EUROPEAN PATENT SPECIFICATION

Date of publication and mention of the grant of the patent:

Application number: 94901797.4

Date of filing: 15.11.1993

Int Cl.6: C07C 203/04, A61K 31/21,
C07D 333/22, C07D 209/46,
C07D 491/04, A61K 31/40,
A61K 31/38, C07D 207/337,
C07D 209/88, C07D 333/24,
A61K 31/16

International application number:
PCT/EP93/03193

International publication number:
WO 94/12483 (09.06.1994 Gazette 1994/13)

NITRIC ESTERS HAVING A PHARMACOLOGICAL ACTIVITY AND PROCESS FOR THEIR PREPARATION

SALPETERSÄUREESTER MIT PHARMAZEUTISCHER WIRKUNG UND VERFAHREN ZU DEREN HERSTELLUNG

ESTERS NITRIQUES AYANT UNE ACTIVITE PHARMACOLOGIQUE ET PROCEDE POUR LEUR PREPARATION

Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI NL PT SE

Priority: 26.11.1992 IT MI922699

Date of publication of application:

Proprietor: NICOX S.A.
75116 Paris (FR)

Inventors:
• ARENA, Barbara
  I-20052 Monza (IT)

Representative: Sama, Daniele, Dr.
Sama Patents
Via Morgagni, 2
20129 Milano (IT)

References cited:
EP-A- 0 300 400
EP-A- 0 359 335
WO-A-92/01668
FR-A- 2 612 185
US-A- 4 585 877
US-A- 4 988 728

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
DESCRIPTION

Object of the present invention are nitric esters with an anti-inflammatory and/or anti-platelet aggregation activity, their pharmaceutical utilization and the process for their preparation.

PRIOR ART

Some derivatives of propionic acid, such as for instance 2-(3-benzoylphenyl)propionic acid, commonly known as ketoprofen, have been used for a long time as pharmaceutical preparations for their anti-inflammatory activity and are sold on the different international markets since many years. The process for the preparation of 2-(3-benzoylphenyl)propionic acid has been described in the South African patent n° 68 00 524, corresponding to the US patent 3 641 127, in the French patent n° M6444 and also in C.A. 75,5528m (1971), G.A. PINNA et al., FARMACO Ed. Sci. 35,684 (1980); while the pharmacokinetics in humans is described in T. ISHIKAI et al., Eur J.Clin. Pharmacol. 18,407 (1980). The use of derivatives of propionic acid, such as, for instance, ketoprofen, as well as the use of other products which are utilized as anti-inflammatory agents, involves, as known, severe adverse reactions, for instance in the gastrointestinal apparatus, as well as possible damages to the liver and the kidneys.

There is much experimental evidence [S. MONCADA, R.M.J PALMER, E.A. HIGGS, Pharmacological Reviews, 43(1), 109 (1991); T.H. LUSHER, C.M. BOULANGER, Y. DOHI, Z. YANG, Hypertension, 19,117 (1992)], on whose basis the integrity of vascular endothelium is thought to be a basic barrier against the onset of pathological processes in several organs and apparatuses.

Such protection barrier, and therefore the integrity of the vascular endothelium, is ensured physiologically by the presence of nitric oxide and prostacyclin.

The treatment with non steroid drugs having an anti-inflammatory activity, such as, for instance, 2-(3-benzoylphenyl)propionic acid or ketoprofen, causes the inhibition of cyclo-oxygenase, an enzyme which synthesizes the precursor of prostacyclin.

As a consequence, having so inhibited the production of prostacyclin, the reserve of same in the tissues is markedly depauperated, and therefore the integrity of vascular endothelium is compromised.

As said, because of this endothelial damage due to the reduction of prostacyclin, diffuse pathological process break out which affect the gastrointestinal apparatus, liver and kidneys.

OBJECTS OF THE INVENTION

Object of the present invention is that to provide a group of products which, while ensuring the maintenance of the pharmacological activity characteristic of the known anti-inflammatory agents, are capable of eliminating the adverse reactions caused by the treatment with said agents.

Another object of the present invention is the realization of a process for the preparation of a group of products having an anti-inflammatory activity while being exempt from the adverse reactions which are typical of anti-inflammatory agents.

DESCRIPTION OF THE INVENTION

These and still other objects and associated advantages which will appear from the following description, are obtained with nitric esters having the following general formula:

\[
\text{R}_2 \quad \text{O} \quad \text{A} \\
\text{R} \quad \text{CH} \quad \text{C} \quad \text{Y} \quad (\text{C}_n \text{H}_2 \text{ON}_2) \quad \text{B}
\]

where:

A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among
R₂ is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, Y is chosen among oxygen, NH, NR₁, where R₁ is a linear or branched alkyl group and n is comprised between 1 and 10.

In fact, it has been observed that the introduction of a group such as a terminal nitric ester in the general formula derivatives (I) allows to maintain the pharmacological activity characteristic of non steroid anti-inflammatory agents, while eliminating the adverse reactions caused by the treatment with such agents.

Besides, it has been observed that derivatives (I) are useful also in the treatment of various morbid conditions, such as, for instance, rheumatic diseases in general, disorders of immunologic nature, and can also assuage light-middle severity painful conditions of any kind.

More still, the derivatives (I) subject matter of this invention, are useful in the treatment of diseases of the cardiovascular apparatus, and in particular in the treatment of myocardial and brain ischémies as well as in artery thrombosis as anti-platelet aggregation agents.

Always according to this invention, a nitric ester of general formula (I) proved particularly advantageous, where: hydrogen is chosen as A and B, methyl is chosen as R₂, and as R is chosen oxygen is chosen as y and n is equal to four, according to the following formula:

Also particularly advantageous according to this invention is the nitric ester of a general formula (I) where: hydrogen is chosen as A and B, as R is chosen methyl is chosen as R₂, oxygen is chosen as Y and n is equal to four, according to the following formula:
Still more, always according to the present invention, particularly advantageous are the nitric esters of general formula derivatives (I) where: hydrogen is chosen as A and B, as R are chosen:

\[
\text{(II)}
\]

\[
\text{(VI)}
\]

\[
\text{(VIII)}
\]

methyl, ethyl and hydrogen are chosen as \( R_2 \), oxygen is chosen as \( y \) and \( n \) is equal to four, according to the following formulae:

\[
\text{(XXIV)}
\]

\[
\text{(XXV)}
\]
For the preparation of general formula nitric esters (I), subject matter of the present invention, particularly advantageous proved to be a first process which, according to the invention, comprises the following steps:

- Preparation of the sodium salt of the products having the following general formula:

\[
\text{R}_2 \quad \text{O} \\
\text{R} \quad \text{CH} - \text{C} - \text{OH}
\]

(XIV)

where \( \text{R}_2 \) is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non-substituted. \( \text{R} \) is chosen among: (II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXI), (XXXV) or preparation of derivatives (XIV) functionalized to the carboxyl group, such as acilic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (XIV) or between said derivatives (XIV) functionalized to the carboxylic group, with a composition having the following general formula:

\[
\text{R}_4 \quad \text{C} - \text{R}_3
\]

(XV)

where:
\( \text{R}_4 \) is chosen among chlorine, bromine, NHRR with \( \text{R}_3 \) chosen among hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, \( \text{R}_3 \) is chosen among chlorine, bromine, and iodine, and \( n \) is comprised between 1 and 10, obtaining in this way the relative monomeric esters or the relative amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as AgNO\(_3\) or the like, obtaining in this way nitric esters of derivatives (I).

Also a second process proved to be particularly advantageous which, always according to the present invention, comprises the following steps:
Preparation of the sodium salt of derivatives having the following general formula:

\[
\begin{align*}
R & \quad \text{CH} \quad \text{C} \quad \text{OH} \\
\text{R}_2 & \quad \text{O} \\
\text{R} &
\end{align*}
\]  
(XIV)

where \( R \) is chosen among:

(II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XXXV)

\( \text{R}_2 \) is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, or, alternatively, preparation of derivatives (XIV) functionalized to the carboxylic group, such as acidic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (XIV) or between said derivatives (XIV) functionalized to the carboxylic group, with a composition having the following general formula:

\[
\begin{align*}
\text{A} & \quad \text{(C)}_n \quad \text{OH} \\
\text{B} &
\end{align*}
\]  
(XVI)

where:

\( \text{R}_4 \) is chosen among chlorine, bromine, \( \text{NHR}_2 \) with \( \text{R}_2 \) equal to hydrogen, or linear or branched alkyl chain. \( \text{A} \) and \( \text{B} \) are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and \( n \) is comprised between 1 and 10, obtaining in this way the relative monomeric esters or amides;

- Reaction of said monomeric esters or said amides with an halogenating composition such as \( \text{PBr}_3 \) or the like, obtaining in this way said monomeric esters or said amides characterized by the presence of a terminal halogen group;

- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group, with a nitrating agent such as \( \text{AgNO}_3 \) or the like, obtaining in this way nitric esters of derivatives (I).

The solvents utilized in the processes subject matter of this invention are preferably chosen among chloroform, methylene chloride, acetonitrile, dimethylformamide, tetrahydrofuran, 1,4-dioxane and the like.

The processes for the preparation of derivatives (I) subject matter of this invention, consist of a limited number of steps, allowing to obtain the products which derive from said processes in a short time and with satisfactory fields even on the industrial plane.

According to the processes subject matter of this invention, the preparation of a nitric ester having the following formula:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
\text{CH} = \text{C} & \quad \text{O} \quad \left(\text{CH}_2\right)_4 \quad \text{NO}_2 \\
\end{align*}
\]  
(XII)
proved to be particularly advantageous, which is prepared as described in the following example, given as a mere indication without limiting the protection scope of this invention.

**EXAMPLE 1**

a) 2 g of 2-fluoro-alpha-methyl-4-diphenylacetic acid were added to a solution constituted by 10 ml of methyl alcohol and 0.23 g of Na. The reaction mix was stirred for 5 minutes, then the solvent was evaporated under reduced pressure, obtaining the sodium salt of 2-fluoro-alpha-methyl-4-diphenylacetic acid.

b) The sodium salt of 2-fluoro-alpha-methyl-4-diphenylacetic acid obtained in this way was suspended in 20 ml of dimethylformamide and 3 ml of 1,4-dibromo-butane were added by dripping to this suspension. The reaction mix was stirred for 22 hours at room temperature, then the NaBr which had formed was filtered and the solvent was evaporated under reduced pressure. The residue so obtained was treated with methylene chloride and, after elimination by filtration of the insoluble residue, the methylene chloride was evaporated under reduced pressure, obtaining 3 g of a dry residue which was purified by silica gel chromatography, utilizing an eluent mix constituted by hexane/methylene chloride 1/1 (V/V).

The head fractions were collected, the solvent was evaporated under reduced pressure and 1.86 g of 2-fluoro-alpha-methyl-4-diphenylacetate of 4-bromobutyl (XXII) were obtained.

IR (cm\(^{-1}\)): C=0.1470

\(^1\)H-NMR (300 MHz) (CDCl\(_3\)): 1.51ppm (d, 3H); 1.56ppm (m, 4H); 3.35ppm (t, 2H); 3.61ppm (q, 1H); 4.1ppm (t, 2H); 7.05ppm (m, 1H); 7.17ppm (s, 1H); 7.3-7.55 (m, aromatics).

c) 1.2 g of AgNO\(_3\) dissolved in 8.3 ml of acetonitrile were added to 1.86 g of (XXII), obtained as described under b) dissolved in 7.5 ml of acetonitrile. The reaction mix was stirred for 48 hours at room temperature and then filtered. The solvent was evaporated from the resulting solution under reduced pressure, obtaining a residue which was treated with methylene chloride. The mix obtained in this way was filtered again and the organic phase was purified by silica gel pressure chromatography, utilizing an eluent mix constituted by diethyl ether/hexane 3/7 (V/V). The fractions containing the products were collected, the solvent was evaporated under reduced pressure and 1.2 g of nitric ester of 2-fluoro-alpha-methyl-4-diphenyl acetate of 4-hydroxybutyl (XII) were obtained.

IR(cm\(^{-1}\)): C=0.1737; ONO\(_2\): 1623, 1274.

\(^1\)H-NMR (300 MHz) (CDCl\(_3\)): 1.53ppm (d, 3H); 1.72ppm (m, 4H); 3.74ppm (q, 1H); 4.13 ppm (t, 2H); 4.4ppm (t, 2H); 7.13ppm (t, 2H, aromatics); 7.32-7.42ppm (m, 4H, aromatics); 7.53ppm (m, 2H, aromatics).

Mass spectrometry (i.e.): (M\(^+\))361; (M+1-NO\(_2\))316; 243, 199.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester having the following formula:

![Chemical structure](image)

proved particularly advantageous, which is prepared as described in the example shown hereunder, given as a mere indication without limiting the protection scope of this invention.

**EXAMPLE 2**

a) 10 g of 2-[(3-benzo[phenyl])propionic acid were added to a solution constituted by 80 ml of methyl alcohol and 1.19 g of Na. The reaction mix was stirred for 15 minutes, then the solvent was evaporated under reduced pressure, obtaining a residue constituted by the sodium salt of 2-(3-benzoinphenyl)propionic acid.

b) 100 ml of dimethylformamide and 28.1 g of 1,4-dibromo-butane were added to the residue obtained in this way. The reaction mix was kept for 24 hours at room temperature and then the solvent was evaporated under reduced pressure. 40 ml of water and 60 ml of methylene chloride were added to the residue obtained in this way and the organic phase was extracted and anhydried on sodium sulphate and the solvent was evaporated under reduced pressure until a dry residue was obtained. The residue was purified by silica gel chromatography, utilizing an eluent
mix constituted by diethyl ether/hexane 1/1 (V/V). The head fractions were collected, the solvent was evaporated under reduced pressure and 8.8 g of 2-(3-benzylphenyl)propanoate of 4-bromobutyryl (XXIII) were obtained.

\[1^H\text{-NMR}(200\text{MHz}) (\text{CDCl}_3): 1.53\text{ppm (d,3H); 1.84ppm (m,4H); 3.32ppm (t,2H); 3.75ppm (q,1H); 4.09ppm (t,2H); 7.27 (m,1H, aromatics); 7.38-7.99 (m,8H aromatics).}\]

Mass spectrometry (i.e.): 388 (M+); 309 (M+-Br); 209.

c) 5.5 g of AgNO_3 dissolved in 38 ml of acetonitrile were added to 8.8 g of (XXIII) obtained as described under b) dissolved in 35 ml of acetonitrile. The reaction mix was stirred for 24 hours at room temperature and, having added 1.76 g of AgNO_3, the reaction mix was stirred for 24 more hours at room temperature and then filtered. The solvent was evaporated from the resulting solution under reduced pressure, obtaining a residue which was treated with methylene chloride.

The mix obtained in this way was filtered again and the organic phase was purified by silica gel pressure chromatography, utilizing an eluent mix constituted by ethyl ether/hexane 3/7 (V/V).

The fractions containing the product were collected, the solvent was evaporated under reduced pressure and 3.4 g of nitric ester of 2-(3-benzylphenyl)propanoate of 4-hydroxybutyl (XVIII) were obtained.

IR (cm\(^{-1}\)): 3017, 1737; OCO, 1632, 1288; OCO, 1660.

\[1^H\text{-NMR (80 MHz)} (\text{CDCl}_3): 1.48\text{ppm (d,3H); 1.64ppm (m,4H); 3.78ppm (q,1H); 4.08ppm (m,2H); 4.3ppm (m,2H); 7.3-7.81 (m, aromatics).}\]

Mass spectrometry (i.e.): 371 (M+); 309 (M+-NO_2); 255. The anti-inflammatory and anti-platelet aggregation activity as well as the gastrointestinal ulcerogeticity, for instance of nitric esters having the following formulae, were tested by means of biological studies:
The anti-inflammatory activity of said nitric esters was determined in Wistar rats utilizing the method of the carrageenan paw edema, as reported in C.A. WINTER, E.RISLEY, G.W.NUSS, Proc. Soc. Exp. Biol. Med. 111,544 (1962), while the anti-platelet aggregation activity of said derivatives was determined on human platelets stimulated by arachidonic acid, according to the method described by V.BERTELE et al., Science 220,517 (1983).

The gastrointestinal ulcerability was evaluated by oral administration in the rat.

The anti-inflammatory and anti-platelet aggregation activity as well as the gastrointestinal ulcerability activity of said derivatives are given on Table 1, and are expressed, for each nitric ester indicated, as the power ratio relative to the corresponding acids non functionalized according to the general formula (I), according to this invention. Each value represents the mean of the values obtained by the treatment of 10 animals.

<table>
<thead>
<tr>
<th>COMPOUND STUDIED</th>
<th>ANTI-INFLAM. ACTIVITY</th>
<th>ANTI-AGGREG. ACTIVITY</th>
<th>GASTROINTESTINAL ULCERABILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>(XVII)</td>
<td>1.25</td>
<td>1.35</td>
<td>0.20</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(XII)</td>
<td>1.25</td>
<td>1.15</td>
<td>0.35</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(XXV)</td>
<td>1.20</td>
<td>1.30</td>
<td>0.35</td>
</tr>
<tr>
<td>Suprofen</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(XXV)</td>
<td>1.05</td>
<td>1.25</td>
<td>0.30</td>
</tr>
<tr>
<td>Indobufen</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(XXVII)</td>
<td>1.40</td>
<td>1.10</td>
<td>0.33</td>
</tr>
<tr>
<td>Etodolac</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

In particular, the derivatives (XVIII) and (XII) submitted to additional studies of a pharmacodynamical nature have given the following results, as shown in the following examples.

- **RAT CARRAGEENAN PAW EDEMA.** Both compounds (XVIII) and (XII) showed an efficacy comparable with the corresponding reference drugs Ketoprofen and Flurbiprofen, the effective doses being in the 1 to 10 mg/kg p.o.
- **RAT ADJUVANT ARTHRITIS.** Animals treated for 19 consecutive days (days 3 through 21 after adjuvant injection) with 3 mg/kg p.o. of either compound (XVIII) or (XII) and their corresponding reference compound showed a significant and comparative reduction in the arthritic symptomatology compared to controls.

- **MOUSE PHENYLQUINONE W R I T H I N G.** At doses ranging from 3 to 10 mg/kg p.o., compound (XVIII) and (XII) proved fully effective and their efficaciousness was almost comparable with that of the corresponding reference compounds.

- **IN VIVO PLATELET AGGREGATION.** While both compositions (XVIII) and Flurbiprofen, when administered at the dose of 20 mg/kg p. o. in the rat, inhibited collagen-induced platelet aggregation, the former (66% inhibition versus controls) was significantly more effective than the latter (40%).

**BIOCHEMISTRY**

- **PROSTAGLANDIN SYNTHESIS IN THE INFLAMMATORY EXUDATE.** Subcutaneous implantation of carrageenan sponge elicits the infiltration of inflammatory cells, as reported in Nature 284, 271 (1980). Both compounds, (XVIII) and (XII) when administered at the dose of 20 mg/kg p.o. inhibited the formation of prostaglandin E2 in exudate by more than 75% compared with controls and have shown comparative efficacy to the corresponding reference compounds Ketoprofen and Flurbiprofen.

- **GASTRIC PROSTAGLANDIN SYNTHESIS.** Both compounds, (XVIII) and (XII) were studied for prostaglandin synthesis at the same doses (5-20 mg/kg p.o.) utilized for gastric injuries studies. They inhibited significantly and comparatively to the corresponding reference compounds Ketoprofen and Flurbiprofen, the synthesis of prostaglandin E2, the percent of inhibition being more than 90% at the highest dose.

- **NO RELEASE.** Evidence that compounds (XVIII) and (XII) released nitric oxide after their administration was obtained by measurements of plasma nitrate/nitrite levels, as reported in J. Clin. Invest., 85, 264 (1990). One hour after the administration of either (XVIII) or (XII) compound, the plasma nitrate/nitrite levels had significantly increased by more than 50%. Ketoprofen or Flurbiprofen did not affect plasma nitrate/nitrite levels significantly.

Besides, additional biological studies were performed on derivatives (XII) and (XVIII); said studies have provided the following results.

**GASTROINTESTINAL TOLERABILITY**

- **RAT GASTRIC MUCOSA INJURY.** (XVIII) and (XII) were studied in comparison with the corresponding reference compounds Ketoprofen and Flurbiprofen at doses ranging from 3 to 30 mg/kg p.o. both (XII) and (XVIII) compounds being significantly better tolerated than reference compounds. Ketoprofen or Flurbiprofen caused the onset of gastric damages already at the dose of 3 mg/kg, the severity of such damages being dose-dependent, while (XVIII) or (XII) compounds were well tolerated even at the dose of 30 mg/kg.

The histological evaluation confirmed these findings. Similar differences in the capacity of these compounds to cause gastric and small intestine injury were also observed upon repeated administration of the compounds.

- **GASTRIC LEUKOCYTE ADHERENCE/VEssel DIAMETER.** An early event in the pathogenesis of NSAID-induced gastric mucosa injury is the adherence of leukocytes to the endothelium of post-capillary venules, as reported in Gastroenterology 103, 146 (1992). Trends Pharmacol. Sci. 13, 129 (1992); Am J. Physiol. 262, G903 (1992). Using intravital microscopy, the leucocyte adherence to mesenteric post-capillary venules could be quantified prior to and during a one hour period of the administration of NSAID. Unlike Ketoprofen or Flurbiprofen, (XVIII) or (XII) did not induce significant leukocyte adherence, while increasing the diameter of vessels significantly. No changes in blood pressure were observed.

**GENERAL PHARMACOLOGY**

A secondary pharmacological evaluation of compound (XVIII) or (XII) was performed in comparison with Ketoprofen or Flurbiprofen. No relevant additional adverse reactions were observed affecting the central nervous, autonomic, cardiovascular, respiratory and gastrointestinal systems.

**TOXICOLOGY**

- **ACUTE TOXICOLOGY IN RODENTS.**

The acute toxicity of said derivatives (XVIII), (XXIV), (XXV), (XII) and (XXVI) was then evaluated by p.o. administration of a single dose of each compound (XVIII), (XXIV), (XXV), (XII) and (XXVI), utilizing, for each derivative,
groups of 10 Swiss mice. Death incidence and the onset of toxic symptoms were reported for a period of 14 days. Even after administration of a dose of 100 mg/kg of each compound (XVIII), (XXIV), (XXV), (XII) and (XXVI), no apparent toxicity symptoms were noticed in the animals studied. In particular, preliminary studies on compounds (XVIII) or (XII) were performed in the mouse by two administration routes. No evident toxicity was observed in the animals treated with oral or intraperitoneal doses of 300 mg/kg of either compound.

- MAXIMUM TOLERATED DOSE IN NON RODENTS. Preliminary studies indicate that compounds (XVIII) and (XII) were very well tolerated in this animal species that is known to be particularly sensitive to this class of compounds. The animals were administered increasing oral doses up to 30 mg/kg of either compound and no apparent symptoms were observed, while the reference compounds Ketoprofen and Flurbiprofen, administered at the dose of 10 mg/kg caused the death of the animals.

Claims

1. Nitric esters characterized in that they have the following general formula:

\[
\begin{array}{c}
R_2O
\end{array}
\]

where:

A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among:

- (II)
- (III)
- (IV)
- (V)
- (VI)
- (VII)
2. Nitric ester according to claim 1, characterized in that R₁ is:

\[ \text{(IV)} \]

R₂ is equal to methyl, A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

3. Nitric ester according to claim 1, characterized in that R₁ is equal to:

\[ \text{(IX)} \]

R₂ is equal to methyl, Y is equal to oxygen, A and B are equal to hydrogen and n is equal to four.

4. Nitric ester according to claim 1, characterized in that R₁ is equal to:

\[ \text{(II)} \]

R₂ is equal to methyl, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

5. Nitric ester according to claim 1, characterized in that R₁ is equal to:
R₂ is equal to ethyl, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

6. Nitric ester according to claim 1, characterized in that R is equal to:

R₂ is equal to hydrogen, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

7. Nitric esters according to claim 1, characterized in that they are utilizable in pharmaceutics as anti-inflammatory agents.

8. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of rheumatic diseases, disorders of immunologic nature, and slight-middle severity painful conditions.

9. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of diseases affecting the cardiovascular system, the treatment of miocardial and brain ischemiae and in cases of arterial thromobosis as platelet anti-aggregation agents.

10. Process for the preparation of nitric esters characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives having the following general formula:

where R is chosen among

where R is chosen among
\[ R_2 \text{ is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, or preparation of derivatives (XIV) functionalized to the carboxylic group as acetic chlorides, anhydrides or the like;}

- Reaction between the sodium salt of said derivatives (XIV) or of said derivatives (XIV) functionalized to the carboxylic group, with a compound having the following general formula:
where:

- Reaction of said monomeric esters or said amides with a nitrating agent such as AgNO₃ or the like, obtaining nitric esters having the following general formula:

\[
\begin{array}{c}
\hat{R}_1 \quad \hat{R}_2 \quad \hat{R}_3 \quad \hat{R}_4 \\
\text{A} \quad \text{B} \\
\end{array}
\]

11. Process for the preparation of nitric esters characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives having the following general formula:

\[
\begin{array}{c}
\hat{R}_1 \quad \hat{R}_2 \\
\text{A} \quad \text{B} \\
\end{array}
\]

where \( R \) is chosen among

\[
\text{II} \\
\text{VI} \\
\text{IV}
\]
R₂ is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, or preparation of derivatives (XIV) functionalized to the carboxylic group, such as acetic chlorides, anhydrides and the like;
- Reaction between the sodium salt of said derivatives (XIV) or of said derivatives (XIV) functionalized to the carboxylic group, with a compound having the following general formula:

$$\begin{align*}
A & \\
\text{R}_n & \text{C} \to \text{OH} \\
\text{B} & \\
\end{align*}$$

where:
- Rₙ is chosen among chlorine, bromine, MHRₖ, with Rₖ hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, obtaining the relative monomeric esters or the relative amides;
- Reaction of said monomeric esters or said amides with an halogenating compound such as PBr₅ or the like, obtaining said monomeric esters or said amides, characterized by the presence of a terminal halogen group;
- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group with a nitrating agent such as AgNO₃ or the like, obtaining nitric esters having the following general formula:
where $Y$ is chosen among oxygen, NH, NR$_1$ where R$_1$ is a linear or branched alkyl chain.

**Patentansprüche**

1. Salpetersäureester, dadurch gekennzeichnet, daß sie die nachstehende allgemeine Formel:

$$
R'\backslash-\text{CH}-\text{C}-Y-(C)_n-O\quad\text{NO}_2
$$

aufweisen, worin:

A und B ausgewählt sind aus Wasserstoff, linearen oder verzweigten, substituierten oder nichtsubstituierten Alkylestern. R ausgewählt ist aus:

- (II)
- (III)
- (IV)
- (V)
- (VI)
- (VII)
- (XXI)
- (XXXV)
R₂ ausgewählt ist aus Wasserstoff, Methyl, Ethyl, linearen oder verzweigten Alkylketten mit 3 bis 12 Kohlenstoffatomen, substituiert oder nichtsubstituiert. Y ausgewählt ist aus Sauerstoff, NH, NR₁, worin R₁ eine lineare oder verzweigte Alkylgruppe darstellt und n zwischen 1 und 10 umfaßt ist.

2. Salpetersäureester nach Anspruch 1, dadurch gekennzeichnet, daß R

3. Salpetersäureester nach Anspruch 1, dadurch gekennzeichnet, daß R

4. Salpetersäureester nach Anspruch 1, dadurch gekennzeichnet, daß R:

5. Salpetersäureester nach Anspruch 1, dadurch gekennzeichnet, daß R:
ist,
R₂ Ethyl ist, A und B Wasserstoff sind, Y Sauerstoff ist und n vier ist.

6. Salpetersäureester nach Anspruch 1, dadurch gekennzeichnet, daß R:

   (VIII)

ist,
R₂ Wasserstoff ist, A und B Wasserstoff sind, Y Sauerstoff ist und n vier ist.

7. Salpetersäureester nach Anspruch 1, dadurch gekennzeichnet, daß sie in Pharmazeutika als entzündungshemmende Mittel verwendbar sind.

8. Salpetersäureester nach Anspruch 1, dadurch gekennzeichnet, daß sie bei der Behandlung von rheumatischen Erkrankungen, Erkrankungen immunologischer Natur und leicht-bis mittelschweren Schmerzzuständen verwendbar sind.

9. Salpetersäureester nach Anspruch 1, dadurch gekennzeichnet, daß sie bei der Behandlung von Erkrankungen, die das cardiovasculäre System angreifen, der Behandlung von myokardialer und cerebraler Ischämie und in Fällen arterieller Thrombose als thromboxylenaggregationshemmende Mittel verwendbar sind.

10. Verfahren zur Herstellung von Salpetersäureestern, dadurch gekennzeichnet, daß es die nachstehenden Schritte umfaßt:

   - Herstellung des Natriumsalzes von Derivaten der nachstehenden allgemeinen Formel:

   \[ \begin{align*}
   & R_2 \\
   & \text{O} \\
   & R \quad \text{CH} \quad \text{C} \quad \text{OH} \\
   \end{align*} \]

   (XIV)

worin R ausgewählt ist aus
R₂ ausgewählt ist aus Wasserstoff, Methyl, Ethyl, linearen oder verzweigten Alkylketten mit 3 bis 12 Kohlenstoffatomen, substituiert oder nichtsubstituiert, oder Herstellung von Derivaten (XIV), funktionalisiert an der Carboxylgruppe, wie Säurechloride, -anhydride oder dergleichen:
- Umsetzung zwischen dem Natriumsalz der Derivate (XIV) oder den an der Carboxylgruppe funktionalisierten Derivaten (XIV) mit einer Verbindung der nachstehenden allgemeinen Formel

\[ R_4 \begin{array}{c} \text{(C)}_n \end{array} R_3 \]

worin:
R₄ ausgewählt ist aus Chlor, Brom, NH₃₋₆ mit R₆ als Wasserstoff, lineare oder verzweigte Alkylkette, A und B ausgewählt sind aus Wasserstoff, linearen oder verzweigten, substituierten oder nichtsubstituierten Alkylketten. R₂ ausgewählt ist aus Chlor, Brom und Jod und n zwischen 1 und 10 umfaßt ist, unter Gewinnung der betreffenden monomeren Ester oder der betreffenden Amide;
- Umsetzung der monomeren Ester oder der Amide mit einem Nitrierungsmittel, wie AgNO₃ oder dergleichen, unter Gewinnung von Salpetersäureestern der nachstehenden allgemeinen Formel:

\[ R_2 \begin{array}{c} \text{(C)}_n \end{array} \text{-ONO}_2 \]

worin Y ausgewählt ist aus Sauerstoff, NH, NR₁, worin R₁ eine lineare oder verzweigte Alkylkette darstellt.

11. Verfahren zur Herstellung von Salpetersäureestern, dadurch gekennzeichnet, daß es die nachstehenden Schritte umfaßt:
- Herstellung des Natriumsalzes von Derivaten der nachstehenden allgemeinen Formel:

\[ R_2 \begin{array}{c} \text{OH} \end{array} \]

worin R ausgewählt ist aus
R₂ ausgewählt ist aus Wasserstoff, Methyl, Ethyl, linearen oder verzweigten Alkyketten mit 3 bis 12 Kohlenstoffatomen, substituiert oder nichtsubstituiert, oder Herstellung von Derivaten (XIV), funktionalisiert an der Carboxylgruppe, wie Säurechloride, -anhydride und dergleichen;

- Umsetzung zwischen dem Natriumsalz der Derivate (XIV) oder den an der Carboxylgruppe funktionalisierten Derivaten (XIV) mit einer Verbindung der nachstehenden allgemeinen Formel:

\[
\begin{align*}
\text{A} & \quad R_4 \quad (C)_n \quad \text{OH} \\
\text{B} &
\end{align*}
\]

worin:

R₄ ausgewählt ist aus Chlor, Brom, NH₂R₅, mit R₅ als Wasserstoff, lineare oder verzweigte Alkykette, A und B ausgewählt sind aus Wasserstoff, linearen oder verzweigten, substituierten oder nichts substituierten Alkyketten und n zwischen 1 und 10 umfaßt ist, unter Gewinnung der betreffenden monomeren Ester oder der betreffenden Amide;
- Umsetzung der monomeren Ester oder der Amide mit einer Halogenierungsverbindung, wie PBr₅ oder dergleichen, unter Gewinnung der monomeren Ester oder der Amide, die durch die Gegenwart einer endständigen Halogengruppe gekennzeichnet sind;
- Umsetzung der monomeren Ester oder der Amide, die durch die Gegenwart einer endständigen Halogengruppe gekennzeichnet sind, mit einem Nitrierungsmittel, wie AgNO₃ oder dergleichen, unter Gewinnung von Salpetersäureester der nachstehenden allgemeinen Formel:

\[
\begin{align*}
\text{II} & : \\
\text{III} & :
\end{align*}
\]

worin Y ausgewählt ist aus Sauerstoff, NH, NR₁, worin R₁ eine lineare oder verzweigte Alkykette darstellt.

**Reivendications**

1. Esters nitrates, caractérisés en ce qu'ils ont la formule générale suivante :

\[
\begin{align*}
\text{II} & : \\
\text{III} & :
\end{align*}
\]

dans laquelle :

A et B sont choisis parmi l'hydrogène, les groupes alkyle substitués ou non substitués à chaîne droite ou ramifiée, R est choisi parmi :

\[
\begin{align*}
\text{IV} & : \\
\text{V} & : \\
\text{VI} & : \\
\text{VII} & : \\
\end{align*}
\]
R₂ est choisi parmi l'hydrogène, le groupe méthyle, éthyle, les groupes alkyle linéaires ou ramifiés ayant de 3 à 12 atomes de carbone et substitués ou non substitués, Y est choisi parmi un oxygène, NH, NR₁ où R₁ est un groupe alkyle à chaîne droite ou ramifiée, et n est compris entre 1 et 10.

2. Ester nitrate selon la revendication 1, caractérisé en ce que R est :

3. Ester nitrate selon la revendication 1, caractérisé en ce que R est :

4. Ester nitrate selon la revendication 1, caractérisé en ce que R est :

5. Ester nitrate selon la revendication 1, caractérisé en ce que R est :
5. \( \text{R}_2 \) est le groupe éthyle, A et B sont des hydrogènes, Y est un oxygène, et \( n \) vaut 4.

6. Ester nitrate selon la revendication 1, caractérisé en ce que \( R \) est :

15. \( \text{(VIII)} \)

20. \( \text{R}_2 \) est un hydrogène, A et B sont des hydrogènes, Y est un oxygène, et \( n \) vaut 4.

7. Esters nitrates selon la revendication 1, caractérisés qu'ils peuvent être utilisés en pharmacie en tant qu'agents anti-inflammatoires.

8. Esters nitrates selon la revendication 1, caractérisés qu'ils peuvent être utilisés dans le traitement des maladies rhumatismales, des troubles de nature immunologique et des états douloureux légers à moyens.

9. Esters nitrates selon la revendication 1, caractérisés qu'ils peuvent être utilisés dans le traitement des maladies affectant le système cardio-vasculaire, dans le traitement de l'ischémie du myocarde et de l'ischémie cérébrale, et dans les cas de thrombose artérielle, en tant qu'agents anti-agrégations plaquettaire.

10. Procédé de préparation d'esters nitrates, caractérisé en ce qu'il comprend les étapes suivantes :

- préparation du sel de sodium de dérivés ayant la formule générale suivante :

40. \( \text{R}_2 \quad \text{O} \quad \text{CH} \quad \text{C} \quad \text{OH} \quad \text{R} \quad \text{(XIV)} \)

où \( R \) est choisi parmi :

50. \( \text{(II)} \)

55. \( \text{(III)} \)
R₂ est choisi parmi l'hydrogène, les groupes méthyle, éthyle, alkyle à chaîne droite ou ramifiée ayant de 3 à 12 atomes de carbone et substitués ou non substitués, ou encore préparation de dérivés (XIV) fonctionnalisés sur le groupe carboxyle en tant que chlorures d'acyle, anhydrides, ou analogues ;
- réaction entre le sel de sodium des dérivés (XIV) ou des dérivés (XIV) fonctionnalisés sur le groupe carboxylique, avec un composé ayant la formule générale suivante :
dans laquelle :

- $R_4$ est choisi parmi le chlore, le brome, NH-$R_6$, $R_5$ étant un hydrogène ou un groupe alkyle à chaîne droite ou ramifiée, A et B sont choisis parmi l'hydrogène, les groupes alkyle à chaîne droite ou ramifiée, substitués ou non substitués, $R_5$ est choisi parmi le chlore, le brome et l'iode, et $n$ est compris entre 1 et 10, de façon à obtenir les esters monomères correspondants ou les amides correspondants ;
- réaction des dits esters monomères ou dits amides avec un agent de nitruration tel que AgNO$_3$ ou analogues, pour obtenir des esters nitrates ayant la formule générale suivante :

$$
\begin{array}{c}
R_2 & O & A \\
\left\| \right\| & \left\| \right\| & \left\| \right\| \\
R & \text{CH} & \text{C} & \text{Y} & \left(\text{C}\right)_{n-\text{NO}_2} & B \\
\end{array}
$$

où Y est choisi parmi l'oxygène, NH, NR$_1$ où $R_1$ est un groupe alkyle à chaîne droite ou ramifiée.

11. Procédé de préparation d'esters nitrates, caractérisé en ce qu'il comprend les étapes suivantes :

- préparation du sel de sodium de dérivés ayant la formule générale suivante :

$$
\begin{array}{c}
R_2 & O \\
\left\| \right\| \\
R & \text{CH} & \text{C} & \text{OH} \\
\end{array}
$$

où $R$ est choisi parmi :

- [IV]
- [VII]
R₂ est choisi parmi l'hydrogène, les groupes méthyle, éthyle, alkyle à chaîne droite ou ramifiée ayant de 3 à 12 atomes de carbone et substitués ou non substitués, ou préparation de dérivés (XIV) fonctionnalisés sur le groupe carboxylique tels que les chlorures d'acyl, les anhydrides, et analogues ;
- réaction entre le sel de sodium desdits dérivés (XIV) ou desdits dérivés (XIV) fonctionnalisés sur le groupe carboxylique, avec un composé ayant la formule générale suivante :

\[
\begin{array}{c}
\text{R₄} \\
\text{(C)ₙ} \\
\text{OH} \\
\end{array}
\]

(XVI)

dans laquelle :
R₄ est choisi parmi le chlore, le brome, NH₅R₆, R₆ étant un hydrogène ou un groupe alkyle à chaîne droite ou ramifiée, A et B sont choisis parmi l'hydrogène, les groupes alkyle à chaîne droite ou ramifiée, substitués ou non substitués, et n est compris entre 10, de façon à obtenir les esters monomères correspondants ou les amides correspondants ;
réaction des dits esters monomères ou des dits amides avec un composé d’halogénation tel que PBr₃ ou analogues, pour obtenir les dits esters monomères ou les dits amides, caractérisée par la présence d’un groupe halogène terminal ;

réaction des dits esters monomères ou des dits amides caractérisée par la présence d’un groupe halogène terminal avec un agent de nitrilation tel que AgNO₃ ou analogues, pour obtenir les esters nitrates ayant la formule générale suivante :

\[
\begin{array}{c}
\text{R₂} \quad \text{O} \quad \text{A} \\
\mid \quad \| \quad \mid \\
\text{R} - \text{CH} - \text{C} - \text{Y} - (\text{C})ₙ\text{ONO₂} \\
\mid \\
\text{B}
\end{array}
\]

où Y est choisi parmi l’oxygène, NH, NR₃ où R₁ est un groupe alkyle à chaîne droite ou ramifiée.