PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/66, C07F 9/117 — A1

(11) International Publication Number: **WO 95/14477**

(43) International Publication Date: 1 June 1995 (01.06.95)

(21) International Application Number: PCT/SE94/01095

(22) International Filing Date: 18 November 1994 (18.11.94)

(30) Priority Data:
9303854-5 22 November 1993 (22.11.93) SE

(71) Applicant *(for all designated States except US)*: PERSTORP AB [SE/SE]; S-284 80 Perstorp (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: PERSSON, Lars [SE/SE]; Möllegången 17, S-281 37 Hässleholm (SE). REHNBERG, Nicola [SE/SE]; Klövergatan 28, S-284 00 Perstorp (SE). GUSTAFSSON, Torgny [SE/SE]; Jättegatan 21, S-284 00 Perstorp (SE).

(74) Agent: STENBERG, Yngve; Perstorp AB, S-284 80 Perstorp (SE).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published
With international search report.

(54) Title: THE USE OF AN ESTER OF INOSITOLTRISPHOSPHATE FOR THE TREATMENT OF INFLAMMATORY CONDITIONS

(57) Abstract

The use of an ester of inositoltrisphosphate for the preparing of a medicament for preventing, alleviating or combatting inflammatory conditions in mammals including man.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

THE USE OF AN ESTER OF INOSITOLTRISPHOSPHATE FOR THE TREATMENT OF INFLAMMATORY CONDITIONS

The present invention relates to the use of an ester of inositoltrisphosphate for the preparing of a medicament for preventing, alleviating or combatting inflammatory conditions in mammals including man.

Injury or destruction of tissues should be understood as damage to an aggregation of specialized cells with a particular function both internally and externally in the body, such as different organs or parts of these, vessels, skin etc.

Tissue damage involves a complex series of events such as dilatation of vessel walls e.g. arterioles, capillaries and venules, increased permeability of fluids including e.g. plasma proteins and increased blood flow. Increased vascular leakage often results in extravasation and oedema formation which characterize the damage of different tissues.

Often tissue damage and inflammatory conditions are characterized by signs of pain, heat, redness, swelling and loss of function.

Tissue damage is not defined as a disease per se but is often a component in different diseases of both acute or chronic nature.

Damage of tissues can be induced in many ways. Inducing factors can be correlated with mechanical effects, immunological effects or chemical effects. Microorganisms such as virus, bacteria and fungus can induce tissue damage and exposure to heat, fire, radiation, cold and blows most often results in such damage. Many diseases like asthma, eczema, psoriasis, rheumatoid arthritis, diabetes and arteriosclerosis also involve different types of tissue damage.

The existing treatments of diseases connected to tissue damage and inflammatory conditions are based on drugs such as non steroid antiinflammatory drugs (NSAID), steroids, antibiotics and cytostatics. In some cases also surgical therapy is used.

Existing drugs often suffer from limited effectiveness in combination with serious side effects. Toxic effects appearing from the treatment with NSAID:s can consist of gastrointestinal side effects, allergic reactions and side effects in the central nervous system. Treatment with steroids often results in side effects such as osteoporosis and fractures, increased susceptibility to infections and peptic ulcerations.

According to the present invention it has surprisingly become possible to overcome and reduce the above mentioned injuries and destructions of tissues by the use of and ester of inositoltrisphosphate for the preparing of a medicament for preventing, alleviating or combatting inflammatory conditions in mammals including man.

The invention also covers the use of an ester of inosi-

toltrisphosphate for the preparing of a medicament for preventing, alleviating or combatting tissue damage in mammals including man.

In preferred embodiments of the invention the medicament is intended to be used for preventing, alleviating or combatting tissue damage related to oedema formation and vascular leakage. In other preferred embodiments of the invention the medicament is intended to be used for preventing, alleviating or combatting tissue damage related to burns, rhinitis, asthma and arthritis.

The invention relates to the use of an ester of inositoltrisphosphate for preparing a medicament for preventing, alleviating or combatting for example the following conditions:

Tissue damage and inflammatory conditions induced mechanically by heat and fire such as burns of first, second or third degree, trauma i.e. wounds or injuries caused by physical damage, or cold;
Tissue damage and inflammatory conditions induced chemically or by microorganisms such as radiation, sepsis and injuries caused by e.g. bee-stings, snake-bites etc;
Tissue damage and inflammatory conditions in diseases where the immunological component is strongly expressed such as rhinitis, hayfever, asthma, psoriasis, vasculitis and eczema. Furthermore the invention relates to treatment of tissue damage and inflammatory conditions related to erythema, herpes and arthritis, injuries caused by or following surgery and operations of grafts, catheters

etc. and injuries caused by or occurring in the border zone of an infarct of cardiac type, cerebral type or any other type.

Other injuries of tissues related to diseases such as uveitis, otitis, stomatitis, peritonitis, sinusitis, gastroenteritis, colitis and cystitis are also related to the invention.

The medicament is effective against tissue damage connected to the above mentioned conditions but also to other conditions where tissue damage and inflammations occurs.

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 inositoltrisphos-

phates 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 pharmaceutically 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 substantialy 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 inositol-trisphosphate 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 zinc 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.

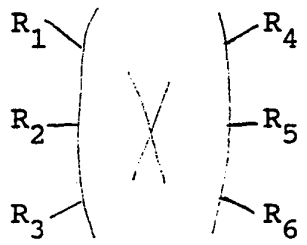
For administration to human patients appropriate dosages can routinely be determined by those skilled in this art by extension of the results obtained in animals at various dosages. The preferred dosage for humans falls within the range of 0,1 to 1000 mg, especially 0.1-200 mg of the compound/day/kg 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, phosphine, phosphinyl, phosphonyl, mercapto, alkylthio, arylthio, silyl, silyloxy,

silylthio, nitro or azido

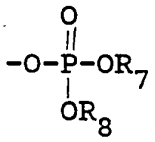
(11) carboxy

(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)  where n is an integer between 1 and 10; preferably n is between 2 and 4

(2)  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) $-OC(=O)(CH_2)_nY(CH_2)_mOH$ 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) $-OC(=O)(CH_2)_nY(CH_2)_mOR_9$ 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) $-OC(=O)(CH_2)_nOCR_9$ 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) $-OC(=O)(CH_2)_nCOOR_{10}$ 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) $-OC(=O)(CH_2)_nOCOR_9$ 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) $-OC(CH_2)_nNR_{10}COR_9$ 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 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 $CH(CH_2)_2(CH)_2$.

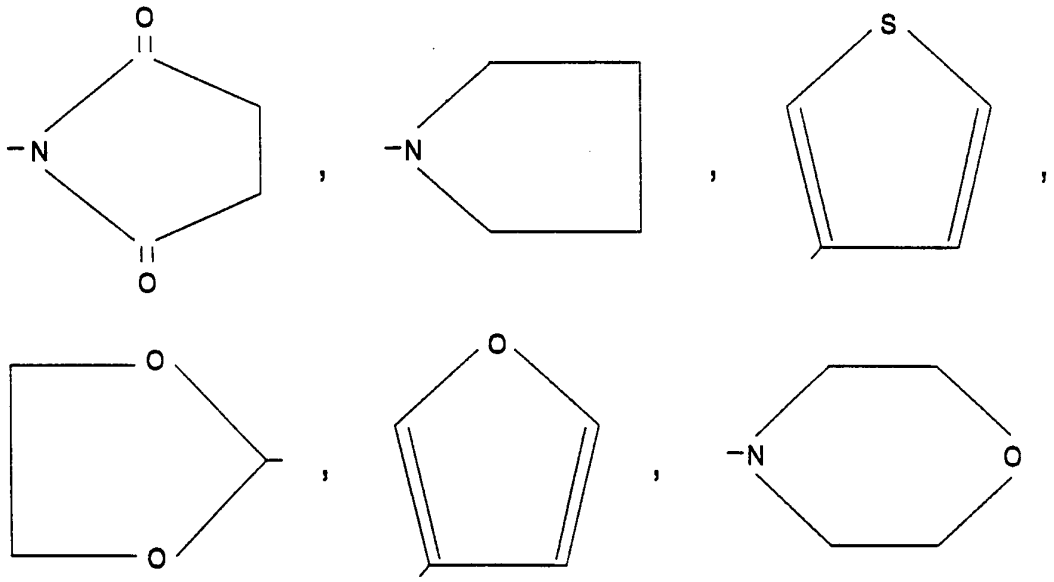
(12) $-OC(CH_2)_nZ^1$ where Z^1 is substituted or unsubstituted cycloalkyl such as $CH(CH_2)_2$, $CH(CH_2)_3$, $CH(CH_2)_4$, $CH(CH_2)_5$, CH(CH2)6 or $CH(CH_2)_2(CH)_2$ and where n is

an integer between 1 and 10; preferably n is 1.

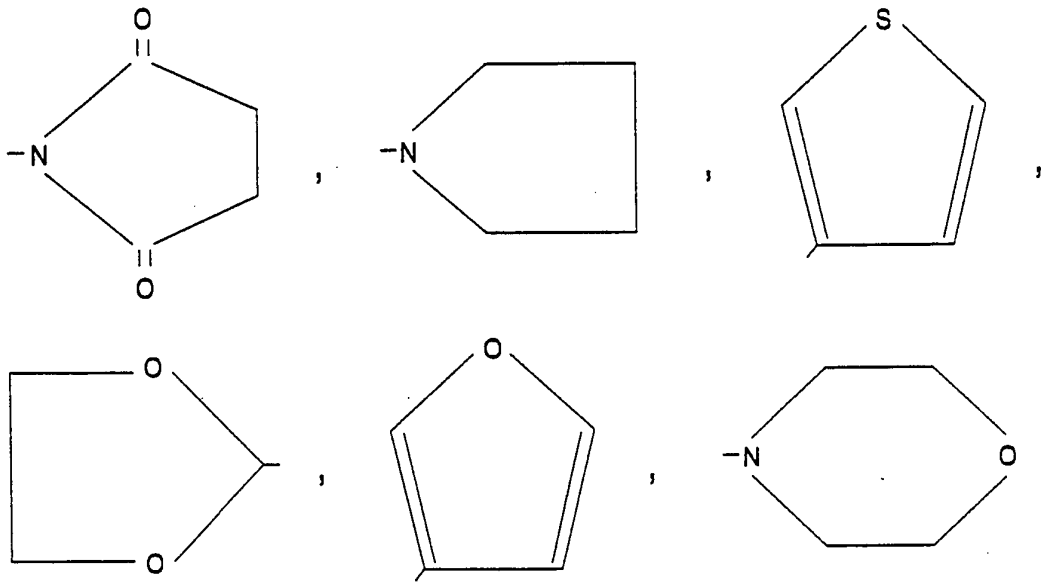
(13) $-O\overset{O}{\overset{\|}{C}}Z^2$ where Z^2 is substituted or unsubstituted phenyl, biphenyl, naphtyl, anthracenyl or phenantrenyl.

(14) $-O\overset{O}{\overset{\|}{C}}(CH_2)_nYZ^2$ 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) $-O\overset{O}{\overset{\|}{C}}Z^3$ where Z^3 is substituted or unsubstituted heterocyclic compound such as



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



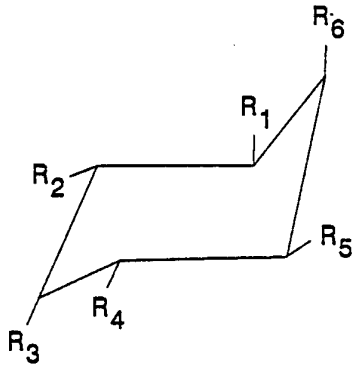
(17) $-OC(CH_2)_nNR_9R_{10}(CH_2)_mOR_{11}$ where n and m is an integer between 1 and 10, where R_9 is a substituted or unsubstituted, straight or branched alkyl, cycloalkyl, aryl, alkaryl and where R_{10} and R_{11} are hydrogen or substituted or unsubstituted straight or branched alkyl, cycloalkyl, 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.

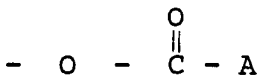
(19) -O-methylcarbamoyl, -O-ethylcarbomoyl, -O-propylcarbamoyl, -O-butylcarbamoyl, -O-phenylcarbamoyl, -O-benzoylcarbamoyl, -O-(2-acetoxy)benzoylcarbamoyl, -O-(2-propionyloxy)benzoylcarbamoyl or chlorosulfonylcarbamoyl.

The formula above discloses specific esters of inositol-trisphosphates 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 the preparing of a medicament effective against inflammatory conditions has the structural formula



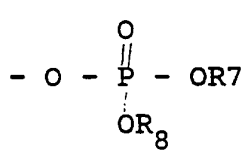
where R_1, R_2 and R_3 are vicinal and all are



where A is

(1) straight or branced 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 yo 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) esterfied 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 and Example 2-6 demonstrate the manufacture of different esters of myo-inositoltrisphosphate and Example 7 and 8 illustrate the inhibiting effect of esters of myo-inositoltrisphosphate against inflammation.

Example 1

Solution of the sodium salt of D-3,4,5-tri-O-hexanyl-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-di-methylamino pyridine. To this solution, 5.30 g

4-acetoxybutyric an hydride dissolved in 10 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 10 ml methanol 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-hydroxypentanoyl-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 hydrogen phosphate) was dissolved in 15 ml methylene chloride. 1.59 g hexanoic anhydride, 1.4 ml N-ethyldiisopropyl amine and 403 mg 4-(dimethylamino)pyride was added and the reaction mix-

ture 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 50 W-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 10 ml dimethylene chloride. 1.44 g 4-(dimethylamino)pyridine and 5 ml ethyldiisopropyl amine was added followed 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 eluated 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

Injection of carrageenan into the subplanar surface of the rat hind-paw induces tissue damage and an inflammatory reaction that results in pronounced oedema. The degree of oedema can be reproducibly quantified by measuring paw circumference.

Two groups of five male rats were injected 2 hours and 1 hour before injection of carrageenan with 80 mg/kg D-3,4,5-tri-O-hexanoyl-myo-inositol-1,2,6-trisphosphate (PP 10-202) or Krebs ringer solution (control) respectively.

Measurement of the paw diameter was made at specific intervals.

The results show that an injection of PP 10-202 reduces the oedema with 41 % one hour after the induction of the damage as compared to control. Two and a half hour after the induction of the damage the oedema was reduced with 49 % compared to control. Thus, the inflammation in the animals treated with PP 10-202 was strongly reduced and the duration of the counteractive effect was prolonged.

Example 8

In an experiment similar to the procedure described in example 7 the antiinflammatory effect D-3,4,5-tri-O-isobutyryl-myo-inositol-1,2,6-trisphosphate (PP10-201) was determined. The results are summarized in the following table:

	Reduction of inflammation	
	after one hour	after three hour
Control	0 %	0 %
Administration of PP10-201	49 %	57 %

The results show that the administration of PP10-201 strongly reduces the inflammation with a long duration.

CLAIMS

1. The use of an ester of inositoltrisphosphate for the preparing of a medicament for preventing, alleviating or combatting inflammatory conditions in mammals including man.

2. The use of an ester of inositoltrisphosphate for the preparing of a medicament for preventing, alleviating or combatting tissue damage in mammals including man.

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

4. The use according to claim 3, wherein said ester of inositoltrisphosphate is a salt of sodium, calcium, zinc or magnesium or a mixture of two or more thereof.

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 any one of claims 1-2, wherein the ester of inositoltrisphosphate is an ester of D-myo-inositol-1,2,6-trisphosphate.

7. The use according to any one of claims 1-6, wherein the medicament is in unit dosage form comprising tablets, granules, capsules, solutions or suspensions.

INTERNATIONAL SEARCH REPORT

Int...ational application No.
PCT/SE 94/01095

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	EP, A2, 0269105 (SIREN, MATTI), 1 June 1988 (01.06.88), see pages 19 and 25 and examples 5 and 8	1-7
	--	
X	EP, A2, 0420428 (SABIN, ROBERT), 3 April 1991 (03.04.91), see the whole document	1-7
	--	
A	WO, A1, 9109601 (PERSTORP AB), 11 July 1991 (11.07.91), see the whole document	1-7
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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 documents, 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	Date of mailing of the international search report
17 February 1995	28.02.1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/01095

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A2, 0359256 (SIREN, MATTI), 21 March 1990 (21.03.90), see the whole document -- --------	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/12/94

International application No.
PCT/SE 94/01095

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0269105	01/06/88	AU-B- 603158	08/11/90
		AU-A- 8168287	02/06/88
		DE-A- 3740152	09/06/88
		GB-A,B- 2198135	08/06/88
		JP-A- 63198694	17/08/88
		US-A- 5157140	20/10/92
		US-A- 5274161	28/12/93
		US-A- 5278332	11/01/94
EP-A2- 0420428	03/04/91	CA-A- 2019878	13/03/91
WO-A1- 9109601	11/07/91	AU-A- 6970091	24/07/91
		EP-A- 0505452	30/09/92
		GB-A- 2255505	11/11/92
		JP-T- 5502864	20/05/93
		US-A- 5342832	30/08/94
EP-A2- 0359256	21/03/90	SE-T3- 0359256	
		DE-U- 6890252	24/09/92
		DE-U- 6890450	04/03/93
		DE-T- 68906106	21/10/93
		DE-D,T- 68914922	01/09/94
		EP-A- 0359257	21/03/90
		EP-A,B- 0359258	21/03/90
		SE-T3- 0359258	
		EP-A,B- 0359259	21/03/90
		SE-T3- 0359259	
		EP-A,B- 0359260	21/03/90
		SE-T3- 0359260	
		ES-T- 2043998	01/01/94
		ES-T- 2045319	16/01/94
		ES-T- 2054965	16/08/94
		ES-T- 2055772	01/09/94
		GB-A,B- 2223167	04/04/90
		GB-A,B- 2223168	04/04/90
		GB-A,B- 2223169	04/04/90
		GB-A,B- 2223403	11/04/90
		GB-A,B- 2223404	11/04/90
		JP-A- 2191217	27/07/90
		JP-A- 2191218	27/07/90
		JP-A- 2191219	27/07/90
		JP-A- 2191220	27/07/90
		JP-A- 2191221	27/07/90
		SE-B- 464059	04/03/91
		SE-A- 8803248	16/03/90
		SE-A- 9003395	25/04/92