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(54) Title: USE OF PLATELET ACTIVATING FACTOR ANTAGONISTS AS ANTI-PRURITIC AGENTS

(57) Abstract

This invention relates to a method for treating pruritus by administering a therapeutically effective amount of a PAF antagonist to a mammal afflicted with pruritus. The PAF antagonists may, for example, be selected from synthetic PAF analogues, natural products isolated from plants having PAF antagonist activity, and triazolobenzodiazepines. The PAF antagonists are preferably applied topically to the afflicted site but systemic such as oral, parenteral, nasal and intrarectal administration, is also possible.

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USE OF PLATELET ACTIVATING FACTOR ANTAGONISTS AS ANTI-PRURITIC AGENTS

Field of the Invention

The present invention relates to methods and means for treating pruritus. More particularly, this invention concerns the use of platelet activating factor (PAF) antagonists or anti-pruritic agents.

Background of the Invention

Itch, or pruritus, is a common and distressing symptom in a variety of diseases. Pruritus typically occurs in peripheral diseases such as allergic conjunctivitis, allergic rhinitis, hemorrhoids, and dermatoses of fungal, allergic and non-allergic origin. Itching can also be a major symptom of certain systemic diseases such as, Hodgkin's disease, chronic renal failure, polycythema vera, hyperthyroidism and cholestasis [see, for example, Herndon, J.H., Jr., Int. J. Derm. 14, 465-484 (1975); Winkelmann, R.K., Med. Clins. N. Am. 66, 1119-1133 (1982)]. The clinical importance of pruritus is undeniable but research efforts in this area have been modest, to great extent due to the absence of established, specific experimental models, especially in preclinical research.

The intracutaneous injection of histamine or proteases elicits itch, and may be used as an experimental model for itch studies [Cormia, F.E., J. Invest. Derm. 19, 21 (1952); Shelley, W.B. and Arthur, R.P., Arch. Derm. (Chicago) 76, 296, 323 (1957)]. It was, therefore, postulated that these agents are involved as mediators in various itching conditions. Since histamine was believed to be the primary mediator of the itch sensation, conventional itch therapy involves H_1-antihistamines as a first-line medication. However, antihistamines have no general anti-pruritic effect, in many instances they are either ineffective or only partially effective. The physician is often obliged to resort to glucocorticoids to relieve pruritus but the potential undesirable side effects from glucocorticoid therapy are of great concern. Glucocorticoids cause skin atrophy and are absorbed systemically to cause Cushings disease-like effects. It has been concluded that although histamine is undoubtedly a potent pruritogen, at least one

other itch-producing substance is involved in the clinically encountered spectrum of diseases where itch is a major symptom.

Although it is known that experimental pruritus may be evoked in human skin by the local administration of diverse pharmacologically active substances, the majority of which cause inflammation, demonstration that a chemical substance causes an itch sensation when locally administered does not necessarily mean that it is involved (as a mediator) in diseases in which itching is a symptom. Substances which have been reported to evoke or facilitate the itch sensation in human skin have not led to accepted anti-itch medications in those instances where compositions of matter are available to block the synthesis or activity of such substances. For example, according to Hagermark et al., J. Invest. Dermatol. 69, 527-539 (1977), prostaglandins E_2 and H_2 produce itch in human skin and potentiate the itch evoked by histamine. However, according to an earlier article by Hagermark [Acta Dermatovener 53, 363-368 (1973)] a known inhibitor of PGE_2 synthesis, aspirin, did not act as an anti-pruritic agent, rather it actually prolonged experimental itch produced by trypsin or histamine. These experimental findings are amply supported by clinical experience where drugs like aspirin and indomethacin are not generally regarded as useful in treating itch.

The pruritogenic activity of other substances has been attributed to an indirect mechanism involving histamine release, these postulates being based on the activity of systemically administered or locally injected H_1-antihistamines. Thus, synthetic platelet activating factor (PAF) has been reported to cause pruritus in human skin [Fjellner and Hagermark, Acta Derm. Venereol. 65, 409-412 (1985)] "via indirect and mainly histamine-dependent mechanism". Based upon their experimental findings, the authors concluded that PAF probably produced itch in human skin by release of mast cell bound histamine.

Given the complicating factors which may confound interpretation of itching studies, proof of involvement of a substance in mediating itch is provided only by studies which demonstrate that a composition of matter which interferes which the synthesis or pharmacological action of the substance in

question attenuates pruritus in either an experimental model of itching disease or in a study involving clinically encountered itch. Further, the beneficial effect of such a composition of matter in relieving itch should be demonstrated as independent of the actions of histamine.

Summary of the Invention

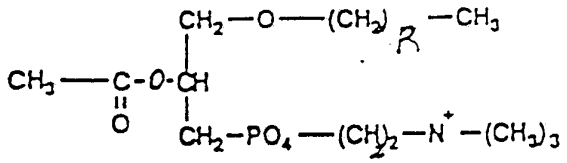
The present invention is based on the unexpected finding that platelet activating factor (PAF) is a very potent pruritogen and platelet activating factor antagonists (PAF antagonists) of highly diverse structures prevent itching episodes of allergic origin. The previously unrecognized anti-pruritic activity of such PAF antagonists is demonstrated as being independent of histaminergic mechanisms.

In one aspect, the present invention relates to a method for treating pruritus by administering a therapeutically effective amount of a PAF antagonist to a mammal afflicted with pruritus. The PAF antagonists may, for example, be selected from synthetic PAF analogues, natural products isolated from plants having PAF antagonist activity, and triazolobenzodiazepines. The PAF antagonists are preferably applied topically to the afflicted site but systemic such as oral, parenteral, nasal and intrarectal administration, is also possible.

In another aspect, the invention relates to the use of PAF antagonists in the preparation of pharmaceutical compositions intended for the treatment of pruritus.

Detailed Description of the Invention

Platelet activating factor (PAF) is a term coined by Benveniste et al. [J. Exp. Med. 136, 1356-1377 (1972)] to describe a fluid phase mediator of unknown chemical structure. This mediator has later been identified as a phospholipid autocoid, which structurally is 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine of the formula (I)



PAF

wherein R is 15 or 17, i.e. the alkyl moiety is hexadecyl or octadecyl. The isolation, chemical synthesis and biological and biochemical characteristics of PAF are, for example, disclosed by Hanahan and Kumar in Prog. Lipid Res. 26, 1-28 (1987).

PAF is not stored in cells but is synthesized in response to appropriate stimuli by a two-step process. The precursor 1-O-alkyl-(R)acyl-glycero-3-phosphatidylcholine is converted to lyso-PAF by phospholipase A_2 and subsequent acetylation results in PAF formation. In fact lyso-PAF is both a precursor and a metabolite of PAF. PAF is known to be an important factor of physiological reactions including platelet aggregation, inflammation, contraction of smooth muscle, alterations in the respiratory and circulatory systems, etc.

PAF antagonists have been discovered comparatively recently, and comprise a series of compounds of diverse structures effective in the treatment of conditions traditionally associated with PAF. The PAF antagonists reported so far in the art may be broadly classified according to their origin and structures as follows: (a) synthetic analogues of the PAF structure; (b) natural products isolated from plants; (c) triazolobenzodiazepines. By virtue of these antagonists, it has become apparent that PAF exerts its known biological effects by stimulating specific PAF-sensitive receptors.

A PAF antagonist, which is a synthetic analogue of the PAF structure is the compound of formula (II),

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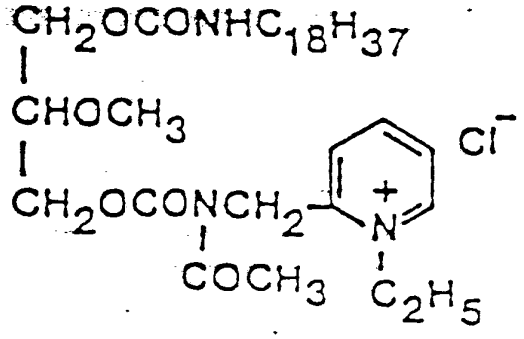
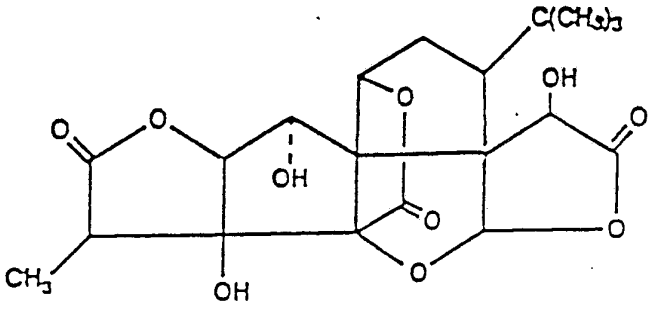


which was disclosed by Terashita et al., in J. Pharm. Exp. Ther. 242, 263-268 (1987). Other synthetic lipid PAF inhibitors are described In the Published European Patent Application 0,157,609 A2 as preventive or therapeutic agents for a variety of circulatory diseases and allergic disorders and as anti-neoplastic agents.

According to the United States Patent No.. 4,734,280, PAF-induced maladies can be effectively treated by the administration of a ginkgolide or a ginkgolide derivative. Ginkgolides were originally isolated from Ginkgo Biloba extracts, and their commonly available representatives include Ginkgolide A, Ginkgolide B, Ginkgolide C, and Ginkgolide M, of which Ginkgolide B (BN 52021) of the formula (III)

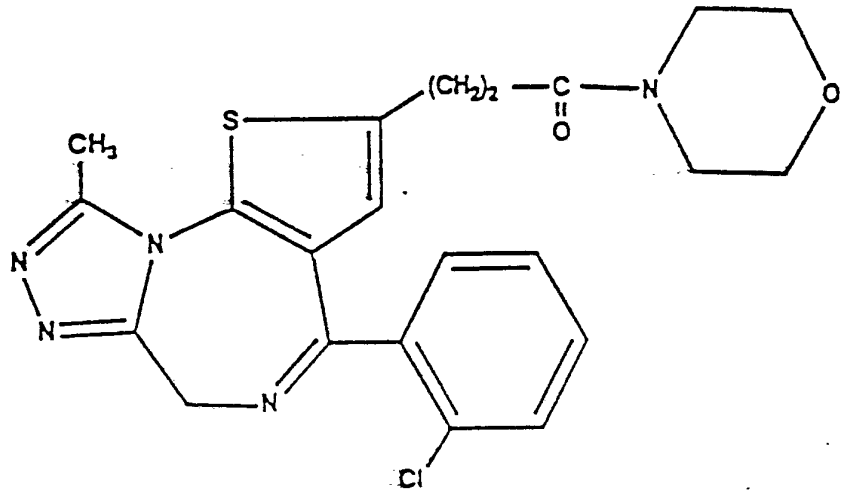


BN 52021

was found to be the most effective [Braquet et al., L. Actualites de Chimie Therapeutique (Paris) 13, 237-254 (1986)]. Known derivatives of ginkgolides include the mono-acetate, the tri-acetate, and the tetrahydro and acetyl derivatives. According to the test data disclosed in the U.S. Patent No. 4,734,280, these compounds show platelet aggregation inhibiting and antianaphylactic activities, and exhibit a protective effect against transvascular fluid escape and shock.

PAF antagonist triazolobenzodiazepine derivatives were, for example, described by Kornecki et al., Science 226, 1454-1456

(1986), and are disclosed in the United States Patent No. 4,820,703 , and in the Published European Patent Application No. 0,194,416 A1. A typical representative of this class of PAF antagonists is the compound of formula (IV)



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(WEB 286) which is disclosed in the above-cited Published European Patent Application. These compounds are described as useful for the prevention or treatment of various PAF-induced diseases, such as diseases associated with platelet aggregation, certain immediate allergic reactions caused by PAF, pain, edema, alteration in the respiratory and circulatory system, etc.

In studies intended to identify pruritogenic substances other than histamine, the inventor of the present application has discovered that PAF is a most potent itch producing substance. Moreover, certain known PAF antagonists were found to specifically block the pruritogen activity of PAF and, more importantly, were found to significantly reduce the pruritus associated with an experimental model of itching diseases. Although PAF had been described as a substance that causes pruritus in human skin by Fjellner and Hagermark, Supra, its action was associated with histamine liberation. Accordingly, it was entirely unexpected that PAF antagonists are capable of relieving itch, and do so in a non-histamine related fashion.

The term "PAF" antagonist as used in accordance with the present invention, refers to synthetic or naturally occurring compounds known in the art or hereinafter discovered, that are effective in the treatment of pruritus via interfering with the pruritogenic action of PAF. This definition includes, but is not restricted to the above-mentioned three classes of PAF antagonists, the preferred representatives being compounds of formulae (II), (III) and (IV) as hereinabove defined.

The term "treatment" is used to cover all aspects of the control of itching including prophylaxis and therapy.

The term "therapeutically effective amount" and grammatical variations thereof, as used herein refer to sufficient quantities of the active compound that can produce the desired therapeutic effect when administered to a mammal afflicted with pruritus. The term "therapeutic effect" is used herein in a broad sense and includes prophylactic effects.

In accordance with the present invention, the PAF antagonists are preferably applied to the afflicted area topically, in admixture with pharmaceutical carriers, in the form of topical pharmaceutical compositions. Such compositions include solutions, suspensions, lotions, gels, creams, ointments, emulsions, skin patches, etc. All of these dosage forms, along with methods for their preparation, are well known in the pharmaceutical and cosmetic art. Typically, such topical formulations contain the active ingredient in a concentration range of 0.001 to 10 mg/ml, in admixture with suitable vehicles. Other desirable ingredients for use in such anti-pruritic preparations include preservatives, co-solvents, viscosity building agents, carriers, etc.

For ophthalmic application, preferably solutions are prepared typically containing from about 0.001 to about 10 mg/ml, preferably from about 0.1 to about 6 mg/ml of active ingredient, and a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 6.5 and 7.2 with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and/or penetration enhancers.

The preferred vehicle that may be used in the ophthalmic solutions of the present invention is purified water, more

preferably a physiological saline solution. Additional suitable vehicles include but are not restricted to, viscosity agents such as polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, carbomer and hydroxyethyl cellulose.

Preferred preservatives that may be used in the ophthalmic formulations of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate.

Penetration enhancers may, for example, be surface active agents; certain organic solvents, such as dimethylsulfoxide and other sulfoxides, dimethylacetamide and pyrrolidone; certain amides of heterocyclic amines, glycols (e.g. propylene glycol); propylene carbonate; oleic acid; alkyl amines and derivatives; various cationic, anionic, nonionic, and amphoteric surface active agents; and the like.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable opthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers for ophthalmic use.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

In addition to topical therapy, other routes of administration such as oral, parenteral, nasal inhalation, and intrarectal are also contemplated. For these uses, additional conventional pharmaceutical preparations such as tablets, granules, powders, capsules, and sprays may be preferentially required. In such formulations further conventional additives such as binding agents, wetting agents, propellants, lubricants, and stabilizers may also be required.

The route of administration, dosage form, and the effective amount vary according to the potency of the selected PAF antagonist, its physicochemical characteristics, and according to the condition to be treated. The selection of proper dosage is well within the skill of an ordinary skilled physician. Topical formulations are usually administered up to four-times a day. A typical dosage of opthalmic solutions is 1-2 drops in the afflicted eye up to four-times a day.

The use of PAF antagonists as anti-pruritics is advantageous in that they relieve itching by a mechanism independent of histaminergic compounds. Thus, they may be effective in itching diseases which are refractory to antihistamine therapy and may be combined with H_1-antihistamines to provide superior therapy via additive or synergistic interaction.

A more complete appreciation of the invention may be obtained from the following Examples. As a means of providing an atraumatic experimental model of itching, the conjunctiva was used as a convenient tissue site. Pruritogenic agents may be administered to the conjunctiva without the need to traumatize the tissue by injection or scarification. The itch sensation is elicited peripherically by local, atraumatic application of the pruritogen. Of equal importance is the ability of this model to identify locally acting anti-pruritic agents without concerns regarding local tissue trauma or, in the case of systemically administered agents, sedation.

Example 1

The pruritogenic activity of numerous and structurally diverse autocoids was examined as follows. A 20 μl drop of a solution of the particular autocoid under evaluation was topically administered to one albino guinea-pig eye, the contralateral eye received 20 μl of vehicle as a control. For PAF studies, the R=15 version of formula I was used and was taken up in 0.5% ultrapure bovine serum albumin. The guinea pig was then replaced in its cage and the number of scratching episodes was recorded over the 15 subsequent minute period. The retention of the experimental animal in familiar surroundings is an important factor in experimental design. Scratching, which is the typical mammalian behavioral response

to the itch sensation, provides an indication of the intensity of the perceived itch sensation and can be quantified by recording the frequency at which itch-scratch episodes occur per unit time: 15 minutes in the case of these examples. The data obtained on several autocoids at physiological dose levels is summarized in Table 1.

TABLE 1

COMPARISON OF THE PRURITOGENIC ACTIVITY OF AUTOCOIDS

AUTOCOID	DOSE (μg)	NO OF SCRATCH EPISODES ($\bar{X} \pm$ SEM)
PAF	1	6.42 ± 1.26
PAF	10	10.17 ± 1.31
PAF	100	13.46 ± 0.88
HISTAMINE	1	1.67 ± 0.45
HISTAMINE	10	8.42 ± 1.12
HISTAMINE	100	20.33 ± 2.55
HISTAMINE	1000	20.33 ± 2.18
PROSTAGLANDIN D_2	1	0.75 ± 0.25
PROSTAGLANDIN D_2	10	4.42 ± 1.36
PROSTAGLANDIN D_2	100	3.08 ± 0.47
PROSTAGLANDIN E_2	1	2.25 ± 0.66
PROSTAGLANDIN E_2	10	3.08 ± 0.48
PROSTAGLANDIN E_2	100	8.17 ± 1.54
PROSTAGLANDIN $F_{2\alpha}$	100	1.75 ± 0.37
CARBACHOL	10	0.75 ± 0.33
CARBACHOL	100	0.83 ± 0.24
CARBACHOL	1000	3.08 ± 0.67
METHACHOLINE	10	0.50 ± 0.19
METHACHOLINE	100	0.67 ± 0.43
METHACHOLINE	1000	2.17 ± 0.77

ECF-A (L-alanylglycyl-L-seryl-L-glutamic acid)	1000	1.42 ± 0.47
ECF-A (L-valylglycyl-L-aspartyl-L-glutamic acid)	100	0.92 ± 0.26
LEUKOTRIENE B_4	10	0.42 ± 0.23
LEUKOTRIENE C_4	10	0.58 ± 0.36
LEUKOTRIENE D_4	1	0.83 ± 0.41
LEUKOTRIENE D_4	10	0.50 ± 0.34
LEUKOTRIENE E_4	1	0.58 ± 0.42
LEUKOTRIENE E_4	10	0.25 ± 0.13
5-Hydroxytetraemoic Acid	10	0.33 ± 0.22
12-Hydroxytetraemoic Acid	10	0.08 ± 0.08
15-Hydroxytetraemoic Acid	10	0.08 ± 0.08
Bradykinin	10	0.50 ± 0.23
Bradykinin	100	4.00 ± 0.90
LYSO-PAF	1	0.92 ± 0.26
LYSO-PAF	10	2.67 ± 0.73
LYSO-PAF	100	13.0 ± 1.58
NORMAL SALINE	--	1.17 ± 0.42
3.6% SALINE	--	2.25 ± 0.57
10mM ACETIC ACID	--	0.42 ± 0.19

n=12, Values are Mean ± SEM

It is apparent from Table 1 that PAF is the most potent pruritogenic agent. The relatively weak activity of lyso-PAF is consistent with a receptor mediated effect. The virtual absence of an itch-scratch response to pain producing stimuli such as hypertonic saline and 10 mM acetic acid provides further validation of the model.

Example 2

The ability of a 30 minute topical pretreatment with selected PAF antagonists to attenuate PAF induced pruritus is shown in Table 2.

TABLE 2

TREATMENT REGIMEN	CONTROL GROUP	TREATED GROUP
Compound of formula (II) (10 mg/ml) vs 1 μg PAF	6.42 ± 1.13	2.67 ± 0.68*
Compound of formula (II) (10 mg/ml) vs 10 μg PAF	10.08 ± 0.82	6.50 ± 1.09*
Compound of formula (III) (10 mg/ml) vs 10 μg PAF	14.33 ± 1.46	8.42 ± 1.37*
Compound of formula (IV) (5 mg/ml) 1 μg PAF	4.00 ± 0.67	0.33 ± 0.19**
Compound of formula (IV) (5 mg/ml) vs 10 μg PAF	11.33 ± 1.53	5.25 ± 0.98**
Pyrilamine (0.1 mg/ml) vs 1 μg PAF	4.67 ± 0.82	4.17 ± 0.91
Pyrilamine (0.1 mg/ml) vs 10 μg PAF	13.67 ± 1.70	14.25 ± 1.75

Values are mean ± SEM
*p < 0.05; ** p <0.01; n=12

Table 2 demonstrates that PAF induced pruritus may be blocked by PAF antagonists but not by the antihistamine pyrilamine: this indicates that PAF does not evoke a pruritic effect by an indirect mechanism involving histamine.

Example 3

In addition to pharmacological studies on pruritogenic autocoids, the conjunctiva may be used as a convenient site for modelling diseases where itching is a major symptom. In animals presensitized to a particular antigen, subsequent topical challenge with that antigen results in conjunctival itching. This may be regarded as

an experimental model of itching which has general relevance to clinically encountered pruritus. In the studies described herein, chicken ovalbumin was used as an antigenic substance and the ability of PAF antagonist pretreatment to block the itching response was examined (Table 3).

TABLE 3

EFFECT OF PAF ANTAGONISTS ON EXPERIMENTAL ALLERGIC ITCHING

TREATMENT REGIMEN	CONTROL GROUP	TREATED GROUP
Compound of formula (II) (1 mg/ml) vs 100 μG antigen	14.38 ± 2.21	7.62 ± 0.96*
Compound of formula (III) (10 mg/ml) vs 100 μG antigen	12.25 ± 1.72	6.87 ± 1.61*
Compound of formula (IV) (10 mg/ml) vs 10 μG antigen	11.00 ± 2.50	5.00 ± 1.10*

*$p < 0.05$ n=8-10

These results demonstrate that PAF is a major mediator of itching diseases and that administration of a PAF antagonist provides an effective method for treating pruritus. In addition, PAF antagonists may also be used in combination with antihistamines or glucocorticoids.

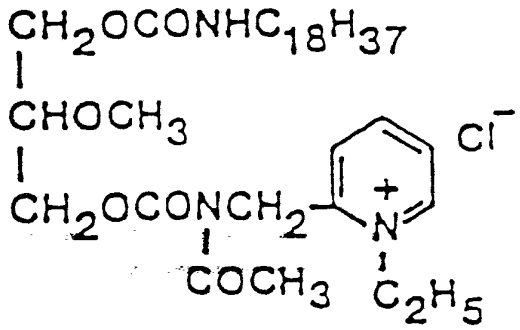
It is understood that this invention may be embodied in a variety of forms without departing from the spirit or essential characteristics. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

Claims:

1. A method for treating pruritus which comprises administering a therapeutically effective amount of a platelet activating factor (PAF) antagonist to a mammal afflicted with pruritus.

2. The method of Claim 1, wherein said PAF antagonist is a synthetic analogue of PAF.

3. The method of Claim 2, wherein said synthetic analog is a compound of formula (II)

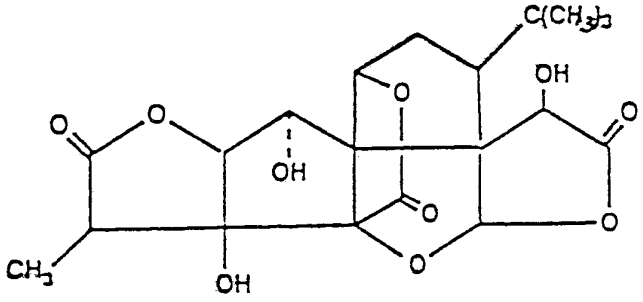


4. The method of Claim 1, wherein said PAF antagonist is a naturally occurring product.

5. The method of Claim 4, wherein said naturally occurring product is a ginkgolide or a ginkgolide derivative.

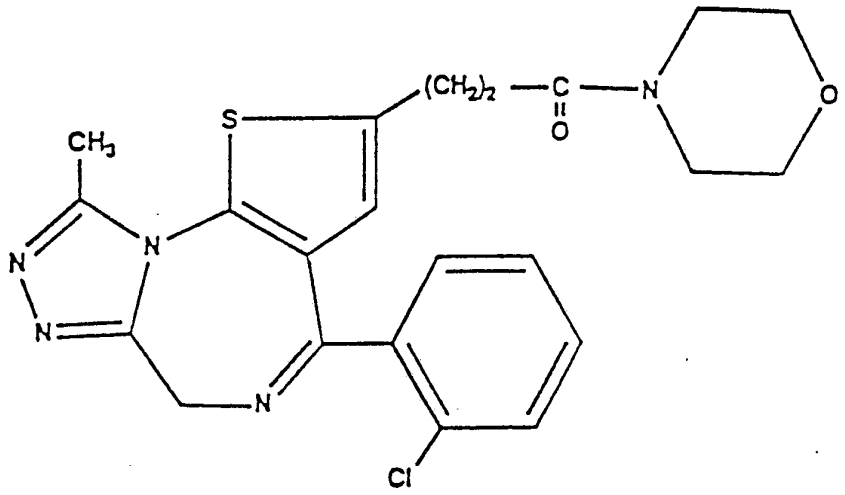
6. The method of Claim 4, wherein said naturally occurring product is selected from the group of Ginkgolide A, Ginkgolide B, Ginkgolide C and Ginkgolide M, and derivatives thereof.

7. The method of Claim 6, wherein said naturally occurring product is Ginkgolide B of the formula (III)



8. The method of Claim 1, wherein said PAF antagonist is a triazolobenzodiazepine.

9. The method of Claim 8, wherein said triazolobenzodiazepine is a compound of the formula (IV)



10. The method of Claim 1, wherein said PAF antagonist is applied topically to the site afflicted with pruritus.

11. The method of Claim 1, wherein said PAF antagonist is administered systemically.

12. The method of Claim 1, wherein said PAF antagonist is administered in the form of a pharmaceutical composition comprising a therapeutically effective amount of said PAF antagonist as active ingredient, in admixture with a pharmaceutical carrier.

13. The method of Claim 12, wherein said pharmaceutical composition is a liquid formulation comprising from about 0.001 to about 10 mg/ml PAF antagonist.

14. The method of Claim 13, wherein said pharmaceutical composition is formulated in a form suitable for topical application.

15. The method of Claim 14, wherein said pharmaceutical composition is formulated as an ophthalmic solution.

16. The method of Claim 1 or Claim 12, wherein said PAF antagonist is administered in combination with at least one further antipruritic agent.

17. The method of Claim 16, wherein said further antipruritic agent is a H_1-antihistamine.

18. Use of a PAF antagonist in the preparation of a pharmaceutical composition intended for the treatment of pruritus, which comprises admixing a therapeutically effective amount of said PAF antagonist with a pharmaceutical carrier.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/02003

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL. A61K 31/55, A61K 31/44, A61K 31/34
U.S. CL. 514/220, 514/357, 514/358, 514/468

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	514/220,514/357,514/358,514/468

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4,734,280 (BRAQUET) 29 MARCH 1988 See entire document	1-18
Y	N, ACTA DERM VENEREOL (SWEDEN) 65 409-412 (FJELLNER ET AL) 1985	1-18
Y	N, J. PHARM. EXP. THER., 242 No. 1, 263-268, (TERASHITA ET AL) 1987 See entire document.	1-18

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier 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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search

24 JUNE 1991

Date of Mailing of this International Search Report

09 JUL 1991

International Searching Authority

ISA/US

Signature of Authorized Officer

LEONARD SCHERKMAN