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(54) **NITRIC OXIDE RELEASING STEROIDS**

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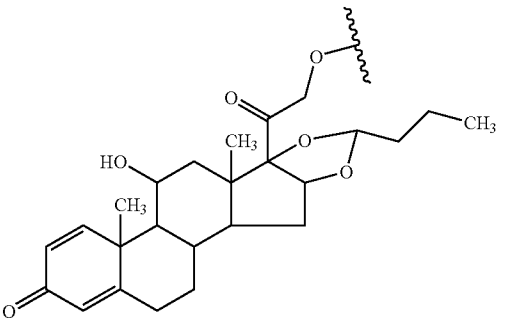
(57) **ABSTRACT**

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.

(II)



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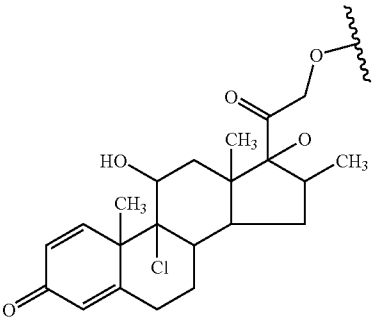

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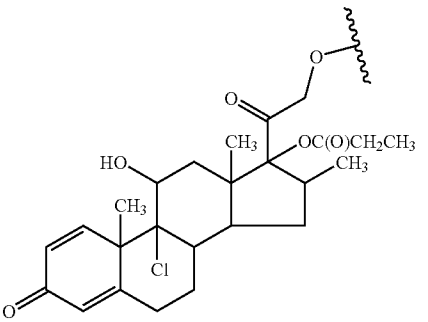

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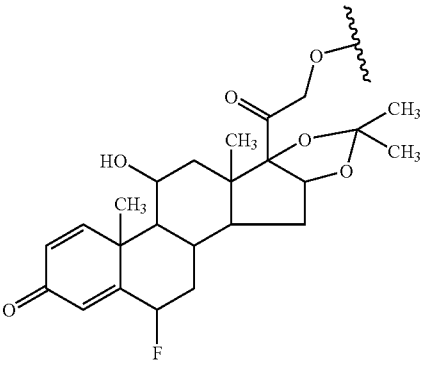


NITRIC OXIDE RELEASING STEROIDS

[0001] 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.

[0002] 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.

[0003] 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

[0004] 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.

[0005] For example, German patent DE 2,222,491 describes the preparation of pregnane derivatives having in position 21 the —CH_2—O—NO_2 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.

[0006] U.S. Pat. No. 3,494,941 describes steroid derivatives from 3-hydroxyextrane 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_2 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 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.

[0007] U.S. Pat. No. 3,183,252 describes derivatives of 16-nitrate-alkylpregnanes wherein the alkyl group is linked to the pregnane 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.

[0008] WO 98/15568 and WO 03/064443 in the name of the Applicant 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.

[0009] Patent application WO 00/61604 in the name of the Applicant 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 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.

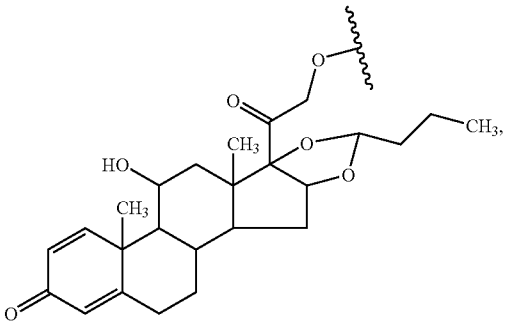
[0010] The Applicant has surprisingly and unexpectedly found a class of nitric oxide releasing compounds with a better efficacy, bioavailability and/or a prolonged release of NO in comparison with the compounds known in prior art. In general the compounds of the present invention have a better drugability in comparison to the corresponding compounds of the prior art.

[0011] An object of the present invention is to provide nitric oxide releasing compounds of general formula (I)

$$R\text{-}(Z)_a\text{-}R_x \qquad (I)$$

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)



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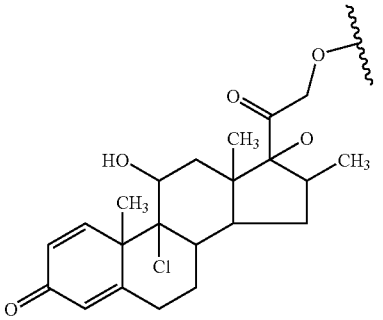

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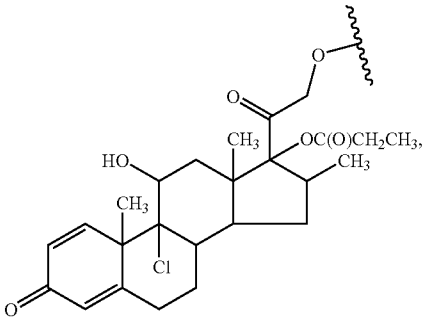

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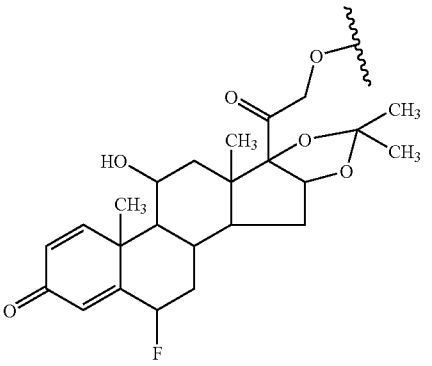


a is 0 or 1,

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:

A)

[0012] (a1) —HN—CH(R^1)—C(O)-(T-Y—ONO_2)

[0013] (a2) —C(O)—CH(R^1)—NH-(T'-Y—ONO_2)

[0014] (a3) —HN—CH(R^{1a}-T"-Y'—ONO_2)—$COOR^{3a}$

[0015] (a4) —C(O)—CH(R^{1a}-T"-Y'—ONO_2)—NHR^{4a}

[0016] (a5) —R^{1b}—CH(NHR^{4a})—C(O)-(T-Y—ONO_2)

[0017] (a6) —R^{1b}—CH($COOR^{1a}$) NH-(T'-Y'—ONO_2)

[0018] (a7) —HN—CH(R^{1a}-T'-Y'—ONO_2)—C(O)-(T-Y—ONO_2)

[0019] (a8) —C(O)—CH(R^{1a}-T"-Y'—ONO_2)—NH-(T'-Y—ONO_2)

[0020] (a9) —R^{1b}—CH(NH-T'-Y'—ONO_2)—C(O)-(T-Y—ONO_2)

[0021] (a10) —R^{1b}—CH(C(O)-T-Y'—ONO_2)—NH-(T'-Y—ONO_2)

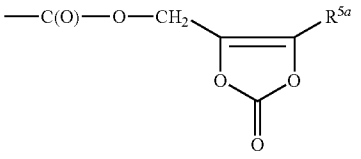
[0022] wherein:

[0023] R^1 is selected from:

[0024] A1) H, —CH_3, isopropyl, isobutyl, sec-butyl, tert-butyl, methylthio-$(CH_2)_2$—, phenyl, benzyl, C_6H, —CH_2—CH_2—, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, C_6H_5CO—; 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, 2-pyrrolidyl, 3-tryptophanyl-CH_2—, 3-benzothienyl-CH_2—, 4-imidazolyl-CH_2—, 9-anthranyl-CH_2—, cyclohexyl, cyclohexyl-CH_2—, cyclohexyl-$(CH_2)_2$—, cyclopentyl-CH_2—, $(C_6H_5)_2CH$—, 4-$B(OH)_2$-benzyl, 4-quinolyl-CH_2—, 3-quinolyl-CH_2—, 2-quinolyl-CH_2—, 2-quinoxalyl-CH_2—, 2-furyl-CH_2—, 1-naphtyl-CH_2—, 2-naphtyl-CH_2—, 2-pyridyl-CH_2—, 3-pyridyl-CH_2—, 4-pyridyl-CH_2—, 2-thienyl-CH_2—, 3-thienyl-CH_2—, C_6H_4—CH═CH—CH_2—, CH_2═CH—CH_2—, CH≡CH—CH_2—, NH_2—CO—CH_2—, NH_2—CO—$(CH_2)_2$—, NH_2(═NH)NH—$(CH_2)_3$—, P(═O)$(OCH_3)_2$, I—CH_2—, preferably R^1 is H, —CH_3, isopropyl, benzyl;

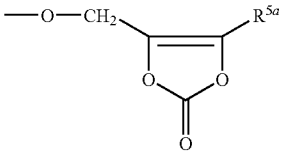
[0025] A2) —CH_2—SH, —CH_2—OH, —$CH(CH_3)$—OH, —CH_2[(C_6H_4)-(4-OH)], —CH_2—[(C_6H_2)-(3,5-diiodo)-(4-OH)]
—CH_2—[(C_6H_3)-(3-nitro)-(4-OH)], preferably R^1 is —CH_2—OH or —CH_2[(C_6H_4)-(4-OH)];

[0026] A3) —CH_2—NHR", —$(CH_2)_2$—NHR", —$(CH_2)_3$—NHR", —$(CH_2)_4$—NHR", wherein R" is H, —C(O)CH_3 or



wherein R^{5a} is H or a linear or branched C_1-C_{10} alkyl chain, preferably R^{5a} is H or a linear (C_1-C_5) alkyl, preferably R^1 is —$(CH_2)_4$—NHR", wherein R" is as above defined,

[0027] A4) —CH_2—C(O)R'", —$(CH_2)_2$—C(O)R'", —$(CH_2)_4$—C(O)R'" wherein R'" is —OR^{5a} or



wherein R^{5a} is as above defined, preferably R^1 is —CH_2—C(O)R'", wherein R'" is as above defined,

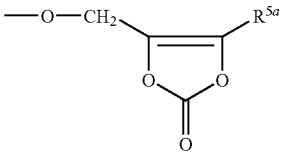
[0028] R^{1a} is selected from:

[0029] A5) —CH_2—S—, —CH_2—O—, —$CH(CH_3)$—O—, —CH_2[(C_6H_4)-(4-O)—], —CH_2-[(3,5-diiodo)-(C_6H_2)-(4-O)—], —CH_2-[(3-nitro)-(C_6H_3)-(4-O)—], preferably R^{1a} is —CH_2—O—;

[0030] A6) —CH_2—NH—, —$(CH_2)_2$—NH—, —$(CH_2)_3$—NH—, —$(CH_2)_4$—NH—, preferably R^{1a} is —$(CH_2)_4$—NH— or —CH_2—NH—,

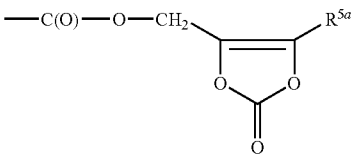
[0031] A7) —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—, preferably R^{1a} is —CH_2—C(O)—;

[0032] R^{3a} is selected from H, —R^{5a} or



[0033] wherein R^{5a} is as above defined,

[0034] R^{4a} is selected from H or —C(O)CH_3 or



[0035] wherein R^{5a} is as above defined,

[0036] R^{1b} is selected from

[0037] A8) —S—CH_2—, —O—$CH(CH_3)$—, —O—CH_2—, [-(4-O)—(C_6H_4)]—CH_2—, [-(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—;

[0038] 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—;

[0039] 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 —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'— 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:

B)

[0040] (b1) —HN—$CH(R^2)$—CH_2—C(O)-(T-Y—ONO_2)

[0041] (b2) —C(O)—CH_2—$CH(R^2)$—NH-(T'-Y—ONO_2)

[0042] (b3) —HN—$CH(R^{2a}$-T"-Y'—$ONO_2)$—CH_2COOR^{3a}

[0043] (b4) —C(O)—CH_2—$CH(R^{2a}$-T"-Y'—$ONO_2)$—NHR^{4a}

[0044] (b5) —R^{2b}—$CH(NHR^{4a})$—$CH_2C(O)$-(T-Y—ONO_2)

[0045] (b6) —R^2—$CH(CH_2COOR^{3a})$NH-(T'-Y—ONO_2)

[0046] (b7) —HN—$CH(R^{2a}$-T"-Y'—$ONO_2)$—CH_2—C(O)-(T-Y—ONO_2)

[0047] (b8) —C(O)—CH_2—$CH(R^{2a}$-T"-Y'—$ONO_2)$—NH-(T'-Y—ONO_2)

[0048] (b9) —R^2—CH(NH-T'-Y'—ONO_2)—$CH_2C(O)$-(T-Y—ONO_2)

[0049] (b10) —R^2—$CH(CH_2C(O)$-T-Y'—$ONO_2)$—NH-(T'-Y—ONO_2)

[0050] wherein

[0051] R^2 is selected from:

[0052] B1) H, —CH_3, CF_3, isopropyl, isobutyl, sec-butyl, methylthio-$(CH_2)_2$—, phenyl, benzyl, 3-tryptophanyl-CH_2—, NH_2—C(O)—CH_2—, NH_2—C(O)—$(CH_2)_2$—, NH_2(═NH)NH—$(CH_2)_3$—, tBuO—$CH(CH_3)$—, benzyl-O—CH_2—, 4-terbutoxy-benzyl, 4-phenylbenzyl, preferably R^2 is H, —CH_3, isopropyl, benzyl,

[0053] B2) —CH_2—SH, —CH_2—OH, —$CH(CH_3)$—OH, —CH_2—[(C_6H_4)-(4-OH)], —CH_2—[(C_6H_2)-(3,5-diiodo)-(4-OH)]
—CH_2—[(C_6H_3)-(3-nitro)-(4-OH)];

[0054] B3) —CH_2—NHR", —$(CH_2)_2$—NHR", —$(CH_2)_3$—NHR", —$(CH_2)_4$—NHR", wherein R" is as above defined, preferably R^2 is —$(CH_2)_4$—NHR";

[0055] B4) —CH_2—C(O)—R'", —$(CH_2)_2$—C(O)—R'", —$(CH_2)_4$—C(O)—R'" wherein R'" is as above defined, preferably R^2 is —CH_2—C(O)—R'";

R^{2a} is selected from:

[0056] B5) CH_2—S—, CH_2—O—, —$CH(CH_3)$—O— or CH_2[(C_6H_4)-(4-O)—], —CH_2-[(3,5-diiodo)-(C_6H_2)-(4-O)—], —CH_2-[(3-nitro)-(C_6H_3)-(4-O)—], preferably R^{2a} is —CH_2—O—;

[0057] B6) —CH_2—NH—, —$(CH_2)_2$—NH—, —$(CH_2)_3$—NH—, —$(CH_2)_4$—NH—, preferably R^{2a} is —$(CH_2)_4$—NH— or —CH_2—NH—;

[0058] B7) —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—, preferably R^{2a} is —CH_2—C(O)—;

R^{2b} is selected from

[0059] B8) —S—CH_2—, —O—$CH(CH_3)$—, —O—CH_2—, [-(4-O)—(C_6H_4)]—CH_2—, [-(4-O)-(3,5-diiodo)-(C_6H_2)]—CH_2—, [-(4-O)-(3-nitro)-(C_6H_3)]—CH_2—, preferably R^{2b} is —O—CH_2— or [-(4-O)—(CH_4)]—CH_2—;

[0060] B9) —HN—CH_2—, —HN—$(CH_2)_2$—, —HN—$(CH_2)_3$—, —HN—$(CH_2)_4$—, preferably R^{2b} is —HN—$(CH_2)_4$— or —HN—CH_2—;

[0061] B10) —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—, preferably R^{2b} is —C(O)—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:

C)

[0062] (c1) —HN—$(CH_2)_b$—C(O)-(T-Y—ONO_2);
(c2) —C(O)—$(CH_2)_b$—NH-(T'-Y—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;

D)

[0063] (d1) —HN—$CH(R^{12})$—CH_2—O-(T'"-Y—ONO_2)
(d2) —O—CH_2—$CH(R^{12})$—NH-(T'-Y—ONO_2)
(d3) —HN—$CH(R^{12a}$-T"-Y'—$ONO_2)$—CH_2OH
(d4) —O—CH_2—$CH(R^{12a}$-T"-Y'—$ONO_2)$—NHR^{4a}
(d5) —R^{12a}—$CH(NHR^{4a})$—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)
(d9) —R^{12b}—CH(NH-T'-Y'—ONO_2)—CH_2—O-(T'"-Y—ONO_2)
(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;
T' and T" are as above defined,
Y and Y' are as below defined;
R^{12} is selected from:

[0064] D1) H, —CH_3, isopropyl, isobutyl, sec-butyl, methylthio-$(CH_2)_2$—, benzyl, 3-triptophanyl-CH_2—, 4-imida-

zolyl-CH_2—, NH_2—CO—CH_2—, NH_2—CO—$(CH_2)_2$—, NH_2(=NH)NH—$(CH_2)_3$—, preferably R^{12} is H;

[0065] 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)] preferably R' is —CH_2—OH or —CH_2[(C_6H_4)-(4-OH)]

[0066] D3) —CH_2—NHR", —$(CH_2)_2$—NHR", —$(CH_2)_3$—NHR", —$(CH_2)_4$—NHR", wherein R" is as above defined, preferably R^{12} is —$(CH_2)_4$—NHR";

[0067] D4) —CH_2—C(O)R'", —$(CH_2)_2$—C(O)R'", —$(CH_2)_4$—C(O)R'" wherein R'" is as above defined, preferably R^{12} is —CH_2—C(O)R'";

R^{12a} is selected from

[0068] D5) —CH_2—O—, —$CH(CH_3)$—O— or —CH_2[(C_6H_2)-(4-O)—], —CH_2-[3,5-diiodo-(C_6H_2)-(4-O)—], —CH_2-[3-nitro-(C_6H_3)-4-O—], preferably R^{12a} is CH_2—O— or —CH_2—[(C_6H_4)-(4-O)—],

[0069] D6) —CH_2—NH—, —$(CH_2)_2$—NH—, —$(CH_2)_3$—NH—, —$(CH_2)_4$—NH—, preferably R^{12a} is —$(CH_2)_4$—NH— or —CH_2—NH—,

[0070] D7) —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—, preferably R^{12a} is —CH_2—C(O)—,

R^{12b} is selected from

[0071] D8) —O—CH_2—, —O—$CH(CH_3)$—, [-(4-O)—(C_6H_4)]—CH_2—, [-(4-O)-(3,5-diiodo)-(C_6H_2)]—CH_2, [-(4-O)-(3-nitro)-(C_6H_3)]—CH_2—, preferably R^{12} is —O—CH_2— or [-(4-O)—(C_6H_4)]—CH_2—;

[0072] D9) —HN—CH_2—, —HN— $(CH_2)_2$—, —HN—(CH_2)—-HN— $(CH_2)_4$—, preferably R^{12b} is —HN— $(CH_2)_4$— or —HN—CH_2—;

[0073] D10) —C(O)—CH_2—, —C(O)— $(CH_2)_2$—, —C(O)—$(CH_2)_4$—, preferably R^{12b} is —C(O)—CH_2—;

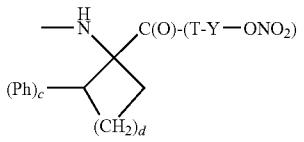
R^{4a} is as above defined;

or R_x is selected from:

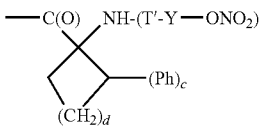
E)

[0074]

(e1)



(e2)

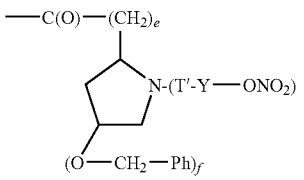


wherein c is equal to 0 or 1, d is an integer from 0 to 3 with the proviso that c is 0 or 1 when d is 0 and c is 0 when d is 1, 2 or 3, T and T' are as above defined and Y is as below defined;

F)

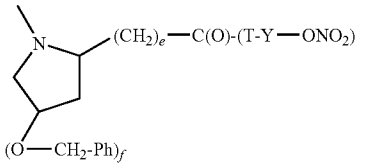
[0075]

(f1)



-continued

(f2)



(XI)

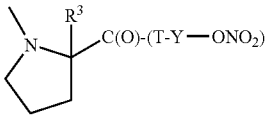
[0076] wherein e and f are equal to 0 or 1, with the proviso that f is 0 when e is 0 and f is 0 or 1 when e is 1,

T and t' are as above defined and y is as below reported;

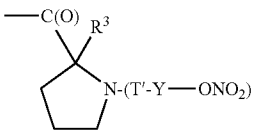
G)

[0077]

(g1)



(g2)

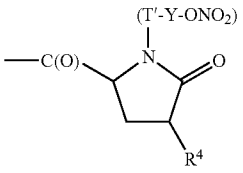


wherein R^3 is H, CH_3, propyl, $(C_6H_5)_2CH$—, 1-naphtyl-CH_2—, benzyl, allyl, 2-bromobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-fluorobenzyl, 4-bromobenzyl, 4-methyl-benzyl, preferably R^3 is H, T and T' are as above defined and Y is as below defined;

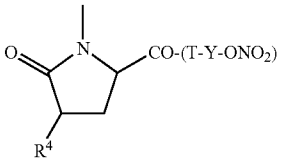
H)

[0078]

(h1)



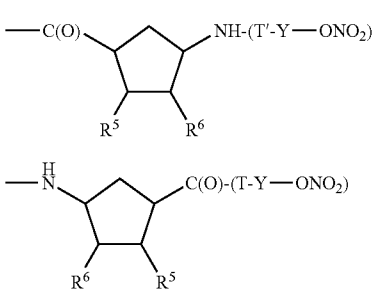
(h2)



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

I)

[0079]



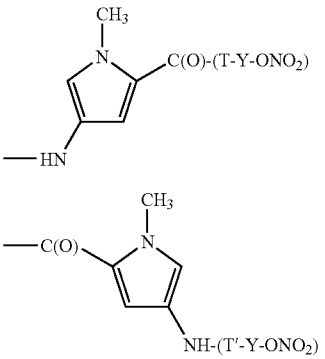
(i1)

(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)

[0080]



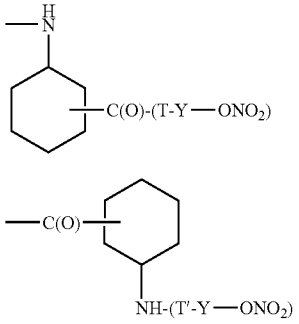
(l1)

(l2)

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

M)

[0081]



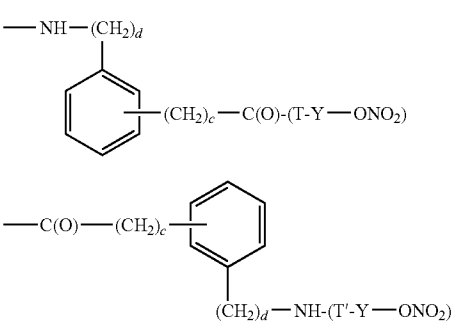
(m1)

(m2)

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

N)

[0082]



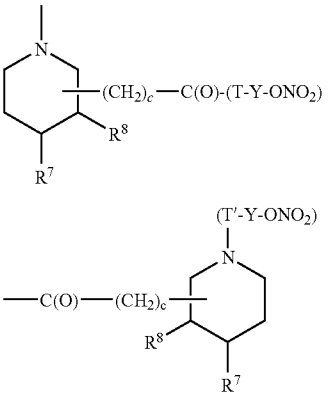
(n1)

(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)

[0083]



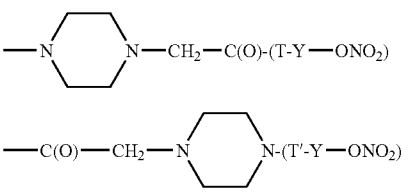
(o1)

(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)

[0084]



(p1)

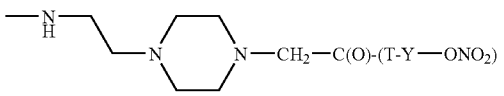
(p2)

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

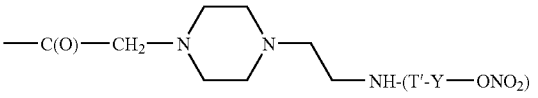
Q)

[0085]

(q1)



(q2)

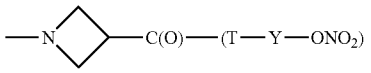


wherein T and T' are as above defined and Y is as below reported;

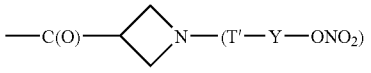
R)

[0086]

(r1)



(r2)

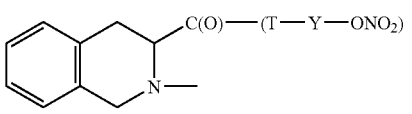


wherein T and T' are as above defined and Y is as below reported;

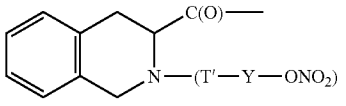
S)

[0087]

(s1)



(s2)

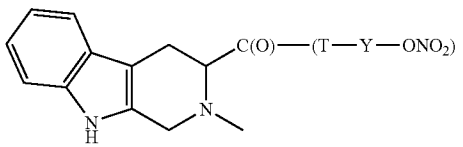


wherein T and T' are as above defined and Y is as below reported;

T)

[0088]

(t1)



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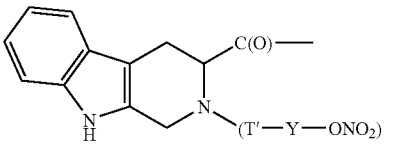
(t2)

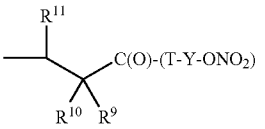


wherein T and T' are as above defined and Y is as below reported;

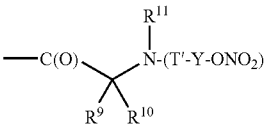
U)

[0089]

(u1)



(u2)

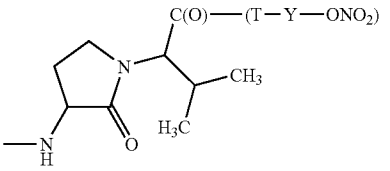


wherein R^9 and R^{10} are H, CH_3, R^{11} is CH_3 or 4-piperidinyl with the proviso that R^9 and R^{10} are H when R^{11} is 4-piperidinyl and R^9 and R^{10} are CH_3 when R^{11} is CH_3, T and T' are as above defined and Y is as below reported;

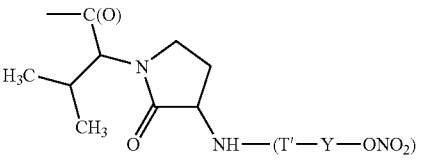
V)

[0090]

(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:

[0091] (a2), (a4) or (a8);

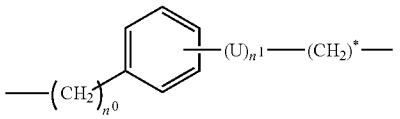
[0092] (a5), (a6), (a9) or (a10) and R^{1b} is selected from the group A10);

[0093] (b2), (b4) or (b8)

[0094] (b5), (b6), (b9) or (b10) and R^{2b} is selected from the group B10);

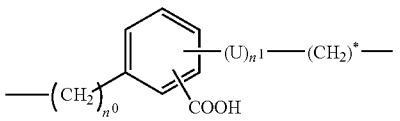
[0095] (c2);
[0096] (d5), (d6), (d9) or (d10) and R^{12b} is selected from the group D10);
[0097] (e2), (f1), (g2), (h1), (i1), (l2), (m2), (n2), (o2), (p2), (q2), (r2), (s2), (t1) or (u2);
a is 1 and Z is —C(O)—, when R_x is:
[0098] (a1), (a3) or (a7);
[0099] (a5), (a6), (a9) or (a10) and R^{1b} is selected from the groups A8) and A9);
[0100] (b1), (b3) or (b7);
[0101] (b5), (b6), (b9) or (b10) and R^{2b} is selected from the groups B8) or B9);
[0102] (c1);
[0103] (d1), (d2), (d3), (d4), (d7) or (d8);
[0104] (d5), (d6), (d9) or (d10) and R^{2b} is selected from the groups D8) or D9);
[0105] (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)
[0106] straight or branched C_1-C_{20} alkylene, preferably a straight or branched C_1-C_{10} alkylene,
[0107] 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} alkyl)-ONO_2 or —O(C_1-C_{10} alkyl)-ONO_2, preferably Y or Y' is a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;
[0108] 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_3;
b)

b)



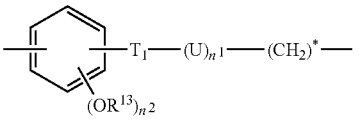
wherein
n^0 is an integer from 0 to 20, preferably n^C is 0 or 1;
n^1 is 0 or 1, preferably n^1 is 1;
[0109] U is a linear or branched C_1-C_{20} alkylene optionally substituted with a ONO_2 group, preferably U is a linear C_1-C_{10} alkylene or U is a linear or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;
c)

c)



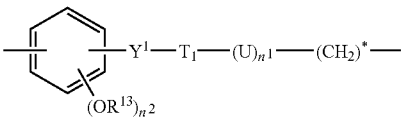
wherein
n^0 is an integer from 0 to 20, preferably n^C is 0 or 1;
n^1 is 0 or 1, preferably n^1 is 1;
[0110] U is a linear or branched C_1-C_{20} alkylene optionally substituted with a —ONO_2 group, preferably U is a linear C_1-C_{10} alkylene or U is a linear or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;
d)

d)



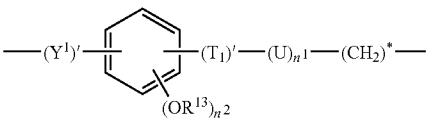
wherein:
n^2 is an integer from 0 to 2, R^{13} is H or CH_3, T_1 is —O—C(O)— or —C(O)O—;
n^1 and U are as above defined;
e)

e)



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═CH—$(CH_2)_2$—, wherein n 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;
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 $n^{2'}$ is 0, T_1 is C(O)O— and U is a linear C_1-C_{10} alkylene;
e')

e')



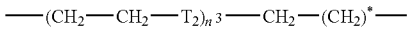
wherein:
n^2 is an integer from 0 to 2, preferably n2 is 1;
R^{13} is H or CH_3, preferably R^{13} is CH_3;
Y^1 is —CH_2—CH_2— or —$(CH_2)_{n^{2'}}$—CH═CH—, wherein n is 0 or 1, preferably Y^1 is —$(CH_2)_{n^{2'}}$—CH═CH— and $n^{2'}$ is 0;

T_1=—O—C(O)—;

[0111] 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;

more preferably 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 —OC(O)— and U is a linear C_1-C_{10} alkylene;

f)

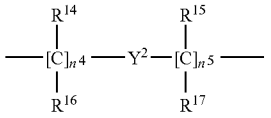


f)

wherein T_2 is —O— or —S—, —NH—, preferably T_2 is —O—, n^3 is an integer from 1 to 6, preferably n^3 is 1;

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'—ONO_2), -(T'"-Y—ONO_2) and -(T'"-Y'—ONO_2) is linked to the —(CH_2)*— group;

g)



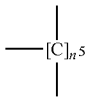
wherein:

n^4 is an integer from 0 to 10, preferably n^4 is 0 or 1;

n^5 is an integer from 1 to 10, preferably n^5 is 1;

[0112] R^{14}, R^{15}, R^{16}, R^{17} are the same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^{14}, R^{15}, R^{16} and R^{17} are H;

wherein the —ONO_2 group is linked to

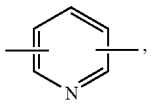


wherein n^5 is as defined above;

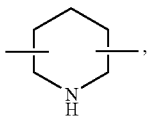
[0113] Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur,

and is selected from the group consisting of:

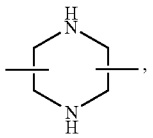
(Y1)



(Y2)



(Y3)



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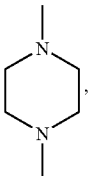
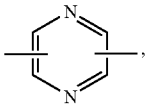
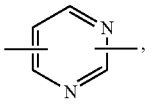
(Y4)



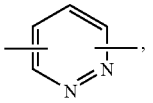
(Y5)



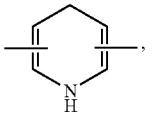
(Y6)



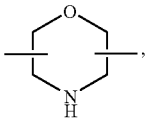
(Y7)



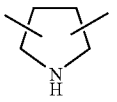
(Y8)



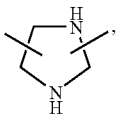
(Y9)



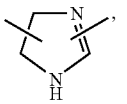
(Y10)



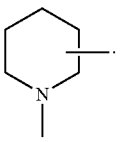
(Y11)



(Y12)



(Y13)



[0114] The term "C_1-C_{10} 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.

[0115] 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_1-C_{10})-alkyl, preferably CH_3.

[0116] 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.

[0117] Respiratory diseases comprises asthma, COPD (chronic obstructive pulmonary diseases), ARDS (Acute Respiratory Distress Syndrome), allergic rhinitis, respiratory tract diseases associated with inflammation.

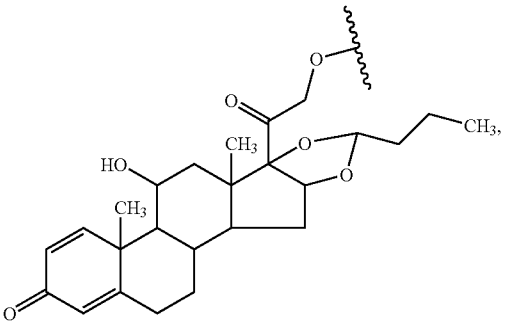
[0118] An embodiment of the invention relates to nitric oxide releasing compounds of general formula (I)

$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

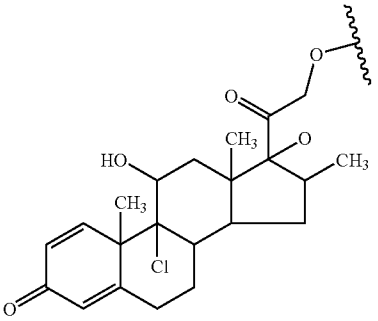
and pharmaceutically acceptable salts or stereoisomers thereof for use in the treatment of respiratory diseases wherein in formula (I)

the corticosteroid residue R is selected from:

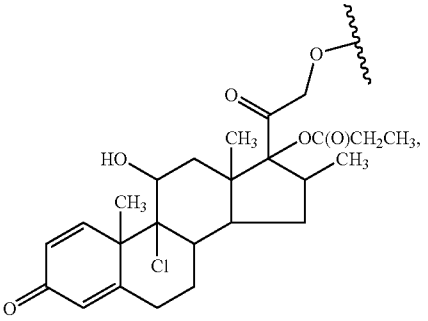
(II)



(III)



(IV)



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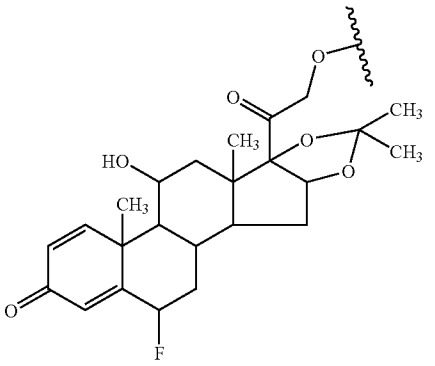
(V)



a is 0 and

R_X is selected from:

(a2) —C(O)—CH(R^1)—NH-(T'-Y—ONO_2)

wherein

R^1 of the group A1) is selected from H, isobutyl, benzyl, C_6H_5—CH_2—CH_2—, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, C_6H_5CO—;

R^1 of the group A2) is selected from —CH_2—OH, —CH(CH_3)OH— or —CH_2[(C_6H_4)-(4-OH)], or

R^1 of the group A3) 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^1 of the group A4) is selected from —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' is —C(O)—, —C(O)—X" wherein X" is —S— or —O—, preferably T' is —C(O)—;

Y is as below defined;

or R_X is

[0119] (a4) —C(O)—CH(R^{1a}-T"-Y'—ONO_2)—NHR^{4a}

wherein 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 selected from —CH_2—C(O)—, —(CH_2)$_2$—C(O)—, —(CH_2)$_4$—C(O)—,

R^{4a} is H or —C(O)CH_3,

[0120] T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} 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_3, when R^{1a} is selected from the group A7),

Y' is as below defined;

or R_X 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)

wherein
R^{1b} of the group A10) is selected from —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—,
R^{3a} is H or a (C_1-C_5) alkyl,

R^{4a} is H or —C(O)CH_3,

[0121] T is —O—, —S—, —NR'— or —O—CH(R')—O—C(O)— wherein R' is H or —CH_3, 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_X is

[0122] (a8) —C(O)—CH(R^{1a}-T"-Y'—ONO_2)—NH-(T'-Y—ONO_2)
wherein
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 selected from —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—,
T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} 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_3, when R^{1a} is selected from the group A7);
[0123] 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,

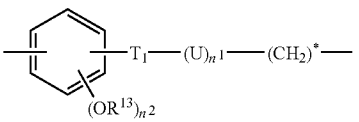
or R_X is

[0124] (b2) —C(O)—CH_2—CH(R^2)—NH-(T'-Y—ONO_2)
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—, preferably T' is —C(O)—;
Y and Y' are each independently selected from a)

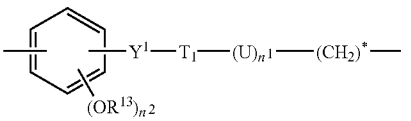
[0125] a straight or branched C_1-C_{10} alkylene,

[0126] a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;

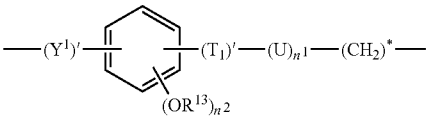
d)



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' 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)



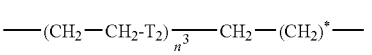
n^2 is 1, R^{13} is CH_3, Y^1 is —CH═CH—$(CH_2)_n{}^{2'}$— and n is 0, T_1 is —C(O)O— and U is a linear C_1-C_{10} alkylene;
e')



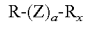
wherein:
n^2 is 1, R^{13} is CH_3;
Y^1 is —$(CH_2)_n{}^{2'}$—CH═CH— and $n^{2'}$ is 0;

T_1=—O—C(O)—;

[0127] n^1 is 1 and U is a linear C_0-C_{10} alkylene or U is a linear or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;
f)

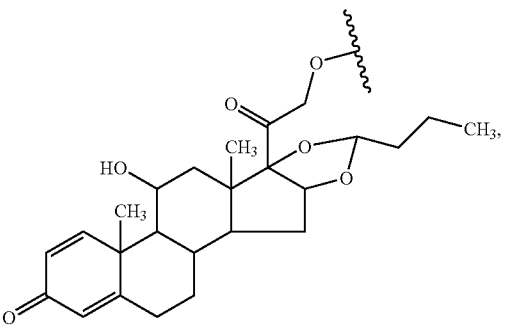


wherein T_2 is —O— or —S—, —NH—, preferably T_2 is —O—, n^3 is 1 or 2;
when Y and Y' are selected from d), e), e') or f), the —ONO_2 group of -(T-Y—ONO_2), -(T'-Y—ONO_2), -(T"-Y'—ONO_2), -(T'-Y'—ONO_2), -(T"'-Y—ONO_2) and -(T""-Y'—ONO_2) is linked to the —(CH_2)*— group.
[0128] Another embodiment of the invention relates to nitric oxide releasing compounds of general formula (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)



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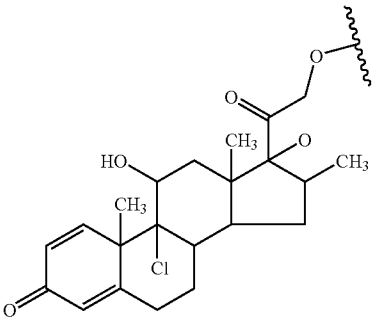

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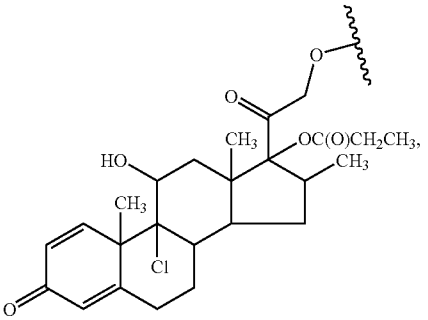

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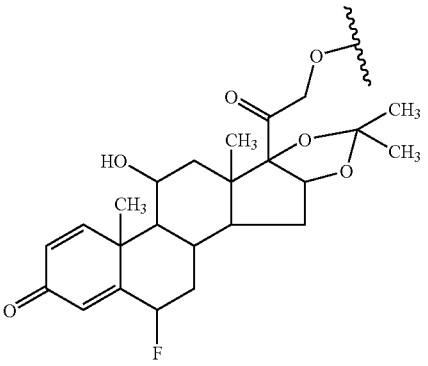


[0129] a is 1 and Z is —C(O)—;

R_X is

[0130] (a1) —HN—CH(R')—C(O)-(T-Y—ONO_2)
wherein
R^1 of the group A1) is selected from H, isobutyl, benzyl, C_6H_5—CH_2—CH_2—, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, C_6H_5CO— or
R^1 of the group A2) is selected from:

—CH_2—OH, —$CH(CH_3)$—OH— or —CH_2—[(C_6H_4)-(4-OH)], or

[0131] R^1 of the group A3) 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^1 of the group A4) 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 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

[0132] (a3) —HN—CH(R^{1a}-T"-Y'—ONO_2)—$COOR^{3a}$
wherein
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)—,
R^{3a} is H or a (C_1-C_5) alkyl,
T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} is selected from the group 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 the group A7);
Y' is as below defined;
or R_X 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)
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

[0133] R^{1b} of the group A9) is selected from —HN—CH_2—, —HN—$(CH_2)_2$—, —HN—$(CH_2)_3$—, —HN—$(CH_2)_4$—,
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—,
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

[0134] (a7) —HN—CH(R^{1a}-T"-Y'—ONO_2)—C(O)-(T-Y—ONO_2)
wherein
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)—;
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—,
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

[0135] (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 —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'", —$(CH_2)_4$—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
(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
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

[0136] 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
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)—,
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}

[0137] (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
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,

[0138] 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_X is selected from:
(d5) —R^{12b}—CH(NHR^{4a})—CH_2—O-(T'"-Y—ONO_2)
(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
R^{12b} of the group D8) is selected from —O—CH(CH_3)—, —O—CH_2—, [-4-O—(CH_4)]—CH_2—, or

[0139] 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.

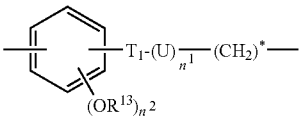
[0140] T' and T'" are each independently selected from —C(O)—, —C(O)—X", wherein X" is —S— or —O—, preferably T' and T'" are —C(O)—,
Y and Y' are each independently selected from
a)

[0141] a straight or branched C_1-C_{10} alkylene,

[0142] a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;

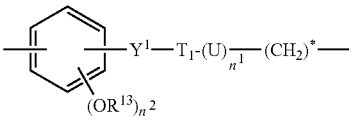
d)

d)



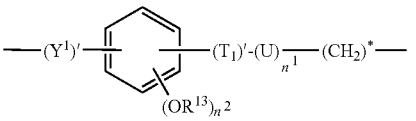
wherein:
n^2 is an integer from 0 to 2, R^{13} is H or CH_3, T_1 is —O—C(O)— or —C(O)O—,
n^1 is 1 and U is a linear C_1-C_{10} alkylene or U is a linear or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;
e)

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')

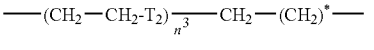
e'



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)—,

[0143] 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)



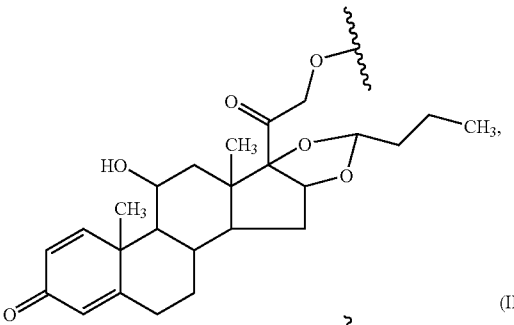
wherein T_2 is —O— or —S—, —NH—, preferably T_2 is —O—, n^3 is 1 or 2,
when Y and Y' are selected from d), e), e') or f), the —ONO_2 group of -(T-Y—ONO_2), -(T''-Y—ONO_2), -(T''-Y'—ONO_2), -(T''-Y'—ONO_2), -(T'''-Y—ONO_2) and -(T'''-Y'—ONO_2) is linked to the —(CH_2)*— group.

[0144] Another embodiment of the present invention is to provide nitric oxide releasing compounds of general formula (I)

$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

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)



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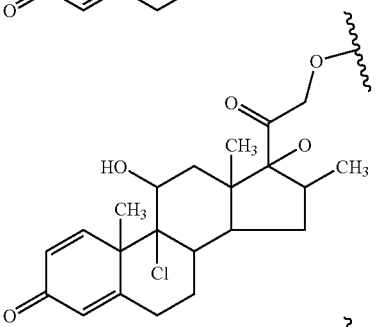

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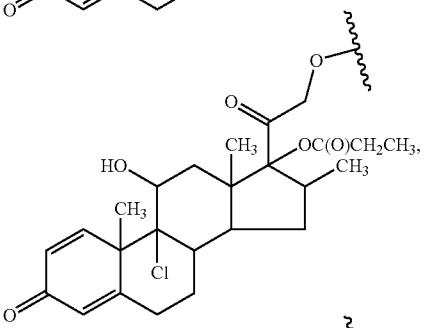

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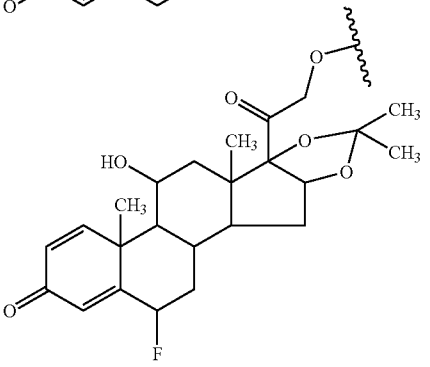


a is 0,

R_X is

[0145] (a2) —C(O)—CH(R^1)—NH-(T'-Y—ONO_2)
wherein
R^1 of the group A1) is H

T' is —C(O)—;

[0146] Y is selected from
a)

[0147] a straight or branched C_1-C_{10} alkylene,

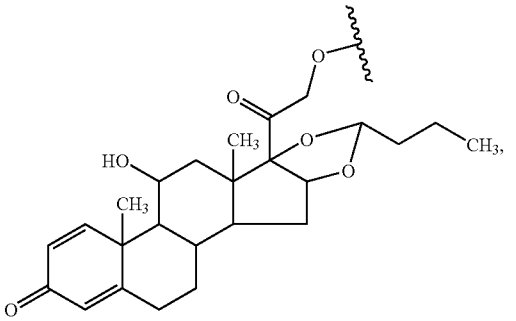
[0148] a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;

[0149] Another embodiment relates to nitric oxide releasing compounds of general formula (I)

$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

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)



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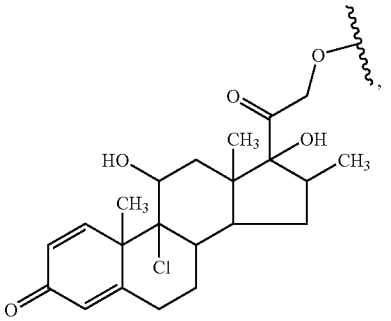

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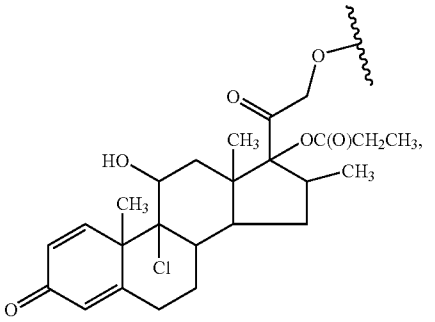

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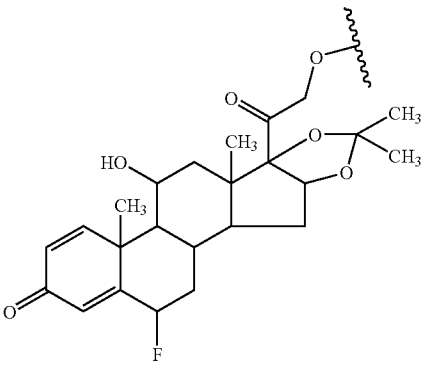


a is 0,

R_X is selected from

R_X is selected from

[0150] (a5) —R^{1b}—CH(NHR^{4a})—C(O)-(T-Y—ONO_2)

[0151] (a6) —R^{1b}—CH(COOR^{1a})NH-(T'-Y—ONO_2) or

[0152] (a9) —R^{1b}—CH(NH-T'-Y'—ONO_2)—C(O)-(T-Y—ONO_2)

wherein

R^{1b} of the group A10) is C(O)—CH_2—,

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

R^{4a} is H or —C(O)CH_3,

[0153] 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)

[0154] a straight or branched C_1-C_{10} alkylene,

[0155] a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group.

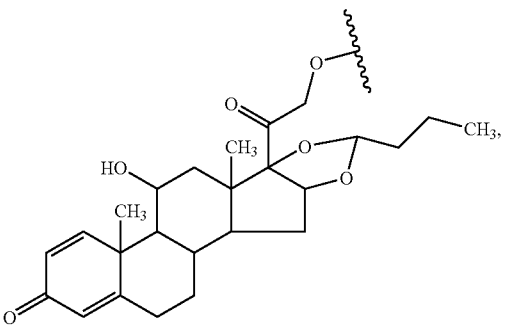
[0156] Another embodiment relates to nitric oxide releasing compounds of general formula (I)

$$R\text{-}(Z)_a\text{-}R_X \quad (I)$$

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)



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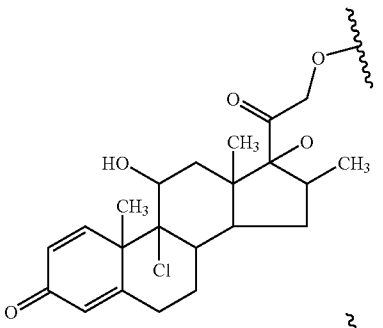

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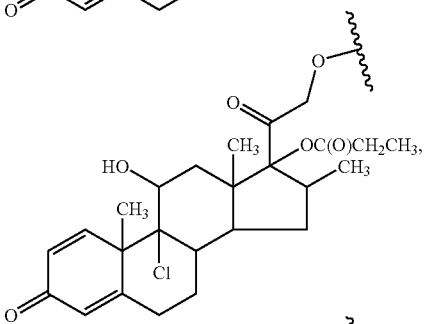

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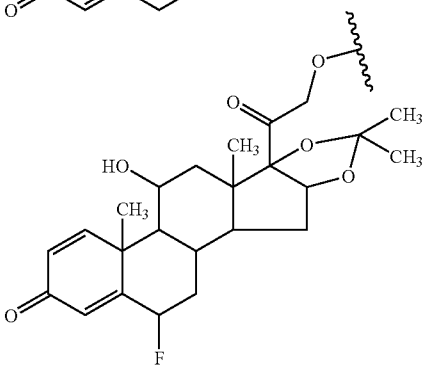


a is 1 and Z is —C(O)—,

R_X is

[0157] (a5) —R^{1b}—CH(NHR^{4a})—C(O)-(T-Y—ONO_2) or

[0158] (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,

[0159] T is selected from —O—, —S—, —NR'— wherein R' is as above defined,

T' is —C(O)— and

[0160] Y and Y' are each independently selected from a)

[0161] a straight or branched C_1-C_{10} alkylene,

[0162] a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group.

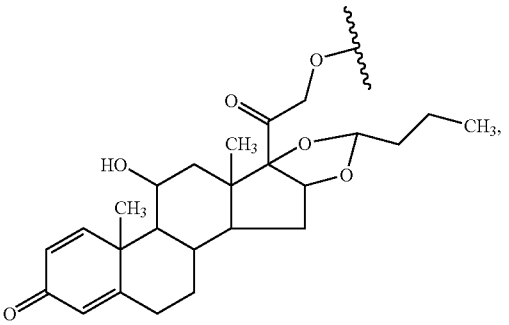
[0163] Another embodiment of the invention relates to nitric oxide releasing compounds of general formula (I)

$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

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)



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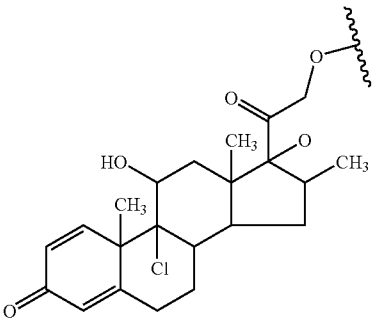

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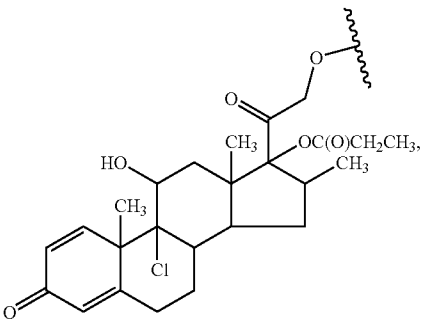

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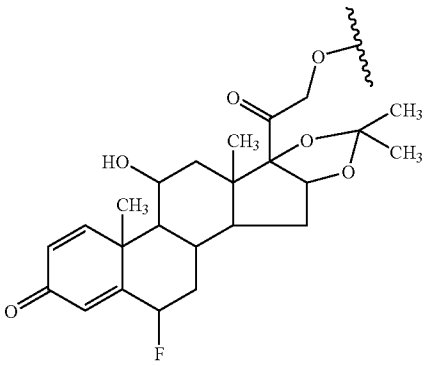


a is 0,

R_X is

[0164] (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)—;

[0165] Y and Y' are each independently selected from

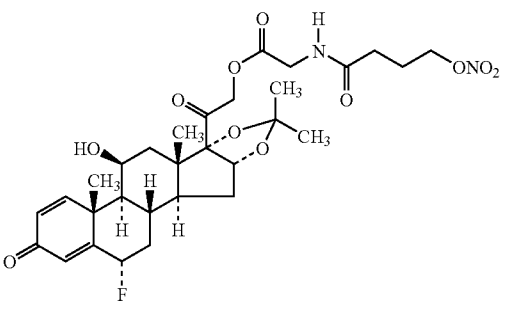
a)

[0166] a straight or branched C_1-C_{10} alkylene,

[0167] a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group.

[0168] The most preferred nitric oxide releasing compounds of general formula (I) for the use in the treatment of respiratory diseases are:

(1)



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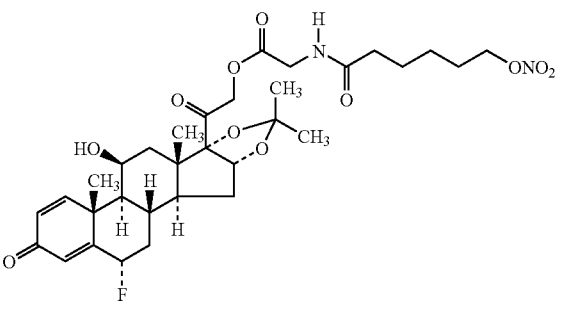

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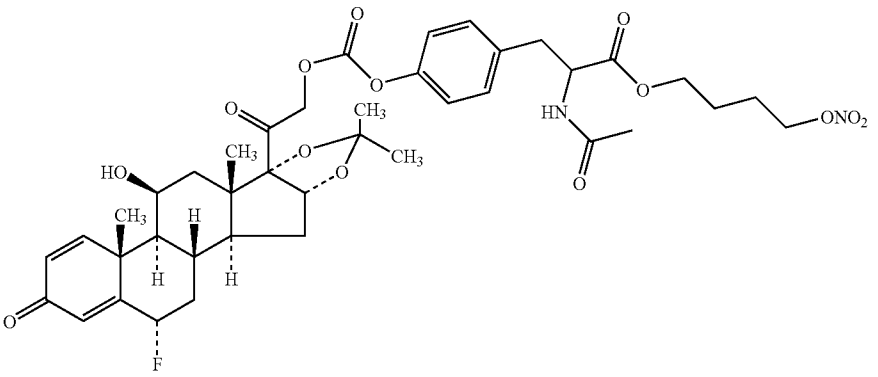

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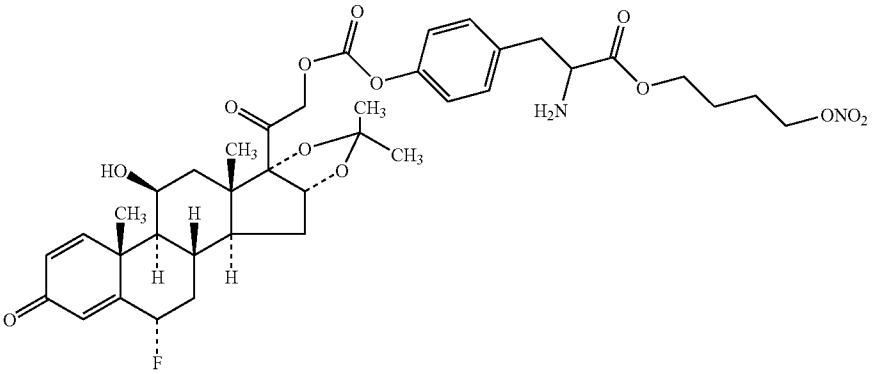

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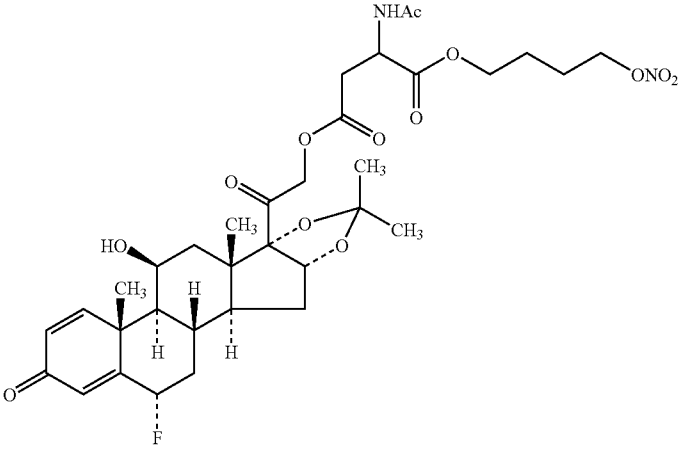

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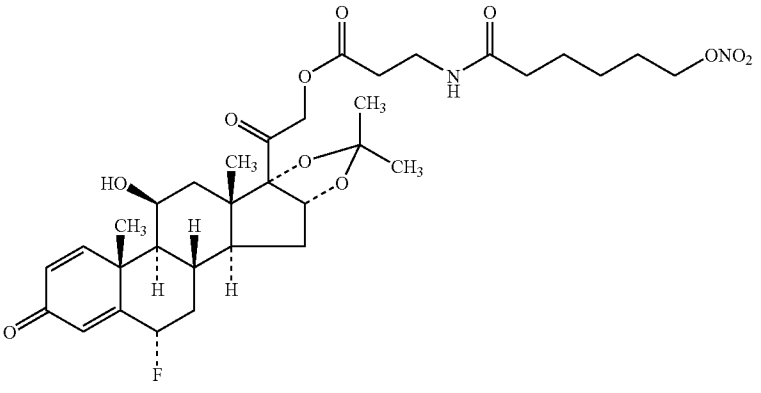

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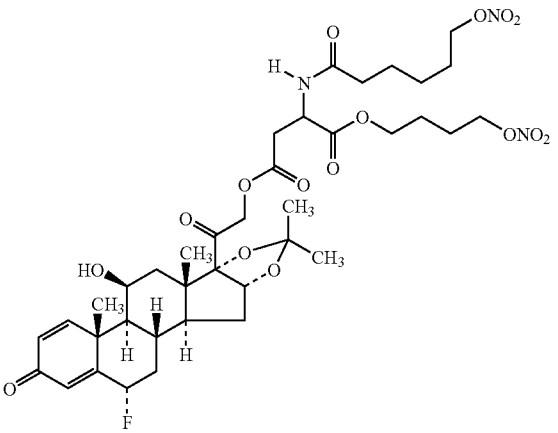

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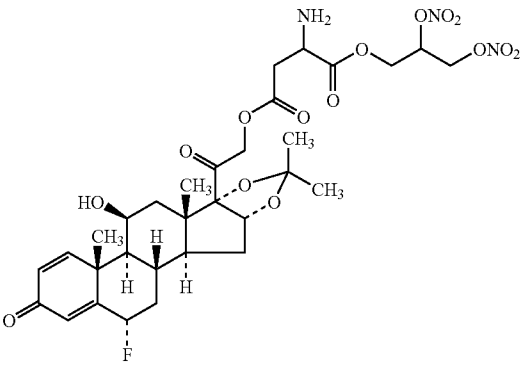

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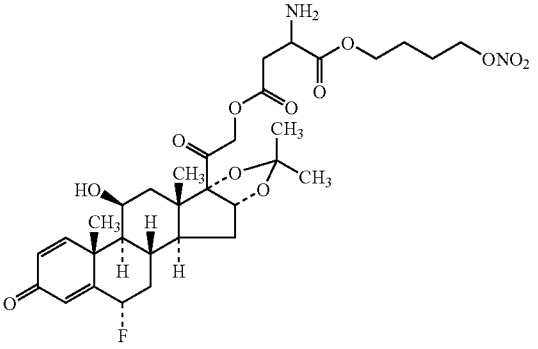

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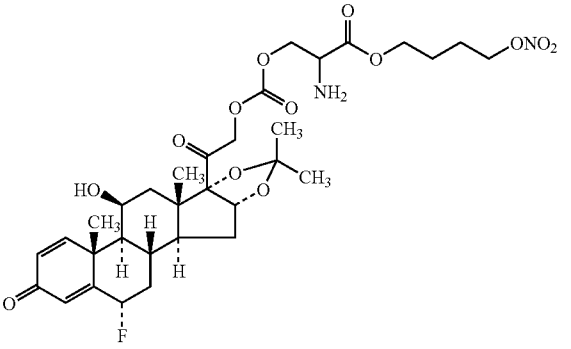

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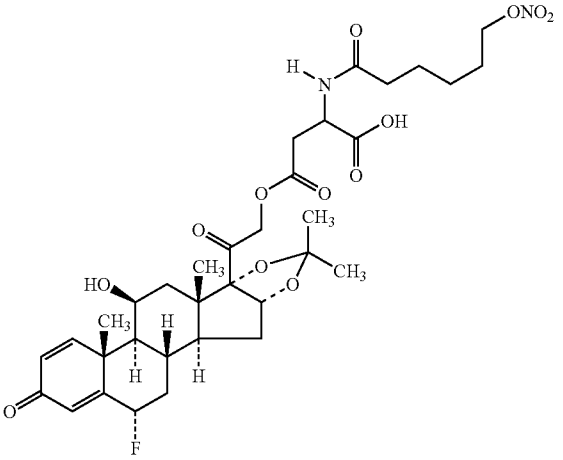

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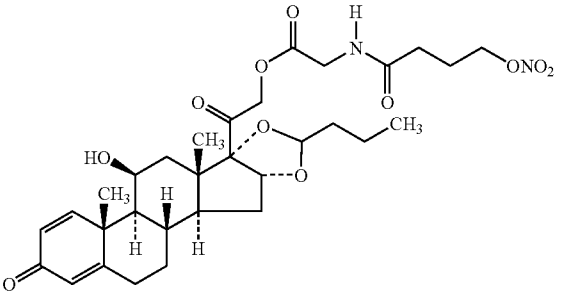

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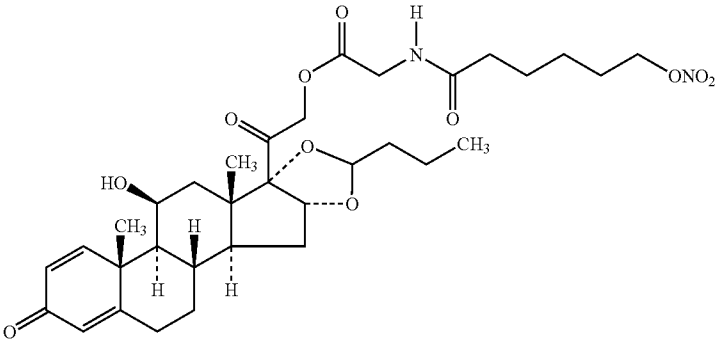

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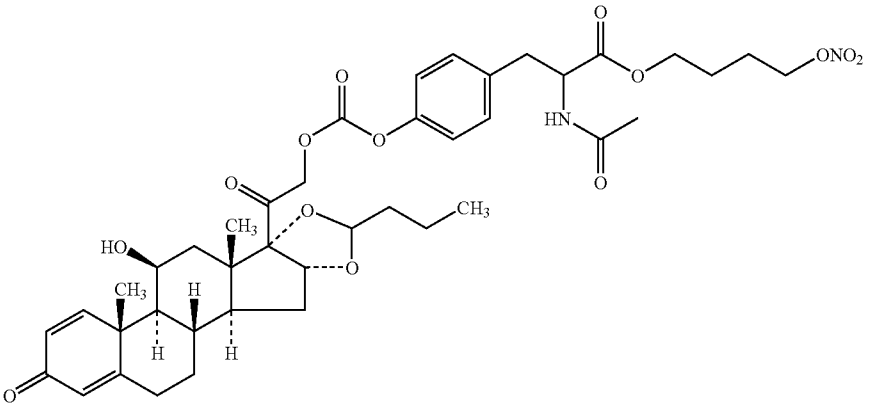

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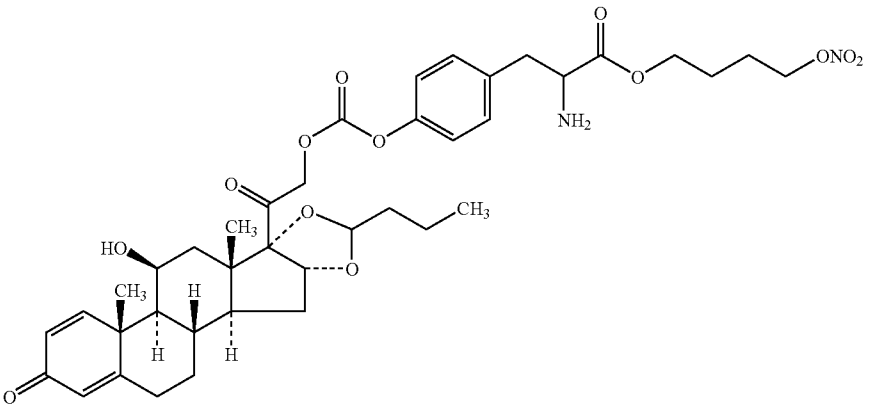

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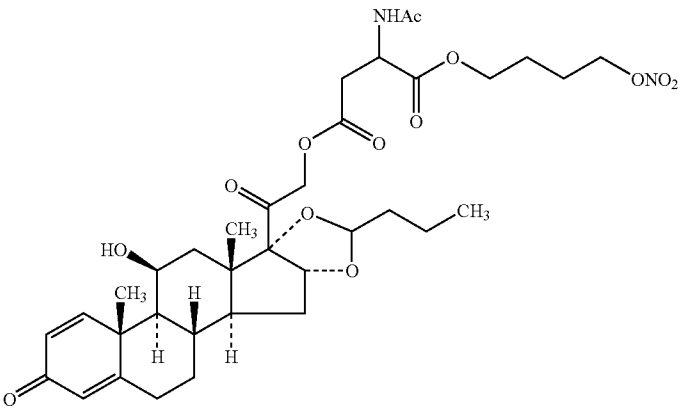

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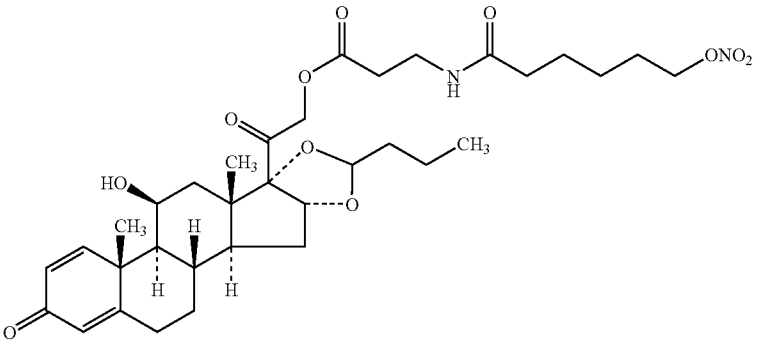

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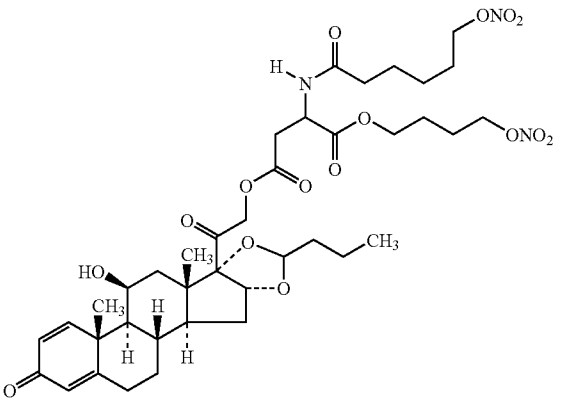

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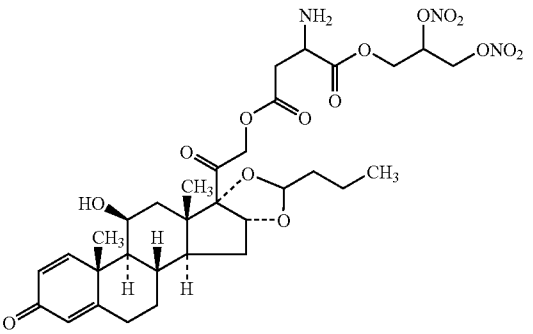

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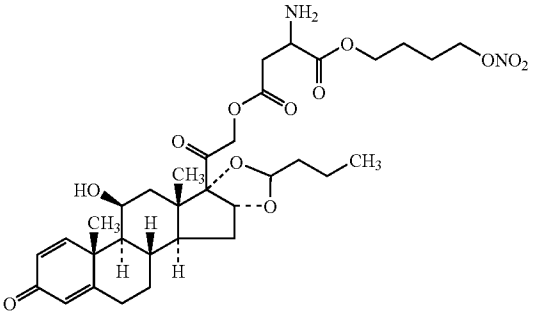

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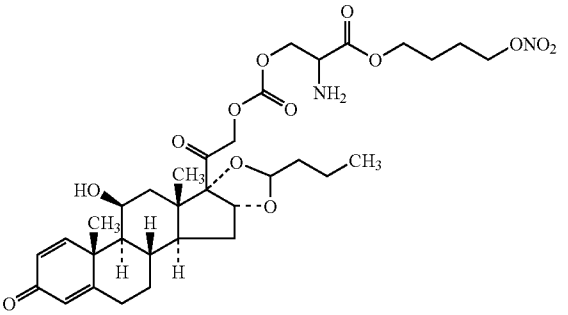

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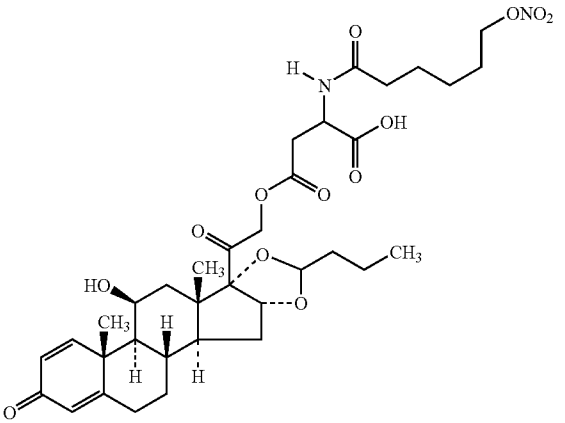

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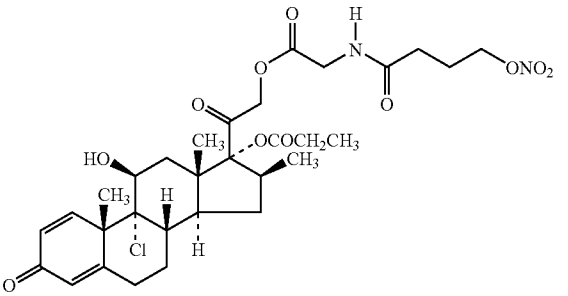

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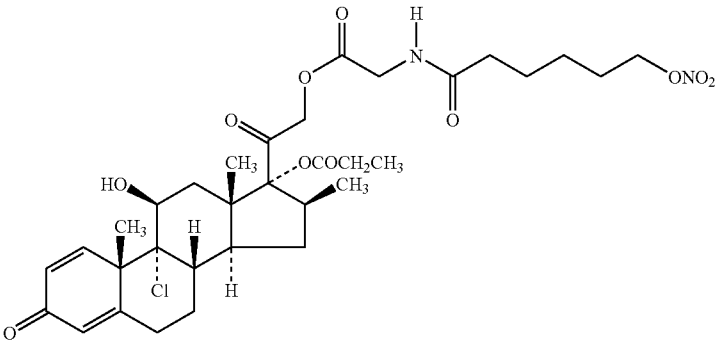

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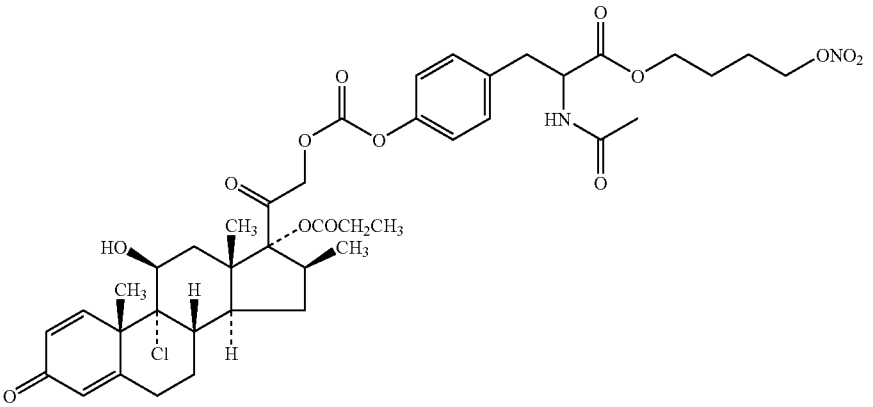

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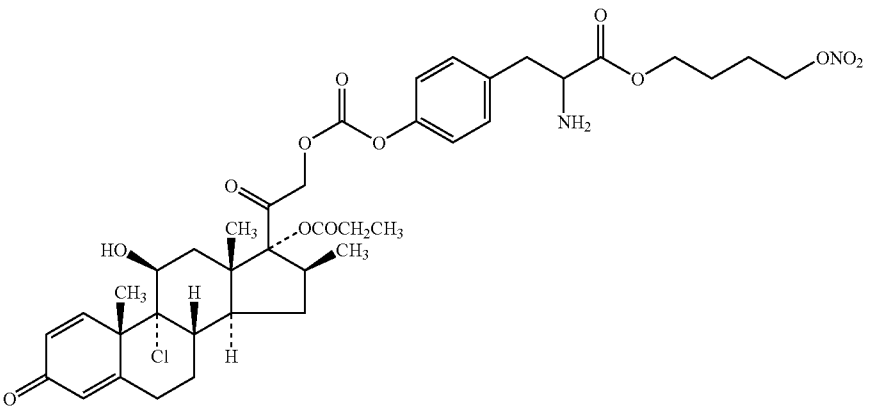

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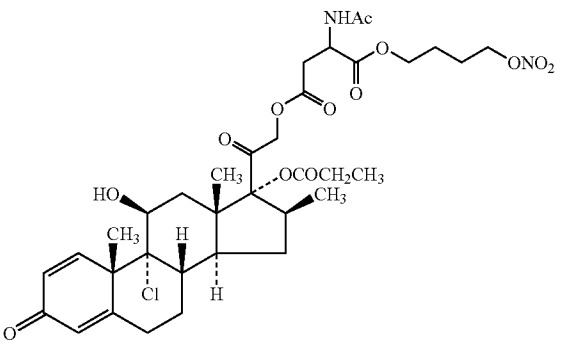

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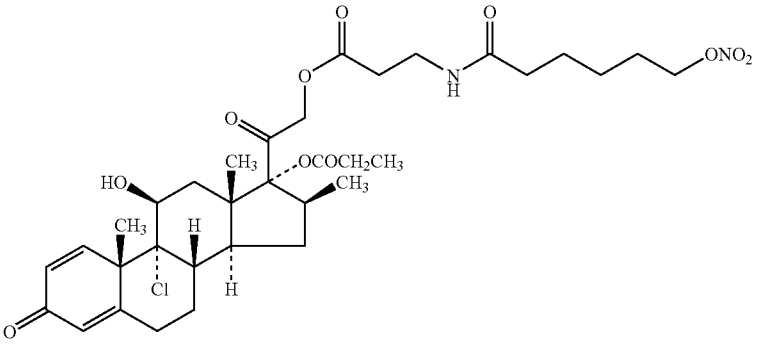

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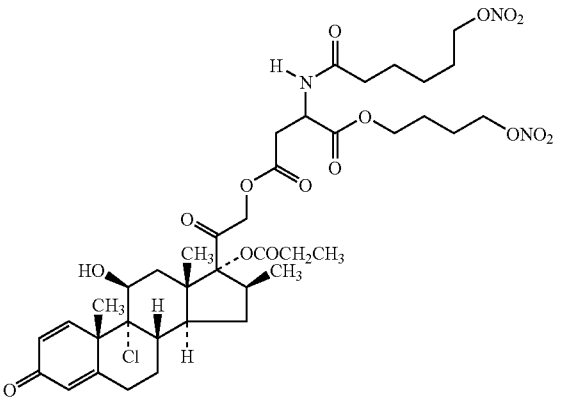

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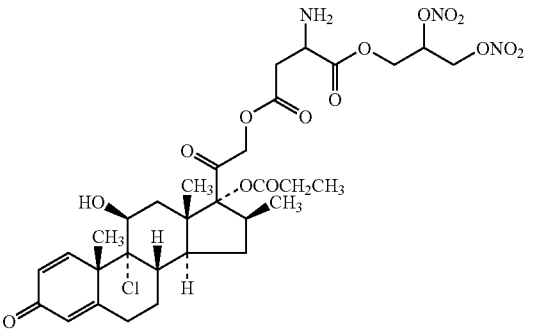

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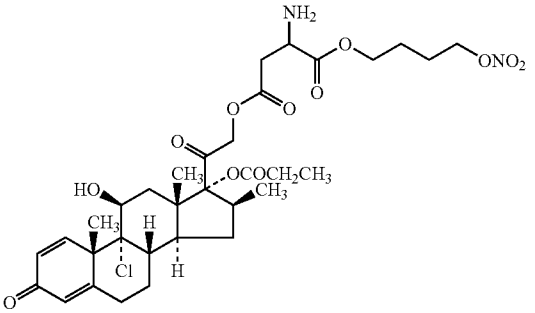

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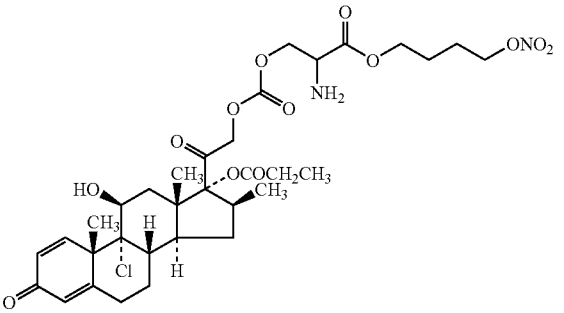

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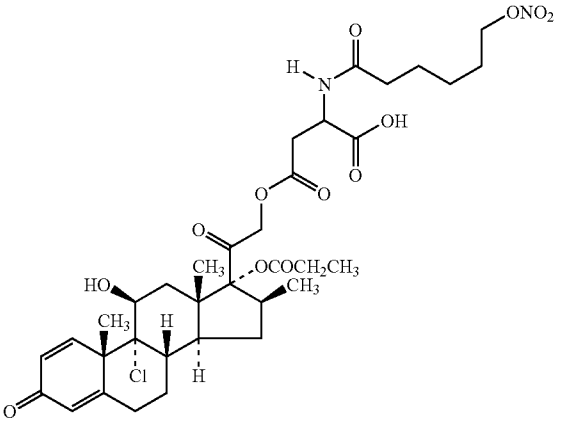

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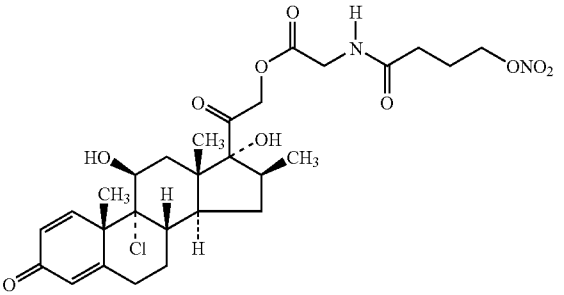

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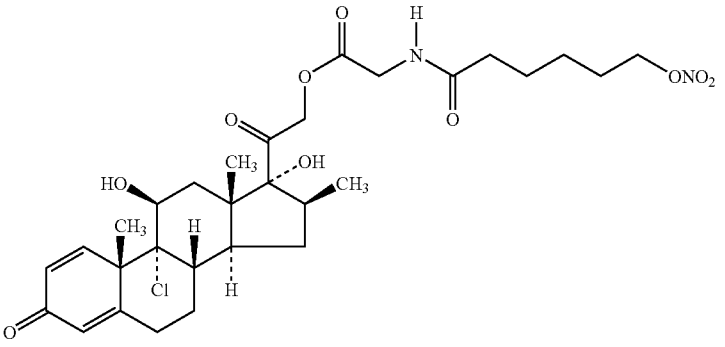

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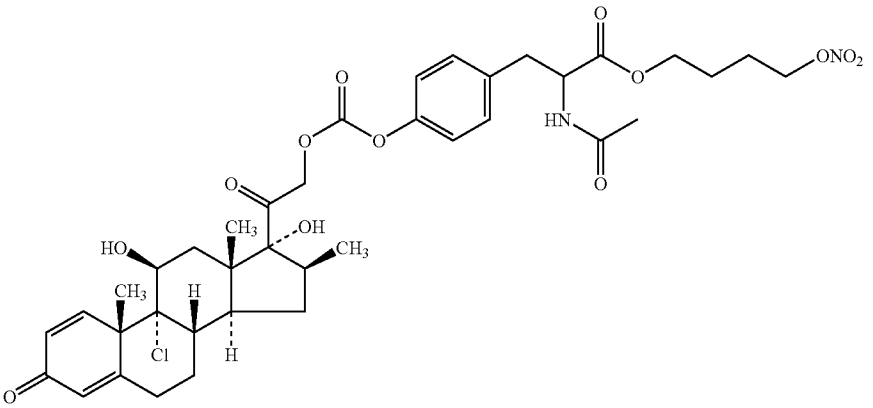

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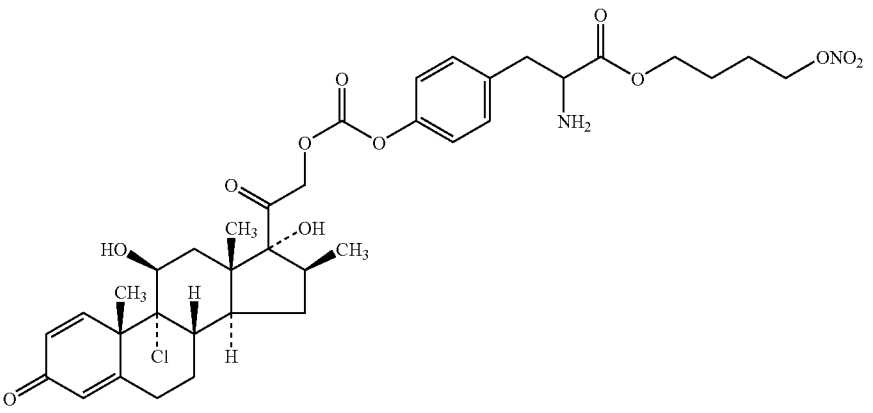

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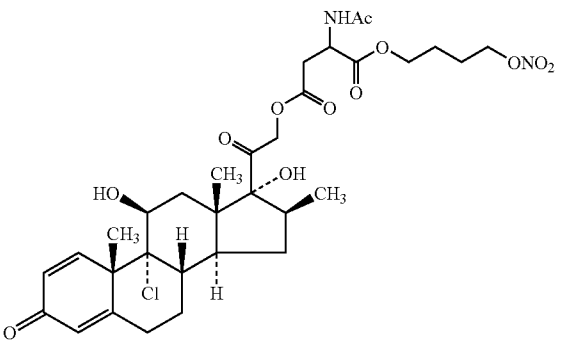

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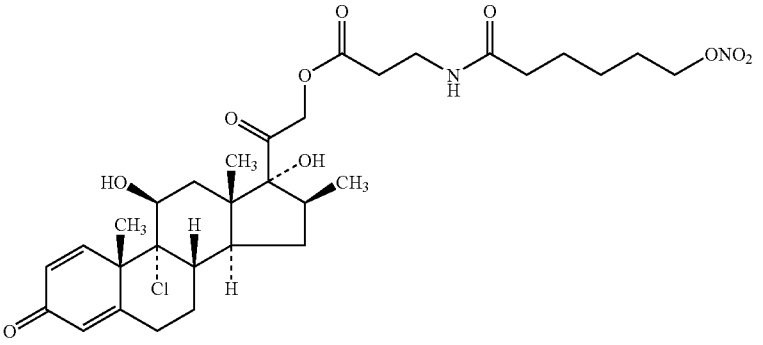

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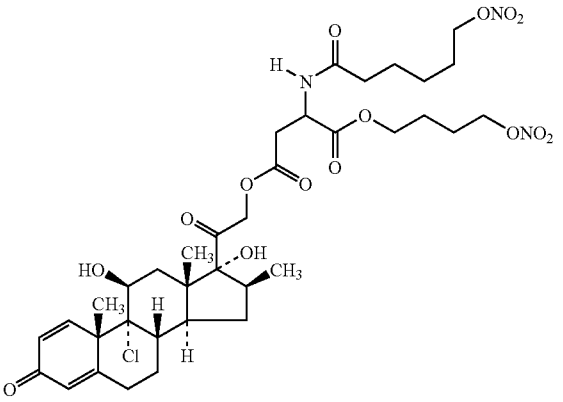

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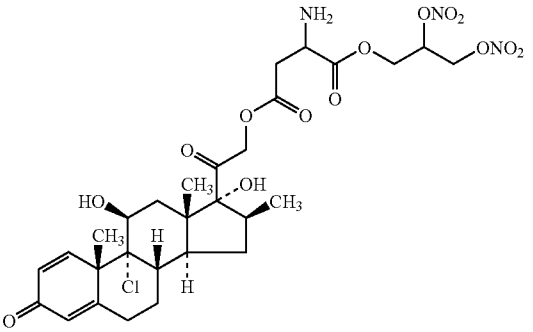

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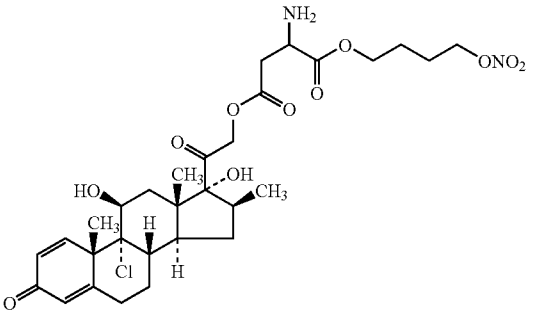

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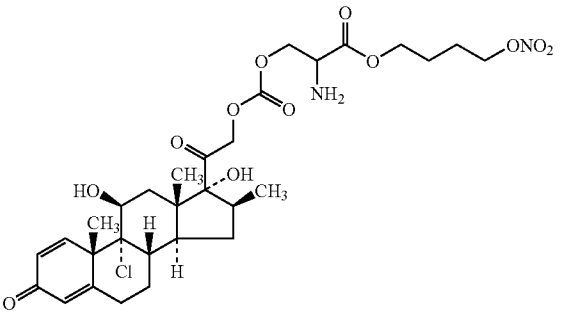

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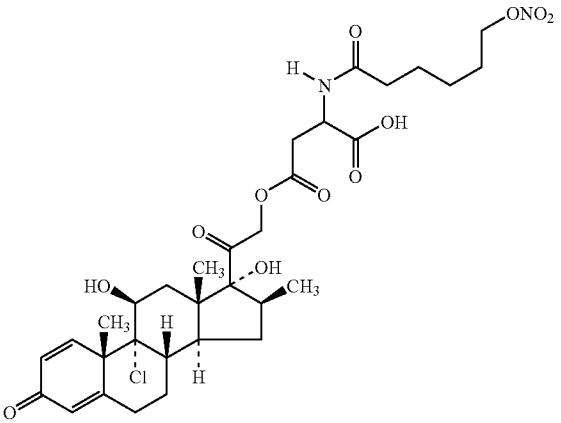
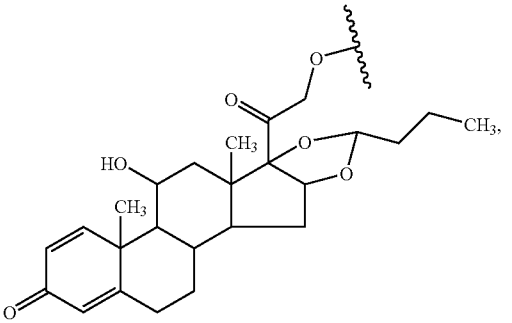


[0169] Another object of the present invention provides nitric oxide releasing compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof

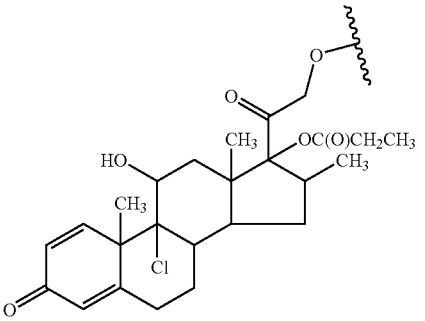
$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

wherein R is a corticosteroid residue selected from:

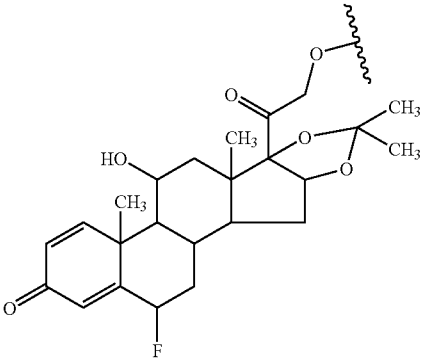
(II)



(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 branched C_1-C_4 alkyl, preferably R' is H or —CH_3;

R_x is a radical selected from the following meanings:

A)

[0170] (a1) —HN—CH(R^1)—C(O)-(T-Y—ONO_2)

[0171] (a2) —C(O)—CH(R^1)—NH-(T'-Y—ONO_2)

[0172] (a3) —HN—CH(R^{1a}-T'-Y'—ONO_2)—$COOR^{3a}$

[0173] (a4) —C(O)—CH(R^{1a}-T"-Y'—ONO_2)—NHR^{4a}

[0174] (a5) —R^{1b}—CH(NHR^{4a})—C(O)-(T-Y—ONO_2)

[0175] (a6) —R^{1b}—CH($COOR^{3a}$)NH-(T'-Y—ONO_2)

[0176] (a7) —HN—CH(R^{1a}-T"-Y'—ONO_2)—C(O)-(T-Y—ONO_2)

[0177] (a8) —C(O)—CH(R^{1d}-T"-Y'—ONO_2)—NH-(T'-Y—ONO_2)

[0178] (a9) —R^{1b}—CH(NH-T'-Y'—ONO_2)—C(O)-(T-Y—ONO_2)

[0179] (a10) —R^{1b}—CH(C(O)-T-Y'—ONO_2)—NH-(T'-Y—ONO_2)

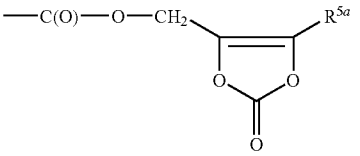
[0180] wherein:

[0181] R^1 is selected from:

[0182] A1) H, —CH_3, isopropyl, isobutyl, sec-butyl, tert-butyl, methylthio-$(CH_2)_2$—, phenyl, benzyl, C_6H_5—CH_2—CH_2—, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, C_6H_5CO—;
2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, 2-pyrrolidyl, 3-triptophanyl-CH_2—, 3-benzothienyl-CH_2—, 4-imidazolyl-CH_2—, 9-anthranyl-CH_2—, cyclohexyl, cyclohexyl-CH_2—, cyclohexyl-$(CH_2)_2$—, cyclopentyl-CH_2—, $(C_6H_5)_2CH$—, 4-B$(OH)_2$-benzyl, 4-quinolyl-CH_2—, 3-quinolyl-CH_2—, 2-quinolyl-CH_2—, 2-quinoxalyl-CH_2—, 2-furyl-CH_2—, 1-naphtyl-CH_2—, 2-naphtyl-CH_2—, 2-pyridyl-CH_2—, 3-pyridyl-CH_2—, 4-pyridyl-CH_2—, 2-thienyl-CH_2—, 3-thienyl-CH_2—, C_6H_4—CH═CH—CH_2—, CH_2═CH—CH_2—, CH≡CH—CH_2—, NH_2—CO—CH_2—, NH_2—CO—$(CH_2)_2$—, NH_2(═NH)NH—$(CH_2)_3$—, P(═O)$(OCH_3)_2$, I—CH_2—, preferably R^1 is H, —CH_3, isopropyl, benzyl;

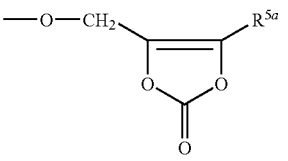
[0183] A2) —CH_2—SH, —CH_2—OH, —CH(CH_3)—OH, —CH_2—[(C_6H_4)-(4-OH)], —CH_2—[(C_6H_2)-(3,5-diiodo)-(4-OH)], —CH_2—[(C_6H_3)-(3-nitro)-(4-OH)], preferably R^1 is —CH_2—OH or —CH_2[(C_6H_4)-(4-OH)];

[0184] A3) —CH_2—NHR", —$(CH_2)_2$—NHR", —$(CH_2)_3$—NHR", —$(CH_2)_4$—NHR", wherein R" is H, —C(O)CH_3 or



wherein R^{5a} is H or a linear or branched C_1-C_{10} alkyl chain, preferably R^{5a} is H or a linear (C_1-C_5) alkyl, preferably R^1 is —$(CH_2)_4$—NHR", wherein R" is as above defined,

[0185] A4) —CH_2—C(O)R'", —$(CH_2)_2$—C(O)R'", —$(CH_2)_4$—C(O)R'" wherein R'" is —OR^{5a} or



wherein R^{5a} is as above defined, preferably R^1 is —CH_2—C(O)R'", wherein R'" is as above defined,

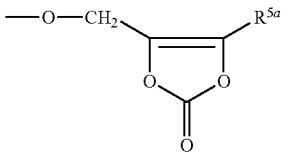
[0186] R^{1a} is selected from:

[0187] A5) —CH_2—S—, —CH_2—O—, —CH(CH_3)—O—, —CH_2[(C_6H_4)-(4-O)—], —CH_2-[(3,5-diiodo)-(C_6H_2)-(4-O)—], —CH_2-[(3-nitro)-(C_6H_3)-(4-O)—], preferably R^{1a} is —CH_2—O—;

[0188] A6) —CH_2—NH—, —$(CH_2)_2$—NH—, —$(CH_2)_3$—NH—, —$(CH_2)_4$—NH—, preferably R^{1a} is —$(CH_2)_4$—NH— or —CH_2—NH—,

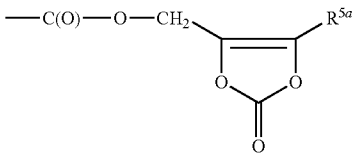
[0189] A7) —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—, preferably R^{1a} is —CH_2—C(O)—;

[0190] R^{3a} is selected from H, —R^{5a} or



[0191] wherein R^{5a} is as above defined,

[0192] R^{4a} is selected from H or —C(O)CH_3 or



[0193] wherein R^{5a} is as above defined,

[0194] R^{1b} is selected from

[0195] A8) —S—CH_2—, —O—CH(CH_3)—, —O—CH_2—, [-(4-O)—(C_6H_4)]—CH_2—, [-(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—;

[0196] 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—;

[0197] 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 —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'— 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:

B)

[0198] (b1) —HN—CH(R^2)—CH_2—C(O)-(T-Y—ONO_2)

[0199] (b2) —C(O)—CH_2—CH(R^2)—NH-(T'-Y—ONO_2)

[0200] (b3) —HN—CH(R^{2a}-T"-Y'—ONO_2)—CH_2COOR^{3a}

[0201] (b4) —C(O)—CH_2—CH(R^{2a}-T"-Y'—ONO_2)—NHR^{4a}

[0202] (b5) —R^{2b}—CH(NHR^{4a})—CH_2—C(O)-(T-Y—ONO_2)

[0203] (b6) —R^{2b}—CH(CH_2COOR^{3a})NH—-(T'-Y—ONO_2)

[0204] (b7) —HN—CH(R^{2a}-T"-Y'—ONO_2)—CH_2—C(O)-(T-Y—ONO_2)

[0205] (b8) —C(O)—CH_2—CH(R^{2a}-T"-Y'—ONO_2)—NH-(T'-Y—ONO_2)

[0206] (b9) —R^{2b}—CH(NH-T'-Y'—ONO_2)—CH_2C(O)-(T-Y—ONO_2)

[0207] (b10) —R^{2b}—CH(CH_2C(O)-T-Y'—ONO_2)—NH-(T'-Y—ONO_2)

[0208] wherein

R^2 is selected from:

[0209] B1) H, —CH_3, CF_3, isopropyl, isobutyl, sec-butyl, methylthio-$(CH_2)_2$—, phenyl, benzyl, 3-triptophanyl-CH_2—, NH_2—C(O)—CH_2—, NH_2—C(O)—$(CH_2)_2$—, NH_2(═NH)NH—$(CH_2)_3$—, tBuO—CH(CH_3)—, benzyl-O—CH_2—, 4-terbutoxy-benzyl, 4-phenylbenzyl, preferably R^2 is H, —CH_3, isopropyl, benzyl,

[0210] B2) —CH_2—SH, —CH_2—OH, —CH(CH_3)—OH, —CH_2—[(C_6H_4)-(4-OH)], —CH_2—[(C_6H_2)-(3,5-diiodo)-(4-OH)], —CH_2—[(C_6H_3)-(3-nitro)-(4-OH)];

[0211] B3) —CH_2—NHR", —$(CH_2)_2$—NHR", —$(CH_2)_3$—NHR", —$(CH_2)_4$—NHR", wherein R" is as above defined, preferably R^2 is —$(CH_2)_4$—NHR";

[0212] B4) —CH_2—C(O)—R'", —$(CH_2)_2$—C(O)—R'", —$(CH_2)_4$—C(O)—R'" wherein R'" is as above defined, preferably R^2 is —CH_2—C(O)—R'";

R^{2a} is selected from:

[0213] B5) —CH_2—S—, —CH_2—O—, —CH(CH_3)—O— or —CH_2[(C_6H_4)-(4-O)—], —CH_2-[(3,5-diiodo)-(C_6H_2)-(4-O)—], —CH_2-[(3-nitro)-(C_6H_3)-(4-O)—], preferably R^{2a} is —CH_2—O—;

[0214] B6) —CH_2—NH—, —$(CH_2)_2$—NH—, —$(CH_2)_3$—NH—, —$(CH_2)_4$—NH—, preferably R^{2a} is —$(CH_2)_4$—NH— or —CH_2—NH—;

[0215] B7) —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—, preferably R^{2a} is —CH_2—C(O)—;

R^{2b} is selected from

[0216] B8) —S—CH_2—, —O—CH(CH_3)—, —O—CH_2—, [-(4-O)—(C_6H_4)]—CH_2—, [-(4-O)-(3,5-diiodo)-(C_6H_2)]—CH_2—, [-(4-O)-(3-nitro)-(C_6H_3)]—CH_2—, preferably R^{2b} is —O—CH_2— or [-(4-O)—(C_6H_4)]—CH_2—;

[0217] B9) —HN—CH_2—, —HN—$(CH_2)_2$—, —HN—$(CH_2)_3$—, —HN—$(CH_2)_4$—, preferably R^{2b} is —HN—$(CH_2)_4$— or —HN—CH_2—;

[0218] B10) —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—, preferably R^{2b} is —C(O)—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:

C)

[0219] (c1) —HN—$(CH_2)_b$—C(O)-(T-Y—ONO_2);
(c2) —C(O)—$(CH_2)_b$—NH-(T'-Y—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;

D)

[0220] (d1) —HN—$CH(R^{12})$—CH_2—O-(T'''-Y—ONO_2)
(d2) —O—CH_2—$CH(R^{12})$—NH-(T'-Y—ONO_2)
(d3) —HN—$CH(R^{12a}$-T''-Y''—$ONO_2)$—CH_2OH
(d4) —O—CH_2—$CH(R^{12a}$-T''-Y'—$ONO_2)$—NHR^{4a}
(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)
(d9) —R^{12}—CH(NH-T'-Y'—ONO_2)—CH_2—O-(T'''-Y—ONO_2)
(d10) —R^{12}—$CH(CH_2$—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;
T' and T'' are as above defined,
Y and Y' are as below defined;
R^{12} is selected from:

[0221] D1) H, —CH_3, isopropyl, isobutyl, sec-butyl, methylthio-$(CH_2)_2$—, benzyl, 3-triptophanyl-CH_2—, 4-imidazolyl-CH_2—, NH_2—CO—CH_2—, NH_2—CO—$(CH_2)_2$—, $NH_2(=NH)NH$—$(CH_2)_3$—, preferably R^{12} is H;

[0222] 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)], preferably R^{12} is —CH_2—OH or —CH_2[(C_6H_4)-(4-OH)];

[0223] D3) —CH_2—NHR'', —$(CH_2)_2$—NHR'', —$(CH_2)_3$—NHR'', —$(CH_2)_4$—NHR'', wherein R'' is as above defined, preferably R^{12} is —$(CH_2)_4$—NHR'';

[0224] D4) —CH_2—C(O)R''', —$(CH_2)_2$—C(O)R''', —$(CH_2)_4$—C(O)R''' wherein R''' is as above defined, preferably R^{12} is —CH_2—C(O)R''';
R^{12a} is selected from

[0225] D5) —CH_2—O—, —$CH(CH_3)$—O— or —CH_2[(C_6H_4)-(4-O)—], —CH_2-[3,5-diiodo-(C_6H_2)-(4-O)—], —CH_2-[3-nitro-(C_6H_3)-4-O—], preferably R^{12a} is CH_2—O— or —CH_2—[(C_6H_4)-(4-O)—],

[0226] D6) —CH_2—NH—, —$(CH_2)_2$—NH—, —$(CH_2)_3$—NH—, —$(CH_2)_4$—NH—, preferably R^{12a} is —$(CH_2)_4$—NH— or —CH_2—NH—,

[0227] D7) —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—, preferably R^{2a} is —CH_2—C(O)—,
R^{12b} is selected from

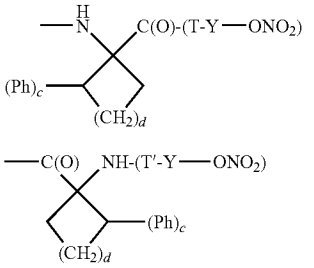
[0228] D8) —O—CH_2—, —O—$CH(CH_3)$—, [-(4-O)—(C_6H_4)]—CH_2—, [-(4-O)-(3,5-diiodo)-(C_6H_2)]—CH_2, [-(4-O)-(3-nitro)-(C_6H_3)]—CH_2—, preferably R^{12} is —O—CH_2— or [-(4-O)—(C_6H_4)]—CH_2—;

[0229] D9) —HN—CH_2—, —HN—$(CH_2)_2$—, —HN—$(CH_2)_3$—, —HN—$(CH_2)_4$—, preferably R^{12b} is —HN—$(CH_2)_4$— or —HN—CH_2—;

[0230] D10) —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—, preferably R^{12b} is —C(O)—CH_2—;
R^{4a} is as above defined;
or R_x is selected from:

HE)

[0231]



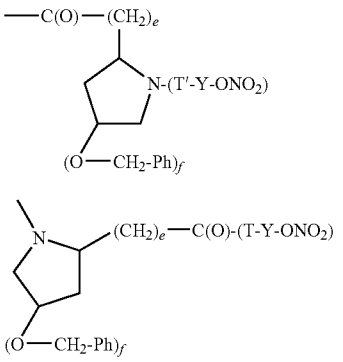
(e1)

(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)

[0232]



(f1)

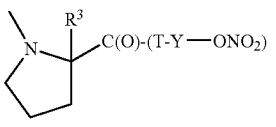
(f2)

(XI)

[0233] 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)

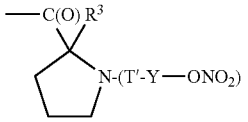
[0234]



(g1)

-continued

(g2)

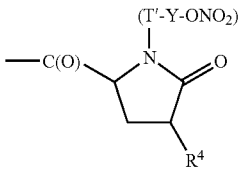


wherein R^3 is H, CH_3, propyl, $(C_6H_5)_2CH$—, 1-naphtyl-CH_2—, benzyl, allyl, 2-bromobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-fluorobenzyl, 4-bromobenzyl, 4-methyl-benzyl, preferably R^3 is H, T and T' are as above defined and Y is as below defined;

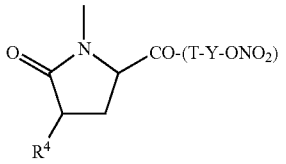
H)

[0235]

(h1)



(h2)

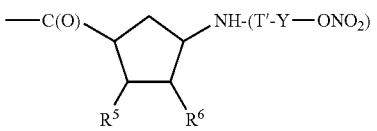


wherein R^4 is H, benzyl, 4-bromobenzyl, 2-bromobenzyl, T and T' are as above defined and Y is as below defined;

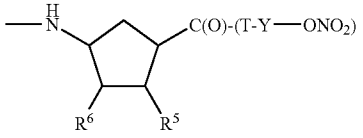
I)

[0236]

(i1)



(i2)

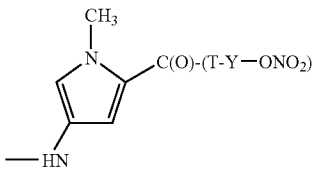


wherein R^5 is H, R^p is H, or R^5 and R when taken together are a double bond, T and T' are as above defined and Y is as below reported;

L)

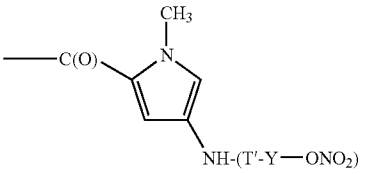
[0237]

(l1)



-continued

(l2)

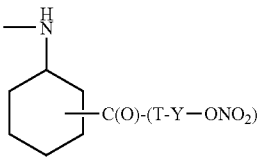


wherein T and T' are as above defined and Y is as below reported;

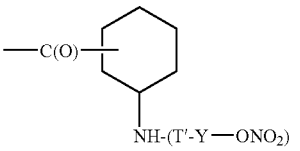
M)

[0238]

(m1)



(m2)

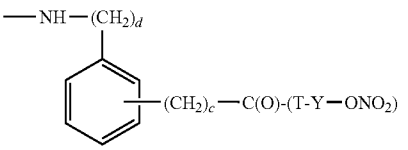


wherein T and T' are as above defined and Y is as below reported;

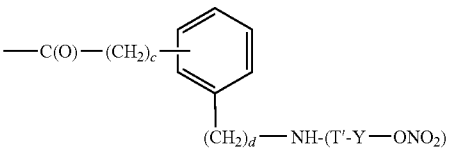
N)

[0239]

(n1)



(n2)

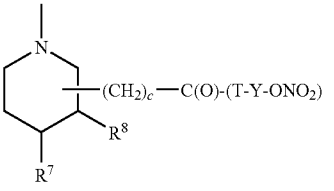


wherein c is as above defined, d is equal to 0 or 1, T and T' are as above defined and Y is as below reported;

O)

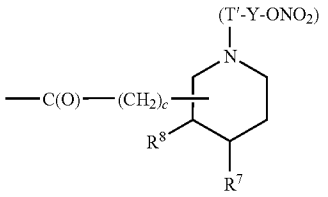
[0240]

(o1)



-continued

(o2)

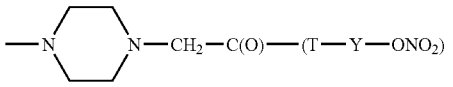


wherein R^7 is H, R^8 is H, or R^7 and R^8 when taken together are a double bond, c is as above defined, T and T' are as above defined and Y is as below reported;

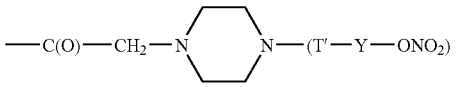
P)

[0241]

(p1)



(p2)

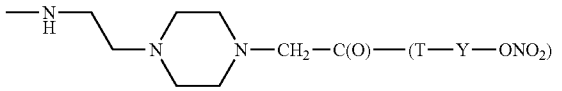


wherein T and T' are as above defined and Y is as below reported;

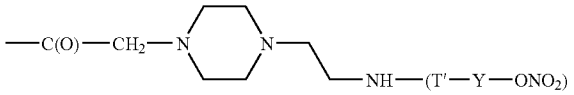
Q)

[0242]

(q1)



(q2)

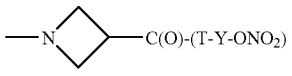


wherein T and T' are as above defined and Y is as below reported;

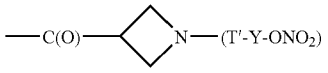
R)

[0243]

(r1)



(r2)

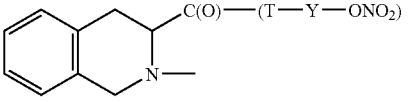


wherein T and T' are as above defined and Y is as below reported;

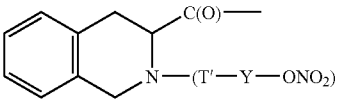
S)

[0244]

(s1)



(s2)

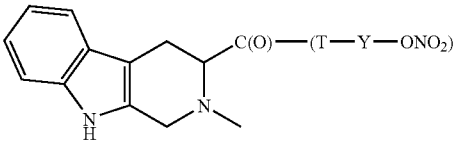


wherein T and T' are as above defined and Y is as below reported;

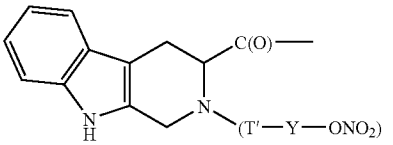
T)

[0245]

(t1)



(t2)

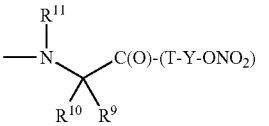


wherein T and T' are as above defined and Y is as below reported;

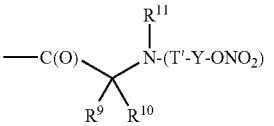
U)

[0246]

(u1)



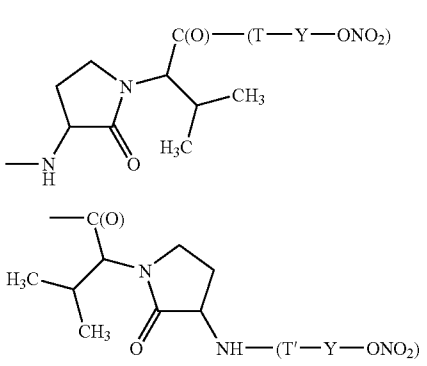
(u2)



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)

[0247]



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:

[0248] (a2), (a4) or (a8);

[0249] (a5), (a6), (a9) or (a10) and R^{1b} is selected from the group A10);

[0250] (b2), (b4) or (b8);

[0251] (b5), (b6), (b9) or (b10) and R^{2b} is selected from the group B10);

[0252] (c2);

[0253] (d5), (d6), (d9) or (d10) and R^{12b} is selected from the group D10);

[0254] (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:

[0255] (a1), (a3) or (a7);

[0256] (a5), (a6), (a9) or (a10) and R^{1b} is selected from the groups A8) and A9);

[0257] (b1), (b3) or (b7);

[0258] (b5), (b6), (b9) or (b10) and R^{2b} is selected from the groups B8) or B9);

[0259] (c1);

[0260] (d1), (d2), (d3), (d4), (d7) or (d8);

[0261] (d5), (d6), (d9) or (d10) and R^{12b} is selected from the groups D8) or D9);

[0262] (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:

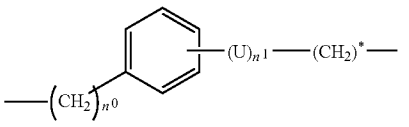
a)

[0263] straight or branched C_1-C_{20} alkylene, preferably a straight or branched C_1-C_{10} alkylene,

[0264] 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} alkyl)-ONO_2 or O(C_1-C_{10} alkyl)-ONO_2, preferably Y or Y' is a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;

[0265] 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_3;

b)



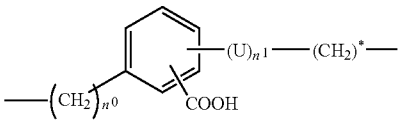
wherein

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

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

c)



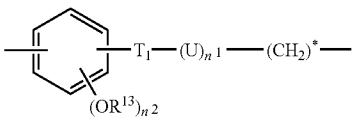
wherein

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

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

[0266] 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;

d)

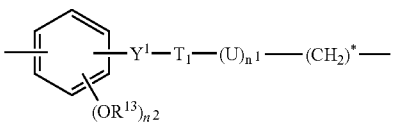


wherein:

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)



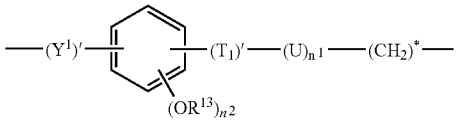
n^2 is an integer from 0 to 2, preferably n^2 is 1;

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

Y^1 is —CH_2—CH_2— or —CH═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;
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 $n^{2'}$ is 0, T_1 is —C(O)O— and U is a linear C_1-C_{10} alkylene;
e')

e')

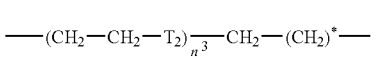


wherein:
n^2 is an integer from 0 to 2, preferably n^2 is 1;
R^{13} is H or CH_3, preferably R^{13} is CH_3;
Y^1 is —CH_2—CH_2— or —$(CH_2)_2$—CH═CH—, wherein n is 0 or 1, preferably Y^1 is —$(CH_2)_{n^{2'}}$—CH═CH— and $n^{2'}$ is 0;

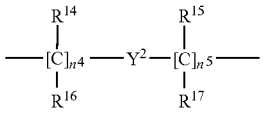
T_1=—O—C(O)—;

[0267] 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;
more preferably 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 —OC(O)— and U is a linear C_1-C_{10} alkylene;
f)

f)



wherein T_2 is —O— or —S—, —NH—, preferably T_2 is —O—, n^3 is an integer from 1 to 6, preferably n^3 is 1;
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'—ONO_2), -(T"'-Y—ONO_2) and -(T"'-Y'—ONO_2) is linked to the —(CH_2)*— group;
g)



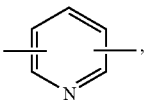
wherein:
n^4 is an integer from 0 to 10, preferably n^4 is 0 or 1;
n^5 is an integer from 1 to 10, preferably n^5 is 1;
[0268] R^{14}, R^{15}, R^{16}, R^{17} are the same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^{14}, R^{15}, R^{16} and R^{17} are H;

wherein the —ONO_2 group is linked to

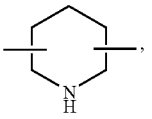
wherein n^5 is as defined above;

[0269] 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:

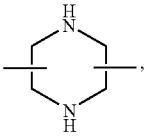
(Y1)



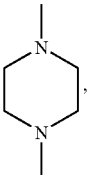
(Y2)



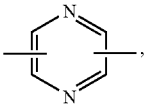
(Y3)



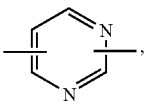
(Y4)



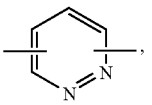
(Y5)



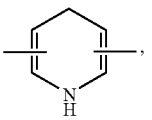
(Y6)



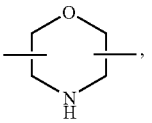
(Y7)



(Y8)



(Y9)



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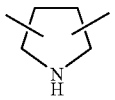
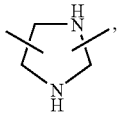
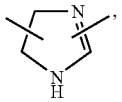
(Y10)



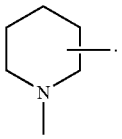
(Y11)



(Y12)



(Y13)

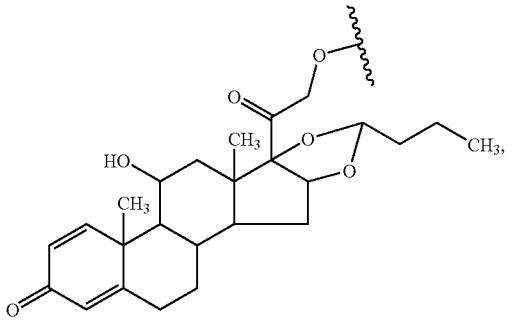


[0270] Another object of the present invention provides nitric oxide releasing compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof

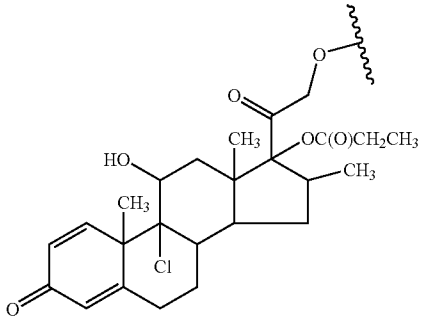
$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

wherein R is a corticosteroid residue selected from:

(II)



(IV)



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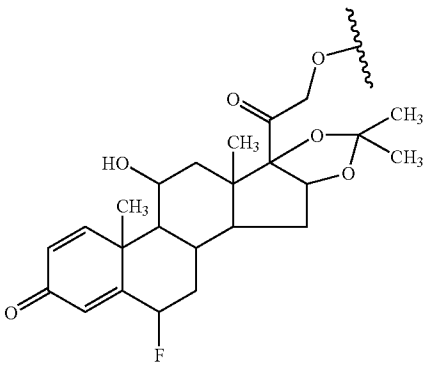
(V)



a is 0 and

R_X is selected from:

(a2) —C(O)—CH(R^1)—NH-(T'-Y—ONO_2)

wherein

R^1 of the group A1) is selected from H, isobutyl, benzyl, C_6H_5—CH_2—CH_2—, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, C_6H_5CO—;

R^1 of the group A2) is selected from —CH_2—OH, —CH(CH_3)OH— or —CH_2[(C_6H_4)-(4-OH)], or

R^1 of the group A3) 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^1 of the group A4) is selected from —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' is —C(O)—, —C(O)—X" wherein X" is —S— or —O—, preferably T' is —C(O)—;

Y is as below defined;

or R_X is

[0271] (a4) —C(O)—CH(R^{1a}-T"-Y'—ONO_2)—NHR^{4a}

wherein 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 selected from —CH_2—C(O)—, —(CH_2)$_2$—C(O)—, —(CH_2)$_4$—C(O)—,

R^{4a} is H or —C(O)CH_3,

[0272] T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} 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_3, when R^{1a} is selected from the group A7),

Y' is as below defined;

or R_X 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)

wherein
R^{1b} of the group A10) is selected from —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—,
R^{3a} is H or a (C_1-C_5) alkyl,

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

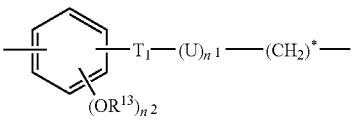
[0273] T is —O—, —S—, —NR'— or —O—CH(R')—O—C(O)— wherein R' is H or —CH_3, preferably T is —O—, T' is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, preferably T' is —C(O)—,
Y and Y' are as below defined;

or R_X is

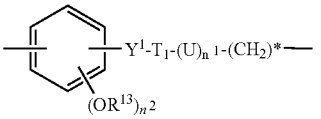
[0274] (a8) —C(O)—CH(R^{1a}-T"-Y'—ONO_2)—NH-(T'-Y—ONO_2)
wherein
R^{1a} of the group A5) is selected from —CH_2—O—, —CH(CH_3)—O— or —CH_2[(C_6H_4)-(4-O)—], or
R^{1a} of the group A6) is selected from —CH_2—NH—, —$(CH_2)_2$—NH—, —$(CH_2)_3$—NH—, —$(CH_2)_4$—NH—, or
R^{1a} of the group A7) is selected from —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—,
T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} 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_3, when R^{1a} 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_X is

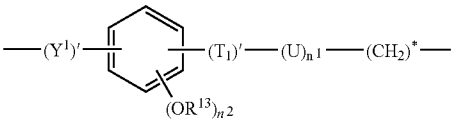
[0275] (b2) —C(O)—CH_2—CH(R^2)—NH-(T'-Y—ONO_2)
wherein
R^2 of the group B1) is selected from H, CH_3, isobutyl, isopropyl, benzyl;
T' is —C(O)—, —C(O)—X" wherein X" is —S— or —O—, preferably T' is —C(O)—;
Y and Y' are each independently selected from
a)
[0276] a straight or branched C_1-C_{10} alkylene,
[0277] a straight or branched C_1-C_{10} alkylene 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 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)



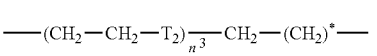
n^2 is 1, R^{13} is CH_3, Y^1 is —CH═CH—$(CH_2)_n{}^{2'}$— and $n^{2'}$ is 0, T_1 is —C(O)O— and U is a linear C_1-C_{10} alkylene;
e')



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)—;

[0278] 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)

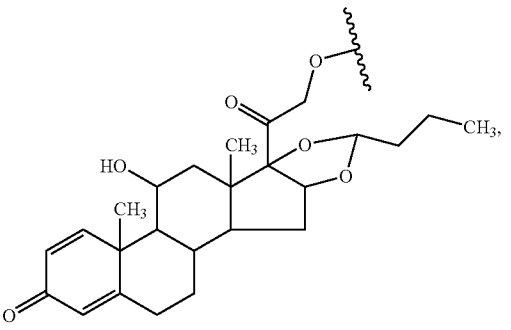


wherein T_2 is —O— or —S—, —NH—, preferably T_2 is —O—, n^3 is 1 or 2;
when Y and Y' are selected from d), e), e') or f), the —ONO_2 group of -(T-Y—ONO_2), -(T'-Y—ONO_2), -(T"-Y'—ONO_2), -(T'-Y'—ONO_2), -(T"'-Y—ONO_2) and -(T"'-Y'—ONO_2) is linked to the —(CH_2)*— group.
[0279] Another object of the 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)



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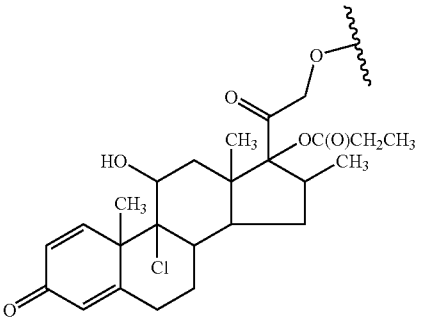
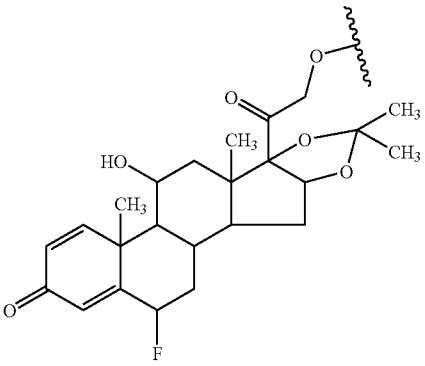
(IV)



(V)



a is 1 and Z is —C(O)—;

R_X is

[0280] (a1) —HN—CH(R^1)—C(O)-(T-Y—ONO_2)
wherein
R^1 of the group A1) is selected from H, isobutyl, benzyl, C_6H_5—CH_2—CH_2—, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, C_6H_5CO— or
R^1 of the group A2) is selected from:

—CH_2—OH, —$CH(CH_3)$—OH— or —$CH_2[(C_6H_4)$-(4-OH)], or

[0281] R^1 of the group A3) 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^1 of the group A4) 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_3-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

[0282] (a3) —HN—CH(R^{1a}-T"-Y'—ONO_2)—$COOR^{3a}$
wherein
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)—,
R^{3a} is H or a (C_1-C_5) alkyl,
T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} is selected from the group 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 the group A7);
Y^1 is as below defined;
or R_X is selected from.
(a5) —R^{1b}—$OCH(NHR^{4a})$—C(O)-(T-Y—ONO_2)
(a6) —R^{1b}—$CH(COOR^{3a})NH$-(T'-Y—ONO_2)
(a9) —R^{1b}—OCH(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)
wherein
R^{1b} of the group AB) 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— $(CH_2)_4$—,
R^{3a} is H or a (C_1-C_5) alkyl,

R^{4a} is H or —C(O)CH_3,

[0283] 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—,
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

[0284] (a7) —HN—CH(R^{1a}-T'-Y'—ONO_2)—C(O)-(T-Y—ONO_2)
wherein
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)—;
T" is —C(O)— or —C(O)—X", wherein X" is —S— or —O—, when R" 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—,
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

[0285] (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 —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,

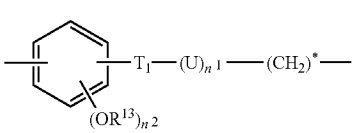
R^2 of the group B4) is —CH_2—C(O)R'", —$(CH_2)_2$—C(O)R'", —$(CH_2)_4$—C(O)R'" wherein R'" is OR^{5a} wherein R^{5a} is H or a linear (C_1-C_5) alkyl;
T is —O—, —S—, —NR'—, —O—CH(R')—O—C(O)— wherein R' is H or a straight or branched C_1-C_4 alkyl, preferably T is —O—,
Y is as below defined;
or R_X is selected from
(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
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
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)—,
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
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,

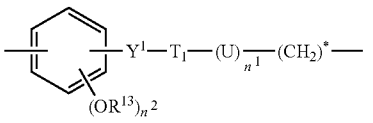
[0286] T" is selected from —C(O)— or —C(O)—X", wherein X" is —S— or —O—, when R^{12a} is selected from D5) or D6), preferably T' and T'" are —C(O)—,
T" is —O—, —S—, —NR'—, —O—CH(R')—O—C(O)—, wherein R' is H or a straight or branched C_1-C_4 alkyl, when R^{12a} is selected from D7), preferably T is —O—,
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_X is selected from:
(d5) —R^{12b}—CH(NHR^{4a})—CH_2—O-(T'"-Y—ONO_2)
(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
R^{12b} of the group D8) is selected from —O—CH(CH_3)—, —O—CH_2—, [-4-O—(C_8H_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,

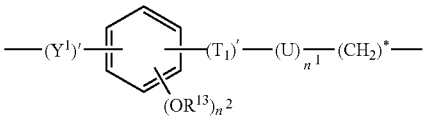
[0287] T' and T'" are each independently selected from —C(O)—, —C(O)—X", wherein X" is —S— or —O—, preferably T' and T'" are —C(O)—,
Y and Y' are each independently selected from
a)
[0288] a straight or branched C_1-C_{10} alkylene,
[0289] a straight or branched C_1-C_{10} alkylene substituted with a 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 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)



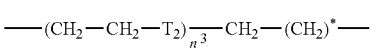
n^2 is 1, R^{13} is CH_3, Y^1 is —CH═CH—$(CH_2)_{n^{2'}}$— and $n^{2'}$ is 0, T_1 is —C(O)O— and U is a linear C_1-C_{10} alkylene;
e')



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)—,

[0290] 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)



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

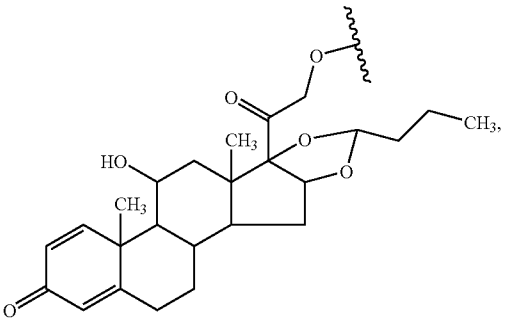
when Y and Y' are selected from d), e), e') or f), the —ONO_2 group of -(T-Y—ONO_2), -(T'-Y—ONO_2), -(T''-Y'—ONO_2), -(T'-Y'—ONO_2), -(T'''-Y—ONO_2) and -(T'''-Y'—ONO_2) is linked to the —(CH_2)*— group.

[0291] Another object of the present invention provides nitric oxide releasing compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof

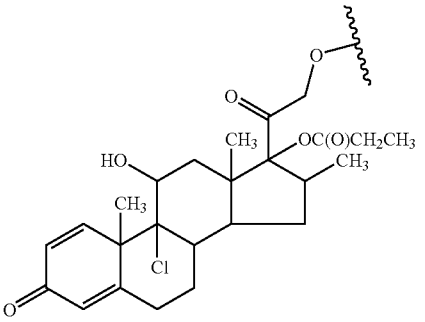
$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

wherein R is a corticosteroid residue selected from:

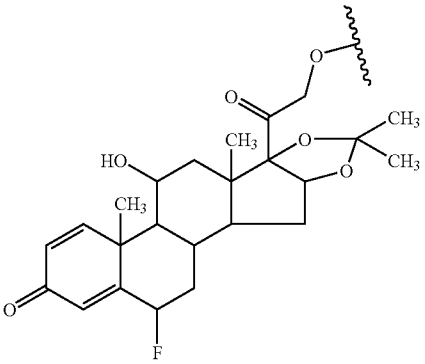
(II)



(IV)



(V)



a is 0,

R_X is

[0292] (a2) —C(O)—CH(R^1)—NH-(T'-Y—ONO_2) wherein

R^1 of the group A1) is H

T' is —C(O)—;

[0293] Y is selected from

a)

[0294] a straight or branched C_1-C_{10} alkylene,

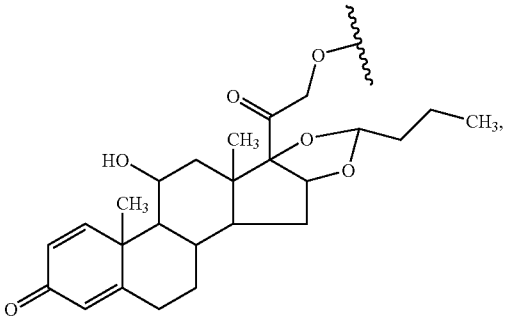
[0295] a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;

[0296] Another object of the present invention provides nitric oxide releasing compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof

$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

wherein R is a corticosteroid residue selected from:

(II)



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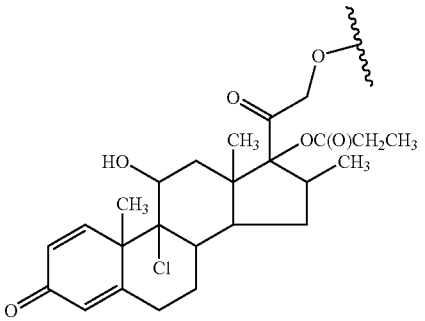

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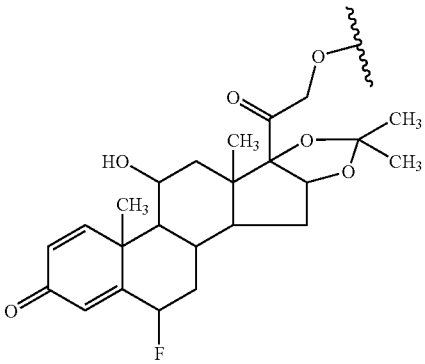


a is 0,

R_X is selected from

R_X is selected from

[0297] (a5) —R^{1b}—CH(NHR^{4a})—C(O)-(T-Y—ONO_2)

[0298] (a6) —R^{1b}—CH($COOR^{3a}$)NH-(T'-Y—ONO_2) or

[0299] (a9) —R^{1b}—CH(NH-T'-Y'—ONO_2)—C(O)-(T-Y—ONO_2)

wherein
R^{1b} of the group A10) is —C(O)—CH_2—,
R^{3a} is H or a (C_1-C_5) alkyl,

R^{4a} is H or —C(O)CH_3,

[0300] T is selected from —O—, —S—, —NR'— wherein R' is as above defined,

T' is —C(O)— and

[0301] Y and Y' are each independently selected from a)

[0302] a straight or branched C_1-C_{10} alkylene,

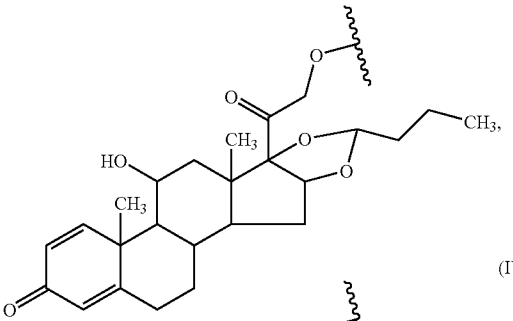
[0303] a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group.

[0304] Another object of the present invention provides nitric oxide releasing compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof

$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

wherein R is a corticosteroid residue selected from:

(II)



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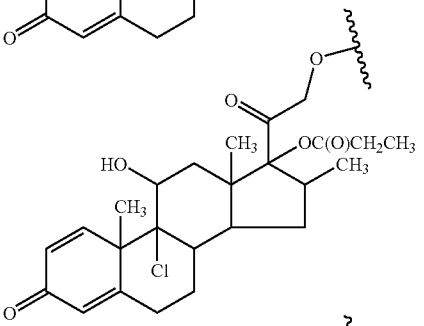

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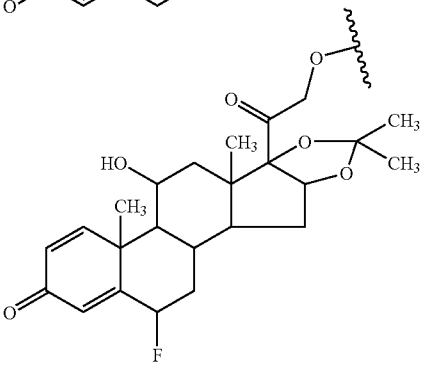


a is 1 and Z is —C(O)—,

R_X is

[0305] (a5) —R^{1b}—CH(NHR^{4a})—C(O)-(T-Y—ONO_2) or

[0306] (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,

[0307] T is selected from —O—, —S—, —NR'— wherein R' is as above defined,

T' is —C(O)— and

[0308] Y and Y' are each independently selected from a)

[0309] a straight or branched C_1-C_{10} alkylene,

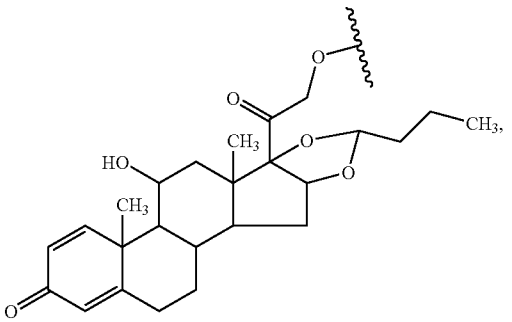
[0310] a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group.

[0311] Another object of the present invention provides nitric oxide releasing compounds of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof

$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

wherein R is a corticosteroid residue selected from:

(II)



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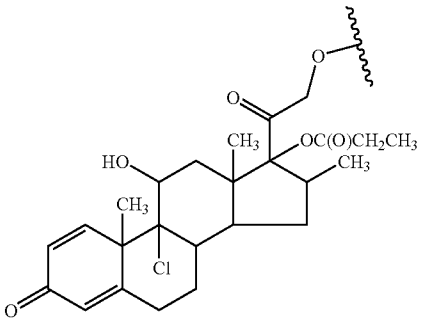

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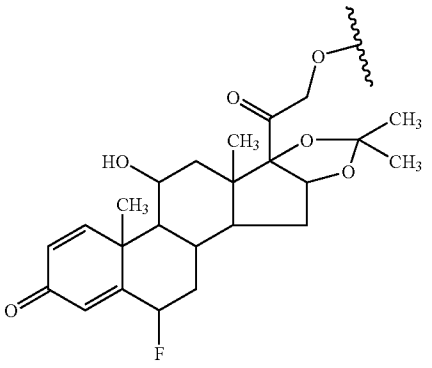


a is 0,

R_X is

[0312] (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)—;

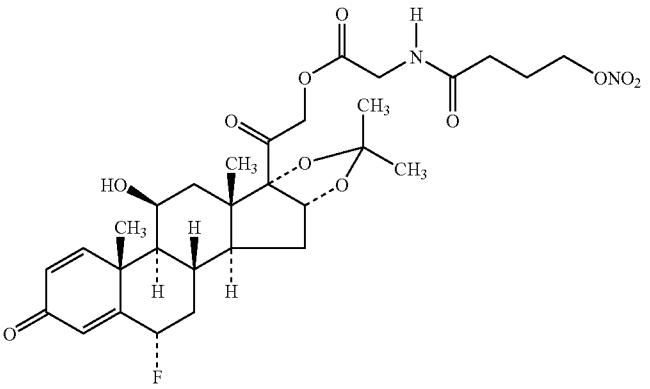
[0313] Y and Y' are each independently selected from a)

[0314] a straight or branched C_1-C_{10} alkylene,

[0315] a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group.

[0316] The most preferred nitric oxide releasing compounds of general formula (I) are:

(1)



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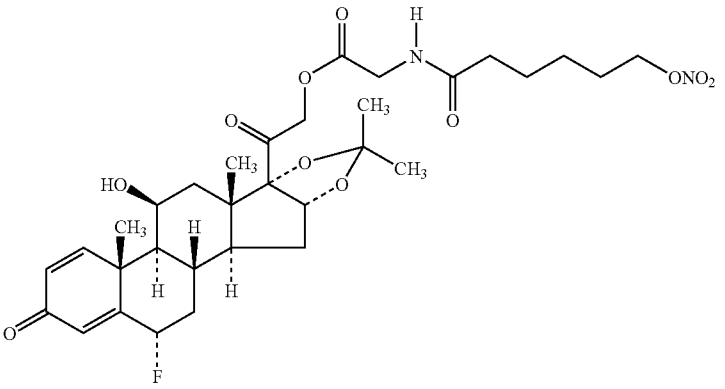

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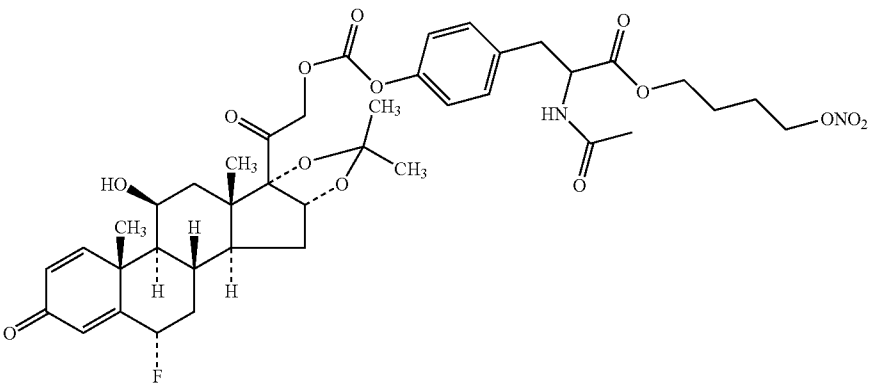

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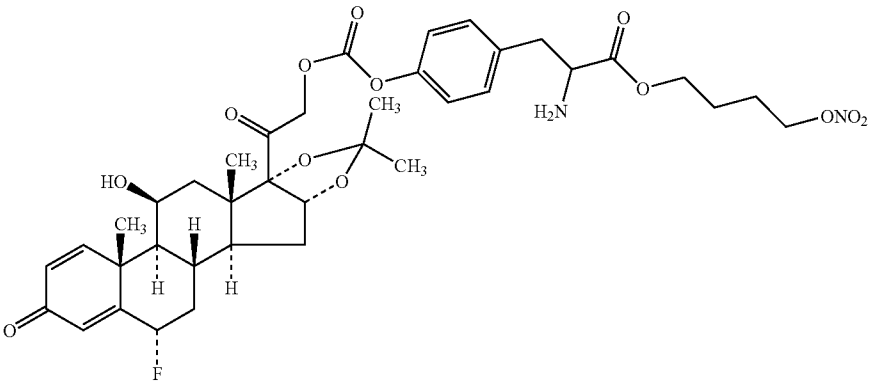

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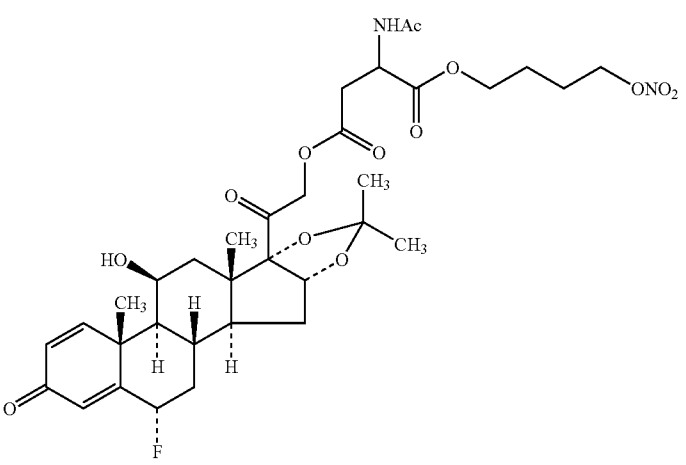

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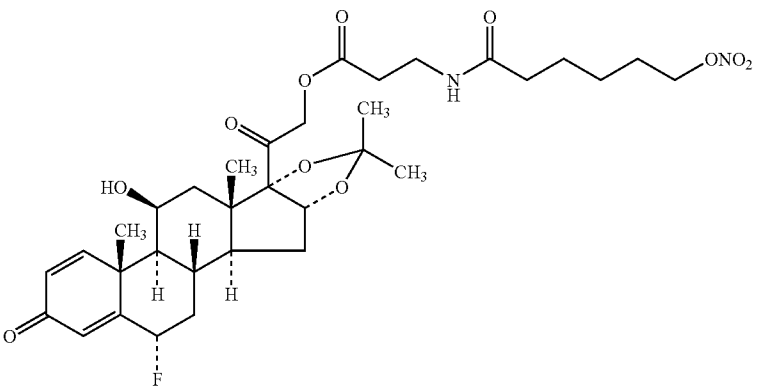

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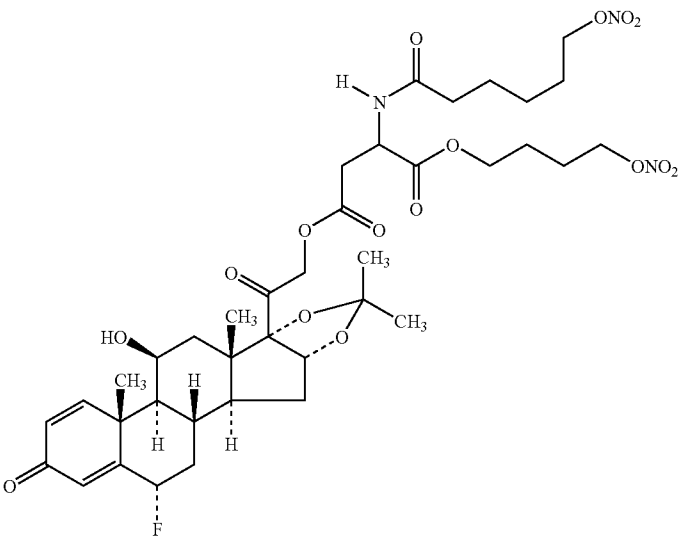

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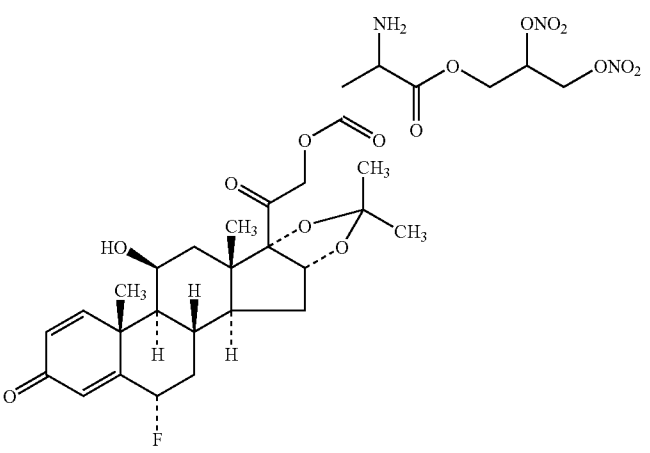

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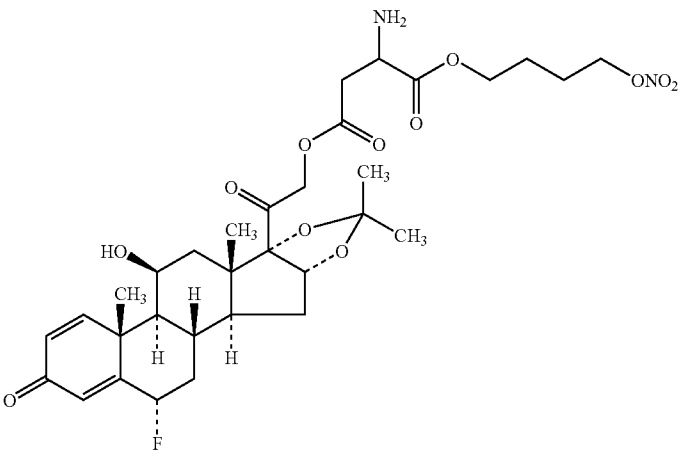

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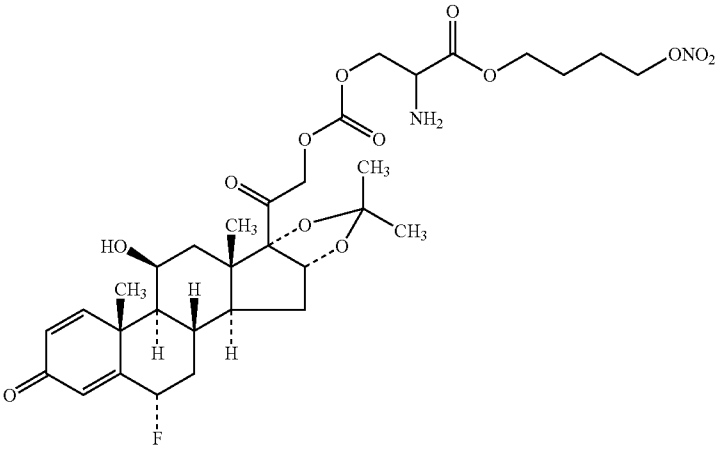

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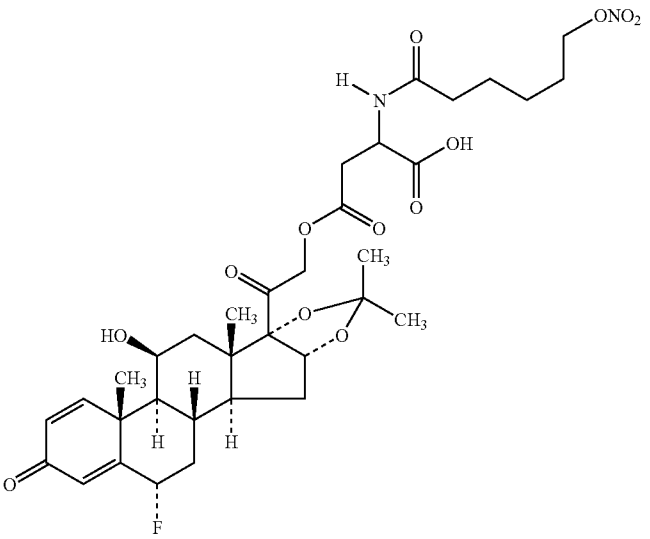

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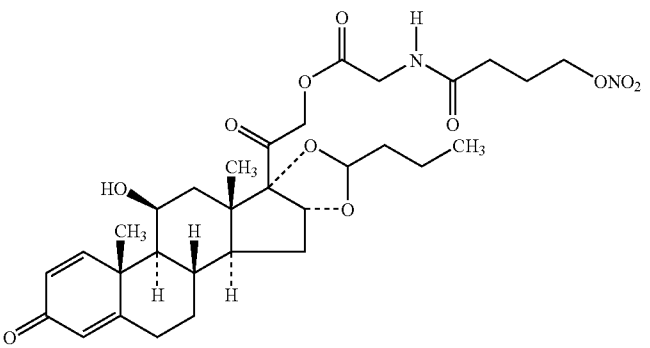

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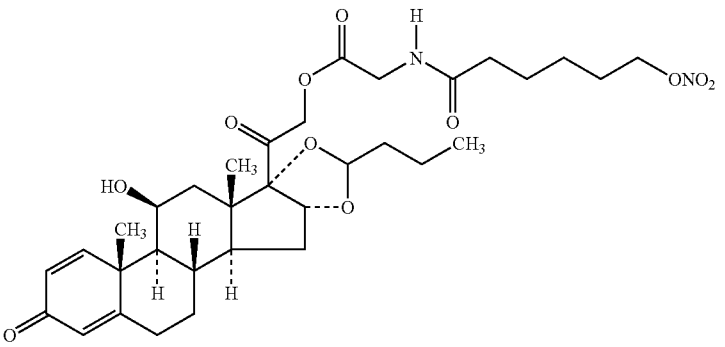

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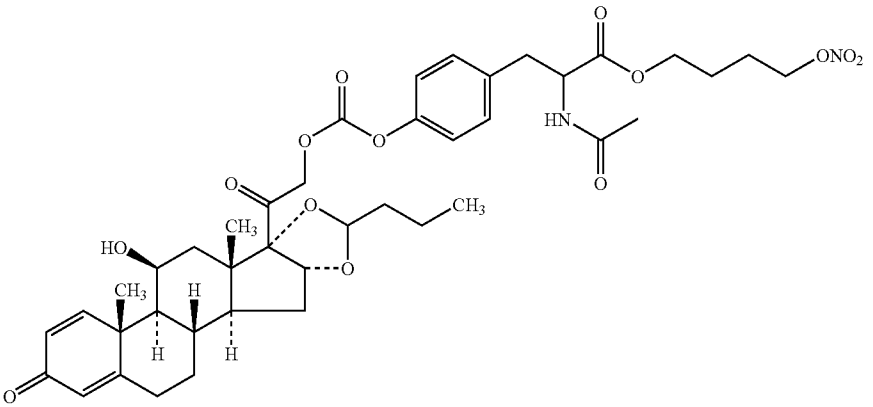

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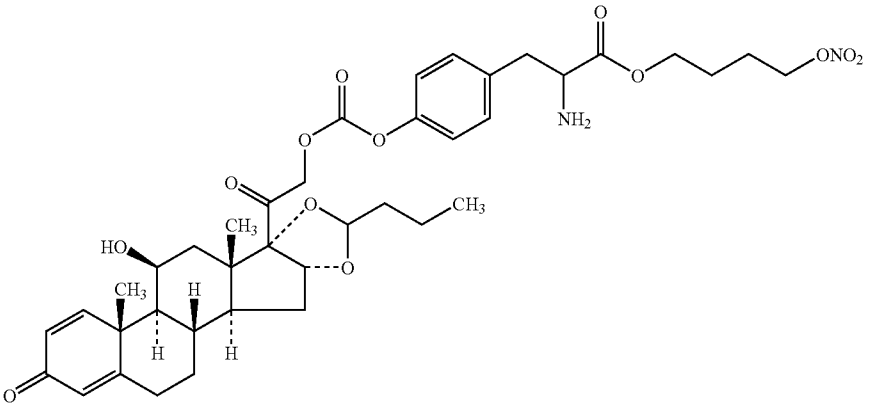

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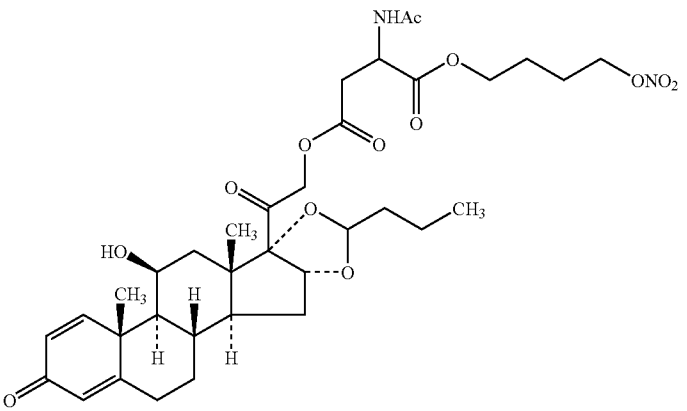

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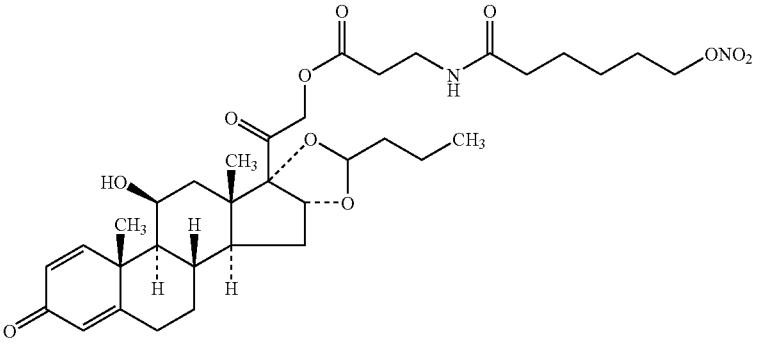

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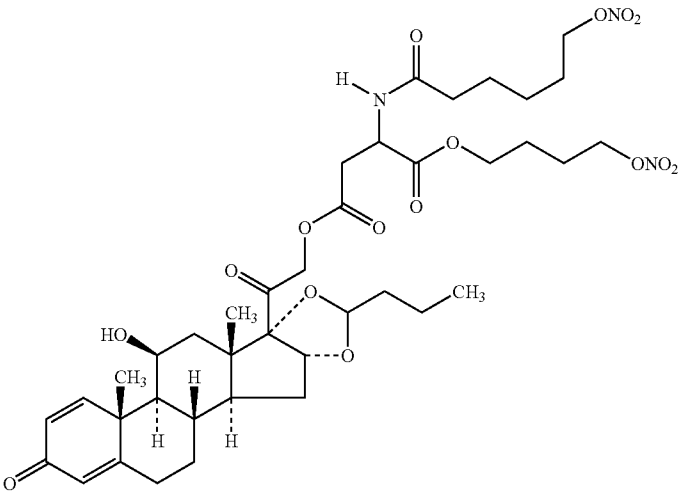

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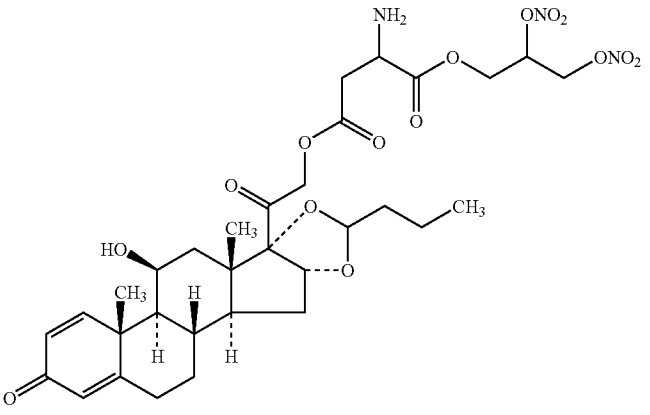

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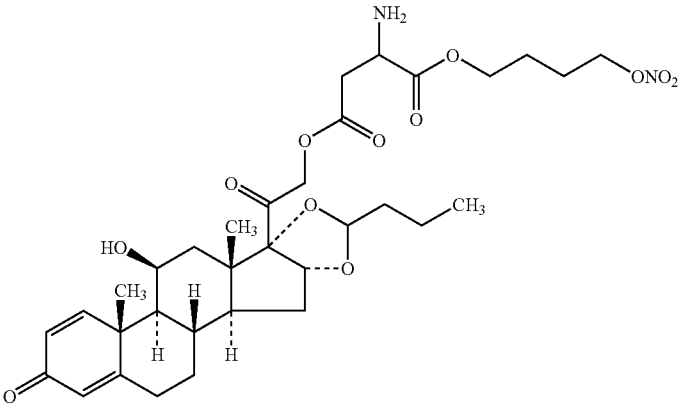

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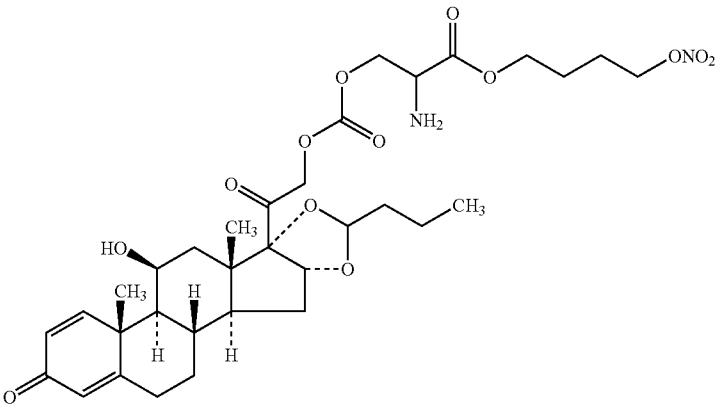

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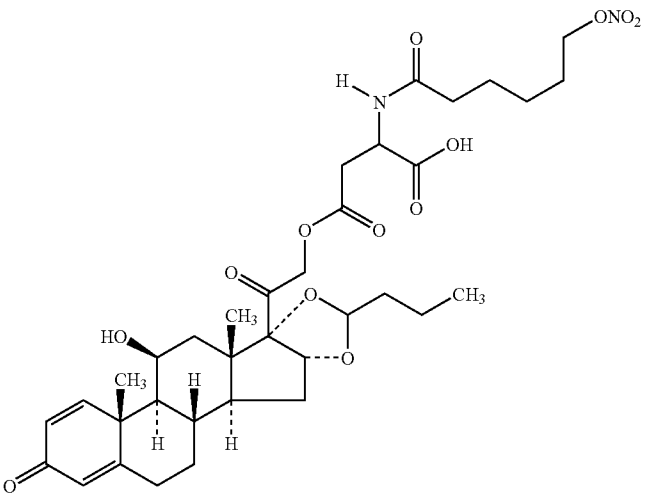

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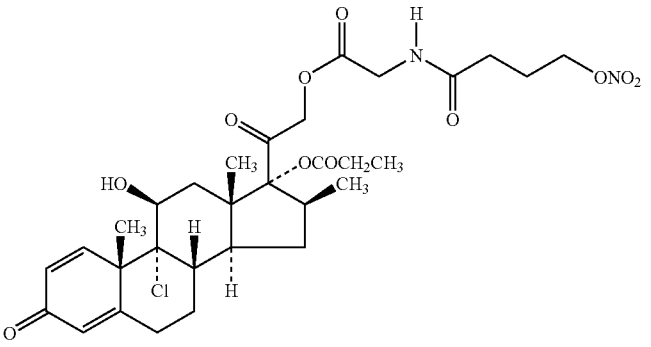

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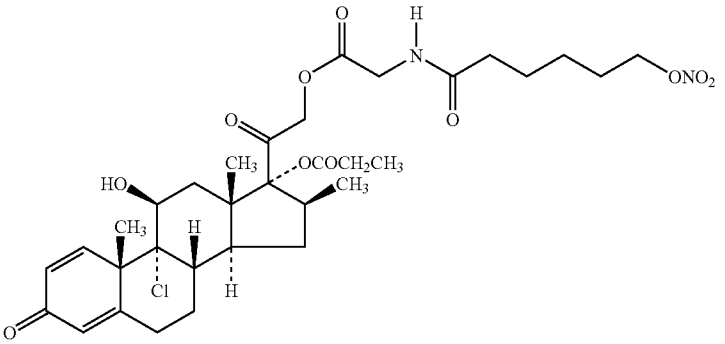

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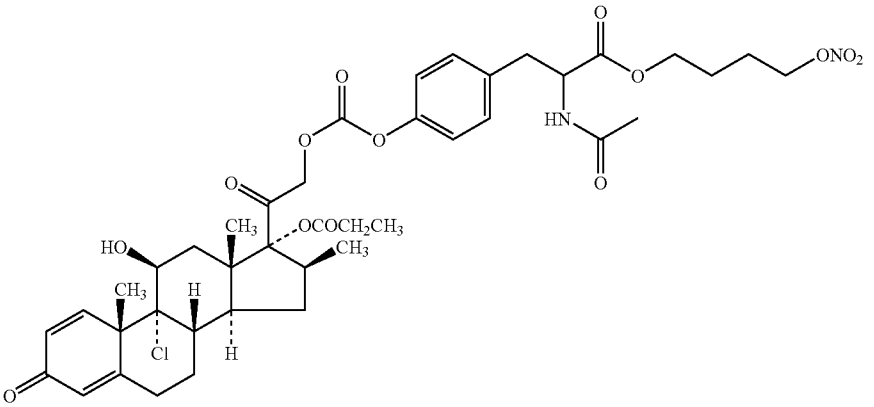

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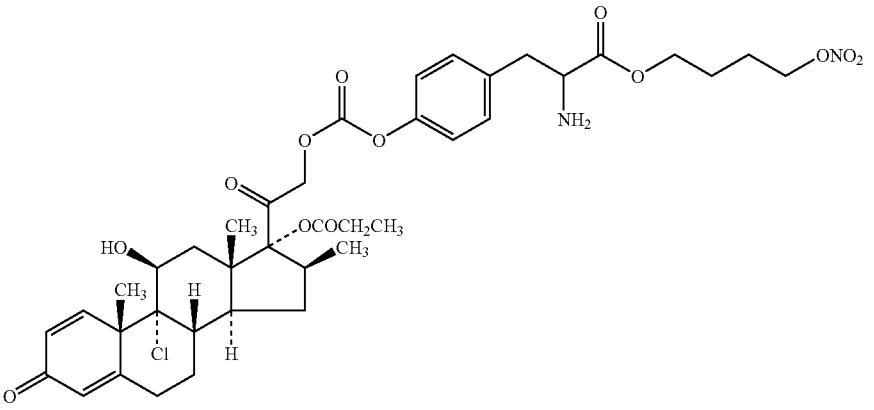

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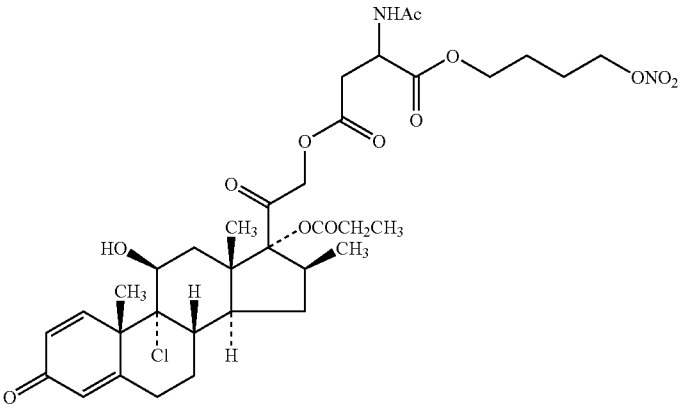

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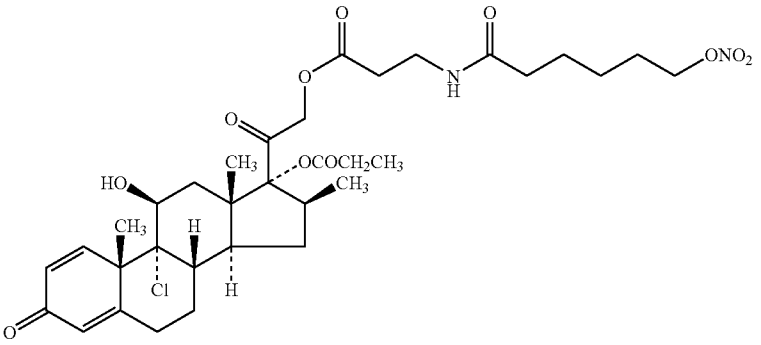

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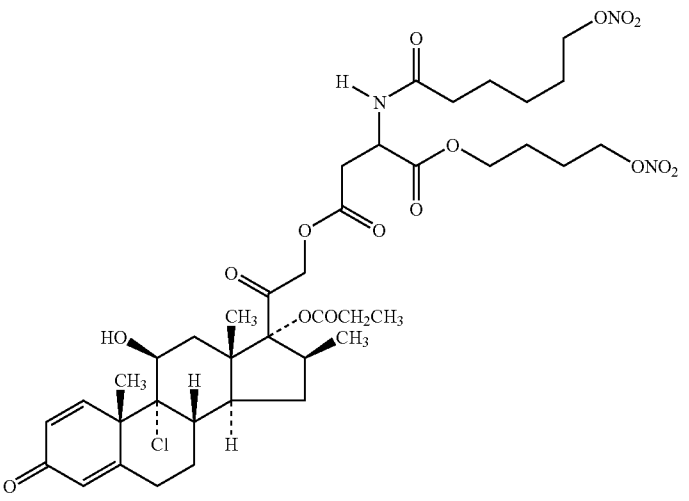

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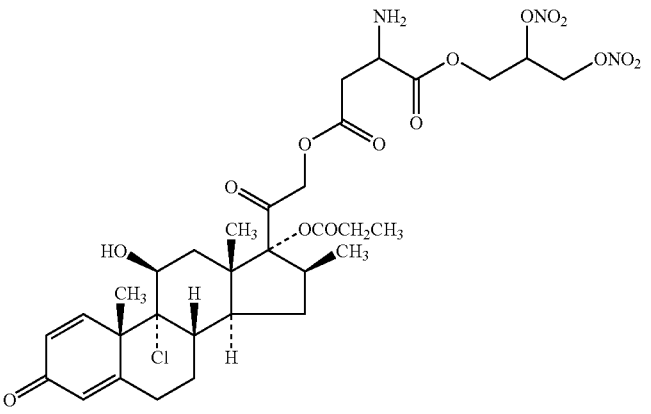

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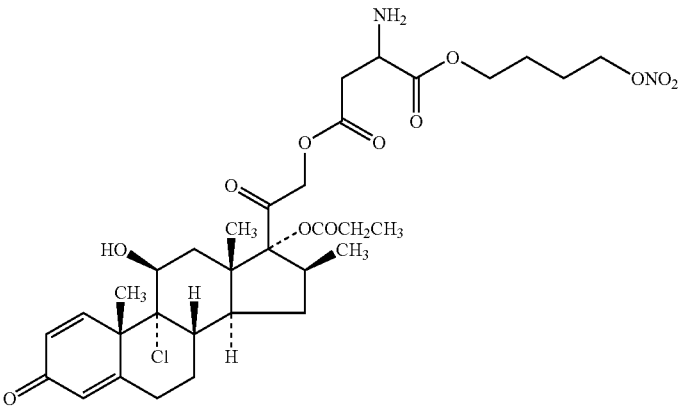

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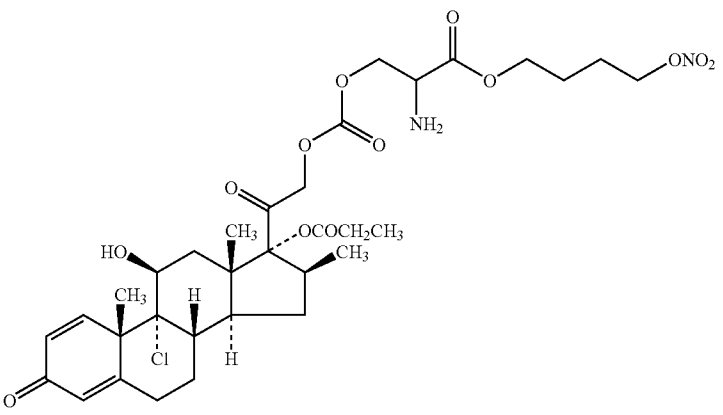

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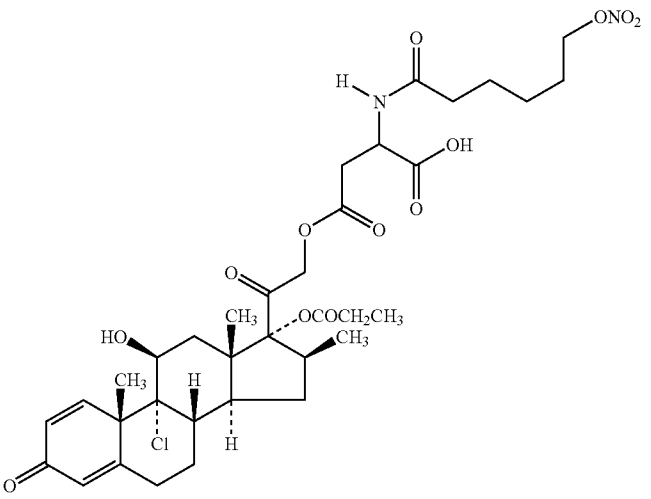


[0317] Another object of the invention is a composition comprising a compound of formula (I) above reported and at least one bronchodilator or a pharmaceutical acceptable salt or solvate thereof.

Bronchodilators that can be used in the composition of the invention include: anticholinergic bronchodilators which includes tiotropium and ipratropium, β_2-agonists which include salbutamol, bitolterol mesylate, formoterol, isoproterenol, levalbuterol, metaproterenol, salmeterol, terbutaline and fenoterol. In addition to β_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.

[0318] In another embodiment, the compound of formula (I) and at least one bronchodilator are administered simultaneously wherein the two components may be administered by the same or different administration pathways.

[0319] In another embodiment, the compound of formula (I) and at least one bronchodilator are administered sequentially wherein 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.

[0320] In another embodiment the invention provides the use of a composition comprising a compound of formula (I) above reported 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 associated with inflammation.

[0321] As stated above, the invention includes also the pharmaceutically acceptable salts of the compounds of formula (I) and stereoisomers thereof.

[0322] Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, triethylamine, dibenzylamine, piperidine and other acceptable organic amines.

[0323] The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in an organic solvent such as acetonitrile, tetrahydrofuran with the corresponding organic or inorganic acids.

[0324] 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.

[0325] The compounds of the invention which have one or more asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures. Within the object of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

[0326] 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 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" 15th Ed.

[0327] The amount on a molar basis of the active principle in said compositions is generally the same, or lower than that of the corresponding precursor drug.

[0328] 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

[0329] 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:

1-i) by reacting a compound of formula (II_1)

R—H (II_1)

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

$$W—X_1 \quad (Ia)$$

wherein W is —OH, Cl, O—R_a wherein R_a is pentafluorophenyl, 4-nitrophenyl or —(N-succimidyl), X_1 is as below defined, to obtain the compounds of formula (II_2)

$$R—X_1 \quad (II_2)$$

wherein X_1 is as below defined,

X_1 is a radical having the following meaning:

[0330] (a2') —C(O)—CH($R^{1'}$)—NH-(T'-Y-Q)

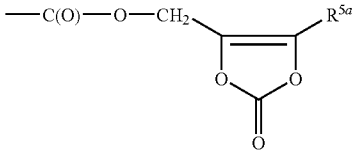
wherein R" is selected from

A1) as defined above or

A2') —CH_2—SP^1, —CH_2—OP^1, —$CH(CH_3)$—OP^1, —CH_2—[(C_6H_4)-4-OP^1], —CH_2—[(C_6H_3)-(3,5-diiodo)-4-OP^1], —CH_2—[(C_6H_3)-3-nitro-4-OP^1] or

A3') —CH_2—NHR"", —$(CH_2)_2$—NHR"", —$(CH_2)_3$—NHR"", —(CH_2), —NHR"",

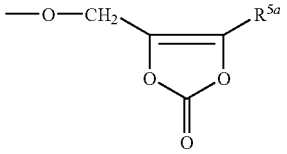
[0331] wherein R"" is P^3 or —C(O)CH_3 or



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

A4') —CH_2—C(O)R"", —$(CH_2)_2$—C(O)R"", —$(CH_2)_4$—C(O)R""

[0332] wherein R"" is P^2, —OR^{5a} or

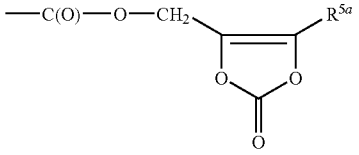


[0333] wherein R^{5a} is as above defined;

[0334] (a4') —C(O)—CH(R^{1a}-T"-Y'-Q)-$NHR^{4a'}$

[0335] (a8') —C(O)—CH(R^{1a}-T"-Y'-Q)-NH-(T'-Y-Q)

wherein R^{1a} is as defined above and R^{4a} is P^3 or —C(O)—CH_3 or



[0336] (b2') —C(O)—CH_2—CH($R^{2'}$)—NH-(T'-Y-Q) wherein $R^{2'}$ is selected from B1) as defined above or

B2') —$CH(CH_3)$—OP^1, —CH_2—[(C_6H_4)-4-OP^1];

B3') —CH_2—NHR"", —$(CH_2)_2$—NHR"", —(CH_2), —NHR"", —$(CH_2)_4$—NHR"",

[0337] wherein R"" is as above defined;

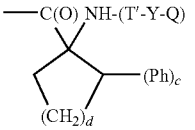
B4') —CH_2—C(O)—R"", —$(CH_2)_2$—C(O)—R"", —$(CH_2)_4$—C(O)—R"" wherein R"" is as above defined;

[0338] (b4') —C(O)—CH_2—CH(R^{2a}-T"-Y'-Q)-$NHR^{4a'}$

[0339] (b8') —C(O)—CH_2—CH(R^{2a}-T"-Y'-Q)-NH-(T'-Y-Q) wherein R^{2a} and $R^{4a'}$ are as defined above;

[0340] (c2') —C(O)—$(CH_2)_b$—NH-(T'-Y-Q);

(e2')



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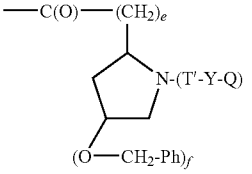

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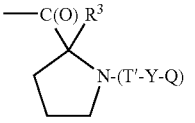

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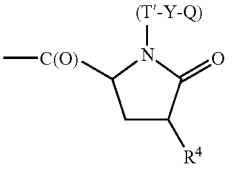

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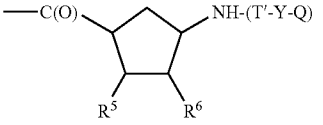

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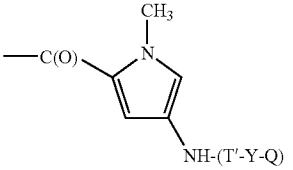

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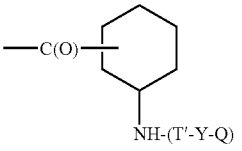

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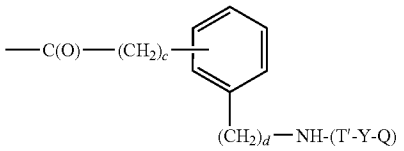

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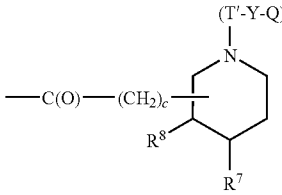

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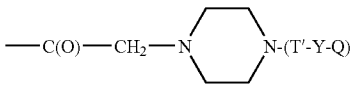

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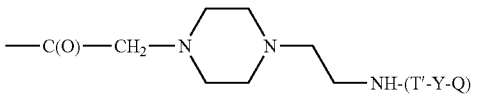

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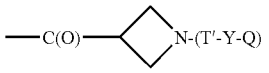

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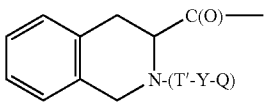

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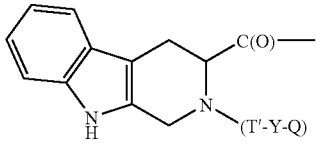

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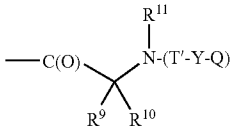

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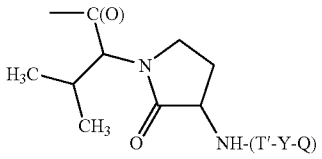


wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, b, c, d, e and f are as above defined;

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, P2 is a carboxylic protecting group such as tert-butyl ester and those 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,

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 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 acetonitrile, tetrahydrofurane, 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^{nd} 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_1 is as above defined, with a compound of formula (II_1) 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).

[0341] 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_a wherein R_a and X_1 are as above defined, with a compound of formula (II_1) 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 $Sc(OTf)_3$ or $Bi(OTf)_3$.

[0342] 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_1 is are as above defined, with a compound of formula (II_1) 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.

[0343] The compounds of formula (II_1) are commercially available.

1a) The compounds of formula (Ia) wherein W is —OH, and X_1 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 $R^{1'}$ is selected from A1), A2'), A3') or A4'), R^{1a} is selected from A5) or A6), R^{2a} is selected from B5) or B6) and $R^{2'}$ is selected from B1), B2'), B3') or B4'), wherein T' and T" are C(O) and Y, Y' and $R^{4a'}$ are as above defined, can be obtained

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

$$P^2—X_2 \quad \text{(IIIa)}$$

wherein P^2 is as above defined, X_2 is a radical having the following meaning

[0344] (a2") —C(O)—CH($R^{1'}$)—NH_2

[0345] (a4") —C(O)—CH(R^{1a}—H)—NH$R^{4a'}$

wherein $R^{1'}$ is selected from A1), A2'), A3'), A4'), R^{1a} is selected from A5) or A6) and $R^{4a'}$ is as defined above

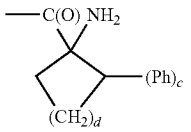
[0346] (b2") —C(O)—CH_2—CH(R^2)—NH_2,

[0347] (b4") —C(O)—CH_2—CH(R^{2a}—H)—NH$R^{4a'}$

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

[0348] (c2") —C(O)—$(CH_2)_b$—NH_2,

(e2")



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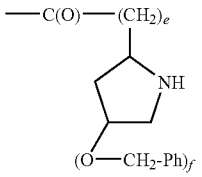

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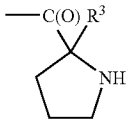

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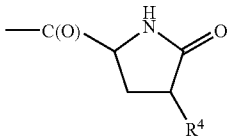

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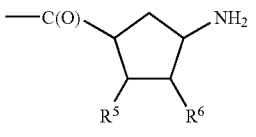

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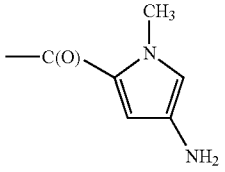

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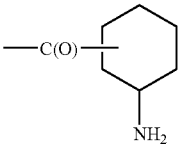

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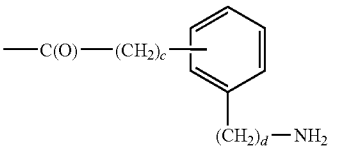

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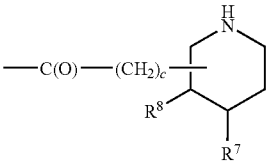

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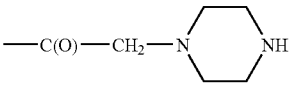

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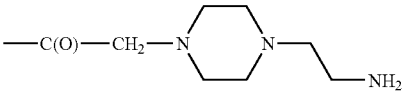

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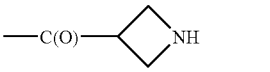

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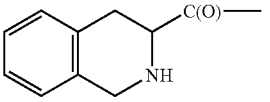

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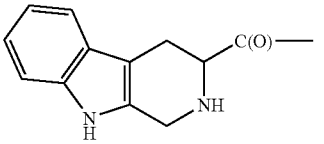

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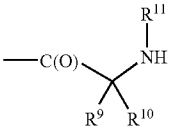

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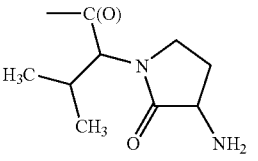


wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, b, c, d, e and f are as above defined;

with a compound of formula (IVa)

$$W_1—(O)C\text{-}y\text{-}Q \quad \text{(IVa)}$$

wherein W_1 is OH or O—R_a and R_a and Q are as above defined, y is 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

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.

[0349] 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'-tetramethyluronium hexafluorophosphate (HATU).

[0350] 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 O—R_a, y, Q are as above defined, may be carried as described in 1-i-2).

[0351] The compounds of formula (IIIa) are commercially available or can be obtained as known in the literature.

[0352] The compounds of formula (IVa) wherein W_1 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 acetic anhydride in a temperature range from −50° C. to 0° C. or from the corresponding derivatives of formula HOOC-y-Z_2 (IVc) wherein Z_2 is as above defined, by reaction with a nitrate source as above described. Alternatively the reaction with $AgNO_3$ can be performed under microwave irradiation in solvents such acetonitrile or THF at temperatures in the range between 100 and 180° C. for time range from 1 to 60 min.

[0353] The compounds of formula (IVb) are commercially available.

[0354] The compounds of formula (IVc) are commercially available or can be obtained as known in the literature.

[0355] The compounds of formula (IVa) wherein W_1 is O—R_a, y, Q are as above defined, can be obtained from the corresponding acids of formula (IVa) wherein W_1 is OH as known in the literature.

[0356] The compounds of formula (Ia) wherein W═Cl or O—R_a, X_1 is selected from (a2'), (a4'), (b2'), (b4'), (c2'), (e2'), (f1'), (g2'), (h1'), (i1'), (l2'), (m2'), (n2'), (o2'), (p2'), (q2'), (r2'), (s2'), (t2'), (u21), (v2'), wherein R" is selected from A1), A2'), A3') or A4'), R^{1a} is selected from A5) or A6), R^{2a} is selected from B5) or B6) and $R^{2'}$ 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.

1b) The compounds of formula (Ia) wherein W is —OH, X_1 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 $R^{1'}$ is selected from A1), A2'), A3') or A4'), R^{1a} is selected from A5) or A6), R^{2a} is selected from B5) or B6) and $R^{2'}$ 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)

$$P^2—X_2 \quad \text{(IIIa)}$$

wherein P^2 and X_2 are as defined above, with a compound of formula (IVd)

$$R_a—O—C(O)—X"\text{-}y\text{-}Q \quad \text{(IVd)}$$

[0357] wherein R_a, X" and Q are as above defined, y is 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 above defined, and

1b-ii) when Q is Z_2, 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 1b-i) or 1b-ii) as above described.

[0358] The reaction of a compound of formula (IIIa) wherein P^2 and X_2 are as above defined, with a compound of formula (IVd) wherein R_a, X", y and Q are as above defined, may be carried out as described in 1-i-2)

[0359] The compounds of formula (IVd) wherein R_a, 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.

[0360] The compounds of formula (IVe) are commercially available or are known in literature.

[0361] The compounds of formula (Ia) wherein W is —Cl or O—R_a, X_1 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 $R^{1'}$ is selected from A1), A2'), A3'), A4'), R^{1a} is selected from A5) or A6), R^{2a} is selected from B5) or B6) and $R^{2'}$ 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_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), 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),

$$P^2—X_{3\ (IIIb)}$$

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

[0362] (a8") —C(O)—CH(R^{1a}—H)—NH_2

[0363] (b8") —C(O)—CH_2—CH(R^{2a}—H)—NH_2

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

$$W_1—(O)C\text{-}y\text{-}Q \quad \text{(IVa)}$$

wherein W_1 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_2, 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.

[0364] The reaction of a compound of formula (IIIb) 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) using a ratio (IIIb)/(IVa) 1:2.

[0365] The reaction of a compound of formula (IIIb) 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) using a ratio (IIIb)/(IVa) 1:2.

[0366] The compounds of formula (IIIb) are commercially available or can be obtained as known in the literature.

[0367] 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, 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)

$$P^2—X_{3'} \quad \text{(Ib)}$$

wherein P^2 is as above defined, $X_{3'}$ is the radical of formula

[0368] (a8''') —C(O)—CH(R^{1a}—H)—NH-(T'-Y-Q)

[0369] (b8''') —C(O)—CH_2—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)

$$W_1—(O)C\text{-}y\text{-}Q \quad \text{(IVa)}$$

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.

[0370] 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).

[0371] 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).

[0372] 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).

[0373] 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).

[0374] 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)

$$P^2—X_3 \quad \text{(IIIb)}$$

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

$$R_a—O—C(O)—X''\text{-}y\text{-}Q \quad \text{(IVd)}$$

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.

[0375] 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.

[0376] 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)

$$P^2—X_{3'} \quad \text{(Ib)}$$

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

$$W_1—O—C(O)—X''\text{-}y\text{-}Q \quad \text{(IVd)}$$

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.

[0377] 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).

[0378] 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).

[0379] 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).

[0380] 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).

[0381] 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)

$$P^2—X_{3'} \quad (1b)$$

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

$$R_a—O—(O)C—NR'\text{-}y\text{-}Q \quad (IVf)$$

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.

[0382] 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).

[0383] 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).

[0384] 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).

[0385] 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.

[0386] 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.

[0387] 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),

$$P^2—X_5 \quad (Ie)$$

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

[0388] (a8"') —C(O)—CH(R^{1a}—OH)—NH-(T'-Y-Q)

[0389] (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)

$$HX"\text{-}y\text{-}Q \quad (IVe)$$

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

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

[0390] 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 in 1-i-1).

[0391] 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).

[0392] The compounds of formula (Ie) wherein T' is C(O)—X", wherein P^2 and X_5 are as above defined, are obtained as described in 1b-i), 1b-ii).

[0393] 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 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", and T" is X" wherein X" is as above defined, can be obtained from the corresponding acids (Ia) wherein W is —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),

$$P^2—X_5 \quad (Ie)$$

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

$$HR'N\text{-}y\text{-}Q \quad (IVg)$$

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 above described and

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

[0394] 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).

[0395] 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

1l) 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 —O—CH(R)—O—C(O)—, wherein R' is as above defined, can be obtained

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

P^2—X_5 (Ie)

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

Hal-CH(R')—O—(O)C-*y*-Q (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 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 above described and

11-iii) optionally deprotecting the compounds obtained in step 11-i) or 11-ii) as above described.

[0396] 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 solvent such as DMF, THF or CH_2Cl_2 at temperature in the range between 0° and 100° C. or in a double phase system H_2O/Et_2O temperature in the range between 20° and 40° C.

[0397] The compounds of formula (IVm) wherein y, Q, R' are as above defined, Hal is an halogen atom may be obtained by reacting a compound R'—CH_2—CHO, commercially available, with a compound of formula Hal-(O)C-y-Q (IVn), wherein y and Q are as above defined, Hal is a chlorine atom and $ZnCl_2$ as known in literature.

[0398] The compounds of formula (IVn) may be obtained as known in literature.

[0399] 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 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 —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.

1m) 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 —O—CH(R')—O—C(O)O—, wherein R' is as above defined, can be obtained

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

P^2—X_5 (Ie)

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

Hal-CH(R')—O—(O)C—O-*y*-Q (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 1m-ii) when Q is Z_2, by converting the compounds obtained in the step 1m-i) into nitro derivative by reaction with a nitrate source such above described and

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

[0400] 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).

[0401] 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.

[0402] 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^4, 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)

P^2—$X_{5'}$ (IIIc)

wherein P^2 is defined above, $X_{5'}$ is

[0403] (a4") —C(O)—CH(R_{1a}—OH)—$NH^{4a'}$

[0404] (b4") —C(O)—CH_2—CH(R_{2a}—OH)—$NHR^{4a'}$

wherein R_a 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', 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 1n-i) or 1-ii) as above described.

[0405] 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).

[0406] 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.

[0407] 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 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 obtained

1o-i) by reacting a compound of formula (IIIc)

P^2—$X_{5'}$ (IIIc)

wherein P^2 and $X_{5'}$ are as above defined, with a compound of formula (IVg)

HR'N-*y*-Q (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 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.

[0408] The reaction of a compound of formula (IIIc) wherein X_5, and P^2 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).

[0409] 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 —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)

$$P^2—X_5 \quad \text{(IIIc)}$$

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

$$\text{Hal-CH(R')—O—(O)C-}y\text{-Q} \quad \text{(IVm)}$$

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 is source as above described and

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

[0410] 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 1l-1).

[0411] 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, 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)

$$P^2—X_5 \quad \text{(IIIc)}$$

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

$$\text{Hal-CH(R')—O—(O)C—O-}y\text{-Q} \quad \text{(IVo)}$$

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_2, 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.

[0412] The reaction of a compound of formula (IIIc) wherein P^2 and X_5, 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 1l-1).

[0413] 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)—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_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), Z is —CH(R')—O— wherein R' is selected from H or straight or branched C_1-C_4 alkyl, can be obtained:

2-i) by reacting a compound of formula (II_1) as above defined with a compound of formula (If)

$$\text{Hal-CH(R')—O—}X_1 \quad \text{(If)}$$

wherein Hal is an halogen atom, R' and X_1 are as above defined and

2-ii) when Q is Z_2, 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.

[0414] The reaction of a compound of formula (If) wherein X_1 and R' are as above defined, with a compound of formula (II_1) may be carried out as described in 1l-i).

[0415] The compounds of formula (If) are obtained by reacting a compound R'—CHO, wherein R' is as above defined with compounds of formula (Ia)

$$W—X_1 \quad \text{(Ia)}$$

wherein W is a chlorine atom, X_1 is as above defined, and $ZnCl_2$ as known in literature.

3) The compounds of general formula (I) as above defined wherein a is equal to 1, the radical R_X 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_3)

$$R—C(O)—O—R_a \quad \text{(II}_3\text{)}$$

wherein R and R_a are as above defined, with a compound of formula (Ig)

$$H—X_2 \quad \text{(Ig)}$$

wherein X_2 is a radical having the following meanings:

[0416] (a1') —HN—CH($R^{1'}$)—C(O)-(T-Y-Q)

[0417] (a3') —HN—CH(R^{1a}-T''-Y'-Q)-COO$R^{3a'}$

[0418] (a7') —HN—CH(R^{1a}-T''-Y∝-Q)-C(O)-(T-Y-Q)

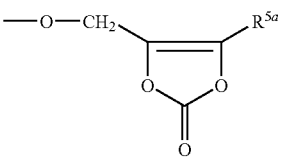
[0419] (b1') —HN—CH($R^{2'}$)—CH_2C(O)-(T-Y-Q)

[0420] (b3') —HN—CH(R^{2a}-T''-Y'-Q)-CH_2CO$R^{3a'}$

[0421] (b7') —HN—CH(R^{2a}-T''-Y'-Q)-CH_2—C(O)-(T-Y-Q)

wherein $R^{1'}$, R_{1a}, $R^{2'}$, R^{2a} are as above defined

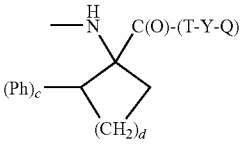
$R^{3a'}$ is selected from P^2, —OR^{5a} or



wherein R_{5a} is as above defined;

[0422] (c1') —HN—$(CH_2)_b$—C(O)-(T-Y-Q);

(e1')



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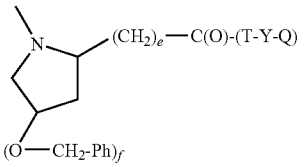

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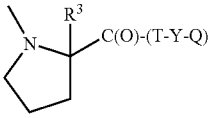

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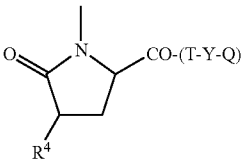

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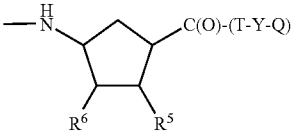

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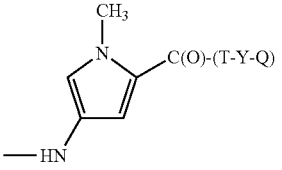

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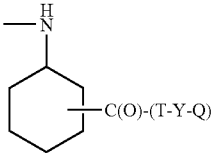

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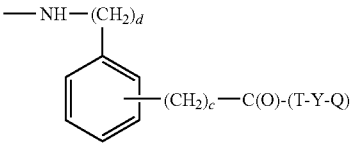

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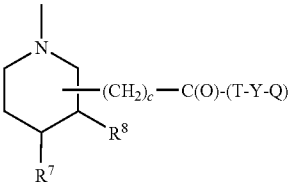

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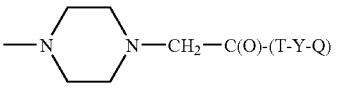

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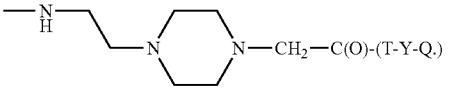

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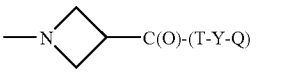

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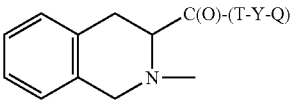

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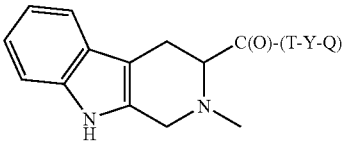

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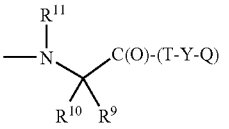

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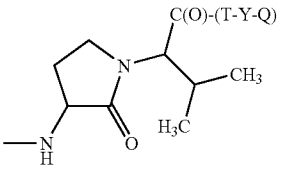


wherein T, T", Y and Y' are as above defined,

3-ii) when Q is Z_2, by converting the compounds obtained in the step 3-i) into nitro derivative by reaction with a nitrate source such above described and

3-iii) optionally deprotecting the compounds obtained in step 3-i) or 3-ii) as above described.

[0423] The reaction of a compound of formula (II3), wherein R and R_a are as above defined, with a compound of formula (Ig) wherein X_1 is as above defined, may be carried out as described in 1-i-2).

[0424] The compounds of formula (II_3) wherein R and R_a are as above defined, are obtained from the compounds of formula (II_1) by reaction with the compounds of formula Cl—C(O)—O—R_a wherein R_a is as above defined, as known in literature.

3a) The compounds of formula (Ig) wherein X_2 is selected from (a1'), (a3'), (b1'), (b3'), (c1'), (e1'), (f2'), (g1'), (h2'), (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'), 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),

P^3—X_6 (IIIe)

wherein P^3 is as above defined, X_6 is a radical having the following meanings:

[0425] (a1") —HN—CH($R^{1'}$)—C(O)—OH

[0426] (a3") —HN—CH(R^{1a}—OH)—$COOR^{3a'}$

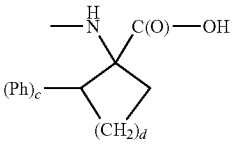
[0427] (b1") —HN—CH($R^{2'}$)$_2$—$CH_2C(O)$—OH

[0428] (b3") —HN—CH(R^{2a}—OH)—$CH_2COOR^{3a'}$

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

[0429] (c1") —HN—$(CH_2)_b$—C(O)—OH;

(e1")



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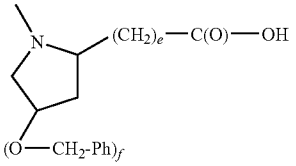

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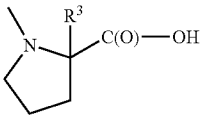

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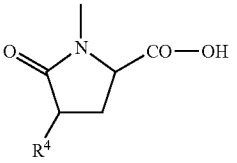

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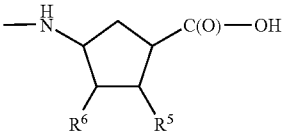

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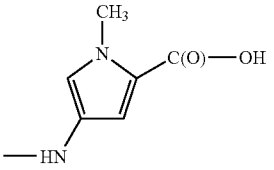

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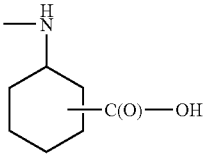

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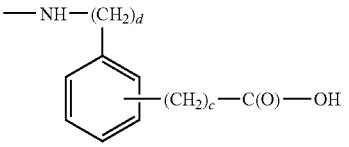

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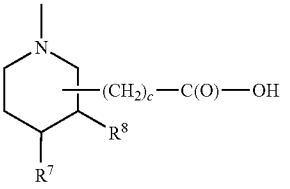

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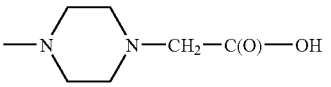

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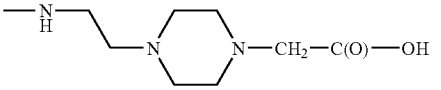

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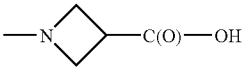

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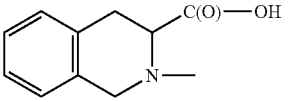

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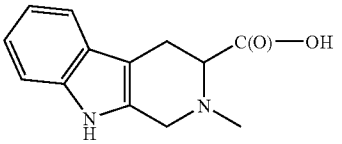

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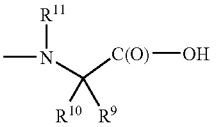

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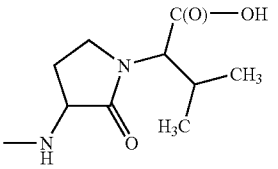


with a compound of formula (IVe)

HX"-*y*-Q (IVe)

wherein Q and X" are as above defined y is the radical Y when X_6 is selected from (a1'), (b1'), (c1'), (e1'), (r2'), (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

3a-ii) when Q is Z_2, by converting the compounds obtained in the step 3a-i) into nitro derivative by reaction with a nitrate source as above described and

3a-iii) optionally deprotecting the compounds obtained in step 3a-i) or 3a-ii) as above described.

[0430] The reaction of a compound of formula (IIIe) wherein P^3 and X_6 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).

[0431] The compounds of formula (IIIe) are commercially available or can be obtained as known in the literature.

3b) The compounds of formula (Ig) wherein X_2 is selected from (a1'), (a3'), (b1'), (b3'), (c1'), (e1'), (r2'), (g1'), (h2'), (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 —NR' wherein R' is as above defined may be obtained

3b-i) by reacting a compound of formula (IIIe),

$$P^3—X_6 \quad \text{(IIIe)}$$

wherein P^3 and X_6 are as above defined, with a compound of formula

$$HR'N\text{-}y\text{-}Q \quad \text{(IVg)}$$

wherein R' and Q are as above defined, y is the radical Y when X_6 is selected from (a1'), (b1'), (c1'), (e1'), (r2'), (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

3b-ii) when Q is Z_2, by converting the compounds obtained in the 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.

[0432] 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 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'), (r2'), (g1'), (h2'), (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

3c-i) by reacting a compound of formula (IIIe)

$$P^3—X_6 \quad \text{(IIIe)}$$

wherein P^3, X_6 are as above defined with compounds of formula (IVm)

$$Hal\text{-}CH(R')—O—(O)C\text{-}y\text{-}Q \quad \text{(IVm)}$$

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'), (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 source as above described and

3c-iii) optionally deprotecting the compounds obtained in step 3c-i) or 3c-ii) as above described.

[0433] 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 1l-i)

3d) The compounds of formula (Ig) wherein X_2 is selected from (a1'), (a3'), (b1'), (b3'), (c1'), (e1'), (r2'), (g1'), (h2'), (i2'), (l1'), (m1'), (n1'), (o1'), (p1'), (q1'), (r1'), (s1'), (t1'), (u1'), (v1'), wherein R1' 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

3d-i) by reacting a compound of formula (IIIe)

$$P^3—X_6 \quad \text{(IIIe)}$$

wherein P^3 and X_6 are as above defined, with compounds of formula (IVo)

$$Hal\text{-}CH(R')—O—(O)C—O\text{-}y\text{-}Q \quad \text{(IVo)}$$

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

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 source as above described and

3d-iii) optionally deprotecting the compounds obtained in step 3d-i) or 3d-ii) as above described.

[0434] 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 1l-i).

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^b 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

3e-i) by reacting a compound of formula (Ih)

$$P^3—X_7 \quad \text{(Ih)}$$

wherein P^3 is as above defined and X_7 is the radical having the following meaning

[0435] (a7") —HN—CH(R^{1a}—H)—C(O)-(T-Y-Q)

[0436] (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)

$$W_1—C(O)\text{-}y\text{-}Q \quad \text{(IVa)}$$

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

3e-iii) optionally deprotecting the compounds obtained in step 3e-i) or 3e-ii) as above described.

[0437] 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).

[0438] The compounds of formula (Ih) wherein P^3 and X_7 are as above defined, T is —X" are obtained as described in 3a).

[0439] The compounds of formula (Ih) wherein P^3 and X_7 are as above defined, T is —NR' are obtained as described in 3b).

[0440] 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).

[0441] 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).

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 Y' are as above defined, may be obtained

3f-i) by reacting a compound of formula (Ih)

$$P^3—X_7 \quad (Ih)$$

wherein P^3 and X_7 are as above defined with compounds of formula (IVd)

$$R_a—O—C(O)—X"\text{-}y\text{-}Q \quad (IVd)$$

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

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)

$$P^3—X_7 \quad (Ih)$$

wherein P^3 and X_7 are as above defined, with compounds of formula (IVf)

$$R_a—O—C(O)—NR'\text{-}y\text{-}Q \quad (IVf)$$

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.

[0442] 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).

[0443] The compounds of formula (Ih) wherein P^3 and X_7 are as above defined, T is —X" are obtained as described in 3a).

[0444] The compounds of formula (Ih) wherein P^3 and X_7 are as above defined, T is —NR' are obtained as described in 3b).

[0445] 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).

[0446] 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).

3h) The compounds of formula (Ig) wherein X_2 is selected from (a7') or (b7') wherein R_a 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

3h-i) by reacting a compound of formula (Ih)

$$P^3—X_7 \quad (Ih)$$

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 compounds of formula (IVe)

$$H—X"\text{-}y\text{-}Q \quad (IVe)$$

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

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.

[0447] 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).

[0448] The compounds of formula (Ih) wherein P^3 and X_7 are as above defined, T is —X" are obtained as described in 3a).

[0449] The compounds of formula (Ih) wherein P^3 and X_7 are as above defined, T is —NR' are obtained as described in 3b).

[0450] 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).

[0451] 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)

$$P^3—X_7 \quad (Ih)$$

wherein P^3 and X_7 are as above defined, with compounds of formula (IVg)

$$H—NR'\text{-}y\text{-}Q \quad (IVg)$$

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

3i-ii) when Q is Z_2, 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.

[0452] The reaction of a compound of formula (Ih) wherein P^3 and X_{87} 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).

3l) 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)—, 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

3l-i) by reacting a compound of formula (Ih)

$$P^3—X_7 \quad (Ih)$$

wherein P^3 and X_8 are as above defined with compounds of formula (IVm)

$$Hal\text{-}CH(R')—O—(O)C\text{-}y\text{-}Q \quad (IVm)$$

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

3l-ii) when Q is Z_2, by converting the compounds obtained in

the step 3l-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.

[0453] 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 1l-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)

$$P^3—X_{7\,(Ih)}$$

wherein P^1 and X_8 are as above defined with a compound of formula (IVo)

$$Hal\text{-}CH(R')—O—(O)C—O\text{-}y\text{-}Q \quad (IVo)$$

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.

[0454] 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 1l-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

3n-i) by reacting a compound of formula (IIIf),

$$P^3—X_9 \quad (IIIf)$$

wherein P^3 is as above defined, X_9 is a radical having the following meaning

[0455] (a3") —HN—CH(R^{1a}—H)—$COR^{3a'}$

[0456] (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)

$$W_1—C(O)\text{-}y\text{-}Q \quad (IVa)$$

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 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.

[0457] The reaction of a compound of formula (IIIf) wherein P^3 and X_9 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), 1a-1).

[0458] The compounds of formula (IIIf) wherein P^3 and X_9 are as above 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

3o-i) by reacting a compound of formula (IIIf)

$$P^3—X_9 \quad (IIIf)$$

wherein P^3 and X_9 are as above defined with a compound of formula (IVd)

$$R_a—O—C(O)—X''\text{-}y\text{-}Q \quad (IVd)$$

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 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.

[0459] The reaction of a compound of formula (IIIf) wherein P^3 and X_9 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 (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 (IIIg),

$$P^3—X_9 \quad (IIIf)$$

wherein P^3 and X_9 are as above defined, with a compound of formula (IVf)

$$R_a—O—(O)C—NR'\text{-}y\text{-}Q \quad (IVf)$$

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

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.

[0460] The reaction of a compound of formula (IIIf) 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).

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_3) as above defined wherein R_a is as above defined, with a compound of formula (Im)

$$H—X_{12} \quad (Im)$$

wherein X_{12} is the radical R_X having the following meaning

[0461] (d1') —HN—CH($R^{12'}$)—CH_2—O-(T'"-Y-Q)

[0462] (d2') —O—CH_2—CH($R^{12'}$)—NH-(T'-Y-Q)

[0463] (d3') —HN—CH(R^{12a}-T"-Y'-Q)-CH_2OH

[0464] (d4') —O—CH_2—CH(R^{12a}-T"-Y'-Q)-NHR^{4a}

[0465] (d7') —HN—CH(R^{12a}-T"-Y'-Q)-CH_2—O-(T'"-Y-Q)

[0466] (d8') —O—CH_2—CH(R^{12a}-T"-Y'-Q)-NH-(T'-Y-Q)

wherein $R^{12'}$ is

D1),

[0467] D2') —CH_2—OP^1, —$CH(CH_3)$—OP^1, —CH_2—[(C_6H_4)-4-OP^1], —CH_2—[(C_6H_3)-(3,5-diiodo)-4-OP^1], —CH_2—[(C_6H_3)-3-nitro-4-OP^1];

D3') —CH_2—NHR"", —$(CH_2)_2$—NHR"", —$(CH_2)_3$—NHR"", —$(CH_2)_4$—NHR"", wherein R"" is as above defined;

D4') —CH_2—C(O)R"", —$(CH_2)_2$—C(O)R"", —$(CH_2)_4$—C(O)R"", wherein R"" is as above defined;

wherein R^{12a} is as above defined; and

4-ii) when Q is 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

4-iii) optionally deprotecting the compounds obtained in step 4-i) or 4-ii) as above described.

[0468] The reaction of a compound of formula (II_3) wherein R and R_a are as above defined, with a compound of formula (Im) wherein X_{12} is as above defined, may be carried out as described in 1-i-2).

4a) The compounds of formula (Im) wherein X_{12} is selected from (d1'), (d2'), (d3') or (d4') wherein $R^{12'}$ is selected from D1), D2'), D3') or D4') and 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

4a-i) by reacting a compound of formula (IIIi),

$$P^4—X_{13} \quad \text{(IIIi)}$$

wherein P^4 is P^3 or P^1 as above defined and X_{13} is a radical having the following meaning

[0469] (d1") —HN—CH($R^{12'}$)—CH_2—OH

[0470] (d2") —O—CH_2—CH($R^{12'}$)—NH_2

[0471] (d3") —HN—CH(R^{2a}—H)—CH_2OP^1

[0472] (d4") —O—CH_2—CH(R^{12a}—H)—$NHR^{4a'}$

wherein $R^{12'}$ is D1), D2'), D3') or D4'), R^{12a} is D5) or D6), $R^{4a'}$ and P^1 are as above defined, with a compound of formula (IVa)

$$W_1—(O)C\text{-}y\text{-}Q \quad \text{(IVa)}$$

wherein Q and W_1 are as above defined, y is the radical Y when X_{13} 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

4a-ii) when Q is Z_2, 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.

[0473] The reaction of a compound of formula (IIIi) wherein X_{13} and P^4 are as above defined, with a compound of formula (IVa) wherein W_1, y and Q are as above defined, may be carried out as described in 1-i-1) and 1-i-2).

[0474] The compounds of formula (IIIi) wherein X_{13} and P^4 are as above described, are commercially available or known in literature.

4b) The compounds of formula (Im) wherein X_{12} is selected from (d1'), (d2'), (d3') or (d4') wherein $R^{12'}$ is selected from D1), D2'), D3') or D4') and R^{2a} 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),

$$P^4—X_{13} \quad \text{(IIIi)}$$

wherein P^4 and X_{13} are defined above, with a compound of formula (IVd)

$$R_a—O—(O)C—X"\text{-}y\text{-}Q \quad \text{(IVd)}$$

wherein Q, R_a and X" are as above defined, y is the radical Y when X_{13} 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.

[0475] 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 is are as above defined, T' and T" and T"' are C(O), can be obtained

4c-i) by reacting a compound of formula (IIII),

$$P^4—X_{14} \quad \text{(IIII)}$$

wherein P^4 is P^1 or P^3, X_{14} is the radical having the following meaning

[0476] (d7") —HN—CH(R^{2a}—H)—CH_2—OH

[0477] (d8") —O—CH_2—CH(R^{12a}—H)—NH_2

wherein R^{12a} is selected from D5) or D6), with a compound of formula (IVa)

$$W_1—(O)C\text{-}y\text{-}Q \quad \text{(IVa)}$$

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.

[0478] The reaction of a compound of formula (IIII) 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 (IIII)/(IVa) 1:2.

[0479] The reaction of a compound of formula (IIII) 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 (IIII)/(IVa) 1:2.

[0480] The compounds of formula (IIII) 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)

$$P^4—X_{15} \quad \text{(In)}$$

wherein P^4 is defined above and X_{15} is the radical having the following meaning

[0481] (d7"') —HN—CH(R^{2a}—H)—CH_2—O-(T"-Y-Q)

[0482] (d8"') —O—CH_2—CH(R^{2a}—H)—NH-(T'-Y-Q)

wherein R^{12a} is selected from D5) or D6), Y, Q, T' and T"' are as above defined, with a compound of formula (IVa)

$$W_1—(O)C\text{-}y\text{-}Q \quad \text{(IVa)}$$

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_2, 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.

[0483] The reaction of a compound of formula (In) wherein P^4 and X_{15} 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).

[0484] The reaction of a compound of formula (In) wherein P^4 and X_{15} 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).

[0485] The compounds of formula (In) wherein P^4 and X_{15} are as above defined, T' and T"' are —C(O)— can by obtained as described in 4a).

4e) 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 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 (IIIl),

(IIIl)

wherein P^4 and X_{14} are as above defined, with a compound of formula (IVd)

(IVd)

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

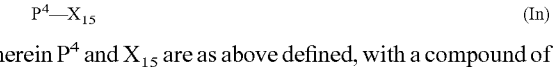
4e-ii) when Q is Z_2, by converting the compounds obtained in the step 4e-i) into nitro derivative by reaction with a nitrate source as above described and

4e-iii) optionally deprotecting the compounds obtained in step 4e-i) or 4e-ii) as above described.

[0486] The reaction of a compound of formula (IIIl) wherein P^4 and X_{14} are as above defined, with a compound of formula (IVd) wherein R_a, 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_{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" 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^4 and X_{15} are as above defined, with a compound of formula (IVd)

(IVd)

wherein R_a, 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_2, 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.

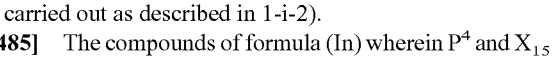
[0487] The reaction of a compound of formula (In) wherein P^4 and X_{15} are as above defined, with a compound of formula (IVd) wherein R_a, X", y and Q are as above defined, may be carried out as described in 1-i-2).

[0488] The compounds of formula (In) wherein T' or T"' are C(O), P^4 and X_{15} are as above defined are obtained as described in 4a-i), 4a-ii).

[0489] The compounds of formula (In) wherein T' or T"' are C(O)—X", wherein P^4 and X_{15} are as above defined are obtained as described in 4b-i), 4b-ii).

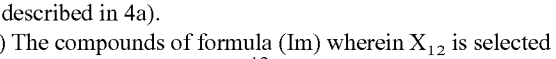
4g) The compounds of formula (Im) wherein X_{12} is selected from (d7') or (d8') wherein R^{2a} is selected from D5) or D6), Q, Y and Y' are as above defined, T" is C(O)—NR'—, T' and T"' are C(O) or C(O)—X", wherein X" is as above defined, can be obtained

4g-i) by reacting a compound of formula (In)



(In)

wherein P^4 and X_{15} 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

4g-ii) when Q is Z_2, 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.

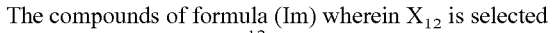
[0490] The reaction of a compound of formula (In) P^4 and X_{15} are as above defined, with a compound of formula (IVf) wherein R_a, R', y, Q are as above defined, may be carried out as described in 1-i-2).

[0491] The compounds of formula (In) wherein T' or T"' are C(O), wherein P^4 and X_{15} are as above defined, are obtained as described in 4a-i), 4a-ii).

[0492] The compounds of formula (In) wherein T' or T"' are C(O)—X", wherein P^4 and X_{15} are as above defined, are obtained as described in 4b-i), 4b-ii).

4h) 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 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

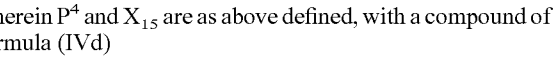
4h-i) by reacting a compound of formula (Ir),



wherein P^4 is defined above and X_{16} is the radical having the following meaning

[0493] (d7"")—HN—CH(R^{12a}—OH)—CH_2—O-(T'-Y-Q)

[0494] (d8"")—O—CH_2—CH(R^{2a}—OH)—NH-(T'-Y-Q) wherein R^{12a} is selected from D7), with a compound of formula (IVe)



(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_2, by converting the compounds obtained in the step 4h-i) into nitro derivative by reaction with a nitrate source as above described and

4h-iii) optionally deprotecting the compounds obtained in step 4h-i) or 4h-ii) as above described.

[0495] 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).

[0496] 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).

[0497] 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 (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),

$$P^4—X_{16} \quad \text{(Ir)}$$

wherein P^4 and X_{16} are as above defined and R^{12a} is selected from D7), with a compound of formula

$$HR'N\text{-}y\text{-}Q \quad \text{(IVg)}$$

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 source such above described and

4i-iii) optionally deprotecting the compounds obtained in step 4i-i) or 4l-ii) as above described.

[0498] 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).

4l) 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

4l-i) by reacting a compound of formula (Ir),

$$P^4—X_{16} \quad \text{(Ir)}$$

wherein P^4 and X_{16} are as above defined and R^{12a} is selected from D7), with a compound of formula (IVm)

$$Hal\text{-}CH(R')—O—(O)C\text{-}y\text{-}Q \quad \text{(IVm)}$$

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

4l-ii) when Q is Z_2, by converting the compounds obtained in the step 4l-i) into nitro derivative by reaction with a nitrate source such above described and 4l-iii) optionally deprotecting the compounds obtained in step 4l-i) or 4l-ii) as above described.

[0499] 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 1l-i).

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),

$$P^4—X_{16} \quad \text{(Ir)}$$

wherein P^4 and X_{16} are as above defined and R^{12a} is selected from D7), with a compound of formula (IVo)

$$Hal\text{-}CH(R')—O—(O)C—O\text{-}y\text{-}Q \quad \text{(IVo)}$$

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

4m-ii) when Q is Z_2, by converting the compounds obtained in the step 4m-i) into nitro derivative by reaction with a nitrate source as above described and

4m-iii) optionally deprotecting the compounds obtained in step 4m-i) or 4m-ii) as above described.

[0500] The reaction of a compound of formula (Ir) wherein P^4 and X_{16} 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 1l-i).

4n) The compounds of formula (Im) wherein X_{12} is selected from (d3') or (d4') wherein R^{2a} is selected from D7), Y' is as above defined, T'' is X'', wherein X'' is defined above, can be obtained

4n-i) by reacting a compound of formula (IIIm),

$$P^4—X_{17} \quad \text{(IIIm)}$$

wherein P^4 is defined above and X_{17} is the radical

[0501] (d3''') —HN—CH(R^{12}—OH)—CH_2OP^1

[0502] (d4''') —O—CH_2—CH(R^{2a}—OH)—$NHR^{4a'}$

[0503] wherein R^{12a} is selected from D7), wherein P^1 and $R^{4a'}$ are as above defined, with a compound of formula (IVe)

$$HX''\text{-}y\text{-}Q \quad \text{(IVe)}$$

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

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.

[0504] The reaction of a compound of formula (IIIm) 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).

[0505] The compounds of formula (IIIm), 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 (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 (IIIm),

$$P^4—X_{17} \quad \text{(IIIm)}$$

wherein P^4 and X_{17} are as defined above, wherein R^{12a} is selected from D7), with a compound of formula

$$HR'N\text{-}y\text{-}Q \quad \text{(IVg)}$$

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_2, by converting the compounds obtained in the step 4o-i) into nitro derivative by reaction with a nitrate source such above described and

4o-iii) optionally deprotecting the compounds obtained in step 4o-i) or 4o-ii) as above described.

[0506] The reaction of a compound of formula (IIIm) wherein P^4 and X_{17} 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 1a-i).

4p) The compounds of formula (Im) wherein X_{12} is selected from (d3') or (d4') wherein R^{12a} 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 (IIIm),

$$P^4—X_{17} \quad \text{(IIIm)}$$

wherein P^4 and X_{17} are as defined above, wherein R^{12a} is selected from D7), with a compound of formula (IVm)

$$\text{Hal-CH(R')—O—(O)C-}y\text{-Q} \quad \text{(IVm)}$$

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

4p-ii) when Q is Z_2, by converting the compounds obtained in the step 4p-i) into nitro derivative by reaction with a nitrate source such above described and

4p-iii) optionally deprotecting the compounds obtained in step 4p-i) or 4p-ii) as above described.

[0507] The reaction of a compound of formula (IIIm) wherein P^4 and X_{17} are as above defined, with a compound of formula (IVm) 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_{12} is selected from (d3') or (d4') wherein R^{12a} 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 (IIIm),

$$P^4—X_{17} \quad \text{(IIIm)}$$

wherein P^4 and X_{17} are as defined above, wherein R^{12a} is selected from D7), with a compound of formula (IVo)

$$\text{Hal-CH(R')—O—(O)C—O-}y\text{-Q} \quad \text{(IVo)}$$

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_2, 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.

[0508] The reaction of a compound of formula (IIIm) wherein P^4 and X_{17} 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_X is a radical selected from (d5), (d6), (d9) or (d10), wherein R^{12b} is selected from D10) can be obtained

5-i) by reacting a compound of formula (II_1) as above defined with a compound of formula (Is)

$$W—X_{18} \quad \text{(Is)}$$

wherein W is as above defined, X_{18} is the radical having the following meanings

[0509] (d5') —R^{12b}—CH(NHR^{4a})—CH_2—O-(T'''-Y-Q)

[0510] (d6') —R^{12b}—CH(CH_2OH)—NH-(T'-Y-Q)

[0511] (d9') —R^{12b}—CH(NH-T'''-Y'-Q)-CH_2—O-(T'-Y-Q)

[0512] (d10') —R^{12b}—CH(CH_2—O-T'''-Y'-Q)-NH-(T'-Y-Q)

wherein R^{12b} is selected from D10), T', T''', Y, Y' and Q are as above defined and

5-ii) when Q is Z_2, 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 5-i) or 5-ii) as above described.

[0513] The reaction of a compound of formula (II_3) as above defined, with a compound of formula (Is) wherein W and X_{11} are as above defined may be carried out as described in 1).

5a) The compounds of formula (Is) wherein X_{18} is a radical of formula (d5') or (d6'), wherein R^{12b} is selected from D10), T' and T''' are C(O) can be obtained

5a-i) by reacting a compound of formula (IIIn),

$$P^2—X_{19} \quad \text{(IIIn)}$$

wherein P^2 is as above defined, X_{19} is the radical having the following meanings

[0514] (d5'') —R^{12b}—CH(NHP^3)—CH_2—OH

[0515] (d6'') —R^{12b}—CH(CH_2OP^1)—NH_2

wherein P^1 and P^3 are as above defined and R^{12b} is selected from D10), with a compound of formula (IVa)

$$W_1—C(O)-y\text{-Q} \quad \text{(IVa)}$$

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

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.

[0516] The reaction of a compound of formula (IIIn) wherein P^2 and X_{19} 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).

[0517] The compounds of formula (IIIn), wherein P^2 and X_{19} are as above 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^{12} is selected from D10), T' and T''' are C(O)—X'', wherein X'' is defined above, can be obtained

5b-i) by reacting a compound of formula (IIIn),

$$P^2—X_{19} \quad \text{(IIIn)}$$

wherein P^2 and X_{19} are as above defined, with a compound of formula (IVd)

$$R_a—O—C(O)—X''-y\text{-Q} \quad \text{(IVd)}$$

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

5b-ii) when Q is Z_2, 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.

[0518] The reaction of a compound of formula (IIIn) wherein P^2 and X_{19} 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).

5c) The compounds of formula (Is) wherein X_{18} is a radical of formula (d9'), wherein R^{12b} 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),

$$P^2—X_{20} \quad \text{(It)}$$

wherein P^2 is as above defined and X_{20} is the radical having the following meanings

[0519] (d9'') —R^{12}—CH(NH_2)—CH_2—O-(T'''-Y-Q)

wherein R^{12b} is selected from D10), T''', Y and Q are as above defined, with a compound of formula (IVa)

$$W_1—C(O)\text{-}y\text{-}Q \quad (IVa)$$

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

5c-ii) when Q is Z_2, 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.

[0520] 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 in 1-i-1), 1-i-2), 1-i-3) and 1a-1).

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),

$$P^2—X_{20} \quad (It)$$

wherein P^2 and X_{20} are as above defined, with a compound of formula (IVd)

$$R_a—O—C(O)—X''\text{-}y\text{-}Q \quad (IVd)$$

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 source as above described and

5d-iii) optionally deprotecting the compounds obtained in step 5d-i) or 5d-ii) as above described.

[0521] 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, 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 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),

$$P^2—X_{20} \quad (It')$$

wherein P^2 is as above defined and $X_{20'}$ is the radical having the following meaning

[0522] (d10") —R^{12b}—$CH(CH_2—OH)$—NH-(T'-Y-Q)

wherein R^{12b} is selected from D10), T', Y and Q are as above defined, with a compound of formula (IVa)

$$W_1—C(O)\text{-}y\text{-}Q \quad (IVa)$$

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

5e-iii) optionally deprotecting the compounds obtained in step 5e-i) or 5e-ii) as above described.

[0523] 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 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 be obtained

5f-i) by reacting a compound of formula (It'),

$$P^2—X_{20'} \quad (It')$$

wherein P^2 and $X_{20'}$ are as above defined, with a compound of formula (IVd)

$$R_a—O—C(O)—X''\text{-}y\text{-}Q \quad (IVd)$$

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.

[0524] 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, 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), is (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_1) as above defined with a compound of formula (Iu)

$$Hal\text{-}CH(R')—O—X_{21} \quad (Iu)$$

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.

[0525] The reaction of a compound of formula (Iu) wherein Hal, X_{21} and R' are as above defined, with a compound of formula (II_1) as above defined may be carried out as described in 11-i).

[0526] The compounds of formula (Iu) are obtained by reacting a compound R'—CHO, wherein R' is as above defined with compounds of formula (IIIo)

$$W—X_{22} \quad (IIIo)$$

wherein W is a chlorine atom, X_{22} is the radical having the following meanings

[0527] (d5''') —R^{12b}—$CH(NHP^3)—CH_2$—O-(T'''-Y-Q)

[0528] (d6''') —R^{12b}—$CH(CH_2OP^1)$—NH-(T'-Y-Q)

[0529] (d9''') —R^{12b}—CH(NH-T'-Y'-Q)-CH_2—O-(T'''-Y-Q)

[0530] (d10''') —R^{12b}—$CH(CH_2—O\text{-}T'''\text{-}Y'\text{-}Q)$-NH-(T'-Y-Q)

wherein R^{12b}, P^3, P^1, T', T''', Y', Y and Q are as above defined, and $ZnCl_2$ as known in literature.

[0531] 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_3) as above defined wherein R_a is as above defined with a compound of formula (Iv)

$$H—X_{23} \quad (Iv)$$

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.

[0532] The reaction of a compound of formula (Iv) wherein X_{23} and is as above defined, with a compound of formula (II_3) as above defined may be carried out as described in 11-i).

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
8-i) by reacting a compound of formula (II_1) as above defined with a compound of formula (Iz)

$$W—X_{24} \quad (Iz)$$

wherein W is as above defined, X_{24} is the radical R_X having the following meanings

[0533] (a5') —R^{1b}—CH(NHR^{4a})—C(O)-(T-Y-Q)
[0534] (a6') —R^{1b}—CH(COOR^{3a})NH-(T'-Y-Q)
[0535] (a9') —R^{1b}—CH(NH-T'-Y'-Q)-C(O)-(T-Y-Q)
[0536] (a10') —R^{1b}—CH(C(O)-T'-Y'-Q)-NH-(T-Y-Q)
[0537] (b5') —R^{2b}—CH(NHR^{4a})—CH_2C(O)-(T-Y-Q)
[0538] (b6') —R^{2b}—CH(CH_2COOR^{3a})NH-(T'-Y-Q)
[0539] (b9') —R^{2b}—CH(NH-T'-Y'-Q)-CH_2C(O)-(T-Y-Q)
[0540] (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, 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 8-i) or 8-ii) as above described.

[0541] The reaction of a compound of formula (II_1) as above defined wherein R is as above defined, with a compound of formula (Iv) wherein W and X_{24} are as above defined may be carried out as described in 1).

8a) The compounds of formula (Iz) wherein X_{24} is a radical of formula (a5'), (a6'), (b5') or (b6'), wherein R^{1b} is selected from A10) and R^{2b} is selected from B10), T and T' are C(O) can be obtained
8a-i) by reacting a compound of formula (IIIq),

$$P^2—X_{25} \quad (IIIq)$$

wherein P^2 is as above defined, X_{25} is the radical having the following meanings

[0542] (a5") —R^{1b}—CH(NHP^3)—C(O)—OH
[0543] (a6") —R^{1b}—CH(COOP^2)—NH_2
[0544] (b5") —R^{2b}—CH(NHP^3)—CH_2C(O)—OH
[0545] (b6") —R^{2b}—CH(CH_2COOP^2)NH_2

wherein P^2 and P^3 are as above defined and R^{1b} is selected from A10), R^{2b} is selected from B10), with a compound of formula (IVa)

$$W_1—C(O)\text{-}y\text{-}Q \quad (IVa)$$

wherein W_1 and Q are as above defined, y is the radical Y, wherein Y is as above defined, and
8a-ii) when Q is Z_2, 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.

[0546] The reaction of a compound of formula (IIIq) wherein P^2 and X_{25} 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).

[0547] The compounds of formula (IIIq), wherein P^2 and X_{25} are as above 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 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),

$$P^2—X_{25} \quad (IIIq)$$

wherein P^2 and X_{25} are as above defined, with a compound of formula (IVd)

$$R_a—O—C(O)—X''\text{-}y\text{-}Q \quad (IVd)$$

wherein R_a, Q and X" are as above defined, y is the radical Y, 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 8b-i) or 8b-ii) as above described.

[0548] 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),

$$P^2—X_{26} \quad (Iy)$$

wherein P^2 is as above defined and X_{26} is the radical having the following meanings

[0549] (a9") —R^{1b}—CH(NH_2)—C(O)-(T-Y-Q)
[0550] (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)

$$W_1—C(O)\text{-}y\text{-}Q \quad (IVa)$$

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.

[0551] 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),

$$P^2—X_{26} \quad \text{(Iy)}$$

wherein P^2 and X_{26} are as above defined, with a compound of formula (IVd)

$$R_a—O—C(O)—X''\text{-}y\text{-}Q \quad \text{(IVd)}$$

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.

[0552] The reaction of a compound of formula (Iy) wherein P^2 and X_{20} is 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'),

$$P^2—X_{26} \quad \text{(Iy')}$$

wherein P^2 is as above defined and X_{26} is the radical having the following meanings

[0553] (a10") —R^{1b}—CH(C(O)—OH)—NH-(T-Y-Q)

[0554] (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)

$$W_1—C(O)\text{-}y\text{-}Q \quad \text{(IVa)}$$

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

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.

[0555] 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).

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

8f-i) by reacting a compound of formula (Iy'),

$$P^2—X_{26'} \quad \text{(Iy')}$$

wherein P^2 and $X_{26'}$ are as above defined, with a compound of formula (IVd)

$$R_a—O—C(O)—X''\text{-}y\text{-}Q \quad \text{(IVd)}$$

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 source as above described and

8f-iii) optionally deprotecting the compounds obtained in step 8f-i) or 8f-ii) as above described.

[0556] 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_3) as above defined with a compound of formula (Ix)

$$H—X_{27} \quad \text{(Ix)}$$

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

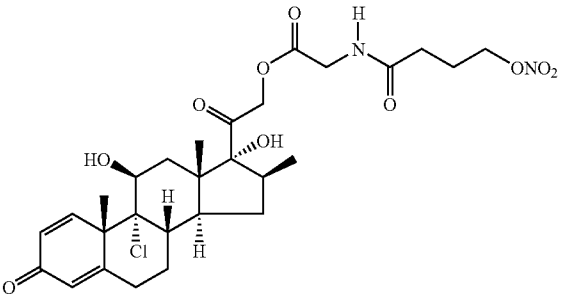
9-iii) optionally deprotecting the compounds obtained in step 9-i) or 9-ii) as above described.

[0557] The reaction of a compound of formula (Ix) wherein X_{27} and is as above defined, with a compound of formula (II_3) may be carried out as described in 11-i).

EXAMPLE 1

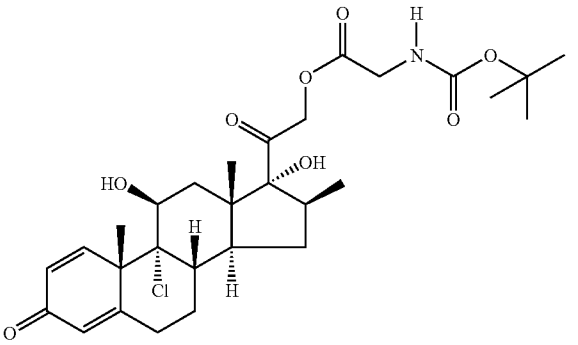
Synthesis of (11β,16β)-9-Chloro-11,17-dihydroxy-16-methyl-21-[1-oxo-((2-(4-(nitrooxy)butyloxy-carbonylamino)acetyl)]-pregna-1,4-diene-3,20-dione

[0558]



(11β,16β)-9-Chloro-11,17-dihydroxy-16-methyl-21-[1-oxo-2-((tert-butylcarbonylamino)acetyl)]-pregna-1,4-diene-3,20-dione

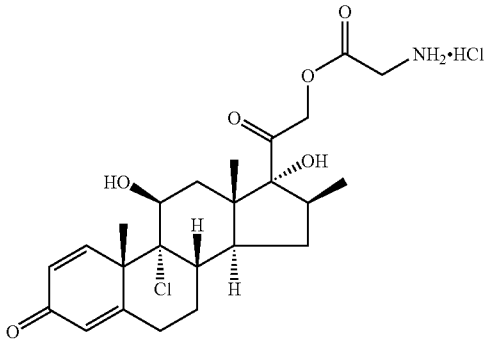
[0559]



[0560] To a solution of beclomethasone (0.6 g, 1.46 mmol) in acetone (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 methylene chloride (50×3 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.

(11β,16β)-9-Chloro-11,17-dihydroxy-16-methyl-21-[1-oxo-2-((carbonylamino)acetyl)]-pregna-1,4-diene-3,20-dione hydrochloride

[0561]



[0562] A solution of compound A (0.8 g, 0.41 mmol) in methylene chloride (70 ml) was stirred at room temperature. HCl gas was buddle in the solution for 1 hour. The solvent was evaporated under reduced pressure. The product was used in the next step without any purification.

(11β,16β)-9-Chloro-11,17-dihydroxy-16-methyl-21-[1-oxo-(2-((4-(nitrooxy)butoxy-carbonylamino) acetyl)]-pregna-1,4-diene-3,20-dione

[0563] 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, 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_3PO_4 (50 ml). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, (Biotage System, 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.

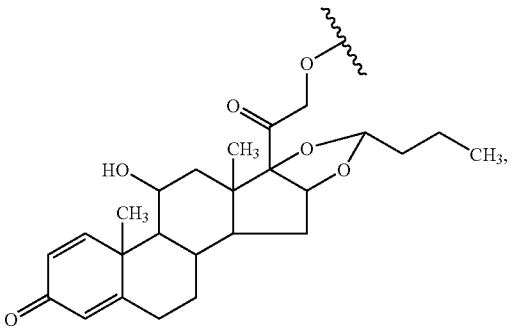
[0564] ^{1}H-NMR: (DMSO), δ: 8.42 (1H, t); 7.30 (1H, d); 6.22 (1H, dd); 5.98 (1H, s); 5.46 (1H, d); 5.42 (2H, s); 5.05 (1H, d); 4.84 (1H, d); 4.5 (2H, t); 4.34 (1H, sb); 3.97 (2H, d); 2.71-2.57 (2H, m); 2.5-2.2 (6H, m); 2.0-1.7 (5H, m); 1.65-1.35 (5H, m); 1.25-0.97 (4H, m); 0.8 (3H, s).

1. Nitric oxide releasing compounds of general formula (I)

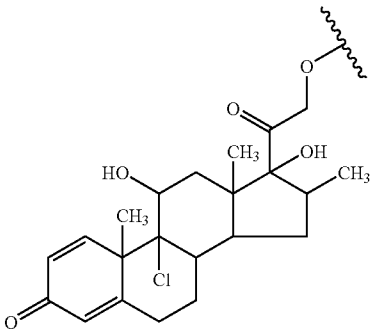
$$R\text{-}(Z)_a\text{-}R_X \quad (I)$$

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:

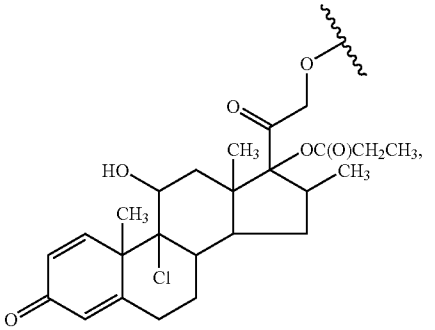
(II)



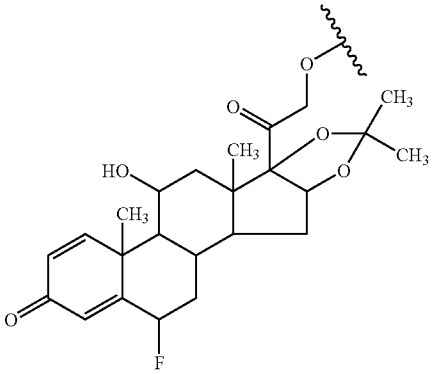
(III)



(IV)



(V)



a is 0 or 1,

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)

(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}

(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)—(O)-(T-Y—ONO_2)

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

wherein:

R^1 is selected from:

A1) H, —CH_3, isopropyl, isobutyl, sec-butyl, tert-butyl, methylthio-$(CH_2)_2$—, phenyl, benzyl, C_6H_5—CH_2—CH_2—,

2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, C_6H_5CO—,

2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, 2-pyrrolidyl, 3-triptophanyl-CH_2—, 3-benzothienyl-CH_2—,

4-imidazolyl-CH_2—, 9-anthranyl-CH_2—, cyclohexyl, cyclohexyl-CH_2—, cyclohexyl-$(CH_2)_2$—, cyclopentyl-CH_2—, $(C_6H_5)_2CH$—,

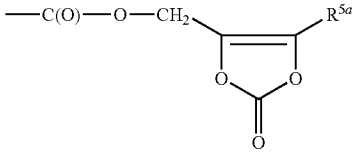
4-B$(OH)_2$-benzyl, 4-quinolyl-CH_2—, 3-quinolyl-CH_2—,

2-quinolyl-CH_2—, 2-quinoxalyl-CH_2—, 2-furyl-CH_2—,

1-naphtyl-CH_2—, 2-naphtyl-CH_2—, 2-pyridyl-CH_2—, 3-pyridyl-CH_2—, 4-pyridyl-CH_2—, 2-thienyl-CH_2—, 3-thienyl-ClF_2—, C_6H_4—CH═CH—CH_2—, CH_2═CH—CH_2—, CH═CH—CH_2—, NH_2—CO—CH_2—, NH_2—CO—$(CH_2)_2$—, NH_2(═NH)NH—$(CH_2)_3$—, P(═O)$(OCH_3)_2$;

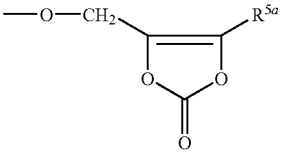
A2) —CH_2—SH, —CH_2—OH, —$CH(CH_3)$—OH, —OCH_2—[(C_6H_4)-(4-OH)], —CH_2—[(C_6H_2)-(3,5-diiodo)-(4-OH)], —CH_2—[(C_6H_3)-(3-nitro)-(4-OH)],

A3) —CH_2—NHR", —$(CH_2)_2$—NHR", —$(CH_2)_3$—NHR", —$(CH_2)_4$—NHR", wherein R" is H, —C(O)CH_3 or



wherein R^{5a} is H or a linear or branched C_1-C_{10} alkyl chain,

A4) —CH_2—C(O)R'", —$(CH_2)_2$—C(O)R'", —$(CH_2)_4$—C(O)R'" wherein R'" is —OR^{5a} or



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

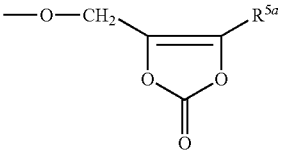
R^{1a} is selected from,

A5) —CH_2—S—, —CH_2—O—, —$CH(CH_3)$—O—, —CH_2[(C_6H_4)-(4-O)—], —CH_2-[(3,5-diiodo)-(C_6H_2)-(4-O)—], —CH_2-[(3-nitro)-(C_6H_3)-(4-O)—],

A6) —CH_2—NH—, —$(CH_2)_2$—NH—, —(CF_{12})—NH—, —$(CH_2)_4$—NH—,

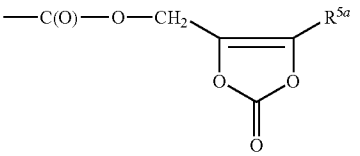
A7) —CH_2—C(O)—, —$(CH_2)_2$—C(O), —$(CH_2)_4$—C(O)—;

R^{3a} is selected from H, —R^{5a} or



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

R^{4a} is selected from H or —C(O)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—, [-(4-O)-(3,5-diiodo)-(C_6H_2)]—CH_2—, [-(4-O)-(3-nitro)-(C_6H_3)]—CH_2—,

A9) —HN—CH_2—, —HN—$(CH_2)_2$—, —HN—$(CH_2)_3$—, —HN—$(CH_2)_4$—,

A10) —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—,

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 —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'— 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:

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}

(b5) —R^{2b}—CH(NHR^{4a})—CH_2—C(O)-(T-Y—ONO_2)

(b6) —R^{2b}—CH(CH_2COOR^{3a})NH-(T-Y—ONO_2)

(b7) —HN—CH(R^{2a}-T"-Y'—ONO_2)—CH_2—C(O)-(T-Y—ONO_2)

(b8) —C(O)CH_2—CH(R^{2a}-T"Y'—ONO_2)—NH-(T'-Y—ONO_2)

(b9) —R^{2b}—CH(NH-T'-Y'—ONO_2)—CH_2C(O)-(T'-Y—ONO_2)

(b10) —R^{2b}—CH(CH_2C(O)-T-Y'—ONO_2)—NH-(T'-Y—ONO_2)

wherein

R^2 is selected from

B1) H, —CH_3, CF_3, isopropyl, isobutyl, sec-butyl, methylthio-$(CH_2)_2$—, phenyl, benzyl, 3-triptophanyl-CH_2—, NH_2—C(O)—CH_2—, NH_2—C(O)—$(CH_2)_2$—, NH_2(═NH)NH—$(CH_2)_3$—, tBuO—CH(CH_3)—, benzyl-O—CH_2—, 4-terbutoxy-benzyl, 4-phenylbenzyl,

B2) —CH_2—SH, —CH_2—OH, —CH(CH_3)—OH, —CH_2—[(C_6H_4)-(4-OH)], —CH_2—[(C_6H_2)-(3,5-diiodo)-(4-OH)], —CH_2—[(C_6H_3)-(3-nitro)-(4-OH)],

B3) —CH_2—NHR", —$(CH_2)_2$—NHR", —$(CH_2)_3$—NHR", —$(CH_2)_4$—NHR", wherein R" is as above defined,

B4) —CH_2—C(O)—R'", —$(CH_2)_2$—C(O)R'", —$(CH_2)_4$—C(O)—R'" wherein R'" is as above defined, preferably R^2 is —CH_2—C(O)—R'";

R^{2a} is selected from:

B5) —CH_2—S—, —CH_2—O—, —CH(CH_3)O— or —CH_2—[(C_6H_4)-(4-O)—], —CH_2-[(3,5-diiodo)-(C_6H_{12})-(4-O)—], —CH_2-[(3-nitro)-(C_6H_3)-(4-O)—],

B6) —CH_2—NH—, —$(CH_2)_2$—NH—, —$(CH_2)_3$—NH—, —$(CH_2)_4$—NH—,

B7) —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—,

R^{2b} is selected from.

B8) —S—CH_2—, —O—CH(CH_3)—, —O—CH_2—, [-(4-O)—(C_6H_4)]—CH_2—, [-(4-O)-(3,5-diiodo)-(C_6H_2)]—CH_2—, [-(4-O)-(3-nitro)-(C_6H_3)]—CH_2,

B9) —HN—CH_2—, —HN—$(CH_2)_2$—, —HN—$(CH_2)_3$—, —HN—$(CH_2)_4$—,

B10) —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, C(O)—$(CH_2)_4$—,

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:

C)

(c1) —HN—$(CH_2)_b$—C(O)-(T'-Y—ONO_2) or

(c2) —C(O)—$(CH_2)_b$—NH-(T'-Y—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;

or R_x is selected from:

D)

(d1) —HN—CH(R^{12})—CH_2—O-(T'"-Y—ONO_2)

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

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

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

(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)

(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,

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-$(CH_2)_2$—, benzyl, 3-triptophanyl-CH_2—, 4-imidazolyl-CH_2—, 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 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)—], —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)—, —$(CH_2)_4$—O(O)—,

R^{12b} is selected from:

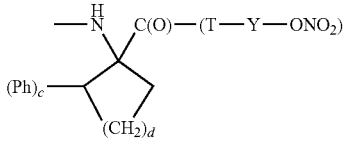
D8) —O—CH_2—, —O—CH(CH_3)—, [-(4-O)(C_6H_4)]—CH_2—, [-(4-O)-(3,5-diiodo)-(C_6H_2)]—CH_2, [-(4-O)-(3-nitro)-(C_6H_3)]—CH_2—,

D9) —HN—CH_2—, —HN—$(CH_2)_2$—, —HN—$(CH_2)_3$—, —HN—$(CH_2)_4$—,

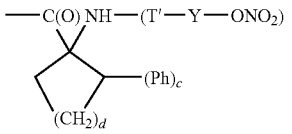
D10) —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—,

R^{4a} is as above defined;
or R_X is selected from:
E)

(e1)

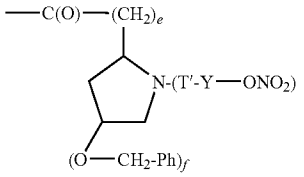


(e2)

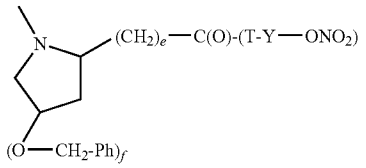


wherein c is equal to 0 or 1, d is an integer from 0 to 3 with the proviso that c is 0 or 1 when d is 0 and c is 0 when d is 1, 2 or 3, T and T' are as above defined and Y is as below defined;
F)

(f1)

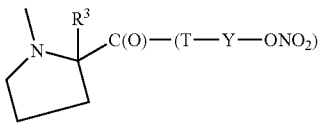


(f2)

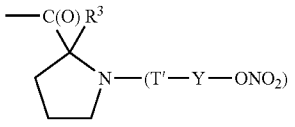


(XI)
wherein e and f are equal to 0 or 1, with the proviso that f is 0 when e is 0 and f is 0 or 1 when e is 1,
T and t' are as above defined and y is as below reported;
G)

(g1)

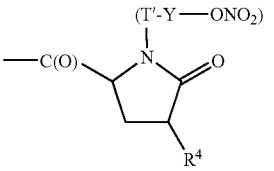


(g2)

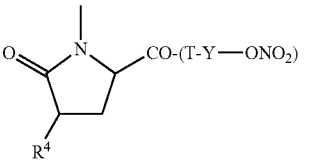


wherein R^3 is H, CH_3, propyl, $(C_6H_5)_2CH$—, 1-naphtyl-CH_2—, benzyl, allyl, 2-bromobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-fluorobenzyl, 4-bromobenzyl, 4-methylbenzyl, T and T' are as above defined and Y is as below defined;
H)

(h1)

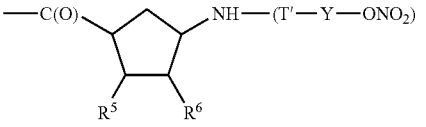


(h2)

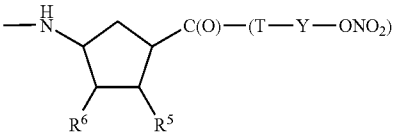


wherein R^4 is H, benzyl, 4-bromobenzyl, 2-bromobenzyl, T and T' are as above defined and Y is as below defined;
I)

(i1)

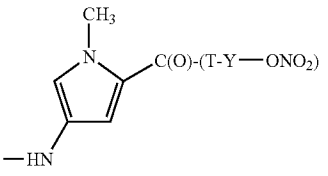


(i2)

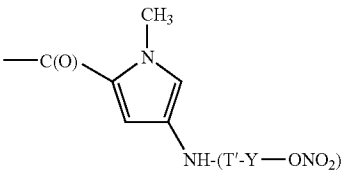


wherein R^5 is H, R^6 is H, or R^5 and R^6 when taken together are a double bond, T and T' are as above defined and Y is as below reported;
L)

(l1)



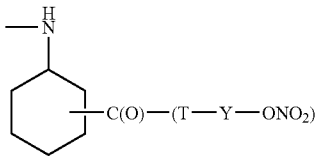
(l2)



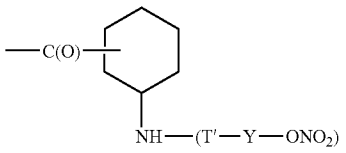
wherein T and T' are as above defined and Y is as below reported;

M)

(m1)



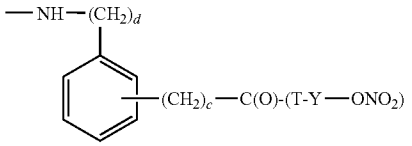
(m2)



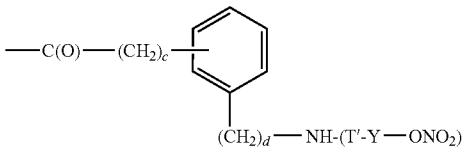
wherein T and T' are as above defined and Y is as below reported;

N)

(n1)



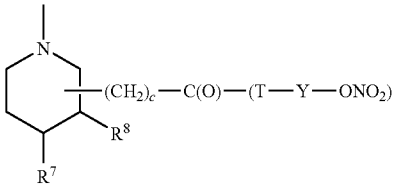
(n2)



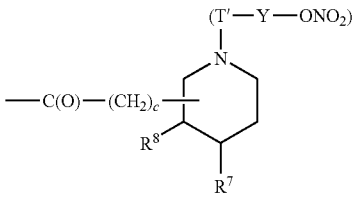
wherein c is as above defined, d is equal to 0 or 1, T and T' are as above defined and Y is as below reported;

O)

(o1)



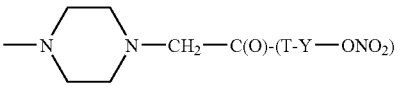
(o2)



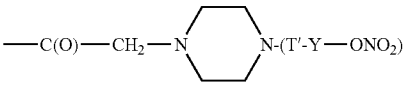
wherein R^7 is H, R^8 is H, or R^7 and R^8 when taken together are a double bond, c is as above defined, T and T' are as above defined and Y is as below reported;

P)

(p1)



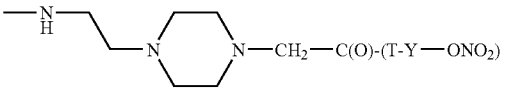
(p2)



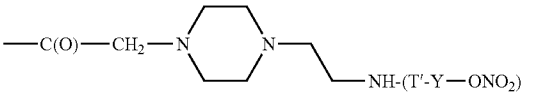
wherein T and T' are as above defined and Y is as below reported;

Q)

(q1)



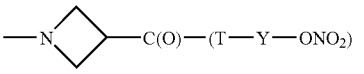
(q2)



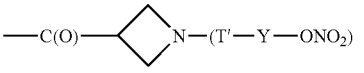
wherein T and T' are as above defined and Y is as below reported;

R)

(r1)



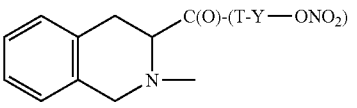
(r2)



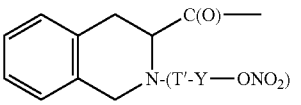
wherein T and T' are as above defined and Y is as below reported;

S)

(s1)



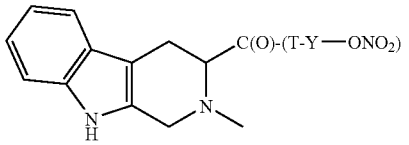
(s2)



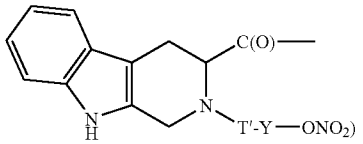
wherein T and T' are as above defined and Y is as below reported;

T)

(t1)



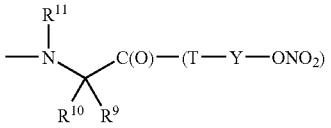
(t2)



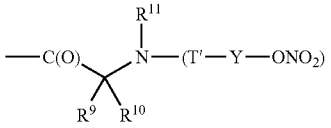
wherein T and T' are as above defined and Y is as below reported;

U)

(u1)



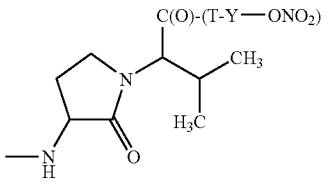
(u2)



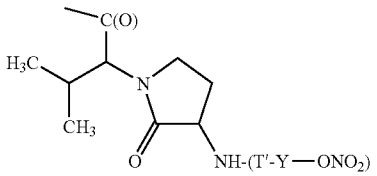
wherein R^9 and R^{10} are H, CH_3, R^{11} is CH_3 or 4-piperidinyl with the proviso that R^9 and R^{10} are H when R^{11} is 4-piperidinyl and R^9 and R^{10} are CH_3 when R^{11} is CH_3, T and T' are as above defined and Y is as below reported;

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);

(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:

(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 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)

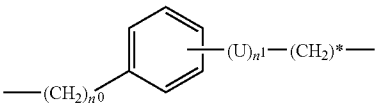
straight or branched C_1-C_{20} alkylene,

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} alkyl)-ONO_2 or —$O(C_1$-C_{10} 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

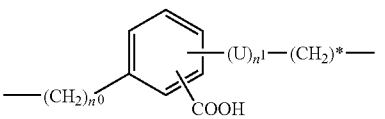
n^0 is an integer from 0 to 20;

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)



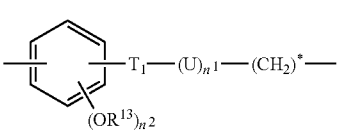
wherein

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)

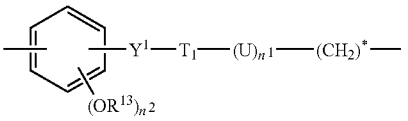


wherein:

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,

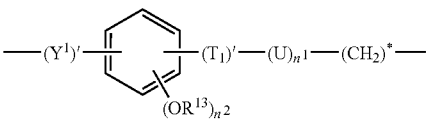
Y^1 is $—CH_2—CH_2—$ or $—CH═CH—(CH_2)_{n^{2'}}—$, wherein $n^{2'}$ is 0 or 1,

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,

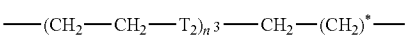
Y^1 is $—CH_2—CH_2—$ or $(CH_2)_{n^{2'}}—CH═CH—$, wherein $n^{2'}$ is 0 or 1,

$(T_1)'$=—O—C(O)—;

n^1 is 0 or 1,

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

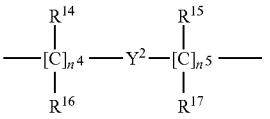
f)



wherein T_2 is —O— or —S—, —NH—, preferably T_2 is —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 $—ONO_2$ 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;

g)



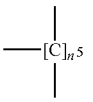
wherein:

n^4 is an integer from 0 to 10,

n^5 is an integer from 1 to 10,

R^{14}, R^{15}, R^{16}, R^{17} are the same or different, and are H or straight or branched C_1-C_4 alkyl,

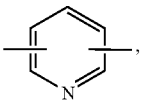
wherein the $—ONO_2$ group is linked to



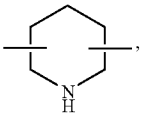
wherein n^5 is as defined above;

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

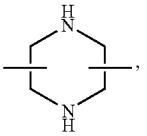
(Y1)



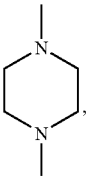
(Y2)



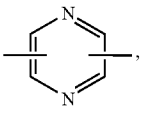
(Y3)



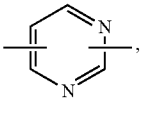
(Y4)



(Y5)

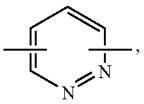


(Y6)

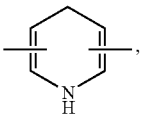


-continued

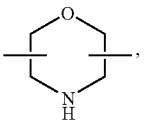
(Y7)



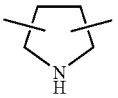
(Y8)



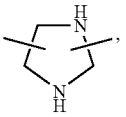
(Y9)



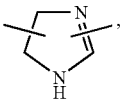
(Y10)



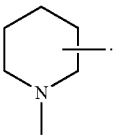
(Y11)



(Y12)



(Y13)



2. The nitric oxide releasing compounds according to claim **1** wherein

a is 1 and Z is —C(O)—;

R_X is

(a1) —HN—CH(R^1)—C(O)-(T-Y—ONO_2)

wherein

R^1 of the group A1) is selected from H, isobutyl, benzyl, C_6H_5—CH_2—CH_2—, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, C_6H_5CO— or

R^1 of the group A2) is selected from —CH_2—OH, —CH(CH_3)—OH— or —CH_2—[(C_6H_4)-(4-OH)], or

R^1 of the group A3) 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^1 of the group A4) 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 is —O—, —S—, —NR'—, —O—CH(R')—O—C(O)— wherein R' is H or a straight or branched C_1-C_4 alkyl,

Y is as below defined;

or R_X is

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

wherein

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)—,

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

T" is —C(O)— or —C(O)—X" wherein X" is S— or —O—, when R^{1a} 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_1-C_4 alkyl, when R^{1a} is selected from the group A7),

Y' is as below defined;

or R_X 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)

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—$(CH_2)_4$,

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

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,

T' is —C(O)— or —C(O)—X" wherein X" is —S— or —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

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)—,

T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} 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_1-C_4 alkyl, when R^{1a} 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_1-C_4 alkyl,

Y and Y' are as below defined;

or R_X is

(b1) —HN—CH(R^2)—CH_2C(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 —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'", —(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,

Y is as below defined;

or R_X is selected from

(d1) —HN—CH(R^2)—CH_2O-(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

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

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—,

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

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,

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),

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),

T'" is selected from —C(O) or —C(O)—X" wherein X" is —S— or —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—$ON)_2$)

(d6) —R^{12b}—CH(CH_2O)—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

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^4, is H or —C(O)—CH_3,

T' and T'" are each independently selected from —C(O)—, —C(O)—X", wherein X" is —S— or —O—,

Y and Y' are each independently selected from

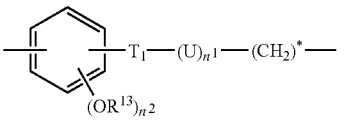
a)

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

a straight or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;

d)

d)



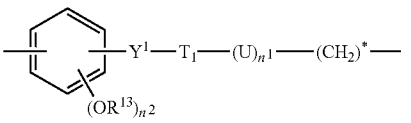
wherein:

n 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 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)

e)

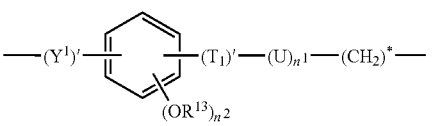


n^2 is 1, R^{13} is CH_3, Y^1 is —CH═CH—(CH_2)$_n^{2'}$— and $n^{2'}$ is 0,

T_1 is —C(O)O— and U is a linear C_1-C_{10} alkylene;

e')

e'



wherein:

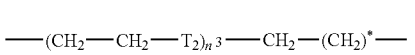
n^2 is 1, R^{13} is CH_3,

Y' is —(CH_2)$_n^{2'}$—CH═CH— and $n^{2'}$ is 0,

(T_1)'=—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— and 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.

3. The nitric oxide releasing compounds according to claim **2** wherein 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_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.

4. The nitric oxide releasing compounds according to claim **1** 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, C_6H_5—CH_2—CH_2—, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, $—NO_2$, $—CF_3$, $—CH_3$, CN, C_6H_5CO—,

R^1 of the group A2) is selected from —CH_2—OH, —CH(CH_3)OH— or

—CH_2—[(C_6H_4)-(4-OH)], or

R^1 of the group A3) 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^1 of the group A4) is selected from —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' is —C(O)—, —C(O)—X_1 wherein X" is —S— or —O—,

Y is as below defined;

or R_X is

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

wherein 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 selected from CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—;

R^{4a} is H or —C(O)CH_3,

T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O— when R^{1a} 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 $—CH_3$ when R^{1a} is selected from the group A7),

Y' is as below defined;

or R_X 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)

wherein

R^{1b} of the group A10) is selected from —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—,

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'— or —O—CH(R')OC(O)— wherein R' is H or

$—CH_3$,

T' is —C(O)— or —C(O)—X" wherein X" is —S— or —O—,

Y and Y' are as below defined;

or R_X is

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

wherein

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 selected from —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—,

T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} 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

$—CH_3$, when R^{1a} 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_X is

(b2) —C(O)—CH_2—CH(R^2)—N-(T'-Y—ONO_2)

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—,

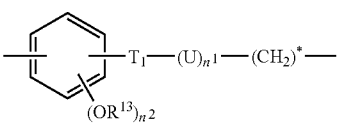
Y and Y' are each independently selected from

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;

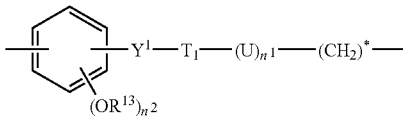
d)



d)

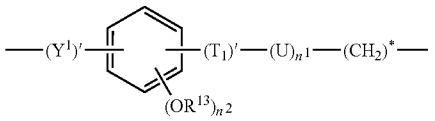
wherein:
n^2 is an integer from 0 to 2, R^{13} is H or CH_3, T_1 is —O—C(O)— or —C(O)O—,
n^1 is 1 and U is a linear C_1-C_{10} alkylene or U is a linear or branched C_1-C_{10} alkylene substituted with a $—ONO_2$ group;
e)

e)



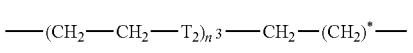
n^2 is 1, R^{13} is CH_3, Y^1 is —CH═CH—$(CH_2)_{n^{2'}}$— and $n^{2'}$ is 0,
T_1 is —C(O)O— and U is a linear C_1-C_{10} alkylene;
e')

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— and 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) is linked to the —(CH_2)*— group.

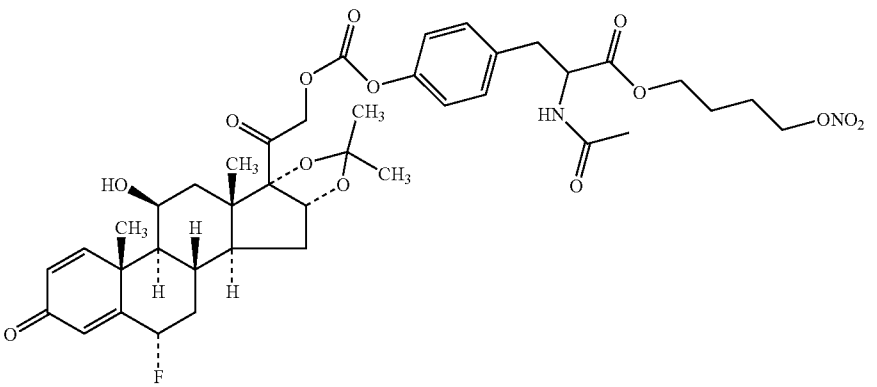
5. The nitric oxide releasing compounds according to claim **4** wherein
R_X is
(a2) —C(O)—CH(R^1)—NH-(T'-Y—ONO_2)
wherein
R^1 of the group A1) is H,
T' is —C(O)—,
Y is selected from
a)
a straight or branched C_1-C_{10} alkylene,
a straight or branched C_1-C_{10} alkylene substituted with a $—ONO_2$ group;

6. The nitric oxide releasing compounds of claim **4** wherein
R_X 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) or
(a9) —R^{1b}—CH(NH-T'-Y'—ONO_2)—C(O)-(T-Y—ONO_2)
wherein
R^{1b} of the group A10) is —C(O)—CH_2—,
R^{3a} is H or a (C_1-C_5) 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_1-C_{10} alkylene,
a straight or branched C_1-C_{10} alkylene substituted with a $—ONO_2$ group.

7. The nitric oxide releasing compounds according to claim **4** wherein
R_X is
(b2) —C(O)—CH_2—CH(R^2)—NH-(T'-Y—ONO_2)
R^2 of the group B1) is H,
T' is —C(O)—,
Y is 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;

8. Nitric oxide releasing compounds according to claim **3**

(3)



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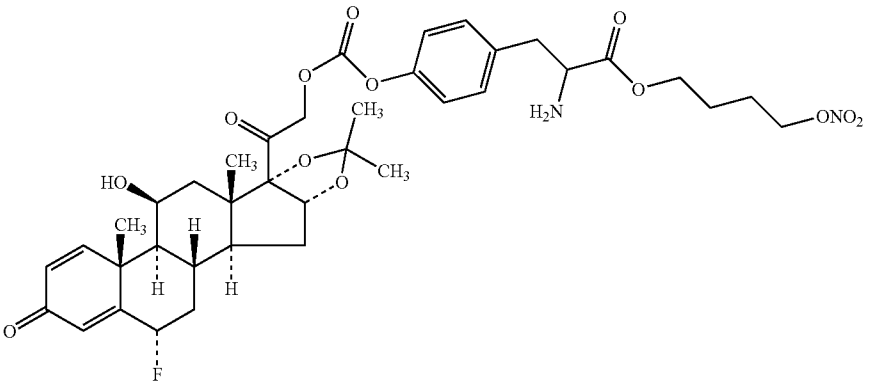

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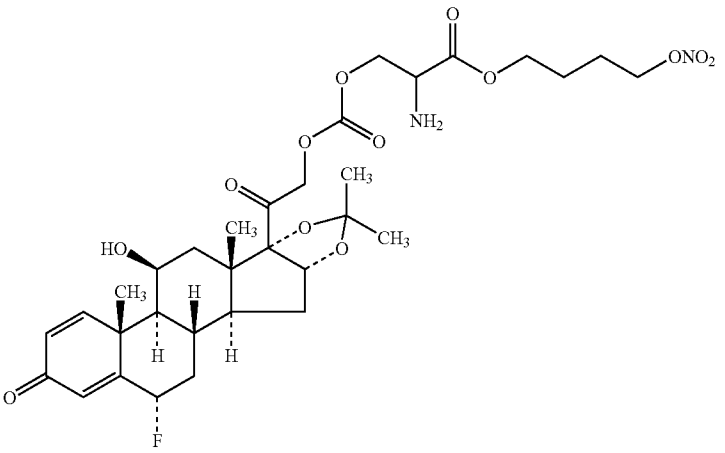

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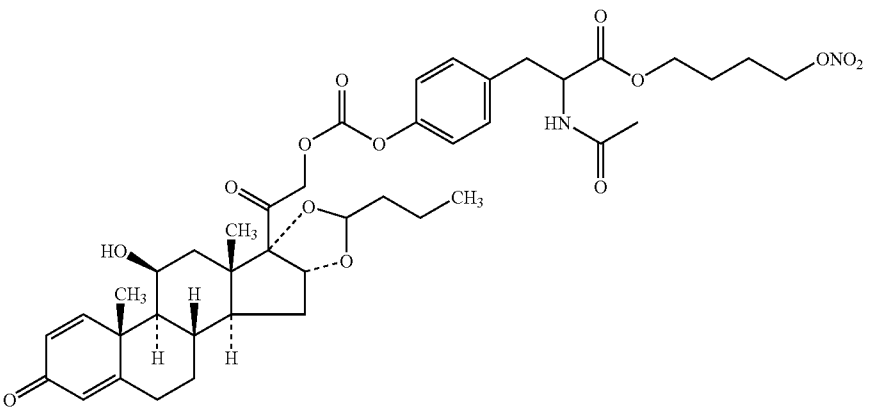

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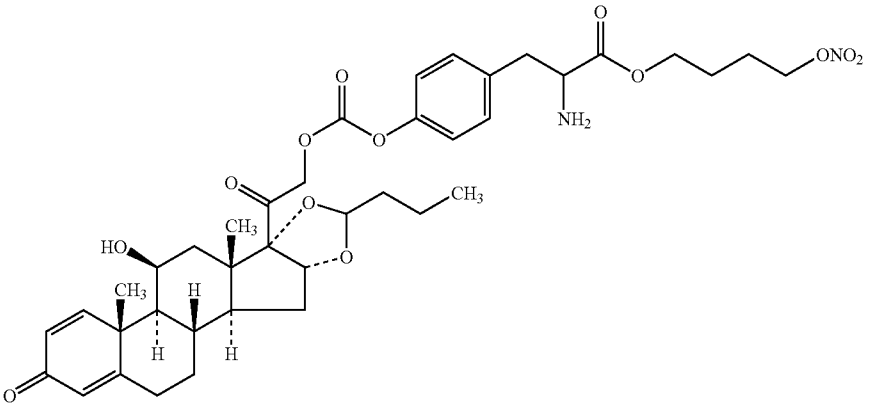

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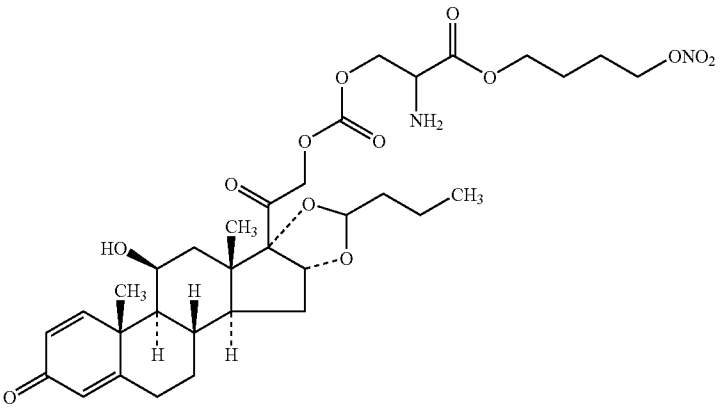

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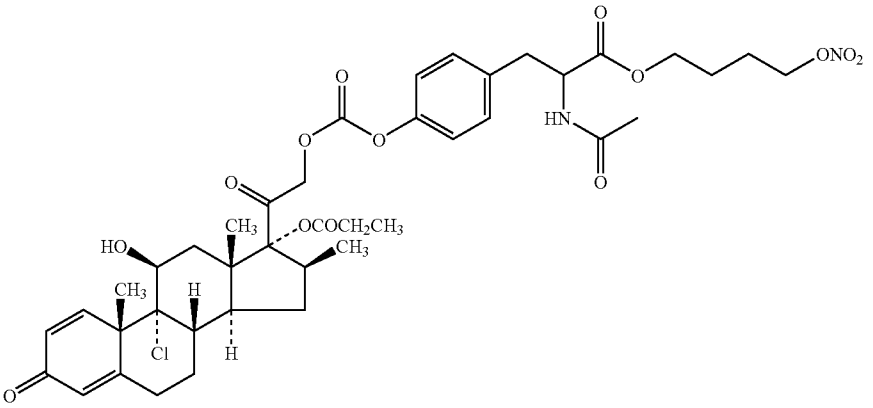

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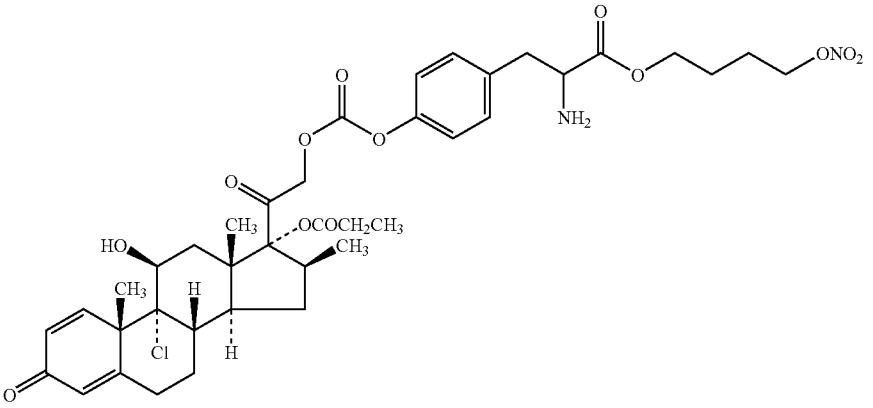

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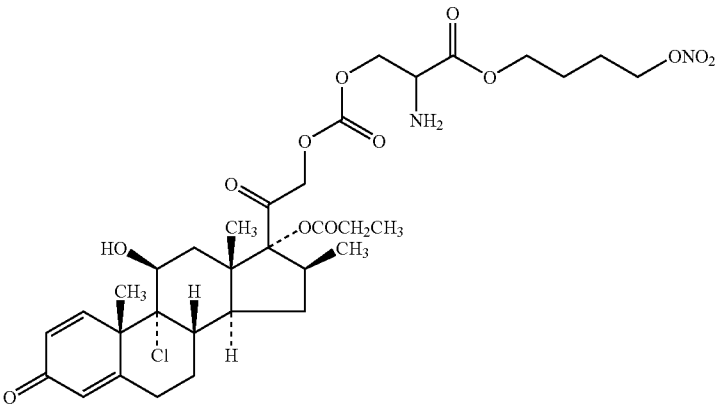

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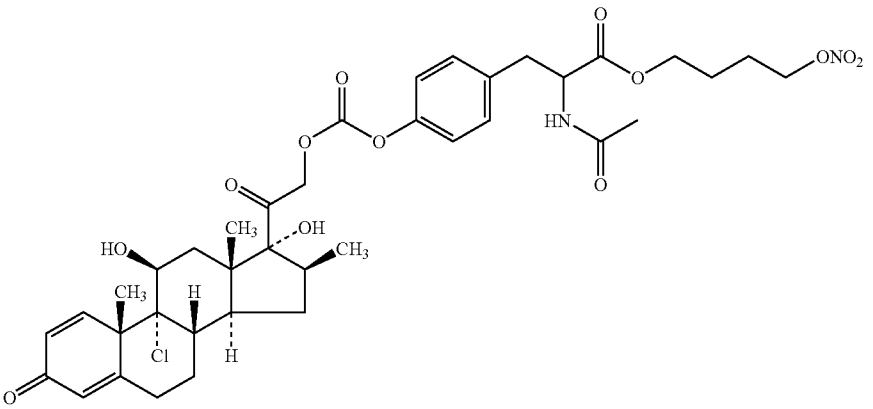

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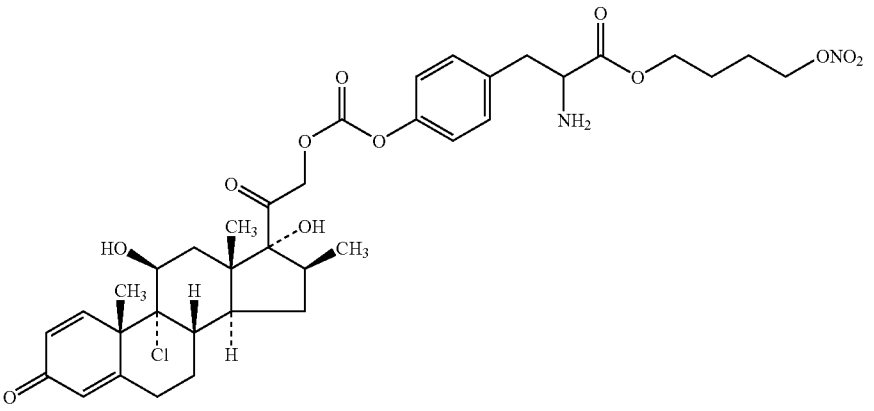

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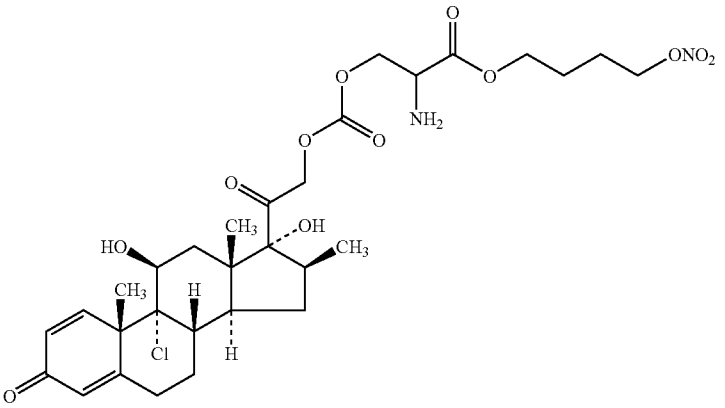

9. Nitric oxide releasing compounds according to claim **5**

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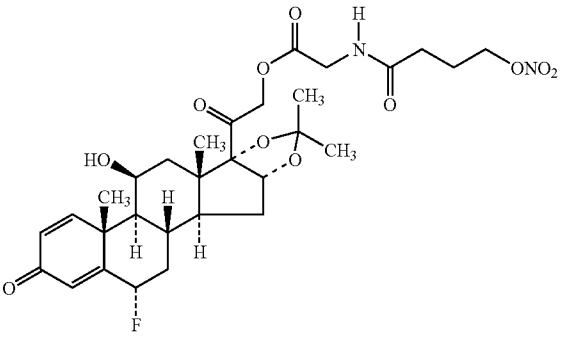
(1)



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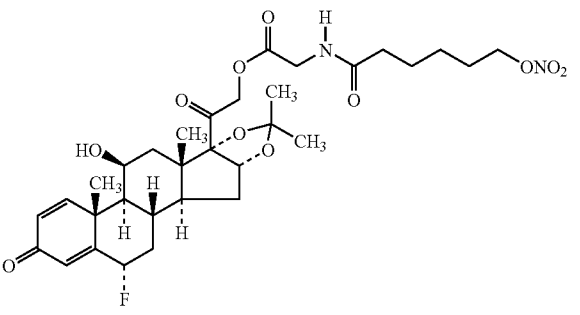

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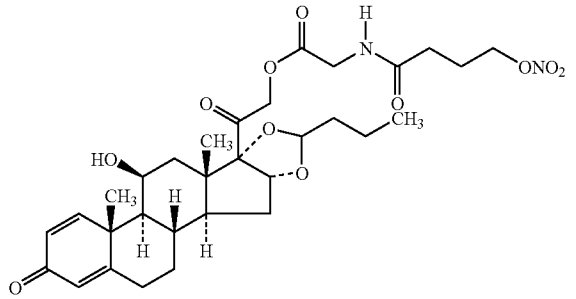

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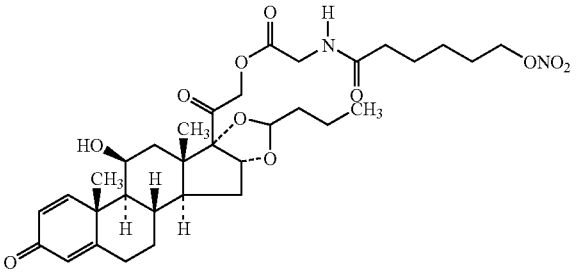

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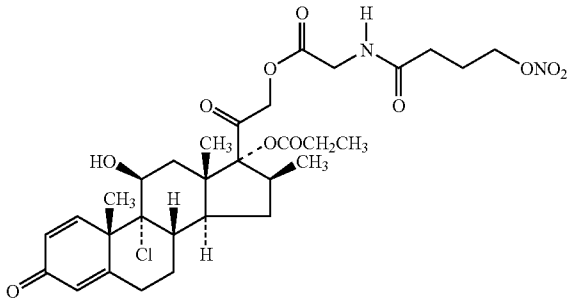

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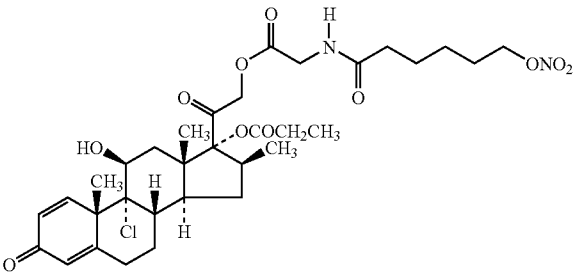

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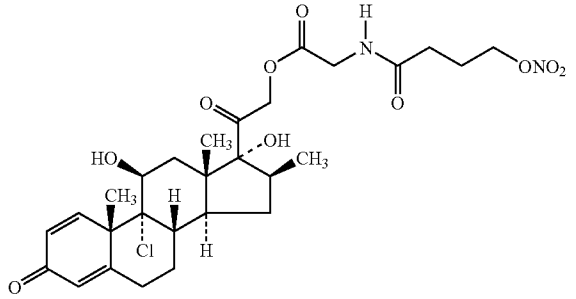

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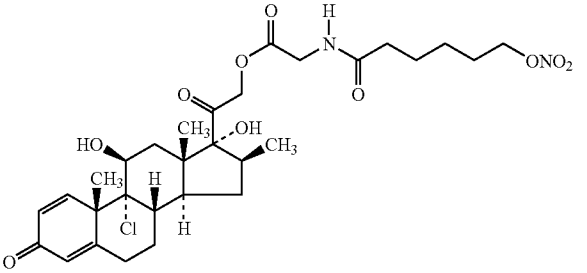
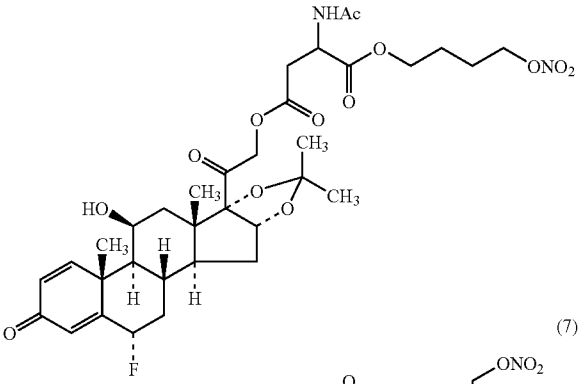


10. Nitric oxide releasing compounds according to claim **6**

(5)



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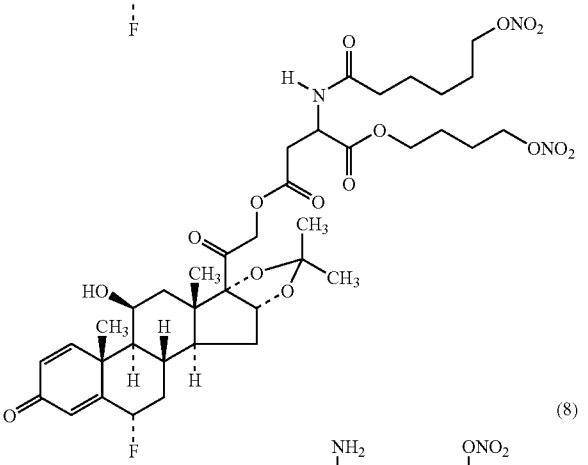

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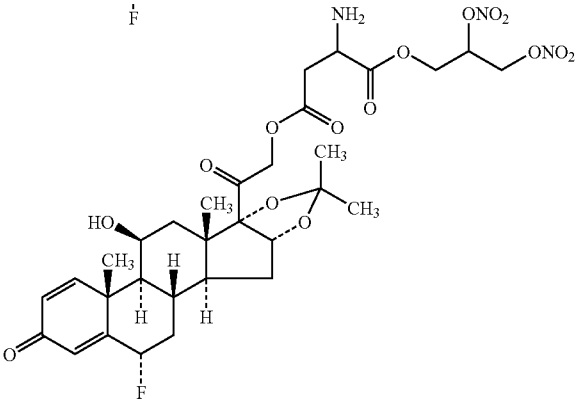

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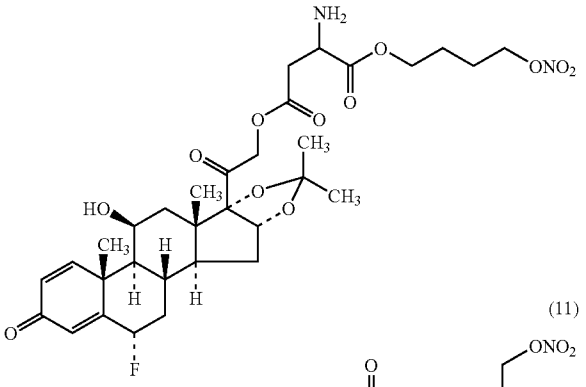

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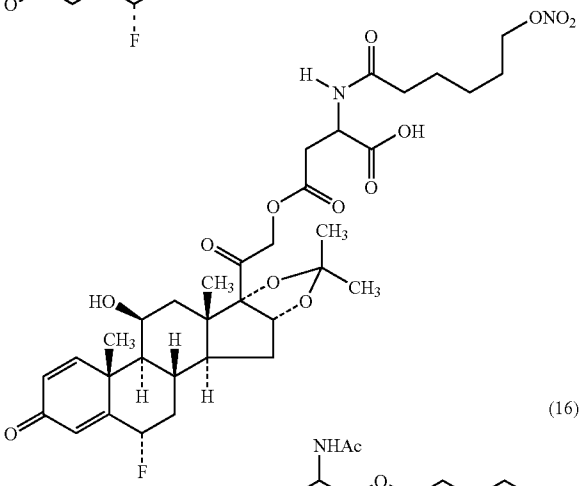

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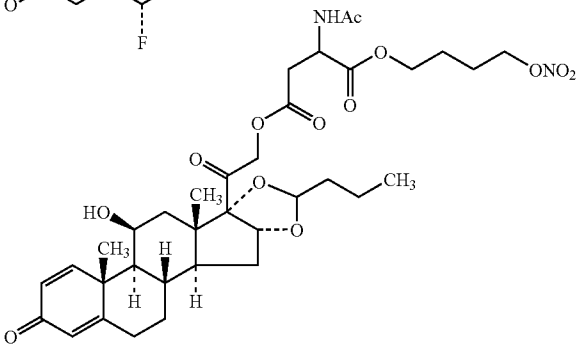

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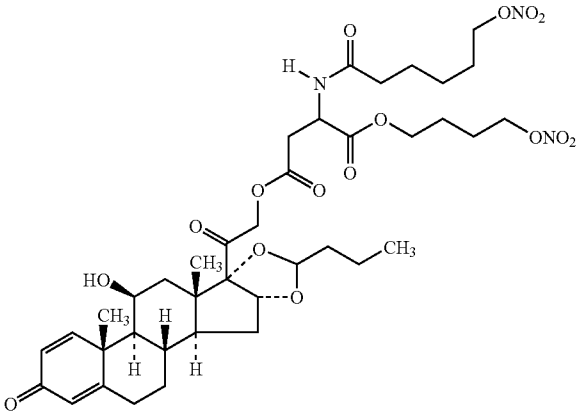

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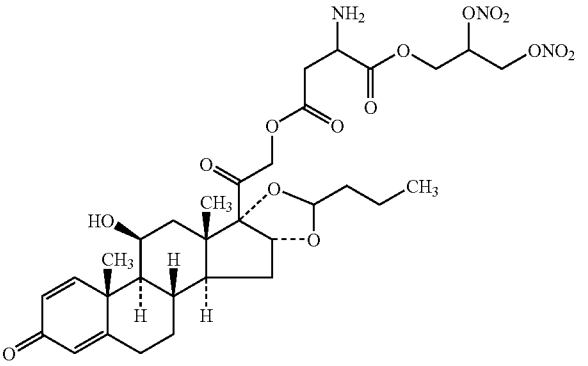

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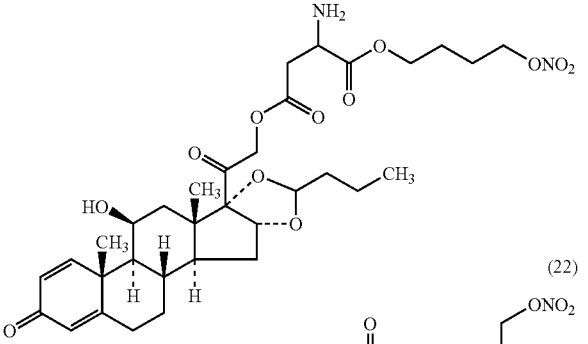

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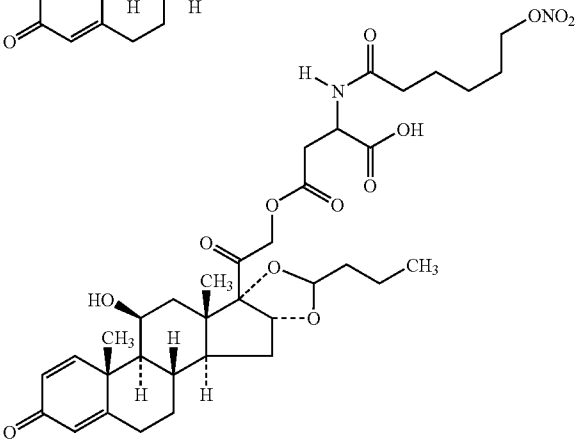

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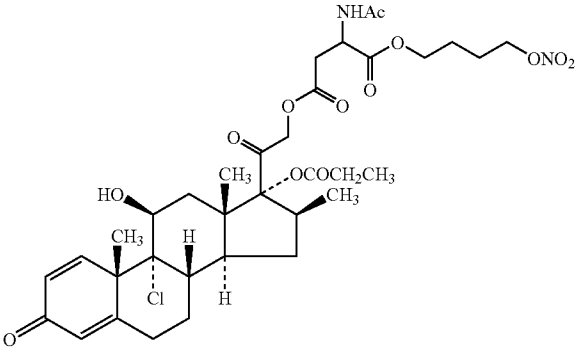

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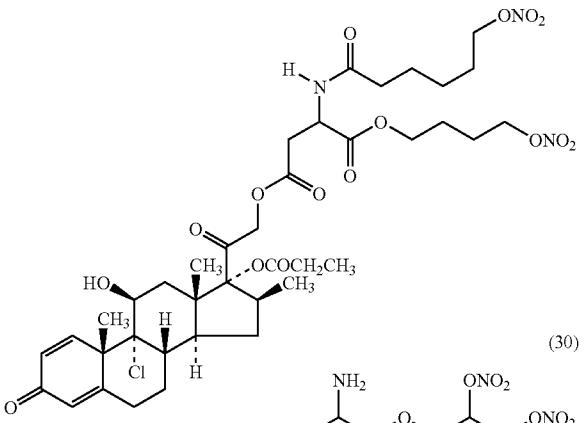

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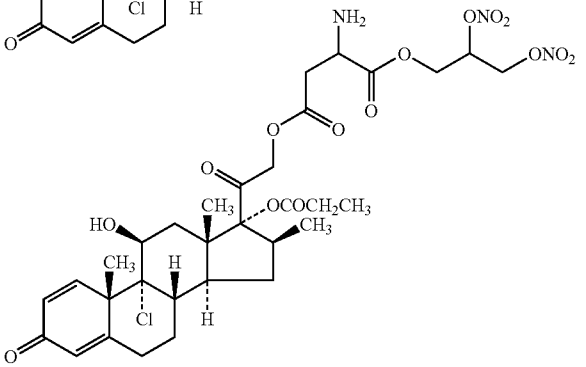

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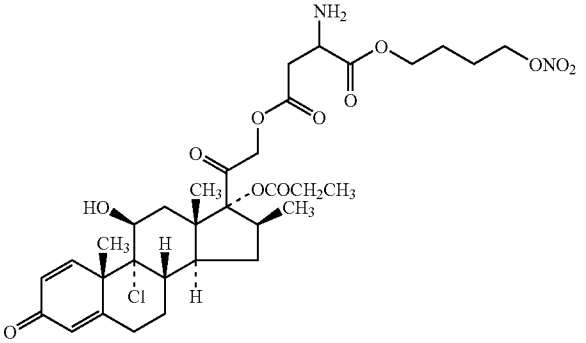

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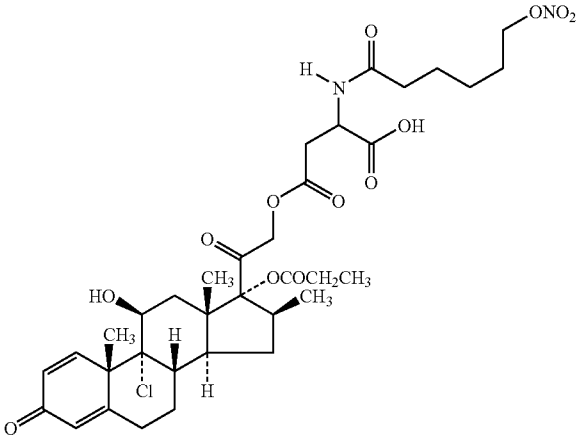

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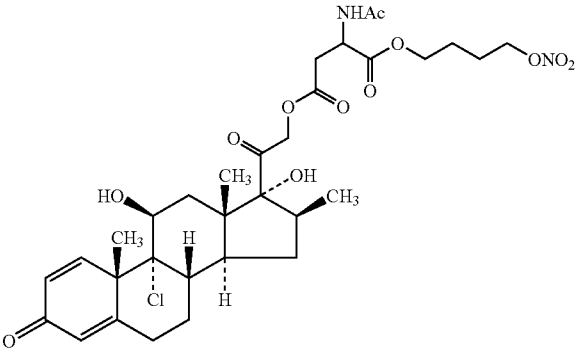

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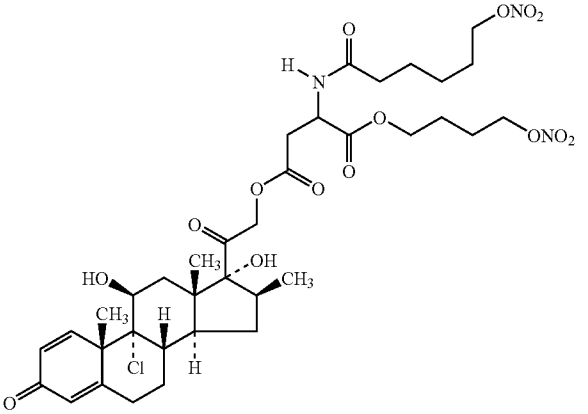

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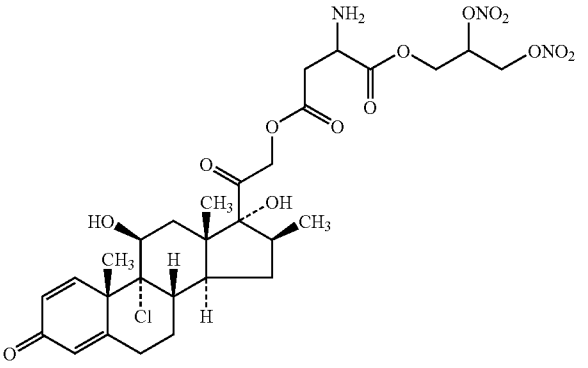

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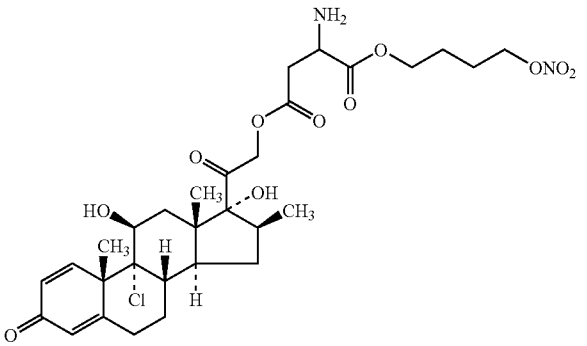

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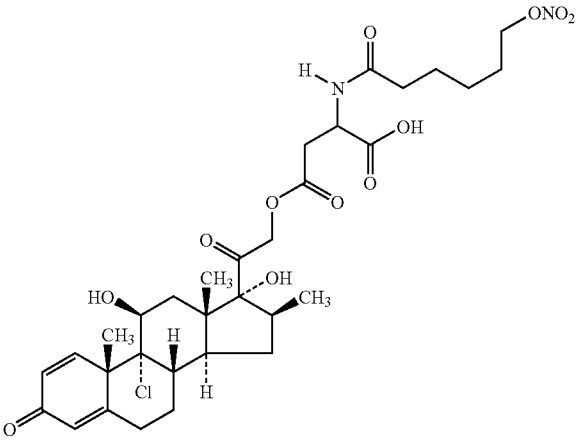
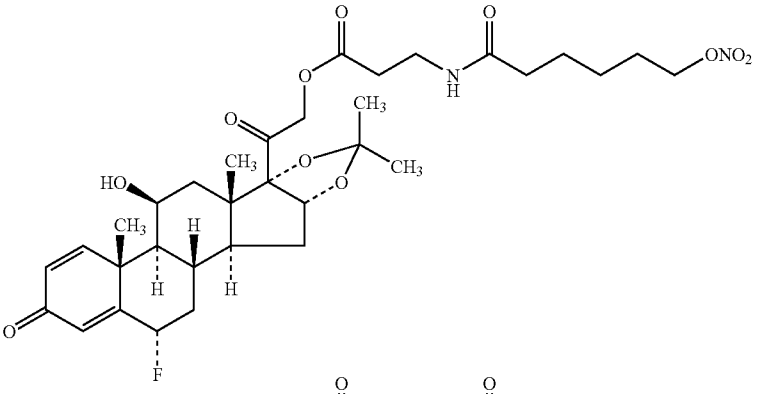


11. Nitric oxide releasing compounds according to claim **7**

(6)



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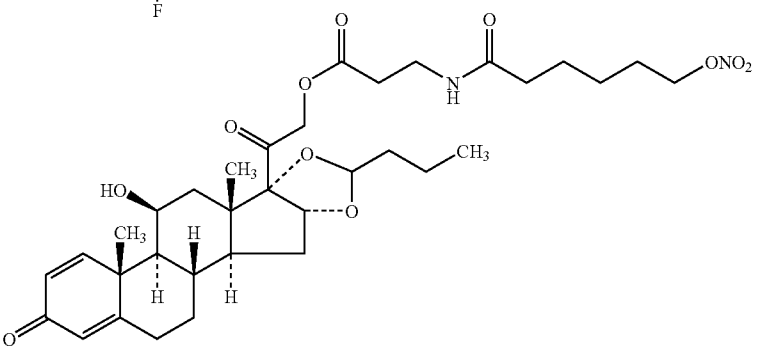

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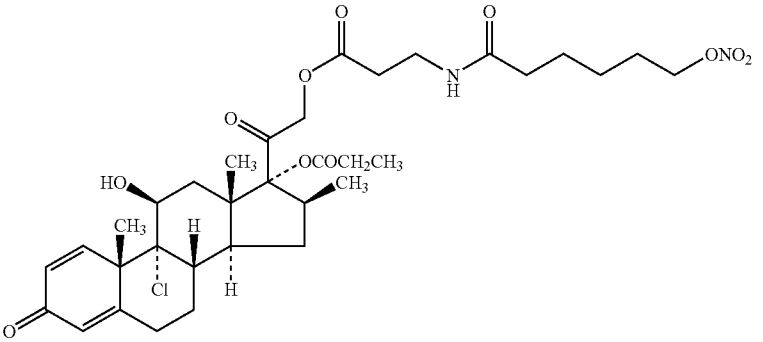

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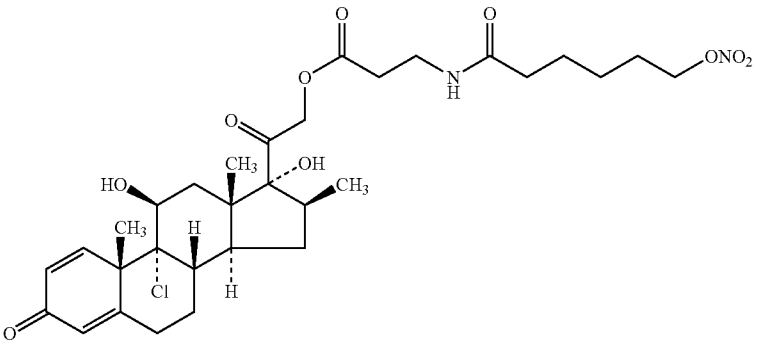


12. Nitric oxide releasing compounds according to claim **1** wherein the respiratory diseases comprise asthma, chronic obstructive pulmonary diseases, Acute Respiratory distress syndrome, allergic rhinitis and respiratory tract diseases associated with inflammation.

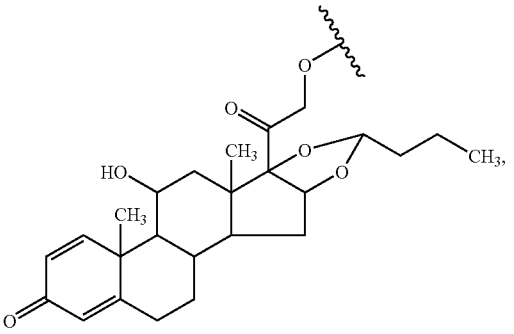
13. Nitric oxide releasing compounds of general formula (I)

$$R\text{-}(Z)_a\text{-}R_x \quad (I)$$

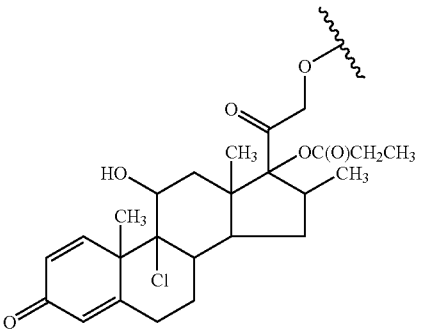
and pharmaceutically acceptable salts or stereoisomers thereof

wherein R is a corticosteroid residue selected from:

(II)



(IV)



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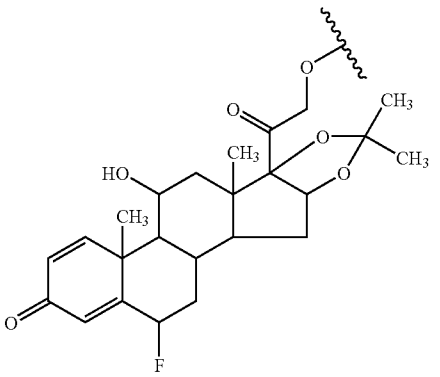
(V)



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 branched C_1-C_4 alkyl, preferably R' is H or —CH_3;

R_X is a radical selected from the Following meanings:

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}

(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)

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

wherein:

R^1 is selected from:

A1) H, —CH_3, isopropyl, isobutyl, sec-butyl, tert-butyl, methylthio-$(CH_2)_2$—, phenyl, benzyl, C_6H_5—CH_2—CH_2—,

2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent

of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, $C6H_5CO$—,

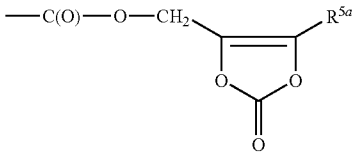
2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 3,4-difluorobenzyl, 2-pyrrolidyl, 3-triptophanyl-CH_2—, 3-benzothienyl-C_1H_2—, 4-imidazolyl-CH_2—, 9-anthranyl-CH_2—, cyclohexyl, cyclohexyl-CH_2—, cyclohexyl-$(CH_2)_2$—, cyclopentyl-CH_2—, $(C_6H_5)_2CH$—, 4-$B(OH)_2$-benzyl, 4-quinolyl-CH_2—, 3-quinolyl-CH_2—, 2-quinolyl-CH_2—,

2-quinoxalyl-CH_2—, 2-furyl-CH_2—, 1-naphtyl-CH_2—, 2-naphtyl-CH_2—, 2-pyridyl-CH_2—, 3-pyridyl-CH_2—, 4-pyridyl-CH_2—,

2-thienyl-CH_2—, 3-thienyl-CH_2—, C_6H_4—CH═CH—CH_2—, CH_2═CH—CH_2—, CH≡CH—CH_2—, NH_2—CO—CH_2—, NH_2—CO—$(CH_2)_2$—, NH_2(═NH)NH—$(CH_2)_3$—, P(═O)$(OCH_3)_2$,

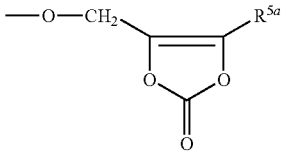
A2) —CH_2—SH, —CH_2—OH, —$CH(CH_3)$—OH, —CH_2[(C_6H_4)-(4-OH)], —CH_2—[(C_6H_2)-(3,5-diiodo)-(4-OH)], —CH_2— [(C_6H_3)-(3-nitro)-(4-OH)],

A3) —CH_2—NHR", —$(CH_2)_2$—NHR", —$(CH_2)_3$—NHR", —$(CH_2)_4$—NHR", wherein R" is H, —C(O)CH_3 or



wherein R^{5a} is H or a linear or branched C_1-C_{10} alkyl chain,

A4) —CH_2—C(O)R'", —$(CH_2)_2$—C(O)R'", —$(CH_2)_4$—C(O)R'" wherein R'" is —OR^{5a} or



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

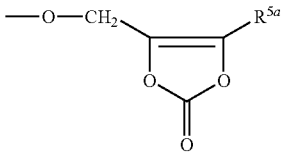
R^{1a} is selected from,

A5) —CH_2—S—, —CH_2—O—, —$CH(CH_3)$—O—, —CH_2[(C_6H_4)-(4-O)—], —CH_2-[(3,5-diiodo)-(C_6H_2)-(4-O)—], —CH_2-[(3-nitro)-(C_6H_3)-(4-O)—], preferably R^{1a} is —CH_2—O—,

A6) —CH_2—NH—, —$(CH_2)_2$—NH—, —$(CH_2)_3$—NH—, —$(CH_2)_4$—NH—,

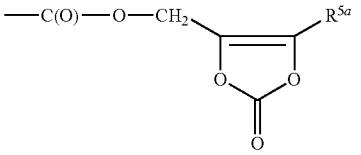
A7) —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—;

R^{3a} is selected from H, —R^{5a} or



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

R^{4a} is selected from H or $C(O)CH_3$ 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—, [-(4-O)-(3,5-diiodo)-(C_6H_2)]—CH_2—, [-(4-O)-(3-nitro)-(C_6H_3)]—H_2—,

A9) —HN—CH_2—, —HN—$(CH_2)_2$—, —HN—$(CH_2)_3$—, —HN—$(CH_2)_4$—,

A10) —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—;

T is selected from —C—, —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 —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'— 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,

B)

(b1) —HN—$CH(R^2)$—CH_2C(O)-(T-Y—ONO_2)

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

(b3) —HN—$CH(R_a$-T"-Y—$ONO_2)$—C—H_2COOR^{3a}

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

(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) —HN—$CH(R^{2a}$-T"-Y'—$ONO_2)$—CH_2—C(O)-(T-Y—ONO_2)

(b8) —C(O)—CH_2—$CH(R^{2a}$-T"-Y'—$ONO_2)$—NH-(T"-Y—ONO_2)

(b9) —R^{2b}—CH(NH-T'-Y'—ONO_2)—CH_2C(O)-(T-Y—ONO_2)

(b10) —R^{2b}—$CH(CH_2$C(O)-T-Y'—$ONO_2)$—NH-(T'-Y—ONO_2)

wherein

R^2 is selected from

B1) H, —CH_3, CF_3, isopropyl, isobutyl, sec-butyl, methylthio-$(CH_2)_2$—, phenyl, benzyl, 3-triptophanyl-CH_2—, NH_2—C(O)—CH_2—, NH_2—C(O)—$(CH_2)_2$—, NH_2(═NH)NH—$(CH_2)_3$—, tBuO—$CH(CH_3)$—, benzyl-O—CH_2—, 4-terbutoxy-benzyl, 4-phenylbenzyl,

B2) —CH_2—SH, —CH_2—OH, —$CH(CH_3)$—OH, —CH_2—[(C_6H_4)-(4-OH)], CH_2—[(C_6H_2)-(3,5-diiodo)-(4-OH)], —CH_2—[(C_6H_3)-(3-nitro)-(4-OH)],

B3) —CH_2—NHR", —$(CH_2)_2$—NHR", —$(CH_2)_3$—NHR", —$(CH_2)_4$—NHR", wherein R" is as above defined,

B4) —CH_2—C(O)—R'", —$(CH_2)_2$—C(O)—R'", —$(CH_2)_4$—C(O)—R'" wherein R'" is as above defined, preferably R^2 is —CH_2—C(O)—R'",

R^{2a} is selected from:

B5) —CH_2—S—, —CH_2—O—, —$CH(CH_3)$—O— or —CH_2—[(C_6H_4)-(4-O)—], —CH_2-[(3,5-diiodo)-(C_6H_2)-(4-O)—], —CH_2-[(3-nitro)-(C_6H_3)-(4-O)—];

B6) —CH_2—NH—, —$(CH_2)_2$—NH—, —$(CH_2)_3$—NH, —$(CH_2)_4$—NH—,

B7) —CH_2—C(O)—, —$(CH_2)_2$—C(O), —$(CH_2)_4$—C(O)—,

R^{2b} is selected from:

B8) —S—CH_2—, —O—$CH(CH_3)$—, —O—CH_2—, [-(4-O)-(C_6H_4)]—CH_2—, [-(4-O)-(3,5-diiodo)-(C_6H_2)]—CH_2—, [-(4-O)-(3-nitro)-(C_6H_3)]—CH_2,

B9) —HN—CH_2—, —HN—$(CH_2)_2$—, —HN—$(CH_2)_3$—, —HN—$(CH_2)_4$—,

B10) —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—,

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,

C)

(c1) —HN—$(CH_2)_b$—C(O)-(T-Y—ONO_2);

(c2) —C(O)—$(CH_2)_b$—NH-(T'-Y—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,

D)

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

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

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

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

(d5) —$R^{12'}$—$CH(NHR^{4a})$—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)

(d9) —R^{12b}—CH(NH-T'-Y'—ONO_2)—CH_2O-(T'"-Y—ONO_2)

(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,

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-$(CH_2)_2$—, benzyl, 3-triptophanyl-CH_2—, 4-imidazolyl-CH_2—, 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 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)—], —CH_2-[3,5-diiodo-$(C_{61}H_2)$-(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—$CH(CH_3)_X$—, [(4-O)—(C_6H_4)]—CH_2—, [-(4-O)-(3,5-diiodo)-(C_6H_2)]—CH_2, [-(4-O)-(3-nitro)-(C_6H_3)]—CH_2—,

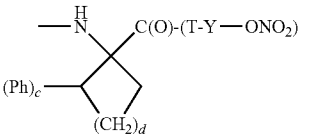
D9) —HN—CH_2—, —HN—$(CH_2)_2$— —HN—$(CH_2)_3$—, —HN—$(CH_2)_4$—,

D10) —C(O)—CH_2—, —C(O)—$(CH_2)_2$, —C(O)—$(CH_2)_4$—,

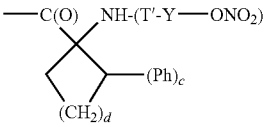
R^{4a} is as above defined,

E)

(e1)



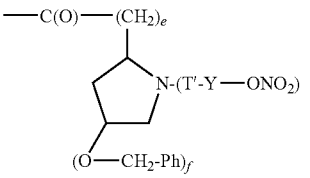
(e2)



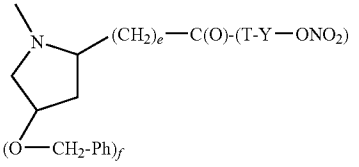
wherein c is equal to 0 or 1, d is an integer from 0 to 3 with the proviso that c is 0 or 1 when d is 0 and c is 0 when d is 1, 2 or 3, T and T' are as above defined and Y is as below defined;

F)

(f1)



(f2)



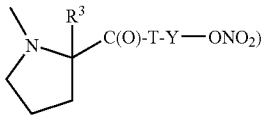
(XI)

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,

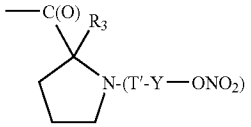
T and T' are as above defined and Y is as below reported;

G)

(g1)



(g2)

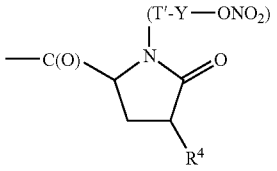


wherein R^3 is H, CH_3, propyl, $(C_6H_5)_2CH$—, 1-naphtyl-CH_2—, benzyl, allyl, 2-bromobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-fluorobenzyl, 4-bromobenzyl, 4-methylbenzyl,

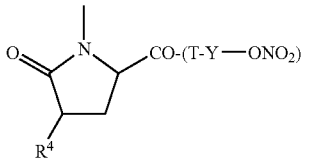
T and T' are as above defined and Y is as below defined,

H)

(h1)



(h2)

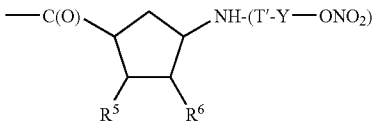


wherein R^4 is H, benzyl, 4-bromobenzyl, 2-bromobenzyl,

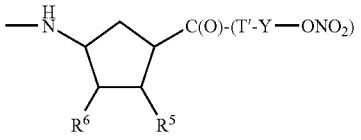
T and T' are as above defined and Y is as below defined;

I)

(i1)



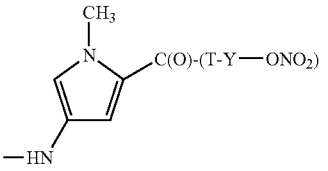
(i2)



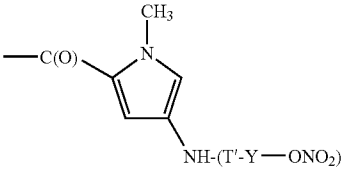
wherein R^5 is H, R^6 is H, or R^5 and R^6 when taken together are a double bond, T and T' are as above defined and Y is as below reported;

L)

(l1)



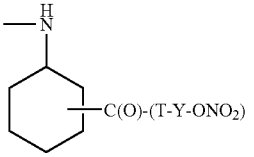
(l2)



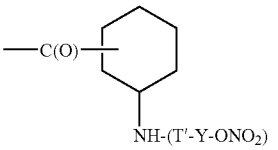
wherein T and T' are as above defined and Y is as below reported;

M)

(m1)



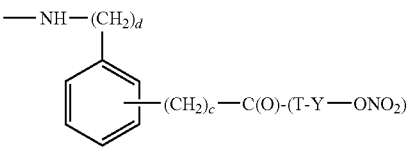
(m2)



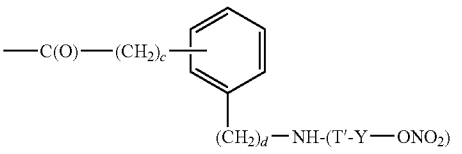
wherein T and T' are as above defined and Y is as below reported;

N)

(n1)



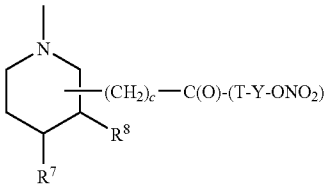
(n2)



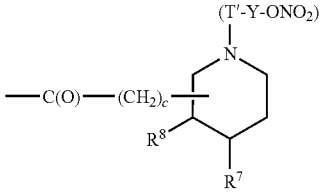
wherein c is as above defined, d is equal to 0 or 1, T and T' are as above defined and Y is as below reported;

O)

(o1)



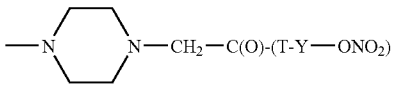
(o2)



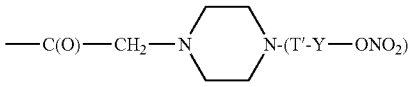
wherein R^7 is H, R^8 is H, or R^7 and R^8 when taken together are a double bond, c is as above defined, T and T' are as above defined and Y is as below reported;

P)

(p1)



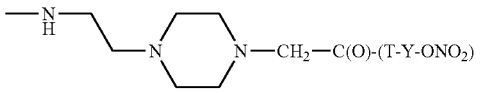
(p2)



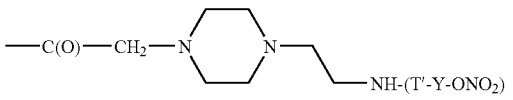
wherein T and T' are as above defined and Y is as below reported;

Q)

(q1)



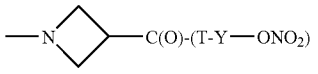
(q2)



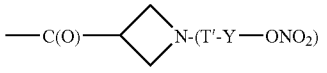
wherein T and T' are as above defined and Y is as below reported;

R)

(r1)



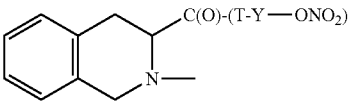
(r2)



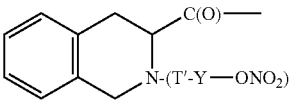
wherein T and T' are as above defined and Y is as below reported;

S)

(s1)



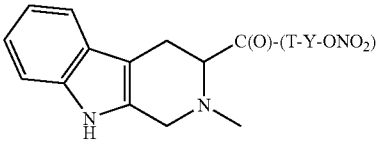
(s2)



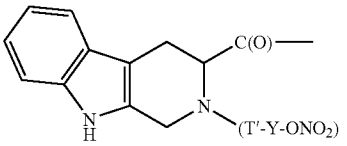
wherein T and T' are as above defined and Y is as below reported;

T)

(t1)



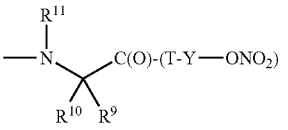
(t2)



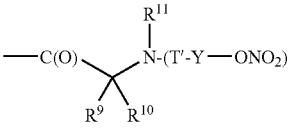
wherein T and T' are as above defined and Y is as below reported;

U)

(u1)



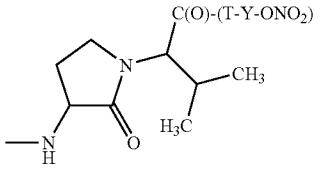
(u2)



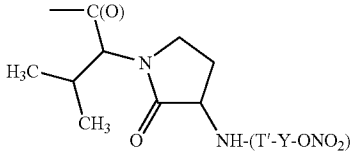
wherein R^9 and R^{10} are H, CH_3, R^{11} is CH_3 or 4-piperidinyl with the proviso that R^9 and R^{10} are H when R^{11} is 4-piperidinyl and R^9 and R^{10} are CH_3 when R^{11} is CH_3, T and T' are as above defined and Y is as below reported;

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);

(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:

(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 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)

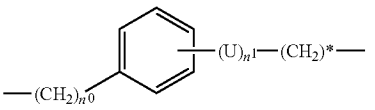
straight or branched C_1-C_{20} alkylene,

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} alkyl)-ONO_2 or —O(C_1-C_{10} 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

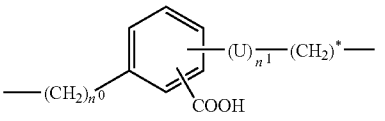
n^0 is an integer from 0 to 20;

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

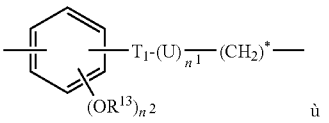
n^0 is an integer from 0 to 20;

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)

d)



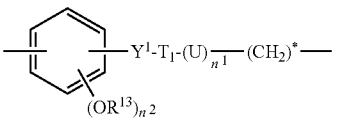
wherein:

n 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,

R^{13} is H or CH_3,

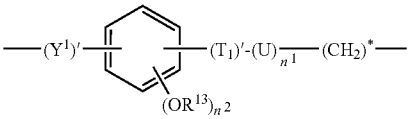
Y^1 is —CH_2—CH_2— or —CH═CH—$(CH_2)_{n^{2'}}$—, wherein $n^{2'}$ is 0 or 1, preferably Y^1 is —CH═CH—$(CH_2)_{n^{2'}}$ and $n^{2'}$ is 0,

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')



e')

wherein:

n^2 is an integer from 0 to 2,

R^{13} is H or CH_3,

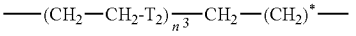
Y^1 is —CH_2—CH_2— or —$(CH_2)_{n^{2'}}$—CH═CH—, wherein $n^{2'}$ is 0 or 1,

$(T_1)'$—O—C(O)—;

n^1 is 0 or 1,

U is a linear or branched C_1-C_{20} alkylene optionally substituted with a —ONO_2 group;

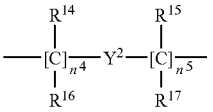
f)



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'—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,

R^{14}, R^{15}, R^{16}, R^{17} are the same or different, and are H or straight or branched C_1-C_4 alkyl,

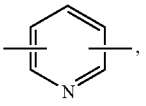
wherein the —ONO_2 group is linked to

wherein n^5 is as defined above;

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

and is selected from the group consisting of:

(Y1)



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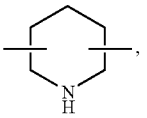
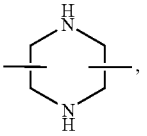
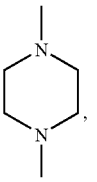
(Y2)



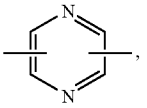
(Y3)



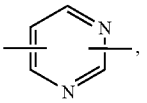
(Y4)



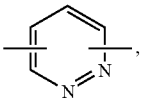
(Y5)



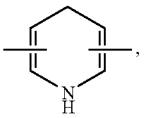
(Y6)



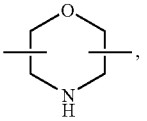
(Y7)



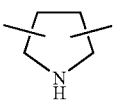
(Y8)



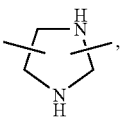
(Y9)



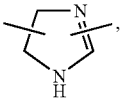
(Y10)



(Y11)



(Y12)



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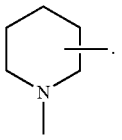
(Y13)



14. The nitric oxide releasing compounds according to claim **13** wherein

a is 1 and Z is —C(O)—;

R_X is

(a1) —HN—CH(R^1)—C(O)-(T-Y—ONO_2)

wherein

R^1 of the group A1) is selected from H, isobutyl, benzyl, C_6H_5—CH_2—CH_2—, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, C_6H_5CO— or

R^1 of the group A2) is selected from —CH_2—OH, —CH(CH_3)—OH— or

—CH_2—[(C_6H_4)-(4-OH)], or

R^1 of the group A3) 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^1 of the group A4) 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 is —O—, —S—, —NR'—, —O—CH(R')—O—C(O)— wherein R' is H or a straight or branched C_1-C_4 alkyl,

Y is as below defined;

or R_X is

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

wherein

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 —(H_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)—,

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

T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} 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_1-C_4 alkyl, when R^{1a} is selected from the group A7),

Y' is as below defined;

or R_X 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)

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—$(CH_2)_4$—,

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

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,

T' is —C(O)— or —C(O)—X" wherein X" is —S— or —O—,

Y and Y' are as below defined;

or R_X is selected from:

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

wherein

R^{1a} of the group A5) is selected from —CH_2O—, —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)—;

T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} 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_1-C_4 alkyl, when R^{1a} 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_1-C_4 alkyl,

Y and Y' are as below defined;

or R_X is selected from:

(b1) —HN—CH(R^2)—CH_2C(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

—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 —(H_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 is —O—, —S—, —NR'—, —O—CH(R')—O—C(O)— wherein R' is H or a straight or branched C_1-C_4 alkyl,

Y is as below defined;

or R_X is selected from:

(d1) —HN—CH(R^{12})—CH_2—O-(T"-Y—ONO_2)

(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

R^{12} of the group D2) is selected from —CH_2—OH, —CH(CH_3)OH— or

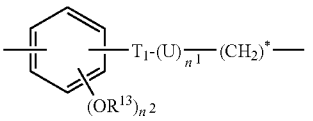
—CH_2—[(C_6H_4)-(4-OH)], or

R^{12} of the group D3) is selected from —CH_2—NHR", —$(CH_2)_2$—NHR",

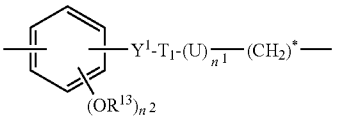
—$(CH_2)_3$—NHR", —$(CH_2)_4$—NHR" wherein R" is H, or

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—,
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
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)—, —(C112)$_2$—C(O)—, —(C H_2)$_4$—C(O)—,
R^{4a} is H or —$C(O)CH_3$,
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),
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),
T'" is selected from —C(O)— or —C(O)X" wherein X" is —S— or —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)
(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
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,
T' and T'" are each independently selected from —C(O)—, —C(O)—X", wherein X" is —S— or —O—,
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;

d)

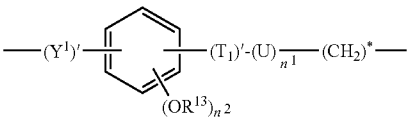


wherein:
n^2 is an integer from 0 to 2 R^{13} is H or CH_3, T_1 is —O—C(O)— or —C(O)O—,
n^1 is 1 and U is a linear C_1-C_{10} alkylene or U is a linear or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;
e)

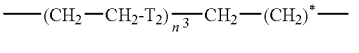


n^2 is 1, R^{13} is CH_3, Y^1 is —CH═CH—$(CH_2)_n{}^{2'}$— and $n^{2'}$ is 0,
T_1 is —C(O)O— and U is a linear C_1-C_{10} alkylene;

e'



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)



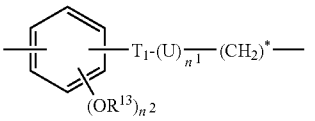
wherein T_2 is —O— or —S—, —NH—,
n^3 is 1 or 2,
when Y and Y' are selected from d), e), e') or f), the —ONO_2 group of -(T-Y—ONO_2), -(T'-Y—ONO_2), -(T"-Y'—ONO_2), (T'-Y'—ONO_2), -(T'"-Y—ONO_2) and -(T'"-Y'—ONO_2) is linked to the —(CH_2)*— group.

15. The nitric oxide releasing compounds according to claim **14** wherein
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_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.

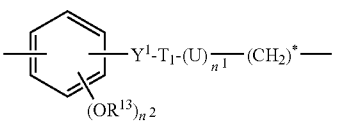
16. The nitric oxide releasing compounds according to claim **13** wherein a is 0 and
R_X is
(a2) —C(O)—CH(R^1)—NH-(T'Y—ONO_2)
wherein
R^1 of the group A1) is selected from H, isobutyl, benzyl, C_6H_5—CH_2—CH_2—, 2-monosubstituted benzyl, or 3-monosubstituted benzyl or 4-monosubstituted benzyl wherein the substituent of the benzyl is selected from —F, —Cl, I, —NO_2, —CF_3, —CH_3, CN, C_6H_5CO—,
R^1 of the group A2) is selected from —CH_2—OH, —CH(CH_3)OH— or
—CH_2—[(C_6H_4)-(4-OH)], or
R^1 of the group A3) 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^1 of the group A4) is selected from —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' is —C(O)—, —C(O)—X" wherein X" is —S— or —O—,
Y is as below defined;
or R_X is
(a4) —C(O)—CH(R_{1a}-T"-Y'—ONO_2)—NHR^{4a}
wherein 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 selected from —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—;
R^{4a} is H or —C(O)CH_3,
T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O— when R^{1a} 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_3 when R^{1a} is selected from the group A7)$_5$
Y' is as below defined;
or R_X 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)
wherein
R^{1b} of the group A10) is selected from —C(O)—CH_2—, —C(O)—$(CH_2)_2$—, —C(O)—$(CH_2)_4$—,
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'— or —O—CH(R')—O—C(O)— wherein R' is H or —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_X is
(a8) —C(O)—CH(R_a-T"-Y'—ONO_2)—NH-(T'-Y—ONO_2)
wherein
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 selected from —CH_2—C(O)—, —$(CH_2)_2$—C(O)—, —$(CH_2)_4$—C(O)—,
T" is —C(O)— or —C(O)—X" wherein X" is —S— or —O—, when R^{1a} is selected from the group A5) or A6),
T" is —O—, —S—, —NR'— or —O—CH(R')—OC(O)— wherein R' is H or —CH_3, when R^{1a} 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_X is
(b2) —C(O)—CH_2—CH(R^2)—NH-(T'-Y—ONO_2)
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
a)
a straight or branched C_1-C_{10} alkylene,
a straight or branched $C_{1\text{-}10}$ alkylene substituted with a —ONO_2 group;
d)

d)



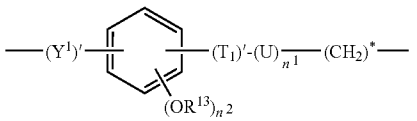
wherein:
n^2 is an integer from 0 to 2, R^{13} is H or CH_3, T_1 is —O—C(O)— or —C(O)O—,
n^1 is 1 and U is a linear C_1-C_{10} alkylene or U is a linear or branched C_1-C_{10} alkylene substituted with a —ONO_2 group;
e)

e)

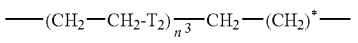


n^2 is 1, R^{13} is CH_3, Y^1 is —CH═CH—$(CH_2)_n$—^{2} and n^2 is 0,
T_1 is —C(O)O— and U is a linear C_1-C_{10} alkylene;

e')



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' 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)



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 $—ONO_2$ 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.

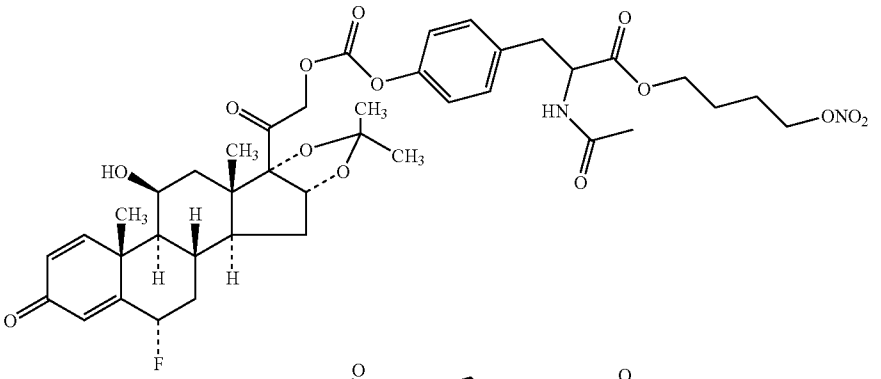
17. The nitric oxide releasing compounds according to claim **16** wherein
R_X is
(a2) —C(O)—CH(R^1)—NH-(T'-Y—ONO_2)
wherein
R^1 of the group A1) is H,
T' is —C(O)—,
Y is selected from
a)
a straight or branched C_1-C_{10} alkylene,
a straight or branched C_1-C_{10} alkylene substituted with a $—ONO_2$ group.

18. The nitric oxide releasing compounds of claim **16** wherein
R_X is selected from
(a5) —R^{1b}—CH(NHR^{4a})—C(O)-(T'-Y—ONO_2)
(a6) —R^{1b}—CH($COOR^3$NH-(T'-Y—ONO_2) or
(a9) —R^{1b}—CH(NH-T'-Y'—ONO_2)—C(O)-(T'-Y—ONO_2)
wherein
R^{1b} of the group A10) is —C(O)—CH_2—,
R^{3a} is H or a (C_1-C_5) 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_1-C_{10} alkylene,
a straight or branched C_1-C_{10} alkylene substituted with a $—ONO_2$ group.

19. The nitric oxide releasing compounds according to claim **16** wherein
R_X is
(b2) —C(O)—CH_2—CH(R^2)—NH-(T'-Y—ONO_2)
R^2 of the group B1) is H,
T' is —C(O)—,
Y is 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;

20. Nitric oxide releasing compounds according to claim **13**

(3)



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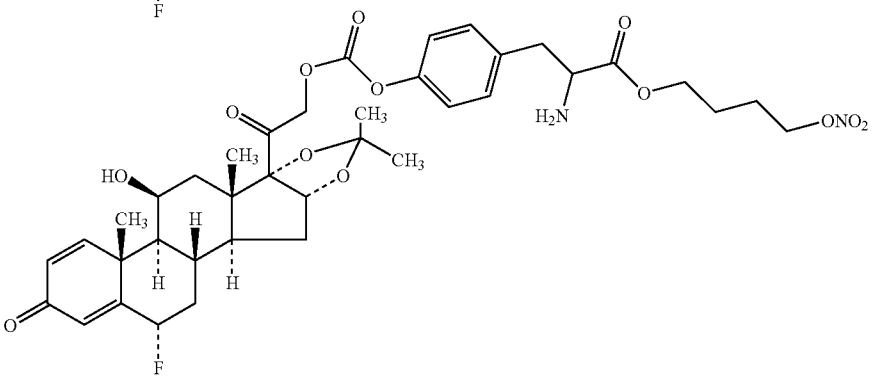

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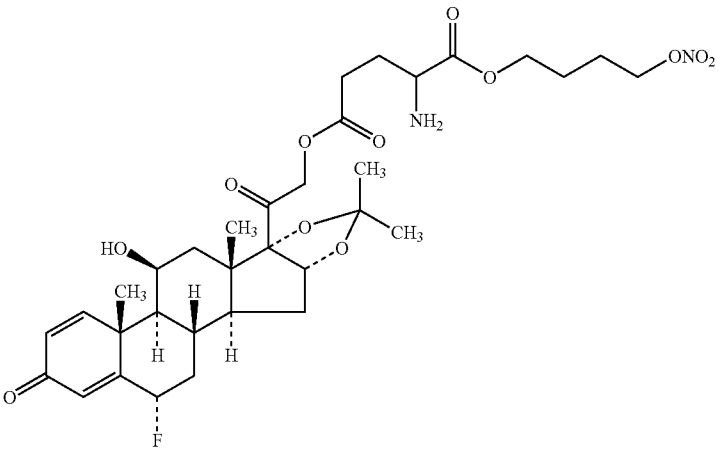

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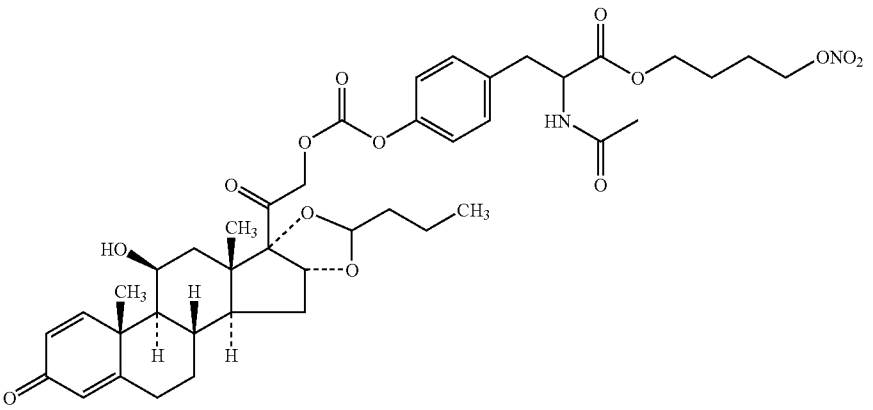

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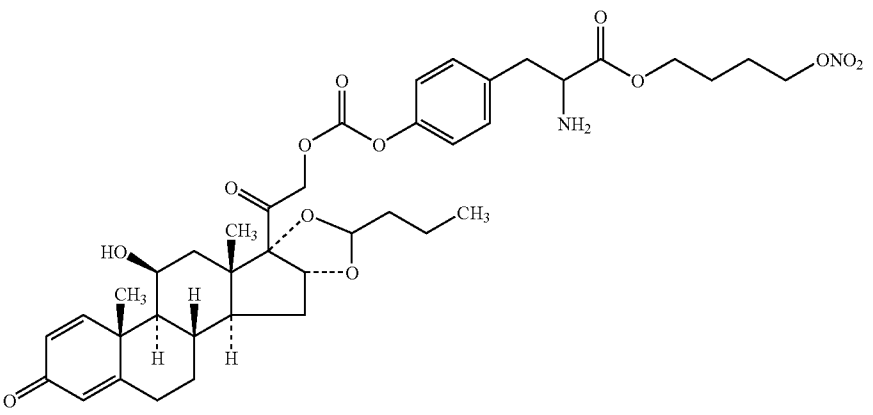

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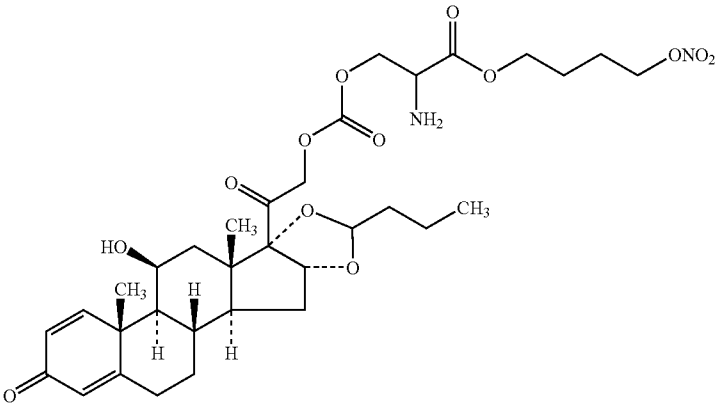

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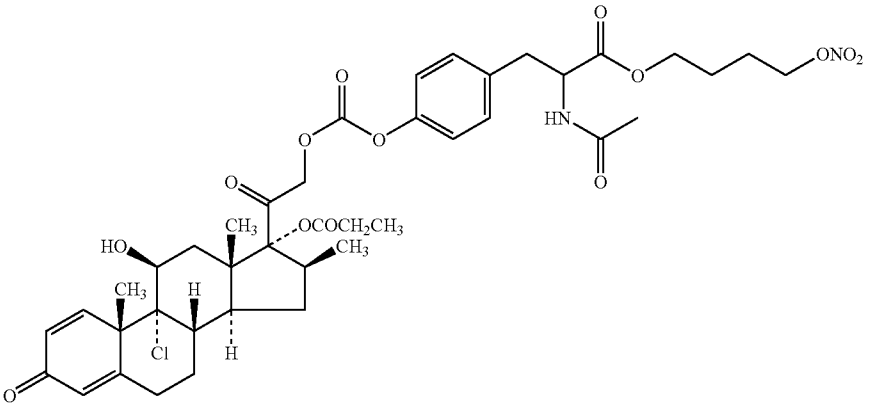

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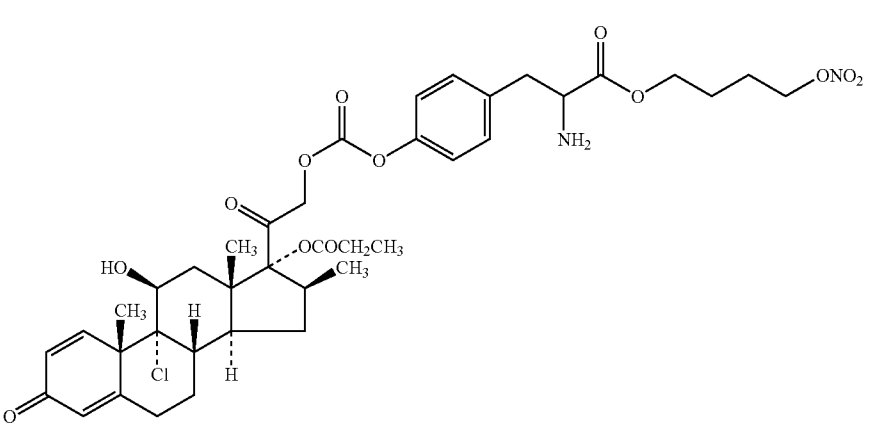

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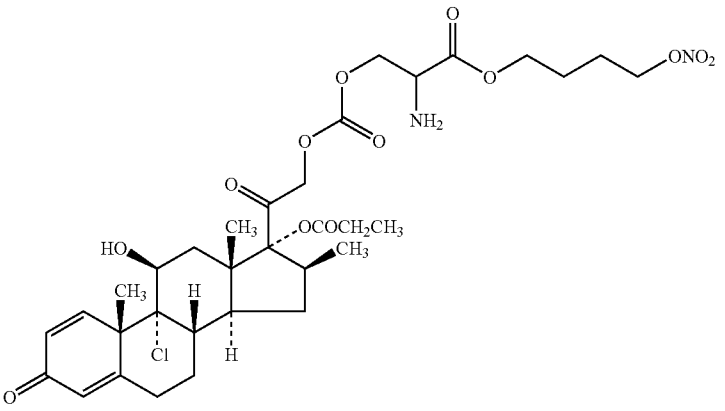
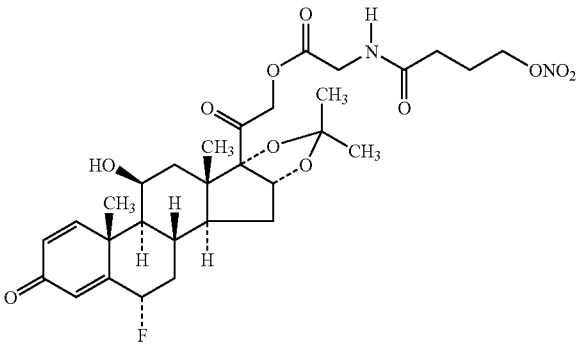


21. Nitric oxide releasing compounds according to claim **17**

(1)



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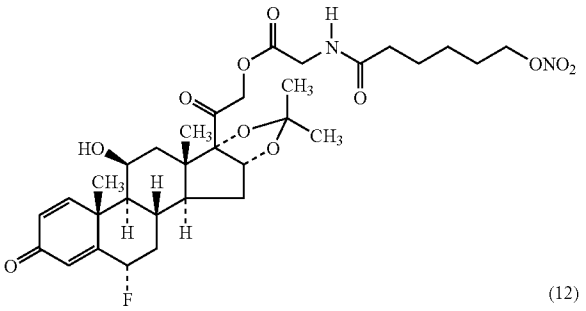

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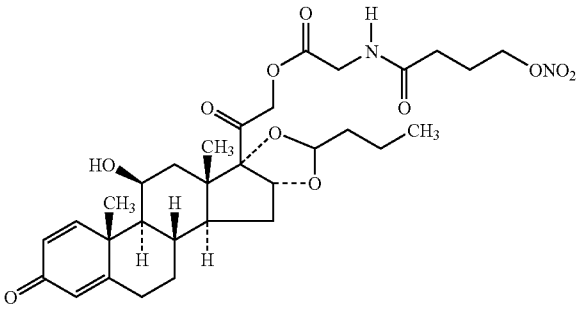

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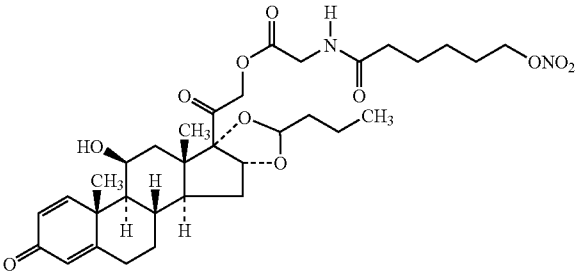
(13)



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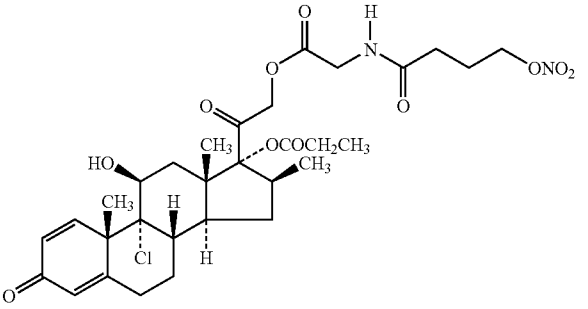

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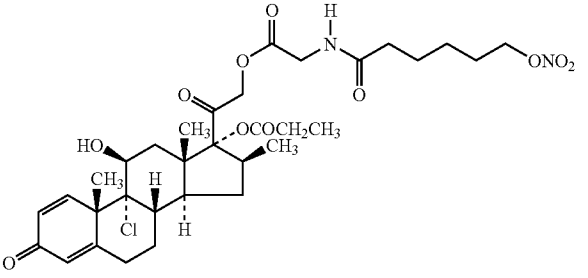
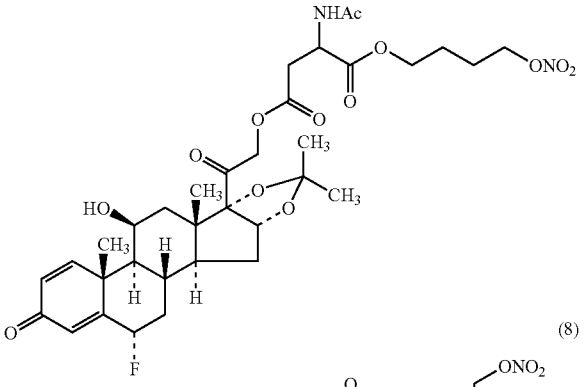


22. Nitric oxide releasing compounds according to claim **18**

(5)



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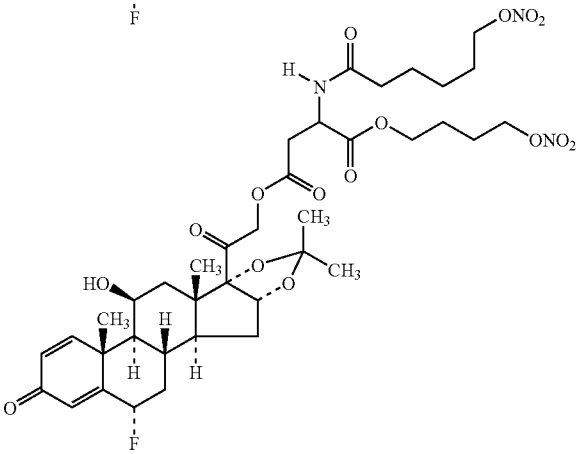

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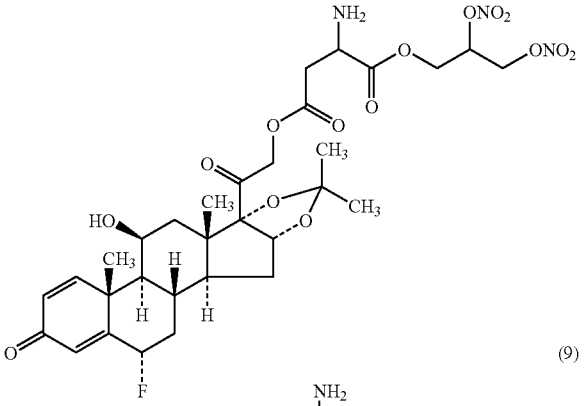

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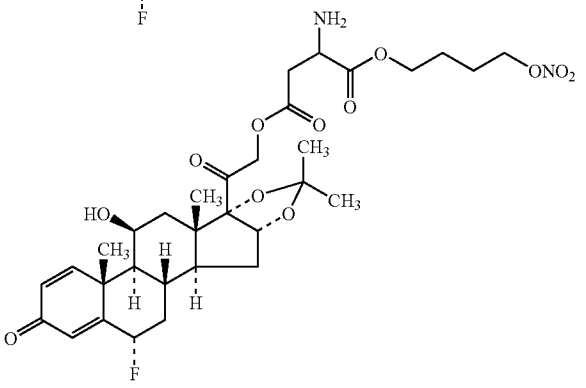

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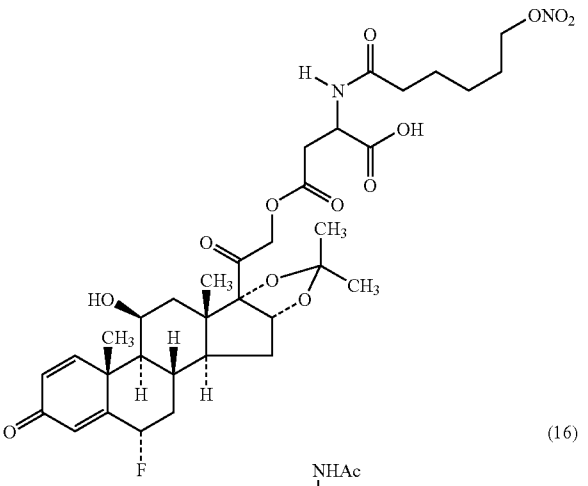

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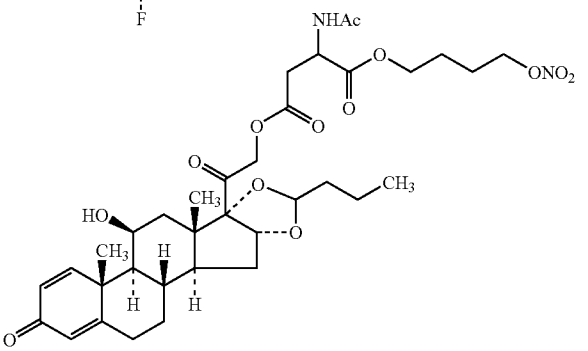

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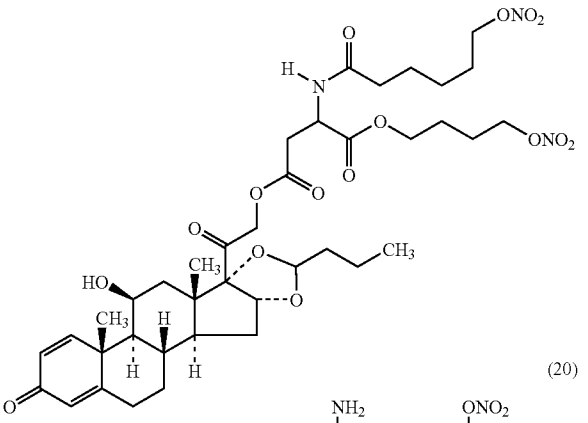

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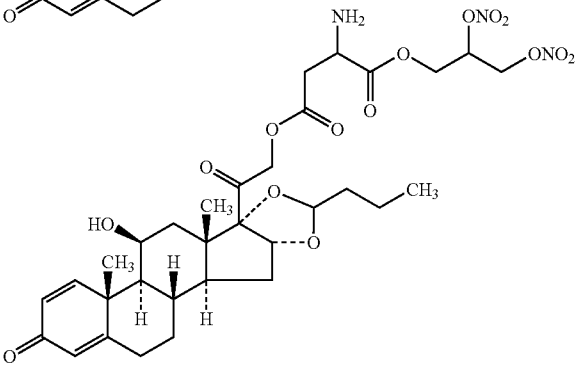

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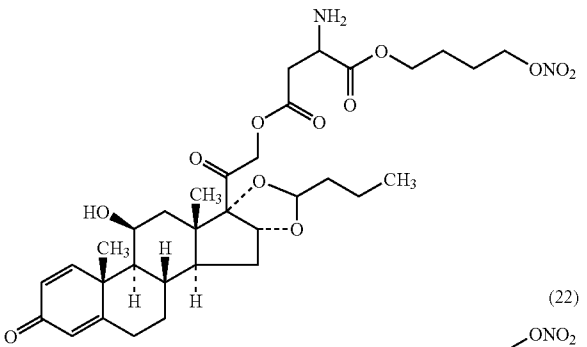

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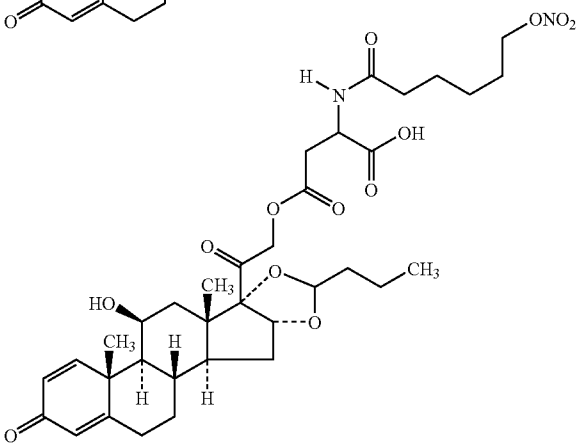

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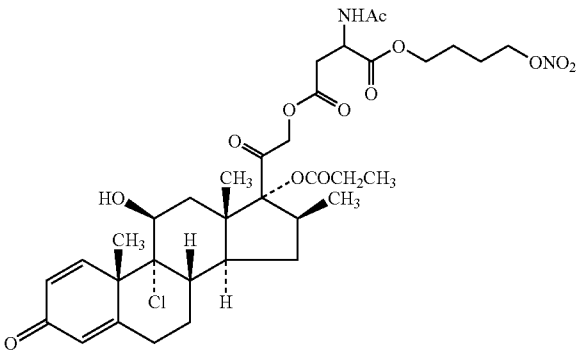

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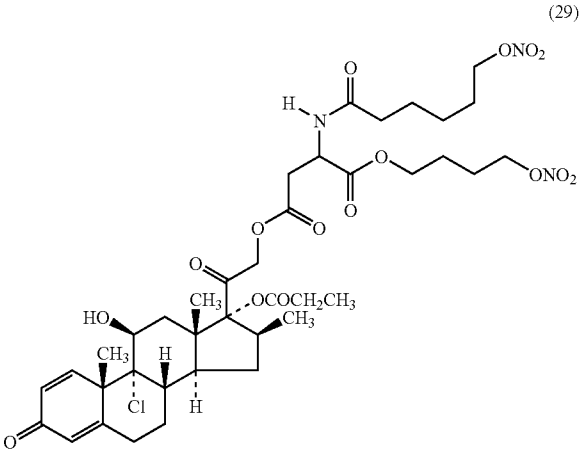

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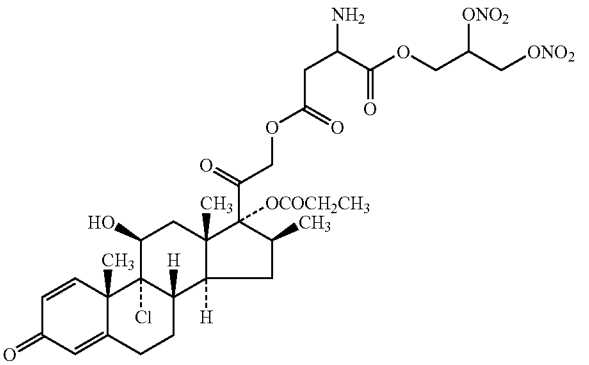

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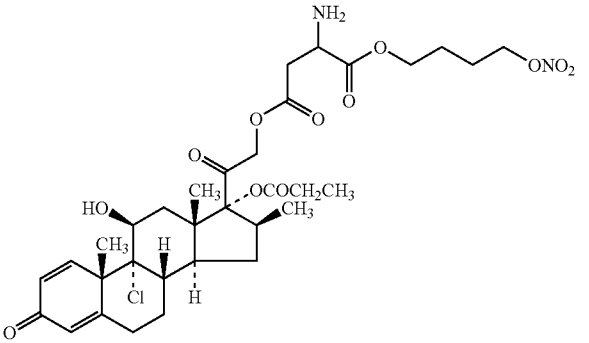

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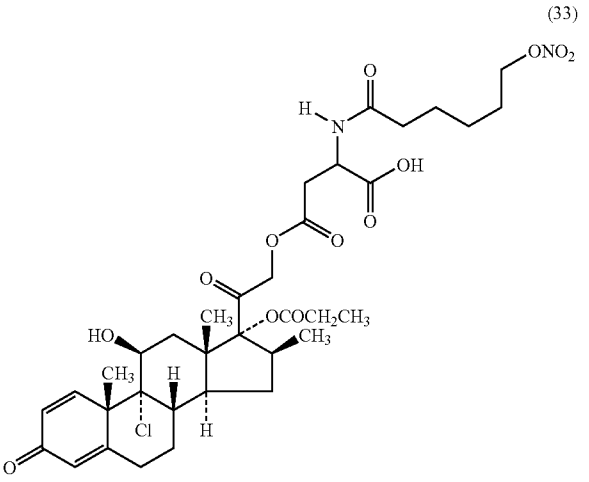
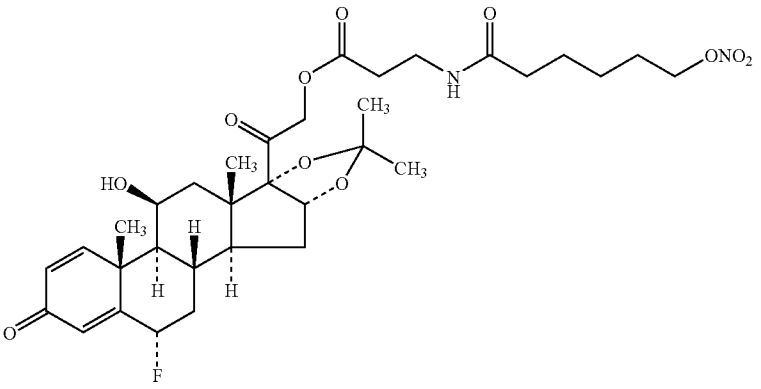


23. Nitric oxide releasing compounds according to claim **19**

(6)



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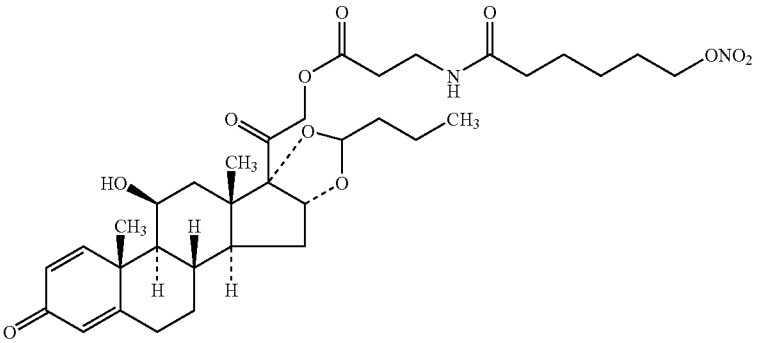

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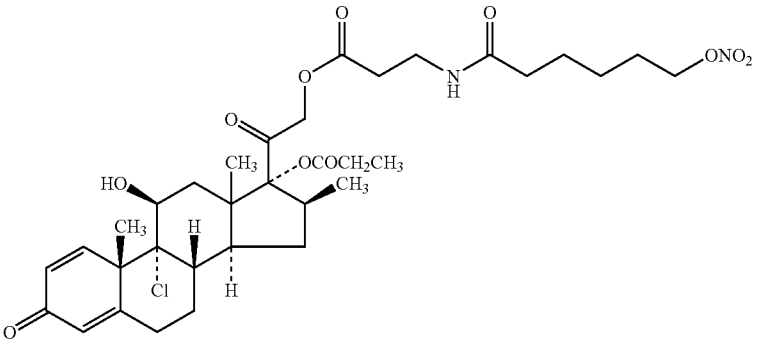

24. Nitric oxide releasing compounds according to claim **13** for use as medicament.

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, β_2-agonists, ephedrine or xanthines.

28. The composition according to claim **25** wherein the nitric oxide releasing compound and the bronchodilator are administered simultaneously.

29. The composition according to claim **25** wherein the nitric oxide releasing compound and the bronchodilator are administered sequentially.

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 claim **25** for use in 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 rhinitis and respiratory tract diseases associated with inflammation.

33. The composition according to claim **25** pharmaceutical acceptable excipient.

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