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(54) **Title:** PROSTAGLANDINS AND ANALOGUES AS AGENTS FOR LOWERING INTRAOCULAR PRESSURE

(57) **Abstract:** The present invention relates to cyclopentane heptenoic acid-5-cis-2-(3α-hydroxy or lower alkyloxy-5-thienylpentyl)-3, 5-dihydroxy, [1α, 2β, 3α, 5α] compounds, lower alkyl, hydroxyl lower alkyl and indole lower alkyl amides and esters thereof as potent ocular hypotensives that are particularly suited for the management of glaucoma.

PROSTAGLANDINS AND ANALOGUES AS AGENTS FOR LOWERING INTRAOCULAR PRESSURE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is based on, and claims the benefit of, U.S. Provisional Application No. 60/733,117, filed November 3, 2005, and which is incorporated herein by reference.

Background of the Invention

1. Field of the Invention

The present invention relates to cyclopentane heptenoic acid-5-cis-2-(3α-hydroxy or lower alkyloxy-5-thienylpentyl)-3, 5-dihydroxy, [1α, 2β, 3α, 5α] compounds lower alkyl, hydroxyl lower alkyl and indole lower alkyl amides and esters thereof as potent ocular hypotensives that are particularly suited for the management of glaucoma.

2. Description of Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

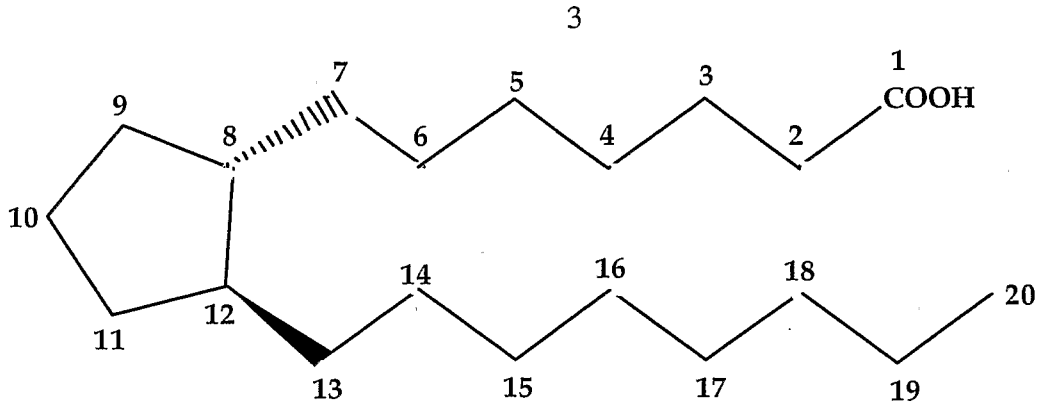
The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In

chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision.

Certain eicosanoids and their derivatives have been reported to possess ocular hypotensive activity, and have been recommended for use in glaucoma management. Eicosanoids and derivatives include numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:



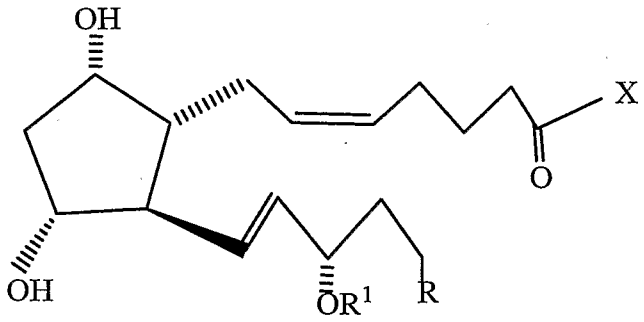
Various prostaglandin derivatives, e.g. latanoprost, travoprost, unoprostone isopropyl, etc. have been commercialized for lowering intraocular pressure and managing glaucoma. Recently, a prostamide, i.e. bimatoprost, has been marketed for treating increased eye pressure caused by open-angle glaucoma or ocular hypertension. Prostamides are structurally similar to prostaglandins but are biologically different. Prostamides, unlike prostaglandins, do not lower intraocular pressure by interaction with the prostaglandin receptor. (See U.S. Patent No. 5,352,708, which hereby is incorporated by reference in its entirety.)

While prostaglandins and prostamides are effective in lowering intraocular pressure without significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been associated with the topical ocular use of such compounds, in particular $PGF_{2\alpha}$ and its prodrugs, e.g., its 1-isopropyl ester, in humans.

Thus, it would be desirable to discover a prostamide or prostaglandin compound which effectively lowers intraocular pressure while not causing excessive hyperemia.

Summary of the Invention

The present invention concerns a method of treating ocular hypertension which comprises administering to a mammal having ocular hypertension a therapeutically effective amount of a compound selected from the group consisting of compounds represented by the following formula:



wherein R^1 is H or methyl;

R is selected from the group consisting of thienyl and substituted thienyl, wherein the substituent may be one or more radicals selected from the group consisting of fluoro, chloro, bromo, methyl and phenyl and X is selected from the group consisting of

R^2
|

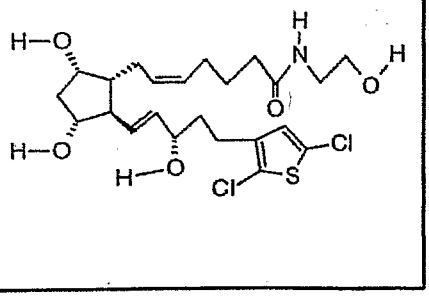
N-R^3 wherein R^2 is H or methyl and R^3 comprises a substituted hydrocarbyl radical, including from 1 to 12 carbon atoms and at least one oxygen atom, e.g. as an ether or a hydroxyl moiety, and, optionally, a nitrogen atom. That is R^3 may be an alkylhydroxy radical or an alkyl ether or a hydroxy indole radical. Thus, R^3 may be an alkyl or an aryl radical which includes an oxygen atom as a hydroxy, alkyloxy, oxo, oxa moiety, etc. Preferably, R^3 is selected from the group consisting of 2-butyl-4-hydroxy, methoxy, 2-ethylhydroxy, and (2-ethyl)(5-hydroxy)indole.

Preferably, said thienyl is substituted with two chloro radicals, or two bromo radicals or one chloro and one methyl radical.

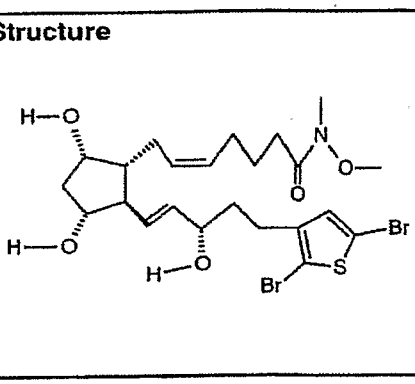
More preferably, when said thienyl is substituted with two chloro radicals, R^2 is H and R^3 is 2-ethylhydroxy, or when said thienyl is substituted with two bromo radicals, R^2 is methyl and R^3 is methoxy, or when said thienyl is substituted with one chloro radical and one methyl radical, R^2 is H and R^3 is (2-ethyl) (5-hydroxy) indole.

Most preferably said compound is selected from the group consisting of the following compounds.

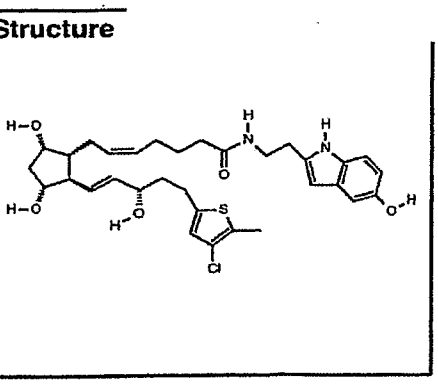
Structure



Structure



Structure



The compounds are very selective FP agonists.

Preferably R is substituted with two or more, e.g. 3, of said radicals.

These compounds effectively lower intraocular pressure while having lower hyperemia.

In another aspect of the invention, a ophthalmic solution comprising one or more of the above compounds in combination with an ophthalmically-acceptable vehicle is contemplated.

In a still further aspect, the present invention relates to a pharmaceutical product, comprising

a container adapted to dispense its contents in a metered form; and

an ophthalmic solution therein, as hereinabove defined.

Finally, certain of the above compounds disclosed herein and utilized in the method of the present invention are novel and unobvious.

Detailed Description of the Invention

The above compounds of the present invention may be prepared by methods that are known in the art. For example, see U.S. Patents 5,834,498; 5,741,810 and 6,124,344 to Burk, which are hereby incorporated by reference.

The compounds of the present invention were tested for in vitro activity as described in U.S. Patents 6,734,206 and 6,747,037 to Old et al which are incorporated by reference.

For the most preferred compounds the in-vitro activity is as follows:

Table 1

FUNCTIONAL_HFP 10.0000	FUNCTIONAL_HTP 300.0000	FEFP_EP4_RATIO 0.0030
FUNCTIONAL_HEP1 98.0000	FUNCTIONAL_HIP 50000.0000	GPEP1
FUNCTIONAL_HEP2 50000.0000	FUNCTIONAL_HDP 50000.0000	GPEP3
FUNCTIONAL_HEP3A 50000.0000	FEFP_OHL 0.2000	RTTPVASC
FUNCTIONAL_HEP4 50000.0000	RBEPVASC_EP4 80.0000	HTPPLAT

FUNCTIONAL_HFP 37.0000	FUNCTIONAL_HTP 374.0000	FEFP_EP4_RATIO 0.0480
FUNCTIONAL_HEP1 599.0000	FUNCTIONAL_HIP 50000.0000	GPEP1
FUNCTIONAL_HEP2 50000.0000	FUNCTIONAL_HDP 50000.0000	GPEP3
FUNCTIONAL_HEP3A 50000.0000	FEFP_OHL 7.0000	RTTPVASC
FUNCTIONAL_HEP4 50000.0000	RBEPVASC_EP4 147.0000	HTPPLAT

FUNCTIONAL_HFP 8.5000	FUNCTIONAL_HTP 1140.0000	FEFP_EP4_RATIO
FUNCTIONAL_HEP1 167.0000	FUNCTIONAL_HIP 50000.0000	GPEP1
FUNCTIONAL_HEP2 50000.0000	FUNCTIONAL_HDP 50000.0000	GPEP3
FUNCTIONAL_HEP3A 50000.0000	FEFP_OHL 9.3000	RTTPVASC
FUNCTIONAL_HEP4 50000.0000	RBEPVASC_EP4	HTPPLAT

Ophthalmic solutions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable acid addition salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using 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 surfactants.

Preferred preservatives that may be used in the ophthalmic solutions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

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 ophthalmically 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. Acids or bases may be used to adjust the pH of these formulations as needed.

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 edentate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate the application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution.

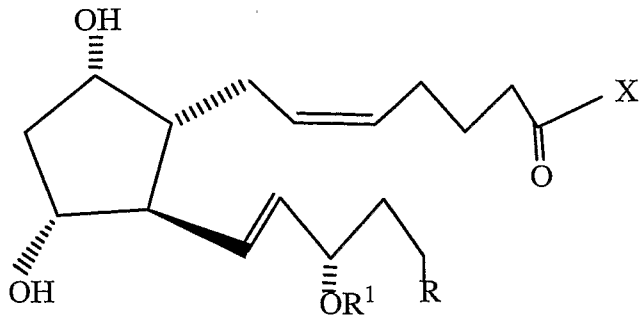
Certain of the compounds of this invention are useful in treating other diseases and conditions which are responsive to prostaglandin analogues, e.g. cardiovascular; e.g. acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris; pulmonary-respiratory; gastrointestinal; reproductive and allergic diseases; osteoporosis and shock.

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode

contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof.

Claims:

1. A method of treating ocular hypertension which comprises administering to a mammal having ocular hypertension a therapeutically effective amount of a compound selected from the group consisting of compounds represented by the following formula:



wherein R^1 is H or methyl;

R is selected from the group consisting of thienyl and substituted thienyl, wherein the substituent may be one or more radicals selected from the group consisting of fluoro, chloro, bromo, methyl and phenyl and X is selected from the group consisting of

R^2
|
N-R^3 wherein R^2 is H or methyl and R^3 comprises a substituted hydrocarbyl radical, including from 1 to 12 carbon atoms and at least one oxygen atom, and, optionally, a nitrogen atom.

2. The method of claim 1 wherein R is a substituted thienyl.

3. The method of claim 1 wherein R is a substituted thienyl comprising one or more chloro, bromo or methyl radicals.

4. The method of claim 3 wherein R is substituted thienyl comprising two chloro radicals.

5. The method of claim 3 wherein R is substituted thienyl comprising two bromo radicals.

6. The method of claim 3 wherein R is substituted thienyl comprising one chloro radical and one methyl radical.

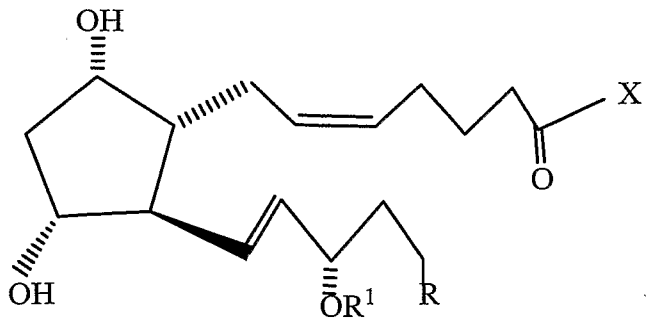
7. The method of claim 2 wherein R^3 is selected from the group consisting of methoxy, 2-ethylhydroxy, and (2-ethyl)(5-hydroxy)indole.

8. The method of claim 4 wherein R^2 is H and R^3 is 2-ethyl hydroxy.

9. The method of claim 5 wherein R^2 is methyl and R^3 is methoxy.

10. The method of claim 6 wherein R^2 is H and R^3 is (2-ethyl)(5-hydroxy) indole.

11. An ophthalmic solution comprising



wherein R^1 is H or methyl;

R is selected from the group consisting of thienyl and substituted thienyl, wherein the substituent may be one or more radicals selected from the group consisting of fluoro, chloro, bromo, methyl and phenyl and X is selected from the group consisting of

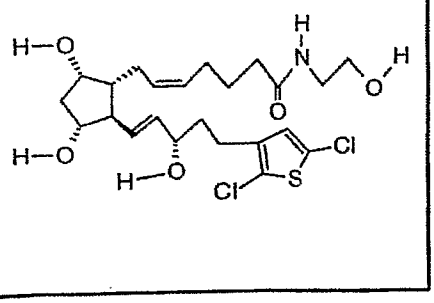
R^2
|

N-R^3 wherein R^2 is H or methyl and R^3 comprises a substituted hydrocarbyl radical, including from 1 to 12 carbon atoms and at least one oxygen atom, and, optionally, a nitrogen atom.

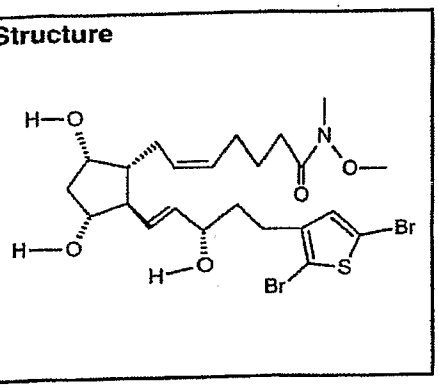
12. A pharmaceutical product comprising a container adapted to dispense its contents in a metered form and the ophthalmic solution of claim 11.

13. A novel compound selected from the group consisting of

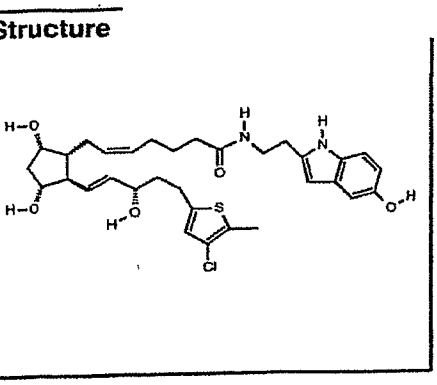
Structure



Structure



Structure



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/042861

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C405/00 A61K31/559 C07D333/04 A61P27/06 C07D209/08

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 124 344 A (BURK ROBERT M [US]) 26 September 2000 (2000-09-26) claim 14, 24; column 6, lines 25-32; column 7, lines 18-24; table	1-13
A	US 647 606 A (DAVID W. OLD (US)) 5 November 2002 (2002-11-05) claims 1-14	1-13

☐ Further documents are listed in the continuation of Box C.

☒ 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" 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 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
18 April 2007	25/04/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	GRAMMENOUDI, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/042861

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/042861

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6124344 A	26-09-2000	US 5906989 A	25-05-1999
US 647606 A		NONE	