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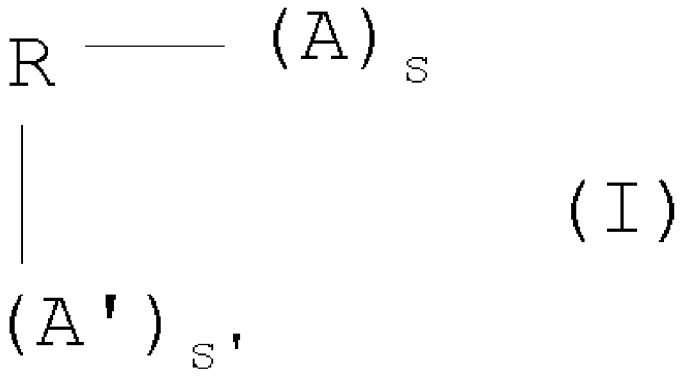

(57) Abstract: New angiotensin II receptor blocker nitroderivatives of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof: and their use for treating cardiovascular, renal and chronic liver diseases, inflammatory processes and metabolic syndromes.

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TITLE OF THE INVENTION

"NEW ANGIOTENSIN II RECEPTOR BLOCKER DERIVATIVES"

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The present invention relates to new Angiotensin II Receptor Blocker (ARB) derivatives. More particularly, the present invention relates to new ARB nitroderivatives, pharmaceutical compositions containing them and their use for the treatment of cardiovascular, renal and chronic liver diseases, inflammatory processes and metabolic syndromes.

With the angiotensin II receptor blockers a class of compounds is intended, comprising as main components Losartan, EXP3174, Candesartan, Telmisartan, Valsartan, Eprosartan, Irbesartan and Olmesartan.

ARBs are approved for the treatment of hypertension, post-myocardial infarction and heart failure, the antihypertensive activity is due mainly to selective blockade of AT_1 receptors and the consequent reduced pressor effect of angiotensin II. Angiotensin II stimulates the synthesis and secretion of aldosterone and raises blood pressure via a potent direct vasoconstrictor effect.

Now, it has been reported that angiotensin II receptor blockers have side-effects such as for example hypotension, hyperkalaemia, myalgia, respiratory-tract disorders, renal disorders, back pain, gastrointestinal disturbances, fatigue, and neutropenia (Martindale, Thirty-third edition, p. 921).

WO 2005/011646 describes angiotensin II receptor blocker nitroderivatives, pharmaceutical compositions containing them and their use for the treatment of cardiovascular, renal and chronic liver diseases,

inflammatory processes and metabolic syndromes. The publication describes a variety of angiotensin II receptor blocker compounds each of which are covalently linked to a bivalent radical capable to release nitric oxide. Specific examples include angiotensin II receptor blockers with one or two nitric oxide-releasing moieties directly linked to the angiotensin II receptor blocker compound through esters or carbonates.

WO 2005/023182 describes nitrosated and nitrosylated cardiovascular compounds, and compositions comprising at least one nitrosated and nitrosylated cardiovascular compound and optionally at least one nitric oxide donor. The cardiovascular compound which is nitrosated or nitrosylated may be an aldosterone antagonist, an angiotensin II receptor antagonist, a calcium channel blocker, an endothelin antagonist, a hydralazine compound, a neutral endopeptidase inhibitor or a renin inhibitor. The nitric oxide donor may be selected from S-nitrosothiols, nitrites, nitrates, N-oxo-N-nitrosamines, furoxans, and sydnonimines.

WO 2006/093864 discloses novel cardiovascular compounds comprising at least one nitric oxide enhancing group, and pharmaceutically acceptable salts thereof. The cardiovascular compounds can be, for example, aldosterone antagonists, angiotensin II antagonists, endothelin antagonists, hydralazine compounds, neutral endopeptidase inhibitors and renin inhibitors. The nitric oxide enhancing groups are nitroxides and/or heterocyclic nitric oxide donor groups such as furoxans, sydnonimines, oxatriazole-5-ones and/or oxatriazole-5-imines.

WO 2007/019448 describes novel nitric oxide enhancing angiotensin II antagonist compounds comprising at least one nitric oxide enhancing group directly or indirectly linked

to the angiotensin II antagonist compound through one or more sites such as carbon, oxygen and/or nitrogen via a bond or moiety that cannot be hydrolyzed.

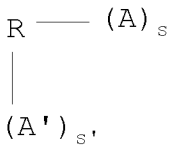
It was now object of the present invention to provide new derivatives of ARBs containing at least a nitric oxide-releasing moiety linked to the angiotensin II receptor blocker through an amino acid bridge.

The Applicant has surprisingly and unexpectedly found a specific class of nitric oxide-releasing ARBs with good pharmacological profile and oral bioavailability, associated with prolonged duration of action.

In particular, it has been recognized that the angiotensin II receptor blocker nitroderivatives of the present invention exhibit a strong anti-inflammatory, antithrombotic and antiplatelet activity and can be furthermore employed for treating or preventing hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, liver fibrosis, portal hypertension, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post-angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, metabolic syndromes and other diseases known to be related to the renin-angiotensin system.

Object of the present invention are, therefore, new angiotensin II receptor blocker nitroderivatives of general

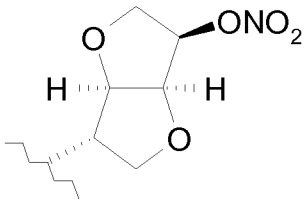
formula (I) and pharmaceutically acceptable salts or stereoisomers thereof:



(I)

wherein:

A and A' are independently selected from the group consisting of -(Y-ONO2), -(Y'-ONO2) or (1a)

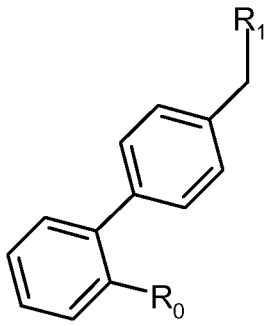


(1a)

s is 1 or 2;

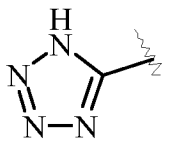
s' is 0, 1 or 2;

R is selected from the following residues of formula (II) or (III):



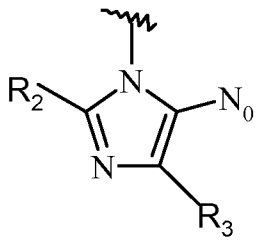
(II)

wherein:

R_0 is the group (IV) 

or N_0 which is a moiety capable to bind the groups A and A' as defined hereinafter;

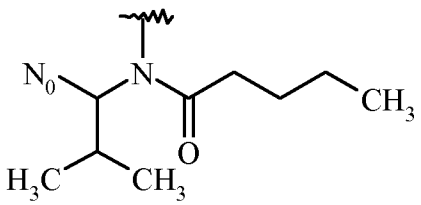
R_1 is selected from the groups (Va-Ve):



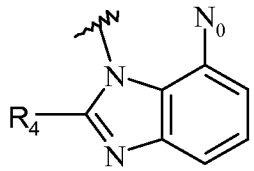
(Va)

wherein R_2 is C_1-C_5 linear or branched alkyl, preferably n-propyl or n-butyl;

R_3 is an halogen atom such as Cl, Br, I, or a perfluorurated C_1-C_4 alkyl chain, preferably C_2F_5, or the group $-C(CH_3)_2OH$;

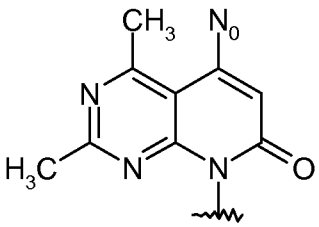


(Vb) ;



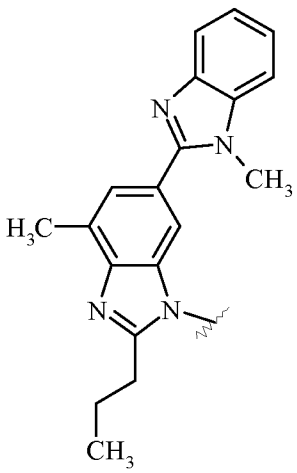
(Vc)

wherein R_4 is n-Bu or –OEt;



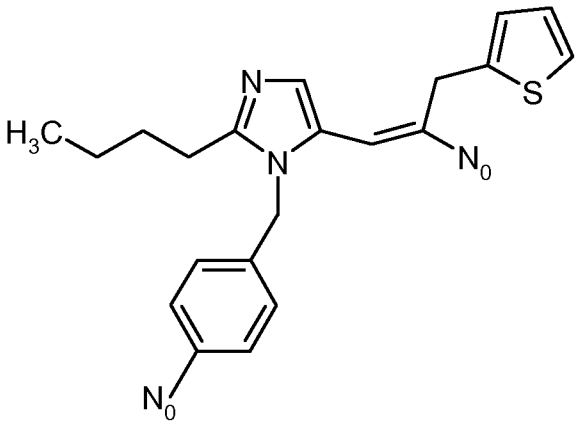
(Vd)

or



(Ve) ;

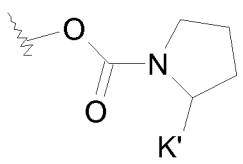
or R is the residue of formula (III):



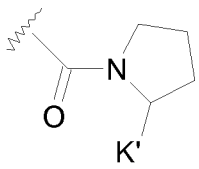
(III)

wherein N_0 is a moiety capable to bind the groups A and A', having one of the following meanings:

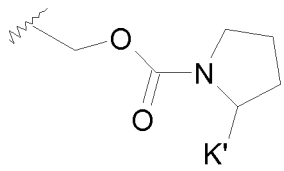
1)



(VIa)



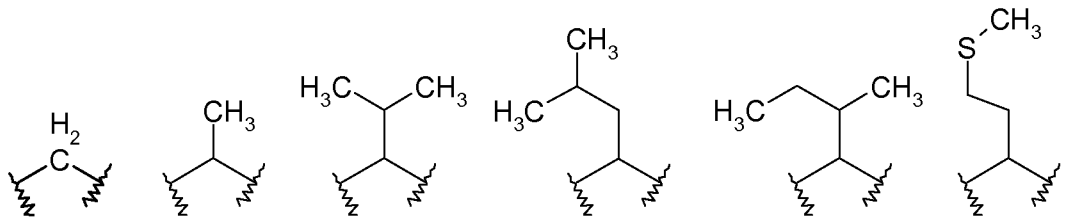
(VIb)



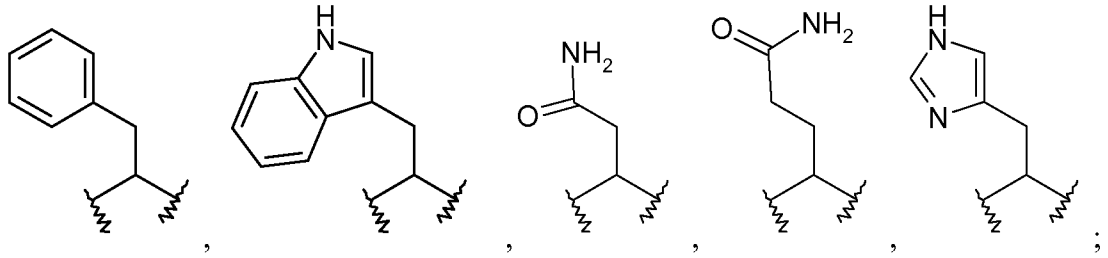
(VIc)

wherein K' is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K' is bound to the group A wherein A is $-(Y-ONO_2)$ or (1a), with the proviso that when A is (1a), then K' is -COO- or $-CH_2-OCOO-$;

2) -OCO-NH-J-K', -CO-NH-J-K' or $-CH_2-O-CO-NH-J-K'$ wherein J is selected among (VIIa-VIIk):



(VIIa) (VIIb) (VIIc) (VIId) (VIIe) (VIIf)

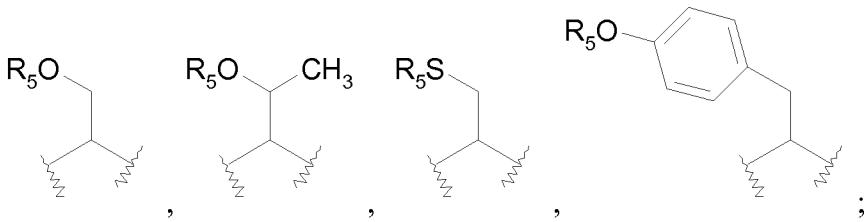


(VIIg) (VIIh) (VIIi) (VIIj) (VIIk)

wherein K' is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K' is bound to the group A wherein A is $-(Y-ONO_2)$ or (1a), with the proviso that when A is (1a), then K' is -COO- or $-CH_2-OCOO-$;

3) -O-CO-NH-K-K*, $-CH_2-O-CO-NH-K-K^*$ or -CO-NH-K-K* wherein K is selected among K_1, K_2 or K_3 wherein:

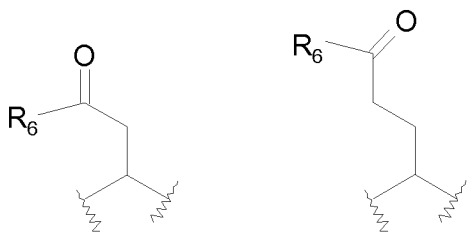
K_1 is selected among (VIIIa-VIIId):



(VIIIa) (VIIIb) (VIIIc) (VIIId)

wherein R_5 is H or a group selected from -CO-, -COO- or -CONH- capable to bind a group A' wherein A' is $-(Y'-ONO_2)$;

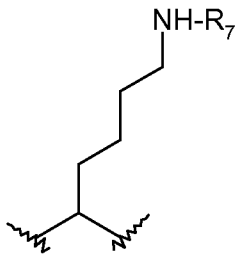
K_2 is selected among (VIIIe-VIIIf):



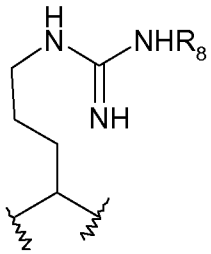
(VIIIe) (VIIIf)

wherein R_6 is -OH or a group selected from -O- or -NH capable to bind a group A', with the proviso that when A' is (1a), then R_6 is -O-;

K_3 is selected among (VIIIg-VIIIh):



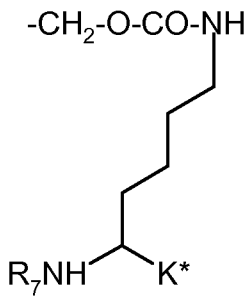
(VIIIg)



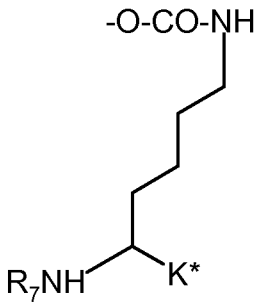
(VIIIh)

wherein R_7 and R_8 are H or a group selected from –CO- or -COO- capable to bind a group A' wherein A' is $-(Y'-ONO_2)$; K* is equal to K' as above defined or -COOH and when K* is equal to K' is bound to the group A, with the proviso that when A is (1a), then K' is –COO- or $-CH_2-OCOO-$;

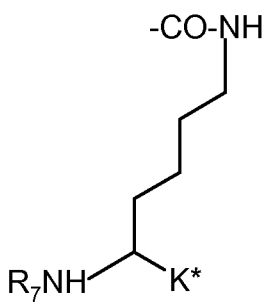
4)



(IXa)



(IXb)



(IXc)

wherein R_7 and K* are as above defined;

with the proviso that:

i) when R_1 is the group (Va), then N_0 is selected from the group consisting of (VIb), (VIc) -CO-NH-J-K', $-CH_2-O-CO-NH-J-K'$, -CO-NH-K-K*, $-CH_2-O-CO-NH-K-K*$, (IXc) and (IXa);

ii) when R_1 is selected from the groups (Vb), (Vc) or (Ve), then N_0 is selected from the group consisting of (VIb), -CO-NH-J-K', -CO-NH-K-K* and (IXc);

iii) when R_1 is the group (Vd), then N_0 is selected from the group consisting of (VIa), -OCO-NH-J-K', -O-CO-NH-K-K* and (IXb);

iv) when R is selected from the residue (III), then N_0 is selected from the group consisting of (VIb), -CO-NH-J-K', -CO-NH-K-K* and (IXc);

v) when R is selected from the residue (II) and R_0 is N_0, then R_1 is the group (V_e)

vi) when R is selected from the residue (II), then s is 1 and s' is 0 or 1;

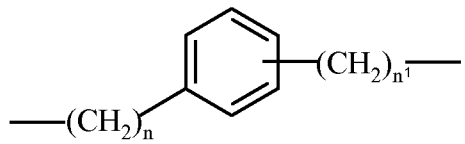
vii) when R is selected from the residue (III), then s is 2 and s' is 0 or 2.

Y and Y' independently are bivalent radicals having the following meaning:

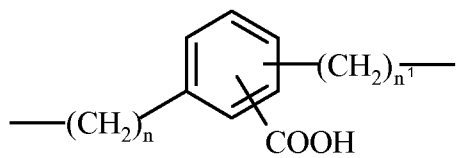
a)

- straight or branched C_1-C_{20} alkylene, preferably C_1-C_{10}, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or R^1, wherein R^1 is $-OC(O)(C_1$-C_{10} alkyl)$-ONO_2$ or $-O(C_1$-C_{10} alkyl)$-ONO_2$;

b)

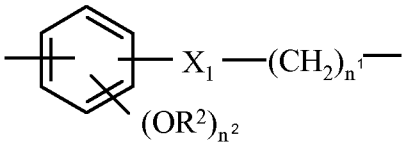


c)



wherein n is an integer from 0 to 20, and n^1 is an integer from 1 to 20;

d)

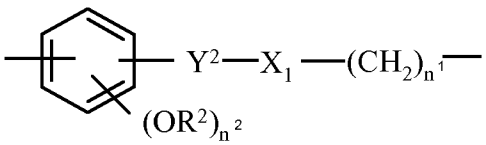


wherein:

n^1 is as defined above and n^2 is an integer from 0 to 2;

X_1 = -OCO- or -COO- and R^2 is H or CH_3;

e)



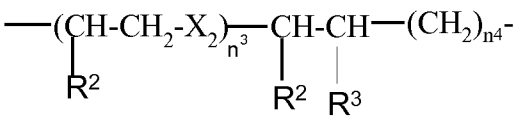
wherein:

n^1, n^2, R^2 and X_1 are as defined above;

Y^2 is $-CH_2-CH_2-$ or $-CH=CH-(CH_2)_{n^2}-$;

with the proviso that when Y or Y' is selected from the bivalent radicals mentioned under b)-e), the $-ONO_2$ group is linked to a $-(CH_2)_{n^1}$ group;

f)



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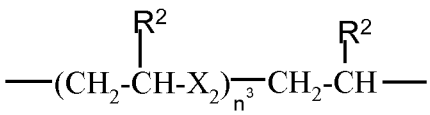


wherein X_2 is -O- or -S-, n^3 is an integer from 1 to 6, preferably from 1 to 4, R^2 is as defined above,

R^3 is H or $-ONO_2$ and n^4 is 0 or 1.

The term "C_1-C_{20} alkylene" as used herein refers to branched or straight chain C_1-C_{20} hydrocarbon, preferably having from 1 to 10 carbon atoms such as methylene, ethylene, propylene, isopropylene, n-butylene, pentylene, n-hexylene and the like.

The term "C_1-C_{10} alkyl" as used herein refers to branched or straight chain alkyl groups comprising one to ten carbon atoms, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, hexyl, octyl and the like.

Another aspect of the present invention provides the use of the compounds of formula (I) in combination with at least a compound used to treat cardiovascular disease selected from the group consisting of: aldosterone antagonists, renin inhibitors, ACE inhibitors, HMGCoA reductase inhibitors, beta-adrenergic blockers, alpha-adrenergic antagonists, sympatholytics, calcium channel blockers, endothelin antagonists, neutral endopeptidase inhibitors, potassium activators, diuretics, vasodilators, antithrombotics such as aspirin. Also it is contemplated the combination with nitrosated compounds of the above reported compounds.

Suitable aldosterone antagonists, renin inhibitors, ACE inhibitors, HMGCoA reductase inhibitors, beta-adrenergic blockers, alpha-adrenergic antagonists, sympatholytics, calcium channel blockers, endothelin antagonists, neutral endopeptidase inhibitors, potassium activators, diuretics, vasodilators and antithrombotics are described in the literature such as The Merck Index (13^{th} edition).

Suitable nitrosated compounds are disclosed in WO 98/21193, WO 97/16405, WO 98/09948, WO 2004/105754, WO 2004/106300, WO 2004/110432, WO 2005/011646, WO 2005/053685, WO 2005/054218, WO 2007/045551.

The administration of the compounds above reported can be carried out simultaneously or successively.

The present invention also provides pharmaceutical kits comprising one or more containers filled with one or

more of the compounds and/or compositions of the present invention and one or more of the compounds used to treat cardiovascular diseases reported above.

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

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

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

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

The compounds of the invention which have one or more 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).

In one embodiment, R is the residue of formula (II) wherein R_0 is the group of formula (IV), R_1 is the group of formula (Va), R_2 is n-butyl, R_3 is Cl and all other variables are as above defined.

In another embodiment, R is the residue of formula (II) wherein R_0 is the group of formula (IV), R_1 is the group of formula (Va), R_2 is n-propyl, R_3 is the group $-C(CH_3)_2OH$ and all other variables are as above defined.

In another embodiment, R is the residue of formula (II) wherein R_0 is the group of formula (IV) as defined above, R_1 is the group of formula (Vc)as defined above, R_4 is -OEt, and all other variables are as above defined.

In another embodiment s_1 is 0 and A is the group (VI_a) or (VI_b) or (VI_c) as defined above wherein K'is -COO-, and all other variables are as above defined.

In another embodiment s_1 is 0 and A is $-CO-NH-J-K'$ or $-CH_2-O-CO-NH-J-K'$ wherein J is the group (VIIa) or (VIIb) as defined above,wherein K'is -COO-, and all other variables are as above defined.

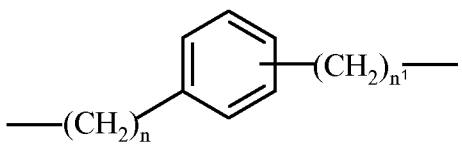
In another embodiment s_1 is 0 and A is $-CH_2-O-CO-NH-K-K^*$ or $-CO-NH-K-K^*$ wherein K is K_3 which is the group (VIIIg) or ($VIII_h$) as defined above, and all other variables are as above defined.

In another embodiment of the invention Y and Y' independently are bivalent radicals having the following meaning:

a)

- straight or branched C_1-C_{10} alkylene, being optionally substituted with one or more $-ONO_2$;

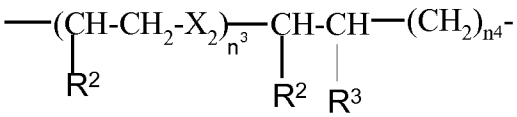
b)



wherein n is an integer from 0 to 5, and n^1 is an integer from 1 to 5;

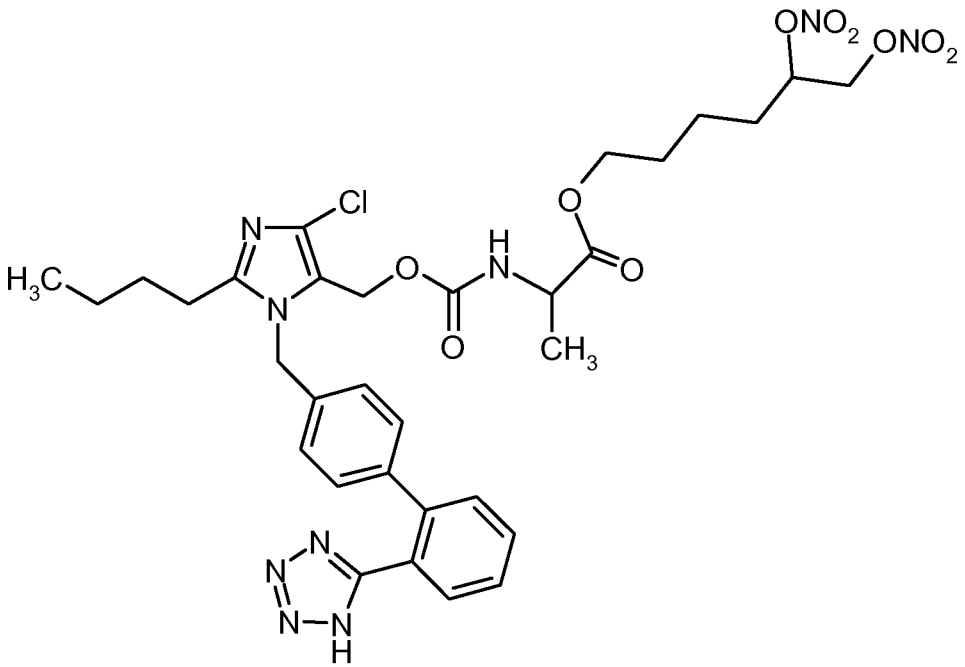
with the proviso that when Y or Y' is selected from the bivalent radical b), the $-ONO_2$ group is linked to a $-(CH_2)_{n^1}$ group;

f)



wherein X_2 is -O- or -S-, n^3 is 1, R^2 is H, R^3 is H or $-ONO_2$ and n^4 is 0 or 1.

The following are preferred compounds according to the present invention:



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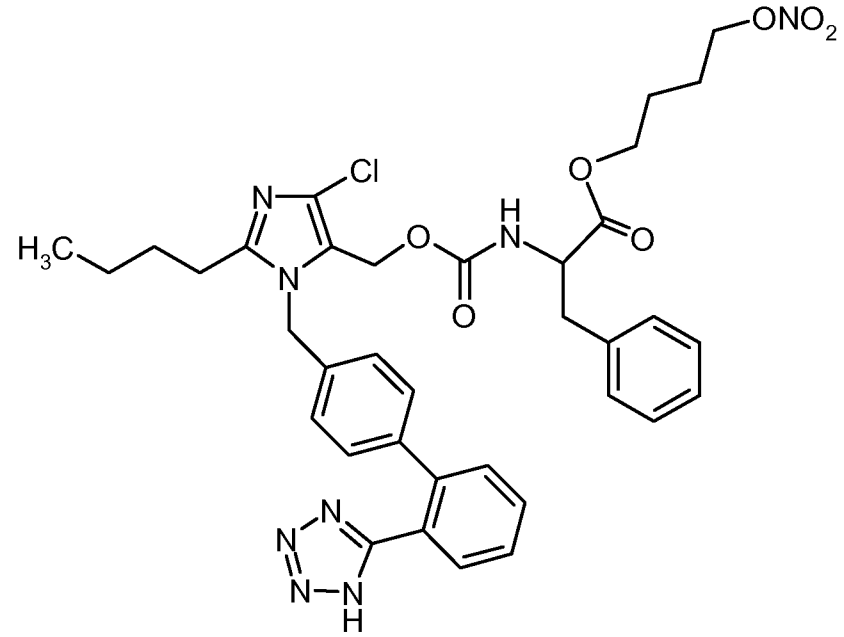

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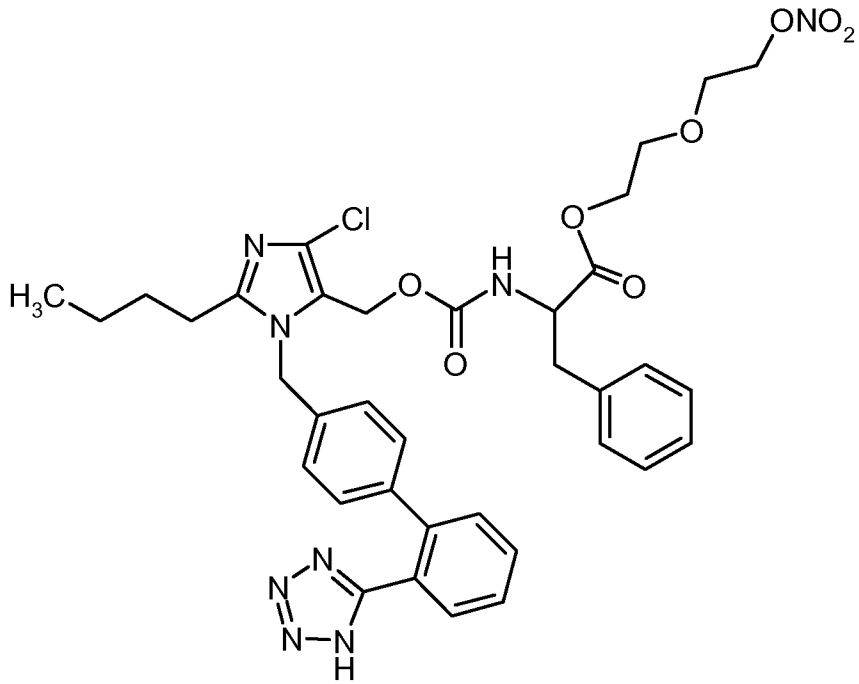

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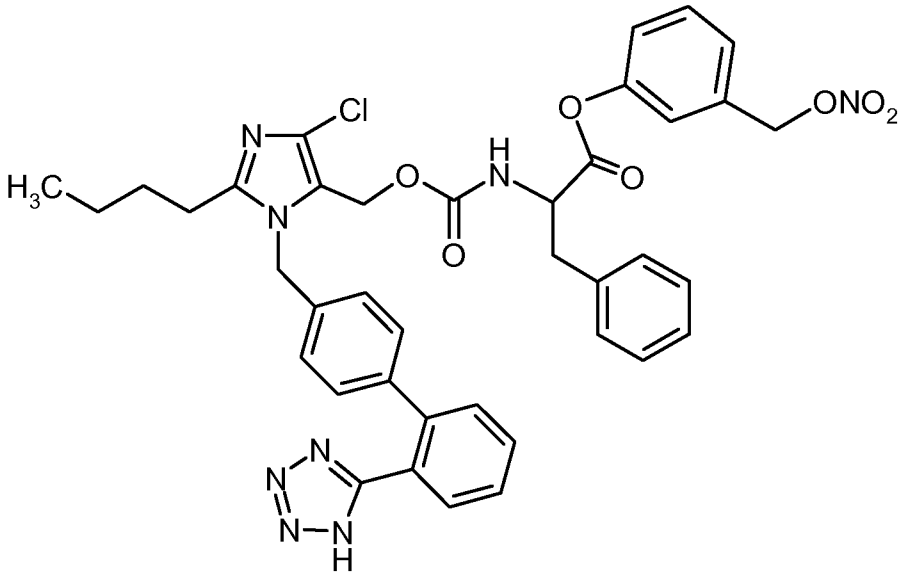

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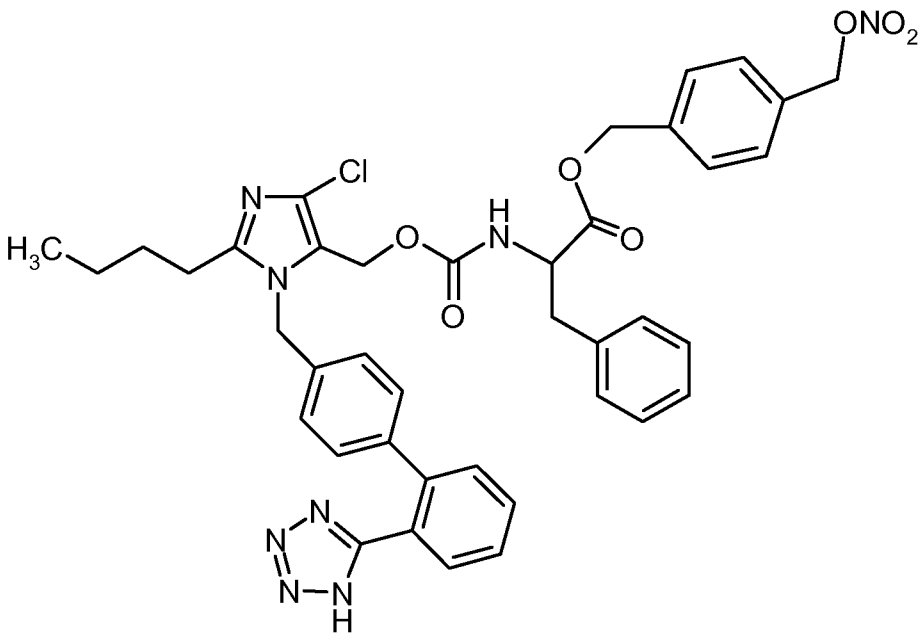

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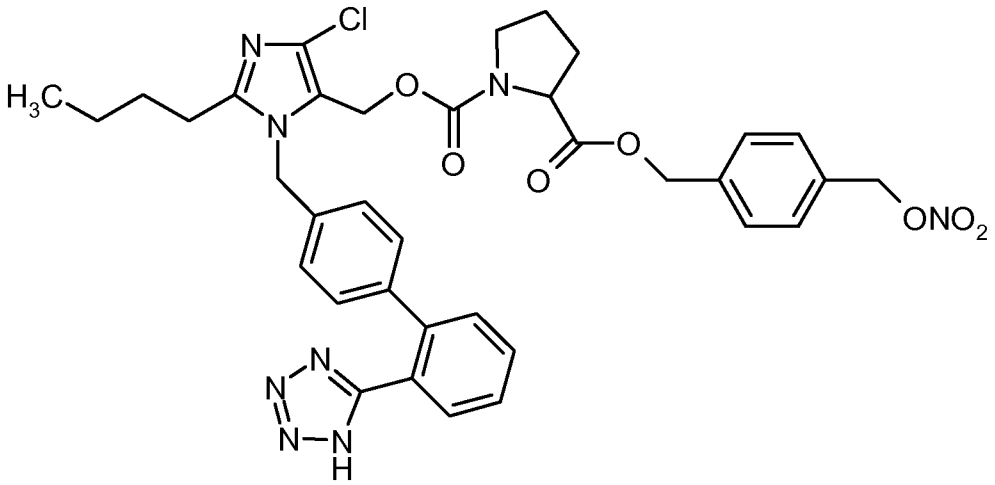

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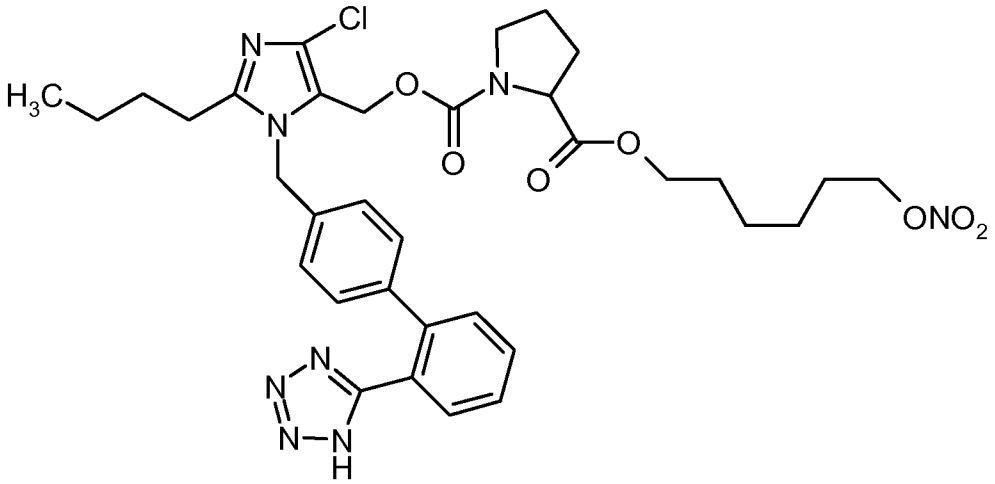

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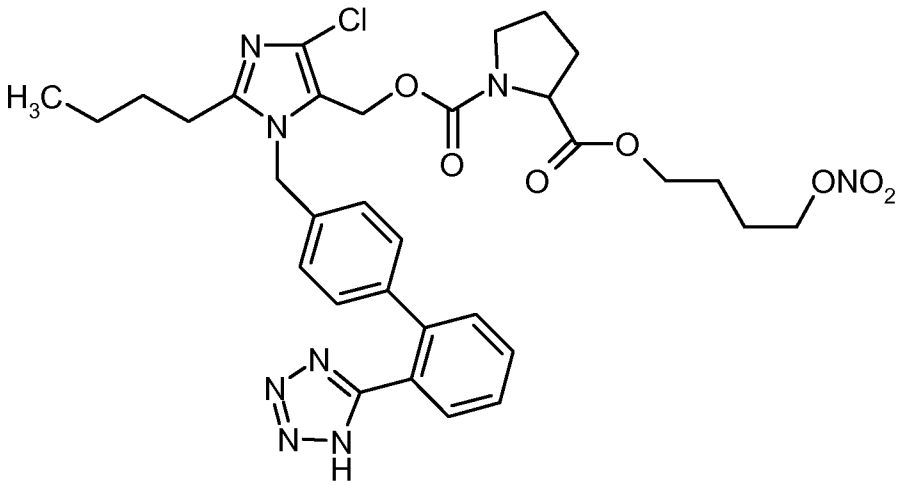

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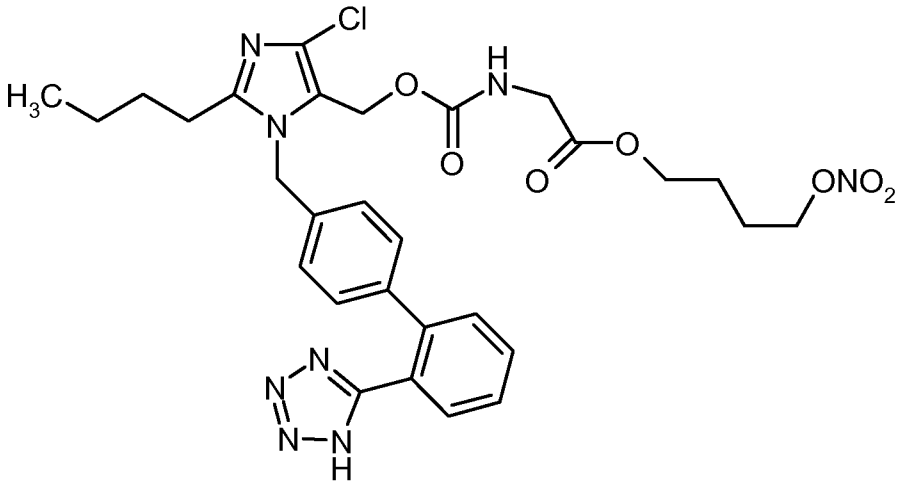

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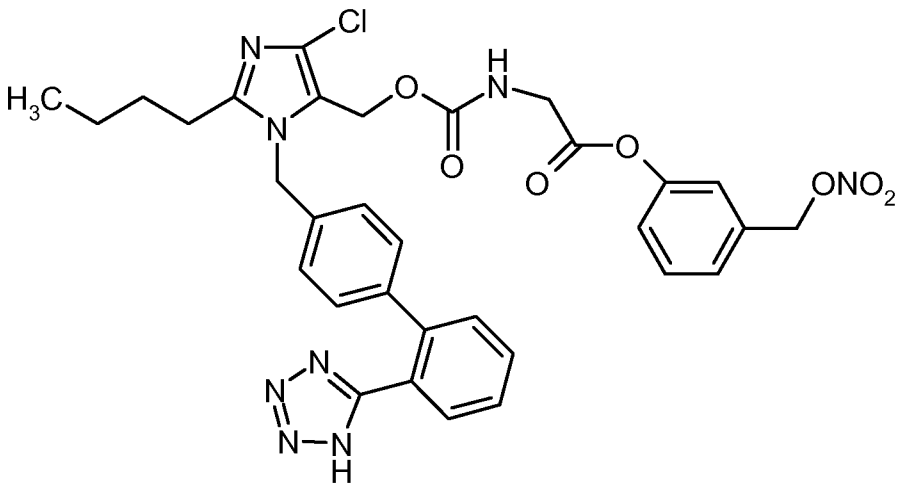

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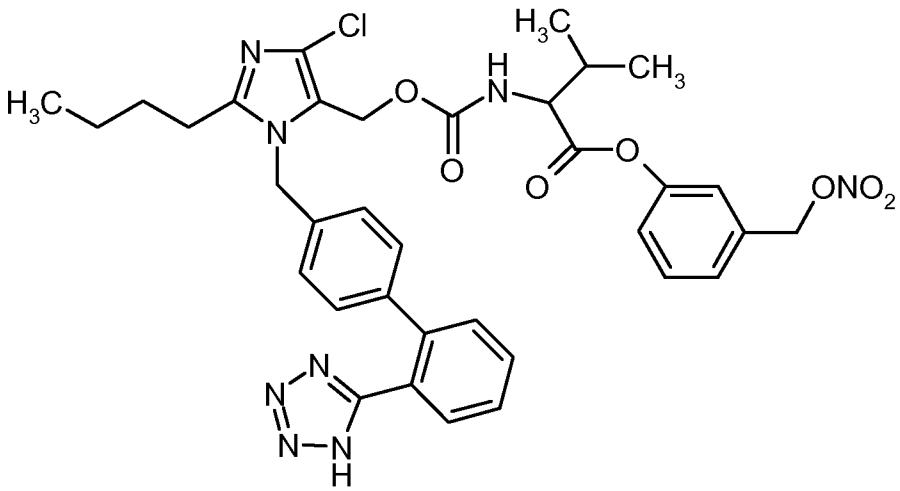

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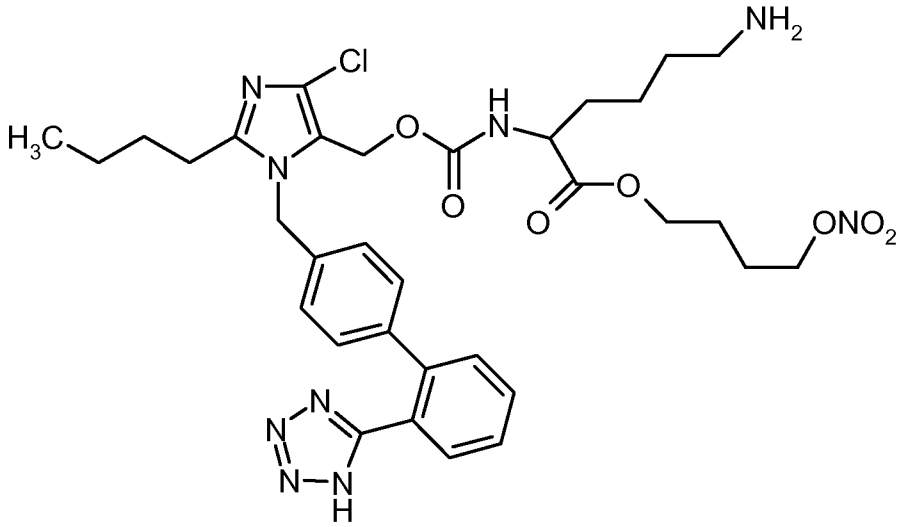

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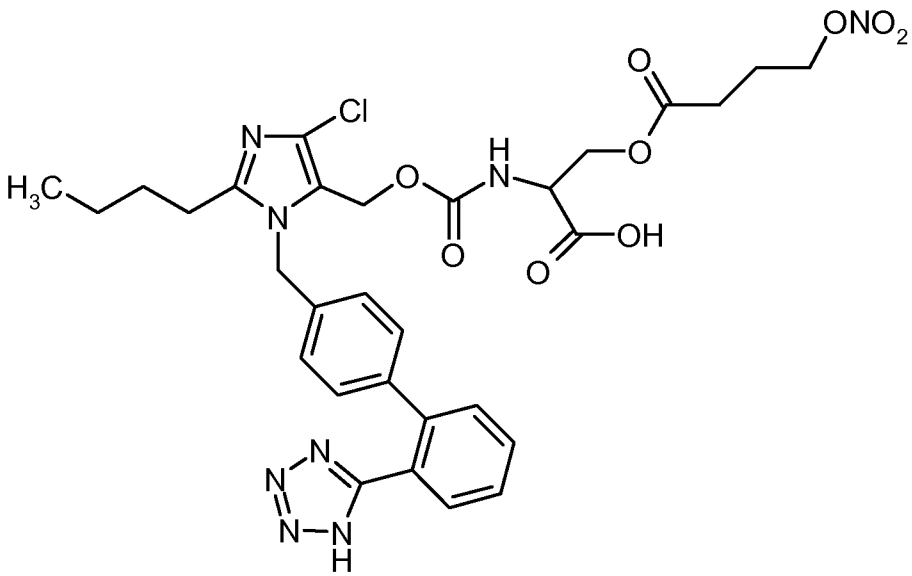

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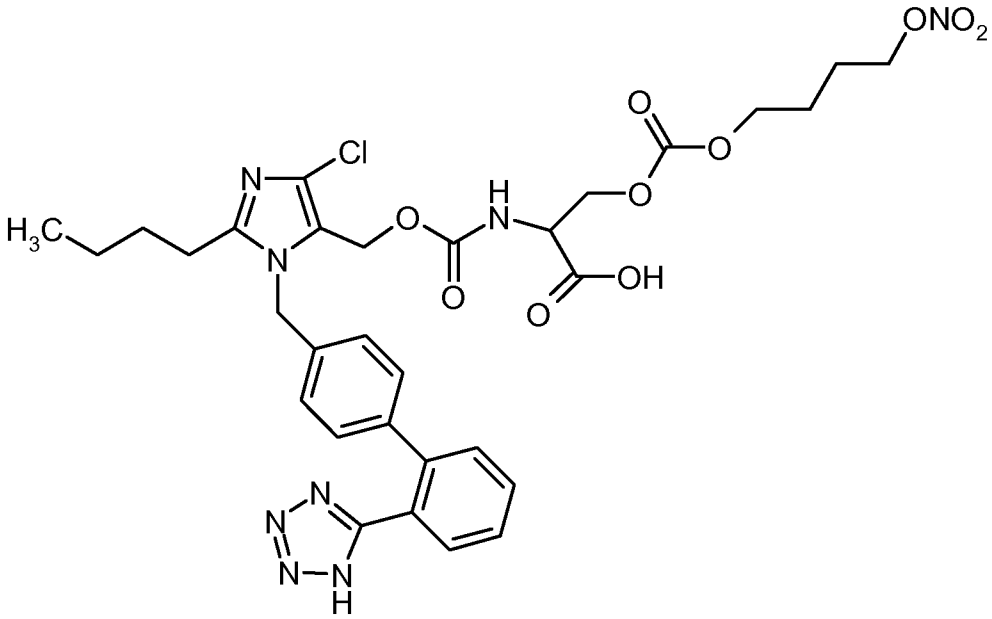

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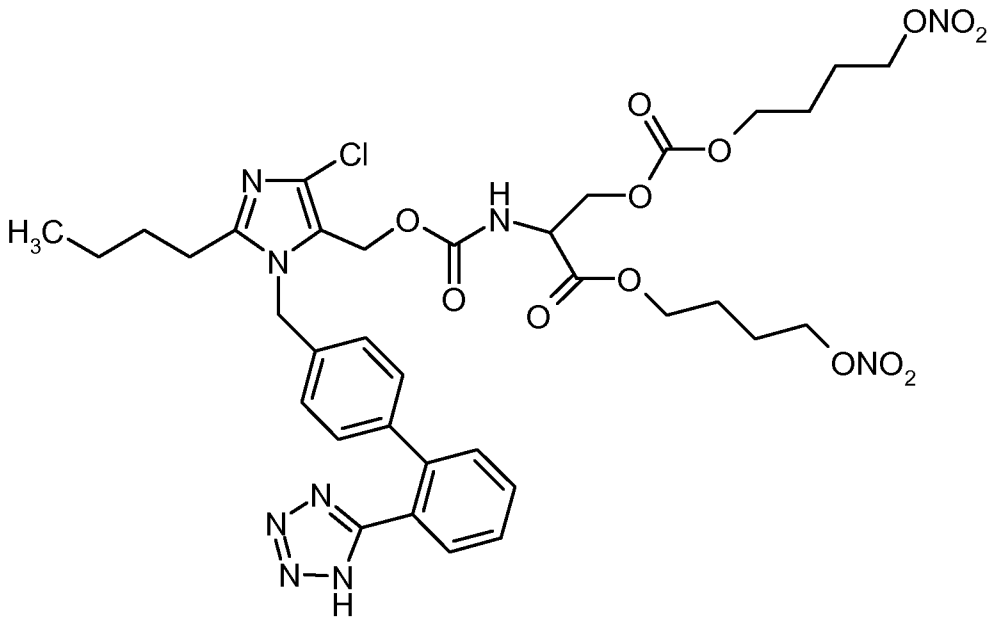

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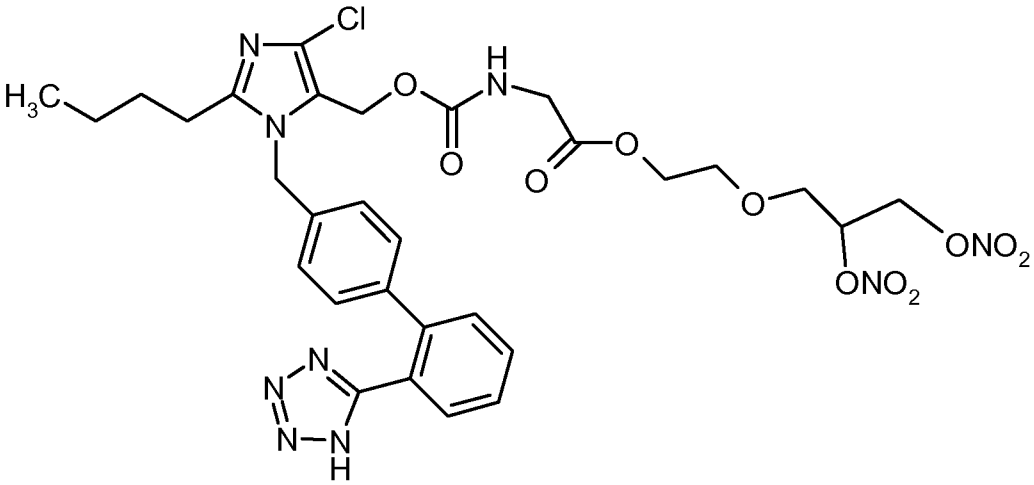

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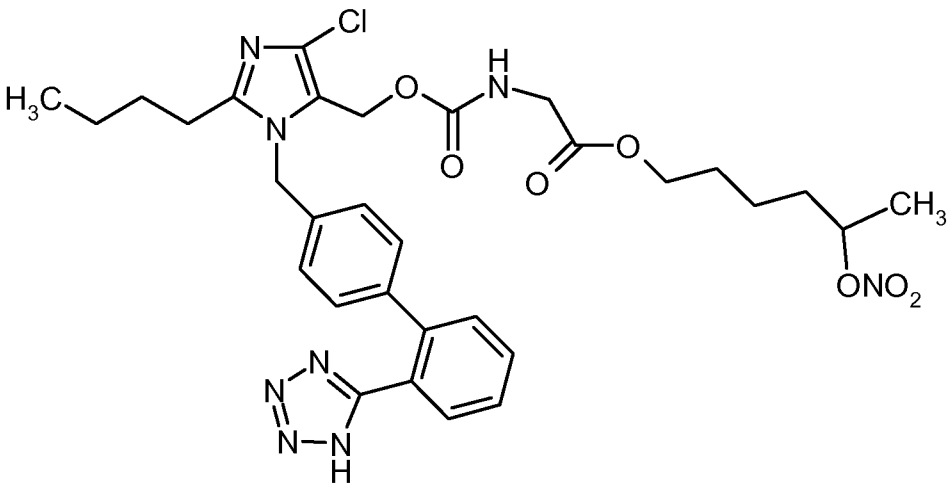

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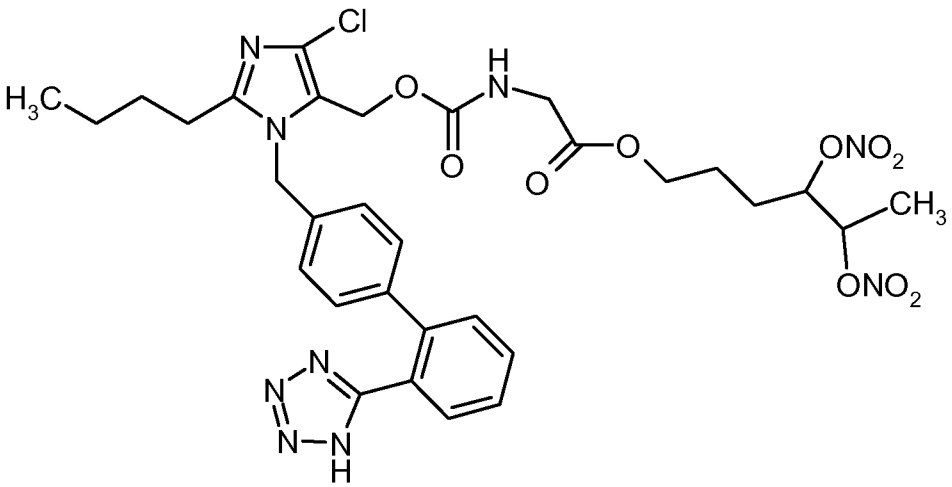

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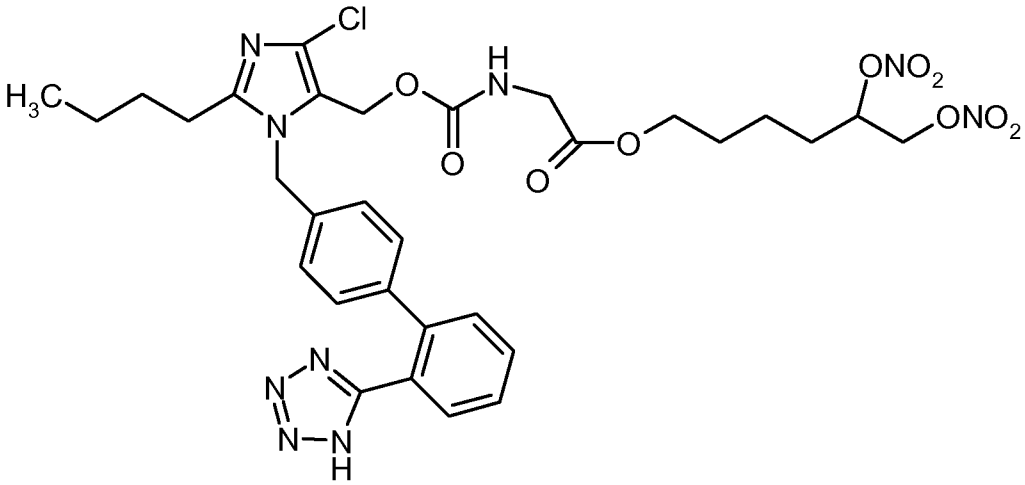

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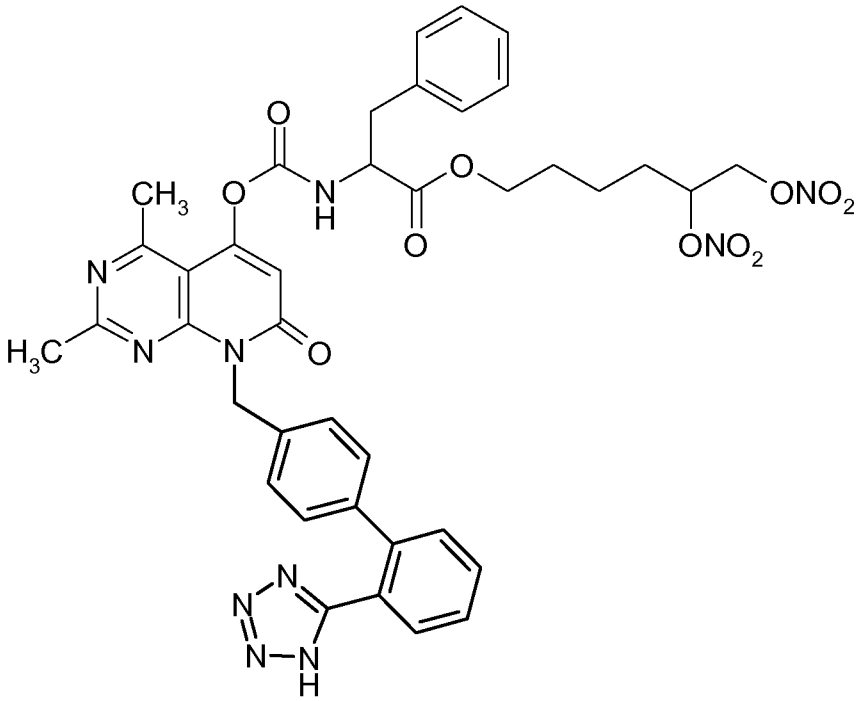

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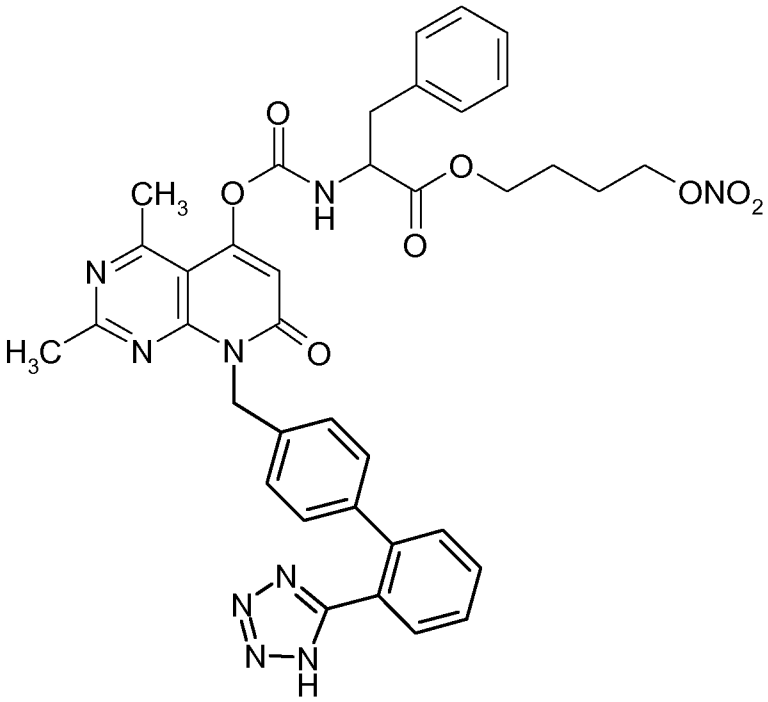

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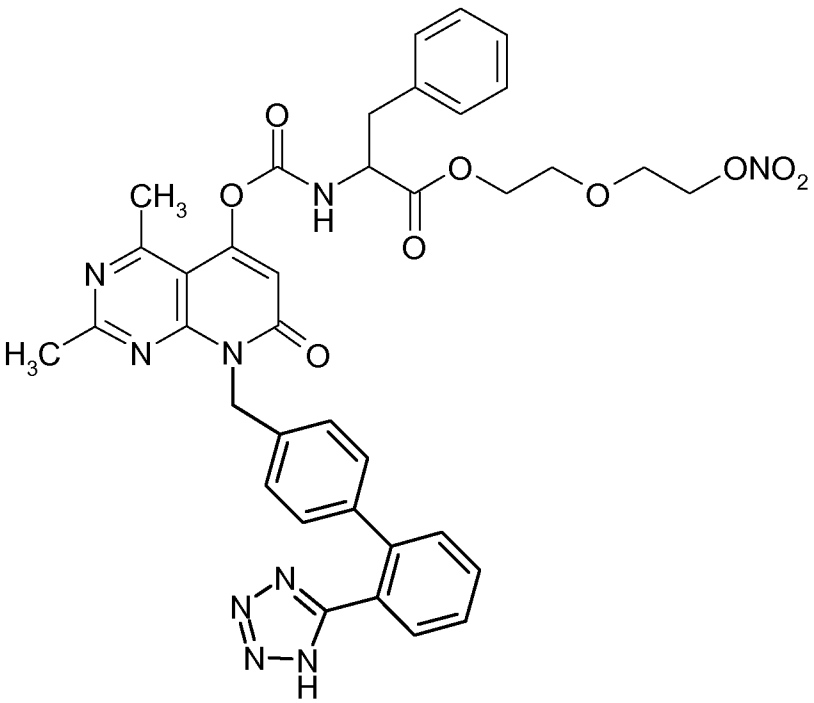

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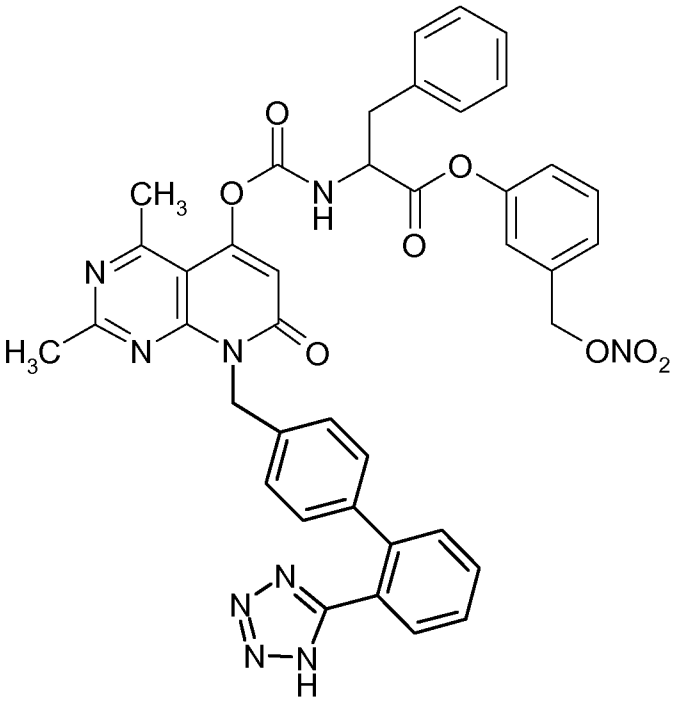

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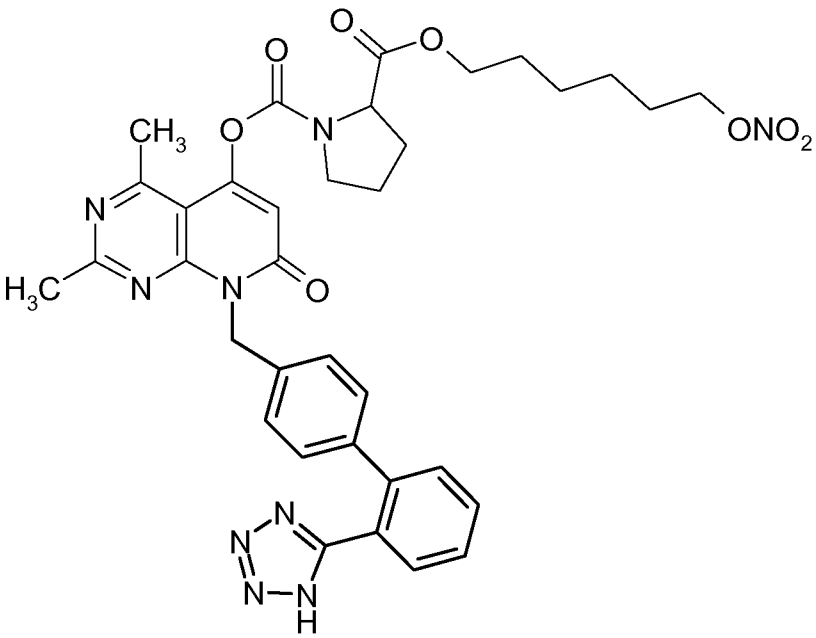

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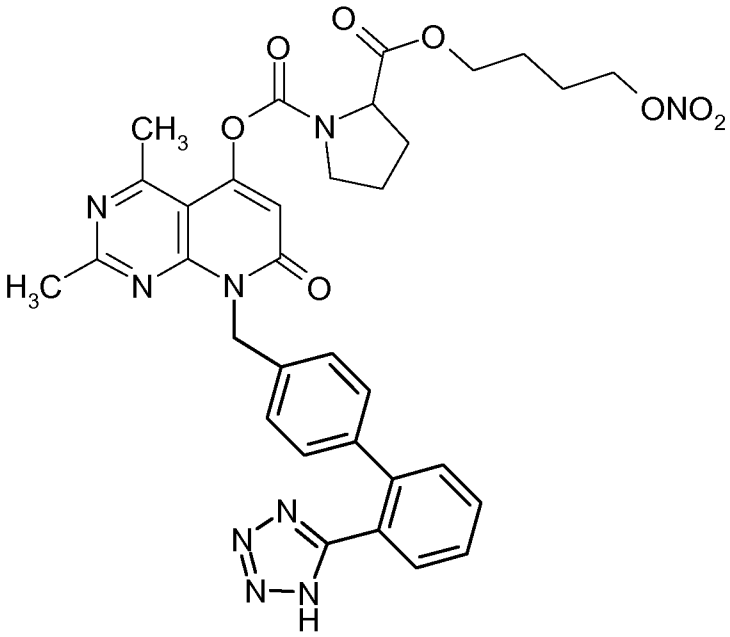

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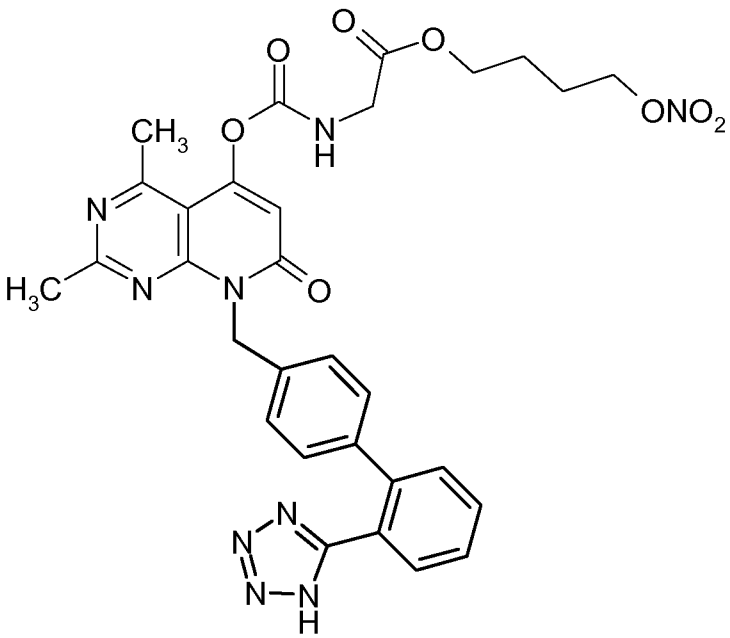

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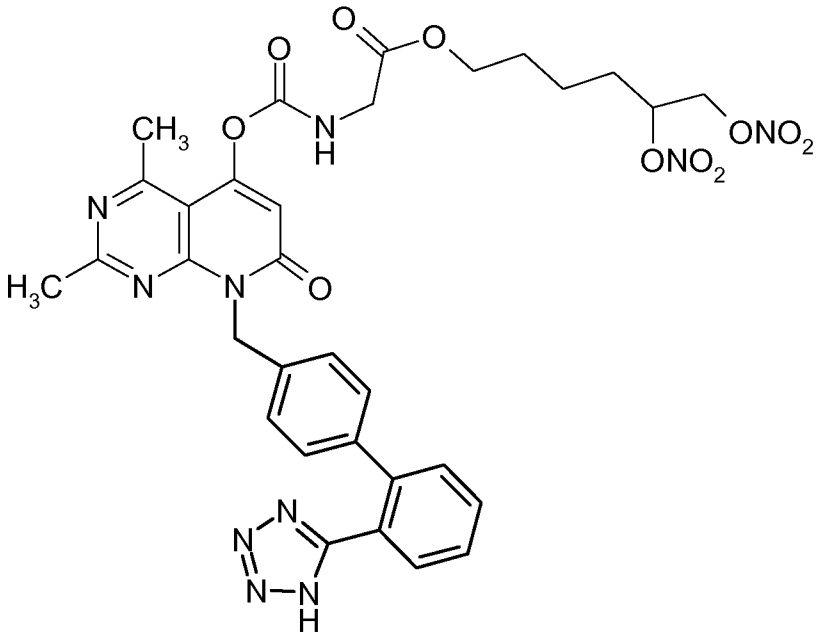

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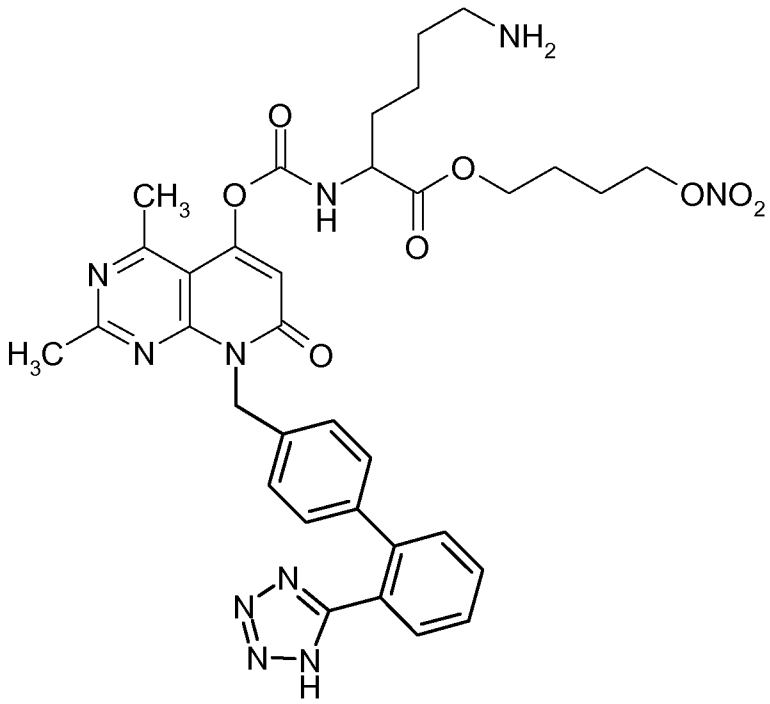

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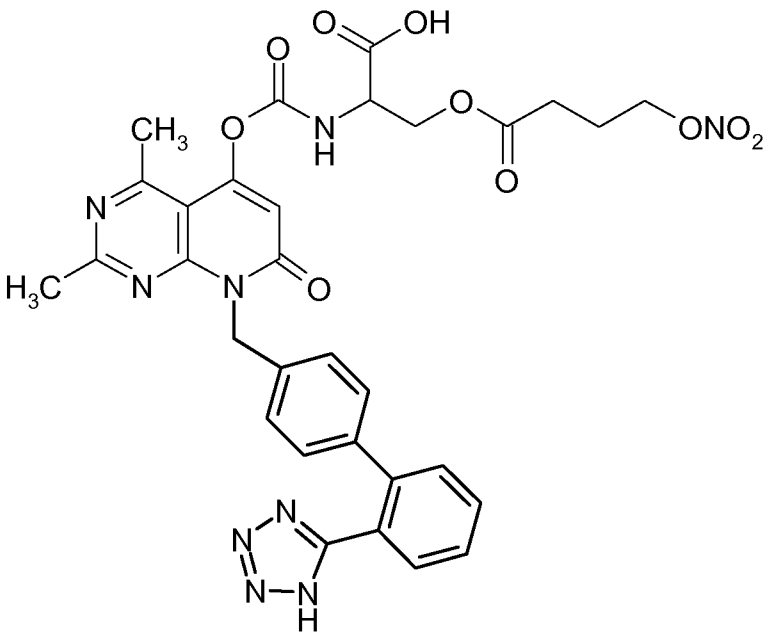

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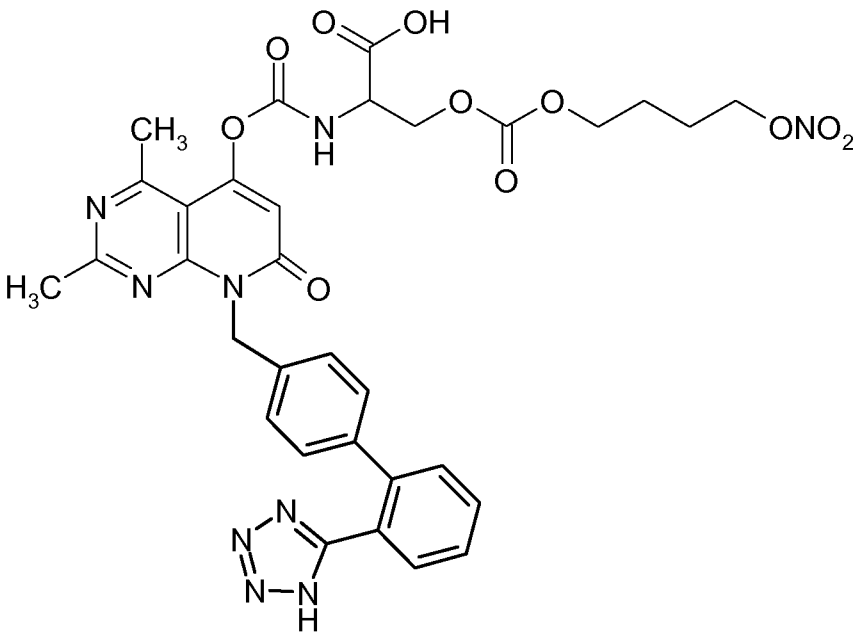

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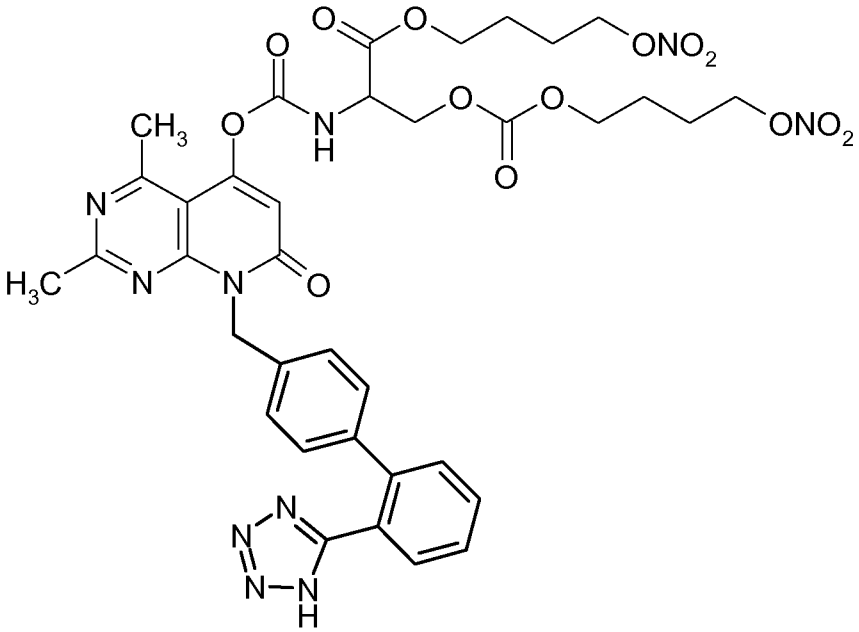

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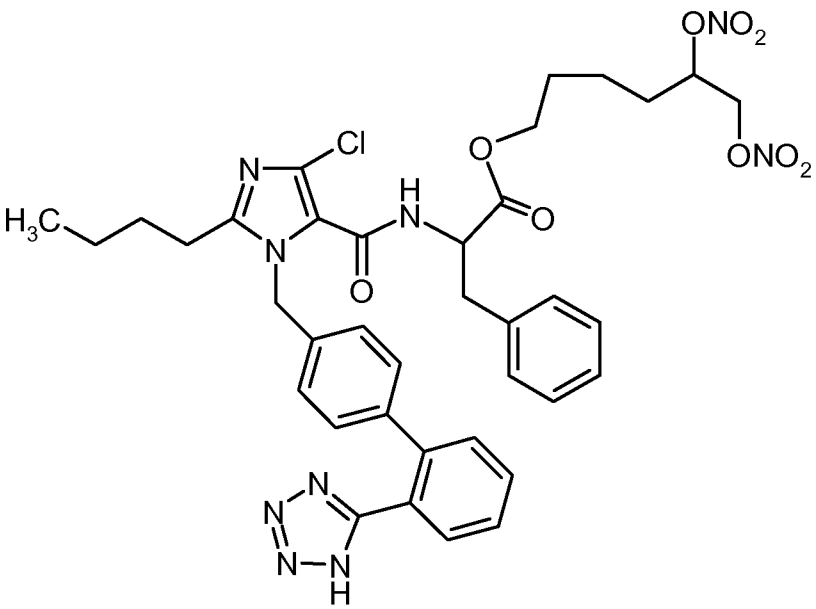

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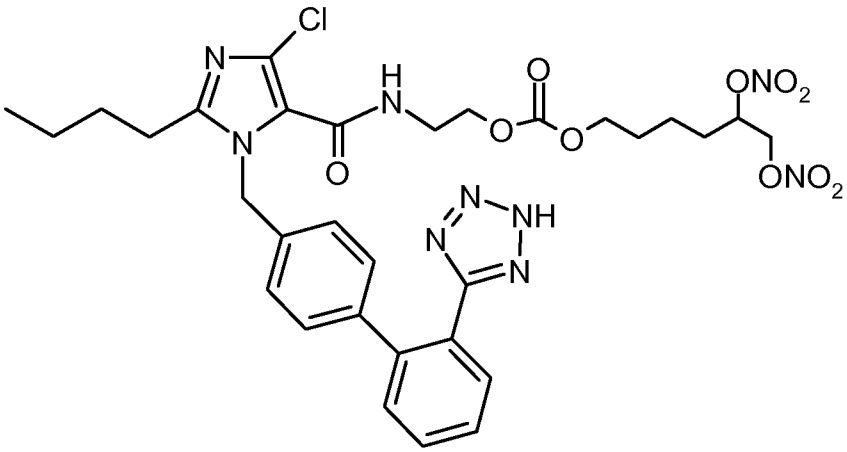

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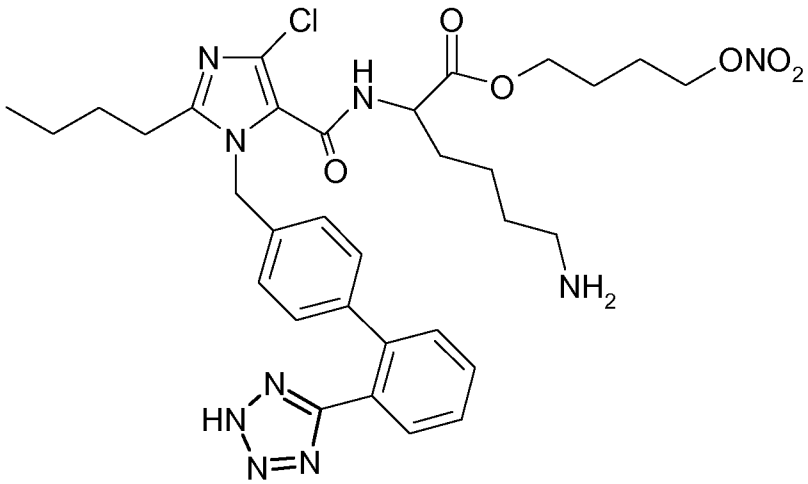

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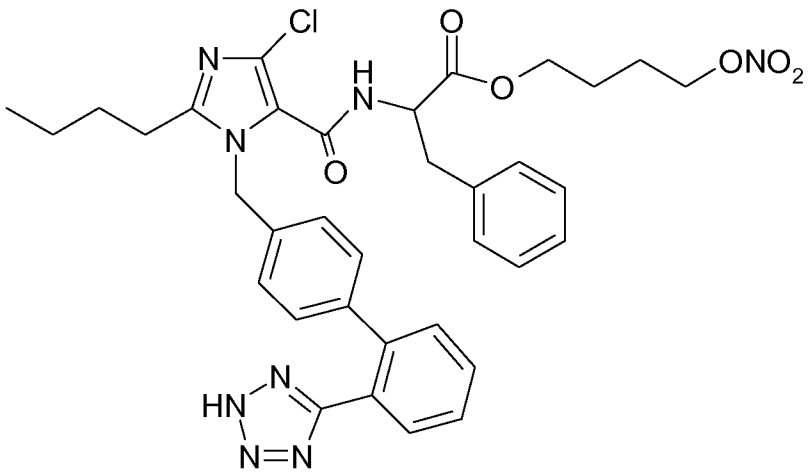

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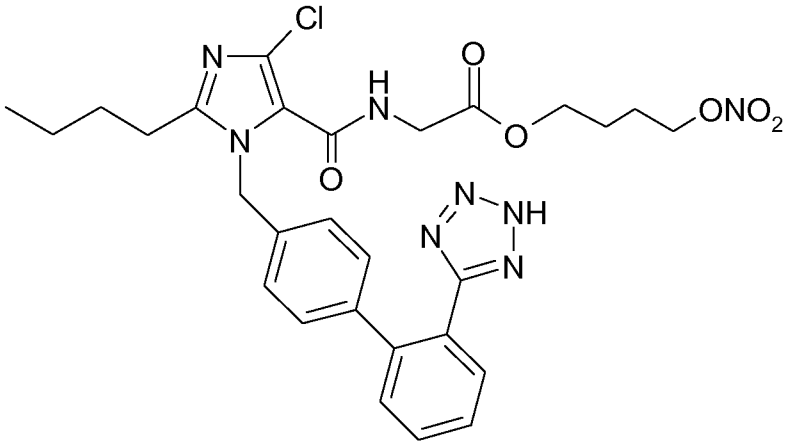

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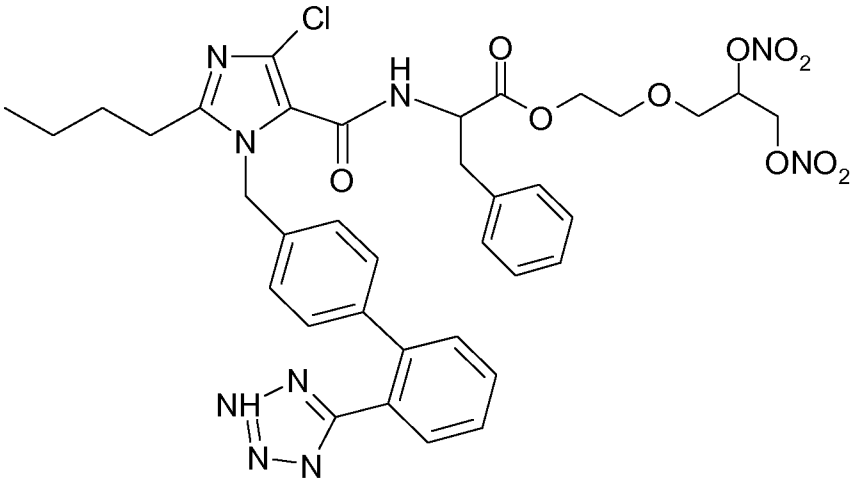

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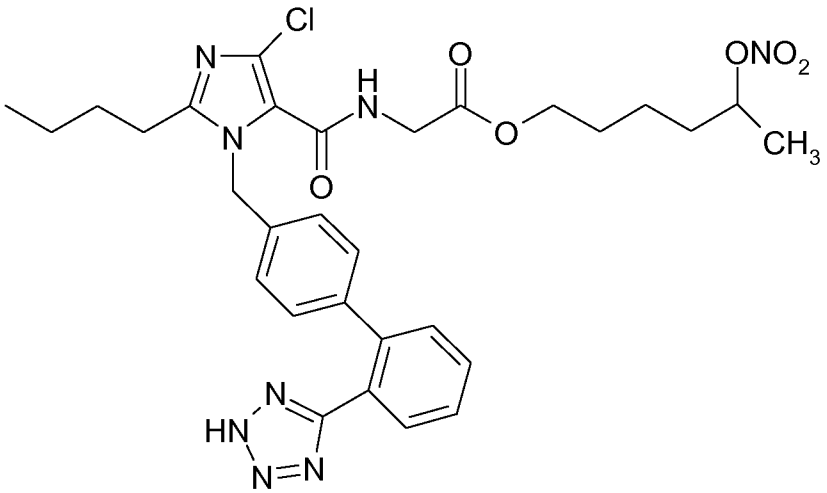

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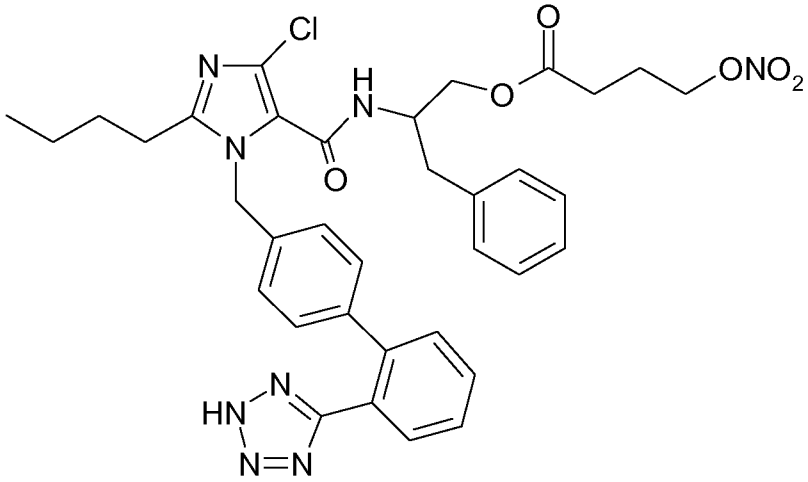

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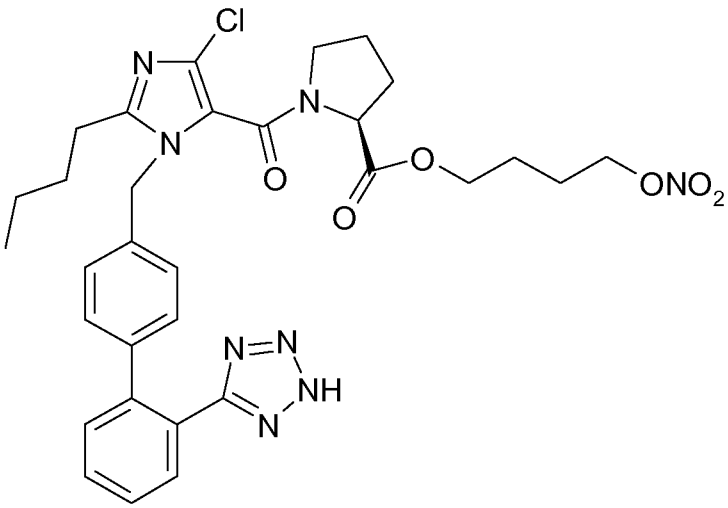

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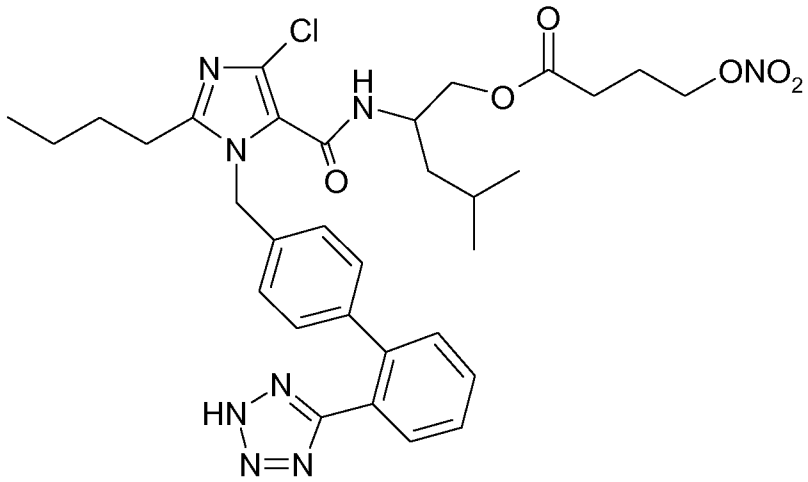

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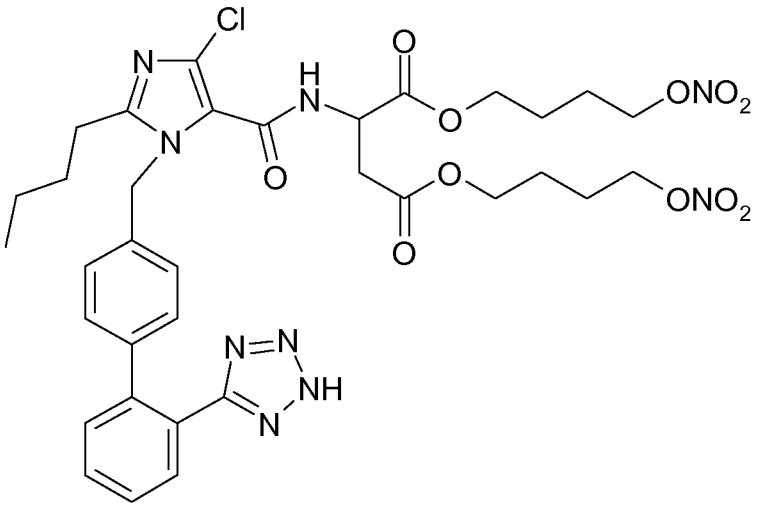

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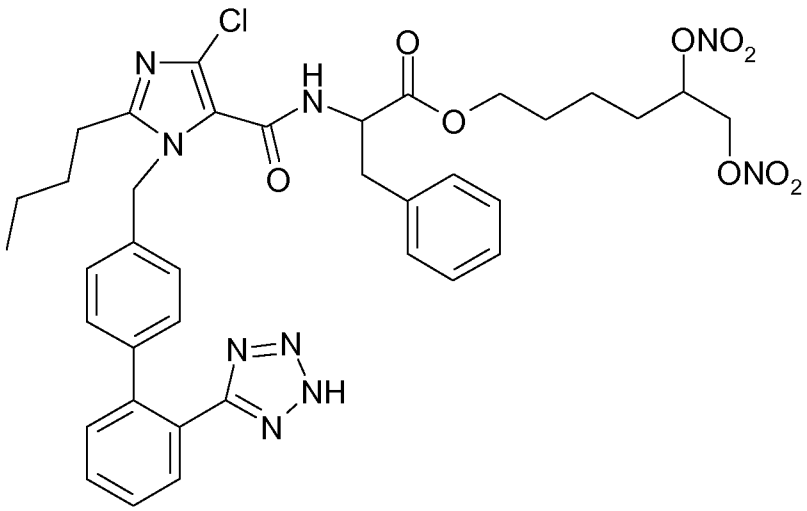

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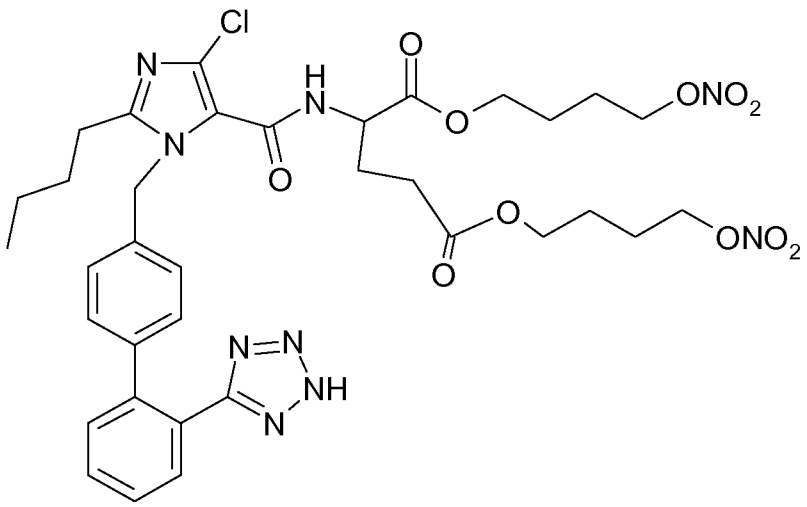

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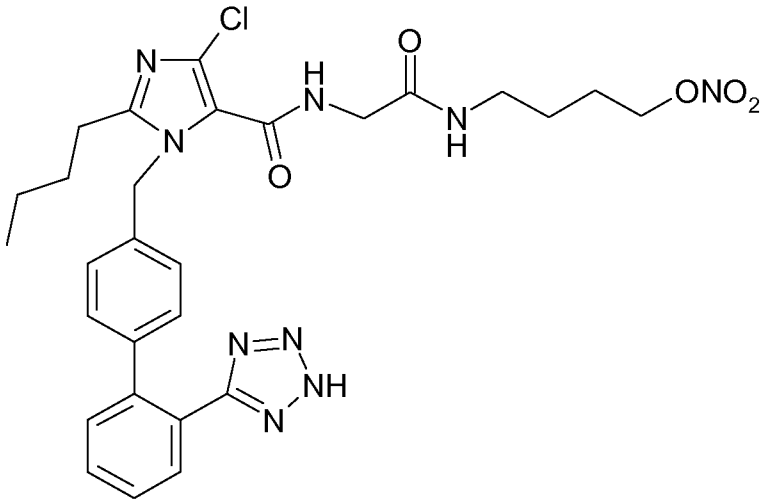

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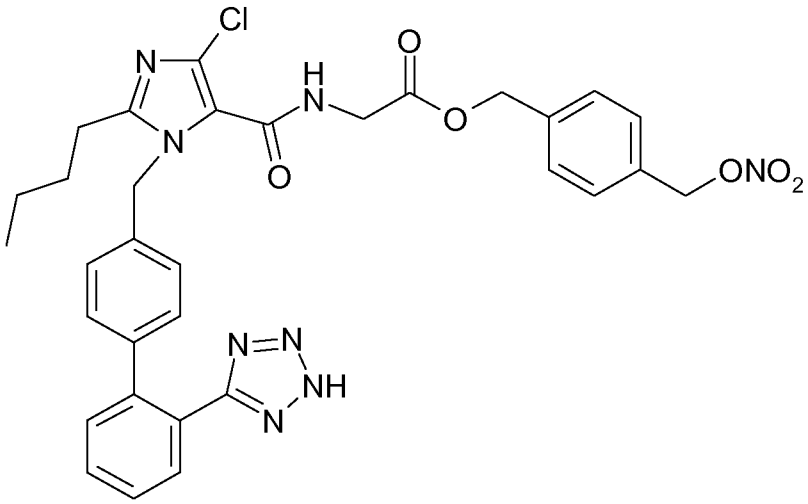

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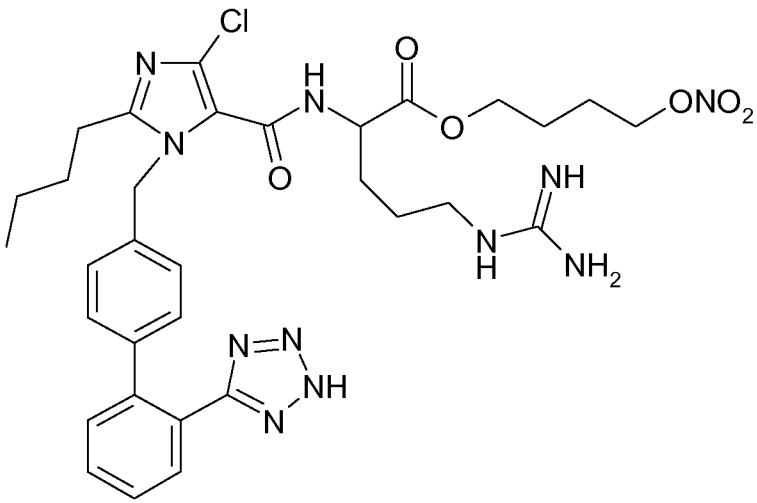

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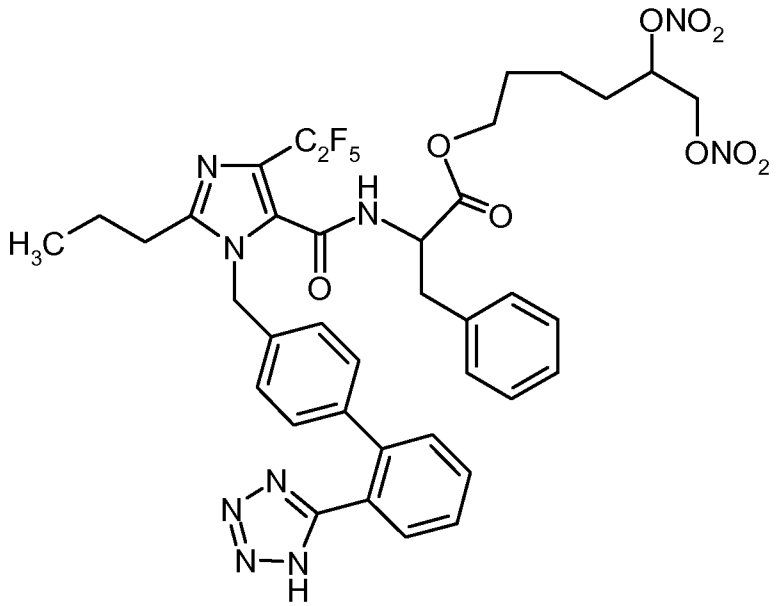

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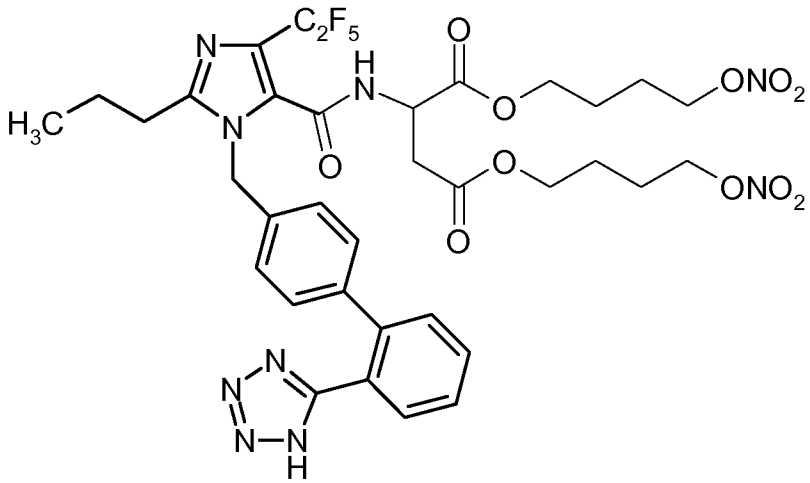

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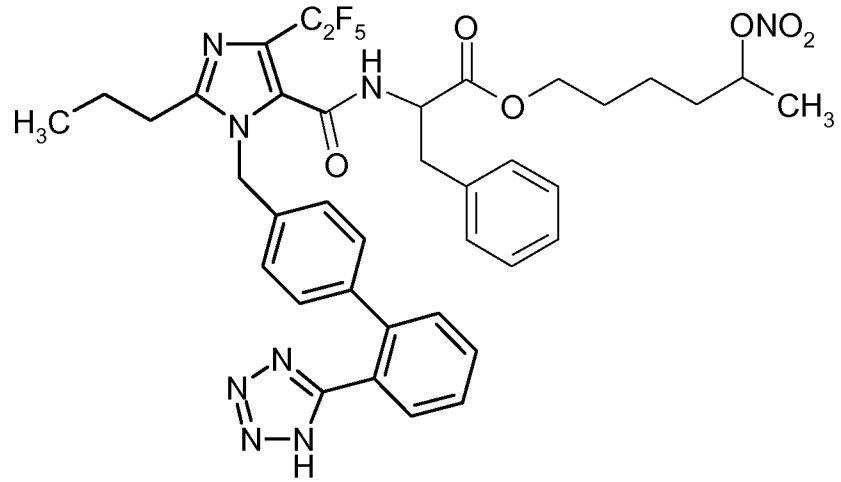

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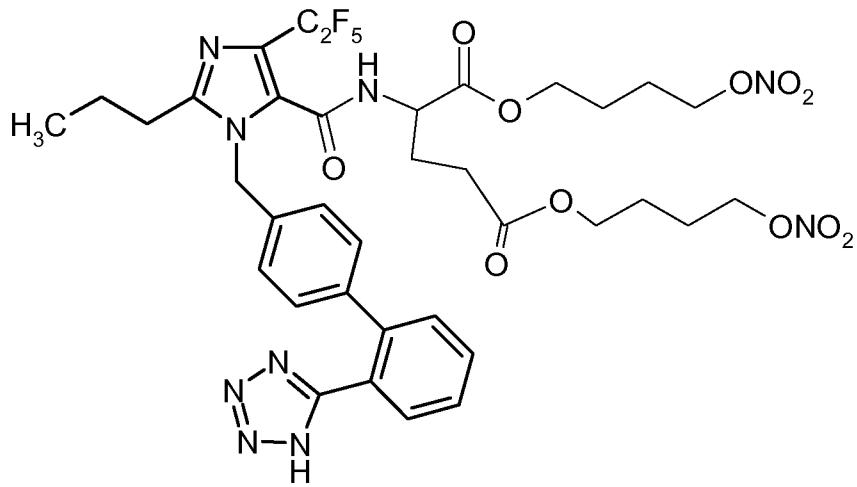

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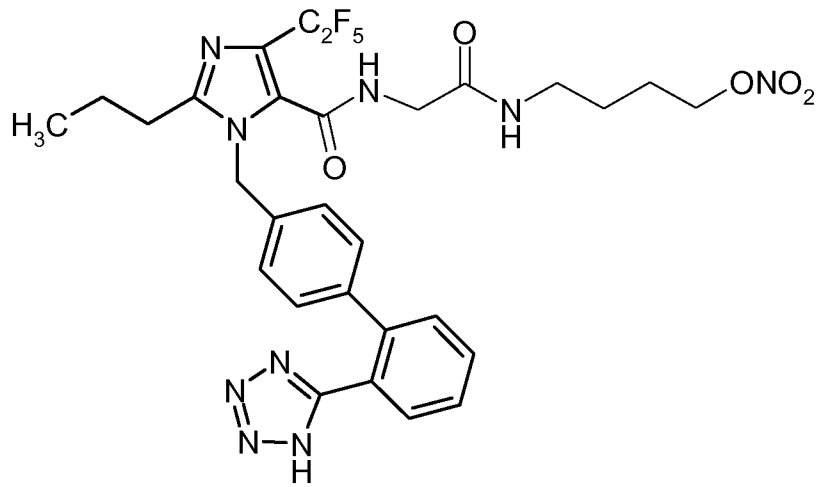

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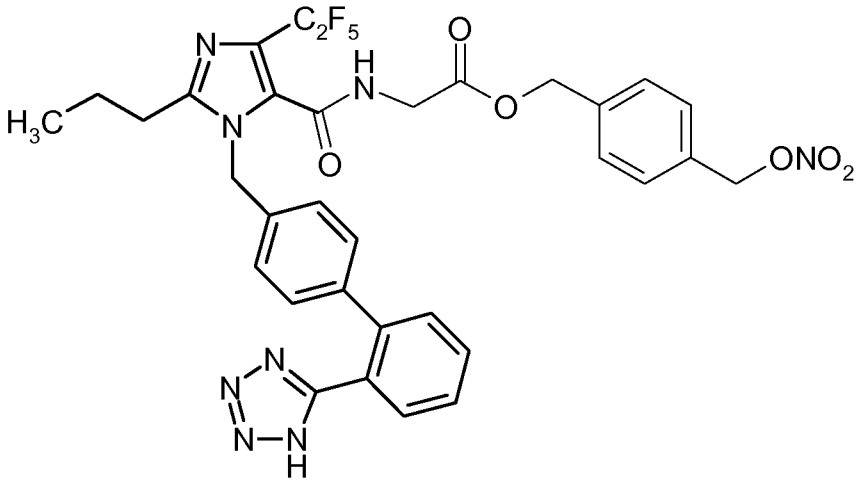

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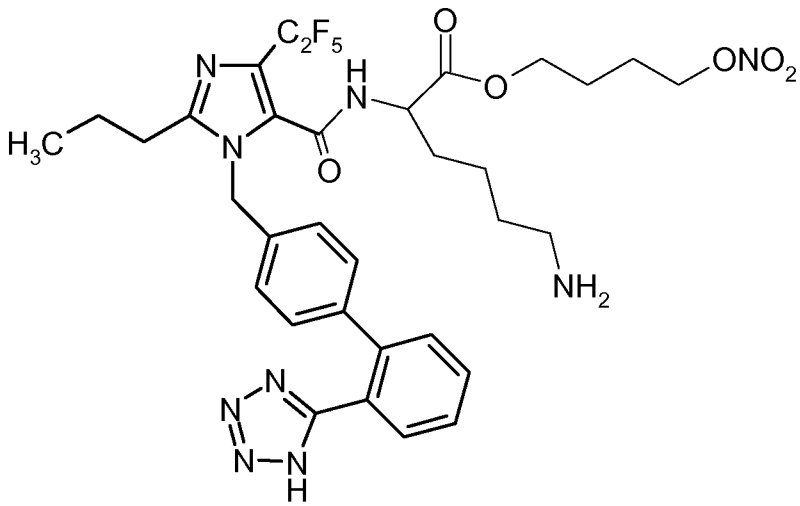

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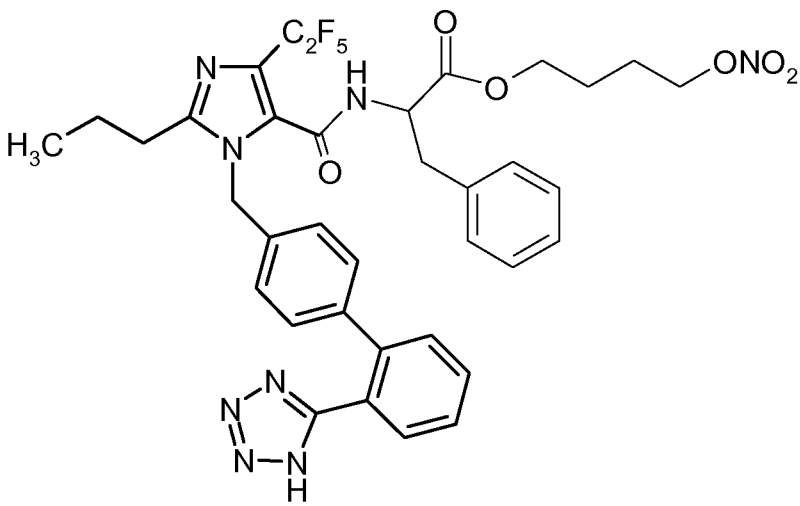

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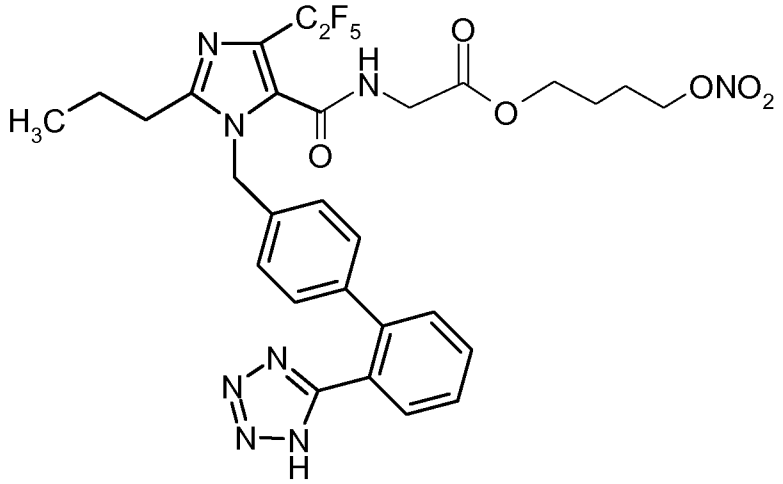

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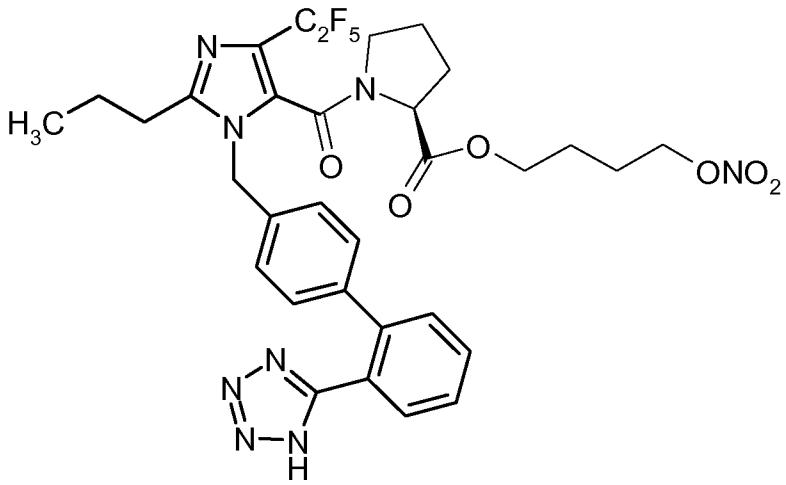

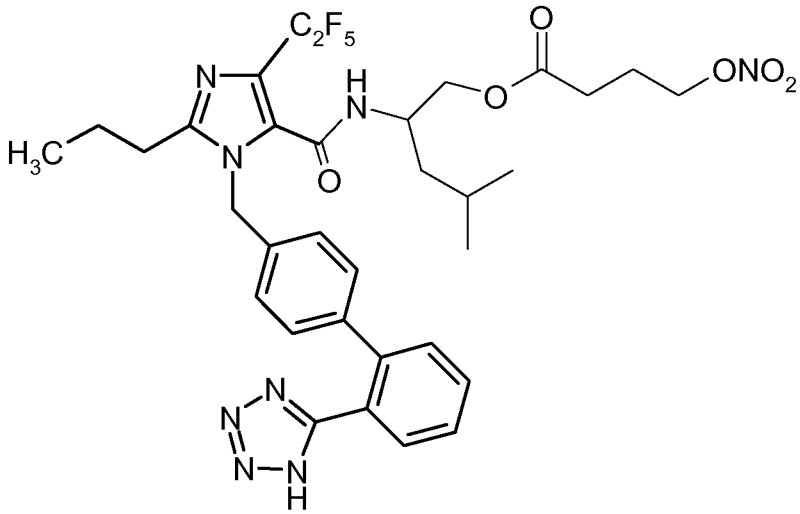

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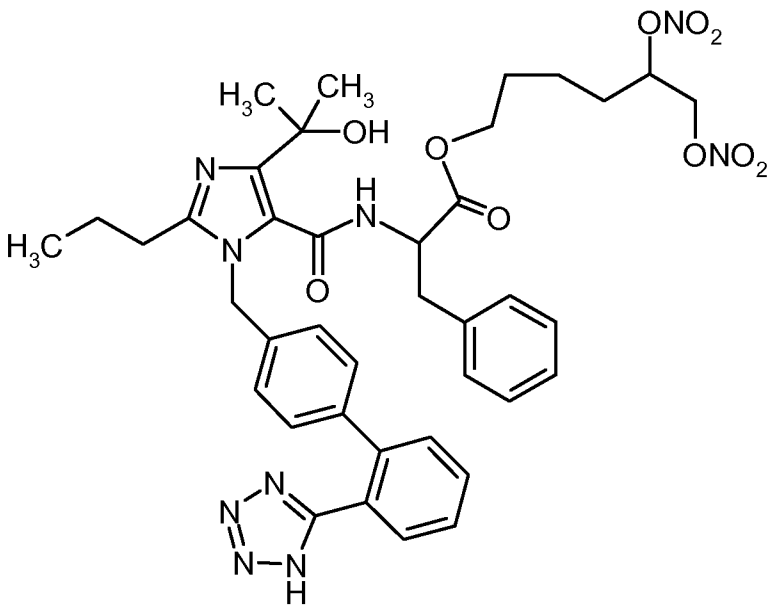

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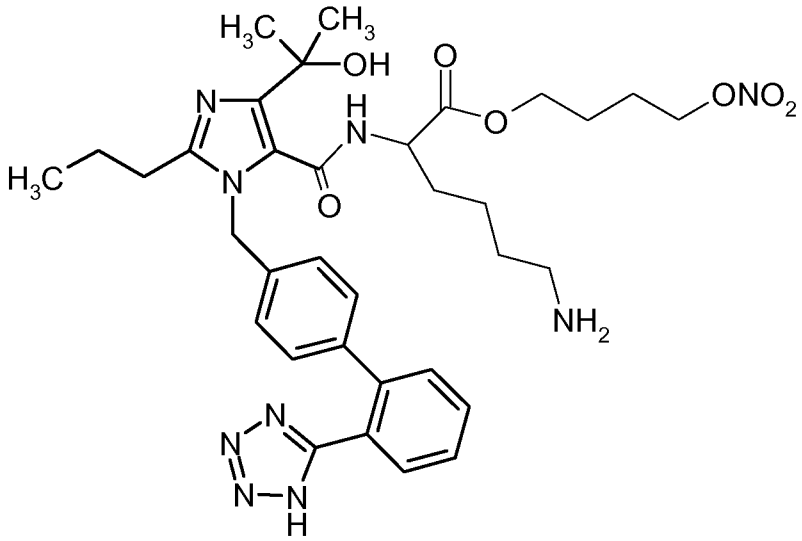

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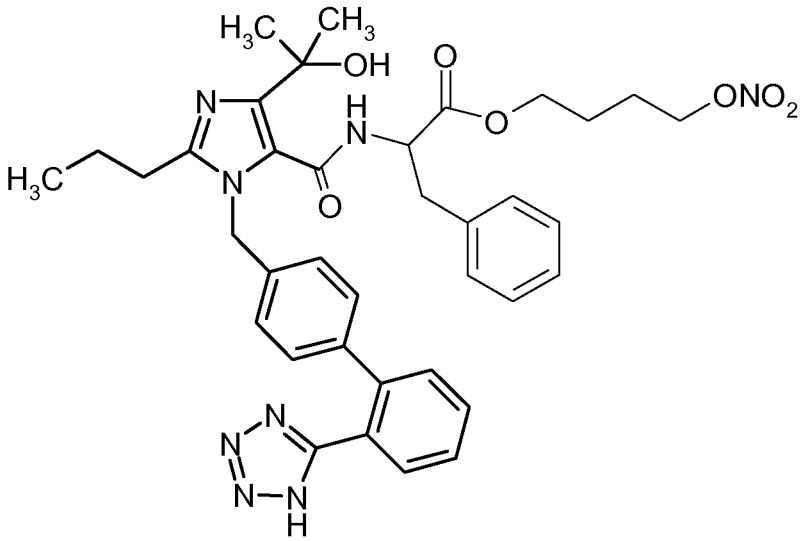

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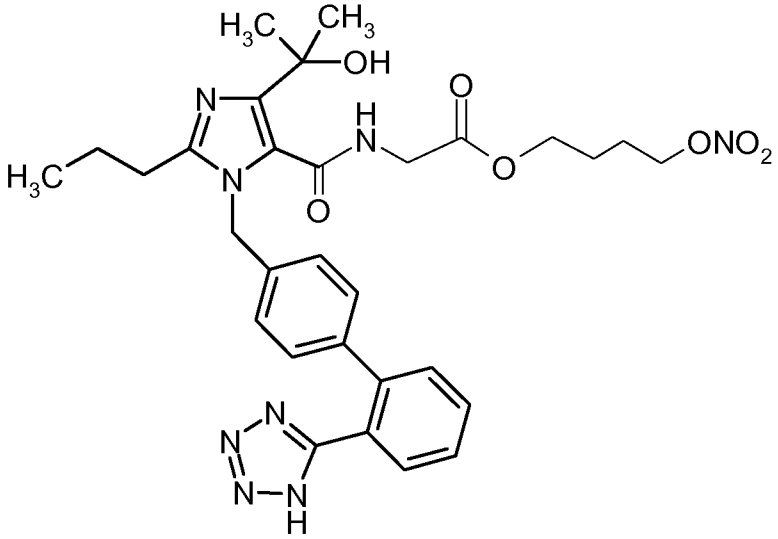

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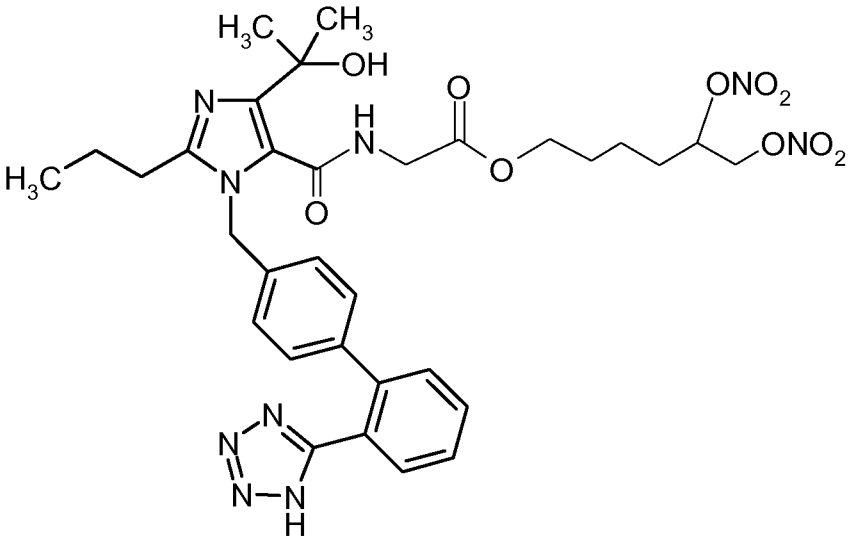

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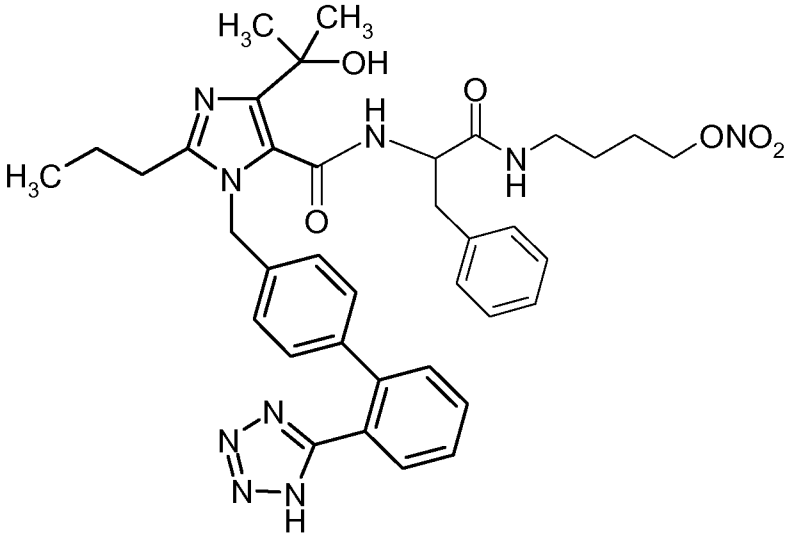

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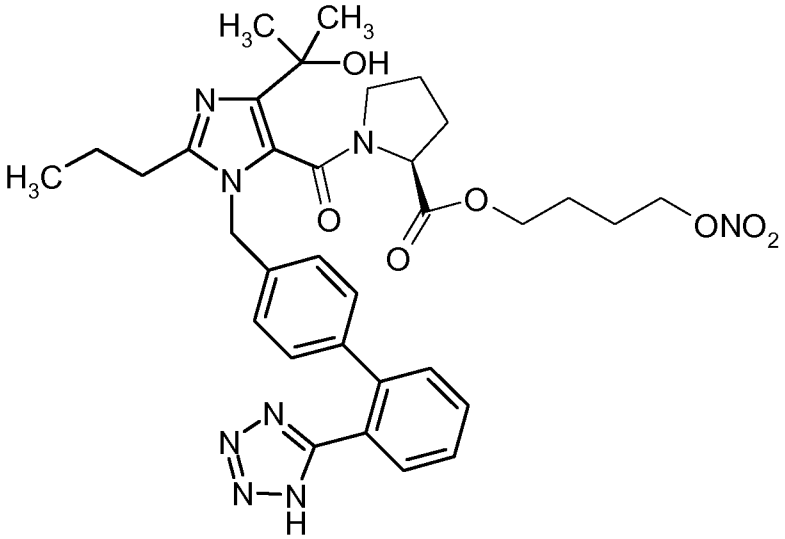

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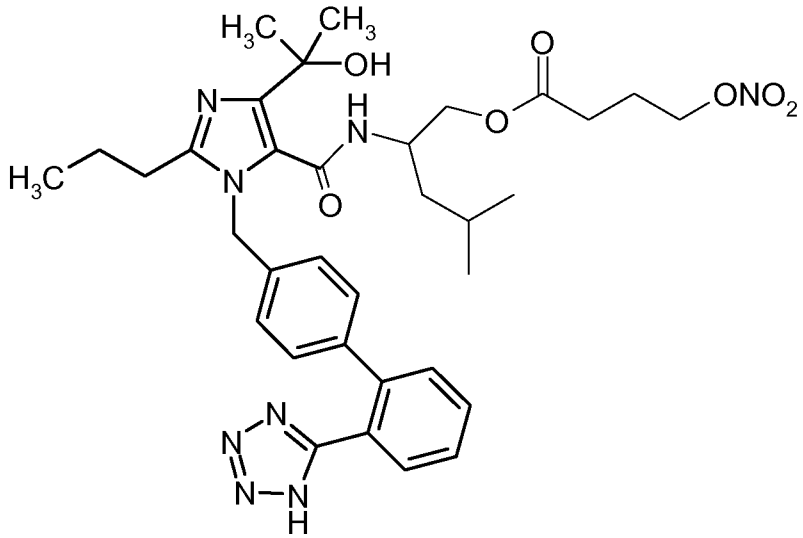

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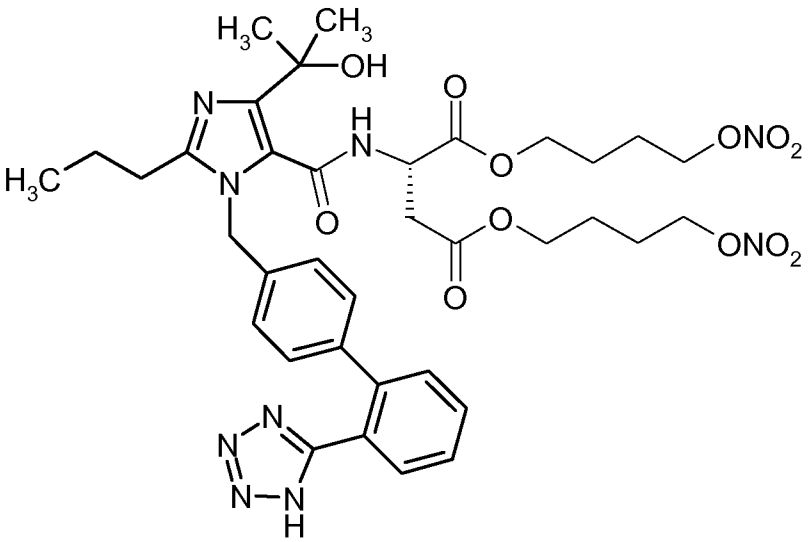

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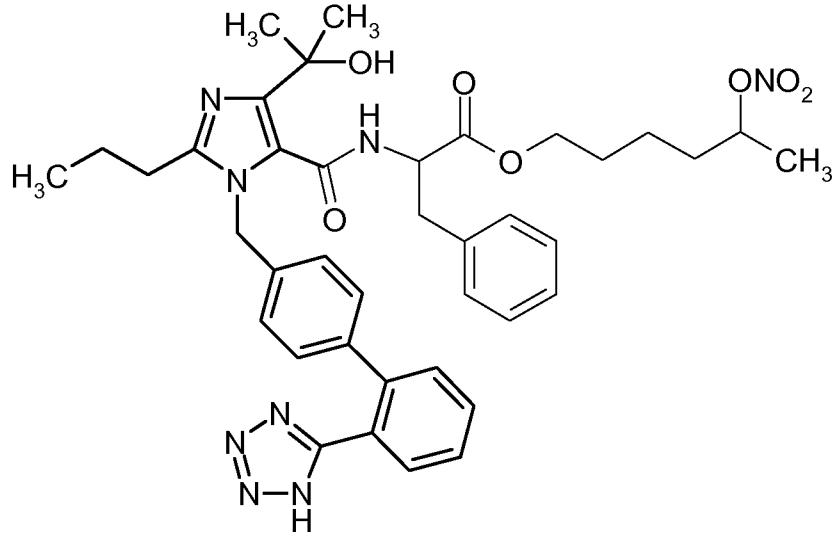

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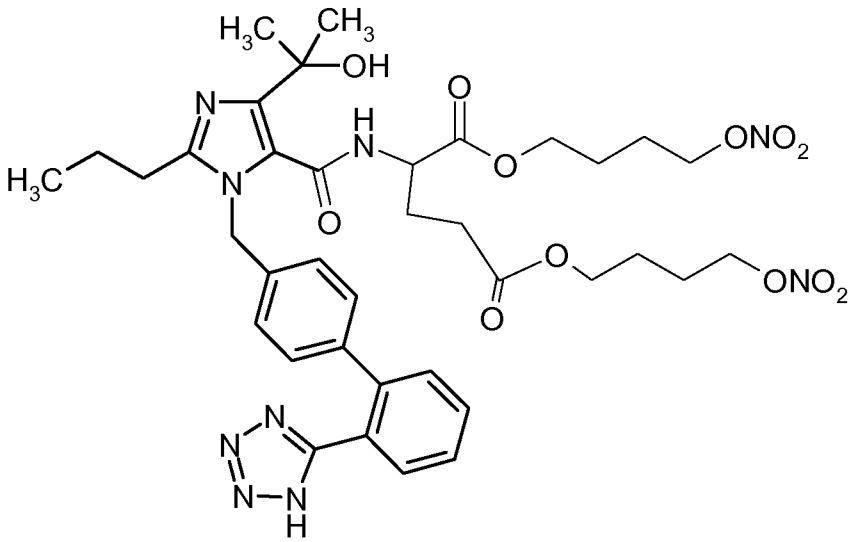

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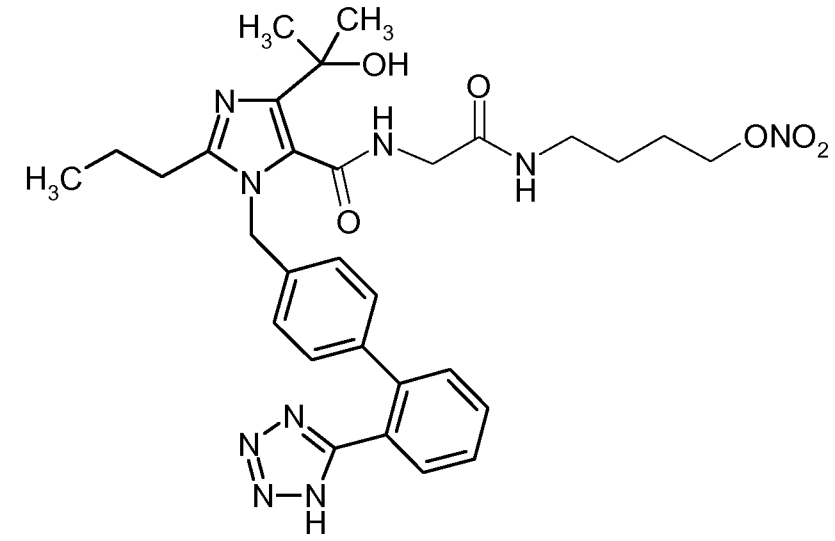

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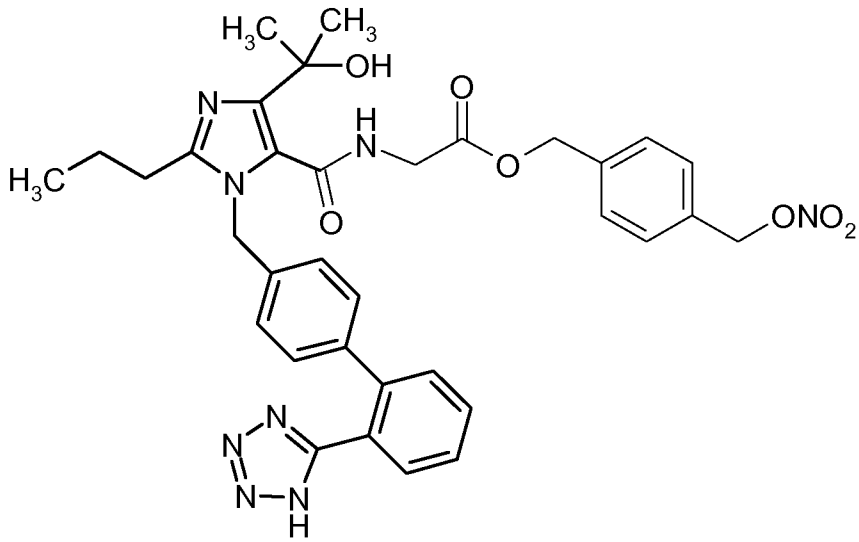

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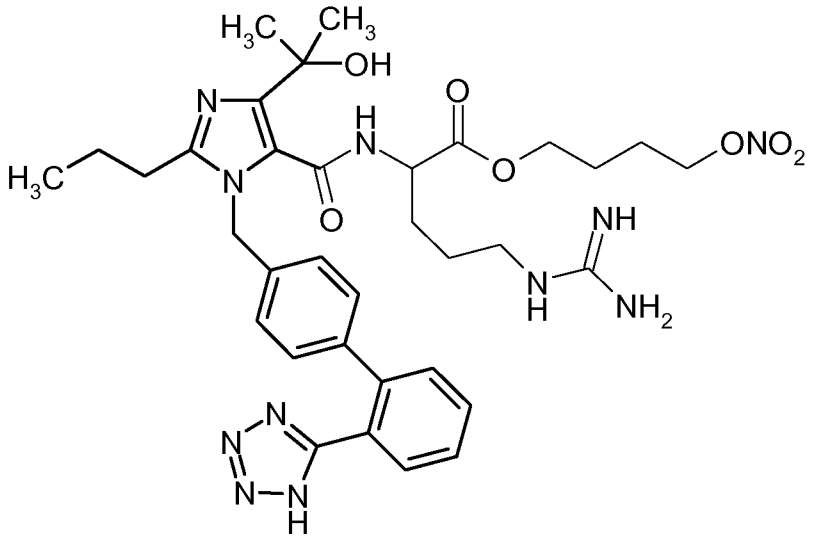

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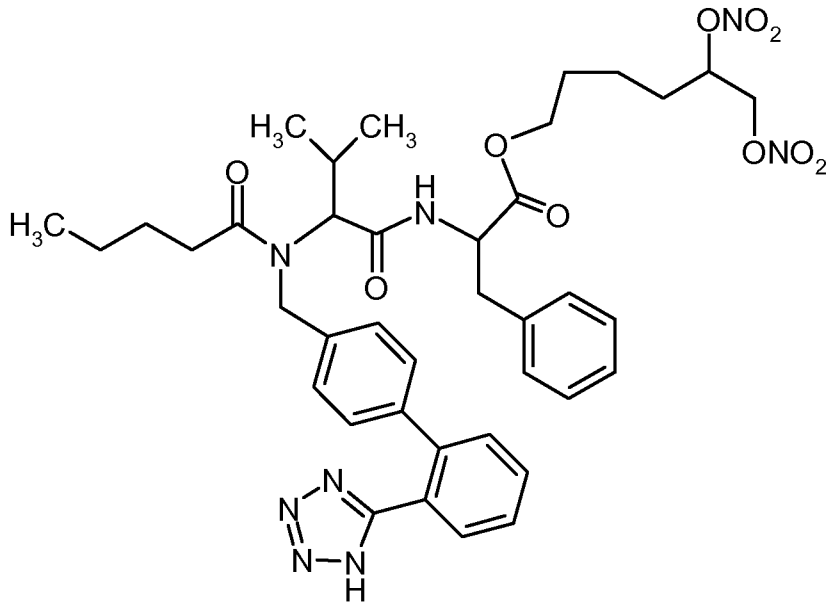

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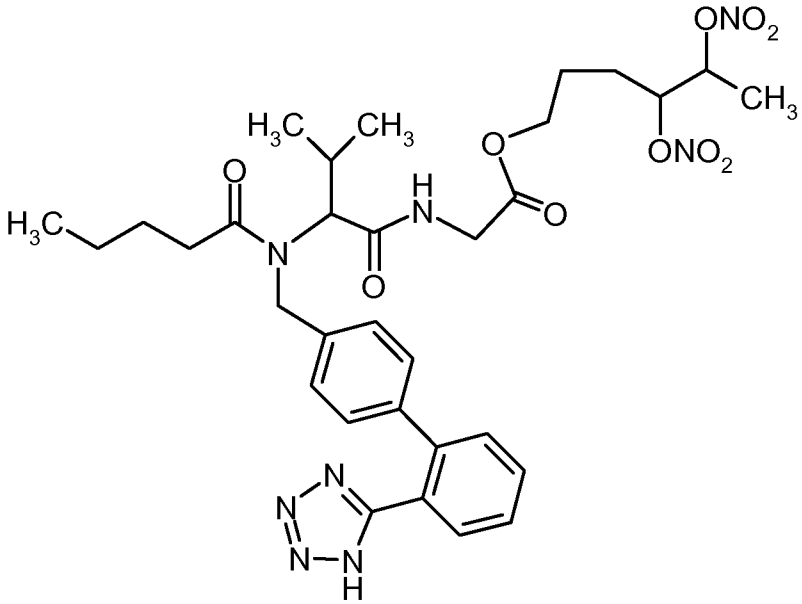

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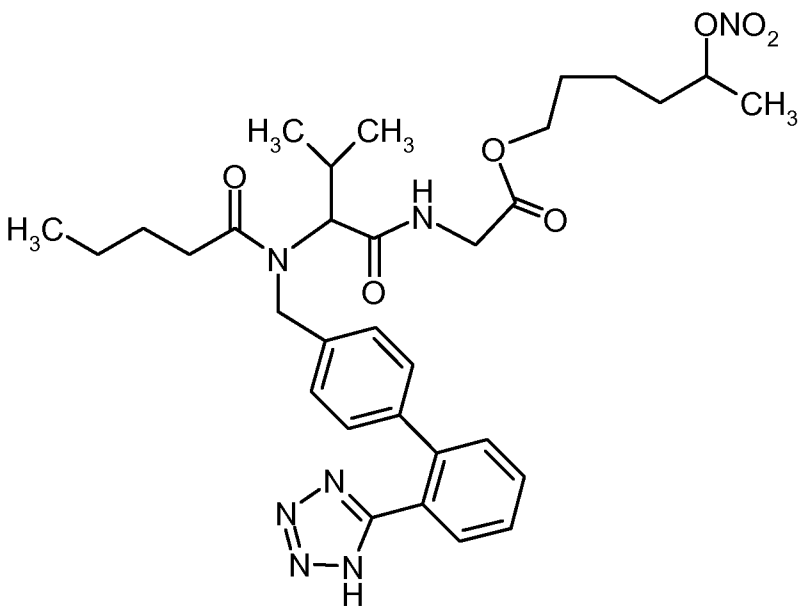

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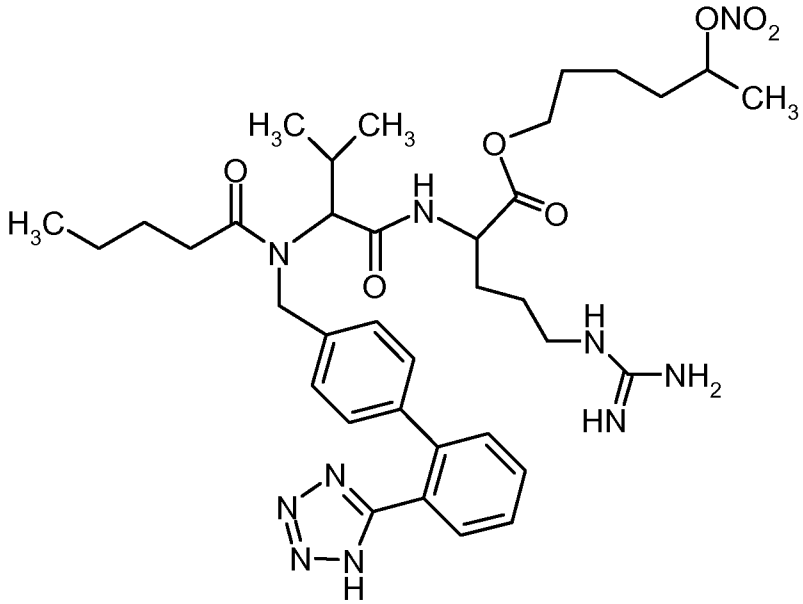

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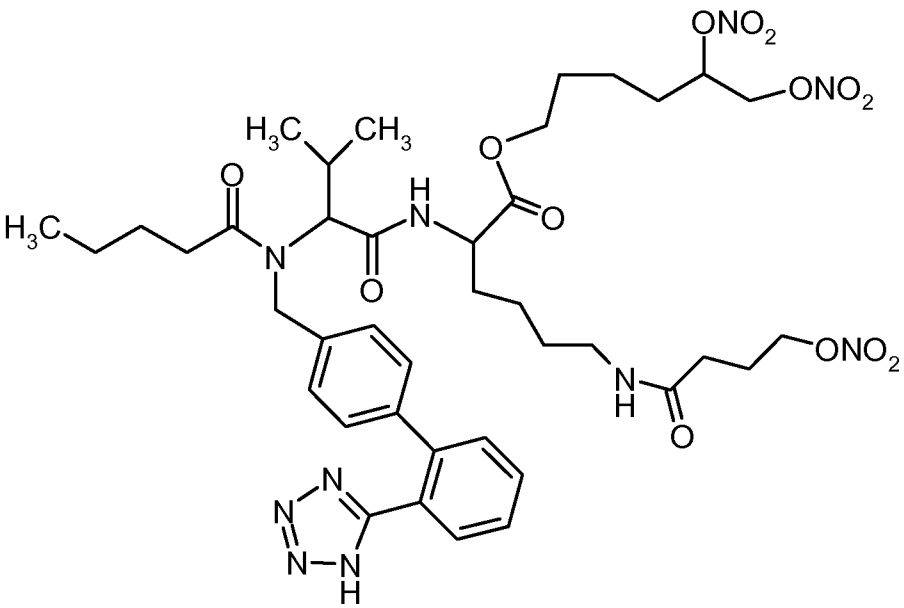

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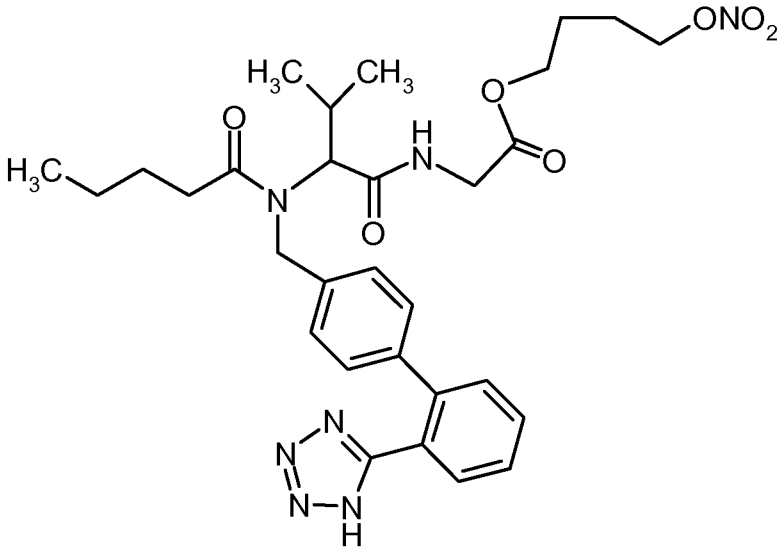

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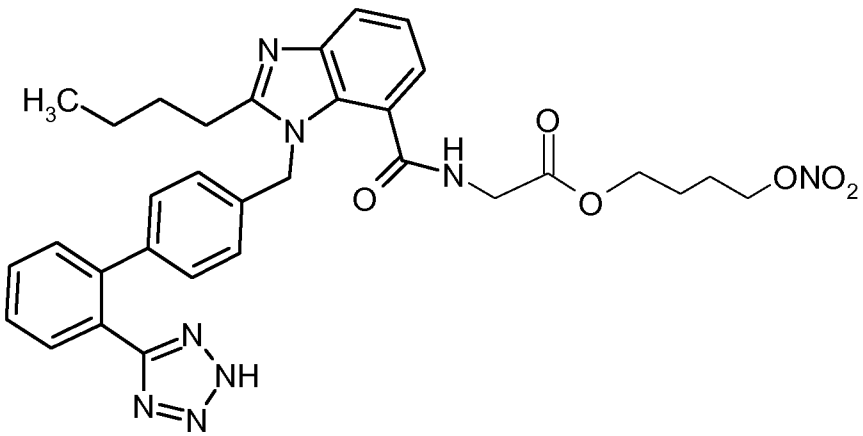

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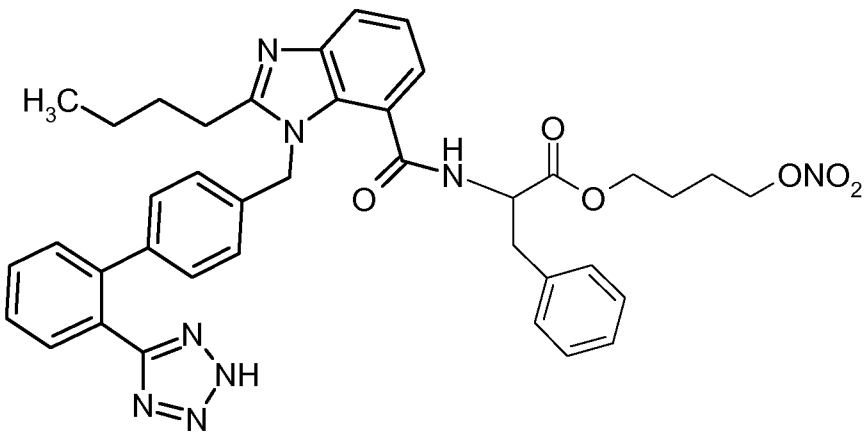

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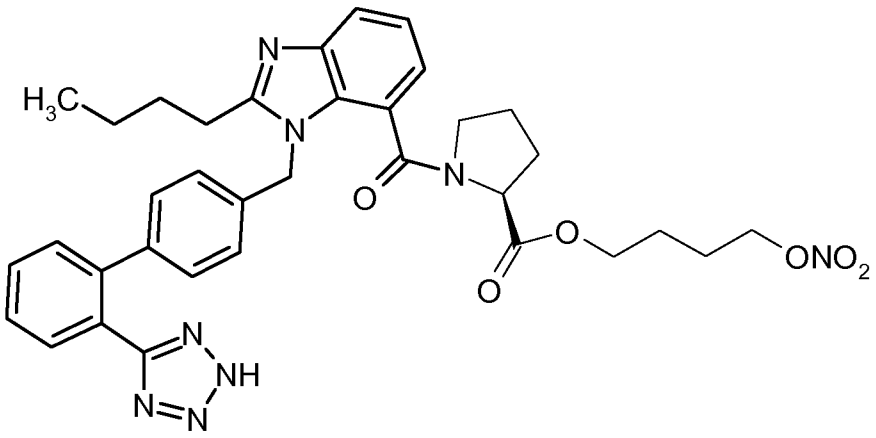

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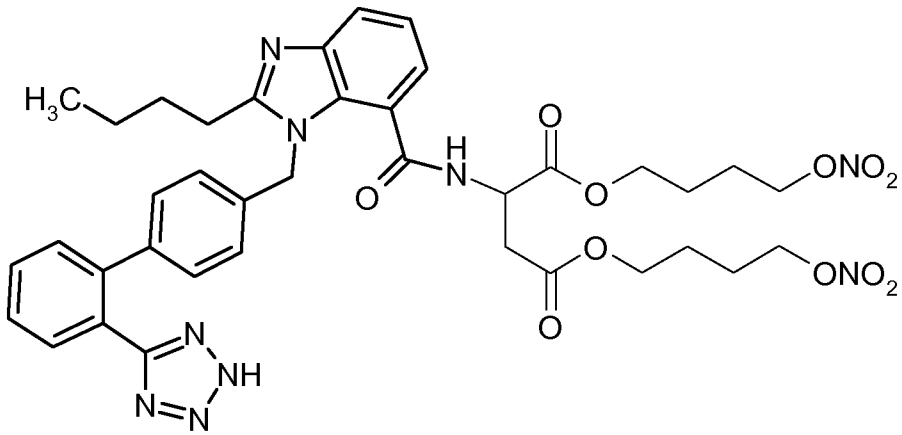

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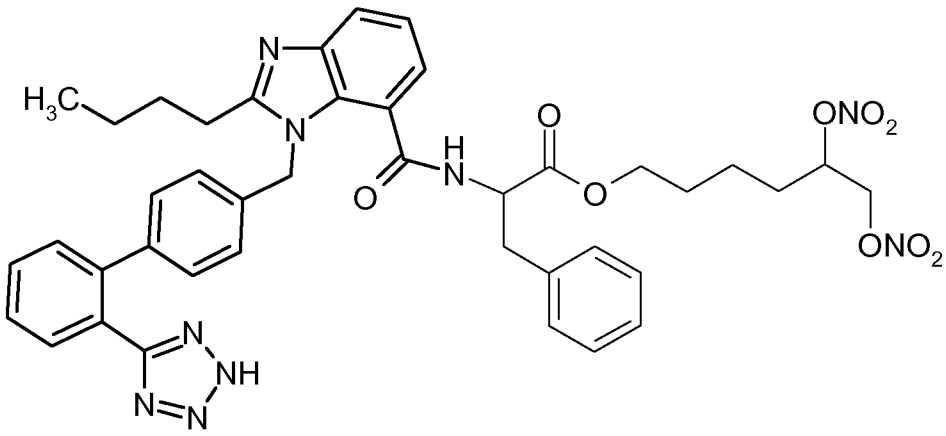

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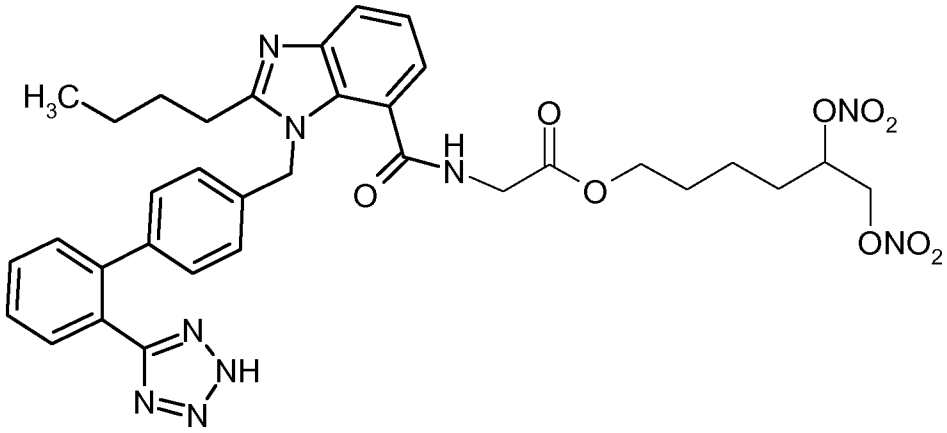

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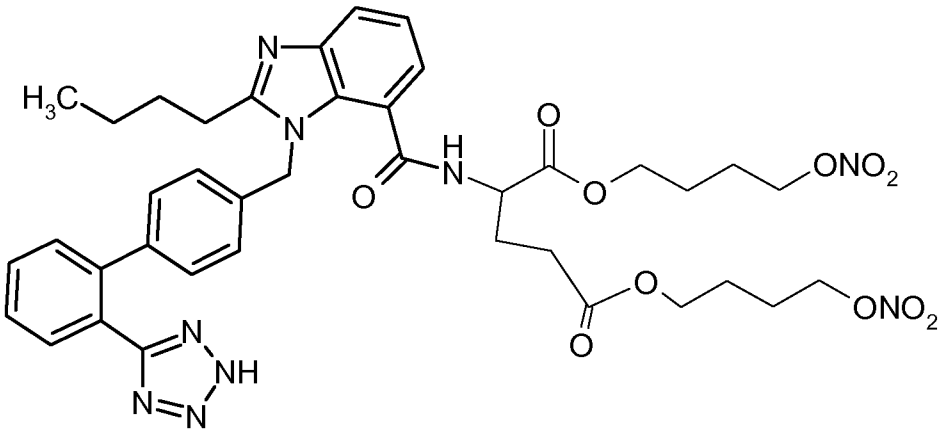

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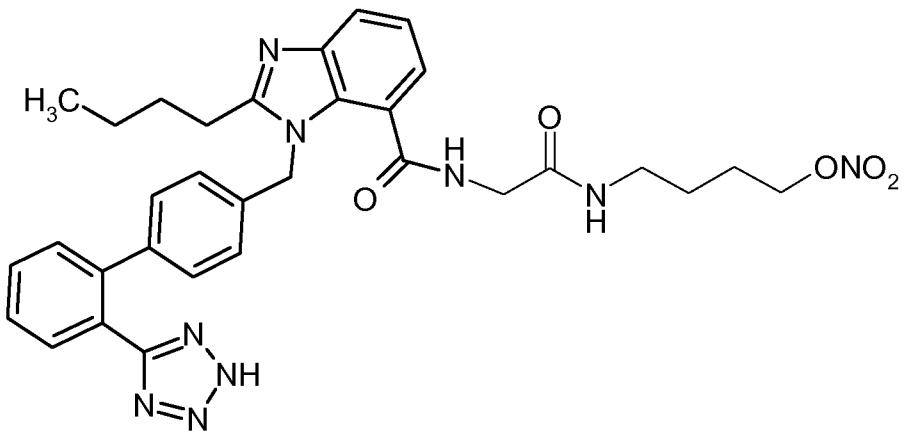

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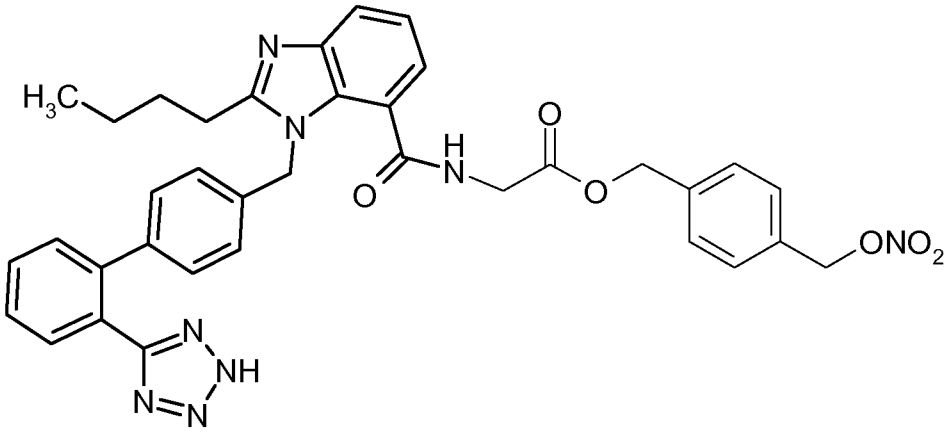

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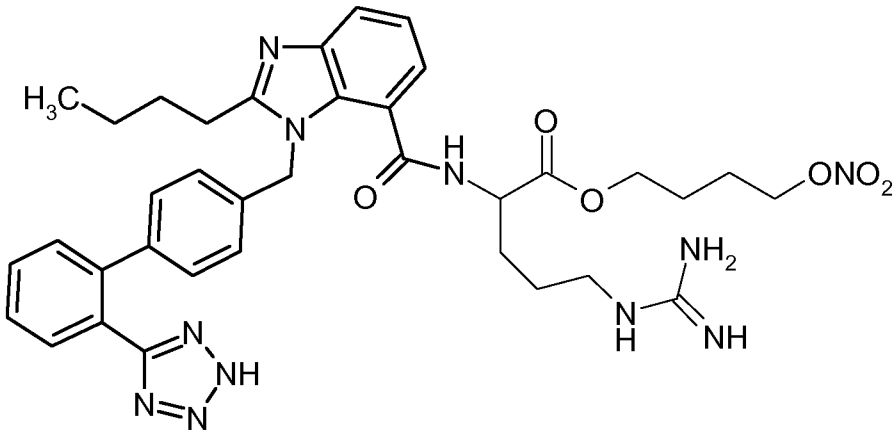

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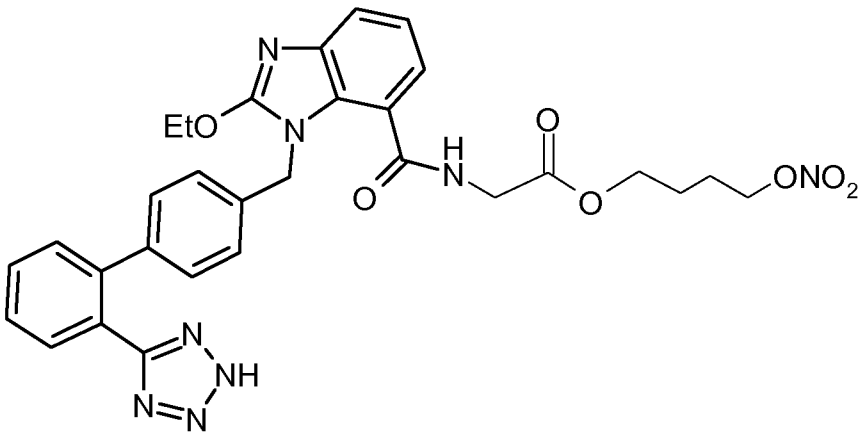

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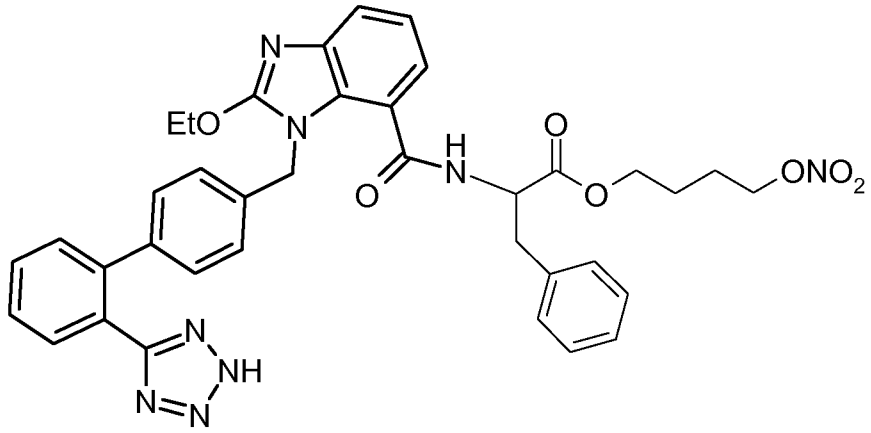

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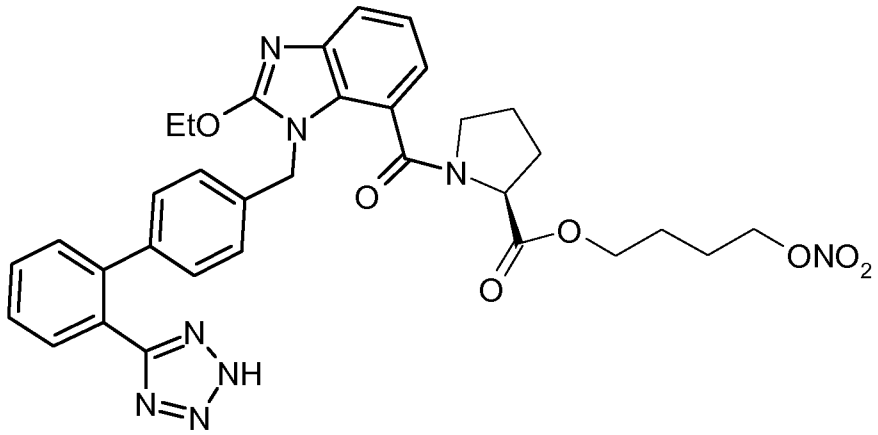

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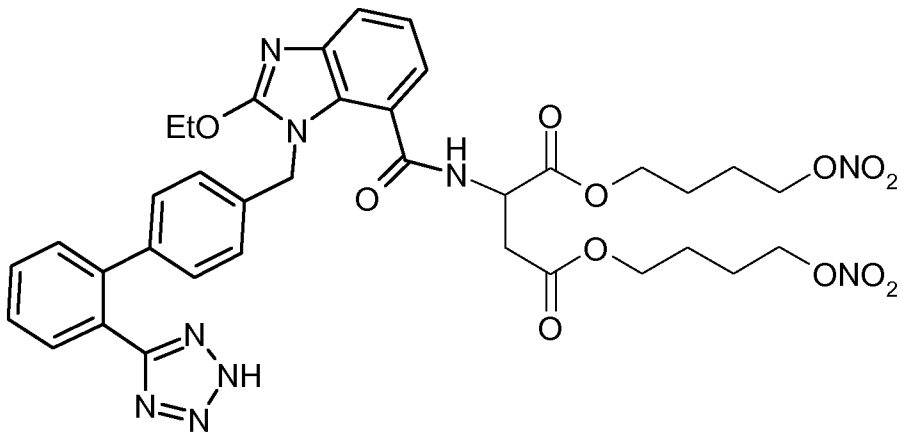

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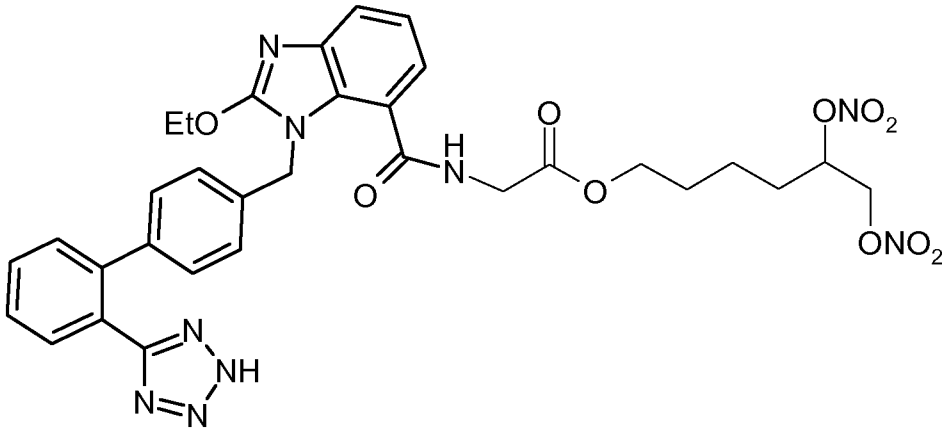

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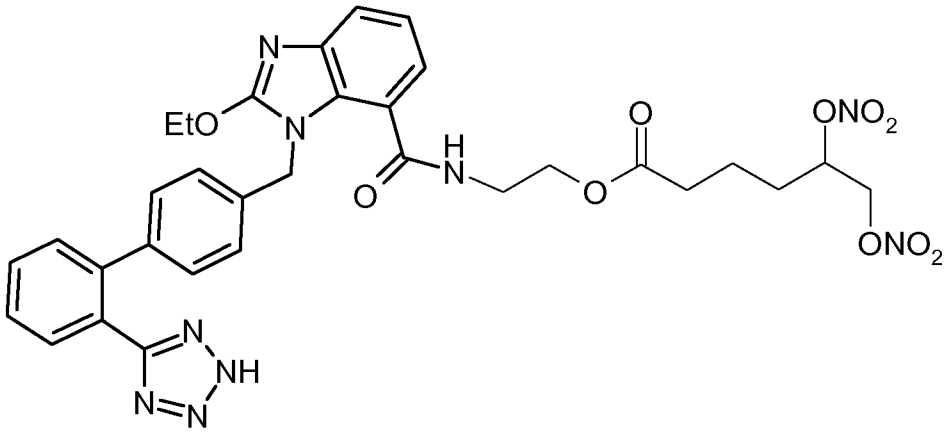

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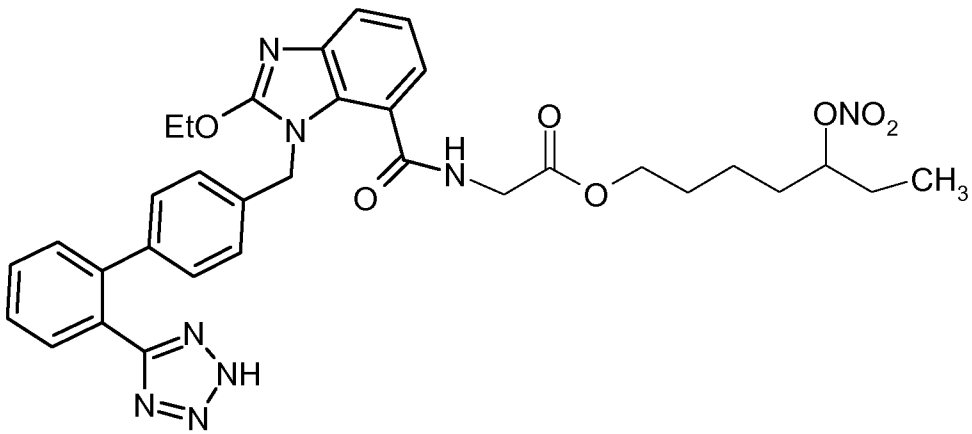

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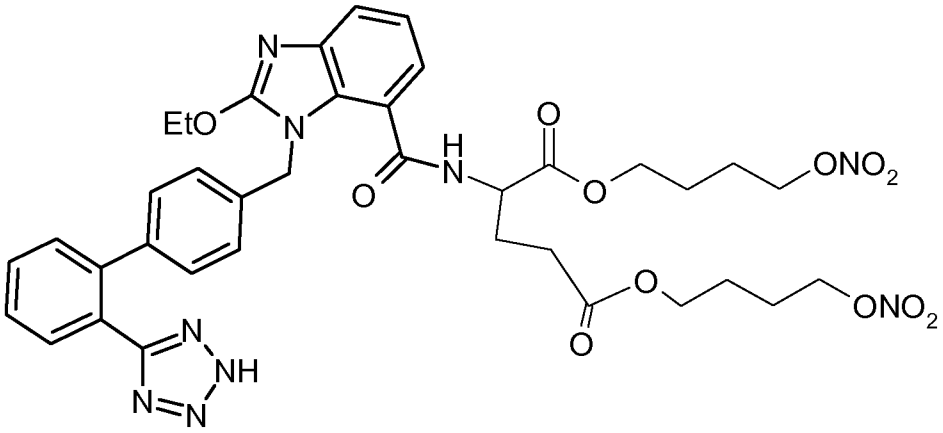

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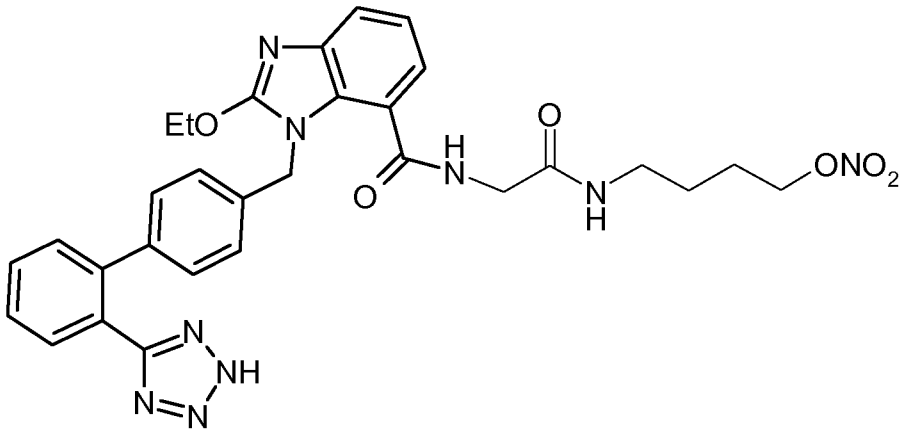

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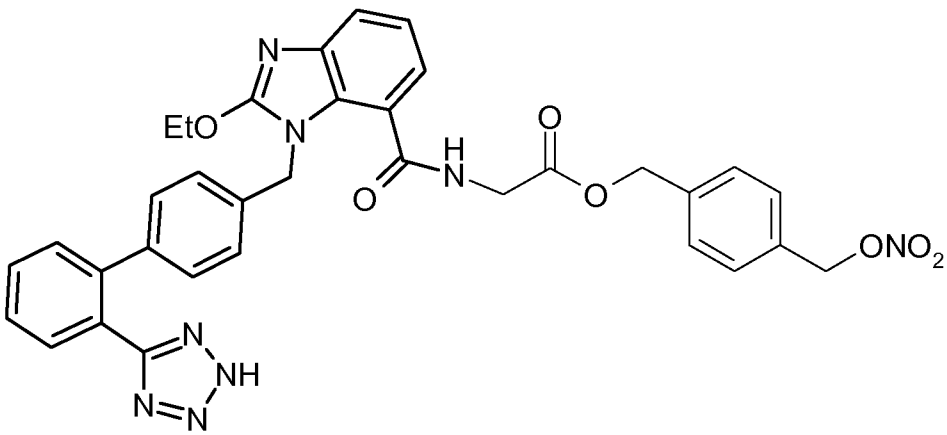

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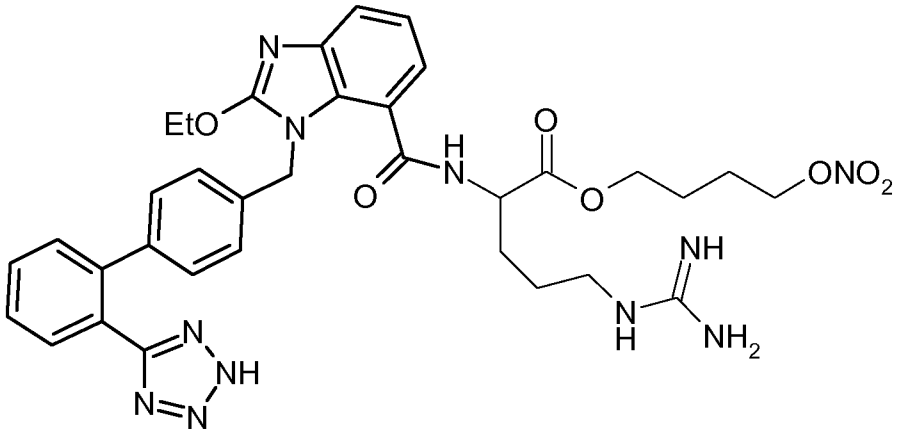

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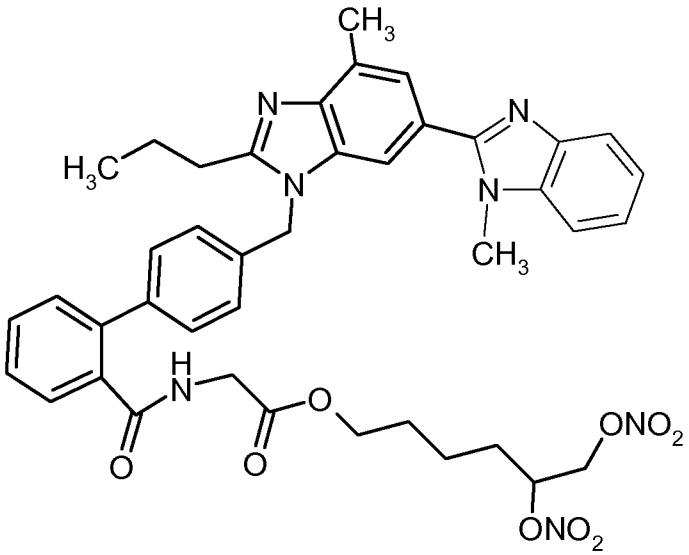

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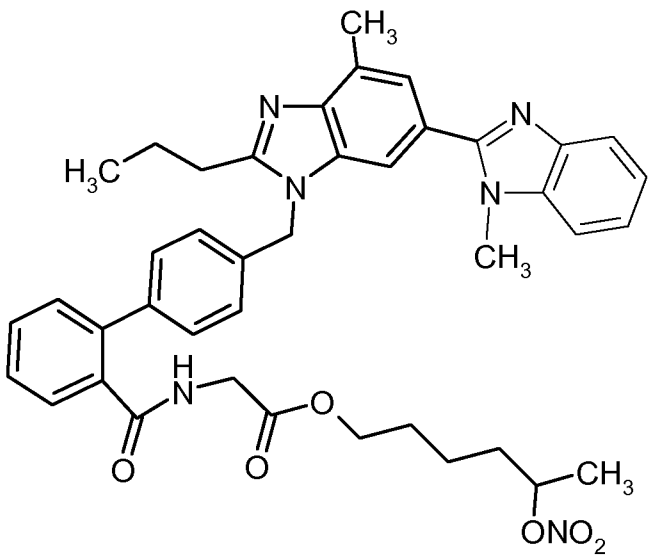

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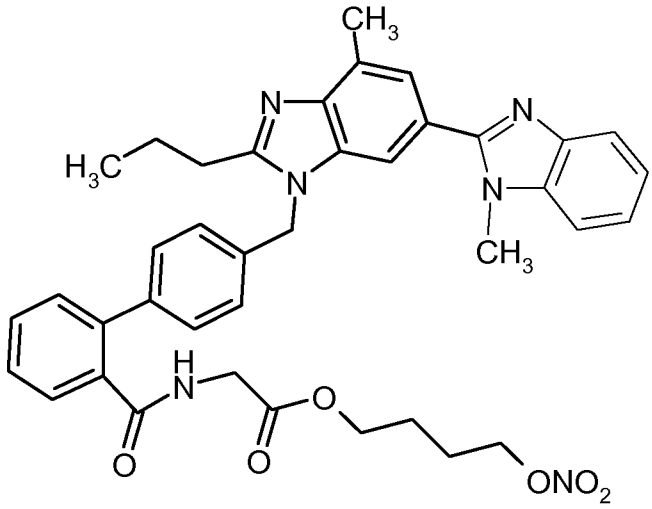

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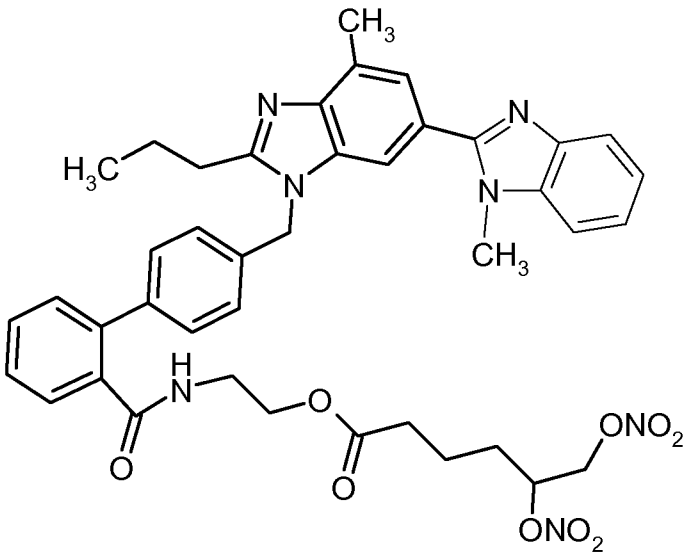

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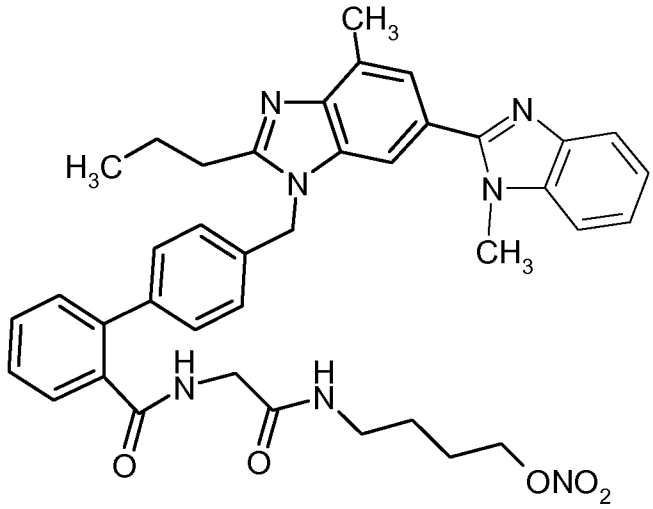

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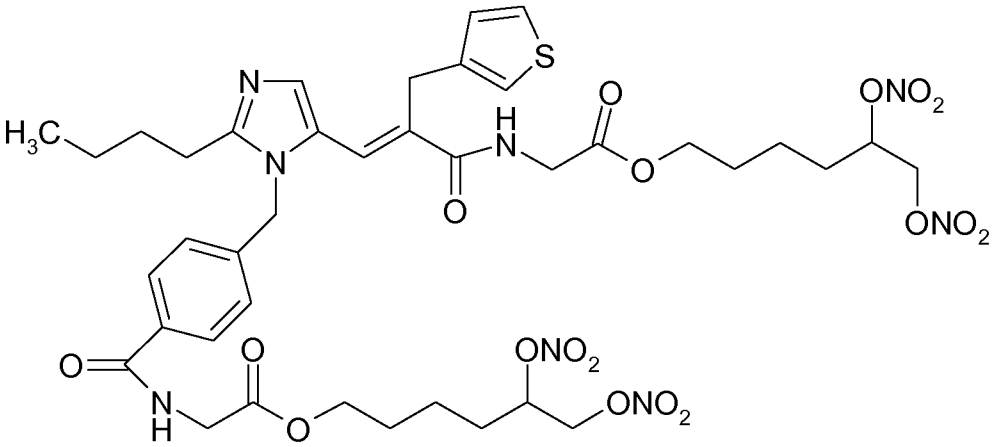

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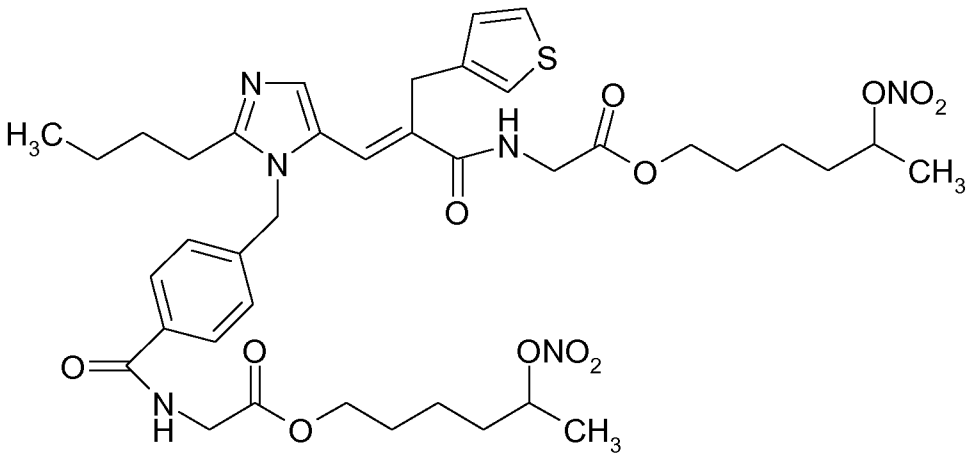

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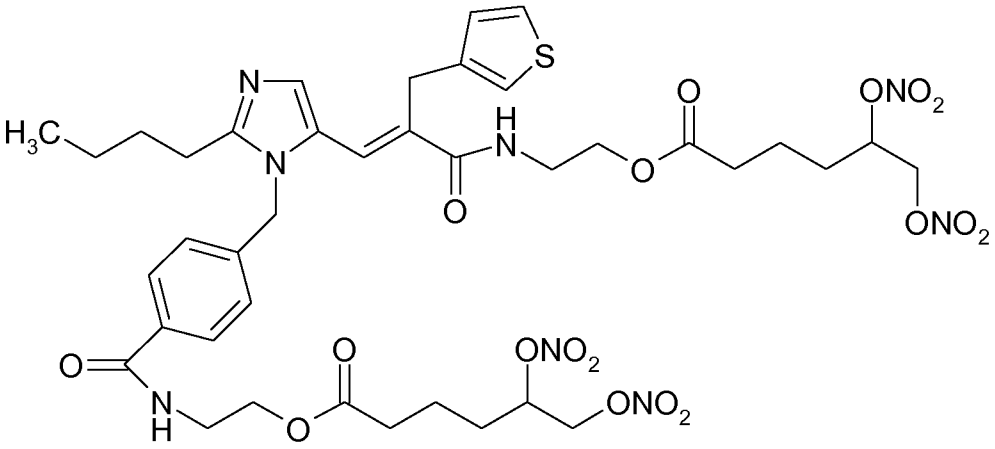

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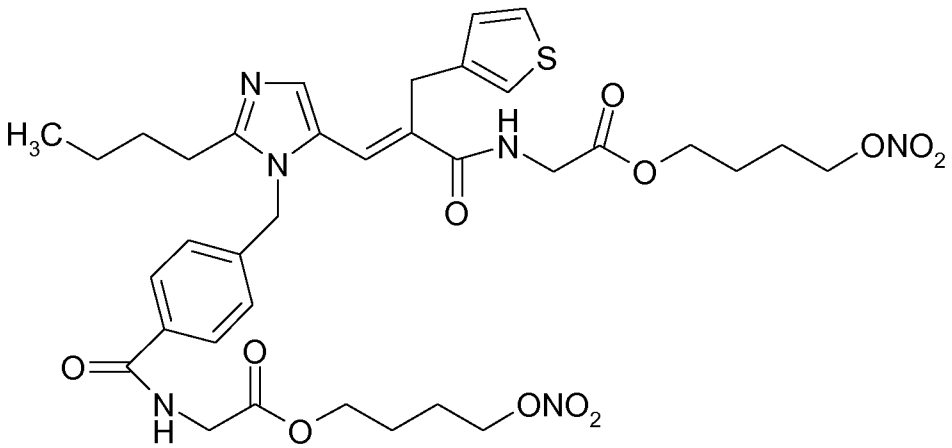

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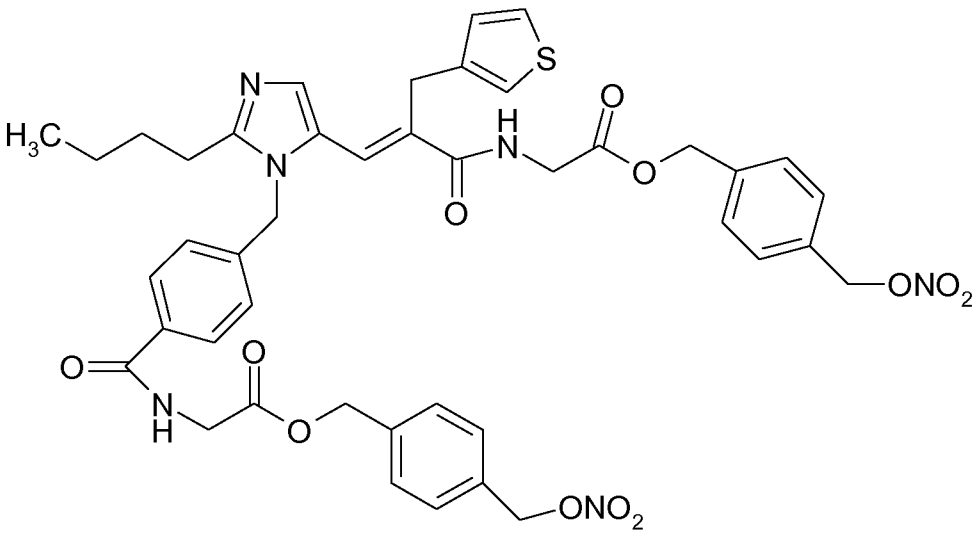
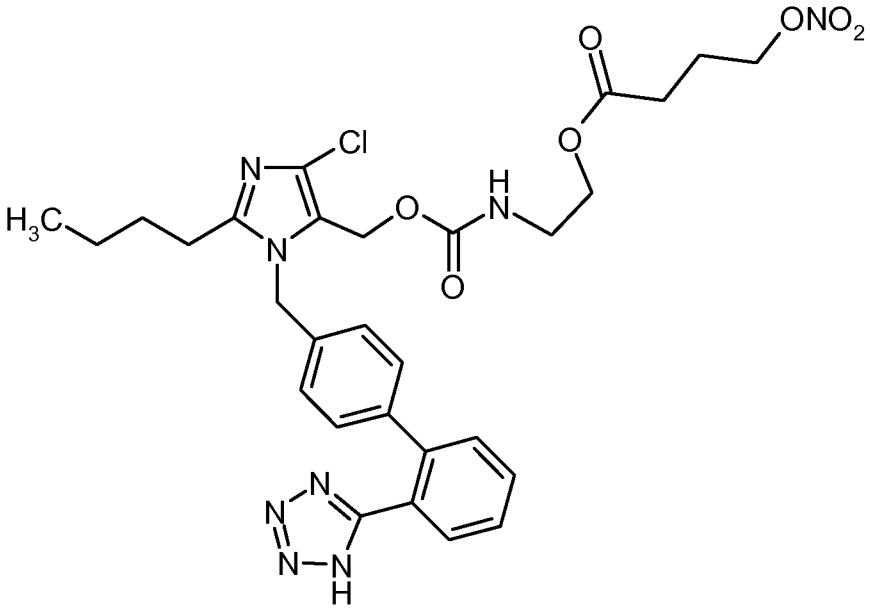
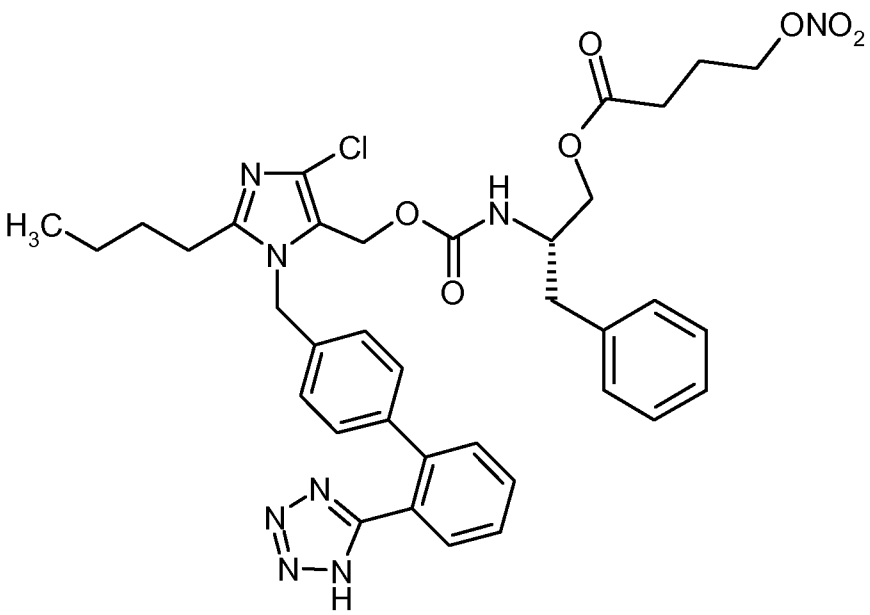


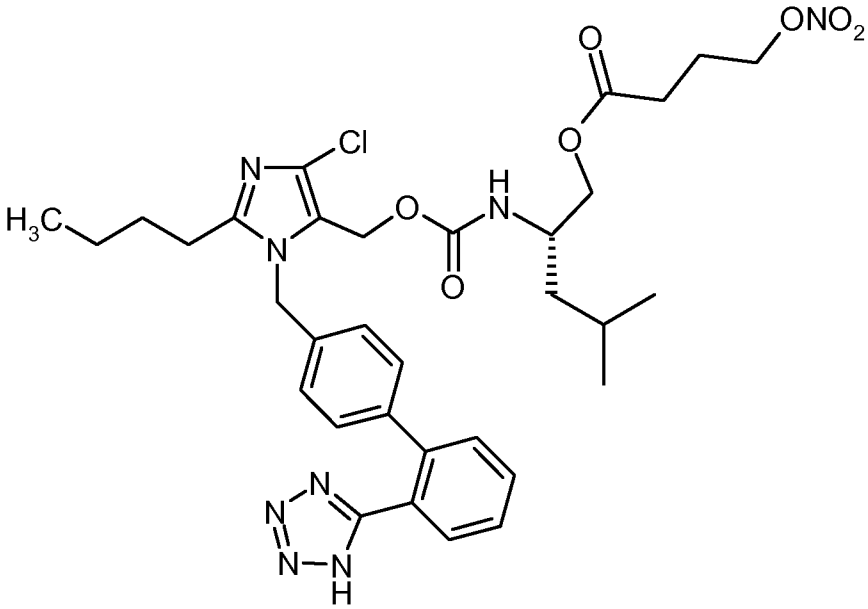
(109)



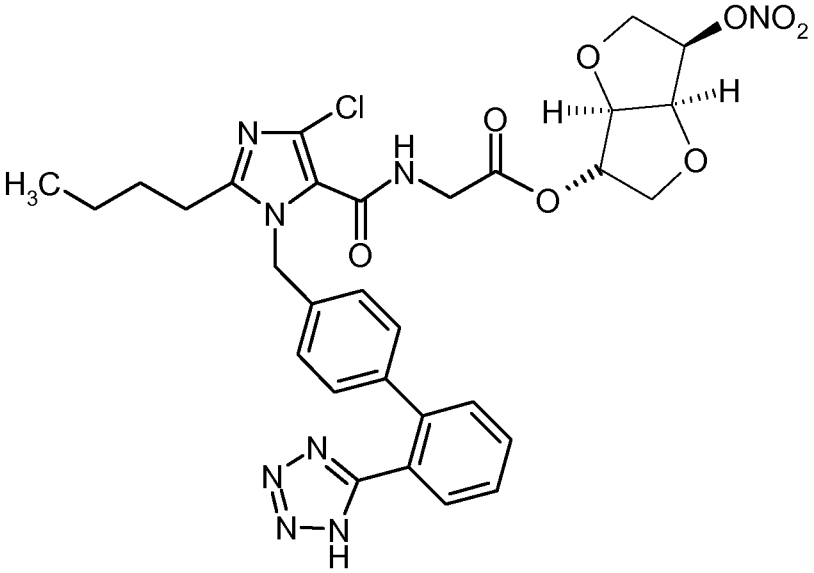
(110)



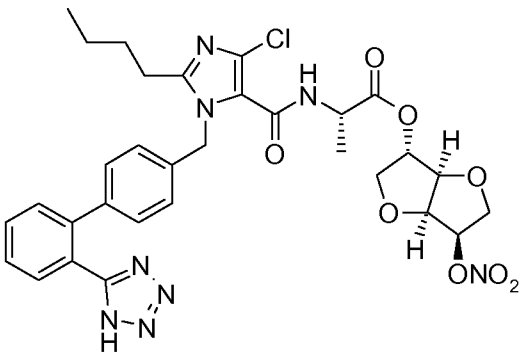
(111)



(112)



(113)



(114)

As mentioned above, object of the present invention are also pharmaceutical compositions containing at least a compound of the present invention of formula (I) together with non toxic adiuvants and/or carriers usually employed in the pharmaceutical field.

The daily dose of active ingredient that should be administered can be a single dose or it can be an effective amount divided into several smaller doses that are to be administered throughout the day. Usually, total daily dose may be in amounts preferably from 50 to 500 mg. The dosage regimen and administration frequency for treating the mentioned diseases with the compound of the invention and/or with the pharmaceutical compositions of the present invention will be selected in accordance with a variety of factors, including for example age, body weight, sex and medical condition of the patient as well as severity of the disease, route of administration, pharmacological considerations and eventual concomitant therapy with other drugs. In some instances, dosage levels below or above the aforesaid range and/or more frequent may be adequate, and this logically will be within the judgment of the physician and will depend on the disease state.

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

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

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

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g. lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

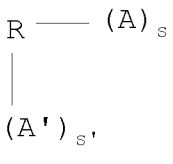
Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents,

emulsifying and suspending agents, and sweetening, flavouring and the like.

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

Synthesis procedure

1. The compounds of general formula (I)



(I)

wherein:

s is equal to 1;

s' is equal to 0

A is $-(Y-ONO_2)$ wherein Y is as above defined;

R is selected from the residue of formula (II) wherein R_0 is (IV) and R_1 is selected from the group (Va) wherein:

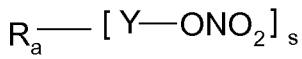
R_2 is n-butyl and R_3 is Cl, and N_0 is selected from:

1) (VIc), wherein K' is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K' is bound to the group $-(Y-ONO_2)$;

2)$-CH_2-O-CO-NH-J-K'$ wherein J is selected among (VIIa-VIIk) and K' is as above defined;

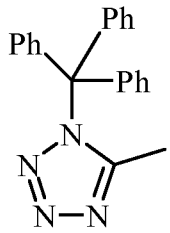
can be prepared as follows:

1a) by reacting a compound of formula (Ia)



(Ia)

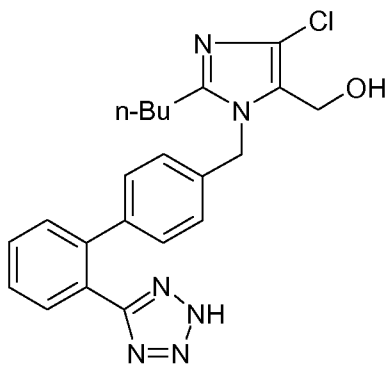
wherein s and Y are as above defined in **1.**, R_a is selected from the residue of formula (II) wherein R_1, R_2, R_3 and N_0 are as above defined in **1.**; R_0 is equal to (IVa) and is equal to:



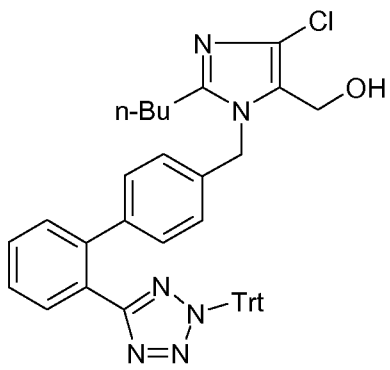
(IVa)

with anhydrous or aqueous organic or inorganic acid to hydrolyze the trityl protective group following procedure well known in the literature; alternatively the trityl protective group can be removed treating with an alcoholic solvent such is metanol or ethanol at temperature from 20-100° C for 1-48 hrs;

1b) by reacting a compound of formula R_{IIa} or $R_{IIa'}$,



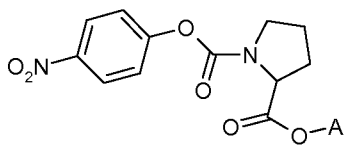
R_{IIa}



$R_{IIa'}$

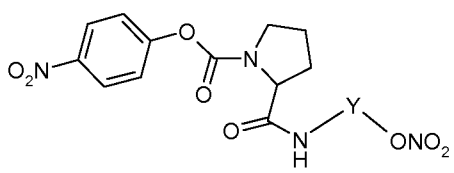
with:

1b.1) a compound of formula (Xa_a)-(Xa_e) depending on the meaning of K'

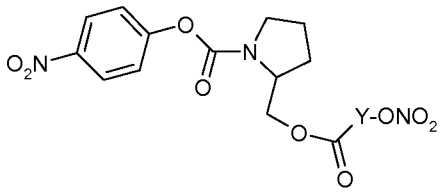


(Xa_a)

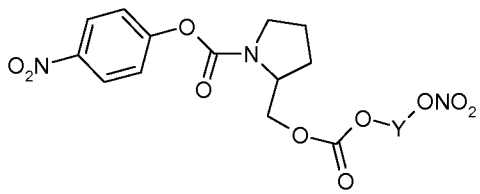
wherein A is $-(Y-ONO_2)$



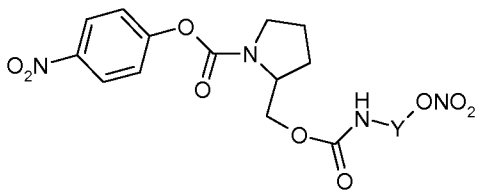
(Xa_b)



(Xa_c)



(Xa_d)



(Xa_e)

wherein Y is as above defined;

9

or

1b.2) compounds of formula (Xb_a)-(Xb_e) depending on the meaning of K':

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}J\text{-}COO\text{-}A$ (Xb_a)

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}J\text{-}CONH\text{-}Y\text{-}ONO_2$ (Xb_b)

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}J\text{-}CH_2O\text{-}CO\text{-}Y\text{-}ONO_2$ (Xb_c)

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}J\text{-}CH_2O\text{-}COO\text{-}Y\text{-}ONO_2$ (Xb_d)

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}J\text{-}CH_2O\text{-}CONH\text{-}Y\text{-}ONO_2$ (Xb_e)

wherein A is $-(Y\text{-}ONO_2)$, Y and J are as above defined;

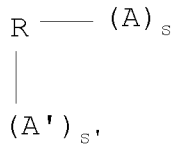
in the presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0°-100°C for time range of 1-60 hrs, or under microwave irradiation in the presence of DMAP and a Lewis acid such as $Sc(OTf)_3$ or $Bi(OTf)_3$ in solvents such as DMF, CH_2Cl_2 at temperatures range between 60°-120°C for time range of 1-120 min,;

Compound R_{IIa} is Losartan and compound $R_{IIa'}$ is trityl losartan: both compounds are known and commercially

available. When R_{IIa} is used the deprotection step described in **1a)** is required.

For the preparation of compounds of formula (Xa_a)-(Xa_e) and (Xb_a)-(Xb_e) see Appendix 1: preparations **A1-A6.**

2. The compounds of general formula (I)



(I)

wherein:

s is equal to 1;

s' is equal to 0

A is $-(Y\text{-}ONO_2)$ wherein Y is as above defined;

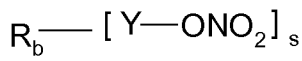
R is selected from the residue of formula (II) wherein R_0 is (IV) and R_1 is selected from the group (Vd) and N_0 is selected from:

1) (VIa), wherein K' is equal to -COO-, -CONH-, $-CH_2$-O-CO-, $-CH_2$-O-COO- or $-CH_2$-O-CONH- and K' is bound to the group $-(Y\text{-}ONO_2)$;

2)-O-CO-NH-J-K' wherein J is selected among (VIIa-VIIk) and K' is as above defined;

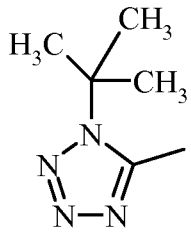
can be prepared as follows

2a) by reacting a compound of formula (Ib)



(Ib)

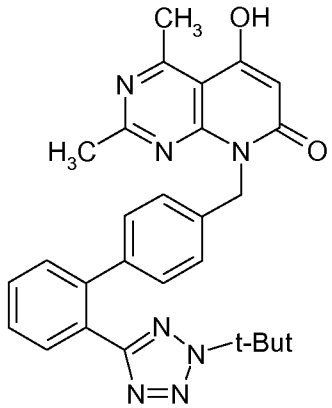
wherein s and Y are as above defined in **1.**, R_b is selected from the residue of formula (II) wherein R_1 and N_0 are as above defined in **2.**; R_0 is equal to (IVb) and is equal to:



(IVb)

with anhydrous or aqueous organic or inorganic acid to hydrolyze the t-butyl protective group following the procedure described in **1a)**;

2b) by reacting a compound of formula R_{IIb}



R_{IIb}

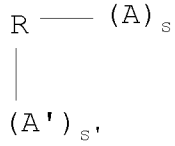
with:

2b.1) a compound of formula (Xa_a)-(Xa_e), described in **1b)**, depending on the meaning of K' ; or

2b.2) a compound of formula (Xb_a)-(Xb_e) above defined **1b)**, depending on the meaning of K';

using the procedure already described in **1b)**. Compound R_{IIb} is the t-Butyl protected Enoltasosartan (the active metabolite of tasosartan) and can be synthesized as described by John W. Ellingboe et al. in *J. Med. Chem.* **1998**, 41, 4251-4260.

3. The compounds of general formula (I)



(I)

wherein:

s is equal to 1;

s' is equal to 0

A is -(Y-ONO_2) wherein Y is as above defined,

R is selected from the residue of formula (II) wherein R_0 is (IV), R_1 is selected from the group:

i) (Va) wherein R_2 is n-butyl and R_3 is Cl;

ii) (Va) wherein R_2 is n-propyl and R_3 is C_2F_5;

iii) (Va) wherein R_2 is n-propyl and R_3 is the group $C(CH_3)_2OH$;

iv) (Vb);

v) (Vc) wherein R_4 is n-butyl;

vi) (Vc) wherein R_4 is -OEt;

wherein N_0 is selected from:

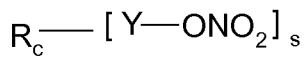
1) (VIb), wherein K' is equal to -COO-, -CONH-, -CH_2-O-CO-, -CH_2-O-COO- or -CH_2-O-CONH- and K' is bound to the group -(Y-ONO_2);

2)-CO-NH-J-K' wherein J is selected among (VIIa-VIIk) and K' is as above defined;

and

can be prepared as follows

3a) by reacting a compound of formula (Ic)

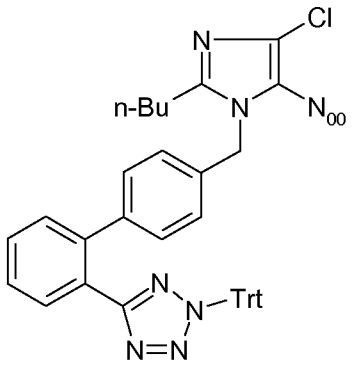


(Ic)

wherein s and Y are as above defined in **1.**, R_c is selected from the residue of formula (II) wherein N_0 is as above defined in **3.** and R_1 is as above defined in the points i)-vi); R_0 is equal to (IVa) and is as previously defined, following the same procedure described in **1a)**;

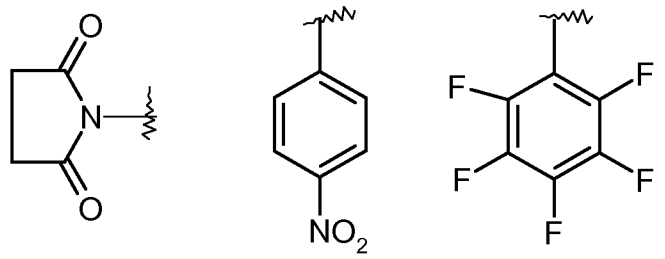
3b) by reacting:

i) a compound of formula R_{IIc}



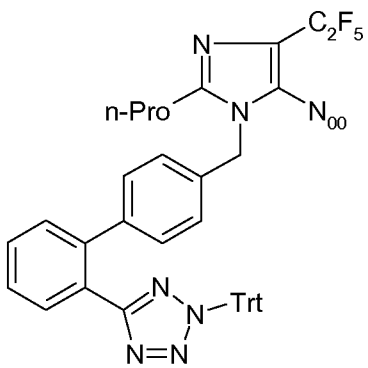
R_{IIc}

Wherein N_{00} is -COOH, -COHal or -COOAct wherein Hal is an halogen atom such as Cl, Br, F; Act is a carboxylic acid activating group used in peptide chemistry such as:

Act = 

; or

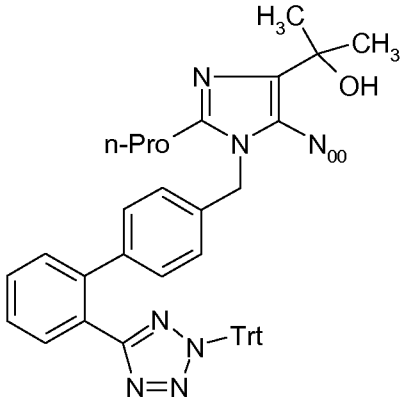
ii) a compound of formula R_{IId}



R_{IId}

wherein N_{00} is as previously defined; or

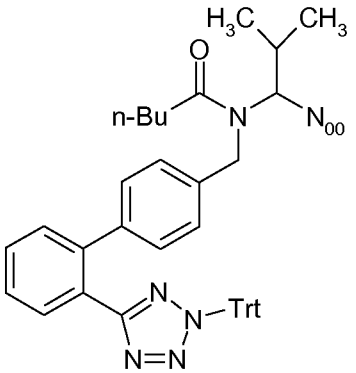
iii) a compound of formula R_{IIe}



R_{IIe}

wherein N_{00} is as previously defined; or

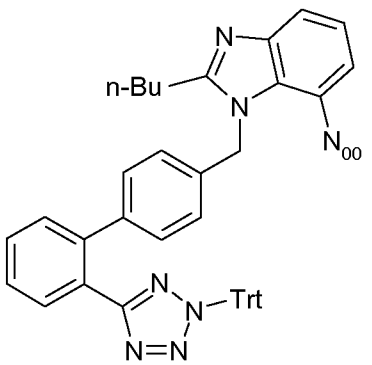
iv) a compound of formula R_{IIf}



R_{IIf}

wherein N_{00} is as previously defined; or

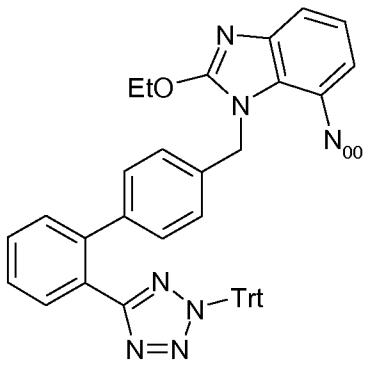
v) a compound of formula R_{IIg}



R_{IIg}

wherein N_{00} is as previously defined; or

vi) a compound of formula R_{IIh}

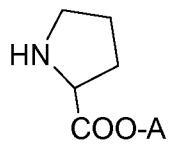


R_{IIh}

wherein N_{00} is as previously defined;

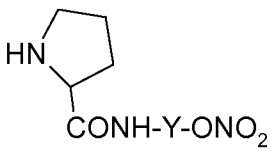
with

3b.1) a compound of formula (Xc_a)-(Xc_e) depending on the meaning of K'

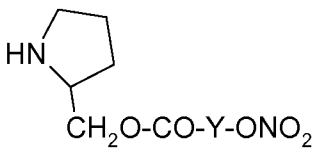


(Xc_a)

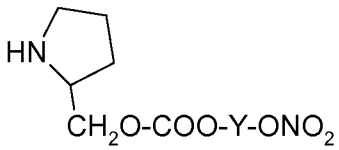
wherein A is $-(Y-ONO_2)$



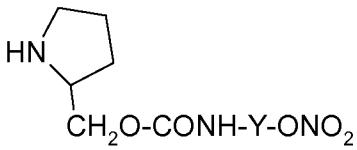
(Xc_b)



(Xc_c)



(Xc_d)



(Xc_e)

wherein Y is as above defined;

or

3b.2) a compound of formula (Xd_a)-(Xd_e), depending on the meaning of K'

NH_2-J-COO-A

(Xd_a)

wherein A is $-(Y-ONO_2)$

$NH_2-J-CONH-Y-ONO_2$

(Xd_b)

$NH_2-J-CH_2O-CO-Y-ONO_2$

(Xd_c)

$NH_2-J-CH_2O-CO-O-Y-ONO_2$

(Xd_d)

$NH_2-J-CH_2O-CO-NH-Y-ONO_2$

(Xd_e)

wherein Y and J are as above defined;

by reaction with:

1) if **N_{00} = -COOH:**

a condensing agent such as dicyclohexylcarbodiimide (DCC) or N,N'-carbonyldiimidazol (CDI) or other known condensing reagents such as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), in the presence or not of 1-Hydroxybenzotriazole (HOBT) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 80°C in the presence or not of a base as for example DMAP.

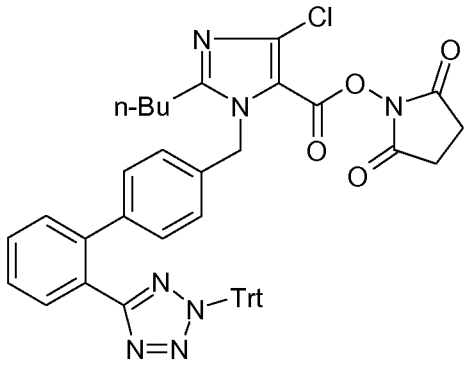
2) if **N_{00} = -COHal or -COOAct:**

the reaction is generally carried out in presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0°-80°C or in a double phase system H_2O/Et_2O at temperatures range between 20°-40°C; or in the presence of DMAP and a Lewis acid such as $Sc(OTf)_3$ or $Bi(OTf)_3$ in solvents such as DMF, CH_2Cl_2.

For the preparation of compounds of formula $(Xc_a)-(Xc_e)$ and $(Xd_a)-(Xd_e)$ see Appendix 1, preparations **A1-A6.**

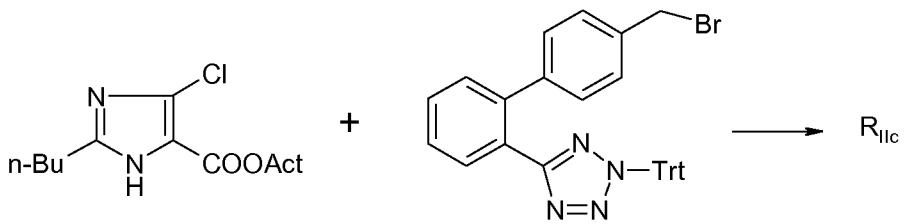
Compounds R_{IIc}-R_{IIh} wherein -N_{00} is -COHal or -COOAct were obtained transforming a compound R_{IIc}-R_{IIh} wherein -N_{00} is -COOH by known procedures.

Alternatively compounds R_{IIc} wherein -N_{00} is -COOAct and preferably -N_{00} is the N-hydroxysuccinimido ester:



R_{IIc}

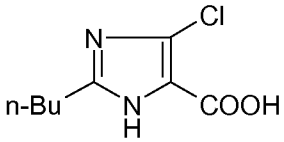
can be prepared more efficiently by reacting compound A with the commercially available compound B:



A B

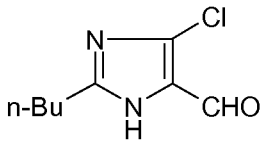
The reaction is generally carried out in presence of a base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between -15°-+80°C or in a double phase system H_2O/Et_2O at temperatures range between 20°- 40°C.

Compounds of formula A can be obtained by reacting compounds of formula C with compound Act-OH, and preferably with N-hydroxysuccinimide following known procedures:



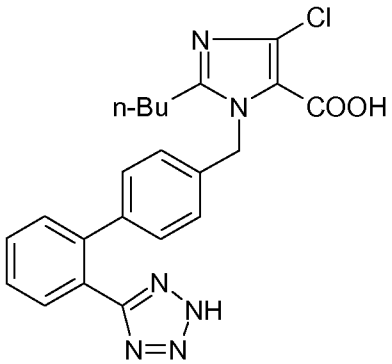
C

Compound C can be prepared by $KMnO_4$ oxidation as described in WO 2005/011646 of the corresponding aldehyde D, commercially available:



D

R_{IIc} wherein $-N_{00}$ is –COOH can be prepared from compound R_{IIcc} known as EXP 3174:



R_{IIcc} (EXP 3174)

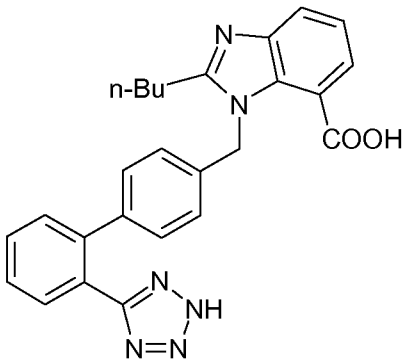
by reacting with trityl chloride and TEA in CH_2Cl_2 following known procedures;

R_{IId} wherein $-N_{00}$ is –COOH is known as trityl DuP 532 and can be prepared as described by Michael E. Pierce in *J. Org. Chem.* **1993**,58,4642-4645;

R_{IIe} wherein $-N_{00}$ is –COOH is known as trityl olmesartan and is commercially available;

R_{IIf} wherein $-N_{00}$ is –COOH is known as trityl valsartan and is commercially available

R_{IIg} wherein $-N_{00}$ is –COOH can be prepared from compound R_{IIgg} known as CV 11194 by reacting with trityl chloride as already described for R_{IIcc};

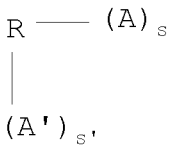


R_{IIgg}, CV-11194

R_{IIgg} can be prepared as decribed by Kubo, K. et al, in *J. Med. Chem.* **1993**,*36*, 1772-1784.

R_{IIh} wherein $-N_{00}$ is –COOH is known as trityl candesartan and is commercially available.

4. The compounds of general formula (I)



(I)

wherein:

s is equal to 1 or 2;

s' is equal to 0,

A is $-(Y-ONO_2)$ wherein Y is as above defined,

R is selected from:

i) **s = 1:** the residue of formula (II) wherein R_1 is selected from (Ve) and R_0 is N_0 and is selected from:

1) (VIb), wherein K' is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K' is bound to the group $-(Y-ONO_2)$;

2)-CO-NH-J-K' wherein J is selected among (VIIa-VIIk) and K' is as above defined;

ii) **s = 2:** the residue of formula (III) wherein N_0 is selected from:

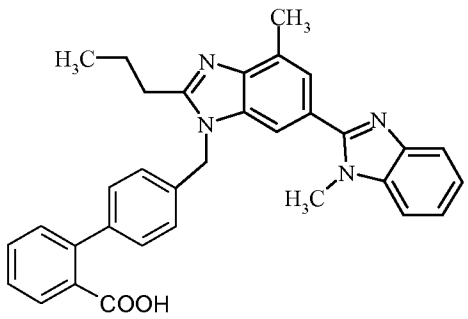
1) (VIb), wherein K' is equal to -COO-, -CONH-, $-CH_2$-O-CO-, $-CH_2$-O-COO- or $-CH_2$-O-CONH- and K' is bound to the group $-(Y-ONO_2)$;

2)-CO-NH-J-K' wherein J is selected among (VIIa-VIIk) and K' is as above defined;

can be prepared as follows:

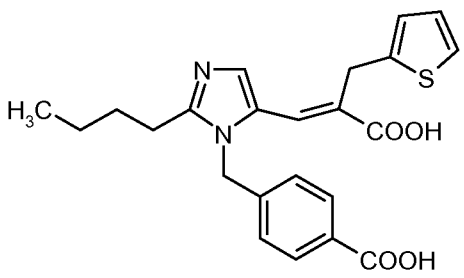
4a) by reacting a compound of formula R_{IIi} or a compound of formula R_{IIIa} with compounds $(Xc_a)-(Xc_e)$ or $(Xd_a)-(Xd_e)$ alredy described, following the same procedure described in **3b)** using a ratio of $(Xc_a)-(Xc_e)$ or $(Xd_a)-(Xd_e)$ 1:1 or 2: 1 if more than one group -COOH is present.

Compound R_{IIi} is known as telmisartan and is commercially available:



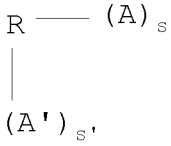
R_{IIi}

Compound R_{IIIa} is known as eprosartan and is commercially available:



R_{IIIa}

5. The compounds of general formula (I)



(I)

wherein:

s is equal to 1;

s' is equal to 0;

A is -(Y-ONO_2) wherein Y is as above defined,

R is selected from the residue of formula (II) wherein R_0 is (IV) and R_1 is selected from the group (Va) wherein:

R_2 is n-butyl, R_3 is Cl, and N_0 is selected from:

1) -CH_2-O-CO-NH-K-K* wherein K* is equal to K' and is equal to -COO-, -CONH-, -CH_2-O-CO-, -CH_2-O-COO- or -CH_2-O-CONH- and K* is bound to the group -(Y-ONO_2); K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5, R_7 and R_8 are -H, R_6 is -OH

2) (IXa) wherein K* is equal to K' and is as above defined and R_7 is -H;

can be prepared as follows:

5a) by reacting a compound of formula (Id)

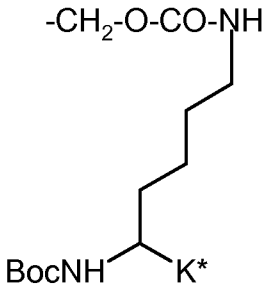
(Id)

wherein s and Y are as above defined in **5.**, R_d is selected from the residue of formula (II) wherein R_1, R_2 and R_3 are as above defined in **5.**; R_0 is equal to (IVa) and is as defined in **1a)**; N_0 is equal to N_{0a} and is equal to:

5a.1) -CH_2-O-CO-NH-K_a-K* wherein K* is as above defined in **5.** and K* is bound to the group -(Y-ONO_2); K_a is selected from (VIIIaa)-(VIIIha) (see Appendix 1, preparation **A7**);

or

5a.2) N_{0a} is the group IXa_a

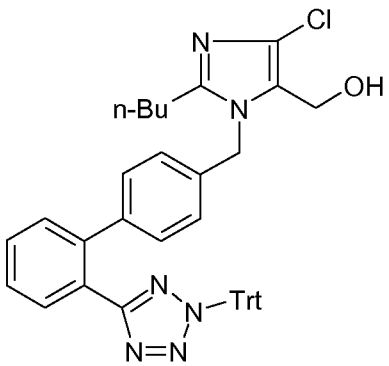


IXa_a

wherein K* and Boc are as previously defined;

with anhydrous or aqueous organic or inorganic acid to hydrolyze the trityl and the other protective groups following procedure well known in the literature;

5b) by reacting a compound of formula R_{IIa}, above described:



R_{IIa},

with:

5b.1) a compound of formula (Xe_a)-(Xe_e) depending on the meaning of K*:

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_a\text{-}COO\text{-}A$

(Xe_a)

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_a\text{-}CONH\text{-}Y\text{-}ONO_2$

(Xe_b)

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_a\text{-}CH_2O\text{-}CO\text{-}Y\text{-}ONO_2$

(Xe_c)

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_a\text{-}CH_2O\text{-}CO\text{-}O\text{-}Y\text{-}ONO_2$

(Xe_d)

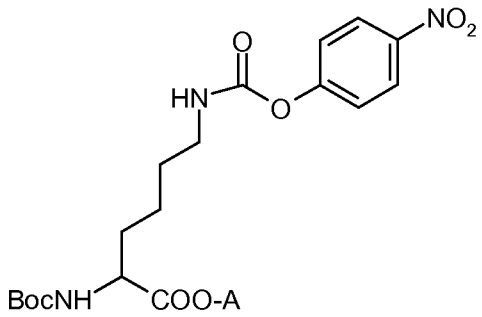
$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_a\text{-}CH_2O\text{-}CO\text{-}NH\text{-}Y\text{-}ONO_2$

(Xe_e)

wherein A is -(Y-ONO_2) and Y and K_a are as above defined;

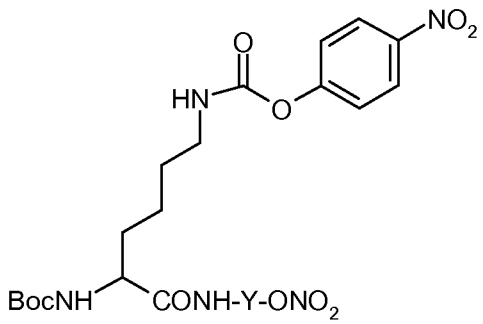
or

5b.2) a compound of formula (Xf_a)- (Xf_e):

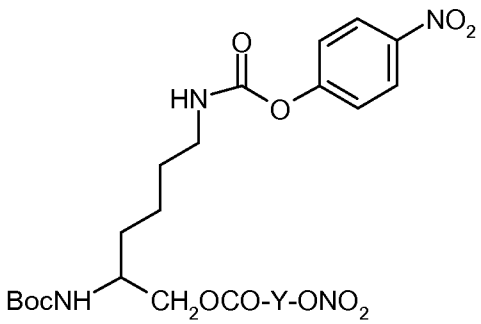


(Xf_a)

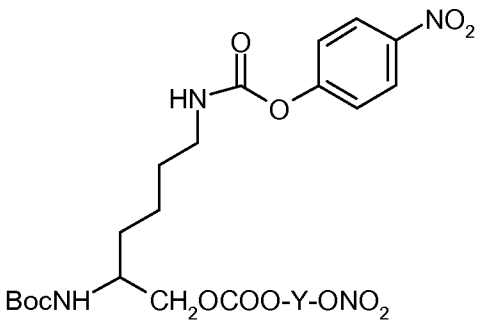
wherein A is -(Y-ONO_2)



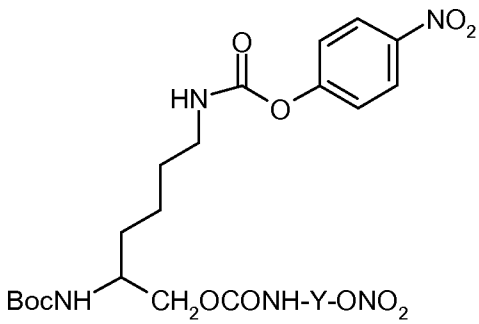
(Xf_b)



(Xf_c)



(Xf_d)



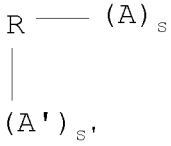
(Xf_e)

wherein Y is as above defined;

following the procedure described in **1b)**.

For the preparation of compounds of formula (Xe_a)-(Xe_e) and (Xf_a)-(Xf_e) see Appendix 1, preparations **A7** and **A8**.

6. The compounds of general formula (I)



(I)

wherein:

s is equal to 1;

s' is equal to 0

A is -(Y-ONO_2) wherein Y is as above defined,

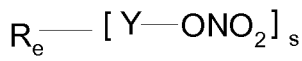
R is selected from the residue of formula (II) wherein R_0 is (IV) and R_1 is selected from the group (Vd) and N_0 is selected from:

1) -O-CO-NH-K-K* wherein K* is equal to K' and is equal to -COO-, -CONH-, -CH_2-O-CO-, -CH_2-O-COO- or -CH_2-O-CONH- and K* is bound to the group -(Y-ONO_2); K is selected from (VIIIa)-(VIIIh) wherein R_5, R_7 and R_8 are -H, R_6 is -OH

2) (IXb) wherein K* is as above defined and R_7 is -H;

can be prepared as follows

6a) by reacting a compound of formula (Ie)

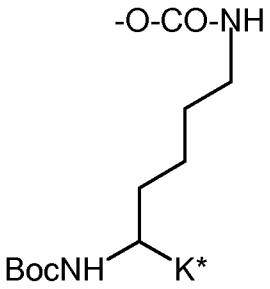


(Ie)

wherein s and Y are as above defined in **6.**, R_e is selected from the residue of formula (II) wherein R_1 and N_0 are as above defined in **6.**; R_0 is equal to (IVb) and is the t-butyl protecting group as defined in **2a)**; N_0 is equal to N_{0b} and is equal to:

6a.1) -O-CO-NH-K_a-K* wherein K* is as above defined in **6.** and K* is bound to the group -(Y-ONO_2); K_a is selected from (VIIIaa)-(VIIIha) as already described in **5a)**; or

6a.2) N_{0b} is the group IXb_a:

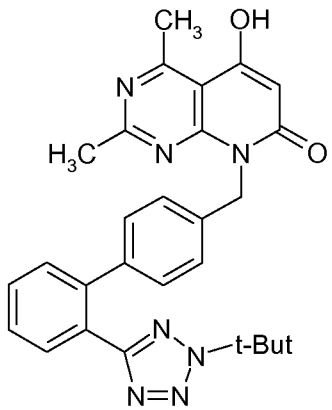


IXb_a

wherein K* and Boc are as previously defined;

with anhydrous or aqueous organic or inorganic acid to hydrolyze the t-butyl and the other protective groups following procedure well known in the literature;

6b) by reacting a compound of formula R_{IIb}:



R_{IIb}

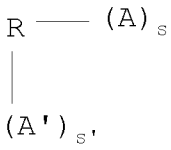
with:

6b.1) compounds of formula (Xe_a)-(Xe_e) above described, depending on the meaning of K*; or

6b.2) compounds of formula (Xf_a)-(Xf_e) above described, depending on the meaning of K*;

following the procedure described in **1b)**.

7. The compounds of general formula (I)



(I)

wherein:

s is equal to 1;

s' is equal to 0;

A is $-(Y-ONO_2)$ wherein Y is as above defined,

R is selected from the residue of formula (II) wherein R_0 is (IV), R_1 is selected from the group:

i) (Va) wherein R_2 is n-butyl and R_3 is Cl;

ii) (Va) wherein R_2 is n-propyl and R_3 is C_2F_5,

iii) (Va) wherein R_2 is n-propyl and R_3 is the group $-C(CH_3)_2OH$;

iv) (Vb);

v) (Vc) wherein R_4 is n-butyl;

vi) (Vc) wherein R_4 is -OEt;

wherein N_0 is selected from:

1) -CO-NH-K-K* wherein K* is equal to K' and is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K* is bound to the group $-(Y-ONO_2)$; K is selected from (VIIIa)-(VIIIh) wherein R_5, R_7 and R_8 are -H, R_6 is -OH;

2) (IXc) wherein K* is as above defined and R_7 is -H;

can be prepared as follows:

7a) by reacting a compound of formula (If)

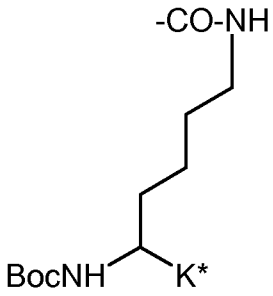
$$R_f-[Y-ONO_2]_s$$

(If)

wherein s and Y are as above defined in **7.**, R_f is selected from the residue of formula (II) wherein R_1 is as above defined in **7.** in the points i)-vi); R_0 is equal to (IVa) and is as previously defined, N_0 is equal to N_{0c} and is equal to:

7a.1) $-CO-NH-K_a-K^*$ wherein K* is as above defined in **7.** and K* is bound to the group $-(Y-ONO_2)$; K_a is as defined in **5a)**; or

7a.2) N_{0c} is the group IXc_a:



IXc_a

wherein K* and Boc are as previously defined;

with anhydrous or aqueous organic or inorganic acid to hydrolyze the trityl and the other protective groups following procedure well known in the literature;

7b) by reacting compounds of formula R_{IIc}-R_{IIh} already defined in **3b)** with:

7b.1) a compound of formula (Xg_a)-(Xg_e), depending on the meaning of K*:

NH_2-K_a-COO-A

(Xg_a)

NH_2-K_a-CONH-Y-ONO_2

(Xg_b)

NH_2-K_a-CH_2O-CO-Y-ONO_2

(Xg_c)

NH_2-K_a-CH_2O-CO-O-Y-ONO_2

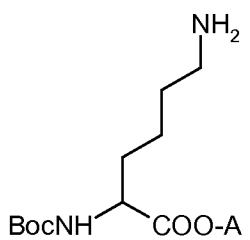
(Xg_d)

NH_2-K_a-CH_2O-CO-NH-Y-ONO_2

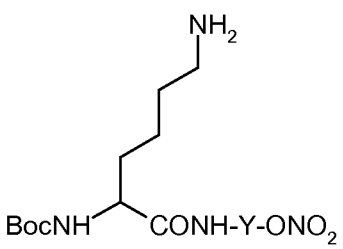
(Xg_e)

wherein A is -(Y-ONO_2), Y and K_a are as above defined; or

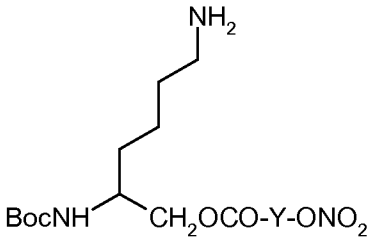
7b.2) a compound of formula (Xh_a)-(Xh_e), depending on the meaning of K*:



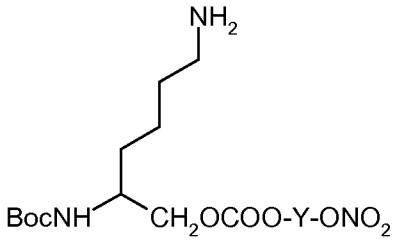
(Xh_a)



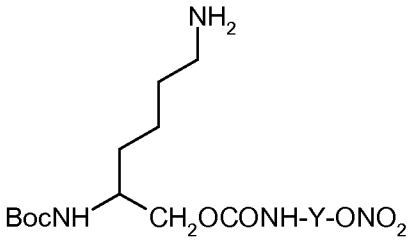
(Xh_b)



(Xh_c)



(Xh_d)



(Xh_e)

wherein A is $-(Y-ONO_2)$ and Y is as above defined;

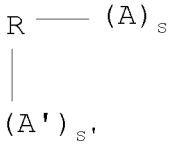
following the procedures reported in **3c)** for:

1) **N_{00} = -COOH:**

2) **N_{00} = -COHal or -COOAct:**

For the preparation of compounds of formula (Xg_a)-(Xg_e) and (Xh_a)-(Xh_e) see Appendix 1, preparations **A7** and **A8.**

8. The compounds of general formula (I)



(I)

wherein:

s is equal to 1 or 2;

s' is equal to 0;

A is $-(Y-ONO_2)$ wherein Y is as above defined,

R is selected from:

i) **s = 1:** the residue of formula (II) wherein R_1 is selected from (Ve) and R_0 is N_0 and is selected from:

1) -CO-NH-K-K* wherein K* is equal to K' and is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K*

is bound to the group $-(Y-ONO_2)$; K is selected from (VIIIa)-(VIIIh) wherein R_5, R_7 and R_8 are -H, R_6 is -OH;

2) (IXc) wherein K* is as above defined and R_7 is -H;

ii) **s = 2:** the residue of formula (III) wherein N_0 is selected from:

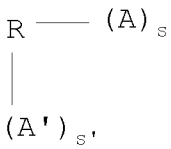
1) -CO-NH-K-K* wherein K* is as above defined and is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K* is bound to the group $-(Y-ONO_2)$; K is selected from (VIIIa)-(VIIIh) wherein R_5, R_7 and R_8 are -H, R_6 is -OH;

2) (IXc) wherein K* is as above defined and R_7 is -H;

can be prepared as follows:

8a) by reacting the compounds of formula R_{IIi} or R_{IIIa} described in **4a)** with compounds $(Xg_a)-(Xg_e)$ and $(Xh_a)-(Xh_e)$ depending on the meaning of K* and described in **7b)** following the same procedure described in **7b)** using a ratio of $(Xg_a)-(Xg_e)$ and $(Xh_a)-(Xh_e)$) 1:1 or 2: 1 if more than one group -COOH is present.

9. The compounds of general formula (I)



(I)

wherein:

s and s' are equal to 1;

A and A' are $-(Y-ONO_2)$ or $-(Y'-ONO_2)$ wherein Y and Y' are equal or different and are as above defined,

R is selected from the residue of formula (II) wherein R_0 is (IV) and R_1 is selected from the group (Va) wherein:

R_2 is n-butyl, R_3 is Cl, and N_0 is selected from:

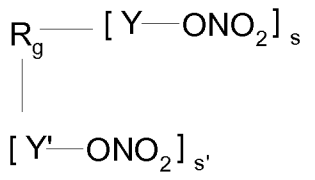
1) $-CH_2-O-CO-NH-K-K^*$ wherein K* is equal to K' is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K* is bound to the group $-(Y-ONO_2)$; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is

selected from –CO-, -COO- or –CONH-; R_6 is selected from –O- or –NH; R_7 and R_8 are selected from –CO- or -COO- and K is bound to the group –(Y'-ONO_2);

2) (IXa) wherein K* is as above defined and R_7 is selected from –CO- or -COO- and R_7 is bound to the group –(Y'-ONO_2);

can be prepared as follows:

9a) by reacting a compound of formula (Ig)



(Ig)

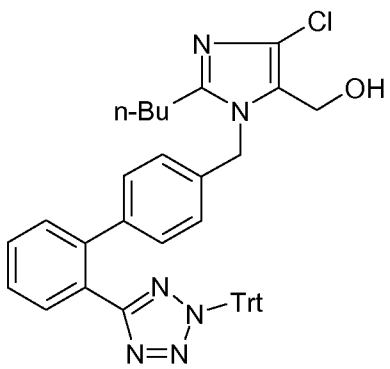
wherein s, s', Y and Y' are as above defined in **9.**, R_g is selected from the residue of formula (II) wherein R_1, R_2 and R_3 are as above defined in **9.**; R_0 is equal to (IVa) and is as defined in **1a)**; N_0 is equal to:

9a.1) $-CH_2-O-CO-NH-K-K^*$ wherein K and K* are as above defined in **9.**;

9a.2) (IXa) wherein K* and R_7 are as above defined in **9.**;

with anhydrous or aqueous organic or inorganic acid to hydrolyze the trityl protective groups following procedure well known in the literature;

9b) by reacting a compound of formula $R_{IIa'}$:



$R_{IIa'}$

with:

9b.1) compound of general formula (Xi_a)-(Xi_o):

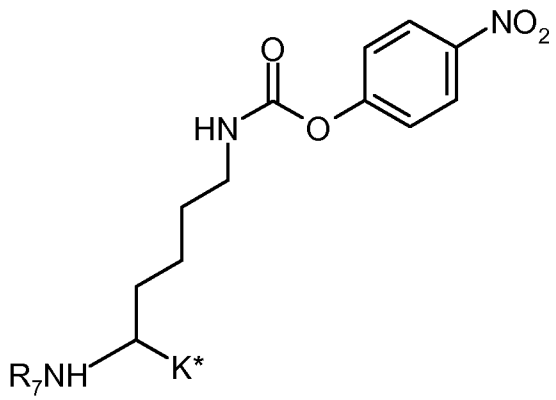
p-$NO_2-C_6H_4$-O-CO-NH-K-K*

$(Xi_a)-(Xi_o)$

wherein K* and K are as above defined in **9.**

For a complete description and for preparations of $(Xi_a)-(Xi_o)$ see Appendix 1, preparations **A9-A23;** or

9b.2) a compound of general formula $(Xj_a)-(Xj_e)$



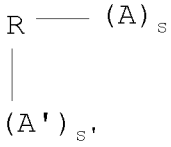
$(Xj_a)-(Xj_e)$

wherein K* is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K* is bound to the group $-(Y-ONO_2)$; R_7 is selected from -CO- or -COO- and R_7 is bound to the group $-(Y'-ONO_2)$.

following the procedure described in **1b);**

For the preparation of compounds of formula $(Xj_a)-(Xj_e)$ see Appendix 1, preparation **A24.**

10. The compounds of general formula (I)



(I)

wherein:

s and s' are equal to 1;

A and A' are $-(Y-ONO_2)$ or $-(Y'-ONO_2)$ wherein Y and Y' are equal or different and are as above defined,

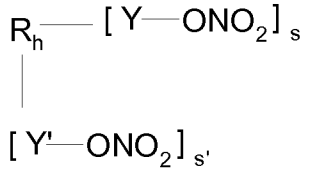
R is selected from the residue of formula (II) wherein R_0 is (IV) and R_1 is selected from the group (Vd) and N_0 is selected from:

1) -O-CO-NH-K-K* wherein K* is equal to K' and is equal to -COO-, -CONH-, $-CH_2$-O-CO-, $-CH_2$-O-COO- or $-CH_2$-O-CONH- and K* is bound to the group $-(Y-ONO_2)$; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is selected from -CO-, -COO- or -CONH-; R_6 is selected from -O- or -NH; R_7 and R_8 are selected from -CO- or -COO- and K is bound to the group $-(Y'-ONO_2)$;

2) (IXb) wherein K* is as above defined and R_7 is selected from -CO- or -COO- and R_7 is bound to the group $-(Y'-ONO_2)$;

can be prepared as follows:

10a) by reacting a compound of formula (Ih)



(Ih)

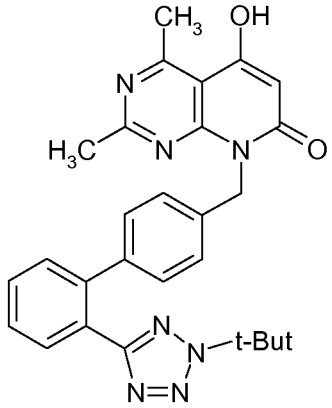
wherein s, s' Y and Y are as above defined in **10.**, R_h is selected from the residue of formula (II) wherein R_1 and N_0 are as above defined in **10.**; R_0 is equal to (IVb) and is the t-butyl protecting group as defined in **2a)**; N_0 is equal to:

10a.1) -O-CO-NH-K-K* wherein K is selected from K_1, K_2 or K_3 and K and K* are as above defined in **10.**; K_1, K_2, K_3 and K* are respectively bound to the group $-(Y'-ONO_2)$ and $-(Y-ONO_2)$;

10a.2) (IXb) wherein K* and R_7 are as above defined in **10.**; R_7 is bound to the group $-(Y'-ONO_2)$;

with anhydrous or aqueous organic or inorganic acid to hydrolyze the t-butyl group following procedure well known in the literature;

10b) by reacting a compound of formula R_{IIb}:



R_{IIb}

with:

10b.1) a compound of general formula $(Xi_a)-(Xi_o)$ as above defined

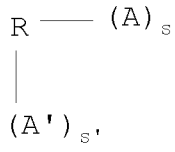
$$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K\text{-}K^*$$

$$(Xi_a)-(Xi_o)$$

following the procedure described in **1b)**; or

10b.2) a compound of general formula $(Xj_a)-(Xj_e)$ defined in **9b)**, following the procedure described in **1b)**.

11. The compounds of general formula (I)



(I)

wherein:

s is equal to 1;

s' is equal to 1;

A and A' are $-(Y\text{-}ONO_2)$ or $-(Y'\text{-}ONO_2)$ wherein Y and Y' are as above defined,

R is selected from the residue of formula (II) wherein R_0 is (IV), R_1 is selected from the group:

i) (Va) wherein R_2 is n-butyl and R_3 is Cl;

ii) (Va) wherein R_2 is n-propyl and R_3 is C_2F_5,

iii) (Va) wherein R_2 is n-propyl and R_3 is the group -$C(CH_3)_2OH$;

iv) (Vb);

v) (Vc) wherein R_4 is n-butyl;

vi) (Vc) wherein R_4 is -OEt;

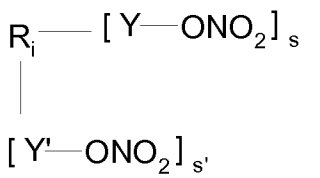
wherein N_0 is selected from:

1) -CO-NH-K-K* wherein K* is equal to K' and is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K* is bound to the group $-(Y-ONO_2)$; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is selected from -CO-, -COO- or -CONH-; R_6 is selected from -O- or -NH; R_7 and R_8 are selected from -CO- or -COO- and K is bound to the group $-(Y'-ONO_2)$;

2) (IXc) wherein K* is as above defined and R_7 is selected from -CO- or -COO- and R_7 is bound to the group-$(Y'-ONO_2)$;

can be prepared as follows:

11a) by reacting a compound of formula (Ii)



(Ii)

wherein s, s', Y and Y' are as above defined in **11.**, R_i is selected from the residue of formula (II) wherein N_0 is as above defined, R_1 is as above defined in **11.** in the points i)-vi); R_0 is equal to (IVa) and is as previously defined, with anhydrous or aqueous organic or inorganic acid to hydrolyze the trityl and the other protective groups following procedure well known in the literature;

11b) by reacting compounds of formula R_{IIc}- R_{IIh} already defined in **3b)** with

11b.1) compounds of general formula $(Xk_a)-(Xk_o)$

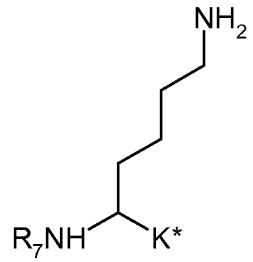
NH_2-K-K^*

$(Xk_a)-(Xk_o)$

wherein K* and K are as defined in **11.**;

or

11b.2) compound of formula $(XL_a)-(XL_e)$, depending on the meaning of K*:



$(XL_a)-(XL_b)$

Wherein R_7 is selected from –CO- or -COO- and R_7 is bound to the group $-(Y'-ONO_2)$;

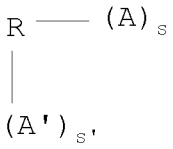
following the procedures reported in **3c)** for:

1) **N_{00} = -COOH:**

2) **N_{00} = -COHal or -COOAct:**

For the preparation of compounds of formula $(Xk_a)-(Xk_o)$ and $(XL_a)-(XL_e)$ see Appendix 1, preparations **A9-A24.**

12. The compounds of general formula (I)



(I)

wherein:

s is equal to 1 or 2;

s' is equal to 1 or 2;

A and A' are $-(Y-ONO_2)$ or $-(Y'-ONO_2)$ wherein Y and Y' are as above defined,

R is selected from:

i) **s = 1, s' = 1:** the residue of formula (II) wherein R_1 is selected from (Ve) and R_0 is N_0 and is selected from:

1) -CO-NH-K-K* wherein K* is equal to K' and is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K*

is bound to the group $-(Y-ONO_2)$; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is selected from –CO-, -COO- or –CONH-; R_6 is selected from –O- or –NH; R_7 and R_8 are selected from –CO- or -COO- and K is bound to the group-$(Y'-ONO_2)$.

2) (IXc) wherein K* is as above defined and R_7 is selected from –CO- or -COO- and R_7 is bound to the group $-(Y'-ONO_2)$;

ii) **s = 2, s' = 2:** the residue of formula (III) wherein N_0 is selected from:

1) -CO-NH-K-K* wherein K* is equal to K' and is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K* is bound to the groups $-(Y-ONO_2)$; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is selected from –CO-, -COO- or –CONH-; R_6 is selected from –O- or –NH; R_7 and R_8 are selected from –CO- or -COO- and K is bound to the groups $-(Y'-ONO_2)$.

2) (IXc) wherein K* is as above defined and R_7 is selected from –CO- or -COO- and R_7 is bound to the group $-(Y'-ONO_2)$;

can be prepared as follows:

12a) by reacting the compounds of formula R_{IIi} or R_{IIIa} described in **4a)** with:

12a.1) compounds of general formula $(Xk_a)-(Xk_o)$

$$NH_2-K-K^*$$

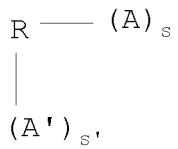
$$(Xk_a)-(Xk_o)$$

defined in **11b)**; or

12a.2) compound of formula $(XL_a)-(XL_e)$, defined in **11b)**;

following the same procedure described in **7b)** using a ratio of $(Xk_a)-(Xk_o)$ and $(XL_a)-(XL_e)$ 1:1 or 2: 1 if more than one group -COOH is present.

13. The compounds of general formula (I)



(I)

wherein:

s is equal to 0;

s' is equal to 1;

A' is $-(Y'-ONO_2)$ wherein Y' is as above defined;

R is selected from the residue of formula (II) wherein R_0 is (IV) and R_1 is selected from the group (Va) wherein:

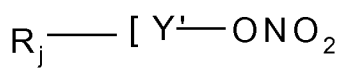
R_2 is n-butyl, R_3 is Cl, and N_0 is selected from:

1) $-CH_2-O-CO-NH-K-K^*$ wherein K* is equal to -COOH; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is selected from -CO-, -COO- or -CONH-; R_6 is selected from -O- or -NH; R_7 and R_8 are selected from -CO- or -COO- and K is bound to the group $-(Y'-ONO_2)$;

2) (IXa) wherein K* is equal to -COOH and R_7 is -CO- or -COO- and R_7 is bound to the group $-(Y'-ONO_2)$;

can be prepared as follows:

13a) by reacting a compound of formula (Ij)



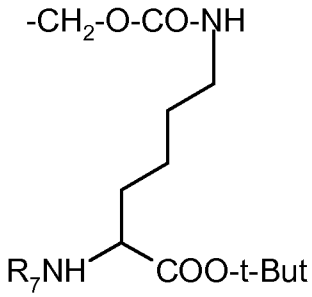
(Ij)

wherein s' and Y' are as above defined in **13.**, R_j is selected from the residue of formula (II) wherein R_1, R_2 and R_3 are as above defined in **13.**; R_0 is equal to (IVa) and is as defined in **1a)**; N_0 is equal to N_{0a} and is equal to:

13a.1) $-CH_2-O-CO-NH-K-K_x^*$ wherein K_x^* is equal to -COOt-But; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is selected from -CO-, -COO- or -CONH-; R_6 is selected from -O- or -NH; R_7 and R_8 are selected from -CO- or -COO- and K is bound to the group $-(Y'-ONO_2)$;

or

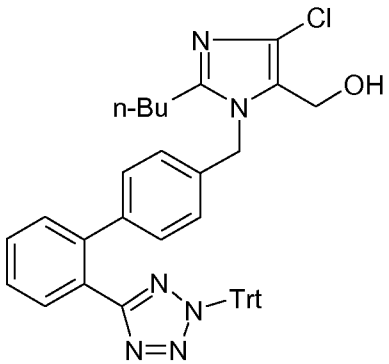
13a.2) N_{0a} is the group IXa_b



IXa_b

wherein t-But is the tert-butyl protecting group and R_7 is selected from –CO- or -COO- and binds the group -(Y'-ONO_2); with anhydrous or aqueous organic or inorganic acid to hydrolyze the trityl and the other protective groups following procedure well known in the literature;

13b) by reacting a compound of formula $R_{IIa'}$ above described:



$R_{IIa'}$

depending on the meaning of K, with:

13b.1) compound of formula (Xi_{a4})-(Xi_{a6})

p-NO_2-C_6H_4-O-CO-NH-K_1-COOtBut

(Xi_{a4})-(Xi_{a6})

wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is selected from respectively:

i) –CO- (Xi_{a4});

ii) -COO- (Xi_{a5}); or

iii) –CONH- (Xi_{a6});

and K_1 is bound to the group $-(Y'-ONO_2)$ (see Appendix 1, preparation **A9/2**);

13b.2) compound of formula $(Xi_{f3}),(Xi_{f4})$:

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_2\text{-}COOtBut$

$(Xi_{f3}),(Xi_{f4})$

wherein K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is selected from respectively:

i) -O- (Xi_{f3}) or

ii) -NH- (Xi_{f4})

and K_2 is bound to the group $-(Y'-ONO_2)$ (see Appendix 1, preparation **A14/2**);

13b.3) compound of formula $(Xi_{k3}),(Xi_{k4})$:

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_3\text{-}COOtBut$

$(Xi_{k3}),(Xi_{k4})$

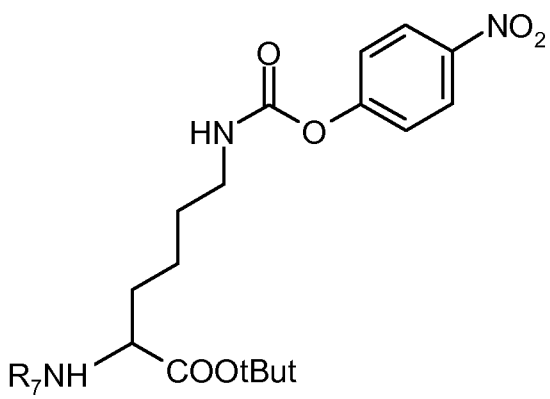
wherein K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xi_{k3}) or

ii) -COO- (Xi_{k4})

and K_3 is bound to the group $-(Y'-ONO_2)$ (see Appendix 1, preparation **A19/2**);

13b.4) compounds of formula (Xj_{a3})- $(Xj_{a4}$:



(Xj_{a3})- (Xj_{a4})

wherein R_7 is selected from respectively:

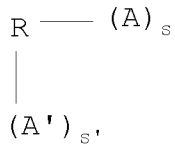
i) -CO- (Xj_{a3}),

ii) -COO- (Xj_{a4}) and R_7 is bound to the group $-(Y'-ONO_2)$

(see Appendix 1, preparation **A24/2**);

following the procedure described in **1b)**.

14. The compounds of general formula (I)



(I)

wherein:

s is equal to 0;

s' is equal to 1

A' is $-(Y'-ONO_2)$ wherein Y' is as above defined;

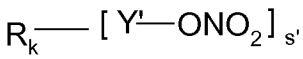
R is selected from the residue of formula (II) wherein R_0 is (IV) and R_1 is selected from the group (Vd) and N_0 is selected from:

1) -O-CO-NH-K-K* wherein K* is equal to -COOH; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is selected from -CO-, -COO- or -CONH-; R_6 is selected from -O- or -NH; R_7 and R_8 are selected from -CO- or -COO- and K is bound to the group $-(Y'-ONO_2)$;

2) (IXb) wherein K* is equal to -COOH and R_7 is -CO- or -COO- and R_7 is bound to the group $-(Y'-ONO_2)$;

can be prepared as follows:

14a) by reacting a compound of formula (Ik)



(Ik)

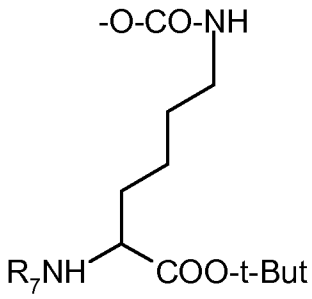
wherein s' and Y' are as above defined in **14.**, R_k is selected from the residue of formula (II) wherein R_1 is as above defined in **14.**; R_0 is equal to (IVb) and is as defined in **2a)**; N_0 is equal to N_{0b} and is equal to:

14a.1) -O-CO-NH-K-K_x* wherein K_x* is equal to -COOt-But; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-

(VIIIh) wherein R_5 is selected from –CO-, -COO- or –CONH-; R_6 is selected from –O- or –NH; R_7 and R_8 are selected from –CO- or -COO- and K is bound to the group –(Y'-ONO_2);

or

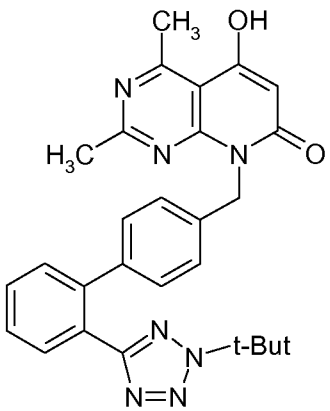
14a.2) N_{0b} is the group IXb_b



IXb_b

wherein t-But is the tert-butyl protecting group and R_7 is selected from –CO- or -COO- and binds the group –(Y'-ONO_2); with anhydrous or aqueous organic or inorganic acid to hydrolyze the trityl and the other protective groups following procedure well known in the literature;

14b) by reacting a compound of formula R_{IIb}:



R_{IIb}

depending on the meaning of K, with:

14b.1) compound of formula (Xi_{a4})-(Xi_{a6})

p-NO_2-C_6H_4-O-CO-NH-K_1-COOtBut

(Xi_{a4})-(Xi_{a6})

described in 13b.1)

14b.2) compound of formula $(Xi_{f3}),(Xi_{f4})$:

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_2\text{-}COOtBut$

$(Xi_{f3}),(Xi_{f4})$

described in 14b.2)

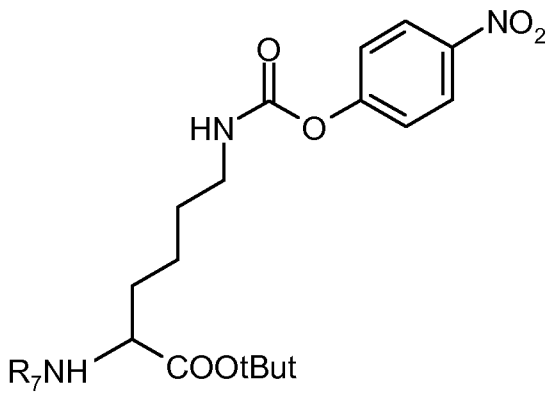
14b.3) compound of formula $(Xi_{k3}),(Xi_{k4})$:

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_3\text{-}COOtBut$

$(Xi_{k3}),(Xi_{k4})$

described in 13b.3)

14b.4) compounds of formula (Xj_{a3})- $(Xj_{a4}$:

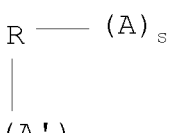


(Xj_{a3})- (Xj_{a4})

described in 13b.4);

following the procedure described in **1b)**.

15. The compounds of general formula (I)



(I)

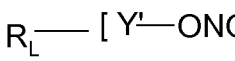
wherein:

s is equal to 0;

s' is equal to 1;

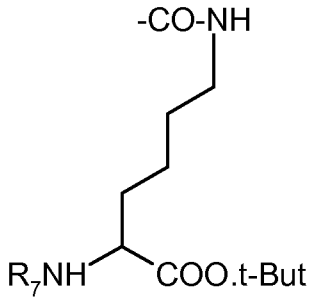
A' is $-(Y'-ONO_2)$ wherein Y' is as above defined;
R is selected from the residue of formula (II) wherein R_0 is (IV), R_1 is selected from the group:
i) (Va) wherein R_2 is n-butyl and R_3 is Cl;
ii) (Va) wherein R_2 is n-propyl and R_3 is C_2F_5,
iii) (Va) wherein R_2 is n-propyl and R_3 is the group $-C(CH_3)_2OH$;
iv) (Vb);
v) (Vc) wherein R_4 is n-butyl;
vi) (Vc) wherein R_4 is -OEt;

wherein N_0 is selected from:
1) -CO-NH-K-K* wherein K* is equal to -COOH; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is selected from -CO-, -COO- or -CONH-; R_6 is selected from -O- or -NH; R_7 and R_8 are selected from -CO- or -COO- and K is bound to the group $-(Y'-ONO_2)$;
2) (IXc) wherein K* is equal to -COOH; and R_7 is selected from -CO- or -COO- and R_7 is bound to the group $-(Y'-ONO_2)$;
can be prepared as follows:
15a) by reacting a compound of formula (IL)



(IL)

wherein s' and Y' are as above defined in **15.**, R_L is selected from the residue of formula (II) wherein R_1 is as above defined in **15.** in the points i)-vi); R_0 is equal to (IVa) and is as previously defined, N_0 is equal to N_{0c} and is equal to:
7a.1) -CO-NH-K-K_x* wherein K_x* is equal to -COOt-But; K is as defined in **15.**; or
7a.2) N_{0c} is the group IXc_b:



IXc_a

wherein R_7 and t-But are as previously defined;

with anhydrous or aqueous organic or inorganic acid to hydrolyze the trityl and the other protective groups following procedure well known in the literature;

15b) by reacting compounds of formula R_{IIc}- R_{IIh} already defined in **3b)**, depending on the meaning of K with:

15b.1) compounds of formula (Xk_{a4})-(Xk_{a6}):

$$NH_2\text{-}K_1\text{-}COOtBut$$
$$(Xk_{a4})\text{-}(Xk_{a6})$$

wherein t-But is as above defined and K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is selected from respectively:

i) -CO- (Xk_{a4});

ii) -COO- (Xk_{a5}); or

iii) -CONH- (Xk_{a6});

and K_1 is bound to the group -(Y'-ONO_2) (see Appendix 1, preparation **A9/2**); or

15b.2) compounds of formula (Xk_{f3}),(Xk_{f4}):

$$NH_2\text{-}K_2\text{-}COOtBut$$
$$(Xk_{f3})\text{-}(Xk_{f4})$$

wherein K_2 is selected from:

i) -O- (Xk_{f3}) or

ii) -NH- (Xk_{f4})

and K_2 is bound to the group $-(Y'-ONO_2)$ (see Appendix 1, preparation **A14/2**); or

15b.3) compounds of formula $(Xk_{k3}),(Xk_{k4})$:

$NH_2-K_3-COOtBut$

$(Xk_{k3})-(Xk_{k4})$

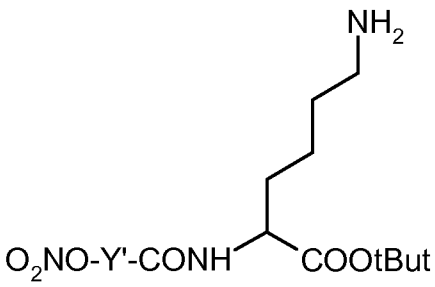
wherein K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) $-CO-$ (Xk_{k3}) or

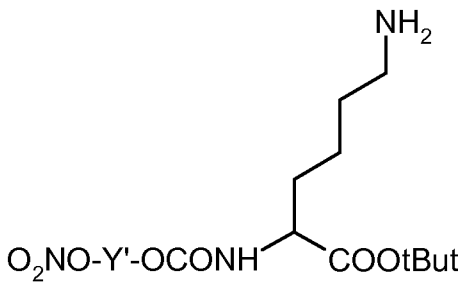
ii) $-COO-$ (Xk_{k4})

and K_3 is bound to the group $-(Y'-ONO_2)$ (see Appendix 1, preparation **A19/2**); or

15b.4) compounds of formula $(XL_{a3}),(XL_{a4})$:



(XL_{a3})



(XL_{a4})

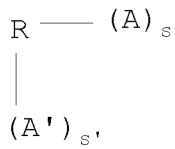
wherein Y' and t-But are as previously defined; (see Appendix 1, preparation **A24/2**);

following the procedures reported in **3c)** for:

1) **N_{00} = -COOH:**

2) **N_{00} = -COHal or -COOAct.**

16. The compounds of general formula (I)



(I)

wherein:

s is equal to 0;

s' is equal to 1 or 2;

A' is $-(Y'-ONO_2)$ wherein Y' is as above defined;

R is selected from:

i) **s = 1:** the residue of formula (II) wherein R_1 is selected from (Ve) and R_0 is N_0 and is selected from:

1) -CO-NH-K-K* wherein K* is equal to –COOH; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is selected from –CO-, -COO- or –CONH-; R_6 is selected from –O- or –NH; R_7 and R_8 are selected from –CO- or -COO- and K is bound to the group $-(Y'-ONO_2)$;

2) (IXc) wherein K* is equal to –COOH; and R_7 is selected from –CO- or -COO- and R_7 is bound to the group $-(Y'-ONO_2)$;

ii) **s = 2:** the residue of formula (III) wherein N_0 is selected from:

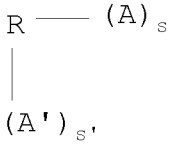
1) -CO-NH-K-K* wherein K* is equal to –COOH; K is selected from K_1, K_2 or K_3 and is selected from (VIIIa)-(VIIIh) wherein R_5 is selected from –CO-, -COO- or –CONH-; R_6 is selected from –O- or –NH; R_7 and R_8 are selected from –CO- or -COO- and K is bound to the group $-(Y'-ONO_2)$;

2) (IXc) wherein K* is equal to –COOH; and R_7 is selected from –CO- or -COO- and R_7 is bound to the group $-(Y'-ONO_2)$;

can be prepared as follows:

16a) by reacting the compounds of formula R_{IIi} or R_{IIIa} described in **4a)** with compounds $(Xk_{a4})-(Xk_{a6})$, or $(Xk_{f3}),(Xk_{f4})$, or $(Xk_{k3})-(Xk_{k4})$ depending on the meaning of K and described in 15b.1-15b.3 or compounds of formula $(XL_{a3}),(XL_{a4})$ described in 15b.4; following the same procedure described in **3c)** using a ratio of $(Xk_{a4})-(Xk_{a6})$, or $(Xk_{f3}),(Xk_{f4})$, or $(Xk_{k3})-(Xk_{k4})$, or $(XL_{a3}),(XL_{a4})$ 1:1 or 2: 1 if more than one group -COOH is present.

17. The compounds of general formula (I)



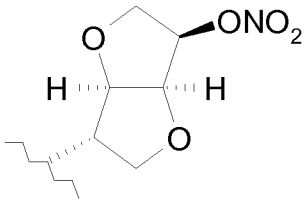
(I)

wherein:

s is equal to 1;

s' is equal to 0

A is equal to (1a) and is the group



(1a),

R is selected from the residue of formula (II) wherein R_0 is (IV), R_1 is selected from the group:

i) (Va) wherein R_2 is n-butyl and R_3 is Cl;

iii) (Va) wherein R_2 is n-propyl and R_3 is the group $C(CH_3)_2OH$;

iv) (Vb);

vi) (Vc) wherein R_4 is -OEt;

wherein N_0 is selected from:

1) (VIb), wherein K' is equal to -COO-, and K' is bound to the group (1a)

2)-CO-NH-J-K' wherein J is selected among (VIIa-VIIk) and K' is as above defined;

can be prepared as follows

17a) by reacting a compound of formula (Ic')

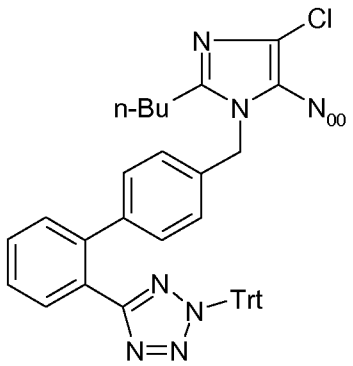
$$R_c\text{-}[A]_s$$

(Ic')

wherein A and s are as defined in **17.** and R_c is selected from the residue of formula (II) wherein N_0 is as above defined in **17.** and R_1 is as above defined in the points i),

iii),iv) and vi); R_0 is equal to (IVa) and is as previously defined, following the same procedure described in **1a)**; **17b)** by reacting:

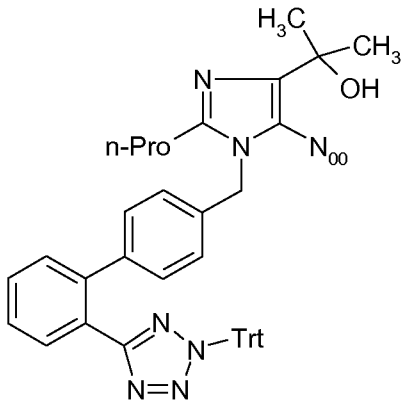
i) a compound of formula R_{IIc}



R_{IIc}

Wherein N_{00} is -COOH, -COHal or -COOAct wherein Hal and Act are as previously defined in **3.**; or

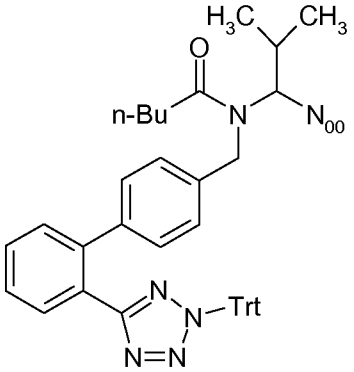
iii) a compound of formula R_{IIe}



R_{IIe}

wherein N_{00} is as previously defined; or

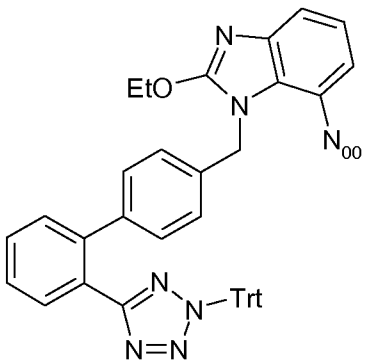
iv) a compound of formula R_{IIf}



R_{IIf}

wherein N_{00} is as previously defined; or

vi) a compound of formula R_{IIh}

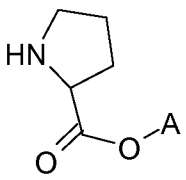


R_{IIh}

wherein N_{00} is as previously defined;

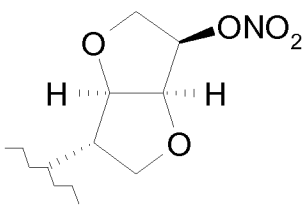
with

3b.1) a compound of formula (Xc_a)



(Xc_a)

wherein A is the group (1a),



(1a)

or

3b.2) a compound of formula (Xd_a)

NH_2-J-COO-A

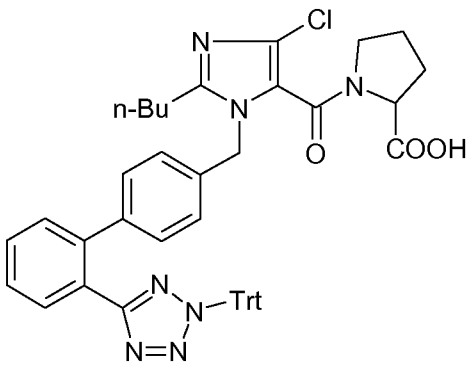
(Xd_a)

wherein A is (1a) and J is as above defined;

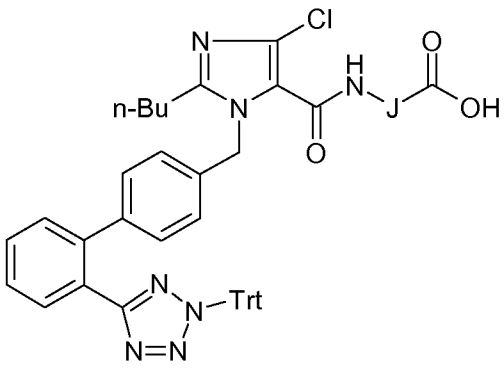
following the procedure described in **3.**

17b') alternatively by reacting:

i) a compound of formula R_{IIca} or R_{IIcb}

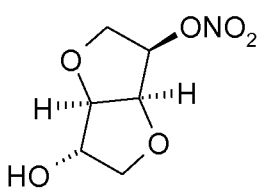


R_{IIca}



R_{IIcb}

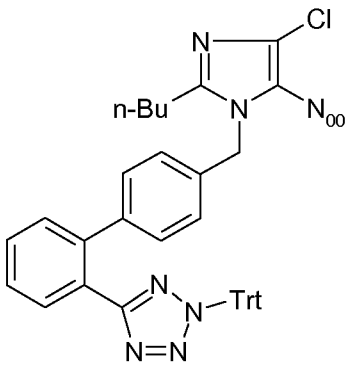
Wherein J is as above defined, with compound (XIa) (see Appendix 1, preparation **A1.**



(XIa)

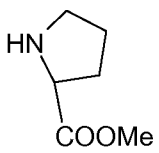
and a condensing agent such as dicyclohexylcarbodiimide (DCC) or N,N'-carbonyldiimidazol (CDI) or 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDC) or other known condensing reagents such as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), in the presence or not of 1-Hydroxybenzotriazole (HOBT) in solvent such as CH_2Cl_2, DMF, THF, chloroform at a temperature in the range from -5°C to 80°C in the presence or not of a base as for example DMAP.

17c) by reacting compound R_{IIc} defined in **3b)**



R_{IIc}

wherein N_{00} is as previously defined, with compounds (1b) or (1c)



(1b)

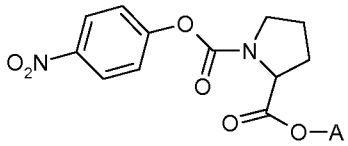
NH-J-COOMe

(1c)

wherein J is as previously defined using a condensing agent as 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole as known in the literature and hydrolysing the final methyl ester with NaOH in solvent such as MeOH as well known in the literature.

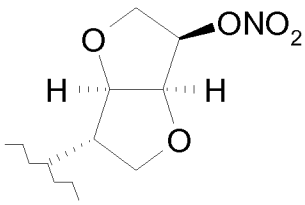
Appendix 1

A1. Synthesis of compounds (Xa_a) and (Xc_a)



(Xa_a)

wherein A is $-(Y-ONO_2)$, and Y is as above defined, or the group (1a)



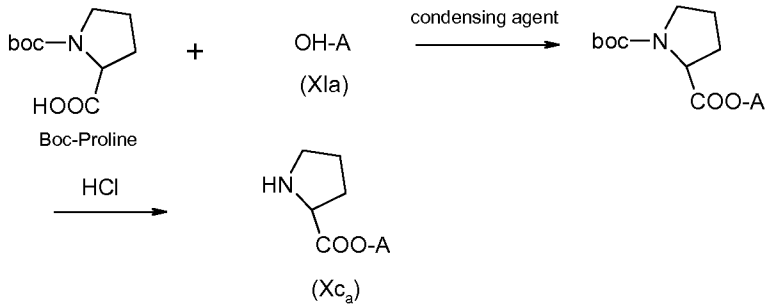
(1a),

can be obtained by reacting compound (Xc_a) wherein A is as above defined with commercially available p-nitrophenylchlorocarbonate in the presence of a base following procedures well known in the literature.

(Xc_a)

Compounds (Xc_a) can be obtained from commercially available Boc-proline by the procedures depicted in the scheme 1 following procedures well known in the literature:

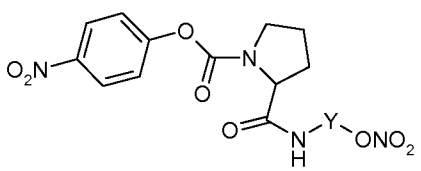
Scheme 1



Compounds of formula (XIa) wherein A is the group (1a) are commercially available.

Compounds of formula (XIa) wherein A is the group -(Y-ONO_2) are obtained by reacting compounds of formula HO-Y-Hal (XIIa) wherein Y is as above defined and Hal is an halogen atom such as Cl, Br, I or compounds of formula HO-Y-OTs (XIIIa) wherein Ts is the tosyl group, with $AgNO_3$ or $MetalNO_3$ wherein Metal is K^+, Na^+ Li^+ in a suitable organic solvent such as acetonitrile or tetrahydrofuran (THF) under nitrogen in the dark at temperatures range between 20°-80°C using a nitrate ammonium salt as catalyst; alternatively the reaction with $AgNO_3$ or $MetalNO_3$ can be performed under microwave irradiation in solvents such acetonitrile or THF at temperatures in the range between about 100-180°C for time range about 1-120 min. The compounds of formula (XIIa) and (XIIIa) are commercially available or can be obtained from commercially available compounds HO-Y-OH (XIIIb) with methods well known in the literature.

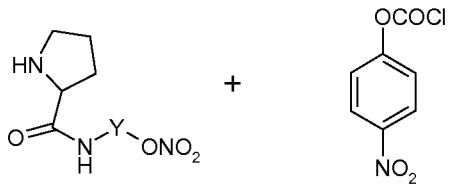
A2. Synthesis of compounds (Xa$_b$) and (Xc$_b$)



(Xa$_b$)

wherein Y is as above defined, can be obtained by reacting compound (Xc$_b$) with commercially available p-

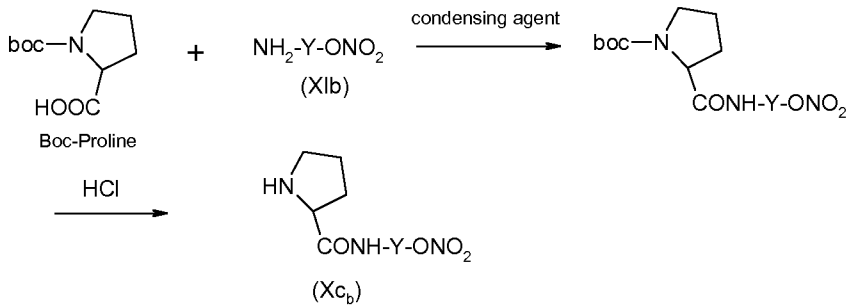
nitrophenylchlorocarbonate in the presence of a base following procedures well known in the literature.



(Xc_b)

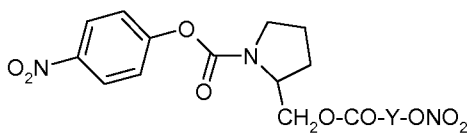
Compounds (Xc_b) can be obtained from commercially available Boc-proline by the procedures depicted in the Scheme 2 following procedures well known in the literature:

Scheme 2



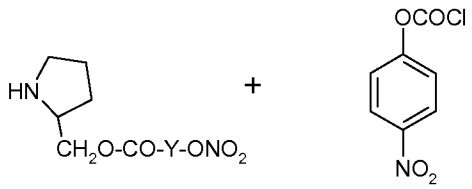
The compounds of formula (XIb) are obtained by reacting compounds of formula BocNH-Y-Hal (XIIb) wherein Y and Hal are as above defined or compounds of formula BocNH-Y-OTs (XIVa) wherein Ts is the tosyl group, with $AgNO_3$ or $MetalNO_3$ as already described in **A1**, eventually acid hydrolysing the Boc protective group. The compounds of formula (XIIb) and (XIVa) are commercially available or can be obtained from commercially available compounds BocNH-Y-OH (XIVb) with methods well known in the literature.

A3. Synthesis of compounds (Xa_c) and (Xc_c)



(Xa_c)

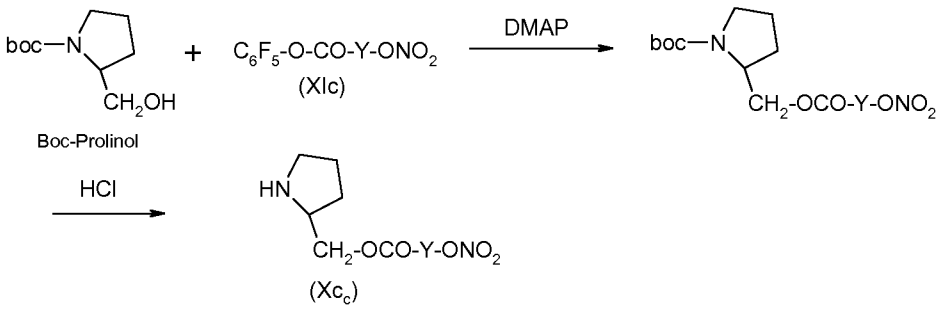
wherein Y is as above defined, can be obtained by reacting compound (Xc_c) with commercially available p-nitrophenylchlorocarbonate as already described:



(Xc_c)

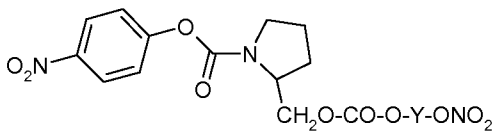
Compounds (Xc_c) can be obtained from commercially available Boc-prolinol by the procedures depicted in the Scheme 3 following methods analogues to those described in WO 2006/008196.

Scheme 3



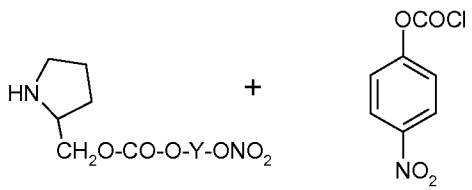
The compounds of formula (XIc) are obtained as described in WO 2006/008196.

A4. Synthesis of compounds (Xa_d) and (Xc_d)



(Xa_d)

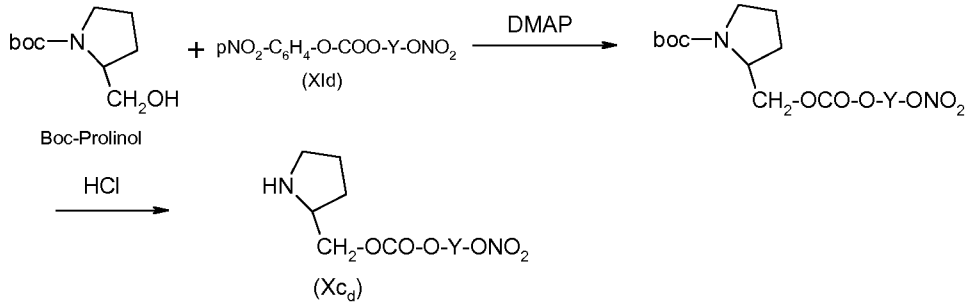
wherein Y is as above defined, can be obtained by reacting compound (Xc_d) with commercially available p-nitrophenylchlorocarbonate as already described:



(Xc_d)

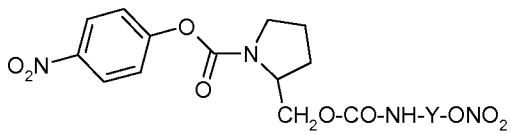
Compounds (Xc_d) can be obtained from commercially available Boc-prolinol by the procedures depicted in the Scheme 4 following methods analogues to those described in WO 2006/008196.

Scheme 4



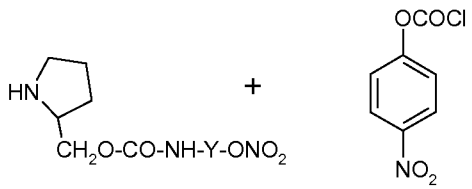
The compounds of formula (XId) are obtained as described in WO 2006/008196.

A5. Synthesis of compounds (Xa_e) and (Xc_e)



(Xa_e)

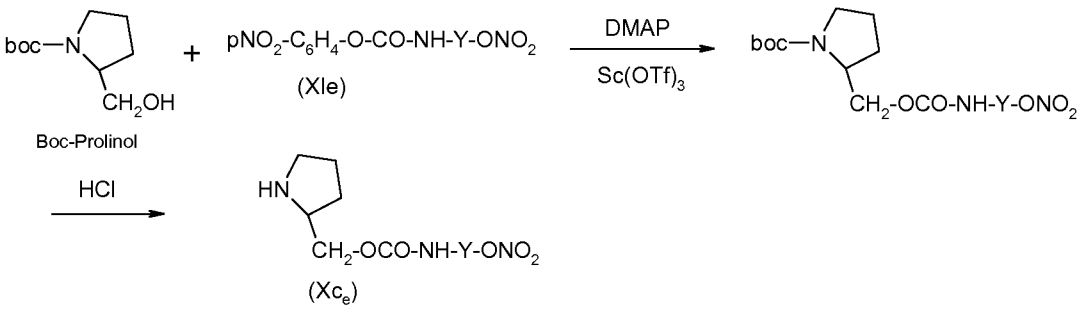
wherein Y is as above defined, can be obtained by reacting compound (Xc_e) with commercially available p-nitrophenylchlorocarbonate as already described:



(Xc_e)

Compounds (Xc_e) can be obtained from commercially available Boc-prolinol by the procedures depicted in the Scheme 5 following methods well known in the literature:

Scheme 5



The compounds of formula (XIe) are new compounds and are obtained from (XIb) described in **A2** following procedure described for analogues compounds:

NH_2-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(XIb)

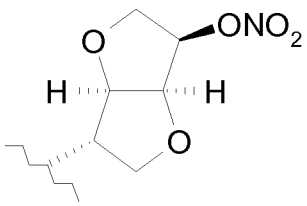
A6. Synthesis of compounds (Xb_a)-(Xb_e) and (Xd_a)-(Xd_e)

The compounds of formula (Xb_a)-(Xb_e) wherein J is as above defined depending on the meaning of K':

pNO_2-C_6H_4-OCONH-J-COO-A

(Xb_a)

wherein J is as previously defined and A is -(Y-ONO_2) or the group (1a)



(1a),

pNO_2-C_6H_4-OCONH-J-CONH-Y-ONO_2

(Xb_b)

pNO_2-C_6H_4-OCONH-J-CH_2O-CO-Y-ONO_2

(Xb_c)

pNO_2-C_6H_4-OCONH-J-CH_2O-CO-O-Y-ONO_2

(Xb_d)

pNO_2-C_6H_4-OCONH-J-CH_2O-CO-NH-Y-ONO_2

(Xb_e)

Wherein J and Y are as previously defined, are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xd_a)-(Xd_e):

NH_2-J-COO-A + pNO_2-C_6H_4-OCOCl

(Xd_a)

Wherein A is as previously defined;

NH_2-J-CONH-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xd_b)

NH_2-J-CH_2OCO-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xd_c)

NH_2-J-CH_2OCO-O-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xd_d)

NH_2-J-CH_2OCO-NH-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xd_e)

Wherei J and y are as previously defined.

Compounds of formula (Xd_a)-(Xd_e) depending on the meaning of J can be obtained starting from the corresponding Boc protected amino acid or Boc protected amino alcohol following the procedure described in **A1-A5** depending on the meaning of K'.

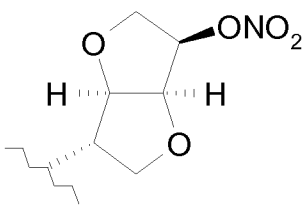
A7. Synthesis of compounds (Xe_a)-(Xe_e) and (Xg_a)-(Xg_e)

The compounds of formula (**Xe_a**)-(Xe_e)

p-NO_2-C_6H_4-O-CO-NH-K_a-COO-A

(Xe_a)

wherein A is -(Y-ONO_2) or the group (1a)



(1a),

p-NO_2-C_6H_4-O-CO-NH-K_a-CONH-Y-ONO_2

(Xe_b)

p-NO_2-C_6H_4-O-CO-NH-K_a-CH_2O-CO-Y-ONO_2

(Xe_c)

p-NO_2-C_6H_4-O-CO-NH-K_a-CH_2O-CO-O-Y-ONO_2

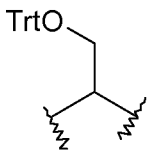
(Xe_d)

p-NO_2-C_6H_4-O-CO-NH-K_a-CH_2O-CO-NH-Y-ONO_2

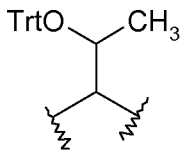
(Xe_e)

wherein:

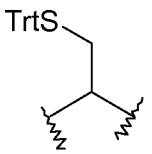
Y is as previously defined, and K_a is selected from (VIIIaa)-(VIIIha):



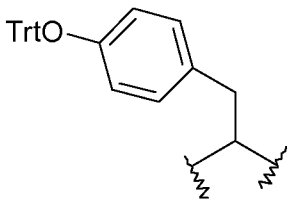
(VIIIaa)



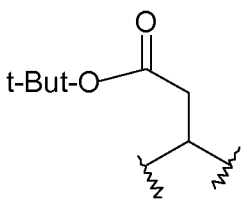
(VIIIba)



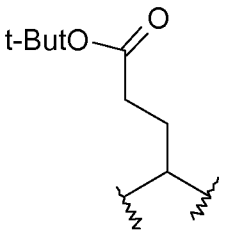
(VIIIca)



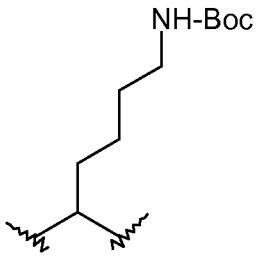
(VIIIda)



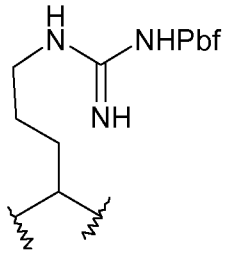
(VIIIea)



(VIIIfa)



(VIIIga)



(VIIIha)

wherein Trt is the trityl protecting group; t-But is the t-Butyl protecting group; Boc is the Boc protecting group; Pfb is the (2,2,4,6,7-pentamethyl-dihydrobenzofuran-5-sulfonyl)- protecting group;

are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xg_a)-(Xg_e):

NH_2-K_a-COO-A + pNO_2-C_6H_4-OCOCl

(Xg_a)

NH_2-K_a-CONH-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xg_b)

NH_2-K_a-CH_2O-CO-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xg_c)

NH_2-K_a-CH_2O-CO-O-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

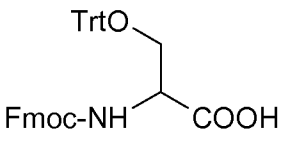
(Xg_d)

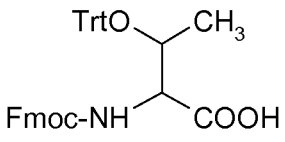
NH_2-K_a-CH_2O-CO-NH-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xg_e)

wherein A, Y and K_a are as previously defined.

Compounds of formula (Xg_a)-(Xg_e) depending on the meaning of K_a can be obtained starting from the corresponding N-Fmoc protected amino acid (VIIIab)-(VIIIhb):



,


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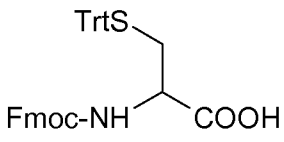
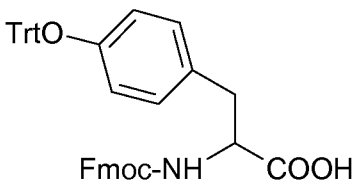
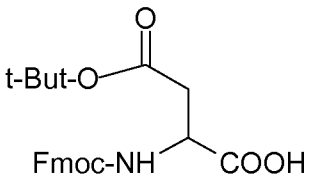
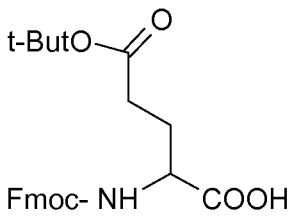


,

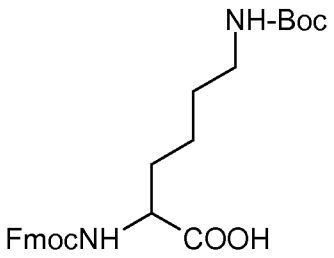
(VIIIab) (VIIIbb) (VIIIcb)







(VIIIdb), (VIIIeb) (VIIIfb)



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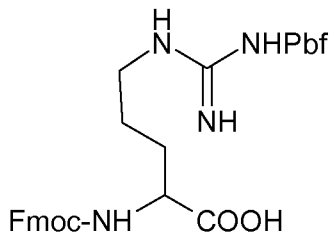
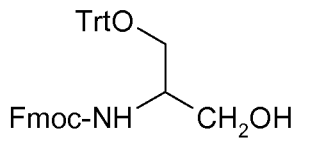


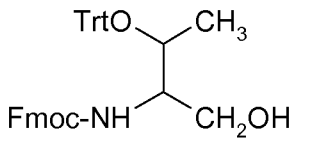
;

(VIIIgb) (VIIIhb)

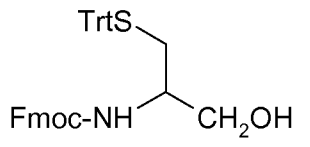
or corresponding N-Fmoc protected amino alcohol (VIIIac)-(VIIIhc):



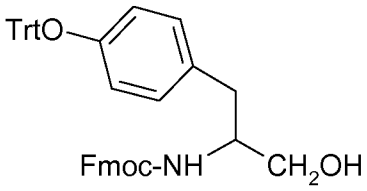
(VIIIac),



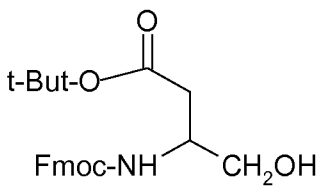
(VIIIbc),



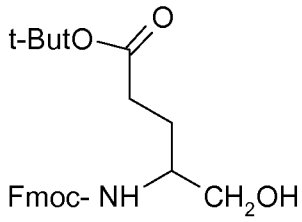
(VIIIcc),



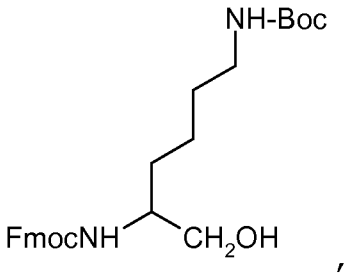
(VIIIdc),



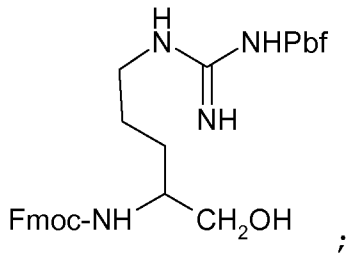
(VIIIec),



(VIIIfc),



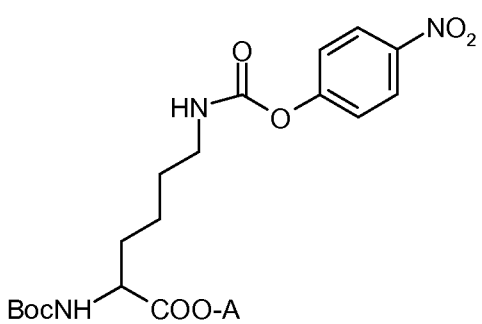
(VIIIgc),



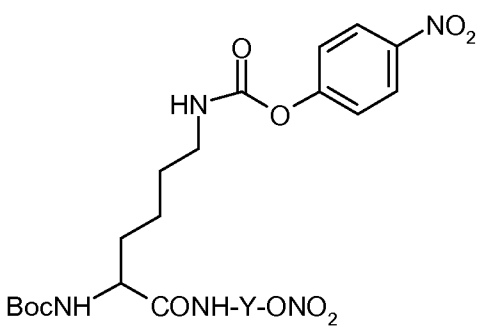
(VIIIhc);

following the procedure described in **A1-A5** depending on the meaning of K* that is equal to K', eventually hydrolyzing the Fmoc protected group following methods well known in the literature.

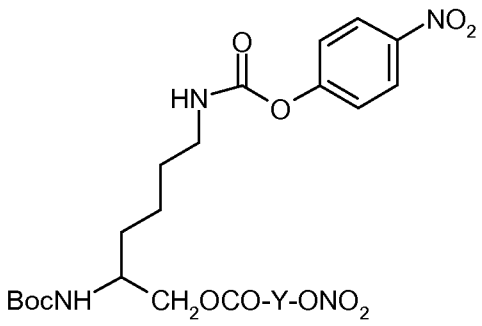
A8. Synthesis of compounds (Xf_a)-(Xf_e) and (Xh_a)-(Xh_e)



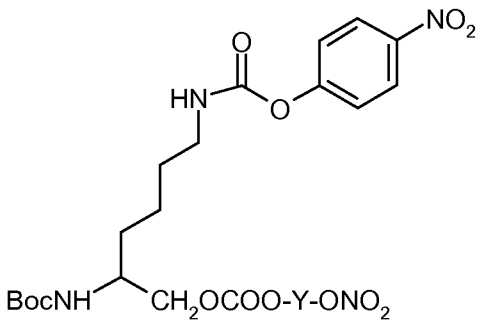
(Xf_a)



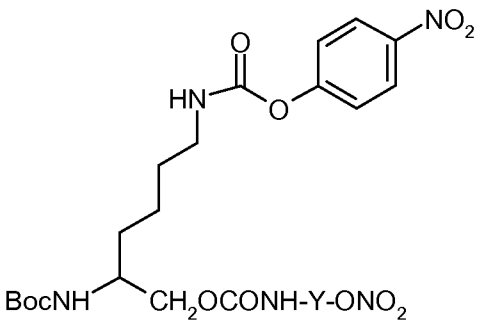
(Xf_b)



(Xf_c)



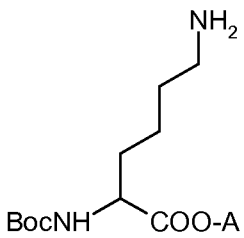
(Xf_d)



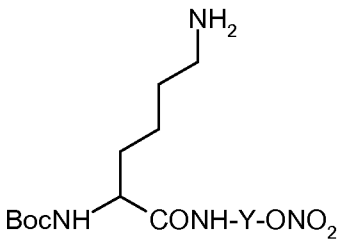
(Xf_e)

Wherein A, Y and are as previously defined in **A1.**

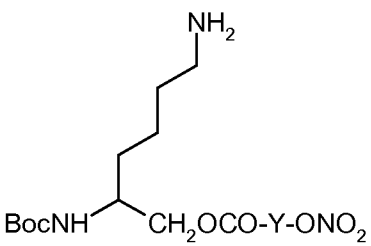
The compounds of formula (Xf_a)-(Xf_e) wherein A and Y are as previously defined in **A1.**, are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xh_a)-(Xh_e):



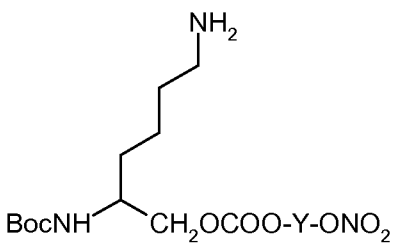
(Xh_a)



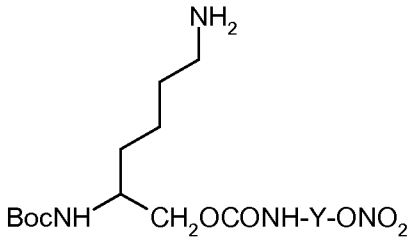
(Xh_b)



(Xh_c)



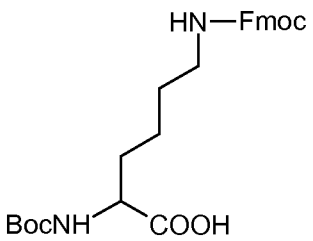
(Xh_d)



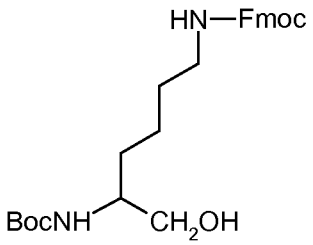
(Xh_e)

wherein A, Y and Boc are as previously defined.

Compounds of formula (Xh_a)-(Xh_e) depending on the meaning of K* that is equal to K' can be obtained starting from the corresponding N-Fmoc protected derivatives (IXaa) or (IXab):



(IXaa)



(IXab)

following the procedure described in **A1-A5** depending on the meaning of K*, eventually hydrolyzing the Fmoc protected group following methods well known in the literature.

A9/1. Synthesis of compounds (Xi_{a1}), (Xi_{a2}), (Xi_{a3}) and (Xk_{a1}), (Xk_{a2}) and (Xk_{a3})

Compounds of formula

$$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_1\text{-}COO\text{-}Y\text{-}ONO_2$$

(Xi_{a1})-(Xi_{a3})

wherein Y is as above described and K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is selected from respectively:

i) -CO- (Xi_{a1});

ii) -COO- (Xi_{a2}); or

iii) -CONH- (Xi_{a3});

and K_1 is bound to the group $-(Y'-ONO_2)$ are obtained by reaction with $pNO_2-C_6H_4-OCOCl$ of the corresponding compounds $(Xk_{a1})-(Xk_{a3})$:

$$NH_2-K_1-COO-Y-ONO_2 \quad + \quad pNO_2-C_6H_4-OCOCl$$
$$(Xk_{a1})-(Xk_{a3})$$

wherein Y is as previously defined and K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is selected from respectively:

i) $-CO-$ (Xk_{a1});

ii) $-COO-$ (Xk_{a2}); or

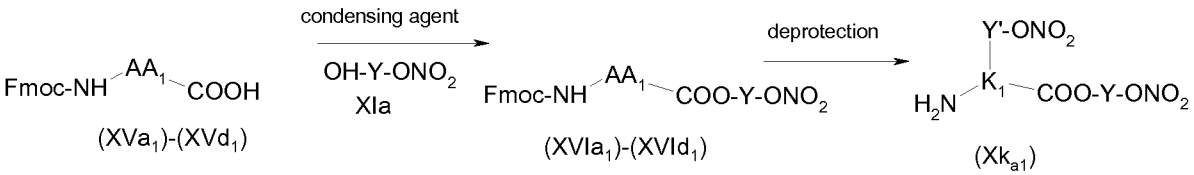
iii) $-CONH-$ (Xk_{a3});

Compounds of formula $(Xk_{a1})-(Xk_{a3})$ can be obtained as follows:

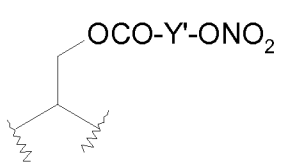
1) **(Xk_{a1}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is $-CO$:

1a) by reacting Fmoc protected compounds of formula $(XVa_1)-(XVd_1)$ (Scheme 6a) with compounds (XIa) applying the same procedure described in **A1**, eventually hydrolyzing the Fmoc protective groups of the resulting $(XVIa_1)-(XVId_1)$ following methods known in the literature.

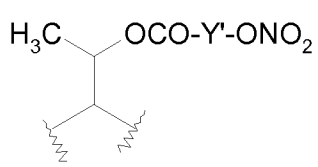
Scheme 6a



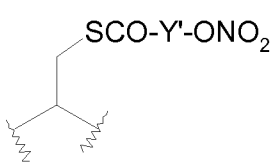
wherein Y is as above described; AA_1 are respectively the residue of formula (XVaa)-(XVad):



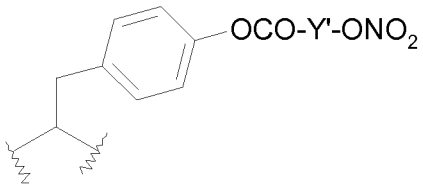
(XVaa)



(XVab)



(XVac)



(XVad)

wherein Y' as above defined; following the procedure already described in **A1**;

1b) Compounds of formula (XVa_1)-(XVd_1) are obtained by reacting respectively the corresponding commercially available Fmoc-serine, Fmoc-treonine, Fmoc-cysteine, or Fmoc-tyrosine with compounds (XIc):

C_6F_5O-CO-Y'-ONO_2

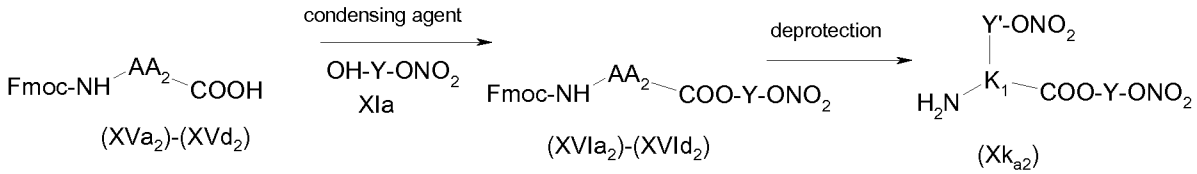
(XIc)

following procedure described in WO 2006/008196. Compounds (XIc) have been already described in **A3.**

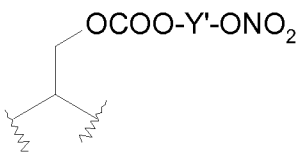
2) **(Xk_{a2}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is -COO:

2a) by reacting Fmoc protected compounds of formula (XVa_2)-(XVd_2) with compounds (XIa) applying the procedure described in Scheme 6b:

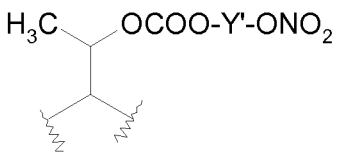
Scheme 6b



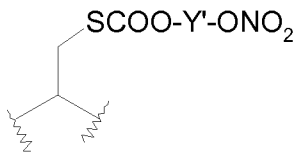
wherein Y is as above described; AA_2 are respectively the residue of formula (XVba)-(XVbd):



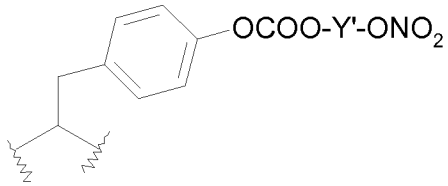
(XVba)



(XVbb)



(XVbc)



(XVbd)

wherein Y' is as above defined;

2b) Compounds of formula (XVa_2)-(XVd_2) are obtained by reacting respectively the corresponding commercially available Fmoc-serine, Fmoc-treonine, Fmoc-cysteine, or Fmoc-tyrosine with compounds (XId):

$p\text{-}NO_2\text{-}C_6H_4O\text{-}COO\text{-}Y'\text{-}ONO_2$

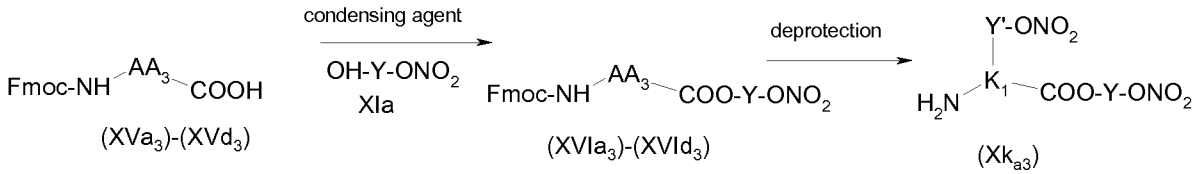
(XId)

following procedure described in WO 2006/008196. Compounds (XId) have been already described in **A4.**

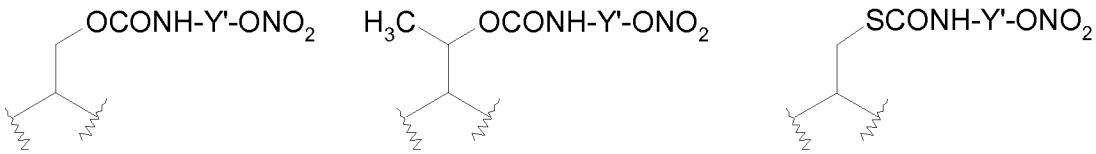
3) **(Xk_{a3}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is –CONH-:

3a) by reacting Fmoc protected compounds of formula (XVa_3)-(XVd_3) with compounds (XIa) applying the procedure described in Scheme 6c:

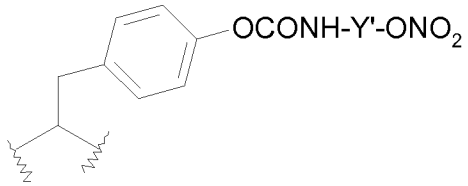
Scheme 6c



wherein Y is as above described; AA_3 are respectively the residue of formula (XVca)-(XVcd):



(XVca) (XVcb) (XVcc)



(XVcd)

wherein Y' is as above defined;

3b) Compounds of formula (XVa_3)-(XVd_3) as above defined are obtained by reacting respectively the corresponding commercially available Fmoc-serine, Fmoc-treonine, Fmoc-cysteine, or Fmoc-tyrosine with compounds (XIe):

$p\text{-}NO_2\text{-}C_6H_4O\text{-}CONH\text{-}Y'\text{-}ONO_2$

(XIe)

following procedure described in **A5.**

A9/2. Synthesis of compounds (Xi_{a4}), (Xi_{a5}), (Xi_{a6}) and (Xk_{a4}), (Xk_{a5}) and (Xk_{a6})

Compounds of formula

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_1\text{-}COOtBut$

(Xi_{a4})-(Xi_{a6})

wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is selected from respectively:

i) -CO- (Xi_{a4});

ii) -COO- (Xi_{a5}); or

iii) -CONH- (Xi_{a6});

and K_1 is bound to the group -(Y'-ONO_2) are obtained by reaction with $pNO_2\text{-}C_6H_4\text{-}OCOCl$ of the corresponding compounds (Xk_{a4})-(Xk_{a6}):

$NH_2\text{-}K_1\text{-}COOtBut + pNO_2\text{-}C_6H_4\text{-}OCOCl$

(Xk_{a4})-(Xk_{a6})

wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is selected from respectively:

i) -CO- (Xk_{a4});

ii) -COO- (Xk_{a5}); or

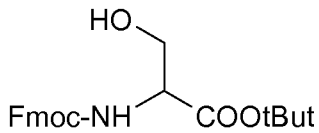
iii) -CONH- (Xk_{a6});

Compounds of formula (Xk_{a4})-(Xk_{a6}) can be obtained

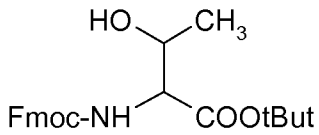
1) **(Xk_{a4}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is -CO are obtained:

by reacting respectively the corresponding commercially available compound (VIIIad), (VIIIbd), (VIIIcd) and (VIIIdd) with compounds (XIc) (Scheme 6d):

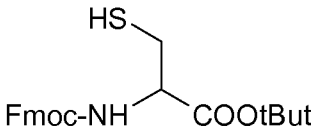
Scheme 6d



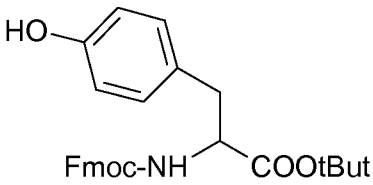
(VIIIad) + C_6F_5O-CO-Y'-ONO_2 (XIc)



(VIIIbd) + C_6F_5O-CO-Y'-ONO_2 (XIc)



(VIIIcd) + C_6F_5O-CO-Y'-ONO_2 (XIc)

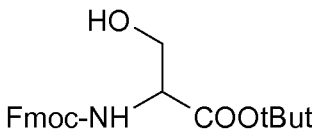


(VIIIdd) + C_6F_5O-CO-Y'-ONO_2 (XIc)

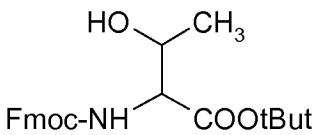
wherein Y' is as above described, following procedure described **A3** and eventually deprotecting the Fmoc group by known methods.

2) **(Xk_{a5}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is -COO:
are obtained by reacting respectively the corresponding commercially available compound (VIIIad), (VIIIbd), (VIIIcd) and (VIIIdd) with compounds (XId) (Scheme 6e):

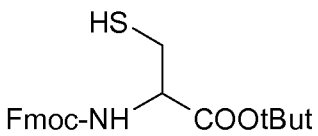
Scheme 6e



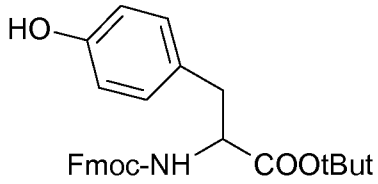
(VIIIad) + p-NO_2-C_6H_4O-COO-Y'-ONO_2 (XId)



(VIIIbd) + p-NO_2-C_6H_4O-COO-Y'-ONO_2 (XId)



(VIIIcd) + p-NO_2-C_6H_4O-COO-Y'-ONO_2 (XId)



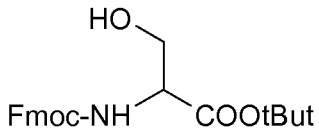
(VIIIdd) + p-NO_2-C_6H_4O-COO-Y'-ONO_2 (XId)

wherein Y' is as above described, following procedure described **A4** and eventually deprotecting the Fmoc group by known methods.

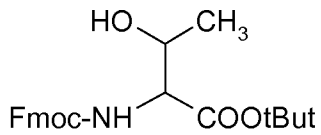
3) **(Xk_{a6}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is –CONH-:

are obtained by reacting respectively the corresponding commercially available compound (VIIIad), (VIIIbd), (VIIIcd) and (VIIIdd) with compounds (XIe) (Scheme 6f):

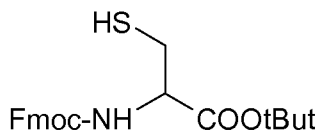
Scheme 6f



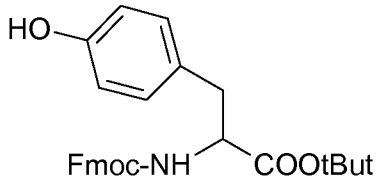
(VIIIad) + p-NO_2-C_6H_4O-CONH-Y'-ONO_2 (XIe)



(VIIIbd) + p-NO_2-C_6H_4O-CONH-Y'-ONO_2 (XIe)



(VIIIcd) + p-NO_2-C_6H_4O-CONH-Y'-ONO_2 (XIe)



(VIIIdd) + p-NO_2-C_6H_4O-CONH-Y'-ONO_2 (XIe)

wherein Y' is as above described, following procedure described **A5** and eventually deprotecting the Fmoc group by known methods.

A10. Synthesis of compounds (Xi_{b1}), (Xi_{b2}), (Xi_{b3}) and (Xk_{b1}), (Xk_{b2}) and (Xk_{b3})

Compounds of formula

p-NO_2-C_6H_4-O-CO-NH-K_1-CONH-Y-ONO_2

(Xi_{b1})-(Xi_{b3})

wherein Y is as above described and K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is selected from respectively:

i) -CO- (Xi_{b1});

ii) -COO- (Xi_{b2}); or

iii) -CONH- (Xi_{b3});

and K_1 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xk_{b1})-(Xk_{b3})

NH_2-K_1-CONH-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xk_{b1})-(Xk_{b3})

wherein Y and K_1 are as above defined;

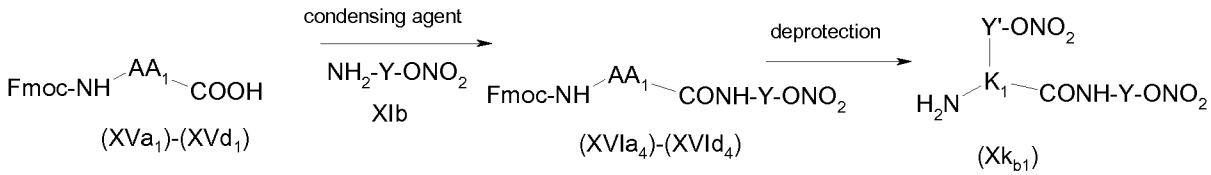
Compounds of formula (Xk_{b1})-(Xk_{b3}) can be obtained as follow:

1) **(Xk_{b1}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is -CO:

1a) by reacting compounds of formula (XVa_1)-(XVd_1) obtained as described in **A9** with compounds (XIb) applying the same

procedure described in **A2**, eventually hydrolyzing the Fmoc protective groups of the resulting ($XVIa_4$)-($XVId_4$) following methods known in the literature (Scheme 7a):

Scheme 7a

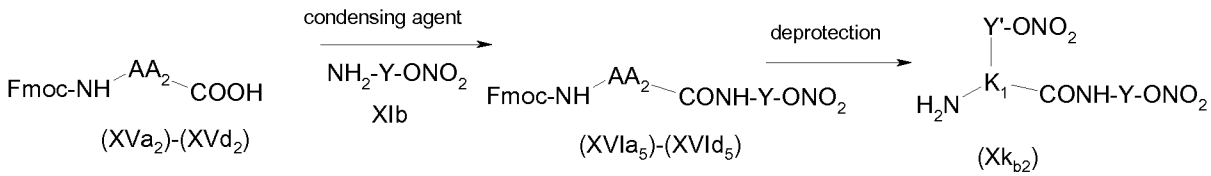


wherein Y and AA_1 are as previously defined.

2) **(Xk_{b2}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is -COO:

2a) by reacting Fmoc protected compounds of formula (XVa_2)-(XVd_2) obtained as described in **A9** with compounds (XIb) then deprotecting the obtained compounds ($XVIa_5$)-($XVId_5$) applying procedures already described (Scheme 7b):

Scheme 7b

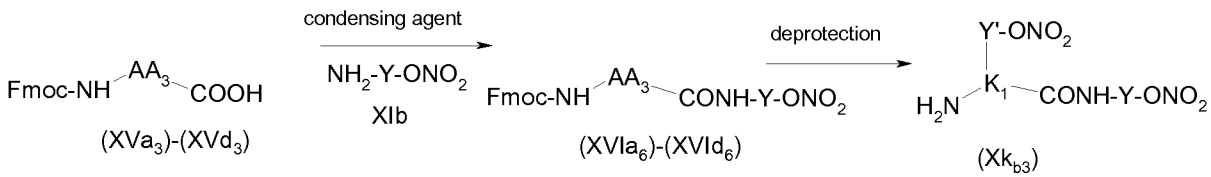


wherein Y and AA_2 are as already described;

3) **(Xk_{b3}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is -CONH-:

3a) by reacting Fmoc protected compounds of formula (XVa_3)-(XVd_3) with compounds (XIb) applying the same procedure described above (Scheme 7c):

Scheme 7c



wherein Y and AA_3 are as previously defined;

A11. Synthesis of compounds (Xi_{c1}), (Xi_{c2}), (Xi_{c3}) and (Xk_{c1}), (Xk_{c2}) and (Xk_{c3})

Compounds of formula

$$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_1\text{-}CH_2O\text{-}CO\text{-}Y\text{-}ONO_2$$

(Xi_{c1})-(Xi_{c3})

wherein Y is as above described and K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is selected from respectively:

i) -CO- (Xi_{c1});

ii) -COO- (Xi_{c2}); or

iii) -CONH- (Xi_{c3});

and K_1 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xk_{c1})-(Xk_{c3}):

$$NH_2\text{-}K_1\text{-}CH_2O\text{-}CO\text{-}Y\text{-}ONO_2 \quad + \quad pNO_2\text{-}C_6H_4\text{-}OCOCl$$

(Xk_{c1})-(Xk_{c3})

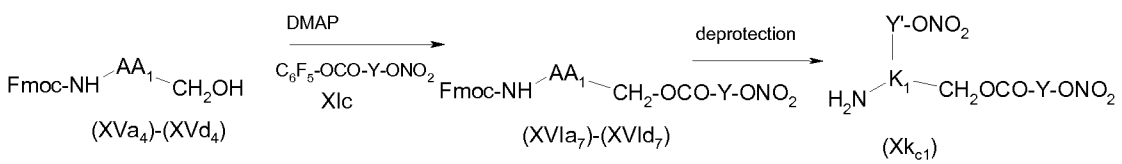
wherein Y and K_1 are as above defined;

Compounds of formula (Xk_{c1})-(Xk_{c3}) can be obtained as follow:

1) **(Xk_{c1}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is -CO:

1a) by reacting Fmoc protected compounds of formula (XVa_4)-(XVd_4) with compounds (XIc) applying the same procedure described in **A3,** eventually hydrolyzing the Fmoc protective groups of the resulting $(XVIa_7)$-$(XVId_7)$ following methods known in the literature (Scheme 8a):

Scheme 8a

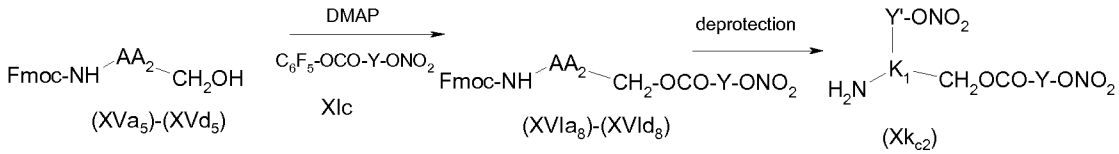


wherein Y is as above defined and AA_1 has been already described in **A9**;

2) **(Xk_{c2})**: wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is –COO:

2a) by reacting Fmoc protected compounds of formula (XVa_5)-(XVd_5) with compounds (XIc) applying the same procedure described above (Scheme 8b):

Scheme 8b

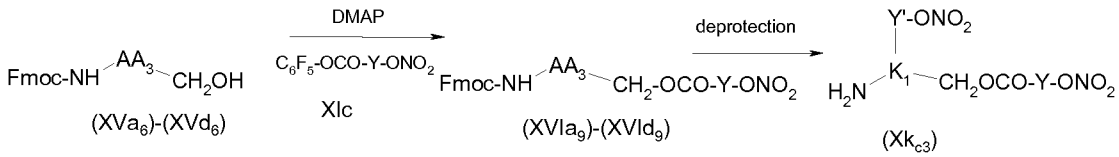


wherein Y and AA_2 havs been already defined;

3) **(Xk_{c3})**: wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is –CONH-:

3a) by reacting Fmoc protected compounds of formula (XVa_6)-(XVd_6) with compounds (XIb) applying the same procedure described above (Scheme 8c):

Scheme 8c



wherein Y and AA_3 have been already described.

A12. Synthesis of compounds (Xi_{d1}), (Xi_{d2}), (Xi_{d3}) and (Xk_{d1}), (Xk_{d2}) and (Xk_{d3})

Compounds of formula:

$$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_1\text{-}CH_2O\text{-}COO\text{-}Y\text{-}ONO_2$$

(Xi_{d1})-(Xi_{d3})

wherein Y is as above described and K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is selected from respectively:

i) –CO- (Xi_{d1});

ii) –COO- (Xi_{d2}); or

iii) –CONH- (Xi_{d3});

and K_1 is bound to the group $-(Y'-ONO_2)$ are obtained by reaction with $pNO_2-C_6H_4-OCOCl$ of the corresponding compounds $(Xk_{d1})-(Xk_{d3})$:

$$NH_2-K_1-CH_2O-COO-Y-ONO_2 \quad + \quad pNO_2-C_6H_4-OCOCl$$
$$(Xk_{d1})-(Xk_{d3})$$

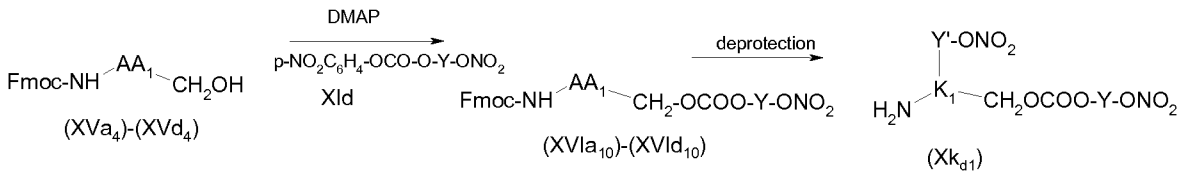
wherein Y and K_1 are as above defined;

Compounds of formula $(Xk_{d1})-(Xk_{d3})$ can be obtained as follow:

1) **(Xk_{d1}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is –CO:

1a) by reacting Fmoc protected compounds of formula $(XVa_4)-(XVd_4)$ with compounds (XId) applying the same procedure described in **A4**, eventually hydrolyzing the Fmoc protective groups of the resulting $(XVIa_{10})-(XVId_{10})$ following methods known in the literature (Scheme 9a):

Scheme 9a

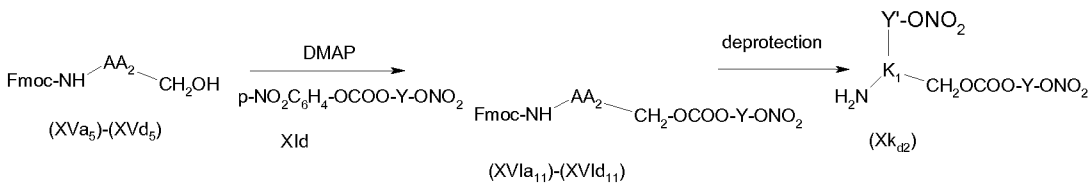


wherein Y and AA_1 have been already described in **A9;**

2) **(Xk_{d2}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is –COO:

2a) by reacting Fmoc protected compounds of formula $(XVa_5)-(XVd_5)$ with compounds (XId) applying the same procedure described above. (Scheme 9b):

Scheme 9b

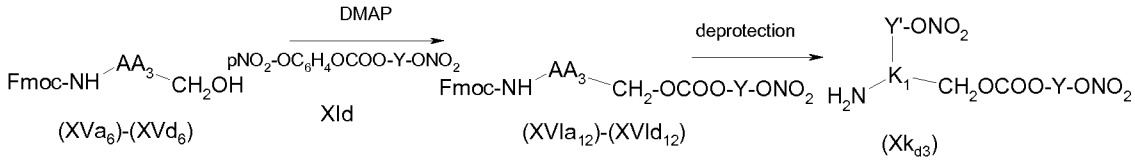


wherein Y and AA_2 have been already defined;

3) **(Xk_{d3}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is –CONH-:

3a) by reacting Fmoc protected compounds of formula (XVa_6)-(XVd_6) with compounds (XId) applying the same procedure described above (Scheme 9c):

Scheme 9c



wherein Y and AA_3 have been already described.

A13. Synthesis of compounds (Xi_{e1}), (Xi_{e2}), (Xi_{e3}) and (Xk_{e1}), (Xk_{e2}) and (Xk_{e3})

Compounds of formula

$$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_1\text{-}CH_2O\text{-}CONH\text{-}Y\text{-}ONO_2$$

(Xi_{e1})-(Xi_{e3})

wherein Y is as above described and K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is selected from respectively:

i) –CO- (Xi_{e1});

ii) -COO- (Xi_{e2}); or

iii) –CONH- (Xi_{e3});

and K_1 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xk_{e1})-(Xk_{e3}):

NH_2-K_1-CH_2O-CONH-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xk_{e1})-(Xk_{e3})

wherein Y and K_1 are as above defined;

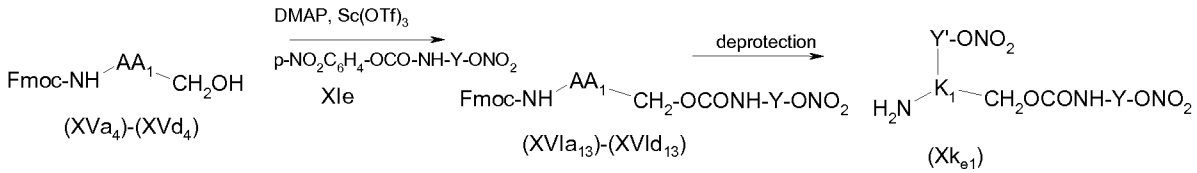
Compounds of formula (Xk_{e1})-(Xk_{e3}) can be obtained as follow:

1) **(Xk_{e1}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is –CO:

1a) by reacting Fmoc protected compounds of formula (XVa_4)-(XVd_4) with compounds (XIe) applying the same procedure

described in **A5,** eventually hydrolyzing the Fmoc protective groups of the resulting ($XVIa_{13}$)-($XVId_{13}$) following methods known in the literature (Scheme 10a):

Scheme 10a

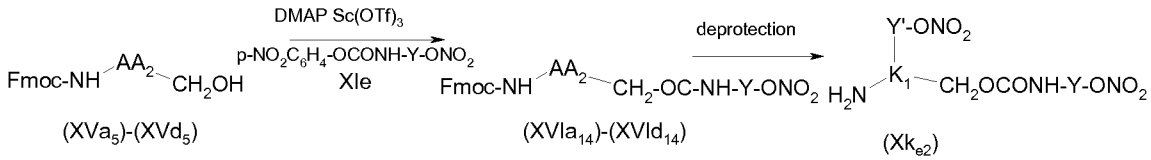


wherein Y and AA_1 have been already described;

2) **(Xk_{e2}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is –COO:

2a) by reacting Fmoc protected compounds of formula (XVa_5)-(XVd_5) with compounds (XIe) applying the same procedure described above (Scheme 10b):

Scheme 10b

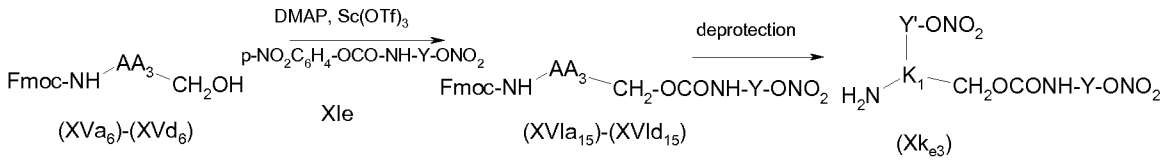


wherein Y and AA_2 have been already defined;

3) **(Xk_{e3}):** wherein K_1 is selected from (VIIIa)-(VIIId) wherein R_5 is –CONH-:

3a) by reacting Fmoc protected compounds of formula (XVa_6)-(XVd_6) with compounds (XIe) applying the same procedure described above (Scheme 10c):

Scheme 10c



wherein Y and AA_3 have been already described.

A14/1. Synthesis of compounds (Xi_{f1}),(Xi_{f2}) and (Xk_{f1})-(Xk_{f2})

Compounds of formula

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_2\text{-}COO\text{-}Y\text{-}ONO_2$

$(Xi_{f1}),(Xi_{f2})$

wherein Y is as above described and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is selected from respectively:

i) -O- (Xi_{f1}) or

ii) -NH- (Xi_{f2})

and K_2 is bound to the group $-(Y'\text{-}ONO_2)$ are obtained by reaction with $pNO_2\text{-}C_6H_4\text{-}OCOCl$ of the corresponding compounds $(Xk_{f1}),(Xk_{f2})$:

$NH_2\text{-}K_2\text{-}COO\text{-}Y\text{-}ONO_2$ + $pNO_2\text{-}C_6H_4\text{-}OCOCl$

$(Xk_{f1})\text{-}(Xk_{f2})$

wherein Y is as previously defined and K_2 is selected from:

i) -O- (Xk_{f1}) or

ii) -NH- (Xk_{f2})

Compounds of formula $(Xk_{f1}),(Xk_{f2})$ can be obtained as follows:

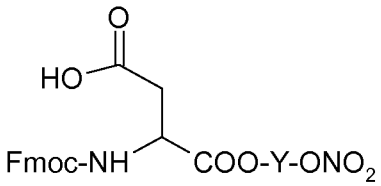
1) **(Xk_{f1}):** wherein Y and Y' are equal and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is -O-:

1a) by reacting the Fmoc-glutamic acid or Fmoc-glutaric acid with compounds (XIa) applying the same procedure described in **A1** and using 2 equivalents of (XIa), eventually hydrolyzing the Fmoc protective groups following methods known in the literature.

1') **(Xk_{f1}):** wherein Y and Y' are different and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is -O-:

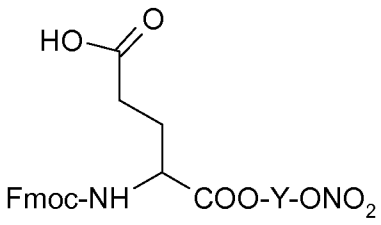
1a') by reacting compounds of formula $(XVIIa_1),(XVIIb_1)$ with compounds (XIa) following procedure already described in **A1** (Scheme 11a):

Scheme 11a



+ HO-Y'-ONO$_2$

(XVIIa$_1$) (XIa)

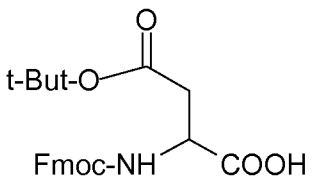


+ HO-Y'-ONO$_2$

(XVIIb$_1$) (XIa)

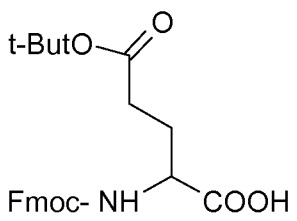
Eventually deprotecting the Fmoc group by known methods.

Compounds (XVIIa$_1$) and (XVIIb$_1$) were obtained by reacting compounds (VIIIeb) and (VIIIfb) above described in **A7** with compounds (XIa), eventually acid hydrolyzing the t-butyl ester group:



+ HO-Y-ONO$_2$

(VIIIeb) (XIa)



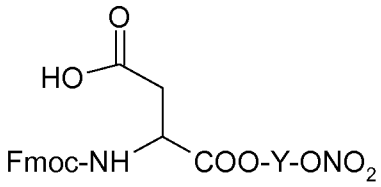
HO-Y-ONO$_2$

(VIIIfb) (XIa)

2) **(Xk_{f2}):** wherein Y is as above defined and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is –NH-:

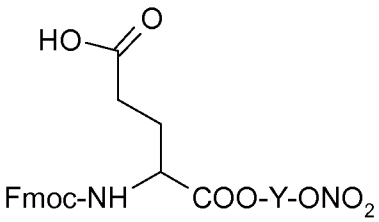
2a) by reacting compounds of formula ($XVIIa_1$),($XVIIb_1$) already defined with compounds (XIb) following procedure already described in **A2** (Scheme 11b):

Scheme 11b



+ NH_2-Y'-ONO_2

($XVIIa_1$) (XIb)



+ NH_2-Y'-ONO_2

($XVIIb_1$) (XIb)

Eventually deprotecting the Fmoc group by known methods.

A14/2. Synthesis of compounds (Xi_{f3}),(Xi_{f4}) and (Xk_{f3})-(Xk_{f4})

Compounds of formula

p-NO_2-C_6H_4-O-CO-NH-K_2-COOtBut

(Xi_{f3}),(Xi_{f4})

wherein K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is selected from respectively:

i) -O- (Xi_{f3}) or

ii) -NH- (Xi_{f4})

and K_2 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xk_{f3}),(Xk_{f4}):

NH_2-K_2-COOtBut + pNO_2-C_6H_4-OCOCl

$(Xk_{f3})-(Xk_{f4})$

wherein K_2 is selected from:

i) -O- (Xk_{f3}) or

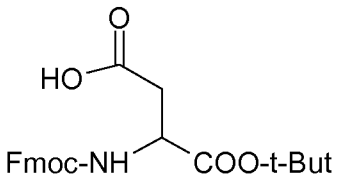
ii) -NH- (Xk_{f4})

Compounds of formula $(Xk_{f3}),(Xk_{f4})$ can be obtained as follows:

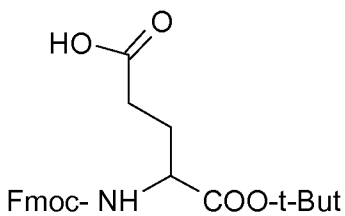
1) **(Xk_{f3}):** wherein K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is -O-:

1a) by reacting commercially available compounds of formula (VIIIde) and (VIIIdf) with compounds (XIa) applying the same procedure described in **A1** (Scheme 11c) eventually hydrolyzing the Fmoc protective groups following methods known in the literature.

Scheme 11c



(VIIIde) + $HO-Y'-ONO_2$ (XIa)

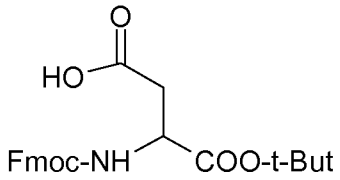


(VIIIdf) + $HO-Y'-ONO_2$ (XIa)

2) **(Xk_{f4}):** wherein K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is -NH-:

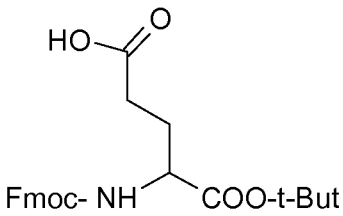
2a) by reacting commercially available compounds of formula (VIIIde) and (VIIIdf) with compounds (XIb) applying the same procedure described in **A2** (Scheme 11d) eventually hydrolyzing the Fmoc protective groups following methods known in the literature.

Scheme 11d



+ NH_2-Y'-ONO_2

(VIIIde) (XIb)



+ NH_2-Y'-ONO_2

(VIIIdf) (XIb)

A15. Synthesis of compounds (Xi_{g1}),(Xi_{g2}) and (Xk_{g1})-(Xk_{g2})

Compounds of formula

p-NO_2-C_6H_4-O-CO-NH-K_2-CONH-Y-ONO_2

(Xi_{g1}),(Xi_{g2})

Wherein Y is as above described and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is selected from respectively:

i) -O- (Xi_{g1}) or

ii) -NH- (Xi_{g2})

and K_2 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xk_{g1}),(Xk_{g2})

NH_2-K_2-CONH-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xk_{g1})-(Xk_{g2})

Wherein Y is as previously defined and K_2 is selected from:

i) -O- (Xk_{g1}) or

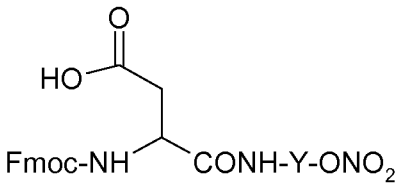
ii) -NH- (Xk_{g2})

Compounds of formula (Xk_{g1}),(Xk_{g2}) can be obtained as follow:

1) **(Xk_{g1}):** wherein Y is as above defined and K_2 is selected from (VIIIe), (VIIIf) wherein R_6 is -O-:

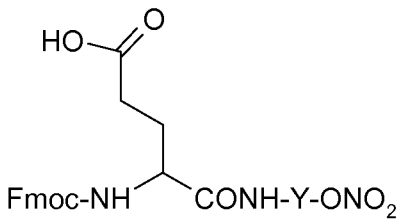
1a) by reacting compounds of formula ($XVIIa_2$),($XVIIb_2$) with compounds (XIa) following procedure already described in **A1** (Scheme 12):

Scheme 12



+ OH-Y'-ONO_2

($XVIIa_2$) (XIa)



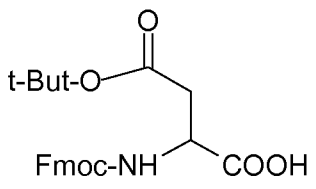
+ HO-Y'-ONO_2

($XVIIb_2$) (XIa)

Eventually deprotecting the Fmoc group by known methods.

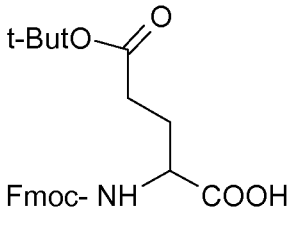
Compounds ($XVIIa_2$) and ($XVIIb_2$) can be obtained by reacting compounds (VIIIeb) or (VIIIfb) with compounds (XIb) following procedure described in **A2** (Scheme 15):

Scheme 15



+ NH_2-Y-ONO_2

(VIIIeb) (XIb)



NH_2-Y-ONO_2

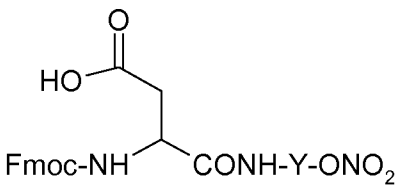
(VIIIfb) (XIb)

2) **(Xk_{g2}):** wherein Y and Y′ are equal or different and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is –NH-:

2a) wherein Y and Y′ are equal: by reacting the Fmoc-glutamic acid or Fmoc-glutaric acid with compounds (XIb) applying the same procedure described in **A2** and using 2 equivalent of (XIb), eventually hydrolyzing the Fmoc protective groups following methods known in the literature.

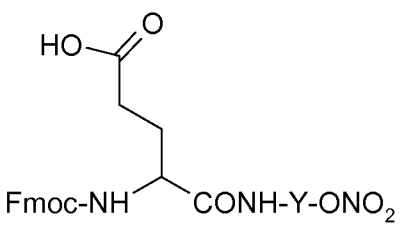
2a′) wherein Y and Y′ are different: by reacting compounds ($XVIIa_2$) and ($XVIIb_2$) above described with compounds (XIb) as above described, (Scheme 16) eventually hydrolyzing the Fmoc protecting group:

Scheme 16



+ NH_2-Y′-ONO_2

($XVIIa_2$) (XIb)



+ NH_2-Y′-ONO_2

($XVIIb_2$) (XIb)

A16. Synthesis of compounds (Xi_{h1}),(Xi_{h2}) and (Xk_{h1})-(Xk_{h2})

Compounds of formula

$$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_2\text{-}CH_2OCO\text{-}Y\text{-}ONO_2$$

(Xi_{h1}),(Xi_{h2})

Wherein Y is as above described and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is selected from respectively:

i) -O- (Xi_{h1}) or

ii) -NH- (Xi_{h2})

and K_2 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xk_{h1}),(Xk_{h2}):

$$NH_2\text{-}K_2\text{-}CH_2OCO\text{-}Y\text{-}ONO_2 \quad + \quad pNO_2\text{-}C_6H_4\text{-}OCOCl$$

(Xk_{h1})-(Xk_{h2})

wherein Y is as previously defined and K_2 is selected from:

i) -O- (Xk_{h1}) or

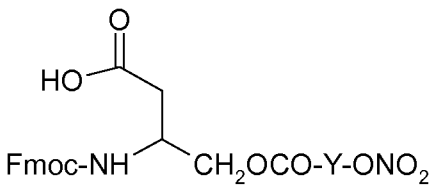
ii) -NH- (Xk_{h2})

Compounds of formula (Xk_{h1}),(Xk_{h2}) can be obtained as follow:

1) **(Xk_{h1})**: wherein Y is as above defined and K_2 is selected from (VIIIe), (VIIIf) wherein R_6 is -O- and K_2 binds a group -Y'-ONO_2:

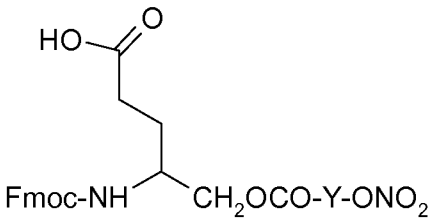
1a) by reacting compounds of formula ($XVIIa_3$),($XVIIb_3$) with compounds (XIa) following procedure already described in **A3** (Scheme 15):

Scheme 15



+ OH-Y'-ONO_2

($XVIIa_3$) (XIa)

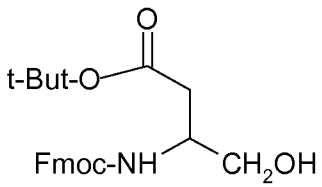


+ HO-Y'-ONO_2

($XVIIb_3$) (XIa)

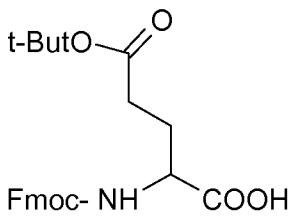
Eventually deprotecting the Fmoc group by known methods. Compounds ($XVIIa_3$) and ($XVIIb_3$) can be obtained by reacting compounds (VIIIec) or (VIIIfc) with compounds (XIc) following procedure described in **A3** (Scheme 16)

Scheme 16



+ C_6F_5O-CO-Y-ONO_2

(VIIIec) (XIc)



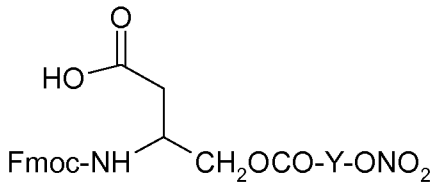
+ C_6F_5O-CO-Y-ONO_2

(VIIIfc) (XIc)

2) **(Xk_{h2}):** wherein Y is as above defined and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is –NH-:

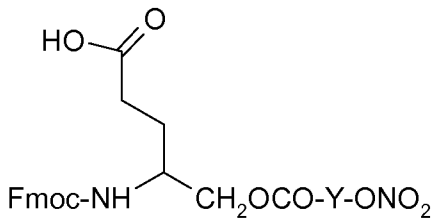
2a) by reacting compounds ($XVIIa_3$) and ($XVIIb_3$) above described with compounds (XIb) as above described, (Scheme 17):

Scheme 17



+ NH_2-Y'-ONO_2

($XVIIa_3$) (XIb)



+ NH_2-Y'-ONO_2

($XVIIb_3$) (XIb)

eventually hydrolyzing the Fmoc protecting group as already described.

A17. Synthesis of compounds (Xi_{i1}),(Xi_{i2}) and (Xk_{i1})-(Xk_{i2})

Compounds of formula

p-NO_2-C_6H_4-O-CO-NH-K_2-CH_2OCOO-Y-ONO_2

(Xi_{i1}),(Xi_{i2})

wherein Y is as above described and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is selected from respectively:

i) -O- (Xi_{i1}) or

ii) -NH- (Xi_{i2})

and K_2 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xk_{i1}),(Xk_{i2})

NH_2-K_2-CH_2OCOO-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xk_{i1})-(Xk_{i2})

Wherein Y is as previously defined and K_2 is selected from:

i) -O- (Xk_{i1}) or

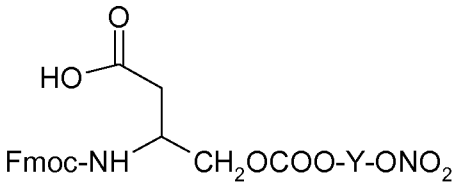
ii) -NH- (Xk_{i2})

Compounds of formula (Xk_{i1}),(Xk_{i2}) can be obtained as follow:

1) **(Xk_{i1}):** wherein Y is as above defined and K_2 is selected from (VIIIe), (VIIIf) wherein R_6 is –O-:

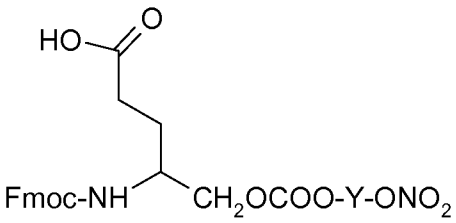
1a) by reacting compounds of formula ($XVIIa_4$),($XVIIb_4$) with compounds (XIa) following procedure already described in **A3** (Scheme 18):

Scheme 18



+ OH-Y'-ONO_2

($XVIIa_4$) (XIa)



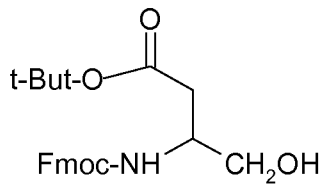
+ HO-Y'-ONO_2

($XVIIb_4$) (XIa)

Eventually deprotecting the Fmoc group by known methods.

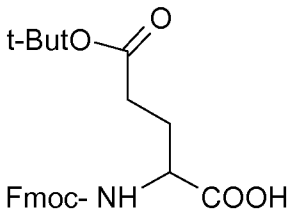
Compounds ($XVIIa_4$) and ($XVIIb_4$) can be obtained by reacting compounds (VIIIec) or (VIIIfc) with compounds (XId) following procedure described in **A4** (Scheme 19):

Scheme 19



+ p-NO_2-C_6H_4O-COO-Y-ONO_2

(VIIIec) (XId)



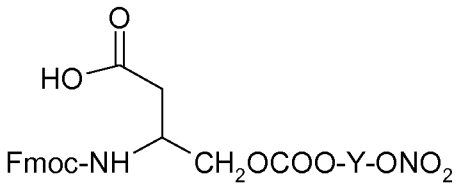
+ p-NO_2-C_6H_4O-COO-Y-ONO_2

(VIIIfc) (XId)

2) **(Xk_{i2}):** wherein Y is as above defined and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is –NH-:

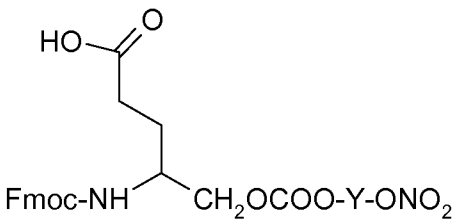
2a) by reacting compounds ($XVIIa_4$) and ($XVIIb_4$) above described with compounds (XIb) as above described, (Scheme 20):

Scheme 20



+ NH_2-Y'-ONO_2

($XVIIa_4$) (XIb)



+ NH_2-Y'-ONO_2

($XVIIb_4$) (XIb)

eventually hydrolyzing the Fmoc protecting group as already described.

A18. Synthesis of compounds (Xi_{j1}),(Xi_{j2}) and (Xk_{j1})-(Xk_{j2})

Compounds of formula

p-NO_2-C_6H_4-O-CO-NH-K_2-CH_2OCONH-Y-ONO_2

(Xi_{j1}),(Xi_{j2})

wherein Y is as above described and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is selected from respectively:

i) -O- (Xi_{j1}) or

ii) -NH- (Xi_{j2})

and K_2 is bound to the group $-(Y'-ONO_2)$ are obtained by reaction with $pNO_2-C_6H_4-OCOCl$ of the corresponding compounds $(Xk_{j1}),(Xk_{j2})$:

$$NH_2-K_2-CH_2OCONH-Y-ONO_2 \quad + \quad pNO_2-C_6H_4-OCOCl$$
$$(Xk_{j1})-(Xk_{j2})$$

wherein Y is as previously defined and K_2 is selected from:

i) $-O-$ (Xk_{j1}) or

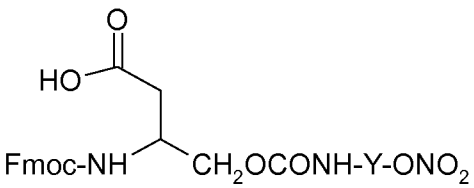
ii) $-NH-$ (Xk_{j2})

Compounds of formula $(Xk_{j1}),(Xk_{j2})$ can be obtained as follow:

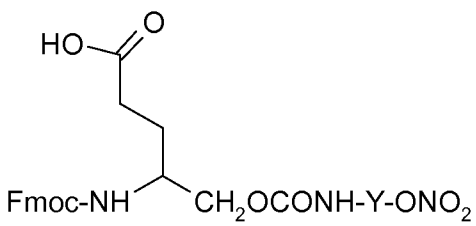
1) **(Xk_{j1}):** wherein Y is as above defined and K_2 is selected from (VIIIe), (VIIIf) wherein R_6 is $-O-$:

1a) by reacting compounds of formula $(XVIIa_5),(XVIIb_5)$ with compounds (XIa) following procedure already described in **A3** (Scheme 21):

Scheme 21



$(XVIIa_5)$ + $OH-Y'-ONO_2$ (XIa)

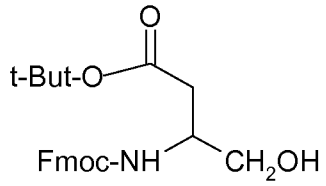


$(XVIIb_5)$ + $HO-Y'-ONO_2$ (XIa)

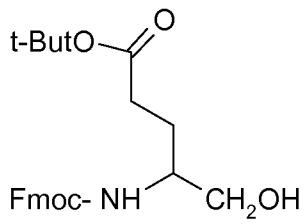
Eventually deprotecting the Fmoc group by known methods.

Compounds $(XVIIa_5)$ and $(XVIIb_5)$ can be obtained by reacting compounds (VIIIec) or (VIIIfc) with compounds (XIe) following procedure described in **A5** (Scheme 22):

Scheme 22



(VIIIec) + $pNO_2-C_6H_4O-CONH-Y-ONO_2$ (XIe)



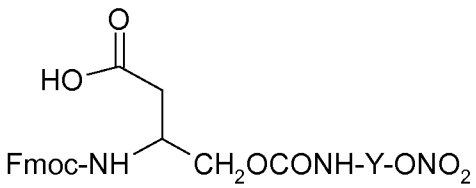
(VIIIfc) + $pNO_2-C_6H_4O-CONH-Y-ONO_2$ (XIe)

Eventually deprotecting the t-But ester by acid hydrolysis following known methods.

2) **(Xk_{j2}):** wherein Y is as above defined and K_2 is selected from (VIIIe),(VIIIf) wherein R_6 is –NH-:

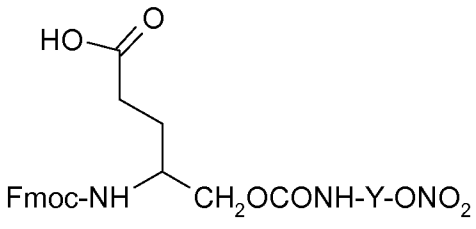
2a) by reacting compounds ($XVIIa_5$) and ($XVIIb_5$) above described with compounds (XIb) as above described, (Scheme 23):

Scheme 23



+ $NH_2-Y'-ONO_2$

($XVIIa_5$) (XIb)



(XVIIb$_5$) + NH_2-Y'-ONO_2 (XIb)

eventually hydrolyzing the Fmoc protecting group as already described.

A19/1. Synthesis of compounds (Xi_{k1}),(Xi_{k2}) and (Xk_{k1})-(Xk_{k2})

Compounds of formula

p-NO_2-C_6H_4-O-CO-NH-K_3-COO-Y-ONO_2

(Xi_{k1}),(Xi_{k2})

wherein Y is as above described and K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xi_{k1}) or

ii) -COO- (Xi_{k2})

and K_3 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xk_{k1}),(Xk_{k2}):

NH_2-K_3-COO-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xk_{k1})-(Xk_{k2})

Wherein Y is as previously defined and K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xk_{k1}) or

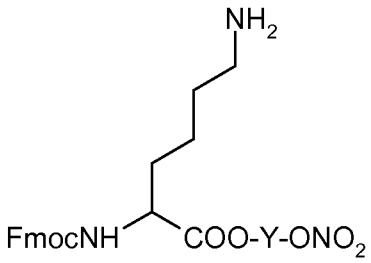
ii) -COO- (Xk_{k2})

Compounds of formula (Xk_{k1}),(Xk_{k2}) can be obtained as follow:

1) **(Xk_{k1}):** wherein Y is as above defined and K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -CO-:

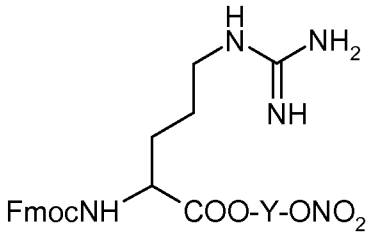
1a) by reacting compounds of formula ($XVIIIa_1$),($XVIIIb_1$) with compounds (XIc) following procedure already described in **A3** (Scheme 24a):

Scheme 24a



+ C_6F_5O-CO-Y'-ONO_2

($XVIIIa_1$) (XIc)

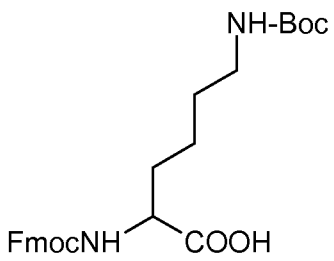


+ C_6F_5O-CO-Y'-ONO_2

($XVIIIb_1$) (XIc)

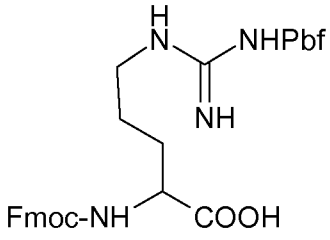
Eventually deprotecting the Fmoc group by known methods. Compounds ($XVIIIa_1$) and ($XVIIIb_1$) can be obtained by reacting compounds (VIIIgb) and (VIIIhb) already described in **A7** with compounds (XIa) as already described, eventually acid hydrolyzing the Boc or Pfb protective groups (Scheme 25):

Scheme 25



+ HO-Y-ONO_2

(VIIIgb) (XIa)



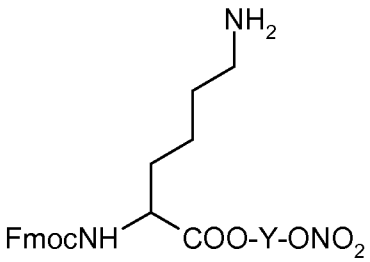
+ HO-Y-ONO_2

(VIIIhb) (XIa)

2) **(Xk_{k2}):** wherein Y is as above defined and K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -COO-:

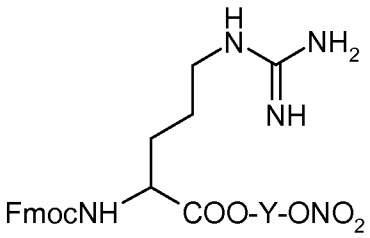
1a) by reacting compounds of formula ($XVIIIa_1$),($XVIIIb_1$) already described above in **A19** with compounds (XId) following procedure already described in **A4** (Scheme 24b):

Scheme 24b



+ p-NO_2-C_6H_4O-COO-Y'-ONO_2

($XVIIIa_1$) (XId)



+ p-NO_2-C_6H_4O-COO-Y'-ONO_2

($XVIIIb_1$) (XId)

Eventually deprotecting the Fmoc group by known methods.

A19/2. Synthesis of compounds (Xi_{k3}),(Xi_{k4}) and (Xk_{k3})-(Xk_{k4})

Compounds of formula

p-NO_2-C_6H_4-O-CO-NH-K_3-COOtBut

(Xi_{k3}),(Xi_{k4})

wherein K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xi_{k3}) or

ii) -COO- (Xi_{k4})

and K_3 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xk_{k3}),(Xk_{k4}):

NH_2-K_3-COOtBut + pNO_2-C_6H_4-OCOCl

(Xk_{k3})-(Xk_{k4})

Wherein K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xk_{k3}) or

ii) -COO- (Xk_{k4})

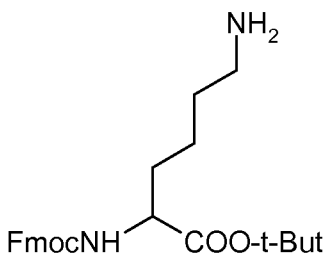
and K_3 is bound to the group -(Y'-ONO_2)

Compounds of formula (Xk_{k3}),(Xk_{k4}) can be obtained as follow:

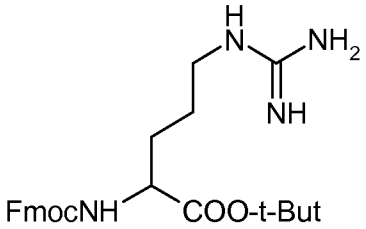
1) **(Xk_{k3})**: wherein K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -CO- and K_3 is bound to the group -(Y'-ONO_2):

1a) by reacting commercially available compounds of formula ($XVIIIc_1$),($XVIIId_1$) with compounds (XIc) following procedure already described in **A3** (Scheme 24c):

Scheme 24c



($XVIIIc_1$) + C_6F_5O-CO-Y'-ONO_2 (XIc)



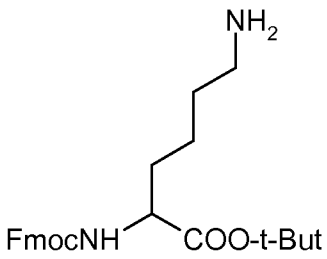
(XVIIId$_1$) + C_6F_5O-CO-Y'-ONO_2 (XIc)

Eventually deprotecting the Fmoc group by known methods.

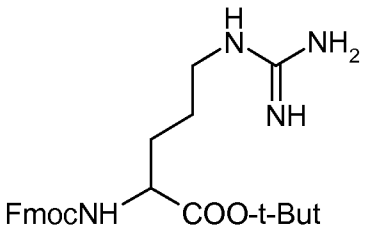
2) **(Xk$_{k4}$):** wherein K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -COO- and K_3 is bound to the group -(Y'-ONO_2):

1a) by reacting compounds of formula (XVIIIc$_1$),(XVIIId$_1$) already described above with compounds (XId) following procedure already described in **A4** (Scheme 24d):

Scheme 24d



(XVIIIc$_1$) + p-NO_2-C_6H_4O-COO-Y'-ONO_2 (XId)



(XVIIId$_1$) + p-NO_2-C_6H_4O-COO-Y'-ONO_2 (XId)

Eventually deprotecting the Fmoc group by known methods.

A20. Synthesis of compounds (Xi$_{L1}$),(Xi$_{L2}$) and (Xk$_{L1}$)-(Xk$_{L2}$)

Compounds of formula

$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_3\text{-}CONH\text{-}Y\text{-}ONO_2$

$(Xi_{L1}),(Xi_{L2})$

wherein Y is as above described and K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xi_{L1}) or

ii) -COO- (Xi_{L2})

and K_3 is bound to the group $-(Y'\text{-}ONO_2)$ are obtained by reaction with $pNO_2\text{-}C_6H_4\text{-}OCOCl$ of the corresponding compounds $(Xk_{L1}),(Xk_{L2})$:

$NH_2\text{-}K_3\text{-}CONH\text{-}Y\text{-}ONO_2$ + $pNO_2\text{-}C_6H_4\text{-}OCOCl$

$(Xk_{L1})\text{-}(Xk_{L2})$

Wherein Y is as previously defined and K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xk_{L1}) or

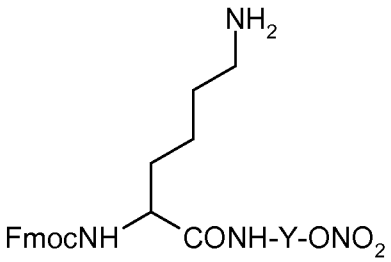
ii) -COO- (Xk_{L2})

Compounds of formula $(Xk_{L1}),(Xk_{L2})$ can be obtained as follow:

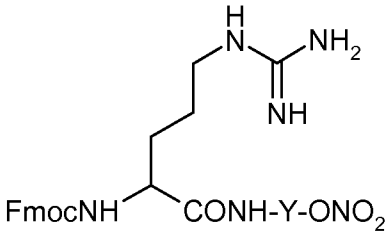
1) **(Xk_{L1}):** wherein Y is as above defined and K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -CO-:

1a) by reacting compounds of formula $(XVIIIa_2),(XVIIIb_2)$ with compounds (XIc) following procedure already described in **A3** (Scheme 26a):

Scheme 26a



$(XVIIIa_2)$ + $C_6F_5O\text{-}CO\text{-}Y'\text{-}ONO_2$ (XIc)

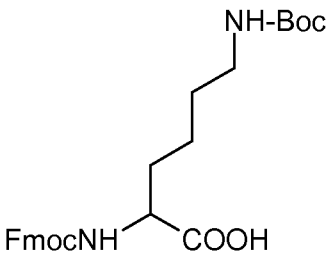


+ C_6F_5O-CO-Y'-ONO_2

($XVIIIb_2$) (XIc)

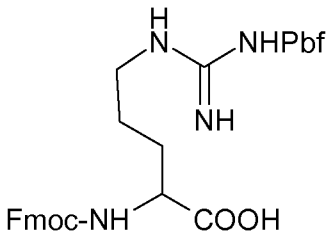
Eventually deprotecting the Fmoc group by known methods. Compounds ($XVIIIa_2$) and ($XVIIIb_2$) can be obtained by reacting compounds (VIIIgb) and (VIIIhb) already described in **A7** with compounds (XIb) as already described, eventually acid hydrolyzing the Boc or Pfb protective groups (Scheme 27):

Scheme 27



+ NH_2-Y-ONO_2

(VIIIgb) (XIb)



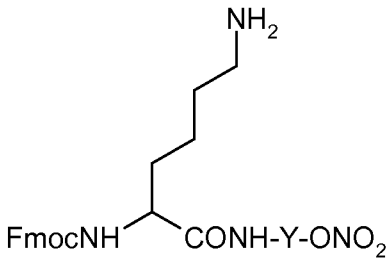
+ NH_2-Y-ONO_2

(VIIIhb) (XIb)

2) **(Xk_{L2}):** wherein Y is as above defined and K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -COO-:

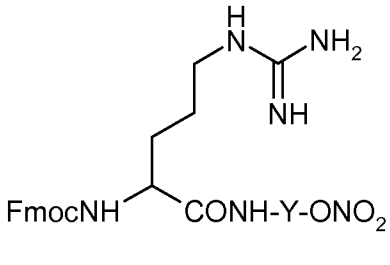
1a) by reacting compounds of formula ($XVIIIa_2$),($XVIIIb_2$) already described above in **A20** with compounds (XId) following procedure already described in **A4** (Scheme 26b):

Scheme 26b



+ $p\text{-}NO_2\text{-}C_6H_4O\text{-}COO\text{-}Y'\text{-}ONO_2$

($XVIIIa_2$) (XId)



+ $p\text{-}NO_2\text{-}C_6H_4O\text{-}COO\text{-}Y'\text{-}ONO_2$

($XVIIIb_2$) (XId)

Eventually deprotecting the Fmoc group by known methods.

A21. Synthesis of compounds (Xi_{m1}),(Xi_{m2}) and (Xk_{m1})-(Xk_{m2})

Compounds of formula

$$p\text{-}NO_2\text{-}C_6H_4\text{-}O\text{-}CO\text{-}NH\text{-}K_3\text{-}CH_2O\text{-}CO\text{-}Y\text{-}ONO_2$$

(Xi_{m1}),(Xi_{m2})

wherein Y is as above described and K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xi_{m1}) or

ii) -COO- (Xi_{m2})

and K_3 is bound to the group -(Y'-ONO_2) are obtained by reaction with $pNO_2\text{-}C_6H_4\text{-}OCOCl$ of the corresponding compounds (Xk_{m1}),(Xk_{m2}):

$NH_2\text{-}K_3\text{-}CH_2O\text{-}CO\text{-}Y\text{-}ONO_2$ + $pNO_2\text{-}C_6H_4\text{-}OCOCl$

$(Xk_{m1})-(Xk_{m2})$

wherein Y is as previously defined and K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xk_{m1}) or

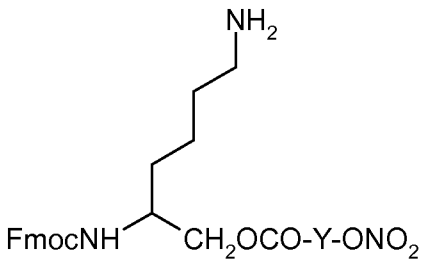
ii) -COO- (Xk_{m2})

Compounds of formula (Xk_{m1}),(Xk_{m2}) can be obtained as follow:

1) **(Xk_{m1}):** wherein Y is as above defined and K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -CO-:

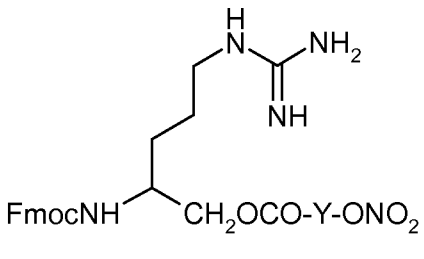
1a) by reacting compounds of formula $(XVIIIa_3)$,$(XVIIIb_3)$ with compounds (XIc) following procedure already described in **A3** (Scheme 28a):

Scheme 28a



+ C_6F_5O-CO-Y'-ONO_2

$(XVIIIa_3)$ (XIc)



+ C_6F_5O-CO-Y'-ONO_2

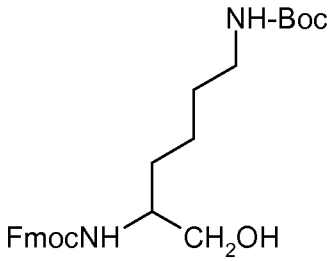
$(XVIIIb_3)$ (XIc)

Eventually deprotecting the Fmoc group by known methods.

Compounds $(XVIIIa_3)$ and $(XVIIIb_3)$ can be obtained by reacting compounds (VIIIgc) and (VIIIhc) already described in **A7** with compounds (XIc) as already described, eventually

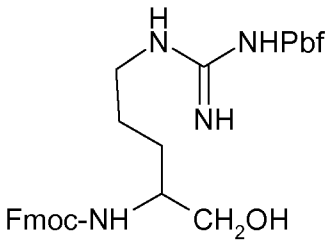
acid hydrolyzing the Boc or Pfb protective groups (Scheme 29):

Scheme 29



+ C_6F_5O-CO-Y'-ONO_2

(VIIIgc) (XIc)



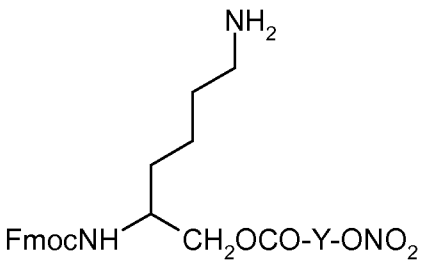
+ C_6F_5O-CO-Y'-ONO_2

(VIIIhc) (XIc)

2) **(Xk_{m2})**: wherein Y is as above defined and K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -COO-:

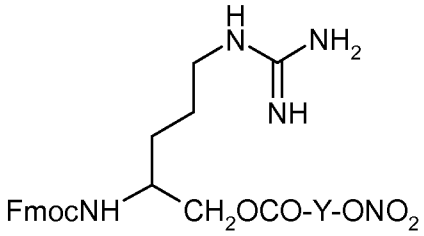
1a) by reacting compounds of formula ($XVIIIa_3$),($XVIIIb_3$) already described above in **A21** with compounds (XId) following procedure already described in **A4** (Scheme 28b):

Scheme 28b



+ p-NO_2-C_6H_4O-COO-Y'-ONO_2

($XVIIIa_3$) (XId)



(XVIIIb$_3$) + p-NO$_2$-C$_6$H$_4$O-COO-Y'-ONO$_2$ (XId)

Eventually deprotecting the Fmoc group by known methods.

A22. Synthesis of compounds (Xi$_{n1}$),(Xi$_{n2}$) and (Xk$_{n1}$)-(Xk$_{n2}$)

Compounds of formula

p-NO$_2$-C$_6$H$_4$-O-CO-NH-K$_3$-CH$_2$O-COO-Y-ONO$_2$

(Xi$_{n1}$),(Xi$_{n2}$)

wherein Y is as above described and K$_3$ is selected from (VIIIh),(VIIIg) wherein R$_7$ and R$_8$ are selected from respectively:

i) -CO- (Xi$_{n1}$) or

ii) -COO- (Xi$_{n2}$)

and K$_3$ is bound to the group -(Y'-ONO$_2$) are obtained by reaction with pNO$_2$-C$_6$H$_4$-OCOCl of the corresponding compounds (Xk$_{n1}$),(Xk$_{n2}$):

NH$_2$-K$_3$-CH$_2$O-COO-Y-ONO$_2$ + pNO$_2$-C$_6$H$_4$-OCOCl

(Xk$_{n1}$)-(Xk$_{n2}$)

Wherein Y is as previously defined and K$_3$ is selected from (VIIIh),(VIIIg) wherein R$_7$ and R$_8$ are selected from respectively:

i) -CO- (Xk$_{n1}$) or

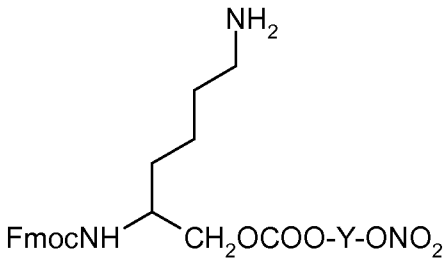
ii) -COO- (Xk$_{n2}$)

Compounds of formula (Xk$_{n1}$),(Xk$_{n2}$) can be obtained as follow:

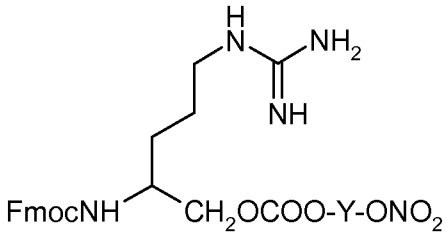
1) **(Xk$_{n1}$)**: wherein Y is as above defined and K$_3$ is selected from (VIIIg),(VIIIh) wherein R$_7$ and R$_8$ are -CO-:

1a) by reacting compounds of formula ($XVIIIa_4$),($XVIIIb_4$) with compounds (XIc) following procedure already described in **A4** (Scheme 30a):

Scheme 30a



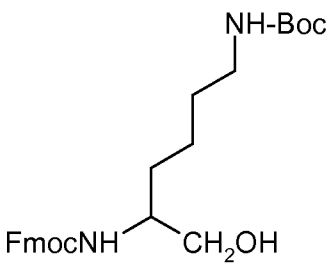
($XVIIIa_4$) + C_6F_5O-CO-Y'-ONO_2 (XIc)



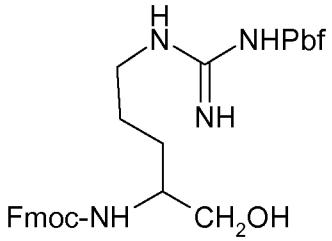
($XVIIIb_4$) + C_6F_5O-CO-Y'-ONO_2 (XIc)

Eventually deprotecting the Fmoc group by known methods. Compounds ($XVIIIa_4$) and ($XVIIIb_4$) can be obtained by reacting compounds (VIIIgc) and (VIIIhc) already described in **A7** with compounds (XId) as already described, eventually acid hydrolyzing the Boc or Pfb protective groups (Scheme 31):

Scheme 31



(VIIIgc) + p-NO_2-C_6H_4O-COO-Y'-ONO_2 (XId)



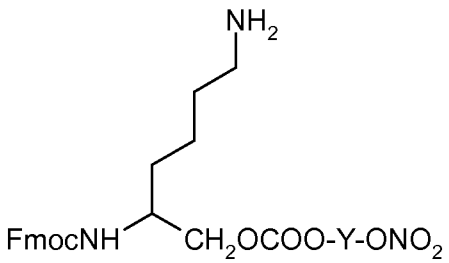
+ p-NO_2-C_6H_4O-COO-Y'-ONO_2

(VIIIhb) (XId)

2) **(Xk_{n2}):** wherein Y is as above defined and K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -COO-:

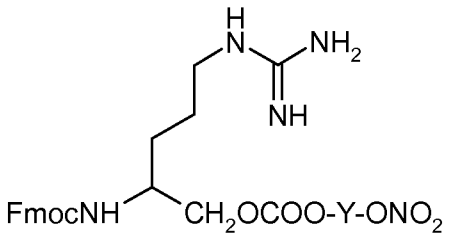
1a) by reacting compounds of formula ($XVIIIa_4$),($XVIIIb_4$) already described above in **A22** with compounds (XId) following procedure already described in **A4** (Scheme 30b):

Scheme 30b



+ p-NO_2-C_6H_4O-COO-Y'-ONO_2

($XVIIIa_4$) (XId)



+ p-NO_2-C_6H_4O-COO-Y'-ONO_2

($XVIIIb_4$) (XId)

Eventually deprotecting the Fmoc group by known methods.

A23. Synthesis of compounds (Xi_{o1}),(Xi_{o2}) and (Xk_{o1})-(Xk_{o2})

Compounds of formula

p-NO_2-C_6H_4-O-CO-NH-K_3-CH_2O-CONH-Y-ONO_2

(Xi_{o1}),(Xi_{o2})

wherein Y is as above described and K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xi_{o1}) or

ii) -COO- (Xi_{o2})

and K_3 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (Xk_{o1}),(Xk_{o2}):

NH_2-K_3-CH_2O-CONH-Y-ONO_2 + pNO_2-C_6H_4-OCOCl

(Xk_{o1})-(Xk_{o2})

wherein Y is as previously defined and K_3 is selected from (VIIIh),(VIIIg) wherein R_7 and R_8 are selected from respectively:

i) -CO- (Xk_{o1}) or

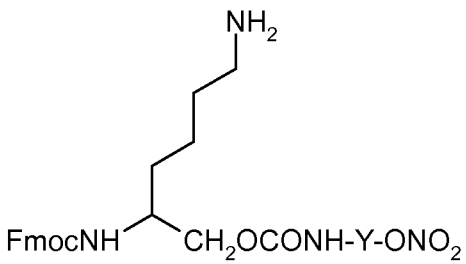
ii) -COO- (Xk_{o2})

Compounds of formula (Xk_{o1}),(Xk_{o2}) can be obtained as follow:

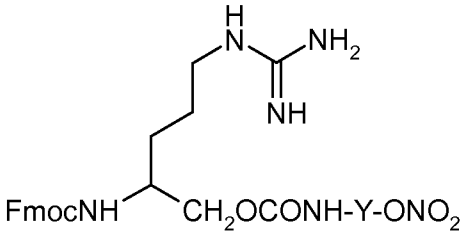
1) **(Xk_{o1})**: wherein Y is as above defined and K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -CO-:

1a) by reacting compounds of formula ($XVIIIa_5$),($XVIIIb_5$) with compounds (XIc) following procedure already described in **A4** (Scheme 32a):

Scheme 32a



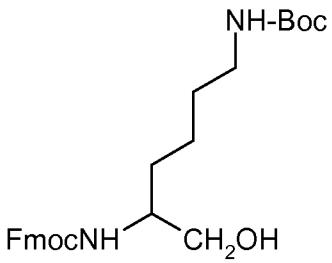
($XVIIIa_5$) + C_6F_5O-CO-Y'-ONO_2 (XIc)



(XVIIIb$_5$) + C_6F_5O-CO-Y'-ONO_2 (XIc)

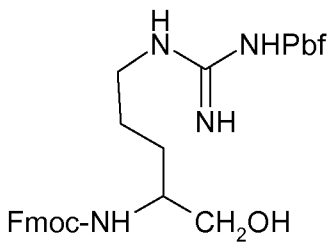
Eventually deprotecting the Fmoc group by known methods. Compounds (XVIIIa$_5$) and (XVIIIb$_5$) can be obtained by reacting compounds (VIIIgc) and (VIIIhc) already described in **A7** with compounds (XIe) as already described, eventually acid hydrolyzing the Boc or Pfb protective groups (Scheme 29):

Scheme 29



+ pNO_2-C_6H_4O-CONH-Y-ONO_2

(VIIIgc) (XIe)



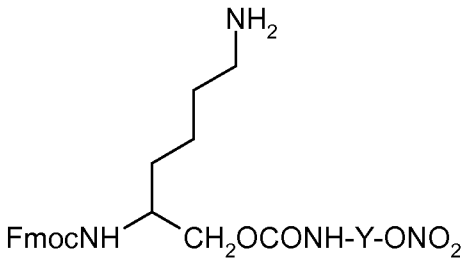
+ pNO_2-C_6H_4O-CONH-Y-ONO_2

(VIIIhb) (XIe)

2) **(Xk_{o2}):** wherein Y is as above defined and K_3 is selected from (VIIIg),(VIIIh) wherein R_7 and R_8 are -COO-:

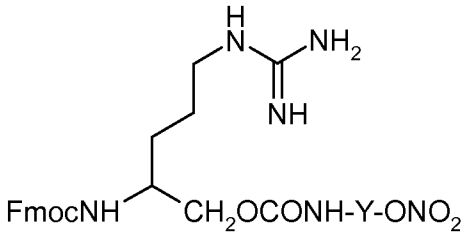
1a) by reacting compounds of formula ($XVIIIa_5$),($XVIIIb_5$) already described above in **A23** with compounds (XId) following procedure already described in **A4** (Scheme 32b):

Scheme 32b



+ p-NO_2-C_6H_4O-COO-Y'-ONO_2

($XVIIIa_5$) (XId)



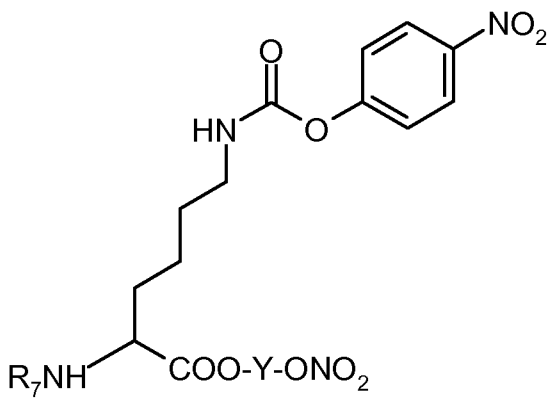
+ p-NO_2-C_6H_4O-COO-Y'-ONO_2

($XVIIIb_5$) (XId)

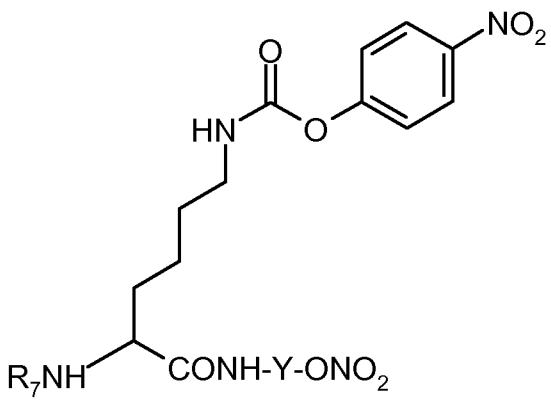
Eventually deprotecting the Fmoc group by known methods.

A24/1. Synthesis of compounds (Xj_{a1}),(Xj_{a2}) and (XL_{a1})-(XL_{a2}); (Xj_{b1}),(Xj_{b2}) and (XL_{b1})-(XL_{b2}); (Xj_{c1}),(Xj_{c2}) and (XL_{c1})-(XL_{c2}); (Xj_{d1}),(Xj_{d2}) and (XL_{d1})-(XL_{d2}); (Xj_{e1}),(Xj_{e2}) and (XL_{e1})-(XL_{e2})

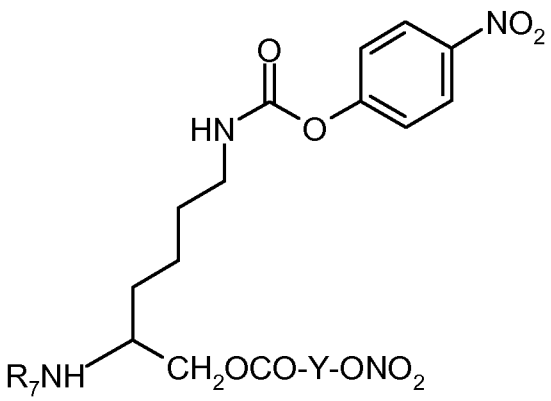
Compounds of formula



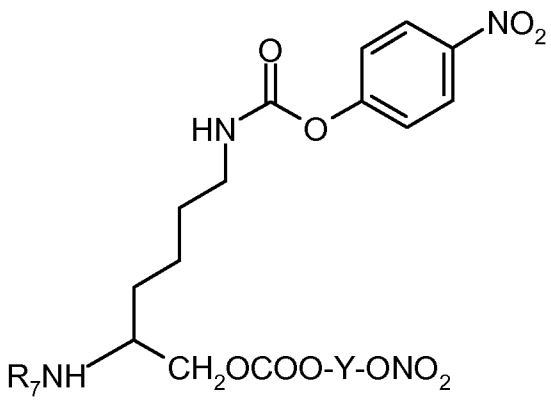
(Xj_{a1})- (Xj_{a2})



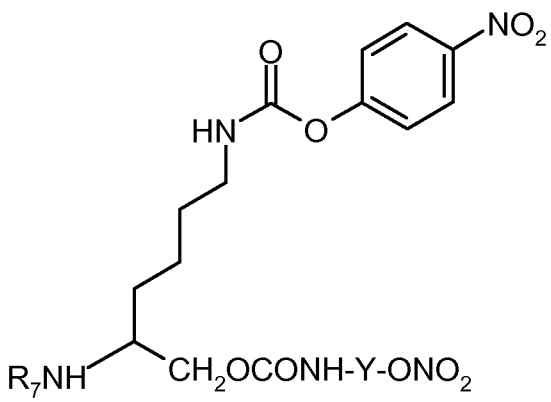
(Xj_{b1})- (Xj_{b2})



(Xj_{c1})- (Xj_{c2})



(Xj_{d1})- (Xj_{d2})



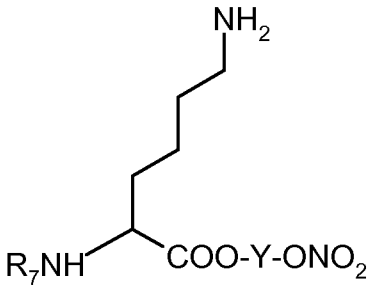
(Xj_{e1})- (Xj_{e2})

wherein Y is as above described and R_7 is selected from respectively:

i) -CO- (Xj_{a1}), (Xj_{b1}), (Xj_{c1}), (Xj_{d1}), (Xj_{e1});

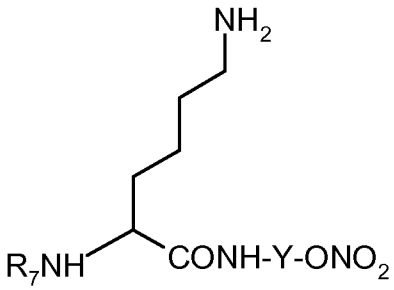
ii) -COO- (Xj_{a2}), (Xj_{b2}), (Xj_{c2}), (Xj_{d2}), (Xj_{e2});

and R_7 is bound to the group -(Y'-ONO_2) are obtained by reaction with pNO_2-C_6H_4-OCOCl of the corresponding compounds (XL_{a1}),(XL_{a2}); (XL_{b1})-(XL_{b2}); (XL_{c1})-(XL_{c2}); (XL_{d1})-(XL_{d2}); (XL_{e1})-(XL_{e2}):



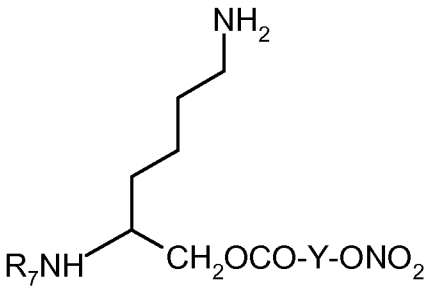
+ $pNO_2-C_6H_4-OCOCl$

$(XL_{a1})-(XL_{a2})$



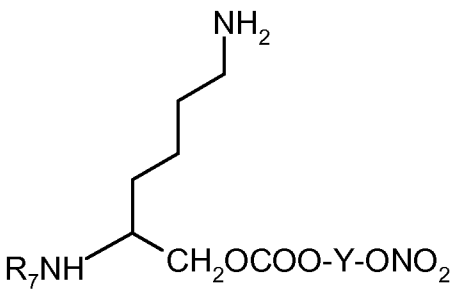
+ $pNO_2-C_6H_4-OCOCl$

$(XL_{b1})-(XL_{b2})$



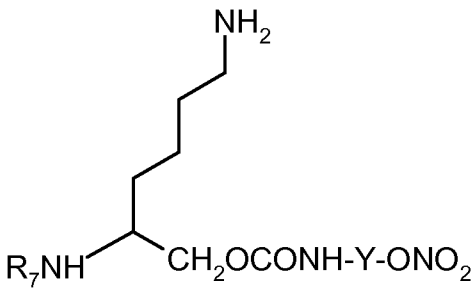
+ $pNO_2-C_6H_4-OCOCl$

$(XL_{c1})-(XL_{c2})$



+ $pNO_2-C_6H_4-OCOCl$

$(XL_{d1})-(XL_{d2})$



+ $pNO_2-C_6H_4-OCOCl$

(XL_{e1})-(XL_{e2})

wherein Y is as previously defined and R_7 is selected from respectively:

i) -CO- (XL_{a1}), (XL_{b1}), (XL_{c1}),(XL_{d1}), (XL_{e1});

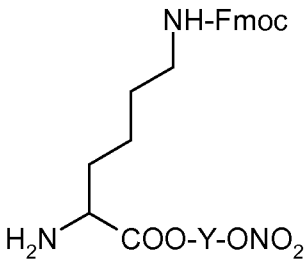
ii) -COO- (XL_{a2}), (XL_{b2}), (XL_{c2}),(XL_{d2}), (XL_{e2})

Compounds of formula (XL_{a1}), (XL_{b1}), (XL_{c1}),(XL_{d1}), (XL_{e1}), (XL_{a2}), (XL_{b2}), (XL_{c2}), (XL_{d2}) and (XL_{e2}) can be obtained as follow:

1) **(XL_{a1}), (XL_{b1}), (XL_{c1}),(XL_{d1}) and (XL_{e1}):** wherein Y is as above defined and R_7 is -CO-:

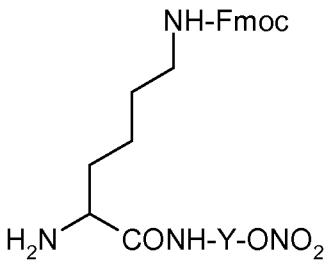
1a) by reacting compounds of formula $(XIXa_1)$-$(XIXa_5)$ with compounds (XIc) following procedure already described in **A3** (Scheme 33):

Scheme 33



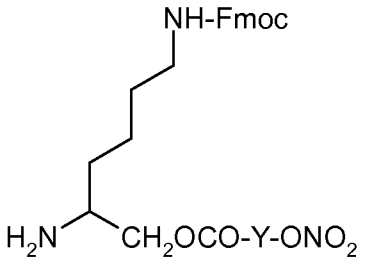
+ C_6F_5O-CO-Y'-ONO_2

$(XIXa_1)$ (XIc)



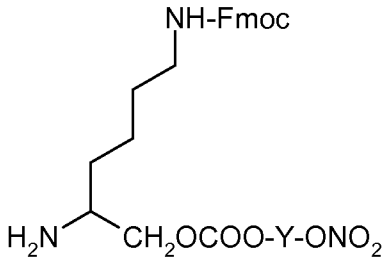
+ C_6F_5O-CO-Y'-ONO_2

$(XIXa_2)$ (XIXc)



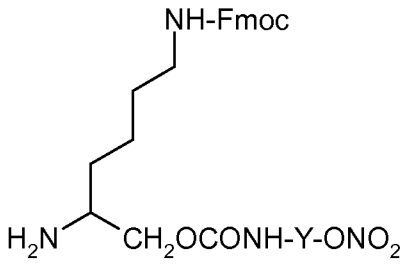
+ C_6F_5O-CO-Y'-ONO_2

$(XIXa_3)$ (XIc)



+ C_6F_5O-CO-Y'-ONO_2

($XIXa_4$) (XIc)



+ C_6F_5O-CO-Y'-ONO_2

($XIXa_5$) (XIc)

Eventually deprotecting the Fmoc group by known methods.

The compounds ($XIXa_1$)-($XIXa_5$) can be obtained by acid hydrolyzing the Boc protective group of compounds (Xh_a)-(Xh_e) already prepared as described in **A8**;

2) **(XL_{a2}), (XL_{b2}), (XL_{c2}), (XL_{d2}), (XL_{e2}):** wherein Y is as above defined and R_7 is –COO-:

1a) by reacting compounds of formula ($XIXa_1$)-($XIXa_5$) above described with compounds (XId):

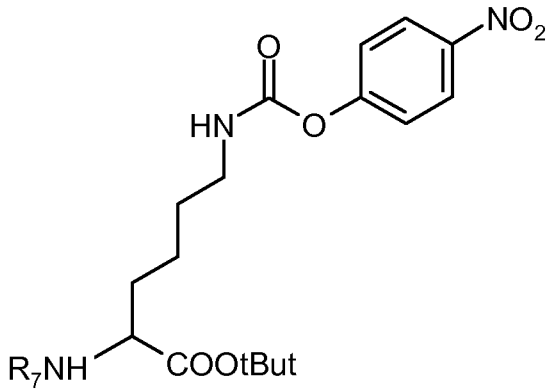
p-NO_2-C_6H_4O-COO-Y'-ONO_2

(XId)

following procedure already described in **A4** and eventually deprotecting the Fmoc group by known methods.

A24/2. Synthesis of compounds (Xj_{a3}),(Xj_{a4}) and (XL_{a3})-(XL_{a4})

Compounds of formula

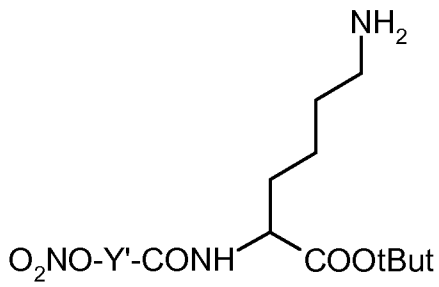


(Xj_{a3})- (Xj_{a4})

wherein R_7 is selected from respectively:

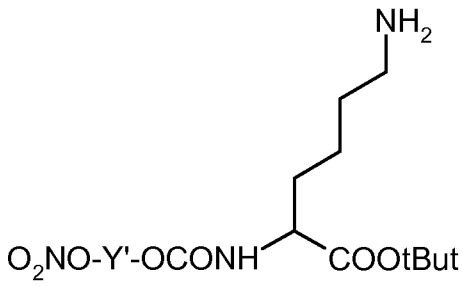
i) -CO- (Xj_{a3}),

ii) -COO- (Xj_{a4}) and R_7 is bound to the group $-(Y'-ONO_2)$ are obtained by reaction with $pNO_2-C_6H_4-OCOCl$ of the corresponding compounds (XL_{a3}),(XL_{a4}):



+ $pNO_2-C_6H_4-OCOCl$

(XL_{a3})



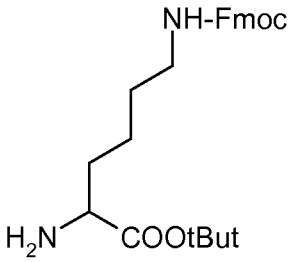
+ $pNO_2-C_6H_4-OCOCl$

(XL_{a4})

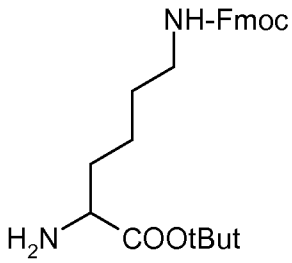
wherein Y' is as previously defined;

Compounds of formula (XL_{a3}) and (XL_{a4}) can be obtained by reacting commercially available compound of formula $(XIXa_6)$ with respectively compounds (XIc) and (XId) following procedure already described in **A3** and **A4** (Scheme 34):

Scheme 34



(XIXa$_6$) + C_6F_5O-CO-Y'-ONO_2 (XIc)

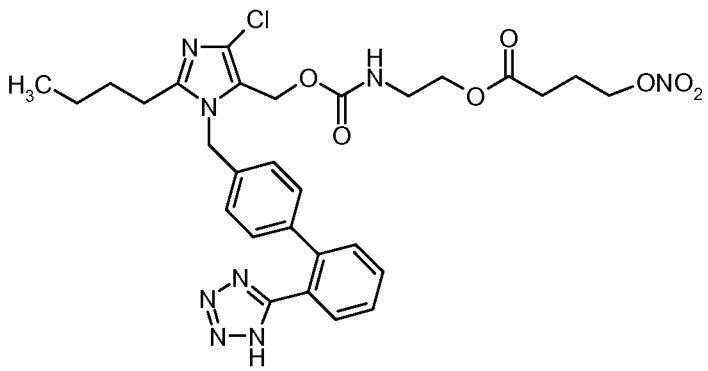


(XIXa$_6$) + p-NO_2-C_6H_4O-COO-Y'-ONO_2 (XId)

Eventually deprotecting the Fmoc group by known methods.

The following examples are to further illustrate the invention without limiting it.

EXAMPLE 1

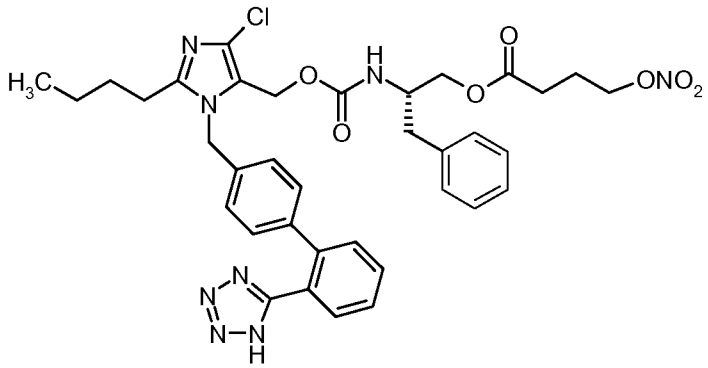


2-(((1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methoxy)carbonylamino)ethyl 4-(nitrooxy)butanoate (corresponding to compound (110)

A mixture of Losartan (2.20 g; 5.20 mmol), N,N-dimethylaminopyridine (DMAP) (1.16 g; 9.46 mmol) and scandium trifluoromethanesulfonate (0.466 g; 0.946 mmol) and 2-((4-nitrophenoxy)carbonylamino)ethyl 4-(nitrooxy)butanoate (**Intermediate 2**) (1.69 g; 4.73 mol) in CH_2Cl_2 (40 ml) was heated in a microwave apparatus (80°C, 40 min). Then the mixture was diluted with CH_2Cl_2 and washed with NaH_2PO_4 (5%, 2 X 40 ml). The organic layer was dried over sodium sulfate and concentrated under reduced pressure.

The residue was purified by flash chromatography (CH_2Cl_2/MeOH: 98/2) yielding the title compound.

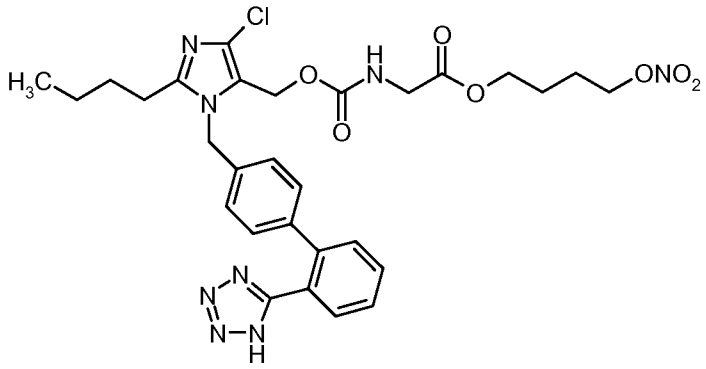
EXAMPLE 2



(S)-2-(((1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methoxy)carbonylamino)-3-phenylpropyl 4-(nitrooxy)butanoate (corresponding to compound (111):

Starting from Losartan and (S)-2-((4-nitrophenoxy)carbonylamino)-3-phenylpropyl 4-(nitrooxy)butanoate (Intermediate 5) and following the same synthetic procedure described in **Example 1** the title compound was obtained.

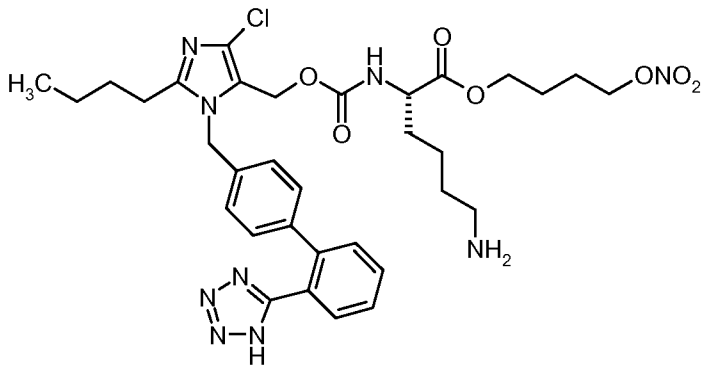
EXAMPLE 3



4-(nitrooxy)butyl 2-(((1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methoxy)carbonylamino)acetate (corresponding to compound (9):

Starting from Losartan and 4-(nitrooxy)butyl 2-((4-nitrophenoxy)carbonylamino)acetate (Intermediate 3) and following the same synthetic procedure described in **Example 1** the title compound was obtained.

EXAMPLE 4



4-(nitrooxy)butyl 2-(((1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methoxy)carbonylamino)-6-aminohexanoate (Corresponding to compound (12)

Step A: (2S)-4-(nitrooxy)butyl 6-(tert-butoxycarbonylamino)-2-(((2-butyl-4-chloro-1-((2'-(1-

trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazol-5-yl)methoxy)carbonylamino)hexanoate

A mixture of trityl Losartan (0.755 g; 1.14 mmol), N,N-dimethylaminopyridine (0.116 g; 0.946 mmol), scandium trifluoromethanesulfonate (0.093 g; 0.189 mmol) and 4-(nitrooxy)butyl 6-(tert-butoxycarbonylamino)-2-((4-nitrophenoxy)carbonylamino)hexanoate (Intermediate 4) (0.500 g; 0.946 mol) in CH_2Cl_2 (14 ml) was heated in a microwave apparatus (80°C, 40 min). Then the mixture was diluted with CH_2Cl_2 and washed with Na_2HPO_4 (5%, 2 X 40 ml). The organic layer was dried over sodium sulfate and concentrated under reduced pressure.

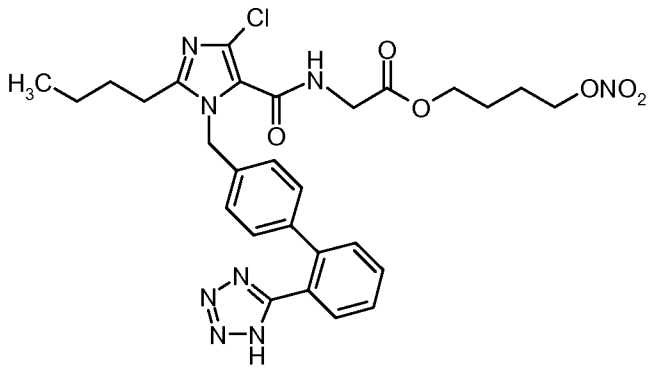
Step B: (S)-4-(nitrooxy)butyl 2-(((1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methoxy)carbonylamino)-6-(tert-butoxycarbonylamino)hexanoate

The crude obtained in Step A was dissolved in MeOH (14 ml) and the reaction was heated in a microwave apparatus (90°C, 23 min). Then the mixture was evaporated under reduced pressure and the residue was purified by flash chromatography (DCM/MeOH:98/2) yielding the title compound.

Step C: 4-(nitrooxy)butyl 2-(((1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methoxy)carbonylamino)-6-aminohexanoate

Compound obtained in Step B was dissolved in CH_2Cl_2 (4 ml) and cooled to 0 °C. Then HCl_{gas} was bubbled for 2 hours. At the end of the addition the solution was concentrated and the residue was treated with diethyl ether, affording the title compound.

EXAMPLE 5



4-(Nitrooxy)butyl 2-(1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)acetate corresponding to compound (36)

Step A: 4-(Nitrooxy)butyl 2-(2-butyl-4-chloro-1-((2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxamido)acetate

To a solution of 4-(nitrooxy)butyl 2-(tert-butoxycarbonylamino)acetate (Intermediate 6) (0.479 g, 2.07 mmol) and TEA (362 µl, 2.59 mmol) in CH_2Cl_2 (20 ml) a solution of 2,5-dioxopyrrolidin-1-yl 2-butyl-4-chloro-1-((2'-(2-trityl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate (1.20 g, 1.73 mmol) (Intermediate 1) in CH_2Cl_2 (10 ml) was added. The reaction was stirred at room temperature for 24 hours. Then the organic layer was washed with a solution of 5% NaH_2PO_4, brine and finally dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (n-hexane/EtOAc 8:2) affording the title compound.

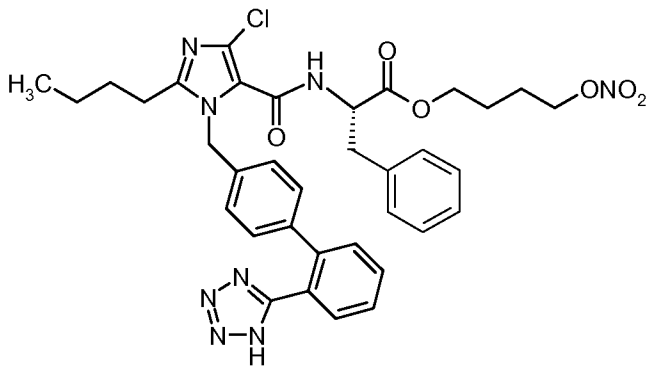
Step B: 4-(Nitrooxybutyl 2-(1-((2'-(2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)acetate

A suspension of compound obtained in Step A (0.800 g, 0.94 mmol) in MeOH (18 ml) was heated in a microwave apparatus

(90°C, 20 min). Then the mixture was concentrated under reduced pressure and the crude was purified by silica gel chromatography (CH_2Cl_2/MeOH 97:3) affording the title compound as a white solid.

^{1}H-NMR (DMSO-δ_6): 8.4(1H,t); 7.71-7.49(4H,m); 7.05(4H,s); 5.47(2H,s); 4.51(2H,t); 4.09(2H,t); 3.99(2H,d);2.55-2.51(2H,m); 1.79-1.61(4H,m); 1.54-1.40(2H,m); 1.31-1.25(2H,m); 0.82(3H,t).

EXAMPLE 6

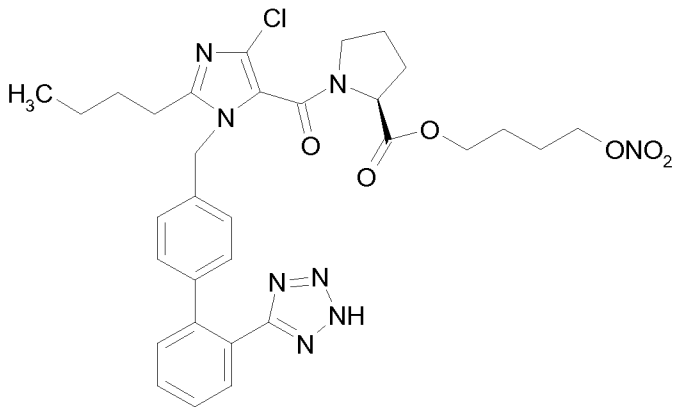


(S)-4-(nitrooxy)butyl 2-(1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)-3-phenylpropanoate (corresponding to compound (35))

Following the same synthetic procedure described in **Example 5** but starting from (S)-4-(nitrooxy)butyl 2-amino-3-phenylpropanoate (Intermediate 7) the title compound was obtained.

^{1}H-NMR (DMSO-δ_6): 8.40 (1H,d); 7.71-7.48 (4H,m); 7.31-7.13 (5H,m); 7.1-6.8 (4H,m); 5.34 (2H,s); 4.69-4.58 (1H,m); 4.47 (2H,t); 4.05 (2H,t); 3.21-3.0 (2H,m); 2.6-2.5 (2H,m); 1.71-1.52 (4H,m); 1.5-1.4 (2H,m); 1.35-1.12 (2H,m); 0.8(3H,t).

EXAMPLE 7

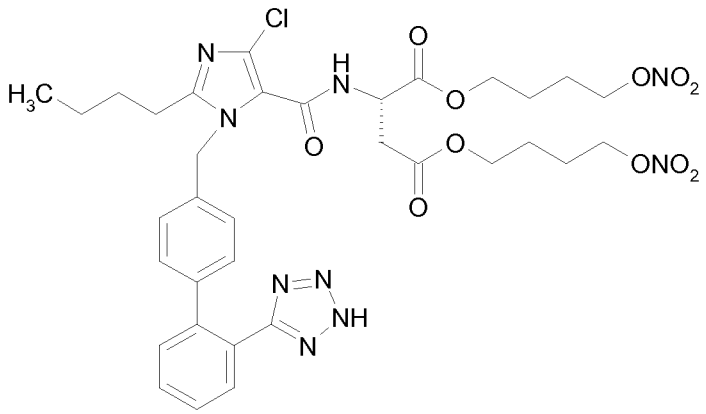


(S)-4-(nitrooxy)butyl 1-(1-((2'-(2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carbonyl)pyrrolidine-2-carboxylate corresponding to compound (40)

Starting from (S)-4-(Nitrooxy)butyl pyrrolidine-2-carboxylate (Intermediate 8) and following the same synthetic procedure described in **Example 5** the title compound was obtained.

^{1}H-NMR (DMSO-δ_6): 7.71-7.4 (3H,m): 7.4-7.3 (1H,m); 7.2-6.9 (4H,m); 5.18 (2H,dd); 4.5 (2H,m); 4.3 (1H,m); 4.07 (2H,M); 3.5-3.0 (2H,m); 2.67 (2H,m); 2.3-2.1 (1H,m); 1.9-1.4 (7H,m); 1. 1.2 (2H,m); 1.85 (3H,t).

EXAMPLE 8

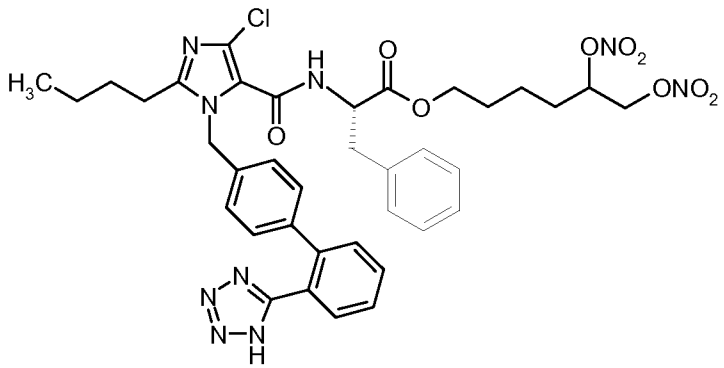


(S)-bis(4-(nitrooxy)butyl) 2-(1-((2'-(2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)succinate (corresponding to compound (42)

Starting from (S)-bis(4-(nitrooxy)butyl) 2-aminosuccinate (Intermediate 9) and following the same synthetic procedure described in **Example 5** the title compound was obtained.

^{1}H-NMR (DMSO-δ_6): 8.49(1H,d); 7.75-7.48(4H,m); 7.05(4H,s); 5.45(2H,s); 4.80(1H,q); 4.58-4.42(4H,m); 4.15-3.9(4H,m); 2.77(2H,dq); 2.61-2.52(2H,m); 1.79-1.55(8H,m); 1.57-1.39(2H,m); 1.31-1.28(2H,m); 0.8(3H,t).

EXAMPLE 9

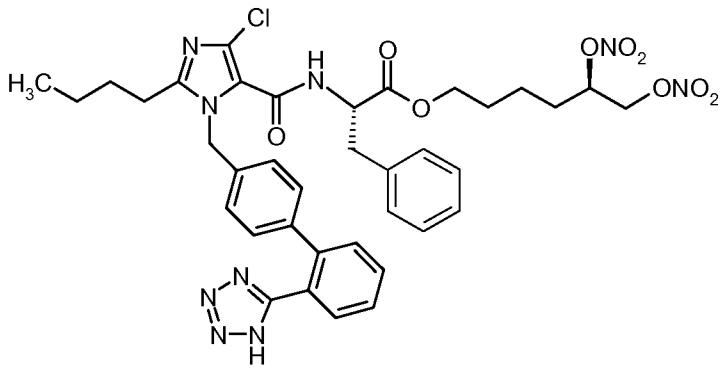


(S)-(5,6-bis(nitrooxy)hexyl) 2-(1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)-3-phenylpropanoate (corresponding to compound (32))

Starting from (S)-((R)-5,6-bis(nitrooxy)hexyl) 2-amino-3-phenylpropanoate (Intermediate 10) and following the same synthetic procedure described in **Example 5** the title compound was obtained.

^{1}H-NMR (DMSO-δ_6): 8.42(1H,d); 7.71-7.48(4H,m); 7.29-7.65(5H,m); 7.11-6.9(4H,m); 5.41-5.32(3H,m); 4.95(1H,m); 4.71-4.58(2H,m); 4.03(2H,t); 3.2-2.9(2H,m); 2.55-2.47(2H,m); 1.75-1.62(2H,m); 1.6-1.3(6H,m); 1.3-1.15(2H,m); 0.8(3H,t).

EXAMPLE 9a



(S)-((R)-5,6-bis(nitrooxy)hexyl) 2-(1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)-3-phenylpropanoate corresponding to compound (32), isomer 5R)

Step A: methyl (2*S*)-2-{[(2-butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazol-5-yl)carbonyl]amino}-3-phenylpropanoate

A mixture of 2-butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazole-5-carboxylic acid (6.5 g, 14.9 mmol) (Intermediate 11) L-phenylalanine, methyl ester (4.16 g, 19.4 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (4.28 g, 22.3 mmol), 1-hydroxybenzotriazole (3.02 g, 22.3 mmol) and triethylamine (7.5 g, 74.5 mmol) in *N*,*N*-dimethylformamide (80 mL) was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was partitioned between water (100 mL) and a mixture of chloroform and isopropanol (3:1) (40 mL). The aqueous layer was extracted with a mixture of chloroform and isopropanol (3:1) (40 mL×3). The organic layers were combined, dried (sodium sulfate), and concentrated in vacuo. The residue was purified by column chromatography to give the title compound, which was used in the next step without further purification. LC-MS: m/z 598 (M+H).

Step B: (2*S*)-2-{[(2-butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazol-5-yl)carbonyl]amino}-3-phenylpropanoic acid

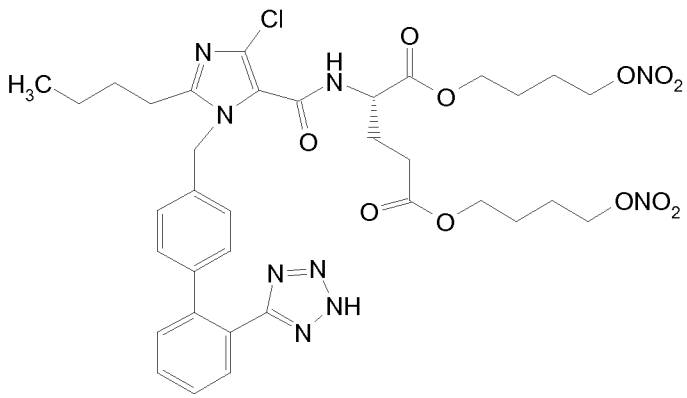
To a methanol (100 mL) solution of methyl (2*S*)-2-{[(2-butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazol-5-yl)carbonyl]amino}-3-phenylpropanoate (6.6 g, 11 mmol) was added 1N aqueous lithium hydroxide (33 mL), and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was then concentrated in vacuo and added 100 mL of water. This mixture was washed with diethyl ether (50 mL × 3), and the organic layers were discarded. The aqueous layer was acidified with diluted hydrochloric acid to pH 3, then extracted with a mixture of chloroform and isopropanol (3:1) (50 mL × 3). The organic layers were combined, dried (sodium sulfate), and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the title compound. ^{1}H NMR (400 MHz, CD_3OD): δ 7.67-7.50 (4H, m), 7.24-7.16 (5H, m), 7.10 (2H, d, *J* = 8.4 Hz), 7.04 (2H, d, *J* = 8.0 Hz), 5.49 (2H, s), 4.80 (1H, m), 3.29 (1H, m), 3.11 (1H, m), 2.62 (2H, t, *J* = 8.0 Hz), 1.56 (2H, m), 1.34 (2H, m), 0.88 (3H, t, *J* = 7.6 Hz). LC-MS: m/z 584 (M+H).

Step C: (S)-((R)-5,6-bis(nitrooxy)hexyl) 2-(1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)-3-phenylpropanoate

(2*S*)-2-{[(2-Butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazol-5-yl)carbonyl]amino}-3-phenylpropanoic acid (0.50 g, 0.86 mmol), (2*R*)-6-hydroxyhexane-1,2-diyl dinitrate (0.19 g, 0.86 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (0.16 g, 0.86 mmol), and *N*,*N*-dimethylaminopyridine (0.11 g, 0.86 mmol) were mixed and stirred in

dichloromethane (10 mL). After 3 days, the reaction mixture was concentrated in vacuo. Purification of the reaction mixture by reversed-phase mass-directed high-performance liquid chromatography afforded the title compound. ^{1}H-NMR ($CDCl_3$): 8.02 (1H, d, *J* = 7.6Hz); 7.63 (1H, t, *J* = 7.5Hz); 7.56 (1H, t, *J* = 7.6Hz); 7.47 (1H, d, *J* = 7.6Hz); 7.34-7.24 (3H, m); 7.22 (2H, d, *J* = 7.3Hz); 7.12 (2H, d, *J* = 8.0Hz); 6.91 (2H, d, *J* = 7.8Hz); 6.79 (1H, d, *J* = 6.0Hz); 5.56 (1H, d, *J* = 15.8Hz); 5.37 (1H, d, *J* = 15.8Hz); 5.33-5.24 (1H, m); 4.76 (1H, dd, *J* = 2.6, 12.9Hz); 4.67 (1H, q, *J* = 6.1Hz); 4.49 (1H, ddd, *J* = 6.6, 8.0, 13.0Hz); 4.18 (1H, td, *J* = 5.9, 11.0Hz); 4.02 (1H, td, *J* = 5.7, 10.7Hz); 3.19 (1H, dd, *J* = 6.2, 13.7Hz); 3.14 (1H, dd, *J* = 8.0, 14.0Hz); 2.70 (2H, t, *J* = 7.6Hz); 1.8-1.6 (m, 5H), 1.55-1.35 (m, 5H), 0.91(3H, t, *J* = 7.4Hz). LC-MS: m/z 790 (M + H).

EXAMPLE 10

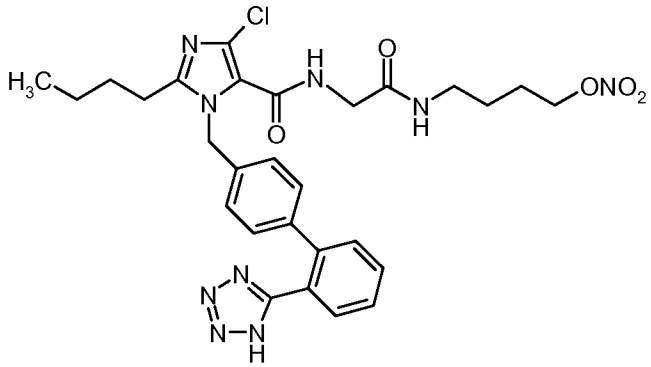


((S)-bis(4-(nitrooxy)butyl) 2-(1-((2'-(2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)pentanedioate (corresponding to compound (44))

Starting from (S)-bis(4-(nitrooxy)butyl) 2-aminopentanedioate (Intermediate 12) and following the same synthetic procedure described in **Example 5** the title compound was obtained

^{1}H-NMR (DMSO-δ_6): 8.6 (1H,d); 7.71-7.45 (4H,m); 7.11-7.05 (4H,m); 5.49-5.3 (2H,m); 4.52-4.38 (5H,m); 4.1-3.98 (4H,m); 2.6-2.5 (2H,m); 2.4 (2H,t); 2.15-1.89 (2H,dm); 1.71-1.52 (8H,m);1.51-1.40 (2H,m); 1.3-1.19 (2H,m); 0.8 (3H,t).

EXAMPLE 11

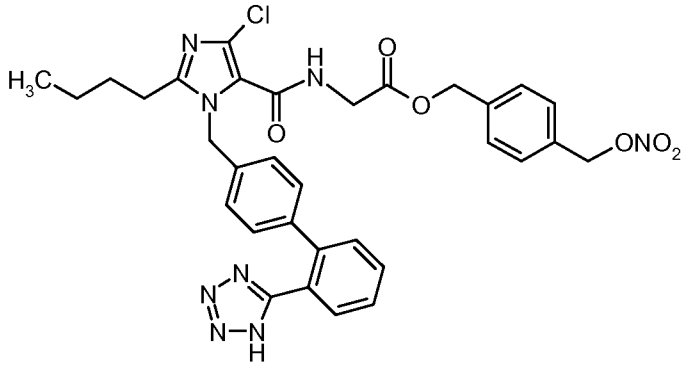


4-(2-(1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)acetamido)butyl nitrate (corresponding to compound (45))

Starting from 4-(2-aminoacetamido)butyl nitrate (Intermediate 13) and following the same synthetic procedure described in **Example 5** the title compound was obtained.

^{1}H-NMR (DMSO-δ_6): 8.06 (1H,t); 7.92 (1H,t); 7.71-7.49 (4H,m); 7.05 (4H,s); 5.52 (2H,s); 4.49 (2H,t); 3.83 (2H,d); 3.15-3.075 (2H,m); 2.6-2.48 (2H,m); 1.7-1.59 (2H,m); 1.507-1.4 (4H,m); 1.31-1.18 (2H,m); 0.802 (3H,t).

EXAMPLE 12

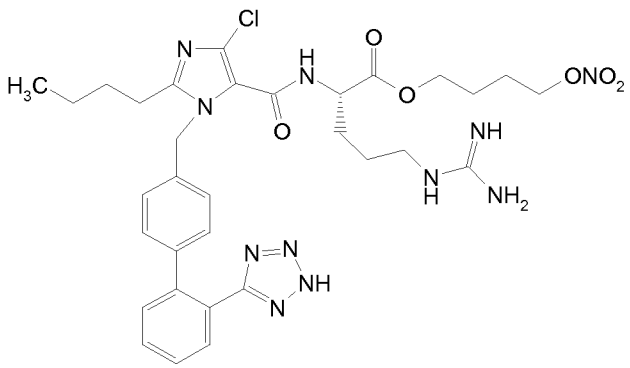


4-(nitrooxymethyl)benzyl 2-(1-((2'-(2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)acetate (corresponding to compound (46))

Starting from 4-[(nitrooxy)methyl]benzyl 2-aminoacetate (Intermediate 14) and following the same synthetic procedure described in **Example 5** the title compound was obtained.

^{1}H-NMR (DMSO-δ_6): 8.49 (1H,t); 7.71-7.41 (8H,m); 7.04 (4H,s); 5.56 (2H,s); 5.45 (2H,s); 5.16 (2H,s); 4.07 (2H,d); 2.59-2.49 (2H,m); 1.51-1.40 (2H,m); 1.32-1.19 (2H,M); 0.804 (3H,t).

EXAMPLE 13

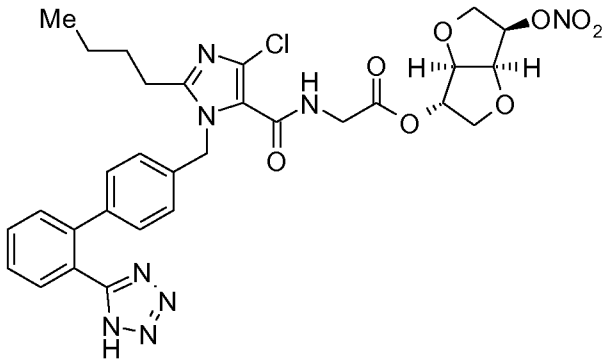


(S)-4-(nitrooxy)butyl 2-(1-((2'-(2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazole-5-carboxamido)-5-guanidinopentanoate (corresponding to compound (47))

Starting from (S)-4-(nitrooxy)butyl 2-amino-5-(3-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-

ylsulfonyl)guanidino)pentanoate (Intermediate 15) and following the same synthetic procedure described in **Example 5** and then acid hydrolizing the Pfb protective group as described for analogue reaction in **Example 4**, the title compound was obtained.

EXAMPLE 14



(3*S*,3a*R*,6*R*,6a*S*)-6-(nitrooxy)hexahydrofuro[3,2-*b*]furan-3-yl {[(2-butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazol-5-yl)carbonyl]amino}acetate (corresponding to compound (113))

Step A: (3*S*,3a*R*,6*R*,6a*S*)-6-(nitrooxy)hexahydrofuro[3,2-*b*]furan-3-yl {[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}acetate

A mixture of Fmoc-glycine (10.0 g, 33.6 mmol), isosorbide-5-mononitrate (7.07 g, 37.0 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (7.74 g, 40.4 mmol), 1-hydroxybenzotriazole (6.18 g, 40.4 mmol), *N*-methylmorpholine (11.1 mL, 101 mmol) and 4-dimethylaminopyridine (0.411 g, 3.36 mmol) was stirred in dichloromethane (300 mL) at room temperature overnight. The solvent was removed in vacuo, and the residue was partitioned between water (300 mL) and ethyl acetate (300 mL). The aqueous layer was extracted with ethyl acetate

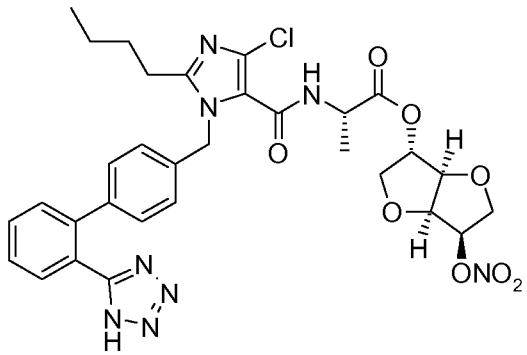
(300 mL × 3), and the combined organic layers were dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography over silica gel to give the title compound. LC-MS: m/z 471 (M+H).

Step B: (3*S*,3a*R*,6*R*,6a*S*)-6-(nitrooxy)hexahydrofuro[3,2-*b*]furan-3-yl {[(2-butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazol-5-yl)carbonyl]amino}acetate

To a *N*,*N*-dimethylformamide solution (100 mL) of (3*S*,3a*R*,6*R*,6a*S*)-6-(nitrooxy)hexahydrofuro[3,2-*b*]furan-3-yl {[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}acetate (8.33 g, 17.7 mmol) was added piperidine (1.75 mL, 17.7 mmol). After 1 hour, 2-butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazole-5-carboxylic acid (3.18 g, 7.27 mmol), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (4.06 g, 7.79 mmol) and triethylamine (4.0 mL, 28.7 mmol) were added, and the reaction mixture was stirred overnight. Purification of the reaction mixture by reversed-phase mass-directed high-performance liquid chromatography afforded the title compound.

^{1}H-NMR ($CDCl_3$): 7.77 (1H, d, *J* = 7.6Hz); 7.57 (1H, t, *J* = 7.7Hz); 7.44-7.52 (2H, m); 7.40 (1H, d, *J* = 7.6Hz); 7.01 (2H, d, *J* = 8.0Hz); 6.94 (2H, d, *J* = 8.0Hz); 5.50 (2H, s); 5.33 (1H, dt, *J* = 2.6, 5.4Hz); 5.20 (1H, d, *J* = 2.8Hz); 4.96 (1H, t, *J* = 5.2Hz); 4.48 (1H, d, *J* = 4.8Hz); 4.11 (2H, d, *J* = 5.2Hz); 3.98 (1H, t, *J* = 10.9Hz); 3.91-3.97 (2H, m); 3.84 (1H, dd, *J* = 5.4, 11.3Hz); 2.78 (2H, t, *J* = 7.8Hz); 1.61 (2H, quintet, *J* = 7.7Hz), 1.32 (2H, sextet, *J* = 7.5Hz), 0.84 (3H, t, *J* = 7.4Hz). LC-MS: m/z 667 (M + H).

EXAMPLE 15



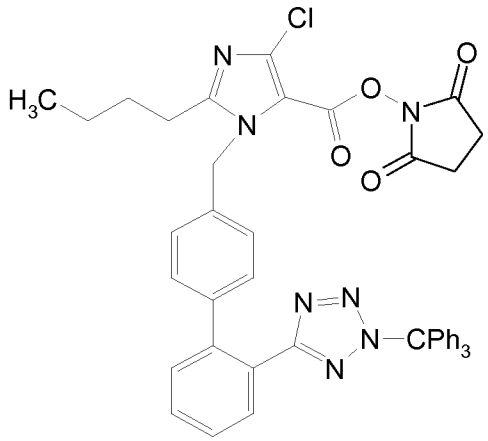
(3*S*,3a*R*,6*R*,6a*S*)-6-(nitrooxy)hexahydrofuro[3,2-*b*]furan-3-yl (2*S*)-2-{[(2-butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazol-5-yl)carbonyl]amino}propanoate

(corresponding to compound (114)

The title compound was prepared by the procedure described for Example 14, except that in Step A the reagent Fmoc-glycine was replaced by Fmoc-L-alanine and in Step B the reagent(3S,3aR,6R,6aS)-6-(nitrooxy)hexahydrofuro[3,2-b] furan-3-yl {[(9H-fluoren-9-ylmethoxy)carbonyl]amino}acetate was replaced by(S)-((3S,3aR,6R,6aS)-6-(nitrooxy)hexahydrofuro[3,2-b]furan-3-yl) (2S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)propanoate.

^{1}H NMR (500 MHz, CD_3CN) δ7.81 (d, *J* = 6.8 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.65 (td, *J* = 7.7, 1.2 Hz, 1H), 7.55 (t, *J* = 7.1 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 5.50 (s, 2H), 5.40 (td, *J* = 5.4, 2.3 Hz, 1H), 5.14 (d, *J* = 3.2 Hz, 1H), 4.91 (t, *J* = 5.4 Hz, 1H), 4.45 (quintet, *J* = 7.2 Hz, 1H), 4.40 (d, *J* = 5.0 Hz, 1H), 3.98-3.92 (m, 2H), 3.89-3.83 (m, 2H), 2.87 (t, *J* = 7.8 Hz, 2H), 1.59 (quintet, *J* = 7.7 Hz, 2H), 1.35 (d, *J* = 7.4 Hz, 3H), 1.32 (sextet, *J* = 7.3 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); LC-MS: *m/z* 681.2 (M + H).

INTERMEDIATE 1



2,5-dioxopyrrolidin-1-yl 2-butyl-4-chloro-1-((2'-(2-trityl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate (Corresponding to compound of formula (R_{IIc}))

Step A: 2,5-dioxopyrrolidin-1-yl 2-butyl-4-chloro-1H-imidazole-5-carboxylate

To a solution of 2-butyl-4-chloro-1H-imidazole-5-carboxylic acid (10.0 g, 49.4 mmol) in THF (100 mL), cooled to 0 °C, 1,1-*N*,*N*-carbonyl diimidazole (12.0 g, 74.1 mmol) was added. The reaction was warmed to room temperature and stirred for 3 hours. Then *N*-hydroxysuccinimide (5.68 g, 49.4 mmol) and sodium ethylate (672 mg, 9.88 mmol) were added and the mixture was stirred overnight. The reaction mixture was partitioned between EtOAc (100 mL) and NaH_2PO_4 (5%, 100 mL). The organic phase was washed with NaH_2PO_4 (3 x 50 mL) and brine (3 x 50 mL), dried over Na_2SO_4 and concentrated. The crude was purified by flash chromatography (BIOTAGE equipment, column diameter 75 + L, EtOAc/Hexane gradient - EtOAc 12%, 999 mL; EtOAc 12% to 100%, 9999 mL; EtOAc 100%, 1998 mL) affording the title compound as a white solid.

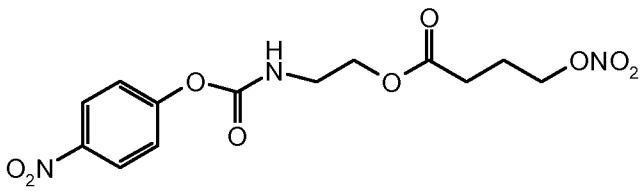
^{1}H-NMR ($CDCl_3$): 10.13(1H,s); 2.91(4H,s); 2.73(2H,t); 1.73(2H,m); 1.36(2H,m); 0.93(3H,t).

Step B: 2,5-dioxopyrrolidin-1-yl 2-butyl-4-chloro-1-((2'-(2-trityl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate

2,5-dioxopyrrolidin-1-yl 2-butyl-4-chloro-1H-imidazole-5-carboxylate (2.13 g, 7.10 mmol), 5-(4'-(bromomethyl)biphenyl-2-yl)-1-trityl-1H-tetrazole (3.96 g, 7.10 mmol) and K_2CO_3 (1.18 g, 8.50 mmol) were dissolved in DMF (25 mL) and stirred overnight. The salts were filtered off and the mixture was partitioned between EtOAc (50 mL) and NaH_2PO_4 (5%, 50 mL). The organic phase was washed with NaH_2PO_4 (5%, 3 x 50 mL), and brine (3 x 50 mL), dried over Na_2SO_4 and concentrated. The crude was purified by flash chromatography (BIOTAGE equipment, column diameter 65i, EtOAc/Hexane gradient - EtOAc 12% 471 mL; EtOAc 12% to 80%, 4710 mL; EtOAc 80% 942 mL-) affording the title compound (R_{IIc}) as a white solid.

^{1}H-NMR ($CDCl_3$): 7.90(1H,dd); 7.49(2H,m); 7.46-7.22(10H,m); 7.11(2H,d); 6.92(6H,m); 6.80(2H,d); 5.34(2H,s); 2.82 (4H,s); 2.52(2H,t); 1.63(2H,m); 1.26(2H,m); 0.85(3H,t)

INTERMEDIATE 2



2-((4-nitrophenoxy)carbonylamino)ethyl 4-(nitrooxy)butanoate (following procedure described in Appendix 1, A3)

Step A: 2-(tert-butoxycarbonylamino)ethyl 4-(nitrooxy)butanoate

tert-butyl 2-hydroxyethylcarbamate

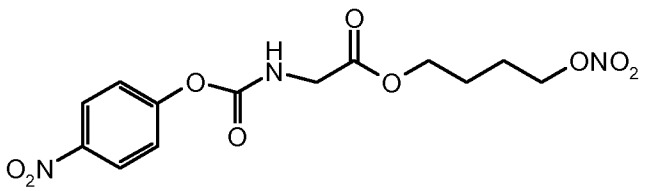
Step B: 2-aminoethyl 4-(nitrooxy)butanoate hydrochloride

Step C: 2-((4-nitrophenoxy)carbonylamino)ethyl 4-(nitrooxy)butanoate

To a solution of 2-aminoethyl 4-(nitrooxy)butanoate hydrochloride (1.16 g; 5.06 mmol) and $NaHCO_3$ (0.850 g; 10.1 mmol) in CH_3CN (32 ml) cooled to 0°C, was added dropwise a solution of 4-nitrophenyl chloroformate (1.02 g; 5.06 mmol) in CH_3CN (16 ml). The resulting mixture was stirred at room temperature for 18 hours. Then the mixture was diluted with EtOAc and washed with aqueous NaH_2PO_4 (5%, 2 X 50 ml) and brine (40 ml). The organic layer was dried over sodium sulfate and concentrated under reduced pressure.

The residue was purified by flash chromatography (hexane/EtOAc=6/4; R_f=0.21), yielding the title compound.

INTERMEDIATE 3



4-(nitrooxy)butyl 2-((4-nitrophenoxy)carbonylamino)acetate (following procedure described in Appendix 1, A1)

Step A: 4-hydroxybutyl 2-(tert-butoxycarbonylamino)acetate

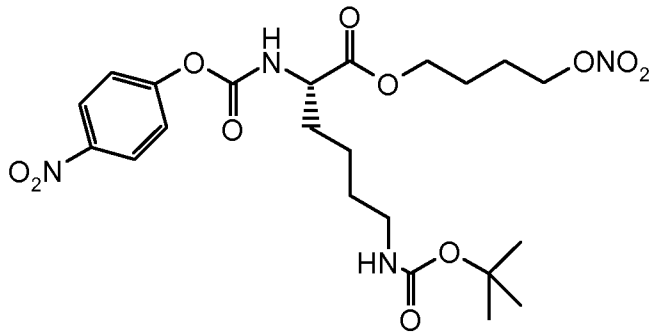
Step B: 4-(nitrooxy)butyl 2-(tert-butoxycarbonylamino)acetate

Step C: 4-(nitrooxy)butyl 2-aminoacetate

Step D: 4-(nitrooxy)butyl 2-((4-nitrophenoxy)carbonylamino)acetate

The title compound was prepared from 4-(nitrooxy)butyl 2-aminoacetate and 4-nitrophenyl chloroformate as described in Intermediate 2 Step C.

INTERMEDIATE 4



(S)-4-(nitrooxy)butyl 6-(tert-butoxycarbonylamino)-2-((4-nitrophenoxy)carbonylamino)hexanoate (following procedure described in Appendix 1, A7).

Step A: (S)-4-(nitrooxy)butyl 1-(9H-fluoren-9-yl)-13,13-dimethyl-3,11-dioxo-2,12-dioxa-4,10-diazatetradecane-5-carboxylate

Commercial N(α)-Fmoc-N(ε)-Boc-L-lysine pentafluorophenyl ester (6.51 mmol) and 4-(nitrooxy)-1-butanol (6.55 mmol) were dissolved in DMF (12 ml) and the mixture was cooled to 0°C. N,N-dimethylaminopyridine (DMAP) (6.55 mmol) were added and the reaction was slowly warmed to room temperature and stirred for 4 hours. Then the mixture was concentrate under reduced pressure and diluted with EtOAc, washed with 5% aqueous Na_2HPO_4 and brine. The organic layer was dried over sodium sulphate and concentrated under reduced pressure.

The residue was purified by flash chromatography (n-hexan/EtOAc 70:30 as eluent) yielding the title compound.

Step B: (S)-4-(nitrooxy)butyl 2-amino-6-(tert-butoxycarbonylamino)hexanoate

To a solution of (S)-4-(nitrooxy)butyl 1-(9H-fluoren-9-yl)-13,13-dimethyl-3,11-dioxo-2,12-dioxa-4,10-diazatetradecane-5-carboxylate (2.52 g, 4.30 mmol) in CH_3CN (30 ml), piperidine (2.12 ml, 21.5 mmol) was added in the dark, the reaction was stirred at r.t. for 25 min. Then the mixture was concentrated to a small volume and diluted with EtOAc (150 ml) and washed with 5% aqueous $NaHPO_4$ (2 x 70 ml). The

organic layer was dried over sodium sulphate and concentrated under reduced pressure.

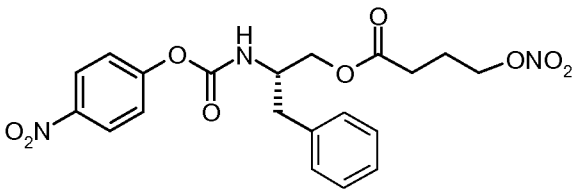
The residue was purified by flash chromatography (CH_2Cl_2/MeOH 98:2 as eluent), yielding the title compound.

1H-NMR (DMSO-d6): 6.78 (1H, t), 4.55 (2H, t), 4.07 (2H,m), 3.26 (2H,t), 2.87 (1H,m), 1.73-1.65 (4H,m), 1.64-1.40 (2H,m), 1.37 (9H,s), 1.36-1.22(4H,s).

Step C: (S)-4-(nitrooxy)butyl 6-(tert-butoxycarbonylamino)-2-((4-nitrophenoxy)carbonylamino)hexanoate

The title compound was prepared starting from (S)-4-(nitrooxy)butyl 2-amino-6-(tert-butoxycarbonylamino)hexanoate as described in Intermediate 2 Step C.

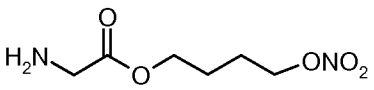
INTERMEDIATE 5



(S)-2-((4-nitrophenoxy)carbonylamino)-3-phenylpropyl 4-(nitrooxy)butanoate

The title compound was obtained from (S)-tert-butyl 1-hydroxy-3-phenylpropan-2-ylcarbamate following the procedure described for Intermediate 2.

INTERMEDIATE 6



4-(nitrooxy)butyl 2-aminoacetate

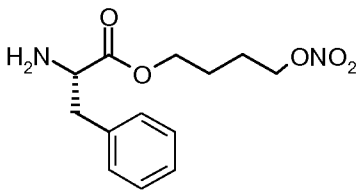
Step A 4-(nitrooxy)butyl 2-(tert-butoxycarbonylamino)acetate

The title compound was obtained from N-Boc-L-glycine, N-hydroxysuccinimido ester following procedures described in Intermediate 4, Step A.

Step B: 4-(nitrooxy)butyl 2-aminoacetate

To a solution of 4-(nitrooxy)butyl 2-(tert-butoxycarbonylamino)acetate (3.00 g, 1.03 mmol) in CH_2Cl_2 (40 ml) cooled to 0 °C, HCl_{gas} was bubbled for 2 hours. The solvent was concentrated and the residue was treated with diethyl ether, affording the title compound as a white solid.

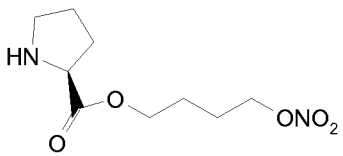
INTERMEDIATE 7



(S)-4-(nitrooxy)butyl 2-amino-3-phenylpropanoate

The title compound was prepared from N-Boc-Phenylalanine following the procedure described in Intermediate 6.

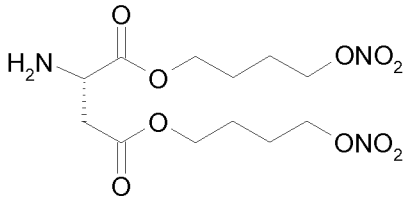
INTERMEDIATE 8



(S)-4-(nitrooxy)butyl pyrrolidine-2-carboxylate

The title compound was prepared as an oil from N-Boc-L-Proline following the procedure described in Intermediate 6.

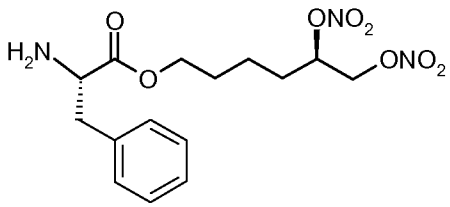
INTERMEDIATE 9



(S)-bis(4-(nitrooxy)butyl) 2-aminosuccinate

The title compound was prepared from Boc-L-glutamic acid following the procedure described in Intermediate 6.

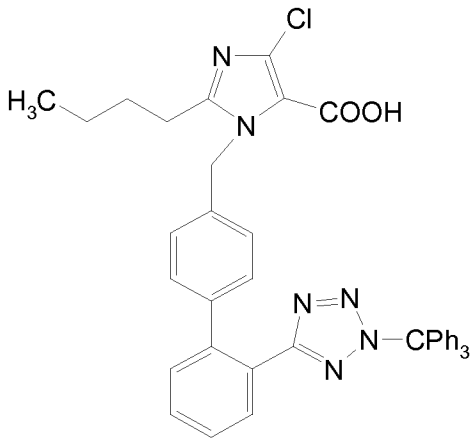
INTERMEDIATE 10



(S)-((R)-5,6-bis(nitrooxy)hexyl) 2-amino-3-phenylpropanoate

The title compound was prepared from Boc-L-Phenylalanine and (2R)-6-hydroxyhexane-1,2-diyl dinitrate (prepared as described in WO2005070868(A1)) following the procedure described in Intermediate 6

INTERMEDIATE 11



2-butyl-4-chloro-1-{[2'-(2-trityl-2H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1H-imidazole-5-carboxylic acid

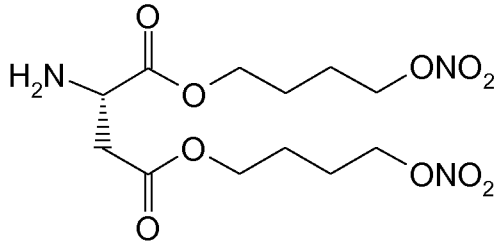
Step A: 2-butyl-4-chloro-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1H-imidazole-5-carboxylic acid

Water (10 L) was added to a 22 L 4-neck round bottom flask. The water was cooled to 0 °C. At 0 °C, potassium hydroxide (855 g, 15.24 mol) was added followed by losartan potassium (500 g, 1.09 mol)), sodium periodate (554 g, 2.59 mol) and ruthenium (III) chloride hydrate (12 g, 0.05 mol) and the reaction mixture was stirred at 0 °C overnight. The reaction mixture was filtered. IPA (90 mL) was added to the filtrate while stirring. The solution was warmed to 25 °C and stirred for 2.5 hrs. After 2.5 hrs., phosphoric acid (1200 mL) was added, maintaining the temperature below +30 °C. The mixture was stirred for 30 min and the product was filtered, washing with water. The residue was dried in the vacuum oven at 55 °C overnight. The solid was dissolved in methanol (4 L) and isopropyl acetate (12 L), and charcoal (activated carbon) (100 g) was added. The mixture was stirred at rt for 3.5 hrs, filtered and concentrated. The product was redissolved in DCM/MeOH and precipitated with heptane to afford the title compound as a greenish/brown foam which was used in subsequent steps without further purification.

Step B: 2-butyl-4-chloro-1-{[2'-(2-trityl-2H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1H-imidazole-5-carboxylic acid

To a solution of E3174 (234.58 g, 0.54 mol) in DCM (4500 mL) was added triethylamine (85 mL, 0.59 mol) followed by a solution of trityl chloride (159 g, 0.56 mol) in DCM (800 mL) and the reaction mixture was stirred at rt overnight. The reaction mixture was washed with water, dried (MgSO4), filtered, and concentrated in vacuo. Chromatography over silica eluting with 20-80% acetone/heptane afforded the title compound as an orange solid.

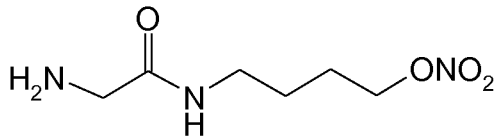
INTERMEDIATE 12



(S)-bis(4-(nitrooxy)butyl) 2-aminosuccinate

The title compound was prepared from Boc-L-aspartic acid following the procedure described in Intermediate

INTERMEDIATE 13



4-(2-aminoacetamido)butyl nitrate

Step A: tert-butyl 2-(4-hydroxybutylamino)-2-oxoethylcarbamate

4-Amino-1-butanol (0.686 g, 7.70 mmol) and triethylamine (0.779 g, 7.70 mmol) were dissolved in CH_2Cl_2 (40 ml) and the mixture was cooled to 0° C. A suspension of commercial N-Boc-glycine N-hydroxysuccinimido estere (2.10 g; 7.70 mmol) in CH_2Cl_2 (40 ml) was added and the reaction was slowly warmed to room temperature and stirred for 24 hours. Then the mixture was diluted with CH_2Cl_2 (150 ml) and washed with 5% aqueous Na_2HPO_4 and brine. The aqueous layer was extracted twice with CH_2Cl_2 and twice with a mixture of EtOAc/MeOH 98:2. The organic layers were dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography (n-hexane/i-prOH 80:20) affording the title compound.

Step B: tert-butyl 2-(4-(nitrooxy)butylamino)-2-oxoethylcarbamate

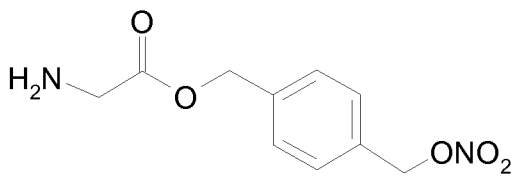
To a solution of tert-butyl 2-(4-hydroxybutylamino)-2-oxoethylcarbamate (2.16 g, 8.77 mmol), tetraethylammonium nitrate (3.37 g, 17.54 mmol) and 2,6-di-tert-butyl-4-methylpyridine (2.71 g, 13.16 mmol) in CH2Cl2 (60 ml) cooled to -70°C and under nitrogen, a solution of trifluoromethansulfonic anhydride (2.72 g, 9.65 mmol) in CH2Cl2 (40 ml) was added drop wise. The resulting mixture was stirred for 3 hours at -65°C. Then the mixture was slowly warmed to room temperature, diluted with CH2Cl2 and washed with 5% aqueous Na2HPO4. The organic layer was dried over sodium sulphate and concentrated under reduced pressure.

The residue was purified by flash chromatography CH_2Cl_2/ CH3CN 70:30 as eluent) affording the title compound

Step C: 4-(2-aminoacetamido)butyl nitrate

To a solution of tert-butyl 2-(4-(nitrooxy)butylamino)-2-oxoethylcarbamate (1.73 g 7.0 mmol)in CH2Cl2 (40 ml) cooled to 0 °C, HCl_{gas} was bubbled for 2 hours. The solvent was concentrated and the residue was treated with diethyl ether, affording the title compound as a white solid.

INTERMEDIATE 14



4-[(nitrooxy)methyl]benzyl 2-aminoacetate

Step A 4-(chloromethyl)benzyl 2-(tert-butoxycarbonylamino)acetate

The title compound was prepared from N-Boc-Glycine N-hydroxysuccinimido ester and 4-(chloromethyl)benzyl alcohol following procedure reported in Intermediate 3 Step A.

Step B: 4-[(nitrooxy)methyl]benzyl 2-(tert-butoxycarbonylamino)acetate

To a solution of 4-(chloromethyl)benzyl 2-(tert-butoxycarbonylamino)acetate ester (0.605 g, 1.78 mmol) in CH_3CN (13 ml), $AgNO_3$ (0.756 g, 4.45 mmol) was added and the reaction was heated in a microwave apparatus (150° C, 20 min). The formed salts were filtered off and the solvent was concentrated, then the residue was diluted with EtOAc (100 ml) and washed with brine. The organic layer was dried over sodium sulphate and concentrated under reduced pressure yielding the title compound.

Step C: 4-[(nitrooxy)methyl]benzyl 2-aminoacetate

The title compound was obtained by acid hydrolysing 4-[(nitrooxy)methyl]benzyl 2-(tert-butoxycarbonylamino) acetate following procedure described in Intermediate 2 Step B.

Studies on vascular tone

The ability of ARB nitroderivatives to induce vasorelaxation in comparison to native ARBs, was tested *in vitro* in isolated rabbit thoracic aorta preparations (Wanstall J.C. et al., Br. J. Pharmacol., 134:463-472, 2001). Male New Zealand rabbits were anaesthetized with thiopental-Na (50 mg/kg, iv), sacrificed by exsanguinations and then the thorax was opened and the aorta dissected. Aortic ring preparations (4 mm in length) were set up in physiological salt solution (PSS) at 37°C in small organ chambers (5 ml). The composition of PSS was (mM): NaCl 130, $NaHCO_3$ 14.9, KH_2PO_4 1.2, $MgSO_4$ 1.2, HEPES 10, $CaCl_2$, ascorbic acid 170 and glucose 1.1 (95% O_2 /5% CO_2 ; pH 7.4). Each ring was mounted under 2 g passive tension. Isometric tension was recorded with a Grass transducer (Grass FT03) attached to a BIOPAC MP150 System. Preparations were allowed to equilibrate for 1h, and then contracted

submaximally with noradrenaline (NA, 1 µM) and, when the contraction was stable, acetylcholine (ACh, 10 µM) was added. A relaxant response to ACh indicated the presence of a functional endothelium. Vessels that were unable to contract NA or showed no relaxation to Ach were discarded. When a stable precontraction was reached, a cumulative concentration-response curve to either of the vasorelaxant agents was obtained in the presence of a functional endothelium. Each arterial ring was exposed to only one combination of inhibitor and vasorelaxant. Moreover, the effect of the soluble guanylyl cyclase inhibitor ODQ (1-H-(1,2,4)-oxadiazol(4,3-a)quinoxalin-1-one) on vasorelaxation elicited by the compounds was examined preincubating the aortic rings with ODQ (10 µM) for 20 min.

Responses to relaxing agents are expressed as a percentage of residual contraction and plotted against concentration of test compound. EC_{50} values (where EC_{50} is the concentration producing 50% of the maximum relaxation to the test compound) were interpolated from these plots.

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

As shown in Table 1, the compounds of the invention were able to induce relaxation in a concentration-dependent manner. Furthermore, in experiments performed in the presence of ODQ (10 µM), the vasorelaxant responses to tested compounds were inhibited.

Table 1

Compound	**EC_{50} (µM)±** sem
Losartan	no effect
EXP 3174	no effect
Candesartan	no effect
Compound of **EX. 1**	23.6 ± 3.9
Compound of **EX. 2**	40.1 ± 2.7
Compound of **EX. 3**	9.2 ± 4.1
Compound of **EX. 4**	46 ± 7.2
Compound of **EX. 5**	9.2 ± 2.5
Compound of **EX. 6**	14.2 ± 8
Compound of **EX. 7**	7.1 ± 1.9
Compound of **EX. 8**	10.4 ± 2.5
Compound of **EX. 9**	3.4 ± 0.8
Compound of **EX. 10**	5.4 ± 1.8
Compound of **EX. 11**	38.7 ± 5.3
Compound of **EX. 13**	30.6 ± 4.7
Compound **(2)**	43.4 ± 11
Compound **(112)**	47.8 ± 16

Study on angiotensin receptor antagonism

Tissue preparation

Thoracic aorta was obtained from male rabbits. Each animal was sacrificed by exsanguinations under pentobarbital-Na anesthesia and the thoracic aorta was rapidly removed.

After removing adhering fat and connecting tissues, the thoracic aorta was cut into 4-5 mm long rings. Each preparation was placed in a 5 ml organ bath containing physiological salt solution (PSS) at the following composition (mM): NaCl 130.0, KCl 3.7, $NaHCO_3$ 14.9, KH_2PO_4 1.2, $MgSO_4 \cdot 7H_2O$ 1.2, Glucose 11.0, HEPES 10.0, $CaCl_2 \cdot 2H_2O$ 1.6. The solution in the bath was constantly aerated with 95% O_2 and 5% CO_2 and kept at 37°C (pH 7.4). Contractile force was measured with isometric transducer (Grass FT03), connected to a BIOPAC MP150 System. After 1 h of equilibration with a appropriate resting tension (2g), the rings were primed by exposure to 90 mM KCl (3 times) with intervening washings. Then each ring was contracted submaximally with methoxamine 3 µM and, when the contraction was stable, acetylcholine (ACh, 3 µM) was added. A relaxant response to ACh indicates the presence of a functional endothelium.

Interaction with Angiotensin II Receptors

The vascular preparations were exposed to increasing concentrations of Angiotensin II (AngII) until the maximal contractile effect was achieved. Then the vascular tissues were washed and recovered to baseline. After an incubation time of 30 minutes with antagonist at the selected concentration, a second concentration-response curve for agonist was constructed. In parallel control experiments, vehicle was given before the second agonist curve was constructed.

Responses are expressed as percentage maximal contractile effect achieved in the first cumulative curve.

Antagonist activity was assessed by the ability of compounds to produce rightward shifts in the dose response

curve for angiotensin II-induced contraction of the isolated rabbit aorta.

All the compounds of the invention showed an angiotensin II receptor antagonism.

Study of antihypertensive activity of ARB nitroderivatives *in vivo*

The ability of the compounds of the invention to decrease blood pressure was evaluated in conscious spontaneously hypertensive rats (SHRs). SHRs (250-300 g) received a single oral dose of EXP 3174 or the corresponding nitroderivative. Systolic blood pressure (SBP) and heart rate were monitored by telemetry for 24 hours after dosing. SBP was evaluated before (baseline) and after (i.e. 6, 24 hours) treatment by oral administration of the compounds. The data were processed both as the absolute value or as a delta between the absolute value and its own baseline.

The Dataquest IV telemetry system (Data Sciences International) was used for measurement of systolic pressure, diastolic pressure, mean arterial pressure, heart rate, and motor activity. The monitoring system consists of a transmitter (radio frequency transducer model TA11PA), receiver panel, consolidation matrix, and personal computer with accompanying software. Before the device was implanted, calibrations were verified to be accurate within ±3 mmHg. Rats were anesthetized with ketamine/xylazine/acepromazine, and the flexible catheter of the transmitter was surgically secured in the abdominal aorta just below the renal arteries. The transmitter was sutured subcutaneously. Rats were housed in individual cages after the operation. Each cage was placed over the receiver panel that was connected to the personal computer for data acquisition. The rats were unrestrained and free

to move within their cages. Hemodynamic data were sampled every 2 minutes for 10 seconds.

As shown in Table 2, the nitroderivatives of the invention were able to induce a reduction in blood pressure levels over the treatment period, associated with prolonged duration of action and resulted more effective than the parent compounds.

Table 2

Δ Systolic blood pressure (mmHg)		
Compound	**6 hrs**	**24 hrs**
EXP 3174 (10 mpk, po)*	-5	2
Compound of **EX. 5**(10 mpk, po)	-7	-11
Compound of **EX. 6**(10 mpk, po)	-12	-13
Compound of **EX. 10**(10 mpk, po)	-6	-11
Compound of **EX. 11**(10 mpk, po)	-6	-17

* Systolic blood pressure for EXP 3174 was evaluated with tail-cuff method (Whitesall S.E et Al.; Am. J. Physiol. Heart Circ. Physiol 286: H2408-H2415, 2004).

Solubility test

The solubility of the tested compounds in PEG 400/H_2O 7/3 was evaluated using a standard curve constructed of six calibration points by plotting the peak areas of the compounds of the invention versus the concentration.

Test solution: 5.0 mg of the nitroderivative were dissolved in 0.7 ml of PEG 400 in a glass volumetric flask and 0.3 ml of water were added. The solution was mixed for 1 hour and filtered through 0.45 µm Acrodisc filter.

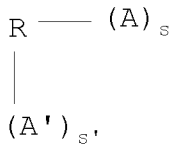
As shown in Table 3, the nitroderivatives of the invention showed a very good solubility.

Table 3

Compound	**Solubility PEG400/H_2O 70:30 (mg/ml) target 5 mg/ml**
(2)	> 5
Compound of **EX. 3**	> 5
Compound of **EX. 2**	> 5
(112)	> 5
Compound of **EX. 1**	4
Compound of **EX. 5**	4.2
Compound of **EX. 6**	> 5
Compound of **EX. 9**	4.9
Compound of **EX. 7**	> 5
Compound of **EX. 11**	4.6
(46)	5.07

CLAIMS

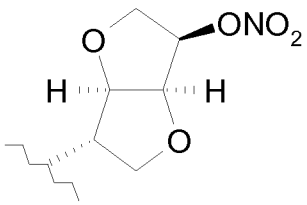
1. A compound of general formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof:



(I)

wherein:

A and A' are independently selected from the group consisting of -(Y-ONO2), -(Y'-ONO2) or (1a)

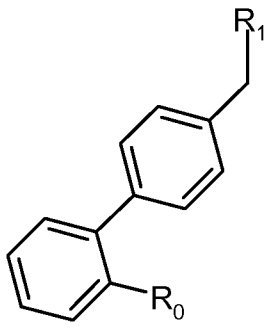


(1a)

s is 1 or 2;

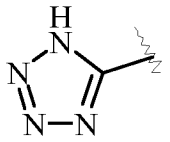
s' is 0, 1 or 2;

R is selected from the following residues of formula (II) or (III):



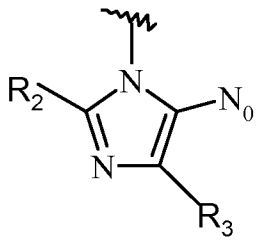
(II)

wherein:

R_0 is the group (IV) 

or N_0 which is a moiety capable to bind the groups A and A' as defined hereinafter;

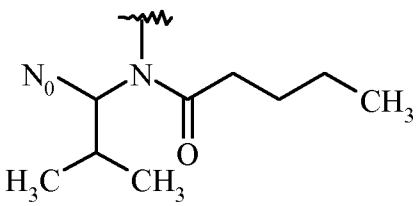
R_1 is selected from the groups (Va-Ve):



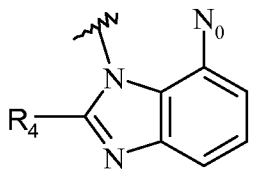
(Va)

wherein R_2 is C_1-C_5 linear or branched alkyl, preferably n-propyl or n-butyl;

R_3 is an halogen atom such as Cl, Br, I, or a perfluorurated C_1-C_4 alkyl chain, preferably C_2F_5, or the group $-C(CH_3)_2OH$;

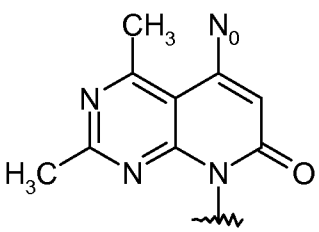


(Vb) ;

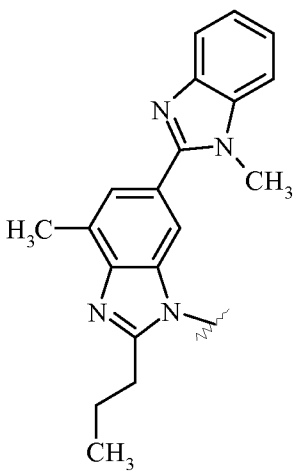


(Vc)

wherein R_4 is n-Bu or -OEt;



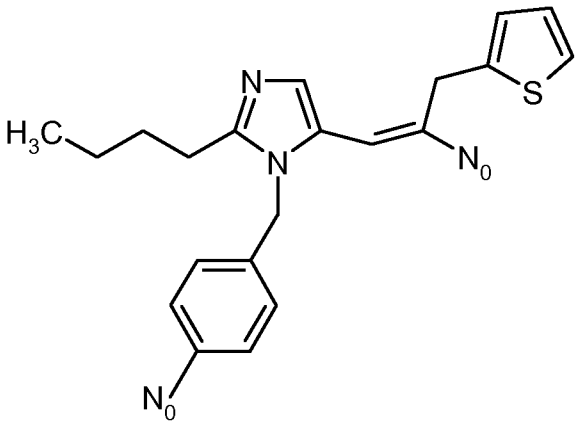
or



;

(Vd) (Ve)

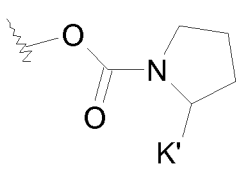
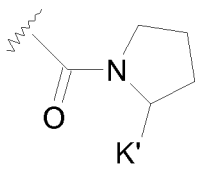
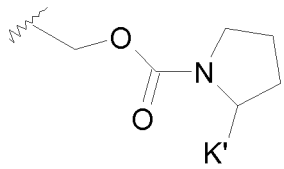
or R is the residue of formula (III):



(III)

wherein N_0 is a moiety capable to bind the groups A and A', having one of the following meanings:

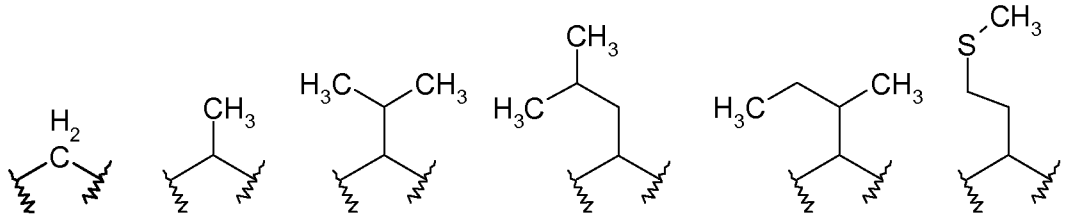
1)

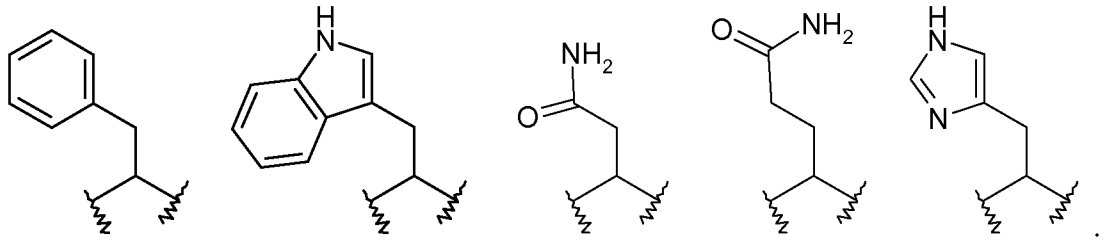
(VIa) (VIb) (VIc)

wherein K' is equal to -COO-, -CONH-, $-CH_2$-O-CO-, $-CH_2$-O-COO- or $-CH_2$-O-CONH- and K' is bound to the group A wherein A is $-(Y-ONO_2)$ or (1a), with the proviso that when A is (1a), then K' is -COO- or $-CH_2$-OCOO-;

2) -OCO-NH-J-K', -CO-NH-J-K' or $-CH_2$-O-CO-NH-J-K' wherein J is selected among (VIIa-VIIk):



(VIIa) (VIIb) (VIIc) (VIId) (VIIe) (VIIf)

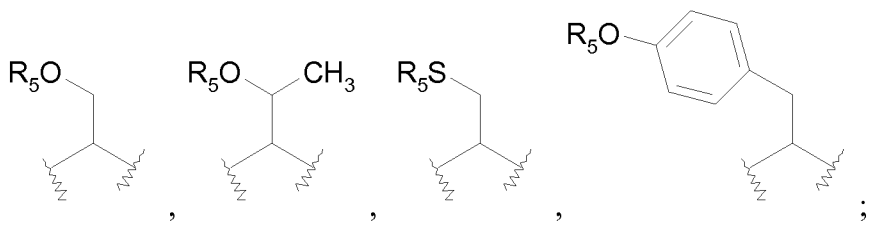


(VIIg) (VIIh) (VIIi) (VIIj) (VIIk)

wherein K' is equal to -COO-, -CONH-, $-CH_2-O-CO-$, $-CH_2-O-COO-$ or $-CH_2-O-CONH-$ and K' is bound to the group A wherein A is $-(Y-ONO_2)$ or (1a), with the proviso that when A is (1a), then K' is -COO- or $-CH_2-OCOO-$;

3) -O-CO-NH-K-K*, $-CH_2-O-CO-NH-K-K^*$ or -CO-NH-K-K* wherein K is selected among K_1, K_2 or K_3 wherein:

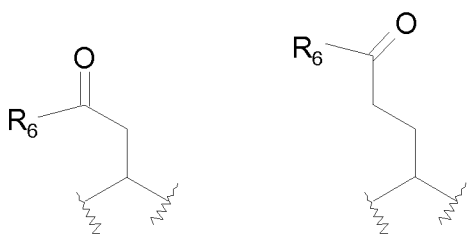
K_1 is selected among (VIIIa-VIIId):



(VIIIa) (VIIIb) (VIIIc) (VIIId)

wherein R_5 is H or a group selected from -CO-, -COO- or -CONH- capable to bind a group A' wherein A' is $-(Y'-ONO_2)$;

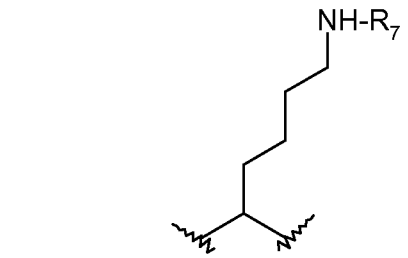
K_2 is selected among (VIIIe-VIIIf):



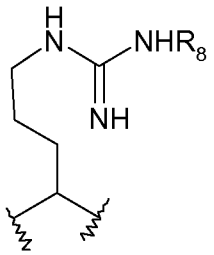
(VIIIe) (VIIIf)

wherein R_6 is -OH or a group selected from –O- or –NH capable to bind a group A', with the proviso that when A' is (1a), then R_6 is –O-;

K_3 is selected among (VIIIg-VIIIh):



,

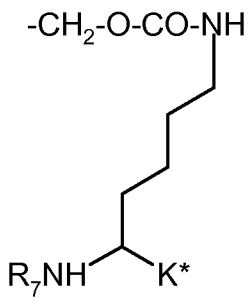


;

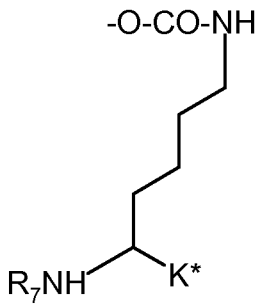
(VIIIg) (VIIIh)

wherein R_7 and R_8 are H or a group selected from –CO- or -COO- capable to bind a group A' wherein A' is $-(Y'-ONO_2)$; K* is equal to K' as above defined or -COOH and when K* is equal to K' is bound to the group A, with the proviso that when A is (1a), then K' is –COO- or $-CH_2-OCOO-$;

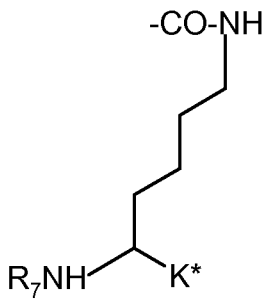
4)



(IXa)



(IXb)



(IXc)

wherein R_7 and K* are as above defined;

with the proviso that:

i. when R_1 is the group (Va), then N_0 is selected from the group consisting of (VIb), (VIc) -CO-NH-J-K',

a. $-CH_2-O-CO-NH-J-K'$, $-CO-NH-K-K^*$, $-CH_2-O-CO-NH-K-K^*$, (IXc) and (IXa);

ii. when R_1 is selected from the groups (Vb), (Vc) or (Ve), then N_0 is selected from the group consisting of (VIb), $-CO-NH-J-K'$, $-CO-NH-K-K^*$ and (IXc);

iii. when R_1 is the group (Vd), then N_0 is selected from the group consisting of (VIa), $-OCO-NH-J-K'$, $-O-CO-NH-K-K^*$ and (IXb);

iv. when R is selected from the residue (III), then N_0 is selected from the group consisting of (VIb), $-CO-NH-J-K'$, $-CO-NH-K-K^*$ and (IXc);

v. when R is selected from the residue (II) and R_0 is N_0, then R_1 is the group (V_e)

vi. when R is selected from the residue (II), then s is 1 and s' is 0 or 1;

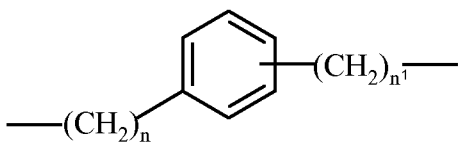
vii. when R is selected from the residue (III), then s is 2 and s' is 0 or 2.

Y and Y' independently are bivalent radicals having the following meaning:

a)

- straight or branched C_1-C_{20} alkylene, preferably C_1-C_{10}, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or R^1, wherein R^1 is $-OC(O)(C_1-C_{10}$ alkyl$)-ONO_2$ or $-O(C_1-C_{10}$ alkyl$)-ONO_2$;

b)



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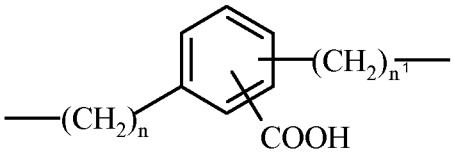
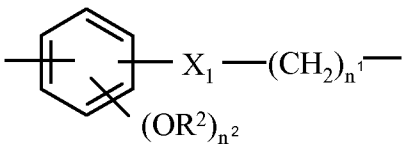


wherein n is an integer from 0 to 20, and n^1 is an integer from 1 to 20;

d)

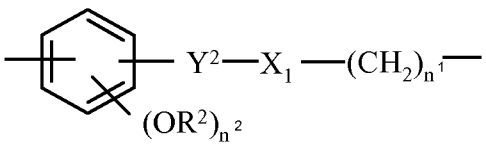


wherein:

n^1 is as defined above and n^2 is an integer from 0 to 2;

X_1 = -OCO- or -COO- and R^2 is H or CH_3;

e)



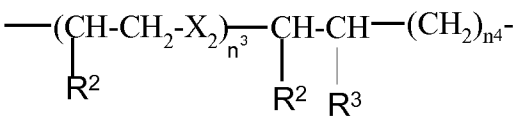
wherein:

n^1, n^2, R^2 and X_1 are as defined above;

Y^2 is $-CH_2-CH_2-$ or $-CH=CH-(CH_2)_{n^2}-$;

with the proviso that when Y or Y' is selected from the bivalent radicals mentioned under b)-e), the $-ONO_2$ group is linked to a $-(CH_2)_{n^1}$ group;

f)



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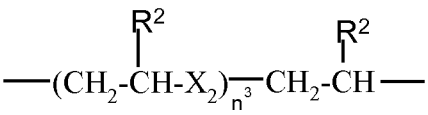


wherein X_2 is -O- or -S-, n^3 is an integer from 1 to 6, preferably from 1 to 4, R^2 is as defined above,

R^3 is H or $-ONO_2$ and n^4 is 0 or 1.

2. The compounds of formula (I) according to claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof wherein R is the residue of formula (II), R_0 is the group of formula (IV), R_1 is the group of formula (Va), R_2 is n-butyl, R_3 is Cl and all other variables are as defined in claim 1.

3. The compounds of formula (I) according to claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof wherein R is the residue of formula (II), R_0 is the group of formula (IV), R_1 is the group of formula (Va), R_2 is n-propyl, R_3 is the group $-C(CH_3)_2OH$ and all other variables are as defined in claim 1.

4. The compounds of formula (I) according to claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof wherein R is the residue of formula (II), R_0 is the group of formula (IV), R_1 is the group of formula (Vc) as defined in claim 1, R_4 is -OEt, and all other variables are as defined in claim 1.

5. The compounds of formula (I) according to claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof wherein s_1 is 0 and A is the group (VI_a) or (VI_b) or (VI_c) wherein K'is -COO-, and all other variables are as defined in claim 1.

6. The compounds of formula (I) according to claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof wherein s_1 is 0 and A is -CO-NH-J-K' or $-CH_2$-O-CO-NH-J-K', J is the group (VIIa) or (VIIb), wherein K'is -COO-, and all other variables are as defined in claim 1.

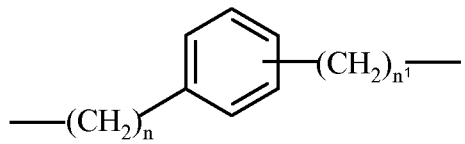
7. The compounds of formula (I) according to claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof wherein s_1 is 0 and A is $-CH_2-O-CO-NH-K-K^*$ or $-CO-NH-K-K^*$, K is K_3 which is the group (VIIIg) or ($VIII_h$), and all other variables are as defined in claim 1.

8. A compound of general formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof according to claim 1-7, wherein Y and Y' independently are a bivalent radical having the following meaning:

a)

- straight or branched C_1-C_{10} alkylene, being optionally substituted with one or more $-ONO_2$;

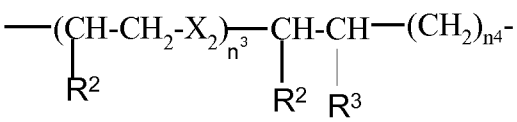
b)



wherein n is an integer from 0 to 5, and n^1 is an integer from 1 to 5;

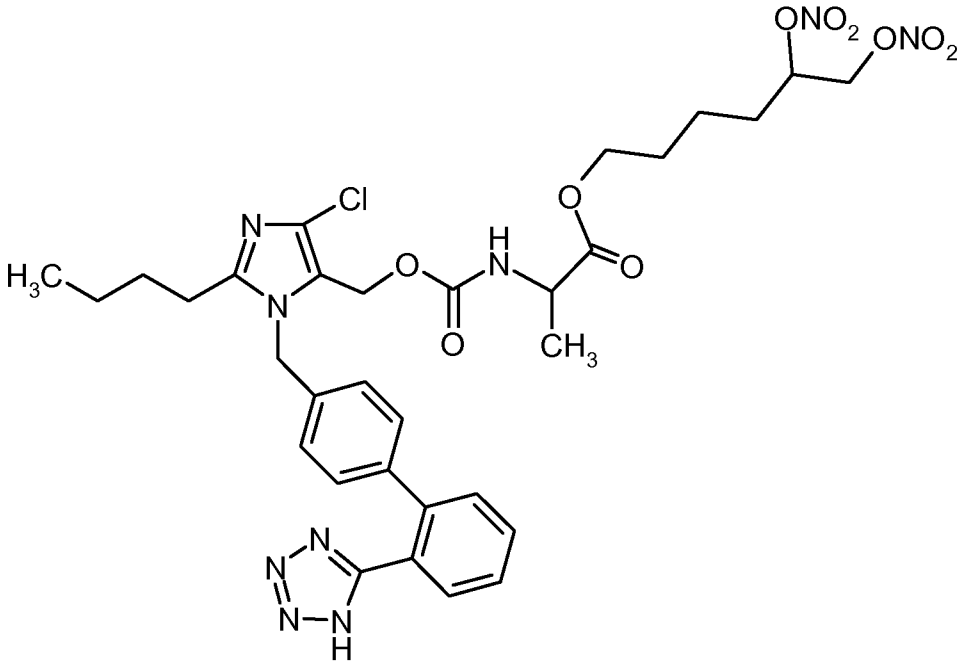
with the proviso that when Y or Y' is selected from the bivalent radical b), the $-ONO_2$ group is linked to a $-(CH_2)_{n^1}$ group;

f)



wherein X_2 is -O- or -S-, n^3 is 1, R^2 is H, R^3 is H or $-ONO_2$ and n^4 is 0 or 1.

9. A compound according to claims 1-8, selected from the group consisting of:



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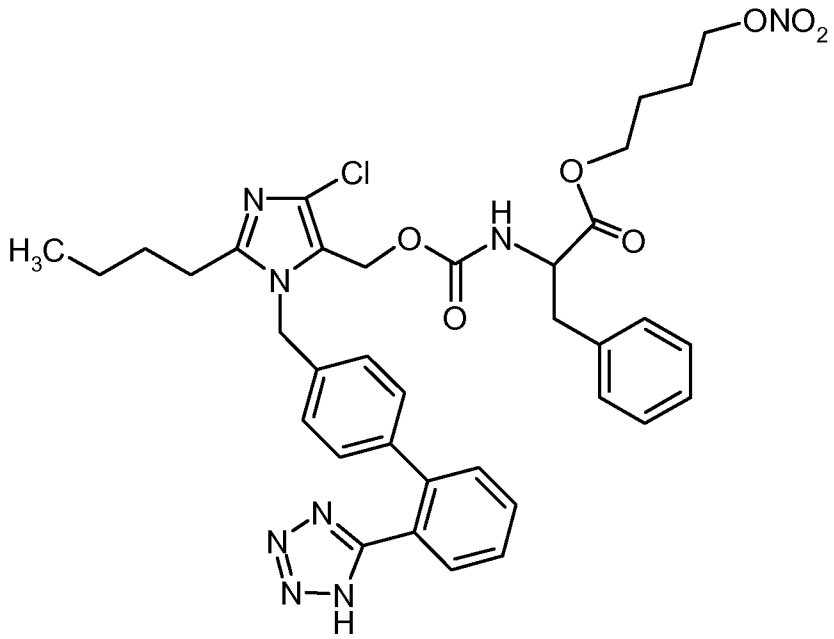

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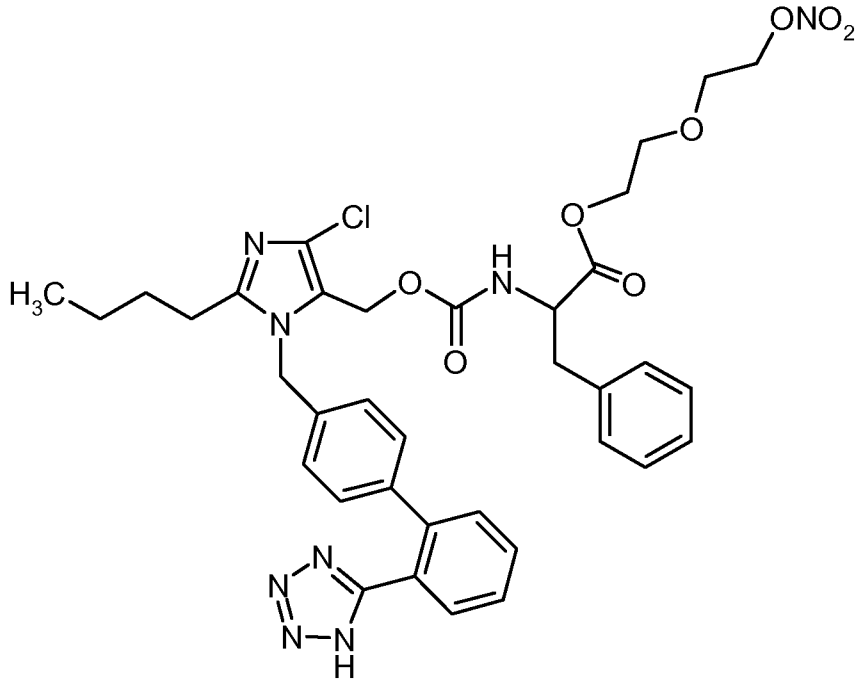

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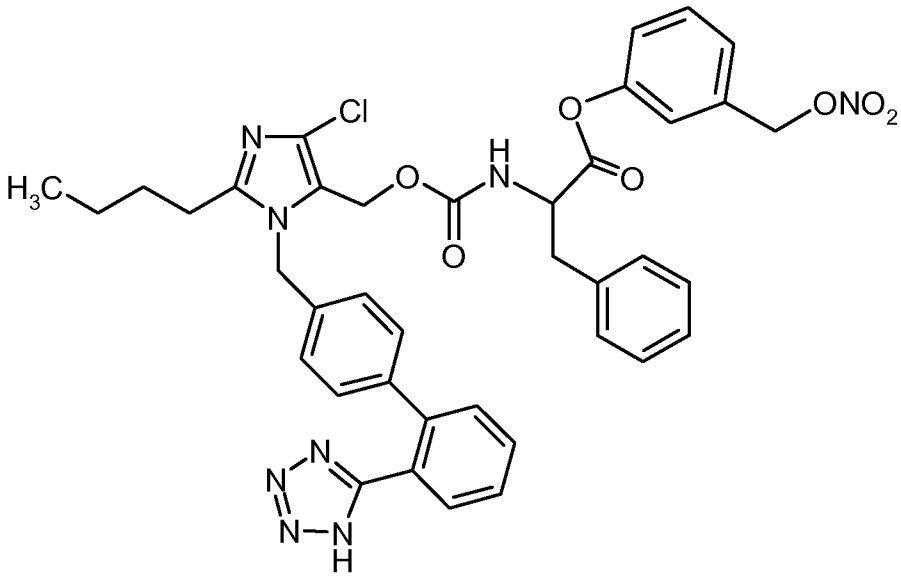

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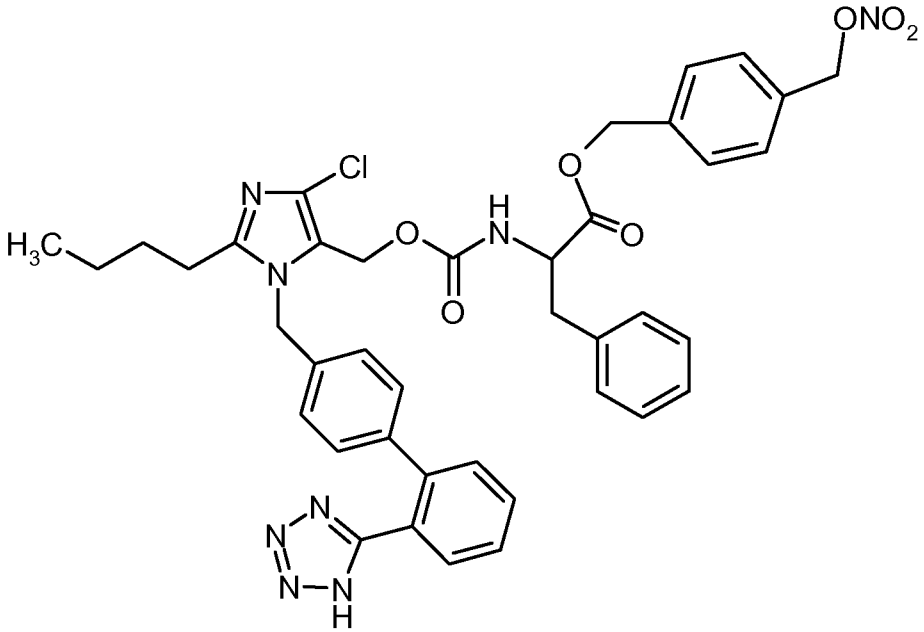

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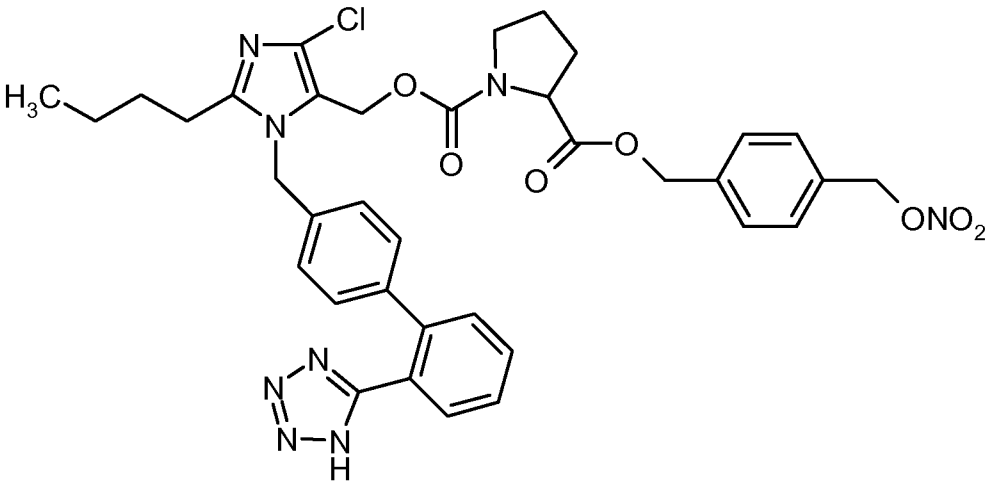

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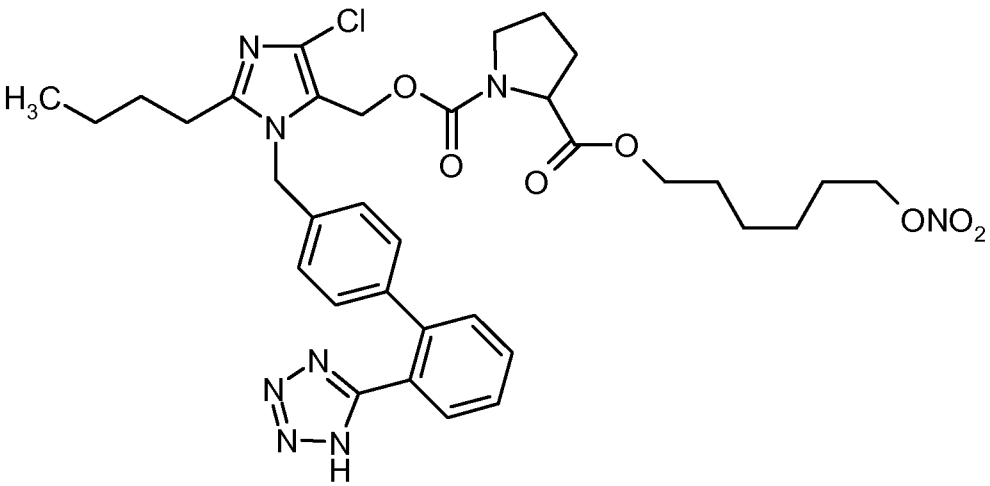

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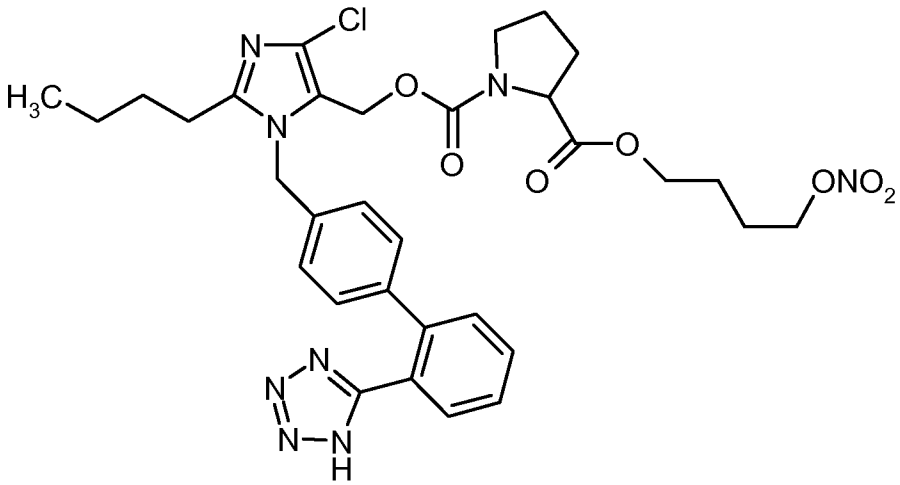

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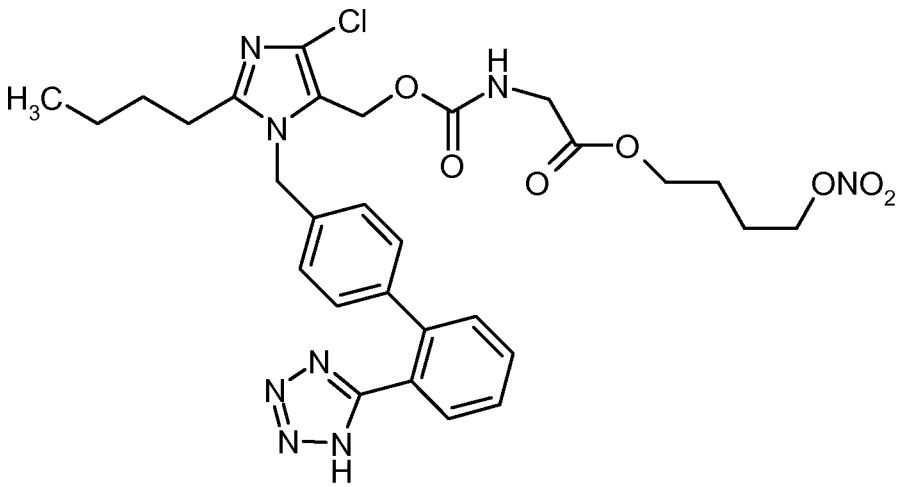

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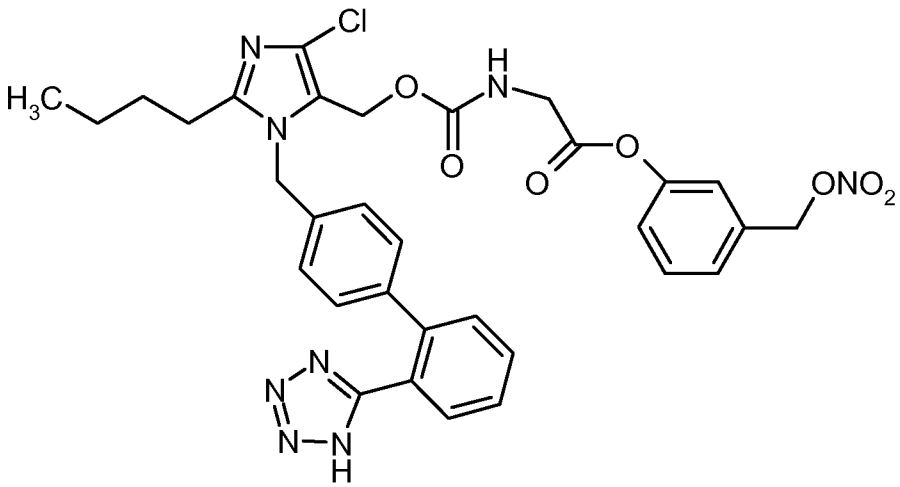

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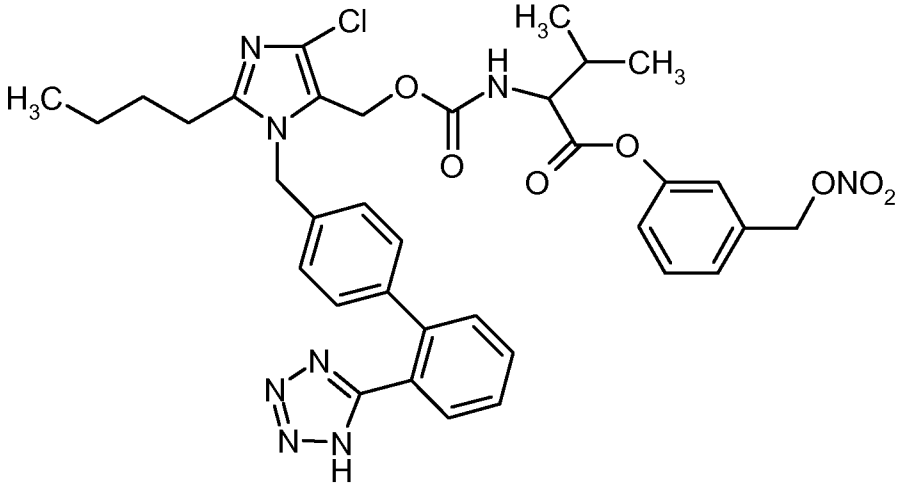

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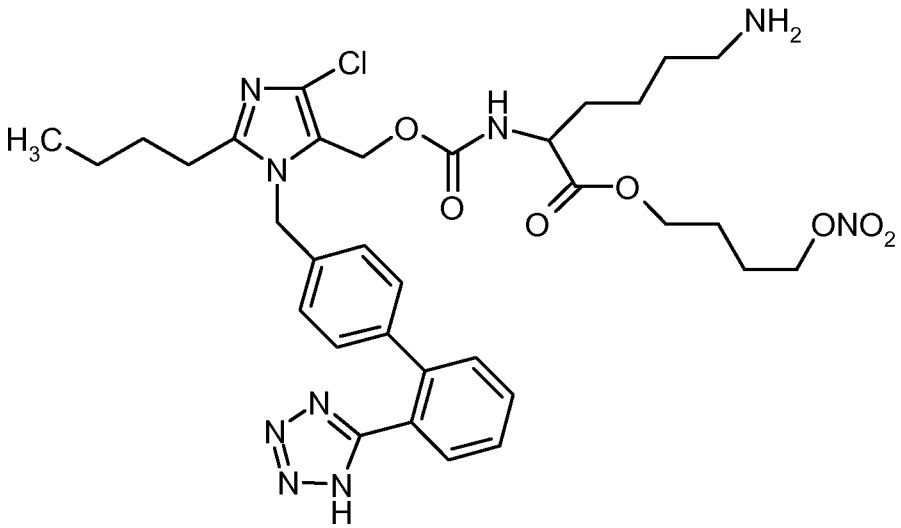

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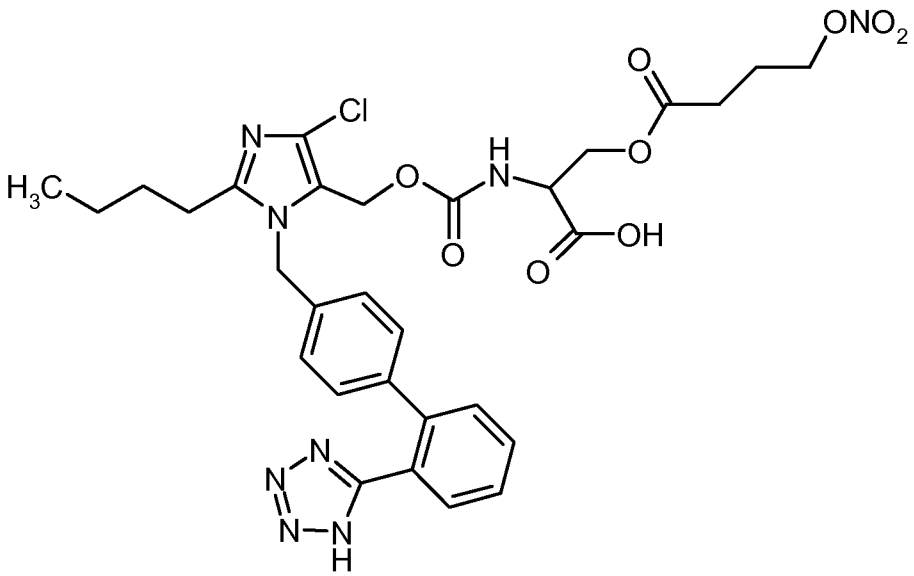

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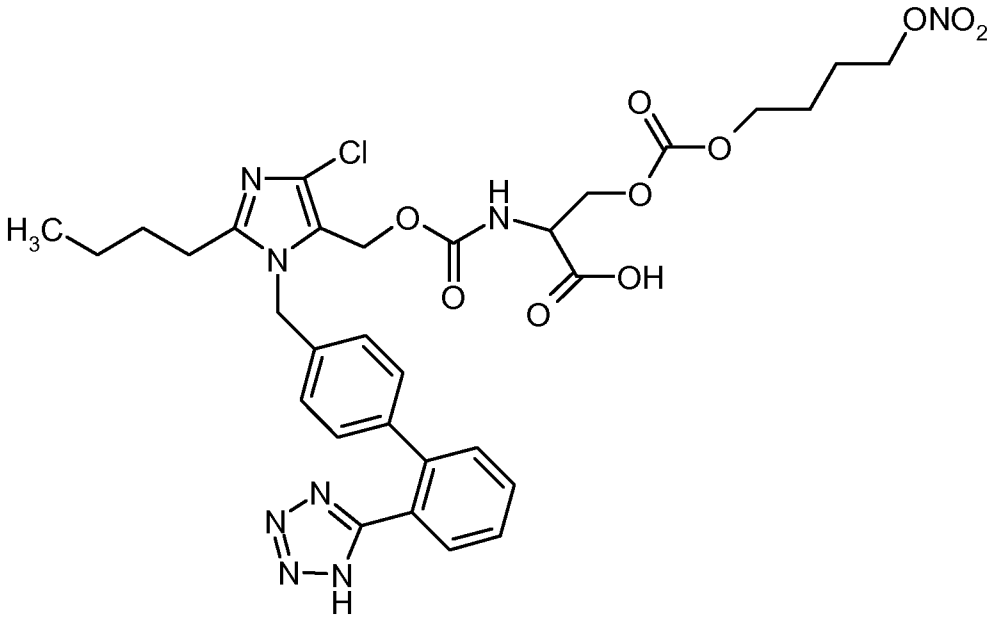

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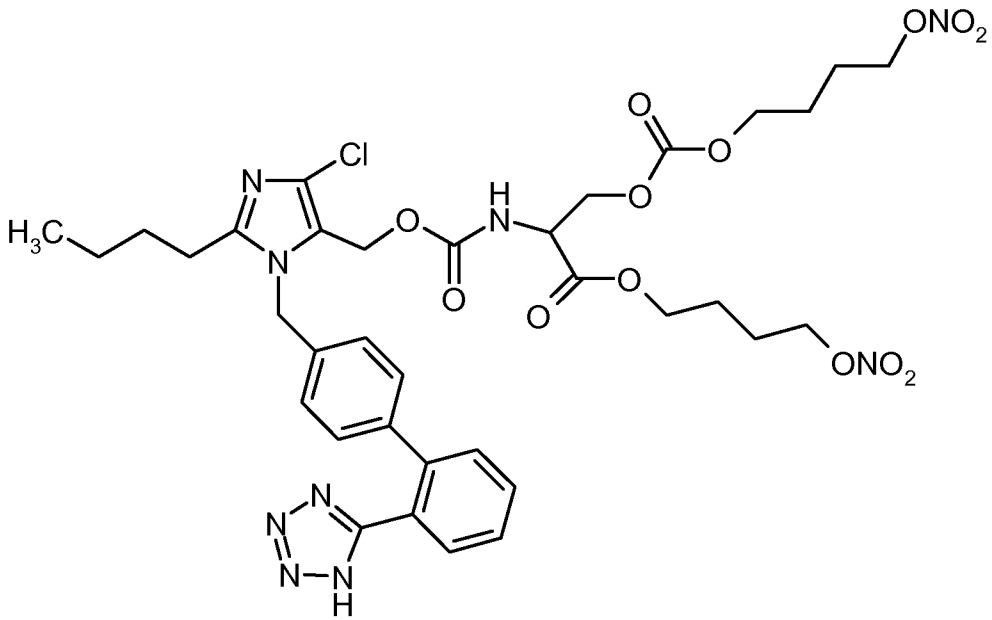

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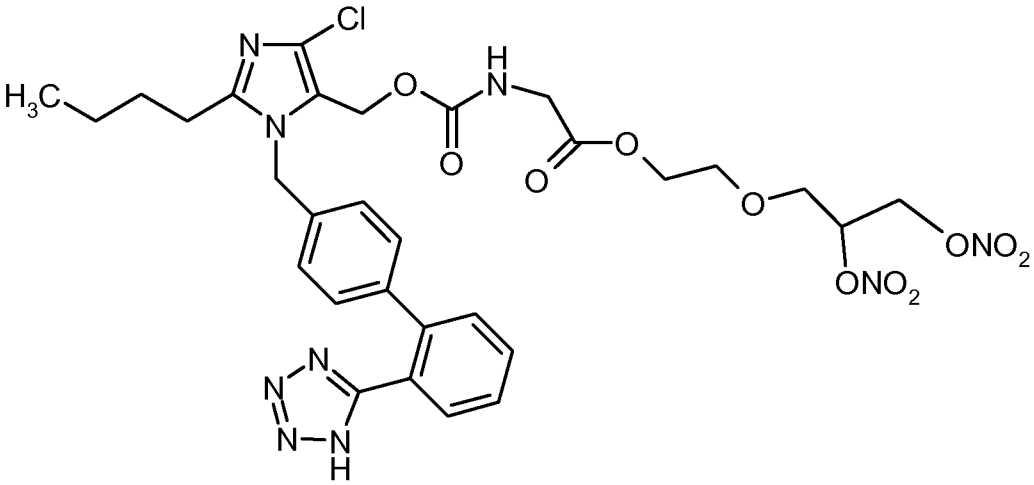

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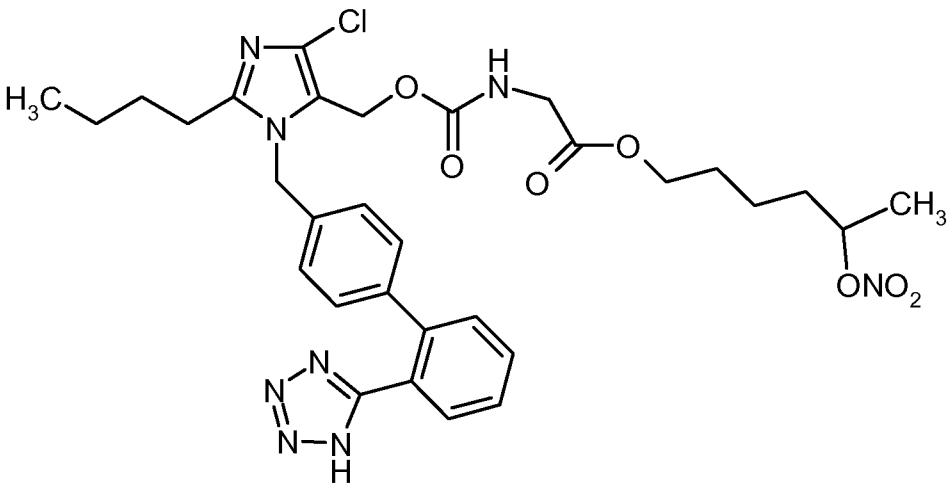

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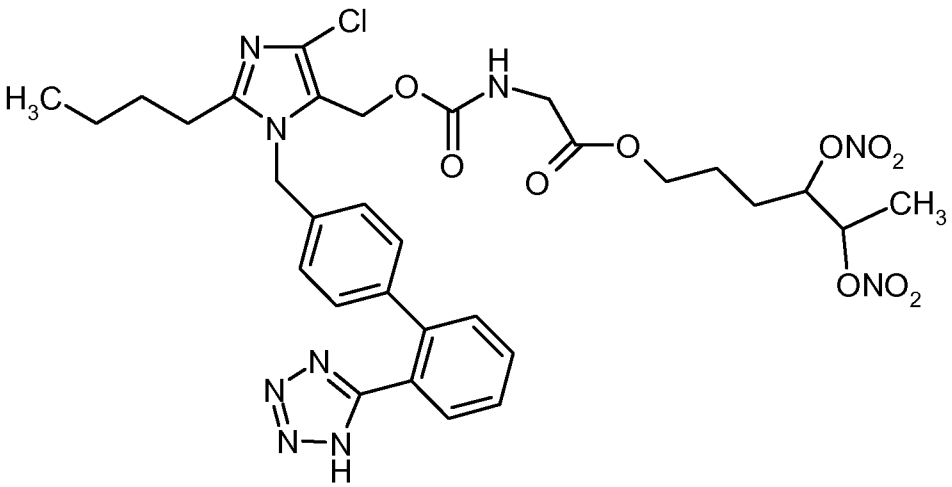

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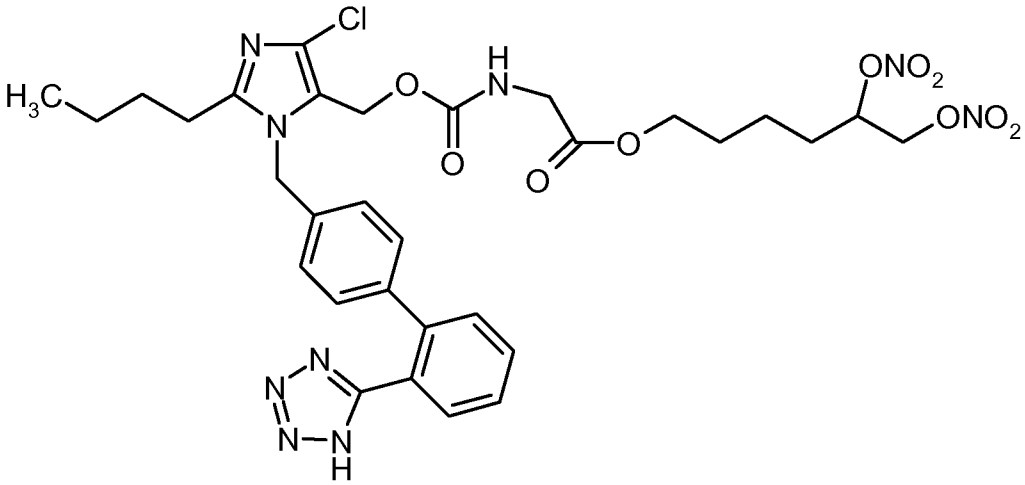

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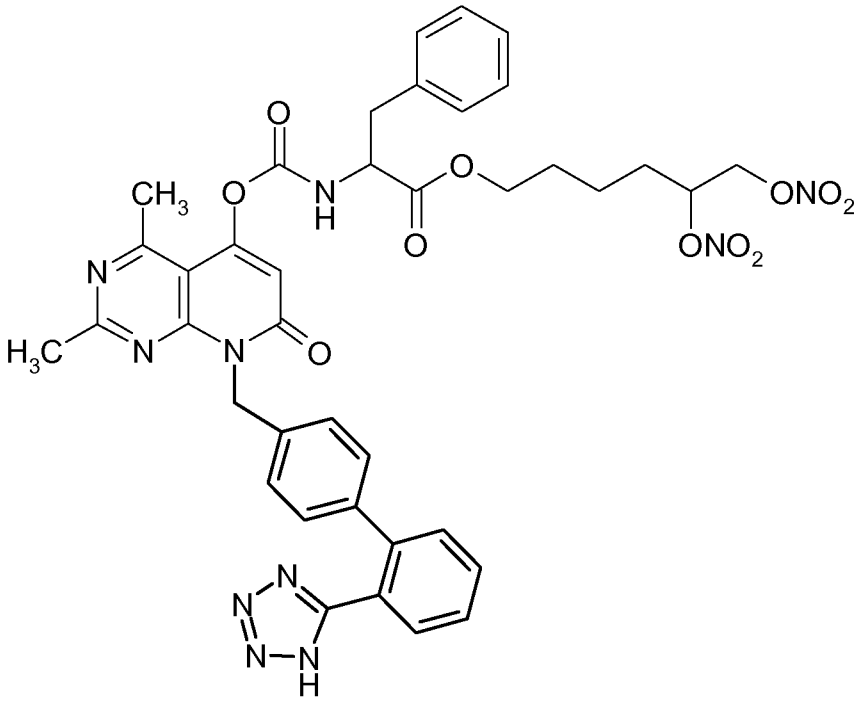

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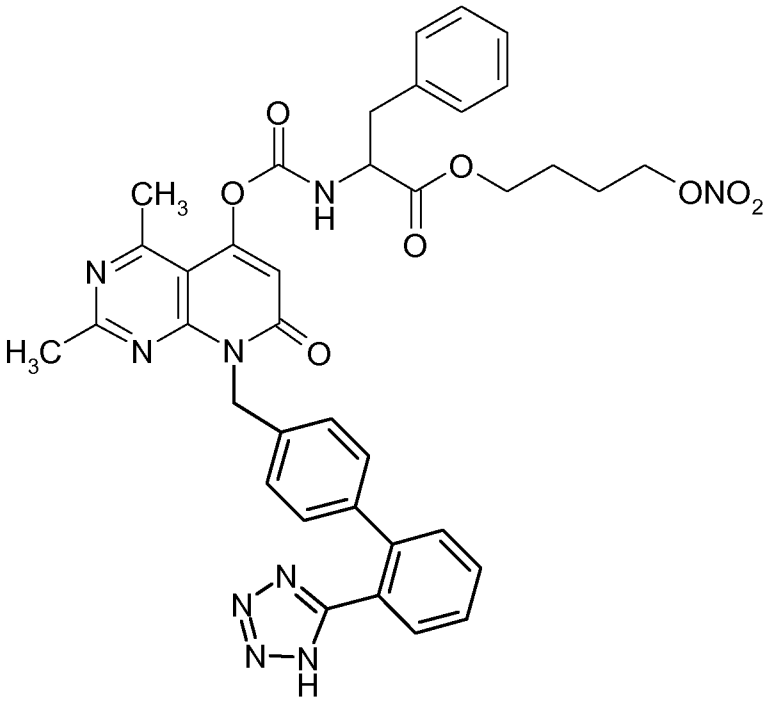

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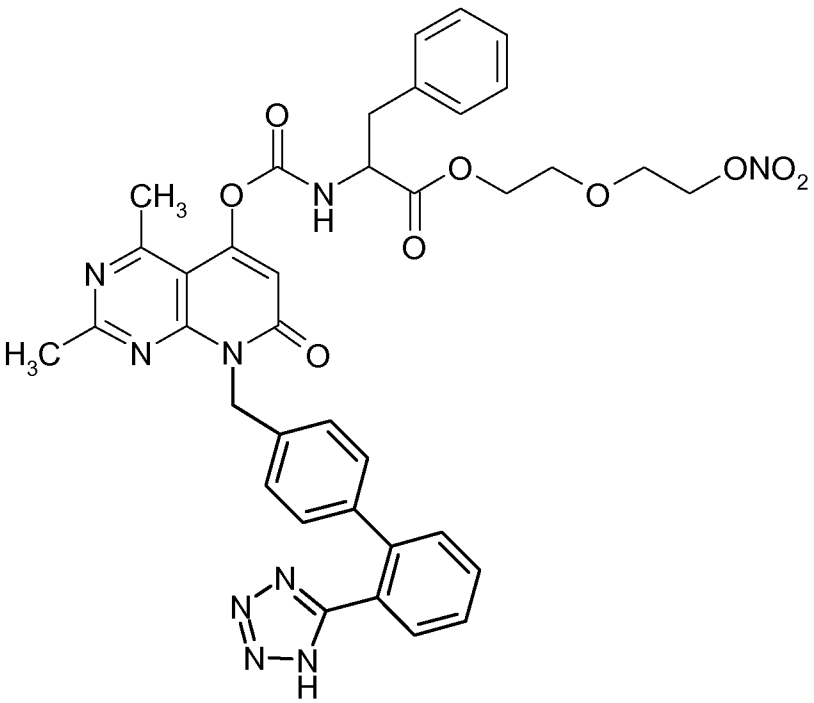

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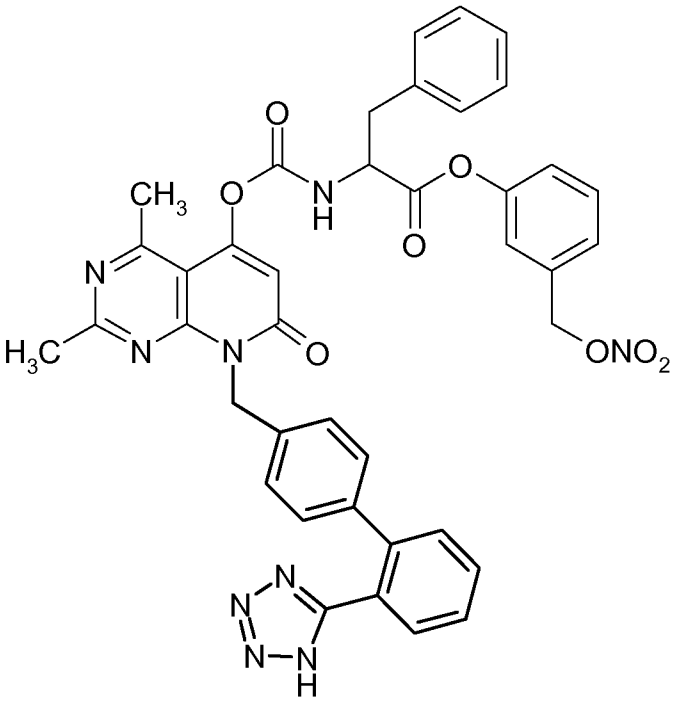

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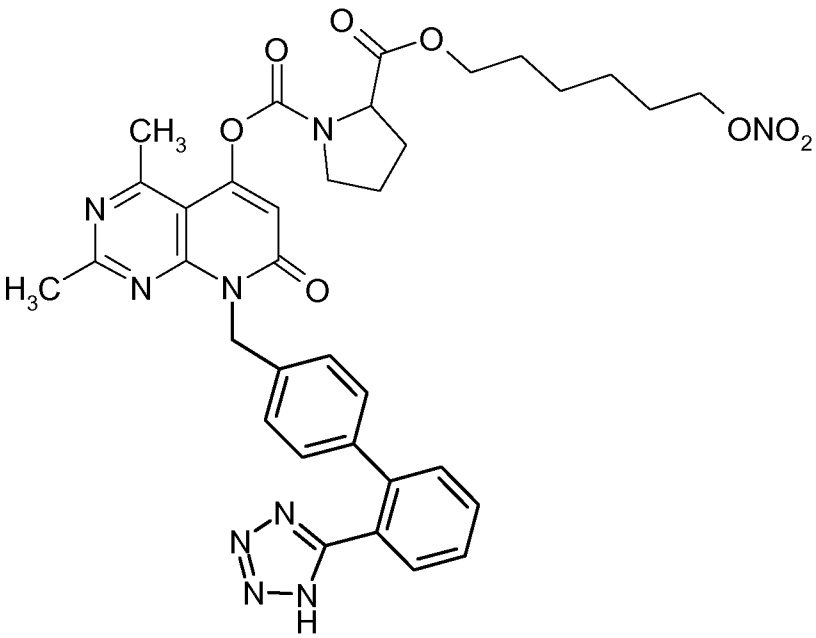

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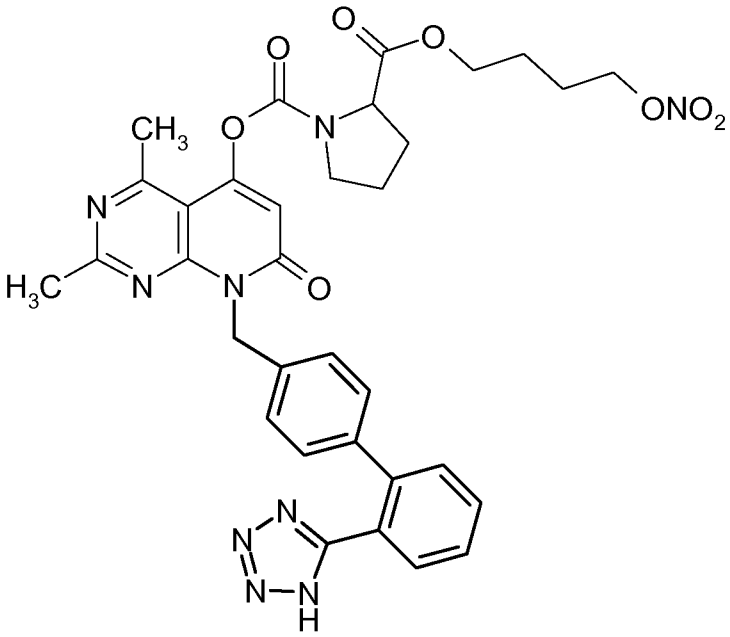

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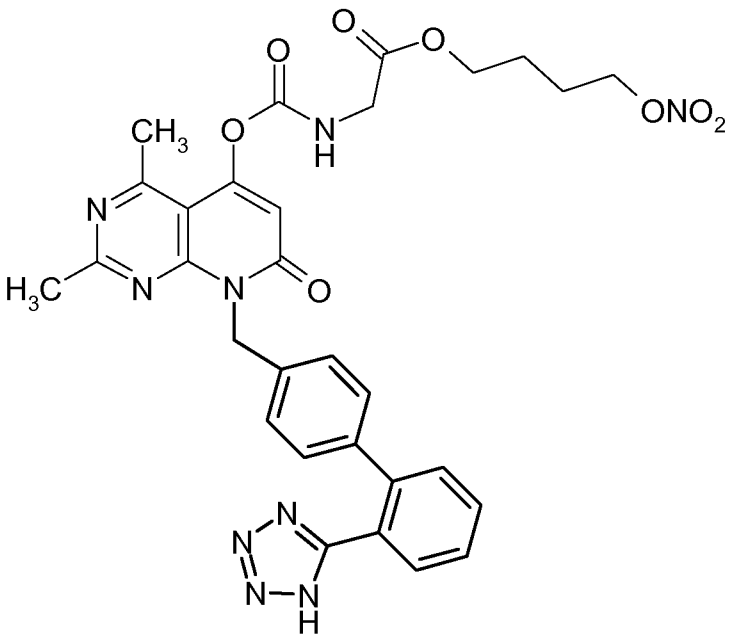

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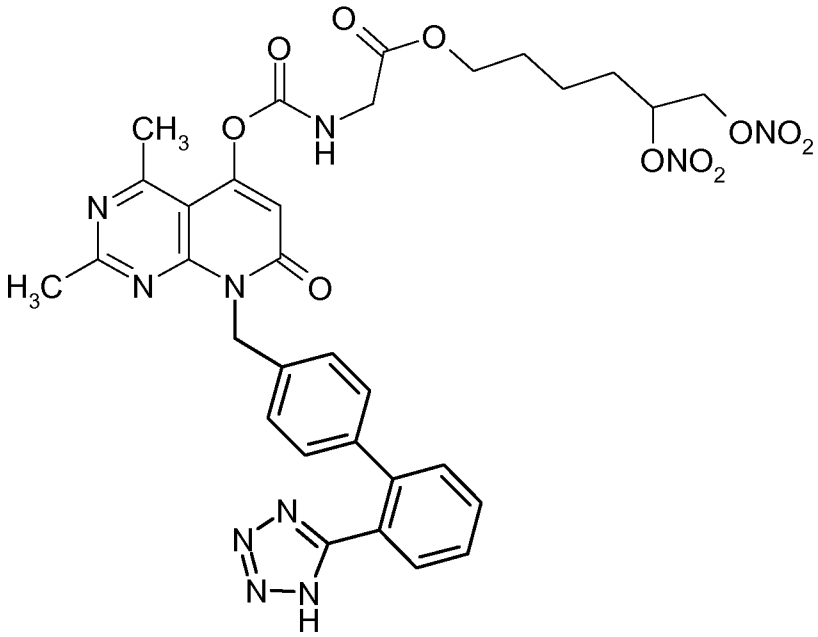

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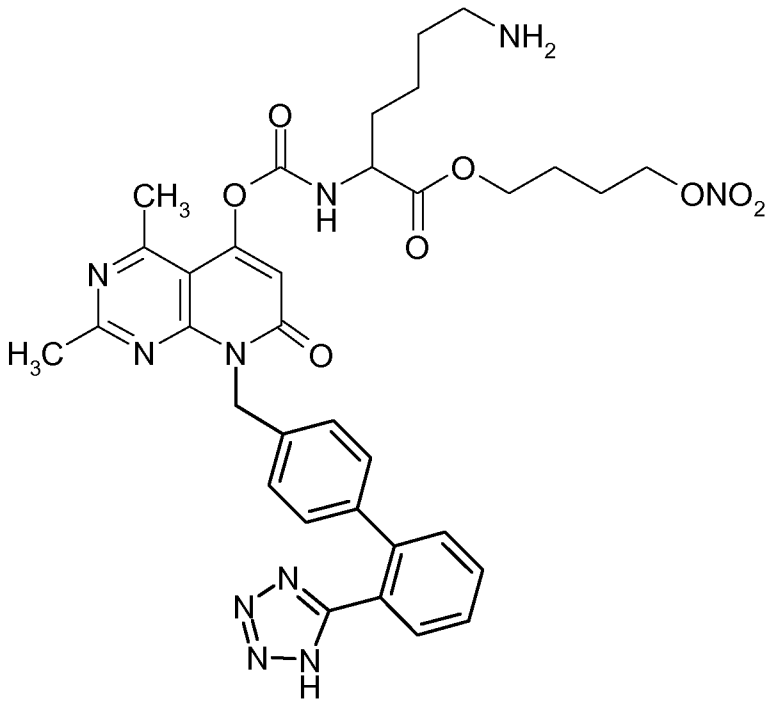

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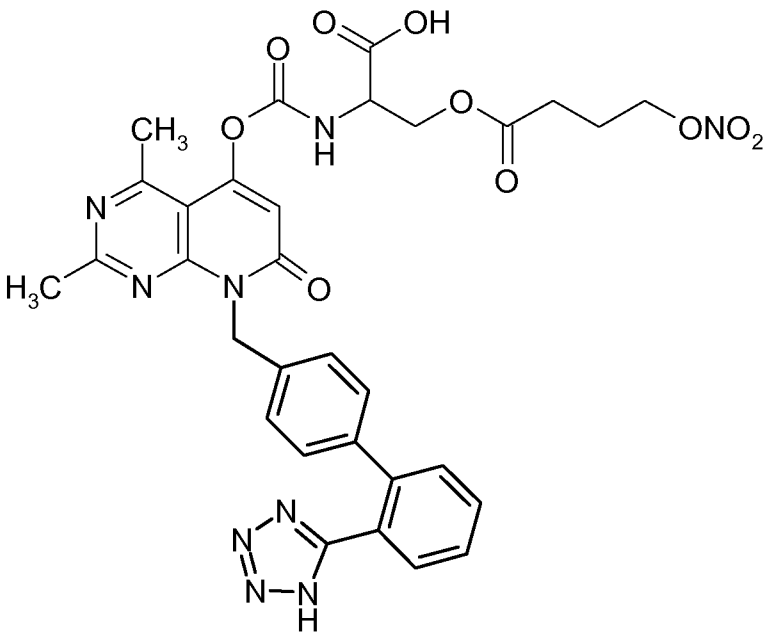

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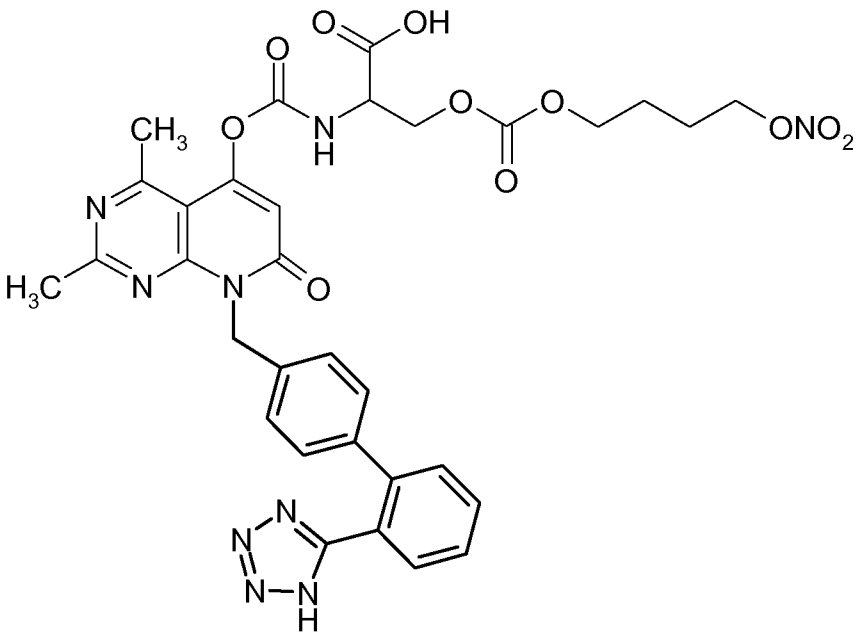

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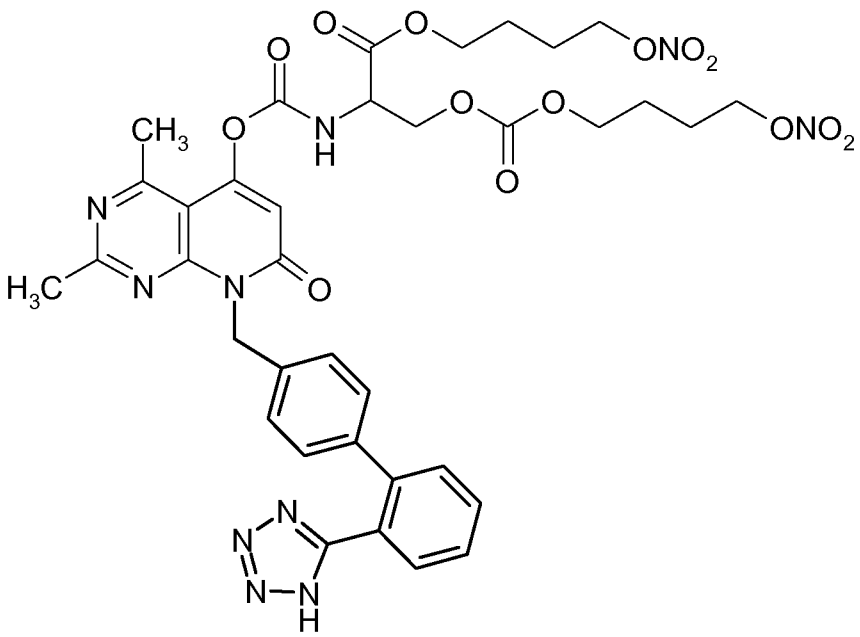

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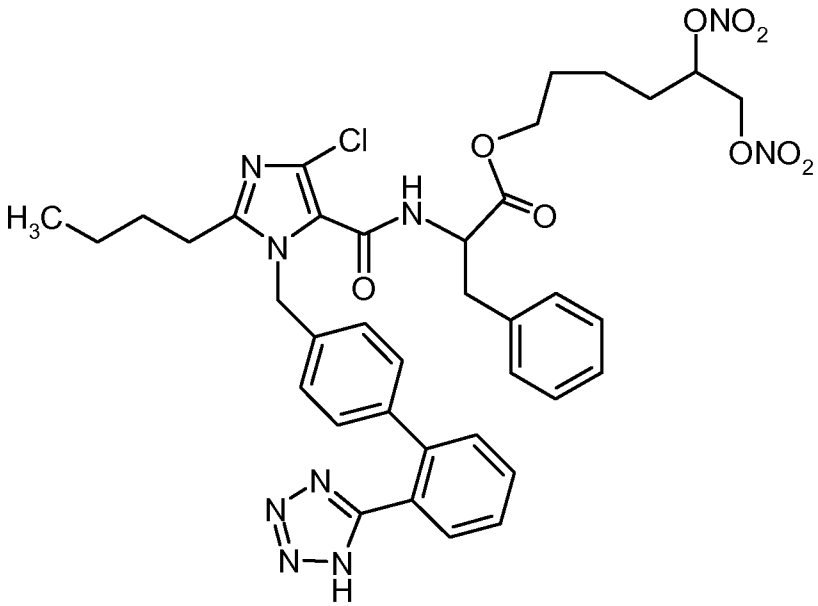

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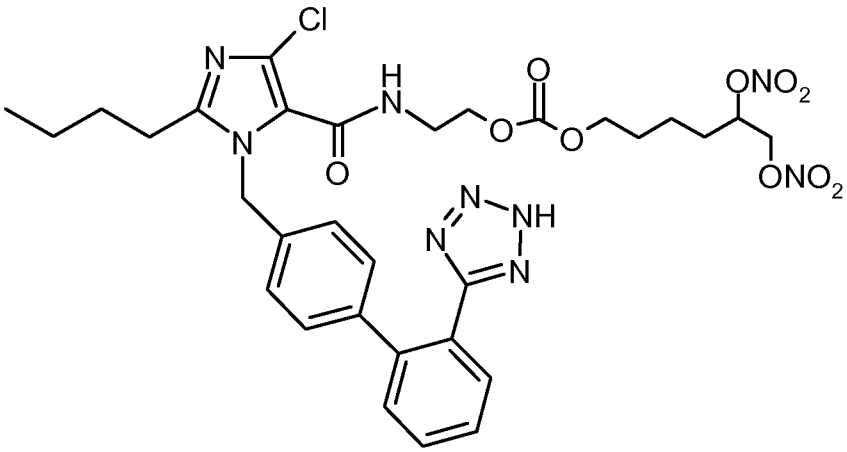

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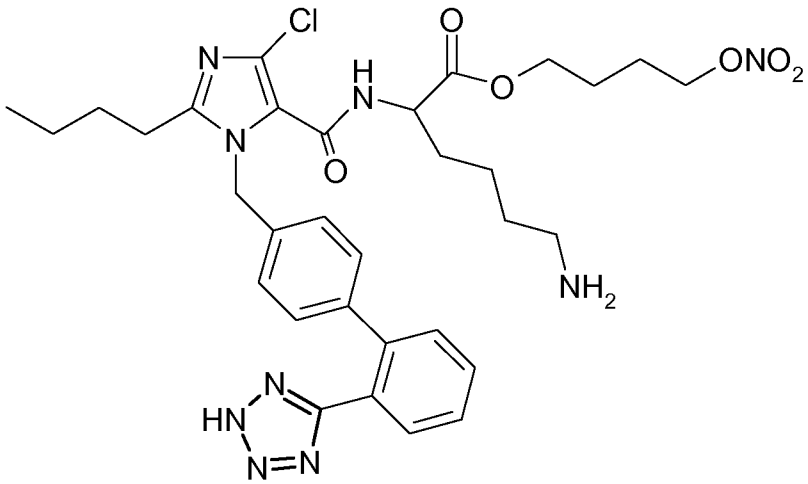

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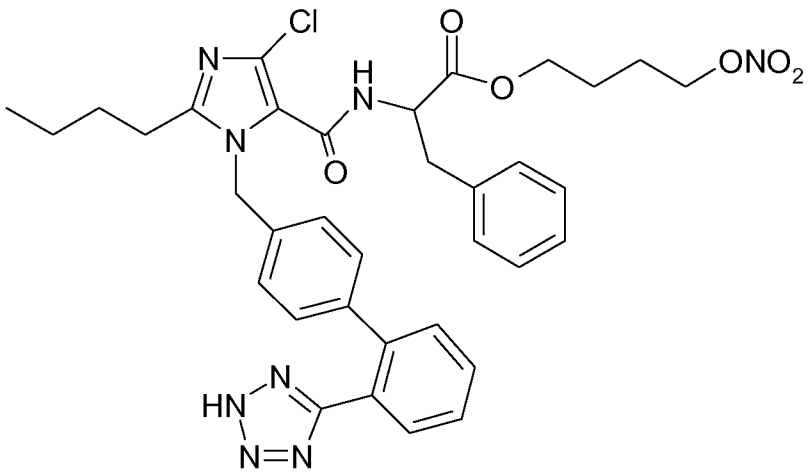

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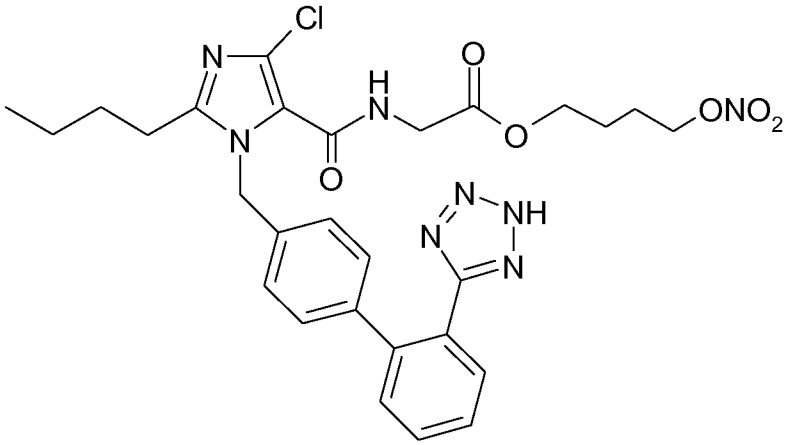

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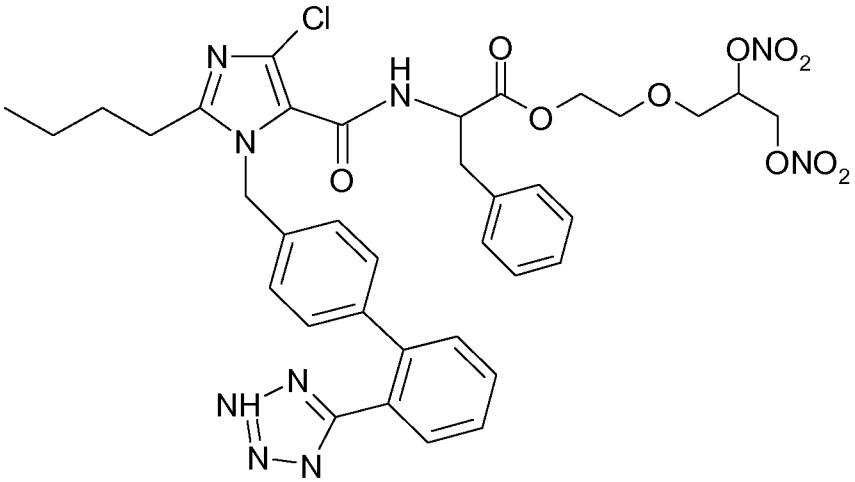

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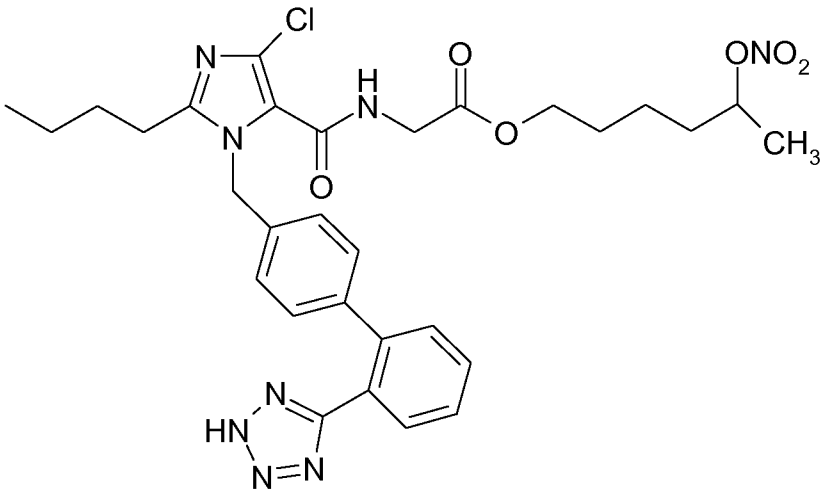

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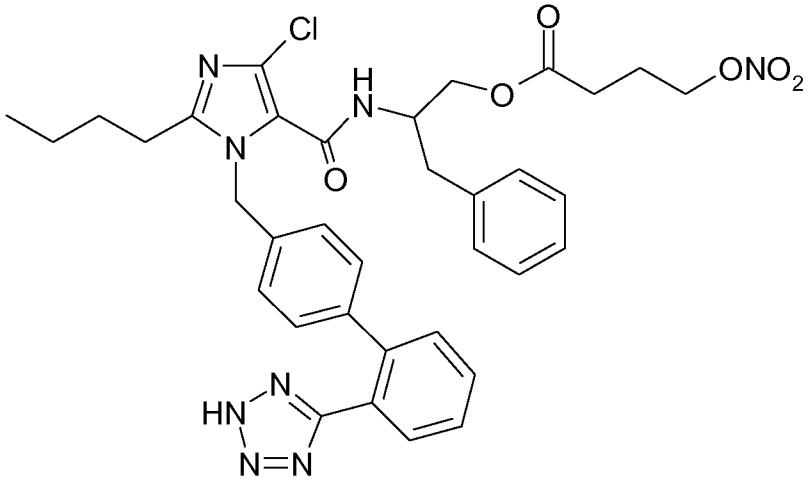

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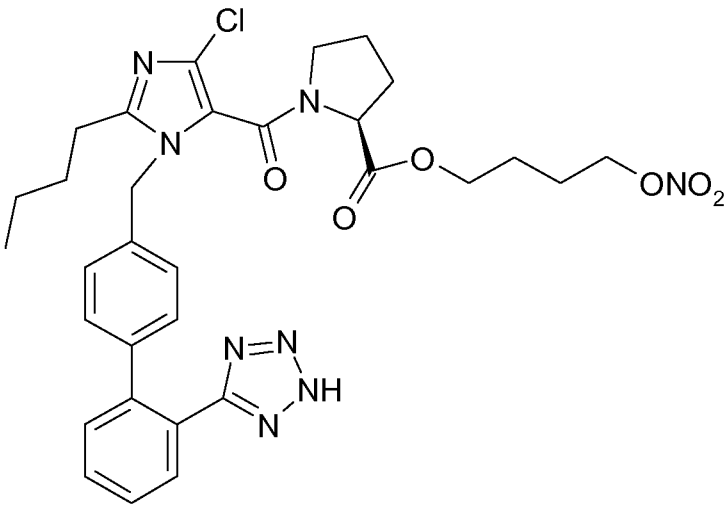

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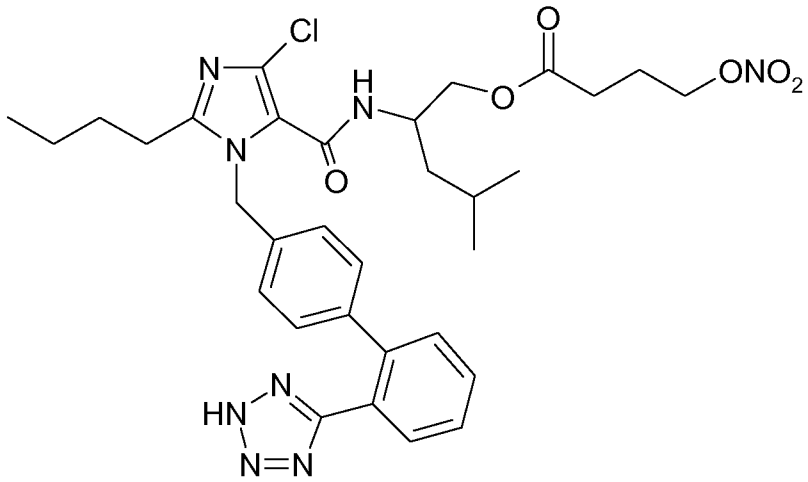

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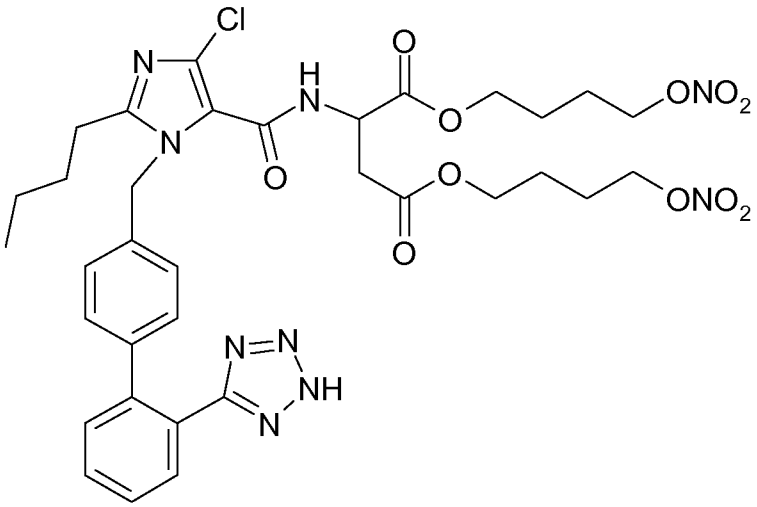

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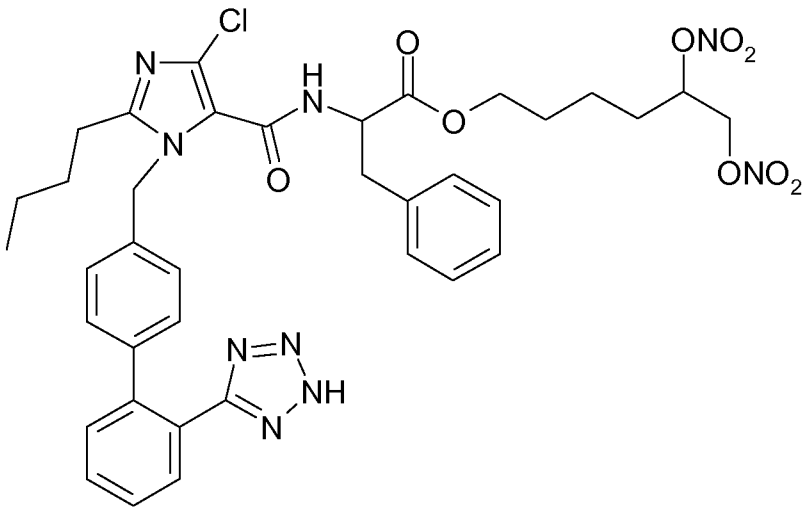

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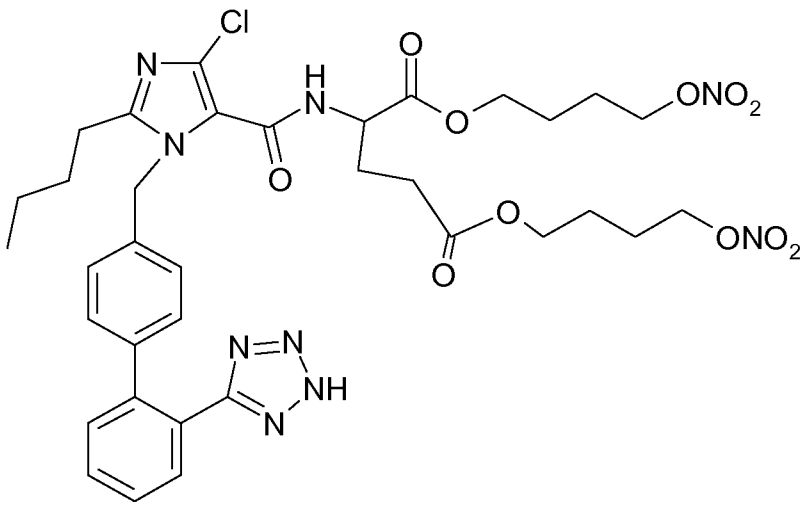

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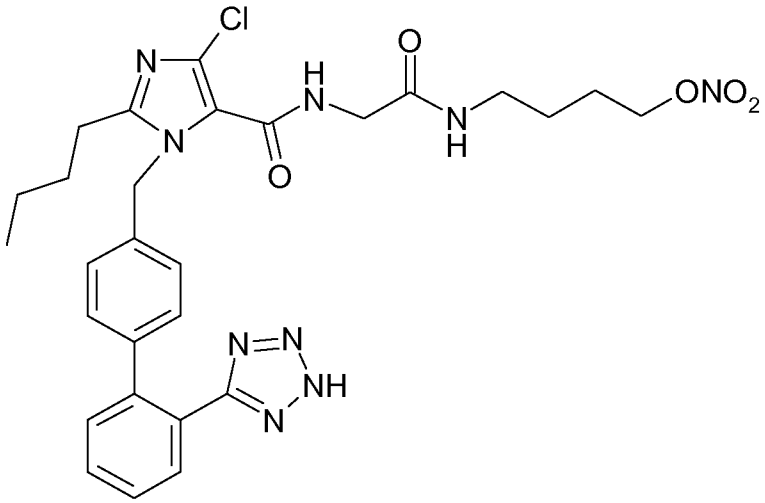

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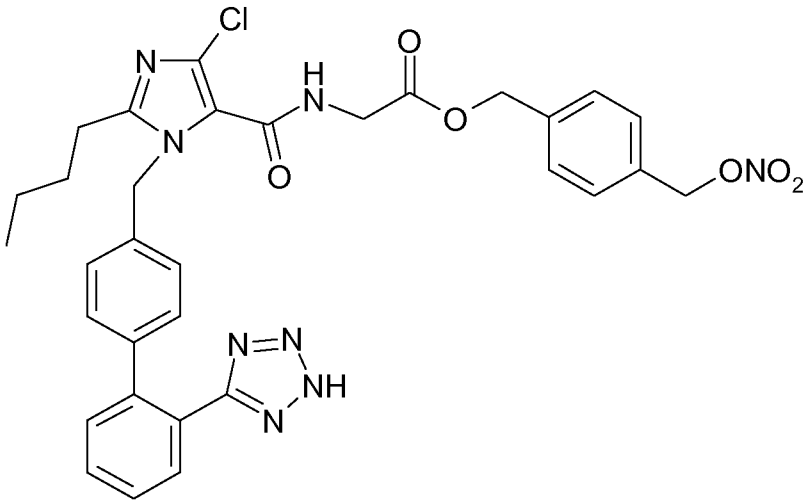

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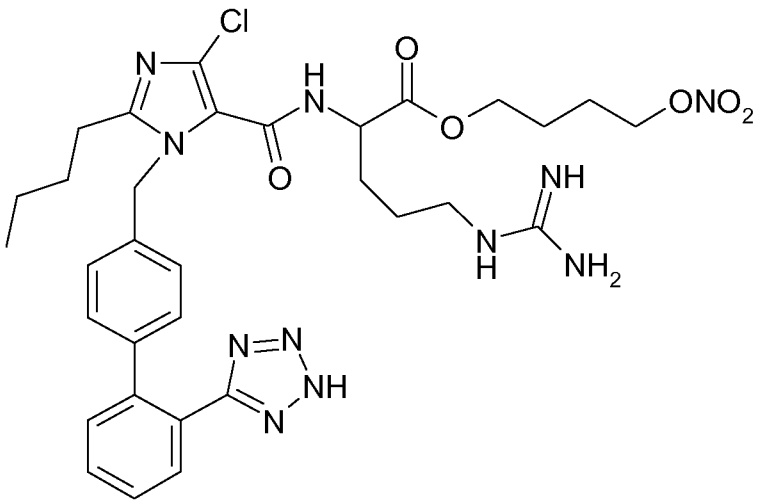

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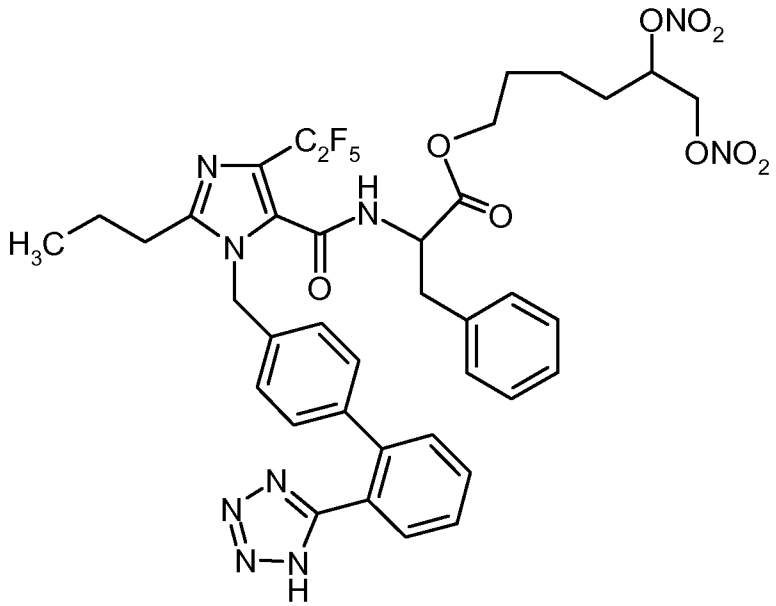

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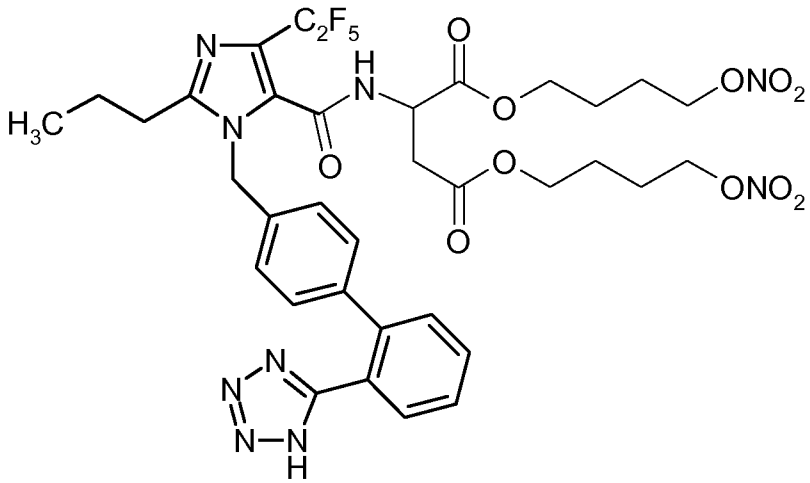

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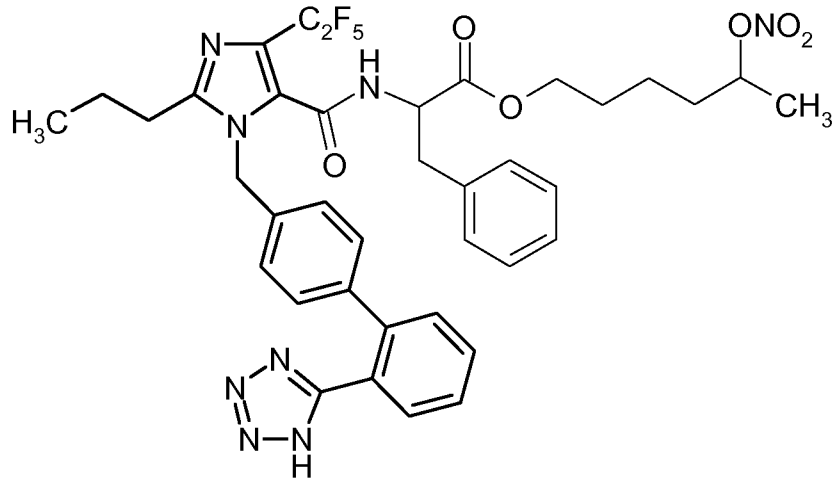

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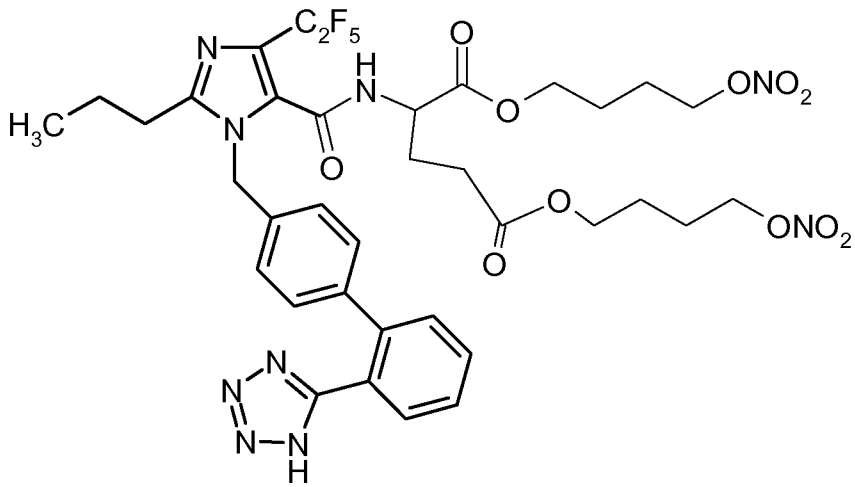

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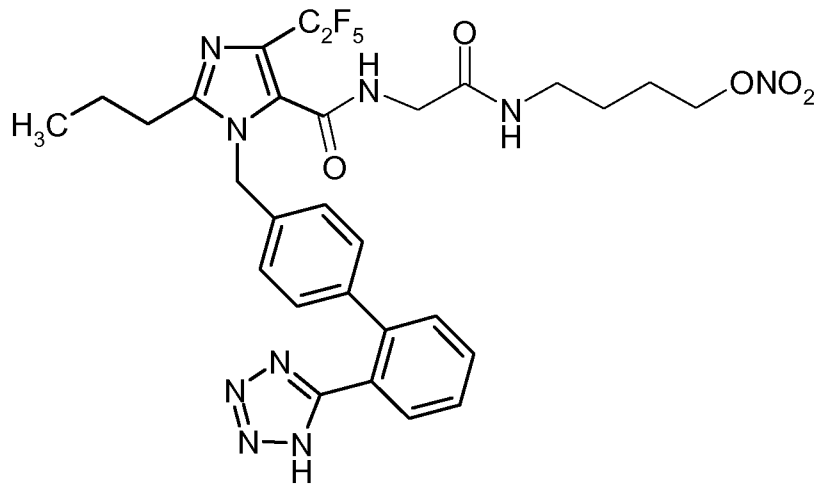

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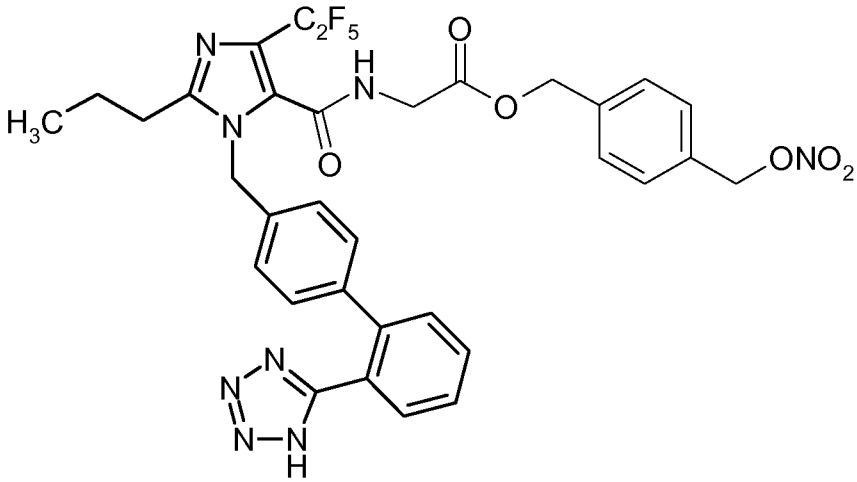

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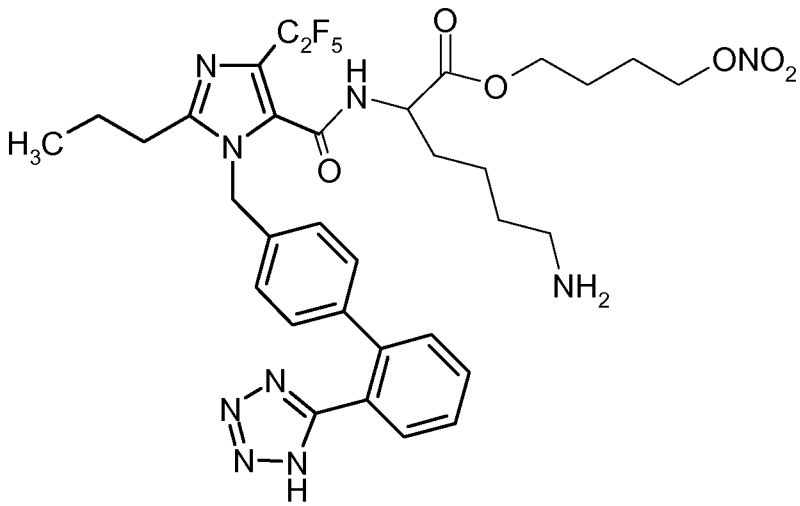

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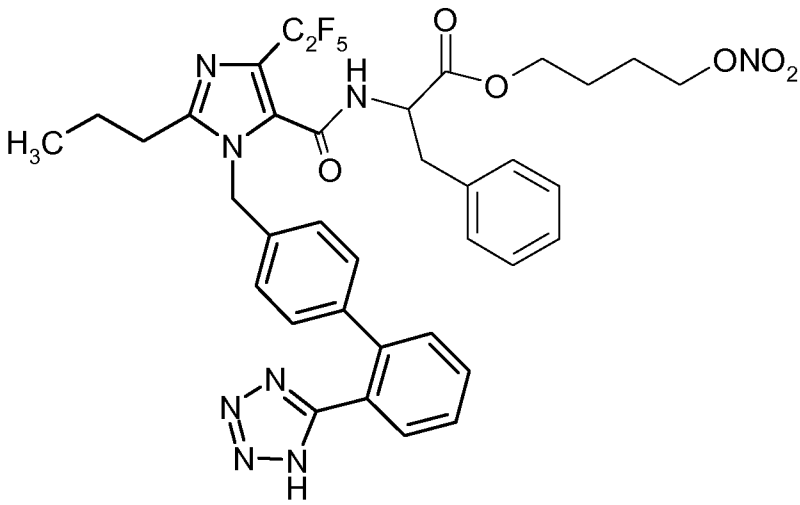

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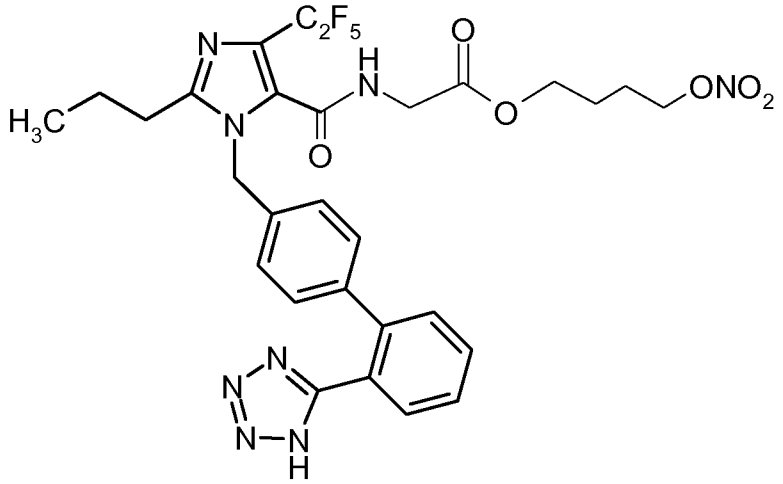

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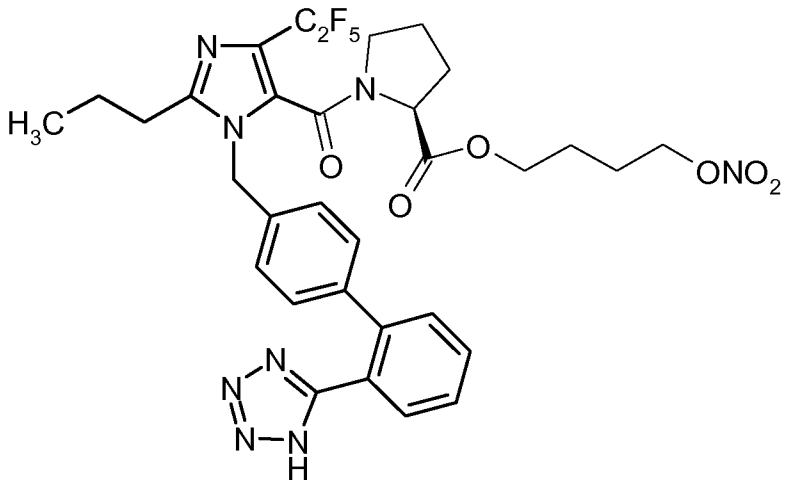

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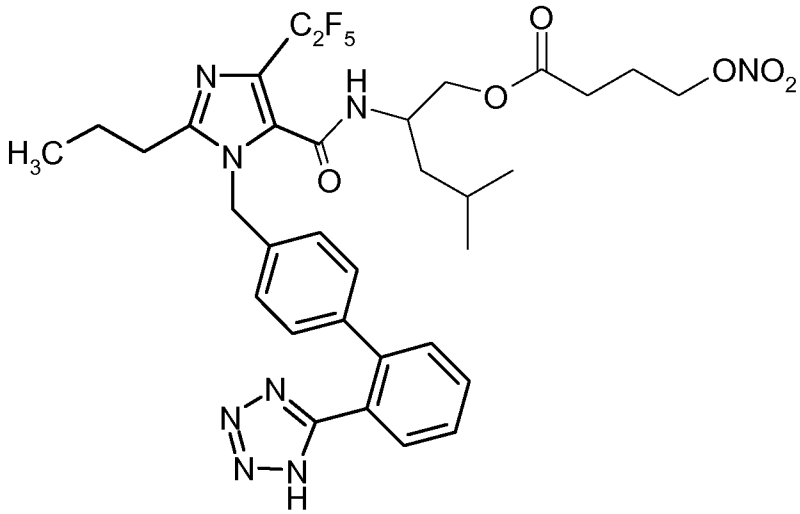

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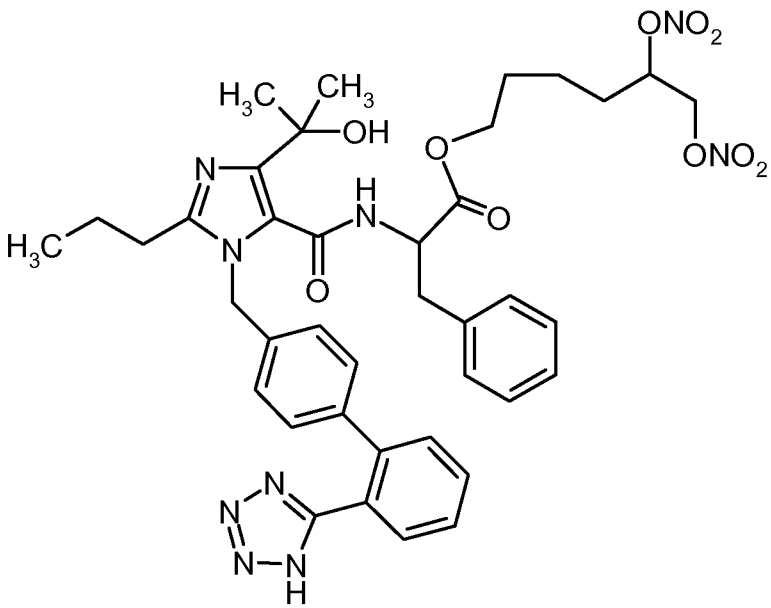

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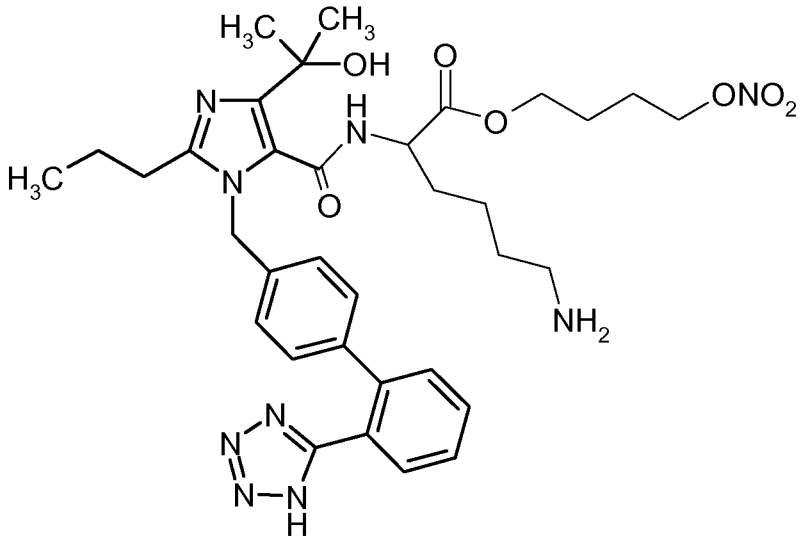

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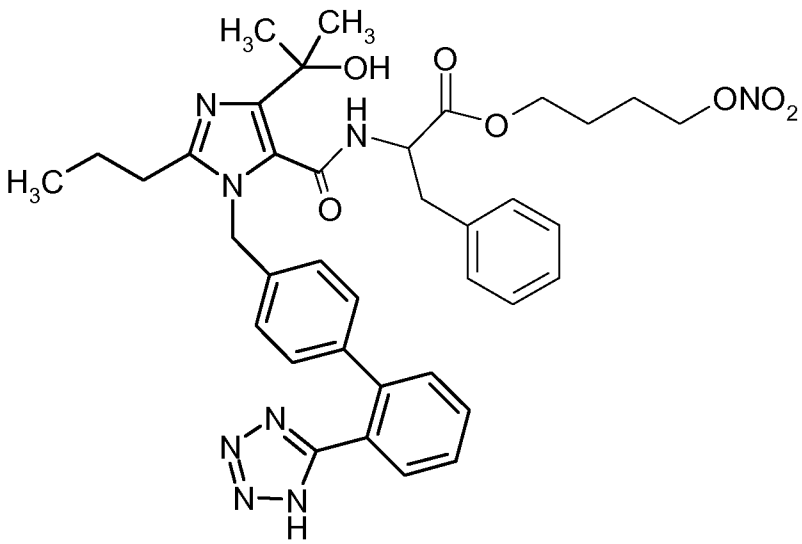

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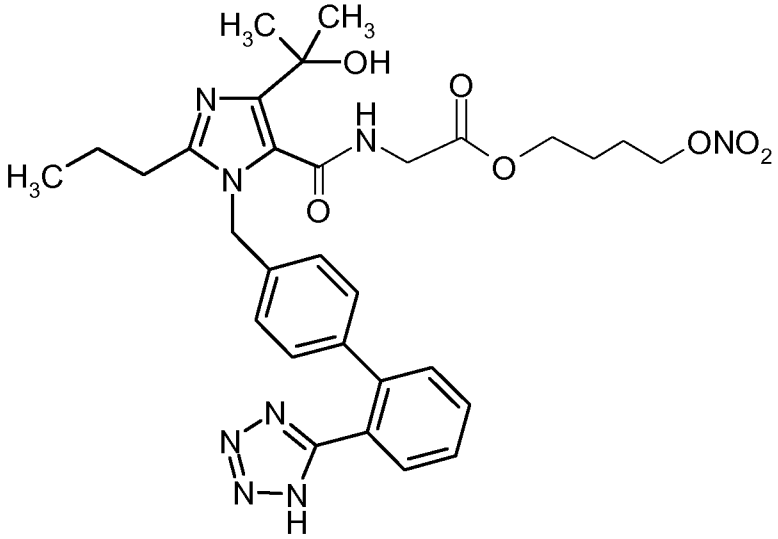

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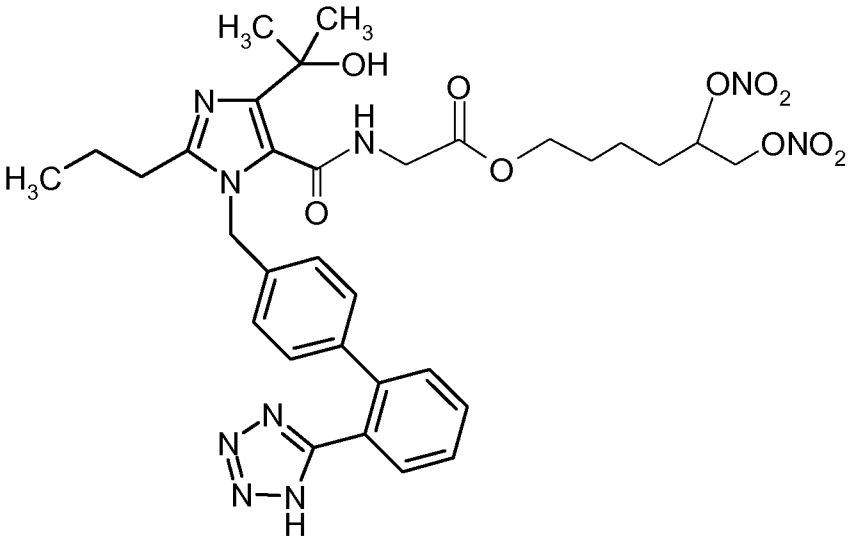

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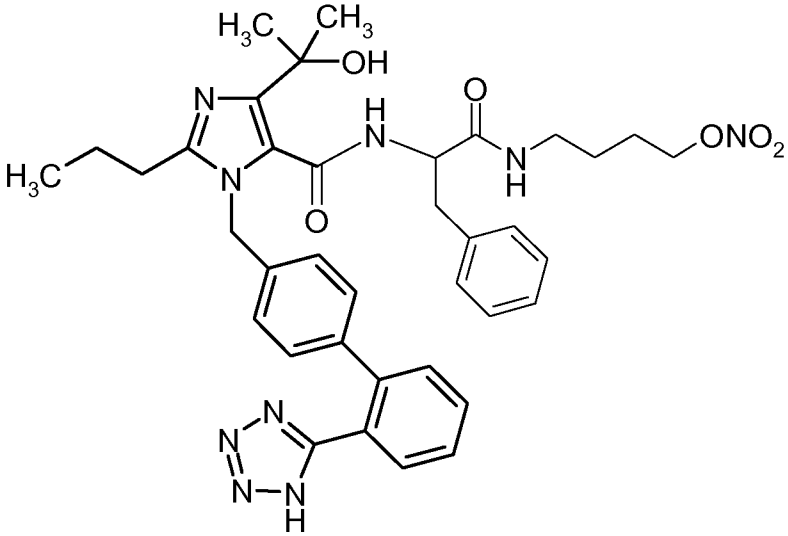

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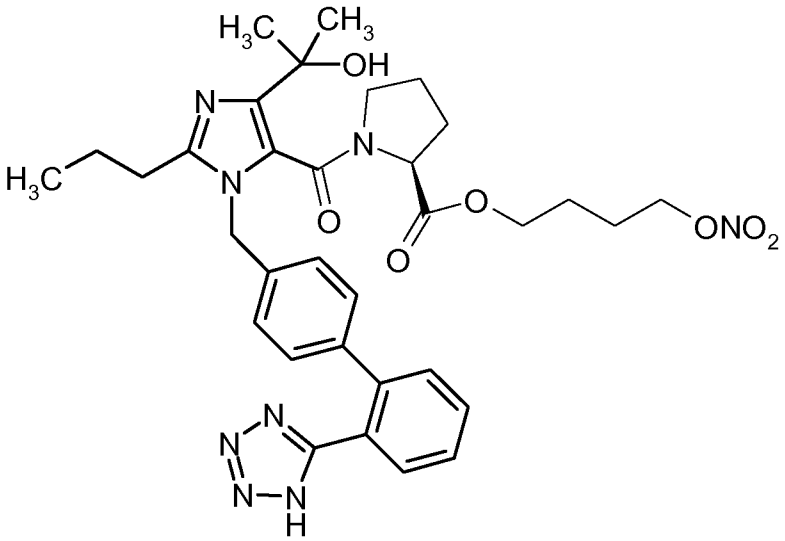

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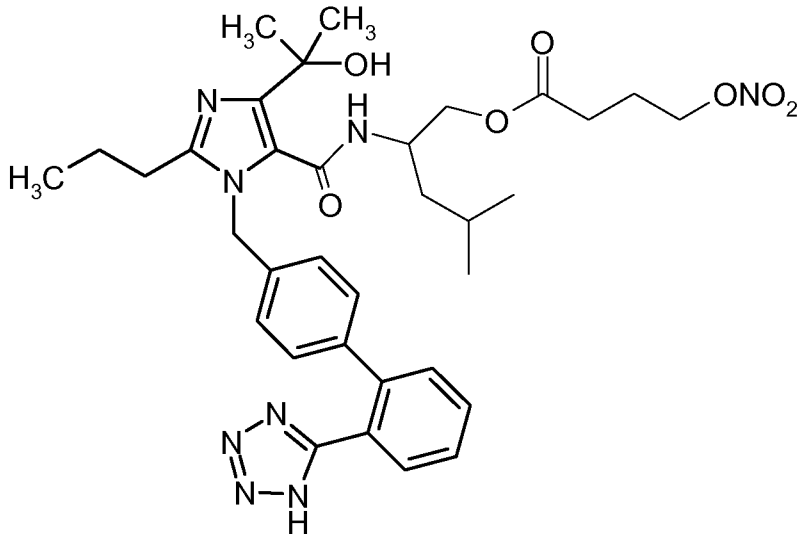

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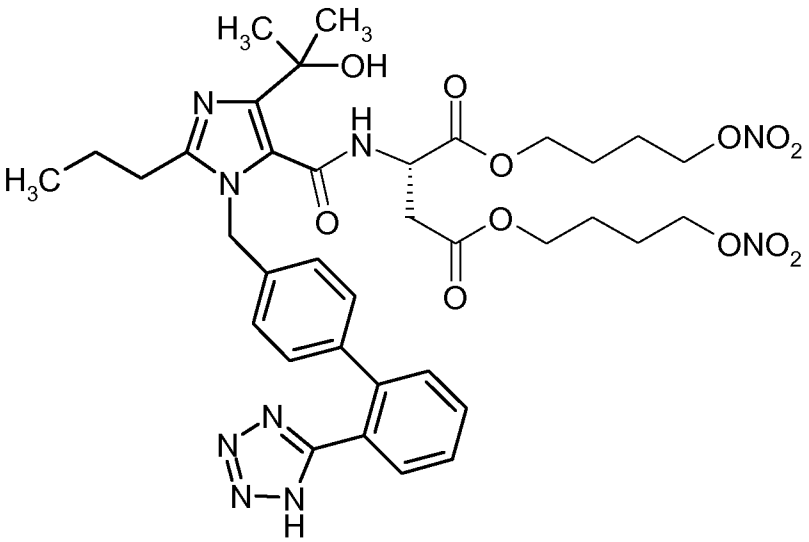

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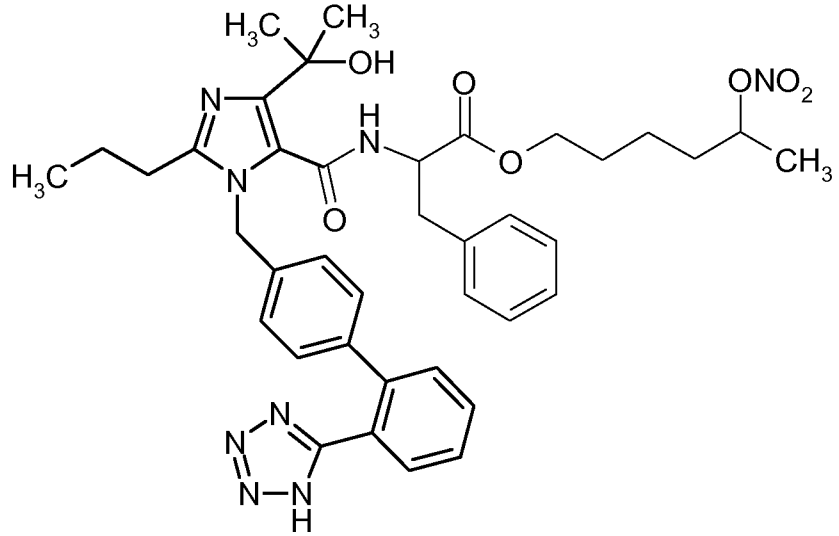

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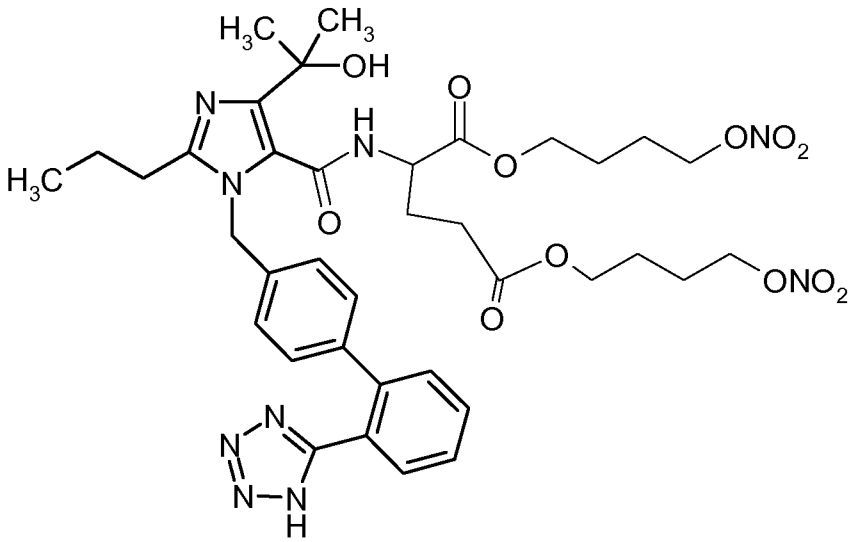

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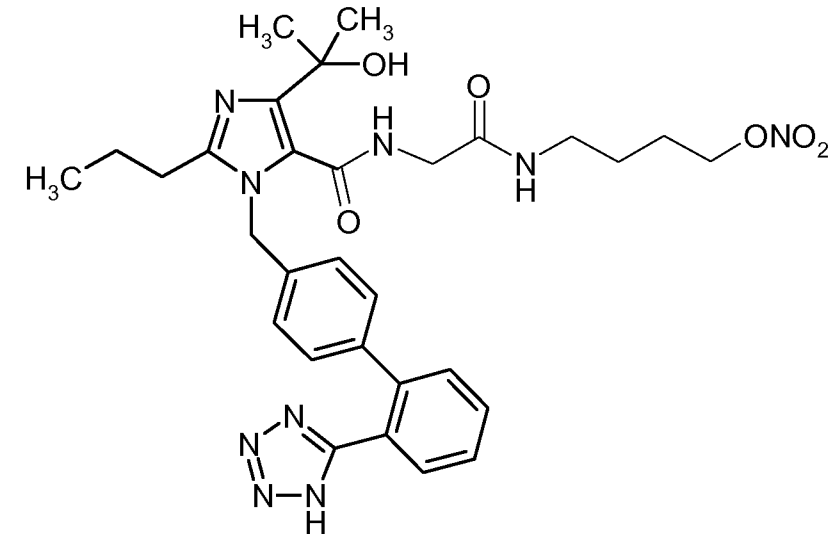

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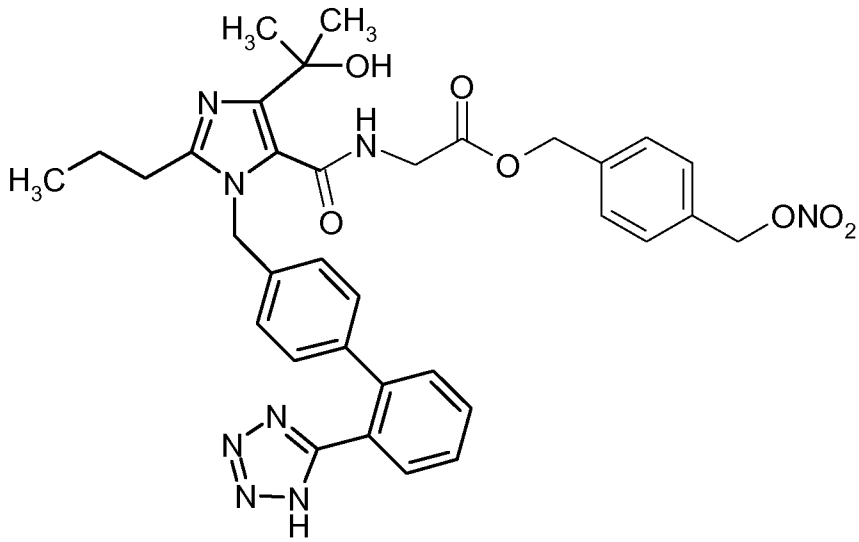

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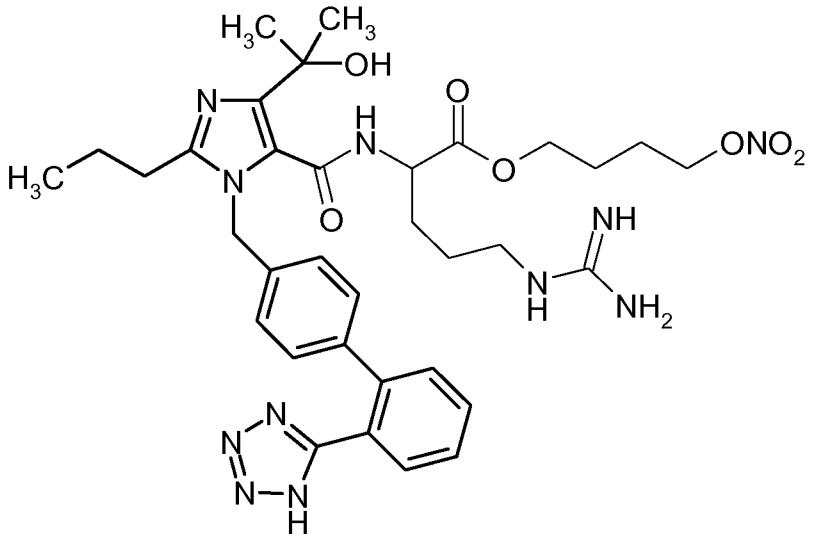

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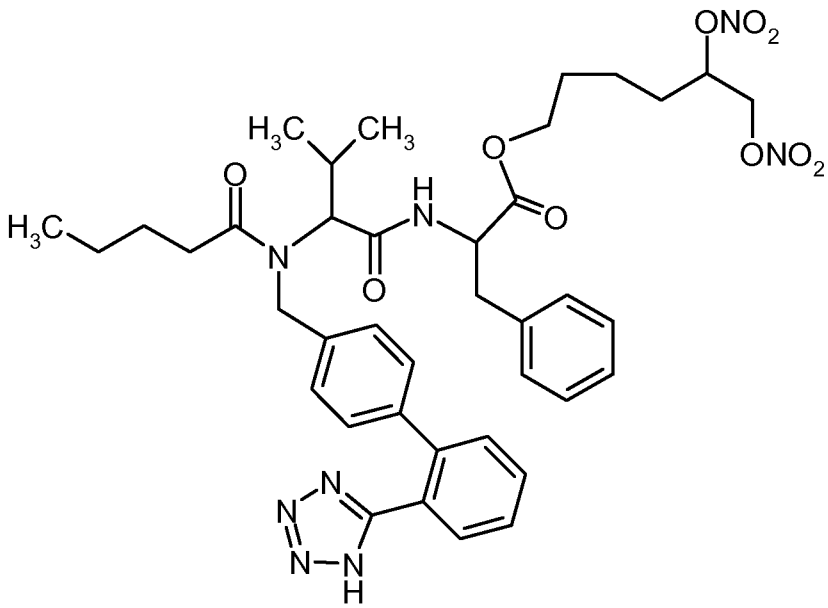

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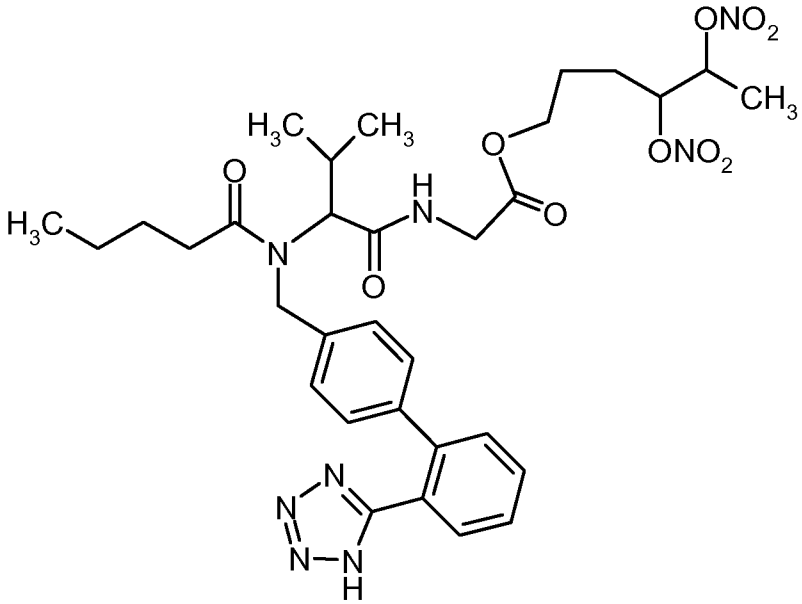

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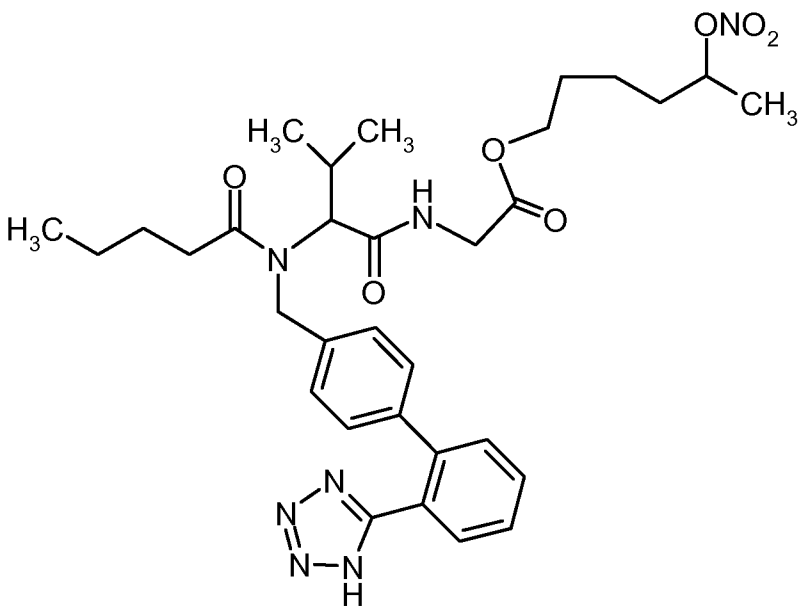

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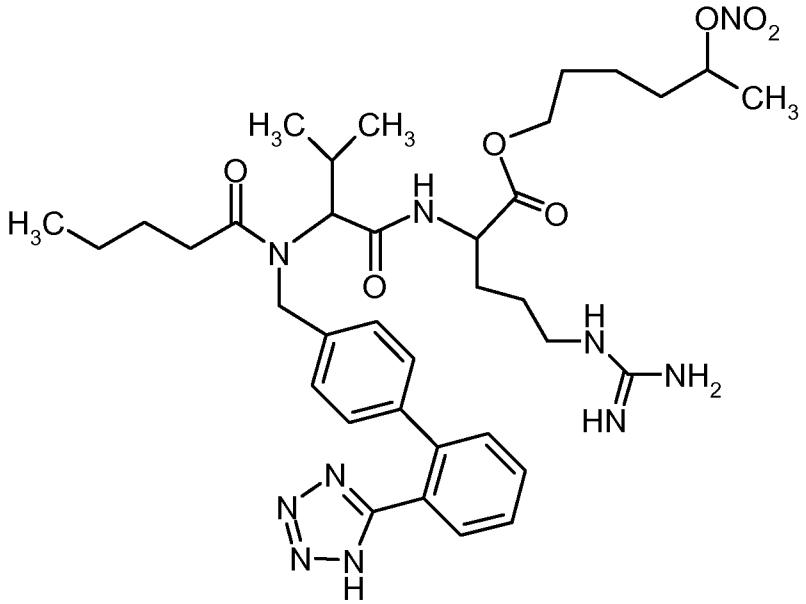

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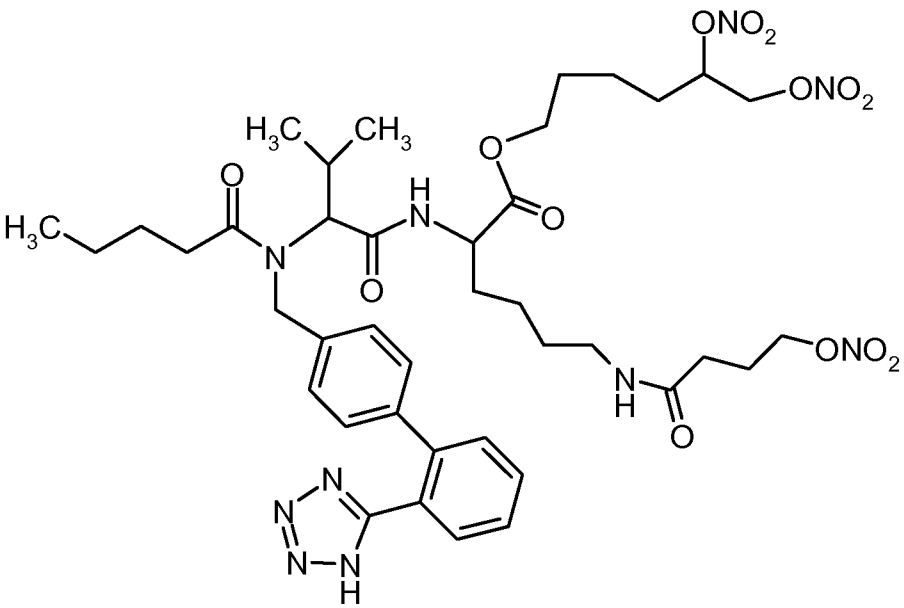

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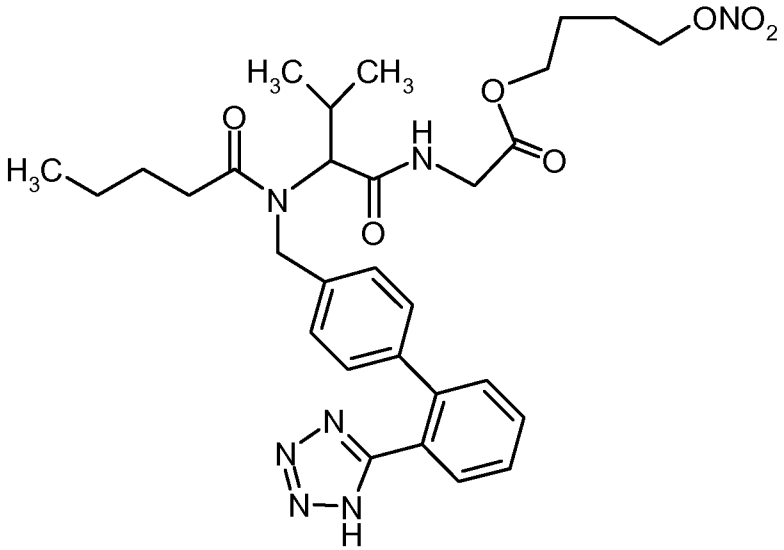

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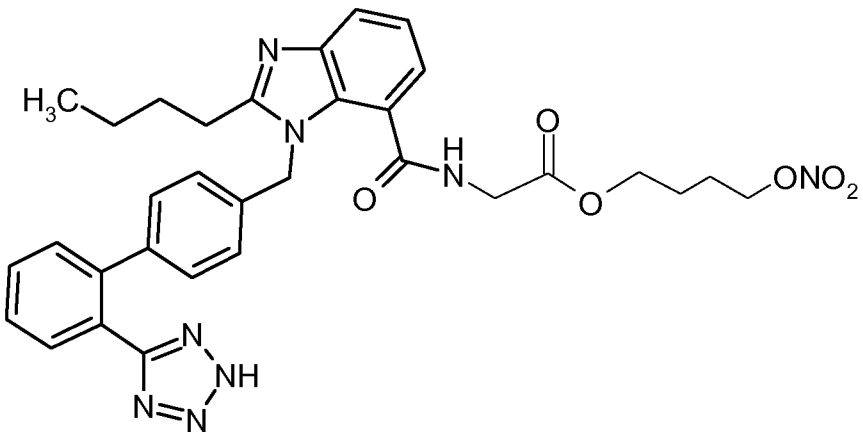

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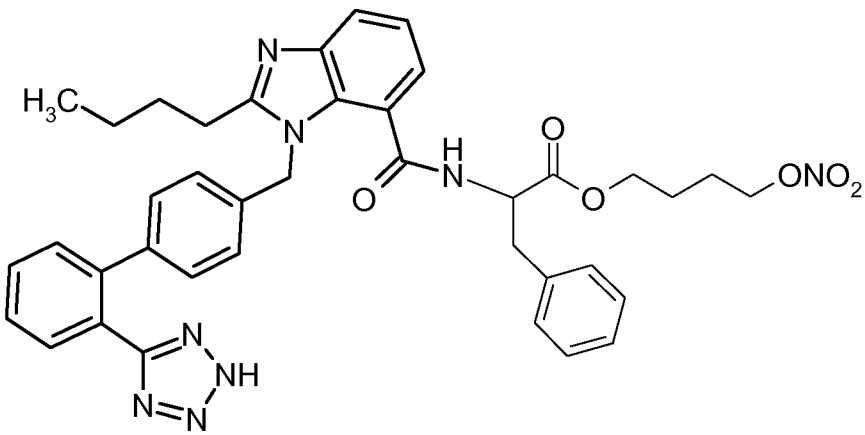

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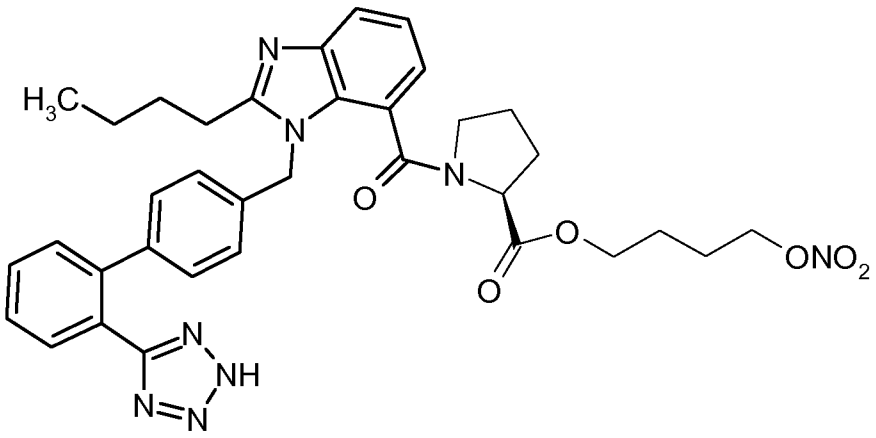

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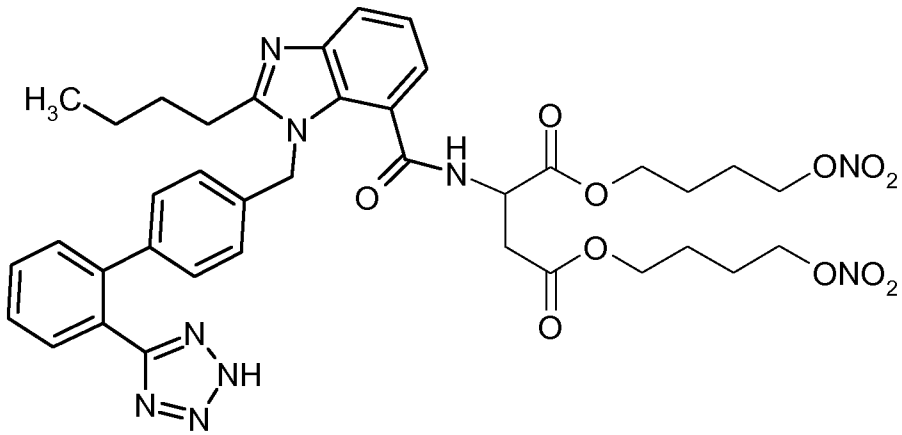

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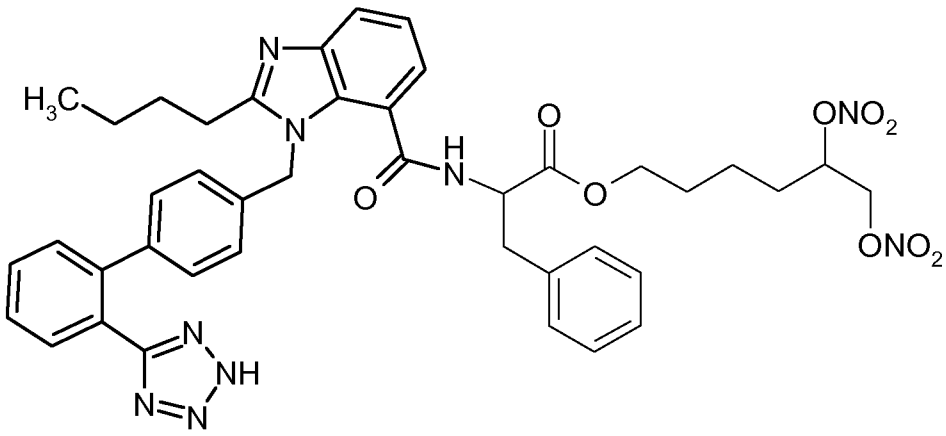

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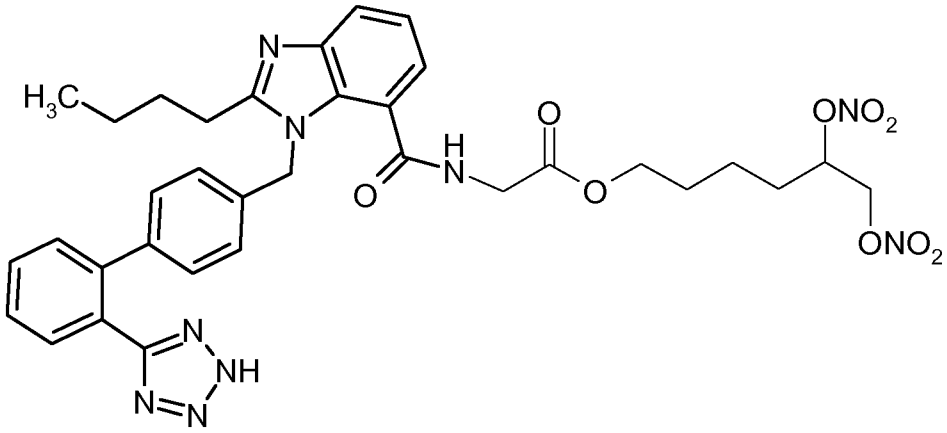

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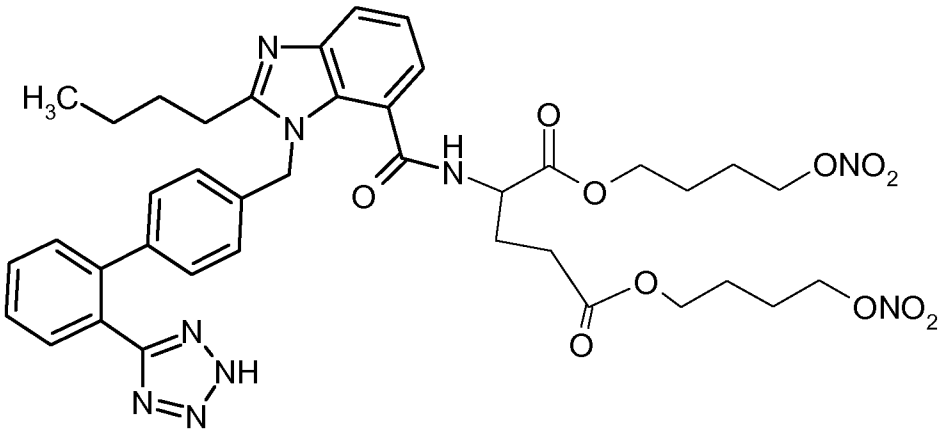

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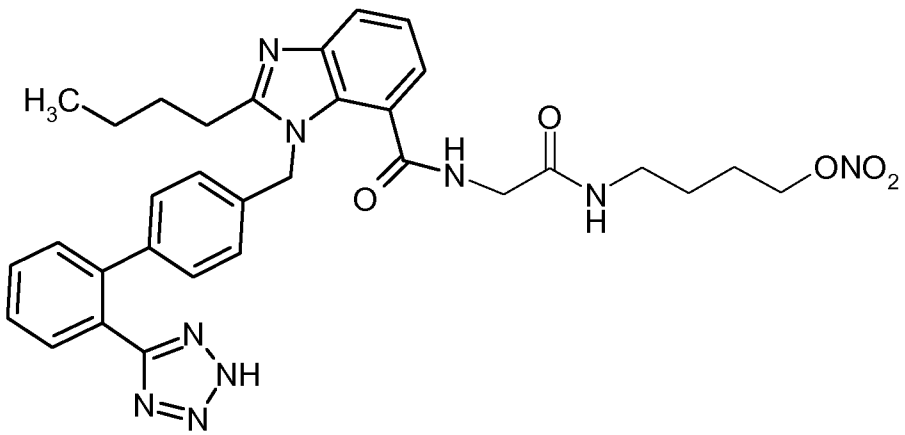

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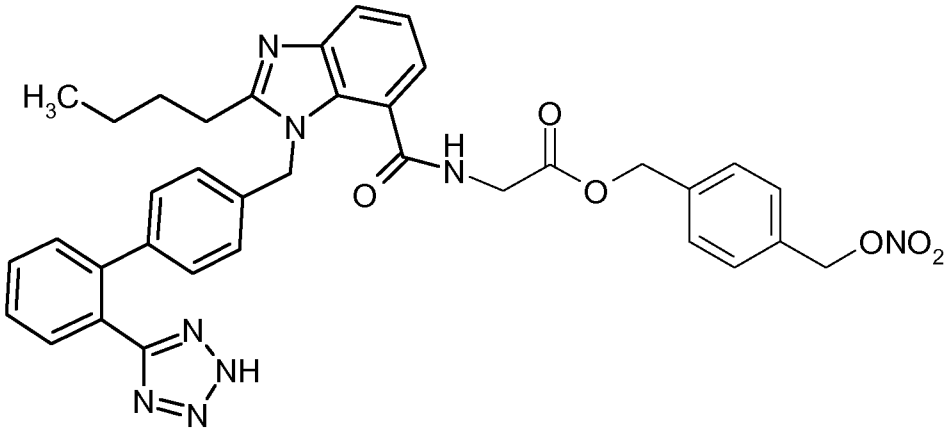

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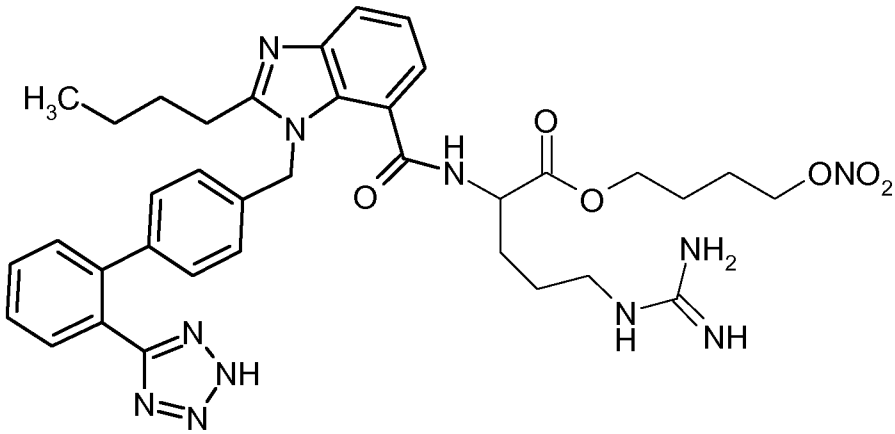

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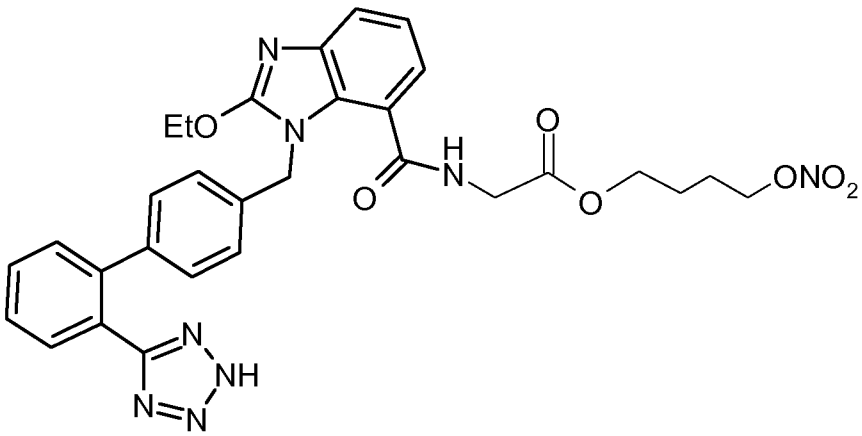

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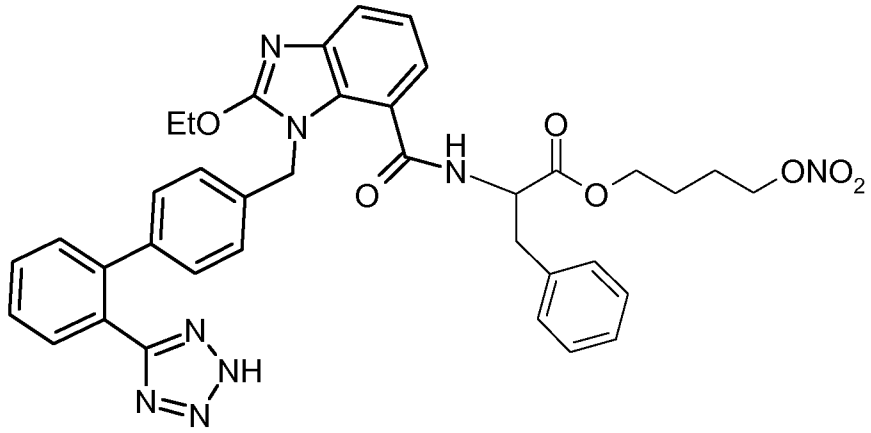

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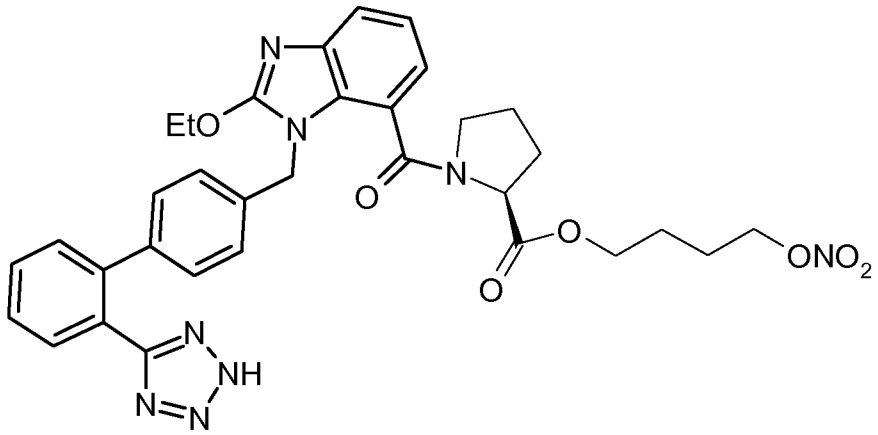

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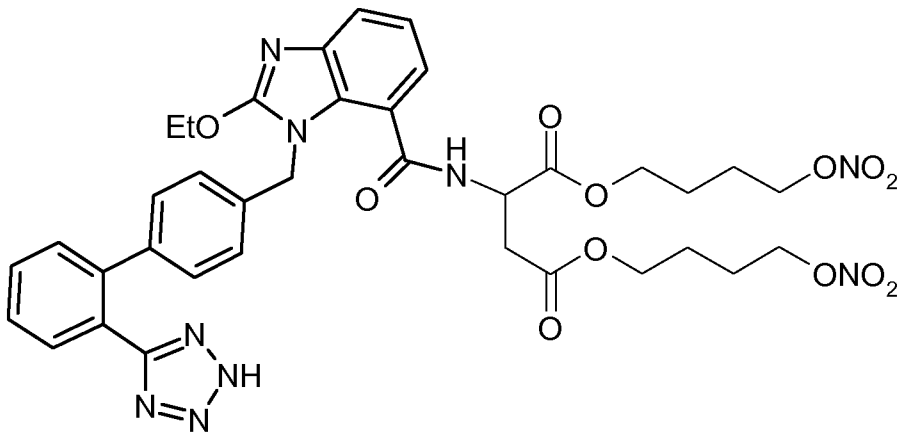

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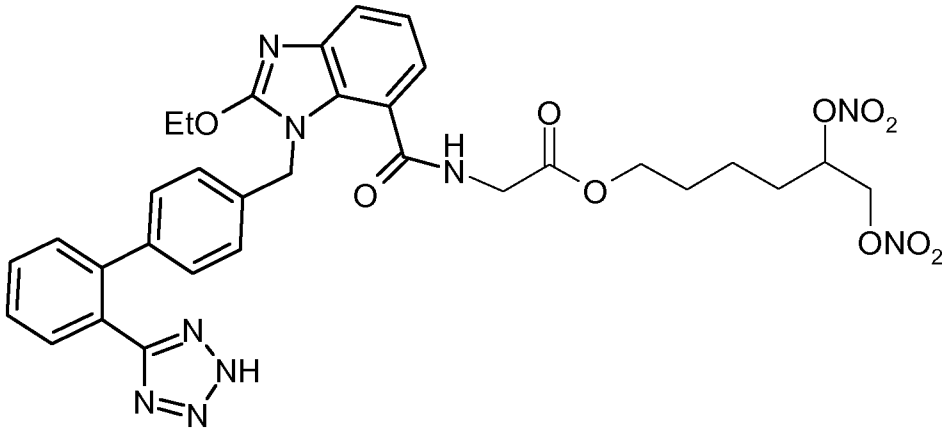

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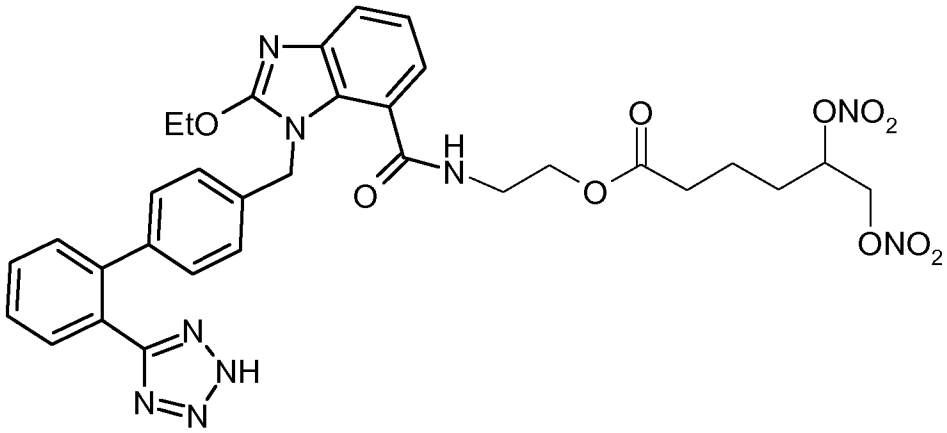

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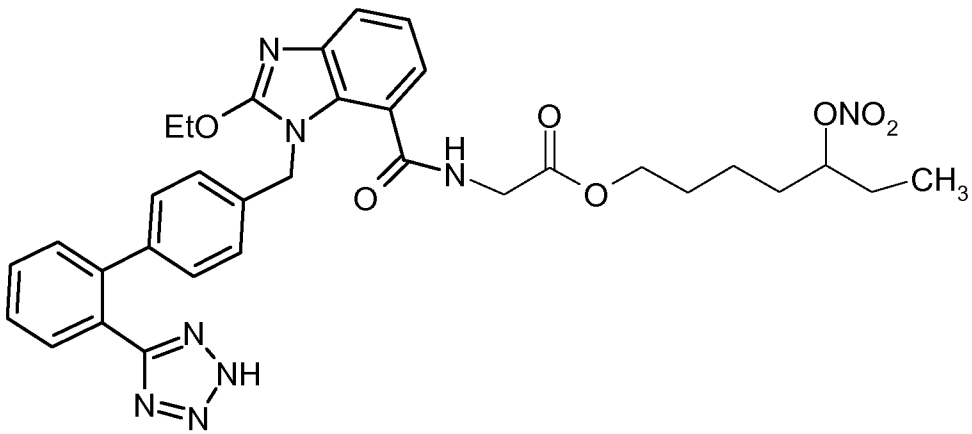

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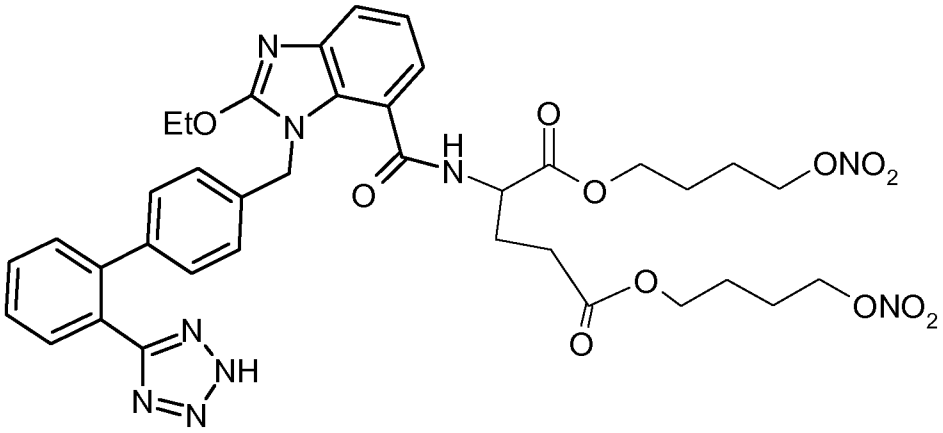

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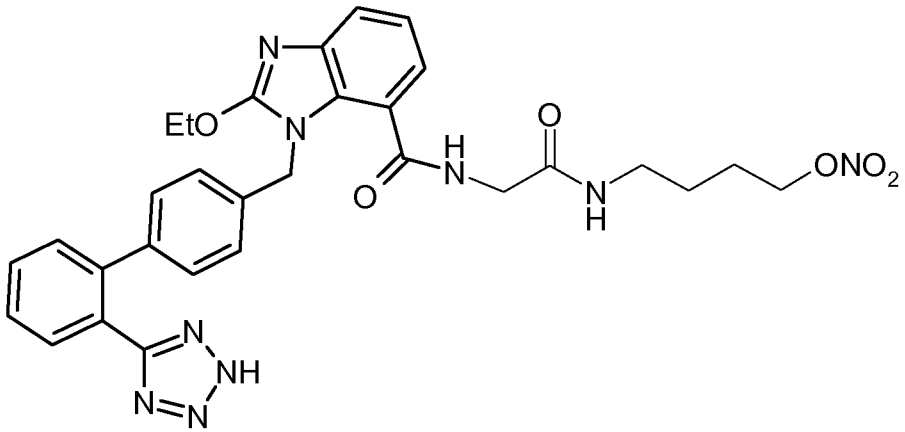

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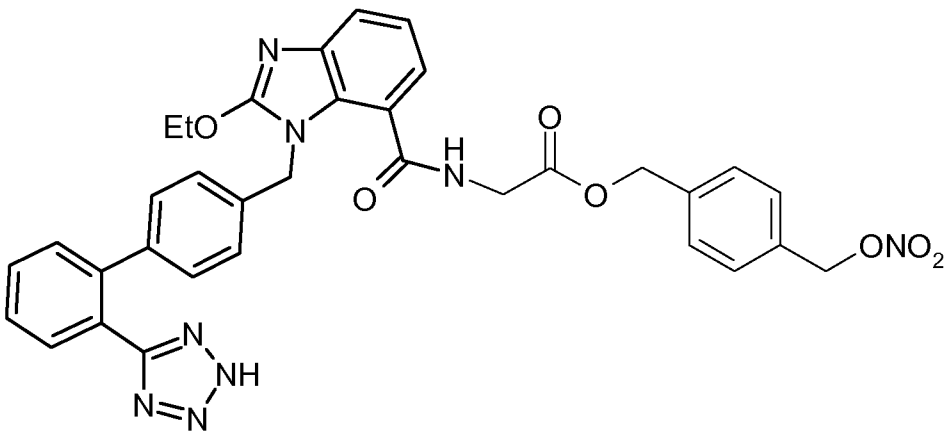

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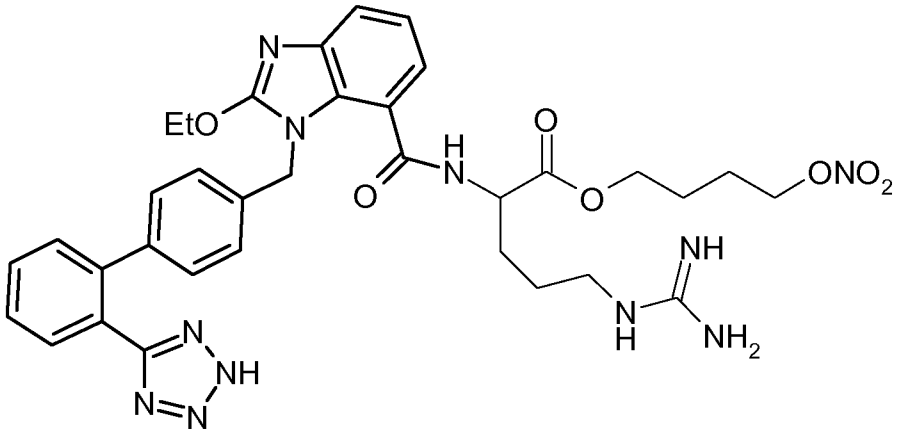

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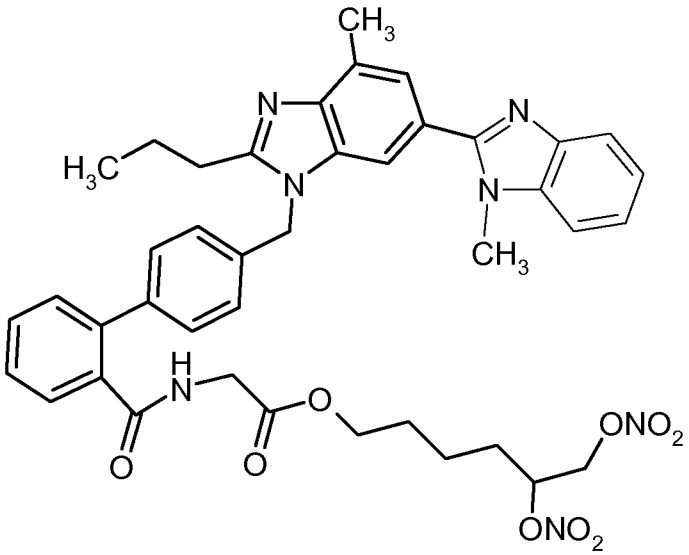

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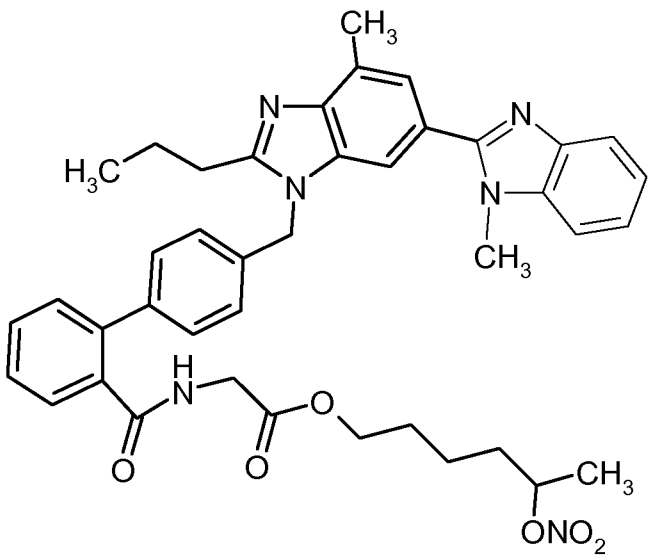

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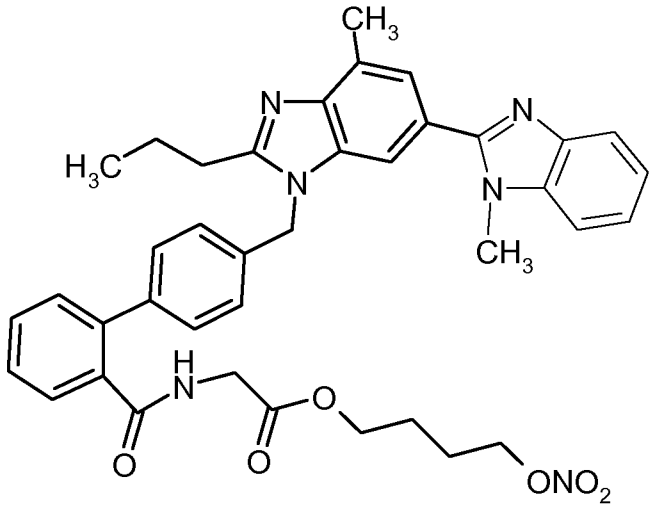

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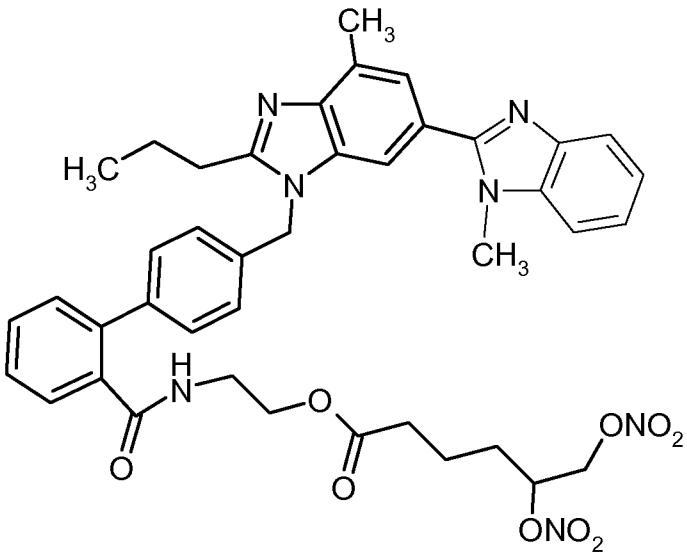
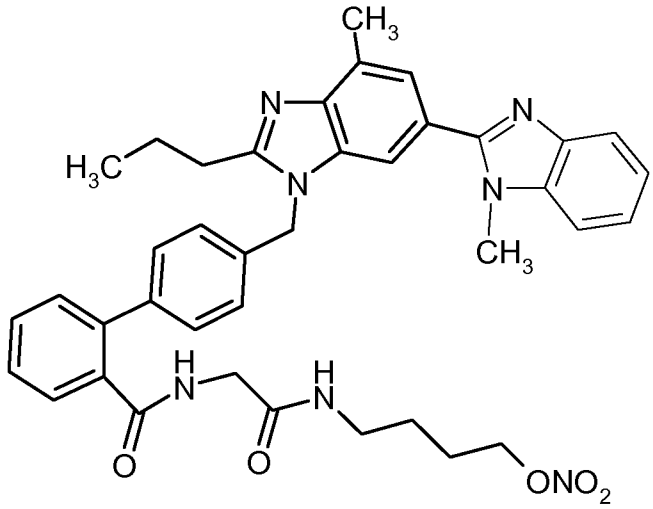
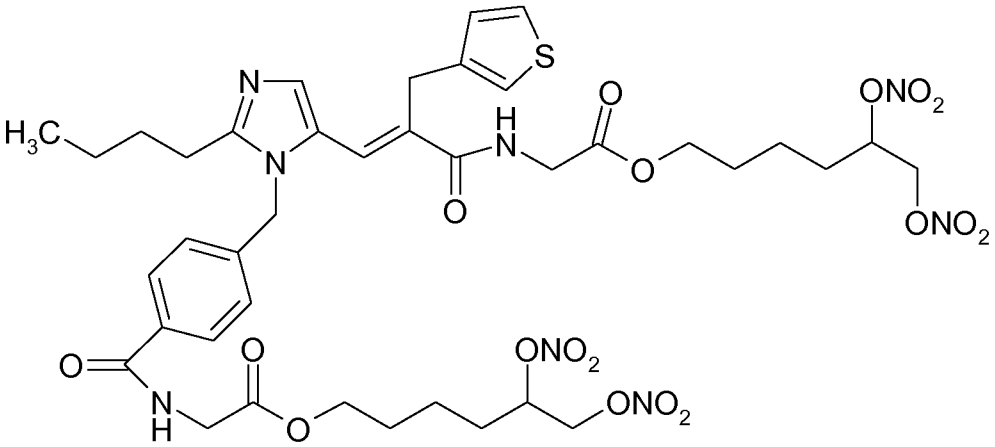


(103)



(104)



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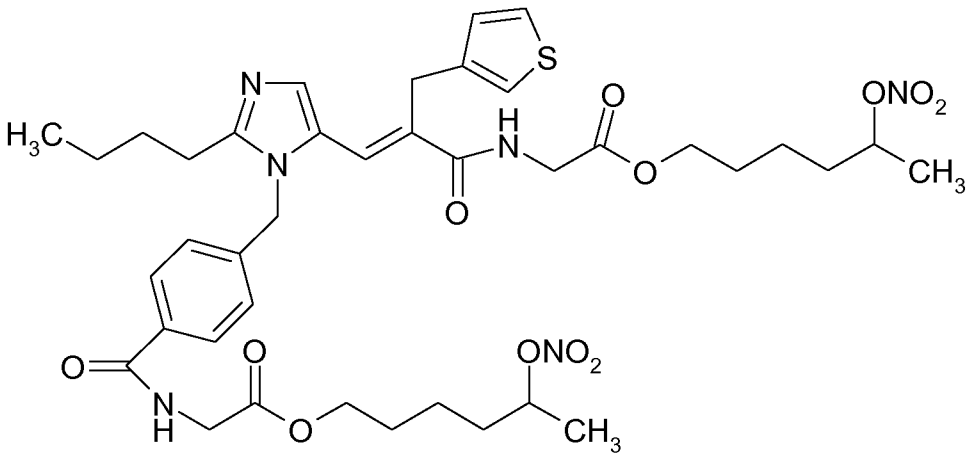

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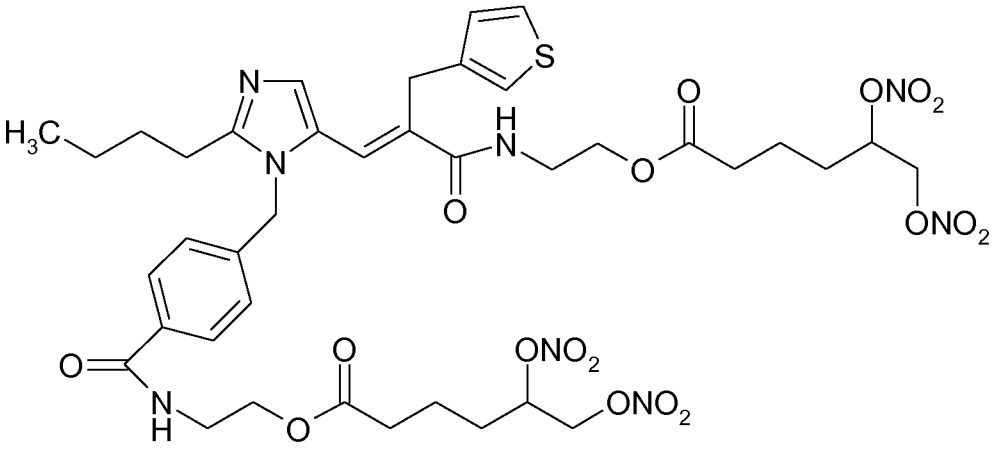
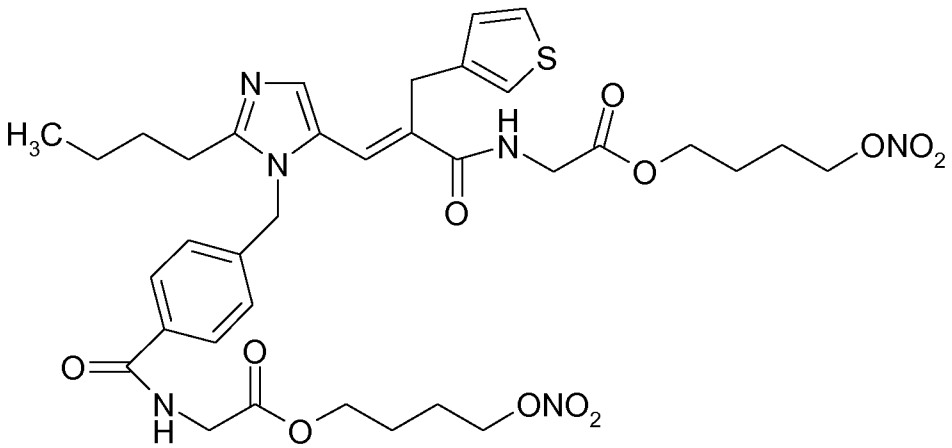


(107)



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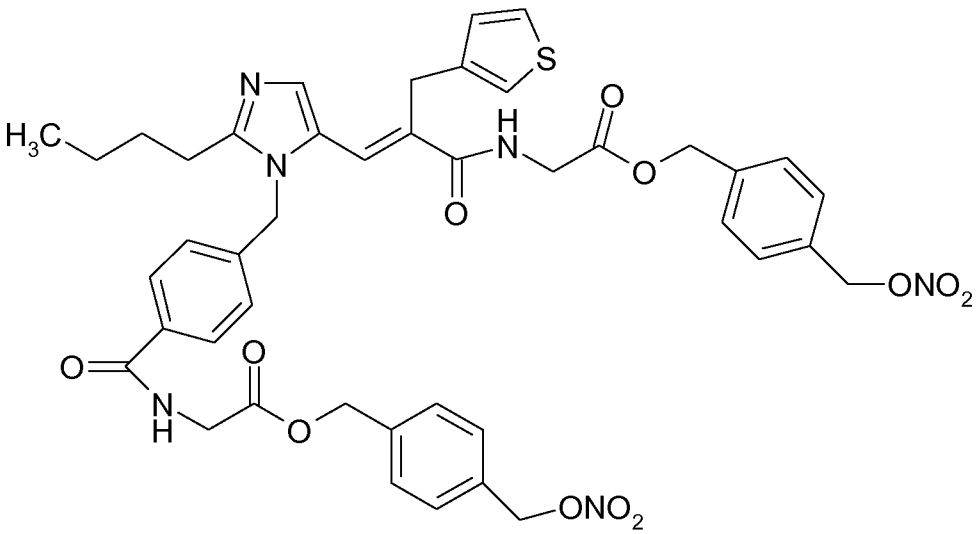

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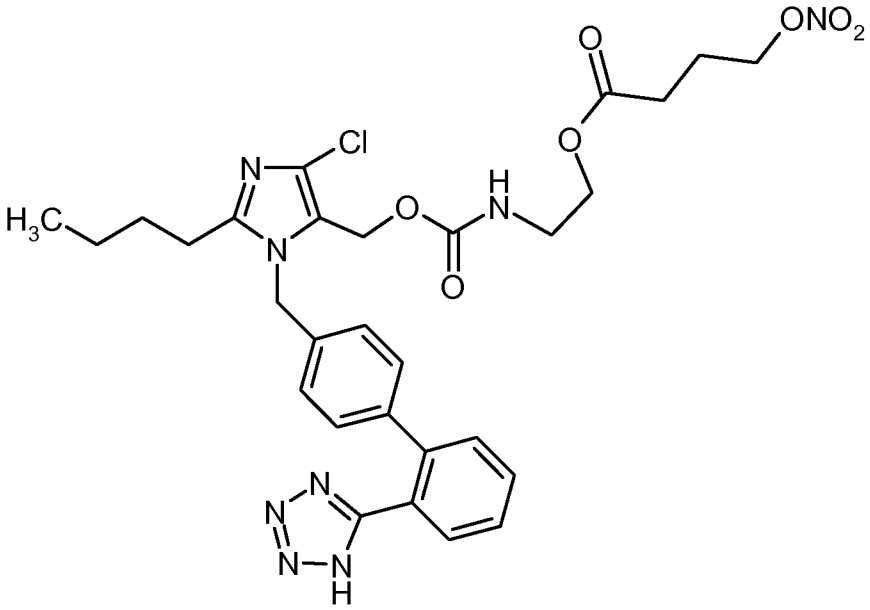

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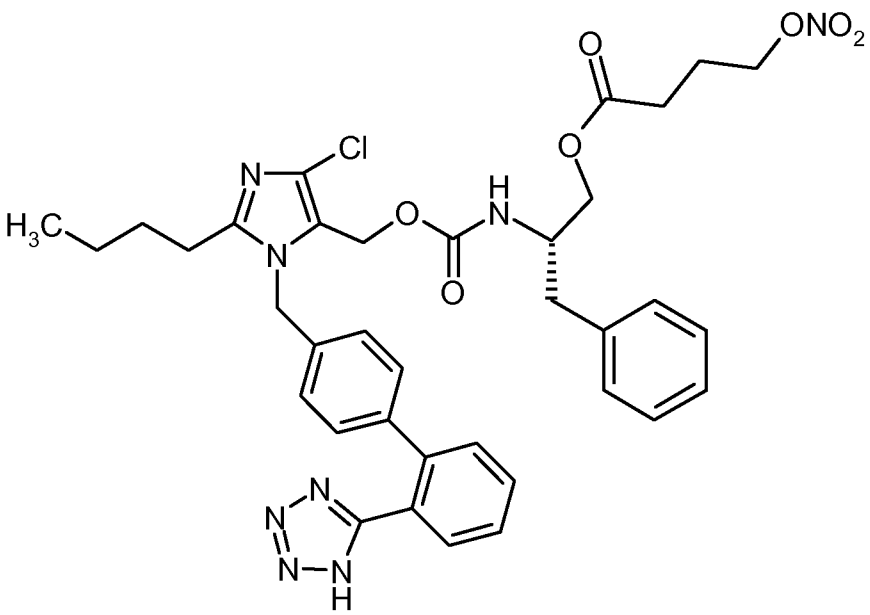
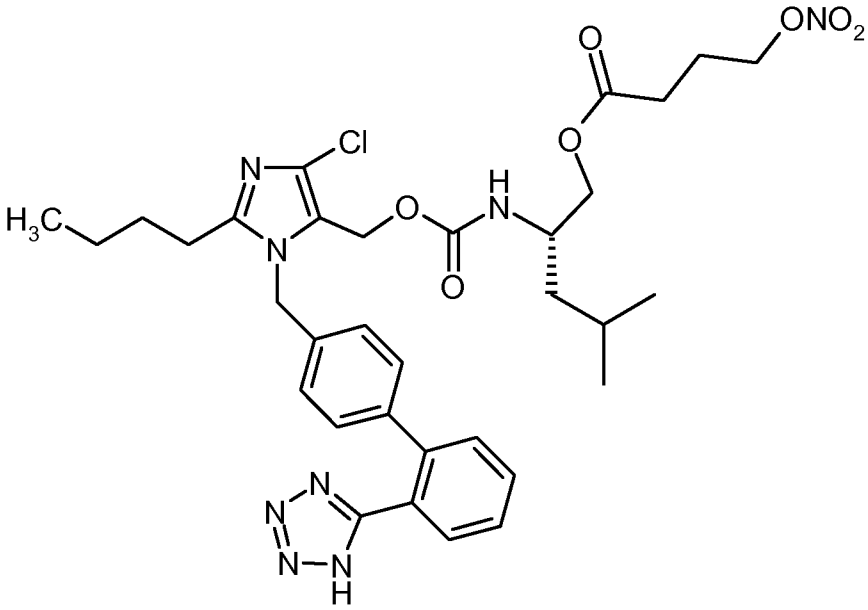
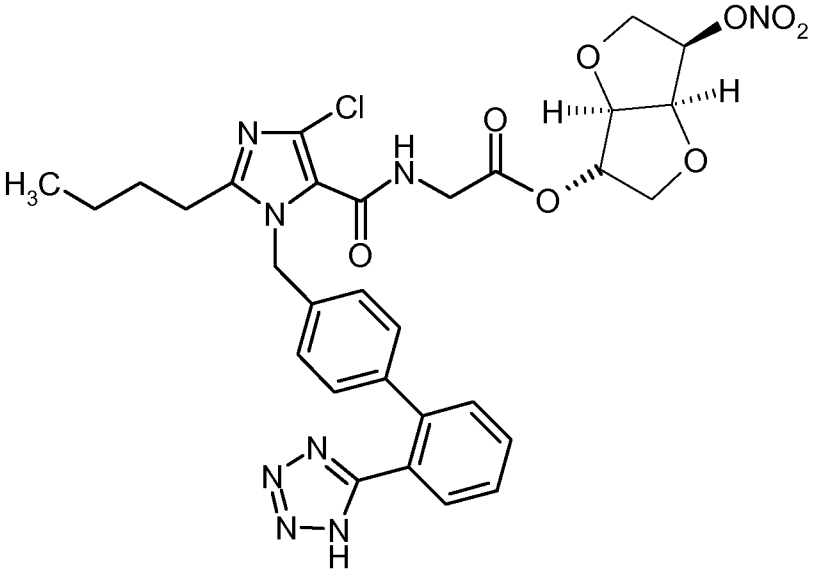


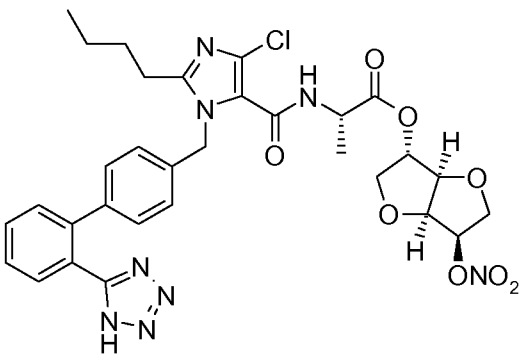
(111)



(112)



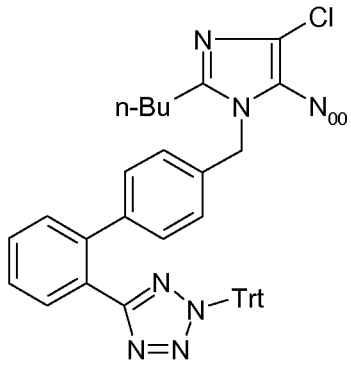
(113)



(114)

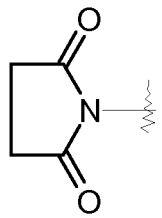
or a pharmaceutically acceptable salt or stereoisomer thereof.

10. A compound of formula R_{IIc}:



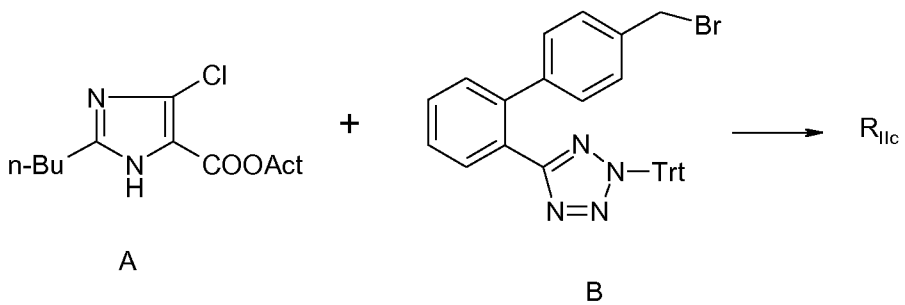
R_{IIc}

wherein Trt is the trityl protecting group, t-But is the t-Butyl protecting group and N_{00} is -COOAct with Act =



.

11. A process for preparing the compound R_{IIc} according to claim 10, by reacting a compound A with the commercially available compound B:



A B

in presence of a base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between -15°-+80°C or in a double phase system H_2O/Et_2O at temperatures range between 20°- 40°C.

12. A compound of general formula (I) according to claims 1-9 for use as a medicament.

13. A compound according to claims 1-9 for use as a drug having anti-inflammatory, antithrombotic and antiplatelet activity.

14. A compound according to claims 1-9, for use in the treatment or prophylaxis of cardiovascular, renal and chronic liver diseases, inflammatory processes and metabolic syndrome.

15. A compound according to claims 1-9, for use in the treatment or prophylaxis of hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, liver fibrosis, portal hypertension, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, metabolic syndromes and other diseases known to be related to the renin-angiotensin system.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of general formula (I) or a salt or stereoisomer thereof according to claims 1-9.

17. A pharmaceutical composition according to claim 16 in a suitable form for the oral, parenteral, rectal, topic and transdermic administration, by inhalation spray or aerosol or iontophoresis devices.

18. Liquid or solid pharmaceutical composition for oral, parenteral, rectal, topic and transdermic administration or inhalation in the form of tablets, capsules and pills eventually with enteric coating, powders, granules, gels, emulsions, solutions, suspensions, syrups, elixir, injectable forms, suppositories, in transdermal patches or liposomes, containing a compound of formula (I) or a salt or stereoisomer thereof according to claims 1-9 and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition comprising a compound of general formula (I) according to claims 1-9, at least a compound used to treat cardiovascular disease and a pharmaceutically acceptable carrier.

20. Pharmaceutical composition according to claim 19 wherein the compound used to treat cardiovascular disease is selected from the group consisting of: aldosterone antagonists, renin inhibitors, ACE inhibitors, HMGCoA reductase inhibitors, beta-adrenergic blockers, alpha-adrenergic antagonists, sympatholytics, calcium channel blockers, endothelin antagonists, neutral endopeptidase

inhibitors, potassium activators, diuretics, vasodilators, antithrombotics such as aspirin or nitrosated compounds thereof.

21. A pharmaceutical kit comprising a compound of general formula (I) as defined in claim 1, a compound used to treat cardiovascular disease as combined preparation for simultaneous, separated or sequential use for the treatment of cardiovascular disease.

22. A pharmaceutical kit according to claim 21 wherein the compound used to treat cardiovascular disease is selected from the group consisting of: aldosterone antagonists, renin inhibitors, ACE inhibitors, HMGCoA reductase inhibitors, beta-adrenergic blockers, alpha-adrenergic antagonists, sympatholytics, calcium channel blockers, endothelin antagonists, neutral endopeptidase inhibitors, potassium activators, diuretics, vasodilators, antithrombotics such as aspirin or nitrosated compounds thereof.