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(54) Title: PROSTAGLANDIN DERIVATIVES

(57) Abstract: Nitroderivatives of prostaglandin amides having improved pharmacological activity and enhanced tolerability are described. They can be employed for the treatment of glaucoma and ocular hypertension.

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PROSTAGLANDIN DERIVATIVES

The present invention relates to new prostaglandin derivatives. More particularly, the present invention relates to nitrooxyderivatives of prostaglandin amides, pharmaceutical compositions containing them and their use as drugs for treating glaucoma and ocular hypertension.

Glaucoma is optic nerve damage, often associated with increased intraocular pressure (IOP), that leads to progressive, irreversible loss of vision.

Almost 3 million people in the United States and 14 million people worldwide have glaucoma; this is the third leading cause of blindness worldwide.

Glaucoma occurs when an imbalance in production and drainage of fluid in the eye (aqueous humor) increases eye pressure to unhealthy levels.

It is known that elevated IOP can be at least partially controlled by administering drugs which either reduce the production of aqueous humor within the eye or increase the fluid drainage, such as beta-blockers, α-agonists, cholinergic agents, carbonic anhydrase inhibitors, or prostaglandin analogs.

Several side effects are associated with the drugs conventionally used to treat glaucoma.

Topical beta-blockers show serious pulmonary side effects, depression, fatigue, confusion, impotence, hair loss, heart failure and bradycardia.

Topical α-agonists have a fairly high incidence of allergic or toxic reactions; topical cholinergic agents (miotics) can cause visual side effects.

The side effects associated with oral carbonic anhydrase inhibitors include fatigue, anorexia, depression, paresthesias and serum electrolyte abnormalities (The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, M. H. Beers and R. Berkow Editors, Sec. 8, Ch. 100).

Finally, the topical prostaglandin analogs (bimatoprost, latanoprost, travoprost and unoprostone) used in the treatment of glaucoma, can produce ocular side effects, such as increased pigmentation of the iris, ocular irritation, conjunctival hyperaemia, iritis, uveitis and macular oedema (Martindale, Thirty-third edition, p. 1445)

U.S. Pat. No. 3,922,293 describes monocarboxyacylates of prostaglandins F-type and their 15β isomers, at the C-9 position, and processes for preparing them; U.S. Pat. No. 6,417,228 discloses 13-aza prostaglandins having functional $PGF_{2\alpha}$ receptor agonist activity and their use in treating glaucoma and ocular hypertension.

WO 90/02553 discloses the use of prostaglandins derivatives of PGA, PGB, PGE and PGF, in which the omega chain contains a ring structure, for the treatment of glaucoma or ocular hypertension.

WO 00/51978 describes novel nitrosated and/or nitrosylated prostaglandins, in particular novel derivatives of PGE_1, novel compositions and their use for treating sexual dysfunctions.

U.S. Pat. No. 5,625,083 discloses dinitroglycerol esters of prostaglandins which may be used as vasodilators, antihypertensive cardiovascular agents or bronchodilators.

U.S. Pat. No. 6,211,233 discloses compounds of the general formula $A\text{-}X_1\text{-}NO_2$, wherein A contains a prostaglandin residue, in particular PGE_1, and X_1 is a bivalent connecting bridge, and their use for treating impotence.

WO 2005/049558 discloses compositions comprising an amide related to a prostaglandin and an amine selected from the group consisting of epinephrine, dopamine, diacetyl dopamine and serotonin, and their use for treating glaucoma.

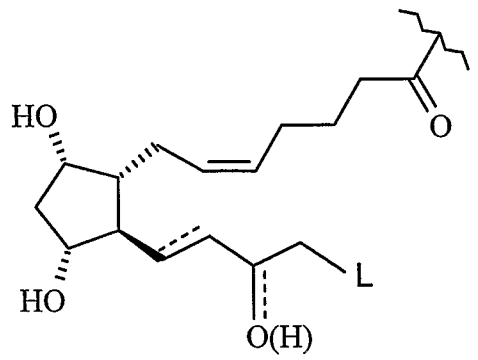
It is an object of the present invention to provide new derivatives of prostaglandins able not only to eliminate or at least reduce the side effects associated with these compounds, but also to possess an improved pharmacological activity. It has been surprisingly found that nitroderivatives of prostaglandin amides have a significantly improved overall profile as compared to native prostaglandins both in terms of wider pharmacological activity, enhanced tolerability and long-acting hypotensive activity. In particular, it has been recognized that the prostaglandin nitroderivatives of the present invention can be employed for treating glaucoma and ocular hypertension. The compounds of the present invention are indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or with chronic angle-closure glaucoma who underwent peripheral iridotomy or laser iridoplasty.

An object of the present invention is, therefore, nitroderivatives of prostaglandin amides of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof

$$R\text{-}X\text{-}(B)_m\text{-}Y\text{-}ONO_2$$

(I)

wherein R is the prostaglandin residue of formula (II):

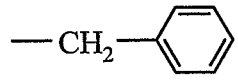
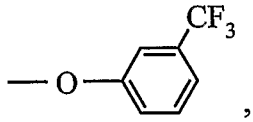


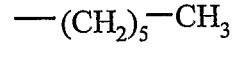
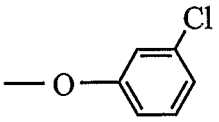
(II)

wherein

the symbol --- represents a single bond or a double bond;

L is selected from the following groups:

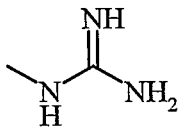
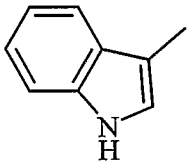
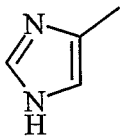
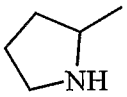
-  ,  ,

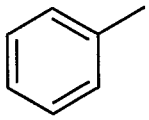
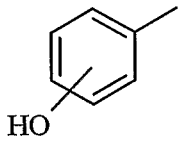
-  ,  ;

X is $-NR^1-$, wherein R^1 = H or C_1-C_6 alkyl;

m is an integer equal to 0 or 1;

B is a radical of the formula –CH(R1')COO-, wherein $R^{1'}$ is H, straight or branched C_1-C_{10} alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: -OH, -COOH, $-CONH_2$, $-NH_2$,

-SH, $-SCH_3$,  ,  ,  ,  ,

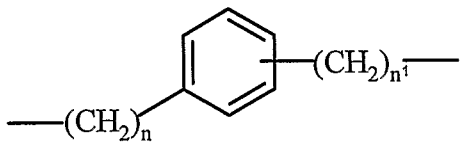
 or  ;

Y is a bivalent radical having the following meaning:

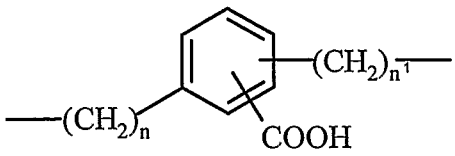
a)

- straight or branched C_1-C_{20} alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or T, wherein T is
  $-OC(O)(C_1$-C_{10} alkyl)-ONO_2 or $-O(C_1$-C_{10} alkyl)-ONO_2;
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1, wherein T_1 is straight or branched C_1-C_{10} alkyl;

b)

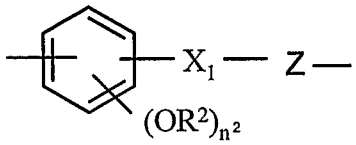


c)



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

d)



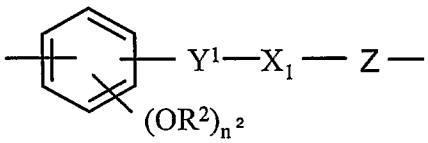
wherein

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

Z is $–(CH_2)_n{}^1$- or the bivalent radical defined above under b);

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

e)



wherein:

Y^1 is $–CH_2-CH_2-(CH_2)_n{}^2$- or $–CH=CH-(CH_2)_n{}^2$-;

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

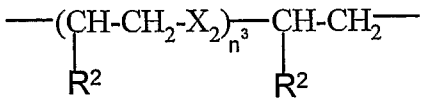
with the proviso that:

i) when Y is selected from the bivalent radicals mentioned under b)-e), then the terminal $–ONO_2$ group is bound to $-(CH_2)_n{}^1$;

ii) when y is selected from the bivalent radicals mentioned under b) or c) and n = 0, then m = 1;

iii) when y is selected from the bivalent radicals mentioned under d) or e), then m = 1;

g)



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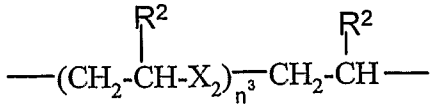
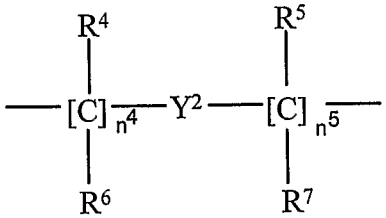


wherein X_2 is –O- or –S-, n^3 is an integer from 1 to 6, R^2 is as defined above;

h)



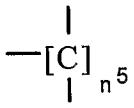
wherein:

n^4 is an integer from 0 to 10;

n^5 is an integer from 1 to 10;

R^4, R^5, R^6, R^7 are the same or different, and are H or straight or branched C_1-C_4 alkyl;

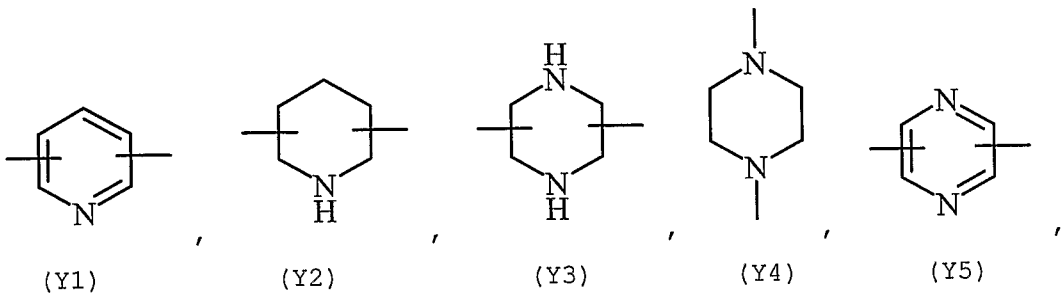
wherein the $–ONO_2$ group is linked to



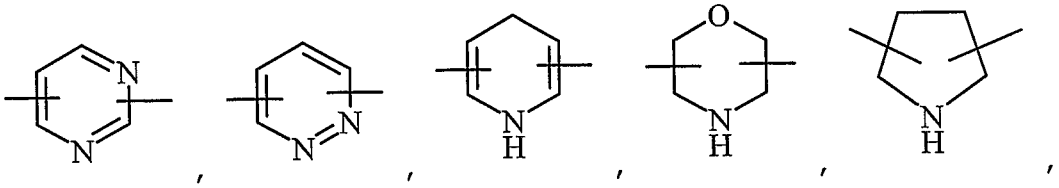
wherein n^5 is as defined above;

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

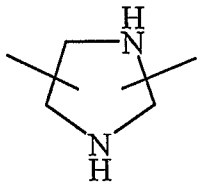
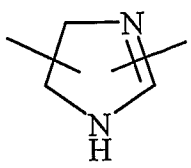
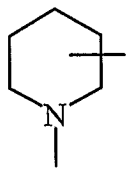
and is selected from



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



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

(Y11) (Y12) (Y13)

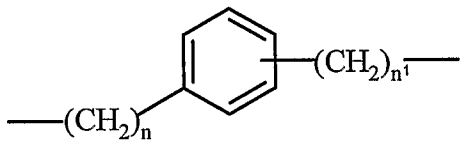
Preferably $R^{1'}$ is H or C_1-C_6 alkyl.

Preferred compounds of formula (I) are those wherein R, L, X, B and m are as above defined and Y is a bivalent radical having the following meaning:

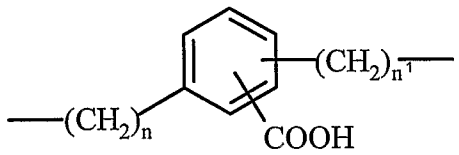
a)

- straight or branched C_1-C_{10} alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or T, wherein T is $-OC(O)(C_1$-C_{10} alkyl)-ONO_2 or $-O(C_1$-C_{10} alkyl)-ONO_2;
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1, wherein T_1 is CH_3;

b)

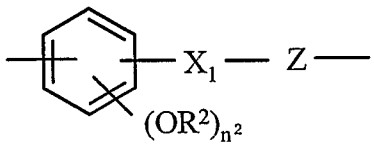


c)



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

d)



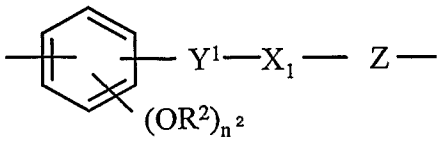
wherein:

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

Z is $-(CH_2)_n{}^1$- or the bivalent radical defined above under b);

n^1 is an integer from 1 to 10 and n^2 is an integer from 0 to 2;

e)



wherein:

Y^1 is $-CH_2-CH_2-$ or $-CH=CH-(CH_2)_n{}^2-$;

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

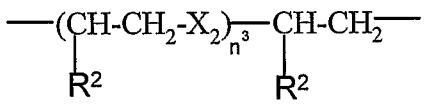
with the proviso that:

i) when Y is selected from the bivalent radicals mentioned under b)-e), then the terminal $-ONO_2$ group is bound to $-(CH_2)_n{}^1$;

ii) when y is selected from the bivalent radicals mentioned under b) or c) and n = 0, then m = 1;

iii) when y is selected from the bivalent radicals mentioned under d) or e), then m = 1;

g)



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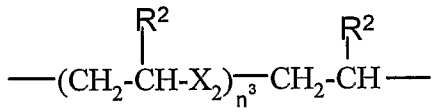
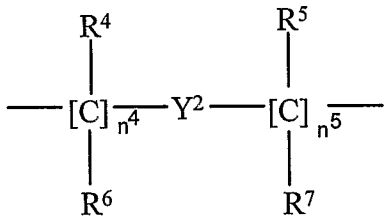


wherein X_2 is –O- or –S-, n^3 is an integer from 1 to 4 and R^2 is as defined above;

h)



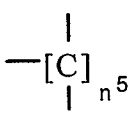
wherein:

n^4 is an integer from 0 to 3;

n^5 is an integer from 1 to 3;

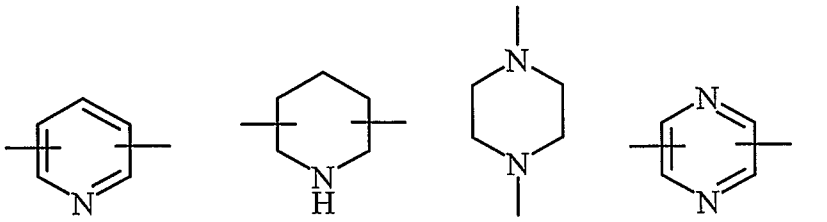
R^4, R^5, R^6, R^7 are H;

wherein the $-ONO_2$ group is linked to

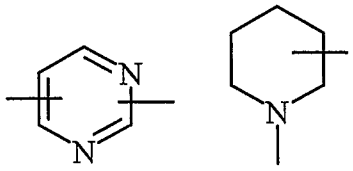


wherein n^5 is as defined above;

Y^2 is selected from



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



(Y6) (Y13)

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.

The term "cycloalkylene" as used herein refers to ring having from 5 to 7 carbon atoms including, but not limited to, cyclopentylene, cyclohexylene optionally substituted with side chains such as straight or branched (C_1-C_{10})-alkyl, preferably CH_3.

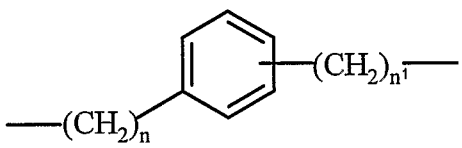
The term "heterocyclic" as used herein refers to saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, such as for example pyridine, pyrazine, pyrimidine, pyrrolidine, morpholine, imidazole and the like.

Preferred compounds of formula (I) are those wherein

the prostaglandin residue R is selected from the group consisting of residues of: latanoprost, travoprost, unoprostone and cloprostenol, preferably R is the residue of latanoprost.

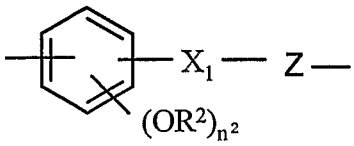
Most preferred meanings of Y are:

b)



wherein n is 0 or 1, and n^1 is 1;

d)



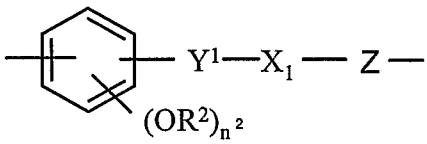
wherein

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

Z is $–(CH_2)_n{}^1$-;

n^1 is an integer from 1 to 5 and n^2 is as as above defined;

e)



wherein:

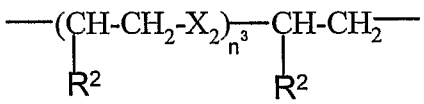
Y^1 is $–CH_2$-CH_2-$(CH_2)_n{}^2$- or –CH=CH-$(CH_2)_n{}^2$-;

Z is $–(CH_2)_n{}^1$- or the bivalent radical defined above under b);

n^1 is an integer from 1 to 5;

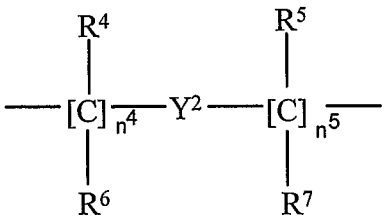
n^2, R^2 and X_1 are as above defined;

g)



wherein X_2 is –O- or –S-, n^3 is 1, R^2 is hydrogen.

h)



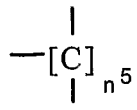
wherein:

n^4 is 2 or 3;

n^5 is 2 or 3;

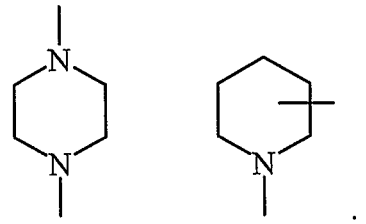
R^4, R^5, R^6, R^7 are H;

wherein the $–ONO_2$ group is linked to



wherein n^5 is as defined above;

Y^2 is selected from



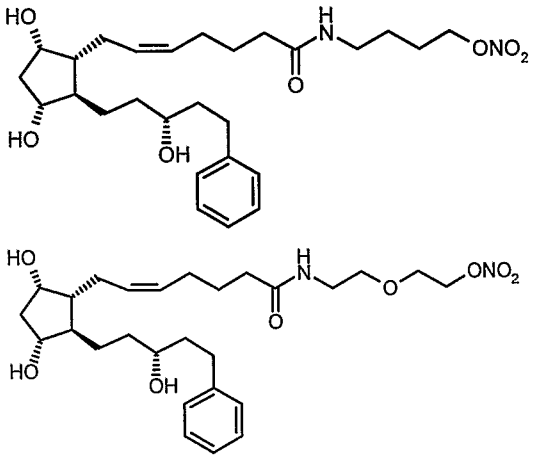
(Y4) (Y13)

When X is $-NR^1-$ and R^1 is C_1-C_6 alkyl, preferably Y is straight or branched C_2-C_6 alkylene, optionally substituted with $-ONO_2$.

When X is $-NR^1-$, and R^1 is H and m is 1, preferably Y is straight or branched C_2-C_6 alkylene, optionally substituted with $-ONO_2$.

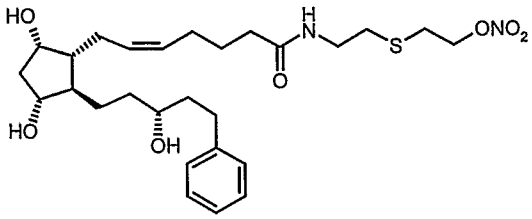
When X is $-NR^1-$, and R^1 is H and m is 0, preferably Y is straight or branched C_4-C_{10} alkylene, optionally substituted with $-ONO_2$.

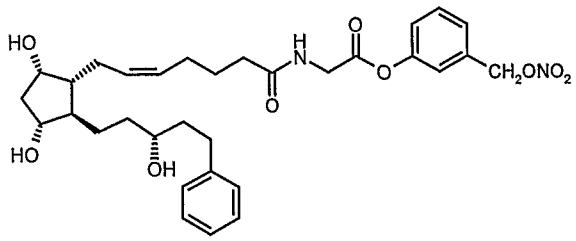
The following are preferred compounds according to the present invention:



(1)

(2)





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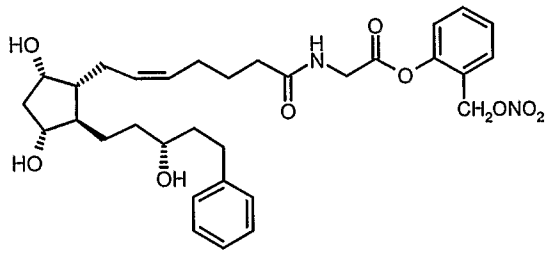

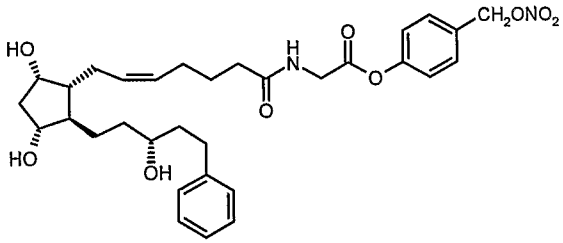

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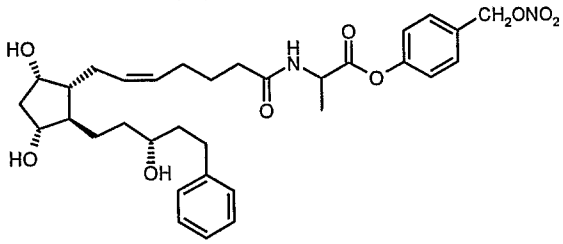

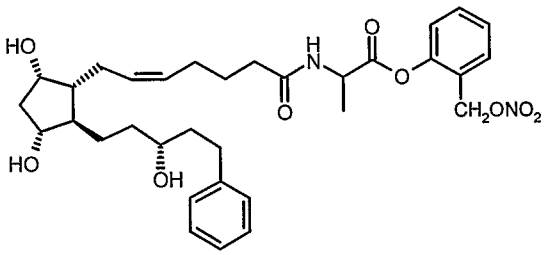

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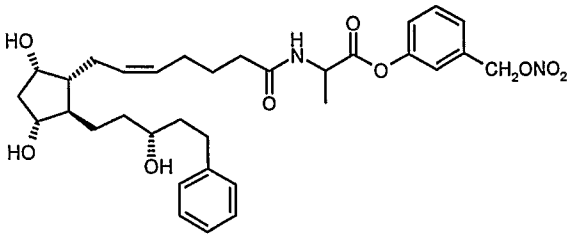

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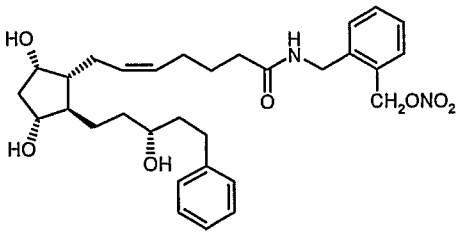

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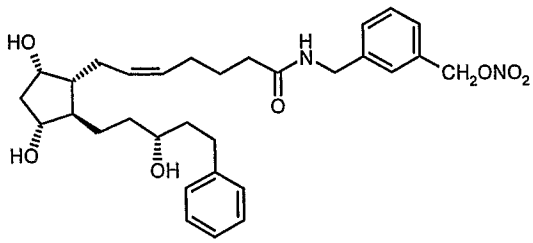

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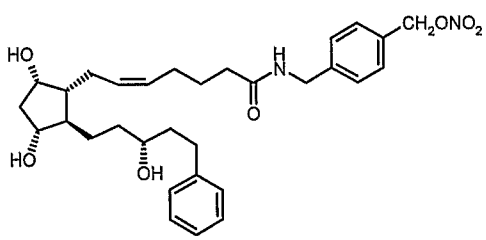

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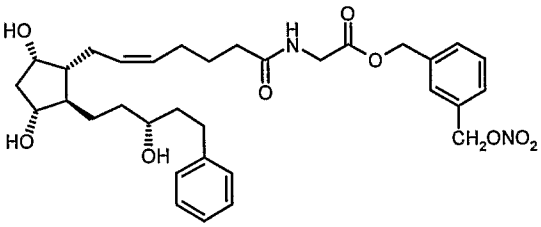

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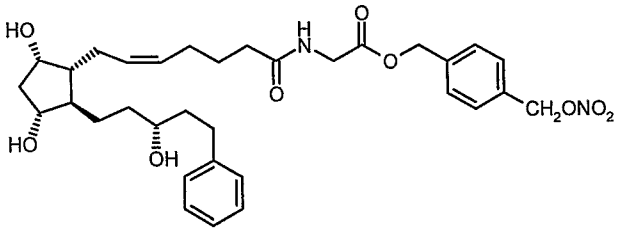

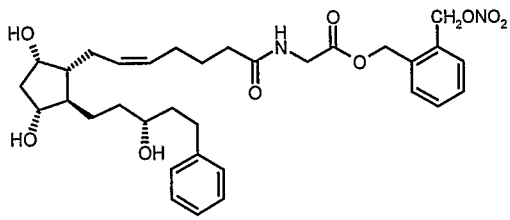

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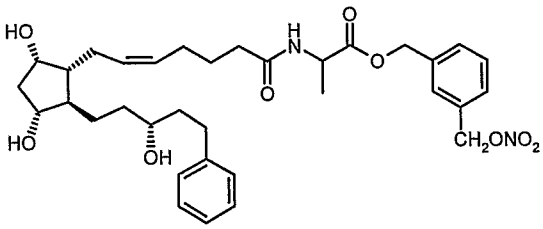

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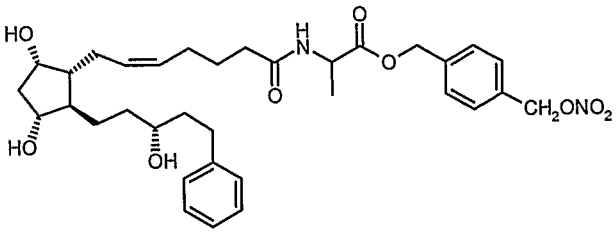

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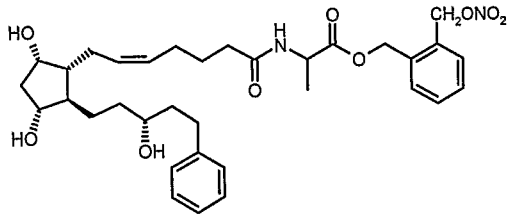

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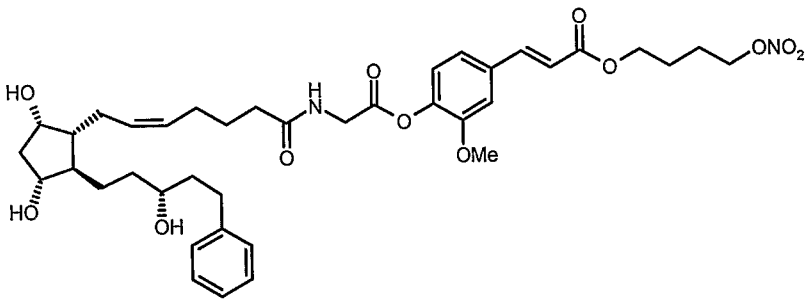

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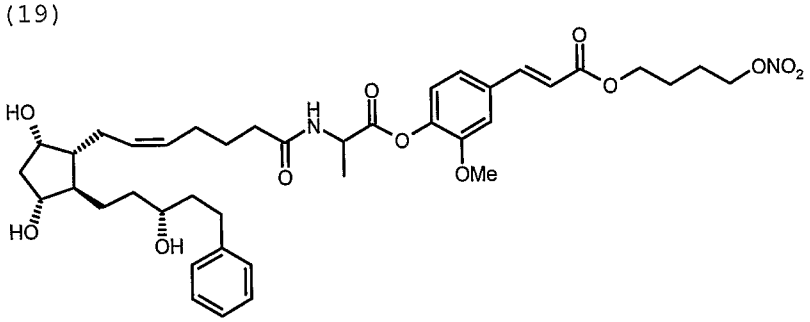

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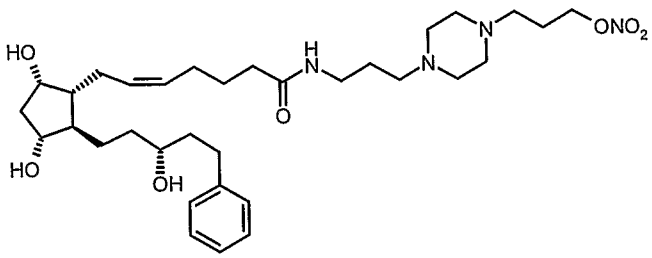

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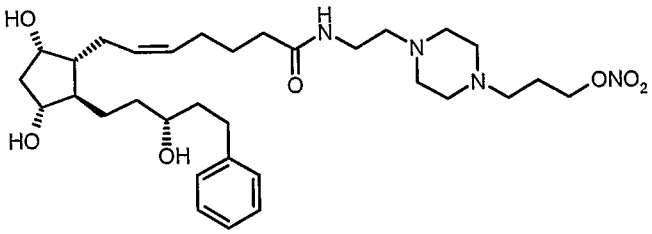

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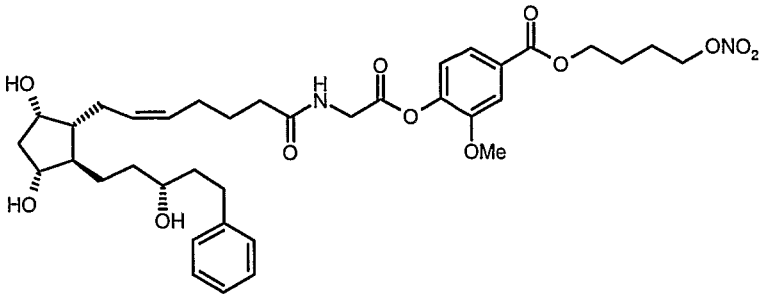

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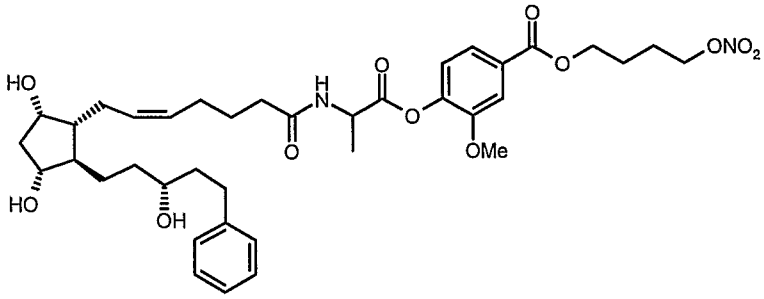

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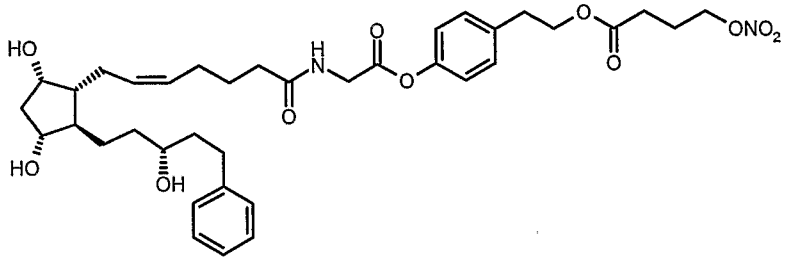

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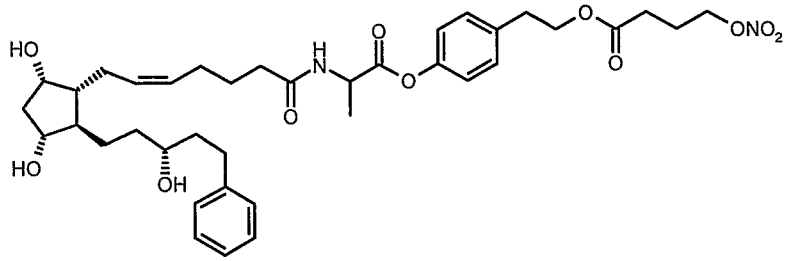

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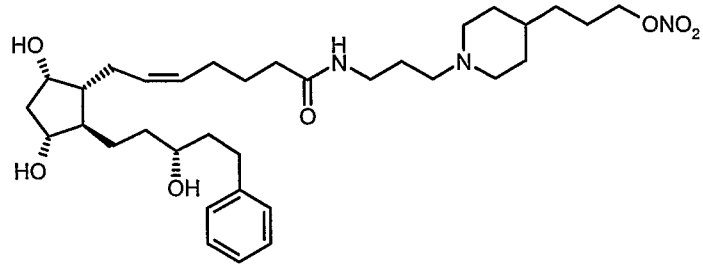

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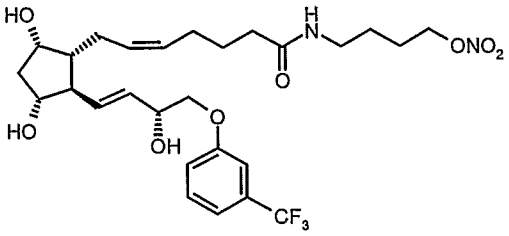

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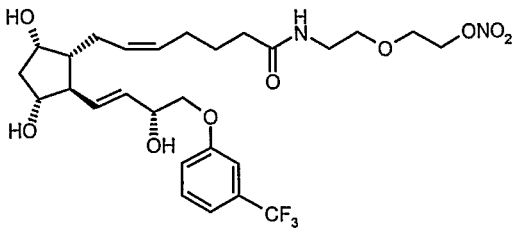

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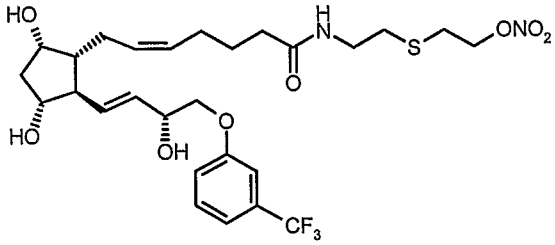

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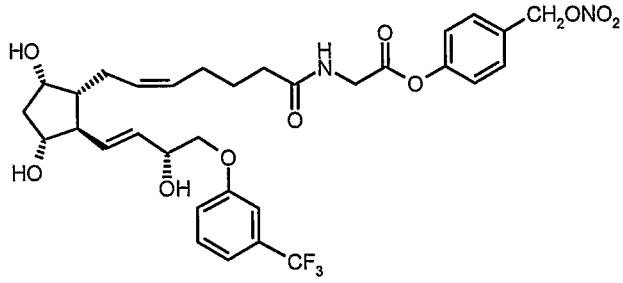

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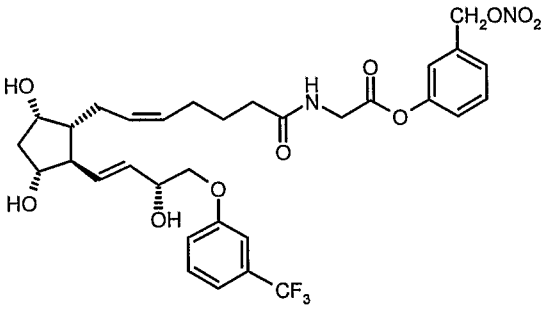

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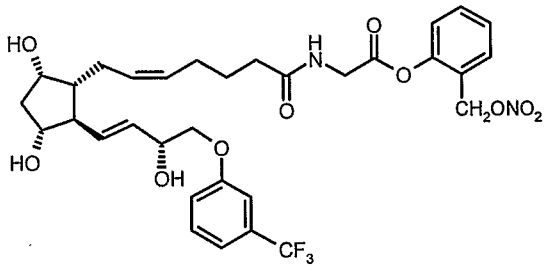

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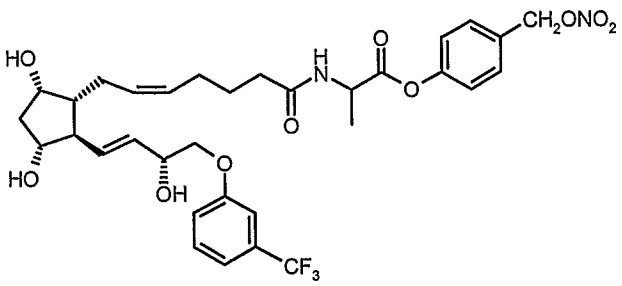

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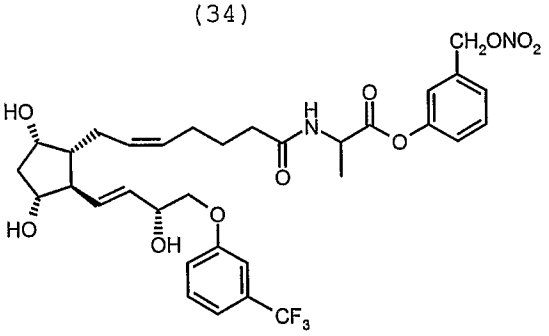

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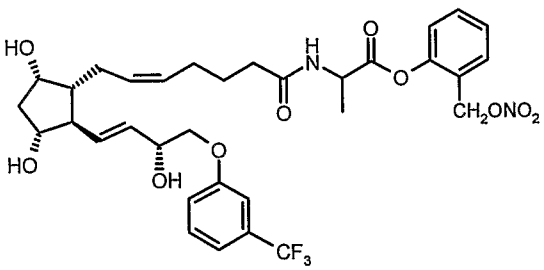

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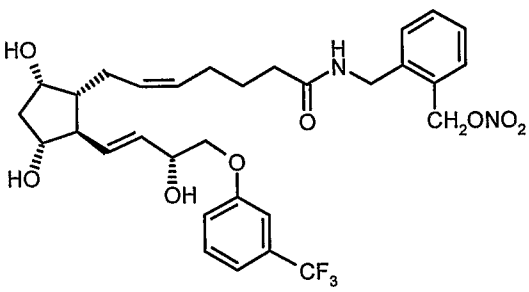

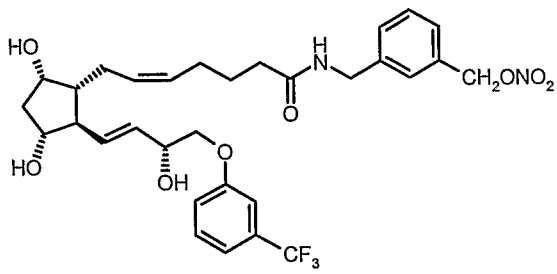

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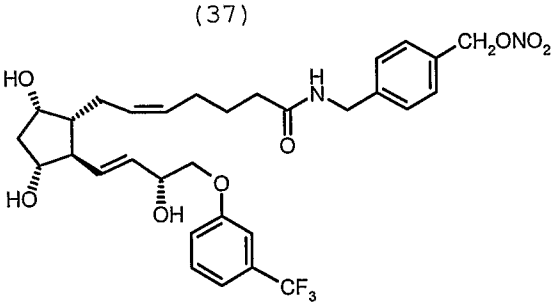

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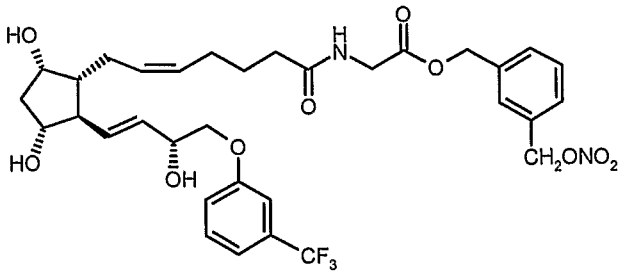

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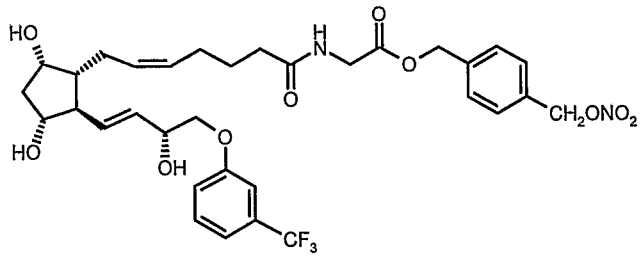

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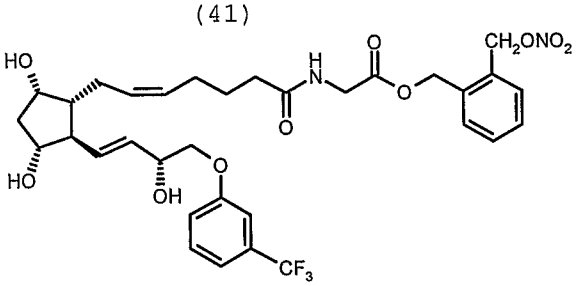

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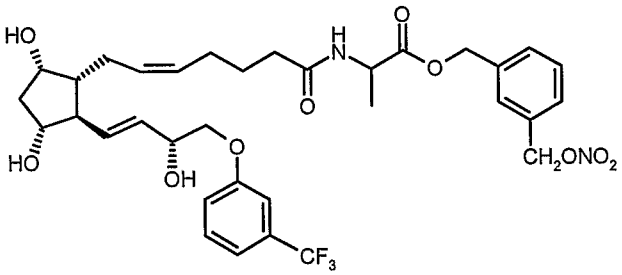

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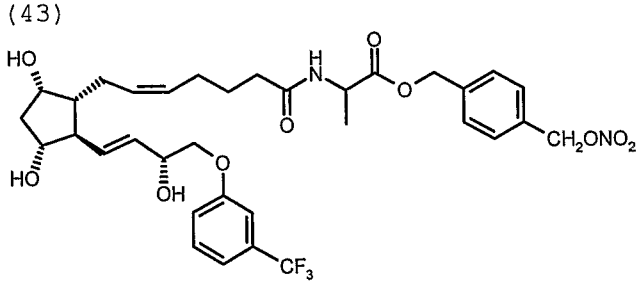

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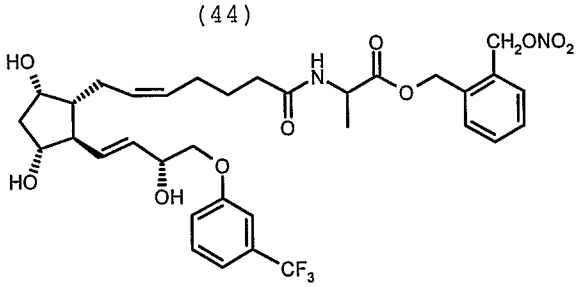

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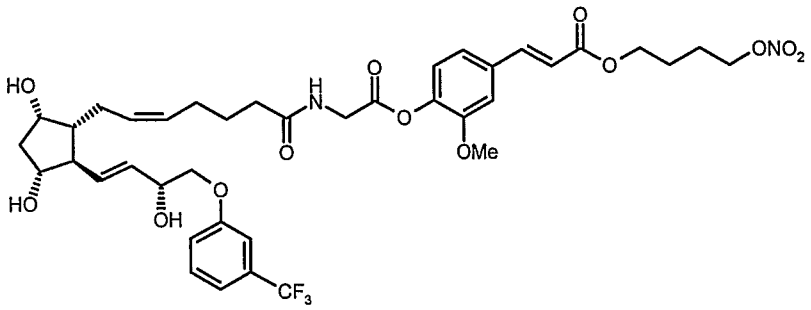

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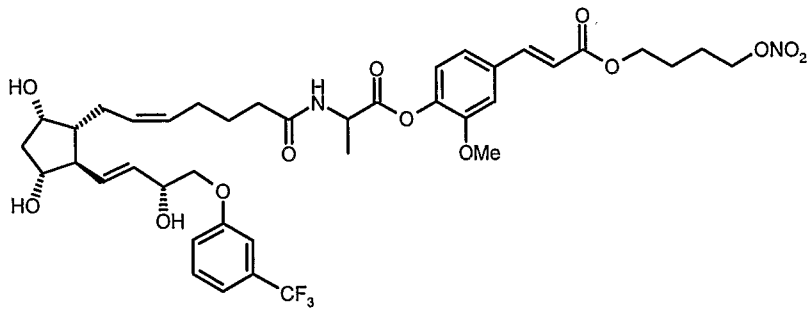

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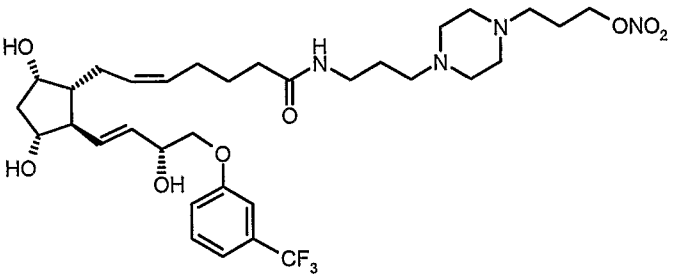

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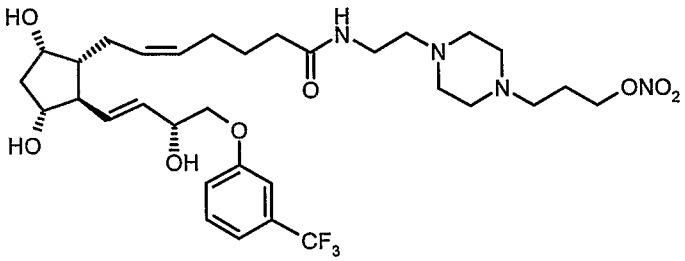

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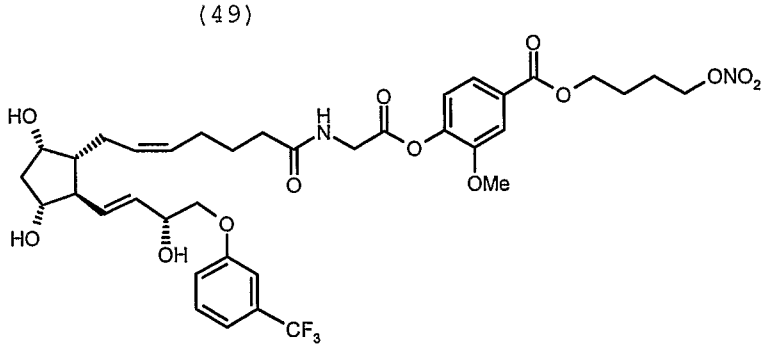

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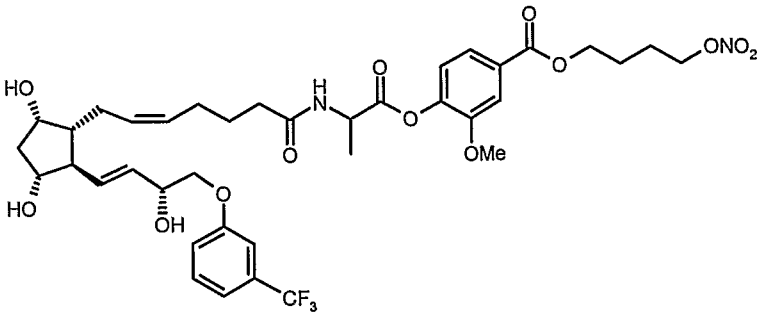

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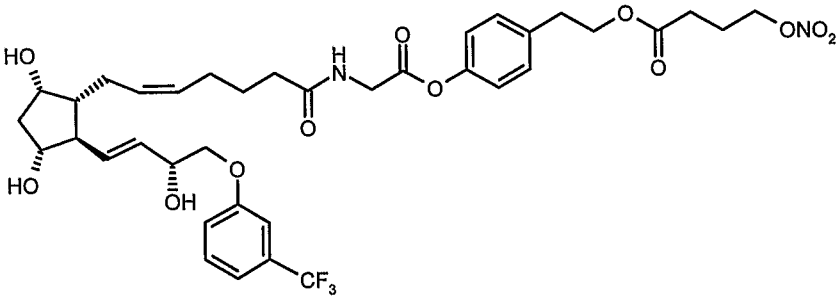

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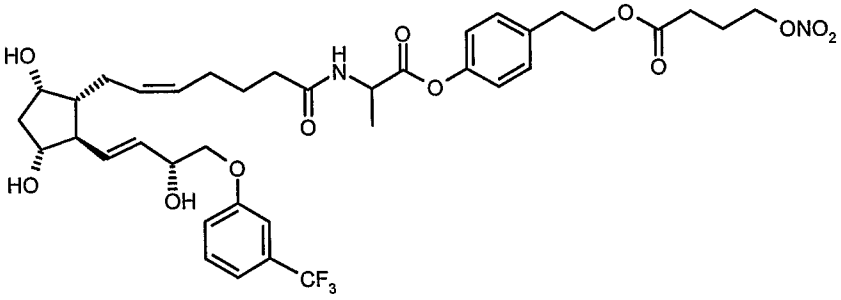

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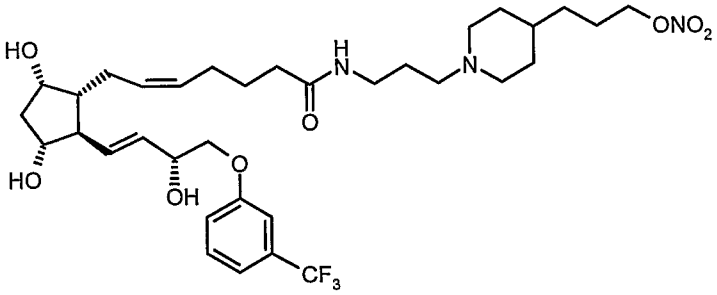

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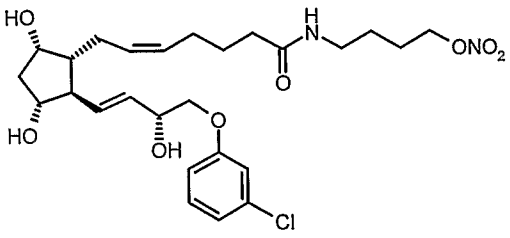

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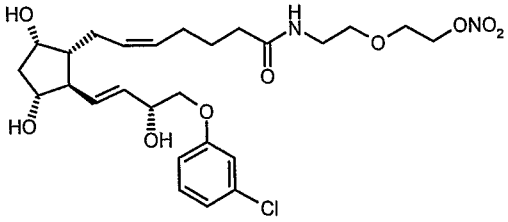

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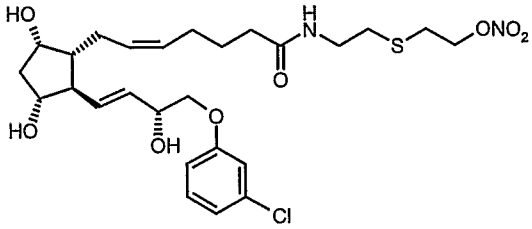

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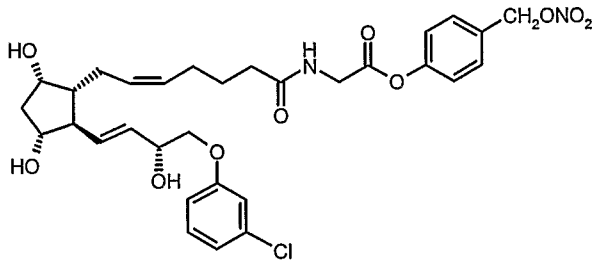

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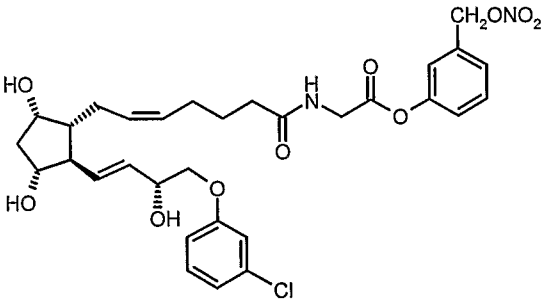

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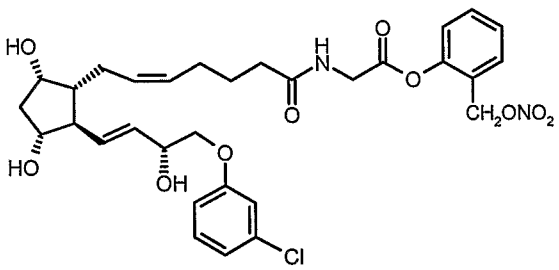

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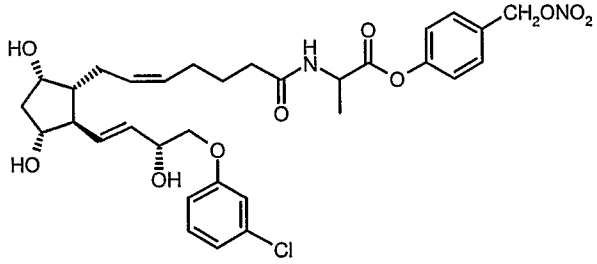

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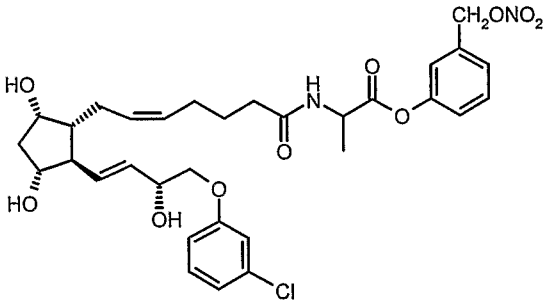

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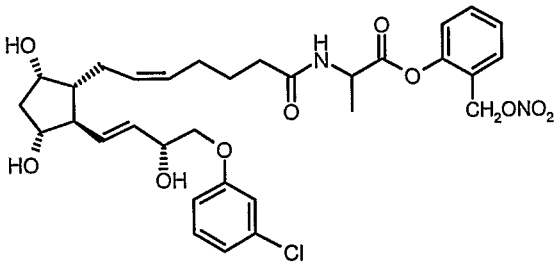

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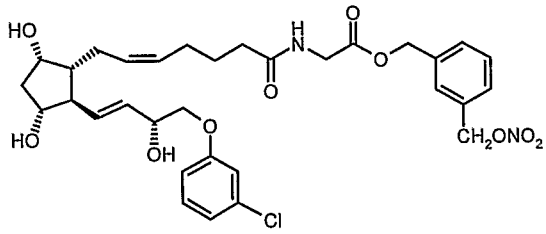

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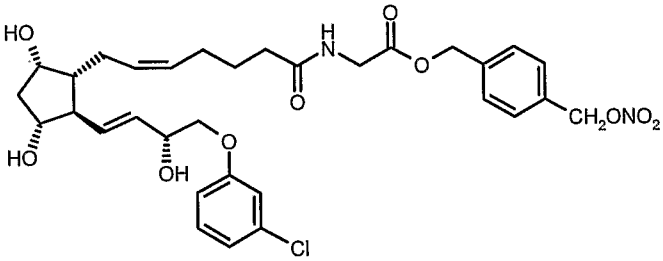

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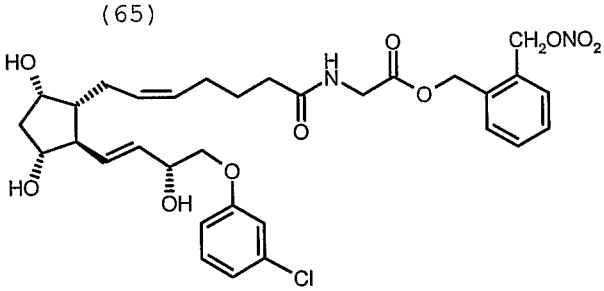

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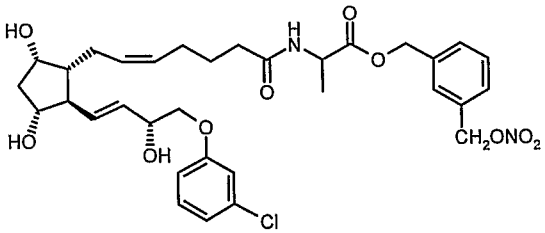

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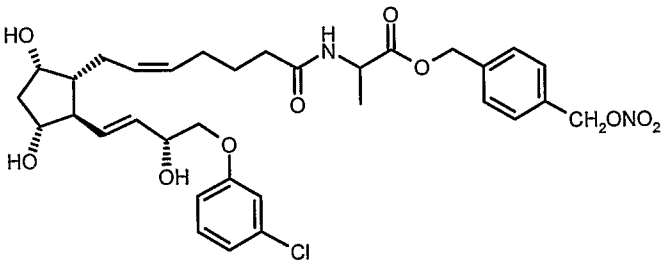

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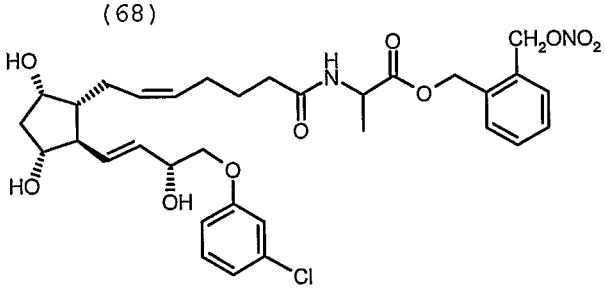

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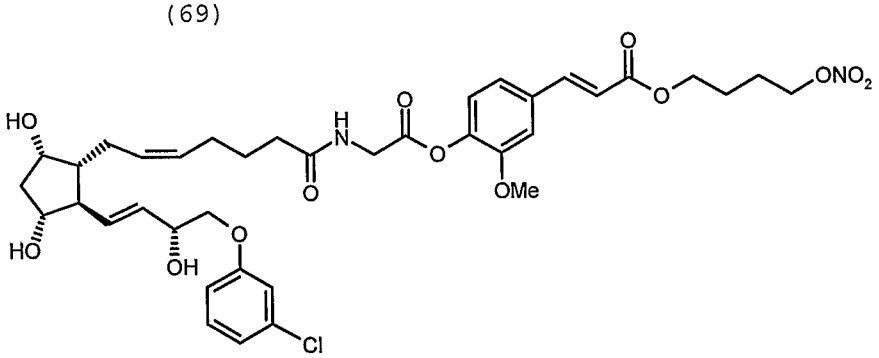

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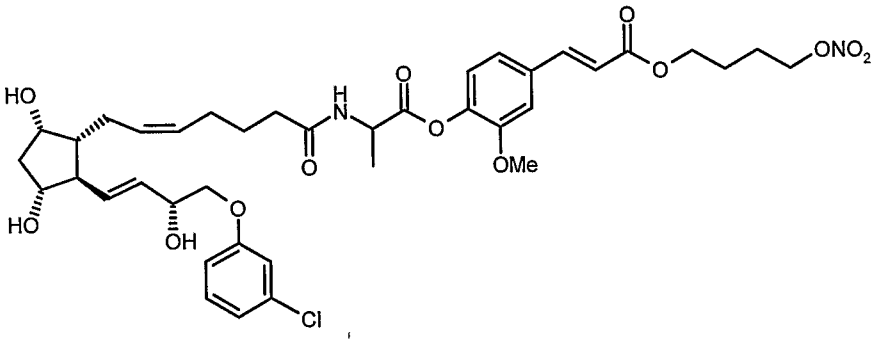

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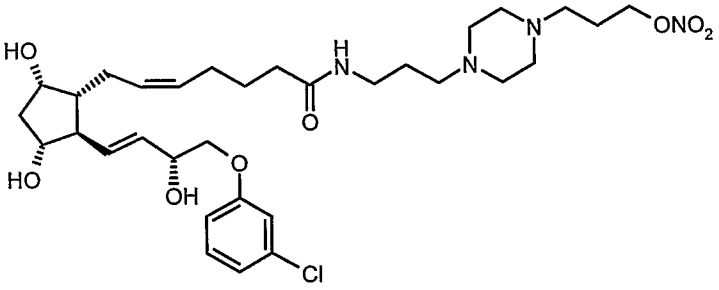

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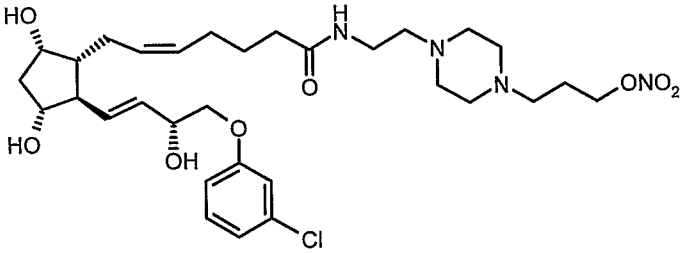

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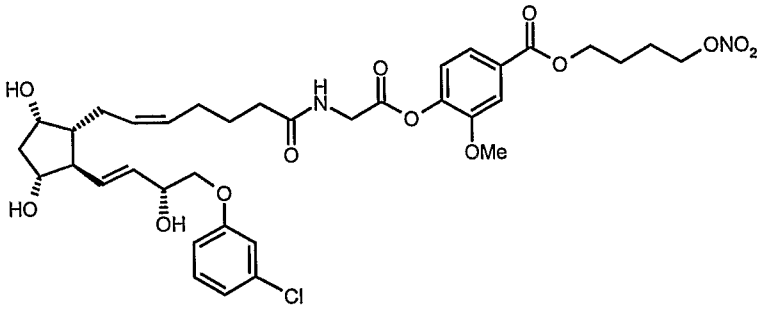

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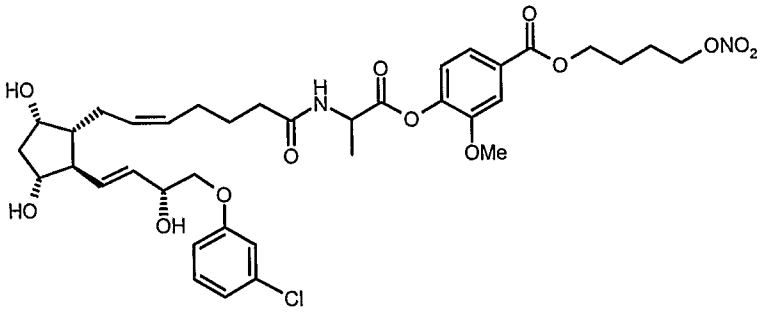

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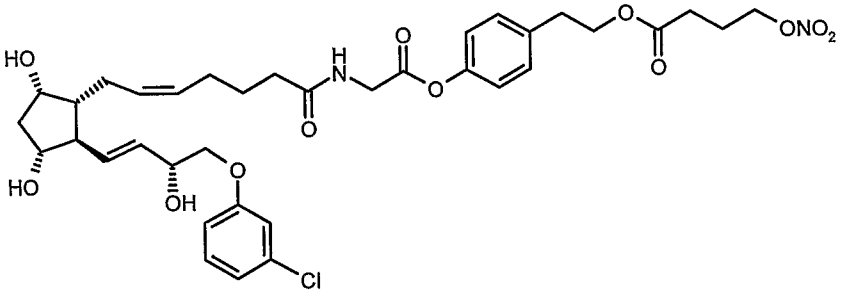

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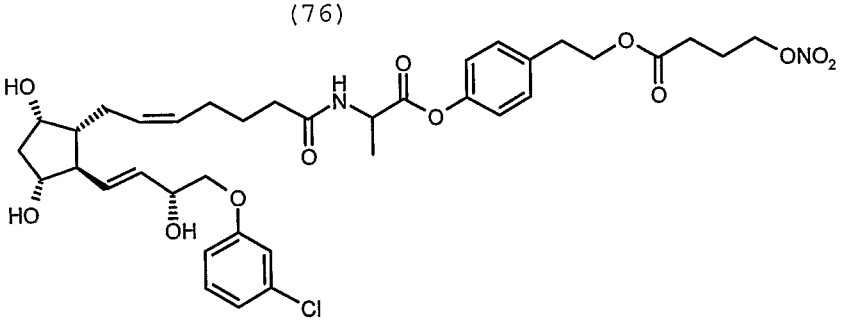

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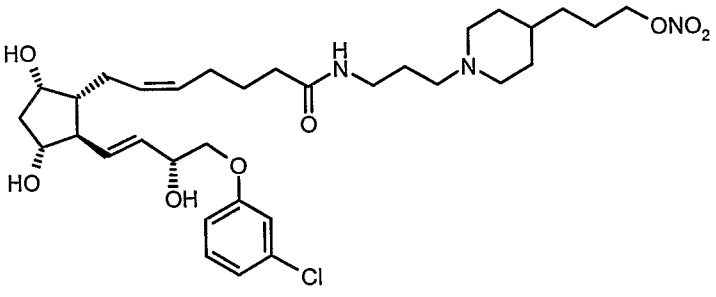

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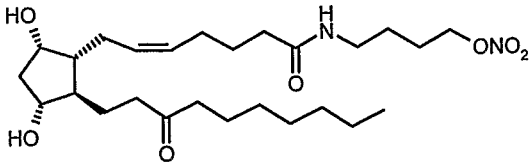

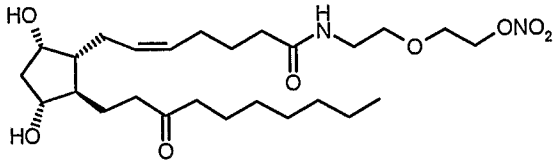

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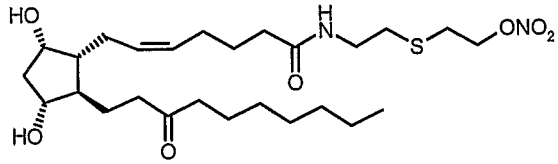

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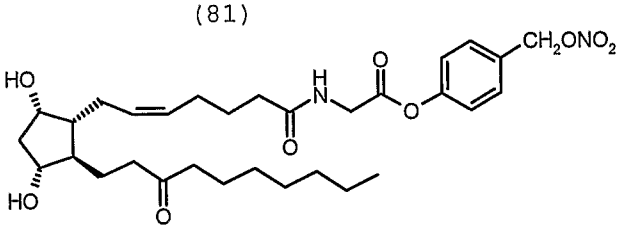

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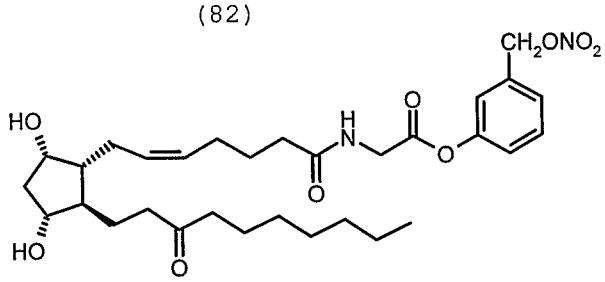

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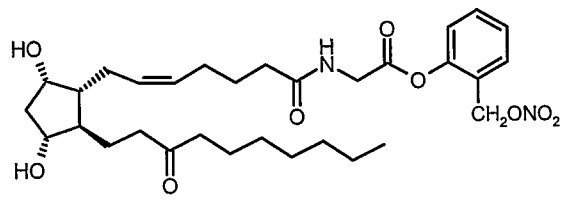

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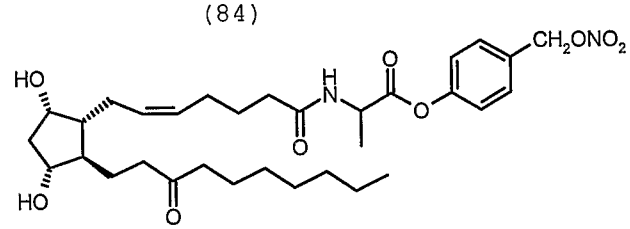

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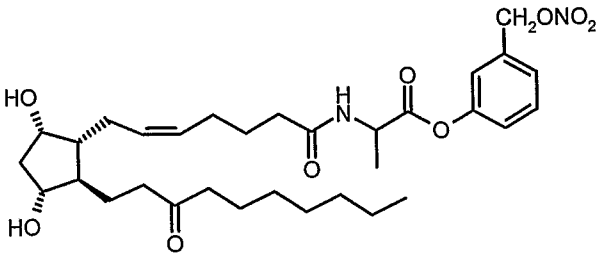

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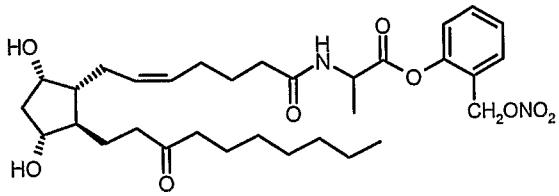

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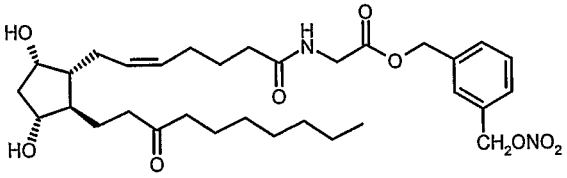

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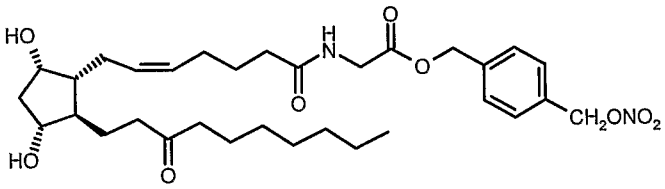

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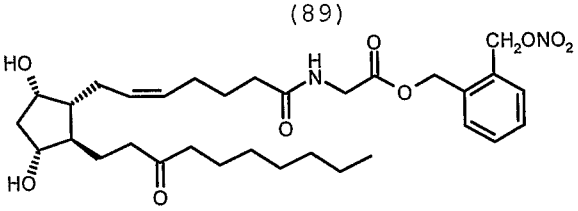

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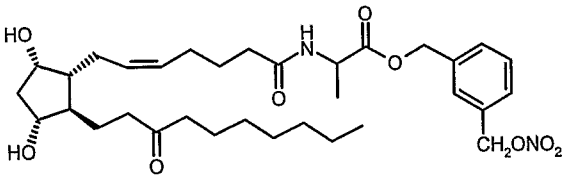

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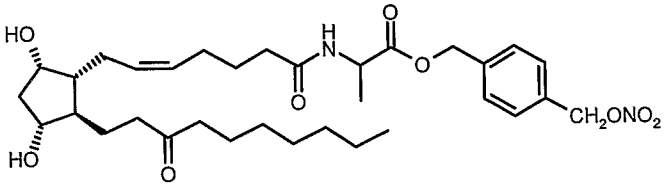

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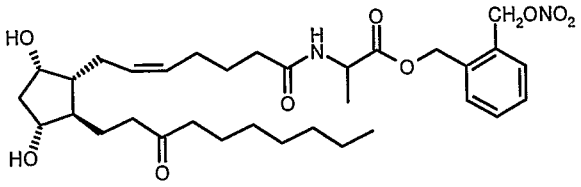

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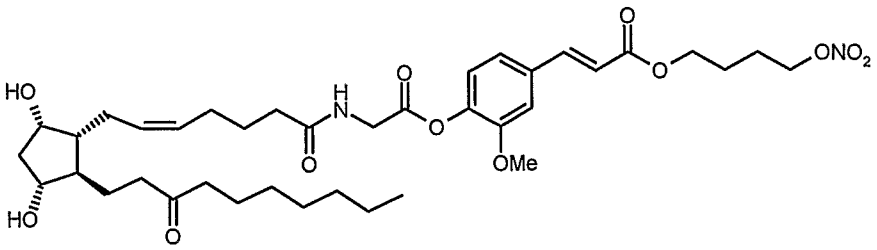

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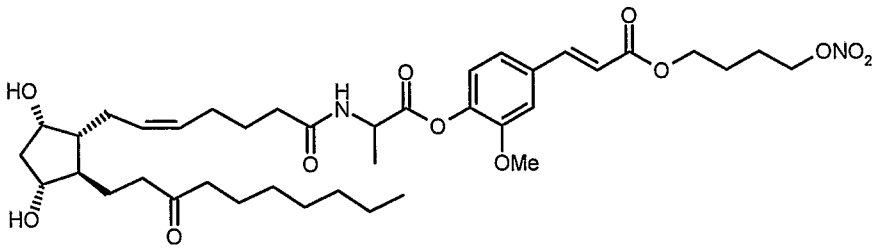

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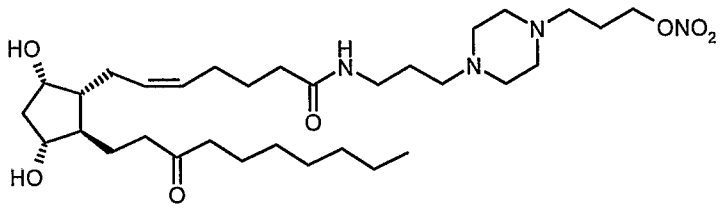

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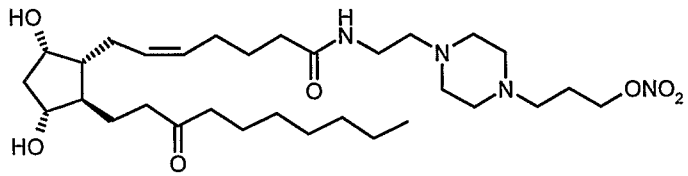

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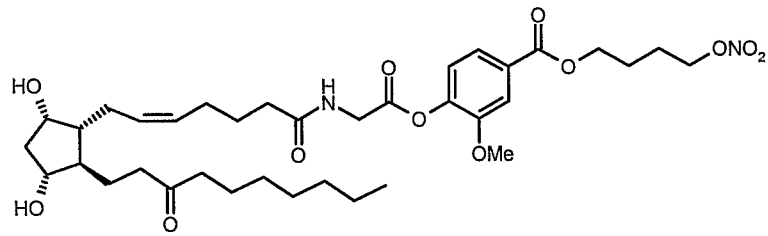

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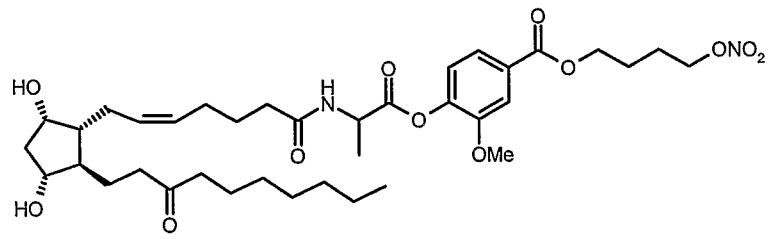

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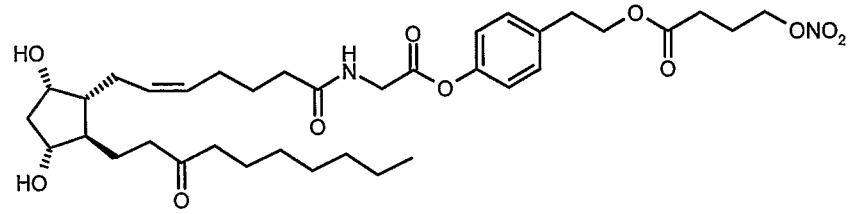

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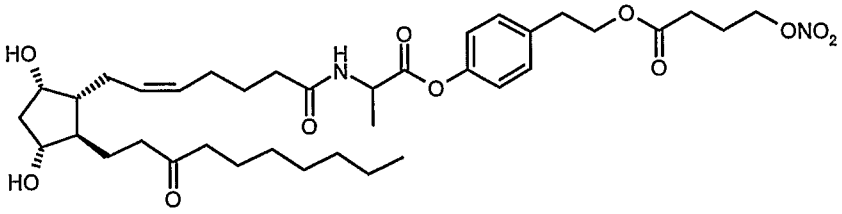

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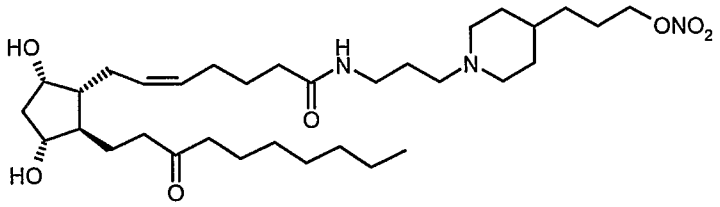

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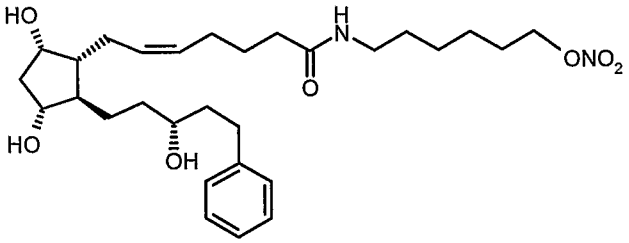

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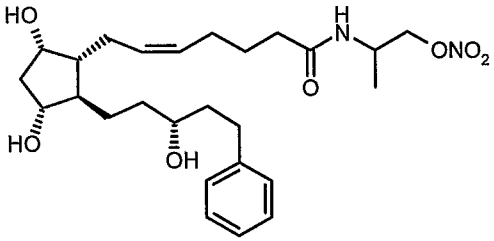

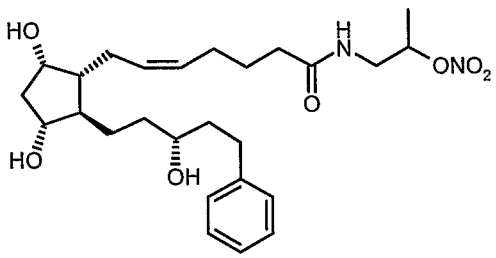

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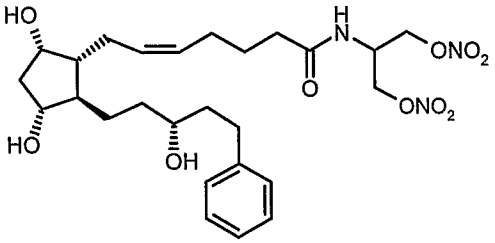

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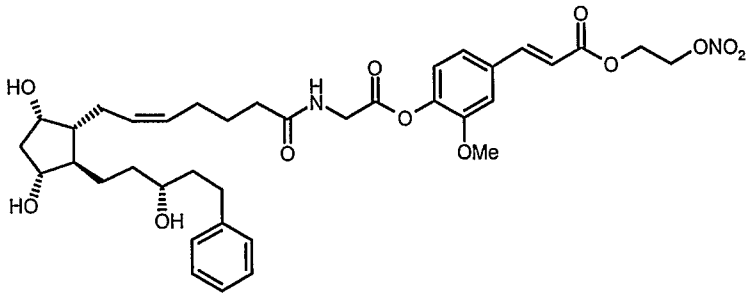

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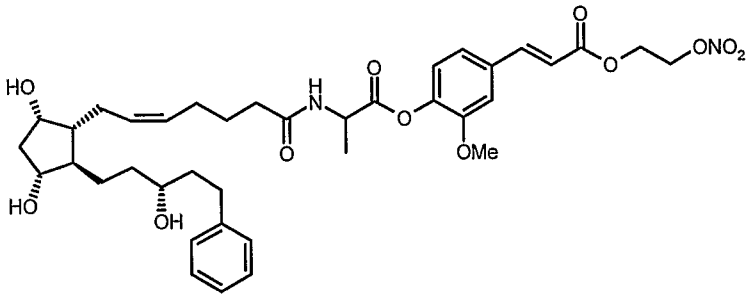

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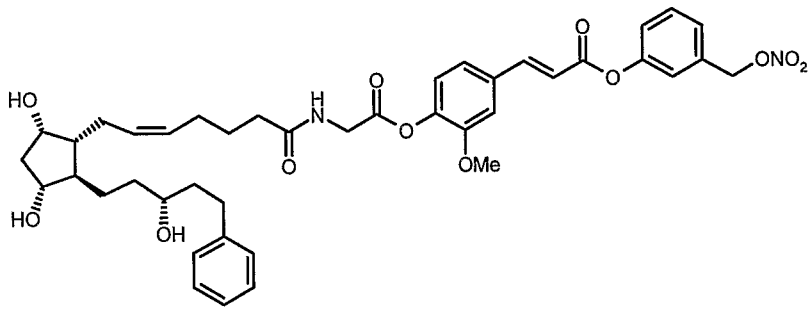

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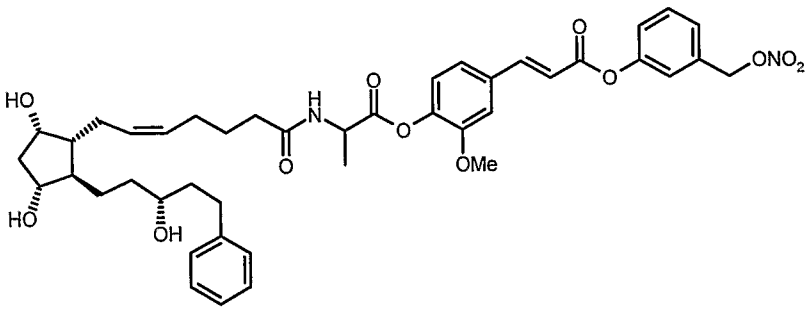

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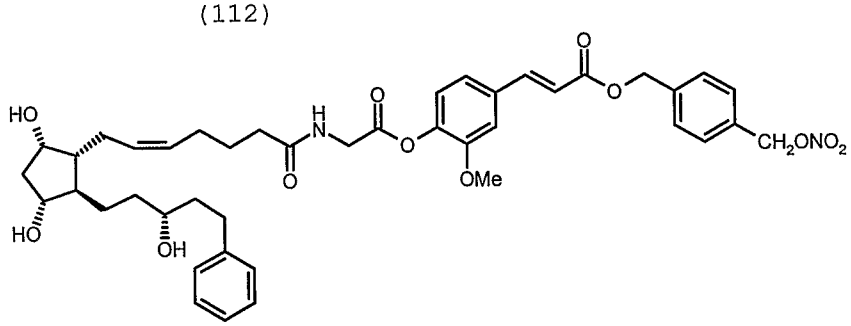

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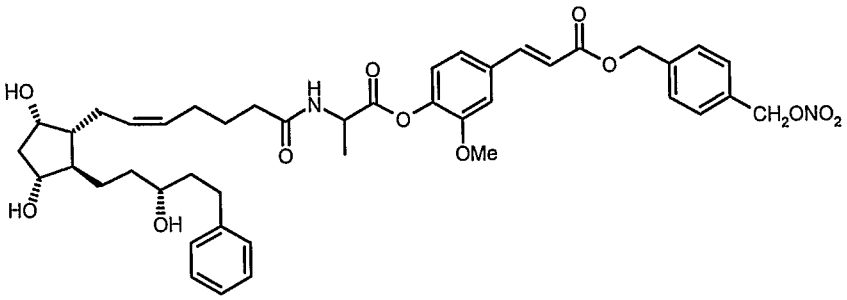

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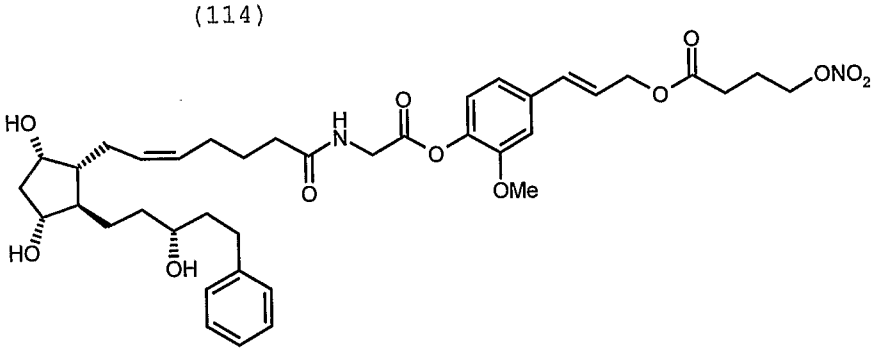

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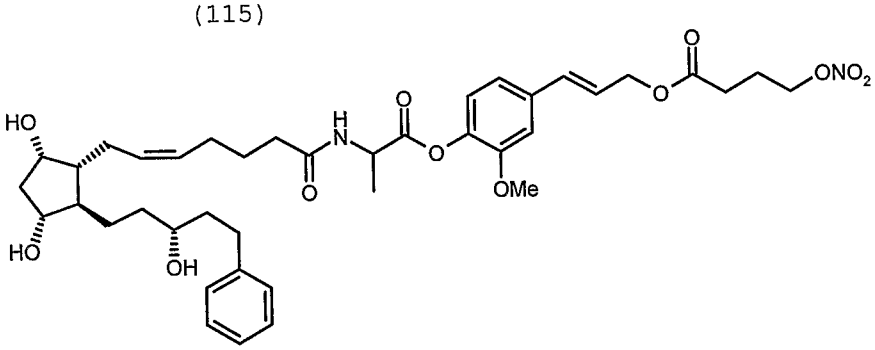

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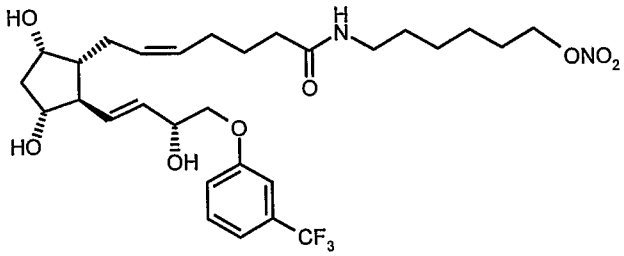

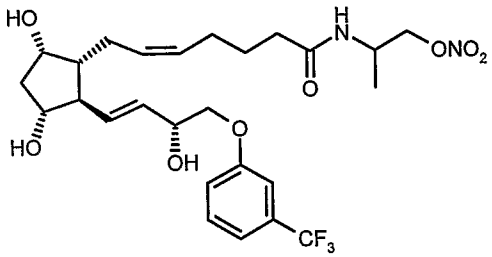

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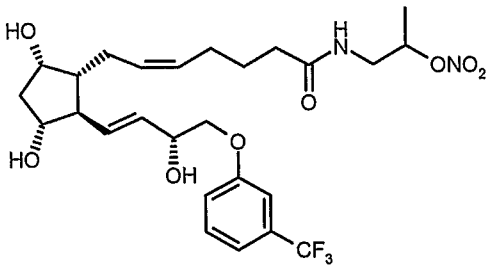

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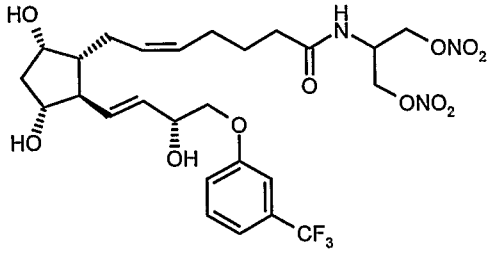

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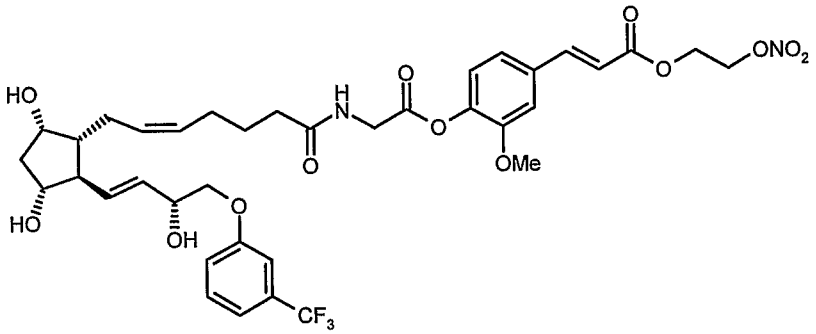

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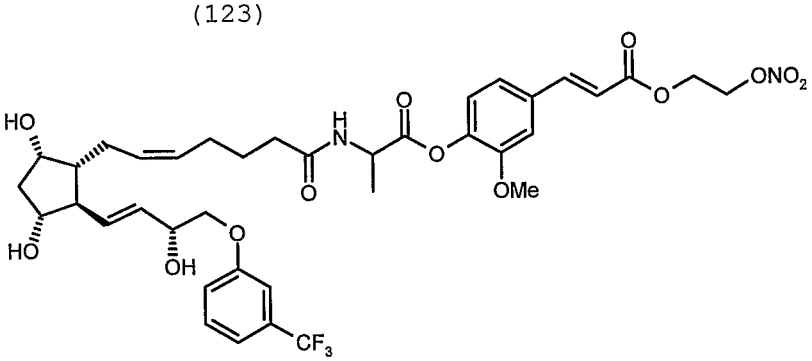

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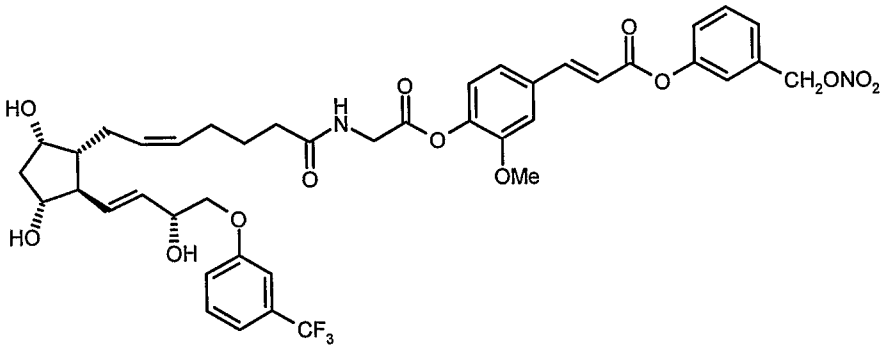

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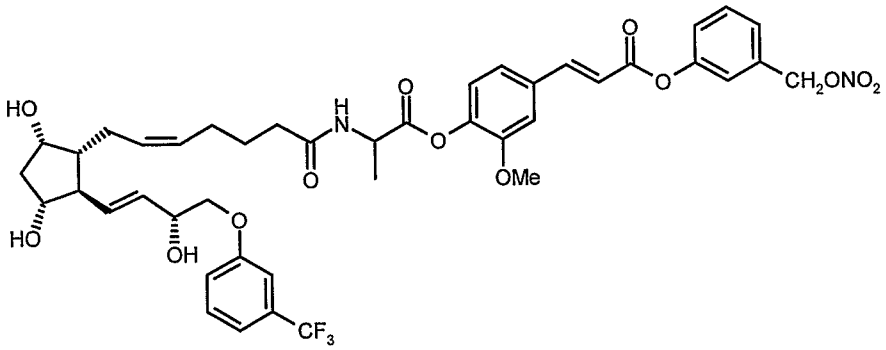

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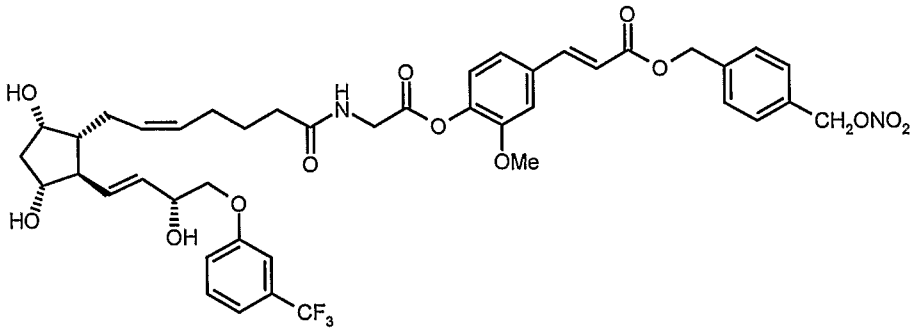

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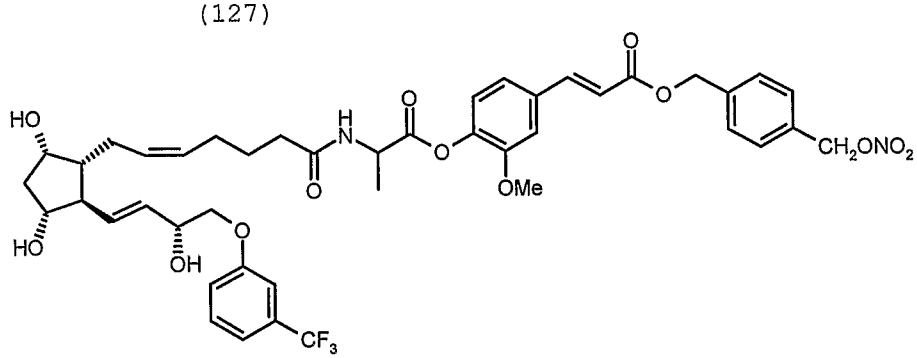

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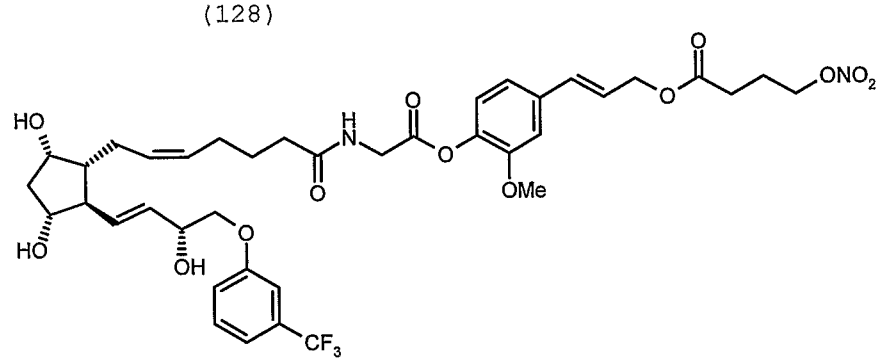

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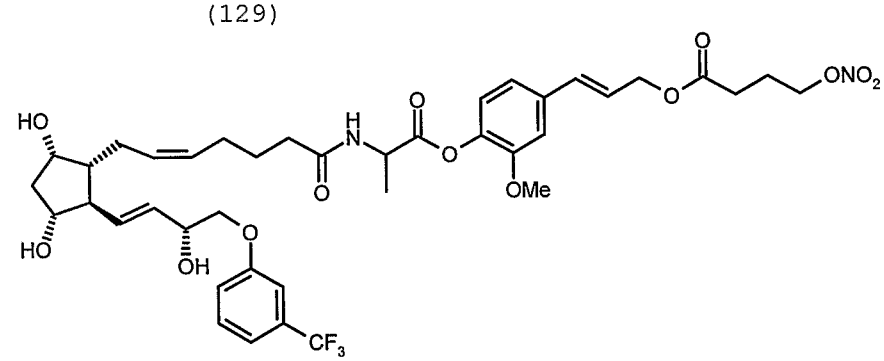

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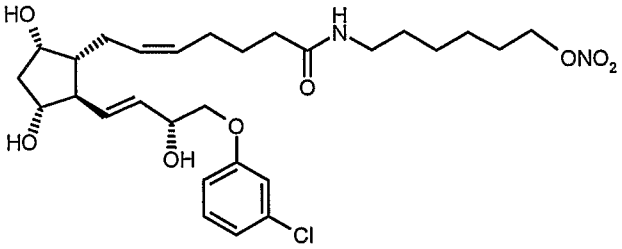

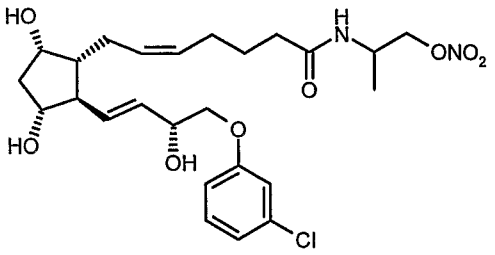

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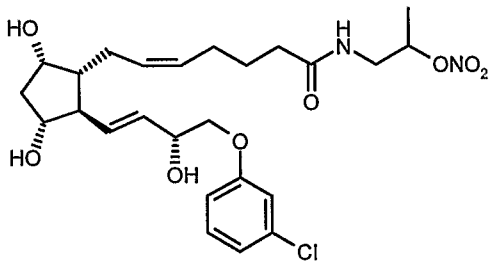

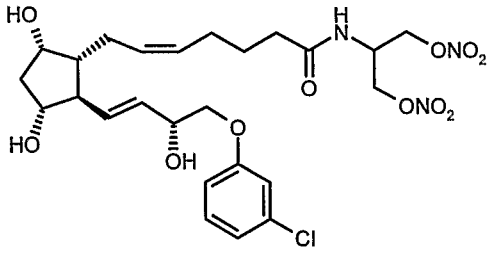

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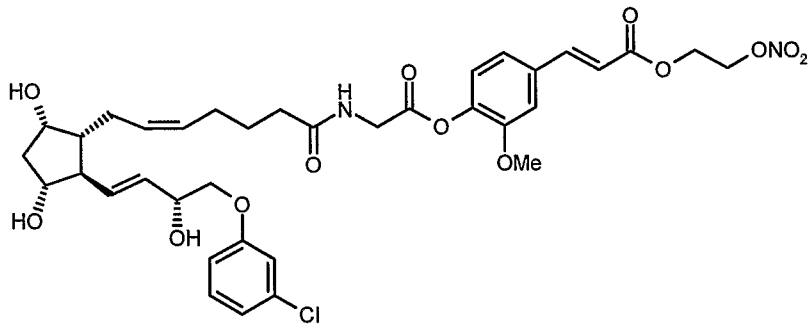

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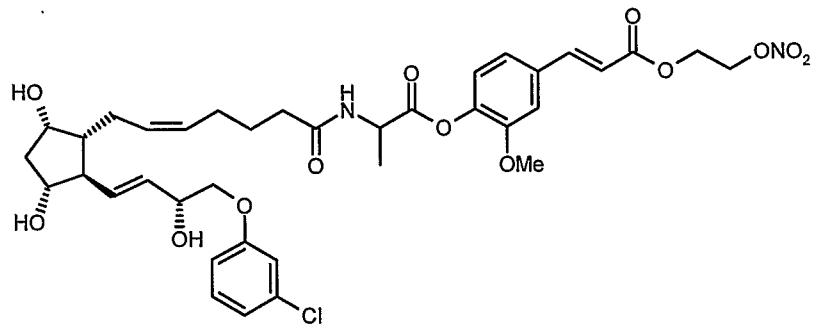

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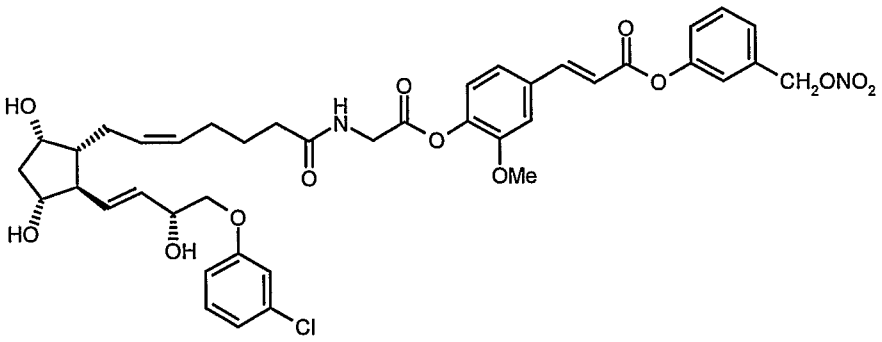

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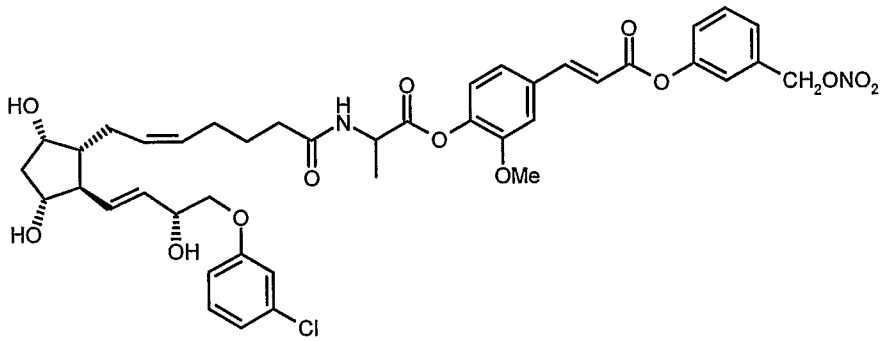

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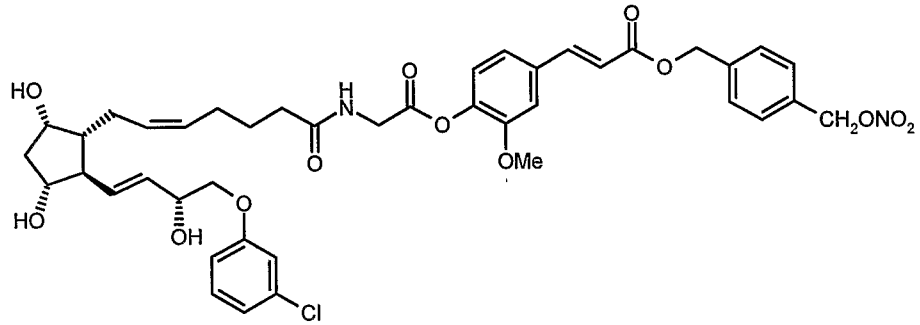

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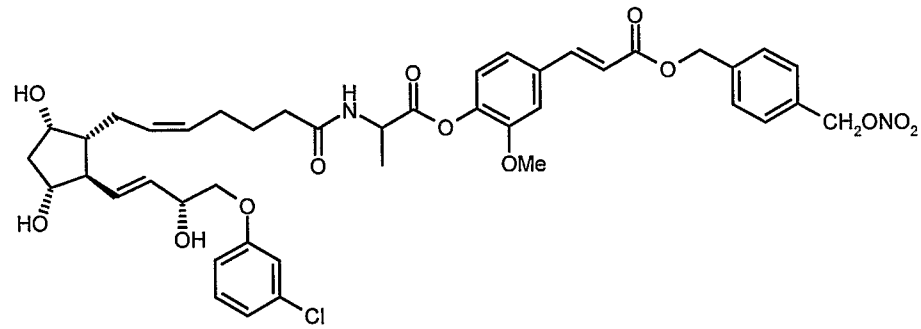

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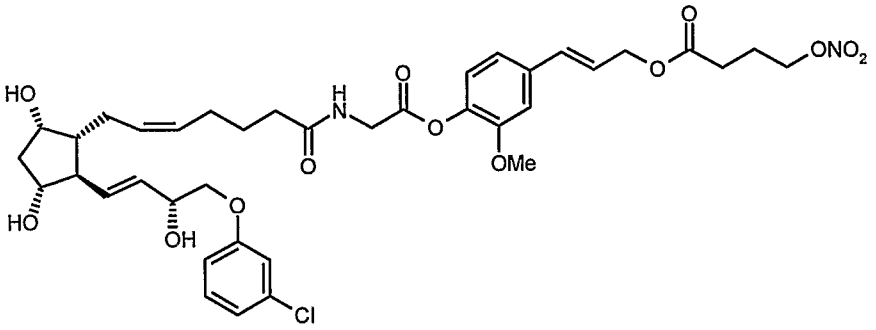

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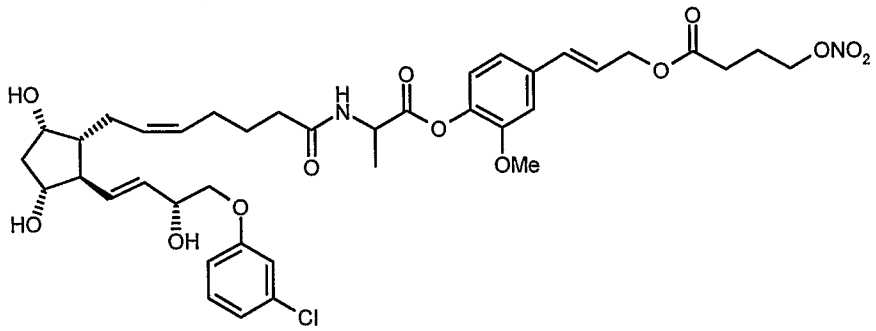

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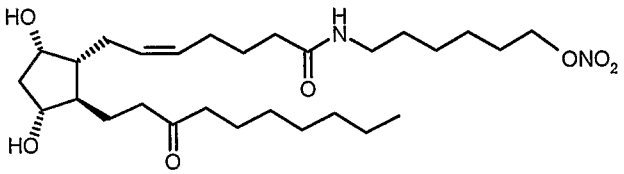

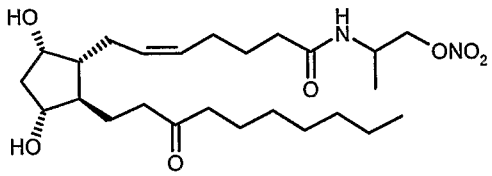

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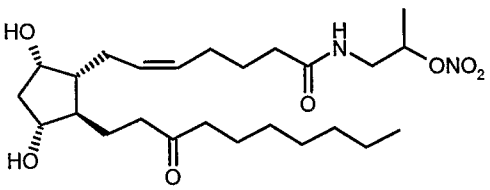

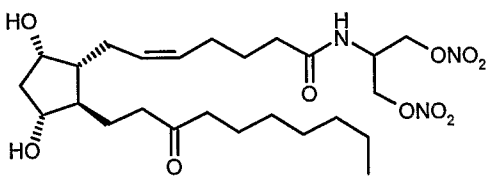

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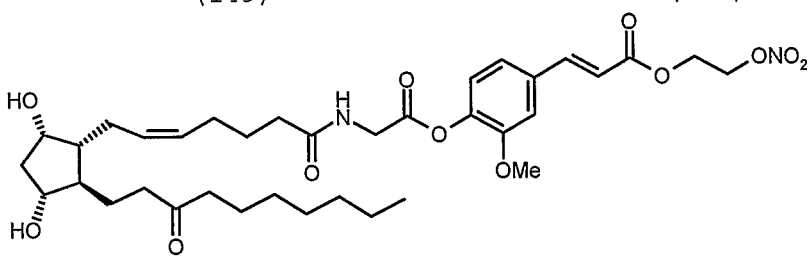

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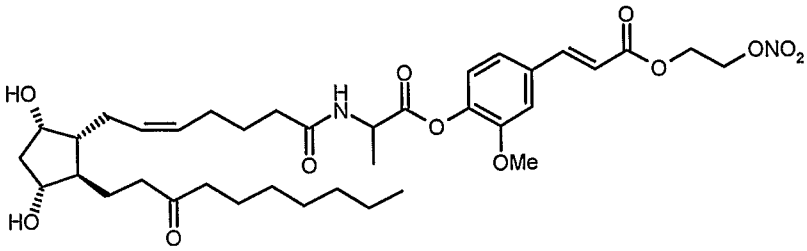

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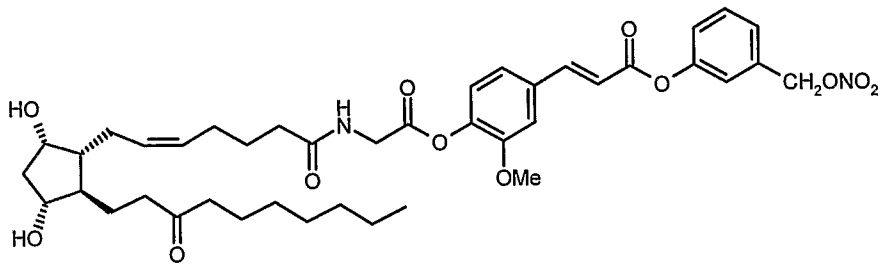

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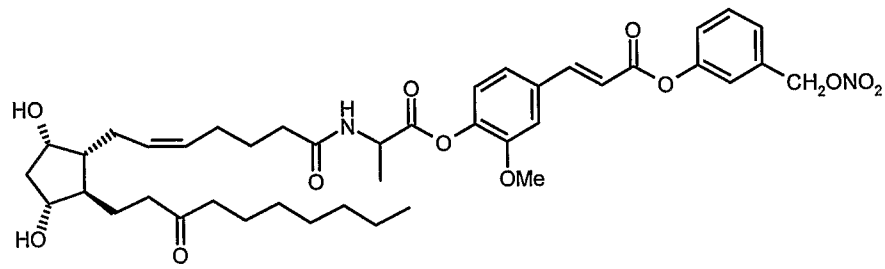

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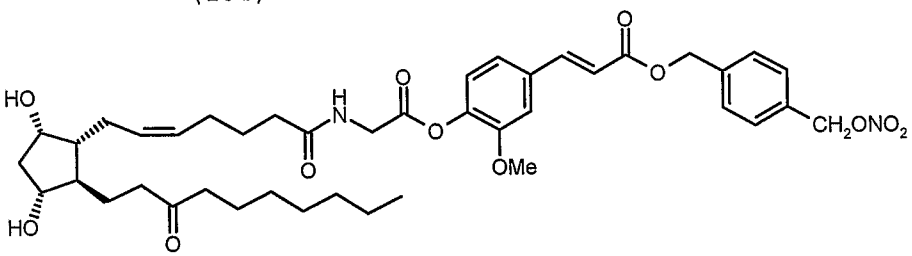

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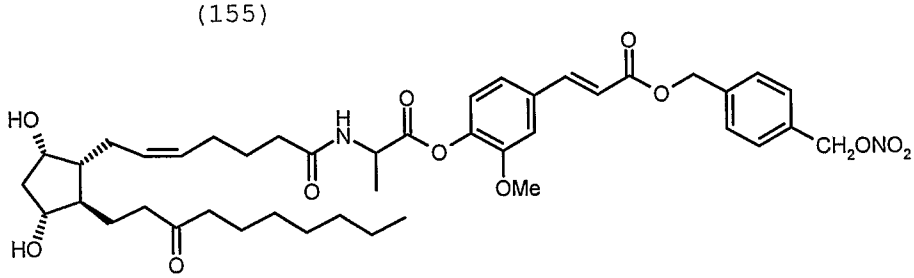

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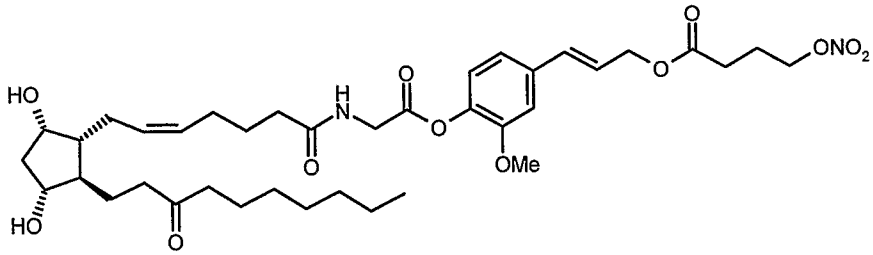

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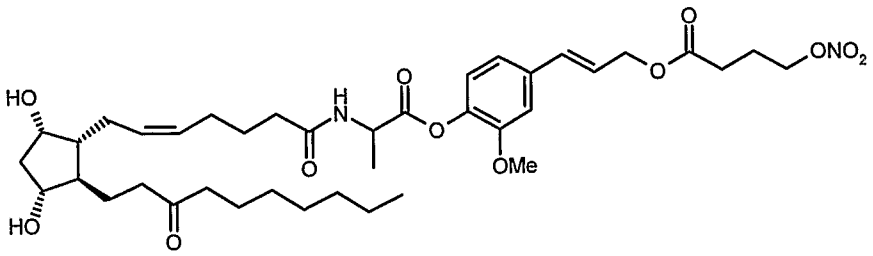

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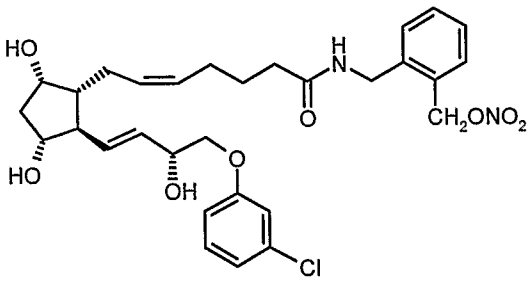

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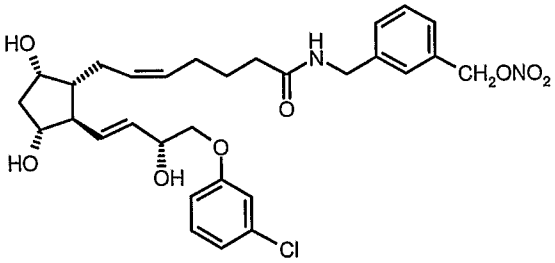

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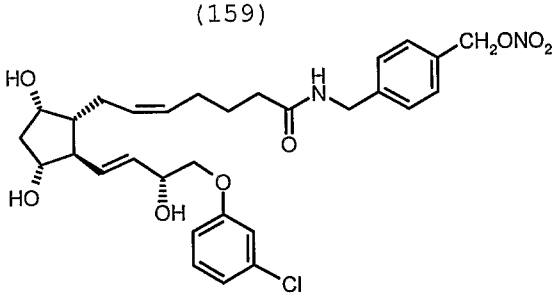

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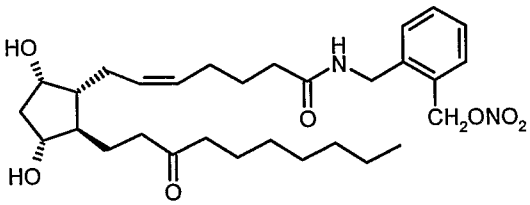

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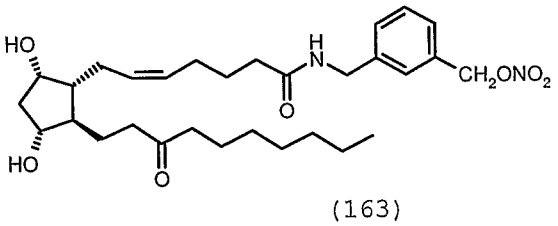

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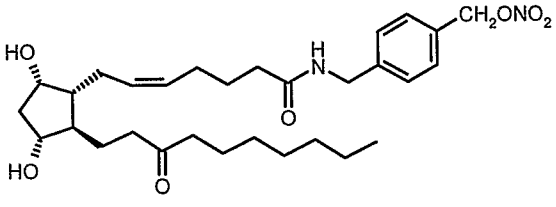

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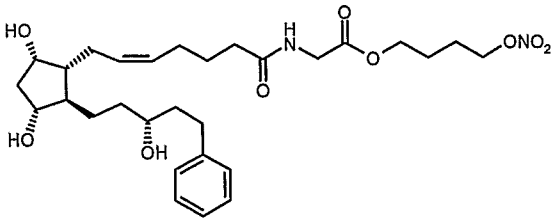

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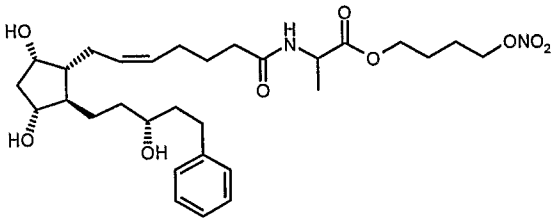

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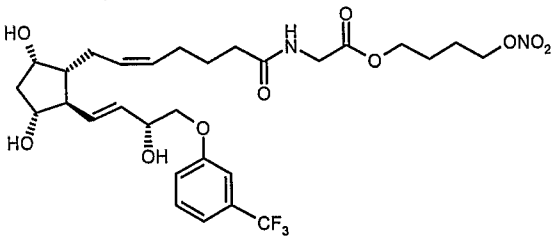

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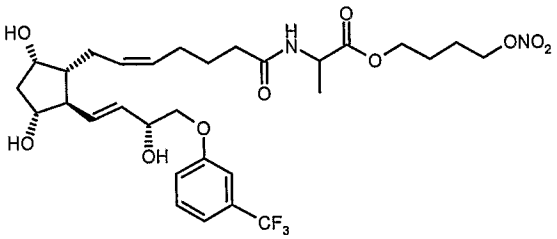

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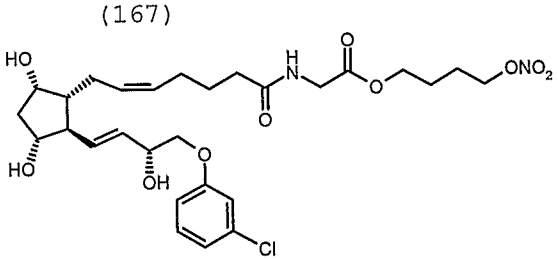

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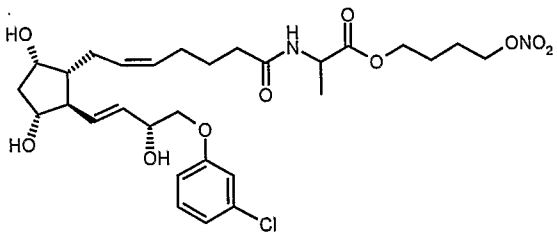

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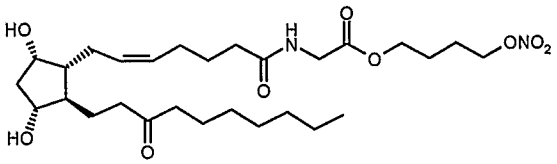

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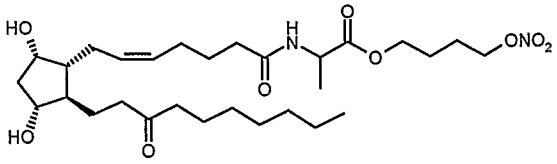

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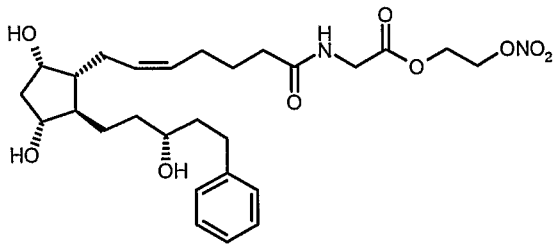

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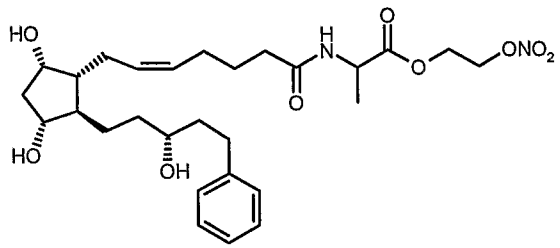

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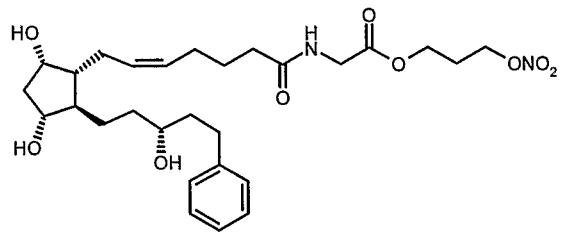

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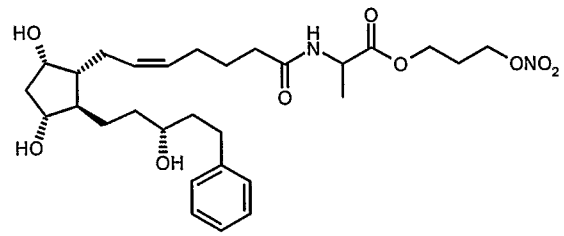

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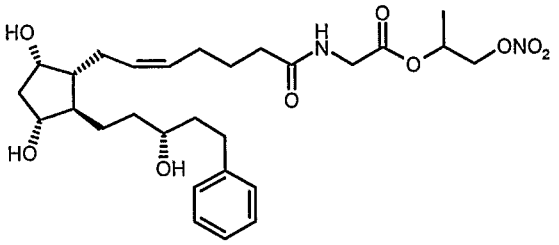

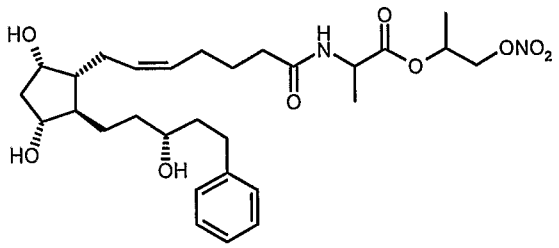

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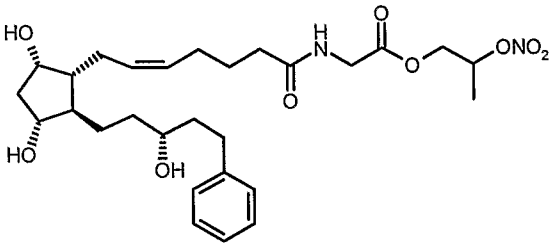

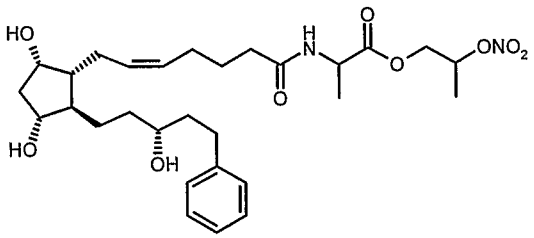

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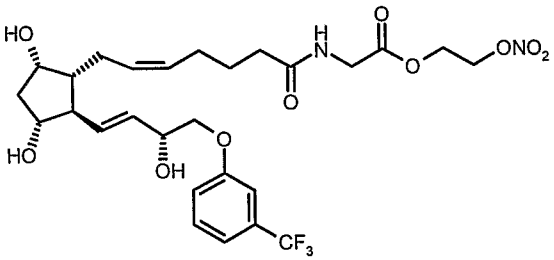

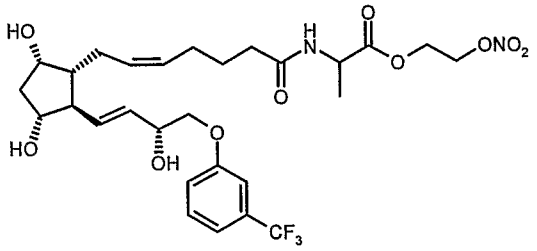

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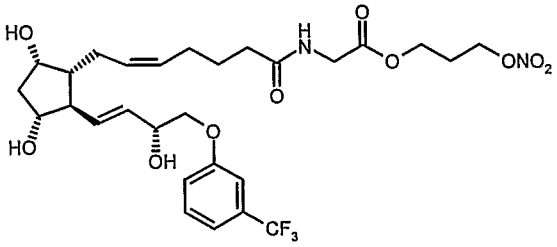

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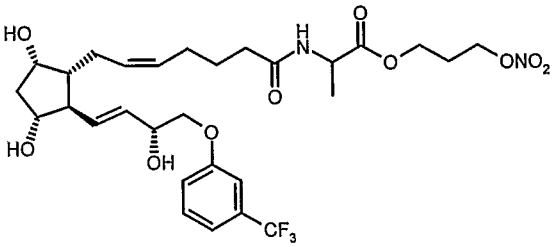

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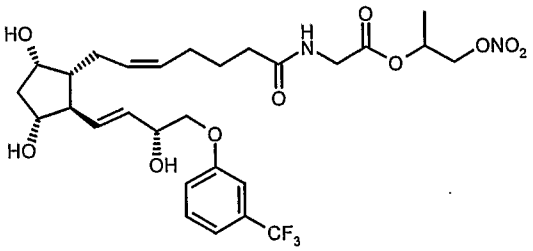

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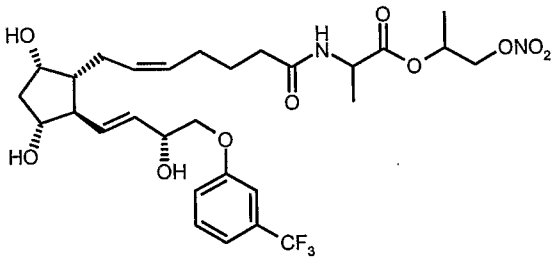

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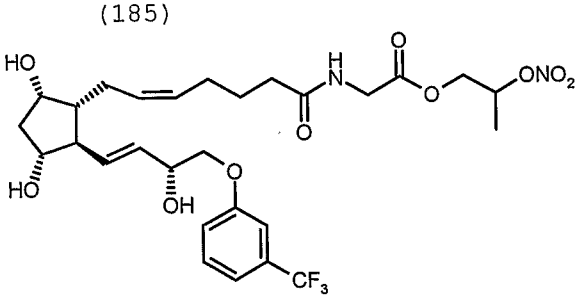

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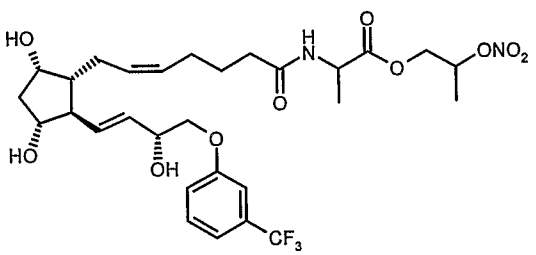

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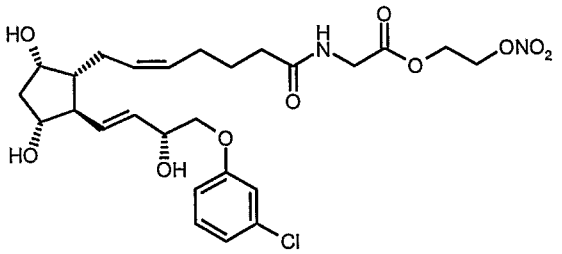

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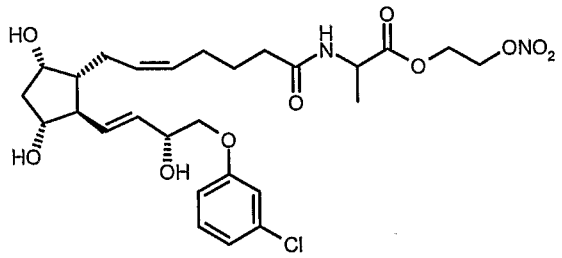

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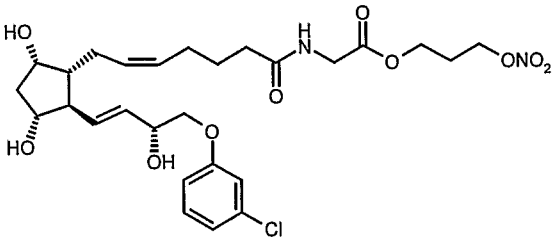

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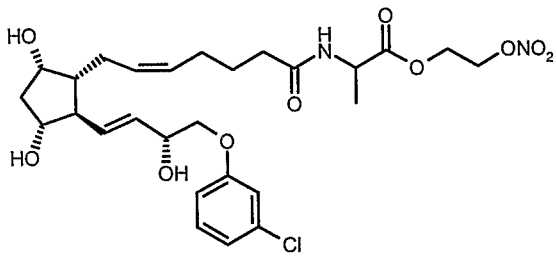

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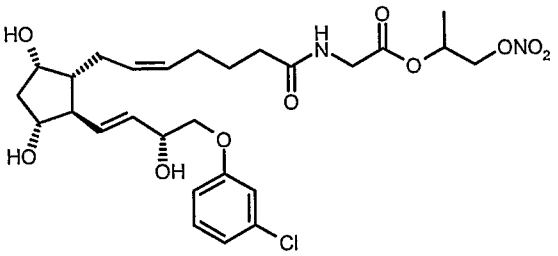

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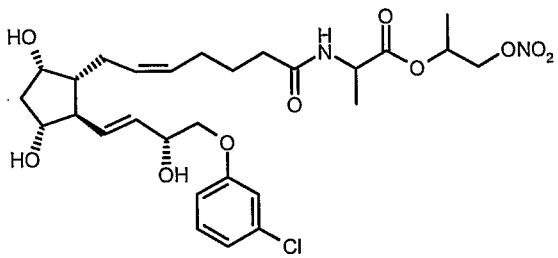

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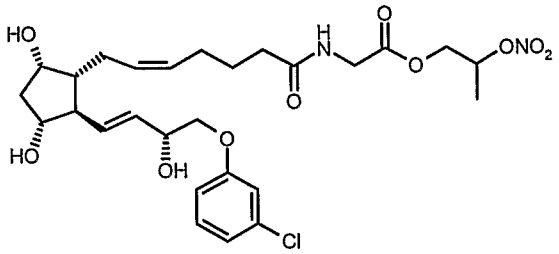

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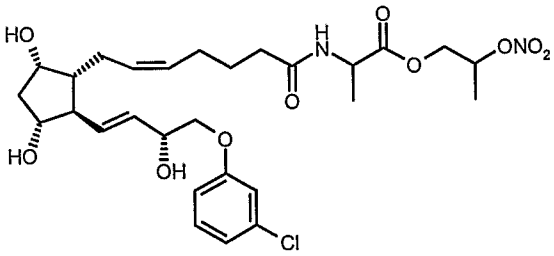

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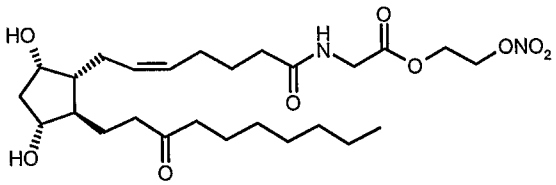

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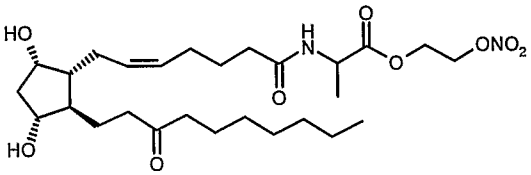

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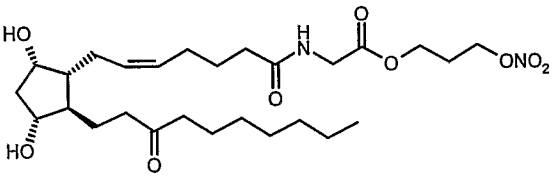

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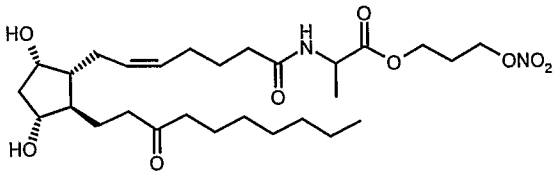

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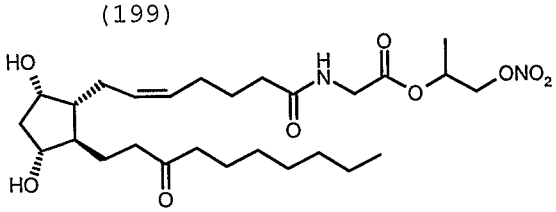

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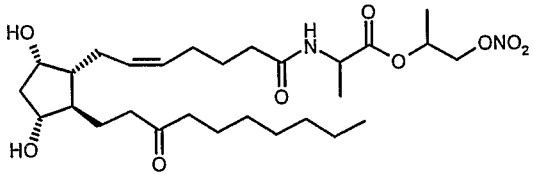

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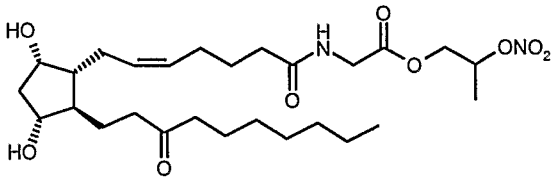

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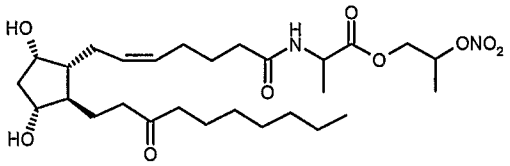

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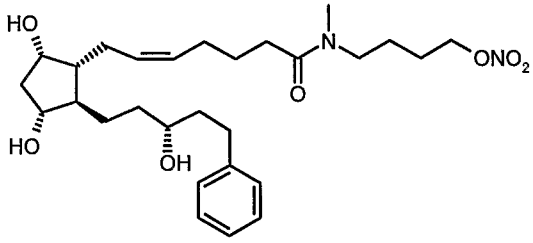

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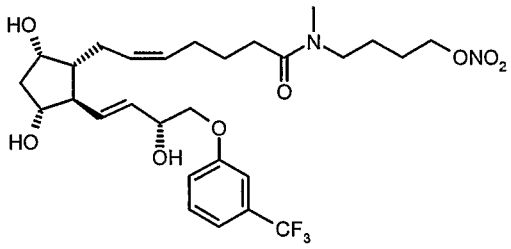

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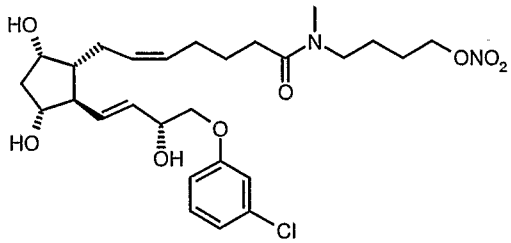

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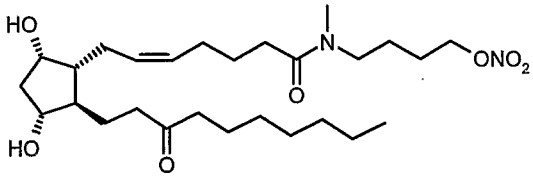

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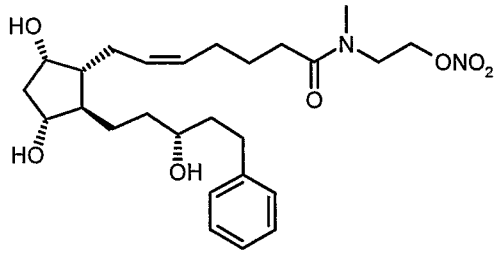

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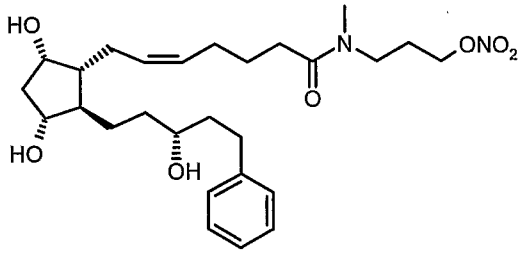

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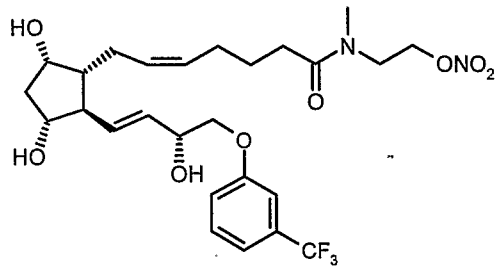

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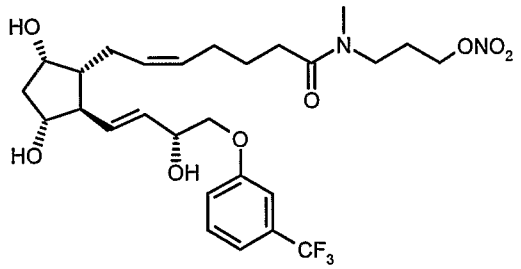

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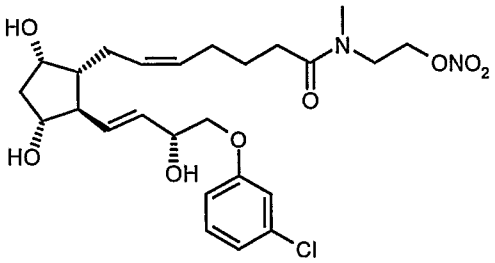

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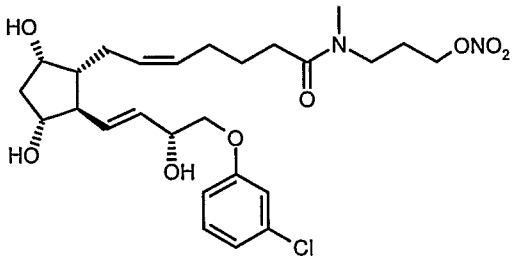

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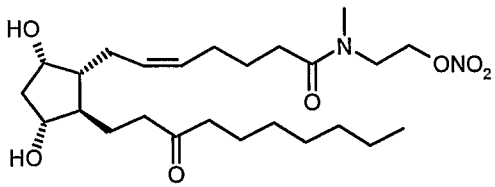

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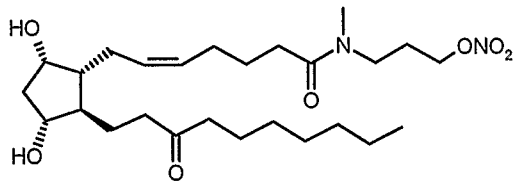

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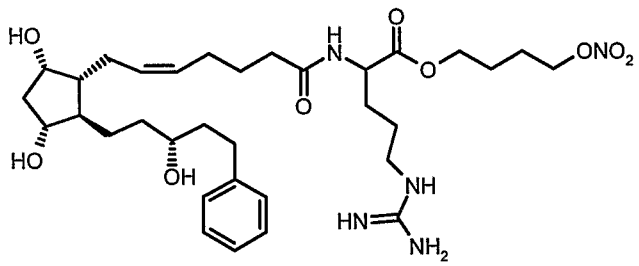

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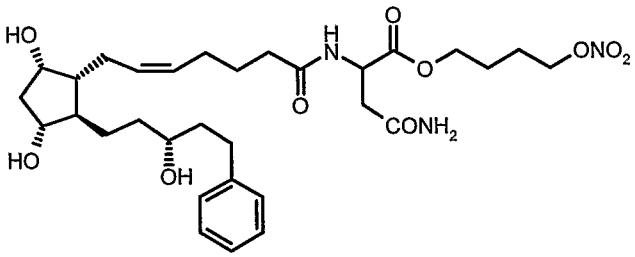

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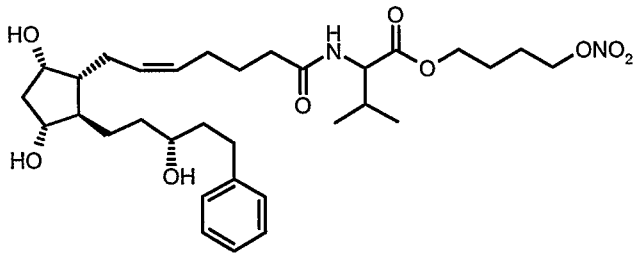

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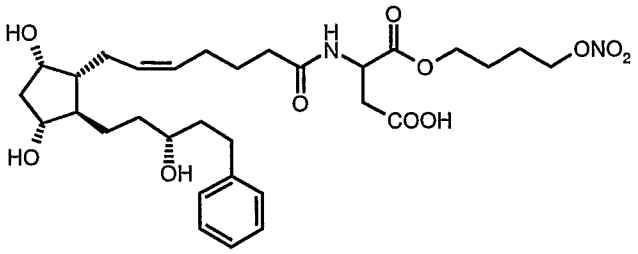

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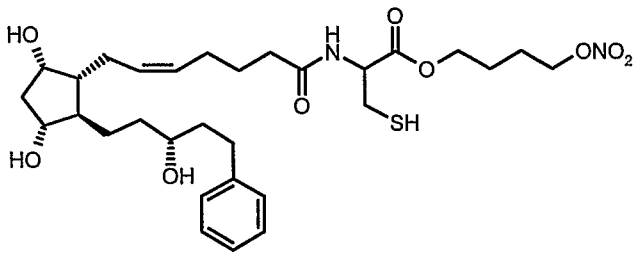

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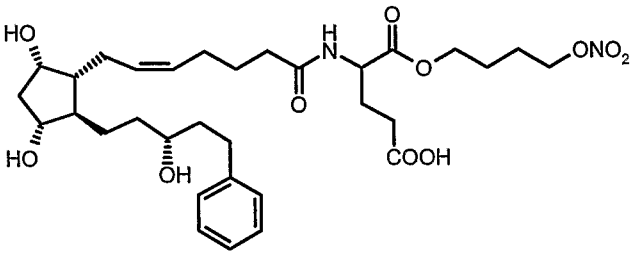

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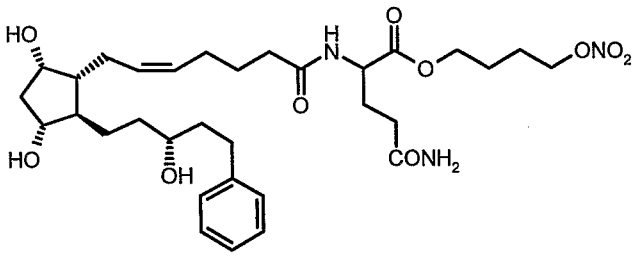

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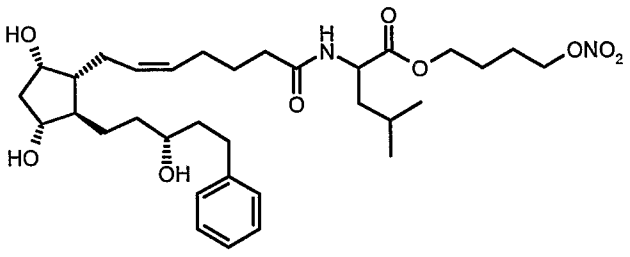

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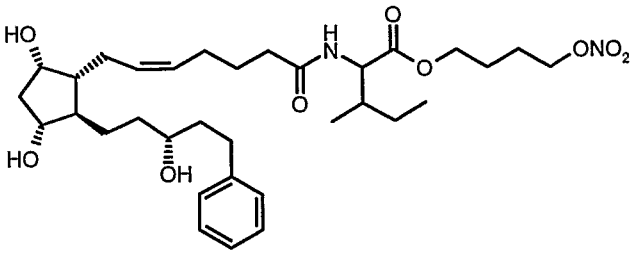

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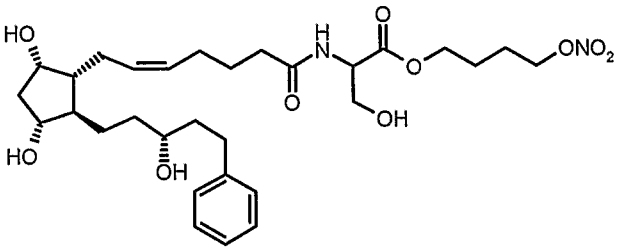

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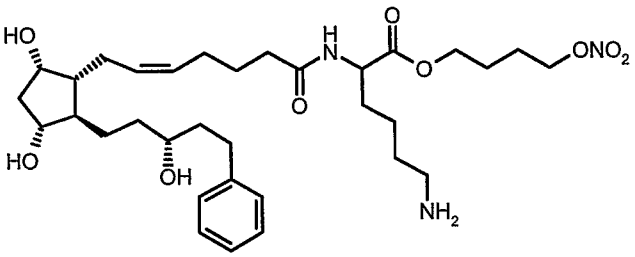

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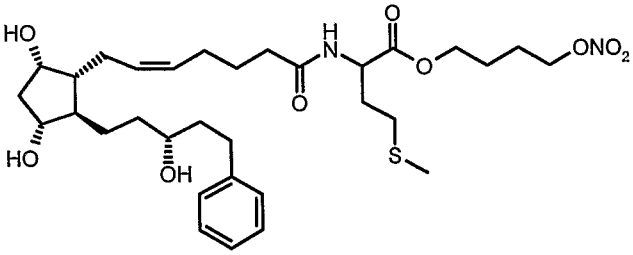

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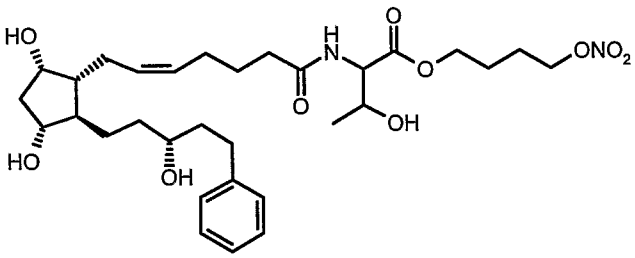

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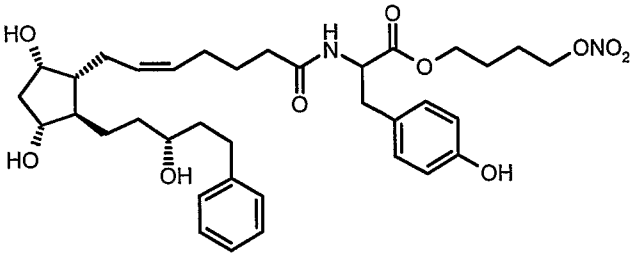

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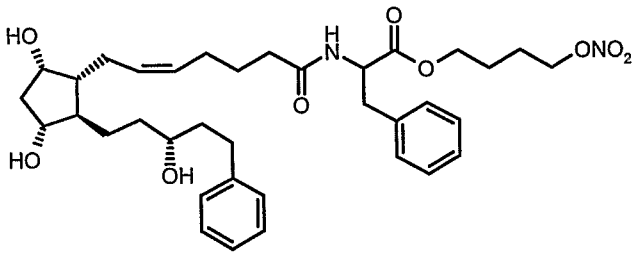

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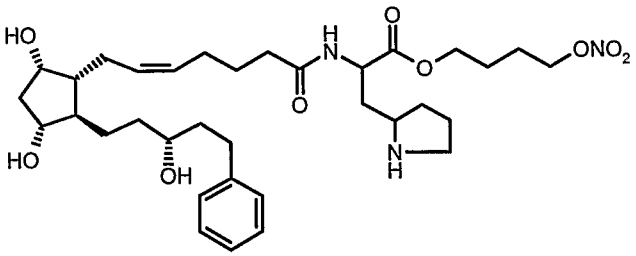

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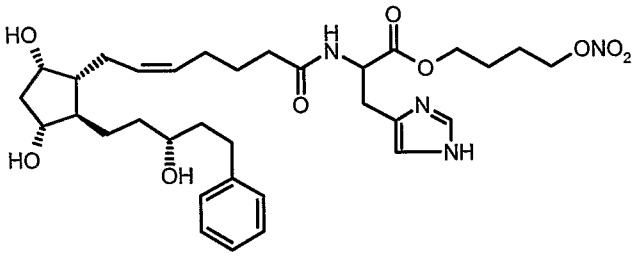

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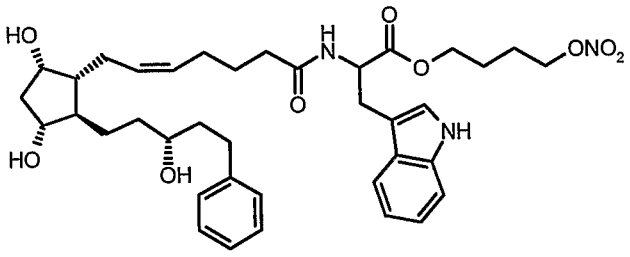


(234)

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 scope of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I), including mixtures enriched in a particular isomer.

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

The preferred route of administration is topical.

The compounds of the present invention can be administered as solutions, suspensions or emulsions (dispersions) in an ophthalmically acceptable vehicle. The term "ophthalmically acceptable vehicle" as used herein refers to any substance or combination of substances which are non-reactive with the compounds and suitable for administration to patient.

Preferred are aqueous vehicles suitable for topical application to the patient's eyes.

Other ingredients which may be desirable to use in the ophthalmic compositions of the present invention include antimicrobials, preservatives, co-solvents, surfactants and viscosity building agents.

The invention also relates to a method for treating glaucoma or ocular hypertension, said method consisting in contacting an effective intraocular pressure reducing amount of a composition with the eye in order to reduce eye pressure and to maintain said pressure on a reduced level.

The doses of prostaglandin nitroderivatives can be determined by standard clinical techniques and are in the same range or less than those described for the corresponding underivatized, commercially available prostaglandin compounds as reported in the: Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 58th Ed., 2004; The pharmacological basis of therapeutics, Goodman and Gilman, J. G. Hardman, L. e. Limbird, Tenth Ed.

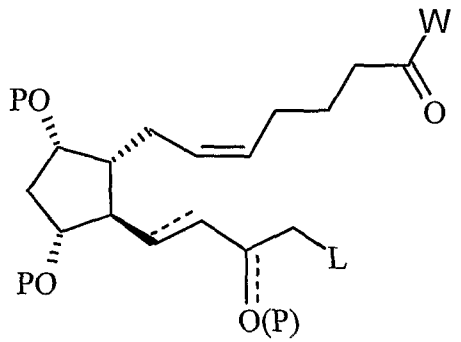
The compositions contain 0.1-0.30 μg, especially 1-10 μg, per application of the active compound.

The treatment may be advantageously carried out in that one drop of the composition, corresponding to about 30 μl, is administered about 1 to 2 times per day to the patient's eye.

It is further contemplated that the compounds of the present invention can be used with other medicaments known to be useful in the treatment of glaucoma or ocular hypertension, either separately or in combination. For example the compounds of the present invention can be combined with (i) beta-blockers, such as timolol, betaxolol, levobunolol and the like (see U.S. Pat. No. 4,952,581); (ii) carbonic anhydrase inhibitors, such as brinzolamide; (iii) adrenergic agonists including clonidine derivatives, such as apraclonidine or brimonidine (see U.S. Pat. No. 5,811,443). Also contemplated is the combination with nitrooxy derivatives of the above reported compounds, for example nitrooxy derivatives of beta-blockers such as those described in U.S. Pat. No. 6,242,432.

The compounds of general formula (I) as above defined, can be obtained by a process comprising the following steps:

a) reacting a compound of formula (III)



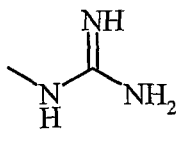
(III)

wherein

L is as above defined; P is H or a hydroxylic protecting group, W is -OH, Cl, or -$OC(O)R_1$ wherein R_1 is a linear or branched C_1-C_5 alkyl;

with a compound of formula (IV)

$$HR^1N\text{-}(B^1)_m\text{-}Y\text{-}Q \quad (IV)$$

wherein R^1, Y and m are as above defined, B^1 is B wherein the possible groups -OH, -COOH, $-CONH_2$,$-NH_2$, -SH,  , were protected as described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980, Q is -ONO_2 or Z_1 wherein Z_1 is selected from the group consisting of:

chlorine, bromine , iodine, mesyl, tosyl; and

b) when Q is Z_1, converting the compound obtained in the step a) into the corresponding nitro derivative by reaction with a nitrate source; and

c) optionally deprotecting the compound obtained in step a) or b).

Step a

Preferred hydroylic protecting groups are silyl ethers, such as trimethylsilyl, tert-butyl-dimethylsilyl, or acetyl and those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980;

- The reaction of a compound of formula (III) wherein W = -OH, P and L are as above defined, with a compound of formula (IV) wherein Q, Y, B,R^1 and m are as above defined may be carried out in presence of a condensing agent as dicyclohexylcarbodiimide (DCC), N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDAC) and a catalyst, such as N,N-dimethylamino pyridine (DMAP) or N,N'-carbonyldiimidazole (CDI). The reaction is carried out in an inert organic solvent dry such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C and 40°C. The reaction is completed within a time range from 30 minutes to 36 hours.
    - The reaction of a compound of formula (III) wherein W = -OC(O)R_1 wherein R_1 and P are as above defined, with a compound of formula (IV) wherein Q, Y, B, R^1 and m are as above defined may be carried out in presence of a catalyst, such as N,N-dimethylamino pyridine (DMAP). The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C and 40°C. The reaction is completed within a time range from 30 minutes to 36 hours.
    - The reaction of a compound of formula (III) wherein W = Cl and P is as above defined, with a compound of formula (IV) wherein Q, Y, B, R^1 and m are as above defined may be carried out in presence of an organic base such as N,N-dimethylamino pyridine (DMAP), triethylamine, pyridine. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C and 40°C. The reaction is completed within a time range from 30 minutes to 36 hours.

Step b)

A nitrate source may be silver nitrate, lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate, calcium nitrate, iron nitrate, zinc nitrate or tetraalkylammonium nitrate (wherein alkyl is C_1-C_{10} alkyl. Preferred nitrate source is silver nitrate. The reaction of step b) is carried out preferably in the dark, in a suitable organic solvent such as acetonitrile, tetrahydrofurane, methyl ethyl ketone, ethyl acetate, DMF, at a temperature from room temperature to the boiling temperature of the solvent.

Step C

The reaction of step C) may be carried out as described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980. The reaction with fluoride ion is the preferred method for removing silyl ether protecting group.

The compounds of formula (III) wherein W = -OH and P = H are commercially available;

The compounds of formula (III) wherein W = -OH and P is a hydroxylic protecting group may be prepared from the corresponding compounds wherein P = H as well known in the art, for example as described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980.

The compounds of formula (III) wherein W = $-OC(O)R_1$ and P is as above defined may be obtained from the corresponding acids wherein W = -OH by reaction with a chloroformate such as isobutylchloroformate, ethylchloroformate in presence of a non-nucleophilic base such as triethylamine in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C and 40°C. The reaction is completed within a time range from 1 to 8 hours.

The compounds of formula (III) wherein W = Cl may be obtained from the corresponding acids wherein W = -OH by reaction with a thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert such as toluene, chloroform, DMF.

The compounds of formula (IV), wherein Q is Z_1 and Y, B, R^1 are as above defined and m=0 can be obtained by reacting a compound of formula (IV_a)

$$HR^1N\text{-}Y\text{-}OH \quad (IV_a)$$

with a suitable reagent such as thionyl or oxalyl chloride, halides of P^{III} or P^{V} , mesyl chloride, tosyl chloride in an inert solvent such as toluene, chloroform, DMF, etc.

The compounds of formula (IV), wherein Q is $-ONO_2$, and Y, B, R^1 are as above defined and m=0 are obtained by conversion of the above compounds of formula(IV_a)as above described in step b). Alternatively the nitration can be carried out in the presence of nitric acid and acetic anhydride in a temperature range from –50°C to 0°C according to methods well known in the literature.

The compounds of formula (IV) wherein R^1, Q, Y, B, Z are as above defined and m=1 can be obtained by a process comprising the following steps:

d) reacting a compound of formula (V)

$$P_1R^1N\text{-}B^1\text{-}W \quad (V)$$

wherein W, B_1 and R^1 are as above defined, P_1 is H or an amino protecting group such as tert-butylcarbamate (BOC), 2,2,2-trichloroethyl carbamate (TROC) and those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980, with a compound of formula (VI)

$$Z_3\text{-}Y\text{-}Q \quad (VI)$$

wherein Y and Q are as above defined, Z_3 is HO or Z_1 wherein Z^1 is as above defined, and optionally deprotecting the obtained compounds as described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980;and

e) when Q is Z_1, converting the compound obtained in the step d) into a nitro derivative by the procedure above described.

The reaction of a compound of formula (V) wherein W = -OH, , with a compound of formula (VI) Z_3-Y-Q wherein Z_3 is –OH, Y and Q are as above defined, may be carried out in presence of a dehydrating agent as dicyclohexylcarbodiimide (DCC) or

N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDAC) and a catalyst, such as N,N-dimethylamino pyridine (DMAP). The reaction is carried out in an inert organic solvent dry such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C and 40°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (V) wherein W = -OH are commercially available or can be synthetized according to methods well known in the literature.

- The reaction of a compound of formula (V) wherein W = $-OC(O)R_1$ wherein R_1 is as above defined with a compound of formula (VI) Z_3-Y-Q wherein Z_3 is –OH, Y and Q are as above defined, may be carried out in presence of a catalyst, such as N,N-dimethylamino pyridine (DMAP). The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C and 40°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (V) wherein W = $-OC(O)R_1$ may be obtained from the corresponding acids wherein W = -OH by reaction with a chloroformate such as isobutylchloroformate, ethylchloroformate in presence of a non-nucleophilic base such as triethylamine in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C and 40°C. The reaction is completed within a time range from 1 to 8 hours.

- The reaction of a compound of formula (V) wherein W = -OH, with a compound of formula (VI) Z_3-Y-Q wherein Z_3 is Z_1, Y and Q are as above defined, may be carried out in presence of a organic base such as 1,8-diazabiciclo[5.4.0]undec-7-ene (DBU), N,N-diisopropylethylamine, diisopropylamine or inorganic base such as alkaline-earth metal carbonate or hydroxide, potassium carbonate, cesium carbonate, in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, acetone, methyl ethyl ketone, acetonitrile, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C and 40°C, preferably from 5°C to 25°C. The reaction is completed within a time range from 1 to 8 hours. When Z_1 is chosen among chlorine or bromine the reaction is carried out in presence an iodine compound such as KI.

- The reaction of a compound of formula (V) wherein W = Cl with a compound of formula (VI) Z_3-Y-Q wherein Z_3 is –OH, Y and Q are as above defined, may be carried out in presence of a of a organic base such as N,N-dimethylamino pyridine (DMAP), triethylamine, pyridine. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene,

dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from -20°C and 40°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (V) wherein W = Cl may be obtained from the corresponding acids wherein W = -OH by reaction with a thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert such as toluene, chloroform, DMF.

The compounds of formula (VI) Z_3-Y-Q wherein Z_3 is –OH, Q is -ONO_2 and Y is as above defined can be obtained by converting the corresponding diol derivative of formula (VII)

HO-Y-OH (VII)

wherein Y is as above defined, in a compound of formula (VIII)

Z_3-Y-Z_1 (VIII)

wherein Z_3, Y, Z_1 are as above defined, by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P^{III} or P^{V} , mesyl chloride, tosyl chloride in solvents inert such as toluene, chloroform, DMF, etc. The final conversion to the nitro derivative is carried out as above described. Alternatively the diol derivative of formula (VII) can be nitrated by reaction with nitric acid and acetic anhydride in a temperature range from –50°C to 0°C according to methods well known in the literature.

Compounds of formula (VII) are commercially available, or can be synthesized by well known reactions.

The compounds of formula (VI) wherein Z_3 is Z_1, Q is -ONO_2 and Y and Z_1 are as above defined can be obtained from the halogen derivative of formula (IX)

Z_1-Y-Hal (IX)

wherein Hal is halogen, by conversion to the nitro derivative following the methods above described.

Compounds of formula (IX) are commercially available or can be synthesized according to methods well known in the literature,

The following examples are to further illustrate the invention without limiting it.

Example 1

Synthesis of [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid 3-(nitrooxy)propyl amide.

A) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-di-TBDMSilyl-oxy-2-(3 TBDMSilyl-oxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid

To a solution of latanoprost acid (1g, 2.56mmol) in dimethylformamide dry (12ml), TBDMSiCl (4.6g, 30.72mmol) and imidazole (2.1g, 30.72mmol) were added. The reaction was stirred at room temperature for 24 hours. The solution was treated with $KHSO_4$ and extracted three times with AcOEt. The organic layers were washed with

brine, dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent n-hexane/ethyl acetate 8/2. The product (1.3g) was obtained as an oil.

B) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-di-TBDMSilyl-oxy-2-(3-TBDMSilyl-oxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid 3-bromopropylamide

To a suspension of 3-bromopropylamine hydrobromide (0.12g, 0.55mmol) in CH_2Cl_2 (50ml), TEA (0.55mg, 0.55mmol) was added. After 30 min compound A (0.2g, 0.27mmol), EDAC (0.77g, 0.40mmol) and DMAP (cat. amount) were added and the reaction was stirred at room temperature for 4 hours. The solution was washed with water and the organic layers were dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent n-hexane/ethyl acetate 8/2. The product (0.13 g) was obtained as an oil.

C) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-di-TBDMSilyl-oxy-2-(3-TBDMSilyl-oxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid 3-(nitrooxy)propylamide

A solution of compound B (0.1g, 0.11mmol) and silver nitrate (0.03g, 0.17mmol) in acetonitrile (50ml) was stirred at 40°C, in the dark, for 4 hours. The precipitated (silver salts) was filtered off and the solvent was evaporated under vacuum. The residue was purified by flash chromatography, eluent n-hexane/ethyl acetate 8/2. The product (0.07g) was obtained as oil.

D) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid 3-(nitrooxy)propylamide

To a solution of compound C (0.05g, 0.06mmol) in THF dry under inert atmosphere a solution of n-Bu_4-NF in THF (1M) (0.27ml, 0.27mmol) was added.
The mixture was stirred at room temperature 3 days and washed with water. AcOEt was added and the organic layers were washed with brine, dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent ethyl acetate/n-hexane 7/3. The product was obtained as an oil.

^{1}H-NMR($CDCl_3$): 7.35-7.10(5H,m); 5.46(2H,m); 4.54(2H,t); 4.10(1H,m); 3.76(1H,m); 3.67(1H,m); 3.35 (2H,m); 2.75(2H,m); 2.40-2.0(8H,m); 1.90-1.45(10H,m); 1.45-1.25(2H,m).

Example 2

Synthesis of [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid N-methyl-N-(3-(nitrooxy)propyl) amide (corresponding to compound of formula 210).

A) N-Methyl-3-iodopropylamine hydrocloride

To a solution of N-methyl-3-cloropropylamine hydrochloride (0.7 g, 4.86mmol) in acetonitrile (20 ml), sodium iodide (3.64 g, 24.3 mmol) was added. The reaction was heated to 150°C for 30 minutes under microwave irradiation. The resulting mixture was cooled, filtered and the solvent was removed under reduced pressure to give a solid product (yield> 95%) which was used without further purification.

B) N-Methyl-3-nitroxypropylamine nitrate salt

To a solution of N-methyl-3-cloropropylamine hydrochloride (1.1 g, 4.67mmol) in acetonitrile (20 ml), silver nitrate (0.8 g, 4.86 mmol)was added. The reaction was heated to 100°C for 4 minutes under microwave irradiation. The resulting mixture was cooled, filtered and used without further purification.

C) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-di-TBDMSilyl-oxy-2-(3-TBDMSilyl-oxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid

To a solution of latanoprost acid (1 g, 2.56 mmol) in dimethylformamide dry (12 ml), TBDMSiCl (4.6 g, 30.72 mmol) and imidazole (2.1g , 30.72 mmol) were added. The reaction was stirred at room temperature for 24 hours. The solution was treated with $KHSO_4$ and extracted three times with AcOEt. The organic layers were washed with brine, dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent n-hexane/ethyl acetate 8/2. The product (1.3g) was obtained as an oil.

D) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-di-TBDMSilyl-oxy-2-(3-TBDM silyl-oxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid N-methyl-N-(3-(nitrooxy)propyl) amide.

To a solution of N-methyl-3-nitroxypropylamine nitrate salt (4.8 mmol, compound B)in acetonitrile (40 ml), compound C (1.6 g, 2.18 mmol), EDAC (1.4 g, 7.3 mmol) and DMAP (cat. amount) were added and the reaction was stirred at room temperature for 4 hours. The solution was concentrated under reduced pressure. The residue was treated with ethyl acetate, washed with water and the organic layers were dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent n-hexane/ethyl acetate 8/2. The product (1 g) was obtained as an oil.

E) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid N-methyl-N-(3-(nitrooxy)propyl) amide.

To a solution of compound D (100 mg, 0.11 mmol) in acetonitrile (50 ml) phosphomolybdic acid hydrate (100 mg) was added.
The mixture was stirred at room temperature 30 minutes and the solvent was removed under reduced pressure. The residue was purified by HPLC Preparative, Column Symmetry C18 7 um 19x150 mm, eluent acetonitrile/water, a gradient flow was used as follows:0 min 20% CH_3CN,12 min 80% CH_3CN,15 min 80% CH_3CN,18 min 100% CH_3CN, 20 min 20% CH_3CN,flow rate 20 ml/min,detector UV λ 200 nm Temp. 25°C. . The product (10 mg) was obtained as an oil.

^{1}H-NMR($CDCl_3$): 7.31-7.13 (5H, m); 5.52-5.32 (2H, m); 4.49 (2H, t); 4.16 (1H, bs); 3.95 (1H, bs); 3.67 (1H, m); 3.47 (2H, m); 3.0 (3H, s); 2.89-2.6 (2H, m); 2.4-0.7 (18H, m).

Example 3

Synthesis of [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid amide with glycine[2-methoxy-4-[2-propenoyloxy(4-nitrooxybutyl)]] phenyl ester (corresponding to compound of formula 19)

F) Ferulic acid 4-(bromo)butyl ester

To a solution of ferulic acid (1 g, 5.15 mmol) in tetrahydrofurane (40 ml), triphenylphosphine (2.7 g, 10.3 mmol) and tetrabromomethane (3.41 g, 10.3 mmol) were added. The mixture was stirred at room temperature for 4 hours. The mixture was filtered and the solvent was evaporated under vacuum. The crude residue was purified by silica gel chromatography, eluent n-hexane/ethyl acetate 7/3. The product (0.77 g) was obtained as a yellow solid. (Yield 46%)

G) Ferulic acid 4-(nitrooxy)butyl ester

A solution of compound A (0.8 g, 2.43 mmol) and silver nitrate (1.2 g, 7.29 mmol) in acetonitrile (50 ml) was stirred at 40°C, in the dark, for 16 hours. The precipitated (silver salts) was filtered off and the solvent was evaporated under vacuum. The residue was purified by flash chromatography, eluent n-hexane/ethyl acetate 75/25. The product (0.4 g) was obtained as white powder (yield 53%)

H) N-Boc-glycine [2-methoxy-4-[2-propenoyloxy(4-nitrooxybutyl)]] phenyl ester

To a solution of N-Boc-glycine (0.508 g, 2.9 mmol) in chloroform (50 ml), ferulic acid 4-(nitrooxy)butyl ester (0.9 g, 2.9 mmol), EDAC (0.83 g, 4.3 mmol) and DMAP (cat. amount)

were added and the reaction was stirred at room temperature for 3 hours. The solution was washed with water and the organic layers were dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent n-hexane/ethyl acetate 7/3. The product (0.8 g) was obtained as an oil.

I) Glycine [2-methoxy-4-[2-propenoyloxy(4-nitrooxybutyl)]] phenyl ester hydrochloride

To a solution of compound H (0.8 g, 1.7 mmol) in ethyl acetate (30 ml), HCl gas was bubbled until the TLC (n-hexane/ethyl acetate 7/3) showed no starting material. The reaction mixture was filtered. The solid was dried under vacuum. The product (0.6 g) was obtained as an oil.

J) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-di-TBDMSilyl-oxy-2-(3-TBDM silyl-oxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid amide with glycine[2-methoxy-4-[2-propenoyloxy(4-nitrooxybutyl)]] phenyl ester

To a solution of compound I (0.40 g, 1.0 mmol)in acetonitrile (100 ml), compound C (0.73 g, 1.0 mmol), EDAC (0.2 g, 1.5 mmol) and DMAP (cat. amount) were added and the reaction was stirred at room temperature for 4 hours. The solvent was evaporated under vacuum. The residue was purified by flash chromatography, eluent n-hexane/ethyl acetate 75/25. The product (0.25 g) was obtained as an oil.

K) Synthesis of [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid amide with glycine[2-methoxy-4-[2-propenoyloxy(4-nitrooxybutyl)]] phenyl ester

To a solution of compound J (250 mg, 0.23 mmol) in acetonitrile (50 ml) phosphomolybdic acid hydrate (250 mg) was added.
The mixture was stirred at room temperature 30 minutes and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using a gradient flow n-hexane/ethyl acetate 50/50, ethyl acetate 100%. The product (15 mg) was obtained as an oil.

^{1}H-NMR($CDCl_3$): 7.63 (1H, d); 7.31-7.05 (8H, m); 6.42-6.32 (2H, m); 5.5-5.27 (2H, m); 4.5 (2H, t); 4.25 (2H, d); 4.23 (2H, t); 4.14 (1H, bs); 3.93 (1H, bs); 2.82 (3H, s); 3.72-3.61 (1H, m); 2.85-2.58 (4H, m); 2.42-2.2 (8H, m); 1.95-1.45 (9H, m); 1.43-1.20 (6H, m).

Example 4

Synthesis of [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid 6-(nitrooxy)hexyl amide (corresponding to compound of formula 105).

Q) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-di-TBDMSilyl-oxy-2-(3-TBDM silyl-oxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid 6-iodohexyl amide

To a suspension of 6-iodohexylamine hydrochloride (1.9g, 8mmol) in CH_2Cl_2 (50ml) compound F) (3g, 4mmol), EDAC (1.15g, 6mmol) and DMAP (cat. amount) were added. The reaction was stirred at room temperature for 4 hours. The solution was washed with water and the organic layers were dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent n-hexane/ethyl acetate 8/2. The product (2 g) was obtained as an oil.

R) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-di-TBDMSilyl-oxy-2-(3-TBDMSilyl-oxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid 6-(nitrooxy)hexylamide

A solution of compound Q (2g, 2mmol) and silver nitrate (0.5g, 3mmol) in acetonitrile (50ml) was stirred at 40°C, in the dark, for 4 hours. The precipitated (silver salts) was filtered off and the solvent was evaporated under vacuum. The residue was purified by flash chromatography, eluent n-hexane/ethyl acetate 8/2. The product (0.88g) was obtained as oil.

S) [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid 6-(nitrooxy)hexylamide

To a solution of compound R) (400mg, 0.45 mmol) in acetonitrile (25 ml) phosphomolybdic acid hydrate (400mg) was added.

The mixture was stirred at room temperature 20 minutes and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using a gradient flow n- ethyl acetate/methanol 100/5. The product (150 mg) was obtained as an oil.

^{1}H-NMR($CDCl_3$): 7.31-7.13 (5H, m); 6.02 (1H, t); 5.46-5.31 (2H, m); 4.41 (2H, t); 4.10 (1H, m); 3.95 (1H, bs); 3.62 (1H, m); 3.42 (1H, bs); 3.32(2H, m); 2.84-2.74 (2H, m); 2.38-1.30 (25H, m).

Example 5

Synthesis of [1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid amide with Omo-phenylalanine(4-nitrooxy)butyl ester (corresponding to compound of formula 231)

L) 4-Bromobutanol

Tetrahydrofuran (12.5 g , 173 mmol) was charged under nitrogen in a reactor cooled to 5-10°C. Hydrogen bromide (7.0 g, 86.5 mmol) was then added slowly and the reaction medium was stirred over a period of 4.5 hours at 5-10°C. The mixture was diluted with 22.5 g of cold water and the pH of this solution was adjusted to pH=5-7 by adding 27.65% sodium hydroxide (2.0 g) keeping the temperature at 5-10°C. The solution was then extracted twice with dichloromethane (13.25 g). The combined organic phases were washed with 25% brine (7.5 g), adjusted to pH=6-7 with 27.65% sodium hydroxide and dried over magnesium sulfate. Dichloromethane was distilled off and crude 4-bromobutanol (10.3 g, 66.9 mmol) was obtained in a yield of about 77%.

M) 4-Bromobutyl nitrate

In reactor cooled to –5 to 5°C, nitric acid fuming (8.5 g, 135 mmol) was slowly added to a solution of 98% sulfuric acid (13.0 g, 130 mmol) in dichloromethane (18.0 g, 212 mmol). 4-Bromobutanol (10.2 g, 66.6 mmol) was then added to this mixture and the reaction medium was stirred at –5 to 5°C over a period of 2-5 hours. The mixture was poured into cold water (110 g) keeping the temperature between –5 °C and 3°C. After decantation, the upper aqueous phase was extracted with dichloromethane and the combined organic phases were washed with water, adjusted to pH=6-7 by addition of 27.65% sodium hydroxide, washed with brine and dried over magnesium sulfate. Dichloromethane was distilled off under vacuum and crude 4-bromobutyl nitrate (12.7 g, 64.1 mmol) was recovered in a yield of about 96%.

N) BOC-omophenylalanine 4-(nitrooxy)butyl ester

To a solution of BOC-omophenylalanine (1 g, 3.58 mmol) in acetone (50 ml) compound M) (8.43 g, 25% w/w in methylene chloride, 7.16 mmol), DBU (1.36 g, 8.95.3 mmol) and KI (0.59 g, 3.58 mmol) were added and the reaction was stirred at room temperature for 4 hours. The solution was washed with water and the organic layers were dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent ethyl acetate. The product (1 g) was obtained.

O) Omophenylalanine 4-(nitrooxy)butyl ester hydrochloride

To a solution of Compound N) (1 g, 2.52 mmol) in ethyl acetate (50 ml), HCl_{gas} was added until the disappearance of starting material (TLC: n-hexane/ethyl acetate 8/2).The solution was concentrated under reduced pressure. The product was used without any further purification.

P)[1R-[1α(Z),2β(R*),3α,5α]]-7-[3,5-di-hudroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid amide with Omo-phenylananine(4-nitrooxy)butyl ester

To a solution of compound O (2 g, 1.97 mmol) in acetonitrile (100 ml) phosphomolybdic acid hydrate (2 g) was added.

The mixture was stirred at room temperature 30 minutes and the solvent was removed under reduced pressure. The residue was treated with methylene chloride, washed with water. The organic layers were dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent ethyl acetate. The product (0.7 g) was obtained.

^{1}H-NMR($CDCl_3$): 7.31-7.15 (10H, m); 6.17 (1H, d); 5.50-5.32 (2H, m); 4.65 (1H, m); 4.47 (2H, t); 4.22-4.10 (3H, m); 3.94 (1H, m); 3.65 (1H, m); 2.89-2.62 (6H, m); 2.45-1.25 (22H, m).

Effects of latanoprost amide nitroderivative in hypertonic saline-induced transient intraocular pressure (IOP) raise

Male White New Zealand rabbits weighting 1,5-2 kg were used in this study. Animals were anaesthetized using 20 mg/mL/kg of sodium pentobarbital and injected with 0.1 mL of hypertonic saline solution (5% in distilled water) into the anterior chamber of both eyes. Intraocular pressure was determined using a tonometer (TONO-PEN ® XL- Medtronic) prior to hypertonic saline injection (basal) and at 30, 60, 90, 180 and 300 min thereafter. Vehicle (0.5 % Tween-80; 0.3 % DMSO; 0.2 mg/mL BAK in phosphate buffer saline pH 6.7), Xalatan® (latanoprost ophthalmic solution) 0.03% or latanoprost amide nitroderivative (compound 105, example 4) 0.03% were instilled immediately after the injection of hypertonic saline. Individual eyes were randomly assigned to different treatment groups. Vehicle or drugs were directly instilled into the conjuntival pocket.

The results are reported in Table 1. The compound of the invention at the dose of 0.03% showed a highly significant IOP-lowering effect at all time points tested as compared to the reference compound Xalatan® at the same dose. Moreover, latanoprost amide nitroderivative elicited significant responses when compared to vehicle treated group at 30 and 180 minutes after treatments.

	IOP $_{mmHg}$ (mean ± SEM)					
	basal	30 min	60 min	90 min	180 min	300 m
Vehicle	14.9±0.9	37.5±1.7	29.4±1.3	31.5±2.5	24.3±2.9	19.2±

Xalatan®	14.6±0.7	38.8±1.3	32.7±2.1	35.6±2.9	25.8±3	19.4±2.2
compound 105	14.7±1.1	31.9±0.8*#	25.6±1.8*	27.1±1.9*	17.2±1.7*#	13.9±1*

* p< 0.05 vs Xalatan®; Student's t-test

# p<0.05 vs vehicle; Student's t-test

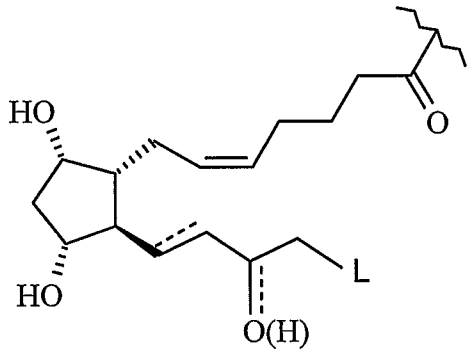
CLAIMS

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

$$R\text{-}X\text{-}(B)_m\text{-}Y\text{-}ONO_2$$

(I)

wherein R is the prostaglandin residue of formula (II):

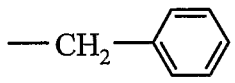
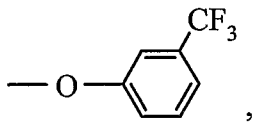


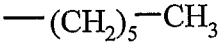
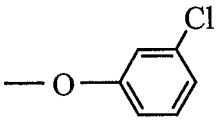
(II)

wherein

the symbol --- represents a single bond or a double bond;

L is selected from the following groups:

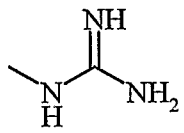
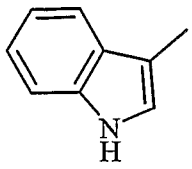
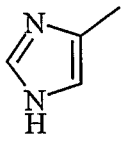
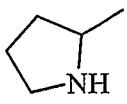
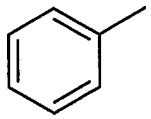
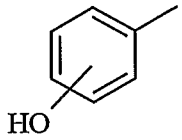
-  ,
 ,

-  ,
 ;

X is $-NR^1-$, wherein R^1 = H or C_1-C_6 alkyl;

m is an integer equal to 0 or 1;

B is a radical of the formula $-CH(R^{1'})COO-$, wherein $R^{1'}$ is H, straight or branched C_1-C_{10} alkyl, being optionally substituted with one or more of the substituents selected from the group consisting of: -OH, -COOH, $-CONH_2$, $-NH_2$,

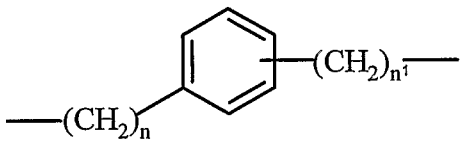
-SH, -SCH_3,  ,  ,  ,  ,  or  ;

Y is a bivalent radical having the following meaning:

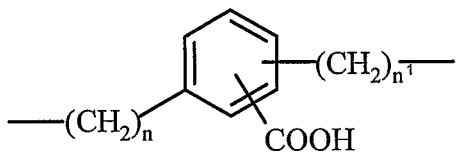
a)

- straight or branched C_1-C_{20} alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, –ONO_2 or T, wherein T is
  –OC(O)(C_1-C_{10} alkyl)-ONO_2 or –O(C_1-C_{10} alkyl)-ONO_2;
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1, wherein T_1 is straight or branched C_1-C_{10} alkyl;

b)

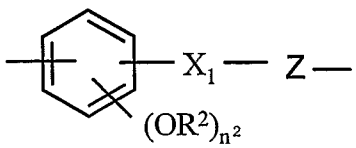


c)



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

d)



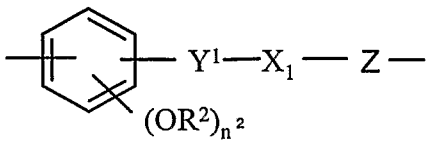
wherein

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

Z is $-(CH_2)_n{}^1-$ or the bivalent radical defined above under b);

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

e)



wherein:

Y^1 is $-CH_2-CH_2-(CH_2)_n{}^2-$ or $-CH=CH-(CH_2)_n{}^2-$;

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

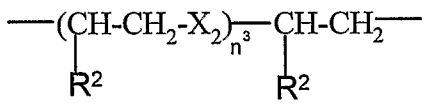
with the proviso that:

i) when Y is selected from the bivalent radicals mentioned under b)-e), then the terminal $-ONO_2$ group is bound to $-(CH_2)_n{}^1$;

ii) when y is selected from the bivalent radicals mentioned under b) or c) and n = 0, then m = 1;

iii) when y is selected from the bivalent radicals mentioned under d) or e), then m = 1;

g)



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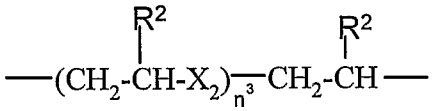
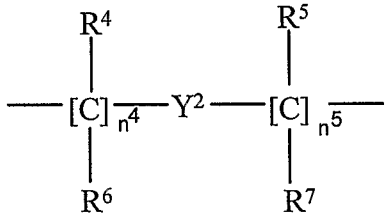


wherein X_2 is –O- or –S-, n^3 is an integer from 1 to 6, R^2 is as defined above;

h)



wherein:

n^4 is an integer from 0 to 10;

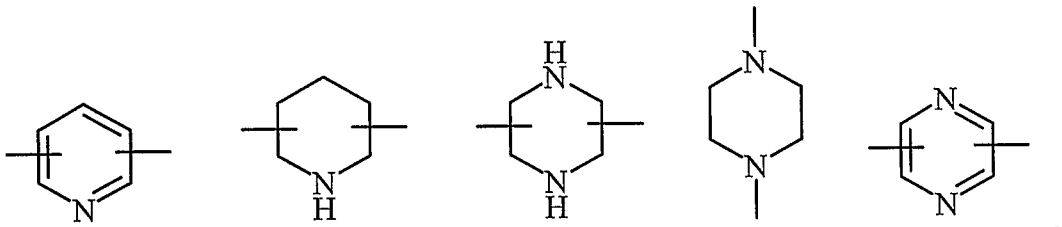
n^5 is an integer from 1 to 10;

R^4, R^5, R^6, R^7 are the same or different, and are H or straight or branched C_1-C_4 alkyl;

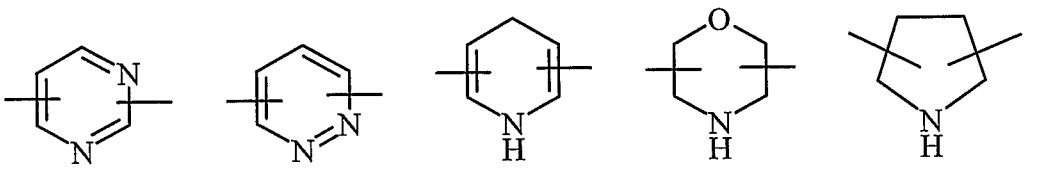
wherein the $-ONO_2$ group is linked to

wherein n^5 is as defined above;

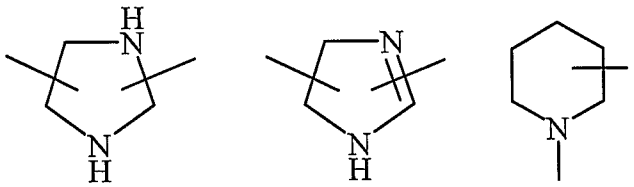
Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur, and is selected from



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



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



(Y11) (Y12) (Y13)

2. A compound of general formula (I) according to claim 1 or a pharmaceutically acceptable salt or stereoisomer thereof wherein R, L, X, Y and m are as defined in claim 1 and B is a radical of formula $-CH(R^{1'})COO-$, wherein $R^{1'}$ is H or C_1-C_6 alkyl;

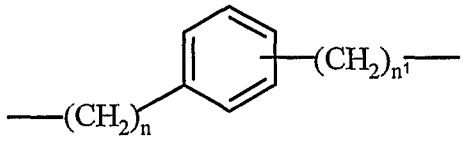
3. A compound of general formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R, L, X, B and m are as defined in claim 1 and Y is a bivalent radical having a meaning selected from the following group:

a)

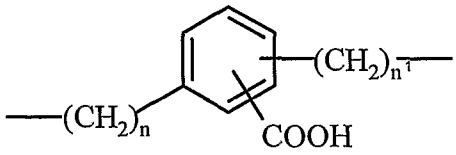
- straight or branched C_1-C_{10} alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or T, wherein T is $-OC(O)(C_1$-C_{10} alkyl)-ONO_2 or $-O(C_1$-C_{10} alkyl)-ONO_2;

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1, wherein T_1 is CH_3;

b)

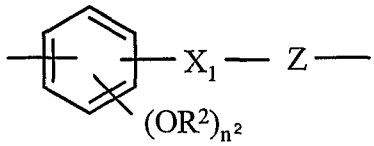


c)



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

d)



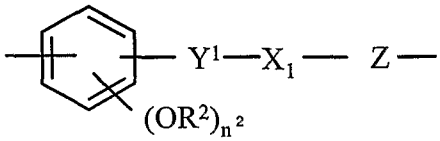
wherein:

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

Z is $-(CH_2)_n{}^1$- or the bivalent radical defined above under b);

n^1 is an integer from 1 to 10 and n^2 is an integer from 0 to 2;

e)



wherein:

Y^1 is $–CH_2–CH_2–$ or $–CH=CH–(CH_2)_n{}^2–$;

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

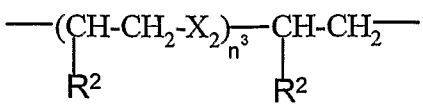
with the proviso that:

i) when Y is selected from the bivalent radicals mentioned under b)-e), then the terminal $–ONO_2$ group is bound to $-(CH_2)_n{}^1$;

ii) when Y is selected from the bivalent radicals mentioned under b) or c) and n = 0, then m = 1;

iii) when Y is selected from the bivalent radicals mentioned under d) or e), then m = 1;

g)



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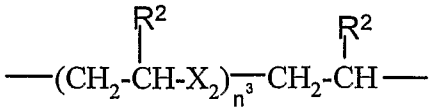
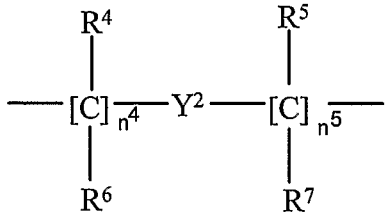


wherein X_2 is –O- or –S-, n^3 is an integer from 1 to 4 and R^2 is as defined above;

h)



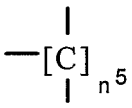
wherein:

n^4 is an integer from 0 to 3;

n^5 is an integer from 1 to 3;

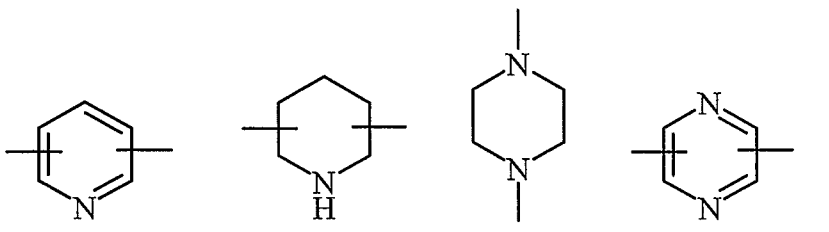
R^4, R^5, R^6, R^7 are H;

wherein the $-ONO_2$ group is linked to

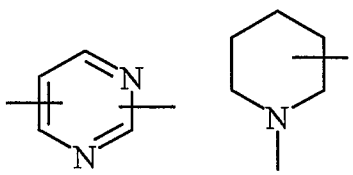


wherein n^5 is as defined above;

Y^2 is selected from



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



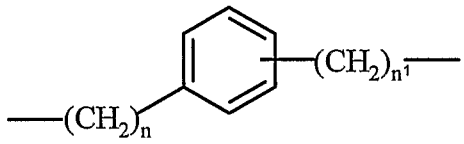
(Y6) (Y13)

4. A compound of general formula (I) according to anyone of claims 1-3, wherein R is the residue of travoprost or unoprostone or cloprostenol.

5. A compound of general formula (I) according to anyone of claims 1-3, wherein R is the residue of latanoprost.

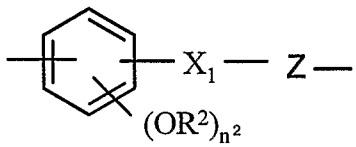
6. A compound of general formula (I) according to anyone of the claims from 1 to 5, wherein Y is a bivalent radical having the following meaning:

b)



wherein n is 0 or 1, and n^1 is 1;

d)



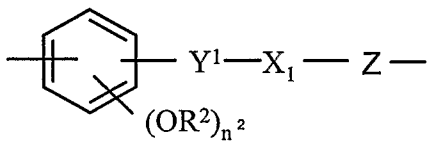
wherein

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

Z is $–(CH_2)_n{}^1$-;

n^1 is an integer from 1 to 5 and n^2 is an integer from 0 to 2;

e)



wherein:

Y^1 is $–CH_2$-CH_2-$(CH_2)_n{}^2$- or –CH=CH-$(CH_2)_n{}^2$-;

Z is $–(CH_2)_n{}^1$- or the bivalent radical defined above under b);

n^1 is an integer from 1 to 5;

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

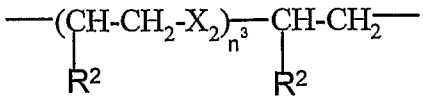
with the proviso that:

i) when Y is selected from the bivalent radicals mentioned under b), d) and e), then the terminal $–ONO_2$ group is bound to $-(CH_2)_n{}^1$;

ii) when y is selected from the bivalent radicals mentioned under b) and n = 0, then m = 1;

iii) when y is selected from the bivalent radicals mentioned under d) or e), then m = 1;

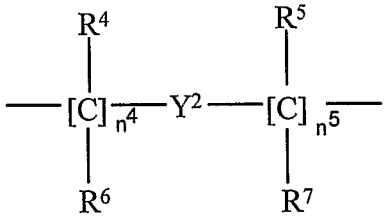
g)



,

wherein X_2 is –O- or –S-, n^3 is 1, R^2 is hydrogen;

h)



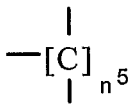
wherein:

n^4 is 2 or 3;

n^5 is 2 or 3;

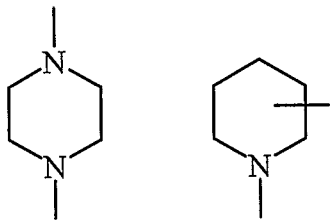
R^4, R^5, R^6, R^7 are H;

wherein the $-ONO_2$ group is linked to



wherein n^5 is as defined above;

Y^2 is selected from



(Y4) (Y13)

7. A compound of general formula (I) according to anyone of the claims from 1 to 6, wherein X is $-NR^1-$ and R^1 is C_1-C_6 alkyl.

8. A compound of general formula (I) according to claim 7, wherein Y is straight or branched C_1-C_6 alkylene, being optionally substituted with $-ONO_2$.

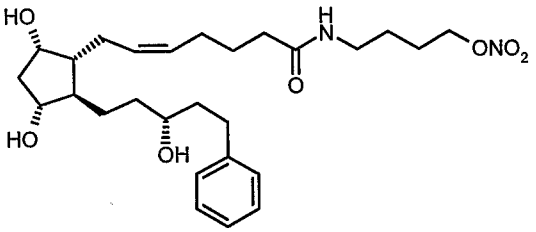
9. A compound of general formula (I) according to anyone of the claims from 1 to 6, wherein X is $-NR^1-$ in which R^1 is H and m is 1.

10. A compound of general formula (I) according to claim 9, wherein and Y is straight or branched C_2-C_6 alkylene, being optionally substituted with $-ONO_2$.

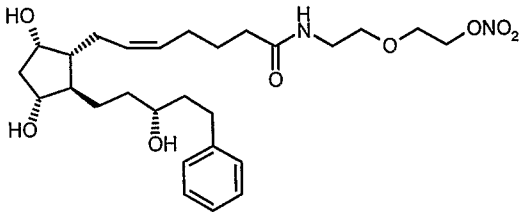
11. A compound of general formula (I) according to anyone of the claims from 1 to 6, wherein X is $-NR^1-$ in which R^1 is H, m is 0.

12. A compound of general formula (I) according to claim 11,wherein Y is straight or branched C_4-C_{10} alkylene, being optionally substituted with $-ONO_2$.

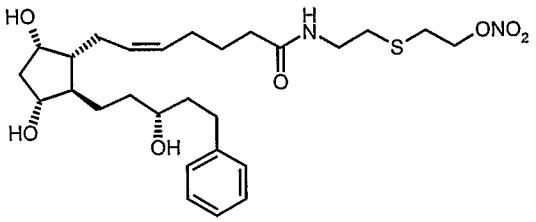
13. A compound according to claim 1, selected from the group consisting of:



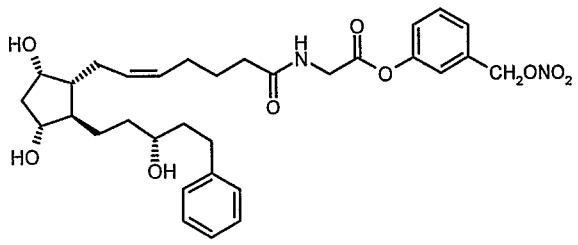
(1)



(2)



(3)



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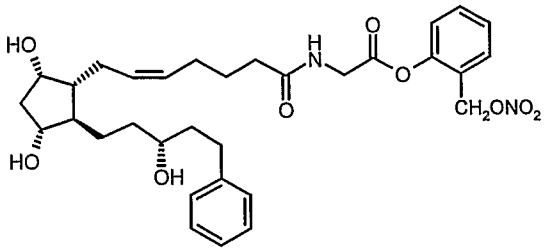
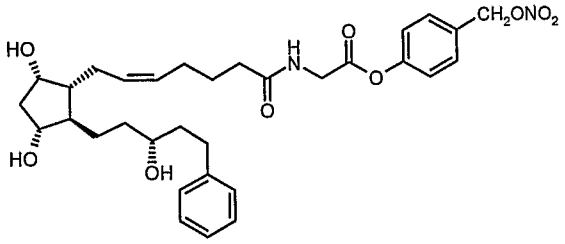
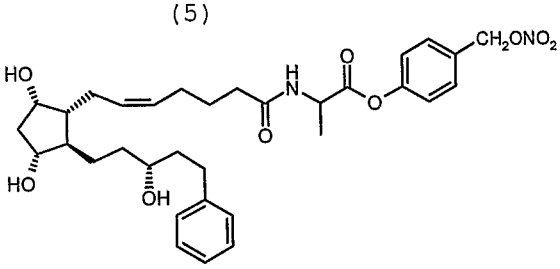
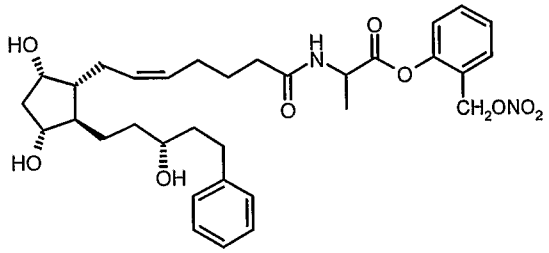




(5) (6)





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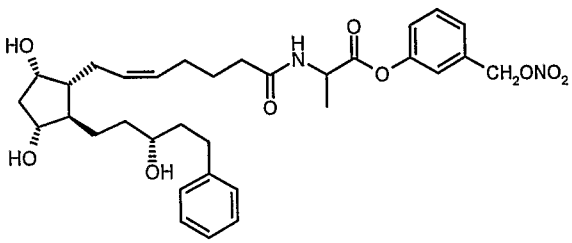

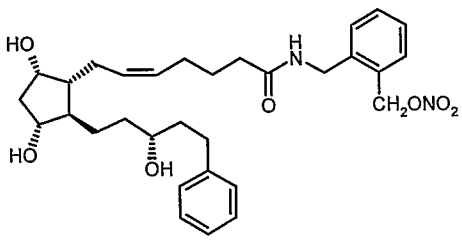

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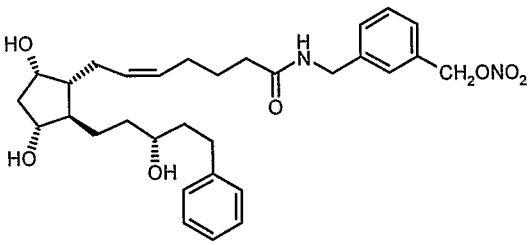
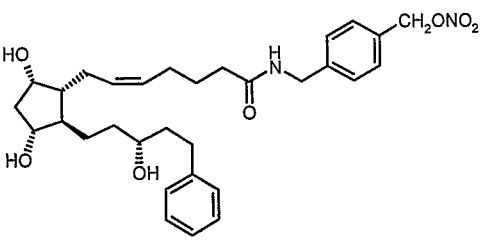
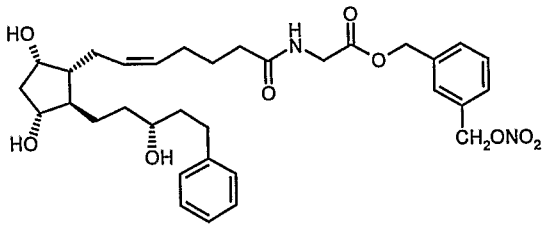




(11) (12)



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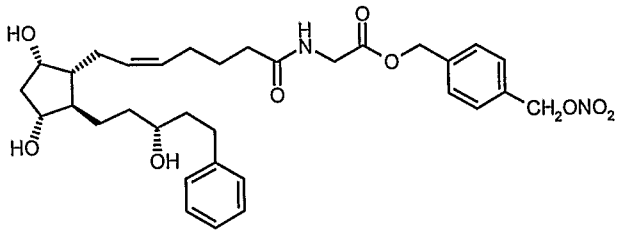

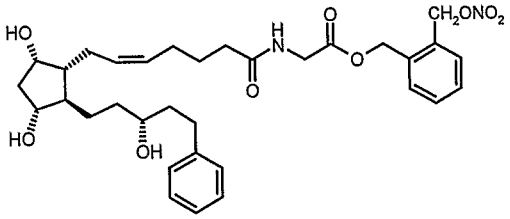

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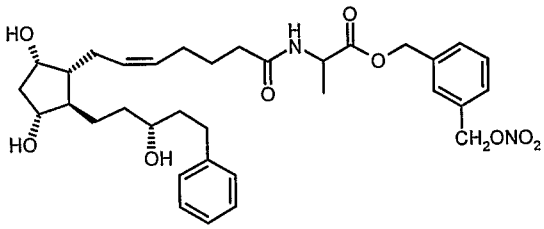
(15)



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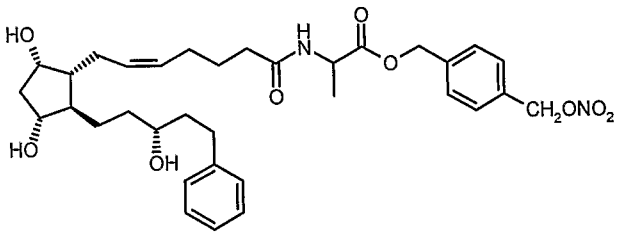

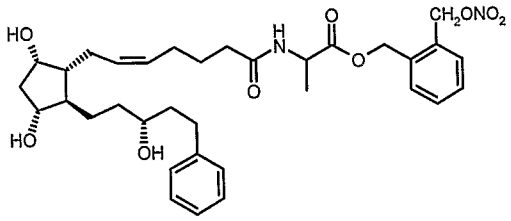

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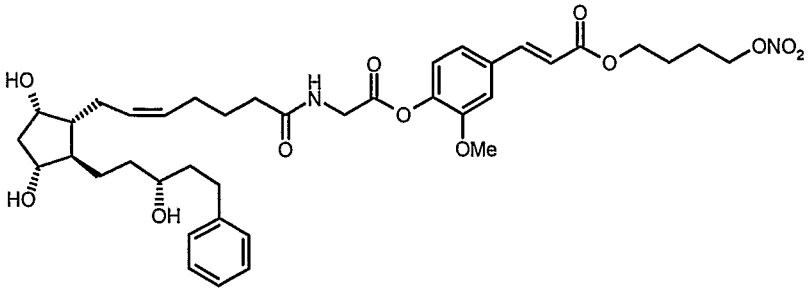

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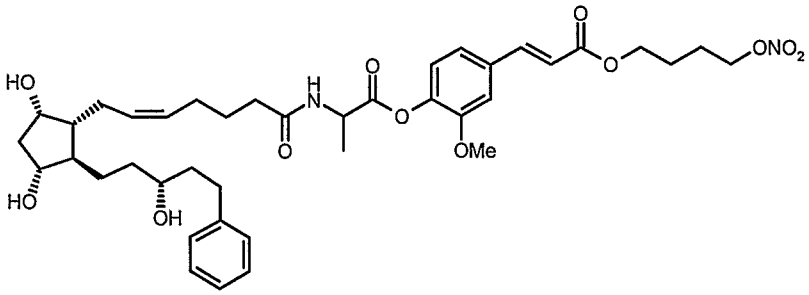

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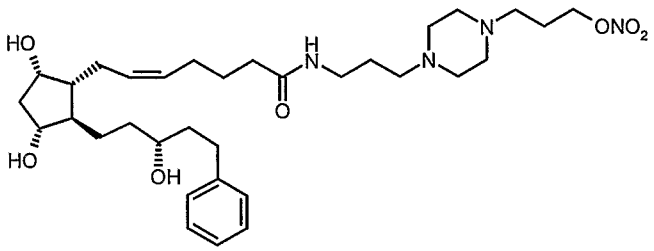

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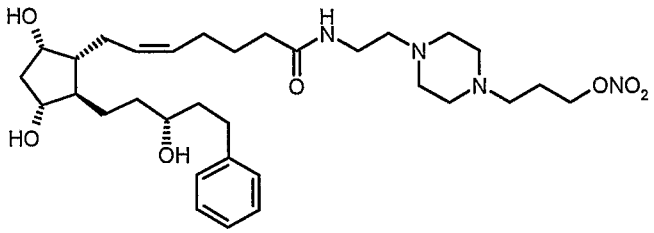

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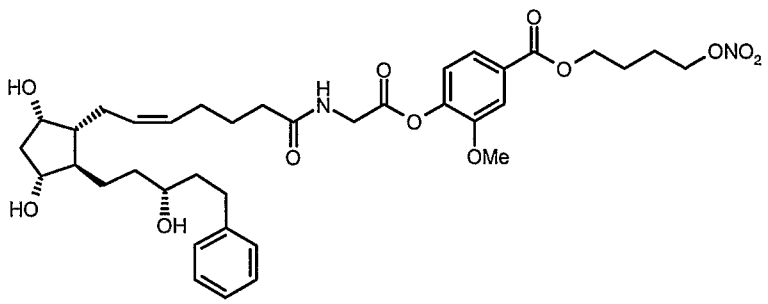

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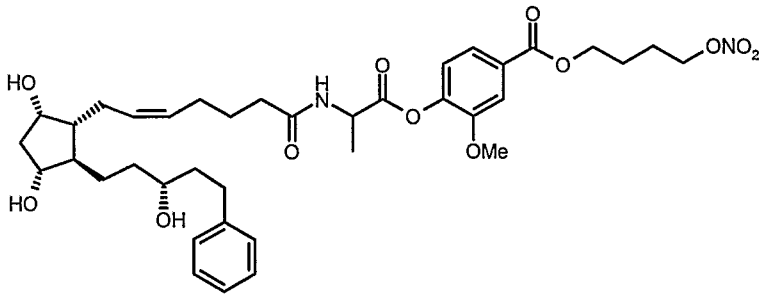

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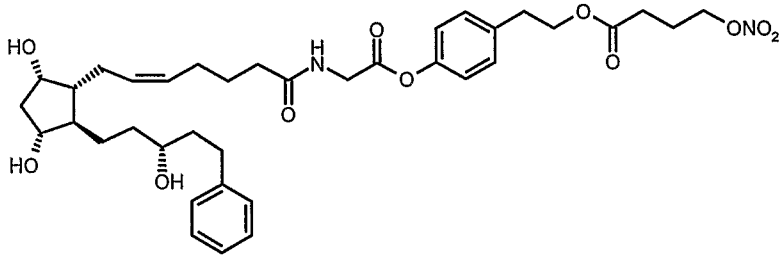

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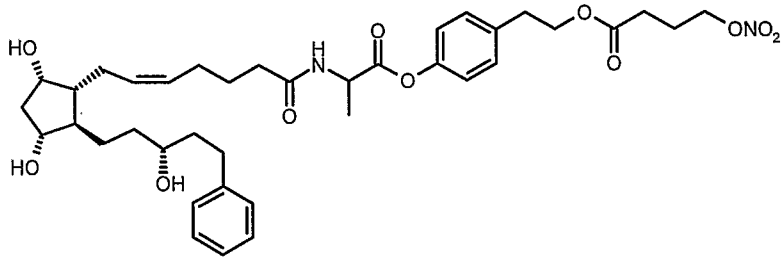

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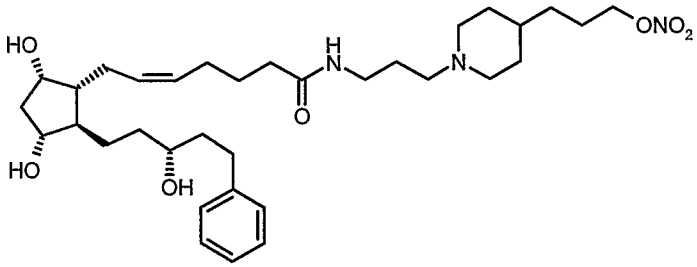

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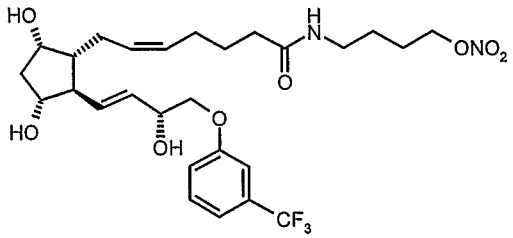

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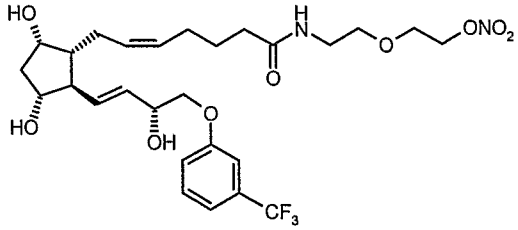

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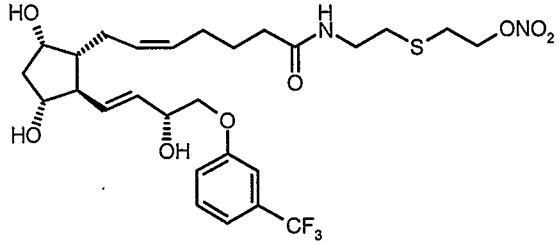

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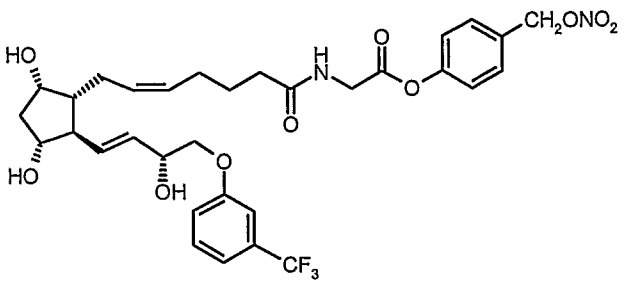

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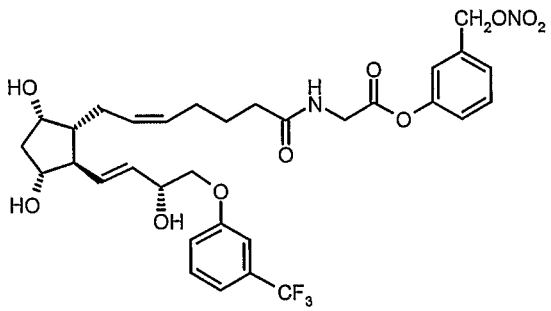

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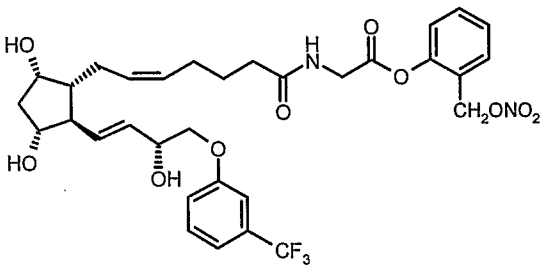

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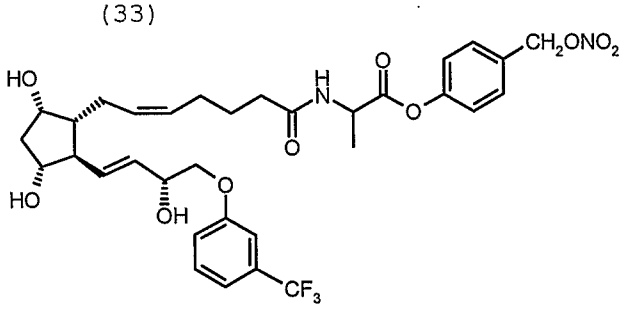

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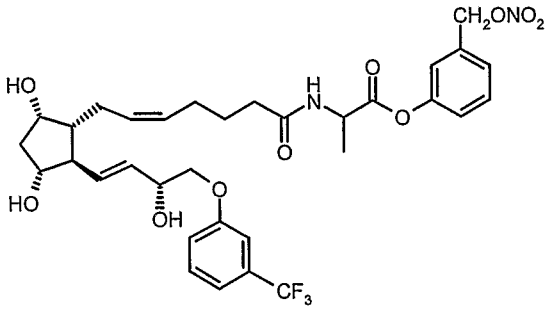

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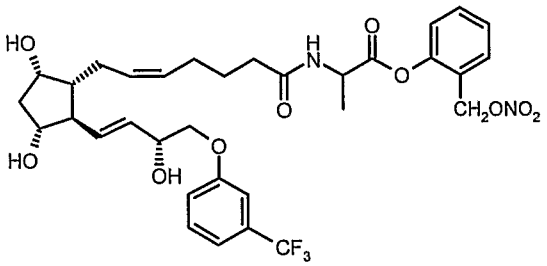

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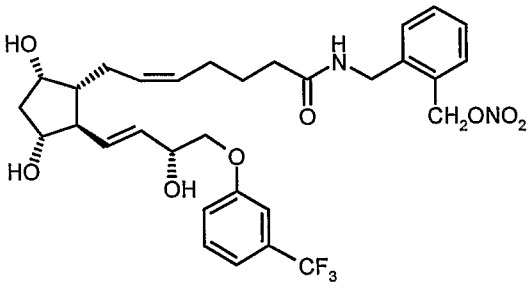

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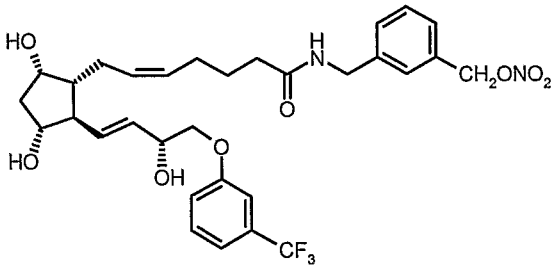

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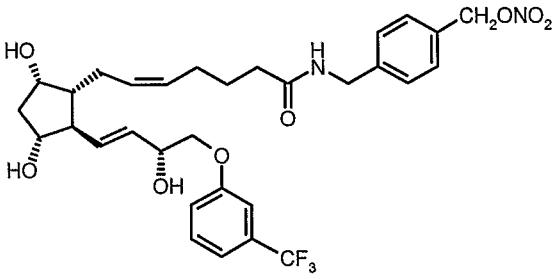

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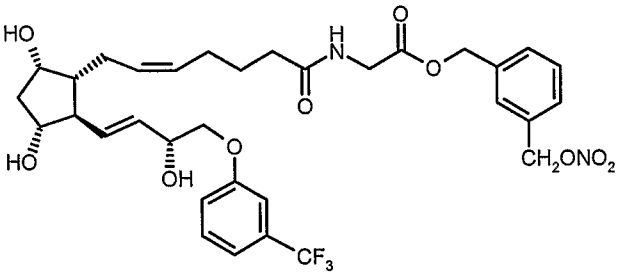

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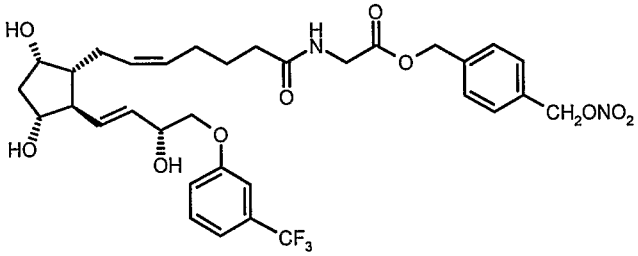

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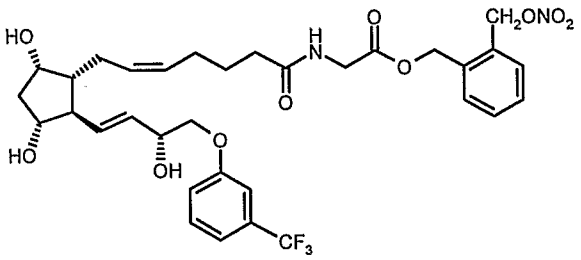

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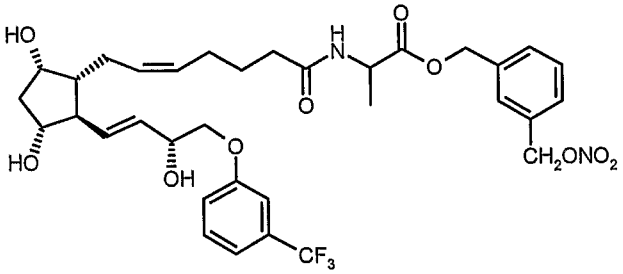

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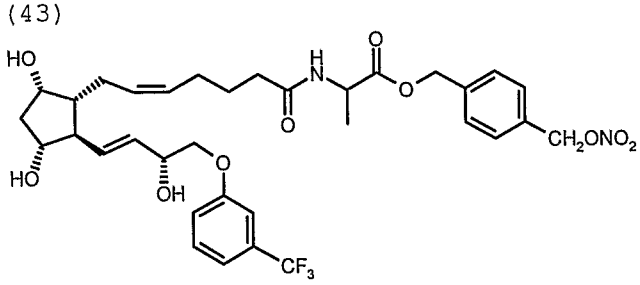

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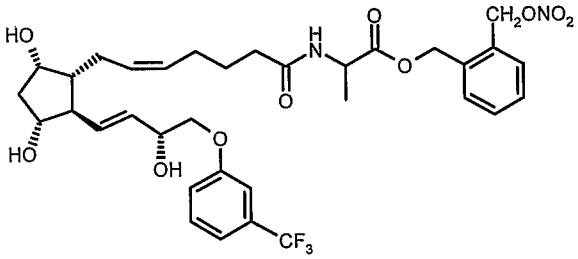

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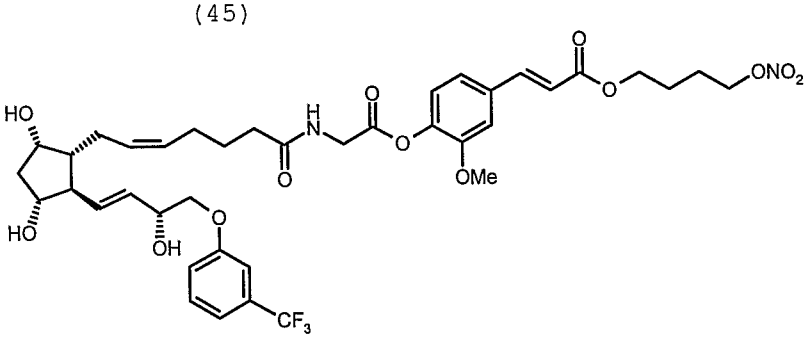

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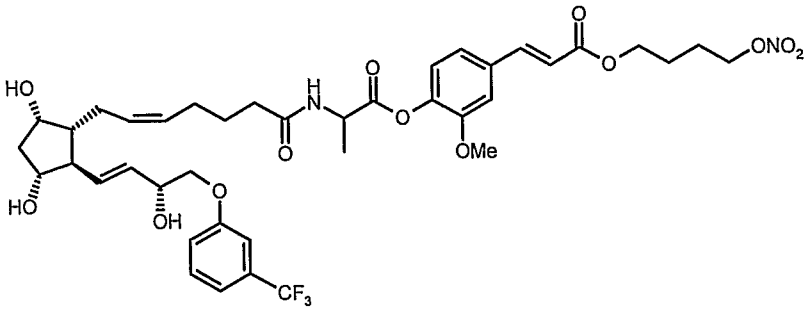

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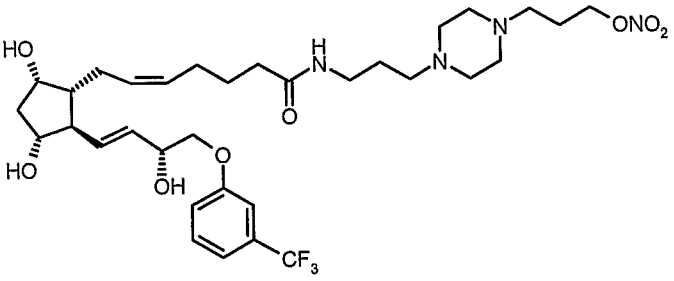

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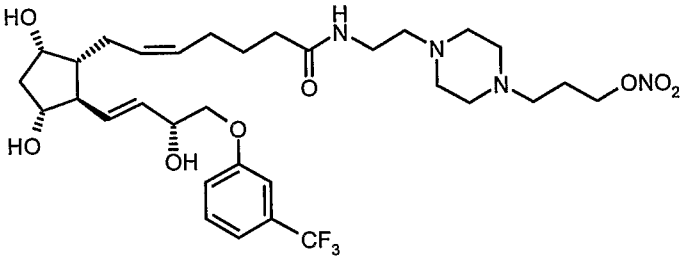

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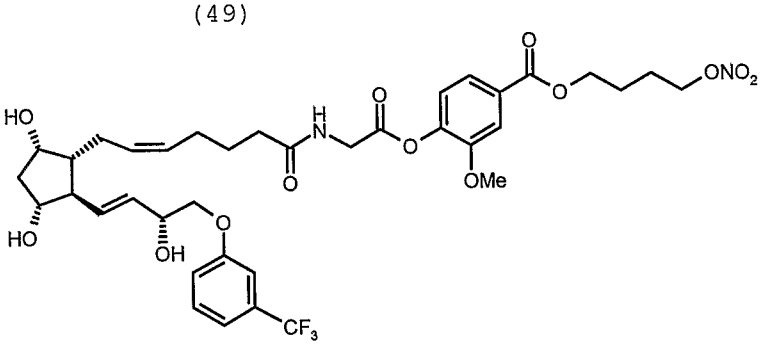

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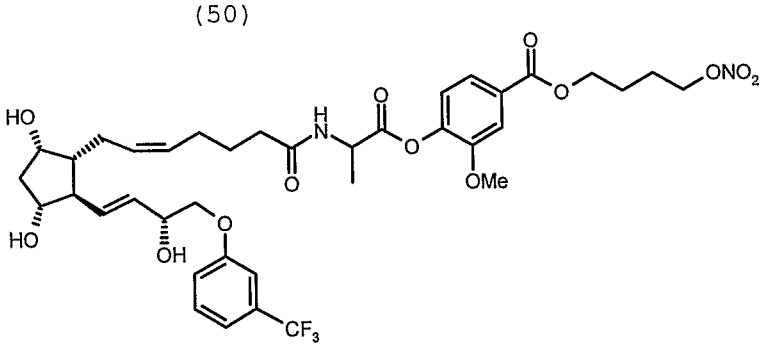

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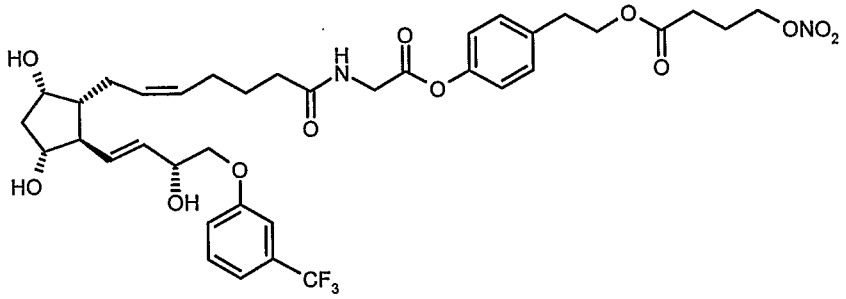

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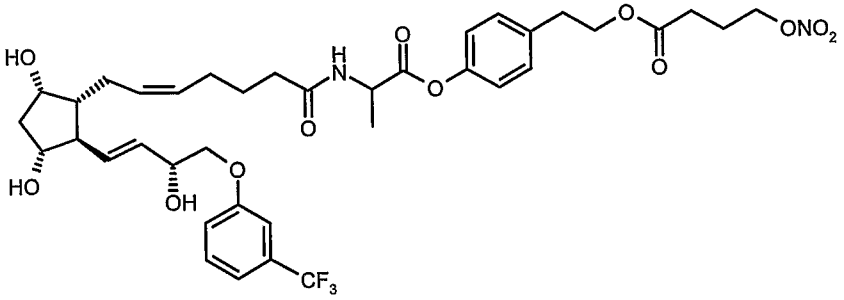

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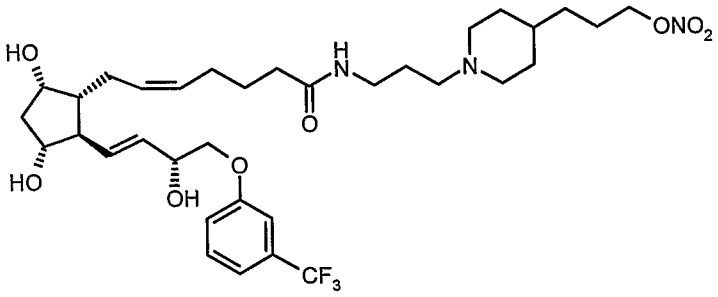

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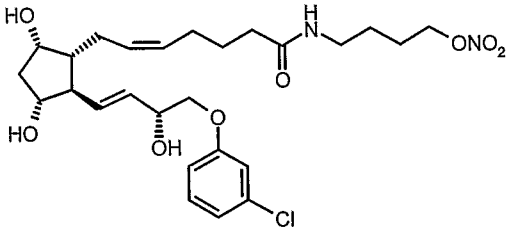

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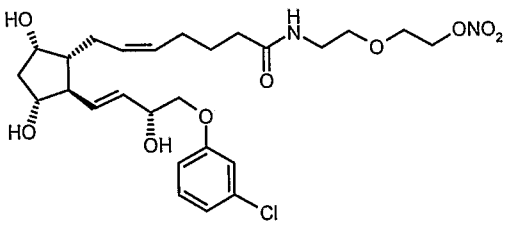

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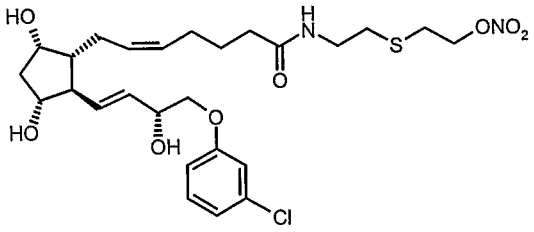

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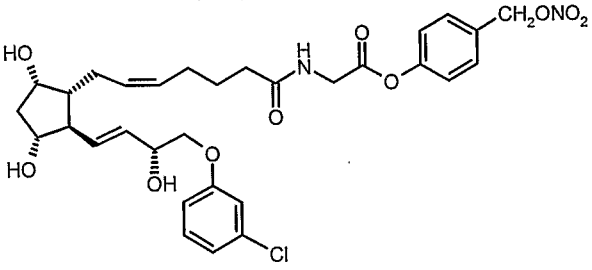

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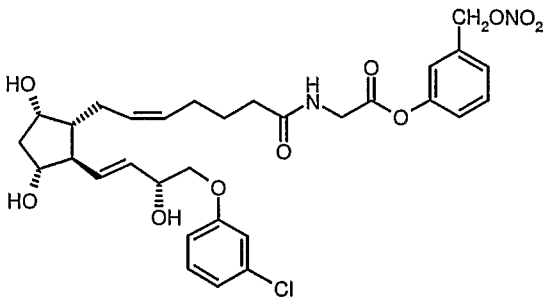

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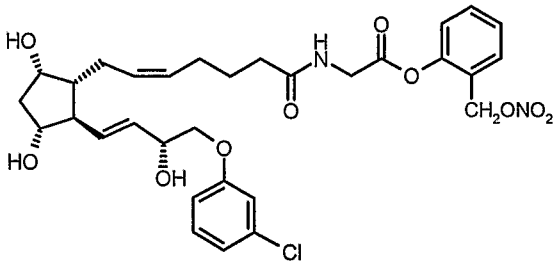

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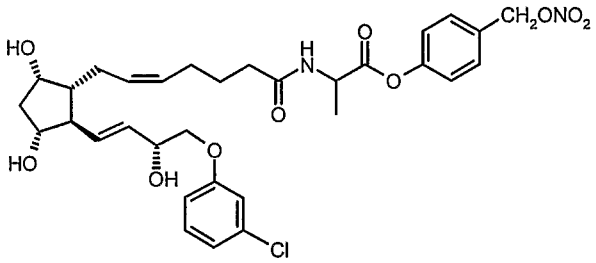

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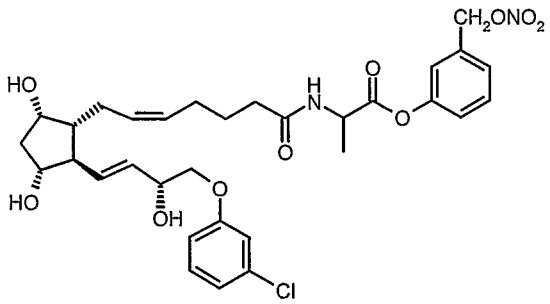

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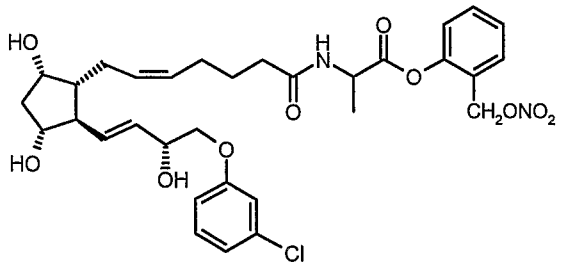

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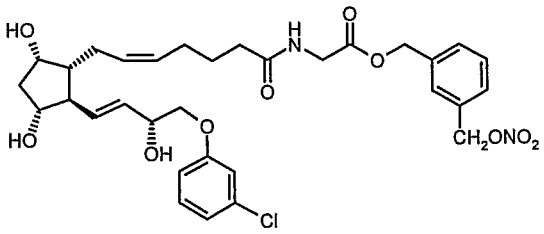

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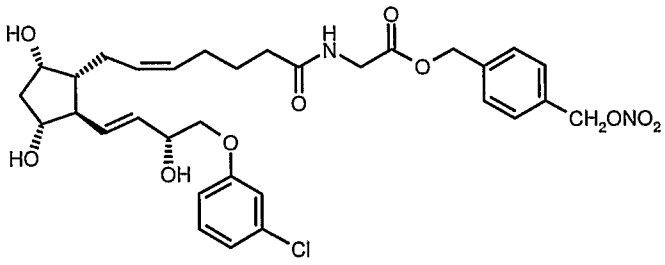

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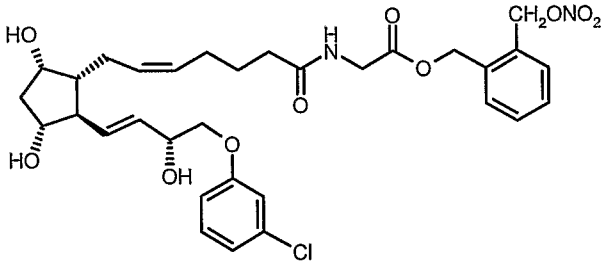

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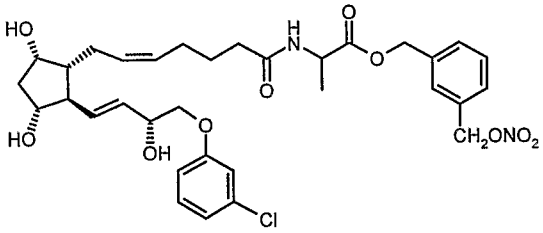

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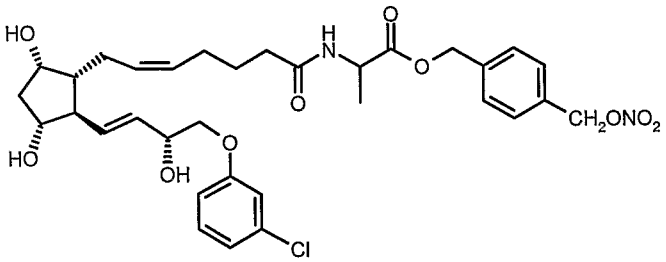

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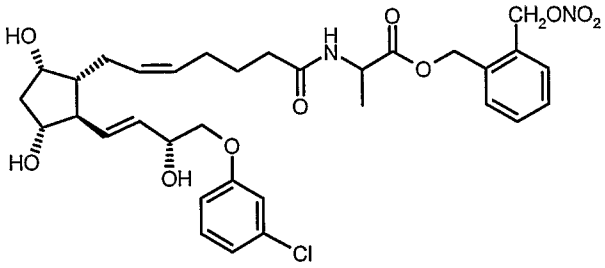

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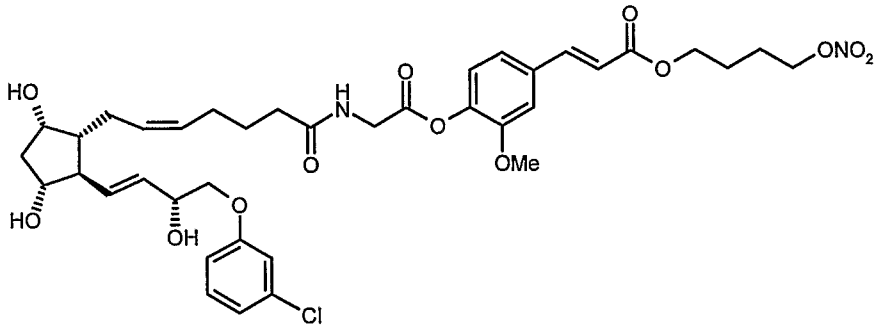

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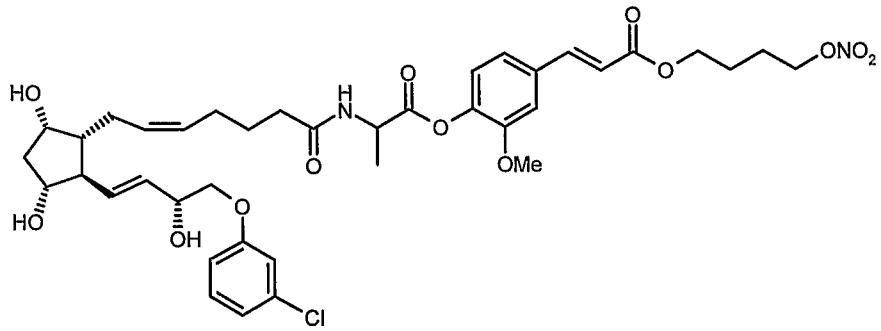

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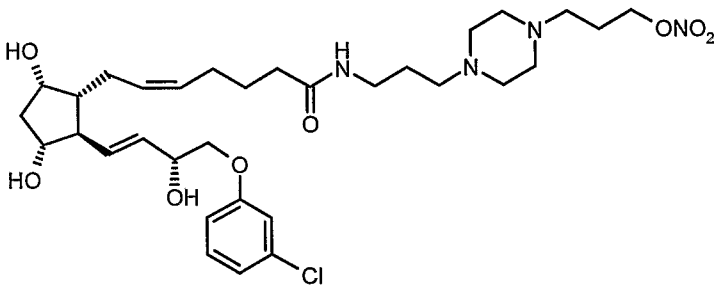

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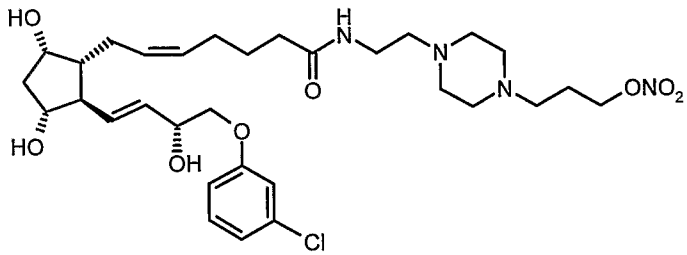

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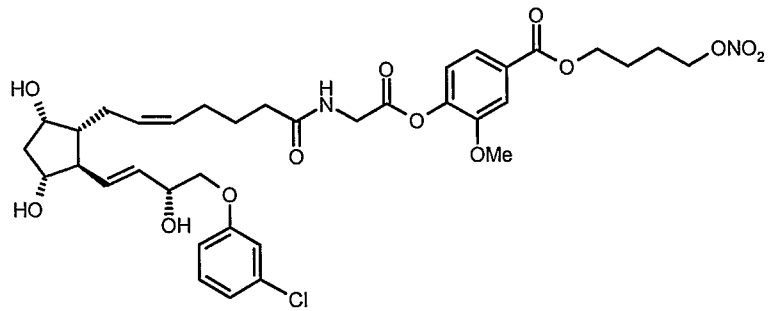

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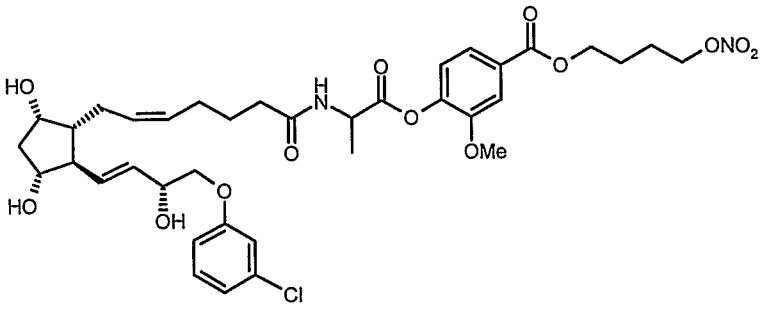

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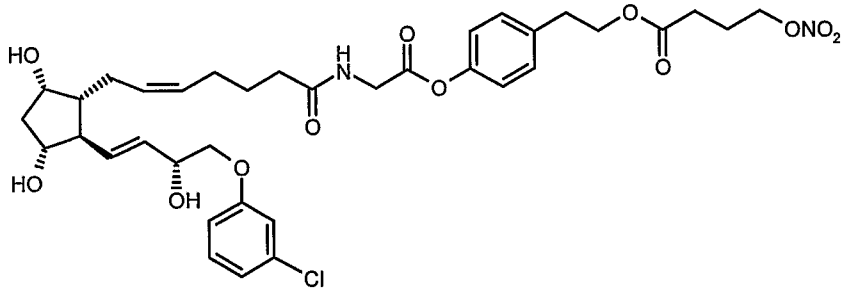

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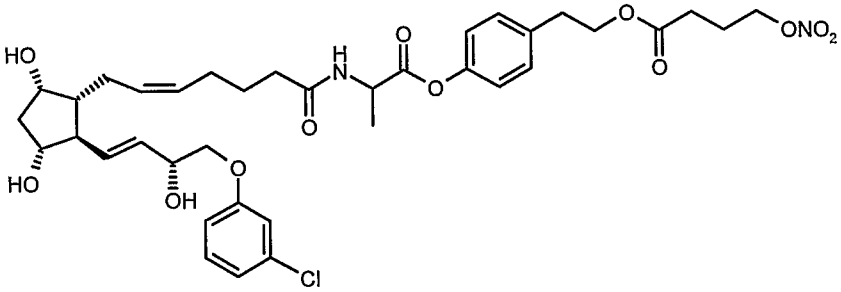

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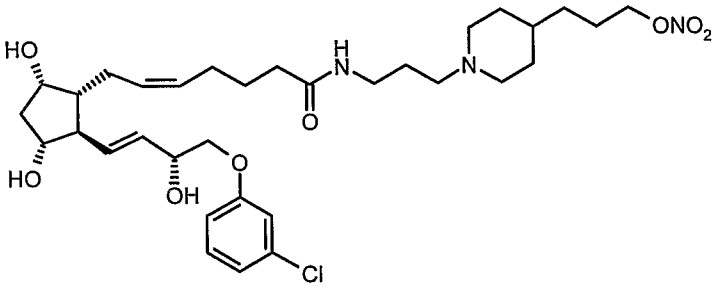

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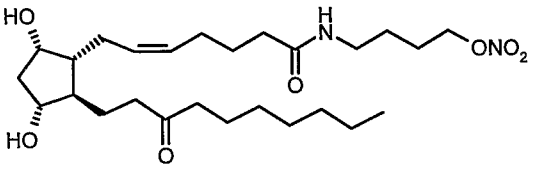

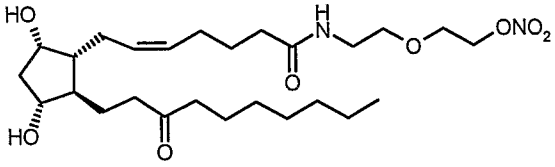

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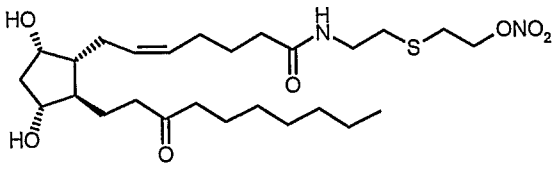

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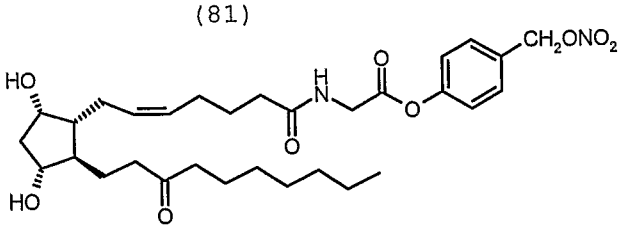

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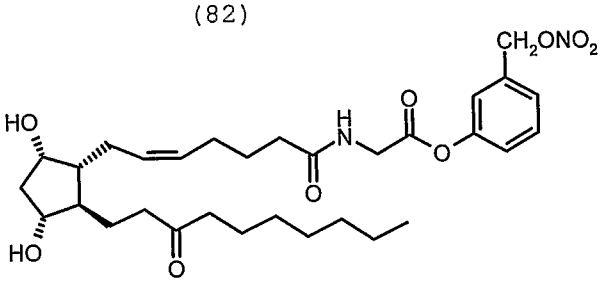

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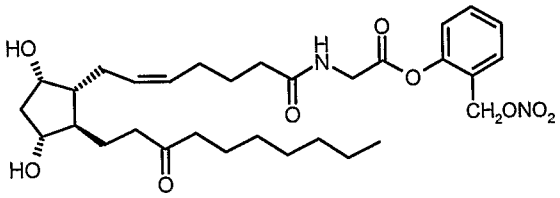

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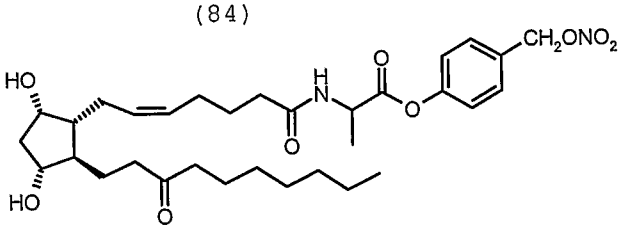

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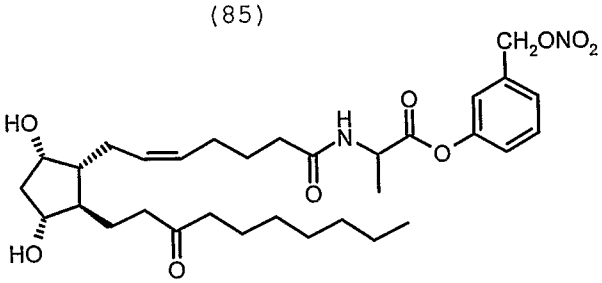

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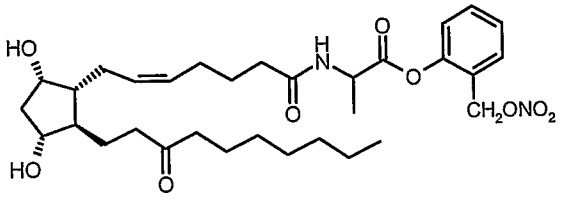

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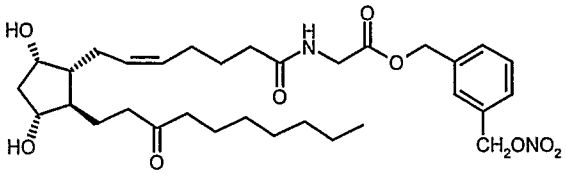

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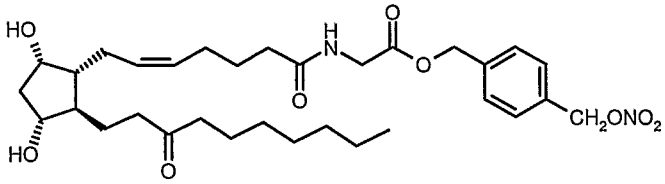

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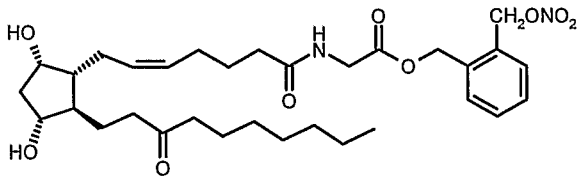

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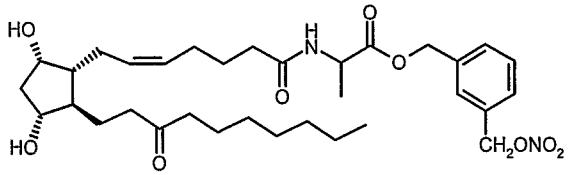

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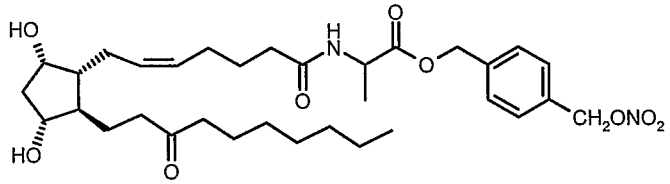

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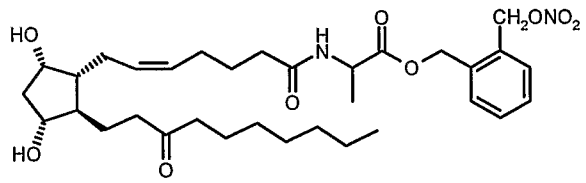

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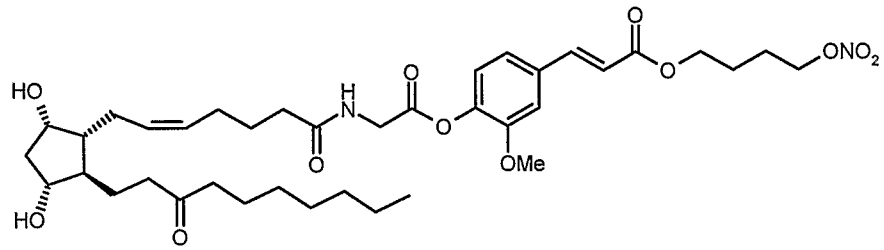

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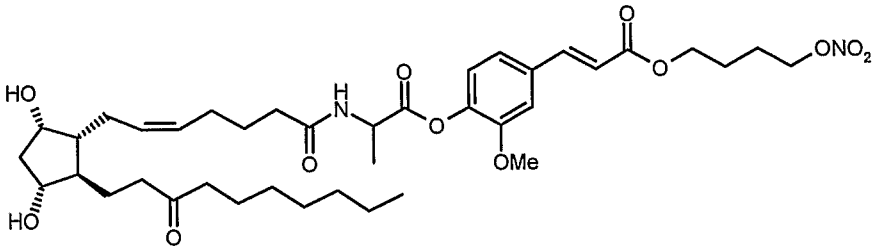

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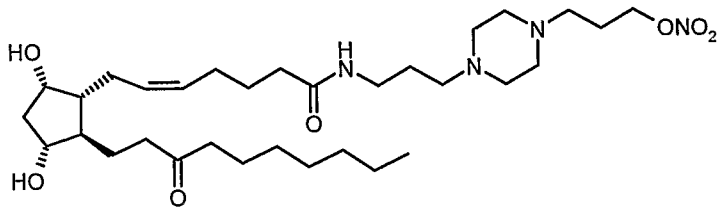

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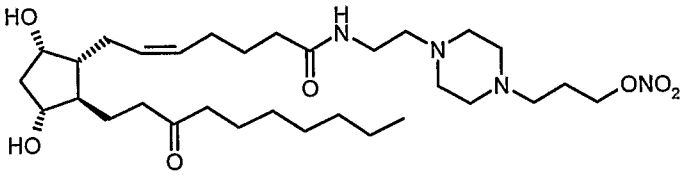

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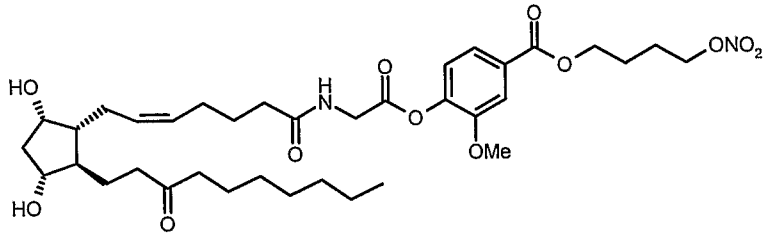

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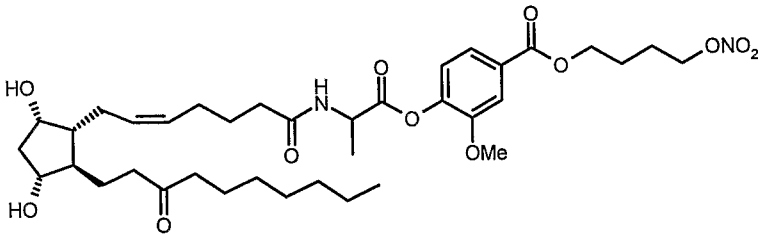

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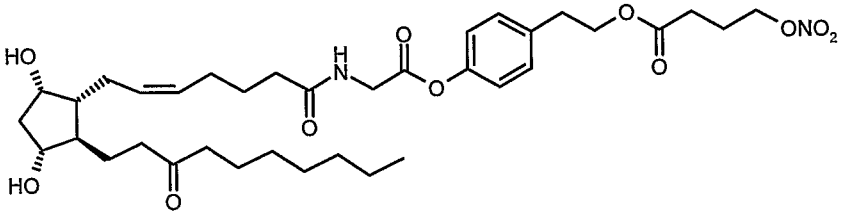

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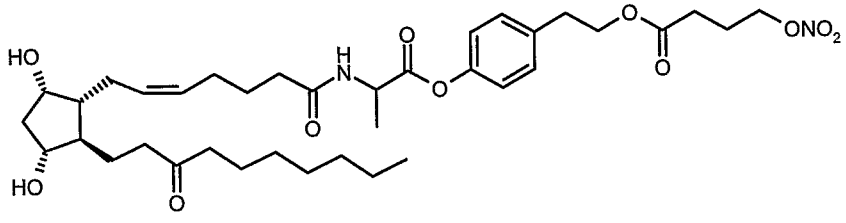

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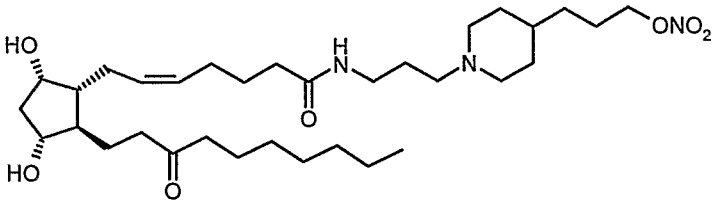

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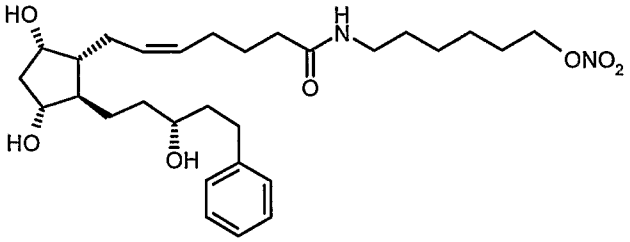

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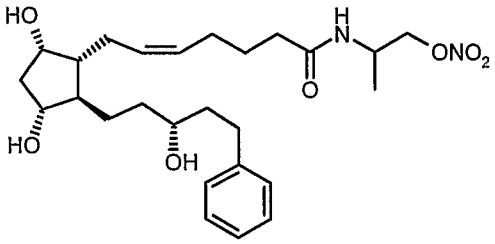

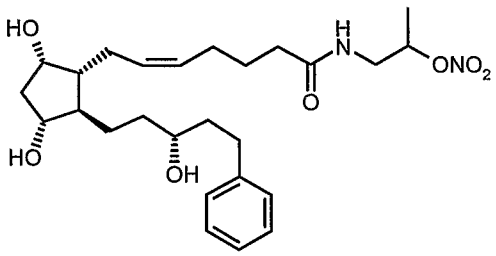

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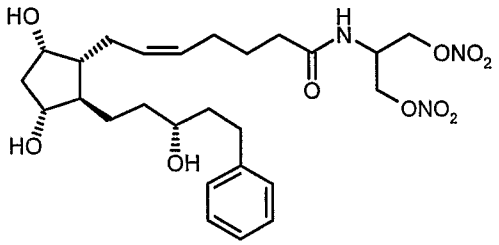

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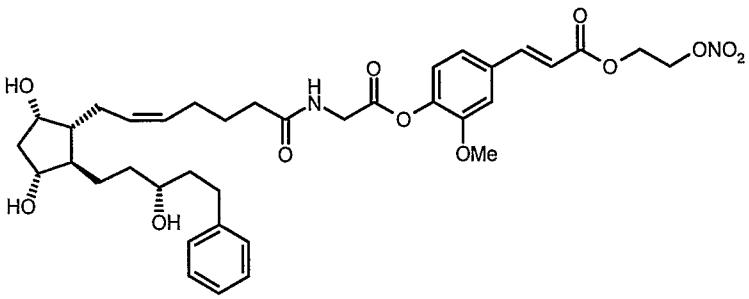

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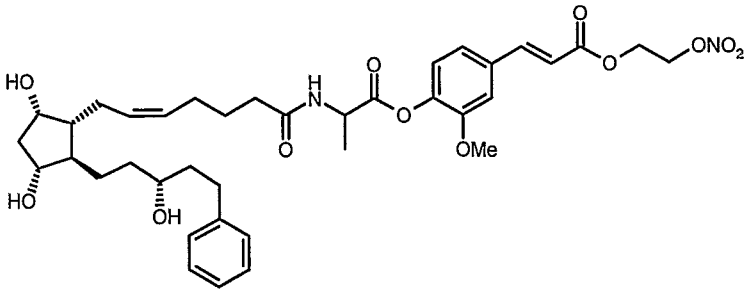

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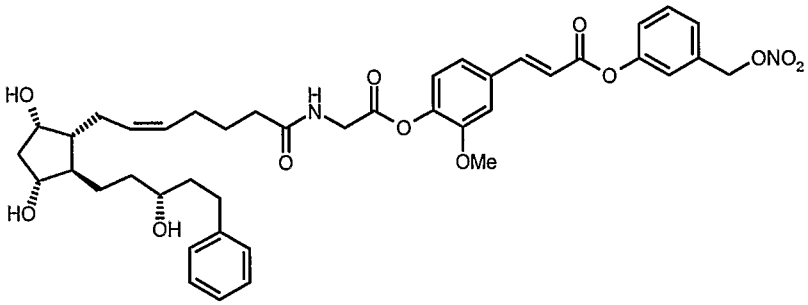

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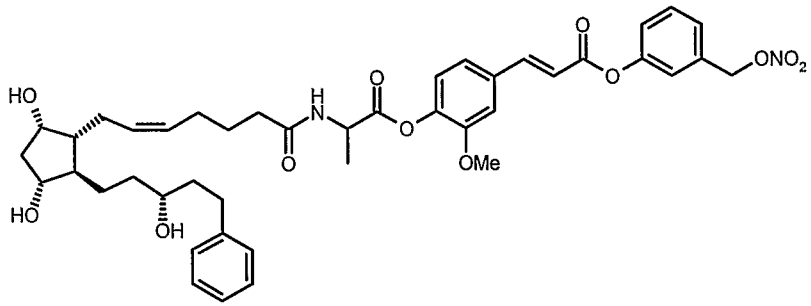

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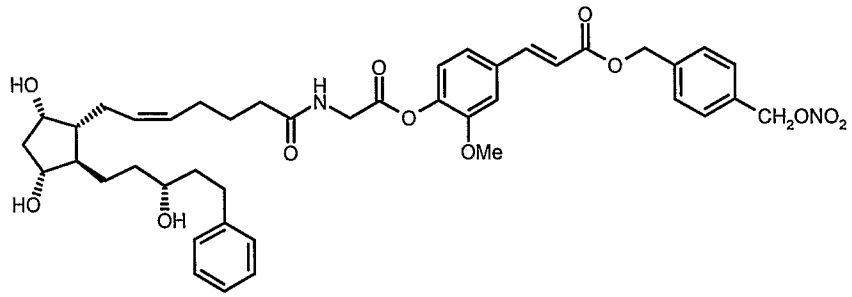

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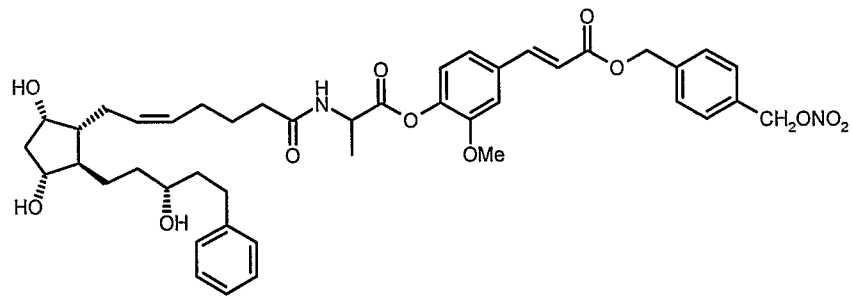

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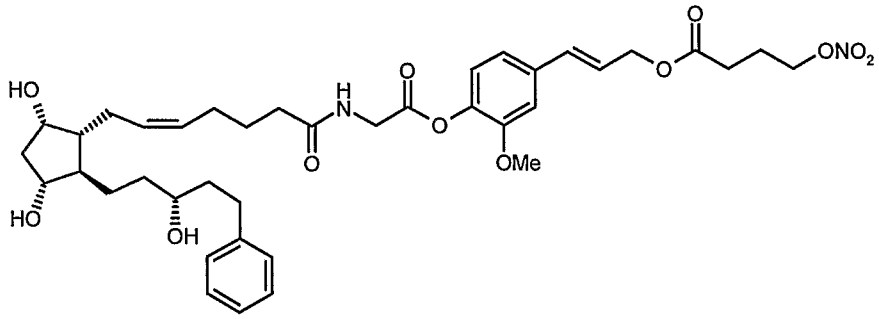

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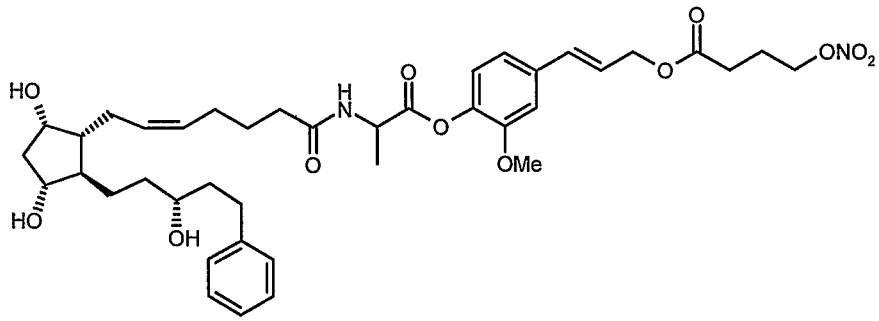

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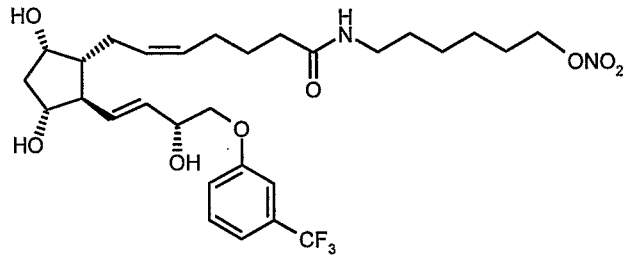

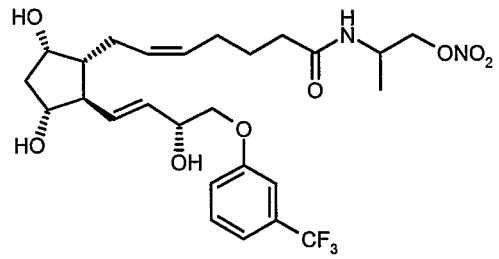

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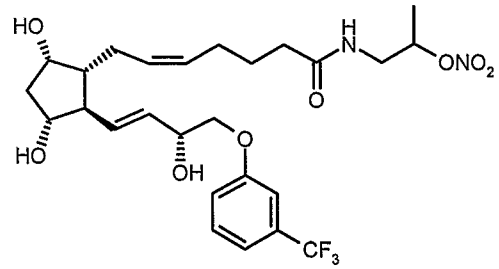

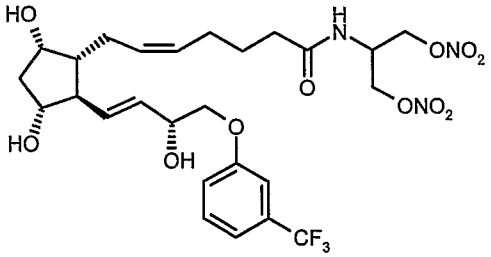

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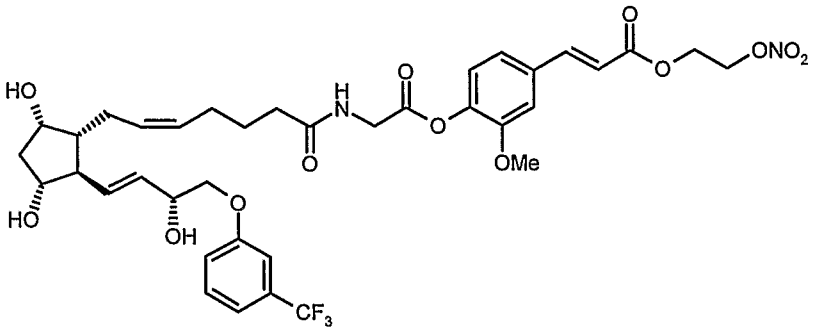

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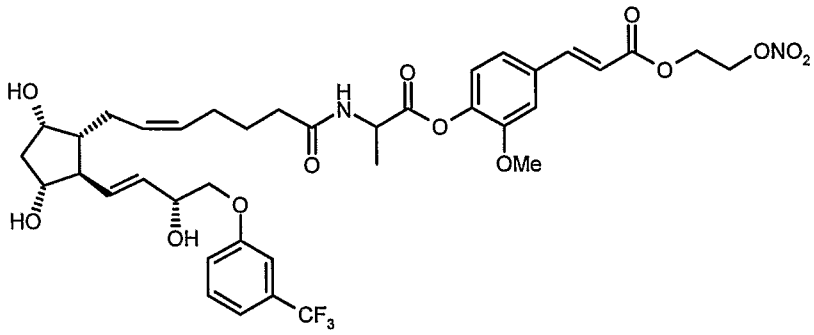

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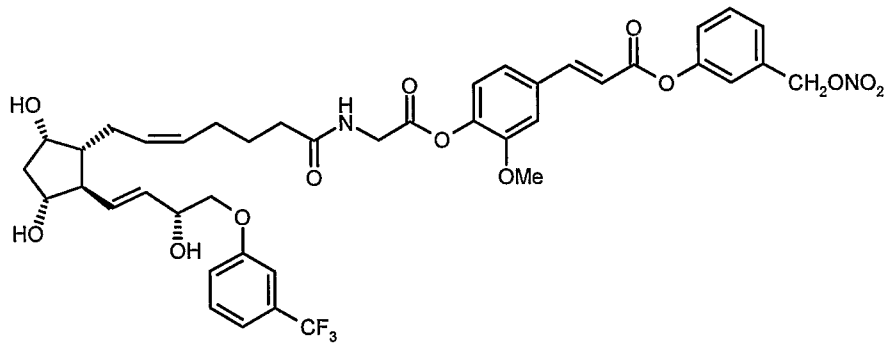

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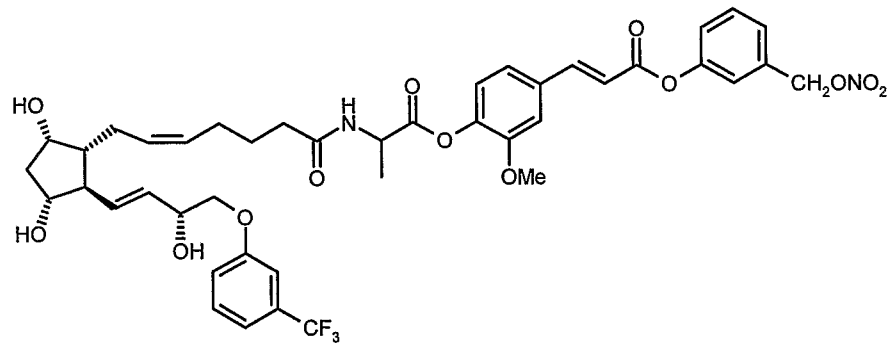

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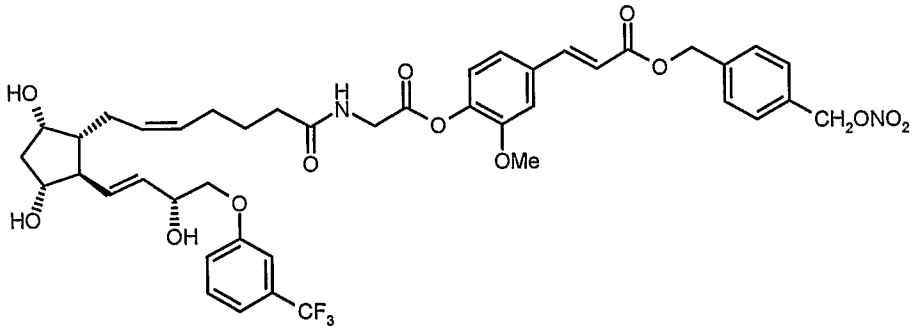

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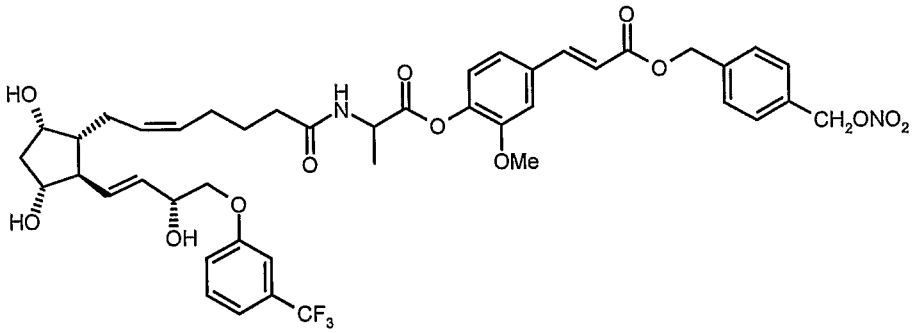

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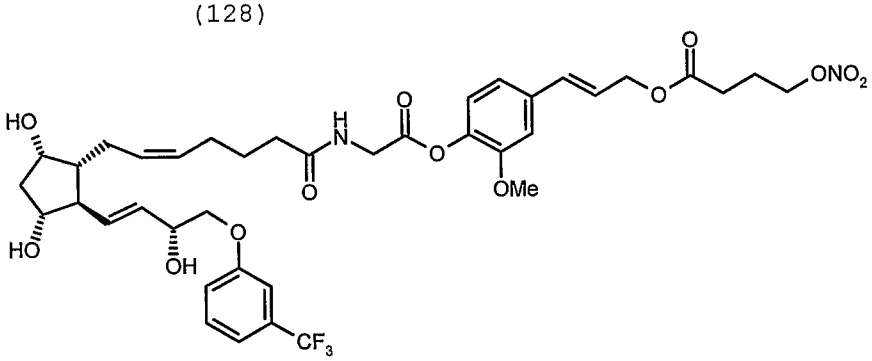

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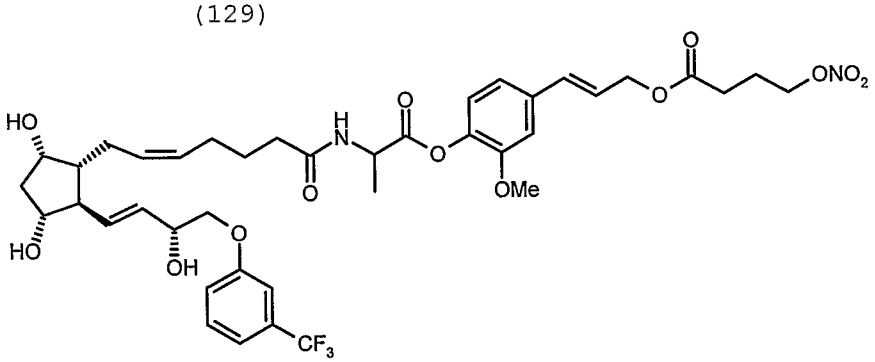

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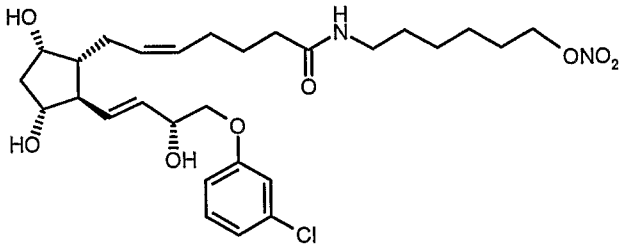

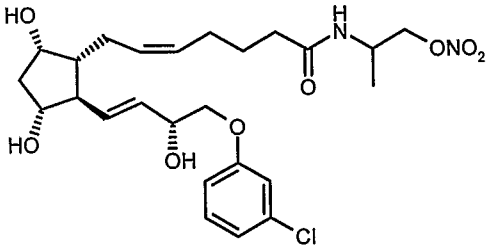

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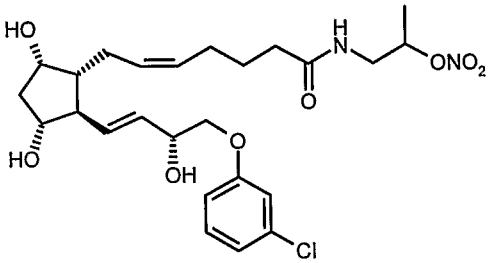

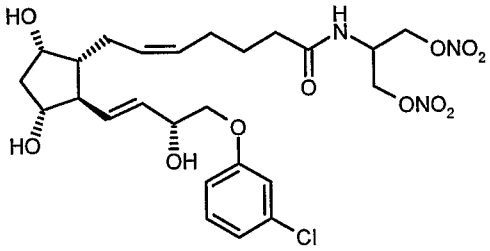

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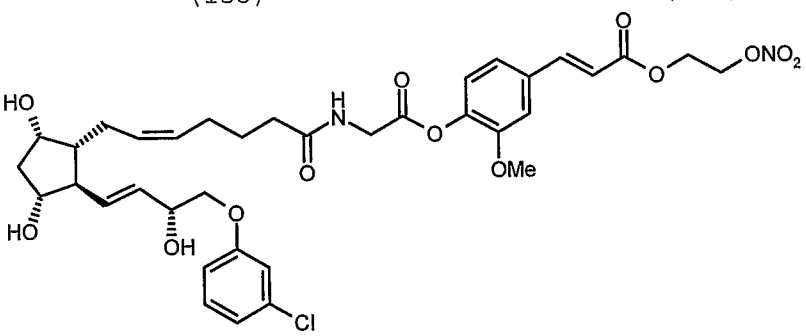

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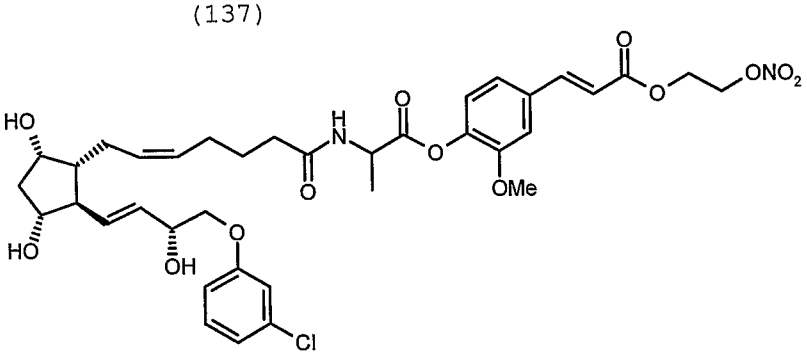

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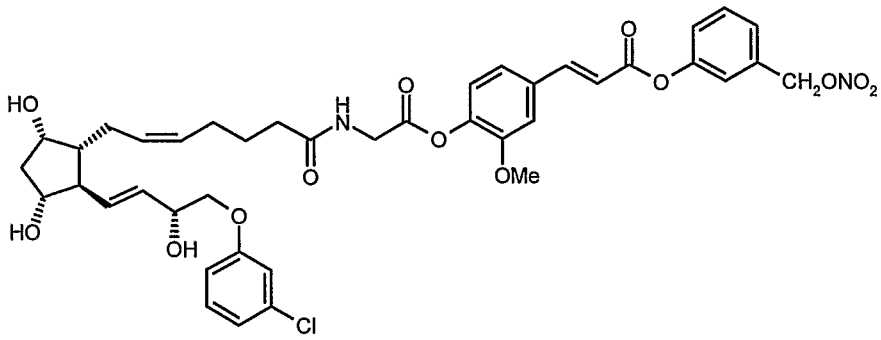

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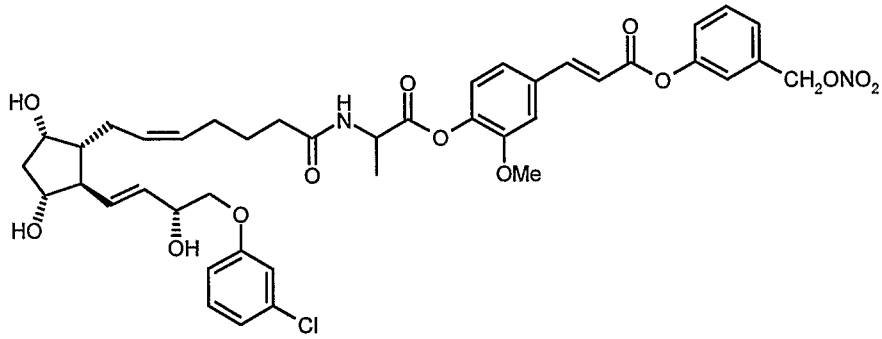

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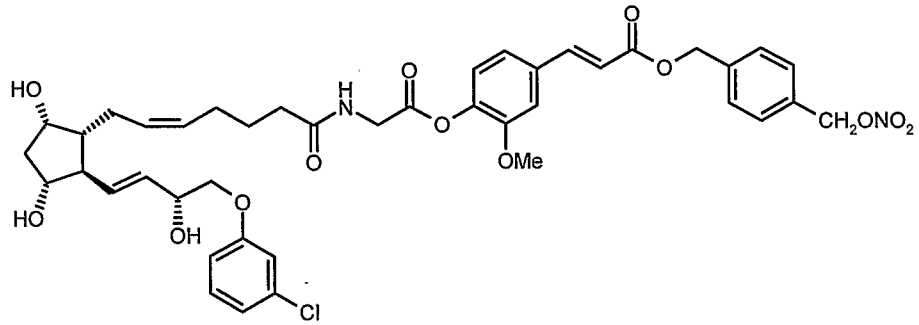

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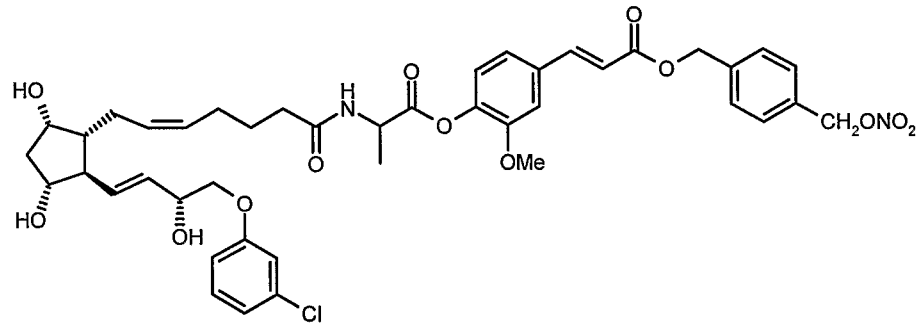

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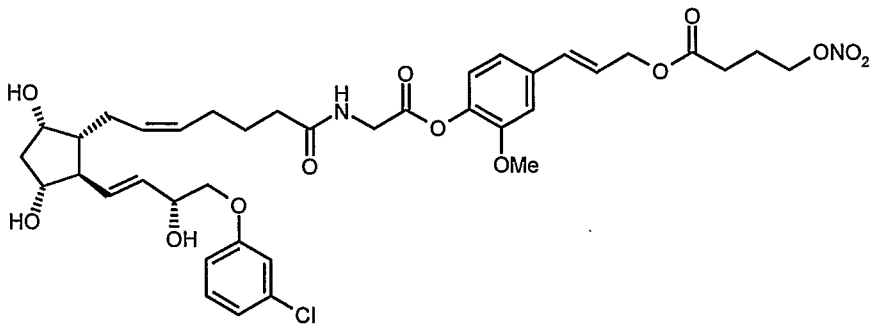

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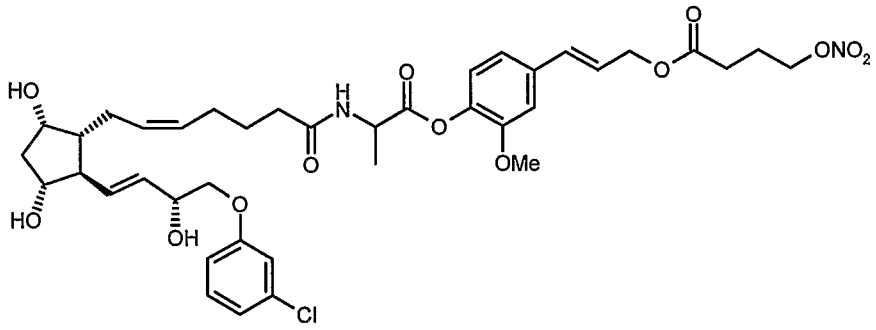

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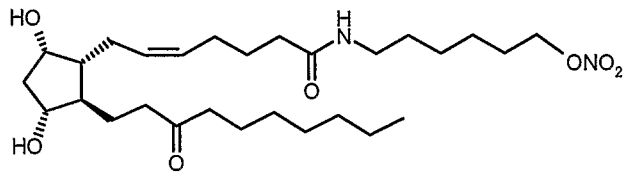

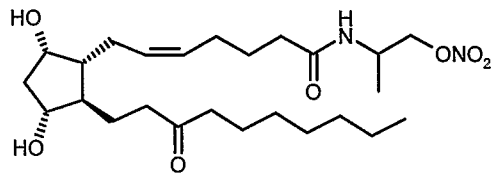

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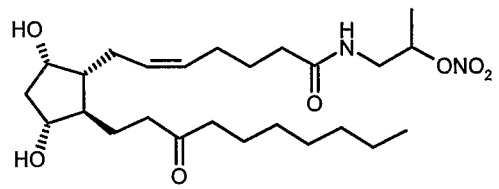

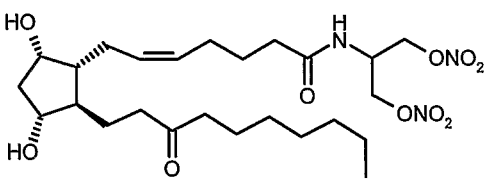

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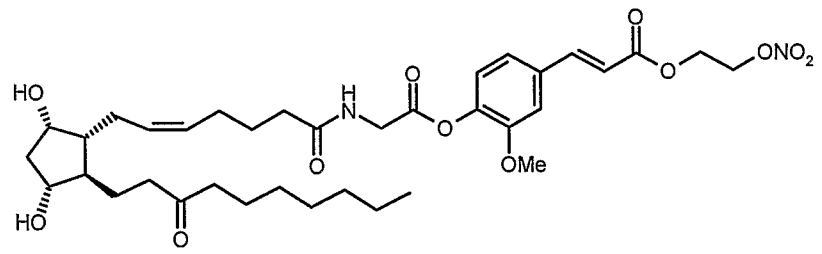

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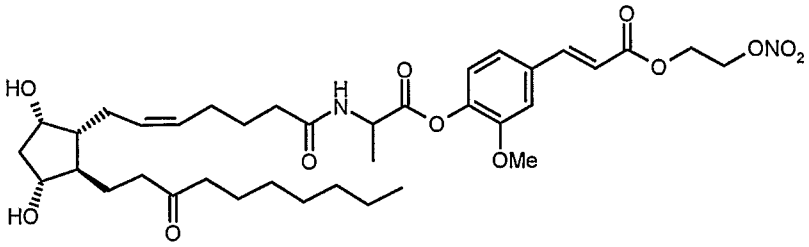

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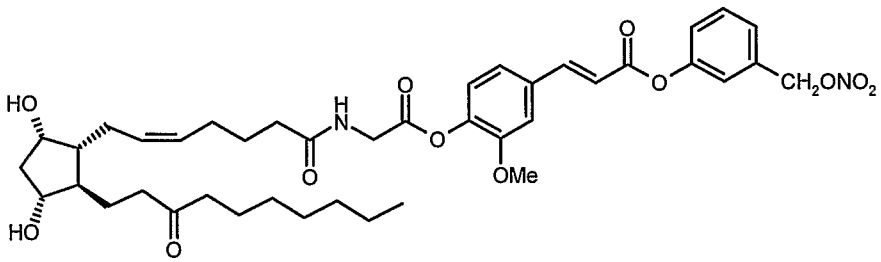

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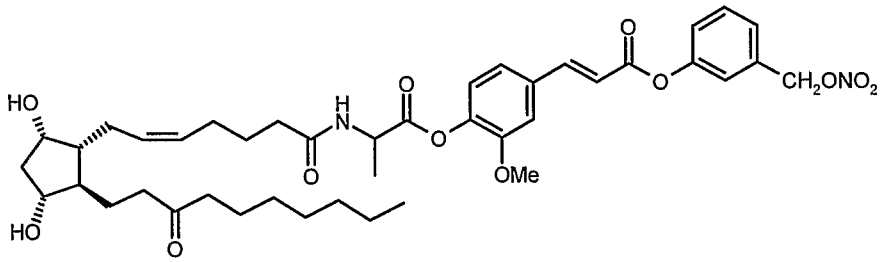

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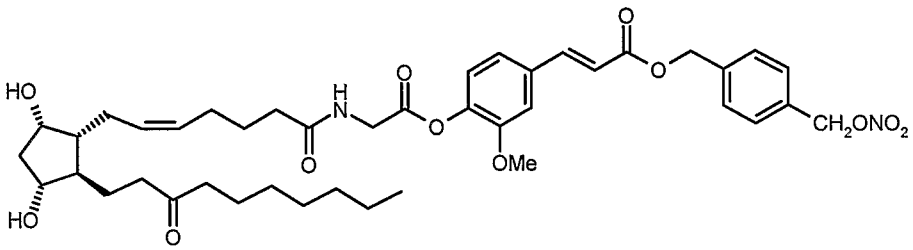

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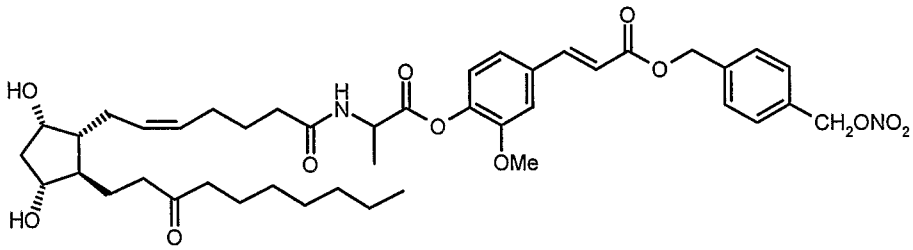

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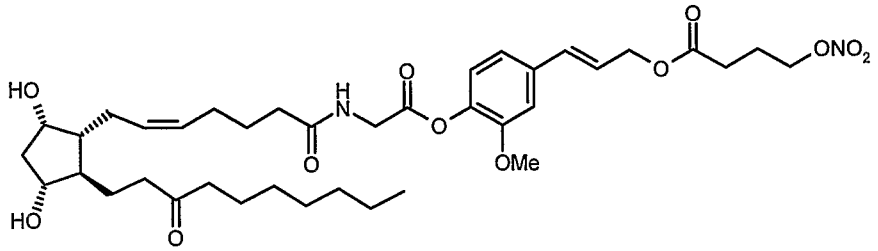

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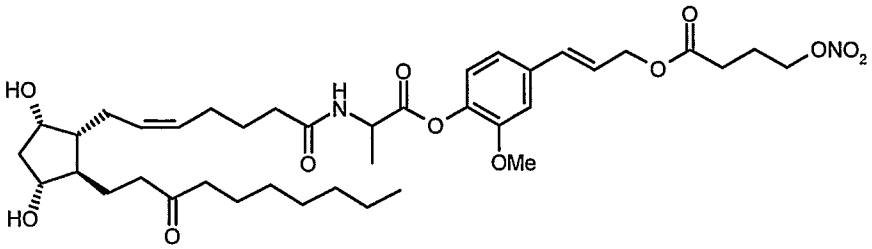

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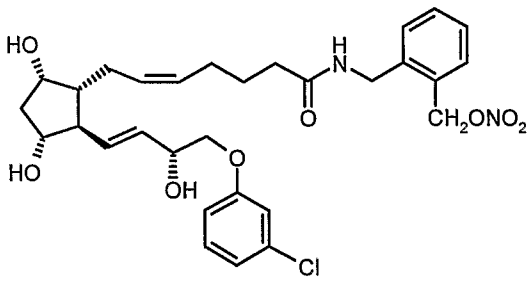

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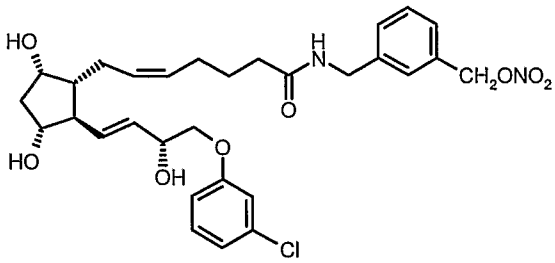

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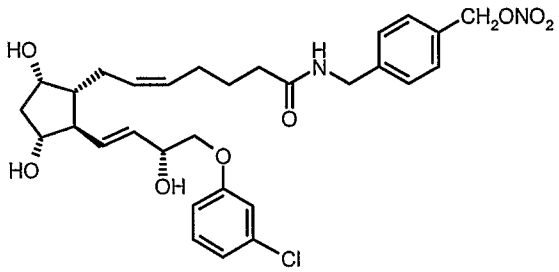

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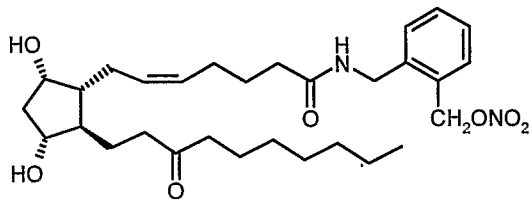

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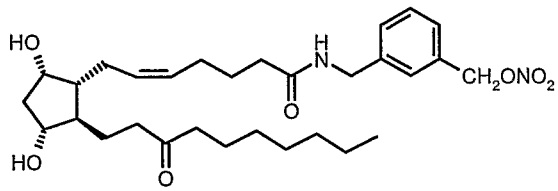

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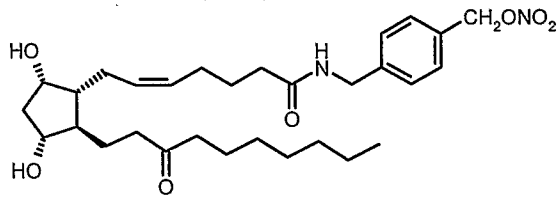

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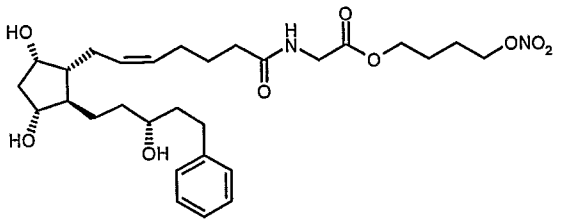

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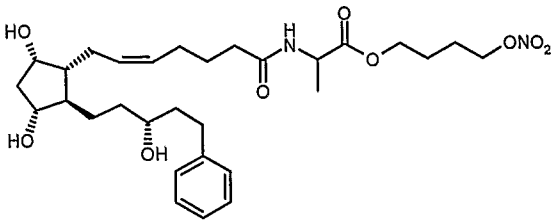

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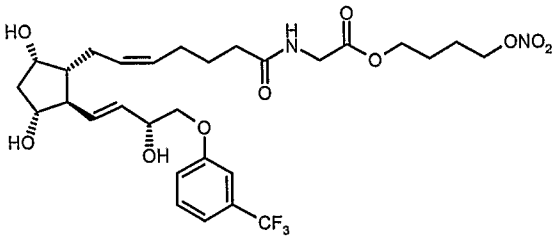

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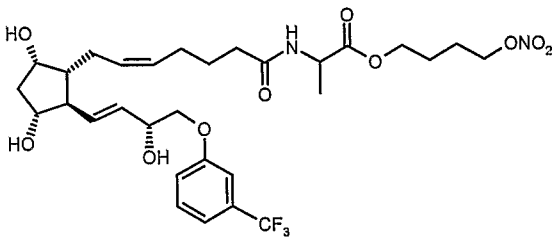

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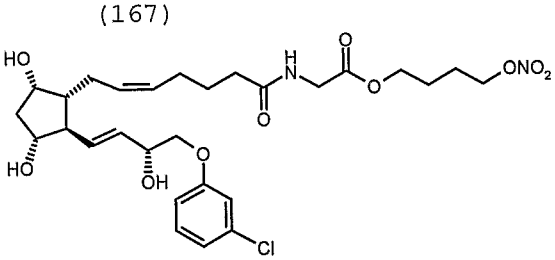

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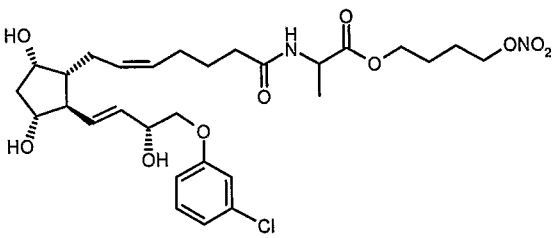

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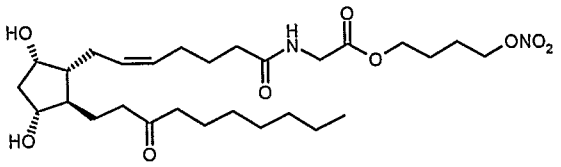

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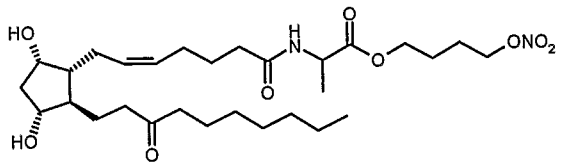

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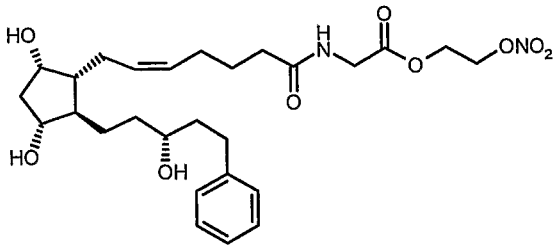

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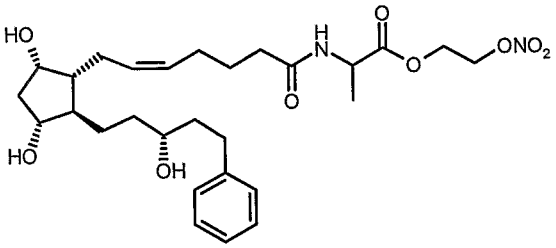

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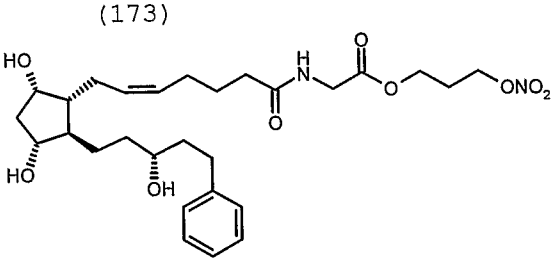

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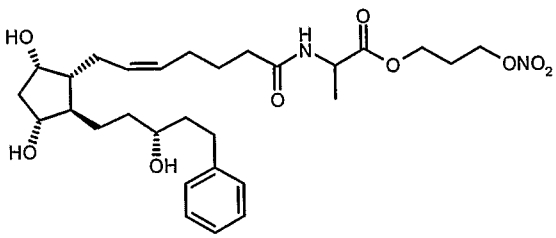

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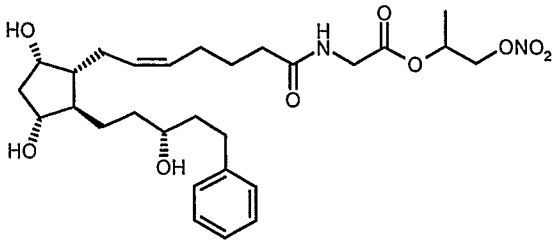

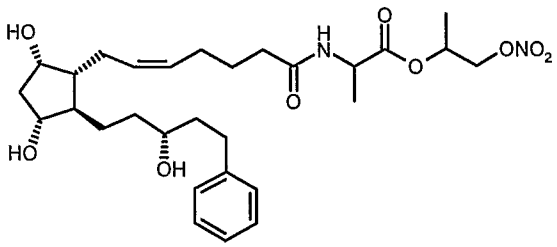

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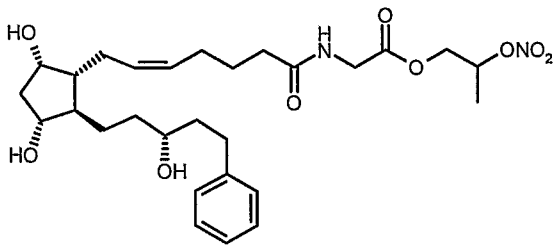

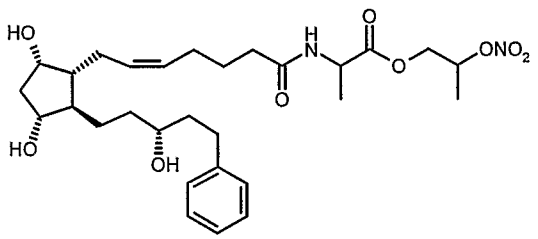

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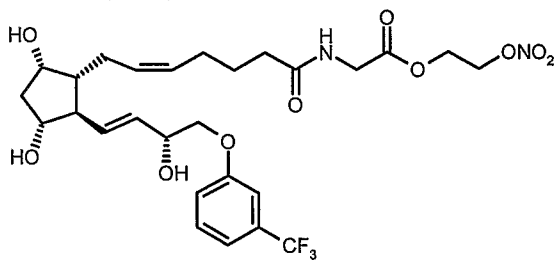

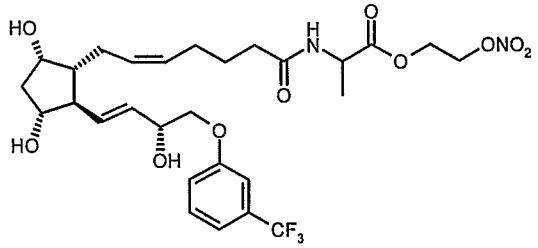

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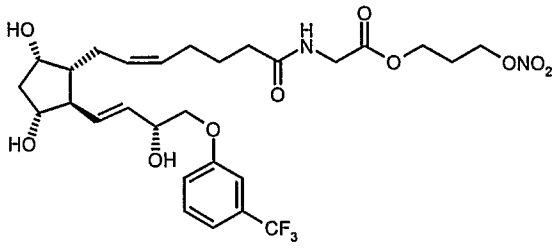

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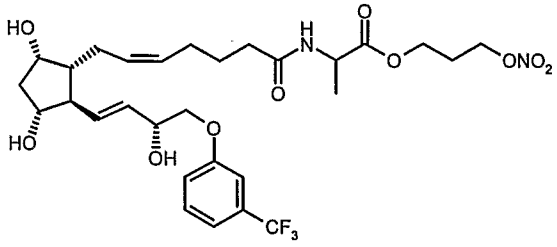

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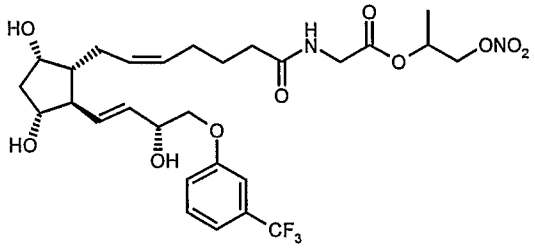

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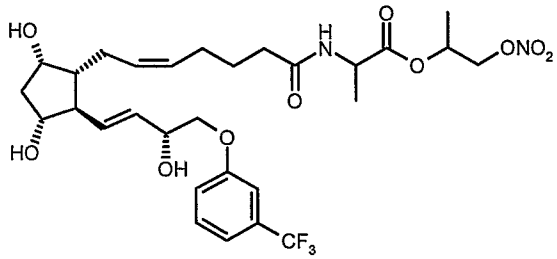

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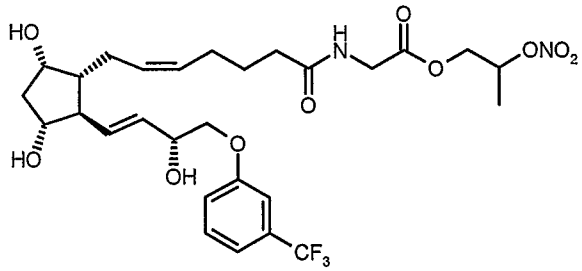

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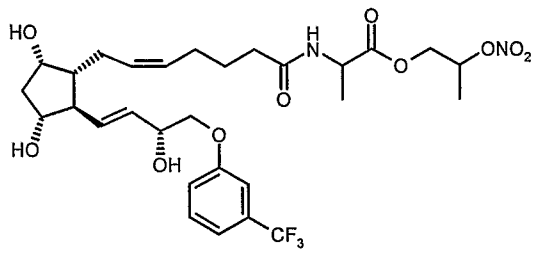

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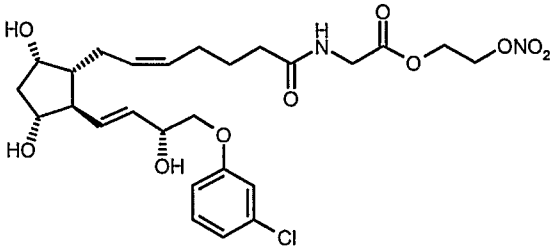

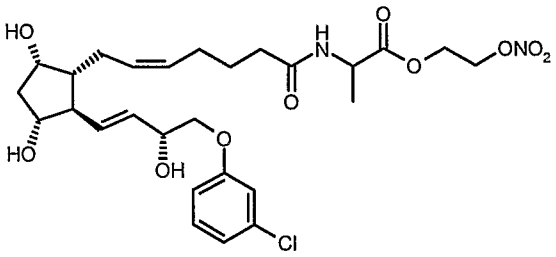

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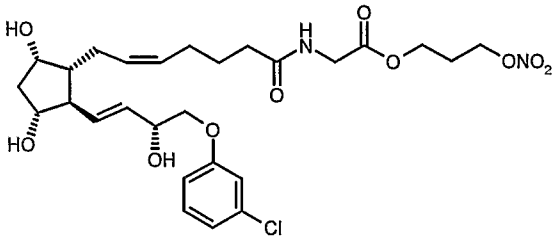

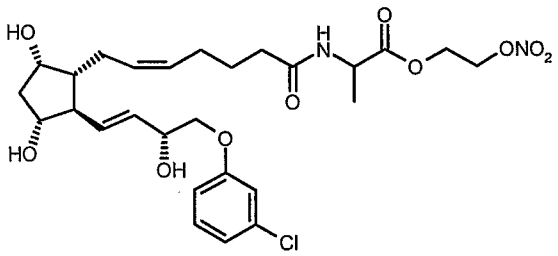

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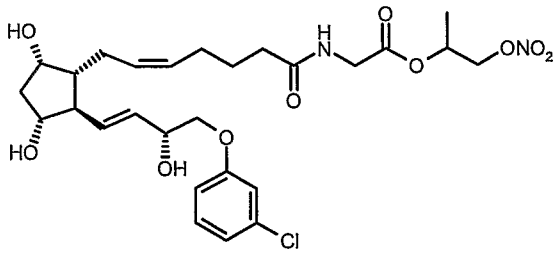

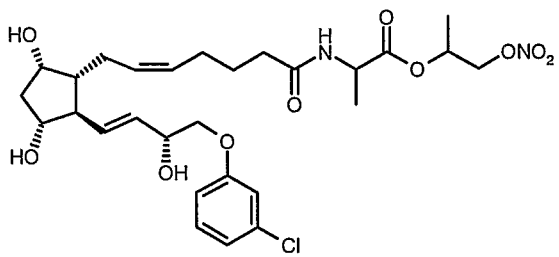

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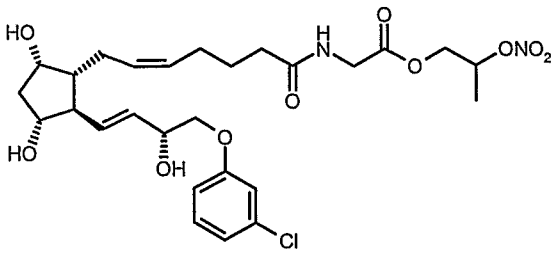

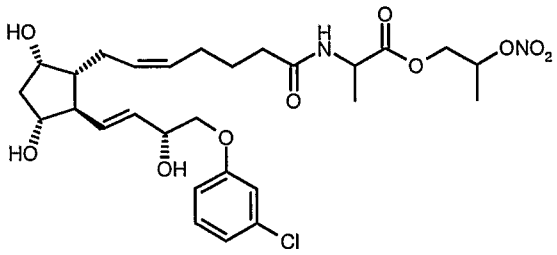

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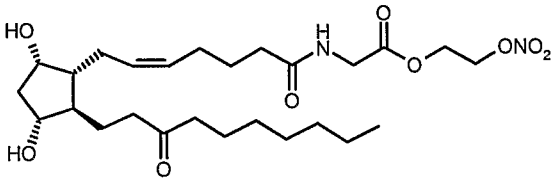

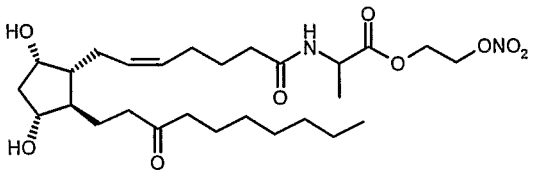

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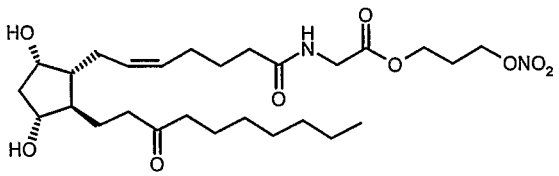

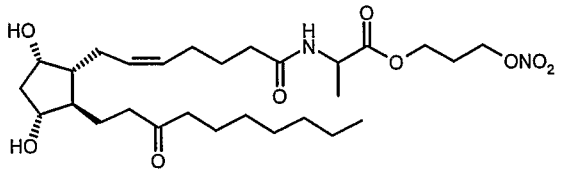

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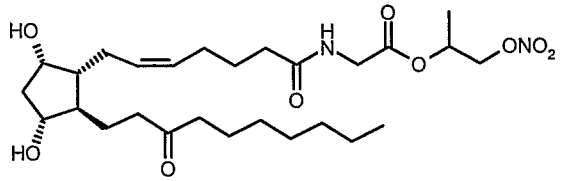

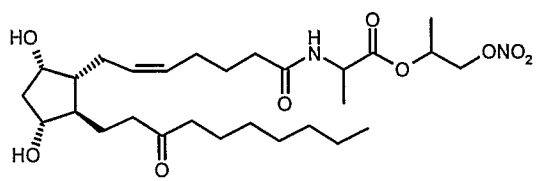

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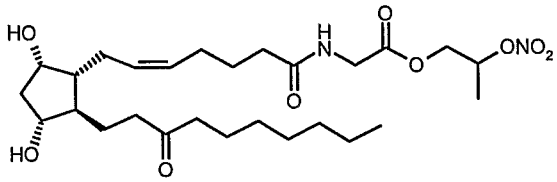

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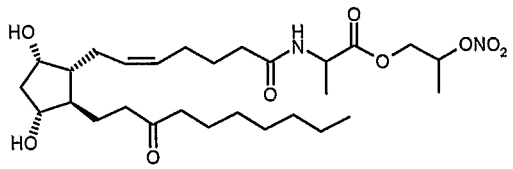

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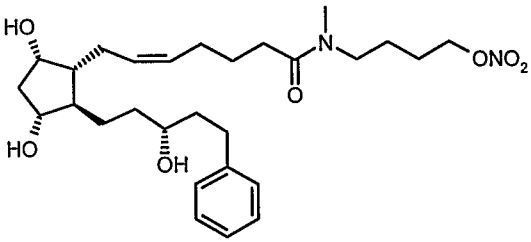

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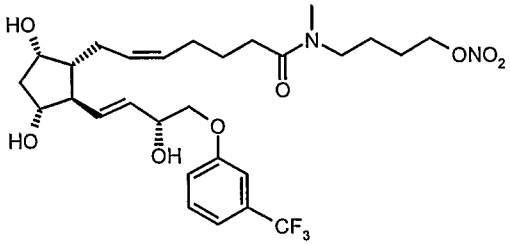

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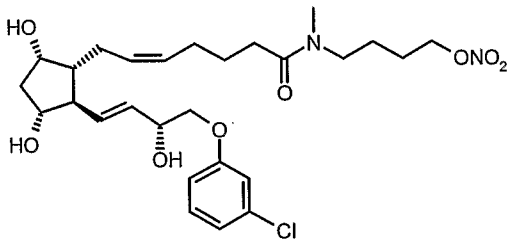

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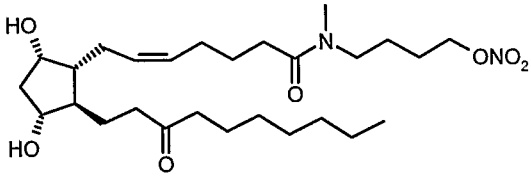

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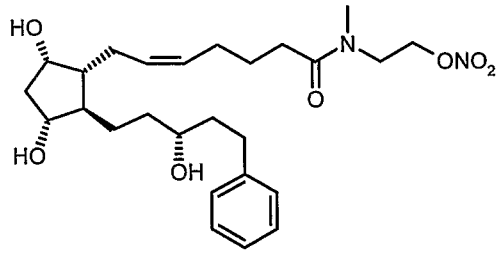

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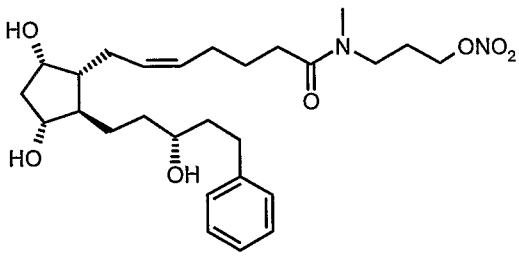

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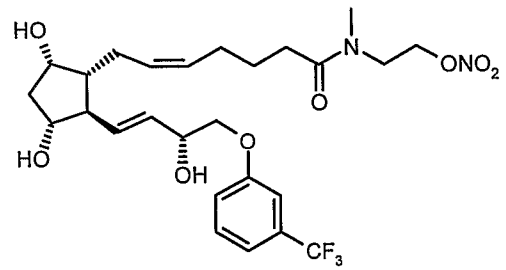

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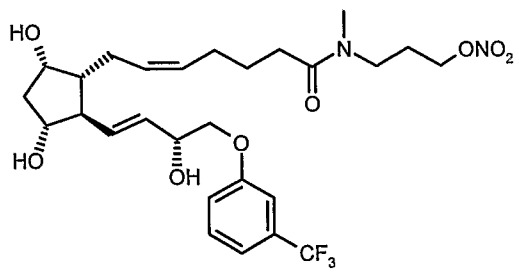

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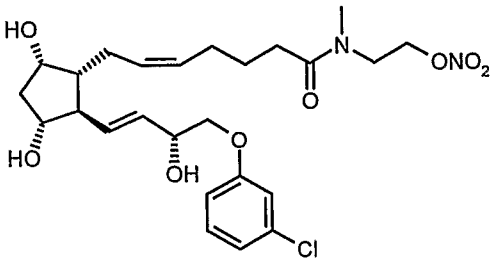

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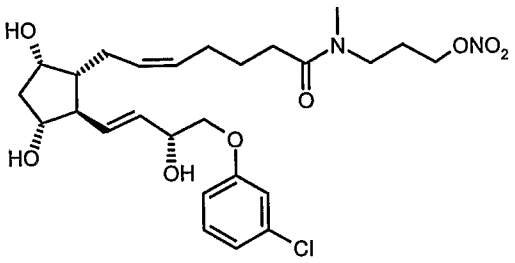

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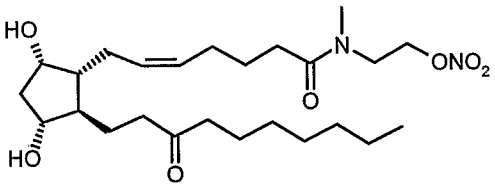

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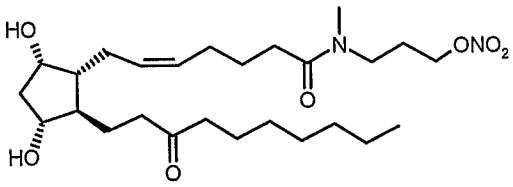

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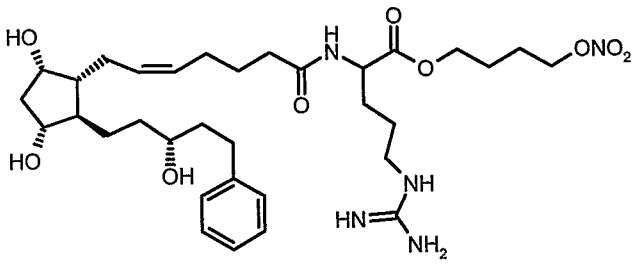

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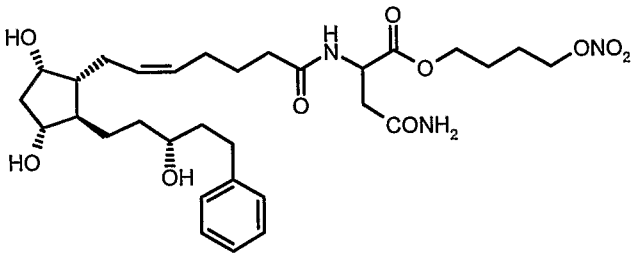

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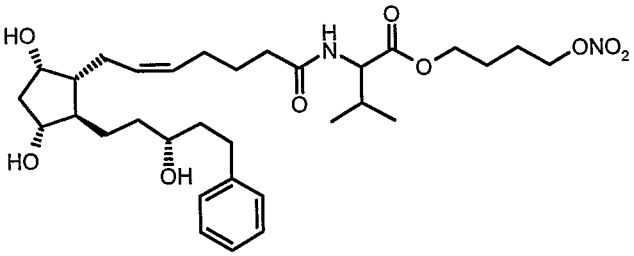

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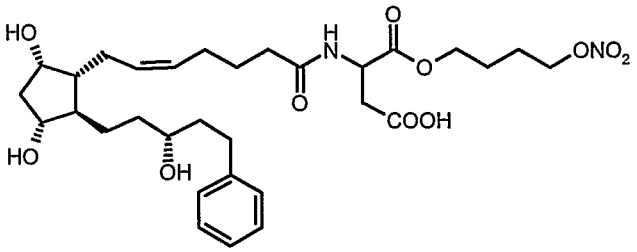

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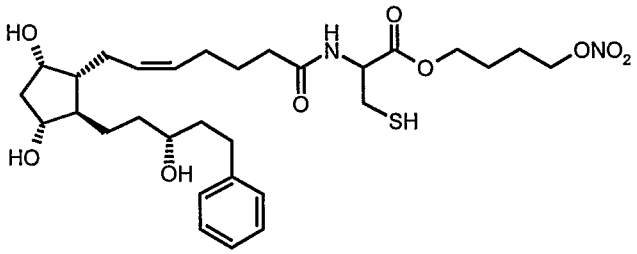

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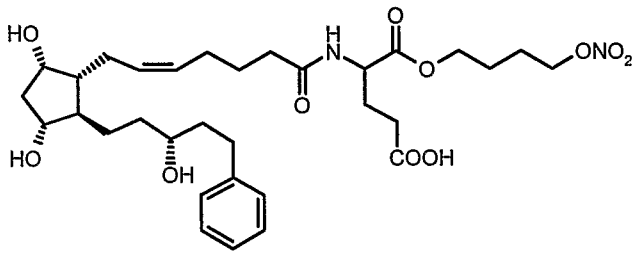

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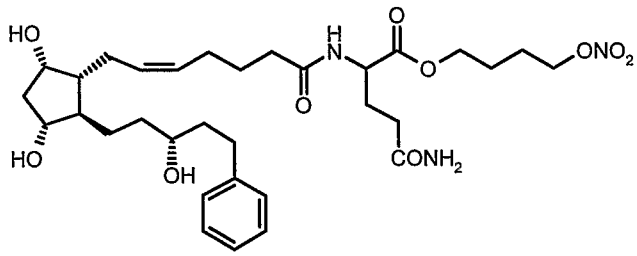

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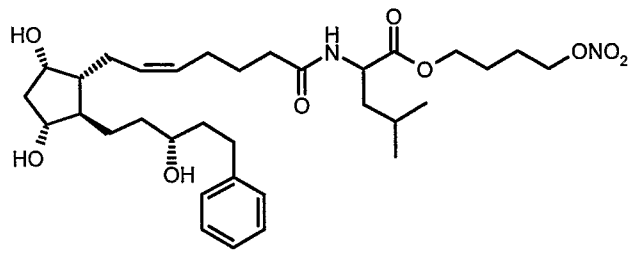

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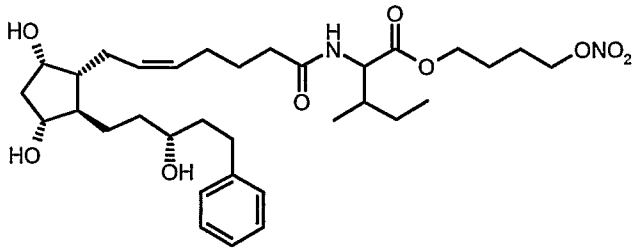

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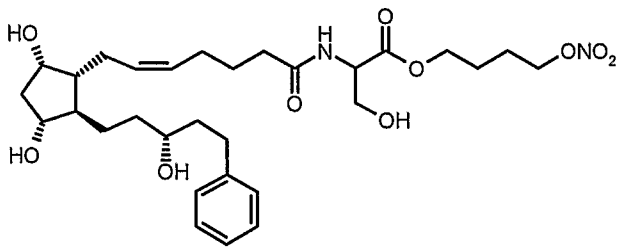

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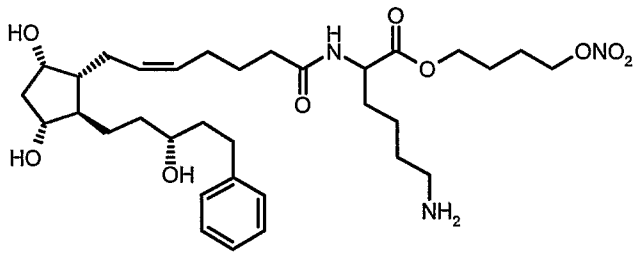

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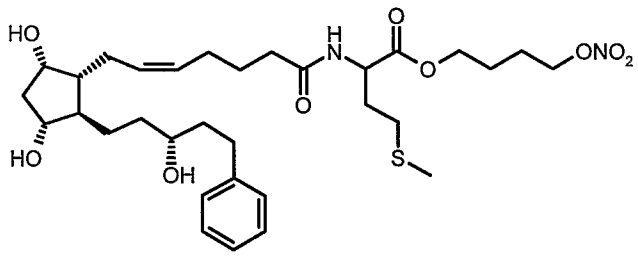

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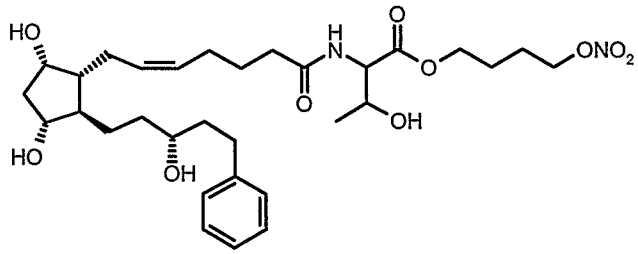

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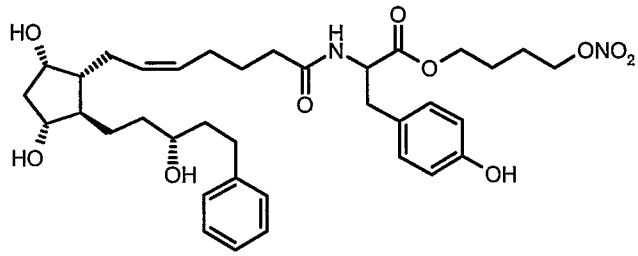

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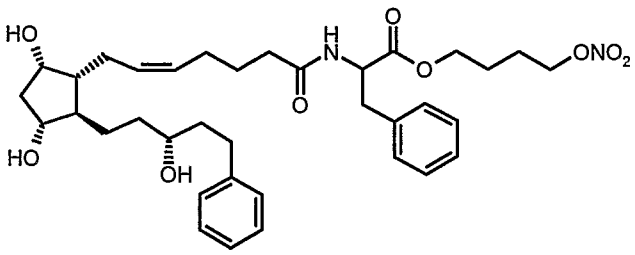

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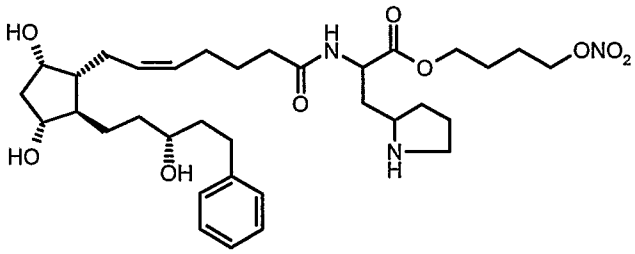

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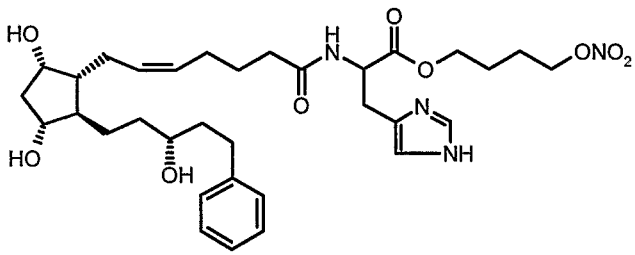

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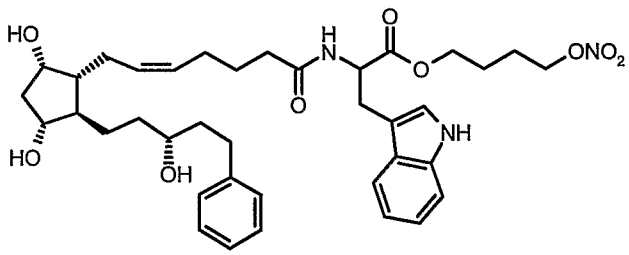
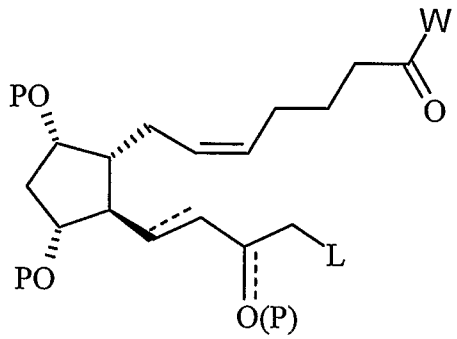


(234)

14. A process for preparing a compound of general formula (I) as defined in claim 1, which process comprises:

a.1) reacting a compound of formula (III)



wherein

L is as defined in claim 1; P is H or a hydroxylic protecting group, W is -OH, Cl, or -$OC(O)R_1$ wherein R_1 is a linear or branched C_1-C_5 alkyl;

with a compound of formula (IV)

$$HR^1N\text{-}(B)_m\text{-}Y\text{-}Q \quad (IV)$$

wherein R^1, Y, B and m are as defined in claim 1, Q is $-ONO_2$ or Z_1 wherein Z_1 is selected from the group consisting of:

chlorine, bromine , iodine, mesyl, tosyl; and

b) when Q is Z_1, converting the compound obtained in the step a) into the corresponding nitrooxy derivative by reaction with a nitrate source; and

c) optionally deprotecting the compound obtained in step a) or b).

15. A compound of general formula (I) according to claims 1-13 for use as a medicament.

16. Use of a compound according to claims 1-13 for the preparation of a medicament for treating glaucoma and ocular hypertension.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of general formula (I) and/or a salt or stereoisomer thereof as defined in claims 1-13.

18. A pharmaceutical composition according to claim 17 in a suitable form for the topical administration.

19. A pharmaceutical composition according to claims 17-18 for the treatment of glaucoma and ocular hypertension.

20. A pharmaceutical composition according to claims 17-19, wherein the compound of general formula (I) is administered as a solution, suspension or emulsion in an ophthalmically acceptable vehicle.

21. A method for treating glaucoma or ocular hypertension, said method consisting in contacting an effective intraocular pressure reducing amount of a pharmaceutical composition according to claims 17-20, with the eye in order to reduce eye pressure and to maintain said pressure on a reduced level.

22. A pharmaceutical composition comprising a mixture of a compound of formula (I) as defined in claim 1 and (i) a beta-blocker or (ii) a carbonic anhydrase inhibitor or (iii) an adrenergic agonist or a nitrooxy derivative thereof.

23. A pharmaceutical composition comprising a mixture of a compound of formula (I) as defined in claim 1 and timolol or a nitrooxy derivative thereof.