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(54) Title: THE USE OF AN ESTER OF INOSITOLTRISPHOSPHATE FOR THE PREPARING OF AN ANALGETIC MEDICAMENT

(57) Abstract

The present invention relates to the use of an ester of inositoltrisphosphate for the preparing of a medicament effective as an analgesic.

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THE USE OF AN ESTER OF INOSITOLTRISPHOSPHATE FOR THE PREPARING OF AN ANALGETIC MEDICAMENT

The present invention relates to the use of an ester of inositoltrisphosphate for the preparing of a medicament effective as an analgesic.

Many diseases and medical procedures are characterized by the sense of pain in different ways for the patient. For example during and after surgical operations the manifestation of pain is high. The same is true for many disorders related to trauma. Thus e.g. burn patients suffer great pain directly after an accident but also during the recovery period. Pain is also mainfested in most inflammatory conditions and in association tumour-related diseases or treatment of those. Different therapeutics are used in order to achieve an analgetic or anaesthetic effect. Various types of local anaesthetics are utilized to abolish the sensation of pain to a limited area of the body around the site of its application. Other drugs such as opioids, for example morphine, are used for reducing severe pain related to surgical operations. Another type of pharmaceuticals used to reduce pain are sedative agents such as barbiturates and benzodiazepines. Many of these drugs have side effects such as depressant action on respiration and circulation and are producing nausea and vomiting, which limit their use to many groups of patients. Furthermore many of the used drugs give hypnotic effects which are undesirable for the patient.

Nonsteroidal anti-inflammatory drugs are used to treat pain and inflammation. This class of compounds works by

preventing the synthesis of prostaglandins and side-effects such as damage to the gastic mucosa often appear.

According to the present invention it has surprisingly become possible to reduce pain without sedative effects by the use of an ester of inositoltrisphosphate for the preparing of a medicament effective as an analgesic.

In preferred embodiments of the invention the medicament is intended to be used for preventing, alleviating and combatting pain.

The medicament can be used for example in the following conditions in order to reduce pain:

Tissue damage induced mechanically or chemically such as burns, trauma i.e. wounds or injuries caused by physical damage.

Injuries following surgery or operations.

Conditions related to tumours.

Inflammatory conditions such as joint inflammations.

The medicament can also be effective in other disorders or conditions where reduction of pain is desirable.

The medicament exerts significant analgesic effects without showing any side-effects and without any sedative effects which is very beneficial for the patient.

From the European Patent No 179439 a pharmaceutical composition comprising as a pharmaceutically active ingredient at least one isomer of inositoltrisphosphate is known. In said patent the effect of this pharmaceutical composition is shown for different areas, such as platelet aggregation.

The production of esters of inositoltrisphosphate and the isolation of the different isomers thereof are disclosed in the European Patent Application No. 0269105.

The therapeutic profile of esters of inositoltrisphosphates differs from the profile of inositoltrisphosphates in many important aspects. Chemical properties such as lipophilicity, solubility and pK_A-values are changed which affect the potency and selectivity of the compound.

Furthermore the susceptibility against enzymatic degradation is markedly lowered for esters of inositoltrisphosphates which result in a prolonged duration.

It is suitable that the medicament used according to the invention exists in unit dosage form. Tablets, granules or capsules are suitable administration forms for such unit dosage. Furthermore, tablets and granules can easily be surface treated such as to provide an enteric coating to prevent an uncontrolled hydrolysis in the stomach and to bring about a desired absorption in the intestine. Other suitable administration forms are slow release and transdermal administration. A usual pharmaceutrically acceptable additive, excipient and/or carrier can be included in the medicament. The tablets or granules can also contain a disintegrant which causes the tablets or

the granules, respectively, to disintegrate easily in the intestine. In certain cases, especially in acute situations, it is preferable to use the unit dosage in the form of a solution for intravenous administration. In other situations suspensions comprising the compound can be preferably used as administration form.

The medicament can also consist as such of esters of inositoltrisphosphate solely without any additive, excipient or carrier.

The medicament can consist of or comprise one or more specific isomers of esters of inositoltrisphosphate, each present in substantially pure form. Thus, the different isomers can be isolated from each other in substantially pure form, which means that they have a purity of 80-100 %, such as 82-100 % or 85-100 %, preferably 90-100 %. Since the isomers can be produced in pure form they can be mixed in any proportion, of course.

It is in most cases suitable that the ester of inositoltrisphosphate used for the preparing of the medicament according to the invention are present in salt form in order not to affect the mineral balance negatively. The salt should preferably consist of a sodium, potassium, calcium or magnesium salt or a mixture of two or more of these salts.

For the above mentioned reasons it is also an advantage if the medicament contains a surplus or an extra addition of at least one pharmaceutically acceptable salt of calcium, zinc or magnesium with a mineral acid or organic acid. This is especially valuable for elderly persons who

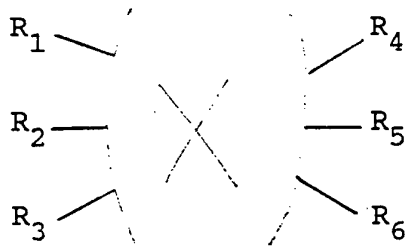
are often deficient in these minerals.

For administration to human patients appropriate dosages can routinely be determined by those skilled in this art by extension of the results obtained in animals at various dosages. The preferred dosage for humans falls within the range of 0.1 to 1000 mg, especially 0.1-200 mg of the compound/day/kg body weight.

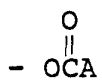
In animal experiments, no toxic effects were seen after administration of very high doses of esters of inositol-trisphosphates, 300 mg/kg body weight by intravenous injection to mice.

The medicament usually contains 0.01-1.5 g, such as 0.05-1.3 g or preferably 0.1-1 g of the compound per unit dosage.

The composition used according to the present invention contains at least one, sometimes two or more of the following compounds which correspond to esters of inositoltrisphosphates with the structural formula:



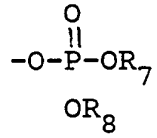
where R_1, R_2 and R_3 are vicinal and all are



where A is

(1) straight or branched chain alkyl containing 1 to 24 carbon atoms
(2) cycloalkyl containing 3 to 16 carbon atoms
(3) alkenyl containing 2 to 24 carbon atoms
(4) cycloalkenyl containing 5 to 16 carbon atoms
(5) aryl containing 6 to 24 carbon atoms
(6) aralkyl containing 7 to 48 carbon atoms
(7) alkaryl containing 7 to 48 carbon atoms
(8) aralkenyl containing 8 to 48 carbon atoms
(9) alkenylaryl containing 8 to 48 carbon atoms
(10) a heterocyclic ring containing at least one atom of oxygen, nitrogen or sulfur said meanings (1) to (10) being unsubstituted or substituted with hydroxy, oxo, alkoxy, aryloxy, halo, cyano, isocyano, carboxy, esterified carboxy, amino, substituted amino, formyl, acyl, acyloxy, acylamino, sulfinyl, sulfonyl, phosphino, phosphinyl, phosphonyl, mercapto, alkylthio, arylthio, silyl, silyloxy, silylthio, nitro or azido
(11) carboxy
(12) esterified carboxy
(13) amino or
(14) substituted amino

where R_4, R_5 and R_6 are vicinal and all are



where R_7 and R_8 are the same or different and are

(1) hydrogen
(2) mono-, di- or trivalent cation

and where X is a radical of myo-inositol or a configuration isomer thereof.

The substituent A could be the same for all R_1, R_2 and R_3 or could have different structures following the above definition.

In another preferred embodiment of the invention R_1, R_2 and R_3 are vicinal and all are

(1) $-OC(CH_2)_nOH$ where n is an integer between 1 and 10; preferably n is between 2 and 4

(2) $-OC(CH_2)_nOR_9$ where n is an integer between 1 and 10 and where R_9 is a substituted or unsubstituted straight or branched alkyl, cycloalkyl, aryl or alkaryl; preferably n is between 2 and 4 and R_9 is a lower alkyl such as methyl, ethyl or propyl.

(3) $-OC(CH_2)_nY(CH_2)_mOH$ where n and m is an integer between 1 and 10 and where Y is oxygen or sulphur; preferably n is 1 and m is between 2 and 4.

(4) $-OC(CH_2)_nY(CH_2)_mOR_9$ where n and m is an integer between 1 and 10, where Y is oxygen or sulphur and where R_9 is a substituted or unsubstituted straight or branched alkyl, cycloalkyl, aryl or alkaryl; preferably n is 1, m is between 2 and 4 and R_9 is a lower alkyl such as methyl, ethyl or propyl.

(5) $-OC(CH_2)_nOCR_9$ where n is an integer between 1 and 10 and where R_9 is a substituted or unsubstituted, straight or branched alkyl, cycloalkyl, aryl or aralkyl; preferably n is 1 or 2 and R_9 is a lower alkyl such as methyl, ethyl or propyl.

(6) $-OC(CH_2)_nCOOR_{10}$ where n is an integer between 1 and 10 and where R_{10} is hydrogen or a substituted or unsubstituted, straight or branched alkyl, cycloalkyl, aryl or aralkyl; preferably n is 2 or 3 and R_{10} is hydrogen or a lower alkyl such as methyl, ethyl or propyl.

(7) $-OC(CH_2)_nOCOR_9$ where n is an integer between 1 and 10 and where R_9 is a substituted or unsubstituted, straight or branched alkyl, cycloalkyl, aryl or aralkyl; preferably n is 1 and R_9 is a lower alkyl such as methyl, ethyl or propyl.

(8) $-OC(CH_2)_nOCNR_9R_{10}$ where n is an integer between 1 and 10 and where R_9 is a substituted or unsubstituted, straight or branched alkyl, cycloalkyl, aryl or aralkyl, and where R_{10} is hydrogen or substituted or unsubstituted, straight or branched alkyl, cycloalkyl, aryl or aralkyl; preferably n is 1, R_9 is lower alkyl such as methyl, ethyl or propyl and R_{10} is hydrogen.

(9) $-OC(CH_2)_nNR_{10}CORH9Y$ where n is an integer between 1 and 10 and where R_9 is a substituted or unsubstituted, straight or branched alkyl, cycloalkyl, aryl or aralkyl and where R_{10} is hydrogen or substituted or

unsubstituted, straight or branched alkyl, cycloalkyl, aryl or aralkyl; preferably n is 1, R_9 is lower alkyl such as methyl, ethyl or propyl and R_{10} is hydrogen.

(10) $-OC(CH)_{2n}R_9$ where n is an integer between 1 and 10 and where R_9 is a substituted or unsubstituted, straight or branched alkyl, cycloalkyl, aryl or aralkyl; preferably n is 1 and R_9 is a lower alkyl such as methyl, ethyl or propyl.

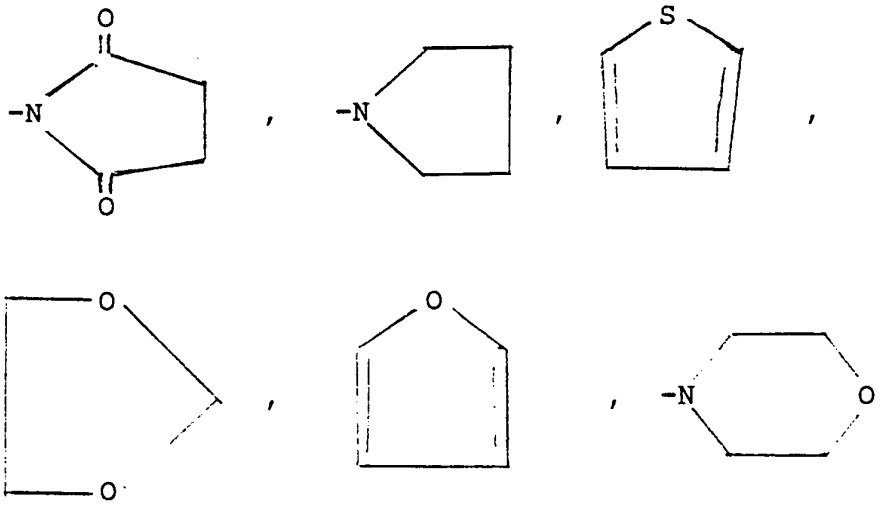
(11) $-OCZ^1$ where Z^1 is substituted or unsubstituted cycloalkyl such as $CH(CH_2)_2$, $CH(CH_2)_3$, $CH(CH_2)_4$, $CH(CH_2)_5$, $CH(CH_2)_6$ or $CH(CH_2)_2(CH)_2$.

(12) $-OC(CH_2)_nZ^1$ where Z^1 is substituted or unsubstituted cycloalkyl such as $CH(CH2)_2$, $CH(CH_2)_3$, $CH(CH_2)_4$, $CH(CH_2)_5$, $CH(CH_2)_6$ or $CH(CH_2)_2(CH)_2$ and where n is an integer between 1 and 10; preferably n is 1.

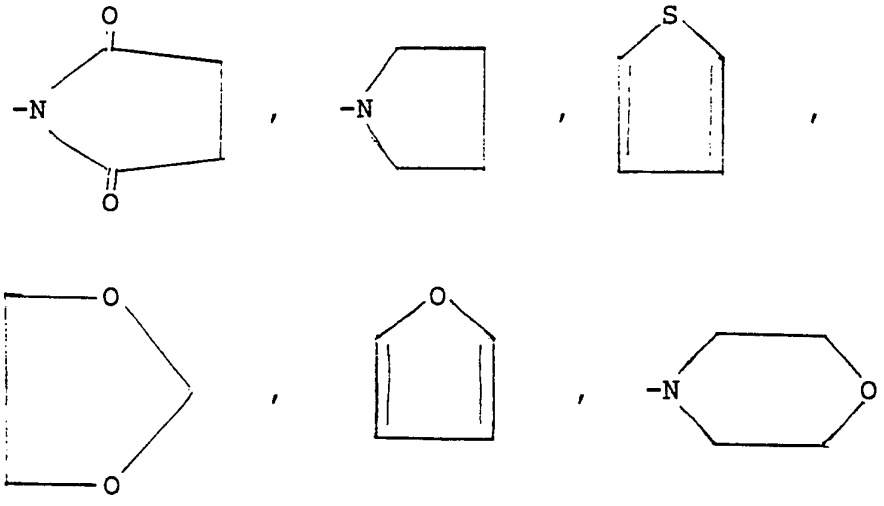
(13) $-OCZ^2$ where Z^2 is substituted or unsubstituted phenyl, biphenyl, naphtyl, anthracenyl or phenantrenyl.

(14) $-OC(CH_2)_nZ^2$ where Z^2 is substituted or unsubstituted phenyl, biphenyl, naphtyl, anthracenyl or phenantrenyl and where n is an integer between 1 and 10; preferably n is 1.

(15) $-\overset{O}{\overset{\|}{O}}CZ^3$ where Z^3 is substituted or unsubstituted heterocyclic compound such as



(16) $-\overset{O}{\overset{\|}{O}}C(CH_2)_nZ^3$ where Z^3 is substituted or unsubstituted heterocyclic compound such as



(17) $-\overset{O}{\overset{\|}{O}}C(CH_2)_nNR_9R_{10}(CH_2)_mOR_{11}$ where n and m is an

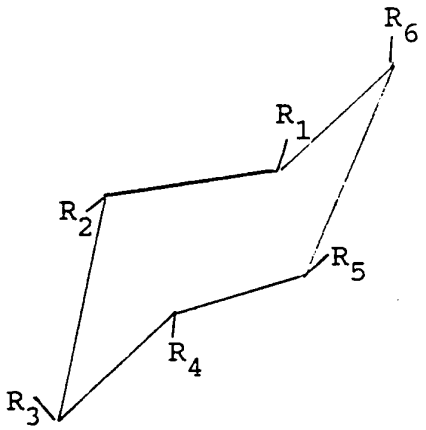
integer between 1 and 10, where R_9 is a substituted or unsubstituted, straight or branched alkyl, cycloalkyl, aryl, alkaryl and where R_{10} and R_{11} are hydrogen or substituted or unsubstituted straight or branched alkyl, cycloalkyl, aryl, alkaryl; preferably n is 1 or 2, m is 2 or 3, R_9 is lower alkyl and R_{10} and R_{11} are hydrogen.

(18) -O-acetyl, -O-propionyl, -O-butyryl, -O-isobutyryl, -O-(4-acetoxy)butyryl, -O-valeryl, -O-isovaleryl, -O-(4-propionyloxy)valeryl, -O-pivaloyl, -O-hexanoyl, -O-octanoyl, -O-decanoyl, -O-dodecanoyl, -O--tetradecanoyl, -O-hexadecanoyl or -O-octadecanoyl.

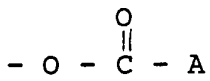
(19) -O-methylcarbamoyl, -O-ethylcarbamoyl, -O-propylcarbamoyl, -O-butylcarbamoyl, -O-phenylcarbamoyl, -O-benzoylcarbamoyl, -O-(2-acetoxy)benzoylcarbamoyl, -O-(2-propionyloxy)benzoylcarbamoyl or chlorosulfonylcarbamoyl.

The formula above discloses specific esters of inositoltrisphosphate where the inositol moiety is selected from the group of myoinositol, cisinositol, epiinositol, alloinositol, neoinositol, mucoinositol, chiroinositol and scylloinositol.

In one preferred embodiment of the invention the compound used for the preparing of a medicament effective as an analgesic has the structural formula



where R_1, R_2 and R_3 are vicinal and all are



where A is

(1) straight or branched chain alkyl containing 1 to 24 carbon atoms
(2) cycloalkyl containing 3 to 16 carbon atoms
(3) alkenyl containing 2 to 24 carbon atoms
(4) cycloalkenyl containing 5 to 16 carbon atoms
(5) aryl containing 6 to 24 carbon atoms
(6) aralkyl containing 7 to 48 carbon atoms
(7) alkaryl containing 7 to 48 carbon atoms
(8) aralkenyl containing 8 to 48 carbon atoms
(9) alkenylaryl containing 8 to 48 carbon atoms
(10) a heterocyclic ring containing at least one atom of oxygen, nitrogen or sulfur said meanings (1) to (10) being unsubstituted or substituted with hydroxy, oxo, alkoxy, aryloxy, halo, cyano, isocyano, carboxy, esterified carboxy, amino, substituted amino, formyl, acyl, acyloxy, acylamino, sulfinyl,

sulfonyl, phosphino, phosphinyl, phosphonyl, mercapto, alkylthio, arylthio, silyl, silyloxy, silylthio, nitro or azido

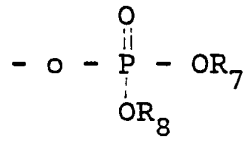
(11) carboxy

(12) esterified carboxy

(13) amino or

(14) substituted amino

and where R_4, R_5 and R_6 all are



where R_7 and R_8 are the same or different and are

(1) hydrogen

(2) mono-, di- or trivalent cation

The compounds contemplated in this embodiment of the invention are esters of myo-inositoltrisphosphates and preferred compounds are esters of D-myo-inositol-1,2,6-trisphosphates.

The invention will be further explained in the following examples where Example 1 shows the manufacturing of a solution of an ester of myo-inositoltrisphosphate for intravenous administration, Example 2-6 demonstrate the manufacture of different esters of myo-inositoltrisphosphate and Example 7 and 8 illustrate the effect of esters of myo-inositoltrisphosphate to reduce pain.

Example 1

Solution of the sodium salt of D-3,4,5-tri-O-hexanoyl--myo-inositol-1,2,6-trisphosphate (PP 10-202) for injection.

0.5 g of the sodium salt of PP 10-202 and 0.77 g sodium chloride were dissolved in 98.73 ml of water for injection to form a solution suitable for injection into a person or an animal.

Example 2

1.92 mmol of the acid form of D-myo-inositol-1,2,6-trisphosphate (IP_3) was evaporated for the elimination of any residue of water and was then dissolved in 25 ml dimethylformamide (DMF). 1.24 g triethylamine was added followed by evaporation and an addition of 1.15 g 4-(dimethylamino)pyridine. To this solution, 5.30 g 4-acetoxybutyric anhydride dissolved in 100 ml dimethylene chloride was added during 30 minutes. The reaction mixture was stirred for 3 hrs at room temperature and then evaporated to dryness.

The residue was dissolved in 100 ml metanol and was extracted with 3x20 ml of heptane. The methanol-fraction was evaporated and the remaining product was analysed with NMR. Structural determination and NMR showed the compound to be D-3,4,5-tri-O-(4-acetoxybutyryl)-myo-inositol-1,2,6-trisphosphate.

Example 3

In experiments similar to the procedure described in example 2 the following esters of D-myo-inositol--1,2,6-trisphosphate were synthesized in good yield;

D-3,4,5-tri-O-propionyl-myo-inositol-1,2,6-trisphosphate
D-3,4,5-tri-O-butyryl-myo-inositol-1,2,6-trisphosphate
D-3,4,5-tri-O-isobutyryl-myo-inositol-1,2,6-trisphosphate
D-3,4,5-tri-O-(4-hydroxy)pentanoyl-myo-inositol-1,2,6-trisphosphate
D-3,4,5-tri-O-dodecanoyl-myo-inositol-1,2,6-trisphosphate.

Example 4

1.4 g of D-myo-inositol-1,2,6-tris(N-ethyldiisopropyl ammonium hydrogenphosphate) was dissolved in 15 ml methylene chloride. 1.59 g hexanoic anhydride, 1.4 ml N-ethyldiisopropylamine and 403 mg 4-(dimethylamino)-pyridin was added and the reaction mixture was stirred for 16 hrs at 40°C. The solvent was removed by evaporation and to the residue was added 15 ml tetrahydrofuran and 20 ml water.

The resulting suspension was purified by ion exchange chromatography (Dowex 50W-X8) with water as eluent. The eluate was neutralized with sodium hydrogen carbonate and the water was removed. The residue was identified with NMR to be D-3,4,5-tri-O-hexanoyl-myo-inositol-1,2,6-trisphosphate.

Example 5

5 g of the N-ethyldiisopropylamine salt of D-myo-inositol-1,2,6-trisphosphate was dissolved in 100 ml dimethylene chloride. 1.44 g 4-(dimethylamino)pyridine and 5 ml ethyldiisopropyl amine was added follow by dropwise addition of 5.75 ml phenylisocyanate during 60 minutes. The reaction mixture was stirred for 6 hours at room temperature and was then evaporated to dryness. The residue was dissolved in 30 ml tetrahydrofuran and 6 ml water followed by treatment with a cation exchange resin in H^+-form. The product was eluted with 200 ml of water and was treated with sodium hydrogen carbonate to reach pH 5.8. After filtration the supernatant was evaporated to dryness and analysed with NMR. The compound was identified as D-3,4,5-tri-O-phenylcarbamoyl-myo-inositol--1,2,6-trisphosphate.

Example 6

In experiments similar to the procedure described in example 5 the following carbamates of D-myo-inositol--1,2,6-trisphosphate were synthesized in good yield:

D-3,4,5-tri-O-(2-acetoxy)benzoyl carbamoyl-1,2,6-trisphosphate
D-3,4,5-tri-O-butylcarbamoyl-1,2,6-trisphosphate
D-3,4,5-tri-O-methylcarbamoyl-1,2,6-trisphosphate

Example 7

Two groups of rats, 10 animals per group, were used in order to investigate the analgetic effect of D-3,4,5-tri-

-O-hexanoyl-myo-inositol-1,2,6-trisphosphate (PP 10-202). The control group was given an intravenous dose of saline while the other group was given a dose of 80 mg/kg of the sodium salt of PP 10-202. Immediately after intravenous dosing, each rat received an intraperifoneal injection of 1 ml of a 1 % (w/w) solution of acetic acid. Directly after that procedure each animal was placed into individual observation chambers and the numbers of writhes elicited during the subsequent 25- minute period were recorded. After the observation period the animals were killed by cervical dislocation. The number of writhes during the observation period is an expression of the pain experienced by the animal. The control group had an average of 48 writhes during the period while the group receiving PP 10-202 had an average of 6 writhes during the period.

The results demonstrate a significant reduction in pain when PP 10-202 is administered.

Example 8

In an experiment similar to the procedure described in example 7 the analgetic effect of D-3,4,5-tri-O-propionyl-myo-inositol-1,2,6-trisphosphate (PP10-305) was determined. The decrease of the number of writhes in the animals receiving PP10-305 was 23 % showing an analgetic effect of the compound.

CLAIMS

1. The use of an ester of inositoltrisphosphate for the preparing of a medicament effective as an analgesic.

2. The use of an ester of inositoltrisphosphate for the preparing of a medicament for preventing, alleviating or combatting pain.

3. The use according to anyone of claims 1-2 wherein said ester of inositoltrisphosphate is in salt form.

4. The use of according to claim 3 wherein said ester of inositoltrisphosphate is a salt of sodium, potassium, calcium or zinc.

5. The use according to anyone of claims 1-2 wherein said ester of inositoltrisphosphate is an ester of myo-inositoltrisphosphate.

6. The use according to anyone of claims 1-2 wherein said ester of inositoltrisphosphate is an ester of D-myo-inositol-1,2,6-trisphosphate.

7. The use according to anyone of claims 1-4 wherein the medicament is in unit dosage forms comprising tablets, granules, capsules, solutions or suspensions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/01092

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/66, C07F 9/117
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)

IPC6: A61K

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

SE,DK,FI,NO classes as above

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

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP, A2, 0269105 (SIREN, MATTI), 1 June 1988 (01.06.88), see pages 19 and 25 and exemples 5 and 8	1-7
Y	P.B. Curtis-Prior, "PROSTAGLANDINS, an Introduction to their Biochemistry, Physiology and Pharmacology", 1976, NORTH-HOLLAND PUBLISHING COMPANY, see page 43	1-7
Y	US, A, 4515722 (SHU S. YANG ET AL), 7 May 1985 (07.05.85), see the whole document	1-7

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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International application No.
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