

TITLE OF THE INVENTION

**"PROCESS FOR PREPARING NITROOXY ESTERS, NITROOXY THIOESTERS
NITROOXY CARBONATES AND NITROOXY THIOCARBONATES,
5 INTERMEDIATES USEFUL IN SAID PROCESS AND PREPARATION
THEREOF"**

The present invention relates to a process for preparing nitrooxy esters, nitrooxy thioesters, nitrooxy
10 carbonates and nitrooxy thiocarbonates of compounds having at least an hydroxyl or thiol functional group, and also to intermediates useful in said process and to their preparation.

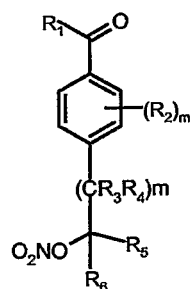
In literature, several methods for synthesizing nitrooxyalkyl/alkylaryl substituted esters from haloalkyl/
15 hydroxyalkyl carboxylic acids or from nitroxyalkylaryl-carboxylic acids are reported.

WO 01/12584 describes the preparation of 4-(acetylamino) phenyl 4-nitrooxybutanoate. The product is obtained by
20 condensation (esterification) of the phenolic group of 4-(acetylamino)phenol with the carboxylic group of 4-bromobutyric acid. The thus obtained 4-bromobutanoate is reacted with silver nitrate.

The principal drawbacks of the above reported synthesis are
25 the use of the silver salts in an amount more than stoichiometric. The use of the silver nitrate in a large amount makes the method expensive and not useful under the point of view of the industrial application. Furthermore the use of a transition metal in the last step of the
30 process, makes difficult the complete removal of the same from the active pharmaceutical product, unless techniques of chromatographic purification are applied.

WO 02/094758 describes a method of synthesis of 21-[4'-(nitrooxyalkyl)benzoate]corticosteroids comprising the reaction of a 21-hydroxyalkylcorticosteroids with a nitrooxyalkyl phenyl carboxylic acid derivatives of formula

5 (I)



(I)

Wherein R' is OH, an halogen atom or $R^{10}C(O)O-$ wherein R^{10} can be an aryl group. The reaction is carried out in the presence of a suitable coupling agent when R' is OH, or in the presence of a suitable base when R' is an halogen atom or the group $R^{10}C(O)O-$.

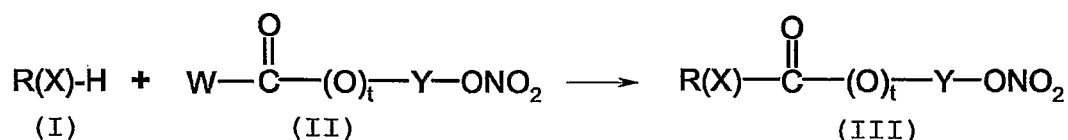
The present application provides a new method of synthesis which overcomes the drawbacks of the previous method using as intermediates nitrooxy-substituted carboxylic acid and nitrooxy-substituted carbonic acid derivatives in the ready-for-use form of activated esters or activated carbonates. Said intermediates are easily isolable in a substantially pure, easy to react, easy to handle and not explosive.

Moreover, it was surprisingly found that if other functional groups are present in the molecule to be derivatised, as for example a carboxylic group, or a N^1H -tetrazole group, they can be unprotected during the reaction.

It was thus an object of the present invention to provide a new process for preparing nitrooxy esters, nitrooxy carbonate, nitrooxy thioesters and nitrooxy

thiocarbonates of compounds having at least an hydroxyl or and thiol functional group.

The object of the invention is a process for preparing compounds of general formula (III), according to the following scheme

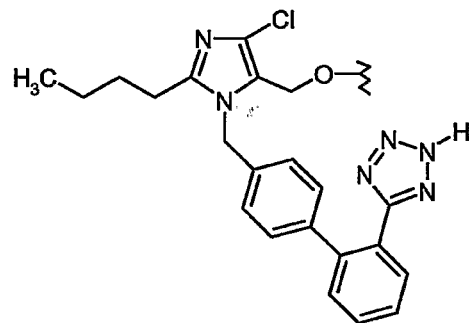


comprising reacting:

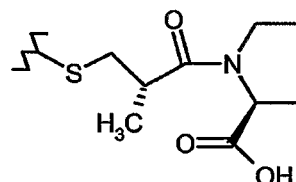
- (a) a compound of formula (I)
 - (b) a compound of formula (II)
- 10 in the presence of dimethylaminopyridine (DMAP) or dimethylaminopyridine and a Lewis acid
wherein:

in formula (I), R(X)-, wherein X is O or S, is the radical of a compound selected from the group comprising:

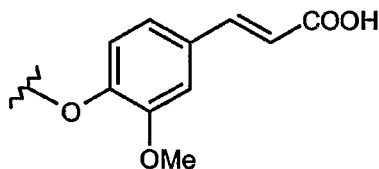
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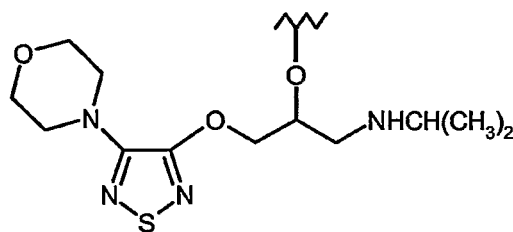
(1a)



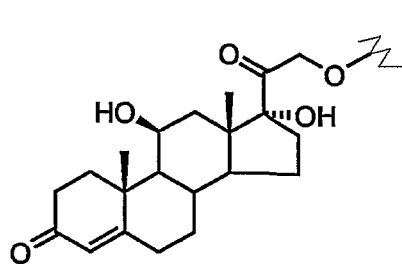
(1b)



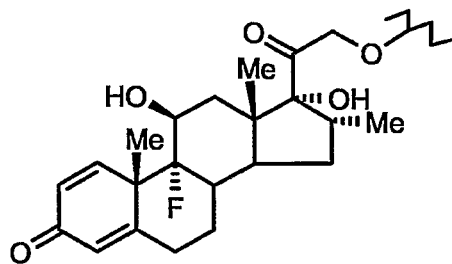
(1c)



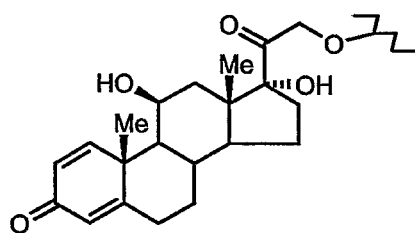
(1d)



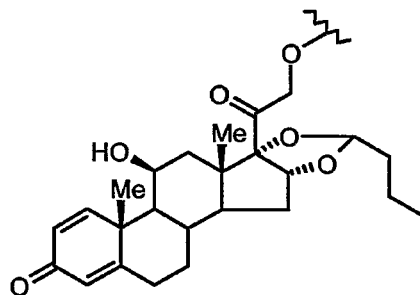
(1e)



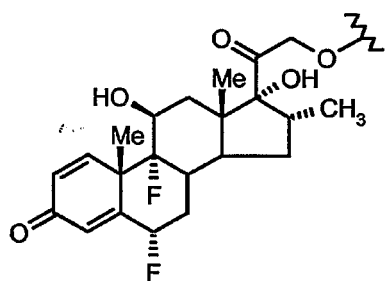
(1f)



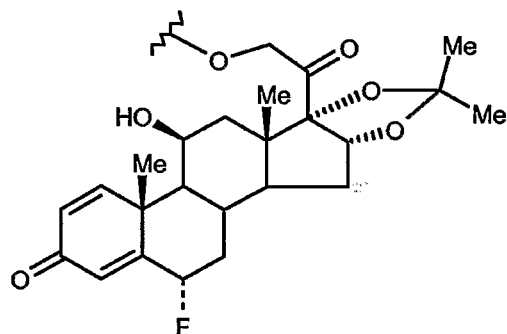
(1g)



(1h)



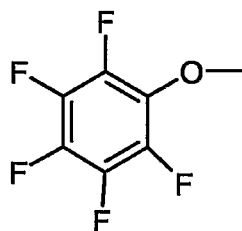
(1i)



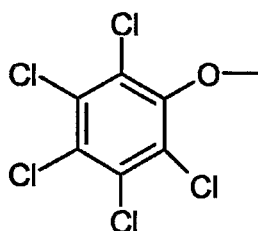
(1l)

- in formula (II), t is 0 or 1,

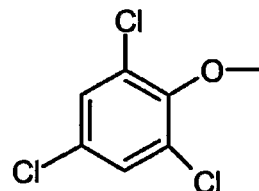
W is selected from



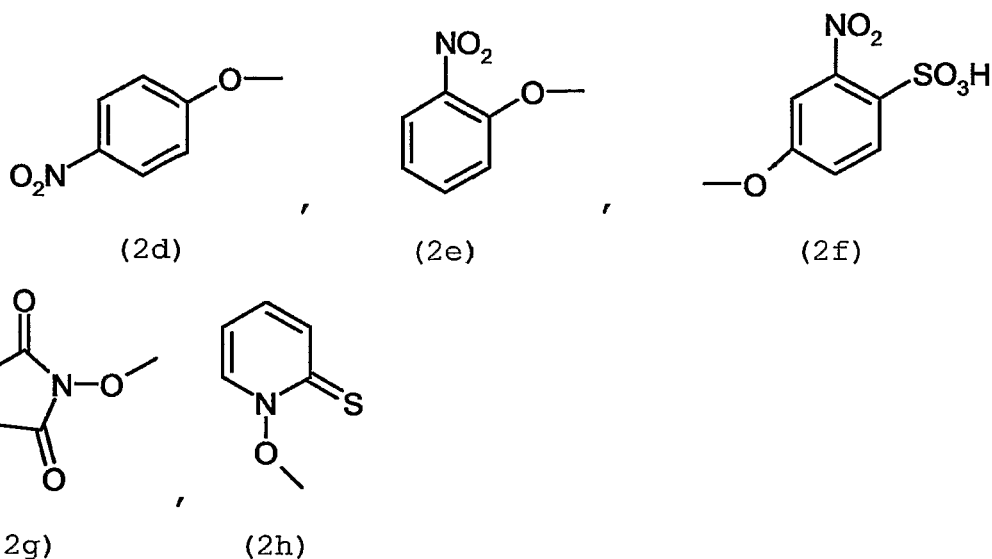
(2a)



(2b)



(2c)



5 Y is as defined below;

- in formula (III), t, R(X)- and X are as above defined,
Y is a bivalent radical having the following meanings:

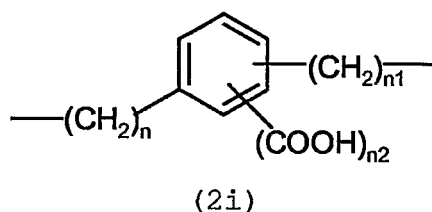
a)

- straight or branched C₁-C₂₀ alkylene, preferably C₁-C₁₀
10 alkylene, more preferably C₃-C₆ alkylene, being optionally
substituted with one or more of the substituents selected
from the group consisting of: halogen atoms, hydroxy, -ONO₂
or T₀, wherein T₀ is

-OC(O)-(C₁-C₁₀ alkyl)-ONO₂ or -O-(C₁-C₁₀ alkyl)-ONO₂;

15 - cycloalkylene having from 5 to 7 carbon atoms, the ring
being optionally substituted with side chains T, wherein T
is straight or branched alkyl with from 1 to 10 carbon
atoms, preferably T is CH₃;

b)



wherein

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

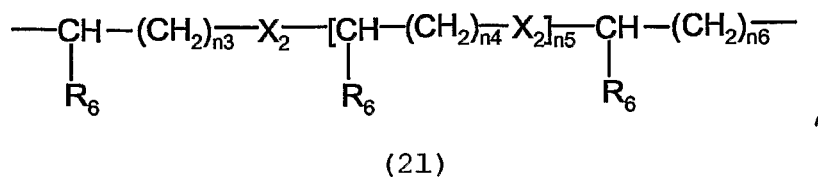
n1 is an integer from 1 to 20, preferably n1 is an integer from 1 to 6, more preferably n1 is 1,

n2 is 0 or 1, preferably n2 is 0;

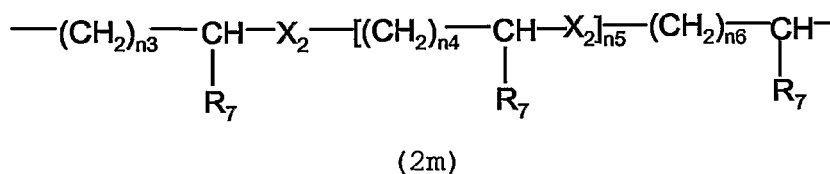
with the proviso that the -ONO₂ group is linked to -(CH₂)_{n1}- group;

5

c)



d)



10

wherein X₂ is O or S,

n3, n4 and n6 are integer independently selected from 0 to 20, preferably n4 and n6 are selected from 1 to 5, more preferably n4 and n6 are 1,

15

preferably n3 is selected from 0 to 4, more preferably n3 is 0,

n5 is an integer from 0 to 6, preferably from 0 to 4, more preferably n5 is 0,

20

R₆ is H, CH₃ or nitrooxy group, preferably R₆ is H,

R₇ is CH₃ or nitrooxy group;

when Y is selected from the bivalent radicals of the group

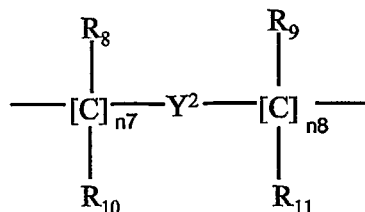
c) the -ONO₂ group is linked to -(CH₂)_{n6}- group;

when Y is selected from the bivalent radicals of the group

25

d) the -ONO₂ group is linked to -CH(R₇)- group;

e)

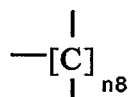


wherein:

n7 is an integer from 0 to 10;

5 n8 is an integer from 1 to 10;

R₈ R₉, R₁₀, R₁₁ are the same or different, and are H or straight or branched C₁-C₄ alkyl, preferably R₈ R₉, R₁₀, R₁₁ are H;

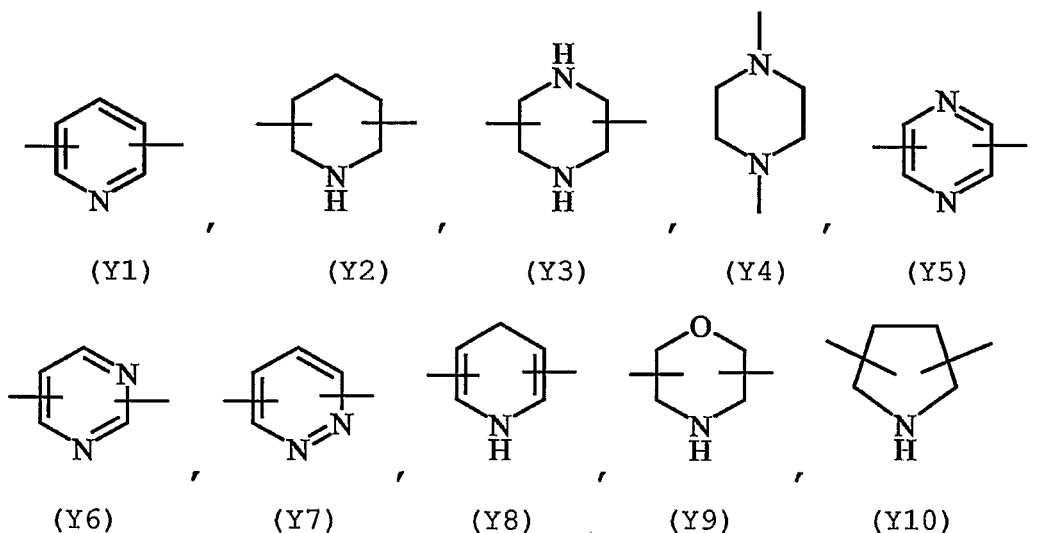
wherein the -ONO₂ group is linked to

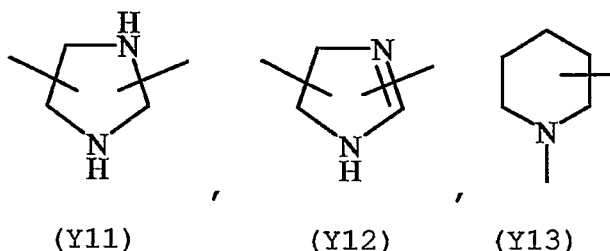
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wherein n8 is as defined above;

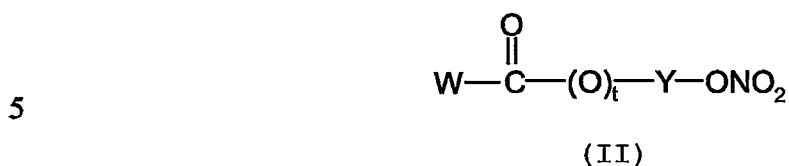
Y² is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur,

15 and is selected from





Another object of the present invention are compounds of formula (II)



wherein W, t, Y are as above defined, said compounds are intermediates of the process above reported.

- When in formula (I) the R(X) residue is as defined by
 10 formula (1a), the compound is known as Losartan;
 when in formula (I) the R(X) residue is represented by
 formula (1b), the compound is known as Captopril;
 when in formula (I) the R(X) residue is represented by
 formula (1c), the compound is known as ferulic acid;
 15 when in formula (I) the R(X) residue is represented by
 formula (1d) and Z is H, the compound is known as timolol;
 when in formula (I) the R(X) residue is represented by
 formula (1e), the compound is known as hydrocortisone;
 when in formula (I) the R(X) residue is represented by
 20 formula (1f), the compound is known as dexamethasone;
 when in formula (I) the R(X) residue is represented by
 formula (1g), the compound is known as prednisolone;
 when in formula (I) the R(X) residue is represented by
 formula (1h), the compound is known as budesonide;
 25 when in formula (I) the R(X) residue is represented by
 formula (1i), the compound is known as flumethasone;
 when in formula (I) the R(X) residue is represented by
 formula (1l), the compound is known as flunisolide;

The compound of formula (I) above reported are commercially available or may be obtained according to processes known in the art; in particular:

Losartan can be prepared as described in D. J. Carini *et al.*, *J. Med. Chem.* 34, 2525 (1991).

Captopril can be prepared as described in M. A. Ondetti, D. W. Cushman, DE 2703828; *eidem*, US 4046889 and US 4105776 (1977, 1977, 1978

Ferulic acid, Timolol, Prednisolone, Hydrocortisone, dexamethasone, budesonide, flumethasone and flunisolide are commercially available.

The term "C₁-C₂₀ alkylene" as used herein refers to branched or straight C₁-C₂₀ saturated hydrocarbon chain that results from the removal of two hydrogen atoms from an acyclic saturated hydrocarbon, preferably having from 1 to 10 carbon atoms such as -CH₂-, -CH₂-CH₂-, -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆- and the like.

The term "C₁-C₁₀ 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, n-pentyl, n-hexyl, n-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 (C₁-C₁₀)-alkyl, preferably CH₃.

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

In one aspect of the invention and as reported above in the general reaction scheme, the reaction between the compound of formula (I) and the nitrooxyderivative of formula (II) is carried out in the presence of dimethylaminopyridine (DMAP) in at least an equimolar amount respect to compound (II).

The molar ratio of compounds of formulas (I):(II) is from 1 to 0.5.

The molar ratio (II):DMAP is 1.

When in the structure of compound (I) of formula $R(X)H$ a free carboxylic acid group or a 1N-H tetrazole group is present an additional equimolar amount of inorganic or organic bases such as DMAP, TEA, pyridine, DIPEA tributylphosphine has added.

The reaction is typically carried out in a temperature range from about -15°C to about 100°C , preferably from -5°C to 40°C ,

Generally, the reaction is carried out in an organic solvent, generally an aprotic solvent, such as pyridine, methylene chloride, or chloroform or dipolar solvents such as acetone, tetrahydrofuran, dimethylformamide (DMF), N-methylpyrrolidone, sulfolane, acetonitrile or in a mixture thereof, depending on the solubility of the compounds involved in the reaction; the preferred solvent are methylene chloride, DMF, a mixture of methylene chloride and THF, or a mixture of methylene chloride and DMF.

In another embodiment the reaction between the compound of formula (I) and the nitrooxyderivative of formula (II) is carried out in the presence of a catalytic amount of a Lewis acid catalyst such as bismuth triflate, scandium triflate, and in the presence of at least an equimolar amount of DMAP respect to compound (II). The preferred Lewis acid catalyst is Scandium triflate.

The molar ratio of compounds of formulas (I):(II) is from 1 to 0.5.

Preferably the molar ratio (II):DMAP is 1.

The molar ratio (II): DMAP: $\text{Sc}(\text{OTf})_3$ is 1:1:0.1.

- 5 When in the structure of compound (I) of formula $\text{R}(\text{X})\text{H}$ a free carboxylic acid group or a 1N-H tetrazole group is present an additional equimolar amount of inorganic or organic bases such as DMAP, TEA, pyridine, DIPEA tributylphosphine has added. The preferred base is DMAP.
- 10 Preferably when the compound of formula (I) has an acidic unprotected function and when in compound of formula (II), Y is the group of formula (2i) wherein n1 is 1 (i.e. Y is a benzylic nitrate) the reaction is always carried out with $\text{Sc}(\text{OTf})_3$ in the presence of an excess of DMAP.
- 15 The reaction is typically carried out in a temperature range from about -15°C to about 100°C , preferably from -5°C to 40°C ,
- 1A) The compounds of formula (II) as above defined are obtained as below reported.
- 20 The compounds of formula (II) wherein W and Y are as above defined and t is 1, are obtained by reacting:
compounds of formula (IVa)



with a compounds of formula (V)

- 25 W-COCl
(V)

wherein W is as above defined, in the presence of DMAP

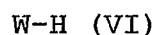
The molar ratio of (V):(IVa):DMAP is 1.2:1:2;

- The reaction is carried out in an organic solvent,
30 generally an aprotic solvent, such as pyridine, methylene chloride, or chloroform or dipolar solvents such as acetone, tetrahydrofuran, dimethylformamide (DMF), N-

methyldpyrrolidone, sulfolane, acetonitrile or in a mixture thereof.

The reaction is typically carried out in a temperature range from about -15°C to about 100°C, preferably from -5°C to 40°C.

2A.1) The compounds of formula (V) as above defined are commercially available or are obtained by reacting compounds of formula (VI)



with phosgene or triphosgene in the presence of a base such as pyridine, TEA or DIPEA in methylene chloride, or THF or DMF or a mixture thereof.

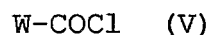
The reaction is typically carried out in a temperature range from about -15°C to about 100°C, preferably from 0°C to 40°C.

2B) Alternatively the compounds of formula (II) wherein W and Y are as above defined and t is 1, are obtained by reacting:

compounds of formula (IVa)



with a compounds of formula (V)



wherein W is as above defined, in the presence of a catalytic amount of a Lewis acid catalyst such as bismuth triflate, scandium triflate, and of at least an equimolar amount of DMAP respect to compound (V).

The molar ratio (V):(IVa):Sc(OTf)₃:DMAP is 1.2:1:0.12:2.

The reaction is carried out in an organic solvent, generally an aprotic solvent, such as pyridine, methylene chloride, or chloroform or dipolar solvents such as acetone, tetrahydrofuran, dimethylformamide (DMF), N-methyldpyrrolidone, sulfolane, acetonitrile or in a mixture thereof.

The reaction is typically carried out in a temperature range from about -15°C to about 100°C, preferably from -5°C to 40°C.

2B.1) The compounds of formula (V) as above defined are
5 commercially available or are obtained using method described in 2A.1).

2B.2) The compounds of formula (IVa)



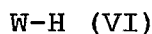
wherein Y is as above defined, are obtained by reacting the
10 commercially available compounds of formula HO-Y-Hal (IVa') wherein Hal is an halogen atom, and Y is as above defined, with AgNO₃ in a suitable organic solvent such as acetonitrile or tetrahydrofuran (THF) under nitrogen in the dark at temperatures range between 20°-80°C; alternatively
15 the reaction with AgNO₃ can be performed under microwave irradiation in solvents such acetonitrile or THF at temperatures in the range between about 100-180°C for time range about 1-60 min.

The compounds of formula (IVa') are commercially available
20 or can be obtained by method well known in the literature;

3A) The compounds of formula (II) wherein W and Y are as above defined and t is 0, are obtained by reacting:
compounds of formula (IVb)



25 wherein Y is as above defined, with a compound of formula (VI)

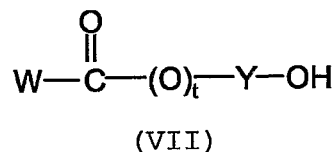


Wherein W is as above defined, in the presence of a condensing agent such as DCC, EDAC.HCl.

30 The reaction is carried out in dichloromethane, THF, DMF or other solvent.

4A) Alternatively, compounds of formula (II) as above defined are obtained by reacting:

a compound of formula (VII)



by *in situ* derivatization and nitration with triflic
 5 anhydride/quaternary ammonium nitrates salts in the
 presence of excess of a base such as DMAP, pyridine, TEA or
 DIPEA.

Preferred quaternary ammonium nitrates is tetraethyl
 ammonium nitrate.

10 The reaction is carried out at a temperature range from
 about -50°C to 100°C. Preferably in a temperature range
 from -50°C to 40°C.

The reaction is carried out in an organic solvent,
 generally in a solvent selected from acetone,
 15 tetrahydrofuran, dimethylformamide, N-methylpyrrolidone,
 sulfolane, acetonitrile, methylene chloride.

Preferred solvent are dichloromethane or dichloro
 methane/DMF.

The molar ratio (VII):triflic anhydride:tetraalkylammonium
 20 nitrate is 1:2:2

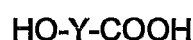
4A.1) Compounds of formula (VII) where t is 1 can be
 obtained from compounds (V) and commercially available
 compounds of formula (VIIa)



25 (VIIa)

using the same procedure described in 2B) using the
 compound (VIIa) instead of compounds (IVa).

4A.2) Compounds of formula (VII) where t is 0 are obtained
 using method described for the preparation of compounds
 30 (II) reacting (VI) with commercially available compounds of
 formula (VIIb)

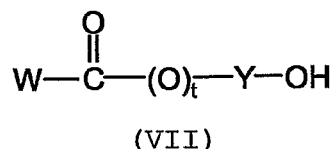


(VIIb)

in the presence of condensing agents as DCC or EDAC.HCl as well known in the art.

5A) Alternatively, compounds of formula (II) as above
5 defined are obtained by reacting:

a compound of formula (VII)



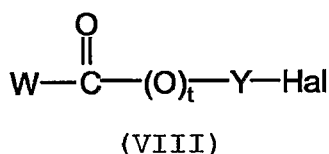
10 with sulfonitric mixture according to the method known in the art.

The compounds of formula (II) may be isolated and stored at -20°C degrees.

5A.1) Compounds of formula (VII) where t is 1 are obtained as described in 4A.1)

15 5A.2) Compounds of formula (VII) where t is 0 are obtained using method described 4A.2).

6A) Alternatively, compounds of formula (II) as above defined are obtained by reacting:
compounds of formula (VIII)



20 wherein Hal is an halogen atom selected from Cl, Br, I, Y and t are as above defined;

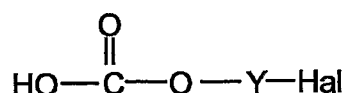
with nitrating agents such as alkaline metal nitrates,
25 quaternary ammonium nitrates, quaternary phosphonium salts and AgNO₃, Zn(NO₃)₂ 6H₂O. Preferably AgNO₃ is used.

The molar ratio (VIII)/nitrating agent is from 1:2 to 1:10, preferably the molar ratio is 1:3.

The reaction is carried out in a temperature range from
30 about 0°C to about 150°C.

The reaction is carried out in solvent such as acetonitrile. High temperature are obtained performing the reaction in a microwave apparatus.

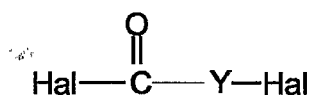
- 6A.1) Compounds of formula VIII where W and Y are as above
 5 described and t is 1 are obtained by reacting compounds of formula (VI) with commercially available compound of formula (VIIIa)



- 10 (VIIIa)

in dichloromethane, THF, DMF or other, in the presence of a base such as Pyridine, TEA, DIPEA and DMAP as known in the art.

- 6A.2) Compounds of formula VIII where W and Y are as above
 15 described and t 0 can be obtained reacting compounds of formula (VI) with commercially available compound of formula (VIIIb)



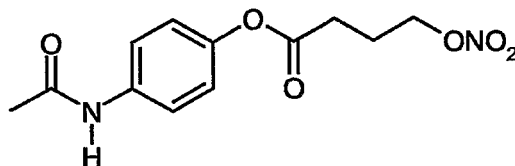
(VIIIb)

- 20 in dichloromethane, THF, DMF or other, in the presence of a condensing agent as DCC or EDAC.HCl and DMAP according to method known in the art.

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

Example 1

Two-step process synthesis of 4-(Nitrooxy)butanoic acid 4-acetamidophenyl ester of formula (IIIa)



5

(IIIa)

Step 1: synthesis of 4-(Nitrooxy)butanoic acid pentafluorophenyl ester (Preparation 1)

To a solution of 4-bromobutyric acid (0.91 g, 5.4 mmol), pentafluorophenol (1.00 g, 5.4 mmol) and DMAP (0.13 g, 1.1 mmol) in CH₂Cl₂ (10 ml) cooled to 0 °C under nitrogen, N,N-dicyclohexylcarbodiimide (1.70 g, 8.1 mmol) was added in portions. After 1 h the reaction was slowly warmed to room temperature and stirred for 5 hours. The dicyclohexylurea was filtered off and the mother liquor was concentrated and purified by flash chromatography (n-Hexane/EtOAc 98:2) affording 4-bromobutyric acid pentafluorophenyl ester as a colourless oil (1.40 g, 78%). A mixture of 4-bromobutyric acid pentafluorophenyl ester (0.65 g, 1.9 mmol) and AgNO₃ (0.83 g, 4.9 mmol) in CH₃CN (8 ml) was warmed at 70 °C for 20 minutes at the microwave. The formed salts were filtered off, the solvent was concentrated and the residue purified by flash chromatography (n-Hexane/EtOAc 95:5) affording 4-nitrooxybutyric acid pentafluorophenyl ester as a clear oil (0.38 g, 62 %).

25

¹H NMR (CDCl₃) δ: 4.60 (2H,t), 2.86 (2H,t), 2.23 (2H,m).

Step 1: synthesis of 4-(Nitrooxy)butanoic acid pentafluorophenyl ester (Preparation 2)

30

To a mixture of pentafluorophenol (3.3 g, 17.96 mmol), 4-bromobutanoic acid (3.0 g, 17.96 mmol) and DMAP (0.440 g,

3.59 mmol) in CH_2Cl_2 (30 ml), cooled to 0°C , EDAC.HCl (5.2 g, 26.94 mmol) was added in portion. The mixture was then stirred at 0°C for 30 minutes. Then it was gradually warmed to room temperature and stirred for 480 minutes. Then the mixture was diluted with NaH_2PO_4 aqueous (5%, 50 ml) and acidified with HCl 1N to pH 3-4. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 ml). The organic phase was washed with brine, dried over Na_2SO_4 and evaporated to give an oil that was purified by flash chromatography (n-Hexane/EtOAc 98:2) to yield 4-bromobutanoic acid pentafluorophenyl ester (5.2 g, 86%) as a colorless oil.

A mixture of 4-bromobutanoic acid pentafluorophenyl ester (5.2 g, 15.61 mmol) and AgNO_3 (6.6 g, 39.03 mmol) in CH_3CN was heated at 60°C for 300 minutes under nitrogen, in the dark.

Then the mixture was cooled, concentrated and diluted with EtOAc. The silver salts were filtered off, the solvent evaporated. After flash chromatography purification (n-Hexane/EtOAc 95:5) 4-(nitrooxy)butanoic acid pentafluorophenyl ester (3.9 g, 80%) was obtained as a colorless oil.

$^1\text{H NMR}$ (CDCl_3) δ : 4.60 (2H,t), 2.86 (2H,t), 2.23 (2H,m).

Step 2: synthesis of 4-(Nitrooxy)butanoic acid 4-acetamidophenyl ester of formula (IIIa)

To a solution of 4-acetamidophenol (Paracetamol) (0.96 g, 6.30 mmol) TEA (0.64 g, 6.3 mmol) and DMAP (0.77 g, 6.3 mmol) in $\text{CH}_2\text{Cl}_2/\text{THF}$ (9:1, 30 ml) kept at 0°C , under stirring and under nitrogen atmosphere, a solution of 4-(nitrooxy)butanoic acid pentafluorophenyl ester (2.0 g, 6.30 mmol) (Preparation 2) in CH_2Cl_2 (10 ml) was added. The resulting solution was kept under stirring for further 240

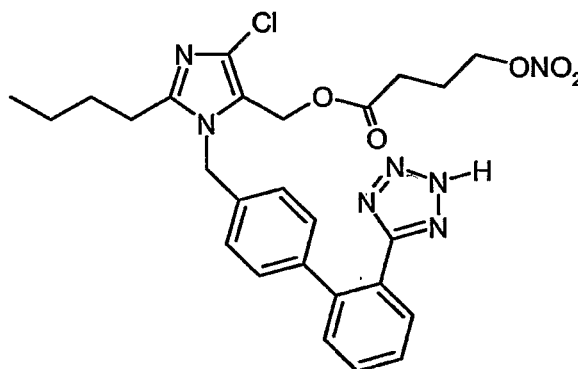
minutes at room temperature. The reaction mixture was poured in a pH 3 buffer solution (about 50 ml), acidified with HCl 1 N to pH 3-4 and extracted with CH₂Cl₂ (2 x 50 ml). The organic phase was washed with brine (100 ml),
 5 dried on sodium sulfate and evaporated under vacuum.

Purification by Flash chromatography of the residue (n-hexane/AcOEt 1:1) gave the title compound as a white solid (1.52 g, 84%). M.p., NMR and HPLC analysis were consistent with data reported in the literature.

10 ¹HNMR (CDCl₃) δ: 7.55 (1H,s); 7.49 (2H,d); 7.02 (2H,d); 4.58 (2H,t); 2.71 (2H,t); 2.19 (2H,m); 2.14 (3H,s).

Example 2

Two-steps process synthesis of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-5-[(3-(nitrooxy) propyl)carbonyloxy]methyl-1H-imidazole of formula (IIIb)
 15



(IIIb)

Step 1: synthesis of 4-(Nitrooxy)butanoic acid pentafluorophenyl ester.
 20

The compound was synthesized using the method described in (Preparation 2)

Step 2: synthesis of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-5-[(3-(nitrooxy) propyl)carbonyloxy]methyl-1H-imidazole;
 25 4-(nitrooxy)butanoic acid

Using the same procedure described in Example 1 but starting from 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (Losartan) (2.13 g, 5.04 mmol) and 4-(nitrooxy)butanoic acid pentafluorophenyl ester (1.59 g, 5.04 mmol) TEA (0.7 ml, 5.04 mmol), DMAP (0.615 g, 5.04 mmol) and using DMF as solvent. Then the mixture was diluted with buffer solution (pH=3); the pH was adjusted to 2-3 and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and evaporated. The residue was purified with Flash chromatography of the residue (CH₂Cl₂/MeOH 98:2) and the title compound was obtained as a white solid (1.48 g, 53%).

m.p. 66-68°C

¹H NMR (CDCl₃) δ: 7.85 (1H, d), 7.58 (2H, m), 7.42 (1H, d), 7.11 (2H, d), 6.79 (2H, d), 5.15 (2H, s), 4.94 (2H, s), 4.42 (2H, t), 2.53 (2H, t); 2.21 (2H, t), 1.93 (2H, m), 1.56 (2H, m), 1.29 (2H, m), 0.85 (3H, t).

20 Example 3

Two-steps process synthesis of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[(3-(nitrooxy)propyl)carbonyloxy]methyl-1H-imidazole of formula (IIb)

Step 1: synthesis of 4-(Nitrooxy)butanoic acid pentafluorophenyl ester.

The compound was synthesized using the method described in (Preparation 1)

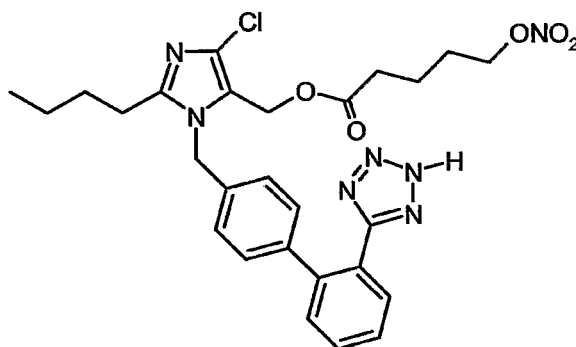
Step 2: synthesis of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[(3-(nitrooxy)propyl)carbonyloxy]methyl-1H-imidazole of formula (IIb)

To a solution of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (0.48 g, 1.1 mmol), TEA (0.16 ml, 1.1 mmol) and DMAP (0.14

mg, 1.1 mmol) in DMF (3 ml), cooled to 0 °C, a solution of 4-nitrooxybutyric acid pentafluorophenyl ester (0.36 g, 1.1 mmol) in DMF (3 ml) was added. The reaction was slowly warmed to room temperature and stirred for 3 hours. Then
 5 the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (10 ml) and washed with a buffer solution (pH=3) then with brine. The organic layer was dried over Na₂SO₄, concentrated and purified by flash chromatography (CH₂Cl₂/ MeOH 98:2) to afford the title
 10 compound (0.41 g, 66%).

Example 4

Two-steps process synthesis of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[(4-(nitrooxy)butyl)carbonyloxy]methyl-1H-imidazole of formula (IIIc);
 15



(IIIc)

Step 1: synthesis of 5-(nitrooxy)pentanoic acid pentafluorophenyl ester (preparation 3)
 20

Starting from 5-bromopentanoic acid (1.0 g, 5.52 mmol) and pentafluorophenol (1.0 g, 5.52 mmol), applying the same procedure described in Preparation 2, 5-bromopentanoic acid pentafluorophenyl ester (1.5 g, 78%) was obtained as a
 25 colorless oil.

From 5-bromopentanoic acid pentafluorophenyl ester (1.5 g, 4.32 mmol) and AgNO₃ (1.8 g, 10.80 mmol), heating to reflux

and applying the same procedure described in Preparation 2, after flash chromatography purification (n-Hexane/EtOAc 98:2) 5-(nitrooxy)pentanoic acid pentafluorophenyl ester (0.72 g, 50%) was obtained as a pale yellow oil.

5 $^1\text{H NMR}$ (CDCl_3) δ : 4.53 (2H, t), 2.77 (2H, t), 2.00–1.85 (4H, m).

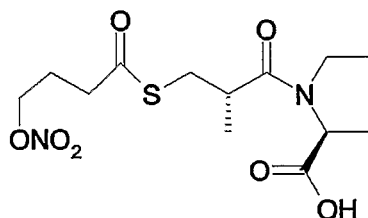
Step 2: synthesis of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[(4-(nitrooxy)butyl)carbonyloxy]methyl-1H-imidazole

10 Using the same procedure described in Example 1 but starting from 2-Butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (Losartan) (0.93 g, 2.19 mmol) and 5-(nitrooxy)pentanoic acid pentafluorophenyl ester (0.72 g, 2.19 mmol) TEA (0.30
15 ml, 2.19 mmol), DMAP (0.27 g, 2.19 mmol) after purification with Flash chromatography of the residue ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2) the title compound (0.72 g, 60%) was obtained as a white foam.

$^1\text{H NMR}$ (CDCl_3) δ : 7.72–7.48 (4H, m); 7.10 (2H, d); 6.94 (2H, d);
20 5.24 (2H, s); 5.00 (2H, s); 4.44 (2H, t); 2.10 (2H, t); 1.57–1.44 (6H, m); 1.29 (4H, m); 0.83 (3H, t).

Example 5

Two-steps process synthesis of 1-[(2S)-3-[(3-(nitrooxy)propyl)carbonylthio]-2-methyl-1-oxopropyl]-L-proline of
25 formula (IIId).



(IIId)

Step 1: synthesis of 4-(Nitrooxy)butanoic acid pentafluorophenyl ester.

The compound was synthesized using the method described in **(Preparation 2)**

5

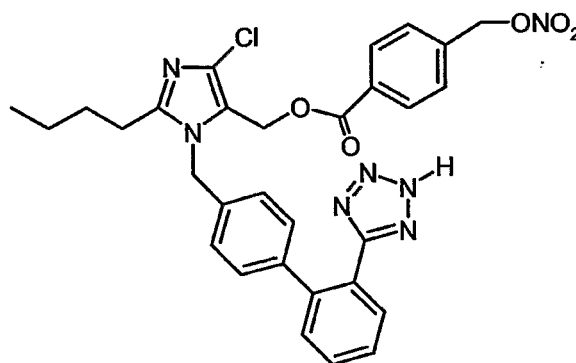
Step 2: synthesis of 1-[(2S)-3-[(3-(nitrooxy)propyl)carbonylthio]-2-methyl-1-oxopropyl]-L-proline.

Using the same procedure described in Example 1 but starting from 1-[(2S)-3-mercapto-2-methyl-1-oxopropyl]-L-proline (Captopril) (0.41 g, 1.9 mmol), 4-(nitrooxy)butanoic acid pentafluorophenyl ester (0.60 g, 1.9 mmol) TEA (0.26 ml, 1.9 mmol) and DMAP (0.23 g, 1.9 mmol) after purification with Flash chromatography of the residue (CH₂Cl₂/Acetone 80:20) the title compound (0.140 g, 20%)
10 was obtained as a white foam.

¹H NMR (CDCl₃) δ: 4.61 (1H,m); 4.51 (2H,t); 3.61 (2H,m); 3.15 (1H,dd); 3.02 (1H,dd); 2.72 (2H,t); 2.39 (1H,m); 2.08 (5H,m); 1.27 (3H,d).

20 **Example 6**

Synthesis of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[[[(4-(nitrooxy)methyl)phenyl]carbonyloxy]methyl]-1H-imidazole of formula (IIIe)



25

(IIIe)

Step 1: synthesis of [4-(nitrooxy)methyl]benzoic acid pentafluorophenyl ester (preparation 4)

Starting from 4-(bromomethyl)benzoic acid (5.0 g, 23.25 mmol) and pentafluorophenol (4.3 g, 23.25 mmol),
5 applying the same procedure described in Preparation 2, 4-(bromomethyl)benzoic acid pentafluorophenyl ester (5.0 g, 56%) was obtained as an off white solid.

From 4-(bromomethyl)benzoic acid pentafluorophenyl ester (5.0 g, 13.12 mmol) and AgNO₃ (5.6 g, 32.80 mmol), heating
10 to reflux and applying the same procedure described in Preparation 2, after flash chromatography purification (n-Hexane/EtOAc 95:5) [4-(nitrooxy)methyl]benzoic acid pentafluorophenyl ester (4.2 g, 88%) was obtained as a white solid.

15 m.p. 75-76°C

¹H NMR (CDCl₃) δ: 8.26 (2H,d), 7.60 (2H,d), 5.55 (2H,s).

Step 2: synthesis of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-5-[[[(4-(nitrooxy)methyl)phenyl]carbonyloxy]methyl]-1H-imidazole

To a solution of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (Losartan) (3.1 g, 7.27 mmol) Sc(OTf)₃ (0.3 g, 0.61 mmol) and DMAP (1.5 g, 12.12 mmol) in CH₂Cl₂ (25 ml) kept at -
25 5°C, under stirring and under nitrogen atmosphere, a solution of [4-(nitrooxy)methyl]benzoic acid pentafluorophenyl ester (2.2 g, 6.06 mmol) in CH₂Cl₂ (5 ml) was added. The resulting solution was kept under stirring for further 16 hrs at room temperature. The reaction mixture was poured
30 into a pH 3 buffer solution (about 50 ml), acidified with HCl 1 N to pH 3-4 and extracted with CH₂Cl₂ (2 x 50 ml). The organic phase was dried on sodium sulfate and evaporated.

After purification with Flash chromatography of the residue ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2) the title compound was obtained as a white solid (1.70 g, 47%).

m.p. 155

- 5 ^1H NMR (DMSO) δ : 7.73–7.56 (5H,m); 7.47 (2H,d); 7.24 (1H,d); 7.00 (4H,m); 5.60 (2H,s); 5.36 (2H,s); 5.27 (2H,s); 2.56 (2H,t); 1.53 (2H,m); 1.28 (2H,m); 0.82 (3H,t).

Example 7

10 Synthesis of 4-(nitrooxy)butyl pentafluorophenyl carbonate

- To a solution of pentafluorophenol (1 g, 5.43 mmol) and TEA (0.91 ml, 6.52 mmol) in CHCl_3 (8 ml), cooled to 0°C and under nitrogen, a solution of 4-chlorobutyl chloroformate (0.76 ml, 5.43 mmol) in CHCl_3 (1 ml) was
15 dropped into. The mixture was allowed to warm to room temperature and stirred for 480 minutes. Then it was diluted with aqueous KHSO_4 (2%), the two phases were separated and the organic phase was dried and evaporated yielding 4-chlorobutyl pentafluorophenyl carbonate (1.69 g,
20 98%) as a colorless oil that was used without further purification.

- A mixture of 4-chlorobutyl pentafluorophenyl carbonate (1.69 g, 5.3 mmol) and NaI (7.99 g, 53.3 mmol) in CH_3CN (20 ml) was refluxed under nitrogen for 960 minutes. Then the
25 solvent was evaporated and the residue taken up with CH_2Cl_2 and washed with water (2 x 50 ml). The organic phase was then dried and evaporated yielding 4-iodobutyl pentafluorophenyl carbonate (1.95 g, 90%) as a yellow oil that was used without further purification.

30

A mixture of 4-iodobutyl pentafluorophenyl carbonate (1.95 g, 4.75 mmol) and AgNO_3 (14.6 mmol) was stirred under nitrogen in the dark at room temperature for 24 hrs.

Then the silver salts were filtered and, following the same procedure already described (Preparation 2), after flash chromatography purification (n-Hexane/EtOAc 95:5) 4-(nitrooxy)butyl pentafluorophenyl carbonate (0.99 g, 60%)
5 was obtained as a colorless oil.

^1H NMR (CDCl_3) δ : 4.51 (2H,t); 4.15 (2H,t); 1.94 (4H,m)

Example 8

Synthesis of [3-(Nitrooxy)methyl]phenyl 4-nitrophenyl carbonate 10

Following the same procedure described in Preparation 3, but starting from 3-(bromomethyl)phenol (9.3 g, 49.6 mmol) and 4-nitrophenyl chloroformate (10 g, 49.6 mmol) after purification of the residue by flash chromatography
15 (n-Hexane/EtOAc 85:15) 3-(bromomethyl)phenyl 4-nitrophenyl carbonate (3.7 g, 21%) was obtained as white solid.

A mixture of 3-(bromomethyl)phenyl 4-nitrophenyl carbonate (3.6 g, 10.2 mmol) and AgNO_3 (8.66 g, 51 mmol) in CH_3CN
20 under nitrogen, in the dark, was heated to 60°C for 48 hrs. Then applying the same procedure described in Preparation 2, after Flash chromatography purification [3-(nitrooxy)methyl]phenyl 4-nitrophenyl carbonate (3.3 g, 96%) was obtained as a pale yellow solid.

25 ^1H NMR (CDCl_3) δ : 8.33 (2H,d); 7.49 (2H,d); 7.49-7.20 (4H,m); 5.58 (2H,s).

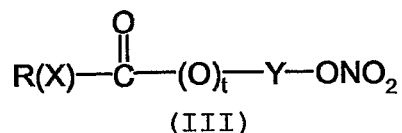
Example 9

Synthesis of 4-(Nitrooxy)butanoic acid N-succinimidyl ester
30 To a mixture of N-hydroxysuccinimide (3.3 g, 28.74 mmol), 4-bromobutanoic acid (4.0 g, 23.95 mmol) and DMAP (0.59 g, 4.82 mmol) in CH_2Cl_2 (40 ml), cooled to 0°C , DCC (7.4 g, 35.93 mmol) was added in portion. The mixture was then

- stirred at 0°C for 30 minutes. Then it was gradually warmed to room temperature and stirred for 480 minutes. Then the mixture was diluted with EtOAc (40 ml) and the solid was filtered off and the solvent was evaporated. The residue
- 5 was taken with EtOAc and the organic phase was washed with brine, dried over Na₂SO₄ and evaporated. The residue was purified by Flash chromatography (n-Hexane: EtOAc 70:30) yielding 4-bromobutanoic acid N-succinimidyl ester (3.0 g, 48%) as a white solid.
- 10 A solution of 4-bromobutanoic acid N-succinimidyl ester (1.8 g, 6.82 mmol) and AgNO₃ (2.9 g, 17.04 mmol) in CH₃CN (18 ml) was heated to 70°C for 18 minutes in a microwave apparatus (Creator®, Biotage). Then the mixture was cooled, diluted with EtOAc and the silver salts were filtered off
- 15 and the solvent evaporated to give 4-(nitrooxy)butanoic acid N-succinimidyl ester (1.4 g, 83%).
- ¹H NMR (CDCl₃) δ: 4.59 (2H,t); 2.87 (4H,m); 2.79 (2H,t); 2.21 (2H,m).

CLAIMS

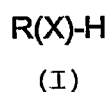
1. A process for preparing compounds of general formula (III)



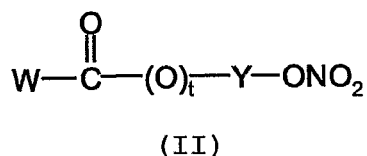
5

comprising reacting:

(a) a compound of formula (I)



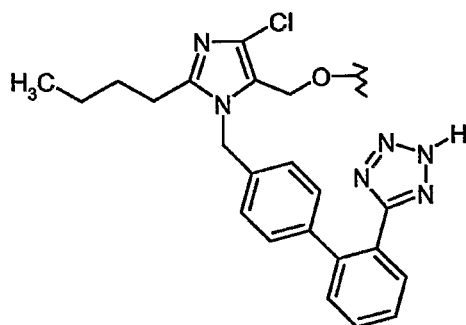
10 (b) a compound of formula (II)



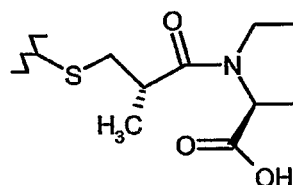
in the presence of dimethylaminopyridine (DMAP)
or dimethylaminopyridine and a Lewis acid

15 wherein:

in formula (I), R(X)-, wherein X is O or S, is the radical of a compound selected from the group comprising:

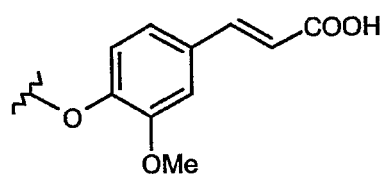


(1a)

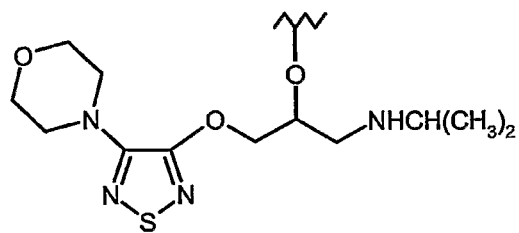


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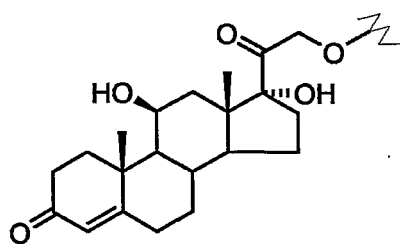
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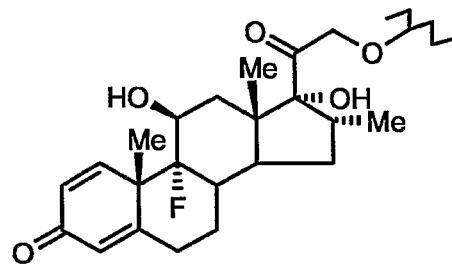
(1c)



(1d)

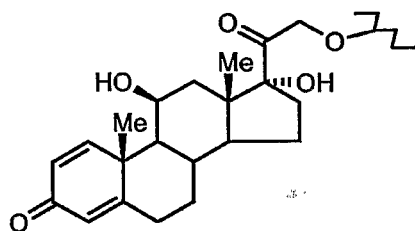


(1e)

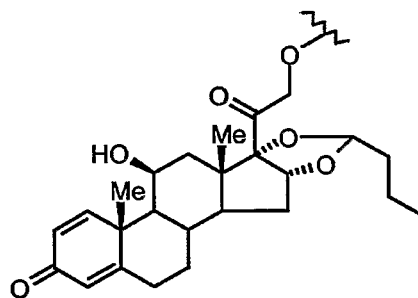


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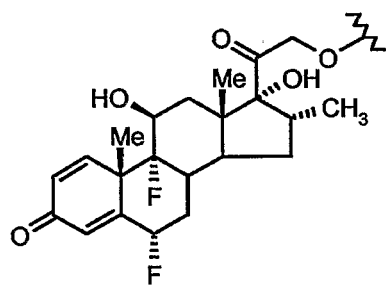
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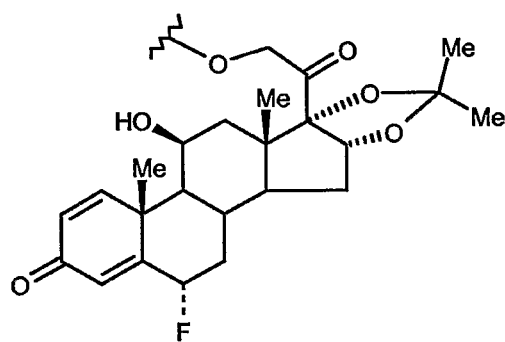
(1g)



(1h)

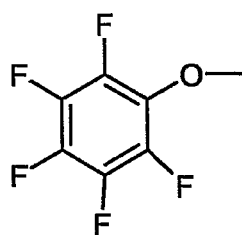


(1i)

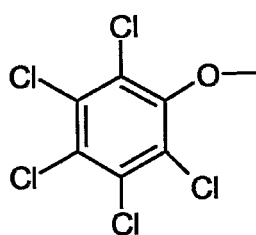


(1j)

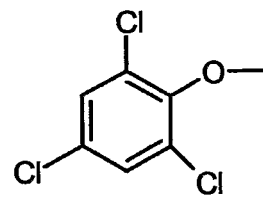
10 - in formula (II), t is 0 or 1,
W is selected from



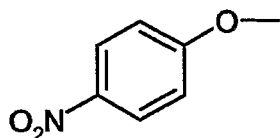
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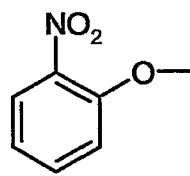
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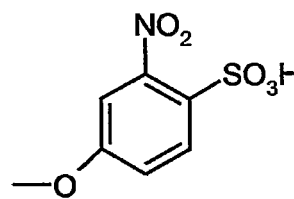
(2c)



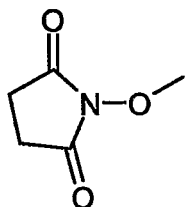
(2d)



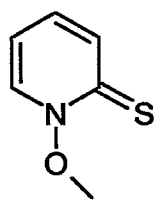
(2e)



(2f)



(2g)



(2h)

Y is as defined below;

- in formula (III), t, R(X)- and X are as above defined,
Y is a bivalent radicals having the following meanings:

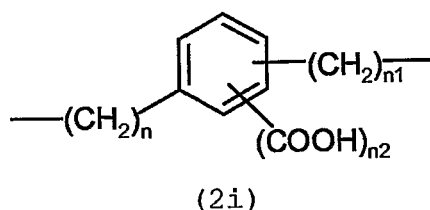
10 a)

- straight or branched C₁-C₂₀ alkylene, preferably C₁-C₁₀ alkylene, more preferably C₃-C₆ alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, -ONO₂ or T₀, wherein T₀ is

-OC(O)-(C₁-C₁₀ alkyl)-ONO₂ or -O-(C₁-C₁₀ alkyl)-ONO₂;

- cycloalkylene having from 5 to 7 carbon atoms, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms, preferably T is CH₃;

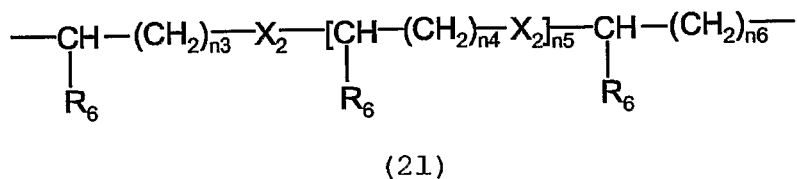
b)



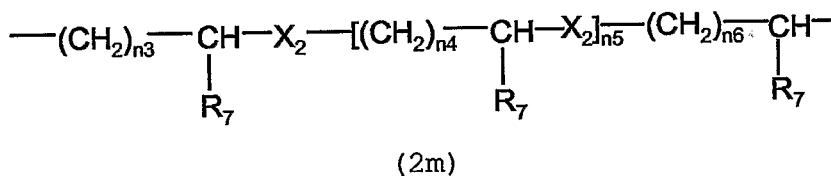
wherein

- 5 n is an integer from 0 to 20, preferably n is 0 or 1,
 n1 is an integer from 1 to 20, preferably n1 is an integer
 from 1 to 6, more preferably n1 is 1,
 n2 is 0 or 1, preferably n2 is 0;
 with the proviso that the -ONO₂ group is linked to -(CH₂)_{n1}-
 10 group;

c)



d)



- wherein X₂ is O or S,
 n3, n4 and n6 are integer independently selected from 0 to
 20, preferably n4 and n6 are selected from 1 to 5, more
 20 preferably n4 and n6 are 1,
 preferably n3 is selected from 0 to 4, more preferably n3
 is 0,
 n5 is an integer from 0 to 6, preferably from 0 to 4, more
 preferably n5 is 0,
 25 R₆ is H, CH₃ or nitrooxy group, preferably R₆ is H,
 R₇ is CH₃ or nitrooxy group;

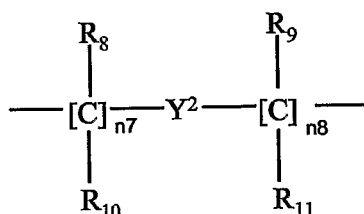
when Y is selected from the bivalent radicals of the group

c) the $-\text{ONO}_2$ group is linked to $-(\text{CH}_2)_{n6}-$ group;

when Y is selected from the bivalent radicals of the group

d) the $-\text{ONO}_2$ group is linked to $-\text{CH}(\text{R}_7)-$ group;

5 e)



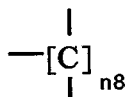
wherein:

$n7$ is an integer from 0 to 10;

$n8$ is an integer from 1 to 10;

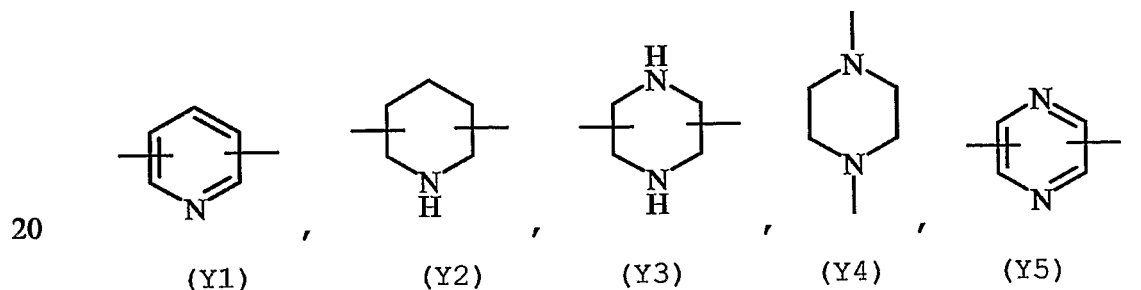
- 10 R_8 , R_9 , R_{10} , R_{11} are the same or different, and are H or straight or branched C_1 - C_4 alkyl, preferably R_8 , R_9 , R_{10} , R_{11} are H;

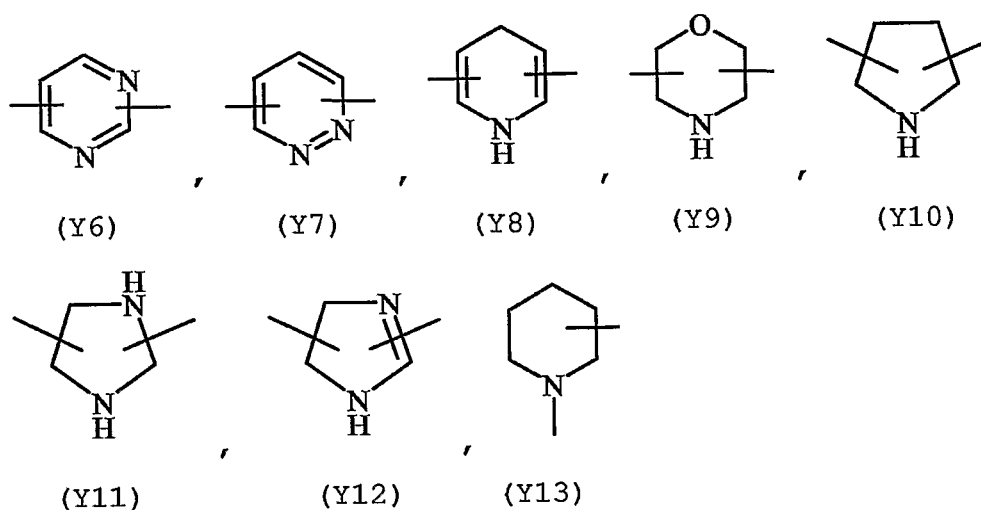
wherein the $-\text{ONO}_2$ group is linked to



- 15 wherein $n8$ 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



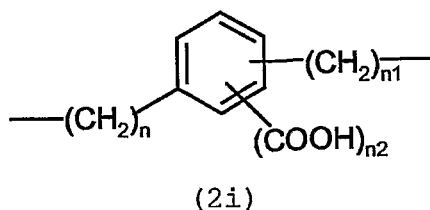


5

2. A process according to claim 1 in which the molar ratio of compounds of formulas (I):(II) is from 1 to 0.5 and the molar ratio (II):DMAP is 1.
3. A process according to claims 1 and 2, wherein in compounds of formula (I), R(X)- is (1a), (1b) or (1c), and an additional equimolar amount of an inorganic or organic bases.
4. A process according to claims 1 to 3, wherein in formulae (II) and (III) Y is a straight or branched C₁-C₂₀ alkylene,
5. A process according to claims 1 and 2, which is carried out in presence of dimethylamminopyridine and a Lewis acid.
6. A process according to claims 5 wherein the molar ratio (II): DMAP: Sc(OTf)₃ is 1:1:0.1.
7. A process according to claims 5 and 6 wherein the Lewis acid is Sc(OTf)₃.
8. A process according to claims 5 to 7, wherein in formulae (II) and (III) Y is

25

b)



wherein

5 n is an integer from 0 to 20,

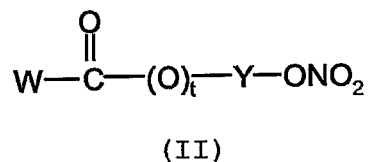
 n₁ is 1,

 n₂ is 0;

 with the proviso that the -ONO₂ group is linked to -
 (CH₂)_{n₁}- group;

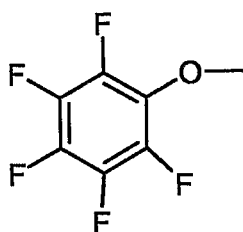
10 9. A process according to claims 5 to 8 wherein in
 compounds of formula (I), R(X)- is (1a), (1b) or (1c),
 and the process is carried out in presence of an
 additional equimolar molar amount of an inorganic or
 organic bases.

15 10. Compounds of formula (II) as intermediates of the
 process of claim 1

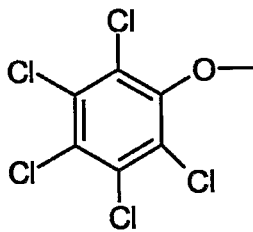


 wherein t is 0 or 1,

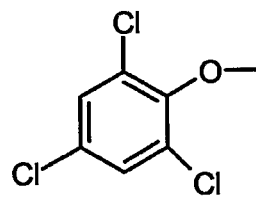
20 W is selected from



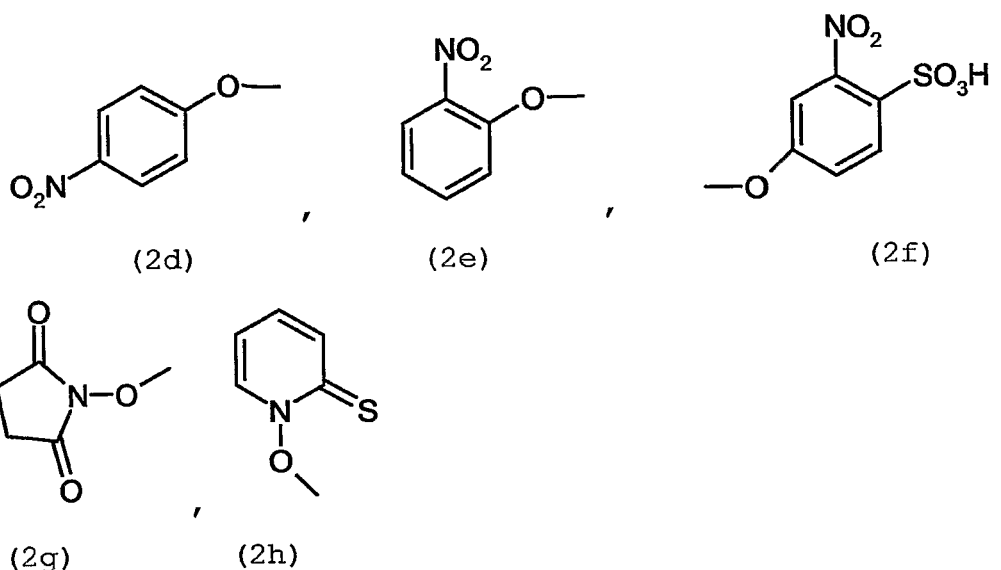
(2a)



(2b)



(2c)

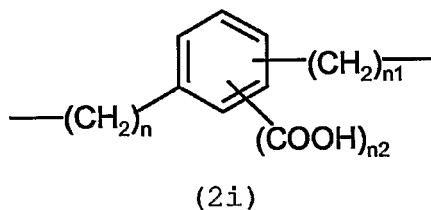


5 Y is a bivalent radical having the following meanings:

a)

- straight or branched C_1 - C_{20} alkylene, preferably C_1 - C_{10} alkylene, more preferably C_3 - C_6 alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or T_0 , wherein T_0 is $-OC(O)-(C_1-C_{10} \text{ alkyl})-ONO_2$ or $-O-(C_1-C_{10} \text{ alkyl})-ONO_2$;
- 10 - cycloalkylene having from 5 to 7 carbon atoms, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms, preferably T is CH_3 ;
- 15

b)



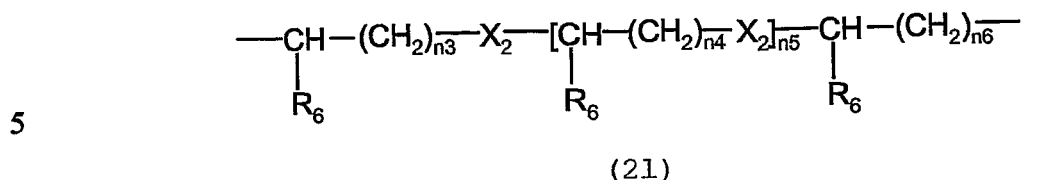
20 wherein

n is an integer from 0 to 20, preferably n is 0 or 1,
 n1 is an integer from 1 to 20, preferably n1 is an integer from 1 to 6, more preferably n1 is 1,

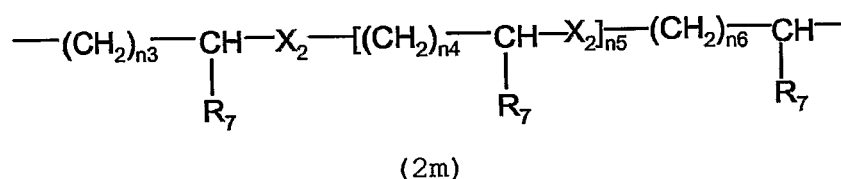
n2 is 0 or 1, preferably n2 is 0;

with the proviso that the -ONO₂ group is linked to -
(CH₂)_{n1}- group;

c)



d)



10 wherein X₂ is O or S,

n₃, n₄ and n₆ are integer independently selected from 0
to 20, preferably n₄ and n₆ are selected from 1 to 5,
more preferably n₄ and n₆ are 1,

preferably n₃ is selected from 0 to 4, more preferably

15 n₃ is 0,

n₅ is an integer from 0 to 6, preferably from 0 to 4,
more preferably n₅ is 0,

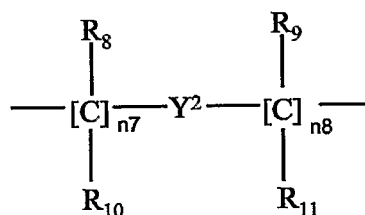
R₆ is H, CH₃ or nitrooxy group, preferably R₆ is H,

R₇ is CH₃ or nitrooxy group;

20 when Y is selected from the bivalent radicals of the
group c) the -ONO₂ group is linked to -(CH₂)_{n6}- group;

when Y is selected from the bivalent radicals of the
group d) the -ONO₂ group is linked to -CH(R₇)- group;

e)



25

wherein:

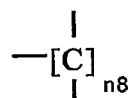
n7 is an integer from 0 to 10;

n8 is an integer from 1 to 10;

R₈, R₉, R₁₀, R₁₁ are the same or different, and are H or straight or branched C₁-C₄ alkyl, preferably R₈, R₉, R₁₀,

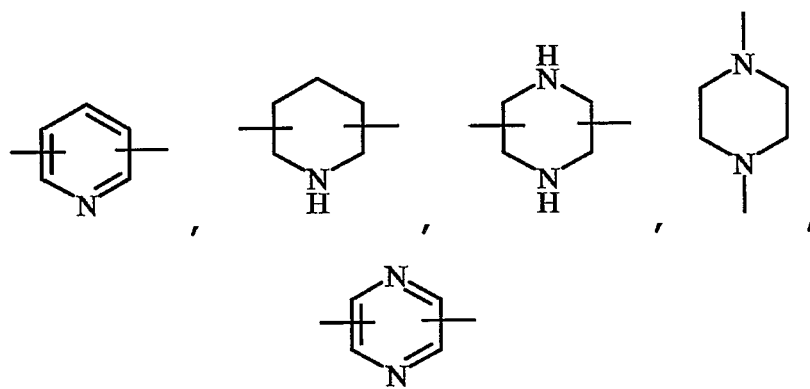
5 R₁₁ are H;

wherein the -ONO₂ group is linked to

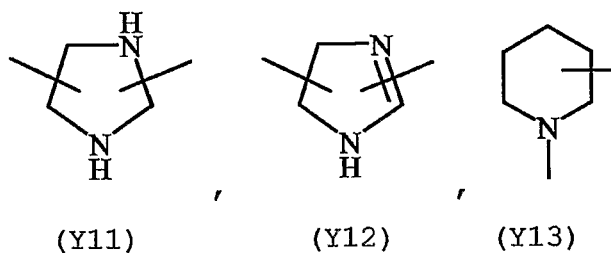
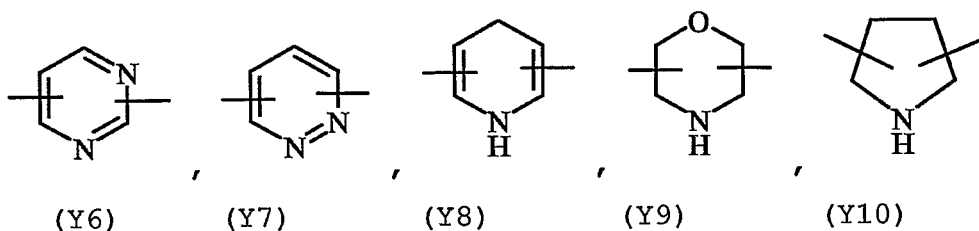


wherein n8 is as defined above;

Y² is an heterocyclic saturated, unsaturated or aromatic
 10 5 or 6 members ring, containing one or more heteroatoms
 selected from nitrogen, oxygen, sulfur,
 and is selected from



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

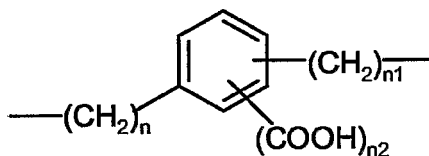


11. Compounds of formula (II) wherein Y

a)

- straight or branched C₁-C₂₀ alkylene, preferably C₁-C₁₀ alkylene, more preferably C₃-C₆ alkylene, being
 5 optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, -ONO₂ or T₀, wherein T₀ is -OC(O)-(C₁-C₁₀ alkyl)-ONO₂ or -O-(C₁-C₁₀ alkyl)-ONO₂;
 - cycloalkylene having from 5 to 7 carbon atoms, the
 10 ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms, preferably T is CH₃;

b)



(2i)

wherein

- n is an integer from 0 to 20, preferably n is 0 or 1,
 n₁ is an integer from 1 to 20, preferably n₁ is an
 integer from 1 to 6, more preferably n₁ is 1,
 20 n₂ is 0 or 1, preferably n₂ is 0;
 with the proviso that the -ONO₂ group is linked to -
 (CH₂)_{n1}- group;

12. Compounds of formula (II) according to claims 10 and 11

- 4-(Nitrooxy)butanoic acid pentafluorophenyl ester,
 25 5-(nitrooxy)pentanoic acid pentafluorophenyl ester,
 [4-(nitrooxy)methyl]benzoic acid pentafluorophenyl
 ester,
 4-(nitrooxy)butyl pentafluorophenyl carbonate,
 [3-(Nitrooxy)methyl]phenyl 4-nitrophenyl carbonate,
 30 4-(Nitrooxy)butanoic acid N-succinimidyl ester.