  is  $-O-C(O)-$  or  $-C(O)O-$ ,

15  $n^1$  is 1 and U is a linear  $C_1-C_{10}$  alkylene or U is a linear or branched  $C_1-C_{10}$  alkylene substituted with a  $-ONO_2$  group;

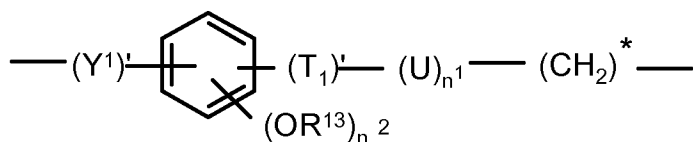
e)



20  $n^2$  is 1,  $R^{13}$  is  $CH_3$ ,  $Y^1$  is  $-CH=CH-(CH_2)_{n^{2'}}-$  and  $n^{2'}$  is 0,

$T_1$  is  $-C(O)O-$  and U is a linear  $C_1-C_{10}$  alkylene;

e')



e')

25 wherein:

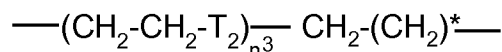
$n^2$  is 1,  $R^{13}$  is  $CH_3$ ,

$Y^1$  is  $-(CH_2)_{n^{2'}}-CH=CH-$  and  $n^{2'}$  is 0,

$(T_1)' = -O-C(O)-$ ,

$n^1$  is 1 and U is a linear  $C_1$ - $C_{10}$  alkylene or U is a linear or branched  $C_1$ - $C_{10}$  alkylene substituted with a  $-\text{ONO}_2$  group;

f)



5 f)

wherein  $T_2$  is  $-\text{O}-$  or  $-\text{S}-$ ,  $-\text{NH}-$  and  $n^3$  is 1 or 2,

when Y and Y' are selected from d), e), e') or f), the  $-\text{ONO}_2$  group of  $-(\text{T}-\text{Y}-\text{ONO}_2)$ ,  $-(\text{T}'-\text{Y}-\text{ONO}_2)$ ,  $-(\text{T}''-\text{Y}'-\text{ONO}_2)$ ,  $-(\text{T}'-\text{Y}'-\text{ONO}_2)$ ,  $-(\text{T}'''-\text{Y}-\text{ONO}_2)$  and  $-(\text{T}'''-\text{Y}'-\text{ONO}_2)$  is linked to the  $-(\text{CH}_2)^*$ -

10 group.

**5.** The nitric oxide releasing compounds according to claim 4 wherein

$R_x$  is

15 (a2)  $-\text{C}(\text{O})-\text{CH}(\text{R}^1)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

wherein

$\text{R}^1$  of the group A1) is H,

$\text{T}'$  is  $-\text{C}(\text{O})-$ ,

Y is selected from

20 a)

- a straight or branched  $C_1$ - $C_{10}$  alkylene,

- a straight or branched  $C_1$ - $C_{10}$  alkylene substituted with a  $-\text{ONO}_2$  group;

25 **6.** The nitric oxide releasing compounds of claim 4 wherein

$R_x$  is selected from

(a5)  $-\text{R}^{1b}-\text{CH}(\text{NHR}^{4a})-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

(a6)  $-\text{R}^{1b}-\text{CH}(\text{COOR}^{3a})\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$  or

(a9)  $-\text{R}^{1b}-\text{CH}(\text{NH}-\text{T}'-\text{Y}'-\text{ONO}_2)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$

30 wherein

$\text{R}^{1b}$  of the group A10) is  $-\text{C}(\text{O})-\text{CH}_2-$ ,

$\text{R}^{3a}$  is H or a  $(C_1-C_5)$  alkyl,

$\text{R}^{4a}$  is H or  $-\text{C}(\text{O})\text{CH}_3$ ,

T is selected from -O-, -S-, -NR'- wherein R' is as above defined,

T' is -C(O)- and

Y and Y' are each independently selected from

5 a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group.

10 **7.** The nitric oxide releasing compounds according to claim 4 wherein

R<sub>x</sub> is

(b2) -C(O)-CH<sub>2</sub>-CH(R<sup>2</sup>)-NH-(T'-Y-ONO<sub>2</sub>)

R<sup>2</sup> of the group B1) is H,

15 T' is -C(O)-,

Y is selected from

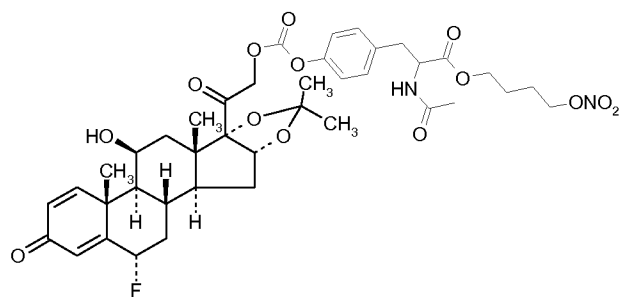
a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub>

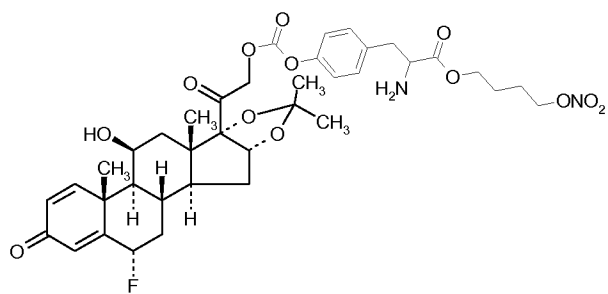
20 group;

**8.** Nitric oxide releasing compounds according to claim 3

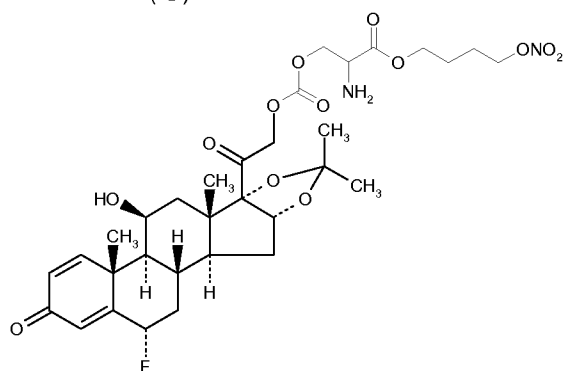


(3)

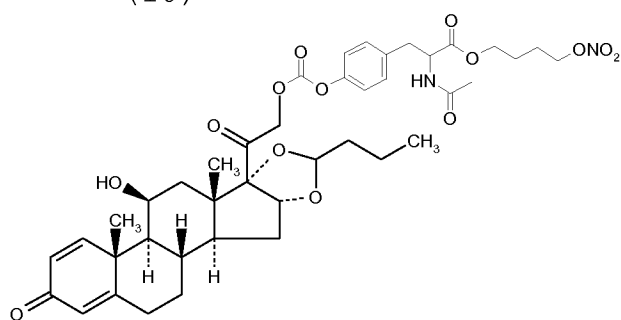
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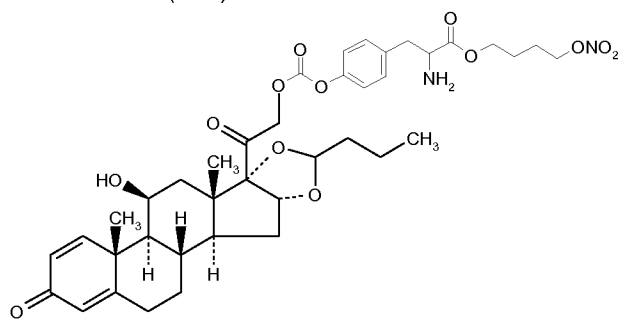
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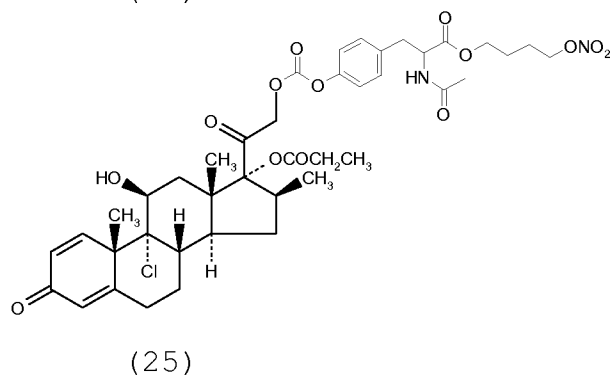
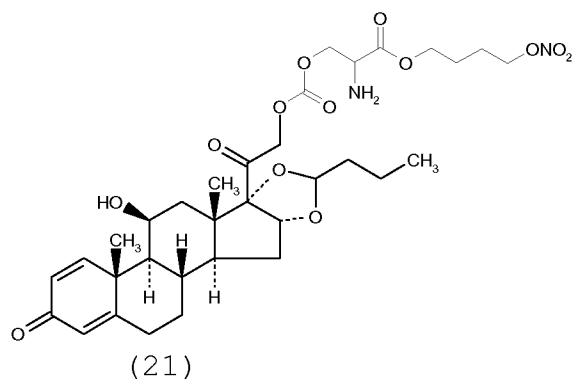
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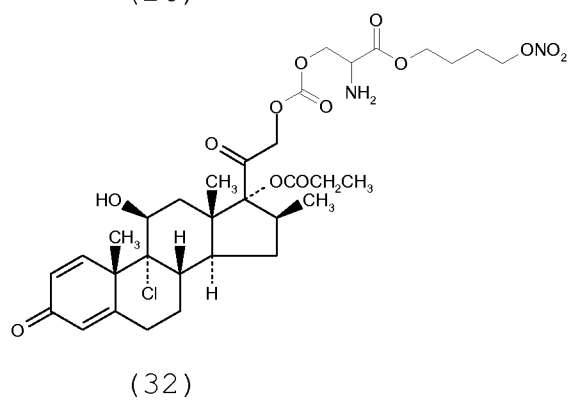
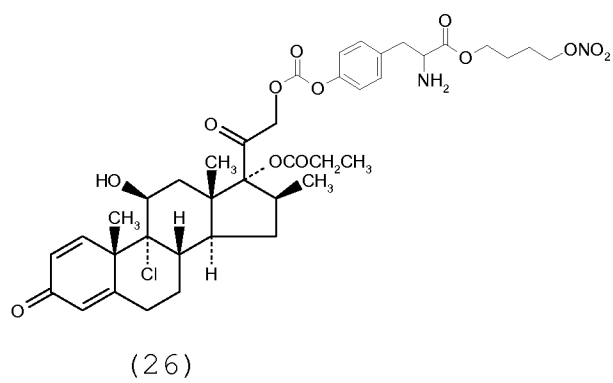
(14)



(15)

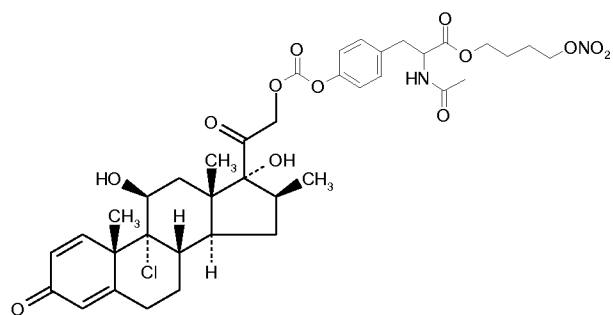


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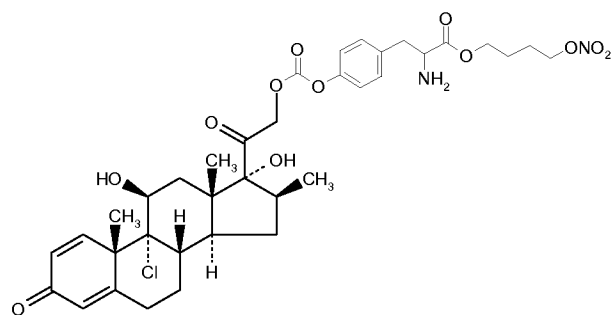




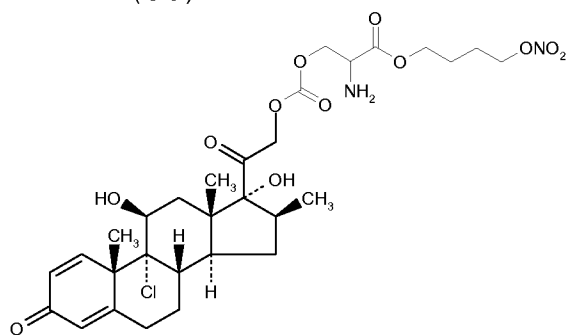
192



(36)



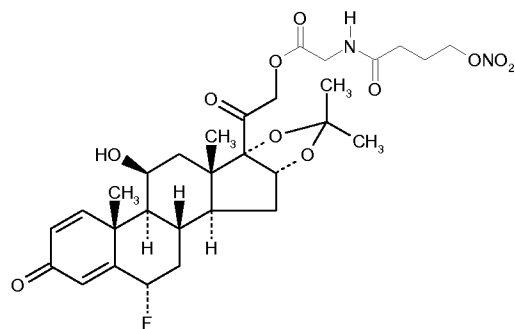
(37)



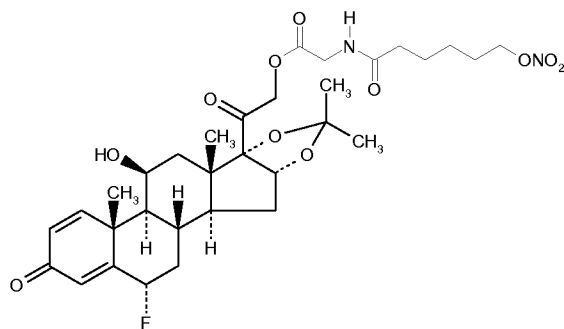
(43)

5

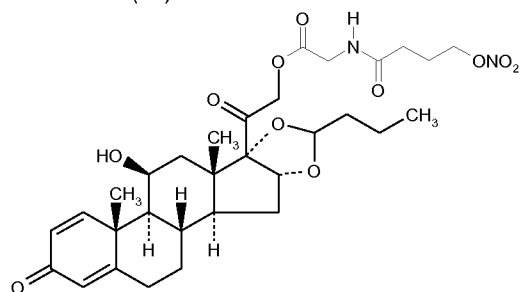
## 9. Nitric oxide releasing compounds according to claim 5



(1)



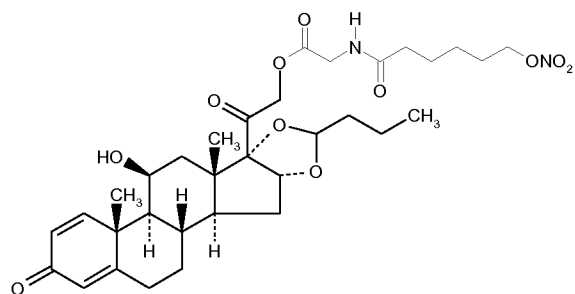
(2)



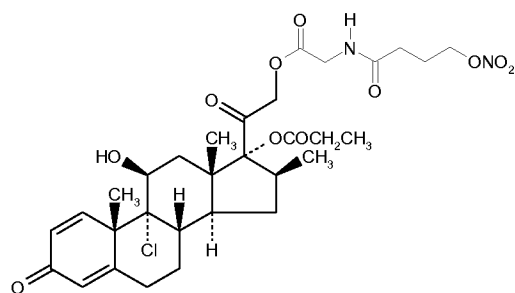
(12)

10

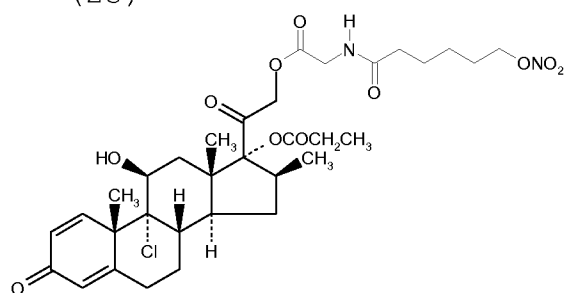
193



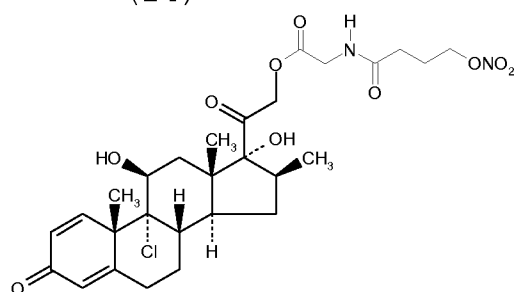
(13)



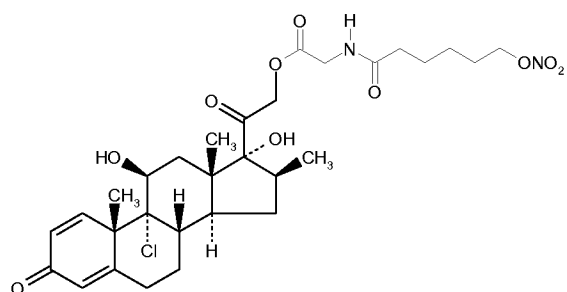
(23)



(24)



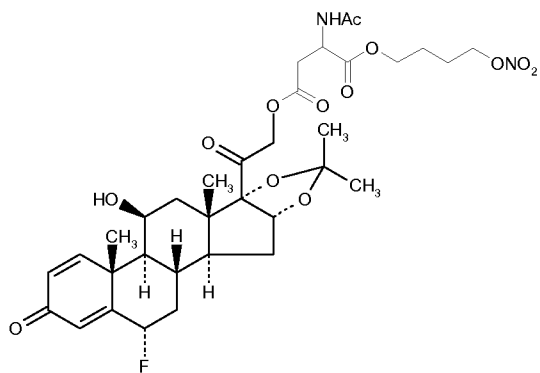
(34)



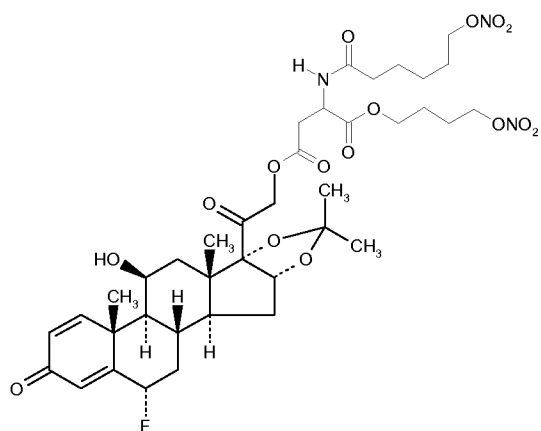
(35)

10

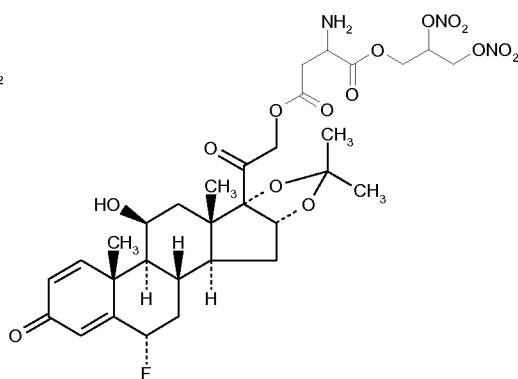
10. Nitric oxide releasing compounds according to claim 6



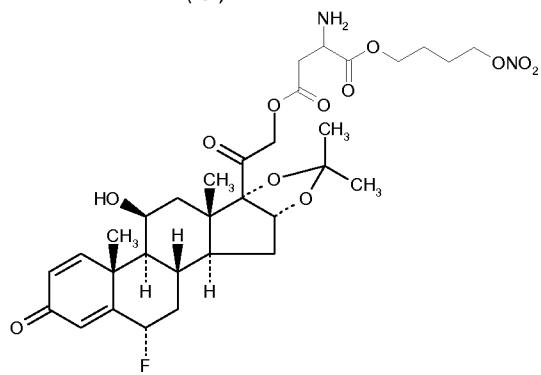
(5)



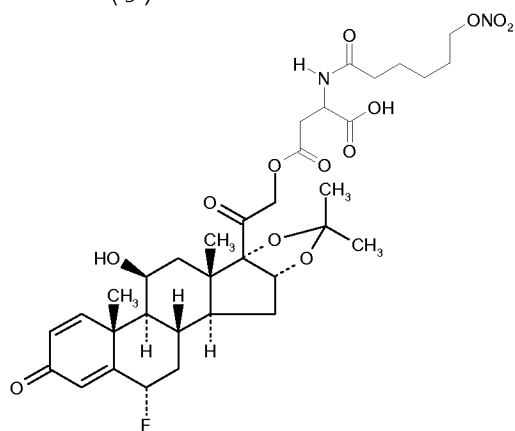
(8)



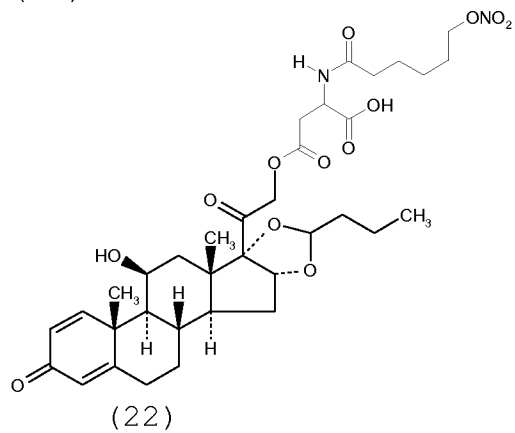
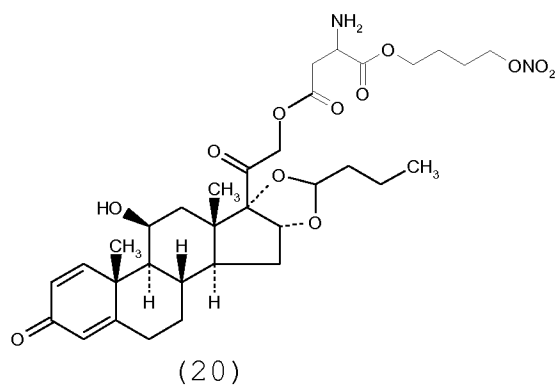
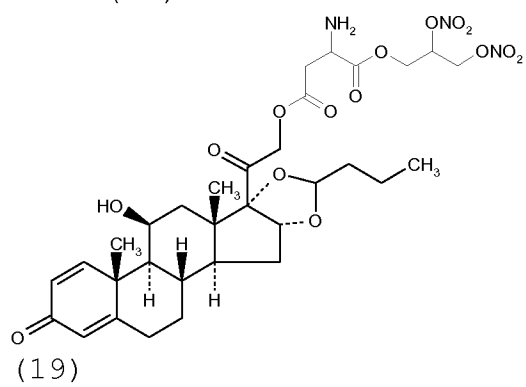
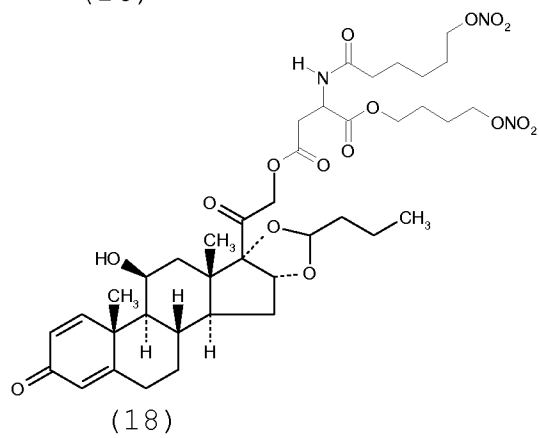
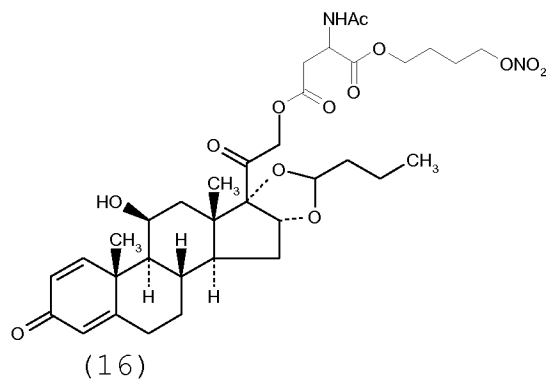
(8)

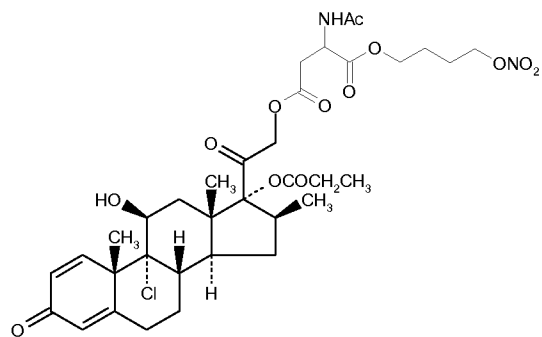


(9)

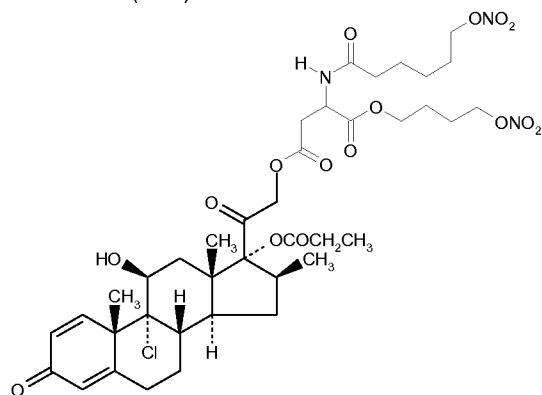


(11)

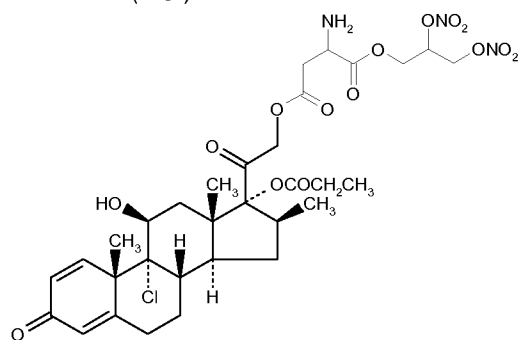




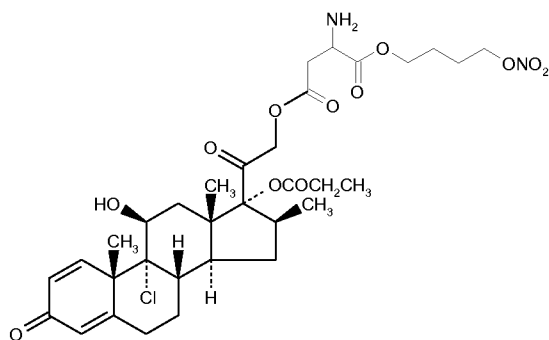
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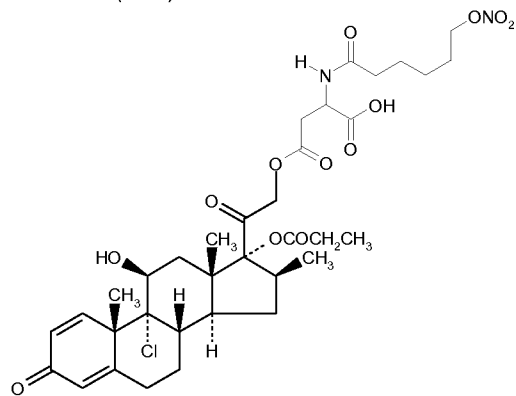
(29)



(30)

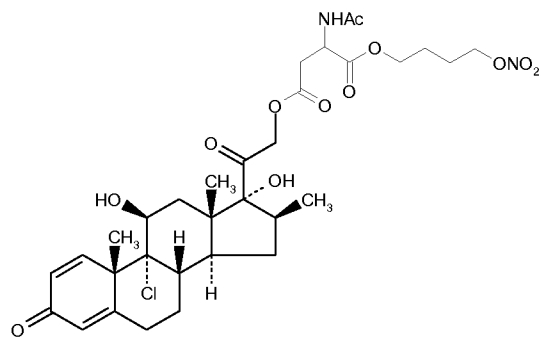


(31)

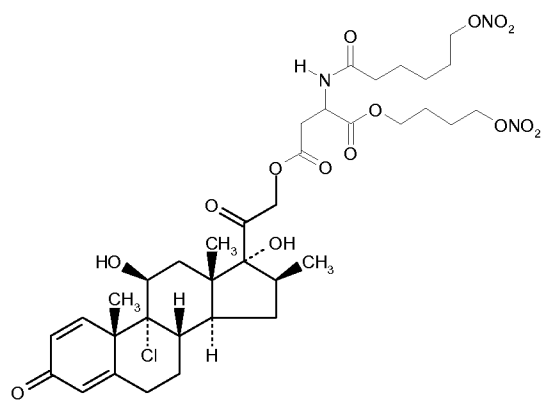


(33)

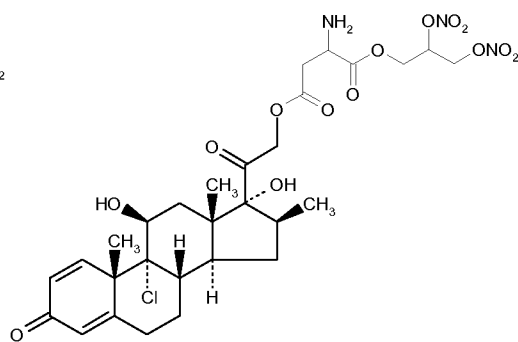
197



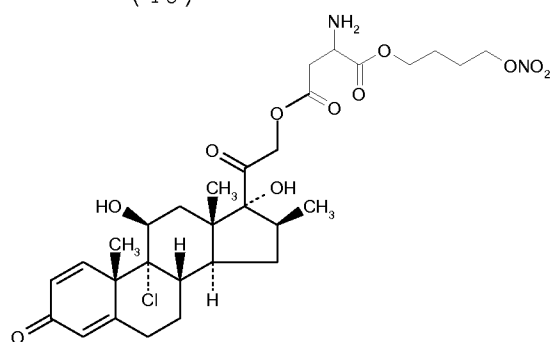
(38)



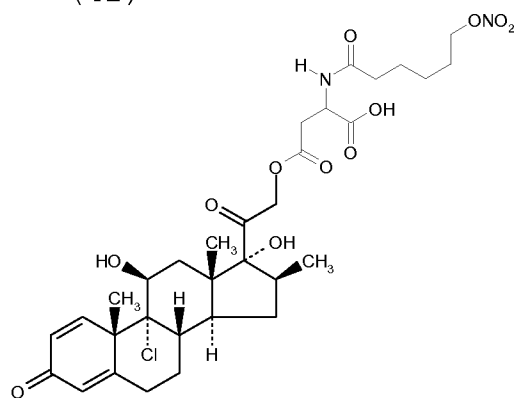
(40)



(41)



(42)

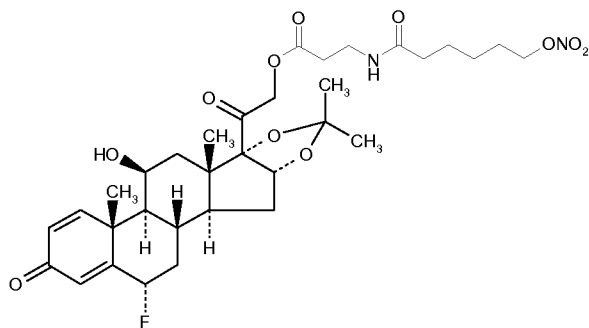


(44)

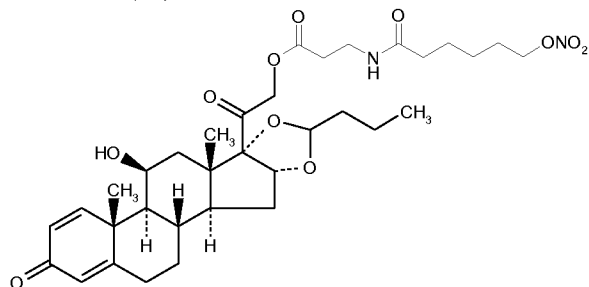
10

11. Nitric oxide releasing compounds according to claim 7

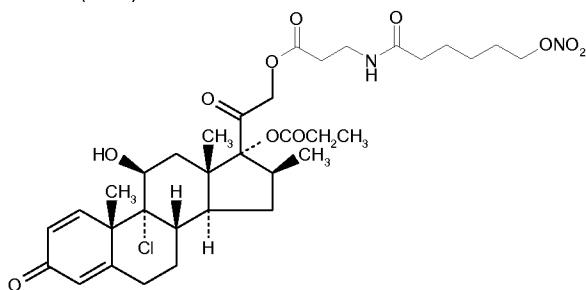
198



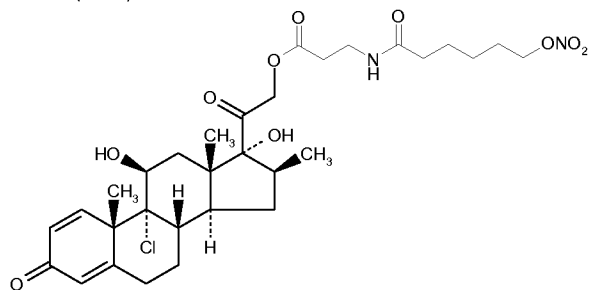
(6)



(17)



(28)

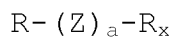


(39)

10 **12.** Nitric oxide releasing compounds according to any of  
claims 1 to 7 wherein the respiratory diseases comprise asthma,  
chronic obstructive pulmonary diseases, Acute Respiratory  
distress syndrome, allergic rhinitis and respiratory tract  
diseases associated with inflammation.

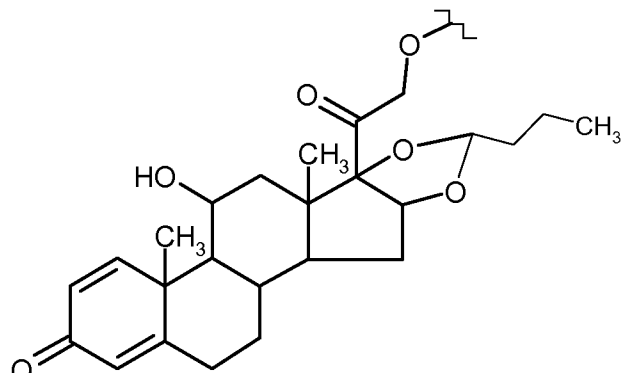
15

**13.** Nitric oxide releasing compounds of general formula (I)

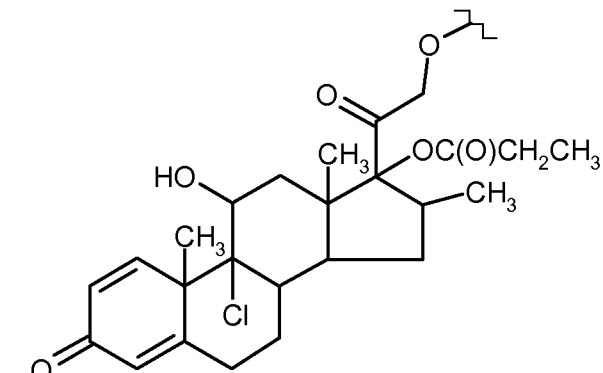


(I)

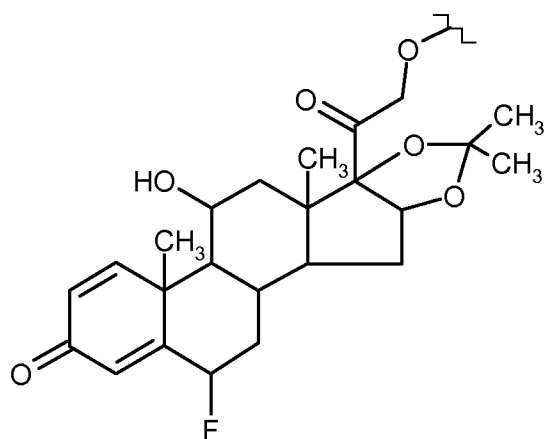
and pharmaceutically acceptable salts or stereoisomers thereof wherein R is a corticosteroid residue selected from:



(II)



(IV)



(V)

a is 0 or 1,

10 Z is a group capable of binding  $R_x$  and is selected from  $-C(O)-$ ,  
or  $-CH(R')-O-$  wherein  $R'$  is selected from H or a straight or  
branched  $C_1-C_4$  alkyl, preferably  $R'$  is H or  $-CH_3$ ;

$R_x$  is a radical selected from the following meanings:

A)

- $$\begin{array}{ll}
15 & \text{(a1)} \quad -\text{HN}-\text{CH}(\text{R}^1)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2) \\
& \text{(a2)} \quad -\text{C}(\text{O})-\text{CH}(\text{R}^1)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2) \\
& \text{(a3)} \quad -\text{HN}-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{COOR}^{3a} \\
& \text{(a4)} \quad -\text{C}(\text{O})-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NHR}^{4a} \\
& \text{(a5)} \quad -\text{R}^{1b}-\text{CH}(\text{NHR}^{4a})-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2) \\
20 & \text{(a6)} \quad -\text{R}^{1b}-\text{CH}(\text{COOR}^{3a})\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)
\end{array}$$

20



- (a7)  $-\text{HN}-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$   
 (a8)  $-\text{C}(\text{O})-\text{CH}(\text{R}^{1a}-\text{T}''-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$   
 (a9)  $-\text{R}^{1b}-\text{CH}(\text{NH}-\text{T}'-\text{Y}'-\text{ONO}_2)-\text{C}(\text{O})-(\text{T}-\text{Y}-\text{ONO}_2)$   
 (a10)  $-\text{R}^{1b}-\text{CH}(\text{C}(\text{O})-\text{T}-\text{Y}'-\text{ONO}_2)-\text{NH}-(\text{T}'-\text{Y}-\text{ONO}_2)$

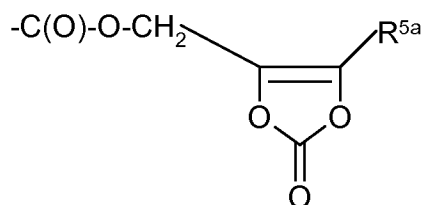
wherein:

$\text{R}^1$  is selected from:

A1) H,  $-\text{CH}_3$ , isopropyl, isobutyl, sec-butyl, tert-butyl, methylthio- $(\text{CH}_2)_2-$ , phenyl, benzyl,  $\text{C}_6\text{H}_5-\text{CH}_2-\text{CH}_2-$ , 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from  $-\text{F}$ ,  $-\text{Cl}$ , I,  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $-\text{CH}_3$ , CN,  $\text{C}_6\text{H}_5\text{CO}-$ , 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, 2-pyrrolidyl, 3-triptyophanyl- $\text{CH}_2-$ , 3-benzothienyl- $\text{CH}_2-$ , 4-imidazolyl- $\text{CH}_2-$ , 9-anthranyl- $\text{CH}_2-$ , cyclohexyl, cyclohexyl- $\text{CH}_2-$ , cyclohexyl- $(\text{CH}_2)_2-$ , cyclopentyl- $\text{CH}_2-$ ,  $(\text{C}_6\text{H}_5)_2\text{CH}-$ , 4-B(OH) $_2$ -benzyl, 4-quinolyl- $\text{CH}_2-$ , 3-quinolyl- $\text{CH}_2-$ , 2-quinolyl- $\text{CH}_2-$ , 2-quinoxalyl- $\text{CH}_2-$ , 2-furyl- $\text{CH}_2-$ , 1-naphtyl- $\text{CH}_2-$ , 2-naphtyl- $\text{CH}_2-$ , 2-pyridyl- $\text{CH}_2-$ , 3-pyridyl- $\text{CH}_2-$ , 4-pyridyl- $\text{CH}_2-$ , 2-thienyl- $\text{CH}_2-$ , 3-thienyl- $\text{CH}_2-$ ,  $\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{CH}_2-$ ,  $\text{CH}_2=\text{CH}-\text{CH}_2-$ ,  $\text{CH}\equiv\text{CH}-\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}-\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}-(\text{CH}_2)_2-$ ,  $\text{NH}_2(=\text{NH})\text{NH}-(\text{CH}_2)_3-$ ,  $\text{P}(=\text{O})(\text{OCH}_3)_2$ ,

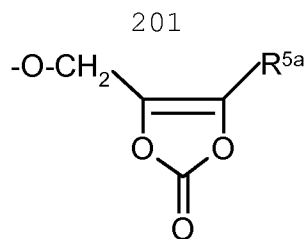
A2)  $-\text{CH}_2-\text{SH}$ ,  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_2)-(3,5\text{-diiodo})-(4-\text{OH})]$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_3)-(3\text{-nitro})-(4-\text{OH})]$ ,

A3)  $-\text{CH}_2-\text{NHR}''$ ,  $-(\text{CH}_2)_2-\text{NHR}''$ ,  $-(\text{CH}_2)_3-\text{NHR}''$ ,  $-(\text{CH}_2)_4-\text{NHR}''$ , wherein  $\text{R}''$  is H,  $-\text{C}(\text{O})\text{CH}_3$  or



wherein  $\text{R}^{5a}$  is H or a linear or branched  $\text{C}_1$ - $\text{C}_{10}$  alkyl chain,

A4)  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''$  wherein  $\text{R}'''$  is  $-\text{OR}^{5a}$  or



wherein  $R^{5a}$  is as above defined,

$R^{1a}$  is selected from,

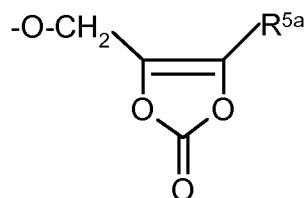
A5)  $-\text{CH}_2-\text{S}-$ ,  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{O}-$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ ,

5  $-\text{CH}_2-[(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)-(4-\text{O})-]$ ,  $-\text{CH}_2-[(3\text{-nitro})-(\text{C}_6\text{H}_3)-(4-\text{O})-]$ , preferably  $R^{1a}$  is  $-\text{CH}_2-\text{O}-$ ,

A6)  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,  $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ ,

A7)  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ ;

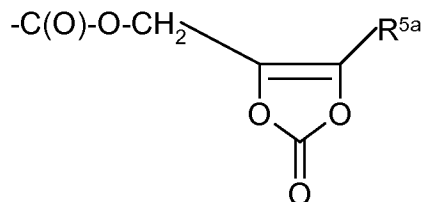
$R^{3a}$  is selected from H,  $-\text{R}^{5a}$  or



10

wherein  $R^{5a}$  is as above defined,

$R^{4a}$  is selected from H or  $-\text{C}(\text{O})\text{CH}_3$  or



wherein  $R^{5a}$  is as above defined,

15  $R^{1b}$  is selected from

A8)  $-\text{S}-\text{CH}_2-$ ,  $-\text{O}-\text{CH}(\text{CH}_3)-$ ,  $-\text{O}-\text{CH}_2-$ ,  $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ,

$[-(4-\text{O})-(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)]-\text{CH}_2-$ ,

$[-(4-\text{O})-(3\text{-nitro})-(\text{C}_6\text{H}_3)]-\text{CH}_2-$ ,

A9)  $-\text{HN}-\text{CH}_2-$ ,  $-\text{HN}-(\text{CH}_2)_2-$ ,  $-\text{HN}-(\text{CH}_2)_3-$ ,  $-\text{HN}-(\text{CH}_2)_4-$ ,

20 A10)  $-\text{C}(\text{O})-\text{CH}_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_4-$ ;

T is selected from  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$  or  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})\text{O}-$  wherein  $\text{R}'$  is as above defined;

$\text{T}'$  is  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{X}''-$  wherein  $\text{X}''$  is  $-\text{O}-$  or  $-\text{S}-$ , or  $\text{T}'$  is  $-\text{C}(\text{O})-\text{NR}'-$  wherein  $\text{R}'$  is as above defined,

25  $\text{T}''$  is independently selected from  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{X}''-$ ,

-C(O)-NR'-, -O-, -S-, -NR'-, -O-CH(R')-O-C(O)-,  
 -O-CH(R')-O-C(O)O-, wherein X'' and R' are as above defined,  
 with the proviso that T'' is -C(O)-, -C(O)-X''- or -C(O)-NR'-  
 when T'' is linked to -NH-, -O-, or -S-, or

5 T'' is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)-, -O-CH(R')-O-C(O)O-  
 when T'' is linked to -C(O)-,

Y and Y' are as below defined,

B)

- (b1) -HN-CH(R<sup>2</sup>)-CH<sub>2</sub>C(O)-(T-Y-ONO<sub>2</sub>)  
 10 (b2) -C(O)-CH<sub>2</sub>-CH(R<sup>2</sup>)-NH-(T'-Y-ONO<sub>2</sub>)  
 (b3) -HN-CH(R<sup>2a</sup>-T''-Y'-ONO<sub>2</sub>)-CH<sub>2</sub>COOR<sup>3a</sup>  
 (b4) -C(O)-CH<sub>2</sub>-CH(R<sup>2a</sup>-T''-Y'-ONO<sub>2</sub>)-NHR<sup>4a</sup>  
 (b5) -R<sup>2b</sup>-CH(NHR<sup>4a</sup>)-CH<sub>2</sub>C(O)-(T-Y-ONO<sub>2</sub>)  
 (b6) -R<sup>2b</sup>-CH(CH<sub>2</sub>COOR<sup>3a</sup>)NH-(T'-Y-ONO<sub>2</sub>)  
 15 (b7) -HN-CH(R<sup>2a</sup>-T''-Y'-ONO<sub>2</sub>)-CH<sub>2</sub>-C(O)-(T-Y-ONO<sub>2</sub>)  
 (b8) -C(O)-CH<sub>2</sub>-CH(R<sup>2a</sup>-T''-Y'-ONO<sub>2</sub>)-NH-(T'-Y-ONO<sub>2</sub>)  
 (b9) -R<sup>2b</sup>-CH(NH-T'-Y'-ONO<sub>2</sub>)-CH<sub>2</sub>C(O)-(T-Y-ONO<sub>2</sub>)  
 (b10) -R<sup>2b</sup>-CH(CH<sub>2</sub>C(O)-T-Y'-ONO<sub>2</sub>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

20 R<sup>2</sup> is selected from

B1) H, -CH<sub>3</sub>, CF<sub>3</sub>, isopropyl, isobutyl, sec-butyl, methylthio-  
 (CH<sub>2</sub>)<sub>2</sub>-, phenyl, benzyl, 3-triptyophanyl-CH<sub>2</sub>-, NH<sub>2</sub>-C(O)-CH<sub>2</sub>-,  
 NH<sub>2</sub>-C(O)-(CH<sub>2</sub>)<sub>2</sub>-, NH<sub>2</sub>(=NH)NH-(CH<sub>2</sub>)<sub>3</sub>-, tBuO-CH(CH<sub>3</sub>)-, benzyl-O-CH<sub>2</sub>-  
 , 4-terbutoxy-benzyl, 4-phenylbenzyl,

25 B2) -CH<sub>2</sub>-SH, -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)-OH, -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-OH)],  
 -CH<sub>2</sub>[(C<sub>6</sub>H<sub>2</sub>)-(3,5-diiodo)-(4-OH)],  
 -CH<sub>2</sub>[(C<sub>6</sub>H<sub>3</sub>)-(3-nitro)-(4-OH)],

B3) -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'', wherein  
 R'' is as above defined,

30 B4) -CH<sub>2</sub>-C(O)-R''', -(CH<sub>2</sub>)<sub>2</sub>-C(O)-R''', -(CH<sub>2</sub>)<sub>4</sub>-C(O)-R''' wherein  
 R''' is as above defined, preferably R<sup>2</sup> is -CH<sub>2</sub>-C(O)-R''',  
 R<sup>2a</sup> is selected from:

B5) -CH<sub>2</sub>-S-, -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)-O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-],  
 -CH<sub>2</sub>[(3,5-diiodo)-(C<sub>6</sub>H<sub>2</sub>)-(4-O)-],

$-\text{CH}_2-[(3\text{-nitro})-(\text{C}_6\text{H}_3)-(4\text{-O})-];$

B6)  $-\text{CH}_2\text{-NH-}, -(\text{CH}_2)_2\text{-NH-}, -(\text{CH}_2)_3\text{-NH-}, -(\text{CH}_2)_4\text{-NH-},$

B7)  $-\text{CH}_2\text{-C(O)-}, -(\text{CH}_2)_2\text{-C(O)-}, -(\text{CH}_2)_4\text{-C(O)-},$

$\text{R}^{2b}$  is selected from:

5 B8)  $-\text{S-CH}_2\text{-}, -\text{O-CH}(\text{CH}_3)\text{-}, -\text{O-CH}_2\text{-}, [- (4\text{-O})-(\text{C}_6\text{H}_4)]\text{-CH}_2\text{-},$   
 $[- (4\text{-O})-(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)]\text{-CH}_2\text{-}, [- (4\text{-O})-(3\text{-nitro})-(\text{C}_6\text{H}_3)]\text{-CH}_2\text{-},$

B9)  $-\text{HN-CH}_2\text{-}, -\text{HN-}(\text{CH}_2)_2\text{-}, -\text{HN-}(\text{CH}_2)_3\text{-}, -\text{HN-}(\text{CH}_2)_4\text{-},$

B10)  $-\text{C(O)-CH}_2\text{-}, -\text{C(O)-}(\text{CH}_2)_2\text{-}, -\text{C(O)-}(\text{CH}_2)_4\text{-},$

$\text{R}^{3a}$  and  $\text{R}^{4a}$  are as above defined,

10 T, T' and T'' are as above defined and Y and Y' are as below defined,

C)

(c1)  $-\text{HN-}(\text{CH}_2)_b\text{-C(O)-(T-Y-ONO}_2\text{)};$

(c2)  $-\text{C(O)-}(\text{CH}_2)_b\text{-NH-(T'-Y-ONO}_2\text{)};$

15 wherein b is an integer from 3 to 6,

T and T' are as above defined and Y and Y' are as below defined,

D)

(d1)  $-\text{HN-CH}(\text{R}^{12})\text{-CH}_2\text{-O-(T'''-Y-ONO}_2\text{)}$

(d2)  $-\text{O-CH}_2\text{-CH}(\text{R}^{12})\text{-NH-(T'-Y-ONO}_2\text{)}$

20 (d3)  $-\text{HN-CH}(\text{R}^{12a}\text{-T''-Y'-ONO}_2\text{)-CH}_2\text{OH}$

(d4)  $-\text{O-CH}_2\text{-CH}(\text{R}^{12a}\text{-T''-Y'-ONO}_2\text{)-NHR}^{4a}$

(d5)  $-\text{R}^{12b}\text{-CH(NHR}^{4a})\text{-CH}_2\text{-O-(T'''-Y-ONO}_2\text{)}$

(d6)  $-\text{R}^{12b}\text{-CH}(\text{CH}_2\text{OH})\text{-NH-(T'-Y-ONO}_2\text{)}$

(d7)  $-\text{HN-CH}(\text{R}^{12a}\text{-T''-Y'-ONO}_2\text{)-CH}_2\text{-O-(T'''-Y-ONO}_2\text{)}$

25 (d8)  $-\text{O-CH}_2\text{-CH}(\text{R}^{12a}\text{-T''-Y'-ONO}_2\text{)-NH-(T'-Y-ONO}_2\text{)}$

(d9)  $-\text{R}^{12b}\text{-CH(NH-T'-Y'-ONO}_2\text{)-CH}_2\text{-O-(T'''-Y-ONO}_2\text{)}$

(d10)  $-\text{R}^{12b}\text{-CH}(\text{CH}_2\text{-O-T'''-Y'-ONO}_2\text{)-NH-(T'-Y-ONO}_2\text{)}$

wherein

T''' is independently selected from  $-\text{C(O)-}, -\text{C(O)X''-}$  wherein X''

30 is  $-\text{O-}$  or  $-\text{S-}$ , or  $-\text{C(O)-NR'-}$  wherein R' is as above defined,

T' and T'' are as above defined,

Y and Y' are as below defined,

$\text{R}^{12}$  is selected from:

D1) H,  $-\text{CH}_3$ , isopropyl, isobutyl, sec-butyl, methylthio-  
 $(\text{CH}_2)_2-$ , benzyl, 3-triptyophanyl- $\text{CH}_2-$ , 4-imidazolyl- $\text{CH}_2-$ ,  
 $\text{NH}_2-\text{CO}-\text{CH}_2-$ ,  $\text{NH}_2-\text{CO}- (\text{CH}_2)_2-$ ,  $\text{NH}_2(=\text{NH})\text{NH}- (\text{CH}_2)_3-$ ,

D2)  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}$ ,  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{OH})]$ ,

5  $-\text{CH}_2-[(\text{C}_6\text{H}_3)-(3,5\text{-diiodo})-(4-\text{OH})]$ ,

$-\text{CH}_2-[(\text{C}_6\text{H}_3)-(3\text{-nitro})-(4-\text{OH})]$ ,

D3)  $-\text{CH}_2-\text{NHR}''$ ,  $-(\text{CH}_2)_2-\text{NHR}''$ ,  $-(\text{CH}_2)_3-\text{NHR}''$ ,  $-(\text{CH}_2)_4-\text{NHR}''$ , wherein  
 $\text{R}''$  is as above defined, preferably  $\text{R}^{12}$  is  $-(\text{CH}_2)_4-\text{NHR}''$ ,

D4)  $-\text{CH}_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})\text{R}'''$  wherein  $\text{R}'''$   
 10 is as above defined,

$\text{R}^{12a}$  is selected from:

D5)  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{O}-$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ ,  
 $-\text{CH}_2-[3,5\text{- diiodo}-(\text{C}_6\text{H}_2)-(4-\text{O})-]$ ,  $-\text{CH}_2-[3\text{-nitro}-(\text{C}_6\text{H}_3)-4-\text{O}-]$ ,

D6)  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,  $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ ,

15 D7)  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ ,

$\text{R}^{12b}$  is selected from:

D8)  $-\text{O}-\text{CH}_2-$ ,  $-\text{O}-\text{CH}(\text{CH}_3)-$ ,  $[-(4-\text{O})-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ ,  
 $[-(4-\text{O})-(3,5\text{-diiodo})-(\text{C}_6\text{H}_2)]-\text{CH}_2$ ,  $[-(4-\text{O})-(3\text{-nitro})-(\text{C}_6\text{H}_3)]-\text{CH}_2-$ ,

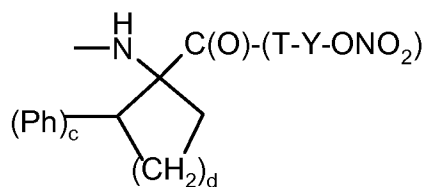
D9)  $-\text{HN}-\text{CH}_2-$ ,  $-\text{HN}-(\text{CH}_2)_2-$ ,  $-\text{HN}-(\text{CH}_2)_3-$ ,  $-\text{HN}-(\text{CH}_2)_4-$ ,

20 D10)  $-\text{C}(\text{O})-\text{CH}_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_2-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_4-$ ,

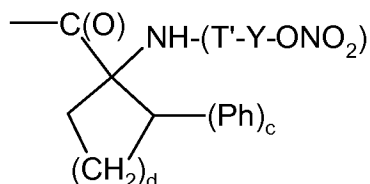
$\text{R}^{4a}$  is as above defined,

E)

(e1)



25 (e2)

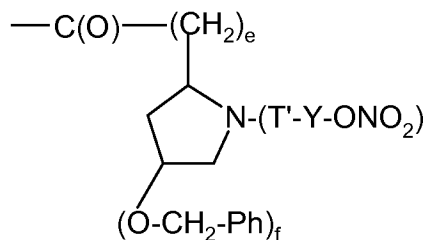


wherein  $c$  is equal to 0 or 1,  $d$  is an integer from 0 to 3 with  
 the proviso that  $c$  is 0 or 1 when  $d$  is 0 and  $c$  is 0 when  $d$  is

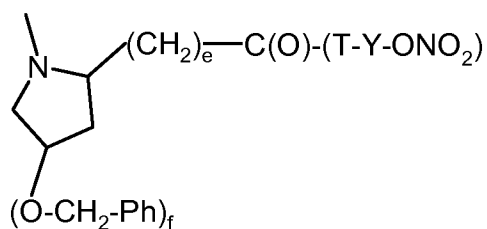
1, 2 or 3, T and T' are as above defined and Y is as below defined;

F)

(f1)



(f2)



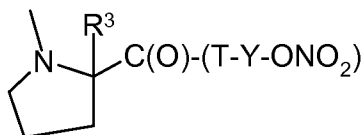
(XI)

wherein e and f are equal to 0 or 1, with the proviso that f is 0 when e is 0 and f is 0 or 1 when e is 1,

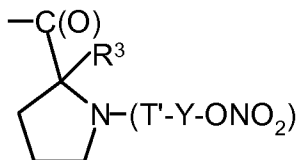
T and T' are as above defined and Y is as below reported;

G)

(g1)



(g2)

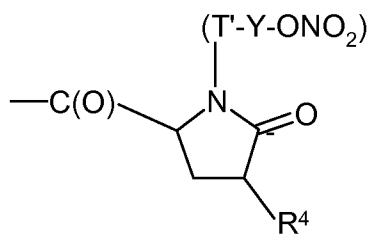


wherein R<sup>3</sup> is H, CH<sub>3</sub>, propyl, (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CH-, 1-naphtyl-CH<sub>2</sub>-, benzyl, allyl, 2-bromobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-fluorobenzyl, 4-bromobenzyl, 4-methylbenzyl,

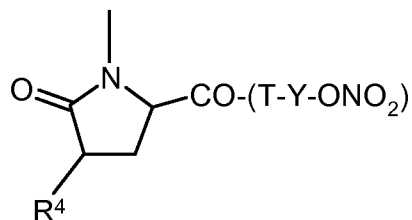
T and T' are as above defined and Y is as below defined,

H)

(h1)



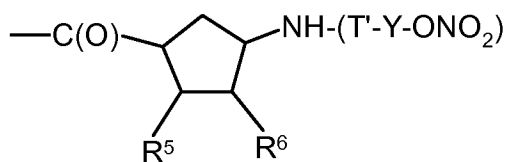
(h2)



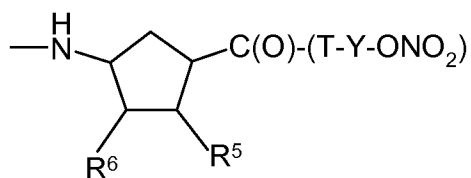
wherein  $R^4$  is H, benzyl, 4-bromobenzyl, 2-bromobenzyl, T and T' are as above defined and Y is as below defined;

I)

(i1)



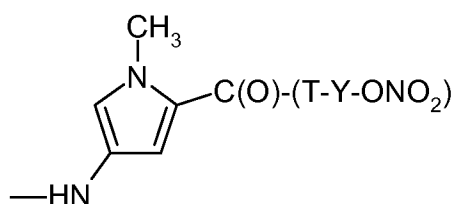
(i2)



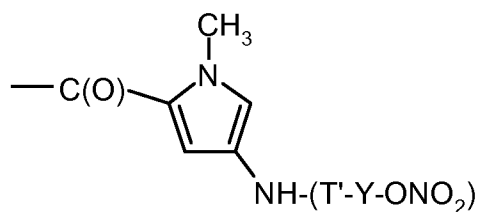
wherein  $R^5$  is H,  $R^6$  is H, or  $R^5$  and  $R^6$  when taken together are a double bond, T and T' are as above defined and Y is as below reported;

L)

(l1)



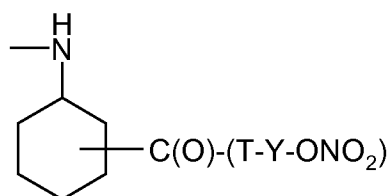
(12)



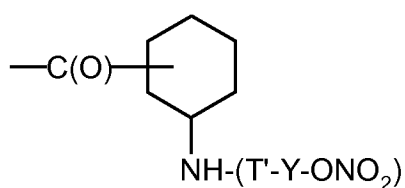
wherein T and T' are as above defined and Y is as below reported;

5 M)

(m1)



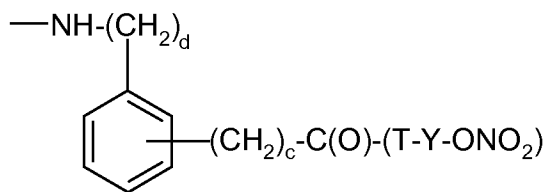
(m2)



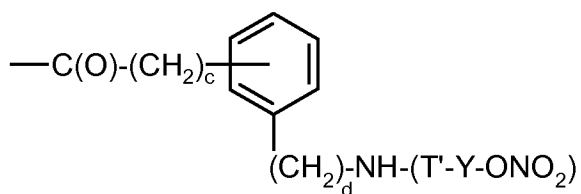
10 wherein T and T' are as above defined and Y is as below reported;

N)

(n1)



15 (n2)

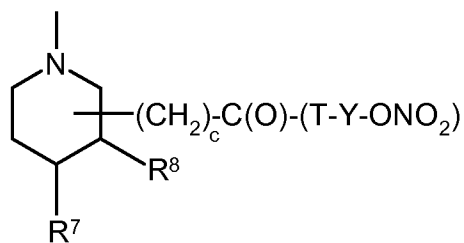


wherein c is as above defined, d is equal to 0 or 1, T and T' are as above defined and Y is as below reported;

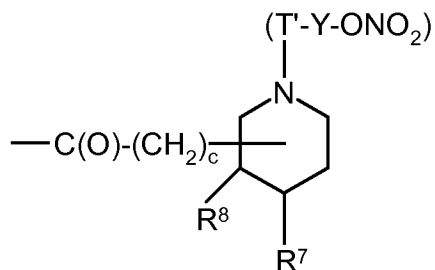
O)



(o1)



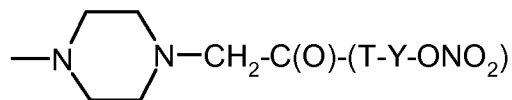
(o2)



5 wherein  $R^7$  is H,  $R^8$  is H, or  $R^7$  and  $R^8$  when taken together are a double bond,  $c$  is as above defined,  $T$  and  $T'$  are as above defined and  $Y$  is as below reported;

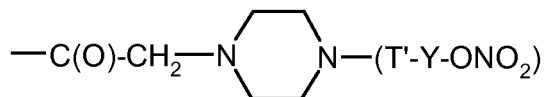
P)

(p1)



10

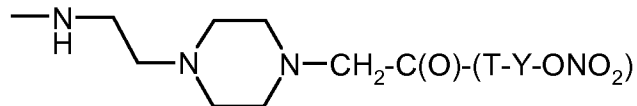
(p2)



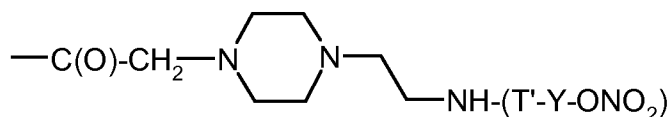
wherein  $T$  and  $T'$  are as above defined and  $Y$  is as below reported;

15 Q)

(q1)



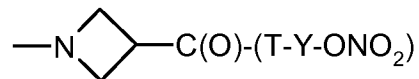
(q2)



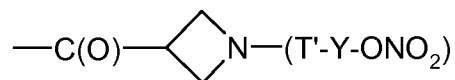
wherein T and T' are as above defined and Y is as below reported;

R)

(r1)



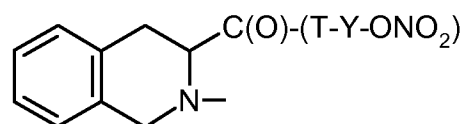
(r2)



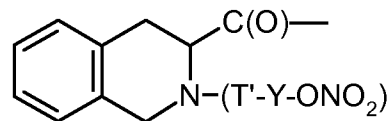
wherein T and T' are as above defined and Y is as below reported;

S)

(s1)



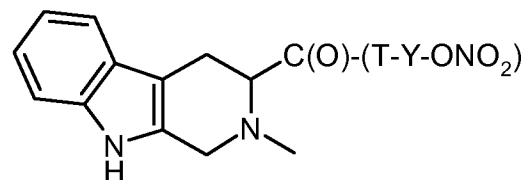
(s2)



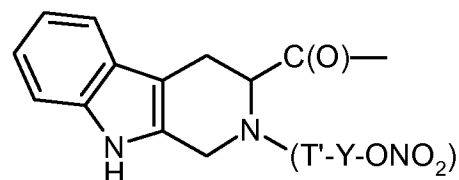
wherein T and T' are as above defined and Y is as below reported;

T)

(t1)



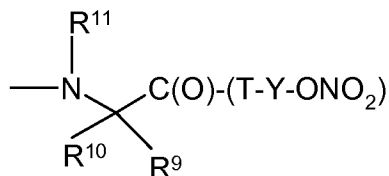
(t2)



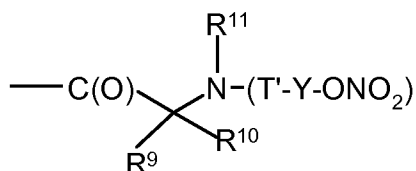
wherein T and T' are as above defined and Y is as below reported;

U)

(u1)



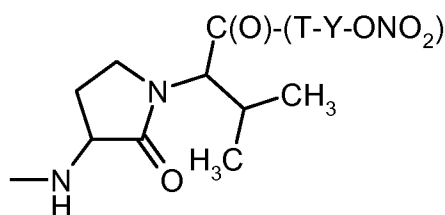
(u2)



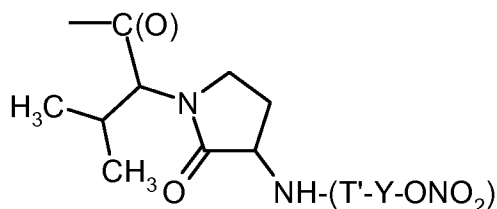
wherein  $R^9$  and  $R^{10}$  are H,  $CH_3$ ,  $R^{11}$  is  $CH_3$  or 4-piperidinyl with the proviso that  $R^9$  and  $R^{10}$  are H when  $R^{11}$  is 4-piperidinyl and  $R^9$  and  $R^{10}$  are  $CH_3$  when  $R^{11}$  is  $CH_3$ , T and T' are as above defined and Y is as below reported;

V)

(v1)



(v2)



wherein T and T' are as above defined and Y is as below reported;

with the proviso that in the formula (I):

a is 0 or a is 1 and Z is  $-CH(R')-O-$  wherein  $R'$  is as above defined, when  $R_x$  is:

- (a2), (a4) or (a8);

- (a5), (a6), (a9) or (a10) and  $R^{1b}$  is selected from the group A10);

- (b2), (b4) or (b8);
- (b5), (b6), (b9) or (b10) and  $R^{2b}$  is selected from the group B10);
- (c2);
- 5 - (d5), (d6), (d9) or (d10) and  $R^{12b}$  is selected from the group D10);
- (e2), (f1), (g2), (h1), (i1), (l2), (m2), (n2), (o2), (p2), (q2), (r2), (s2), (t1) or (u2);

a is 1 and Z is -C(O)-, when  $R_x$  is:

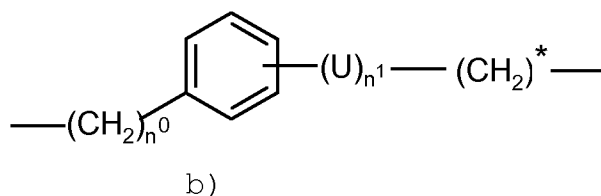
- 10 - (a1), (a3) or (a7);
- (a5), (a6), (a9) or (a10) and  $R^{1b}$  is selected from the groups A8) and A9);
- (b1), (b3) or (b7);
- (b5), (b6), (b9) or (b10) and  $R^{2b}$  is selected from the groups
- 15 B8) or B9);
- (c1);
- (d1), (d2), (d3), (d4), (d7) or (d8);
- (d5), (d6), (d9) or (d10) and  $R^{12b}$  is selected from the groups D8) or D9);
- 20 - (e1), (f2), (g1), (h2), (i2), (l1), (m1), (n1), (o1), (p1), (q1), (r1), (s1), (t2) or (u1).

Y and Y' are bivalent radicals each independently selected from the following meanings:

a)

- 25 - straight or branched  $C_1$ - $C_{20}$  alkylene,
- straight or branched  $C_1$ - $C_{20}$  alkylene substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, -ONO<sub>2</sub> or T<sub>2</sub>, wherein T<sub>2</sub> is -OC(O)( $C_1$ - $C_{10}$  alkyl)-ONO<sub>2</sub> or -O( $C_1$ - $C_{10}$  alkyl)-ONO<sub>2</sub>;
- 30 - cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with one or more straight or branched  $C_1$ - $C_{10}$  alkyl chains;

b)



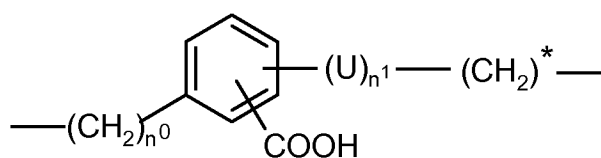
wherein

$n^0$  is an integer from 0 to 20;

5  $n^1$  is 0 or 1;

U is a linear or branched  $C_1$ - $C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group;

c)



10

wherein

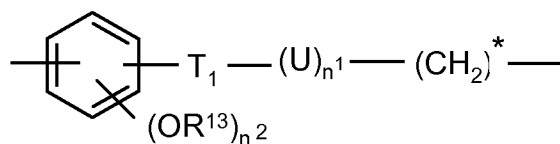
$n^0$  is an integer from 0 to 20;

$n^1$  is 0 or 1;

U is a linear or branched  $C_1$ - $C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group;

15

d)



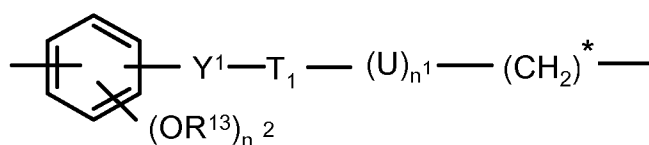
ù

wherein:

20  $n^2$  is an integer from 0 to 2,  $R^{13}$  is H or  $CH_3$ ,  $T_1$  is  $-O-C(O)-$  or  $-C(O)O-$ ;

$n^1$  and U are as above defined;

e)



25

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$n^2$  is an integer from 0 to 2,

$R^{13}$  is H or  $CH_3$ ,

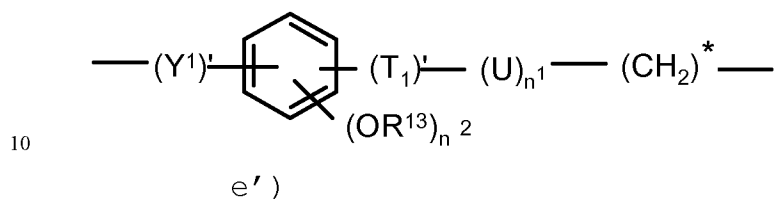
$Y^1$  is  $-CH_2-CH_2-$  or  $-CH=CH-(CH_2)_{n^{2'}}-$ , wherein  $n^{2'}$  is 0 or 1, preferably  $Y^1$  is  $-CH=CH-(CH_2)_{n^{2'}}-$  and  $n^{2'}$  is 0,

5  $T_1 = -O-C(O)-$  or  $-C(O)O-$ ,

$n^1$  is 0 or 1, preferably  $n^1$  is 1;

U is a linear or branched  $C_1-C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group;

e')



wherein:

$n^2$  is an integer from 0 to 2,

$R^{13}$  is H or  $CH_3$ ,

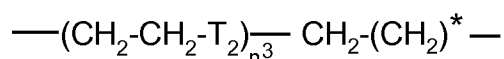
15  $Y^1$  is  $-CH_2-CH_2-$  or  $-(CH_2)_{n^{2'}}-CH=CH-$ , wherein  $n^{2'}$  is 0 or 1,

$(T_1)' = -O-C(O)-$ ;

$n^1$  is 0 or 1,

U is a linear or branched  $C_1-C_{20}$  alkylene optionally substituted with a  $-ONO_2$  group;

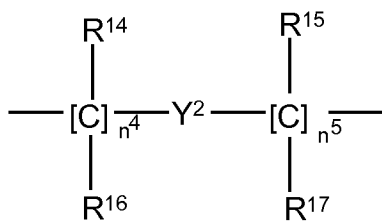
20 f)



wherein  $T_2$  is  $-O-$  or  $-S-$ ,  $-NH-$ ,

when Y and Y' are selected from b), c), d), e), e') or f), the  $-ONO_2$  group of  $-(T-Y-ONO_2)$ ,  $-(T'-Y-ONO_2)$ ,  $-(T''-Y'-ONO_2)$ ,  $-(T'-Y'-$   
 25  $ONO_2)$ ,  $-(T'''-Y-ONO_2)$  and  $-(T'''-Y'-ONO_2)$  is linked to the  $-(CH_2)^*$ -group;

g)

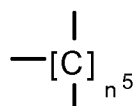


wherein:

$n^4$  is an integer from 0 to 10,

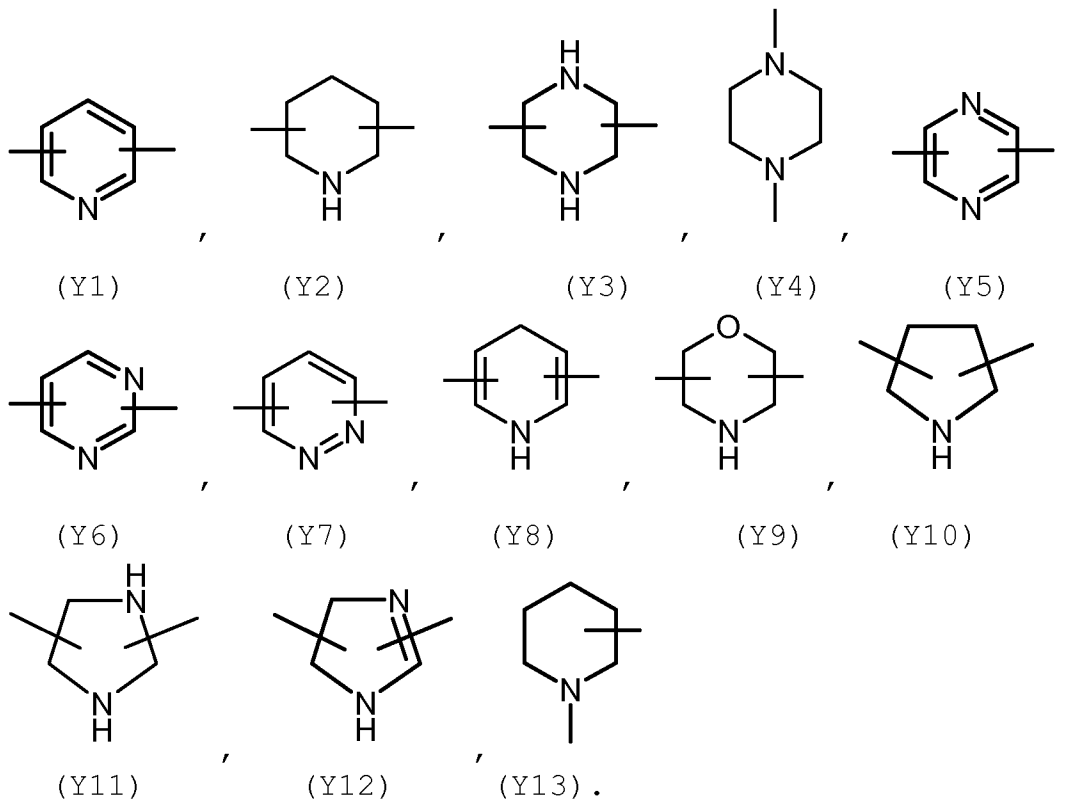
$n^5$  is an integer from 1 to 10,

- 5  $\text{R}^{14}$ ,  $\text{R}^{15}$ ,  $\text{R}^{16}$ ,  $\text{R}^{17}$  are the same or different, and are H or straight or branched  $\text{C}_1$ - $\text{C}_4$  alkyl, wherein the  $-\text{ONO}_2$  group is linked to



wherein  $n^5$  is as defined above;

- 10  $\text{Y}^2$  is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, and is selected from the group consisting of:



**14.** The nitric oxide releasing compounds according to claim 13 wherein

a is 1 and Z is -C(O)-;

R<sub>x</sub> is

5 (a1) -HN-CH(R<sup>1</sup>)-C(O)-(T-Y-ONO<sub>2</sub>)

wherein

R<sup>1</sup> of the group A1) is selected from H, isobutyl, benzyl, C<sub>6</sub>H<sub>5</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the  
10 benzyl is selected from -F, -Cl, I, -NO<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>3</sub>, CN, C<sub>6</sub>H<sub>5</sub>CO- or

R<sup>1</sup> of the group A2) is selected from -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)-OH- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-OH)], or

R<sup>1</sup> of the group A3) is selected from -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'',  
15 -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'', wherein R'' is H, or -C(O)CH<sub>3</sub>,  
R<sup>1</sup> of the group A4) is -CH<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>4</sub>-C(O)R''' wherein R''' is OR<sup>5a</sup> wherein R<sup>5a</sup> is H or a linear (C<sub>1</sub>-C<sub>5</sub>) alkyl,

T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a  
20 straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl,

Y is as below defined;

or R<sub>x</sub> is

(a3) -HN-CH(R<sup>1a</sup>-T''-Y'-ONO<sub>2</sub>)-COOR<sup>3a</sup>

wherein

25 R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-, or

R<sup>1a</sup> of the group A7) is -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>4</sub>-C(O)-,  
30 R<sup>3a</sup> is H or a (C<sub>1</sub>-C<sub>5</sub>) alkyl,

T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from the group A5) or A6),



T'' is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, when R<sup>1a</sup> is selected from the group A7),

Y' is as below defined;

5 or R<sub>x</sub> is selected from:

(a5) -R<sup>1b</sup>-CH(NHR<sup>4a</sup>)-C(O)-(T-Y-ONO<sub>2</sub>)

(a6) -R<sup>1b</sup>-CH(COOR<sup>3a</sup>)NH-(T'-Y-ONO<sub>2</sub>)

(a9) -R<sup>1b</sup>-CH(NH-T'-Y'-ONO<sub>2</sub>)-C(O)-(T-Y-ONO<sub>2</sub>) or

(a10) -R<sup>1b</sup>-CH(C(O)-T-Y'-ONO<sub>2</sub>)-NH-(T'-Y-ONO<sub>2</sub>)

10 wherein

R<sup>1b</sup> of the group A8) is selected from -O-CH(CH<sub>3</sub>)-, -O-CH<sub>2</sub>-, [-4-O-(C<sub>6</sub>H<sub>4</sub>)]-CH<sub>2</sub>-, or

R<sup>1b</sup> of the group A9) is selected from -HN-CH<sub>2</sub>-, -HN-(CH<sub>2</sub>)<sub>2</sub>-, -HN-(CH<sub>2</sub>)<sub>3</sub>-, -HN-(CH<sub>2</sub>)<sub>4</sub>-,

15 R<sup>1b</sup> of the group A10) is -O-CH<sub>2</sub>- or [-4-O-(C<sub>6</sub>H<sub>4</sub>)]-CH<sub>2</sub>-,

R<sup>3a</sup> is H or a (C<sub>1</sub>-C<sub>5</sub>) alkyl;

R<sup>4a</sup> is H or -C(O)CH<sub>3</sub>,

T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl,

20 T' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-,

Y and Y' are as below defined;

or R<sub>x</sub> is selected from:

(a7) -HN-CH(R<sup>1a</sup>-T''-Y'-ONO<sub>2</sub>)-C(O)-(T-Y-ONO<sub>2</sub>)

wherein

25 R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)-O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-, or

R<sup>1a</sup> of the group A7) is -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>4</sub>-C(O)-;

30 T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from A5) or A6),

T'' is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, when R<sup>1a</sup> is selected from A7),

T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl,

Y and Y' are as below defined;

or R<sub>x</sub> is selected from:

5 (b1) -HN-CH(R<sup>2</sup>)-CH<sub>2</sub>C(O)-(T-Y-ONO<sub>2</sub>)

wherein

R<sup>2</sup> of the group B1) is selected from H, CH<sub>3</sub>, isobutyl, isopropyl, benzyl;

10 R<sup>2</sup> of the group B2) is selected from -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)-OH- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)(4-OH)], or

R<sup>2</sup> of the group B3) is selected from -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'', wherein R'' is H, or -C(O)CH<sub>3</sub>,

15 R<sup>2</sup> of the group B4) is -CH<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>4</sub>-C(O)R''' wherein R''' is OR<sup>5a</sup> wherein R<sup>5a</sup> is H or a linear (C<sub>1</sub>-C<sub>5</sub>) alkyl,

T is -O-, -S-, -NR'-, -O-CH(R')-O-C(O)- wherein R' is H or a straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl,

Y is as below defined;

or R<sub>x</sub> is selected from:

20 (d1) -HN-CH(R<sup>12</sup>)-CH<sub>2</sub>-O-(T'''-Y-ONO<sub>2</sub>)

(d2) -O-CH<sub>2</sub>-CH(R<sup>12</sup>)-NH-(T'-Y-ONO<sub>2</sub>)

wherein

R<sup>12</sup> of the group D1) is selected from H, CH<sub>3</sub>, isobutyl, isopropyl, benzyl, or

25 R<sup>12</sup> of the group D2) is selected from -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)OH- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-OH)], or

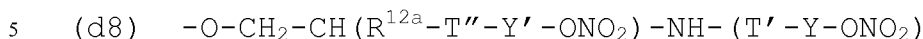
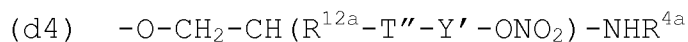
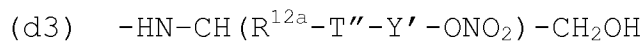
R<sup>12</sup> of the group D3) is selected from -CH<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>2</sub>-NHR'', -(CH<sub>2</sub>)<sub>3</sub>-NHR'', -(CH<sub>2</sub>)<sub>4</sub>-NHR'' wherein R'' is H, or

30 R<sup>12</sup> of the group D4) is -CH<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>2</sub>-C(O)R''', -(CH<sub>2</sub>)<sub>4</sub>-C(O)R''' wherein R''' is OR<sup>5a</sup> wherein R<sup>5a</sup> is H or a linear (C<sub>1</sub>-C<sub>5</sub>) alkyl,

T' and T''' are each independently selected from -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-,

Y is as below defined;

or  $R_x$  is selected from:



wherein

$\text{R}^{12a}$  of the group D5) is selected from  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}(\text{CH}_3)-\text{O}-$  or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4-\text{O})-]$ , or

$\text{R}^{12a}$  of the group D6) is selected from  $-\text{CH}_2-\text{NH}-$ ,  $-(\text{CH}_2)_2-\text{NH}-$ ,

10  $-(\text{CH}_2)_3-\text{NH}-$ ,  $-(\text{CH}_2)_4-\text{NH}-$ , or

$\text{R}^{12a}$  of the group D7) is  $-\text{CH}_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_2-\text{C}(\text{O})-$ ,  $-(\text{CH}_2)_4-\text{C}(\text{O})-$ ,  $\text{R}^{4a}$  is H or  $-\text{C}(\text{O})\text{CH}_3$ ,

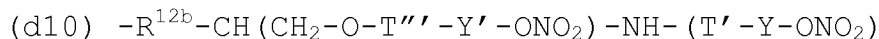
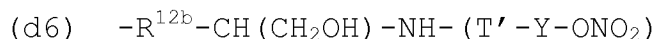
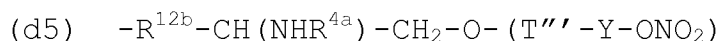
$\text{T}''$  is selected from  $-\text{C}(\text{O})-$  or  $-\text{C}(\text{O})-\text{X}''$  wherein  $\text{X}''$  is  $-\text{S}-$  or  $-\text{O}-$  when  $\text{R}^{12a}$  is selected from D5) or D6),

15  $\text{T}''$  is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{O}-\text{CH}(\text{R}')-\text{O}-\text{C}(\text{O})-$  wherein  $\text{R}'$  is H or a straight or branched  $\text{C}_1-\text{C}_4$  alkyl when  $\text{R}^{12a}$  is selected from D7),

$\text{T}'''$  is selected from  $-\text{C}(\text{O})-$  or  $-\text{C}(\text{O})-\text{X}''$  wherein  $\text{X}''$  is  $-\text{S}-$  or  $-\text{O}-$ ,

$\text{Y}$  and  $\text{Y}'$  are as below defined;

20 or  $R_x$  is selected from:



25 wherein

$\text{R}^{12b}$  of the group D8) is selected from  $-\text{O}-\text{CH}(\text{CH}_3)-$ ,  $-\text{O}-\text{CH}_2-$ ,  $[-4-\text{O}-(\text{C}_6\text{H}_4)]-\text{CH}_2-$ , or

$\text{R}^{12b}$  of the group D9) is selected from  $-\text{HN}-\text{CH}_2-$ ,  $-\text{HN}-(\text{CH}_2)_2-$ ,  $-\text{HN}-(\text{CH}_2)_3-$ ,  $-\text{HN}-(\text{CH}_2)_4-$ ,

30  $\text{R}^{4a}$  is H or  $-\text{C}(\text{O})-\text{CH}_3$ ,

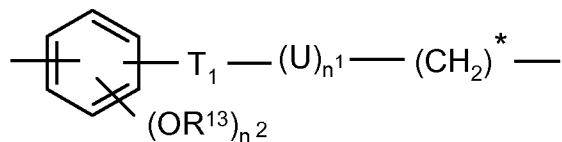
$\text{T}'$  and  $\text{T}'''$  are each independently selected from  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{X}''$ , wherein  $\text{X}''$  is  $-\text{S}-$  or  $-\text{O}-$ ,

$\text{Y}$  and  $\text{Y}'$  are each independently selected from

a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,
- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

d)



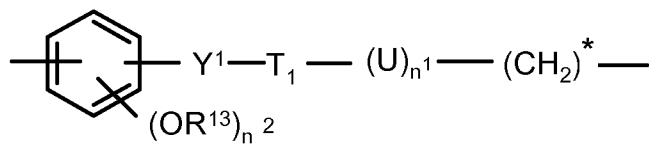
d)

wherein:

n<sup>2</sup> is an integer from 0 to 2, R<sup>13</sup> is H or CH<sub>3</sub>, T<sub>1</sub> is -O-C(O)- or -C(O)O-,

- 10 n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

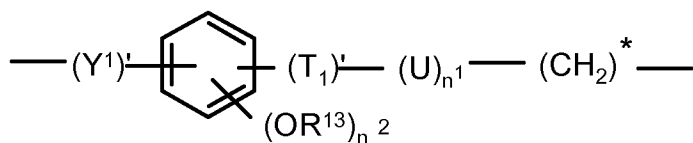
e)



e)

- 15 n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>, Y<sup>1</sup> is -CH=CH-(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>- and n<sup>2'</sup> is 0, T<sub>1</sub> is -C(O)O- and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene;

e')



e')

- 20 wherein:

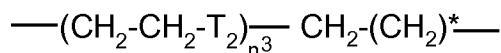
n<sup>2</sup> is 1, R<sup>13</sup> is CH<sub>3</sub>,

Y<sup>1</sup> is -(CH<sub>2</sub>)<sub>n<sup>2'</sup></sub>-CH=CH- and n<sup>2'</sup> is 0,

(T<sub>1</sub>)' = -O-C(O)-,

- 25 n<sup>1</sup> is 1 and U is a linear C<sub>1</sub>-C<sub>10</sub> alkylene or U is a linear or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

f)



wherein  $T_2$  is -O- or -S-, -NH-,

$n^3$  is 1 or 2,

when Y and Y' are selected from d), e), e') or f), the -ONO<sub>2</sub> group of -(T-Y-ONO<sub>2</sub>), -(T'-Y-ONO<sub>2</sub>), -(T''-Y'-ONO<sub>2</sub>), -(T'-Y'-ONO<sub>2</sub>),  
 5 -(T'''-Y-ONO<sub>2</sub>) and -(T'''-Y'-ONO<sub>2</sub>) is linked to the -(CH<sub>2</sub>)\*-group.

**15.** The nitric oxide releasing compounds according to claim 14 wherein

10  $R_x$  is

(a5)  $-R^{1b}-CH(NHR^{4a})-C(O)-(T-Y-ONO_2)$  or

(a9)  $-R^{1b}-CH(NH-T'-Y'-ONO_2)-C(O)-(T-Y-ONO_2)$

$R^{1b}$  of the group A10) is -O-CH<sub>2</sub>- or [-4-O-(C<sub>6</sub>H<sub>4</sub>)]-CH<sub>2</sub>-,

$R^{4a}$  is H or -C(O)CH<sub>3</sub>,

15 T is selected from -O-, -S-, -NR'- wherein R' is as above defined,

T' is -C(O)- and

Y and Y' are each independently selected from

a)

20 - a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group.

**16.** The nitric oxide releasing compounds according to claim

25 13 wherein a is 0 and

$R_x$  is

(a2)  $-C(O)-CH(R^1)-NH-(T'-Y-ONO_2)$

wherein

$R^1$  of the group A1) is selected from H, isobutyl, benzyl,

30 C<sub>6</sub>H<sub>5</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from -F, -Cl, I, -NO<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>3</sub>, CN, C<sub>6</sub>H<sub>5</sub>CO-,

$R^1$  of the group A2) is selected from -CH<sub>2</sub>-OH, -CH(CH<sub>3</sub>)OH- or

$-\text{CH}_2[(\text{C}_6\text{H}_4)-(4\text{-OH})]$ , or

$\text{R}^1$  of the group A3) is selected from  $-\text{CH}_2\text{-NHR}''$ ,  $-(\text{CH}_2)_2\text{-NHR}''$ ,  
 $-(\text{CH}_2)_3\text{-NHR}''$ ,  $-(\text{CH}_2)_4\text{-NHR}''$ , wherein  $\text{R}''$  is H or  $-\text{C}(\text{O})\text{CH}_3$ ,

$\text{R}^1$  of the group A4) is selected from  $-\text{CH}_2\text{-C}(\text{O})\text{R}'''$ ,

5  $-(\text{CH}_2)_2\text{-C}(\text{O})\text{R}'''$ ,  $-(\text{CH}_2)_4\text{-C}(\text{O})\text{R}'''$  wherein  $\text{R}'''$  is  $\text{OR}^{5a}$  wherein  $\text{R}^{5a}$   
 is H or a linear ( $\text{C}_1\text{-C}_5$ ) alkyl,

$\text{T}'$  is  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{-X}''$  wherein  $\text{X}''$  is  $-\text{S}-$  or  $-\text{O}-$ ,

$\text{Y}$  is as below defined;

or  $\text{R}_x$  is

10 (a4)  $-\text{C}(\text{O})\text{-CH}(\text{R}^{1a}\text{-T}''\text{-Y}'\text{-ONO}_2)\text{-NHR}^{4a}$

wherein  $\text{R}^{1a}$  of the group A5) is selected from  $-\text{CH}_2\text{-O}-$ ,  $-\text{CH}(\text{CH}_3)\text{O}-$   
 or  $-\text{CH}_2[(\text{C}_6\text{H}_4)-(4\text{-O})-]$ , or

$\text{R}^{1a}$  of the group A6) is selected from  $-\text{CH}_2\text{-NH}-$ ,  $-(\text{CH}_2)_2\text{-NH}-$ ,  
 $-(\text{CH}_2)_3\text{-NH}-$ ,  $-(\text{CH}_2)_4\text{-NH}-$ , or

15  $\text{R}^{1a}$  of the group A7) is selected from  $-\text{CH}_2\text{-C}(\text{O})-$ ,  $-(\text{CH}_2)_2\text{-C}(\text{O})-$ ,  
 $-(\text{CH}_2)_4\text{-C}(\text{O})-$ ;

$\text{R}^{4a}$  is H or  $-\text{C}(\text{O})\text{CH}_3$ ,

$\text{T}''$  is  $-\text{C}(\text{O})-$  or  $-\text{C}(\text{O})\text{-X}''$  wherein  $\text{X}''$  is  $-\text{S}-$  or  $-\text{O}-$  when  $\text{R}^{1a}$  is  
 selected from the group A5) or A6),

20  $\text{T}''$  is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$  or  $-\text{O-CH}(\text{R}')\text{-O-C}(\text{O})-$  wherein  $\text{R}'$  is H or  
 $-\text{CH}_3$  when  $\text{R}^{1a}$  is selected from the group A7),

$\text{Y}'$  is as below defined;

or  $\text{R}_x$  is selected from:

(a5)  $-\text{R}^{1b}\text{-CH}(\text{NHR}^{4a})\text{-C}(\text{O})\text{-(T-Y-ONO}_2)$

25 (a6)  $-\text{R}^{1b}\text{-CH}(\text{COOR}^{3a})\text{NH-(T'-Y-ONO}_2)$

(a9)  $-\text{R}^{1b}\text{-CH}(\text{NH-T'-Y'-ONO}_2)\text{-C}(\text{O})\text{-(T-Y-ONO}_2)$  or

(a10)  $-\text{R}^{1b}\text{-CH}(\text{C}(\text{O})\text{-T-Y'-ONO}_2)\text{-NH-(T'-Y-ONO}_2)$

wherein

$\text{R}^{1b}$  of the group A10) is selected from  $-\text{C}(\text{O})\text{-CH}_2-$ ,  $-\text{C}(\text{O})\text{-(CH}_2)_2-$ ,  
 30  $-\text{C}(\text{O})\text{-(CH}_2)_4-$ ,

$\text{R}^{3a}$  is H or a ( $\text{C}_1\text{-C}_5$ ) alkyl,

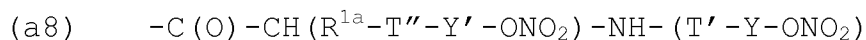
$\text{R}^{4a}$  is H or  $-\text{C}(\text{O})\text{CH}_3$ ,

$\text{T}$  is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$  or  $-\text{O-CH}(\text{R}')\text{-O-C}(\text{O})-$  wherein  $\text{R}'$  is H or  
 $-\text{CH}_3$ ,

T' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-,

Y and Y' are as below defined;

or R<sub>x</sub> is



5 wherein

R<sup>1a</sup> of the group A5) is selected from -CH<sub>2</sub>-O-, -CH(CH<sub>3</sub>)-O- or -CH<sub>2</sub>[(C<sub>6</sub>H<sub>4</sub>)-(4-O)-], or

R<sup>1a</sup> of the group A6) is selected from -CH<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>2</sub>-NH-, -(CH<sub>2</sub>)<sub>3</sub>-NH-, -(CH<sub>2</sub>)<sub>4</sub>-NH-, or

10 R<sup>1a</sup> of the group A7) is selected from -CH<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>2</sub>-C(O)-, -(CH<sub>2</sub>)<sub>4</sub>-C(O)-,

T'' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-, when R<sup>1a</sup> is selected from the group A5) or A6),

15 T'' is -O-, -S-, -NR'- or -O-CH(R')-O-C(O)- wherein R' is H or -CH<sub>3</sub>, when R<sup>1a</sup> is selected from the group A7);

T' is -C(O)- or -C(O)-X'' wherein X'' is -S- or -O-,

Y and Y' are as below defined;

or R<sub>x</sub> is



20 wherein

R<sup>2</sup> of the group B1) is selected from H, CH<sub>3</sub>, isobutyl, isopropyl, benzyl;

T' is -C(O)-, -C(O)-X'' wherein X'' is -S- or -O-,

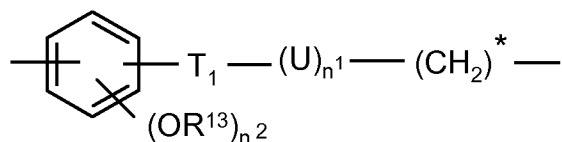
Y and Y' are each independently selected from

25 a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

d)



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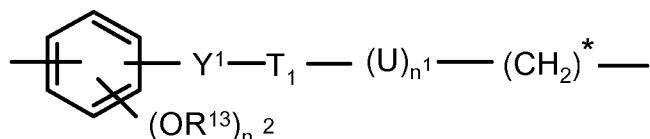
d)

wherein:

$n^2$  is an integer from 0 to 2,  $R^{13}$  is H or  $\text{CH}_3$ ,  $T_1$  is  $-\text{O}-\text{C}(\text{O})-$  or  $-\text{C}(\text{O})\text{O}-$ ,

$n^1$  is 1 and U is a linear  $\text{C}_1$ - $\text{C}_{10}$  alkylene or U is a linear or branched  $\text{C}_1$ - $\text{C}_{10}$  alkylene substituted with a  $-\text{ONO}_2$  group;

5 e)

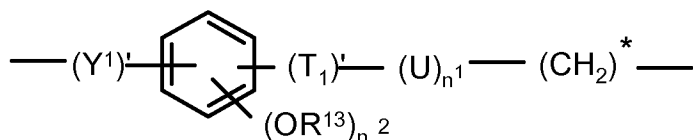


e)

$n^2$  is 1,  $R^{13}$  is  $\text{CH}_3$ ,  $\text{Y}^1$  is  $-\text{CH}=\text{CH}-(\text{CH}_2)_{n^{2'}}-$  and  $n^{2'}$  is 0,

$\text{T}_1$  is  $-\text{C}(\text{O})\text{O}-$  and U is a linear  $\text{C}_1$ - $\text{C}_{10}$  alkylene;

10 e')



e'

wherein:

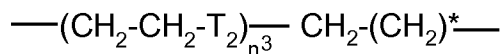
$n^2$  is 1,  $R^{13}$  is  $\text{CH}_3$ ,

15  $\text{Y}^1$  is  $-(\text{CH}_2)_{n^{2'}}-\text{CH}=\text{CH}-$  and  $n^{2'}$  is 0,

$(\text{T}_1)' = -\text{O}-\text{C}(\text{O})-$ ,

$n^1$  is 1 and U is a linear  $\text{C}_1$ - $\text{C}_{10}$  alkylene or U is a linear or branched  $\text{C}_1$ - $\text{C}_{10}$  alkylene substituted with a  $-\text{ONO}_2$  group;

f)



20

wherein  $\text{T}_2$  is  $-\text{O}-$  or  $-\text{S}-$ ,  $-\text{NH}-$ ,

$n^3$  is 1 or 2,

when Y and  $\text{Y}'$  are selected from d), e), e') or f), the  $-\text{ONO}_2$  group of  $-(\text{T}-\text{Y}-\text{ONO}_2)$ ,  $-(\text{T}'-\text{Y}-\text{ONO}_2)$ ,  $-(\text{T}''-\text{Y}'-\text{ONO}_2)$ ,  $-(\text{T}'-\text{Y}'-\text{ONO}_2)$ ,

25  $-(\text{T}'''-\text{Y}-\text{ONO}_2)$  and  $-(\text{T}'''-\text{Y}'-\text{ONO}_2)$  is linked to the  $-(\text{CH}_2)^*$ -group.

**17.** The nitric oxide releasing compounds according to claim 16 wherein



R<sub>x</sub> is



wherein

R<sup>1</sup> of the group A1) is H,

5 T' is -C(O)-,

Y is selected from

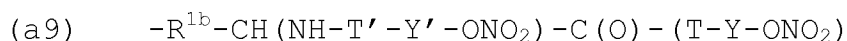
a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

10 - a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group.

**18.** The nitric oxide releasing compounds of claim 16 wherein

R<sub>x</sub> is selected from



wherein

R<sup>1b</sup> of the group A10) is -C(O)-CH<sub>2</sub>-,

R<sup>3a</sup> is H or a (C<sub>1</sub>-C<sub>5</sub>) alkyl,

20 R<sup>4a</sup> is H or -C(O)CH<sub>3</sub>,

T is selected from -O-, -S-, -NR'- wherein R' is as above defined,

T' is -C(O)- and

Y and Y' are each independently selected from

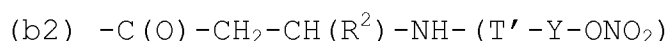
25 a)

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group.

30 **19.** The nitric oxide releasing compounds according to claim 16 wherein

R<sub>x</sub> is



R<sup>2</sup> of the group B1) is H,

T' is -C(O)-,

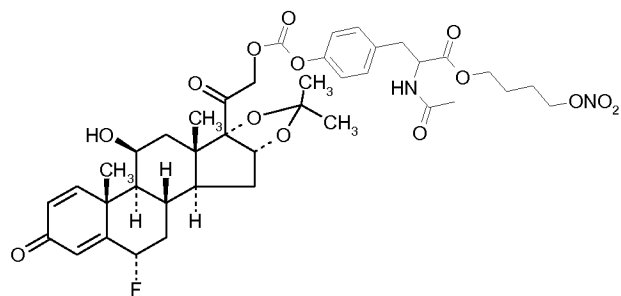
Y is selected from

a)

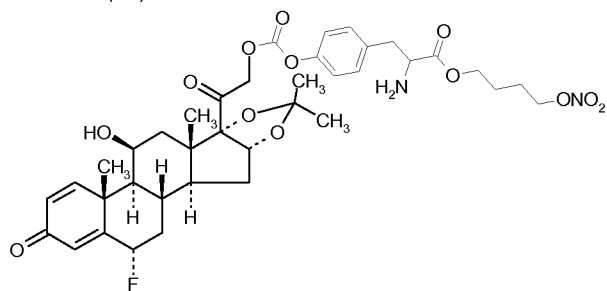
- a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene,

5 - a straight or branched C<sub>1</sub>-C<sub>10</sub> alkylene substituted with a -ONO<sub>2</sub> group;

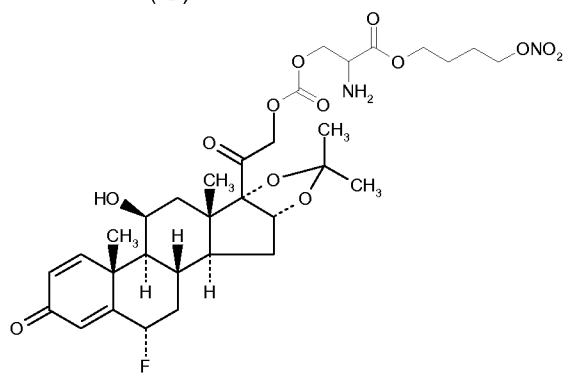
**20.** Nitric oxide releasing compounds according to claim 13



(3)

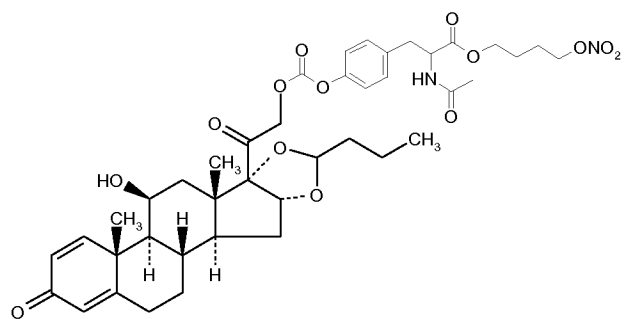


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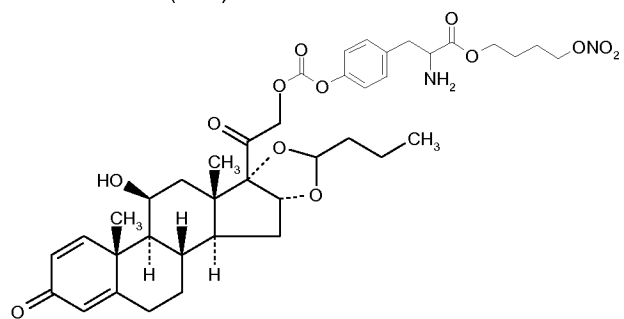


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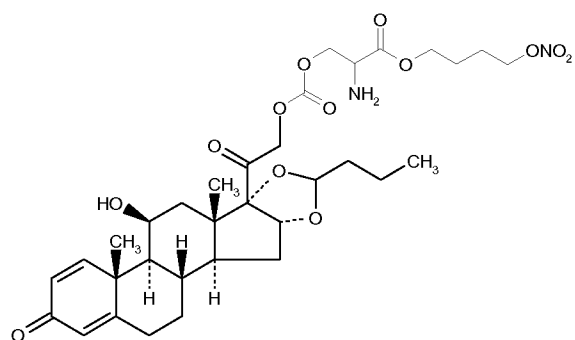


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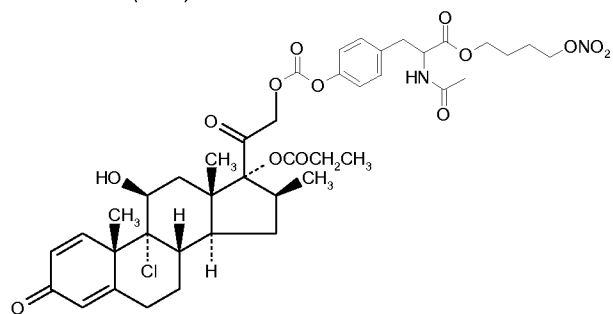


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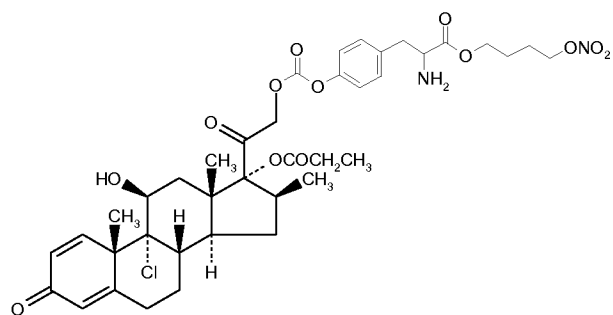
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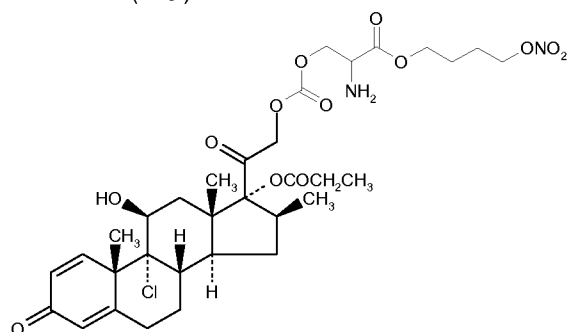
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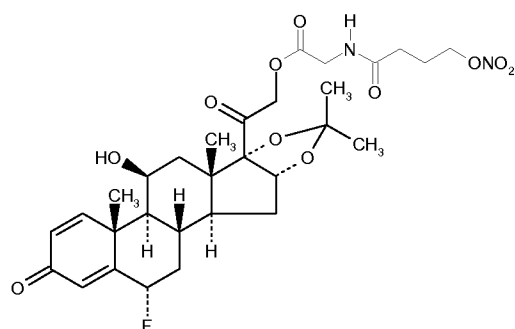
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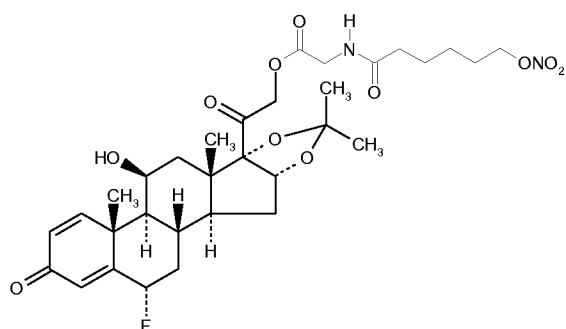
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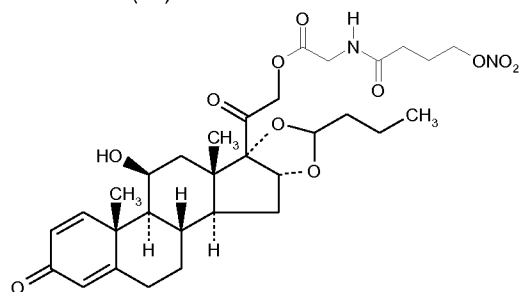
# **21.** Nitric oxide releasing compounds according to claim 17



(1)



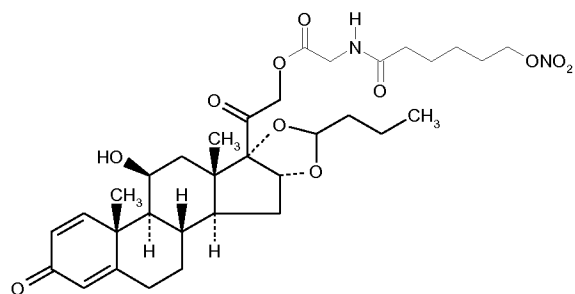
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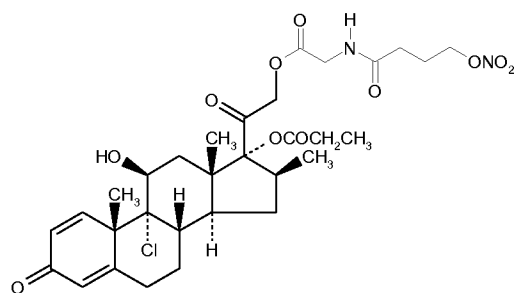
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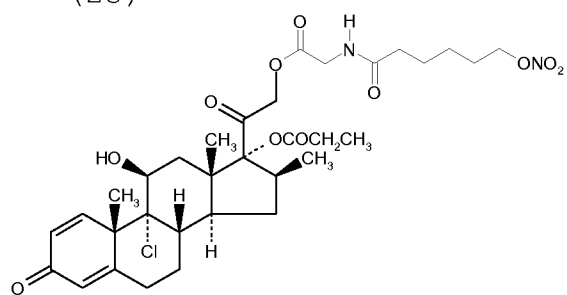
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(13)

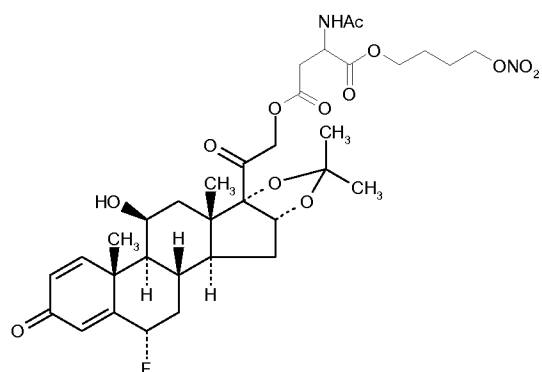


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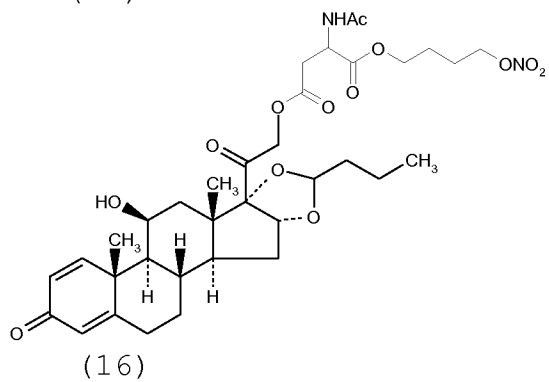
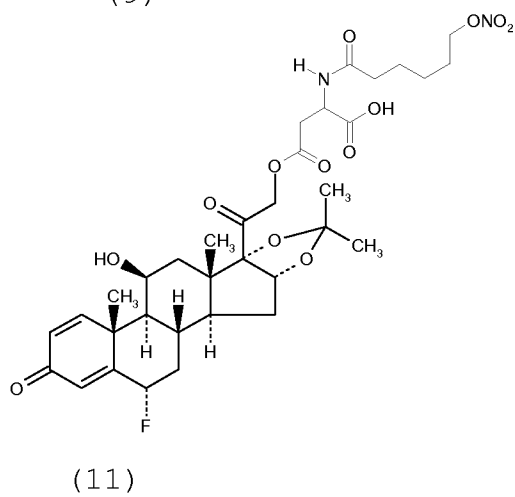
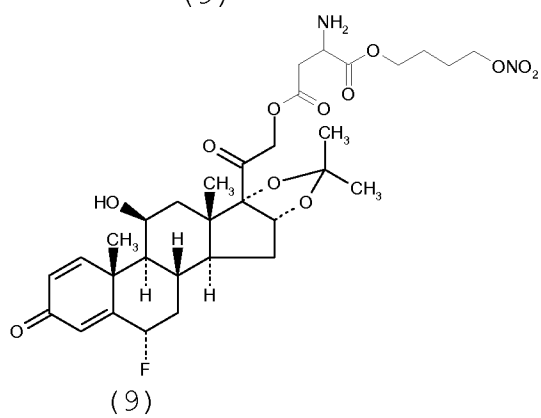
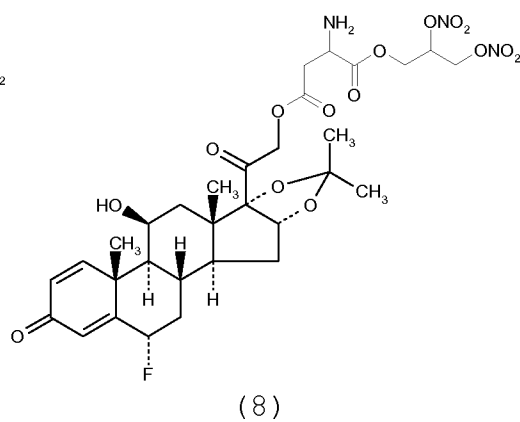
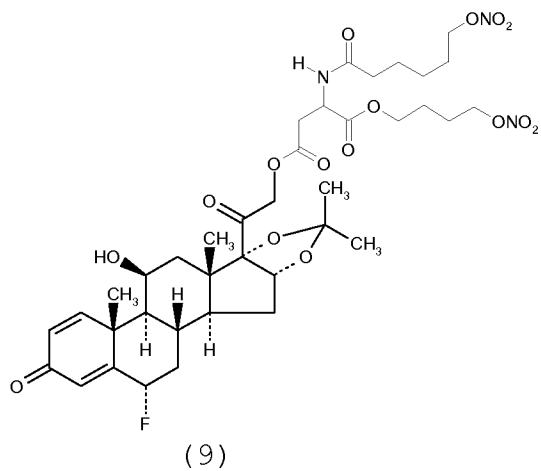


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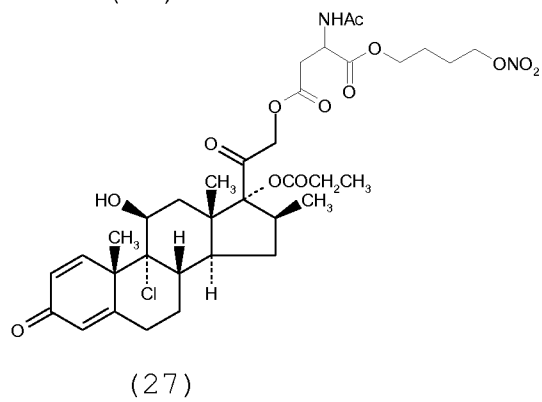
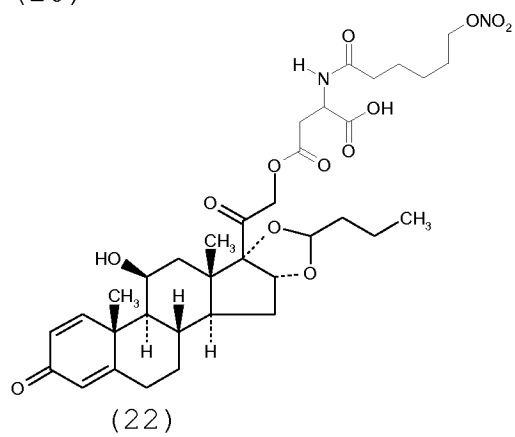
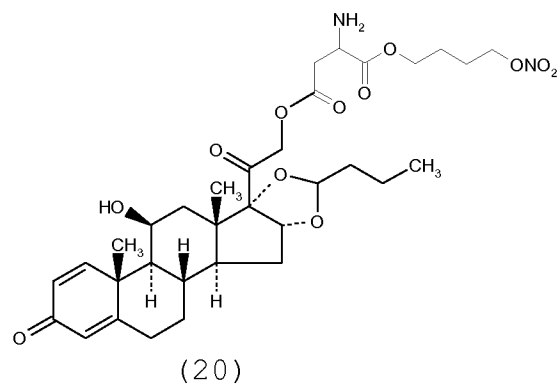
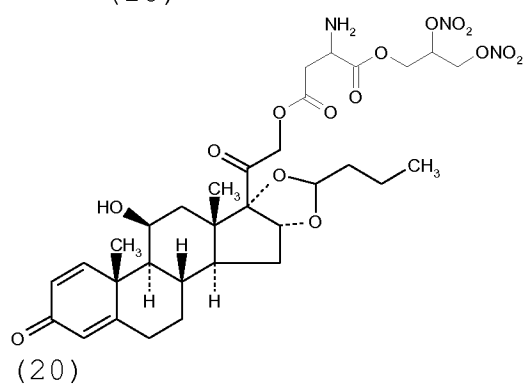
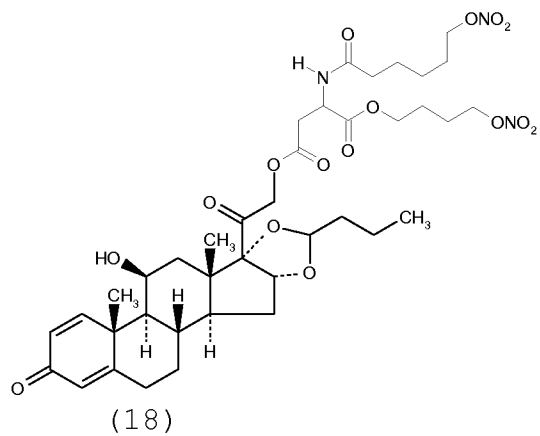
22. Nitric oxide releasing compounds according to claim 18



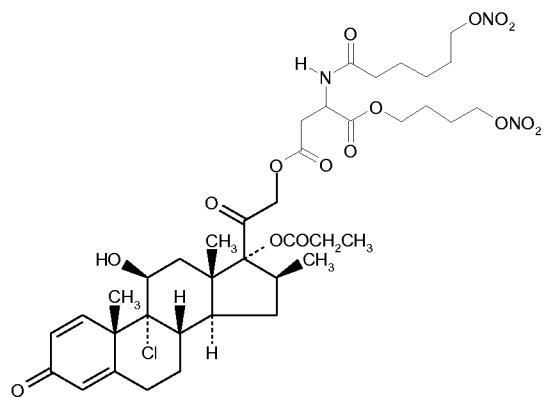
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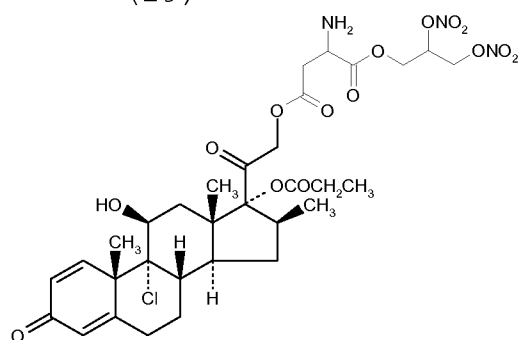
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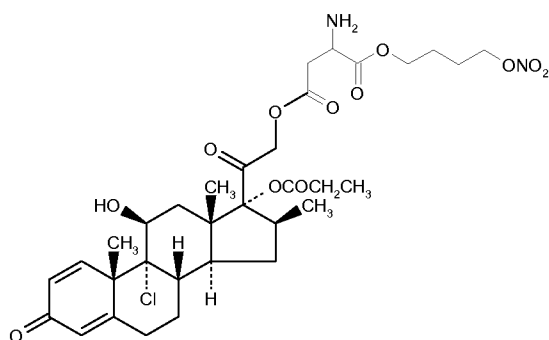
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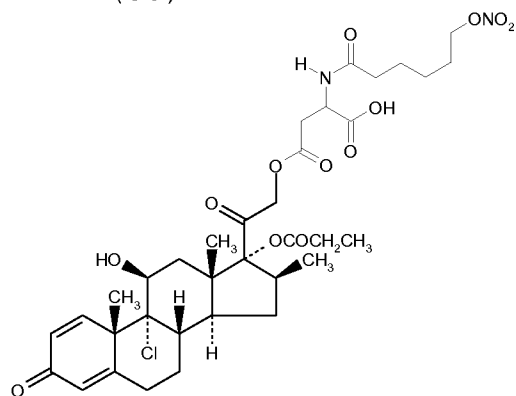
(29)



(30)

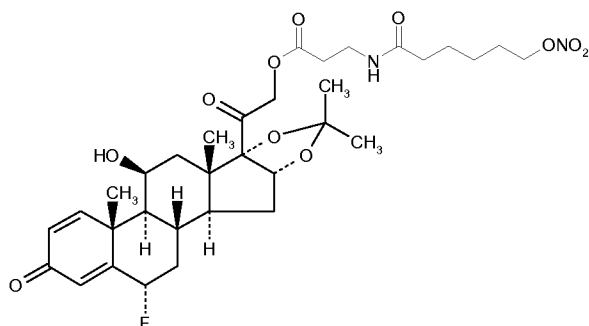


(31)



(33)

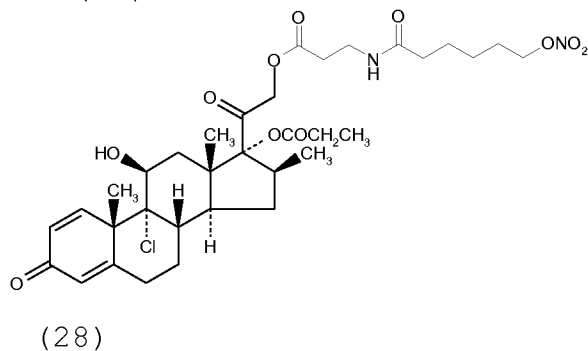
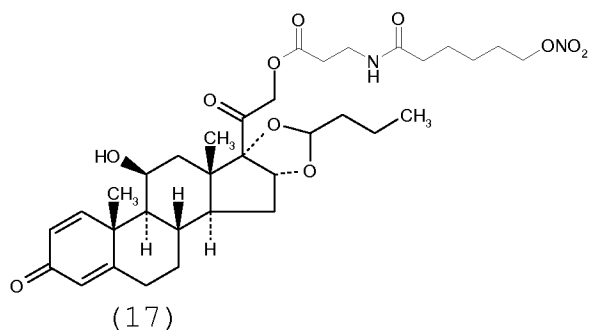
## 23. Nitric oxide releasing compounds according to claim 19



(6)



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5

**24.** Nitric oxide releasing compounds according to claims 13 to 19 for use as medicament.

**25.** Pharmaceutical composition comprising a nitric oxide releasing compound of formula (I) according to claim 13 and a pharmaceutical acceptable excipient.

**26.** A composition comprising a nitric oxide releasing compound of formula (I) according to claim 13 and at least one bronchodilator or a pharmaceutical acceptable salt or solvate thereof.

**27.** The composition according to claim 26 wherein the bronchodilator is selected from anticholinergic bronchodilators,  $\beta_2$ -agonists, ephedrine or xanthines.

**28.** The composition according to claims 25 or 26 wherein the nitric oxide releasing compound and the bronchodilator are administered simultaneously.

25

**29.** The composition according to claims 25 or 26 wherein the nitric oxide releasing compound and the bronchodilator are administered sequentially.

5 **30.** The composition according to claim 29 wherein the nitric oxide releasing compound is administered before or after the bronchodilator.

**31.** The composition according to claims 25 or 26 for use in  
10 the treatment of respiratory diseases.

**32.** The composition according to claim 31 wherein respiratory diseases comprise asthma, chronic obstructive pulmonary diseases, acute respiratory distress syndrome, allergic  
15 rhinitis and respiratory tract diseases associated with inflammation.

**33.** The composition according to claims 25 or 26 pharmaceutical acceptable excipient.

20

25

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# INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/050947

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07J41/00 A61K31/573 A61P5/44

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)

C07J A61K A61P

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, CHEM ABS Data, BEILSTEIN Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/064443 A (NICOX SA [FR]; DEL SOLDATO PIERO [IT]; ONGINI ENNIO [IT]) 7 August 2003 (2003-08-07) page 57 - page 65; claim 8	1-33
X	BARALDI, PIER GIOVANNI ET AL: "Synthesis of Nitro Esters of Prednisolone, New Compounds Combining Pharmacological Properties of Both Glucocorticoids and Nitric Oxide" JOURNAL OF MEDICINAL CHEMISTRY, 47(3), 711-719 CODEN: JMCMAR; ISSN: 0022-2623, 2004, page 712, XP002475140 figure 1	1-33
X	WO 00/61604 A (NICOX SA [FR]; DEL SOLDATO PIERO [IT]) 19 October 2000 (2000-10-19) page 55 - page 59; examples 3-5	1-33
	-/-	



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
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\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

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\*G\* document member of the same patent family

Date of the actual completion of the international search

25 April 2008

Date of mailing of the international search report

13/05/2008

Name and mailing address of the ISA/

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Authorized officer

Mezzato, Stefano

# INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/050947

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/15568 A (NICOX SA [FR]; DEL SOLDATO PIERO [IT]) 16 April 1998 (1998-04-16) page 27; compound III -----	1-33
X	PERRETTI, M. ET AL: "Generation of innovative anti-inflammatory and anti-arthritic glucocorticoid derivatives that release NO: the nitro-steroids" DIGESTIVE AND LIVER DISEASE, 35(SUPPL. 2), S41-S48 CODEN: DLDIFK; ISSN: 1590-8658, 2003, XP002475141 page S43; figure 2 -----	1-33
X	EP 1 336 602 A (SCARAMUZZINO GIOVANNI [IT]) 20 August 2003 (2003-08-20) page 166; compounds 11-12 -----	1-33
X,P	WO 2007/025632 A (NICOX SA [FR]; FERRER INTERNAC S A [ES]; BENEDINI FRANCESCA [IT]; ONGI) 8 March 2007 (2007-03-08) page 74 - page 83; claim 5 -----	1-33

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/050947

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03064443	A	07-08-2003	BR 0307027 A CA 2473249 A1 EP 1470150 A2 IT MI20020148 A1 JP 2005516070 T MX PA04007337 A NZ 534147 A US 2006052594 A1	03-11-2004 07-08-2003 27-10-2004 29-07-2003 02-06-2005 26-11-2004 29-09-2006 09-03-2006
WO 0061604	A	19-10-2000	AT 274521 T AU 766798 B2 AU 3820100 A BR 0009696 A CA 2370446 A1 CN 1420891 A CN 1916013 A DE 60013266 D1 DE 60013266 T2 EP 1169337 A2 ES 2226805 T3 HU 0201872 A2 IT MI990751 A1 JP 2002542162 T KR 20060123788 A MX PA01010212 A NO 20014925 A NZ 514572 A PL 350775 A1 PT 1169337 T RU 2240325 C2 TR 200102929 T2 TR 200201899 T2 US 6909007 B1 ZA 200108124 A	15-09-2004 23-10-2003 14-11-2000 08-01-2002 19-10-2000 28-05-2003 21-02-2007 30-09-2004 20-01-2005 09-01-2002 01-04-2005 28-10-2002 13-10-2000 10-12-2002 04-12-2006 18-09-2002 13-12-2001 26-03-2004 10-02-2003 30-11-2004 20-11-2004 22-04-2002 21-11-2002 21-06-2005 03-01-2003
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EP 1336602	A	20-08-2003	NONE	
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## INTERNATIONAL SEARCH REPORT

### Information on patent family members

International application No

PCT/EP2008/050947

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007025632 A		UY 29779 A1	29-12-2006