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(54) Title: NITRIC OXIDE RELEASING COMPOUNDS FOR THE TREATMENT OF NEUROPATHIC PAIN

(57) Abstract: The invention relates to nitrooxyderivatives of Gamma- aminobutyric acid analogs (GABA analogs) for treating neuropathic pain and in particular diabetic neuropathy. The invention also relates to pharmaceutical formulation comprising such derivatives, to a process for their preparation.



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Nitric oxide releasing GABA analogs for the treatment of neuropathic pain.

The present invention relates to nitrooxyderivatives of Gamma-aminobutyric acid analogs (GABA analogs) for treating
5 neuropathic pain and in particular diabetic neuropathy. The present invention also relates to pharmaceutical formulation comprising such derivatives, to a process for their preparation.

Neuropathic pain is a form of chronic pain that can be
10 classified as peripheral or central. Peripheral neuropathic pain is caused by injury or infection of peripheral sensory nerves, whereas central neuropathic pain is caused by damage to the CNS or/and the spinal cord. Both peripheral and central neuropathic pain can occur without obvious initial nerve
15 damage

Neuropathic pain is common in cancer as a direct result of cancer on peripheral nerves (e.g., compression by a tumor), or as a side effect of chemotherapy, radiation injury or surgery.

The clinical causes of neuropathic pain are widespread and
20 include both trauma and disease. Various metabolic diseases may be the cause of neuropathic changes and may subsequently be implicated in neuropathic pain. An example of such a neuropathy is diabetic neuropathy, which occurs in a large number of patients suffering from diabetes and may be
25 associated with a large number of clinical symptoms such as a feeling of numbness, tingling sensation, or pain. The most common form of diabetic neuropathy is distal symmetrical sensomotor polyneuropathy

There are a wide range of treatments available to physicians
30 for neuropathic pain, some of which have specific indications, and some of which are used off-label.

Common analgesics such as opioids and NSAIDs, insufficiently address chronic abnormal pain syndromes such as peripheral and

central neuropathic pain due to insufficient efficacy or limiting side effects, although a subset of patients with neuropathic pain responds to opioids. In the search for alternative treatment regimes to produce satisfactory and sustained pain relief, corticosteroids, conduction blockade, glycerol, antidepressants, local anesthetics, gangliosides and electrostimulation have been tried. Anticonvulsants have been found useful against various types of peripheral neuropathic pain conditions.

Regarding the treatment of neuropathic pain in diabetic patients, amitriptyline, gabapentin and pregabalin are among the primary treatments for painful diabetic neuropathy (PDN), and it is clear that they produce beneficial effects, but there are questions about these treatments that have not been adequately addressed. For example, although there is a growing consensus that the therapeutic effects of amitriptyline in pain patients are independent of its effects on mood, it is not clear that amitriptyline has specific and direct effects on pain. There is also a fairly broad consensus that gabapentin is safe and well tolerated, but the side-effect profile of gabapentin has not been adequately assessed in pain populations

Pregabalin induces weight gain in Type I or II diabetes patients by edema formation. Increased weight is an established risk factor for cardiovascular disease, particularly in Type II diabetic patients.

WO 01/90052 discloses gabapentin analogues wherein the amine and/or the acid group is substituted with a labile organic group that becomes removed in the human or animal body. Said compounds, when administered to humans or animals, provide an increased duration of active compound in the plasma.

WO 03/000642 discloses Nitric oxide (NO) releasing derivatives of drugs used for the treatment of neuropathic

pain, including GABA analogs. The nitric-oxide releasing part of the molecule is attached to the carboxyl group of the precursor drugs.

In particular, WO 03/000642 discloses nitrooxy derivatives
5 of gabapentin that showed good efficacy in models of pain but they are unstable and they are rapidly converted upon contact to aqueous medium, such as plasma, to the gabapentin gamma-lactam that is toxic.

Consequently, formation of gamma-lactam during formulation
10 and/or storage and/or administration of the drug must be minimized for safety reasons.

WO 02/100347 discloses prodrugs of the GABA analogs such as gabapentin and pregabalin; said compounds show a better bioavailability than their precursors gabapentin and
15 pregabalin respectively.

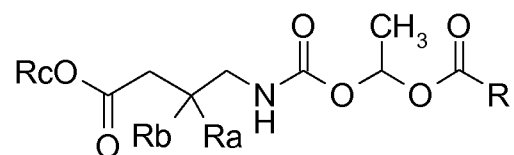
WO 2004/054965 discloses nitrooxyderivatives of drugs for chronic pain including gabapentin. These compounds show a good efficacy in animal models of pain, however these compounds exhibit poor oral absorption consequently they require high
20 doses to achieve a therapeutic concentration in the systemic circulation. These high doses prevent the successful clinical use of these compounds.

Despite the broad spectrum of drugs available with different modes of action, at present there is no effective treatment
25 for neuropathic pain and in particular for painful diabetic neuropathy that addresses all the clinical unmet needs such as drugs having a reduced time to onset of action, an improved efficacy or an improved side effects profile.

It was thus object of the present invention to provide drugs
30 having an improved therapeutic profile and/or lower side effects in the treatment of chronic pain, in particular neuropathic pain.

It has been now surprisingly and unexpectedly found that this problem can be solved with the class of GABA analogs nitrooxyderivatives described below.

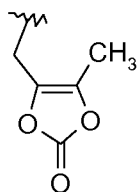
The present invention relates to GABA analogs
5 nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



(I)

wherein

10 Rc is a hydrogen, or

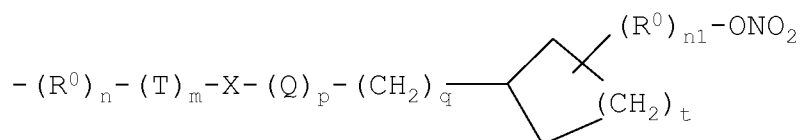


or Rc is pharmaceutically acceptable cation;

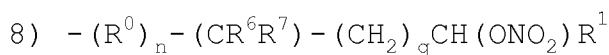
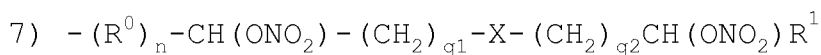
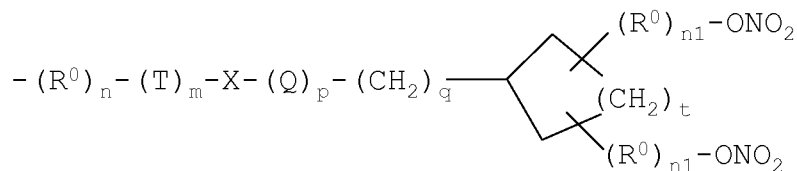
Ra is hydrogen and Rb is $(\text{CH}_3)_2\text{CHCH}_2-$, or Ra and Rb taken together with the carbon atom to which they are attached form
15 a cyclohexyl;

R is selected from the group consisting of:

- 1) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)\text{R}^1$,
- 2) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)-\text{CH}(\text{ONO}_2)\text{R}^{1a}$
- 3) $-(\text{R}^0)_n-(\text{T})_m-\text{X}-(\text{Q})_p-(\text{CH}_2)_q-\text{CH}(\text{ONO}_2)\text{R}^1$,
- 20 4) $-(\text{R}^0)_n-(\text{T})_m-\text{X}-(\text{Q})_p-(\text{CH}_2)_q-\text{CH}(\text{ONO}_2)\text{CH}(\text{ONO}_2)\text{R}^{1a}$,
- 5) 5)



6)



5 wherein

n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

n1 is 0 or 1;

10 q is an integer from 0 to 10, preferably q is from 0 to 6;

q1 is an integer from 1 to 10, preferably q is from 1 to 6;

q2 is an integer from 1 to 10, preferably q is from 1 to 6;

t is an integer from 1 to 4, preferably t is 2 or 3;

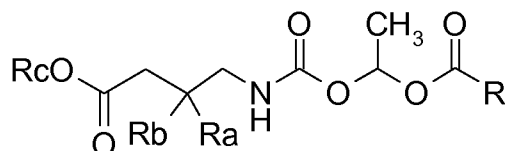
R⁰ is a straight or branched C₁-C₁₀ alkylene; preferably R⁰ is a15 straight or branched C₁-C₆ alkylene, more preferably R⁰ is-C(CH₃)₂- or -C(CH₃)₂-CH₂-;R¹ is selected from hydrogen, a straight or branched C₁-C₄ alkyl, -(CH₂)OCH₃, preferably R¹ is hydrogen, -CH₃, -(CH₂)OCH₃, -CH(CH₃)₂;20 R^{1a} is hydrogen or a straight or branched C₁-C₄ alkyl, preferably R^{1a} is hydrogen or -CH₃;X is selected from an oxygen atom, -NH-, -N(CH₃)- or a covalent bond, preferably X is oxygen or a covalent bond;T and Q are -CR²R³-, wherein R² and R³ at each occurrence are independently selected from hydrogen, C₁-C₄ linear or branched alkyl, OR⁴, NHR⁵, preferably R² and R³ are hydrogen or R² is hydrogen and R³ is NHR⁵;25 R⁴ is hydrogen or C₁-C₄ linear or branched alkyl, preferably R⁴ is hydrogen or -CH₃;30 R⁵ is hydrogen, C₁-C₄ linear or branched alkyl, -C(O)CH₃ or

$-\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$ (Boc), more preferably R^5 is $-\text{C}(\text{O})\text{CH}_3$ or $-\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$;

R^6 is hydrogen or C_1 - C_4 linear or branched alkyl, preferably R^6 is $-\text{CH}_3$;

5 R^7 is $(\text{CH}_2)_q\text{CH}(\text{ONO}_2)\text{R}^1$ wherein q and R^1 are as above defined.

In another embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



10 (I)

wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation;

Ra is hydrogen and Rb is $(\text{CH}_3)_2\text{CHCH}_2-$, or Ra and Rb taken together with the carbon atom to which they are attached form

15 a cyclohexyl;

R is

1) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)\text{R}^1$

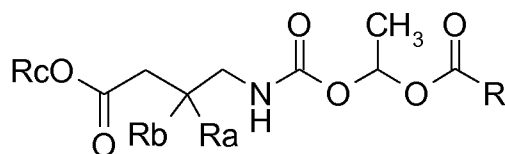
wherein

n is 0 or 1

20 R^0 is a straight or branched C_1 - C_6 alkylene, preferably R^0 is $-\text{C}(\text{CH}_3)_2-$ or $-\text{C}(\text{CH}_3)_2-\text{CH}_2-$;

R^1 is hydrogen, $-\text{CH}_3$, $-(\text{CH}_2)\text{OCH}_3$, or $-\text{CH}(\text{CH}_3)_2$.

In one embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



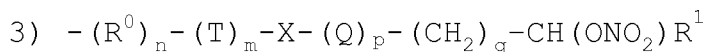
(I)

wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation;

Ra is hydrogen and Rb is (CH₃)₂CHCH₂-, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

5 R is



wherein

n is 0 or 1

m is 1

10 p is 1

q is from 0 to 6;

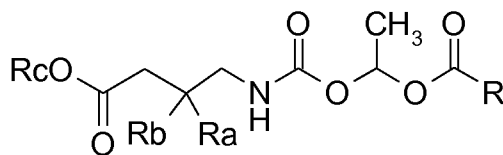
R⁰ is a straight or branched C₁-C₆ alkylene, more preferably R⁰ is -C(CH₃)₂- or -C(CH₃)₂-CH₂-;

R¹ is hydrogen, -CH₃, -(CH₂)OCH₃, or -CH(CH₃)₂;

15 X is oxygen;

T and Q are -CR²R³-, wherein R² and R³ are hydrogen.

In one embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



20

(I)

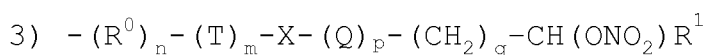
wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation;

Ra is hydrogen and Rb is (CH₃)₂CHCH₂-, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

25

R is



wherein

30 n is 0 or 1;

m is 0;

p is 1;

q is from 0 to 6;

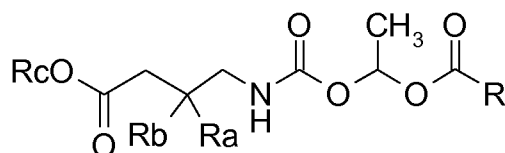
R^0 is a straight or branched C_1 - C_6 alkylene;

5 R^1 is hydrogen, $-CH_3$, $-(CH_2)OCH_3$, or $-CH(CH_3)_2$;

X is a covalent bond;

Q is $-CR^2R^3-$, wherein R^2 is hydrogen and R^3 is NHR^5 wherein R^5 is $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$.

10 In another embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



(I)

wherein

15 Rc is a hydrogen, or a pharmaceutically acceptable cation;

Ra is hydrogen and Rb is $(CH_3)_2CHCH_2-$, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

R is

20 2) $-(R^0)_n-CH(ONO_2)-CH(ONO_2)R^{1a}$

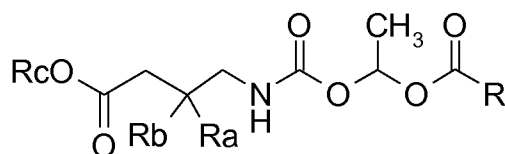
wherein

n is 1;

R^0 is a straight or branched C_1 - C_{10} alkylene;

R^{1a} is hydrogen or $-CH_3$;

25 In another embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



(I)

wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation;

5 Ra is hydrogen and Rb is (CH₃)₂CHCH₂-, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

R is

4) $-(R^0)_n-(T)_m-X-(Q)_p-(CH_2)_q-CH(ONO_2)CH(ONO_2)R^{1a}$,

wherein

10 n is 0 or 1;

m is 1;

p is 1;

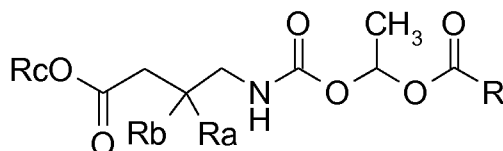
q is from 0 to 6;

R⁰ is a straight or branched C₁-C₆ alkylene, more preferably R⁰15 is -C(CH₃)₂- or -C(CH₃)₂-CH₂-;

X is oxygen;

T and Q are -CR²R³-, wherein R² and R³ are hydrogen;R^{1a} is hydrogen or -CH₃.

In another embodiment of the invention, there is provided
20 GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



(I)

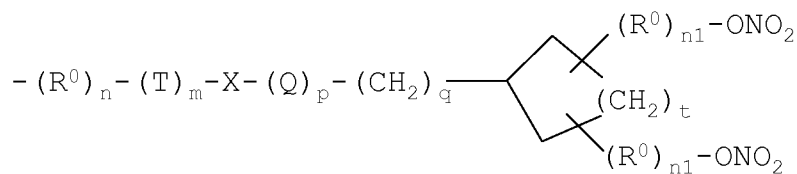
wherein

25 Rc is a hydrogen, or a pharmaceutically acceptable cation;

Ra is hydrogen and Rb is (CH₃)₂CHCH₂-, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

R is

30 6)



wherein

n is 0;

m is 0;

5 p is 0;

n1 is 0 or 1;

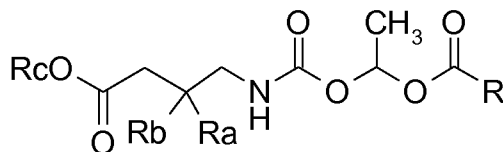
q is an integer from 0 to 10;

t is 2 or 3;

R⁰ is a straight or branched C₁-C₁₀ alkylene;

10 X is a covalent bond.

In another embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



15

(I)

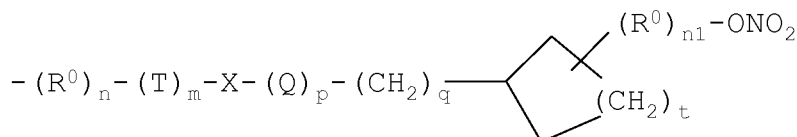
wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation;

20 Ra is hydrogen and Rb is (CH₃)₂CHCH₂-, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

R is

5)



wherein

25 n is 0;

m is 0;

p is 0;

n1 is 0 or 1;

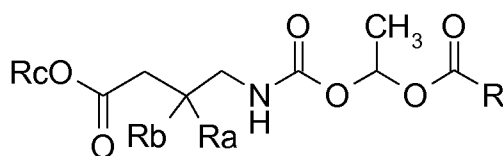
q is an integer from 0 to 10,

t is 2 or 3;

5 R^0 is a straight or branched C_1 - C_{10} alkylene;

X is a covalent bond.

In another embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



10

(I)

wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation;

15 Ra is hydrogen and Rb is $(CH_3)_2CHCH_2-$, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

R is

7) $-(R^0)_n-CH(ONO_2)-(CH_2)_{q1}-X-(CH_2)_{q2}CH(ONO_2)R^1$

wherein

20 n is 0;

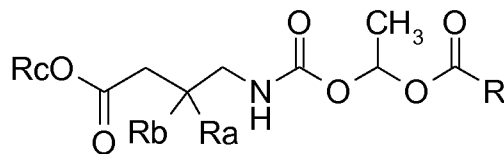
q1 is an integer from 1 to 10;

q2 is an integer from 1 to 10;

X is oxygen or a covalent bond;

25 R^1 is selected from hydrogen, a straight or branched C_1 - C_4 alkyl, $-(CH_2)OCH_3$, preferably R^1 is H.

In another embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



(I)

wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation;

5 Ra is hydrogen and Rb is $(\text{CH}_3)_2\text{CHCH}_2-$, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

R is

8) $-(\text{R}^0)_n - (\text{CR}^6\text{R}^7) - (\text{CH}_2)_q \text{CH}(\text{ONO}_2)\text{R}^1$

10 wherein

n is 0;

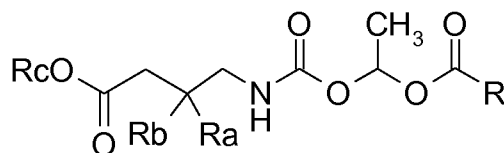
q is an integer from 0 to 10, preferably q is from 0 to 6;

R^6 is hydrogen or C_1 - C_4 linear or branched alkyl, preferably R^6 is $-\text{CH}_3$;

15 R^7 is $(\text{CH}_2)_q \text{CH}(\text{ONO}_2)\text{R}^1$ wherein q is as above defined

R^1 is hydrogen.

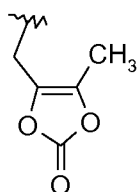
In another embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



(I)

wherein

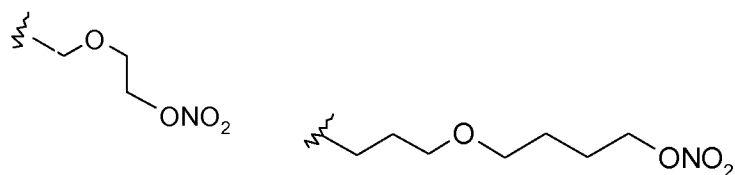
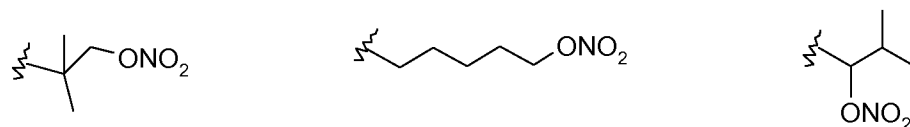
Rc is a hydrogen, or



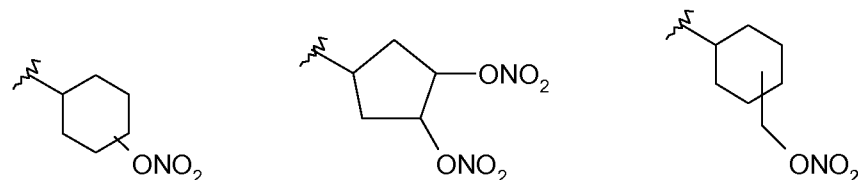
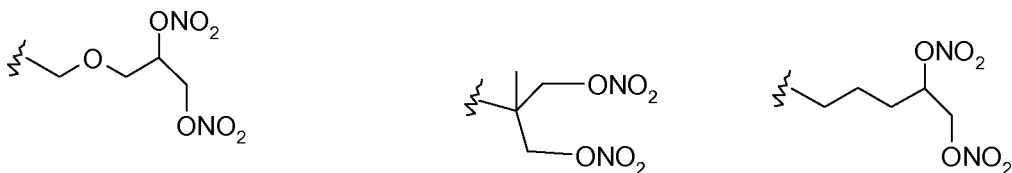
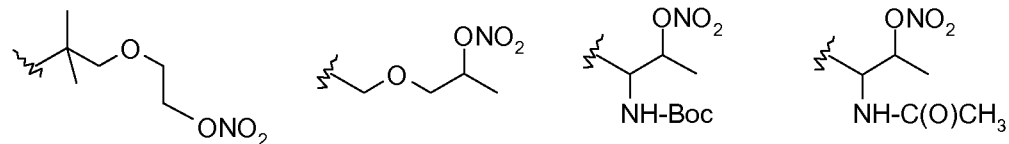
or a pharmaceutically acceptable cation;

Ra is hydrogen and Rb is $(\text{CH}_3)_2\text{CHCH}_2-$, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

5 R is selected from the group consisting of:



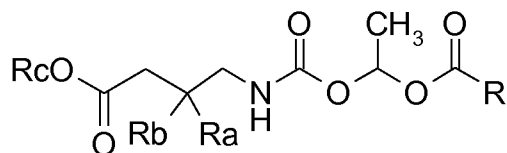
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In another embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



5

(I)

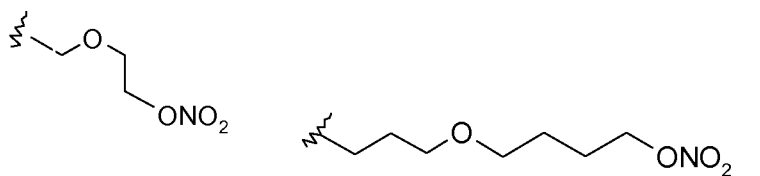
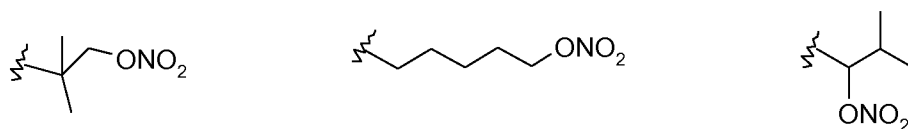
wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation;

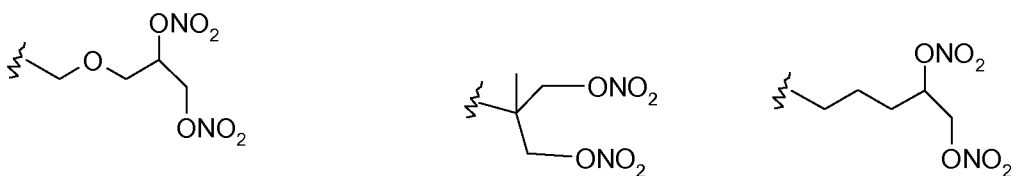
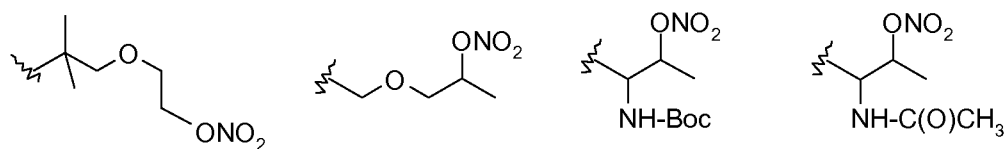
Ra is hydrogen and Rb is $(\text{CH}_3)_2\text{CHCH}_2-$;

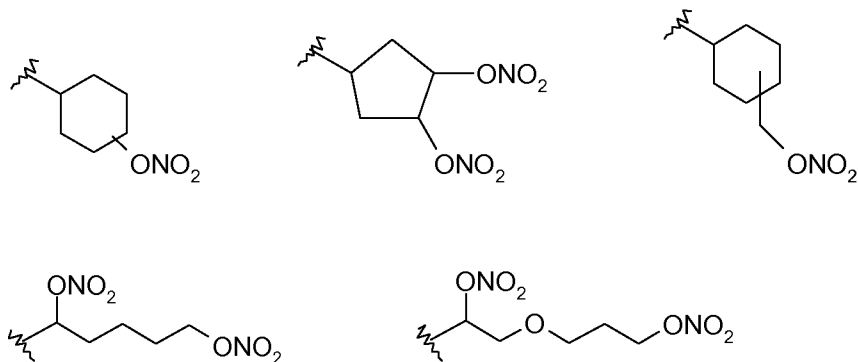
R is selected from the group consisting of:

10

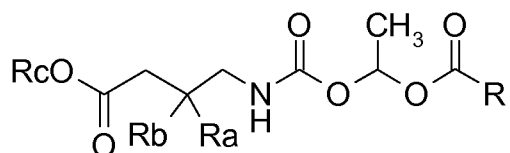


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5 In another embodiment of the invention, there is provided GABA analogs nitrooxyderivatives or salts or stereoisomers thereof having the general formula (I):



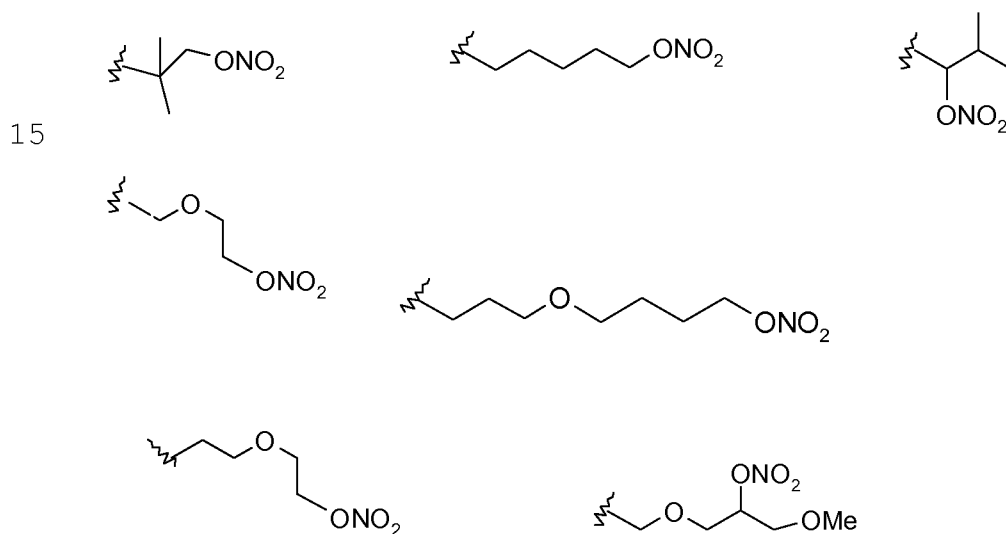
(I)

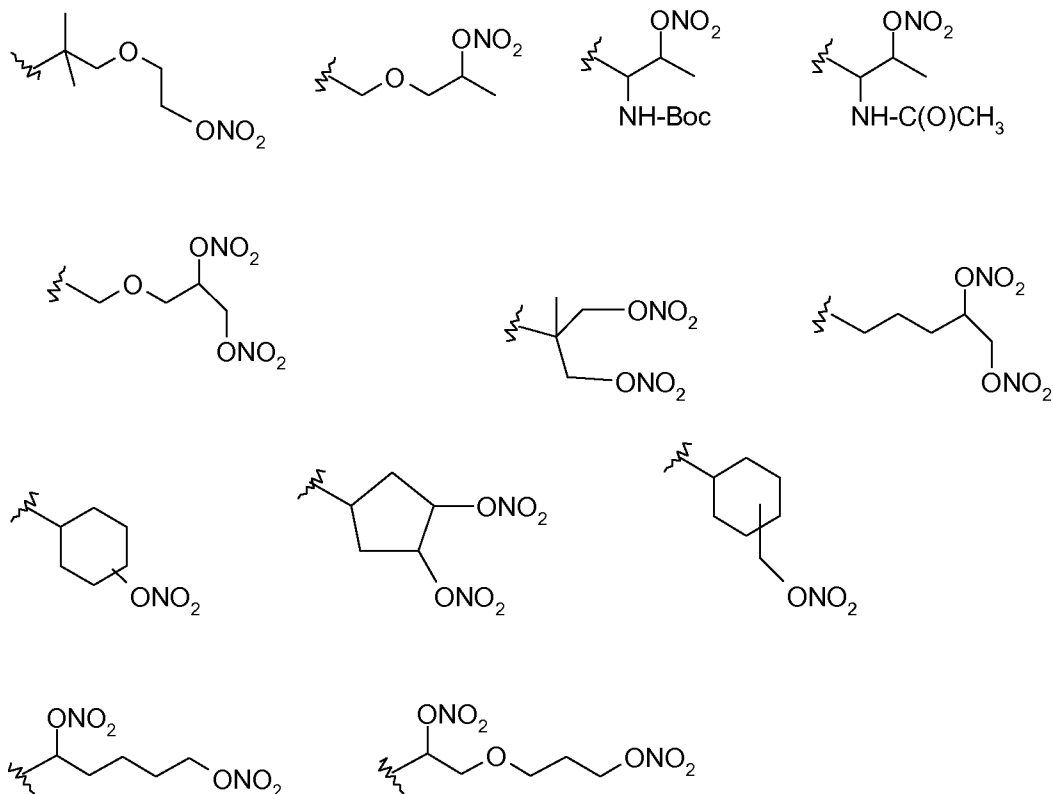
10 wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation;

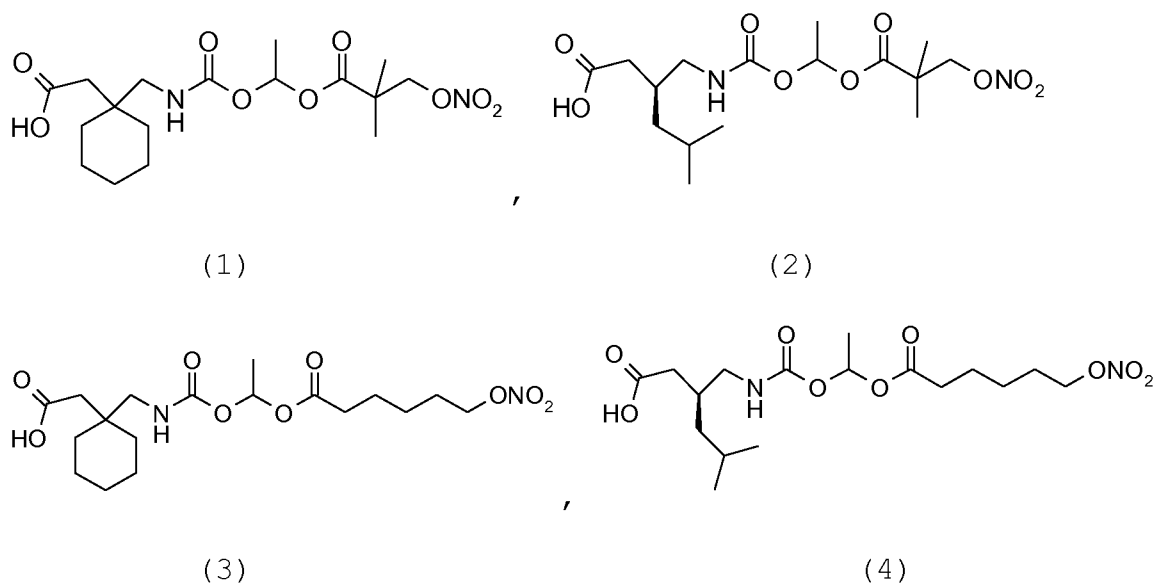
Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

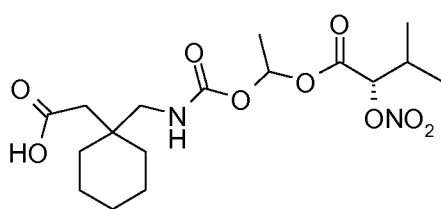
R is selected from the group consisting of:



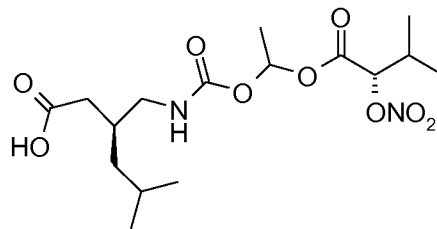


In another embodiment, the compound of formula (I) is selected from the group of compounds shown below:

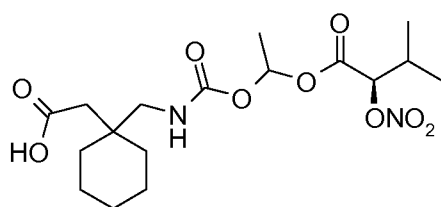




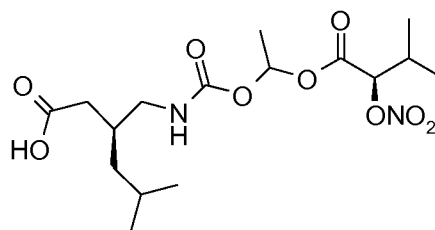
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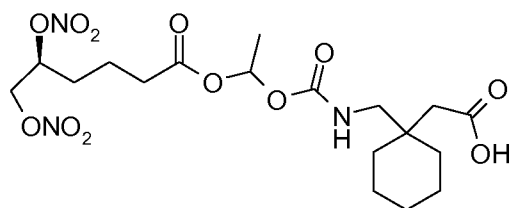
(6)



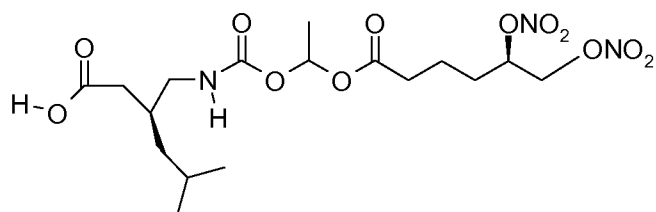
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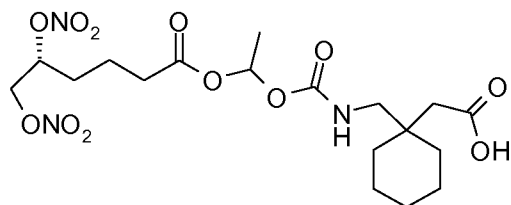
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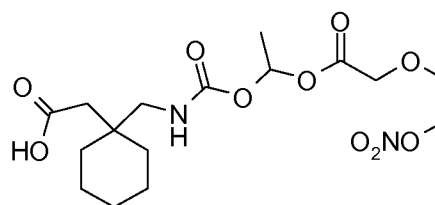
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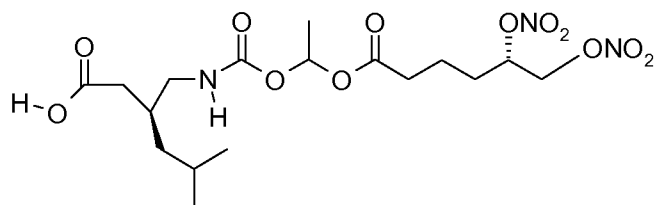
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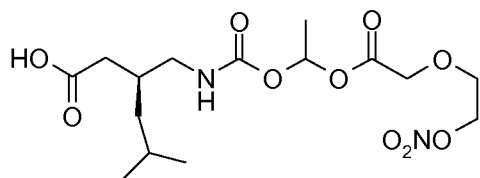
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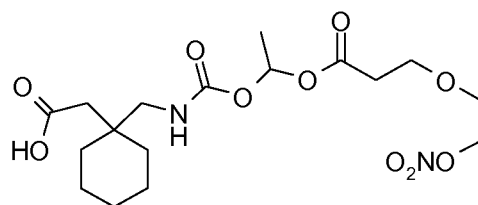
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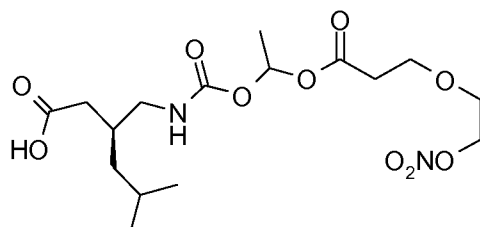
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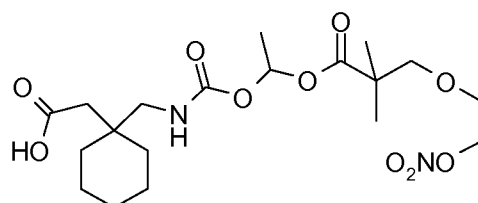
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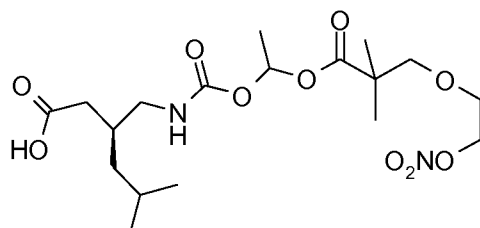
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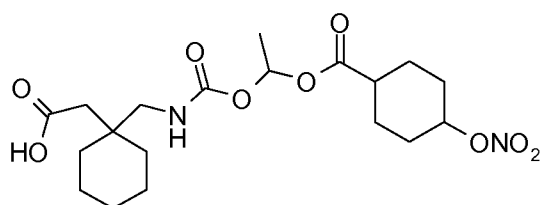
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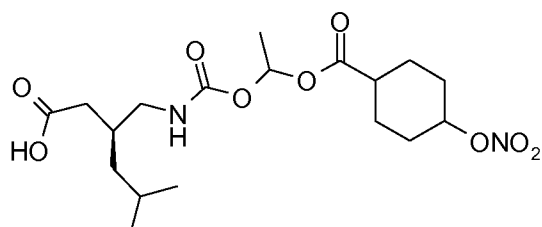
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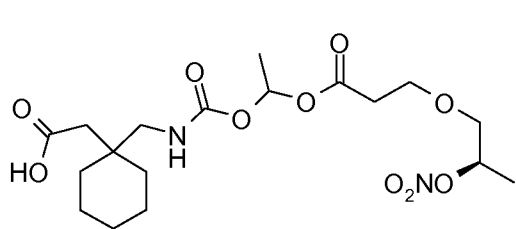
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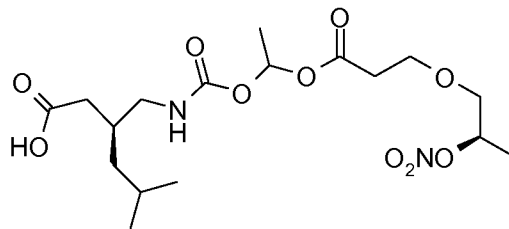
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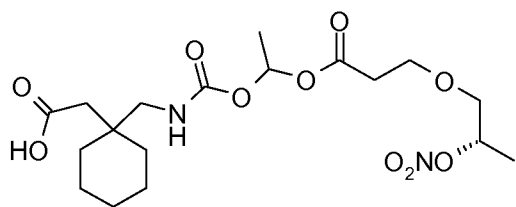
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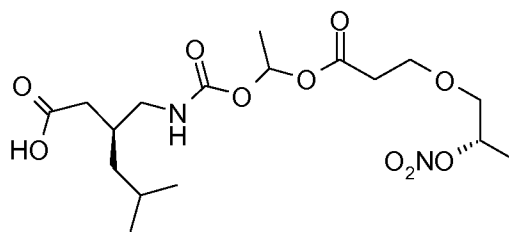
(21)



(22)

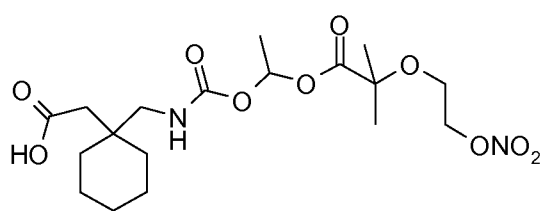


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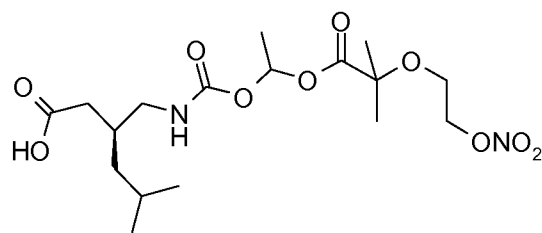


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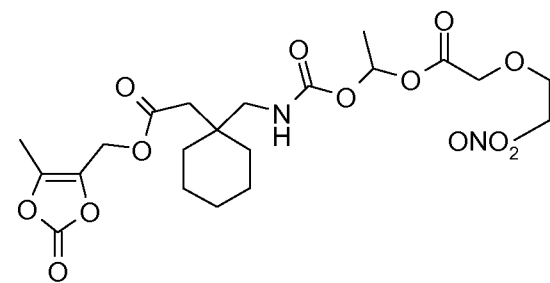
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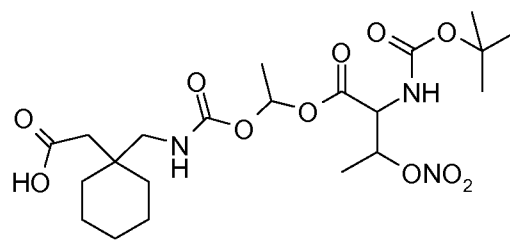
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(26)

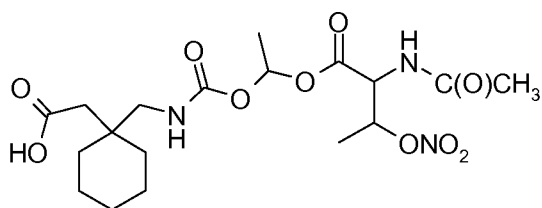


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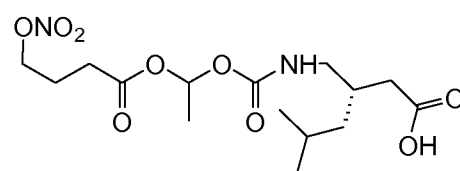


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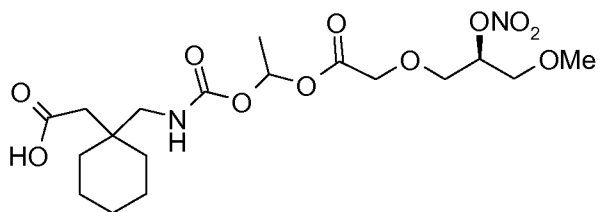
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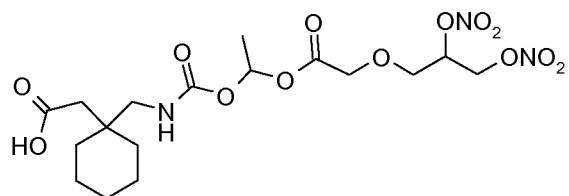
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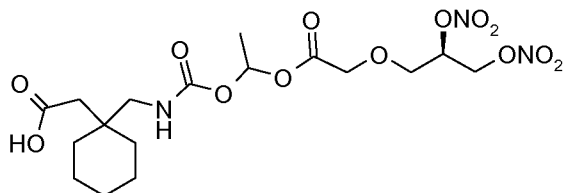
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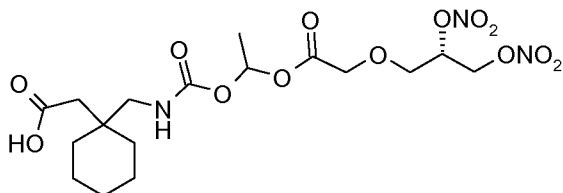
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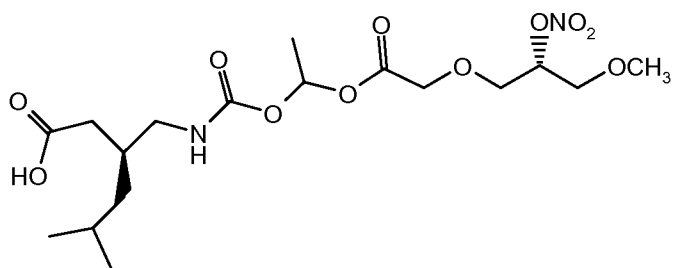
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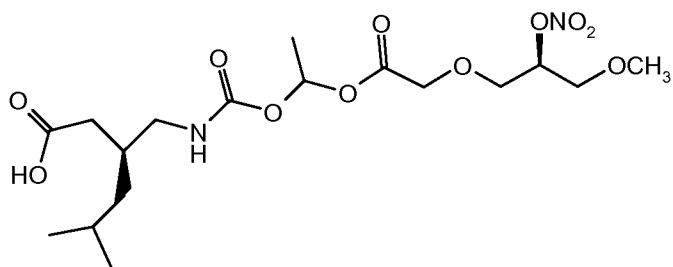
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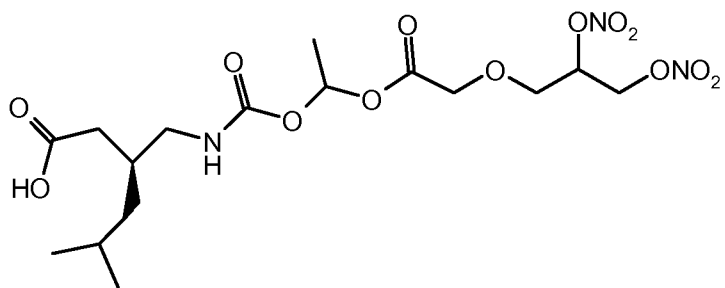
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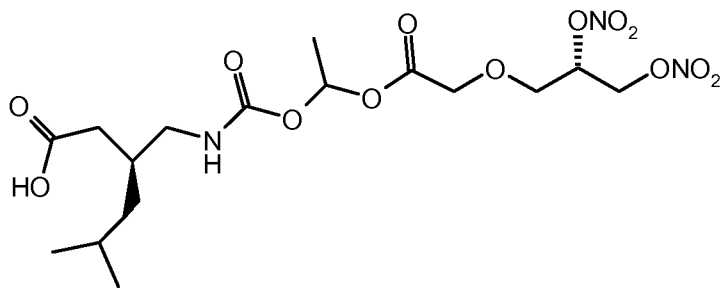
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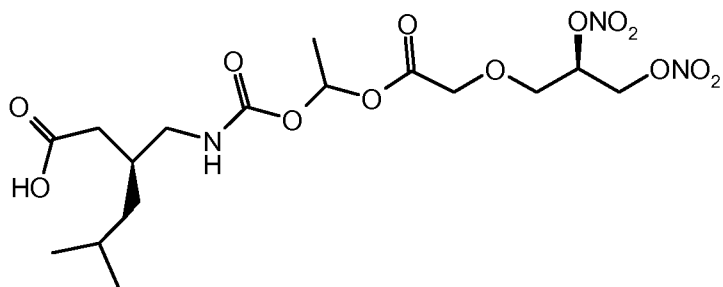
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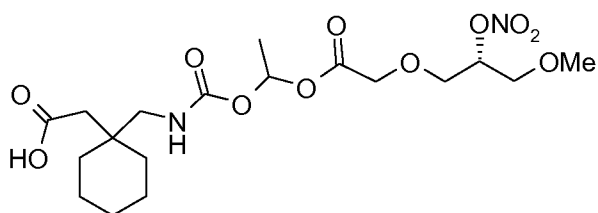
(37)



(38)



(39)



(40).

The compounds of the present invention have a better efficacy than the correspondent parent drugs in reducing neuropathic pain and, in particular, in reducing neuropathic pain associated with diabetes.

The compounds of the inventions have a better efficacy than gabapentin and pregabalin in counteracting the development of pain sensitization in painful diabetic neuropathy.

The compounds of the present invention induce less side effects such as less sedation than the correspondent parent drugs.

Moreover the compounds of the present inventions have a good bioavailability and better plasma stability, namely they do not form gabapentin lactam, than other known gabapentin derivatives.

Pharmaceutically acceptable cations includes ammonium cation, alkali metal salts such sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, cations of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, and cations of amino acids such as arginine, lysine.

In another embodiment, of the invention, there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula (I) and/or a salt or stereoisomer thereof and at least a pharmaceutically acceptable excipient. The pharmaceutical composition can be used for oral or systemic administration of the compound of formula (I).

The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of the excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on the stability, and the nature of the dosage form.

In another embodiment of the invention, there is provided a pharmaceutical composition wherein the compound of the invention is administered as a solution, suspension or emulsion in an acceptable vehicle.

In one embodiment, the invention relates to the use of the GABA analogs nitrooxyderivatives of formula (I) for treating or preventing a neuropathic pain condition, such as restless legs syndrome (RLS), in particular to treating or preventing a diabetes-associated neuropathic pain.

In one embodiment, the invention relates to the use of the GABA analogs nitrooxyderivatives of formula (I) for treating or preventing a diabetes-associated neuropathic pain.

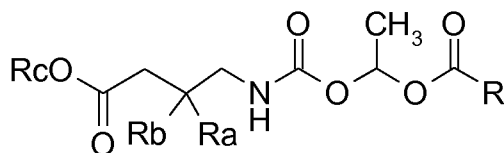
In one embodiment, the invention relates to a method for treating or preventing a neuropathic condition in a subject,

the method consisting essentially of administering to the subject at least one GABA analogs nitrooxyderivatives of formula (I).

In one embodiment, the invention relates to a method for treating or preventing diabetes-associated neuropathic pain in a subject, the method consisting essentially of administering to the subject at least one GABA analogs nitrooxyderivatives of formula (I).

In one embodiment, relates to GABA analogs nitrooxyderivatives of formula (I) in neutral form, the form of acid, in the form of a salt, preferably a physiologically acceptable salt, in the form of a solvate or of a polymorph and/or in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, and/or in any mixing ratio.

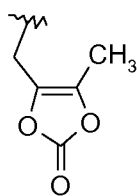
In yet another embodiment of the invention, there is provided a process for the preparation of compounds of formula (I) or stereoisomers thereof



(I)

wherein

Rc is a hydrogen, or

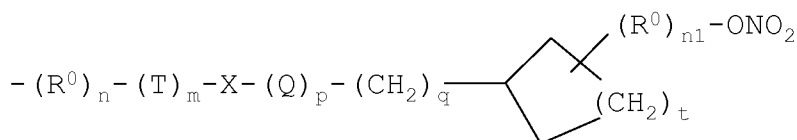


or Rc is the pharmaceutically acceptable cation as described above;

Ra is hydrogen and Rb is $(\text{CH}_3)_2\text{CHCH}_2-$, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl ring;

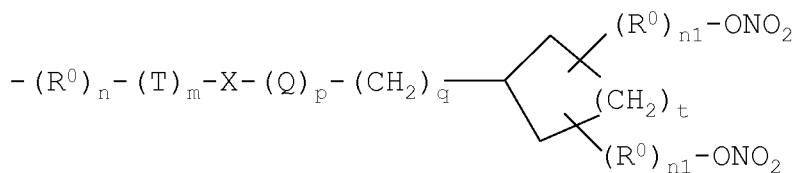
R is selected from the group consisting of:

- 5 1) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)\text{R}^1$,
- 2) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)-\text{CH}(\text{ONO}_2)\text{R}^{1a}$
- 3) $-(\text{R}^0)_n-(\text{T})_m-\text{X}-(\text{Q})_p-(\text{CH}_2)_q-\text{CH}(\text{ONO}_2)\text{R}^1$,
- 4) $-(\text{R}^0)_n-(\text{T})_m-\text{X}-(\text{Q})_p-(\text{CH}_2)_q-\text{CH}(\text{ONO}_2)\text{CH}(\text{ONO}_2)\text{R}^{1a}$,
- 5)



10

6)



- 7) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)-(\text{CH}_2)_{q1}-\text{X}-(\text{CH}_2)_{q2}\text{CH}(\text{ONO}_2)\text{R}^1$
- 8) $-(\text{R}^0)_n-(\text{CR}^6\text{R}^7)-(\text{CH}_2)_q\text{CH}(\text{ONO}_2)\text{R}^1$

15 wherein

n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

n1 is 0 or 1;

20 q is an integer from 0 to 10, preferably q is from 0 to 6;

q1 is an integer from 1 to 10, preferably q is from 1 to 6;

q2 is an integer from 1 to 10, preferably q is from 1 to 6;

t is an integer from 1 to 4, preferably t is 2 or 3;

R⁰ is a straight or branched C₁-C₁₀ alkylene; preferably R⁰ is a

25 straight or branched C₁-C₆ alkylene, more preferably R⁰ is

$-\text{C}(\text{CH}_3)_2-$ or $-\text{C}(\text{CH}_3)_2\text{CH}_2-$;

R^1 is selected from hydrogen, a straight or branched C_1 - C_4 alkyl, $-(CH_2)OCH_3$, preferably R^1 is hydrogen, $-CH_3$, $-(CH_2)OCH_3$, $-CH(CH_3)_2$;

R^{1a} is hydrogen or a straight or branched C_1 - C_4 alkyl, preferably R^{1a} is hydrogen or $-CH_3$;

X is selected from an oxygen atom, $-NH-$, $-N(CH_3)-$ or a covalent bond, preferably X is oxygen or a covalent bond;

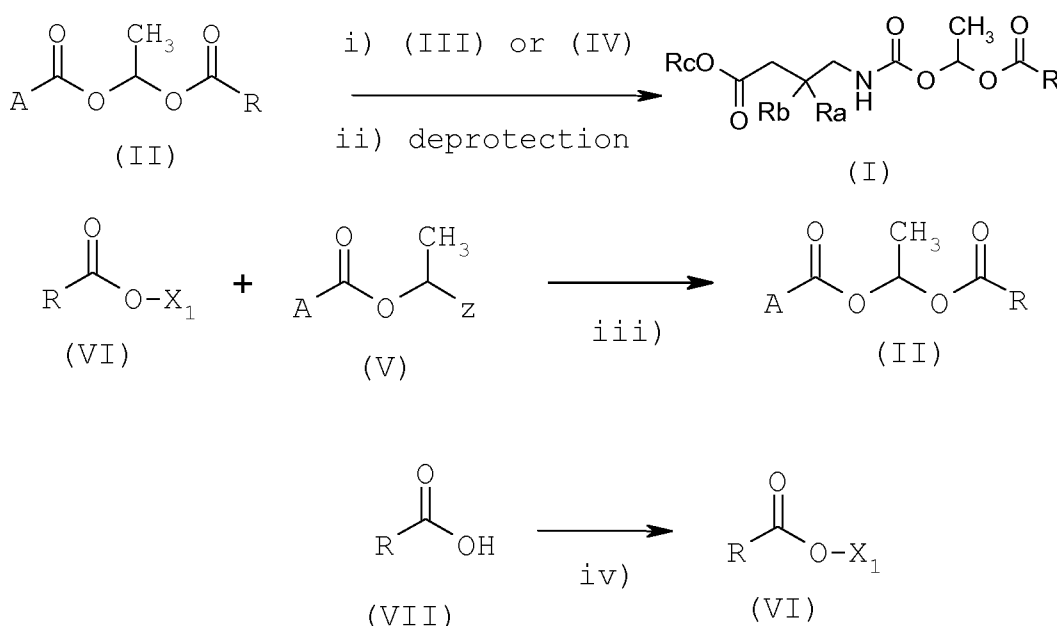
T and Q are $-CR^2R^3-$, wherein R^2 and R^3 at each occurrence are independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, OR^4 , NHR^5 , preferably R^2 and R^3 are hydrogen or R^2 is hydrogen and R^3 is NHR^5 ;

R^4 is hydrogen or C_1 - C_4 linear or branched alkyl, preferably R^4 is hydrogen or $-CH_3$;

R^5 is hydrogen, C_1 - C_4 linear or branched alkyl, $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$ (Boc), more preferably R^5 is $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$;

R^6 is C_1 - C_4 linear or branched alkyl or hydrogen, preferably R^6 is $-CH_3$;

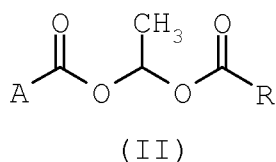
R^7 is $(CH_2)_qCH(ONO_2)R^1$ wherein q and R^1 are as above defined, said process, as depicted in Scheme 1



Scheme 1

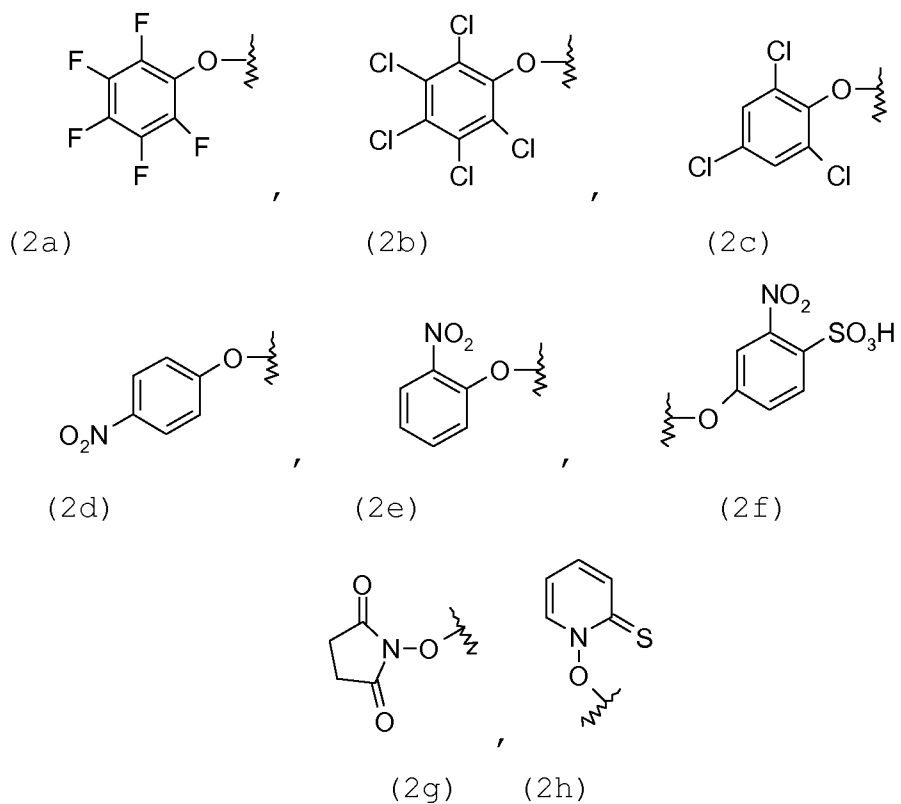
comprises:

i) reacting a compound of formula (II)



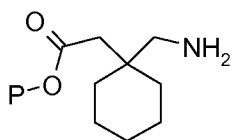
wherein A is an activating group selected from the formulas

5 (2a) - (2h)

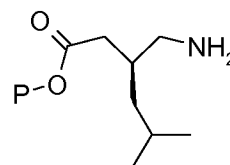


10

with a compound of formula (III) or (IV)



(III)

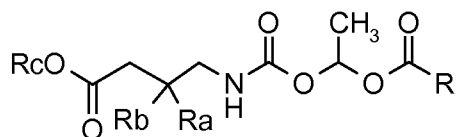


(IV)

15

wherein P is a carboxylic protecting group such as a t-butyl group, or a silyl protecting group, in an aprotic polar/non polar solvent in the presence of an organic or inorganic base;

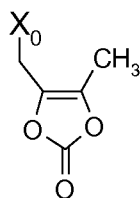
ii) removing the protective group P by acidic work-up or with known methods depending on the group P to obtain a compound of formula (I) wherein Rc is H and all the other variable are as previously defined



(I)

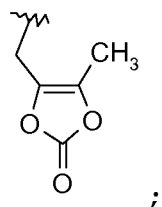
;

5 **iaa)** optionally reacting the compound of formula (I) with a compound (XIII)



(XIII)

10 wherein X₀ is Cl, Br or I, in the presence of an inorganic or organic base, in an aprotic polar/non polar, to obtain a compound of formula (I) wherein Rc is



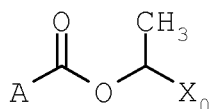
;

15 **iib)** optionally reacting the compounds of formula (I) wherein Rc is H with the appropriate base to obtain a compound of formula (I) wherein Rc is the pharmaceutically acceptable cation;

iii) reacting a compound of formula (VI)

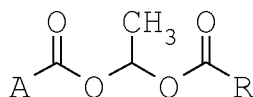


20 wherein R is as above defined and X₁ is Ag⁺ or Hg⁺, with a compound of formula (V)



(V)

wherein A is as above defined, X_0 is Cl, Br or I, in a molar ratio of compounds of formulas (VI):(V) from 2 to 0.5, in an organic solvent to obtain a compound of formula (II)



5

(II)

wherein A and R are as above defined;

iv) reacting a nitrate carboxylic acid of formula (VII)



10 wherein R is as above defined, with Ag_2O or Hg_2O in a molar ratio compound of formula (VII):(Ag_2O) or Hg_2O of from 1 to 0.5 in an organic solvent, to obtain the carboxylic acid salt of formula (VI)



15 wherein X_1 is Ag^+ or Hg^+ .

In step i) the silyl protecting group is trimethylsilyl or tert-butyldimethylsilyl, the organic or inorganic base is selected from pyridine or triethylamine or Cs_2CO_3 , the aprotic polar/non polar solvent is for example THF, DMF or CH_2Cl_2 . The
20 reaction is carried out at temperature ranging from -80°C to 60°C .

In step iia) the inorganic or organic base is selected from Cs_2CO_3 or pyridine or triethylamine. The aprotic polar/non polar solvent can be THF, DMF or CH_2Cl_2 . The reaction is
25 carried at temperature ranging from -80°C to 60°C ,
Compounds (XIII) of step iia) are commercially available or synthesized according to methods well known in the art.

In step iii) the reaction is typically carried out in a temperature range from about -20°C to about 120°C , preferably
30 from 10°C to 30°C . Generally, the reaction is carried out in an organic solvent, generally an aprotic solvent, such as toluene, methylene chloride, tetrahydrofuran or chloroform or

dipolar solvents such as, dimethylformamide (DMF), N-methylpyrrolidone, acetonitrile or in a mixture thereof, depending on the solubility of the compounds involved in the reaction; the preferred solvent are toluene, methylene
 5 chloride, THF, a mixture of methylene chloride and THF.

Compounds of formula (V) of step iii) are prepared by known compounds following procedures well known in the art (Jose Alexander,* Robyn Cargill, Stuart R. Michelson, and Harvey Schwamt, (Acyloxy)alkyl Carbamates as Novel Bioreversible
 10 Prodrugs for Amines: Increased Permeation through Biological Membranes, J. Med. Chem., 1988, 31, 318-322)

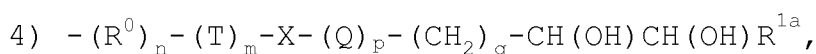
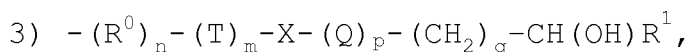
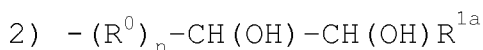
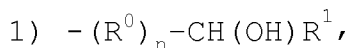
In step iv) the organic solvent is an aprotic solvent, such as toluene, methylene chloride, or chloroform or polar/dipolar solvents such as acetonitrile, water, tetrahydrofurane,
 15 dimethylformamide (DMF), N-methylpyrrolidone, or in a mixture thereof, depending on the solubility of the compounds involved in the reaction; the preferred solvent are acetonitrile, water a mixture of acetonitrile and water.

The reaction is generally carried out in a temperature range
 20 from about -20°C to about 80°C, preferably from 10°C to 30°C in the dark.

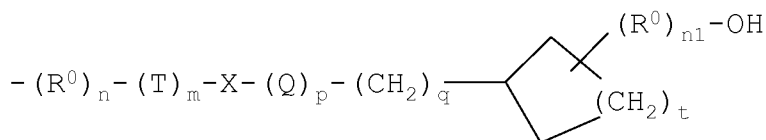
The compound of general formula (VII) of step iv) are known in the literature or can be obtained from the corresponding compounds of formula (VIII)



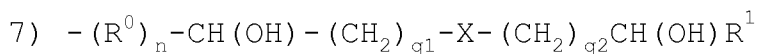
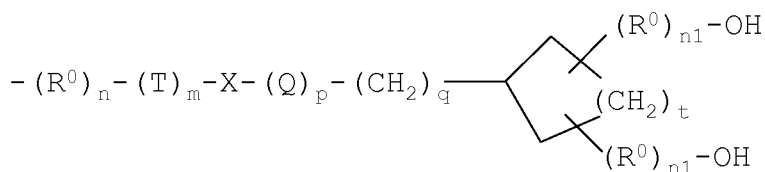
wherein R' is selected from the group consisting of:



5)



6)



wherein

n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

10 n1 is 0 or 1;

q is an integer from 0 to 10, preferably q is from 0 to 6;

q1 is an integer from 1 to 10, preferably q is from 1 to 6;

q2 is an integer from 1 to 10, preferably q is from 1 to 6;

t is an integer from 1 to 4, preferably t is 2 or 3;

15 R^0 is a straight or branched C_1 - C_{10} alkylene; preferably R^0 is a straight or branched C_1 - C_6 alkylene, more preferably R^0 is $-C(CH_3)_2-$ or $-C(CH_3)_2-CH_2-$;

R^1 is selected from hydrogen, a straight or branched C_1 - C_4 alkyl, $-(CH_2)OCH_3$, preferably R^1 is hydrogen, $-CH_3$, $-(CH_2)OCH_3$, $-CH(CH_3)_2$;

20 R^{1a} is hydrogen or a straight or branched C_1 - C_4 alkyl, preferably R^{1a} is hydrogen or $-CH_3$;

X is selected from an oxygen atom, $-NH-$, $-N(CH_3)-$ or a covalent bond, preferably X is oxygen or a covalent bond;

25 T and Q are $-CR^2R^3-$, wherein R^2 and R^3 at each occurrence are independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, OR^4 , NHR^5 , preferably R^2 and R^3 are hydrogen or R^2 is hydrogen and R^3 is NHR^5 ;

R^4 is hydrogen or C_1 - C_4 linear or branched alkyl, preferably R^4 is hydrogen or $-CH_3$;

R^5 is hydrogen, C_1 - C_4 linear or branched alkyl, $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$ (Boc), more preferably R^5 is $-C(O)CH_3$ or

5 $-C(O)OC(CH_3)_3$;

R^6 is C_1 - C_4 linear or branched alkyl or hydrogen, preferably R^6 is $-CH_3$;

R^7 is $(CH_2)_qCH(OH)R^1$ wherein q and R^1 are as above defined,

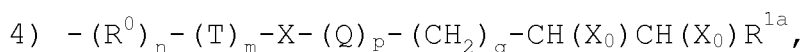
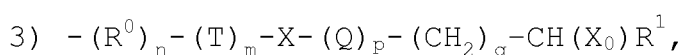
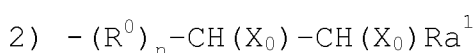
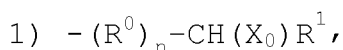
by reacting with nitric acid and acetic anhydride in a
10 temperature range from $-50^\circ C$ to $0^\circ C$, or by reacting with triflic anhydride/tetraalkylammonium nitrate salt in an aprotic polar/non polar solvent such as DMF, THF or CH_2Cl_2 at temperature ranging from $-80^\circ C$ to $65^\circ C$

Compounds (VIII) are commercially available or are known in
15 the literature or can be prepared by known compounds by methods well known in the art.

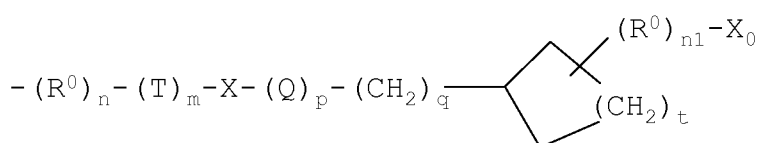
Alternatively, compounds (VII) can be prepared by reacting compound (IX)



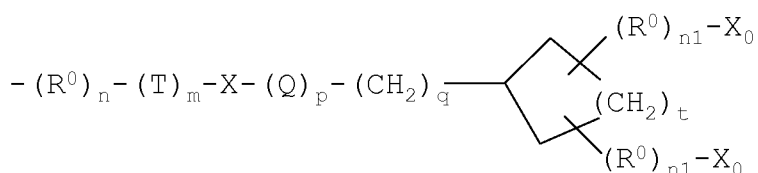
20 wherein R'' is selected from the group consisting of:

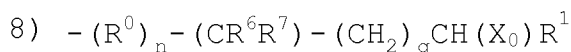
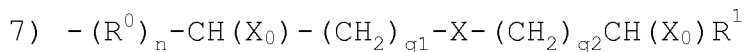


25 5)



6)





wherein

n is 0 or 1;

5 m is 0 or 1;

p is 0 or 1;

n1 is 0 or 1;

q is an integer from 0 to 10, preferably q is from 0 to 6;

q1 is an integer from 1 to 10, preferably q is from 1 to 6;

10 q2 is an integer from 1 to 10, preferably q is from 1 to 6;

t is an is an integer from 1 to 4, preferably t is 2 or 3;

R^0 is a straight or branched C_1 - C_{10} alkylene; preferably R^0 is a straight or branched C_1 - C_6 alkylene, more preferably R^0 is $-C(CH_3)_2-$ or $-C(CH_3)_2-CH_2-$;

15 R^1 is selected from hydrogen, a straight or branched C_1 - C_4 alkyl, $-(CH_2)OCH_3$, preferably R^1 is hydrogen, $-CH_3$, $-(CH_2)OCH_3$, $-CH(CH_3)_2$;

R^{1a} is hydrogen or a straight or branched C_1 - C_4 alkyl, preferably R^{1a} is hydrogen or $-CH_3$;

20 X is selected from an oxygen atom, $-NH-$, $-N(CH_3)-$ or a covalent bond, preferably X is oxygen or a covalent bond;

T and Q are $-CR^2R^3-$, wherein R^2 and R^3 at each occurrence are independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, OR^4 , NHR^5 , preferably R^2 and R^3 are hydrogen or R^2 is hydrogen and R^3 is NHR^5 ;

25 R^4 is hydrogen or C_1 - C_4 linear or branched alkyl, preferably R^4 is hydrogen or $-CH_3$;

R^5 is hydrogen, C_1 - C_4 linear or branched alkyl, $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$ (Boc), more preferably R^5 is $-C(O)CH_3$ or

30 $-C(O)OC(CH_3)_3$;

R^6 is C_1 - C_4 linear or branched alkyl or hydrogen, preferably R^6 is $-CH_3$;

R^7 is $(CH_2)_qCH(X_0)R^1$ wherein q and R^1 are as above defined,

X_0 is as above defined

with AgNO₃ as described in the international application WO 2006/008196.

5 Alternatively (VII) can be obtained by oxidation of compound
(X)



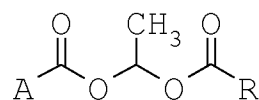
wherein R is as above defined, by oxidation with TCCA or NaOCl or NaIO₄ in the presence of a catalyst such as TEMPO or 10 ruthenium (IV) oxide hydrate in an aprotic polar/protic polar/non polar solvent such as acetone, CH₃CN, water, CH₃Cl or CH₂Cl₂ or mixtures, at temperatures ranging from -80°C to 65°C. Compounds (X) can be obtained by nitration of compounds (XI) or (XII)

$$15 \quad R'CH_2OP' \quad (XI)$$
$$R'' \text{CH}_2\text{OH} \quad (\text{XII})$$

wherein R' and R'' are as above defined and P' is a suitable hydroxyl protecting group

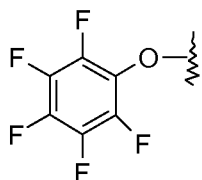
using the procedures above described, followed by the removal
20 of the protecting group by methods well known in the art.

Another embodiment of the invention provides a compound of formula (II):

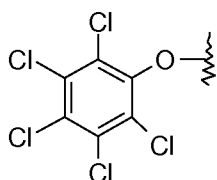


(II)

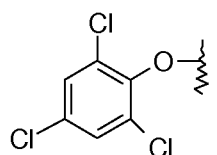
25 wherein A is an activating group selected from the formulas
(2a)-(2h)



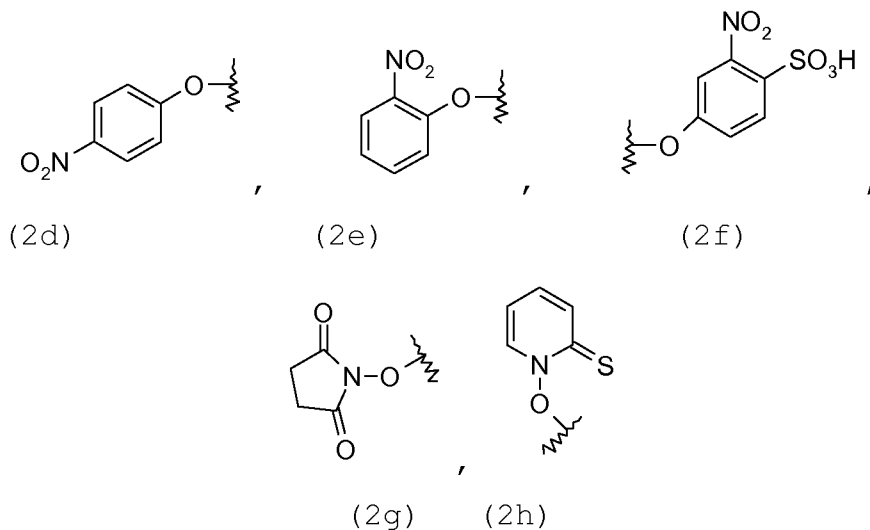
(2a)



(2b)



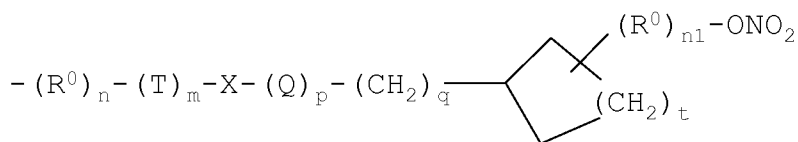
(2c)



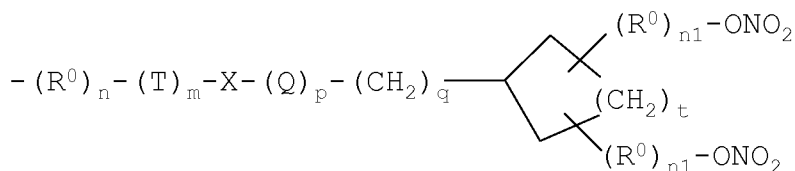
5 preferably A is 2d or 2a or 2g;

R is selected from the group consisting of:

- 1) $-(R^0)_n-CH(ONO_2)R^1$,
- 2) $-(R^0)_n-CH(ONO_2)-CH(ONO_2)R^{1a}$
- 3) $-(R^0)_n-(T)_m-X-(Q)_p-(CH_2)_q-CH(ONO_2)R^1$,
- 10 4) $-(R^0)_n-(T)_m-X-(Q)_p-(CH_2)_q-CH(ONO_2)CH(ONO_2)R^{1a}$,
- 5) 5)



6)



- 15 7) $-(R^0)_n-CH(ONO_2)-(CH_2)_{q1}-X-(CH_2)_{q2}CH(ONO_2)R^1$
- 8) $-(R^0)_n-(CR^6R^7)-(CH_2)_qCH(ONO_2)R^1$

wherein

n is 0 or 1;

m is 0 or 1;

20 p is 0 or 1;

n1 is 0 or 1;

q is an integer from 0 to 10, preferably q is from 0 to 6;

q1 is an integer from 1 to 10, preferably q is from 1 to 6;

q2 is an integer from 1 to 10, preferably q is from 1 to 6;

t is an is an integer from 1 to 4, preferably t is 2 or 3;

R^0 is a straight or branched C_1 - C_{10} alkylene; preferably R^0 is a

5 straight or branched C_1 - C_6 alkylene, more preferably R^0 is

$-C(CH_3)_2-$ or $-C(CH_3)_2-CH_2-$;

R^1 is selected from hydrogen, a straight or branched C_1 - C_4

alkyl, $-(CH_2)OCH_3$, preferably R^1 is hydrogen, $-CH_3$, $-(CH_2)OCH_3$,

$-CH(CH_3)_2$;

10 R^{1a} is hydrogen or a straight or branched C_1 - C_4 alkyl, preferably R^{1a} is hydrogen or $-CH_3$;

X is selected from an oxygen atom, $-NH-$, $-N(CH_3)-$ or a covalent bond, preferably X is oxygen or a covalent bond;

T and Q are $-CR^2R^3-$, wherein R^2 and R^3 at each occurrence are

15 independently selected from hydrogen, C_1 - C_4 linear or branched

alkyl, OR^4 , NHR^5 , preferably R^2 and R^3 are hydrogen or R^2 is hydrogen and R^3 is NHR^5 ;

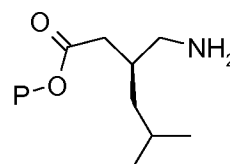
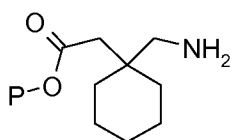
R^4 is hydrogen or C_1 - C_4 linear or branched alkyl, preferably R^4 is hydrogen or $-CH_3$;

20 R^5 is hydrogen, C_1 - C_4 linear or branched alkyl, $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$ (Boc), more preferably R^5 is $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$;

R^6 is C_1 - C_4 linear or branched alkyl or hydrogen, preferably R^6 is $-CH_3$;

25 R^7 is $(CH_2)_qCH(ONO_2)R^1$ wherein q and R^1 are as above defined.

The nitrate derivatives of formula (II) are stable compounds obtainable in high yields and purity, suitable for long term storage. Said compounds can react with the compound of formula (III) or (IV)

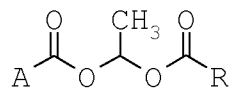


(III)

(IV)

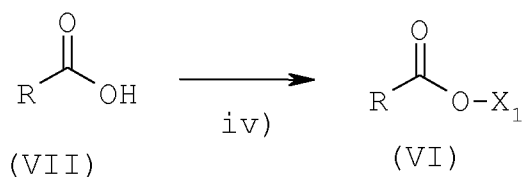
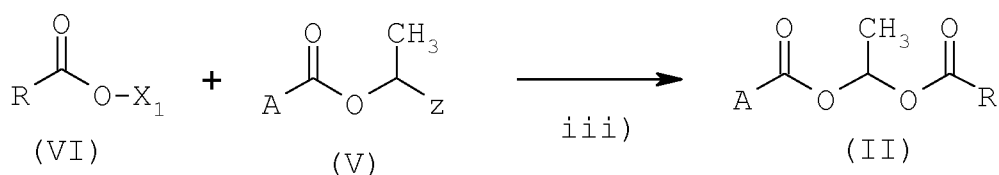
under mild reaction conditions, allowing to obtain nitrooxyderivatives of formula (I) in high yield and purity.

The compounds of formula (II)



(II)

wherein the variables A and R are as above defined are synthesized by the process, as depicted in Scheme 2



Scheme 2

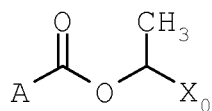
comprising:

iii) reacting a compound of formula (VI)



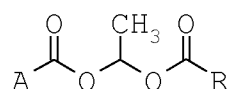
wherein R is as above defined and X₁ is Ag⁺ or Hg⁺,

with a compound of formula (V)



(V)

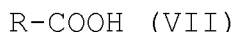
wherein A is as above defined, X₀ is Cl, Br or I, in a molar ratio of compounds of formulas (VI):(V) from 2 to 0.5, in an organic solvent to obtain a compound of formula (II)



(II)

wherein A and R are as above defined;

iv) reacting a nitrate carboxylic acid of formula(VII)



wherein R is as above defined, with Ag₂O or Hg₂O in a molar
5 ratio compound of formula (VII):(Ag₂O) or Hg₂O of from 1 to 0.5
in an organic solvent, to obtain the carboxylic acid salt of
formula (VI)



wherein X₁ is Ag⁺ or Hg⁺.

10 In step iii) the reaction is typically carried out in a
temperature range from about -20°C to about 120°C, preferably
from 10°C to 30°C. Generally, the reaction is carried out in
an organic solvent, generally an aprotic solvent, such as
toluene, methylene chloride, tetrahydrofurane or chloroform or
15 dipolar solvents such as, dimethylformamide (DMF), N-
methylpyrrolidone, acetonitrile or in a mixture thereof,
depending on the solubility of the compounds involved in the
reaction; the preferred solvent are toluene, methylene
chloride, THF, a mixture of methylene chloride and THF.

20 Compounds of formula (V) of step iii), wherein A and X₀ are as
above defined, are prepared by known compounds following
procedures well known in the art (Jose Alexander,* Robyn
Cargill, Stuart R. Michelson, and Harvey Schwamt,
(Acyloxy)alkyl Carbamates as Novel Bioreversible Prodrugs for
25 Amines: Increased Permeation through Biological Membranes, *J.*
Med. Chem., 1988, 31, 318-322).

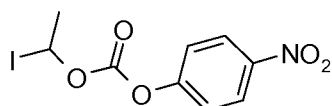
In step iv) the organic solvent is an aprotic solvent, such
as toluene, methylene chloride, or chloroform or polar/dipolar
solvents such as acetonitrile, water, tetrahydrofurane,
30 dimethylformamide (DMF), N-methylpyrrolidone, or in a mixture
thereof, depending on the solubility of the compounds involved
in the reaction; the preferred solvent are acetonitrile, water
a mixture of acetonitrile and water.

The reaction is generally carried out in a temperature range from about -20°C to about 80°C, preferably from 10°C to 30°C in the dark.

The compound of general formula (VII) of step iv) are known in the literature or can be prepared as reported above.

Example 1

Synthesis of 1-iodoethyl 4-nitrophenyl carbonate



STEP A: 1-chloroethyl 4-nitrophenyl carbonate

To a solution of 4-nitrophenol (3.0 g, 21.6 mmol) and pyridine (1.9 mL, 24 mmol) cooled to 0°C, 1-chloroethyl chloroformate (2.3 mL, 21.6 mmol) was added. The reaction was stirred at room temperature for 5-6 hours, then washed with NaH₂PO₄ (5%) and brine, dried over Na₂SO₄ and concentrated affording the title compound (4.88 g, 92%) as a pale yellow solid.

¹H-NMR (CDCl₃): 8.32 (2H,m); 7.44(2H,m); 6.52(1H,q, J=5.8 Hz); 1.94(3H,d, J=5.5Hz).

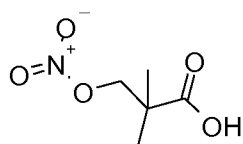
STEP B: 1-iodoethyl 4-nitrophenyl carbonate

1-chloroethyl 4-nitrophenyl carbonate (4.88 g, 20 mmol) and NaI (20.8 g, 139 mmol) were dissolved in CH₃CN (40 mL) and the mixture was refluxed overnight. CH₃CN was removed and the residue was diluted with EtOAc, washed with brine, Na₂S₂O₅ (10%), K₂CO₃ (10%) and brine, dried over Na₂SO₄ and concentrated affording the title compound as a pale oil (3.56 g, 53%)

¹H-NMR (CDCl₃): 8.34 (2H,m); 7.47(2H,m); 6.86(1H,q, J=6.2 Hz); 2.35(3H,d, J=6.2Hz).

Example 2

Synthesis of 2,2-dimethyl-3-(nitrooxy)propanoic acid



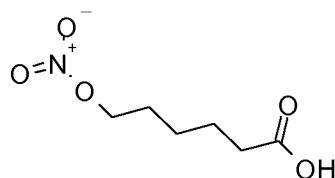
HNO₃ (2.4 mL, 54 mmol) was dissolved in Ac₂O (7.5 mL, 80 mmol), cooled to 0°C, and methyl 3-hydroxy-2,2-dimethylpropanoate (4 mL, 31 mmol) was added. The mixture was stirred for 1 hour, then poured into iced NaHCO₃ (5%) and diluted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated affording methyl 2,2-dimethyl-3-(nitrooxy)propanoate as a clear oil

The residue was dissolved in NaOH (2.5 M, 20 mL) and MeOH (20 mL) and the solution was stirred at room temperature for 6 hours, and then acidified with HCl (5%) to pH 3-4. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated affording the title compound as a pale yellow solid (5.00 g, 98%)

¹H-NMR (CDCl₃): 4.53 (2H, s); 1.34 (6H, s).

Example 3

Synthesis of 6-(nitrooxy)hexanoic acid

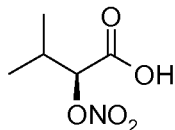


6-Bromohexanoic acid (1.0 g, 5.1 mmol) was dissolved in CH₃CN (20 mL) and AgNO₃ (1.74 g, 19.2 mmol) was added. The reaction was heated by microwave at 90°C for 14 minutes. The precipitate was filtered off and the reaction was concentrated under reduced pressure; EtOAc (20 mL) was added and the organic phase was washed with water and brine, dried over Na₂SO₄ and concentrated affording the title compound as a yellow oil (840 mg, 93%).

¹H-NMR (CDCl₃): 4.47 (2H, t, J=6.6Hz); 2.40 (2H, t, J=7.3Hz); 1.84-1.63 (4H, m); 1.50 (2H, m).

Example 4

Synthesis of (S)-3-methyl-2-(nitrooxy)butanoic acid

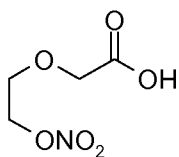


HNO₃ (3 mL, 76 mmol) was dissolved in Ac₂O (10 mL), cooled to
5 0°C, and (S)-(+)-2-Hydroxy-3-methylbutyric acid (1.5 g, 12.7
mmol) was added. The mixture was stirred for 1 hour, then
poured into iced NaHCO₃ (10%) and diluted with CH₂Cl₂. The
organic phase was washed with brine, dried over Na₂SO₄ and
concentrated affording the title compound as a clear oil (1.75
10 g, 85%)

¹H-NMR (CDCl₃): 5.17 (2H, d, J=4.3Hz); 2.25 (1H, m); 0.98
(6H, dd, J=6.9Hz).

Example 5

Synthesis of 2-(2-(nitrooxy)ethoxy)acetic acid



15

STEP A: 2-(2-hydroxyethoxy)ethyl nitrate

Dietilenglycol monochloride (10 mL, 94.3 mmol) was dissolved
in CH₃CN (250 mL) and NaI (141 g, 943 mmol) was added. The
20 reaction was refluxed for 16 hours. The solvent was removed
and CH₂Cl₂ (100 mL) was added, the mixture was filtered and the
organic phase was washed with a solution of Na₂S₂O₅ (10%),
dried and evaporated. The crude material was dissolved in CH₃CN
(250 mL), AgNO₃ (55 g, 330 mmol) was added and the reaction
25 refluxed for 2 hours. The mixture was concentrated and diluted
with EtOAc, then filtered. The organic phase was washed with
water and brine, dried over Na₂SO₄ and concentrated affording
the title compound as a clear oil. (8.5 g, 60%)

¹H-NMR (CDCl₃): 4.66 (2H, m); 3.80 (4H, m); 3.63 (2H, m).

STEP B: 2-(2-(nitrooxy)ethoxy)acetic acid

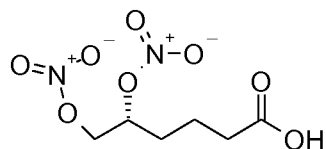
2-(2-hydroxyethoxy)ethyl nitrate (17 g, 112 mmol) was dissolved in acetone and cooled to 0°C; NaHCO₃ (15%, 150 mL), NaBr (2 g, 22 mmol) and TEMPO (170 mg, 1.12 mmol) were added.

5 Trichloroisocyanuric acid (50 g, 224 mmol) was added in portions in 15 minutes. The reaction was stirred at room temperature for 3 hours, then cooled to 0°C and 2-propanol (60 mL) was slowly added in 15 minutes. The reaction was stirred at 0°C for 30 minutes then the precipitate was filtered. The
10 solvent was concentrated and NaOH (10%) was added to pH=9. The aqueous phase was extracted with EtOAc, then HCl was added to pH=3 and the aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄ and concentrated affording the title compound as an oil. (8.7 g, 47%)

15 ¹H-NMR (DMSO): 4.67 (2H,m); 4.06 (2H,s); 3.78 (2H,m).

Example 6

Synthesis of (R)-5,6-bis(nitrooxy)hexanoic acid



20 STEP A: *tert*-butyl (5*R*)-5,6-dihydroxyhexanoate

Tert-butyl hex-5-enoate (5 g, 29.4 mmol) was added to a suspension of AD-mix-β (41 g) in H₂O/*t*-BuOH (125 mL/125 mL) at 0°C and the reaction was stirred overnight at 5°C. EtOAc (100 mL) was added followed by Na₂S₂O₅ (7.0 g) in portions and the
25 reaction was stirred for 30 minutes at 5°C and 1 hour at room temperature. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na₂SO₄ and concentrated affording the title compound as an oil (5.8 g, 98%)

30 ¹H-NMR (CDCl₃): 3.67 (2H,m); 3.47 (1H,m); 2.27 (2H,m); 1.73 (4H,m); 1.46 (9H,s).

STEP B: *tert*-butyl (5*R*)-5,6-bis(nitrooxy)hexanoate

HNO₃ (5.23 mL, 126.2 mmol) was dissolved in Ac₂O (20 mL), cooled to 0°C, and *tert*-butyl (5*R*)-5,6-dihydroxyhexanoate (5.15 g, 25.2 mmol) was added. The mixture was stirred for 1 hour, then poured into iced NaOH (10%) and diluted with CH₂Cl₂. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated affording the title compound as a brown oil (7.0 g, 95%)

¹H-NMR (CDCl₃): 5.29 (1H,m); 4.77 (1H,m); 4.50 (1H,m); 2.30 (2H,m); 1.77 (4H,m); 1.46 (9H,s).

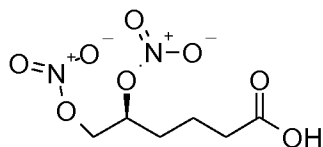
STEP C: (i>R)-5,6-bis(nitrooxy)hexanoic acid

Tert-butyl (5*R*)-5,6-bis(nitrooxy)hexanoate (7.0 g, 29.4 mmol) was dissolved in CH₂Cl₂ and cooled to 0°C. BF₃·Et₂O (3 mL, 32.3 mmol) was added and the reaction stirred 30 minutes at 0°C and 4 hours at room temperature. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The crude material was purified by silica gel chromatography (CH₂Cl₂/MeOH 95:5) affording the title compound as a brown oil. (4.0 g, 60%)

¹H-NMR (CDCl₃): 5.30 (1H,m); 4.77 (1H,m); 4.51 (1H,m); 2.46 (2H,m); 1.83 (4H,m).

Example 7

Synthesis of (i>S)-5,6-bis(nitrooxy)hexanoic acid



Title compound was synthesized following the procedure of Example 6 except that in STEP A AD-mix-α was used instead of AD-mix-β.

¹H-NMR (CDCl₃): 5.30 (1H,m); 4.77 (1H,m); 4.51 (1H,m); 2.46 (2H,m); 1.83 (4H,m).

Example 8

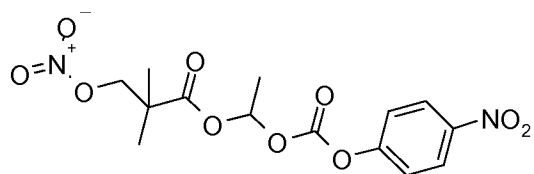
Synthesis of silver(I) 2,2-dimethyl-3-(nitrooxy)propanoate

2,2-dimethyl-3-(nitrooxy)propanoic acid (obtained in Example 2) (5.12 g, 31 mmol) was dissolved in CH₃CN (134 mL). To the solution Ag₂O (4.86 g, 21 mmol) and H₂O (67 mL) were added and the mixture was stirred at room temperature for 5 hours, and then filtered over celite. The filtrate was concentrated affording the title compound as a pale yellow solid (6.60 g, 78%)

¹H-NMR (CDCl₃): 4.55 (2H, s); 1.30 (6H, s)

Example 9

Synthesis of 1-((4-nitrophenoxy)carbonyloxy)ethyl-2,2-dimethyl-3-(nitrooxy)propanoate



silver(I) 2,2-dimethyl-3-(nitrooxy)propanoate (obtained in Example 8) (3.13 g, 12 mmol) and 1-iodoethyl 4-nitrophenyl carbonate (obtained in Example 1) (3.56 g, 11 mmol) were dissolved in dry toluene (50 mL) and the suspension was stirred overnight, filtered and purified by BIOTAGE (eluting with EtOAc/Hexane 5 to 20%) affording the title compound (1.5 g, 38%) as a pale oil.

¹H-NMR (CDCl₃): 8.31 (2H, m); 7.42 (2H, m); 6.87 (1H, q, *J*=5.4 Hz); 4.54 (2H, m); 1.65 (3H, d); 1.34 (6H, s).

Example 10

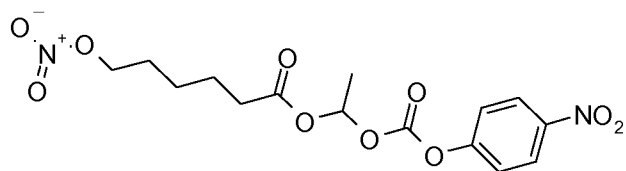
Synthesis of Silver(I) 6-(nitrooxy)hexanoate

Title compound was synthesized following the procedure of Example 8 except that 6-(nitrooxy)hexanoic acid (prepared in Example 3) was used instead of 2,2-dimethyl-3-(nitrooxy)propanoic acid.

¹H-NMR (DMSO): 4.50 (2H, t, *J*=6.6 Hz); 1.65 (2H, m); 1.53 (2H, m); 1.35 (2H, m).

Example 11

1-((4-nitrophenoxy)carbonyloxy)ethyl 6-(nitrooxy) hexanoate



Starting from Silver(I) 6-(nitrooxy)hexanoate (prepared in
 5 Example 10) and 1-iodoethyl 4-nitrophenyl carbonate (obtained
 in Example 1), the title compound was synthesized following
 the procedure of Example 9.

¹H-NMR (CDCl₃): 8.31 (2H,m); 7.42 (2H,m); 6.87 (1H,q, *J*=5.4 Hz);
 4.47 (2H,t, *J*=6.5Hz); 2.43 (2H,m); 1.88-1.66 (4H,m); 1.64
 10 (3H,d, *J*=5.5Hz); 1.50 (2H,m).

Example 12

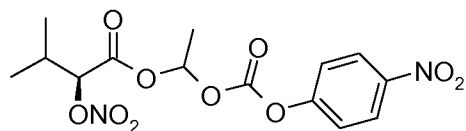
Synthesis of Silver(I) (S)-3-methyl-2-(nitrooxy)butanoate

Title compound was synthesized following the procedure of
 Example 8 except that (S)-3-methyl-2-(nitrooxy)butanoic acid
 15 (prepared in Example 4) was used instead of 2,2-dimethyl-3-
 (nitrooxy)propanoic acid.

¹H-NMR (DMSO): 5.17 (1H,d, *J*=4.3Hz); 2.26 (1H,m); 0.98
 (6H,dd, *J*=6.9Hz)

Example 13

20 Synthesis of (2S)-1-((4-nitrophenoxy)carbonyloxy)ethyl-3-
 methyl-2-(nitrooxy)butanoate



Starting from Silver(I) (S)-3-methyl-2-(nitrooxy)butanoate
 (prepared in Example 12) title compound was synthesized
 25 following the procedure of Example 9.

¹H-NMR (CDCl₃): 8.31 (2H,m); 7.41 (2H,m); 6.93 (1H,m); 5.02
 (1H,d, *J*=4.7Hz); 2.36 (1H,m); 1.69 (3H,m); 1.11 (6H,m).

Example 14

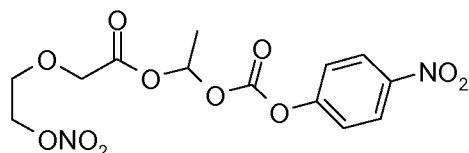
Synthesis of Silver(I) 2-(2-(nitrooxy)ethoxy)acetate

Title compound was synthesized following the procedure of Example 8 except that 2-(2-(nitrooxy)ethoxy)acetic acid (prepared in Example 5) was used instead of 2,2-dimethyl-3-(nitrooxy)propanoic acid.

5 $^1\text{H-NMR}$ (DMSO): 4.66 (2H,m); 3.92 (2H,s); 3.77 (2H,m)

Example 15

Synthesis of 1-((4-nitrophenoxy)carbonyloxy)ethyl 2-(2-(nitrooxy)ethoxy) acetate



10

1-iodoethyl 4-nitrophenyl carbonate (10.55 g, 31.3 mmol) obtained in Example 1 was dissolved in dry toluene (15 mL) under nitrogen atmosphere at r.t. To this solution Silver(I) 2-(2-(nitrooxy)ethoxy)acetate (11 g, 40.7 mmol) obtained in
15 Example 14 was added and the suspension was stirred in the dark at room temperature for 5 hours. The precipitate was filtered and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel chromatography (eluting with EtOAc/Hexane from 5 to 40%) affording the title
20 compound (7.5 g, 68%) as a pale oil.

$^1\text{H-NMR}$ (CDCl_3): 8.30 (2H,m); 7.4 (2H,m); 6.92 (1H,q, $J=5.4\text{Hz}$); 4.67 (2H,m); 4.20 (2H,s); 3.90 (2H,m); 1.67 (3H,d, $J=5.4\text{Hz}$).

Example 16

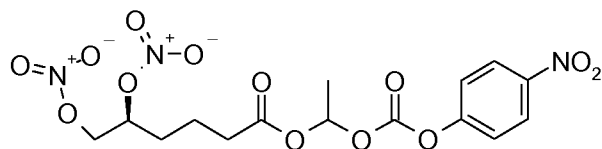
Synthesis of Silver(I) (S)-5,6-bis(nitrooxy)hexanoate

25 Title compound was synthesized following the procedure of Example 8 except that (S)-5,6-bis(nitrooxy)hexanoic acid (prepared in Example 7) was used instead of 2,2-dimethyl-3-(nitrooxy)propanoic acid.

30 $^1\text{H-NMR}$ (DMSO): 5.42 (1H,m); 4.92 (1H,m); 4.68 (1H,m); 2.5 (2H,m); 2.16 (2H,m); 1.81-1.51 (4H,m).

Example 17

Synthesis of (5S)-1-((4-nitrophenoxy)carbonyloxy)ethyl-5,6-bis(nitrooxy) hexanoate



Starting from Silver(I) (S)-5,6-bis(nitrooxy)hexanoate
 5 (prepared in Example 16) title compound was synthesized following the procedure of Example 9.

$^1\text{H-NMR}$ (CDCl_3): 8.30 (2H,m); 7.42 (2H,m); 6.85 (1H,m); 5.28 (1H,m); 4.74 (1H,m); 4.47 (1H,m); 2.47 (2H,m); 1.83 (4H,m); 1.64 (3H,m).

10 Example 18

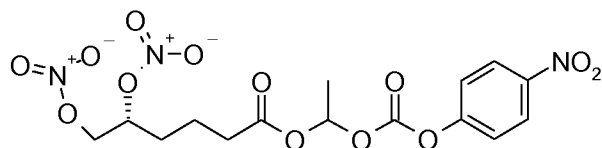
Synthesis of Silver(I) (R)-5,6-bis(nitrooxy)hexanoate

Title compound was synthesized following the procedure of Example 8 except that (R)-5,6-bis(nitrooxy)hexanoic acid
 15 (prepared in Example 6) was used instead of 2,2-dimethyl-3-(nitrooxy)propanoic acid.

$^1\text{H-NMR}$ (DMSO): 5.42 (1H,m); 4.92 (1H,m); 4.68 (1H,m); 2.5 (2H,m); 2.16 (2H,m); 1.81-1.51 (4H,m).

Example 19

Synthesis of (5R)-1-((4-nitrophenoxy)carbonyloxy)ethyl-5,6-
 20 bis(nitrooxy) hexanoate

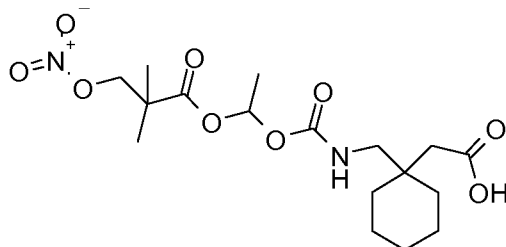


Starting from Silver(I) (R)-5,6-bis(nitrooxy)hexanoate
 (prepared in Example 18), title compound was synthesized following the procedure of Example 9.

25 $^1\text{H-NMR}$ (CDCl_3): 8.30 (2H,m); 7.42 (2H,m); 6.85 (1H,m); 5.28 (1H,m); 4.74 (1H,m); 4.47 (1H,m); 2.47 (2H,m); 1.83 (4H,m); 1.64 (3H,m).

Example 20

Synthesis of 2-(1-(((1-(2,2-dimethyl-3-(nitrooxy)propanoyloxy)ethoxy) carbonylamino)methyl)cyclohexyl)acetic acid (compound 1)



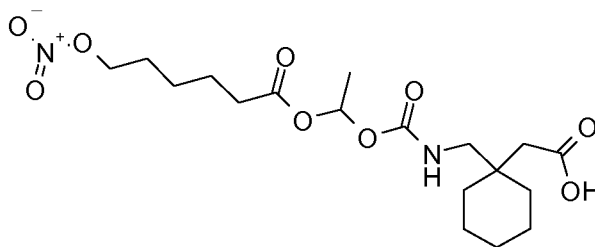
5 (1)

To a solution of Gabapentin (670 mg, 3.9 mmol) in CH₂Cl₂ (20 mL), cooled to 0°C, triethylamine (1.4 mL, 11 mmol) and trimethylsilylchloride (1 mL, 7.8 mmol) were added. The reaction was stirred at 0°C for 2 hours, then 1-((4-nitrophenoxy)carbonyloxy)ethyl-2,2-dimethyl-3-(nitrooxy)propanoate (Example 9) (1.5 g, 4 mmol) was added. The reaction was stirred at room temperature overnight, then washed with NaH₂PO₄ (5%) and brine, dried over Na₂SO₄ and concentrated. The crude material was purified by BIOTAGE (eluting with EtOAc/Hexane from 20 to 80%) affording the title compound (1.29 g, 80%) as a clear oil.

¹H-NMR (CDCl₃): 6.81 (1H, q, J=5.5Hz); 5.28 (1H, bt); 4.52 (2H, m); 3.26 (2H, m); 2.36 (2H, s); 1.51-1.29 (13H, d+m); 1.29 (6H, s).

20 Example 21

Synthesis 2-(1-(((1-(6-(nitrooxy)hexanoyloxy)ethoxy) carbonylamino)methyl)cyclohexyl)acetic acid (compound 3)



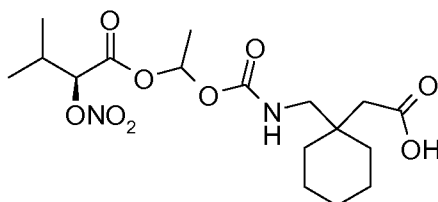
(3)

Title compound was synthesized following the procedure of Example 20, starting from compound obtained in Example 11.

$^1\text{H-NMR}$ (CDCl_3): 6.81 (1H,m); 5.27 (1H, bt); 4.45 (2H,m); 3.25 (2H,m); 2.34 (4H,m); 1.82-1.63 (4H,m); 1.66-1.34 (15H,m).

5 Example 22

Synthesis of 2-(1-(((1-((S)-3-methyl-2-(nitrooxy)butanoyloxy)ethoxy)carbonylamino)methyl)cyclohexyl)acetic acid (compound 7)



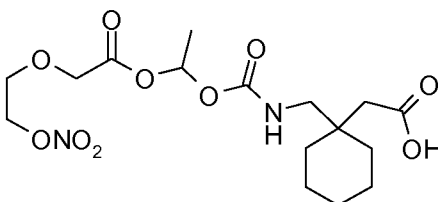
10 (7)

Title compound was synthesized following the procedure of Example 20 Starting from compound obtained in Example 13.

$^1\text{H-NMR}$ (CDCl_3): 6.92 (1H,m); 5.33 (1H, bt); 4.93 (1H,m); 3.27 (2H,m); 2.33 (3H,m); 1.66-1.34 (13H,m); 1.07 (6H,m).

15 Example 23

Synthesis of 2-(1-(5-methyl-11-(nitrooxy)-3,7-dioxo-4,6,9-trioxa-2-azaundecyl)cyclohexyl)acetic acid (corresponding to compound 12)



20 (12)

To a solution of Gabapentin (3.45 g, 20 mmol) in CH_2Cl_2 (200 mL), cooled to 0°C , triethylamine (5.2 mL, 46 mmol) and trimethylsilylchloride (5.2 mL, 41 mmol) were added. The reaction was stirred at 0°C for 2 hours, then 1-((4-nitrophenoxy)carbonyloxy)ethyl 2-(2-(nitrooxy)ethoxy) acetate (Example 15) (7.5 g, 20 mmol) was added. The reaction was

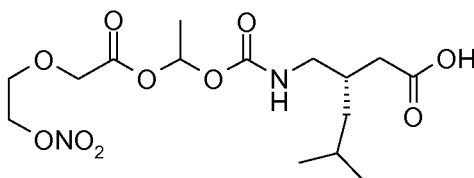
stirred at room temperature overnight, then washed with NaH_2PO_4 (5%) and brine, dried over Na_2SO_4 and concentrated.

The crude material was purified by BIOTAGE (eluting with EtOAc/Hexane from 20 to 80%) affording the title compound (6.0 g, 74 %) as a clear oil.

$^1\text{H-NMR}$ (CDCl_3): 6.86 (1H, q, $J=5.4\text{Hz}$); 5.31 (1H, bt); 4.66 (2H, m); 4.14 (2H, m); 3.88 (2H, m); 3.24 (2H, m); 2.35 (2H, s); 1.63-1.33 (13H, m).

Example 24

- 10 Synthesis of (12S)-12-isobutyl-7-methyl-1-(nitrooxy)-5,9-dioxo-3,6,8-trioxa-10-azatetradecan-14-oic acid (corresponding to compound 14)



(14)

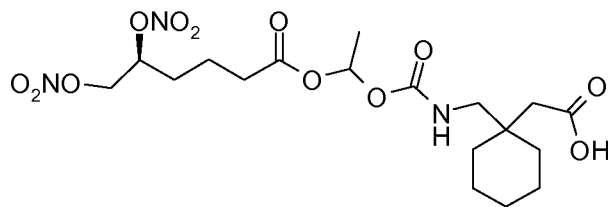
- 15 To a solution of pregabalin (510 mg, 3.2 mmol) in CH_2Cl_2 (25 mL), cooled to 0°C , triethylamine (1.2 mL, 10 mmol) and trimethylsilylchloride (800 μL , 6.3 mmol) were added. The reaction was stirred at 0°C for 2 hours, then 1-((4-nitrophenoxy)carbonyloxy)ethyl 2-(2-(nitrooxy)ethoxy) acetate (Example 15) (1.2 g, 3.2 mmol) was added. The reaction was stirred at room temperature overnight, then washed with NaH_2PO_4 (5%) and brine, dried over Na_2SO_4 and concentrated.

- The crude material was purified by BIOTAGE (eluting with EtOAc/Hexane from 15 to 60 %) affording the title compound (950 mg, 75 %) as a clear oil.

$^1\text{H-NMR}$ (CDCl_3): 6.86 (1H, m); 5.06 (1H, m); 4.66 (2H, m); 4.14 (2H, m); 3.88 (2H, m); 3.22 (2H, m); 2.34 (3H, m); 1.67 (1H, m); 1.52 (3H, m); 1.19 (2H, m); 0.92 (6H, m).

Example 25

Synthesis of 2-(1-(((1-((S)-5,6-bis(nitrooxy)hexanoyloxy)ethoxy)carbonylamino)methyl)cyclohexyl)acetic acid (compound 9)



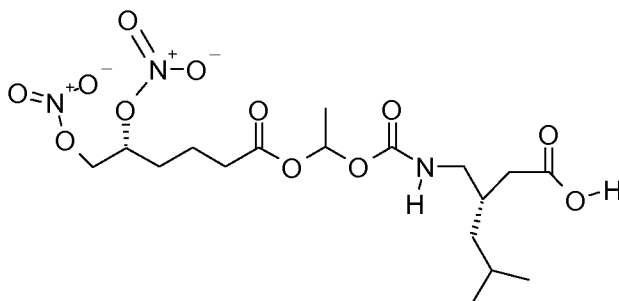
5 (9)

Title compound was synthesized following the procedure of Example 20 starting from compound obtained in Example 17.

¹H-NMR (CDCl₃): 6.80 (1H,m); 5.89 (1H,bt); 4.77 (1H,m); 4.49 (1H,m); 3.25 (2H,m); 2.38 (4H,m); 1.81 (4H,m); 1.62-1.30 (13H,m).

Example 26

Synthesis of (3S)-3-(((1-((R)-5,6-bis(nitrooxy)hexanoyloxy)ethoxy)carbonylamino)methyl)-5-methylhexanoic acid (compound 10)



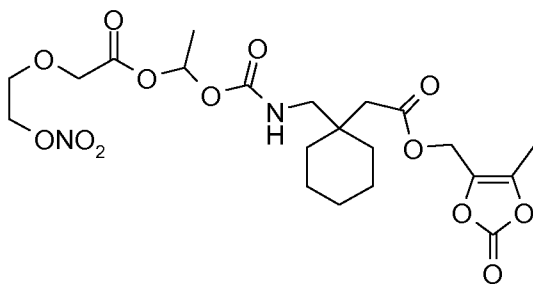
15 (10)

Title compound was synthesized following the procedure of Example 24 starting from compound obtained in Example 19.

¹H-NMR (CDCl₃): 6.79 (1H,m); 5.303 (1H,m); 5.02 (1H,m); 4.78 (1H,m); 4.49 (1H,m); 3.26 (2H,m); 2.41-2.30 (5H,m); 1.81-1.65 (5H,m); 1.49 (3H,m); 1.25 (2H,m); 0.94 (6H,m).

Example 27

Synthesis of 5-methyl-2-oxo-1,3-dioxol-4-yl{2-(1-(5-methyl-11-(nitrooxy)-3,7-dioxo-4,6,9-trioxa-2-azaundecyl)cyclohexyl} acetate (compound 27)



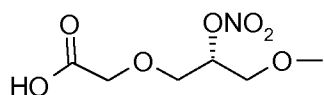
(27)

To a stirred solution of 2-(1-(5-methyl-11-(nitrooxy)-3,7-dioxo-4,6,9-trioxa-2-azaundecyl)cyclohexyl)acetic acid
 5 (Example 23) (600 mg, 1.47 mmol) in dry DMF (20 mL) was added 4-chloromethyl-5-methyl-1,3-dioxol-2-one (241 mg, 1.62 mmol) and Cs₂CO₃ carbonate (327 mg, 1.62 mmol). The mixture was stirred at room temperature for 2 hours. The reaction was diluted with NaH₂PO₄ 5% and extracted with EtOAc. The organic
 10 phase was washed with brine and dried over Na₂SO₄. The crude material was purified by silica gel chromatography (eluting with EtOAC/Hexane 20 to 80 %) affording the product (450 mg, 60 %) as a clear oil.

¹H-NMR (CDCl₃): 6.86 (1H, m); 5.23 (1H, bt); 4.85 (2H, s); 4.65
 15 (2H, t); 4.14 (2H, m); 3.86 (2H, m); 3.19 (2H, m); 2.36 (2H, s); 2.20 (3H, s); 1.6-1.3 (13H, m).

Example 28

Synthesis of (R)-2-(3-methoxy-2-(nitrooxy)propoxy)acetic acid



20 STEP A: methyl {[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl] methoxy} acetate

(S)-(+)-1,2-isopropylideneglycerol (14 mL, 112.8 mmol) was slowly added to a suspension of NaH (60, 9.0 g, 225 mmol) in dry THF (350 mL) at 0°C under nitrogen atmosphere. 15-crown-5
 25 (3 mL, 0.15 mmol) was then added. The reaction was stirred for 20 minutes at 0°C and methyl bromoacetate (31 mL, 338 mmol) in THF (30 mL) was slowly added. The reaction was stirred at room temperature for 2 hours. The reaction was quenched by adding a

saturated solution of NH_4Cl (300 mL) and the aqueous phase was extracted with Et_2O . The combined organic phases were dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel chromatography (Hex/AcOEt 8:2) affording the
5 title compound as a oil. (7.15 g, 31%) ^1H -NMR (CDCl_3): 4.33 (1H,m); 4.17 (2H,s); 4.08 (1H,m); 3.79 (1H,m); 3.76 (3H,s); 3.62 (2H,d); 1.43 (3H,s); 1.36 (3H,s).

STEP B: Methyl {[(2R)-2,3-dihydroxypropyl]oxy}acetate

10 Methyl {[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}acetate (8.2 g; 40 mmol) was dissolved in MeOH (100 mL) and HCl_{gas} was bubbled in the solution. The reaction was stirred at room temperature for 3 hours. The mixture was concentrated affording the title compound as an oil (6.4 g, 98%)
15 ^1H -NMR (CDCl_3): 4.32 (1H,m) 4.14 (2H,s); 3.90 (2H,m); 3.76 (3H,s); 3.74-3.58 (2H,m).

STEP C: methyl {[(2S)-2-hydroxy-3-(tert-Butyldiphenylsilyl) propyl]oxy}acetate

20 To a solution of methyl {[(2R)-2,3-dihydroxypropyl]oxy}acetate (1.7 g, 10.4 mmol) in dry DMF (18 mL), tert-butyldiphenyl silylchloride (3 mL, 11.5 mmol) and imidazole (1.42 g, 20.9 mmol) were added. The solution was stirred 6 hours at room temperature. The organic phase was diluted with NaH_2PO_4 (5%, 60
25 mL) and extracted with EtOAc, dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel chromatography (Hex/AcOEt 8:2) affording the title compound as an oil. (1.0 g, 24%)
30 ^1H -NMR (CDCl_3): 7.66 (4H,m); 7.41 (6H,m); 4.13 (3H,m); 3.94 (1H,m); 3.71 (5H,m); 3.61 (1H,m) 1.06 (9H,m).

STEP D: methyl {[(2S)-2-(nitrooxy)-3-(tert-butyl diphenyl silyl)propyl]oxy}acetate

HNO₃ (0.247 mL, 5.95 mmol) was dissolved in Ac₂O (0.655 mL, 6.9 mmol) and CH₂Cl₂ (30 mL), cooled to 0°C, and methyl {[(2S)-2-hydroxy-3-(tert-Butyldiphenylsilyl)propyl]oxy}acetate (2.0 g, 4.96 mmol) was added. The mixture was stirred for 6 hours, then poured into iced NaOH (10%). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated affording the title compound as an oil (2.0 g, 90%)

¹H-NMR (CDCl₃): 7.65 (4H,m); 7.42 (6H,m); 5.32 (1H,m); 4.10 (2H,m); 3.86 (2H,m); 3.74 (3H,m); 1.05 (9H,m).

STEP E: methyl {[(2R)-3-hydroxy-2-(nitrooxy)propyl]oxy}acetate
To a solution of methyl {[(2S)-2-(nitrooxy)-3-(tert-butyl-
diphenylsilyl)propyl]oxy}acetate (2.0 g, 4.47 mmol) in dry THF (30 mL) at 0°C, acetic acid (0.9 mL, 15.7 mmol) was added and a tetrabutylammonium fluoride solution (1M in THF, 13.4 mL, 14.4 mmol) was added dropwise. The mixture was stirred 4 hours at room temperature. The reaction was diluted with EtOAc (30 mL) and the organic phase was washed with NaH₂PO₄ (5%), dried over Na₂SO₄ and concentrated. The crude material was purified by silica gel chromatography (Hex/AcOEt 1:1) affording the title compound as an oil. (600 mg, 65%)

¹H-NMR (CDCl₃): 5.22 (1H,m); 4.15 (2H,m); 3.95 (2H,m); 3.86 (2H,m); 3.78 (3H,s).

STEP F: methyl {[(2R)-3-methoxy-2-(nitrooxy)propyl]oxy}acetate
To a solution of methyl {[(2R)-3-hydroxy-2-(nitrooxy)propyl]oxy}acetate (0.60 g, 2.87 mmol) in dry CH₂Cl₂ (18 mL) at 0°C, 2,6-di-tert-butyl-4-methylpyridine (2.36 g, 11.5 mmol) and MeOSO₂CF₃ (1.3 mL, 11.5 mmol) were added. The solution was stirred 30 minutes at 0°C and then irradiated by microwave for 1 hour at 80°C. The reaction was washed with NaH₂PO₄ (5%), dried over Na₂SO₄ and concentrated. The crude material was

purified by silica gel chromatography (Hex/AcOEt 8:2) affording the title compound as a oil. (520 mg, 82%).

$^1\text{H-NMR}$ (CDCl_3): 5.35 (1H,m); 4.15 (2H,s); 3.82 (2H,m); 3.75 (3H,s); 3.66 (2H,m); 3.39 (3H,s).

5

STEP G: {[(2R)-3-methoxy-2-(nitrooxy)propyl]oxy}acetic acid

To a solution of methyl {[(2R)-3-methoxy-2-(nitrooxy)propyl]oxy}acetate (0.45 g, 2.0 mmol) in acetone (13 mL), phosphate buffer (PH=8, 50 mL), water (50 mL) and pig liver esterase in ammonium sulfate suspension (0.533 mL) were added. The reaction was stirred overnight at room temperature then acidified with HCl (1N) to pH=3. It was extracted with EtOAc, dried over Na_2SO_4 and concentrated affording the title compound as an oil. (350 mg, 85%)

15 $^1\text{H-NMR}$ (CDCl_3): 5.33 (1H,m); 4.18 (2H,s); 3.85 (2H,m); 3.68 (2H,d); 3.40 (3H,s).

Example 29

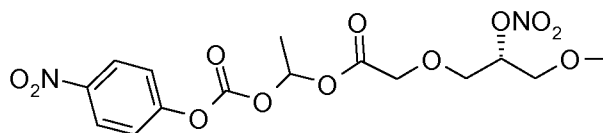
Synthesis of silver(I) (R)-2-(3-methoxy-2-(nitrooxy)propoxy)acetate

20 Title compound was synthesized following the procedure described in Example 8 except that {[(2R)-3-methoxy-2-(nitrooxy)propyl]oxy}acetic acid (prepared in Example 28) was used instead of 2,2-dimethyl-3-(nitrooxy)propanoic acid.

25 $^1\text{H-NMR}$ (DMSO): 5.40 (1H,m); 4.92 (2H,s); 3.73 (2H,m); 3.98 (2H,m); 3.26 (3H,s).

Example 30

Synthesis of 1-((4-nitrophenoxy)carbonyloxy)ethyl 2-((R)-2-hydroxy-3-methoxypropoxy)acetate



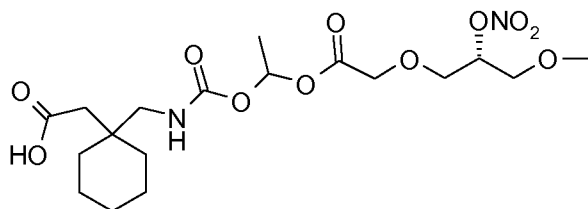
30 Starting from silver(I) (R)-2-(3-methoxy-2-(nitrooxy)propoxy)acetate (prepared in Example 29) and 1-iodoethyl 4-nitrophenyl

carbonate (obtained in Example 1), the title compound was synthesized following the procedure of Example 9.

¹H-NMR (CDCl₃): 8.30 (2H,d); 7.42 (2H,d); 6.90 (1H,m); 5.35 (1H,m); 4.29 (2H,s); 3.85 (2H,m); 3.65 (2H,m); 3.37 (3H,s); 1.65 (3H,d).

Example 31

Synthesis of 2-(1-((11R)-11-hydroxy-5-methyl-3,7-dioxo-4,6,9,13-tetraoxa-2-azatetradecyl)cyclohexyl)acetic acid (compound 23)



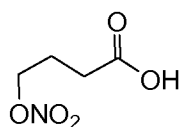
(23)

Title compound was synthesized following the procedure of Example 20, starting from compound obtained in Example 30.

¹H-NMR (CDCl₃): 6.85 (1H,m); 5.32 (2H,m); 4.12 (2H,s); 3.83 (2H,m); 3.66 (2H,m); 3.38 (3H,s); 3.25 (2H,d); 2.34 (2H,s); 1.62-1.32 (13H,m).

Example 32

Synthesis of 4-(nitrooxy)butanoic acid



STEP A: methyl 4-bromobutanoate

To a solution of 4-bromobutanoic acid (6.5 g, 38.9 mmol) in MeOH (120 ml) at 0°C under nitrogen atmosphere, thionyl chloride (2.8 ml, 38.9 mmol) was slowly added and the reaction was stirred overnight at r.t. Solvent was evaporated and the crude material was used directly in next step. (6.0 g, 85%)

¹H-NMR (CDCl₃): 3.71 (3H,s); 3.49 (2H,t J=6.44); 2.53 (2H,t J=7.16); 2.20 (2H,m).

STEP B: methyl 4-(nitrooxy)butanoate

Methyl 4-bromobutanoate (6.0 g; 33 mmol) was dissolved in CH₃CN (120 mL) and silver nitrate (14.0 g, 82.6 mmol) was added. The reaction was heated at 80°C in the dark for 4 hours. Solvent was evaporated and the crude was dissolved in EtOAc (80 ml). Precipitate was filtered off and organic phase was washed with water (2 x 100 ml) and brine (1 x 100 ml), dried over Na₂SO₄ and concentrated affording the title compound as an oil. (5.0 g, 93%)

¹H-NMR (CDCl₃): 4.54 (2H, t J=6.31); 3.73 (3H, s); 2.48 (2H, t J=7.15); 2.08 (2H, m).

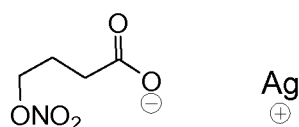
STEP C: 4-(nitrooxy)butanoic acid

Methyl 4-(nitrooxy)butanoate (10.0 g; 61.0 mmol) was dissolved in MeOH (240 mL) at 5°C and LiOH 2N (60 ml) was added. The reaction was stirred overnight at 5°C. Solution was acidified to pH 3 with HCl 1N and MeOH was evaporated. Aqueous phase was extracted with CH₂Cl₂, dried over Na₂SO₄ and concentrated affording the title compound as an oil. (7.2 g, 79%)

¹H-NMR (CDCl₃): 4.55 (2H, t J=6.30); 2.54 (2H, t); 2.10 (2H, m).

Example 33

Synthesis of silver(I) 4-(nitrooxy)butanoate



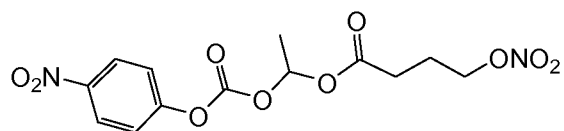
Title compound was synthesized following the procedure described in Example 8 except that 4-(nitrooxy)butanoic acid (prepared in Example 32)

was used instead of 2,2-dimethyl-3-(nitrooxy)propanoic acid.

¹H-NMR (DMSO): 4.56 (2H, t J=6.71); 2.42 (2H, t J=6.54); 2.15 (2H, m)

Example 34

Synthesis of 1-((4-nitrophenoxy)carbonyloxy)ethyl 4-(nitrooxy)butanoate

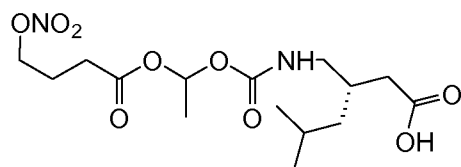


Starting from silver(I) 4-(nitrooxy)butanoate (Example 33) and 1-iodoethyl 4-nitrophenyl carbonate (obtained in Example 1), the title compound was synthesized following the procedure of Example 9.

$^1\text{H-NMR}$ (CDCl_3): 8.30 (2H, d); 7.42 (2H, d); 6.91 (1H, m); 4.55 (2H, t); 2.56 (2H, t); 2.11 (2H, m); 1.65 (3H, s).

Example 35

Synthesis of (3S)-5-methyl-3-(((1-(4-(nitrooxy)butanoyloxy)ethoxy)carbonylamino)methyl)hexanoic acid (compound 30)



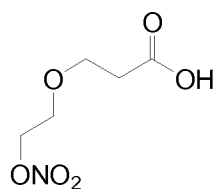
(30)

Title compound was synthesized following the procedure of Example 24 starting from compound obtained in Example 34.

$^1\text{H-NMR}$ (CDCl_3): 6.82 (1H, m); 5.05 (1H, t); 4.53 (2H, t); 3.30 (1H, m); 3.13 (1H, m); 2.50-2.39 (7H, m); 1.67 (1H, m); 1.52 (3H, d); 1.20 (2H, t); 0.91 (6H, m).

Example 36

Synthesis of 3-(2-(nitrooxy)ethoxy)propanoic acid



STEP A: 2-(but-3-en-1-yloxy)ethyl nitrate

To a solution of HNO_3 fuming (3.2 ml, 78.3 mmol) and Acetic anhydride (6.5 ml, 68.5 mmol) in dry CH_2Cl_2 (30 ml) cooled at -50°C , a solution of 2-allyloxyethanol (5.0 g, 48.9 mmol) in CH_2Cl_2 (30 ml) was added dropwise. The solution was stirred at -50°C 1.5 hours then it was allowed to reach r. t. and stirred

for 4h. The solution was then poured into ice, the two phases were separated and the organic phase was washed with brine, dried on Na_2SO_4 and concentrated. The residue was purified by flash chromatography with SP1 Biotage instrument (SNAP 100 g column, n-Hex/EtOAc 95:5, 10 CV) affording the desired product as a colourless oil (6.6 g, yield: 92%).

^1H -NMR (CDCl_3): 6.05 - 5.77 (1 H, m), 5.39-5.14 (2 H, m), 4.69 - 4.57 (2 H, m), 4.08 - 4.00 (2 H, m), 3.78 - 3.68 (2 H, m).

STEP B: 2-(3-hydroxypropoxy)ethyl nitrate

To a solution of 2-(but-3-en-1-yloxy)ethyl nitrate (6.6 g, 44.8 mmol) in dry THF (100 ml) cooled at 0 °C, 9-BBN 0.5M in THF (269 ml, 134.5 mmol) was added dropwise. The solution was stirred at r.t. overnight. Then It was cooled at 0 °C and NaOH 2M (112 ml, 224.2 mmol) and H_2O_2 30% (77 ml) were added dropwise at the same time. The solution was stirred at 0°C for 1 hour. Then It was diluted with H_2O (200 ml) and extracted with Et_2O (5x 200 ml). The combined organic phases were dried on Na_2SO_4 and concentrated affording 20 g of a clear oil. The residue was purified by flash chromatography (SP1 Biotage instrument, SNAP 340 g column, n-Hex/EtOAc from 10:90 to 20:80 in 10 CV) affording the desired product as a clear oil (1.8 g, yield: 24%).

^1H NMR (CDCl_3) : 4.63 (t, 2H), 3.86 - 3.71 (m, 4H), 3.67 (t, 2H), 1.93 - 1.81 (m, 2H).

STEP C: 3-(2-(nitrooxy)ethoxy)propanoic acid

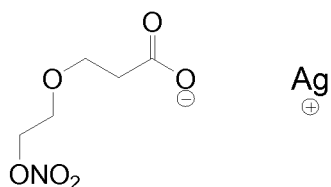
To a solution of 2-(3-hydroxypropoxy)ethyl nitrate (1.8 g, 10.9 mmol) in acetone (50 ml) cooled at 0°C, NaHCO_3 saturated solution (15 ml), NaBr (0.23 mg, 2.2 mmol), TEMPO (0.17 mg, 1.1 mmol) and tricholoisocyanuric acid (5.0 g, 21.8 mmol) were added. The mixture was stirred at r.t. for 3 hours. Then the solution was cooled at 0°C and Isopropanol (8 ml) was added dropwise. The solution was stirred at 0°C for 30 minutes. The precipitate was filterd off and the solution concentrated. The

residue was diluted with NaOH 2N (100 ml) and washed with EtOAc (2X50 ml). The aqueous phase was acidified with HCl conc. until pH=2 and extracted with EtOAc (5X 30 ml). The combined organic phases were dried on Na₂SO₄ and concentrated
 5 affording the desired product as a clear oil (1.7 g, yield: 89%).

¹H NMR (CDCl₃): 4.70 – 4.56 (m, 2H), 3.86 – 3.73 (m, 4H), 2.66 (t, 2H).

Example 37

10 Synthesis of silver(I) 3-(2-(nitrooxy)ethoxy)propanoate



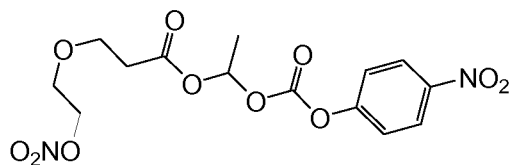
Title compound was synthesized following the procedure described in Example 8 except that 3-(2-(nitrooxy)ethoxy)propanoic acid (prepared in Example 36)

15 was used instead of 2,2-dimethyl-3-(nitrooxy)propanoic acid.

¹H NMR (DMSO): 4.71 – 4.55 (m, 2H), 3.76 – 3.53 (m, 4H), 2.36 (t, 2H).

Example 38

20 Synthesis of 1-((4-nitrophenoxy)carbonyloxy)ethyl 3-(2-(nitrooxy)ethoxy)propanoate

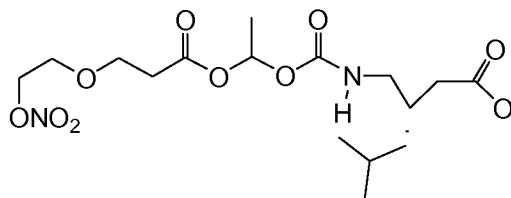


Starting from silver(I) 3-(2-(nitrooxy)ethoxy)propanoate (Example 37) and 1-iodoethyl 4-nitrophenyl carbonate (obtained in Example 1), the title compound was synthesized following
 25 the procedure of Example 9.

¹H NMR (CDCl₃): 8.40 – 8.22 (m, 2H), 7.53 – 7.34 (m, 2H), 6.98 – 6.80 (m, 1H), 4.60 (t, 2H), 3.90 – 3.70 (m, 4H), 2.68 (t, 2H), 1.74 – 1.59 (m, 3H).

Example 39

Synthesis of (13S)-13-isobutyl-8-methyl-1-(nitrooxy)-6,10-dioxo-3,7,9-trioxa-11-azapentadecan-15-oic acid (compound 16)



5 (16)

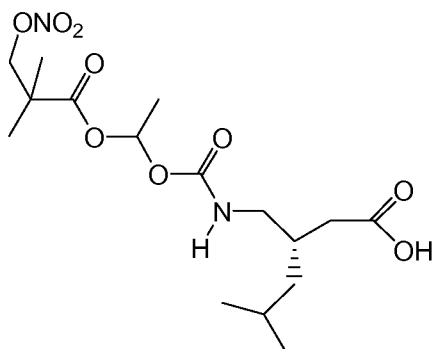
Title compound was synthesized following the procedure of Example 24 starting from compound obtained in Example 38.

¹H NMR (CDCl₃): 6.93 - 6.76 (m, 1H), 5.17 - 4.97 (m, 1H), 4.62 (t, 2H), 3.85-3.68 (m, 4H), 3.41-3.21 (m, 1H), 3.21 - 3.01 (m, 1H), 2.59 (t, 2H), 2.46 - 2.05 (m, 3H), 1.79 - 1.57 (m, 1H), 1.50 (d, 3H), 1.19 (t, 2H), 1.0-0.8 (t, 6H).

Example 40

Synthesis of (3S)-3-(((1-(2,2-dimethyl-3-(nitrooxy)propanoyl oxy)ethoxy)carbonylamino)methyl)-5-methylhexanoic acid

15 (compound 2)



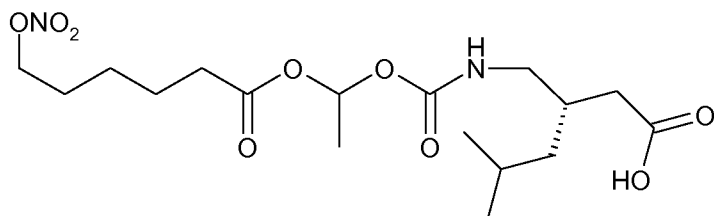
(2)

Title compound was synthesized following the procedure of Example 24 starting from compound obtained in Example 9.

20 ¹H NMR (CDCl₃): 6.88- 6.67 (m, 1H), 5.14- 4.88 (m, 1H), 4.60- 4.37 (m, 2H), 3.45 - 2.87 (m, 2H), 2.46 - 2.03 (m, 3H), 1.78- 1.56 (m, 1H), 1.48 (d, 3H), 1.24 - 1.08 (m, 2H), 1.01-0.76 (t, 6H).

Example 41

Synthesis of (3S)-5-methyl-3-(((1-(6-(nitrooxy)hexanoyloxy)ethoxy)carbonylamino)methyl)hexanoic acid (compound 4)



(4)

5 Title compound was synthesized following the procedure of Example 24 starting from compound obtained in Example 11.

^1H NMR (CDCl_3): 6.80 (1H, m); 5.03 (1H, m); 4.46 (2H, t); 3.29 (1H, m); 3.17 (1H, m); 2.37-2.11 (5H, m); 1.70 (5H, m); 1.47 (5H, m); 1.19 (2H, m); 0.92 (6H, m).

10

Example 42

Evaluation of the efficacy of the compounds in a Mouse Chronic Constriction Injury Model (CCI model)

Test compounds:

15 Compound 12 (prepared according to example 23): 71 mg Kg^{-1} = 0.175 mmol Kg^{-1}

Gabapentin (reference compound): 30 mg Kg^{-1} = 0.175 mmol Kg^{-1}

General Procedure and surgery

24 Male C57/black mice weighting 25-28 g caged with free access to food and water under 12h light/dark cycles were used. Experiments were carried out according to the Declaration of Helsinki and internally approved animal care protocols. Efforts were made to minimize animal suffering.

25 The method described by Bennet and Xie was generally followed (1988). Mice were anesthetized by tribromoethanol at the dose of 400 mg kg^{-1} . The right common sciatic nerve was exposed at the level of the middle of the thigh by blunt dissection through the biceps femoris. Proximal to the sciatic nerve trifurcation, about 6 mm of the nerve was freed of adhering tissue and 3 ligatures (7/0 silk suture) were tied loosely

30

around it with about 1 mm spacing. Ligatures were tied such that the diameter of the nerve was only barely constricted. The incision was closed in layers (3/0 silk suture).

The experiment was carried out 10 days after surgery.

5 Reference gabapentin (Sigma Chemicals St Louis, MO, USA) and compound 12 were administered to 8 mice at the indicated doses dissolved in a vehicle containing PEG400: water (70:30) by oral gavage, and a group of 8 mice was administered with the vehicle (PEG400: water (70:30), 5 ml/kg). 1 hour after the
10 treatment the thermal hyperalgesia test was performed on the three groups of mice.

Thermal Hyperalgesia Assessment.

Thermal hyperalgesia to radiant heat was assessed using the Plantar analgesia meter with the heated glass provided by 2B-
15 Biological system (Besozzo, Varese, Italy). Mice are individually placed in a closed transparent plastic box (5 x 5 x 4 cm) on a glass heated floor which is taken 20 cm over the experimental table and with the help of a small mirror, an infrared heat source is positioned under the plantar surface
20 of the animal hind paw.

The animal paws are tested alternatively with at least 5 minutes interval between consecutive measurements.

The withdrawal latency that is the time taken by the mice to remove or shake its hind paw from the heat source was
25 detected.

Results

The results reported in Table I as delta withdrawal latency (sec) versus basal value (taken before treatment) showed that compound 12 is more efficacious than gabapentin in reversing
30 established pain behavior.

Table I: Thermal Hyperalgesia Assessment in a mouse CCI model		
Treatment	Dose (mg)	1h post-treat (delta vs basal) (sec)
Vehicle	-	-0.50 ± 0.40
Gabapentin	30	1.04 ± 0.49
Compound 12	71	2.97 ± 0.48

Example 43**Evaluation of the efficacy of the compounds in a mouse STZ-induced neuropathic pain model (chronic treatment)**

5 The streptozotocin (STZ)-induced diabetic mice is the most commonly employed animal model used to study mechanisms of painful diabetic neuropathy and to evaluate potential therapies.

10 Mice develop tactile allodynia to stimulation of the plantar surface of the hindpaw with von Frey filaments within 20 days of streptozotocin-induced diabetes.

Tactile allodynia is a common type of pain in painful diabetic neuropathy patients.

Test compounds:

15 Compound 12 (disclosed in example 23): 71 mg Kg⁻¹ = 0.175 mmoli Kg⁻¹

Gabapentin (reference compound): 30 mg Kg⁻¹ = 0.175 mmoli Kg⁻¹

General Procedure

56 Male C57/black mice weighting 25-28 g caged with free access to food and water under 12h light/dark cycles were used. Experiments were carried out according to the Declaration of Helsinki and internally approved animal care protocols. Efforts were made to minimize animal suffering.

Diabetes was induced by the intraperitoneal injection of streptozotocin (STZ) at 120 mg kg⁻¹. Two days later the animals were fasted for 12h and diabetes confirmed by measuring glucose concentration in blood samples obtained by
5 tail prick using a glucose oxidase-impregnated test strips (OneTouch® Ultra2®, LifeScan, CA, USA).

Only STZ-injected animals with glucose concentration above 300 mg dl⁻¹ were considered diabetic and included in further compound testing. Hyperglycaemia was also confirmed at the
10 time of behavioral testing.

After 1 week of the single i.p. injection of STZ mice were divided in three groups and Gabapentin and compound 12 were administered daily, for 21 days consecutively, to 2 groups of mice at 0.175 mmoli kg⁻¹ dissolved in a vehicle made with
15 phosphate buffer at pH 7 by oral gavage, and a group of mice was administered with the vehicle (phosphate buffer at pH 7). 24 hours after the last treatment the tactile allodynia in the three groups of mice was evaluated as below reported.

Tactile Allodynia Assessment.

20 A standardized testing procedure modified for mice was performed to address tactile allodynia (Chaplan SR, Bach FW, Pogrel JW, Chung JM, Yaksh TL, J Neurosci Methods. (1994), 53: 55-63.). Mice were transferred to the testing cage with a wire mesh bottom and allowed to acclimatize for 60 min.

25 Tactile allodynia was assessed by recording the pressure at which the affected paw was withdrawn from graded stimuli (Von Frey monofilaments bending force from 0.02 to 3.6 g) applied perpendicularly to the plantar surface of the paw.

These filaments were used to determine the 50% mechanical
30 threshold using the up and down method previously described by Chaplan SR, Bach FW, Pogrel JW, Chung JM, Yaksh TL, J Neurosci Methods. (1994), 53: 55-63. With an algorithm, using the response of the animal to the different filaments, the

threshold at which the animal withdraws the paw the 50% of the times is calculated.

All behavioral testing were performed by investigators blind to the treatments.

5 Results are expressed as median of the 50% mechanical threshold (g).

The results reported in Table II, show that diabetes induced a profound allodynic effects (see vehicle value). This study showed that after chronic administration only Compound 12 is
10 efficacious in counteracting the development of tactile allodynia in a model of neuropathic pain.

Table II: Tactile Allodynia Assessment in a mouse STZ-induced neuropathic pain model		
Treatment	Dose (mg)	24h post-treatment 50% mechanical threshold (median g)
Naive	-	2.00
Vehicle	-	0.25
Gabapentin	30	0.20
Compound 12	71	1.02

Example 44

15 **Evaluation of the efficacy of the compounds in a Rat Spinal Nerve Ligation Model (SNL model)**

Test compounds:

Compound 12 (prepared according to example 23): $71 \text{ mg Kg}^{-1} = 0.175 \text{ mmoli Kg}^{-1}$

20 Gabapentin (reference compound): $30 \text{ mg Kg}^{-1} = 0.175 \text{ mmoli Kg}^{-1}$

General Procedure and surgery

34 Male Sprague-Dawley rats weighting 150-200g caged with free access to food and water under 12h light/dark cycles were used. Experiments were carried out according to the
5 Declaration of Helsinki and internally approved animal care protocols. Efforts were made to minimize animal suffering.

The method described by Kim and Chung (1992, *Pain*. 50(3): 355-363) was generally followed. Rats were anesthetized by chloral hydrate at the dose of 400 mg kg⁻¹. Briefly, neuropathic injury
10 was produced by tightly ligating the right L5 and L6 spinal nerves.

The experiment was than carried out 14 days after surgery.

Reference gabapentin (Sigma Chemicals St Louis, MO, USA) and compound 12 were administered to 10-12 rats at the indicated
15 doses dissolved in a vehicle containing PEG400: water (70:30) by oral gavage, and a group of 12 rats was administered with the vehicle (PEG400: water (70:30), 5 ml/kg). 2 hour after the treatment the mechanical sensitivity was measured to the three groups of rats.

20 Mechanical allodynia Assessment.

A standardized testing procedure was performed to address tactile allodynia (Chaplan et al., *J Neurosci Methods*. 53: 55-63, 1994). Briefly, rats were transferred to the testing cage with a wire mesh bottom and allowed to acclimatize for 60 min.

25 Von Frey monofilaments (Stoelting, Wood Dale IL, bending force from 0.15 to 15 g applied using a single, steady > 1s application) were used to determine the 50% mechanical threshold for foot withdrawal using the up and down method previously described by Chaplan et al., 1994. All behavioral
30 testing were performed by investigators blind to the treatments.

Results

The results reported in Table III as 50% mechanical threshold (g) taken 2h post-treatment showed that compound 12 is more efficacious than gabapentin in reversing established pain behavior.

Table III: Mechanical Allodynia Assessment in a Rat SNL model		
Treatment	Dose (mg/Kg)	2h post-treat (50% mechanical threshold) (g)
Vehicle	-	4.43 ± 1.85
Gabapentin	30	3.83 ± 1.20
Compound 12	71	10.67 ± 2.20

Example 45

Evaluation of the efficacy of the compounds in the Mouse Formalin test

Test compounds:

Compound 12 (prepared according to example 23): $71 \text{ mg Kg}^{-1} = 0.175 \text{ mmoli Kg}^{-1}$

Gabapentin (reference compound): $30 \text{ mg Kg}^{-1} = 0.175 \text{ mmoli Kg}^{-1}$

Compound 30 (prepared according to example 35): $23.76 \text{ mg Kg}^{-1} = 0.0628 \text{ mmoli Kg}^{-1}$

Pregabalin (reference compound): $10 \text{ mg Kg}^{-1} = 0.0628 \text{ mmoli Kg}^{-1}$

General Procedure

39 Male C57/black mice weighting 25-28 g caged with free access to food and water under 12h light/dark cycles were used. Experiments were carried out according to the Declaration of Helsinki and internally approved animal care protocols. Efforts were made to minimize animal suffering. Mice were habituated in the test environment for 30 minutes and the behavioral testing was performed in a blinded manner.

Reference gabapentin and pregabalin (Sigma Chemicals St Louis, MO, USA) and compound 12/30 were administered to 6-9 mice at the indicated doses dissolved in a vehicle containing PEG400: water (70:30) by oral gavage, and a group of 8 mice was administered with the vehicle (PEG400: water (70:30), 5 ml/kg). 30 minutes after the treatment a solution of formalin (20 μ l at 1.5%) was injected subcutaneously into the dorsal surface of the right hindpaw using an Hamilton syringe with a 26-gauge needle. The efficacy of the compounds in formalin-evoked spontaneous inflammatory pain was assessed by measuring the time (in seconds) spent licking and flinching the affected paw every 5 minutes for 30 minutes, starting from 15 minutes till to 45 minutes after formalin injection (second phase of the test). The efficacy of the compounds assessed in the second phase of the test is an evaluation of their efficacy in chronic pain.

Results

The results reported in Table IV show that compound 12 and compound 30 were more efficacious than gabapentin and pregabalin respectively.

Table IV: Evaluation of the efficacy of the compounds in the Mouse Formalin test		
Treatment	Dose (mg/Kg)	time spent licking/flinching the paw (sec)
Vehicle	-	417.0 $\pm$ 45.7
Gabapentin	30	301.0 $\pm$ 36.6
Compound 12	71	195.4 $\pm$ 30.1
Pregabalin	10	387.3 $\pm$ 36.7
Compound 30	24	196.8 $\pm$ 48.4

Example 46

Evaluation of the efficacy of the compounds on allodynic response in streptozotocin (STZ)-treated diabetic mice.

5 Test compounds:

Compound 30 (prepared according to example 35): 23.76 mg Kg^{-1}
 $= 0.0628 \text{ mmoli Kg}^{-1}$

Compound 16 (prepared according to Example 39) $25.65 \text{ mg Kg}^{-1} =$
 $0.0628 \text{ mmoli Kg}^{-1}$ (single dose)

10 Compound Pregabalin (reference compound): $10 \text{ mg Kg}^{-1} = 0.0628$
 mmoli Kg^{-1} (single dose)

General procedure

Male CD1 mice, weighting 25-35 g were used. Animals were kept under standard conditions of temperature (21-22°C) and
15 illumination (12:12-h light/darkness) and allowed to adjust to this environment in cages with mesh bottoms with free access to tap water and food for at least 7 days before the experiment began. All experiments were performed to minimize animal suffering and in accordance with approved protocols.

20 Diabetes was induced by injecting 200 mg/kg i.p. of streptozotocin (STZ). Blood glucose levels were assessed from the 2nd day until the end of the experiment using an Accu-Chek blood glucose monitoring system. Only animals reaching glucose plasma levels above 200mg/dl within 24-48 h post-STZ-injection
25 were included in the following behavioral experiments which started 14 days after the STZ treatment.

Paw withdrawal threshold (PWT) was determined using the Dynamic Plantar Aesthesiometer (Ugo Basile, Italy), an apparatus that generates a mechanical force linearly
30 increasing with time. More specifically, mice were placed individually in plastic cages with a wire mesh bottom and allowed to acclimatize for at least 2 h. Increasing mechanical stimulation (0.25 g/s, cut-off force: 10 g) was applied to the

plantar surface of a hind paw so to address the respective nociceptive threshold which is defined as the force, in grams, at which the mouse withdraw its paw. When a withdrawal response occurred, the stimulus was terminated and the response threshold electronically determined.

Results

The effects of test compounds were assayed following an acute challenge at the indicated dose by addressing the allodynic threshold at 30, 60, 90, 120 min time points after the oral treatment.

Compound 30 and compound 16 showed a better efficacy than reference compound pregabalin in this test as indicated by the greater mechanical threshold reached by both compounds at all time-points. (Table V)

Table V Acute anti-allodynic effect in mice with STZ-induced diabetes					
Compound	Paw withdrawal threshold (g)				
	Pre	30 min	60 min	90 min	120 min
Vehicle	1.1 ± 0.1	1.5 ± 0.1	2.0 ± 0.3	2.5 ± 0.3	2.5 ± 0.3
Pregabalin	1.1 ± 0.2	2.5 ± 0.3	3.2 ± 0.1	2.9 ± 0.2	2.5 ± 0.3
Compound 30	1.2 ± 0.1	3.5 ± 0.3	3.8 ± 0.5	3.9 ± 0.2	3.2 ± 0.3
Compound 16	1.2 ± 0.1	2.7 ± 0.3	4.7 ± 0.3	4.9 ± 0.3	3.4 ± 0.2

Example 47

Evaluation of the efficacy of the compounds after repeated daily treatment on allodynic response in streptozotocin (STZ)-treated diabetic mice.

5 Test compounds

Compound 12 (prepared according to example 23): $71 \text{ mg Kg}^{-1} = 0.175 \text{ mmoli Kg}^{-1}$ (repeated daily oral treatment)

Gabapentin (reference compound): $30 \text{ mg Kg}^{-1} = 0.175 \text{ mmoli Kg}^{-1}$ (repeated daily oral treatment)

10 General Procedure

Male CD1 mice, weighting 25-35 g were used. Animals were kept under standard conditions of temperature (21-22°C) and illumination (12:12-h light/darkness) and allowed to adjust to this environment in cages with mesh bottoms with free access to tap water and food for at least 7 days before the experiment began. All experiments were performed to minimize animal suffering and in accordance with approved protocols.

Diabetes was induced by injecting 200 mg/kg i.p. of streptozotocin (STZ). Blood glucose levels were assessed from the 2nd day until the end of the experiment using an Accu-Chek blood glucose monitoring system. Only animals reaching glucose plasma levels above 200mg/dl within 24-48 h post-STZ-injection were included in the following behavioral experiments which started 14 days after the STZ treatment.

Paw withdrawal threshold (PWT) was determined using the Dynamic Plantar Aesthesiometer (Ugo Basile, Italy), an apparatus that generates a mechanical force linearly increasing with time. More specifically, mice were placed individually in plastic cages with a wire mesh bottom and allowed to acclimatize for at least 2 h. Increasing mechanical stimulation (0.25 g/s, cut-off force: 10 g) was applied to the plantar surface of a hind paw so to address the respective nociceptive threshold which is defined as the force, in grams,

at which the mouse withdraw its paw. When a withdrawal response occurred, the stimulus was terminated and the response threshold electronically determined.

Results

5 The effects of the test compounds were assayed by addressing the allodynic threshold 18-24 h after the last repeated (1- 2- or 3-week) daily oral treatment.

The results reported in Table VI showed that the animals treated daily for 1, 2, or 3 weeks with compound 12 developed
10 significantly less mechanical allodynia than animals received vehicle or gabapentin with similar treatment schedule.

These data suggest that compound 12 is more efficacious in hampering the development of pain sensitization in hyperglycemic conditions.

15

Table VI:

Mechanical allodynia 18 h following 1, 2, or 3-week daily treatment in mice with STZ-induced diabetes

Treatment	Paw withdrawal threshold (g)		
	1-week	2-week	3-week
Vehicle	1.7 ± 0.1	1.5 ± 0.1	1.3 ± 0.1
Gabapentin	2.0 ± 0.1	1.9 ± 0.3	1.9 ± 0.2
Compound 12	3.2 ± 0.2*	3.8 ± 0.2*	4.1 ± 0.2*

Example 48

Measure of Pharmacokinetic parameters

This study investigated the bioavailability following oral
20 administration of a compound of the present invention and of a compound disclosed by WO 2004/054965 (compound XVA).

Test compounds:

- Compound 12 (disclosed in example 23)

- 1[4-(nitrooxymethyl)benzoylaminomethyl]cyclohexanacetic acid (compound (XVA) of WO 2004/054965 disclosed in example 1 of WO 2004/054965) (comparative compound)

The integral of the plasma concentration of the test compounds versus an interval of definite time were calculated (AUC)

Significant difference was obtained in the calculated areas under the curve (AUC) of the two compounds, showing that compound (XVA) exhibits poor oral absorption (AUC is 0.358 $\mu\text{g}/\mu\text{L}/\text{min}$) whereas compound 12 is rapidly absorbed from the gastrointestinal tract (AUC is 1.853 $\mu\text{g}/\mu\text{L} \cdot \text{min}$) and it has a good bioavailability.

Pharmacokinetic assessments were performed in blood samples withdrawn intracardially from anesthetized mice (chloral hydrate 380 mg kg^{-1} , ip from Sigma Chemicals, St Louis, MO, USA) at the 5, 15, 30, 60, 120, 240 and 360 time points after oral administration of 71 mg Kg^{-1} (0.175 mmol kg^{-1}) of compound 12 and of 61 mg Kg^{-1} (0.174 mmol kg^{-1}) of compound (XVA). Animals were sacrificed thereafter.

Blood samples were added with eparine to avoid coagulation then blood samples were quenched with methanol to prevent further conversion and analyzed immediately by a sensitive and specific LC/MS/MS method for simultaneous determination of gabapentin, gabapentin lactam and the above reported test compounds.

The plasma levels of compound 12 was evaluated on the basis of the plasma levels of gabapentin because compound 12 forms rapidly gabapentin.

Method for simultaneous determination of gabapentin, gabapentin lactam and the test compounds

The system was an Acquity UPLC (Waters, Milford, MA). The detector was a Quattro microTM API LC/MS/MS (Waters, Milford, MA).

The analytical conditions were:

Column: ACQUITY BEH Phenyl 50 x 2.1 mm (5µm) @ 40°C

Mobile Phase: A. water + 0.1% formic acid; B. methanol + 0.1% formic acid

Flow Rate: 0.5mL/min

5 Gradient profile

	Time (min)	A(%) / B(%)
	0.0	95/5
	1.0	95/5
	2.0	0/100
10	3.0	0/100
	3.2	95/5

Injection Volume: 2µL

Detector Wavelength: 210nm

MRM transitions (Multiple Reaction Monitoring) were m/z 172.10
15 → 137.00 for gabapentin, m/z 154.30 → 94.00 for gabapentin lactam and m/z 350.90 → 180.15 for compound (XVA).

The raw data (average peak area at each time point) were interpolated using Quanlynx v4.1 software to obtain the concentration of compound (XVA), gabapentin and gabapentin
20 lactam at each time point.

The results showed that compound (XVA) does not form gabapentin and only a little amount of gabapentin lactam (under quantification limit of 1µM) was observed at all time points.

25 Compound 12 forms rapidly gabapentin (within 5 minute after administration) and formation of gabapentin lactam was not observed.

The calculated total AUC of compound (XVA) is 0.358 µg/µL/min.

The calculated total AUC of compound 12 is 1.853 µg/µL/min.

30 **Example 49**

Evaluations of Rat and human plasma stabilities

In this study the plasma stability of some compounds of the invention and of a compound of the prior art were evaluated.

Test compounds:

- Compound 12 (disclosed in example 23)
- Compound 7 (disclosed in example 22)
- 1-(aminomethyl)cyclohexanecetic acid 3-(nitrooxymethyl)phenyl (compound XVI of WO03/000642, disclosed in example 3 of WO 03/000642) (comparative compound)

The stability of drug candidates is an important parameter, which strongly can influence the *in vivo* efficacy. In particular it is known that gabapentin lactam, that is a degradation product of gabapentin, is toxic and the specification for the maximum allowable limit for lactam is 0.5% in any dosage form.

The data reported in Table III show that compound XVI undergoes a fast degradation via intramolecular cyclization to 3,3-pentamethylene-4-butyrolactam (gabapentin lactam), the half-life ($t_{1/2}$) of compound (XVI) is less than 5 minutes in both matrix (rat and human plasma) and the only metabolite is gabapentin lactam.

Whereas the half-life of compounds 12 and 7 after incubation in human plasma is about 30 minutes and no gabapentin lactam formation was observed.

Example 50

Rat and human liver stabilities methods

A calibration curve (CC) for test compounds 12, 7 and (XVI), for gabapentin and for gabapentin-lactam in both human and rat plasma was prepared in the range 1 - 100 μ M.

Working solutions (WS) of test compounds in DMSO and of gabapentin and gabapentin-lactam in water were prepared by serial dilution of 10 mM stock solutions to the following final concentrations:

<u>WS</u> (μ M)	500	/	250	/	100	/	50	/	25	/	10	/	5
----------------------	-----	---	-----	---	-----	---	----	---	----	---	----	---	---

1 mL of human or rat plasma were protein precipitated using 10 mL of methanol; 550 μ L of each deproteinized matrix were spiked with 10 μ L of each working solution to create a

calibration curve for each analyte in each matrix to the following final nominal concentrations:

CC (μM) 100 / 50 / 20 / 10 / 5 / 2 / 1

990μL of plasma at 37°C were spiked with 10μL of a 1 mM
5 solution of test compound in DMSO. At each time point (5, 10,
15, 30 and 60 min), 50μL of the test solution were protein
precipitated in duplicate using 500μL of acetonitrile, vortex
mixed and centrifuged 10 minutes at 4°C at 4000 rpm. The
supernatant was transferred to a clean plate together with all
10 the calibration curves and injected onto a UPLC-UV system.
Analytical conditions were as follows:

Column: ACQUITY BEH Phenyl 50 x 2.1 mm (5μm) at 40°C

Mobile Phase: A. water + 0.1% formic acid; B. methanol + 0.1%
formic acid

15 Flow Rate: 0.5mL/min

Gradient profile

Time (min) A(%) / B(%)

0.0	95/5
1.0	95/5
20 2.0	0/100
3.0	0/100
3.2	95/5

Injection Volume: 2μL

Detector Wavelength: 210nm

25 MRM transitions (Multiple Reaction Monitoring) were:

m/z 172.10 → 137.00 for gabapentin,

m/z 154.30 → 94.00 for gabapentin lactam

m/z 322.95 → 276.25 for compound (XVI)

m/z 429.1 → 323.0 for compound 12

30 m/z 427.0 → 337.9 for compound 7

The raw data (average peak area at each time point) were
interpolated using Quanlynx v4.1 software to obtain the
concentration of test compounds, gabapentin and gabapentin
lactam at each time points. The extrapolated concentrations

were used to calculate the half-life ($t_{1/2}$) of compound in each matrix and they are reported in Table VII.

Table VII: Plasma half -life ($t_{1/2}$)			
Compound	$t_{1/2}$ (min)		Gabapentin lactam formation
	RAT	HUMAN	
Compound (XVI)	<5	<5	Yes
Compound 7	45	32	No
Compound 12	<5	32.2	No

5 Example 51

Measure of Pharmacokinetic parameters in Rat

In this study the bioavailability following oral administration in rats of a compound of the present invention and of gabapentin as reference compound were investigated.

10 Test compounds:

Test compounds

Compound 12 (prepared according to example 23): $71 \text{ mg Kg}^{-1} = 0.175 \text{ mmoli Kg}^{-1}$

Gabapentin (reference compound): $30 \text{ mg Kg}^{-1} = 0.175 \text{ mmoli Kg}^{-1}$

15 General procedure

Male Wistar rats (Harlan, Concorezzo, Italy) underwent permanent cannulation of the jugular vein to sample blood. The second day after surgery, animals were fasted overnight and in the morning they were treated with gabapentin (30 mg Kg^{-1} , equal to $0.175 \text{ mmoli Kg}^{-1}$) or compound 12 (71 mg Kg^{-1} equal to $0.175 \text{ mmoli Kg}^{-1}$).

A dosing regimen of 5 ml/kg (by gavage) was adopted.

At each time point (0.08, 0.25, 0.5, 1, 2, 4, and 6 hrs), 100 μ l of blood were taken from the cannula and treated as described below. Animals were then sacrificed by a lethal injection (Pentothal).

Blood samples were added with eparine to avoid coagulation then blood samples were quenched with methanol to prevent further conversion and analyzed immediately by a sensitive and specific LC/MS/MS method for simultaneous determination of gabapentin, gabapentin lactam and the above reported test compounds.

The plasma levels of compound 12 was evaluated on the basis of the plasma levels of gabapentin because compound 12 forms rapidly gabapentin.

10 **Results**

The integral of the plasma concentration of the test compounds versus an interval of definite time were calculated (AUC)

Significant differences were obtained in the calculated areas under the curve (AUC) of the two compounds, showing that compound 12 is rapidly absorbed from the gastrointestinal tract (AUC is 3689 $\mu\text{g}/\mu\text{L}\cdot\text{min}$) and it has a good bioavailability.

20 **Method for simultaneous determination of gabapentin, gabapentin lactam and the test compounds**

The system was an Acquity UPLC (Waters, Milford, MA). The detector was a Quattro microTM API LC/MS/MS (Waters, Milford, MA).

The analytical conditions were:

25 Column: ACQUITY BEH Phenyl 50 x 2.1 mm (5 μm) @ 40°C

Mobile Phase: A. water + 0.1% formic acid; B. methanol + 0.1% formic acid

Flow Rate: 0.5mL/min

Gradient profile

30	Time (min)	A(%) / B(%)
	0.0	95/5
	1.0	95/5
	2.0	0/100
	3.0	0/100
35	3.2	95/5

Injection Volume: 2 μ L

MRM transitions (Multiple Reaction Monitoring) in ESI positive mode were m/z 172.10 $\rightarrow$ 137.00 for gabapentin, m/z 154.04 $\rightarrow$ 94.78 for gabapentin lactam and m/z 429.10 $\rightarrow$ 323.00 for

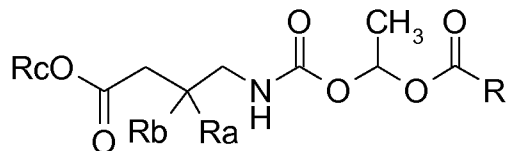
5 compound 12

The raw data (average peak area at each time point) were interpolated using Quanlynx v4.1 software to obtain the concentration of compound 12, gabapentin and gabapentin lactam at each time point.

10 Compound 12 forms gabapentin ($T_{\max}$ 240 minute) and the calculated total AUC of compound 12 is 3689 μ g/ μ L*min.

Claims

1. A compound of formula (I) or salts or stereoisomers thereof

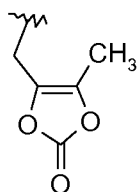


5

(I)

wherein

Rc is a hydrogen, or

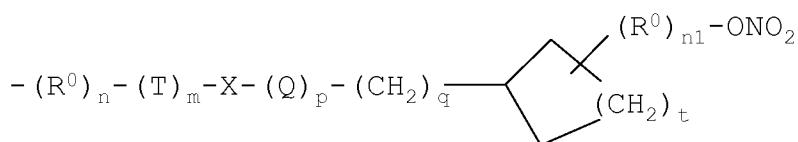


or Rc is pharmaceutically acceptable cation;

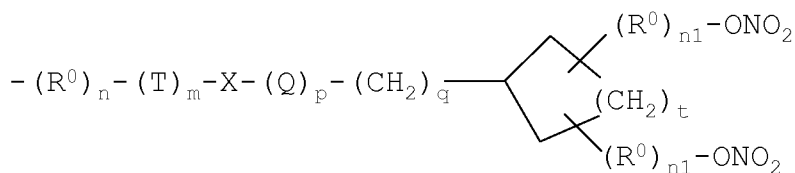
10 Ra is hydrogen and Rb is $(\text{CH}_3)_2\text{CHCH}_2-$, or Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl;

R is selected from the group consisting of:

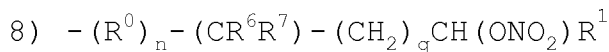
- 1) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)\text{R}^1$,
- 15 2) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)-\text{CH}(\text{ONO}_2)\text{R}^{1a}$
- 3) $-(\text{R}^0)_n-(\text{T})_m-\text{X}-(\text{Q})_p-(\text{CH}_2)_q-\text{CH}(\text{ONO}_2)\text{R}^1$,
- 4) $-(\text{R}^0)_n-(\text{T})_m-\text{X}-(\text{Q})_p-(\text{CH}_2)_q-\text{CH}(\text{ONO}_2)\text{CH}(\text{ONO}_2)\text{R}^{1a}$,
- 5) 5)



20 6)



- 7) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)-(\text{CH}_2)_{q1}-\text{X}-(\text{CH}_2)_{q2}-\text{CH}(\text{ONO}_2)\text{R}^1$



wherein

n is 0 or 1;

m is 0 or 1;

5 p is 0 or 1;

n1 is 0 or 1;

q is an integer from 0 to 10;

q1 is an integer from 1 to 10;

q2 is an integer from 1 to 10;

10 t is an is an integer from 1 to 4;

R^0 is a straight or branched C_1 - C_{10} alkylene;

R^1 is selected from hydrogen, a straight or branched C_1 - C_4 alkyl, $-(CH_2)OCH_3$;

R^{1a} is hydrogen or a straight or branched C_1 - C_4 alkyl;

15 X is selected from an oxygen atom, $-NH-$, $-N(CH_3)-$ or a covalent bond;

T and Q are $-CR^2R^3-$, wherein R^2 and R^3 at each occurrence are independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, OR^4 , NHR^5 ;

20 R^4 is hydrogen or C_1 - C_4 linear or branched alkyl;

R^5 is hydrogen, C_1 - C_4 linear or branched alkyl, $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$;

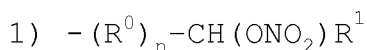
R^6 is hydrogen or C_1 - C_4 linear or branched alkyl;

R^7 is $(CH_2)_q CH(ONO_2)R^1$ wherein q and R^1 are as above defined.

25

2. A compound according to claim 1 wherein R_c is a hydrogen, or a pharmaceutically acceptable cation;

R is



30 wherein

n is 0 or 1

R^0 is a straight or branched C_1 - C_6 alkylene,

R^1 is hydrogen, $-CH_3$, $-(CH_2)OCH_3$, or $-CH(CH_3)_2$.

3. A compound according to claim 2 wherein R^0 is $-C(CH_3)_2-$ or $-C(CH_3)_2-CH_2-$.

5

4. A compound according to claim 1 R_c is a hydrogen, or a pharmaceutically acceptable cation;

R is

3) $-(R^0)_n-(T)_m-X-(Q)_p-(CH_2)_q-CH(ONO_2)R^1$

10 wherein

n is 0 or 1

m is 1

p is 1

q is from 0 to 6;

15 R^0 is a straight or branched C_1 - C_6 alkylene;

R^1 is hydrogen, $-CH_3$, $-(CH_2)OCH_3$, or $-CH(CH_3)_2$;

X is oxygen;

T and Q are $-CR^2R^3-$, wherein R^2 and R^3 are hydrogen.

20 **5.** A compound according to claim 4 wherein R^0 is $-C(CH_3)_2-$ or $-C(CH_3)_2-CH_2-$;

6. A compound according to claim 1 wherein R_c is a hydrogen, or a pharmaceutically acceptable cation;

25 R is

3) $-(R^0)_n-(T)_m-X-(Q)_p-(CH_2)_q-CH(ONO_2)R^1$

wherein

n is 0 or 1;

m is 0;

30 p is 1;

q is from 0 to 6;

R^0 is a straight or branched C_1 - C_6 alkylene;

R^1 is hydrogen, $-CH_3$, $-(CH_2)OCH_3$, or $-CH(CH_3)_2$;

X is a covalent bond;

Q is $-CR^2R^3-$, wherein R^2 is hydrogen and R^3 is NHR^5 wherein R^5 is $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$.

5

7. A compound according to claim 1 wherein Rc is a hydrogen, or a pharmaceutically acceptable cation,

R is

2) $-(R^0)_n-CH(ONO_2)-CH(ONO_2)R^{1a}$

10 wherein

n is 1;

R^0 is a straight or branched C_1 - C_{10} alkylene;

R^{1a} is hydrogen or $-CH_3$.

15 **8.** A compound according to claim 1 wherein Rc is a hydrogen, or a pharmaceutically acceptable cation,

R is

4) $-(R^0)_n-(T)_m-X-(Q)_p-(CH_2)_q-CH(ONO_2)CH(ONO_2)R^{1a}$,

wherein

20 n is 0 or 1;

m is 1;

p is 1;

q is from 0 to 6;

R^0 is a straight or branched C_1 - C_6 alkylene;

25 X is oxygen;

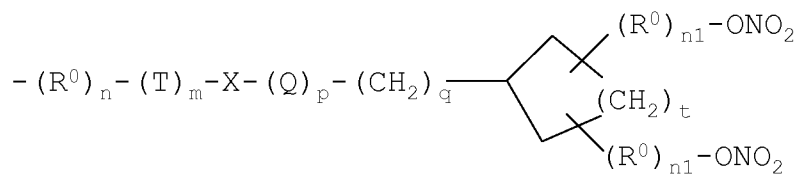
T and Q are $-CR^2R^3-$, wherein R^2 and R^3 are hydrogen;

R^{1a} is hydrogen or $-CH_3$.

30 **9.** A compound according to claim 1 wherein Rc is a hydrogen, or a pharmaceutically acceptable cation,

R is

6)



wherein

n is 0;

m is 0;

5 p is 0;

n1 is 0 or 1;

q is an integer from 0 to 10;

t is 2 or 3;

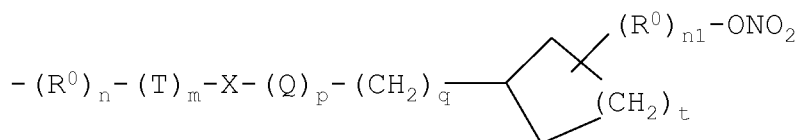
R⁰ is a straight or branched C₁-C₁₀ alkylene;

10 X is a covalent bond.

10. A compound according to claim (I) wherein Rc is a hydrogen, or a pharmaceutically acceptable cation,

R is

15 5)



wherein

n is 0;

m is 0;

20 p is 0;

n1 is 0 or 1;

q is an integer from 0 to 10,

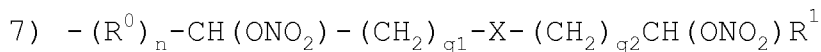
t is 2 or 3;

R⁰ is a straight or branched C₁-C₁₀ alkylene;

25 X is a covalent bond.

11. A compound according to claim 1 wherein Rc is a hydrogen, or a pharmaceutically acceptable cation,

R is



wherein

n is 0;

q₁ is an integer from 1 to 10;

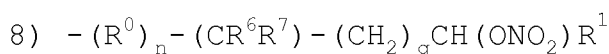
5 q₂ is an integer from 1 to 10;

X is oxygen or a covalent bond;

R¹ is H.

12. A compound according to claim 1 wherein R_c is a hydrogen,
10 or a pharmaceutically acceptable cation,

R is



wherein

n is 0;

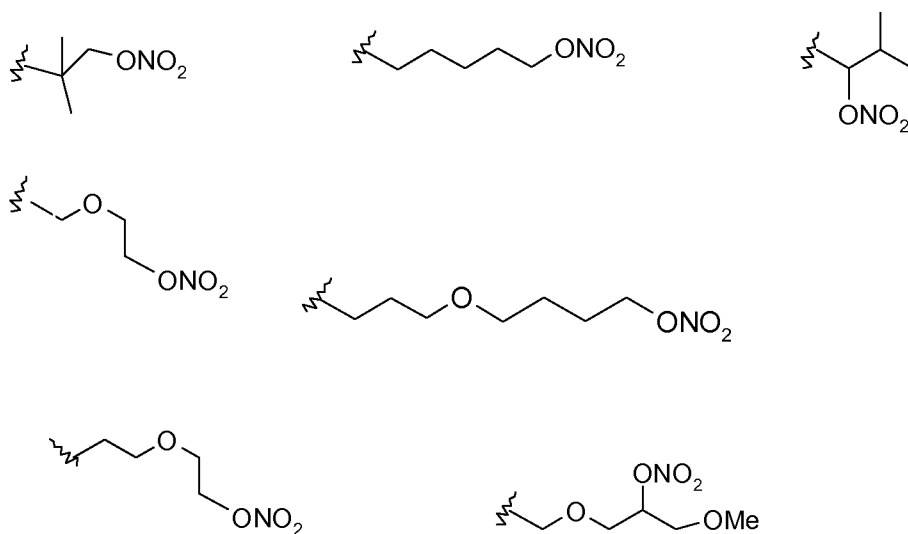
15 q is an integer from 0 to 10;

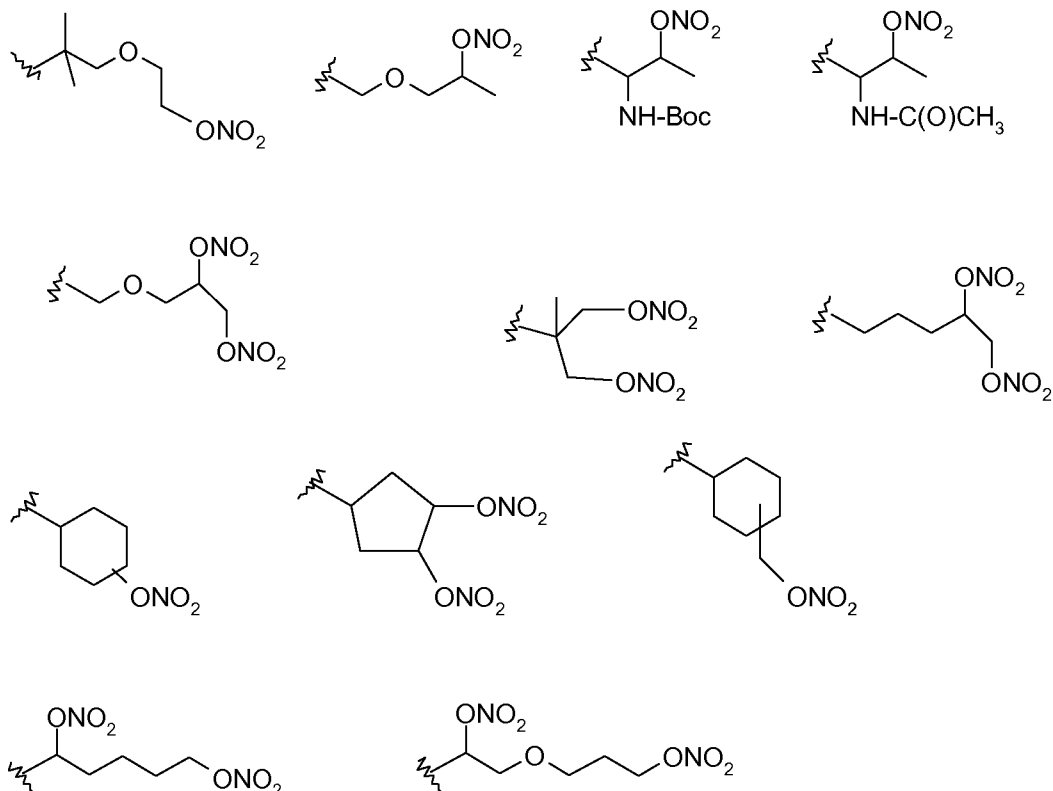
R⁶ is hydrogen or C₁-C₄ linear or branched alkyl;

R⁷ is (CH₂)_qCH(ONO₂)R¹ wherein q is as above defined

R¹ is hydrogen.

20 13. A compound according to claim 1 wherein R is selected from the group consisting of:





14. A compound according to claim 13 wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation,

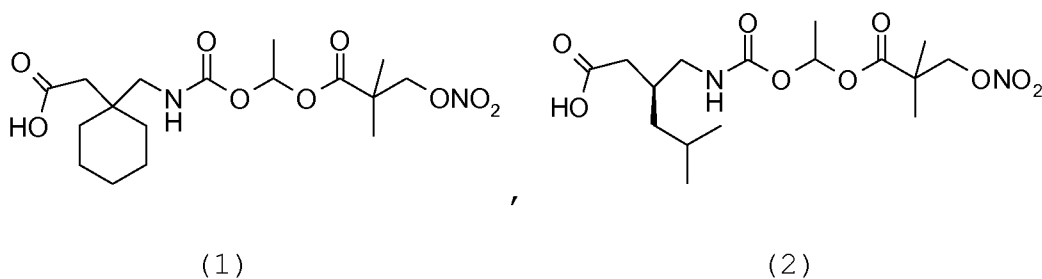
10 Ra is hydrogen and Rb is $(\text{CH}_3)_2\text{CHCH}_2-$.

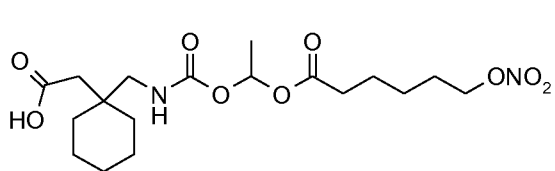
15. A compound according to claim 13 wherein

Rc is a hydrogen, or a pharmaceutically acceptable cation,

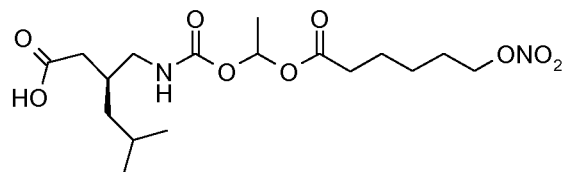
15 Ra and Rb taken together with the carbon atom to which they are attached form a cyclohexyl.

16. A compound according to claim 1 selected from the group:

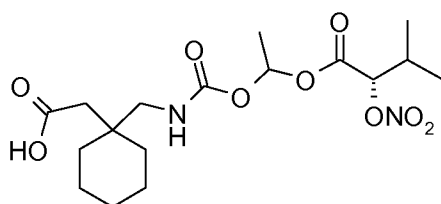




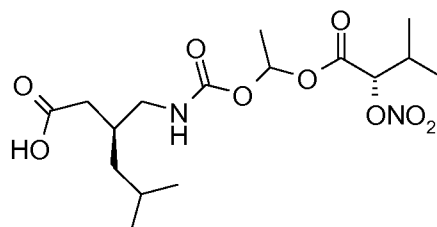
(3)



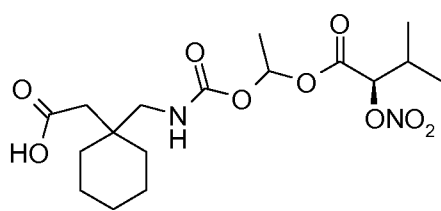
(4)



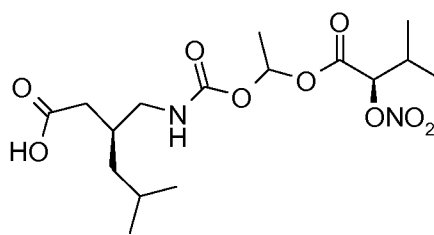
(5)



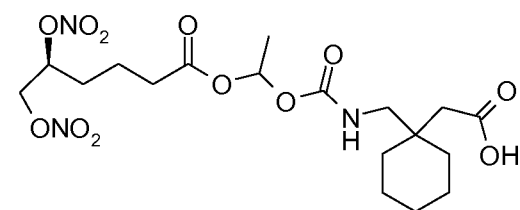
(6)



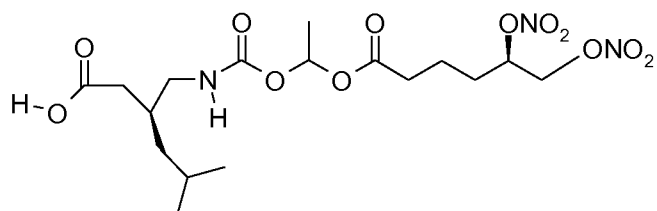
(7)



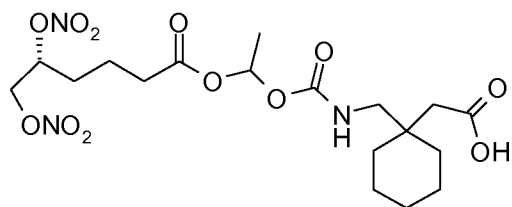
(8)



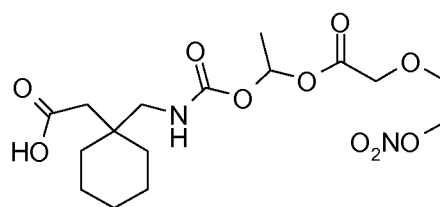
(9)



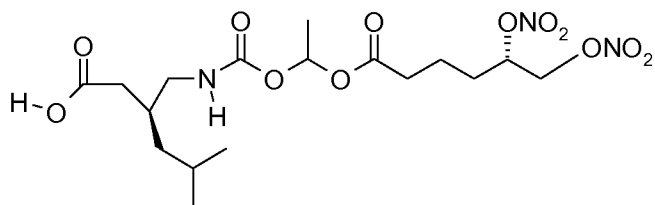
(10)



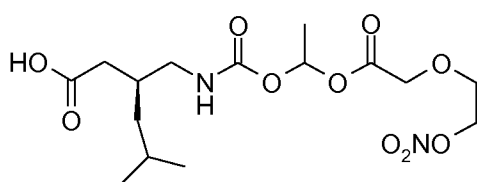
(11)



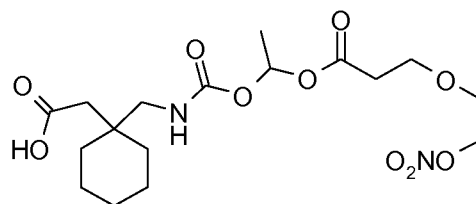
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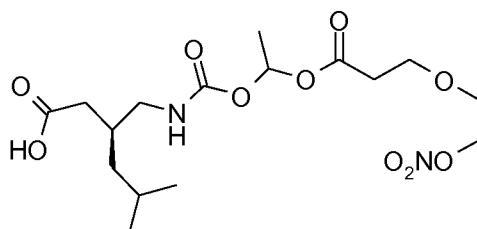
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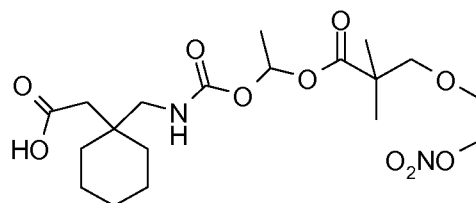
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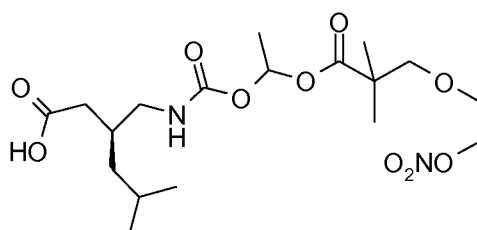
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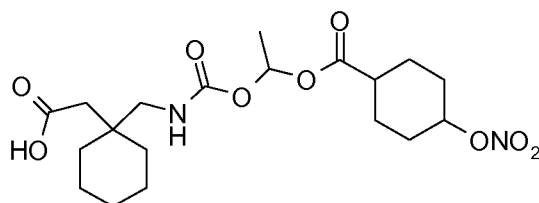
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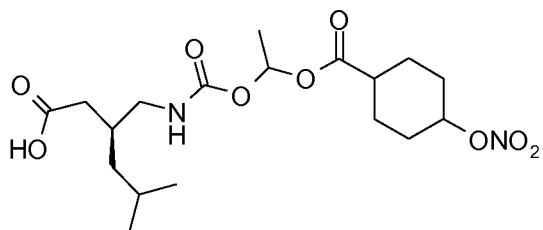
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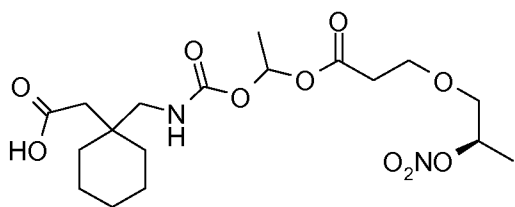
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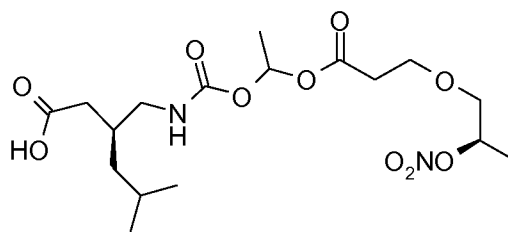
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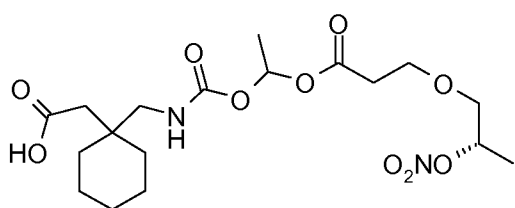
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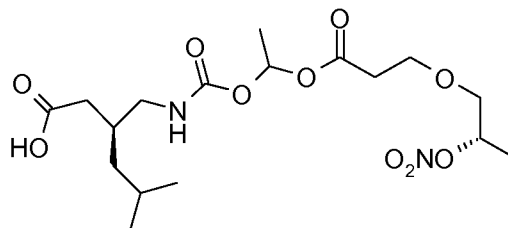
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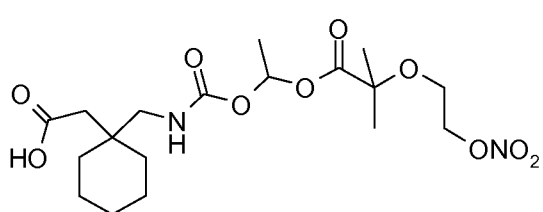
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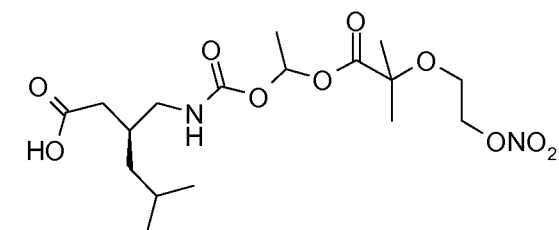
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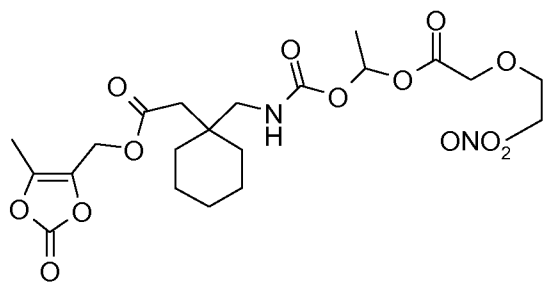
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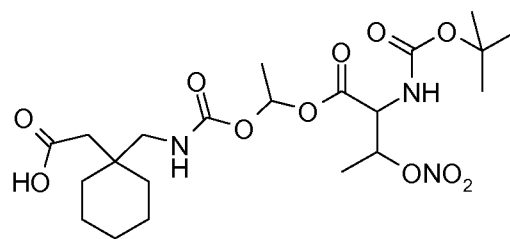
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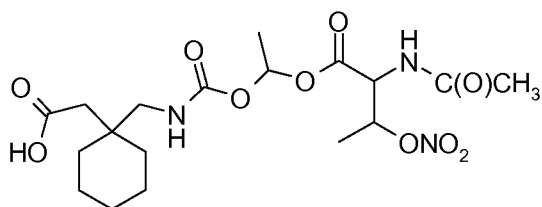
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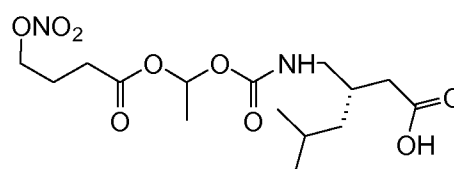
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(28)

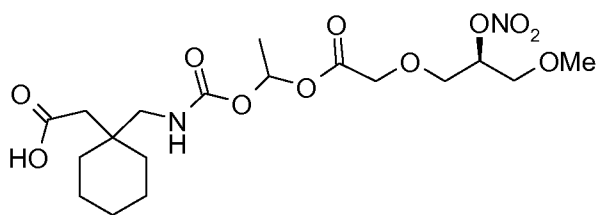


(29)

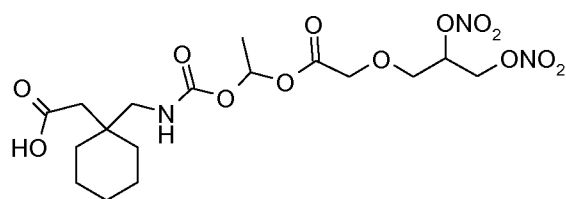


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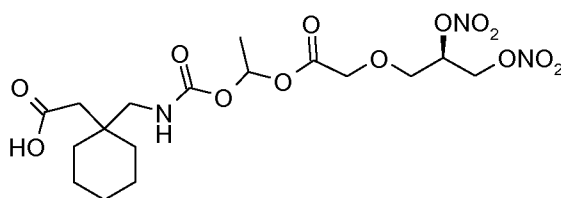
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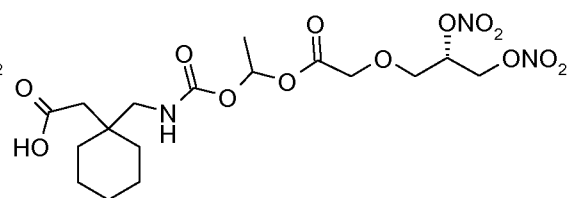
(31)



(32)

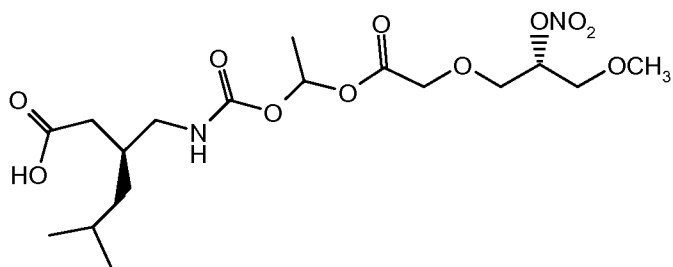


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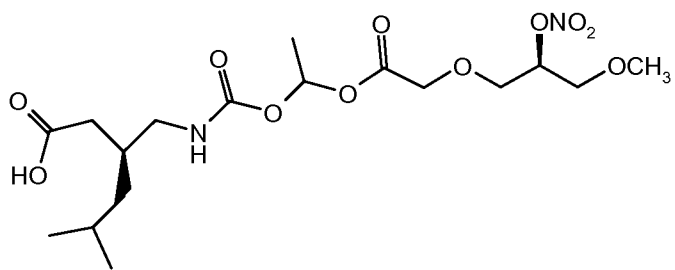


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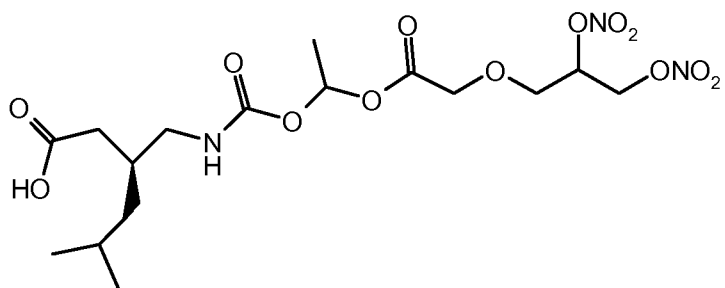
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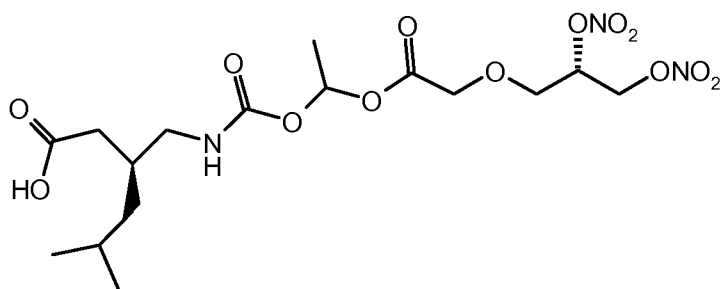
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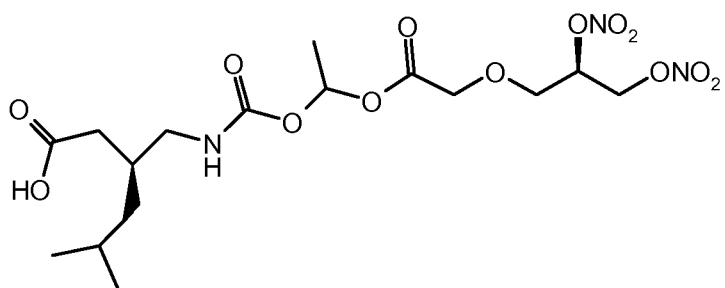
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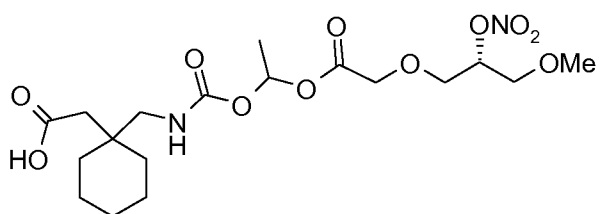
(37)



(38)



(39)



(40)

17. A compound according to anyone of claims 1 to 16 for use as medicament.

18. A compound according to anyone of claims 1 to 16 for use
5 for treating or preventing neuropathic pain.

19. A compound according to anyone of claims 1 to 16 for use for treating or preventing diabetes-associated neuropathic pain.

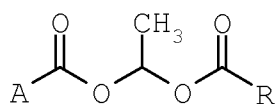
10

20. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula (I) according to anyone of claims 1 to 16 and at least a pharmaceutically acceptable excipient.

15

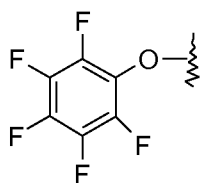
21. A process for the preparation of compounds of formula (I) according to claim 1 comprising:

i) reacting a compound of formula (II)

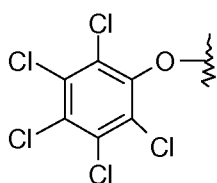


(II)

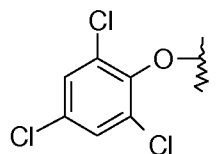
20 wherein A is an activating group selected from the formulas (2a) - (2h)



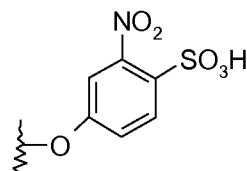
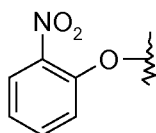
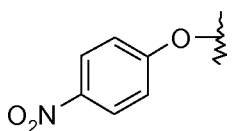
(2a)



(2b)



(2c)

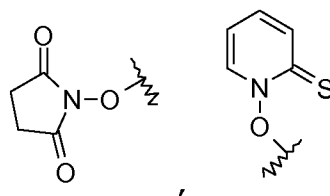


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(2d)

(2e)

(2f)



(2g) (2h)

and R is selected from the group consisting of

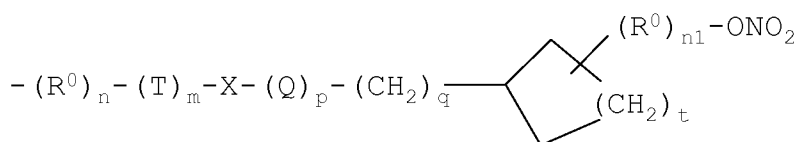
5 1) $-(R^0)_n-CH(ONO_2)R^1$,

2) $-(R^0)_n-CH(ONO_2)-CH(ONO_2)R^{1a}$

3) $-(R^0)_n-(T)_m-X-(Q)_p-(CH_2)_q-CH(ONO_2)R^1$,

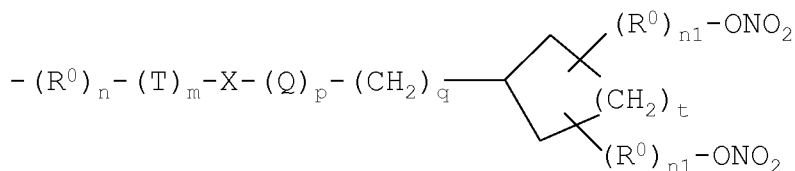
4) $-(R^0)_n-(T)_m-X-(Q)_p-(CH_2)_q-CH(ONO_2)CH(ONO_2)R^{1a}$,

5)



10

6)



7) $-(R^0)_n-CH(ONO_2)-(CH_2)_{q1}-X-(CH_2)_{q2}CH(ONO_2)R^1$

8) $-(R^0)_n-(CR^6R^7)-(CH_2)_qCH(ONO_2)R^1$

15 wherein

n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

n1 is 0 or 1;

20 q is an integer from 0 to 10;

q1 is an integer from 1 to 10;

q2 is an integer from 1 to 10;

t is an integer from 1 to 4;

R^0 is a straight or branched C_1 - C_{10} alkylene;

R^1 is selected from hydrogen, a straight or branched C_1 - C_4 alkyl, $-(CH_2)OCH_3$;

R^{1a} is hydrogen or a straight or branched C_1 - C_4 alkyl;

X is selected from an oxygen atom, $-NH-$, $-N(CH_3)-$ or a covalent
5 bond;

T and Q are $-CR^2R^3-$, wherein R^2 and R^3 at each occurrence are independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, OR^4 , NHR^5 ;

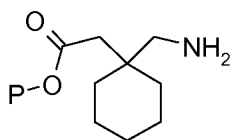
R^4 is hydrogen or C_1 - C_4 linear or branched alkyl;

10 R^5 is hydrogen, C_1 - C_4 linear or branched alkyl, $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$;

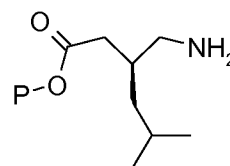
R^6 is hydrogen or C_1 - C_4 linear or branched alkyl;

R^7 is $(CH_2)_qCH(ONO_2)R^1$ wherein q and R^1 are as above defined.

with a compound of formula (III) or (IV)



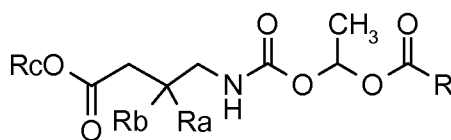
(III)



(IV)

wherein P is a carboxylic protecting group such as a t-butyl group, or a silyl protecting group, in an aprotic polar/non polar solvent in the presence of an organic or inorganic base;

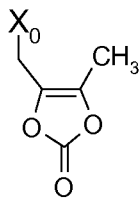
20 ii) removing the protective group P by acidic work-up or with known methods depending on the group P to obtain a compound of formula (I) wherein Rc is H, R is as above defined and the other variables are as defined in claim 1



(I)

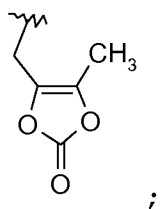
;

25 **ia)** optionally reacting the compound of formula (I) with a compound (XIII)



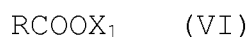
(XIII)

wherein X_0 is Cl, Br or I, in the presence of an inorganic or organic base, in an aprotic polar/non polar, to obtain a compound of formula (I) wherein R_c is

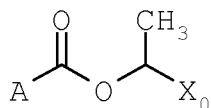


iib) optionally reacting the compounds of formula (I) wherein R_c is H with the appropriate base to obtain a compound of formula (I) wherein R_c is the pharmaceutically acceptable cation;

iii) reacting a compound of formula (VI)

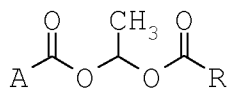


wherein R is as above defined and X_1 is Ag^+ or Hg^+ , with a compound of formula (V)



(V)

wherein A is as above defined, X_0 is Cl, Br or I, in a molar ratio of compounds of formulas (VI):(V) from 2 to 0.5, in an organic solvent to obtain a compound of formula (II)



(II)

wherein A and R are as above defined;

iv) reacting a nitrate carboxylic acid of formula (VII)

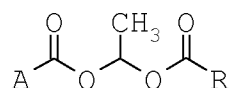


wherein R is as above defined, with Ag₂O or Hg₂O in a molar ratio compound of formula (VII):(Ag₂O) or Hg₂O of from 1 to 0.5 in an organic solvent, to obtain the carboxylic acid salt of formula (VI)

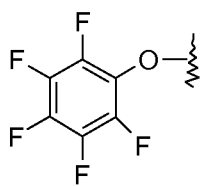


wherein X₁ is Ag⁺ or Hg⁺.

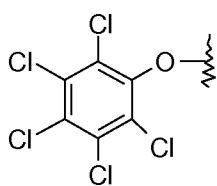
22. A compound of formula (II)



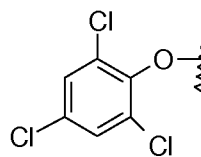
wherein A is an activating group selected from the formulas (2a) - (2h)



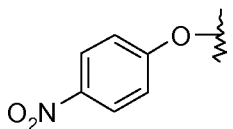
(2a)



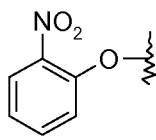
(2b)



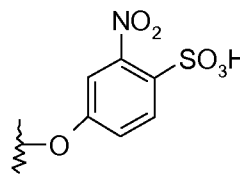
(2c)



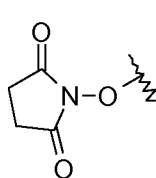
(2d)



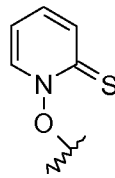
(2e)



(2f)



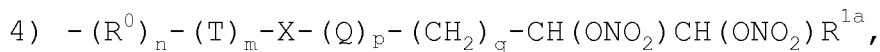
(2g)



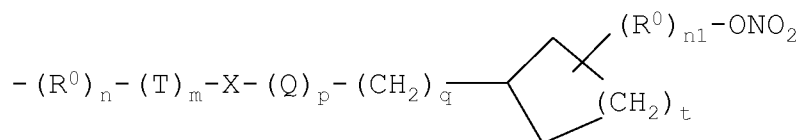
(2h)

R is selected from the group consisting of:

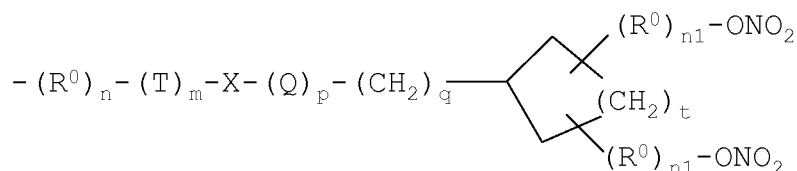
- 20 1) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)\text{R}^1$,
 2) $-(\text{R}^0)_n-\text{CH}(\text{ONO}_2)-\text{CH}(\text{ONO}_2)\text{R}^{1a}$
 3) $-(\text{R}^0)_n-(\text{T})_m-\text{X}-(\text{Q})_p-(\text{CH}_2)_q-\text{CH}(\text{ONO}_2)\text{R}^1$,



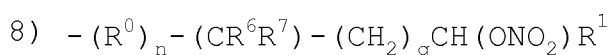
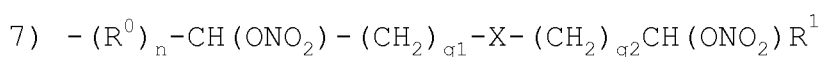
5)



6)



5



wherein

n is 0 or 1;

10 m is 0 or 1;

p is 0 or 1;

n1 is 0 or 1;

q is an integer from 0 to 10;

q1 is an integer from 1 to 10;

15 q2 is an integer from 1 to 10;

t is an is an integer from 1 to 4;

R⁰ is a straight or branched C₁-C₁₀ alkylene;

R¹ is selected from hydrogen, a straight or branched C₁-C₄ alkyl, $-(CH_2)OCH_3$;

20 R^{1a} is hydrogen or a straight or branched C₁-C₄ alkyl;

X is selected from an oxygen atom, $-NH-$, $-N(CH_3)-$ or a covalent bond;

T and Q are $-CR^2R^3-$, wherein R² and R³ at each occurrence are independently selected from hydrogen, C₁-C₄ linear or branched

25 alkyl, OR⁴, NHR⁵;

R⁴ is hydrogen or C₁-C₄ linear or branched alkyl;

R⁵ is hydrogen, C₁-C₄ linear or branched alkyl, $-C(O)CH_3$ or $-C(O)OC(CH_3)_3$;

R^6 is hydrogen or C_1 - C_4 linear or branched alkyl;

R^7 is $(CH_2)_qCH(ONO_2)R^1$ wherein q and R^1 are as above defined.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/051484

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C203/04 C07C271/16 C07D317/40
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/000642 A2 (NICOX SA [FR]; DEL SOLDATO PIERO [IT]; ONGINI ENNIO [IT]) 3 January 2003 (2003-01-03) cited in the application the whole document	1-22
A	WO 2008/095841 A2 (NICOX SA [FR]; ALMIRANTE NICOLETTA [IT]; BIONDI STEFANO [IT]; ONGINI E) 14 August 2008 (2008-08-14) the whole document	1-22



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or
which is cited to establish the publication date of another
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"O" document referring to an oral disclosure, use, exhibition or
other means

"P" document published prior to the international filing date but
later than the priority date claimed

"T" later document published after the international filing date
or priority date and not in conflict with the application but
cited to understand the principle or theory underlying the
invention

"X" document of particular relevance; the claimed invention
cannot be considered novel or cannot be considered to
involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention
cannot be considered to involve an inventive step when the
document is combined with one or more other such docu-
ments, such combination being obvious to a person skilled
in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 June 2011

Date of mailing of the international search report

07/07/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Bedel, Christian

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/051484

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03000642	A2	03-01-2003	CA 2450538 A1 03-01-2003
		EP 1417165 A2 12-05-2004	
		IT MI20011308 A1 23-12-2002	
		US 2004171682 A1 02-09-2004	

WO 2008095841	A2	14-08-2008	CA 2677387 A1 14-08-2008
		EP 2125695 A2 02-12-2009	
		US 2010099729 A1 22-04-2010	
