

00001
165

SUPERINDUSTRIA Y COMERCIO

Radicación: 03095323 00000006

Folios: 119

Señora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Fecha (HH): 2005-05-06 17:22:51

Trámite: 011 PCT-PATENT 379 FASE NACI 329 COMPLEN

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Referencia: Expediente No. 03.095.323

Solicitud de Patente de Invención titulada: "Composiciones de timolol y de
lípidos hipotensivos y los métodos para utilizarlas"

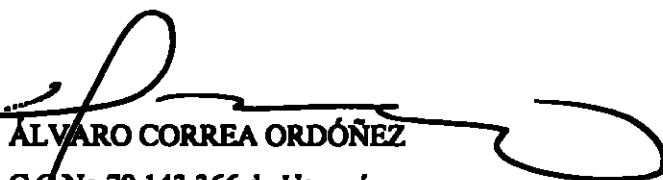
Solicitante: Allergan, Inc.

MEMORIAL DE ALCANCE

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según
aparece al pie de mi firma, en mi condición de apoderado de la sociedad en referencia,
manifiesto lo siguiente:

1. Presento copia del reporte de búsqueda y del reporte de examen preliminar
internacional con sus respectivos anexos. De igual manera, presento una traducción al
español de cada uno de los reportes, sin incluir los anexos.

Atentamente,


ÁLVARO CORREA ORDÓÑEZ
C.C.No.79.143.366 de Usaquén
T.P.20.281

Anexo: Reporte de Búsqueda
Examen preliminar internacional
Traducción

INFORME DE BÚSQUEDA INTERNACIONAL - Solicitud internacional No. PCT/US 02/17291.-

Casillero 1 - Observaciones en donde ciertas reivindicaciones no pudieron ser objeto de búsqueda (continuación de punto 1 de primera página).-

Este informe de búsqueda internacional no ha podido establecerse con respecto a ciertas reivindicaciones conforme al Artículo 17(2) (a) por las siguientes razones:

[X] Reivindicaciones Nos: (en blanco) debido a que se relacionan a materia sobre la que no se requiere búsqueda por parte de esta autoridad, a saber: Aunque las reivindicaciones 6-17 se refieren a un método de tratamiento del cuerpo humano /animal, la búsqueda se ha llevado a cabo y se basa en los supuestos efectos del compuesto/composición.-

1. [X] Reivindicaciones Nos. 1-5, 18-22; 6-7 y 23 (en parte), debido a que se relacionan a partes de la Solicitud Internacional que no cumplen con los requisitos establecidos en la medida en que no puede realizarse búsqueda internacional significativa, específicamente: ver INFORMACIÓN ADICIONAL PCT/ISA/210.-

Casillero II. Observaciones en donde no existe unidad de invención (Continuación del punto 2 de la primera página).- (no se consignan datos en este punto).- INFORMACIÓN ADICIONAL DE PCT/ISA/210.-

Continuación de Casillero I.2 - Reivindicaciones 1-5; 18-22; 6-7 y 23 (en parte).-

Las actuales reivindicaciones 1 y 18 se refieren a un número extremadamente grande de posibles compuestos. En realidad, las

reivindicaciones contienen tantas opciones, variables y condiciones que surge falta de claridad (y/o precisión) dentro del significado del Artículo 6 PCT en una medida tal que hace imposible una búsqueda significativa de las reivindicaciones. En consecuencia, la búsqueda se ha realizado con respecto a aquellas partes de la solicitud que sí aparecen claras (y/o concisas), tal como las reivindicaciones 10-16 y 26-33.-

Las actuales reivindicaciones 2-5, 19-22 se refieren a una composición definida mediante referencia a una característica o propiedad conveniente, tal como "efecto secundario relativo con relación a una composición similar...", "con relación a la aplicación de una composición...".

Las reivindicaciones cubren todas las composiciones que poseen esta característica o propiedad, con lo cual la solicitud provee una sustentación dentro del significado del Artículo 6 de PCT y/o provee una revelación dentro del significado del Artículo 5 PCT para solamente un número muy limitado de tales composiciones. En el presente caso, la búsqueda significativa con respecto a la totalidad del alcance reivindicado es imposible. Independientemente del razonamiento anterior, las reivindicaciones también carecen de claridad (Art. 6 PCT). Se intenta definir a las composiciones mediante referencia a un resultado a ser obtenido. Nuevamente, esta falta de claridad en el presente caso es tal que hace imposible una búsqueda significativa sobre la totalidad del alcance reivindicado. En consecuencia, la búsqueda se ha llevado a cabo con respecto a aquellas partes de las reivindicaciones que aparecen con claridad, sostenidas y reveladas.-

Además, las reivindicaciones 4 y 5, así como 21 y 22, respectivamente, resultan confusas, y aún contradictorias con respecto a las reivindicaciones independientes a las cuales se subordinan. Las reivindicaciones independientes se refieren a combinaciones en donde aquellas reivindicaciones excluyen uno de los agentes. En consecuencia, parece que la subordinación es incorrecta.

Se llama la atención del solicitante sobre el hecho que las reivindicaciones, o partes de las reivindicaciones, referidas a invención con respecto a las cuales no se ha establecido un informe de búsquedas internacional no necesitan ser el objeto de un examen preliminar internacional (Norma 66.1(e)PCT). Se informe al solicitante que la política de la Oficina de Patentes Europea cuando actúa como una Autoridad de Examen Preliminar Internacional es normalmente la de no realizar un examen preliminar sobre materia que no ha sido objeto de búsqueda. Este es el caso independientemente de si las reivindicaciones han sido modificadas o no luego de recibir el informe de búsquedas o durante cualquier procedimiento del Capítulo II.-

TRATADO DE COOPERACION DE PATENTES – PCT/US02/17291.-

“PCT” INFORMACIÓN RELACIONADA CON OFICINAS ELEGIDAS Y NOTIFICADAS DE SU ELECCIÓN.- (Norma PCT 61.3).-

DE: OFICINA INTERNACIONAL.- A: FISHER, Carlos A. – Allergan, Inc., 2525 Dupont Drive, Irvine, CA 926612 – Estados Unidos de América.-

Fecha de envío por correo : 17 de julio de 2003 (17.07.03).- Expediente referencia de solicitante o agente: 17441PCTBAR.- INFORMACIÓN IMPORTANTE.- Solicitud Internacional No. PCT/US02/17291.- Fecha de presentación internacional: 30 de mayo de 2002.- Fecha de prioridad: 31 de mayo de 2001.- Solicitante: ALLERGAN, Inc. y otros.-

1. Por el presente se informa al solicitante que la Oficina Internacional, de acuerdo con el Artículo 31(7) ha notificado a cada una de las siguientes Oficinas sobre la elección de las mismas: EP: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, IE, IT, LU, MC, NL, PT, SE, TR.- Nacionales: AU, BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US.-

2. Las siguientes Oficinas han renunciado al requisito de notificación de su elección; la notificación se les enviará mediante la Oficina Internacional solamente cuando se lo solicite:

AP. GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW.-

EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM.-

OA: BF, BJ, CR, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TH.-

Nacional: AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SD, SE, SG, SI, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.-

3. Se recuerda al solicitante que debe iniciar la “fase nacional” antes del vencimiento de 30 meses a partir de la fecha de prioridad ante cada uno de las oficinas indicadas anteriormente. Esto debe realizarse mediante el pago del arancel nacional y presentado, si se requiriera, una traducción de la solicitud internacional (Artículo 39 (1)(a), así como, cuando fuera aplicable, mediante la presentación de una traducción de cualquiera de los anexos del informe de examen preliminar internacional (Artículo 36(3)(b) y Norma 74.1).-

Algunas oficinas han fijado límites de tiempo fijos que vencen más tarde que la fecha antes indicada. Para información detallada acerca de los tiempos aplicables y los actos a realizarse en la fase nacional ante una Oficina particular, ver Volumen II de la Guía PCT para Solicitantes.-

Oficina Internacional de OMPI – 34, chemin des Colombettes – 1211 Ginebra 20, Suiza.- Funcionario autorizado: Olivia TEFY (hay una firma ilegible) Teléfono No. (41-22) 338 8616.-

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL -

Solicitud Internacional No. PCT/US 02/17291.-

I. Base del informe.-

La base del examen preliminar internacional es la solicitud tal como se presentó originalmente.-

III. No emisión de opinión con respecto a novedad, actividad inventivo y utilidad industrial.-

La cuestión de si la invención reivindicada parece ser novedosa, o comprender un paso inventivo, o ser de aplicación industrial no ha sido objeto del examen preliminar internacional con respecto a las reivindicaciones que no han sido objeto de búsqueda (Artículo 17(2)(a) o (3) y Norma 66 1(e)PCT); ver también informe de búsqueda internacional).-

V. Declaración razonada conforme a la Norma 66 .2(a)(ii) con respecto a novedad, paso inventivo o utilidad industrial.-

En la medida en que se ha realizado el examen preliminar internacional (ver punto III anterior), se destaca lo siguiente:

A la luz de los documentos citados en el informe de búsqueda internacional, se considera que la invención tal como se define en por lo menos algunas de las reivindicaciones, que han sido objeto de una búsqueda internacional, no parece cumplir con los criterios mencionados en el Artículo 33(1) PCT, es decir, no parece ser novedosa y/o comprender un paso inventivo (ver informe de búsqueda internacional, en particular los documentos citados X y/o Y y referencias a reivindicaciones correspondientes).

TRANSMITTAL LETTER TO THE
UNITED STATES RECEIVING OFFICE

Date	May 29, 2002
International Application No.	
Attorney Docket No.	17441PCTBAR

I. Certification under 37 CFR 1.10 (if applicable)

EL385557152US
Express Mail mailing number

May 30, 2002
Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

<i>Mary Lou McNow</i>
Signature of person mailing correspondence

Mary Lou McNow
Typed or printed name of person mailing correspondence

II. ☒ New International Application

TITLE	HYPOTENSIVE LIPID AND TIMOLOL COMPOSITIONS AND METHODS OF USING SAME
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Earliest priority date (Day/Month/Year)
31/05/01

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. ☐ The invention disclosed was not made in the United States.
B. ☐ There is no prior U.S. application relating to this invention.
C. ☒ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority.)

application no.	60/294,845	filed on	31 May 2001
application no.		filed on	

- D. ☐ The present international application contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages and ☐ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

- ☐ A Response to an Invitation from the RO/US. The following document(s) is(are) enclosed:

- A. ☐ A Request for An Extension of Time to File a Response
B. ☐ A Power of Attorney (General or Regular)
C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. ☐ Submission of Priority Documents

Priority document		Priority document	
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- E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

V. ☐ Other (please specify):

The person
signing this
form is the:

☐ Applicant
☒ Attorney/Agent (Reg. No.) 36,510
☐ Common Representative

Carlos A. FISHER
Typed name of signer
<i>Carlos A. Fisher</i>
Signature

U.S. Department of Commerce: Patent and Trademark Office

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum)

17441PCTBAR

Box No. I TITLE OF INVENTION

HYPOTENSIVE LIPID AND TIMOLOL COMPOSITIONS AND METHODS OF USING SAME

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
United States of America

Telephone No.

(714) 246-4920

Facsimile No.

(714) 246-4249

Teleprinter No.

None

Applicant's registration No. with the Office

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant
for the purposes of:☐ all designated
States☒ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

CHEN, June
28771 Via Los Arboles
San Juan Capistrano, CA 92675
United States of America

This person is:

☐ applicant only☒ applicant and inventor☒ inventor only (if this check-box
is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent☐ common
representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

FISHER, Carlos A.; BARAN, Robert J.; DONOVAN, Stephen
and VOET, Martin A.
c/o Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
United States of America

Telephone No.

(714) 246-4920

Facsimile No.

(714) 246-4249

Teleprinter No.

None

Agent's registration No. with the Office

36,510

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

WOODWARD, David F.
22736 Islamare Lane
Lake Forest, CA 92630
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☒ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KHARLAMB, Alexander B.
1 Pandora
Irvine, CA 92604
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☒ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (If other kind of protection or treatment desired, specify on dotted line)
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (If other kind of protection or treatment desired, specify on dotted line)

National Patent (If other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|--|
| ☒ AE United Arab Emirates | ☒ GM Gambia | ☒ NZ New Zealand |
| ☒ AG Antigua and Barbuda | ☒ HR Croatia | ☒ OM Oman |
| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
| ☒ AM Armenia | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AT Austria | ☒ IL Israel | ☒ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Romania |
| ☒ AZ Azerbaijan | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ JP Japan | |
| ☒ BB Barbados | ☒ KE Kenya | ☒ SD Sudan |
| ☒ BG Bulgaria | ☒ KG Kyrgyzstan | ☒ SE Sweden |
| ☒ BR Brazil | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BY Belarus | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ BZ Belize | ☒ KZ Kazakhstan | ☒ SK Slovakia |
| ☒ CA Canada | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LK Sri Lanka | ☒ TJ Tajikistan |
| ☒ CN China | ☒ LR Liberia | ☒ TM Turkmenistan |
| ☒ CO Colombia | ☒ LS Lesotho | ☒ TN Tunisia |
| ☒ CR Costa Rica | ☒ LT Lithuania | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LU Luxembourg | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LV Latvia | ☒ TZ United Republic of Tanzania |
| ☒ DE Germany | ☒ MA Morocco | ☒ UA Ukraine |
| ☒ DK Denmark | ☒ MD Republic of Moldova | ☒ UG Uganda |
| ☒ DM Dominica | | ☒ US United States of America |
| ☒ DZ Algeria | ☒ MG Madagascar | |
| ☒ EC Ecuador | ☒ MK The former Yugoslav Republic of Macedonia | ☒ UZ Uzbekistan |
| ☒ EE Estonia | ☒ MN Mongolia | ☒ VN Viet Nam |
| ☒ ES Spain | ☒ MW Malawi | ☒ YU Yugoslavia |
| ☒ FI Finland | ☒ MX Mexico | ☒ ZA South Africa |
| ☒ GB United Kingdom | ☒ MZ Mozambique | ☒ ZM Zambia |
| ☒ GD Grenada | ☒ NO Norway | ☒ ZW Zimbabwe |
| ☒ GE Georgia | | |
| ☒ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☐ ☐ ☐
- ☐ ☐ ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM				
The priority of the following earlier application(s) is hereby claimed:				
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) (31.05.01) 31 May 2001	60/294,845	US		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items
 ☒ item (1)
 ☐ item (2)
 ☐ item (3)
 ☐ item (4)
 ☐ item (5)
 ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(11)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY		
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):		
ISA / EP		
Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):		
Date (day/month/year)	Number	Country (or regional Office)

Box No. VIII DECLARATIONS		
The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets) : 5
description (excluding sequence listing part) : 24
claims : 13
abstract : 1
drawings : 2

Sub-total number of sheets : 45

sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) : ..

Total number of sheets : 45

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(II), in right column):

This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):

1. ☒ fee calculation sheet :
2. ☐ original separate power of attorney :
3. ☐ original general power of attorney :
4. ☒ copy of general power of attorney; reference number, if any: :
5. ☐ statement explaining lack of signature :
6. ☐ priority document(s) identified in Box No. VI as item(s): :
7. ☐ translation of international application into (language): :
8. ☐ separate indications concerning deposited microorganisms or other biological material :
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other)) :
(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :
(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column :
10. ☒ other (specify): Postcard; Transmittal Letter to US/RO Re

Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).



Carlos A. FISHER

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Applicant's or agent's
file reference

17441PCTBAR

Date stamp of the receiving Office

Applicant

Allergan, Inc.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE

240

T

2. SEARCH FEE

866

S

International search to be carried out by ISA/EP

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) of Box No. IX applies, enter Sub-total number of sheets

45

Where item (b) of Box No. IX does not apply, enter Total number of sheets

407

b1 first 30 sheets

b1

b2

15

x

\$9

fee per sheet

135

b2

b3

additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(I), or both in that form and on paper, under Section 801(a)(II):

400

x

fee per sheet

542

b3

Add amounts entered at b1, b2 and b3 and enter total at B

B

Designation Fee

93

The international application contains designations.

5

x

\$88

amount of designation fee payable (maximum 6)

440

D

Add amounts entered at B and D and enter total at I

982

I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

15

P

FEE FOR PRIORITY DOCUMENT (if applicable)

2,103 USD

5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☒ authorization to charge deposit account (see below)

☐ postal money order

☐ cash

☐ coupons

☐ cheque

☐ bank draft

☐ revenue stamps

☐ other (specify):

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

☒ Authorization to charge the total fees indicated above.

☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

☒ Authorization to charge the fee for priority document.

Receiving Office: RO/ US

Deposit Account No.: 01-0885

Date: 29 May 2002

Name: Carlos A. FISHER

Signature: Carlos A. Fisher

PCT

179

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s) :

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

VOET, Martin A., Assistant Secretary
 Allergan, Inc.
 2525 Dupont Drive
 Irvine, CA 92612
 United States of America

hereby appoint(s) the following person as:

☒ agent☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BARAN, Robert J., Registration No. 25,806
 FISHER, Carlos A., Registration No. 36,510
 VOET, Martin A., Registration No. 25,208
 DONOVAN, Stephen, Registration No. 33,433
 c/o Allergan, Inc.
 2525 Dupont Drive
 Irvine, CA 92612
 United States of America

to represent the undersigned before

☒ all the competent International Authorities☐ the International Searching Authority only☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

US and EP

as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) (where there are several persons, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power).

ALLERGAN SALES, INC.

By:


 Martin A. Voet, Assistant Secretary

Date: May 4, 1999

RECEIVED 0018

PATENT COOPERATION TREATY

JUL 10 2002

LEGAL/PATENTS

180

From the RECEIVING OFFICE

PCT

NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

To:
CHALOS A. FISHER
C/O ALLERGAN, INC.
2525 DUPONT DRIVE
IRVINE, CALIFORNIA 92612

Date of mailing
(day/month/year)

05 JUL 2002

Applicant's or agent's file reference

17441PCTBAR

IMPORTANT NOTIFICATION

International application No.

PCT/US02/17291

International filing date (day/month/year)

30 May 2002

Priority date (day/month/year)

31 May 2001

Applicant

ALLERGAN, INC.

Title of the Invention

HYPOTENSIVE LIPID AND TIMOLOL COMPOSITIONS AND METHODS OF USING SAME

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

05 JUL 2002



was transmitted to the International Bureau on _____



has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:



because the necessary national security clearance has not yet been obtained.



because (reason to be specified):

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

3. FOREIGN TRANSMITTAL LICENSE INFORMATION

Completed by: TS



Additional license for foreign transmittal not required. This subject matter is covered by a license already granted or the equivalent U.S. national application. Refer to that license for information concerning its scope.



License for foreign transmittal not required. 37 CFR 5.11(e)(1) or 37 CFR 5.11(e)(2). However, a license may be required for additional subject matter. See 37 CFR 5.15(b).



Foreign transmittal license granted. 35 U.S.C. 184; 37 CFR 5.11 on 29 Jun 2002

(date)



37 CFR 5.15(a)



37 CFR 5.15(b)

Name and mailing address of the receiving Office

Assistant Commissioner for Patent, Box PCT
Washington, D.C. 20231 Attn:RO/US

Facsimile No. 703-305-3230

Authorized officer

Tyetta Staton

Telephone No. 703-305-3671

JS

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

RECEIVED

To:

(11) - 2002

FISHER, Carlos, A.
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
United States of America

LEGAL/PATENTS

Date of mailing (day/month/year) 10 September 2002 (10.09.02)	
Applicant's or agent's file reference 17441PCTBAR	IMPORTANT NOTIFICATION
International application No. PCT/US02/17291	International filing date (day/month/year) 30 May 2002 (30.05.02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 31 May 2001 (31.05.01)
Applicant ALLERGAN, Inc. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
31 May 2001 (31.05.01)	60/294,845	US	22 July 2002 (22.07.02)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Khema BRAHMI Telephone No. (41-22) 338.63.38
--	---

From the INTERNATIONAL BUREAU

PCTNOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

RECEIVED

DEC 17 2002

LEGAL/PATENTSFISHER, Carlos, A.
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
ETATS-UNIS D'AMERIQUE

Date of mailing(day/month/year)

05 December 2002 (05.12.02)

Applicant's or agent's file reference

17441PCTBAR

IMPORTANT NOTICE

International application No.

PCT/US02/017291

International filing date(day/month/year)

30 May 2002 (30.05.02)

Priority date(day/month/year)

31 May 2001 (31.05.01)

Applicant

ALLERGAN, Inc., et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 05 December 2002 (05.12.02) under No. WO 02/096432.

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.(41-22) 740.14.35

Authorized officer

Judith Zahra

Telephone No.(41-22) 338.91.11

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 December 2002 (05.12.2002)

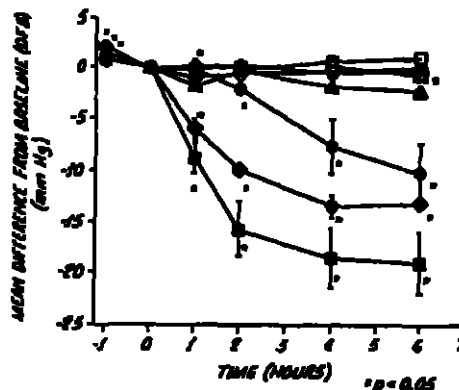
PCT

(10) International Publication Number
WO 02/096432 A3

- (51) International Patent Classification: A61K 31/5575, A61P 27/06 // (A61K 31/5575, 31:535) (74) Agents: FISHER, Carlos, A. et al.; Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92612 (US).
- (21) International Application Number: PCT/US02/17291 (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 30 May 2002 (30.05.2002) (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/294,845 31 May 2001 (31.05.2001) US
- (71) Applicant (for all designated States except US): ALLERGAN, Inc. [US/US]; 2525 Dupont Drive, Irvine, CA 92612 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): CHEN, June [US/US]; 28771 Via Los Arboles, San Juan Capistrano, CA 92675 (US). WOODWARD, David, R. [US/US]; 22736 Islamare Lane, Lake Forest, CA 92630 (US). KHARLAMBA, Alexander, B. [US/US]; 1 Pandora, Irvine, CA 92604 (US).
- Published:
— with international search report

[Continued on next page]

(54) Title: HYPOTENSIVE LIPID (PROSTAGLANDIN DERIVATIVES) AND TIMOLOL COMPOSITIONS AND METHODS OF USING SAME



— VEHICLE (n=5)
— SALINE (VEHICLE GROUP, n=5)
— 0.001% HYPO LIP (n=5)
— SALINE (0.001% HYPO LIP GROUP, n=6)
— 0.05% TIMOLOL MALEATE (n=8)
— SALINE (0.05% TIMOLOL MALEATE GROUP, n=9)
— 0.001% HYPO LIP + 0.05% TIMOLOL MALEATE (n=8)
— SALINE (0.001% HYPO LIP + 0.05% TIMOLOL MALEATE GROUP, n=8)

(57) Abstract: New compositions for and methods of treating ocular hypertension provide for effective treatment of ocular hypertension often using reduced concentrations of active components. Such compositions include a timolol component and a hypotensive lipid component. The present compositions and methods are relatively straightforward, can be easily produced, for example, using conventional manufacturing techniques, and can be easily and conveniently practiced, for example, using application or administration techniques or methodologies which are substantially similar to those employed with prior compositions used to treat ocular hypertension.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 02/17291.

00020

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/5575 A61P27/06 //(A61K31/5575,31:535)

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)
IPC 7 A61K

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, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 30710 A (ALLERGAN INC) 28 August 1997 (1997-08-28) page 4, line 29,30 page 4, line 32 page 4, line 35 page 5, line 2 page 13, line 15 -page 14, line 15 page 5, line 1 - page 7, line 18 formulas I-V	6-17, 23-33
Y	EP 0 286 903 A (PHARMACIA AB ;UNIV COLUMBIA (US)) 19 October 1988 (1988-10-19) column 3, line 39-48 column 5, line 2-4 column 5, line 8-10 --- -/-	6-17, 23-33

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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.

S document member of the same patent family

Date of the actual completion of the international search

19 December 2002

Date of mailing of the international search report

03/01/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 apo nl,
Fax: (+31-70) 340-3016

Authorized officer

Baumgärtner, H

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/17291

00021

185

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 6-17 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.: 1-5, 18-22; 6-7 and 23 (in part)
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 II Observations where unity of invention is lacking (Continuation of Item 2 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/US 02/17291

00022

186

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9730710	A	28-08-1997	US 5688819 A	18-11-1997
			AU 2272197 A	10-09-1997
			WO 9730710 A1	28-08-1997
			US 5972991 A	26-10-1999
			US 6037364 A	14-03-2000
			US 6403649 B1	11-06-2002
			US 6204287 B1	20-03-2001
			US 5834498 A	10-11-1998
			US 2001016597 A1	23-08-2001
EP 0286903	A	19-10-1988	AT 76750 T	15-06-1992
			AU 607981 B2	21-03-1991
			AU 1387088 A	06-10-1988
			CA 1314220 A1	09-03-1993
			DE 3871596 D1	09-07-1992
			DE 3871596 T2	21-01-1993
			EP 0286903 A1	19-10-1988
			ES 2042625 T3	16-12-1993
			GR 3004794 T3	28-04-1993
			GR 3033721 T3	31-10-2000
			HU 9500519 A3	30-10-1995
			JP 2726672 B2	11-03-1998
			JP 63313728 A	21-12-1988
			US 4952581 A	28-08-1990

PATENT COOPERATION TREATY

RECEIVED 2/2

00023

(AN) - 7 503

187

PCT LEGAL/PATENTS

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FISHER, Carlos A.
ALLERGAN, INC.
2525 Dupont Drive,
Irvine, CA 92612
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

30-12-2002

Applicant's or agent's file reference
17441PCTBAR

IMPORTANT NOTIFICATION

International application No.

PCT/US 02/ 17291

International filing date (day/month/year)

30/05/2002

Priority date (day/month/year)

31/05/2001

Applicant

ALLERGAN, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

17/12/2002

2. This date of receipt is:



the actual date of receipt of the demand by this Authority (Rule 61.1(b)).



the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).



the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

- 3.



ATTENTION: That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide, Volume II*.



(if applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/

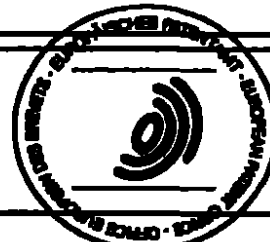


European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

LODOLO F

Tel. (+49-89) 2399-2039



PATENT COOPERATION TREATY

RECEIVED

JAN - 8 2003

LEGAL/PATENTS

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:
ALLERGAN, INC.
Attn. Fisher, Carlos A.
2525 Dupont Drive,
Irvine, CA 92612
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 03/01/2003	
Applicant's or agent's file reference 17441PCTBAR	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 02/17291	International filing date (day/month/year) Feb. 3, 2003 30/05/2002
Applicant ALLERGAN, INC.	

RESPONSE DU

ACTION

*Wish to file my
Voluntary Amendments
under Article 17(2) (3-3)*

- ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.
Filing of amendments and statement under Article 18:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):
When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.
Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.36
For more detailed instructions, see the notes on the accompanying sheet.
- ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.
- ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
- Further action(s): The applicant is reminded of the following:
Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for International publication.
Within 18 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).
Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 18 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 6818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 851 epo nl, Fax: (+31-70) 340-3016	Authorized officer Dominique Hundt
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These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 25 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added," or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Office, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

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LEGAL/PATENTS

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 17441PCTBAR	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/US 02/ 17291	International filing date (day/month/year) 30/05/2002	(Earliest) Priority Date (day/month/year) 31/05/2001
Applicant ALLERGAN, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

HYPOTENSIVE LIPID (PROSTAGLANDIN DERIVATIVES) AND TIMOLOL COMPOSITIONS AND METHODS OF USING SAME

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

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☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/17291

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/5575 A61P27/06 //(A61K31/5575,31:535)

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)

IPC 7 A61K

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, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 30710 A (ALLERGAN INC) 28 August 1997 (1997-08-28) page 4, line 29,30 page 4, line 32 page 4, line 35 page 5, line 2 page 13, line 15 -page 14, line 15 page 5, line 1 - page 7, line 18 formulas I-V	6-17, 23-33
Y	EP 0 286 903 A (PHARMACIA AB ;UNIV COLUMBIA (US)) 19 October 1988 (1988-10-19) column 3, line 39-48 column 5, line 2-4 column 5, line 8-10 -/-	6-17, 23-33

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in 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.

"Z" document member of the same patent family

Date of the actual completion of the international search

19 December 2002

Date of mailing of the international search report

03/01/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-8040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Baumgärtner, H

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RESUL B ET AL: "STRUCTURE-ACTIVITY RELATIONSHIPS AND RECEPTOR PROFILES OF SOME OCULAR HYPOTENSIVE PROSTANOIDS" SURVEY OF OPHTHALMOLOGY, SURVEY OF OPHTHALMOLOGY INC, XX, vol. 41, no. SUPPL 2, February 1997 (1997-02), pages S47-S52, XP001057296 ISSN: 0039-6257 page S50, column 1, last paragraph page S50; figure 4 page S50, column 2, paragraphs 1,2	6-17, 23-33
P,X	ALEXANDER, CHRISTY L. ET AL: "Prostaglandin analog treatment of glaucoma and ocular hypertension" ANNALS OF PHARMACOTHERAPY (2002), 36(3), 504-511 XP009002398 page 505, column 2, paragraph 3 page 508, column 2, paragraph 2	6-17, 23-33

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5, 18-22; 6-7 and 23 (in part)

Present claims 1 and 18 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely claims 10-16 and 26-33.

Present claims 2-5, 19-22 relate to a composition defined by reference to a desirable characteristic or property, namely "reduced side effect relative to a similar composition", "relative to applying a composition ...".

The claims cover all compositions thus having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compositions by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, cf. supra.

Furthermore, claims 4 and 5 as well as 21 and 22 respectively are unclear, even contradictory to the independent claims they depend on. The independent claims refer to combinations whereas those claims exclude one of the agents. Consequently, it appears that the dependency is incorrect.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-17 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.: 1-5, 18-22; 6-7 and 23 (in part)
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 II Observations where unity of invention is lacking (Continuation of item 2 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

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Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9730710	A	28-08-1997	US	5688819 A	18-11-1997
			AU	2272197 A	10-09-1997
			WO	9730710 A1	28-08-1997
			US	5972991 A	26-10-1999
			US	6037364 A	14-03-2000
			US	6403649 B1	11-06-2002
			US	6204287 B1	20-03-2001
			US	5834498 A	10-11-1998
			US	2001016597 A1	23-08-2001
EP 0286903	A	19-10-1988	AT	76750 T	15-06-1992
			AU	607981 B2	21-03-1991
			AU	1387088 A	06-10-1988
			CA	1314220 A1	09-03-1993
			DE	3871596 D1	09-07-1992
			DE	3871596 T2	21-01-1993
			EP	0286903 A1	19-10-1988
			ES	2042625 T3	16-12-1993
			GR	3004794 T3	28-04-1993
			GR	3033721 T3	31-10-2000
			HU	9500519 A3	30-10-1995
			JP	2726672 B2	11-03-1998
			JP	63313728 A	21-12-1988
			US	4952581 A	28-08-1990

XP-001057296

Structure-Activity Relationships and Receptor Profiles of Some Ocular Hypotensive Prostanoids

BAHRAM RESUL, PhD,¹ JOHAN STJERNŠCHANTZ, MD, PhD,¹ GÖRAN SELÉN, PhD,¹
AND LASZLO BITÓ, PhD²

¹Prostaglandin Research Laboratories, Pharmacia & Upjohn, Uppsala, Sweden and ²Department of Ophthalmology, Columbia University, New York, New York, USA

Abstract. A novel series of prostaglandin F (PGF) analogues have been prepared and evaluated *in vivo* and *in vitro*. Their intraocular pressure (IOP) lowering effects and potential side-effects, as prodrug eye drops, have been tested in cats, monkeys and rabbits. Furthermore, the PGF-analogues were tested as free acids for FP-receptor agonistic activity on cat iris sphincter. The results were compared to that of PGF_{2α} (C#1). Based on the structure-activity relationship investigations, inversion of the configuration, at carbon-9 (C#9) or carbon-11 (C#4), changes the potency and the receptor profile of PGF_{2α}. Replacement part of the omega-chain of PGF_{2α} with a benzene ring changes the potency and receptor profile of PGF_{2α}. The optimal position of the benzene ring is on carbon-17, 17-phenyl-18,19,20-trinor PGF_{2α}-isopropyl ester (C#8), and exhibited a much higher therapeutic index in the eye than PGF_{2α} or its ester. The biological activity of different substituents on the C#8 benzene ring have also been studied. Interestingly, introduction of a methyl group at positions 2 or 3 of the benzene ring (C#16 or C#17) affords compounds which are biologically more active than the methyl group at the 4-position (C#18). Furthermore, one of the analogues 13,14-dihydro-17-phenyl-18,19,20-trinor PGF_{2α}-isopropyl ester (latanoprost), has been found in clinical studies to be a highly potent and efficacious IOP-reducing agent for the treatment of glaucoma. (*Surv Ophthalmol* 41 [Suppl 2]: S47-S52, 1987)

Key words. cat • FP-receptors • intraocular pressure • irritation •latanoprost • monkey • prostaglandins • structure-activity relationships

The potent IOP-reducing effect of prostaglandins (PGs), particularly PGE and PGF analogues, in animals as well as in humans,^{1,2,3,4,5,6} has attracted the attention of ocular pharmacologists. Of particular interest is the ability of F-type PGs to reduce IOP in primates, including humans, by increasing the uveoscleral outflow of aqueous humor.⁶ However, the frequent and clinically unacceptable ocular side effects of the naturally occurring PGs, namely ocular irritation, foreign body sensation and conjunctival hyperemia, have led to a demand for the development of PG analogues with improved therapeutic indices. We have conducted a structure-activity relationship program, utilizing naturally-occurring PGs, in particular PGF_{2α}, as a lead compound, to design a new PG agent with better separation between the IOP lowering effect and the side-effects in the treatment of glaucoma.

These efforts have resulted in the discovery oflatanoprost (Fig. 1) as a potent and selective IOP-reducing agent.^{3,12,14,16} Latanoprost has been launched

on the market. Practical ways of synthesizing phenyl-substituted PGs and of screening their IOP-lowering potency and efficacy based on structure-activity relationships have been described.^{12,13} This paper provides a short overview of the structure-activity relationships of PGF_{2α} alkyl esters, PGF_{2α} isomers and the omega-chain modified phenyl-substituted PGF_{2α} compounds with regard to their ocular hypotensive potency and efficacy on FP receptors. The biological activities of these analogues have been compared with those of PGF_{2α} or PGF_{2α}-isopropyl ester (PGF_{2α}-IE).

The PG analogues were subjected to a battery of tests designed to demonstrate specific biological actions^{3,12,14,16} and were tested for IOP-reducing effect, effect on the pupil and ocular irritation in the cat. The IOP was measured using pneumatonometry under local anesthesia with oxibuprocaine. The horizontal diameter of the pupil was measured with a millimeter ruler under constant illumination conditions. The irritation was estimated on an arbitrary scale of 0-3 based on the degree of lid closure: 0

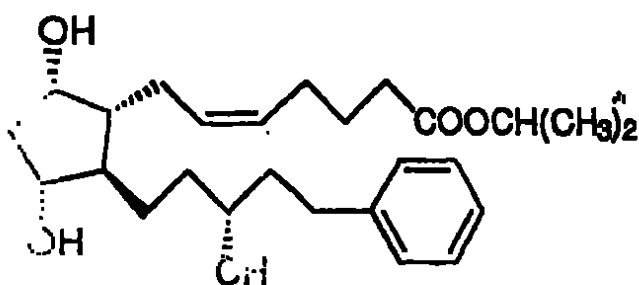


Fig. 1. Structure of latanoprost.

indicating absence of irritation and 3 marked irritation, i.e., complete closure of the lids. The effects of the analogues on the conjunctival blood vessels have been studied in the rabbit eye. The conjunctival hyperemia was documented by color photography. Many of these compounds were also tested for an IOP-reducing effect in cynomolgus monkeys. One eye of each animal was treated with the drug while the contralateral eye received vehicle solution.

In addition, selected PG-analogues were also tested *in vitro*, in the free acid form. The functional receptor studies were performed, using isolated cat iris sphincters expressing FP receptors in an ordinary tissue bath set-up.

The structure-activity relationships of PG analogues were based on the following approaches: 1) prodrugs, 2) stereochemical modifications, 3) omega-chain modifications and 4) aromatic substitutions.

Prodrug Approach

It is essential that drugs are accessible to their site of action. In the case of topically applied anti-glaucoma drugs, the active molecule must cross the tight-junctional surface epithelium to reach its intraocular target site. Therefore, the physiochemical properties of PGs must contribute favorably to the penetration through the corneal epithelium in order to increase the PG concentration at the active site.

Prostaglandins, particularly of the F-series, are relatively polar, hydrophilic molecules, due to their carboxylic acid moiety and several hydroxyl groups. Such molecules penetrate biological membranes poorly. PG-acids can be modified to less polar, more lipophilic compounds, by esterification of the acid moiety. This increases the penetration through lipid membranes, e.g., in the corneal epithelium.

A series of PGF_{2α}-ester prodrugs was prepared and their intraocular agonist potencies were measured. Since PGF_{2α} is a potent miotic in cats in contrast to rabbits and primates, the more easily measured pupillary constriction was used to compare the relative potencies of the esterified prodrugs.¹⁰ PGF_{2α}-isopropyl ester (PGF_{2α}-IE) is given as an example to

illustrate the process of esterification and deesterification in Fig. 2.

As seen in Fig. 1, PGF_{2α}-IE (C:#2) was a more potent miotic in the cat than the PGF_{2α} acid (C:#1). This result shows that the bioavailability has been markedly increased by esterification of PGF_{2α}. In addition, it has been shown that the prodrug PGF_{2α} esters are inactive until they are hydrolysed to the parent molecule, PGF_{2α} acid (Fig. 2).

Thus, the measurement of the extent of the miosis following the topical application of the various PGF_{2α} esters provides a measure of both the ease of the hydrolysis of the prodrug and the ease of the delivery of the drug into the intraocular site.

The prodrug principle also increases the therapeutic index of the PGs in the eye, as is evident from a comparison of the clinical findings with PGF_{2α} tromethamine salt⁸ that resulted in the severe ocular hyperemia, corneal irritation and even headaches, although less side-effects were obtained after the topical application of PGF_{2α}-IE to eyes of normal volunteers. However, even this prodrug, PGF_{2α}-IE, proved to be clinically unacceptable for routine use for the management of IOP in glaucoma.¹ Therefore, the development of new analogues was undertaken.

Stereochemical Approach

It is generally believed that fit of the drug molecule and receptor is necessary to evoke maximal bio-

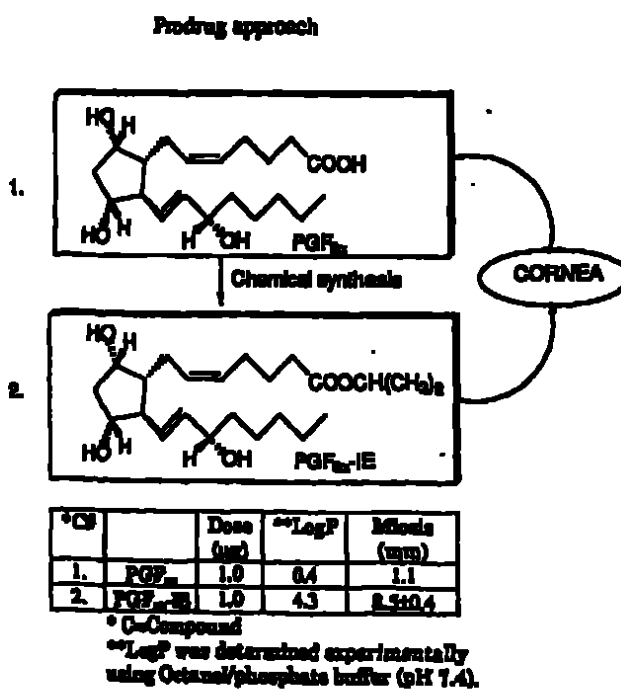


Fig. 2. Influence of the esterification of PGF_{2α} as a prodrug, on the penetration through corneal epithelium. Maximum miotic effect of PGF_{2α} and PGF_{2α}-IE in the cat (n = 6; Mean(SEM)).

logical response. The purpose of this stereochemical approach was to investigate the influence of the spatial orientations of the three hydroxyl groups of PGF analogues on the drug-receptor interaction.

Fig. 3 illustrates the effect of configurational differences in the PGF_{2α} molecule (C#2) on biological responses and receptor profile. Naturally-occurring PGF_{2α} possesses three hydroxyl groups pointing below the plane of the molecule. PGF_{2α} is a potent IOP-reducing agent and also induces miosis and causes strong irritation in the cat eye. In the monkey eye PGF_{2α} is a potent ocular hypotensive. Furthermore, it exhibits potent FP receptor agonist activity. Interestingly, inversion of the configuration at carbon-9 (C#3) changes the type of biological activity and affords a potent IOP-reducing agent which does not induce miosis and is a lesser irritant than PGF_{2α} in the cat eye. In the monkey eye it exhibited somewhat less potent IOP-reducing properties compared to PGF_{2α}. This PG is about 100-fold less potent than PGF_{2α} on the FP receptor. Inversion of the configuration at C-11 (C#4) surprisingly yields a compound which has no significant effect on IOP reduction. However, it is a potent miotic which causes little irritation in the cat eye and is a potent FP agonist. Inversion of the 15-hydroxyl group (C#5) decreased the biological activity in general.

Unfortunately, these compounds also exhibited some clinically unacceptable side effects, such as ocular irritation and conjunctival hyperemia; therefore, new PG analogues had to be designed in an attempt to improve the therapeutic index.

Omega-chain Modifications:

The main emphasis in the structure-activity program has been on the influence of omega-chain modification and the introduction of a phenyl ring in the omega chain on the biological activity and receptor profile. The results are summarized in Fig. 4 and Table 1.

Replacement of the 5 carbon atoms, carbons 16-20, with a benzene ring, yielding 15-phenyl-pentanoic PGF_{2α} (C#6), resulted in a marked loss of biological activity in general. Interestingly, the substitution of carbons 17-20 of PGF_{2α} with a benzene ring, 16-phenyl-tetranor PGF_{2α} (C#7), afforded an active compound with PGF_{2α}-like properties, although it failed to produce miosis in the cat eye. In the monkey eye it is a potent IOP-reducing agent. It was found to be a relatively potent FP receptor agonist, although less potent than PGF_{2α}. Surprisingly, replacement of carbons 18-20 with a benzene ring, 17-phenyl-18,19,20-trinor-PGF_{2α} (C#8), changed the receptor profile dramatically. This compound has no

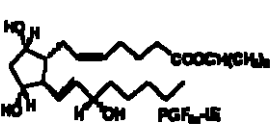
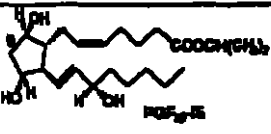
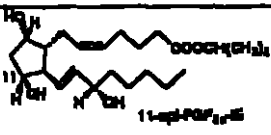
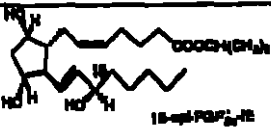
C#	Stereochemistry	Cat (Dose 1µg)			Monkey		FP Receptor
		Reduction of IOP, mmHg	Reduction in pupil diameter mm	Irritation	Dose	Reduction of IOP, mmHg	EC ₅₀ Acid
2		7.5±1.3	9.3±0.4	3.0	3.0	2.5±0.3	1X10 ⁻⁶
3		8.3±1.5	0.0	1.5	1.5	1.1±0.8	3.6X10 ⁻⁶
4		0.0	7.0±0.7	1.0	2.4	2.0±0.9	3.3X10 ⁻⁶
5		7.2±0.4	6.2±1.0	1.0	3.0	0.0	7X10 ⁻⁴

Fig. 3. Effect of stereochemistry in the PGF_{2α} molecule upon biological responses and receptor profile (Mean±SEM).

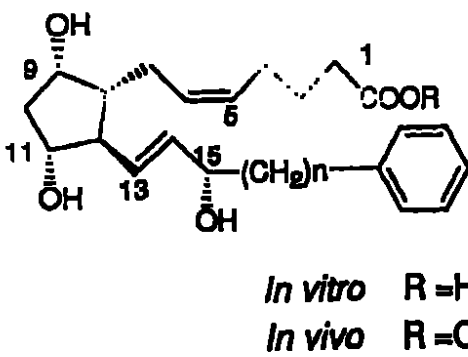


Fig. 4. The structure of the omega chain modified phenyl substituted PGF_{2a} analogues.

significant effect on IOP in cats, although it induced marked and dose-dependent miosis without irritation in the cat eye. The compound exhibits a good IOP-reducing effect in primates. *In vitro*, compound (C#8) exhibited a 10-fold greater potency on FP receptor than PGF_{2a}. As can be seen, increasing the chain length to 18-phenyl dinor PGF_{2a} (C#9) yields a product which is considerably less potent than PGF_{2a}, both *in vivo* and *in vitro*. Increasing the chain length to 19-phenyl or longer diminishes the biological activity or renders the molecules practically inactive.

It is obvious that FP receptors play an important role in the IOP-reducing effect in primates. Furthermore, Fig. 4 and Table 1 illustrate that 17-phenyl-18,19,20-trinor-PGF_{2a}-IE was the most optimal PG analogue in this series of analogues, in that this compound exhibited high biological activity without an irritating effect; it also possesses a good therapeutic index in the eye. This provides evidence that the po-

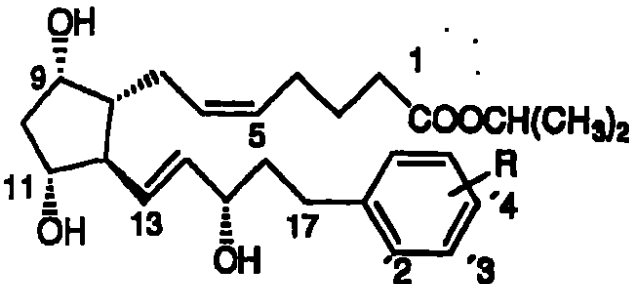


Fig. 5. The structure of different substituents in the benzene ring of 17-phenyl-18,19,20-trinor-PGF_{2a} analogues.

sition of the phenyl ring in the omega chain in PGF_{2a} plays an important role in the type of activity, affinity and efficacy. Thus, the structural requirements for an IOP-reducing effect are very specific and C#8 possesses a nearly optimal structure.

Additional saturation of the trans 13,14-double bond of the C#8 yields a potent ocular hypotensive compound 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF_{2a}-IE (latanoprost) that lacks significant irritative and conjunctival hyperemic side effects. Furthermore, latanoprost was beneficial both from a biological and a chemical point of view, and it is chemically more stable than C#8.

Aromatic Substitution

The purpose of this approach was to investigate the influence on the receptor interaction and receptor profile of the introduction of different groups into the benzene ring of C#8 (Fig. 5 and Table 2). Introduction of a methyl group into the ortho (2-CH₃, C#16) or meta (3-CH₃, C#17) position afforded compounds which induced miosis with a poor

TABLE 1
Maximum Ocular Responses of the Omega Chain Modified PGF_{2a}-IE in Cat and Monkey.
All compounds were applied topically. (n=6, Mean±SEM).
The EC-50 value of the compounds on FP receptors compared with PGF_{2a}.

C#	n	Cat				Monkey		<i>In vitro</i> EC ₅₀ (mol/l)
		Dose µg	Reduction of IOP mm Hg	Reduction in pupil diameter mm	Irritation	Dose µg	Reduction of IOP mmHg	
6	0	3.0	2.0 ± 0.7	0.3 ± 0.3	0.4 ± 0.1			
7	1	1.0	6.7 ± 0.9	1.0 ± 0.0	2.3 ± 0.3	3.0	3.9 ± 0.4	3 × 10 ⁻⁷
8	2	1.0	0.0	9.7 ± 0.3	0.0	3.0	3.9 ± 0.4	2 × 10 ⁻⁶
9	3	1.0	2.0 ± 0.6	4.3 ± 0.6	0.7 ± 0.1	3.0	0.6 ± 0.3	2 × 10 ⁻⁶
10	4	1.0	3.5 ± 1.1	0.0	0.5 ± 0.1	3.0	0.6 ± 0.3	5 × 10 ⁻⁷
11	5	5.0	3.3 ± 0.4	1.7 ± 0.1	0.8 ± 0.2	10.0	0.3 ± 0.3	3 × 10 ⁻⁷
12	6	10.0	1.8 ± 0.8	2.8 ± 0.4	1.3 ± 0.3	3.0	0.5 ± 0.1	3 × 10 ⁻⁶
13	7	1.0	1.3 ± 1.2	0.3 ± 0.3	0.3 ± 0.1			2 × 10 ⁻⁶
14	8	1.0	0.3 ± 1.7	0.0	0.4 ± 0.3			1 × 10 ⁻⁶
15	9	10.0	1.5 ± 0.8	1.0 ± 0.5	0.9 ± 0.2	10.0	0.0 ± 0.3	8 × 10 ⁻⁶
PGF _{2a} -IE	1.0		7.2 ± 0.4	8.2 ± 0.7	3.0 ± 0.2	3.0	2.5 ± 0.3	1 × 10 ⁻⁶
latanoprost	1.0		0.7 ± 0.2	7.5 ± 0.5	0.0	3.0	2.6 ± 0.4	2 × 10 ⁻⁶

Blank denotes not tested.

TABLE 2

Influence of Different Substituents in the Benzene Ring of 17-phenyl-18,19,20-trinor-PGF_{2α} on the Biological Effects in Cat and Monkey Eyes (n=6; Mean±SEM)

Cat						Monkey	
C#	R	Dose µg	Reduction of IOP, mmHg	Reduction in pupil diameter, mm	Irritation	Dose µg	Reduction of IOP, mmHg
16	2-CH ₃	1.0	2.0 ± 0.7	8.3 ± 0.6	0.0	10.0	2.3 ± 0.3
17	3-CH ₃	1.0	1.0 ± 0.9	6.8 ± 0.8	0.3 ± 0.2	1.0	2.5 ± 0.7
18	4-CH ₃	1.0	0.8 ± 0.4	2.5 ± 0.2	0.0	3.0	1.7 ± 0.1
19	2-CF ₃	1.0	2.3 ± 0.8	2.8 ± 0.5	0.3 ± 0.1		
20	3-CF ₃	1.0	1.2 ± 0.7	7.0 ± 0.9	0.2 ± 0.2	3.0	0.7 ± 0.6
21	4-CF ₃	1.0	1.7 ± 0.6	0.6 ± 0.2	0.0	10.0	1.0 ± 0.4
22	2-OCH ₃	1.0	1.1 ± 0.4	1.2 ± 1.1	0.3 ± 0.8		
23	3-OCH ₃	10.0	2.3 ± 0.5	8.2 ± 0.5	0.7 ± 0.1	10.0	0.7 ± 0.3
24	4-OCH ₃	10.0	3.5 ± 0.7	1.7 ± 0.5	0.2 ± 0.1	10.0	1.4 ± 0.5
25	2-F	1.0	2.2 ± 2.0	6.8 ± 1.1	0.4 ± 0.2	3.0	1.4 ± 0.5
26	3-F	1.0	4.3 ± 1.4	7.4 ± 0.7	0.3 ± 0.2		
27	4-F	1.0	0.0	8.2 ± 0.2	0.0	1.0	3.0 ± 0.7

Blank denotes not tested.

ocular hypotensive response, although without irritation in the cat. In the monkey, (C#16) and (C#17) reduced IOP, although less effective than the parent compound. Shifting the methyl substituent to the para position (4-CH₃, C#18) in the benzene ring further reduced the biological activity. In vitro (C#17) was 10 times more potent than (C#18) on the FP receptor. This maneuver was tolerated, but provided no increase in potency compared to the parent compound (C#8).

Introduction of trifluoromethyl into the ortho (2-CF₃, C#19), meta (3-CF₃, C#20) or para (4-CF₃, C#21) position resulted in compounds having no or weak IOP-reducing effect. Among them only (C#20) induced marked miosis in the cat. Introduction of the methoxy group into meta (3-OCH₃, C#23) or para (4-OCH₃, C#24) position has a weak IOP-reducing effect. However, the 3-methoxy analogue (C#23) exhibits potent miosis. The methoxy analogues did not appear to have significant effect on IOP in the monkey. Introduction of a fluorine atom onto any position of the benzene ring did not appear to cause a change in the biologic activity of the parent compound. Thus, introduction of fluorine at different positions in the ring is tolerated. These compounds are potent FP agonists, equipotent to the parent compound. These modifications indicate that almost all compounds with 17-phenyl-18,19,20-trinor-PGF_{2α} substitution show evidence of FP agonistic activity.

Comments and Conclusions

Esterification of the carboxylic acid group of PGF_{2α}

increases the ocular hypotensive potency by enhancing the penetration of the drug into the eye. Inversion of the hydroxyl configuration at carbon-9 or carbon-11 of PGF_{2α} changes the potency and receptor profile of PGF_{2α}, but yields no improvement with respect to IOP reduction. Substituting part of the omega chain of PGF_{2α} with a benzene ring greatly alters the potency and receptor profile of PGF_{2α}. The highest potency is gained when the benzene ring replaces the last 3-carbon atoms of PGF_{2α}. The biological activity of C#8 can further be altered by substitutions in the benzene ring. However, none of these substitutions improved the ocular hypotensive therapeutic index significantly.

In contrast, saturation of the 13,14-double bond of C#8 to yield latanoprost increases the therapeutic index and the chemical stability of C#8. Latanoprost lacks clinically significant conjunctival hyperemic side effects, without loss of ocular hypotensive potency or efficacy as compared to C#8. In fact, this PGF_{2α} analogue prodrug, which is highly selective for the FP-receptor, has been found in Phase II and Phase III clinical studies to be the most potent ocular hypotensive agent in primary open-angle glaucoma or normal tension glaucoma, as described in other reviews in this issue.¹⁴ Most importantly, when applied to the eye once a day at a concentration of 0.005%, latanoprost has been shown to provide a remarkably stable reduction of IOP. This reduction in IOP is achieved by increasing the uveoscleral outflow during both the day and night as described in this issue.¹⁴ The foregoing demonstrates the power of the rational use of structure-

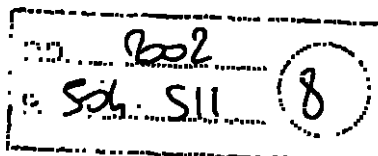
activity relationships in appropriate in vitro and in vivo models in the development of new therapeutic agents, in this case, highly potent and efficacious ocular hypotensive agents for the management of glaucoma.

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Drs. Resul, Sjöstrand and Selén are employed by Pharmacia & Upjohn, Uppsala, Sweden. Dr. Bito has a proprietary interest in the use of prostaglandins for the medical management of glaucoma, through patents he has assigned to Columbia University according to the policies of the National Institutes of Health (USPHS), that has supported the research program of his laboratory in this field, between 1970 and 1989. He is currently a consultant to Pharmacia and Upjohn.

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Prostaglandin Analog Treatment of Glaucoma and Ocular Hypertension

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OBJECTIVE: To review available data related to the use of prostaglandin analogs (bimatoprost, latanoprost, travoprost, unoprostone) in the management of ocular hypertension and open-angle glaucoma.

DATA SOURCES: Primary and review articles were identified from a MEDLINE search (1986–May 2001) and requested information from product manufacturers.

STUDY SELECTION AND DATA EXTRACTION: All available information, including that published in articles and abstracts, which was deemed relevant was included in this review. Limited data have been published to date.

DATA SYNTHESIS: The prostaglandin analogs appear to be effective, well-tolerated agents for the reduction of intraocular pressure (IOP) in patients with primary open-angle glaucoma and ocular hypertension. This drug class offers an alternative for patients who do not achieve control with another topical antiglaucoma agent or for those with a contraindication to first-line therapy with β -adrenergic antagonists. Based on preliminary clinical data, bimatoprost, latanoprost, and travoprost appear to be at least as effective as timolol, while the effectiveness of unoprostone is similar or slightly less. Prostaglandin analogs may be used in conjunction with other antiglaucoma medications, although further studies must establish the optimal combination. Whether clinical experience will yield outcomes in favor of one of the prostaglandin analogs remains to be determined. Patients should be educated on adverse events associated with prostaglandin analogs, particularly the potential for changes in the pigmentation of the iris and eyelashes.

CONCLUSIONS: Bimatoprost, latanoprost, and travoprost appear to be equivalent to the current standard of therapy in the topical treatment of elevated IOP. Further clinical data published in article versus abstract format is required to better assess potential differences among these 3 agents.

KEY WORDS: bimatoprost, glaucoma, latanoprost, prostaglandin analogs, prostamides, travoprost, unoprostone.

Ann Pharmacother 2002;36:504–11.

THIS ARTICLE IS APPROVED FOR CONTINUING EDUCATION CREDIT.

ACPE UNIVERSAL PROGRAM NUMBER: 407-000-02-008-H01.

Prostaglandin, prostamide, and docosanoid analogs are a novel group of ocular hypotensive agents used in the treatment of open-angle glaucoma (OAG) and ocular hypertension (OH). Although these drugs are structurally unique, they share similar characteristics and are often referred to as prostaglandin analogs, the term used for the purpose of this review. Latanoprost was the sole prostaglandin analog approved by the Food and Drug Administration (FDA) until 2000. Three additional prostaglandin analogs, bimatoprost, travoprost, and unoprostone, recently received FDA approval.¹ This review provides an update of

the pharmacology, pharmacokinetics, clinical efficacy, and safety of prostaglandin analogs in the treatment of OAG and OH.

Glaucoma encompasses a group of ocular diseases associated with progressive optic neuropathy that may ultimately result in vision loss.^{2,3} These conditions affect up to 2 million Americans and are a leading cause of blindness worldwide.⁴ Open-angle and angle-closure are the most common types of glaucoma. These diagnoses may be further classified as primary (POAG, no identifiable cause) or secondary (an identifiable cause). Open-angle glaucoma is characterized by an impairment in aqueous humor drainage. In contrast, closed-angle glaucoma is associated with obstruction of aqueous humor drainage.² Open-angle is the

Author information provided at the end of the text.

most prevalent glaucoma, affecting 1–3% of patients in the US >70 years old.¹ Because closed-angle glaucoma is typically an emergency situation requiring surgical intervention, discussion of its treatment is not included in this review. Of note, patients presenting with elevated intraocular pressure (IOP) in the absence of optic nerve damage or visual field loss are classified as having OH.

The exact etiology of primary open-angle glaucoma is unknown; however, key risk factors for the disease include advanced age, African American race, a family history of glaucoma, and elevated IOP.² Diabetes mellitus, hypertension, myopia, genetics, long-term steroid therapy, and previous eye injury may also contribute to the pathogenesis of glaucoma. Elevated IOP does not need to be present to establish the diagnosis; however, it is widely known that many patients with POAG have elevated IOP secondary to the obstruction of aqueous humor outflow.³ Elevated IOP may damage the retinal ganglion cells and the respective axons making up the optic nerve, subsequently reducing the visual field. Multiple studies^{3,4} have demonstrated that elevations in mean and peak IOP correlate with a progression in visual field loss.

Elevated IOP is the only risk factor for the type of glaucoma that is currently amenable to therapy. Healthy adults have a mean IOP of 15–16 mm Hg, with 21 mm Hg considered the upper limit of normal.⁵ The primary goal in the treatment of glaucoma is the reduction of IOP, thereby slowing progression of the disease. Patients with OH may also benefit from IOP reduction because of a decreased risk in future development of glaucoma. Laser surgery, filtration surgery, and chronic drug therapy are interventions that may reduce IOP; the latter is the preferred first-line therapy. Pharmacologic agents can reduce IOP by decreasing aqueous humor production or by increasing its outflow through the trabecular network or uveoscleral pathway. Five classes of topical medications for OAG and OH are available: β -adrenergic blockers (e.g., timolol), carbonic anhydrase inhibitors (e.g., dorzolamide), α_2 -adrenergic agonists (e.g., brimonidine), direct-acting cholinergic agonists (e.g., pilocarpine), and the focus of this review, the prostaglandin analogs.

Selecting an appropriate pharmacologic intervention for a patient with glaucoma or OH is challenging. In general, factors to consider include the agent's efficacy, safety, cost, patient convenience, and long-term effects. Because of its relative efficacy and clinical experience, timolol is the gold standard to which other agents are compared.⁶ However, the β -blockers are limited by the potential for systemic absorption and are contraindicated for use in patients with respiratory or cardiac disease.⁷

The addition of the prostaglandin analog class provides an alternative mode to reduce IOP without inducing significant systemic effects. Bimatoprost, latanoprost, travoprost, and unoprostone are approved by the FDA for the reduction of elevated IOP in patients with OAG or OH who are intolerant of or insufficiently responsive to other IOP-lowering medications.^{10–13} Although this indication classifies the prostaglandin analog class as a second-line treatment

alternative, treatment for glaucoma is highly individualized, and practitioners may select various agents for initial therapy because of favorable efficacy and tolerability.

Literature Selection and Assessment

A MEDLINE search (1966–May 2001) of English-language literature was performed using the terms prostaglandin analogs, glaucoma, latanoprost, bimatoprost, unoprostone, and travoprost. The manufacturers of the respective agents were contacted for additional information. References in the identified articles were reviewed for possible inclusion. With the exception of latanoprost, the majority of clinical data for this drug were available only in abstract form or from the manufacturer at the time of manuscript creation. Therefore, specific details regarding patient demographics, trial design, and complete results were not available in all cases. Because a significant number of new publications became available during the review process for this article, the authors have updated citations from abstracts or data from the manufacturer to reflect new published literature.

Pharmacology

Prostaglandins are endogenous fatty acids existing throughout the body. With ocular administration, various subtypes of prostaglandins reduce IOP. Latanoprost and travoprost are analogs of prostaglandin $F_{2\alpha}$ and act as selective agonists of the prostanoid FP receptor to lower IOP.^{14,15} Unoprostone is structurally distinct from latanoprost and travoprost. It is a docosanoid, which is an Ω -3 polyunsaturated fatty acid analog of a derivative of docosahexaenoic acid.¹⁶ Of the 4 commercially available drugs in the prostaglandin analog class, unoprostone has the lowest affinity for the prostanoid FP receptor and may exert its pharmacologic effects through a unique mechanism of action that is not well understood.¹⁷ Although bimatoprost is classified as a prostaglandin analog, it is actually a synthetic analog of fatty-acid amides (prostanamides), which are endogenous compounds that possess ocular hypotensive activity.^{18,19} In contrast to prostaglandins, which are biosynthesized from arachidonic acid, the precursors to prostanamides are anandamides. Whether this structural difference results in different clinical outcomes remains to be determined.

Unlike other topical ocular hypotensive drug classes (e.g., β -adrenergic blockers), prostaglandin analogs have minimal to no effect on the production of aqueous humor. Although the exact mechanism of action has yet to be elucidated, these agents appear to increase aqueous humor outflow. The uveoscleral outflow through the iris ciliary body may be increased through relaxation of the ciliary muscles or a decrease in extracellular matrix surrounding the muscle bundle.^{10–13} In addition to these actions on the uveoscleral route, bimatoprost may affect the trabecular network.¹⁴ Topical administration of any of the prostaglandin analogs ultimately results in a reduction in IOP.^{10–13}

Pharmacokinetics

Latanoprost, travoprost, and unoprostone are formulated as isopropyl ester prodrugs of their corresponding unbound acids. These agents undergo ester hydrolysis on topical administration during passage and absorption through the cornea. Following topical administration, the concentration of prostaglandin analogs in the systemic circulation is very small compared with the concentration of endogenous prostaglandins. Although data are limited, the pharmacokinetic parameters available to date are provided in Table 1.¹⁰⁻¹²

LATANOPROST

Peak concentrations of latanoprost in the aqueous humor are achieved approximately 2 hours after ocular administration. Latanoprost has a volume of distribution of 0.16 ± 0.02 L/kg. Once in the systemic circulation, the biologically active acid form of latanoprost is primarily metabolized by the liver. The acid form of latanoprost undergoes fatty acid β -oxidation to form the 1,2-dinor and 1,2,3,4-tetranor metabolites. The acid form of latanoprost has an elimination half-life of 17 minutes and a systemic clearance of approximately 7 mL/min/kg after either intravenous or ocular administration. The 1,2-dinor and 1,2,3,4-tetranor metabolites are primarily eliminated by the kidneys. Approximately 88% of an ocular dose and 98% of an intravenous dose is recovered in the urine.¹²

TRAVOPROST

Peak plasma concentrations of travoprost unbound acid (≥ 25 pg/mL) are reached within 30 minutes following ocular administration. The biologically active acid of the drug reaching the systemic circulation is primarily metabolized by the liver. The acid form of travoprost undergoes β -oxidation to form the inactive 1,2-dinor and 1,2,3,4-tetranor metabolites. Following ocular administration, travoprost unbound acid is rapidly eliminated from human plasma and is below the detectable limit (<10 pg/mL) within 1 hour. Although it has not been reported, the estimated half-life of travoprost unbound acid (based on plasma concentration data over time) is <30 minutes.^{11,12}

UNOPROSTONE

The mean peak unoprostone unbound acid concentration is <1.5 ng/mL, with little to no expected accumula-

tion.^{11,12} The acid form of unoprostone is rapidly eliminated from human plasma, with an elimination half-life of 14 minutes. Plasma concentrations of unoprostone unbound acid are undetectable (<0.25 ng/mL) within 1 hour after ocular administration. The metabolites of unoprostone unbound acid are predominantly excreted in the urine.

BIMATOPROST

Unlike the other prostaglandin analogs, bimatoprost is not a prodrug. Bimatoprost is absorbed through the cornea and has a steady-state volume of distribution of about 0.67 L/kg.^{10,17} Bimatoprost resides mainly in the plasma, and approximately 12% of the drug remains unbound. Blood concentrations peak within 10 minutes and are below the lower limit of detection (0.025 ng/mL) within 1.5 hours after dosing. Steady-state is achieved during the first week of ocular dosing, and there is no systemic accumulation over time. Once in the systemic circulation, bimatoprost is the major circulating compound in the blood. It is mainly metabolized by the liver where it undergoes oxidation, *N*-deethylation, and glucuronidation to form a variety of metabolites. Bimatoprost has an elimination half-life of approximately 45 minutes and a total blood clearance of 1.5 L/h/kg. Metabolites are eliminated in the urine (67%) and the feces (25%).

Clinical Efficacy

Important outcomes in the evaluation of a new antiglaucoma agent are the mean IOP reduction, the response rate in different populations, and the diurnal control provided by the agent.¹³ The primary measurable outcome is typically the mean IOP reduction. Unfortunately, this value can be skewed by patients who do not respond or by those who respond very favorably to therapy. Furthermore, IOP widely varies based on circadian rhythms, particularly in patients with POAG. IOP is generally highest in the early morning hours and tapers off throughout the day. Studies^{18,19} show that large fluctuations in diurnal IOP may be detrimental, resulting in a need for agents that provide stable and continuous control. Reporting the mean IOP may not accurately account for these potential fluctuations. Therefore, the diurnal variability should also be assessed and reported, along with the standard deviation.

In registration trials,¹⁰⁻¹² latanoprost, travoprost, and bimatoprost produced a mean IOP reduction of 6–8 mm Hg in patients with OAH or OH (baseline IOP 24–27), corresponding to a 22–33% reduction of IOP. The pivotal studies¹³ with unoprostone yielded a smaller, yet significant reduction of 3–4 mm Hg (13–17%) from a baseline of 23 mm Hg. Because much of the data have not been published to date, details regarding the study methodology and statistical analyses employed were not available for review in all cases.

BIMATOPROST

Two multicenter, randomized, double-masked clinical trials²⁰ were performed to compare the efficacy of bimatop-

Table 1. Pharmacokinetic Parameters of Prostaglandin Analogs¹⁰⁻¹²

Drug	Onset (h)	Peak (h)	Duration (h)
Bimatoprost	~4	8–12	unknown
Latanoprost	~3–4	8–12	unknown
Travoprost	~2	12	unknown
Unoprostone	15 min–1 h	unknown	10–12

prost 0.03% given once ($n = 474$) or twice ($n = 483$) daily with timolol maleate 0.5% twice daily ($n = 241$). Patients were required to have glaucoma or OH and a baseline IOP of 22–34 mm Hg. The primary end point of both studies was the diurnal IOP at 0800, 1000, 1600, and 2000. Patients were evaluated at preenrollment, baseline, week 2, week 6, month 3, and month 6. The baseline IOP (26 mm Hg) was not significantly different among groups in either trial.

The results of the 2 trials were pooled because of their identical design. Bimatoprost 0.03% once daily demonstrated greater reduction in mean IOP than did timolol 0.5% twice daily at each time period and at every study visit ($p \leq 0.001$). Efficacy was sustained for the duration of the 6-month evaluation, with an 8.1-mm Hg (33%) IOP reduction from baseline at month 6 (1000) with bimatoprost 0.03% once daily compared with a 5.6-mm Hg (23%) reduction with timolol 0.5% twice daily ($p \leq 0.029$). Twice-daily administration of bimatoprost 0.03% also demonstrated similar or superior efficacy to that of timolol 0.5% twice daily but was less effective than timolol with once-daily dosing. Additional studies were performed in order to determine the percentage of patients achieving different levels of IOP. Based on a target IOP of ≤ 17 mm Hg, 67% of patients treated with bimatoprost 0.03% once daily were deemed responders compared with 37.3% of patients receiving timolol 0.5% twice daily ($p \leq 0.001$). Likewise, a target of ≤ 15 mm Hg was achieved by more patients in the bimatoprost 0.03% once-daily group (36%) than the timolol 0.5% twice-daily arm (36% vs. 20%, respectively; $p \leq 0.001$).

UNOPROSTONE

Although unoprostone has been commercially available in Japan since 1994, the compound was reformulated for use in the US and additional clinical trials were conducted to support its FDA application. Unoprostone was compared with timolol maleate in 2 pivotal, triple-masked, randomized, international trials.^{16,21} Patients with POAG or OH (mean baseline IOP 24 mm Hg) were enrolled. The primary end point in both studies was the 12-hour diurnal IOP change from baseline at 6 months.

The first study¹⁶ involved 571 patients in the US and Canada. Subjects receiving unoprostone 0.15% twice daily demonstrated an IOP reduction of 3–4 mm Hg; patients in the timolol 0.5% twice-daily group had an IOP reduction of 4–5 mm Hg. The IOP reduction was consistent during the day and was sustained for the study duration in both groups. The second study²¹ randomized 560 patients in Europe and Israel to twice-daily treatment with unoprostone 0.15%, timolol maleate 0.5%, or betaxolol hydrochloride 0.5%. Similar to the results found in the first study, IOP reductions with unoprostone ranged from 4 to 5 mm Hg compared with 5 to 6 mm Hg with timolol and 5 mm Hg with betaxolol. A relatively flat diurnal curve was reported in both studies.

TRAVOPROST

Travoprost was compared with timolol maleate in 2 large studies.^{22,23} In the first international, multicenter, double-blind study, travoprost (0.0015% or 0.004%) given once daily in the evening was compared with timolol maleate 0.5% given twice daily. The primary end point was the mean IOP at 0900, 1100, and 1600. Patients treated with either concentration of travoprost had a significant reduction in IOP ($p = 0.0001$). The greatest reduction was in the travoprost 0.0015% group (8–8.9 mm Hg), whereas the timolol patients had a smaller reduction (6.3–7.9 mm Hg). The second trial also compared travoprost 0.0015% and 0.004% administered once daily in the evening with timolol maleate 0.5% twice daily in patients with POAG or OH. The primary end point was mean IOP at 0800, 1000, and 1600 at 6 months. The IOP-lowering effect of both doses of travoprost was significantly greater than with timolol ($p \leq 0.0130$). The mean percent IOP reduction from baseline was 24–27% for travoprost 0.0015%, 26–29% for travoprost 0.004%, and 20–26% for timolol.

The efficacy of travoprost was compared with latanoprost and timolol in a 12-month, multicenter, randomized, double-masked study.²⁴ Patients with OAG or OH were randomized to receive travoprost 0.0015% or 0.004% once daily in the evening, latanoprost 0.005% once daily in the evening, or timolol 0.5% twice daily. The primary end point was the mean IOP at 0800, 1000, and 1600. Pooled data from treatment groups showed a mean IOP reduction of 6.2–7.2 mm Hg for travoprost 0.0015%, 6.8–7.7 mm Hg for travoprost 0.004%, 6.4–7.7 mm Hg for latanoprost 0.005%, and 5.2–6.7 mm Hg for timolol 0.5%. The authors reported a significantly greater IOP reduction (0.8 mm Hg; $p = 0.00191$) with travoprost 0.004% than latanoprost 0.005% in the 1600 end point analysis. The percentage of patients achieving at least a 30% reduction in IOP or an IOP of ≤ 17 mm Hg was 49.8% for travoprost 0.0015%, 56.3% for travoprost 0.004%, 49.6% for latanoprost 0.005%, and 40.4% for timolol 0.5%. The authors concluded that travoprost 0.004% was more effective than timolol and at least as effective as latanoprost in reducing IOP in patients with POAG or OH.

A subgroup analysis¹¹ assessing the efficacy of travoprost in African Americans detected a 1.8 mm Hg larger reduction in IOP in this population than in non-African American patients. Pooled results from 3 studies²⁵ showed statistically superior IOP reduction with travoprost 0.004% compared with timolol in both African Americans (mean 3.2 mm Hg) and non-African Americans (mean 1.4 mm Hg) ($p \leq 0.0001$). In addition, in 1 study, the mean reduction in IOP in African American patients was 1.4 mm Hg greater with travoprost (to 17.2 mm Hg) than with latanoprost (to 18.6 mm Hg) ($p = 0.0064$). The reason for this difference in response to travoprost is postulated to be due to race or heavily pigmented irises. Because the incidence of glaucoma is approximately 3 times higher in African Americans than non-African Americans, this response may be clinically significant. To date, travoprost is

the only prostaglandin analog that has been specifically analyzed in this population subset.¹¹

LATANOPROST

Multiple studies support the use of latanoprost for the reduction of IOP in patients with POAG and OH. Latanoprost 0.005% given once daily was compared with timolol maleate 0.5% given twice daily in a 6-month, randomized, double-masked study in 294 patients with OH or POAG.²⁶ The primary end point was the diurnal IOP (0900, 1300, 1700) at 6 months. IOP reduction was similar with latanoprost (33.7%) and timolol (32.7%). In an additional trial²⁷ using similar methodology, latanoprost 0.005% administered once daily in the evening reduced IOP by 35% compared with a 27% reduction with timolol 0.5% given twice daily ($p \leq 0.001$). The efficacy of latanoprost appears to be sustained, with a reduction in IOP from 25.3 to 17.1 mm Hg ($p < 0.001$) in 198 patients treated for 1 year.²⁸ Latanoprost 0.005% once daily has also been shown²⁹ to be more effective than timolol 0.5% twice daily in reducing IOP in patients with pigmentary glaucoma.

COMPARISONS

Limited head-to-head analyses were available comparing the prostaglandin analogs at the time of this review. However, in addition to the previously described trial²⁴ comparing travoprost with latanoprost, a small investigation has compared bimatoprost and unoprostone with latanoprost.

A Phase II, multicenter, randomized, double-masked trial³⁰ was conducted to compare the efficacy of once-daily bimatoprost 0.03% ($n = 21$) with latanoprost 0.005% ($n = 22$). Patients with OAG or OH with a baseline IOP between 23 and 34 mm Hg received treatment at 2000 for 29 days. The mean reductions in IOP from baseline with bimatoprost and latanoprost were 5.9–8.9 mm Hg (25–34%) and 4.4–7.0 mm Hg (20–31%), respectively. Although the IOP reduction with bimatoprost was numerically greater at each time point assessed, the difference was not statistically significant. The percentage of patients who achieved a target IOP < 17 mm Hg at 2000 at study end point was 42.1% for bimatoprost 0.03% once daily and 33.3% for latanoprost 0.005% once daily ($p = 0.567$).

Latanoprost was also compared with unoprostone in an 8-week, double-masked, randomized, clinical trial.³¹ Patients ($n = 118$) with POAG or OH received latanoprost 0.005% once daily in the evening or unoprostone 0.12% twice daily. Although this concentration of unoprostone is marketed in multiple countries, the FDA-approved formulation is 0.15%. IOP was assessed at week 2 (1200) and at week 8 (1000, 1700). At study end point, the mean IOP reduction from baseline (24.1 mm Hg) was 6.7 mm Hg (28%) with latanoprost and 3.3 mm Hg (14%) with unoprostone ($p \leq 0.001$). The response rate, defined as $\geq 30\%$ reduction in IOP from baseline, was 44% with latanoprost

and 8% with unoprostone. There was no apparent difference in IOP response due to gender, age, iris color, or type of glaucoma.

COMBINATION THERAPY

Prostaglandin analogs possess a unique mechanism of action that may be synergistic or complementary with other antiglaucoma medications, such as β -adrenergic blockers, oral carbonic anhydrase inhibitors, or topical carbonic anhydrase inhibitors.³² The addition of latanoprost 0.005% once daily or unoprostone 0.15% twice daily to timolol maleate 0.5% twice daily was evaluated in a 4-week study.³³ The IOP reductions from baseline were 2–4 mm Hg (unoprostone plus timolol), 5–6 mm Hg (latanoprost plus timolol), and 1–2 mm Hg (placebo plus timolol). Additional short-term trials^{34,35} have assessed adjunctive therapy with latanoprost in patients treated with dipivefrin 0.1% twice daily, acetazolamide 250 mg twice daily, pilocarpine 2% 3 times daily, and timolol 0.5%/dorzolamide 2% twice daily. In these investigations, latanoprost produced an additional reduction in IOP of 1.5–9.1 mm Hg. In another study,³⁶ travoprost was added to patients receiving monotherapy with timolol maleate 0.5% twice daily (baseline IOP 25 mm Hg). This combination resulted in an additional IOP reduction of 5.7–7.2 mm Hg in the travoprost 0.004% once-daily plus timolol group compared with an IOP reduction of 1.3–2.8 mm Hg in the placebo plus timolol treatment arm.

Data suggest that bimatoprost, latanoprost, and travoprost are at least as effective as timolol in the reduction of IOP, whereas unoprostone may provide slightly less IOP reduction. Latanoprost is the most widely studied and clinically used prostaglandin analog. Full critique of the trials performed with the recently approved agents will be necessary on publication. Important distinguishing factors include the demographics of enrolled patients, the respective dropout rates, patient compliance with therapy, efficacy in population subsets, and the standard deviation in mean IOP reduction. Current data suggest travoprost may be an appropriate choice for African American patients, but comparative analyses of the alternative prostaglandin analogs in this population subset would be helpful. Of note, the clinical trials with the prostaglandin analogs were performed against timolol 0.5% administered twice daily. Investigations are needed to compare the prostaglandin analogs with the widely used once-daily formulation of timolol.

As shown in Table 2, the current average wholesale prices of the prostaglandin analogs are similar.³⁷ Pharmacoeconomic analyses comparing these agents with other IOP-reducing agents and in-class comparisons will yield useful results pertaining to the ultimate role of this drug class. Finally, data are necessary regarding effects of the prostaglandin analogs on the progression of glaucoma, specifically relating to vision loss. Although IOP reduction is helpful as a surrogate outcome, glaucoma is multifactorial, and analyses of the ultimate long-term effects of pharmacologic interventions are essential.

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Safety

Prostaglandin analogs should be used with caution in patients who have active intraocular inflammation (iritis/uveitis), in patients who have known risk factors for macular edema, in aphakic patients, and in pseudophakic patients with torn posterior lens capsules because of the high risk of developing macular edema, including cystoid macular edema.¹⁰⁻¹² These agents should also be used with caution in the treatment of patients with angle closure, inflammatory, or neovascular glaucoma because of a lack of data in these conditions. Limited data are available evaluating the prostaglandin analogs in pediatric, pregnant, or nursing patients. Likewise, data are not available concerning their use in patients with hepatic or renal failure.

Women who are pregnant or plan to become pregnant should exercise caution in handling the prostaglandin analogs because they are biologically active and may be absorbed through the skin. If accidental contact does occur, the exposed area should be washed immediately with soap and water. The prostaglandin analogs are contraindicated in patients with a known hypersensitivity to the active drug, benzalkonium chloride, or any other ingredients in these products.

As depicted in Table 3, the most commonly reported adverse events for this drug class are ocular burning and stinging, ocular itching, and dry eyes. The incidence of these events compared with placebo or active control is not provided in the current literature. In registration trials for the prostaglandin analogs, the incidence of systemic ad-

verse events was not significantly different from placebo. In clinical trials, these agents did not affect heart rate, blood pressure, or other vital signs, and they do not cause bronchoconstriction.¹⁰⁻¹²

The most bothersome adverse event associated with the prostaglandin analogs is a change in pigmented tissue that may be permanent. This phenomenon appears to be related to stimulation of melanin production in melanocytes of the iris stroma. It is most noticeable in patients with green-brown, blue/gray-brown, or yellow-brown irises. The incidence of this event appears to be similar between travoprost, latanoprost, and bimatoprost, whereas it has rarely been reported with unoprostone (Table 3). Of note, there is limited experience with unoprostone in patients with a mixed iris color since the preliminary clinical trials¹⁰⁻¹² were performed in Japan in patient populations with predominantly dark irises.

Prostaglandin analogs may also change the length, thickness, and/or number of eyelashes. The changes in eye color and eyelashes may be permanent and may not be noticeable for months to years after initiation of therapy. These events are particularly problematic in patients receiving treatment in only 1 eye because of the cosmetic difference. Currently, the long-term effects on the corneal epithelium caused by continuous administration of the prostaglandin analogs are not known.¹⁰⁻¹²

Dosage and Administration

With the exception of unoprostone, a primary advantage of the prostaglandin analogs is once-daily dosing. Travoprost, latanoprost, and bimatoprost should be administered in the evening for optimal results. Because of a paradoxical effect of these 3 drugs at higher concentrations, they should not be administered more frequently than recommended in the product labeling.

Many patients receiving therapy with prostaglandin analogs may receive treatment with concomitant ophthalmic medication. Patients should be educated on the need to wait at least 10–15 minutes between administration of different ocular products to allow for maximal absorption.¹⁰⁻¹² Prostaglandin analogs are formulated with benzalkonium chloride, which may be absorbed by contact lenses. Therefore, contact lenses should be removed prior

Table 2. Cost of Recommended Dosage Regimens for Prostaglandin Analogs^{10-12,27}

Drug	Dose	Cost (\$)
Bimatoprost	1 drop in the affected eye(s) once daily in the evening	50.13
Latanoprost	1 drop in the affected eye(s) once daily in the evening	50.06
Travoprost	1 drop in the affected eye(s) once daily in the evening	47.44
Unoprostone	1 drop in the affected eye(s) twice daily	46.82

Table 3. Incidence of Most Common Adverse Events in Pivotal Trials with Prostaglandin Analogs¹⁰⁻¹²

Adverse Event	Bimatoprost	Latanoprost	Travoprost	Unoprostone
Burning/stinging (%)	3–10	5–15	5–10	10–25
Dry eyes (%)	3–10	1–4	1–4	10–25
Itching (%)	15–45	5–15	5–10	10–25
Increased length of eyelashes (%)	15–45	only identified in postmarketing use; frequency not reported	not specified	10–14
Conjunctival infection/conjunctival hyperemia (%)	15–45	5–15	35–50	11.8
Increased pigmentation of iris (%)	1–3	5–15	1–4	<1
Foreign body sensation (%)	3–10	5–15	5–10	5–10

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to administration of these medications and may be reinserted 15 minutes after administration. IOP-lowering effects of bimatoprost, latanoprost, travoprost, and unoprostone may be additive if administered simultaneously with topical β -adrenergic blocking agents, topical dipivefrin, topical epinephrine, oral carbonic anhydrase inhibitors, and/or topical carbonic anhydrase inhibitors.

Bimatoprost, unoprostone, and travoprost may be stored at room temperature (Table 4). Latanoprost should be stored under refrigeration prior to opening and at room temperature thereafter. Patients should be educated about the risk of contaminating topical ophthalmic products caused by allowing the tip of the dispensing container to touch the eye or surrounding structures. Contamination of ophthalmic products has been associated with bacterial keratitis, which may severely damage the eye and result in subsequent loss of vision.¹⁶⁻¹⁸

Summary

Prostaglandin analogs appear to be effective, well-tolerated agents for the reduction of IOP in patients with OAG and OH. This drug class offers an alternative for patients who do not achieve control with another topical antiglaucoma agent or for patients with a contraindication to first-line therapy with β -adrenergic blockers. As clinical experience with this class expands, providers may select the appropriate prostaglandin analog for the initial therapy of patients with OAG or OH. Based on preliminary clinical data, bimatoprost, latanoprost, and travoprost appear to be at least as effective as timolol, while the effectiveness of unoprostone is similar or slightly less than that of timolol. Prostaglandin analogs may be used in conjunction with other antiglaucoma medications; future studies must establish the optimal combination. Whether clinical experience will yield outcomes in favor of one of the prostaglandin analogs remains to be determined. Patients should be educated on adverse events associated with these agents, particularly the potential for changes in the pigmentation of the iris and eyelashes.

Table 4. Storage Conditions¹⁶⁻¹⁸

Formulation	How Supplied (mL)	Storage
Bimatoprost 0.03% solution	2.5 5 7.5	store in original container at 15–25 °C
Latanoprost 0.005% solution	2.5	refrigerate (2–8 °C) prior to opening; after opening, store at room temperature up to 25 °C for up to 6 wk
Travoprost 0.004% solution	2.5	store in the original container at 2–25 °C; discard the container within 6 wk of removing it from the sealed pouch
Unoprostone 0.15% solution	5	store in original container at 2–25 °C

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EXTRACTO

OBJETIVO: Revisar los datos disponibles relacionados con el uso de los análogos de la prostaglandina (bimatoprost, latanoprost, travoprost, unoprostone) en el tratamiento de hipertensión ocular y de glaucoma de ángulo estrecho.

IDENTIFICACIÓN DE INFORMACIÓN: Se identificaron artículos primarios y revisiones después de buscar una búsqueda bibliográfica en MEDLINE

(1966-2001) y de solicitar información de los fabricantes de los productos.

EXTRACCIÓN DE INFORMACIÓN: La información disponible considerada pertinente, incluso la publicada en artículos y abstractos, fue incluida en este resumen. Al momento, la información publicada es limitada.

SÍNTESIS: Los análogos de la prostaglandina parecen ser agentes eficaces y bien tolerados para la reducción de la presión intraocular en pacientes con glaucoma de ángulo estrecho primario e hipertensión ocular. Esta clasificación de fármacos ofrece una alternativa en pacientes que utilizan otros agentes tópicos para el glaucoma pero no se logra el control de la condición o en aquellos en que la terapia de primera línea con bloqueadores β-adrenérgicos está contraindicada. A base de los datos clínicos preliminares, el bimatoprost, el latanoprost y el travoprost parecen ser tan eficaces como el timolol, mientras que la eficacia de la unoprostone es similar o un poco menor. Los análogos de la prostaglandina pueden ser utilizados junto con otros medicamentos para el glaucoma, aunque los estudios futuros deberán establecer la combinación óptima. Para determinar, si los resultados de la experiencia clínica favorecerán a alguno de los análogos de la prostaglandina. Los pacientes deben conocer los eventos adversos relacionados con los análogos de la prostaglandina, particularmente, el potencial de cambios en la pigmentación del iris y de las pestañas.

CONCLUSIONES: El bimatoprost, el latanoprost y el travoprost parecen ser equivalentes a la terapia estándar actual en el tratamiento tópico de presión intraocular elevada. Datos clínicos adicionales obtenidos de artículos en lugar de abstractos son necesarios para evaluar mejor las diferencias potenciales entre estos 3 agentes.

Rafaela Marm de Jiménil

RÉSUMÉ

OBJECTIF: Évaluer les données disponibles relatives à l'utilisation des analogues de prostaglandines (PG; bimatoprost, latanoprost, travoprost, unoprostone) dans la prise en charge de l'hypertension oculaire et du glaucome à angle ouvert.

RECHERCHE DE L'INFORMATION: Des documents primaires et articles de revues ont été identifiés par une recherche MEDLINE (1966-2001), et dans des informations demandées aux laboratoires fabricants.

EXTRAIT DES ÉTUDES ET EXTRACTION DES DONNÉES: Toutes les informations disponibles, y compris celles publiées sous forme d'articles et d'abstracts qui ont été considérées pertinentes ont été incluses dans cette revue. Les données publiées pour l'instant sont limitées.

SYNTHÈSE DES DONNÉES: Les analogues de PG se révèlent efficaces et bien tolérés dans la diminution de la pression intraoculaire chez des patients atteints de glaucome à angle ouvert et d'hypertension oculaire. Cette classe thérapeutique offre une alternative aux patients qui n'obtiennent pas de résultats avec d'autres antiglaucomeux locaux ou pour ceux présentant une contre-indication au traitement de première intention par les β-bloquants. Selon les données cliniques préliminaires, le bimatoprost, le latanoprost et le travoprost s'avèrent au moins aussi efficaces que le timolol, tandis que l'efficacité de l'unoprostone est similaire ou légèrement moindre. Les analogues de PG peuvent être utilisés en association à d'autres médicaments antiglaucomeux, bien que des études ultérieures doivent encore établir la combinaison optimale. Il reste à déterminer si l'expérience clinique fournira des résultats en faveur de l'un des analogues de PG. Les patients devraient être éduqués sur les effets indésirables associés aux analogues de PG, en particulier sur le risque de modification de pigmentation de l'iris et des cils.

CONCLUSIONS: Le bimatoprost, le latanoprost et le travoprost s'avèrent être équivalents à la thérapeutique actuelle de référence de traitement local de l'élévation de pression intraoculaire. Il faudra disposer de plus de données cliniques, publiées sous forme d'articles plutôt que d'abstracts, pour établir les différences potentielles entre ces 3 agents.

Michel Le Duff



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/557	A1	(11) International Publication Number: WO 97/30710 (43) International Publication Date: 28 August 1997 (28.08.97)
(21) International Application Number: PCT/US97/02269 (22) International Filing Date: 13 February 1997 (13.02.97) (30) Priority Data: 08/605,567 22 February 1996 (22.02.96) US (71) Applicant: ALLERGAN [US/US]; 8301 Mars Drive, Waco, TX 76712 (US). (72) Inventors: WOODWARD, David, L.; 23152 Tulip Street, El Toro, CA 92630 (US). ANDREWS, Steven, W.; 3931 Cedron Street, Irvine, CA 92714 (US). BURK, Robert, M.; 1337 Cerritos Drive, Laguna Beach, CA 92651 (US). GARST, Michael, E.; 2627 Raqueta, Newport Beach, CA 92660 (US). (74) Agents: BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, T-2 2-E, P.O. Box 19534, Irvine, CA 92623-9534 (US).		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NON-ACIDIC CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS (57) Abstract The present invention provides cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds, which may be substituted in the 1-position with amino, amido, ether or ester groups, e.g., a 1-OH cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compound. The cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compounds of the present invention are potent ocular hypotensives, and are particularly suitable for the management of glaucoma. Moreover, the cyclopentane heptanoic, 2-(cycloalkyl or arylalkyl) compounds of this invention are smooth muscle relaxants with broad application in systemic hypertensive and pulmonary diseases; smooth muscle relaxants with application in gastrointestinal disease, reproduction, fertility, incontinence, shock, etc.		

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**NON-ACIDIC CYCLOPENTANE HEPTANOIC ACID,
2-CYCLOALKYL OR ARYLALKYL DERIVATIVES
AS THERAPEUTIC AGENTS**

5 Crossreference to Related Applications

10 This patent application is a continuation-in-part of U.S. Patent Application Serial No. 08/371,339, filed on January 11, 1995 which is a continuation of U.S. Patent Application Serial No. 08/154,244 which was filed on November 18, 1993, which is a divisional of U.S. Patent Application Serial No. 07/948,056, filed on September 21, 1992, now U.S. Patent No. 5,352,708 issued on October 4, 1994, all of which are hereby incorporated by reference.

15 Background of the Invention

1. Field of the Invention

20 The present invention provides cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds, which may be substituted in the 1-position with amino, amido, ether or ester groups, e.g., a 1-OH cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compound. The cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compounds of the present invention are potent ocular hypotensives, and are particularly suitable for the management of glaucoma. Moreover, the
25 cyclopentane heptanoic, 2-(cycloalkyl or arylalkyl) compounds of this invention are smooth muscle relaxants with broad application in systemic hypertensive and pulmonary diseases; smooth muscle relaxants with application in gastrointestinal disease, reproduction,
30 fertility, incontinence, shock, etc.

2. Description of the 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 pupillary 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. In cases where surgery is not

indicated, topical b-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Prostaglandins were earlier regarded as potent ocular hypertensives; however, evidence accumulated in the last two decades shows that some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of glaucoma. (See, for example, Starr, M.S. Exp. Eye Res. 1971, 11, pp. 170-177; Bito, L. Z. Biological Protection with Prostaglandins Cohen, M. M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231-252; and Bito, L. Z., Applied Pharmacology in the Medical Treatment of Glaucomas Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477-505). Such prostaglandins include PGF_{2a}, PGF_{1a}, PGE₂, and certain lipid-soluble esters, such as C₁ to C₅ alkyl esters, e.g. 1-isopropyl ester, of such compounds.

In the United States Patent No. 4,599,353 certain prostaglandins, in particular PGE₂ and PGF_{2a} and the C₁ to C₅ alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management.

Although the precise mechanism is not yet known, recent experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et al., Invest. Ophthalmol. Vis. Sci. 28(suppl), 284 (1987)].

The isopropyl ester of PGF_{2a} has been shown to have significantly greater hypotensive potency than the parent compound, which was attributed to its more effective penetration through the cornea. In 1987 this compound was described as "the most potent ocular hypotensive agent ever reported." [See, for example, Bito, L. Z., Arch. Ophthalmol. 105, 1036 (1987), and Siebold et al., Prodrug 5, 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular PGF_{2a} and its prodrugs, e.g. its 1-isopropyl ester, in humans. The clinical potential of prostaglandins in the management of conditions associated with

increased ocular pressure, e.g. glaucoma, is greatly limited by these side effects.

5 Certain phenyl and phenoxy mono, tri and tetra nor prostaglandins and their 1-esters are disclosed in European Patent Application 0,364,417 as useful in the treatment of glaucoma or ocular hypertension.

10 In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending USSN 386,835 (filed 27 July 1989), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl $\text{PGF}_{2\alpha}$. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the co-pending application USSN 357,394 (filed 25 May 1989). Similarly, 15 11,15- 9,15- and 9,11-diester of prostaglandins, for example 11,15-bis-pivaloyl $\text{PGF}_{2\alpha}$ are known to have ocular hypotensive activity. See the co-pending patent applications USSN No. 385,645 filed 27 July 1990, now U.S. Patent No. 4,494,274; 584,370 which is a continuation of USSN No. 386,312, and 585,284, now U.S. Patent No. 5,034,413 which is 20 a continuation of USSN 386,834, where the parent applications were filed on 27 July 1989. The disclosures of these patent applications are hereby expressly incorporated by reference.

Summary of the Invention

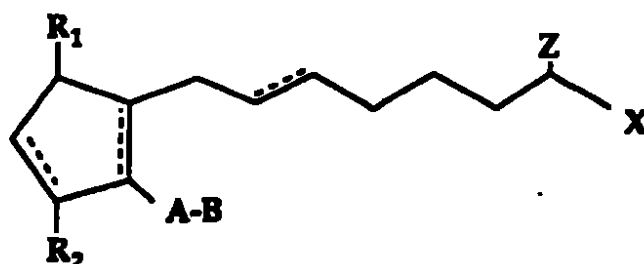
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We have found that certain cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds and derivatives thereof wherein the carboxylic acid group is replaced by a non-acidic substituent have pronounced effects on smooth muscle and are potent ocular 30 hypotensive agents. We have further found that such compounds, in certain instances, may be significantly more potent than their respective parent compounds and, in the case of glaucoma surprisingly, cause no or significantly lower ocular surface hyperemia than the parent compounds.

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The present invention relates to methods of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive,

allergic disease, shock and ocular hypertension which comprises administering an effective amount of a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compound represented by the formula I



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wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of -OR⁴ and -N(R⁴)₂ wherein R⁴ is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

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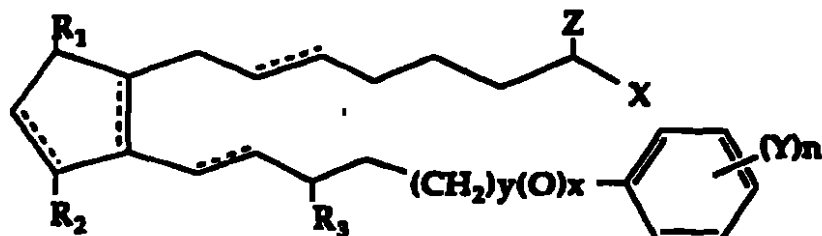
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carbon atoms, R⁵-C- or R⁵-O-C- wherein R⁵ is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; one of R₁ and R₂ is =O, -OH or a -O(CO)R₆ group, and the other one is -OH or -O(CO)R₆, or R₁ is =O and R₂ is H, wherein R₆ is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or -(CH₂)_mR₇ wherein m is 0 or an integer of from 1 to 10, and R₇ is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided, however, that when B is not substituted with a pendant heteroatom-containing radical, and Z is =O, then X is not -

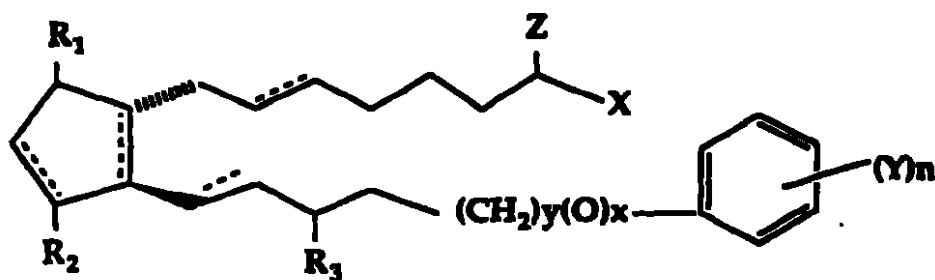
OR⁴. (That is, the cycloalkyl or hydrocarbyl aryl or heteroaryl radical is not substituted with a pendant radical having an atom other than carbon or hydrogen.)

5 More preferably the method of the present invention comprises administering a cyclopentane heptanoic acid, 2-(phenyl alkyl or phenyloxyalkyl) represented by the formula II



10 wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, e.g. fluoro, chloro, etc., nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, etc. and n is 0 or an integer of from 1 to about 3 and R₃ is 15 =C, -OH or -O(CO)R₆ wherein R₆ is as defined above. Preferably, n is 1 or 2.

Preferably the compound used in the above method of treatment is a compound of formula (III).

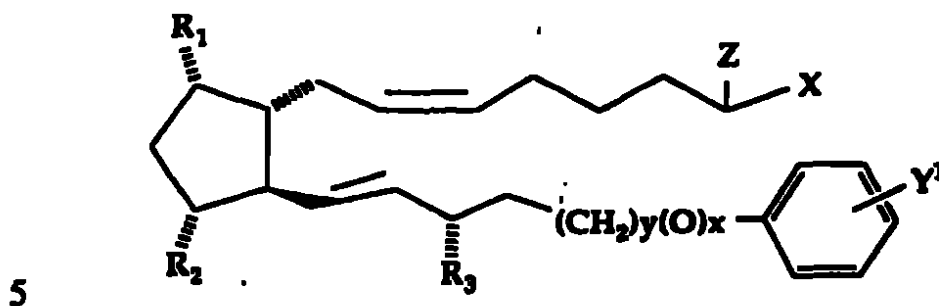


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wherein hatched lines indicate a configuration, solid triangles are used to indicate β configuration

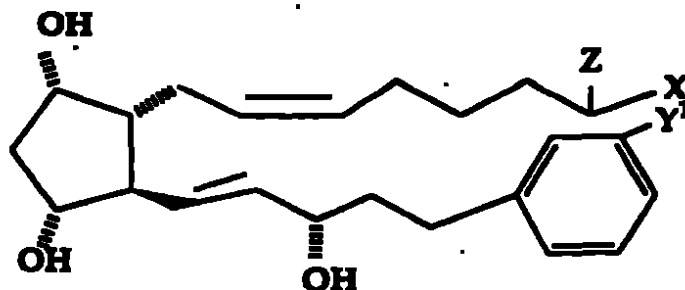
25 In another aspect, the present invention relates to a method of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases, shock and ocular hypertension

which comprises administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (IV)



wherein Y¹ is Cl or trifluoromethyl and the other symbols and substituents are as defined above, in combination with a pharmaceutical carrier.

10 Finally, the method of the present invention relates to a method of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases, shock and ocular hypertension which comprises administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula V



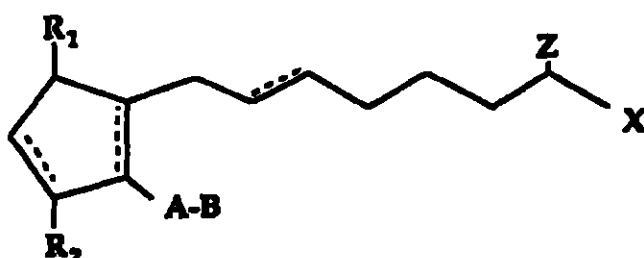
and the 9-and/or 11- and/or 15 esters thereof.

20 In a further aspect, the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formulae (I), (II), (III), (IV) or (V) wherein the symbols have the above meanings, or a pharmaceutically acceptable salt thereof in admixture with a non-toxic, pharmaceutically acceptable liquid vehicle.

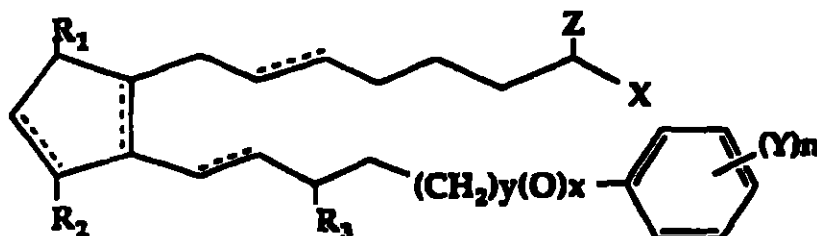
In a still further aspect, the present invention relates to cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds of the above formulae, wherein the substituents and symbols are as defined hereinabove, or a pharmaceutically acceptable salt of such compounds.

Detailed Description of the Invention

The present invention relates to the use of cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds as therapeutic agents, e.g. as ocular hypotensives. These therapeutic agents are represented by compounds having the formula I,

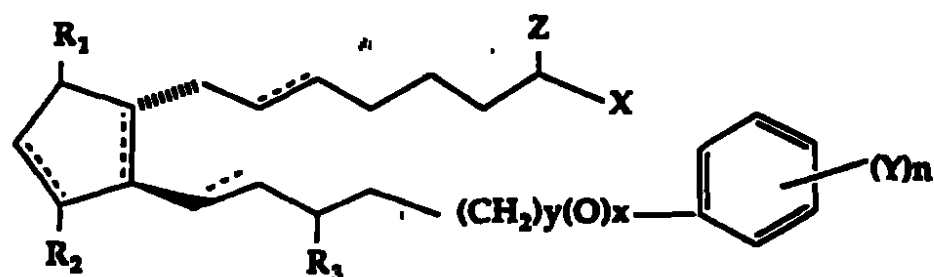


as defined above. The preferred nonacidic cyclopentane heptanoic acid, 2-(phenyl alkyl or phenyloxyalkyl) compounds used in accordance with the present invention are encompassed by the following structural formula (II)

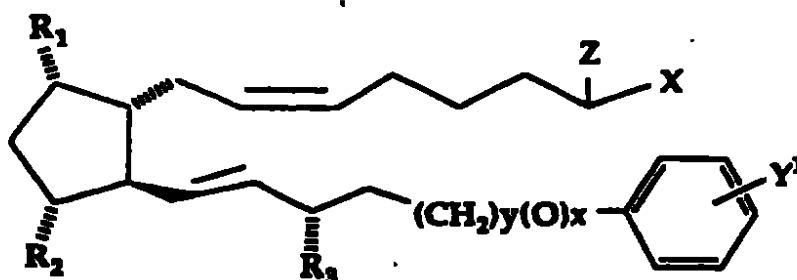


wherein the substituents and symbols are as hereinabove defined. More preferably the compounds are represented by formula (III).

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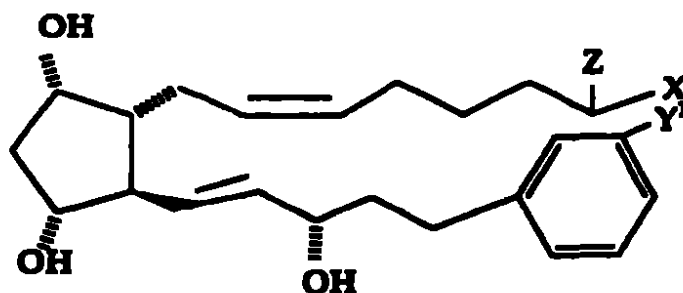


wherein the substituents and symbols are as defined above. More preferably, the compounds utilized in the present invention are compounds represented by the formula (IV)



wherein the substituents and the symbols are as defined above.

Most preferably the present invention utilizes the novel compounds of the formula (V)



and their 9- and/or 11- and/or 15-esters.

In all of the above formulae, as well as in those provided hereinafter, the dotted lines on bonds between carbons 5 and 6 (C-5), between carbons 13 and 14 (C-13), between carbons 8 and 12 (C-8), and

between carbons 10 and 11 (C-10) indicate a single or a double bond which can be in the cis or trans configuration. If two solid lines are used that indicates a specific configuration for that double bond. Matched lines at positions C-9, C-11 and C-15 indicate the α configuration. If one were to draw the β configuration, a solid triangular line would be used.

In the compounds used in accordance with the present invention, compounds having the C-9 or C-11 or C-15 substituents in the α or β configuration are contemplated. As hereinabove mentioned, in all formulas provided herein broken line attachments to the cyclopentane ring indicate substituents in the α configuration. Thickened solid line attachments to the cyclopentane ring indicate substituents in the β configuration. Also, the broken line attachment of the hydroxyl group or other substituent to the C-11 and C-15 carbon atoms signifies the α configuration.

For the purpose of this invention, unless further limited, the term "alkyl" refers to alkyl groups having from one to ten carbon atoms, the term "cycloalkyl" refers to cycloalkyl groups having from three to seven carbon atoms, the term "aryl" refers to aryl groups having from four to ten carbon atoms. The term "saturated or unsaturated acyclic hydrocarbon group" is used to refer to straight or branched chain, saturated or unsaturated hydrocarbon groups having from one to about 6, preferably one to about 4 carbon atoms. Such groups include alkyl, alkenyl and alkynyl groups of appropriate lengths, and preferably are alkyl, e.g. methyl, ethyl, propyl, butyl, pentyl, or hexyl, or an isomeric form thereof.

The definition of R_6 may include a cyclic component, $-(CH_2)_mR_7$, wherein n is 0 or an integer of from 1 to 10, R_7 is an aliphatic ring from about 3 to about 7 carbon atoms, or an aromatic or heteroaromatic ring. The "aliphatic ring" may be saturated or unsaturated, and preferably is a saturated ring having 3-7 carbon atoms, inclusive. As an aromatic ring, R_7 preferably is phenyl, and the heteroaromatic rings have oxygen, nitrogen or sulfur as a heteroatom, i.e. R_7 may be thienyl, furanyl, pyridyl, etc. Preferably m is 0 or an integer of from 1 to 4.

Z is =O or represents two hydrogen atoms.

X may be selected from the group consisting of -OR⁴ and -N(R⁴)₂ wherein R⁴ is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

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carbon atoms, R⁵-C- or R⁵-O-C- wherein R⁵ is a lower alkyl radical having from one to six carbon atoms.

10

Preferred representatives of the compounds within the scope of the present invention are the compounds of formula V wherein X is -OH, i.e. cyclopentane heptenoic acid, 5-cis-2-(3- α hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, [1 α , 2 β , 3 α , 5 α] and cyclopentane methylheptenoate-5-cis-2(3- α hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5 dihydroxy, [1 α , 2 β , 3 α , 5 α] and the 9- and/or 11- and/or 15-esters of this compound. (The numbered designations in brackets refer to the positions on the cyclopentane ring.)

15

20

The following novel compounds may be used in the pharmaceutical compositions and the methods of treatment of the present invention.

25

30

- (1) cyclopentane heptenol-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]
- (2) cyclopentane heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]
- (3) cyclopentane N,N-dimethylheptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]
- (4) cyclopentane heptenyl methoxide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

- (5) cyclopentane heptenyl ethoxide-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]
- 5 (6) cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]
- 10 (7) cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-trifluoromethylphenoxy-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]
- 15 (8) cyclopentane N-isopropyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]
- (9) cyclopentane N-ethyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5 dihydroxy, [1 α , 2 β , 3 α , 5 α]
- 20 (10) cyclopentane N-methyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]
- 25 (11) cyclopentane heptenol-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]
- 30 (12) cyclopentane heptenamide-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]
- (13) cyclopentane heptenol-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

5 A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Such salts are those formed with pharmaceutically acceptable cations, e.g., alkali metals, alkali earth metals, etc.

10 Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable 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.

15 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 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain
20 conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for
25 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, cyclodextrin and purified water.
30

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.

35 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.

5 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.

10 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 of or in conjunction with it.

The ingredients are usually used in the following amounts:

<u>Ingredient</u>	<u>Amount (% w/v)</u>
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	0-10
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%

15 The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

20 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 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. One package may contain one or more unit doses.

Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20-35 ml.

The invention is further illustrated by the following non-limiting Examples.

Example 1

Cyclopentane heptenoic acid, 5-cis-2-(3 α -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

This compound may be purchased from Cayman Chemical Company of Ann Arbor, Michigan or synthesized by methods known in the art.

Example 2

Cyclopentane methylheptenoate-5-cis-2
(3 α -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)
-3,5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

To a stirred solution of cyclopentane heptenoic acid, 5-cis-2-(3 α -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, [1 α , 2 β , 3 α , 5 α] (24 mg, 0.0565 mmol) in acetone (0.6 ml) at room temperature was added 1, 8-diazabicyclo [5.4.0.] undec-7-ene (DBU) (40, μ l, 0.27 mmol) and methyl iodide (20 μ l, 0.32 mmol). The reaction turned yellow with the DBU addition. The reaction was maintained at room temperature for 6.5 hours, then was diluted with ethyl acetate (30 ml) and filtered through a plug of celite with the aid of ethyl acetate. After concentration *in vacuo*, the residue was flushed with ethylacetate (EtOAc) through a 20 mm x 160 mm column of silica to give the desired methyl ester.

Example 3

5 Cyclopentane heptenamide-5-cis-2-
 (3 α -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)
 -3,5-dihydroxy [1 α , 2 β , 3 α , 5 α]

10 A mixture of the methyl ester of the compound of Example 1
 (9.2 mg, 0.0222 mmol) and NH₄Cl (10 mg, 0.187 mmol) in NH₃ was
 heated at 80°C for 12 hours. After cooling to room temperature, the
 solvents were evaporated and the residue was subjected to column
 chromatography to provide the named amide as 7.2 mg of a clear,
 colorless liquid.

15 **Example 4**

Cyclopentane heptenoic acid-5-cis-2-(3 α -hydroxyl-4-m-
 trifluoromethylphenoxy-1-trans-butenyl)-3,5-dihydroxy [1 α , 2 β , 3 α , 5 α]

20 This compound may be purchased from Cayman Chemical
 Company of Ann Arbor, Michigan or synthesized by methods known
 in the art.

Example 5

25 Cyclopentane heptenamide-5-cis-2-(3 α -hydroxyl-4-m-
 trifluoromethylphenoxy-1-trans-butenyl)-3,5-dihydroxy [1 α , 2 β , 3 α , 5 α]

30 A mixture of the methyl ester of the compound of Example 4
 (fluprostenol) and NH₄Cl in NH₃ is heated at 80° C for 12 hours. After
 cooling to room temperature the solvents are evaporated and the
 residue is subjected to column chromatography to provide the named
 amide.

35

Example 6

Measurement of intraocular pressure studies in dogs involved pneumatonometry performed in conscious, Beagle dogs of both sexes (10-15 kg). The animals remained conscious throughout the study and were gently restrained by hand. Drugs were administered topically to one eye as a 25 μ L volume drop, the other eye received 25 μ : vehicle (0.1% polysorbate 80:10 mM TRIS) as a control. 0.1% proparacaine was used for corneal anesthesia during tonometry. Intraocular pressure was determined just before drug administration and at 2, 4 and 6 hour thereafter on each day of the 5 day study. Drug was administered twice a day, with a 6 hour interval between doses that spanned the intraocular pressure measurement time frame. The result reported in Table 1, below.

Table 1. Comparison of effects of certain compounds of the invention on dog intraocular pressure. Values indicate mean changes from baseline intraocular pressure ($\pm$ SEM) at predetermined times post-dosing. n=8, *p<0.05, **p<0.01.

INTRAOCULAR PRESSURE (mmHg) CHANGE AT
PREDETERMINED TIMES (HR)

<u>COMPOUND</u>	<u>DOSE%</u>	<u>2</u>	<u>4</u>	<u>6</u>	<u>24</u>
Example 1	0.01	-0.1 $\pm$ 0.8	-5.2 $\pm$ 1.4**	-4.3 $\pm$ 0.8	-4.4 $\pm$ 0.8
Example 1	0.1	-3.1 $\pm$ 0.8**	-3.2 $\pm$ 0.7	-2.7 $\pm$ 0.8	-
Example 3	0.01	-2.2 $\pm$ 1.0*	5.5 $\pm$ 1.1**	-4.0 $\pm$ 1.4*	2.7 $\pm$ 1.1*
Example 3	0.1	-1.3 $\pm$ 0.4*	2.3 $\pm$ 0.7**	-2.6 $\pm$ 0.6**	-
Example 5	0.1	-2.7 $\pm$ 0.8*	-3.4 $\pm$ 0.9*	-2.8 $\pm$ 0.4**	-2.1 $\pm$ 1.6*

Example 4	0.01	-0.9±0.7	-2.5±0.7*	-3.2±0.7**	-1.3±0.7
Fluprostenol	0.1	-1.3±0.1	-2.1±1.1	-2.7±1.3	-3.1±0.9*

Example 7

5

Measurement of ocular surface hyperemia was visually assessed and scored according to the following schematic:

10	<u>Hyperemia Score</u>	<u>Assigned Value</u>
	<1	1
	1 slight	2
	>1<2	3
15	2 moderate	4
	>2>3	5
	3 severe	6
	(baseline scores for dogs are typically < 1)	

20 The hyperemia value for each dog at a single time point (x) is obtained as follows: (treated eye value at hr x - baseline value)-(control eye value at hr x-baseline value). A composite value is then obtained by dividing the sum of the post-treatment measurement at each time point by the number of animals in the group: i.e. $\frac{m}{n}$ where $m =$

25 measurements of ocular surface hyperemia. Ocular surface hyperemia is evaluated at the same time points as intraocular pressure measurement. It should be noted that untreated dog eyes frequently have a pink/red tone. Thus, values of <1 and 1 are essentially within
30 the normal range. The results are reported in Table 2, below.

Table 2. Comparison of effects of certain compounds of the invention on dog ocular surface hyperemia. Values are composite scores as indicated in the methods.

5	<u>COMPOUND</u>	<u>DOSE%</u>	<u>OCULAR SURFACE HYPEREMIA: COMPOSITE SCORE</u>
	Example 1	0.01	-
10	Example 1	0.1	0.33
	Example 3	0.01	-
15	Example 3	0.1	0.81
	Example 5	0.1	0.81
20	Example 4	0.01	1.08
	Fluprostenol	0.1	1.50

It is clear that the compounds of Examples 1, 3 and 5, unexpectedly, show better efficacy at lowering IOP than Example 4 while showing less hyperemia.

25 The compounds of the invention may also be useful in the treatment of various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris, in which case the compounds may be administered by any means that effect vasodilation and thereby
30 relieve the symptoms of the disease. For example, administration may be by oral, transdermal, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes.

The compounds of the invention may be used alone, or in combination with other of the known vasodilator drugs.

35 The compounds of the invention may be formulated into an ointment containing about 0.10 to 10% of the active ingredient in a suitable base of, for example, white petrolatum, mineral oil and

petroatum and lanolin alcohol. Other suitable bases will be readily apparent to those skilled in the art.

5 The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional dissolving or suspending the compounds, which are all either water soluble or suspendable. For administration in the treatment of the other mentioned pathophysiological disorders. The pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as
10 well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in liquid form that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the
15 active compounds are preferably dissolved or suspended in suitable liquids, such as in buffered salt solution. In addition, stabilizers may be added.

In addition to being provided in a liquid form, for example in gelatin capsule or other suitable vehicle, the pharmaceutical
20 preparations may contain suitable excipients to facilitate the processing of the active compounds into preparations that can be used pharmaceutically. Thus, pharmaceutical preparations for oral use can be obtained by adhering the solution of the active compounds to a solid support, optionally grinding the resulting
25 mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as sugars, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium
30 phosphate or calcium hydrogen phosphate, as well as binders such as starch, paste using for example, maize starch, wheat starch, rich starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may
35 be added such as the above-mentioned starches and also carboxymethyl-starch, crosslinked polyvinyl pyrrolidone, agar, or

algenic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which if desired, are resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally containing gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tables or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Suitable formulations for intravenous or parenteral administration include aqueous solutions of the active compounds. In addition, suspensions of the active compounds as oily injection suspensions may be administered. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, soribitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

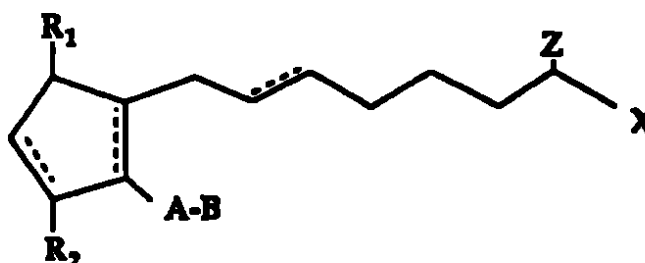
The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. For example, the present invention contemplates certain prodrugs of the

above disclosed compounds, wherein R^4 is R^5-C- or R^5-O-C- . These compounds may be made by acylation or esterification of the corresponding hydroxy or amino derivative. 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; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

CLAIMS

1. A method of treating ocular hypertension which comprises applying to the eye an amount sufficient to treat ocular hypertension of a compound of formula I

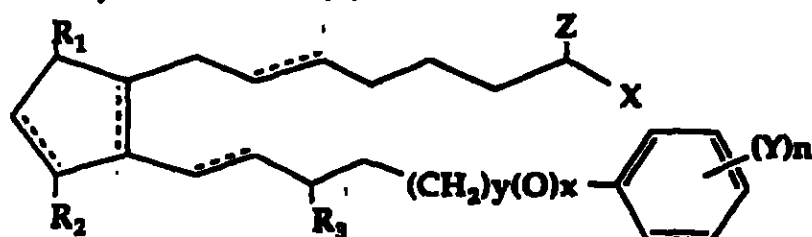


wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of -OR^4 and $\text{-N(R}^4\text{)}_2$ wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

carbon atoms, $\text{R}^5\text{-C-}$ or $\text{R}^5\text{-O-C-}$ wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; one of R_1 and R_2 is =O , -OH or a -O(CO)R_6 group, and the other one is -OH or -O(CO)R_6 , or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $\text{-(CH}_2\text{)}_m\text{R}_7$ wherein m is 0-10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided however that

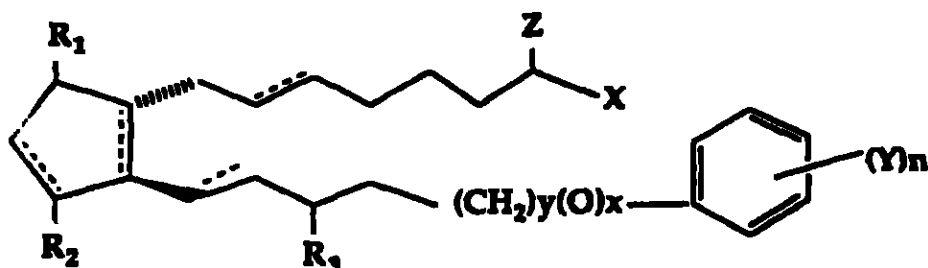
when B is not substituted with a pendant heteroatom-containing radical and Z is =O, then X is not -OR⁴.

2. The method of Claim 1 wherein said compound is a
5 represented by the formula (II)



wherein y is 0 or 1, x is 0 or 1 and x + y are not both 1, Y is a radical
10 selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy and halosubstituted alkyl, wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to 3 and R₃ is =O, -OH or -O(CO)R₆.

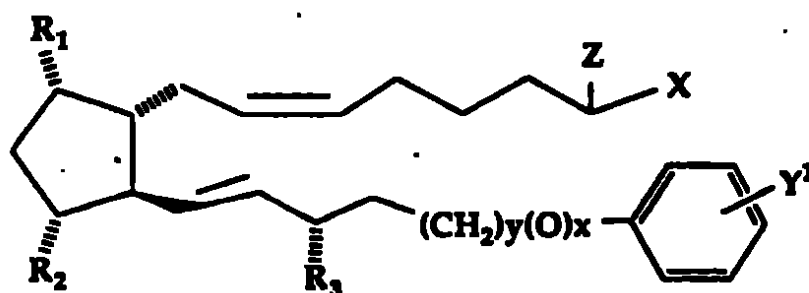
3. The method of claim 2 wherein said compound is represented
15 by formula III.



wherein hatched lines indicate the α configuration and solid
triangles indicate the β configuration.

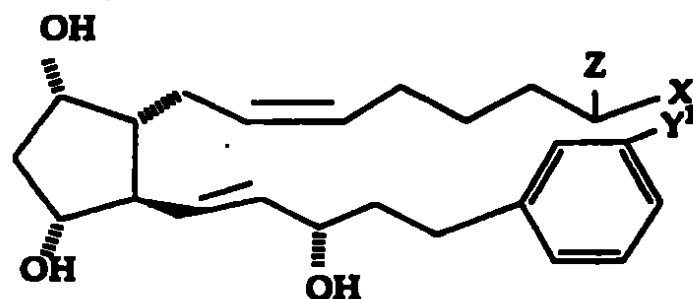
4. The method of claim 3 wherein said compound is represented
20 by the formula IV.

25



wherein Y^1 is Cl or trifluoromethyl.

5. The method of claim 4 wherein said compound is a
5 represented by the formula V



and the 9- and/or 11- and/or 15 esters, thereof.

6. The method of claim 5 wherein Z is =O and X is selected from
10 the group consisting of NH_2 or OCH_3 .

7. The method of claim 5 wherein Y is O, Z is =O and X is selected
15 from the group consisting of alkoxy and amido radicals.

8. The method of claim 1 wherein said compound is selected from
the group consisting of:

cyclopentane heptenol-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-
20 pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

cyclopentane heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-
pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

cyclopentane N,N-dimethylheptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

5 cyclopentane heptenyl methoxide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

cyclopentane heptenyl ethoxide-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

10 cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

15 cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

cyclopentane N-isopropyl hepteneamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

20 cyclopentane N-ethyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

cyclopentane N-methyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

25

cyclopentane heptenol-5-cis-2-(3 α -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

30 cyclopentane heptenamide-5-cis-2-(3 α -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α] and

cyclopentane heptenol-5-cis-2-(3 α -hydroxy-5-phenylpentyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

9. The method of claim 7 wherein X is selected from the group consisting of NH₂ and OCH₃.

10. The method of claim 1 wherein said compound is selected from the group consisting of:

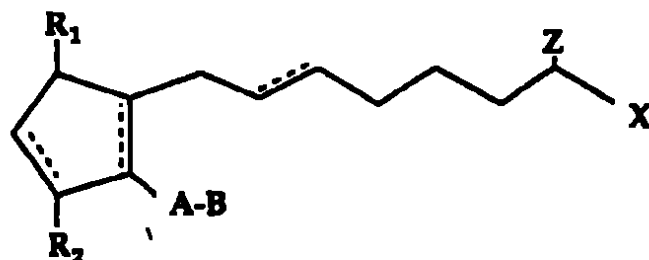
cyclopentane heptenoic acid-5-cis-2-(3 α -hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

10 cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

15 cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-trifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]; and

cyclopentane heptenonic acid-5-cis-2-(3 α -hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α].

11. A method of treating cardiovascular pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases and shock in a human which comprises administering to said human an effective amount of a compound of formula I

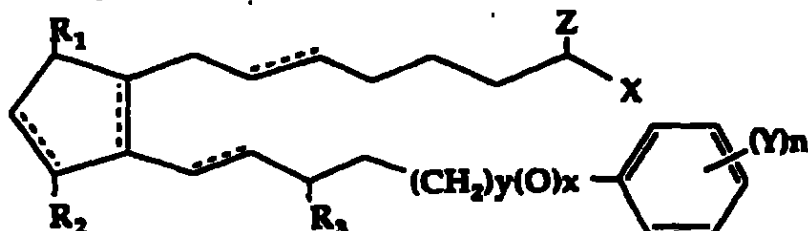


wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon

atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of $-OR^4$ and $-N(R^4)_2$ wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

carbon atoms, R^5-C- or R^5-O-C- wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is $=O$ or represents 2 hydrogen radicals; one of R_1 and R_2 is $=O$, $-OH$ or a $-O(CO)R_6$ group, and the other one is $-OH$ or $-O(CO)R_6$, or R_1 is $=O$ and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $-(CH_2)_mR_7$ wherein m is 0-10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided however that when B is not substituted with a pendant heteroatom-containing radical and Z is $=O$, then X is not $-OR^4$.

12. The method of Claim 1 wherein said compound is a represented by the formula (II)



wherein y is 0 or 1, x is 0 or 1 and $x+y$ are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy and halosubstituted alkyl, wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to 3 and R_3 is $=O$, $-OH$ or $-O(CO)R_6$.

INTERNATIONAL SEARCH REPORT

Int'l application No.

PCT/US 97/02269

00078

221

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. ☒ Claims Nos.: 1-20,25
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-20,25
is(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 II Observations where unity of invention is lacking (Continuation of item 2 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.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5352708 A	04-10-94	AU 676492 B	13-03-97
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INTERNATIONAL SEARCH REPORT

Information on patent family members

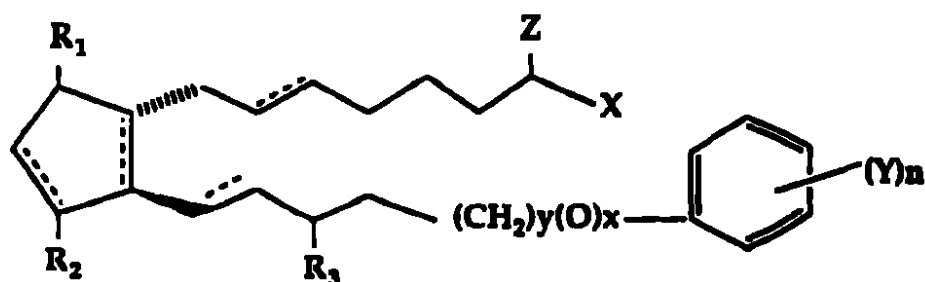
International Application No

PCT/US 97/02269

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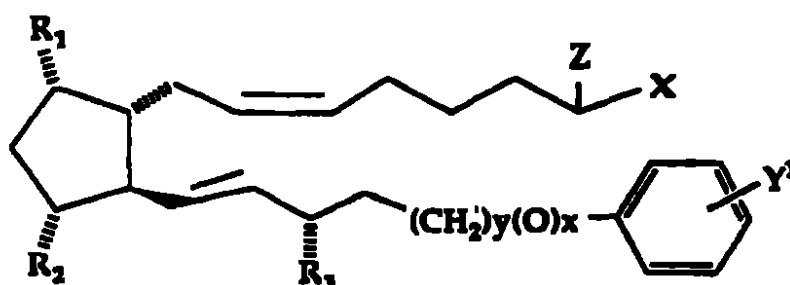
13. The method of claim 2 wherein said compound is represented by formula III.



5 wherein hatched lines indicate the α configuration and solid triangles indicate the β configuration.

14. The method of claim 3 wherein said compound is represented by the formula IV.

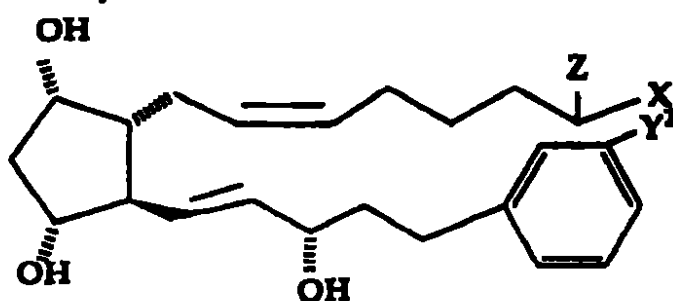
10



wherein Y^1 is Cl or trifluoromethyl.

15. The method of claim 4 wherein said compound is a represented by the formula V

15



and the 9- and/or 11- and/or 15 esters, thereof.

cyclopentane N-methyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

5 cyclopentane heptenol-5-cis-2-(3 α -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

cyclopentane heptenamide-5-cis-2-(3 α -hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α] and

10 cyclopentane heptenol-5-cis-2-(3 α -hydroxy-5-phenylpentyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]

15 19. The method of claim 7 wherein X is selected from the group consisting of NH₂ and OCH₃.

20. The method of claim 1 wherein said compound is selected from the group consisting of:

20 cyclopentane heptenoic acid-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

25 cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]; and

30 cyclopentane heptenonic acid-5-cis-2-(3 α -hydroxy-4-meta-trifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α].

35 21. A compound useful for treating cardiovascular pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases and

16. The method of claim 5 wherein Z is =O and X is selected from the group consisting of NH₂ or OCH₃.
17. The method of claim 5 wherein Y is O, Z is =O and X is selected from the group consisting of alkoxy and amido radicals.
18. The method of claim 1 wherein said compound is selected from the group consisting of:
- 10 cyclopentane heptenol-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];
- cyclopentane heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];
- 15 cyclopentane N,N-dimethylheptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];
- 20 cyclopentane heptenyl methoxide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];
- cyclopentane heptenyl ethoxide-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];
- 25 cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];
- cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];
- 30 cyclopentane N-isopropyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];
- 35 cyclopentane N-ethyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

22. The compound of claim 21 wherein said compound is selected from the group consisting of

5 cyclopentane heptenoic acid-5-cis-2-(3 α -hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α];

cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]; and

10

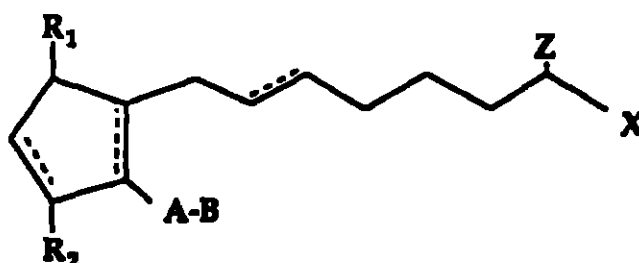
cyclopentane heptenylamide-5-cis-2-(3 α -hydroxy-4-meta-trifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α].

15 23. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 21 in admixture with a non-toxic, pharmaceutically acceptable liquid vehicle.

20 24. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 22 in admixture with a non-toxic, pharmaceutically acceptable liquid vehicle.

25 25. A method of treating ocular hypertension which comprises applying to the eye an amount sufficient to treat ocular hypertension of a compound selected from the group consisting of cloprostenol, fluprostenol and their pharmaceutically acceptable esters and salts.

lowering ocular hypertension which comprises a compound of formula I



- 5 wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy
- 10 groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group
- 15 consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of $-OR^4$ and $-N(R^4)_2$ wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six
- 20 carbon atoms, R^5-C- or R^5-O-C- wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is $=O$ or represents 2 hydrogen radicals; one of R_1 and R_2 is $=O$, $-OH$ or a $-O(CO)R_6$ group, and the other one is $-OH$ or $-O(CO)R_6$, or R_1 is $=O$ and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group
- 25 having from 1 to about 20 carbon atoms, or $-(CH_2)_mR_7$ wherein m is 0-10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided however that when B is not substituted with a pendant heteroatom-containing
- 30 radical and Z is $=O$, then x is not $-OR^4$.

FIG. 2.

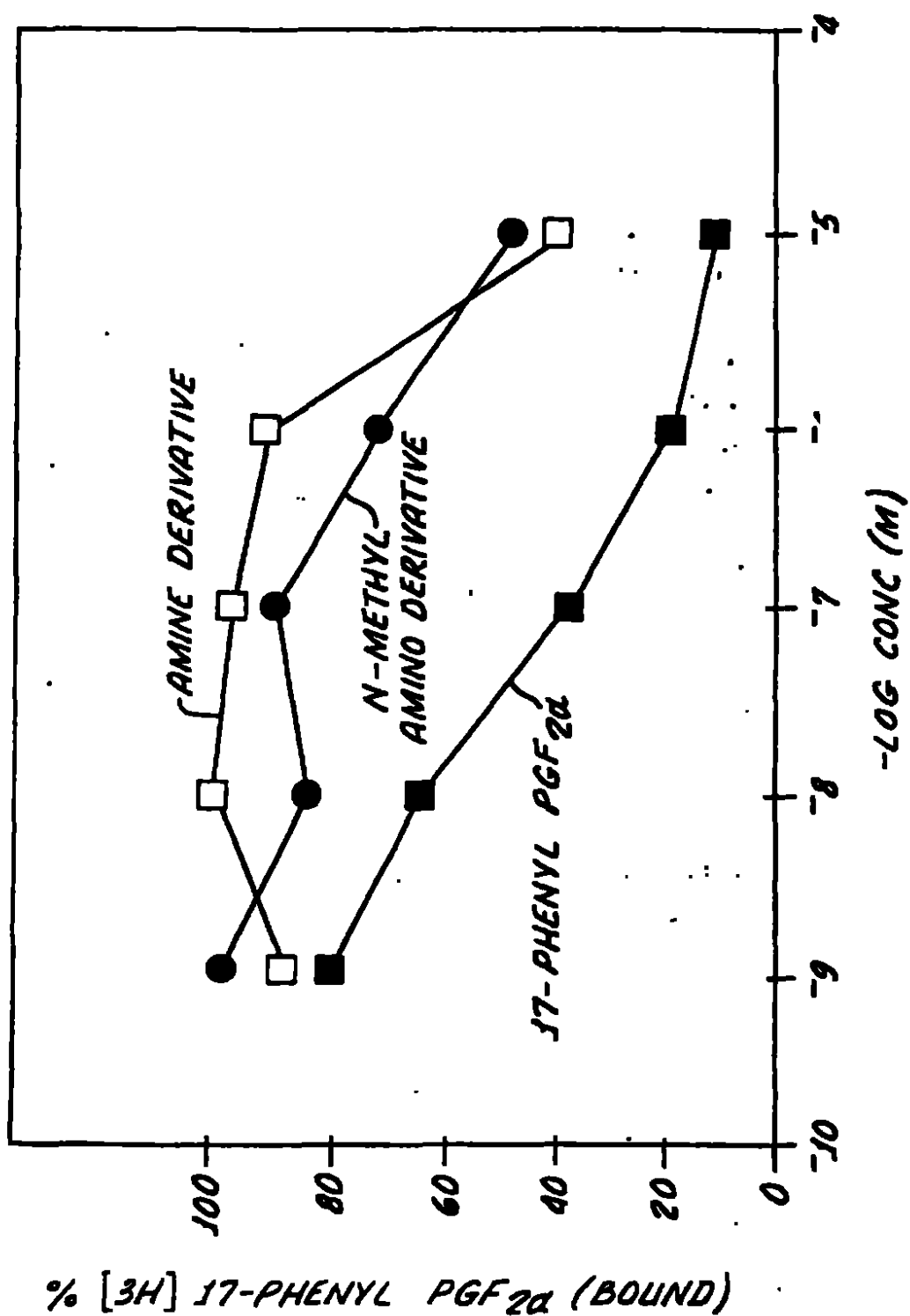
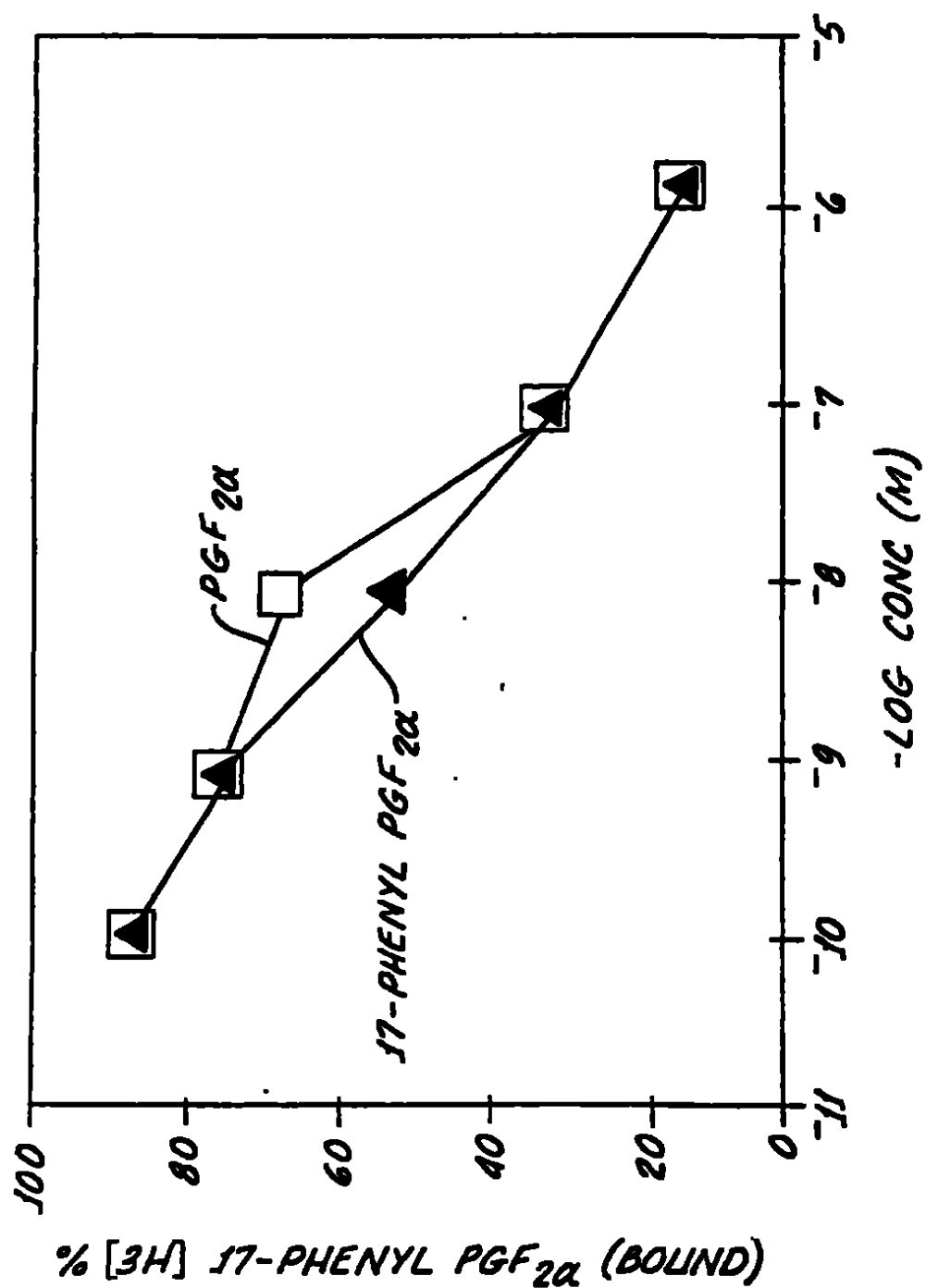


FIG. 1.



INTERNATIONAL SEARCH REPORT

 Internat. Application No
 PC1/US 97/82269

227

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K31/557

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbol)

IPC 6 A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 352 708 A (DAVID F. WOODWARD) 4 October 1994 cited in the application see the whole document ---	1-24
X	EP 0 603 800 A (ALCON LABORATORIES) 29 June 1994 see the whole document ---	1-7, 9, 10, 12-17, 19-25
X	EP 0 364 417 A (PHARMACIA AB) 18 April 1990 cited in the application see the whole document ---	1-5, 12-15, 21, 23

-/-

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in 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

"A" document member of the same patent family

Date of the actual completion of the international search

30 May 1997

Date of making of the international search report

20.06.97

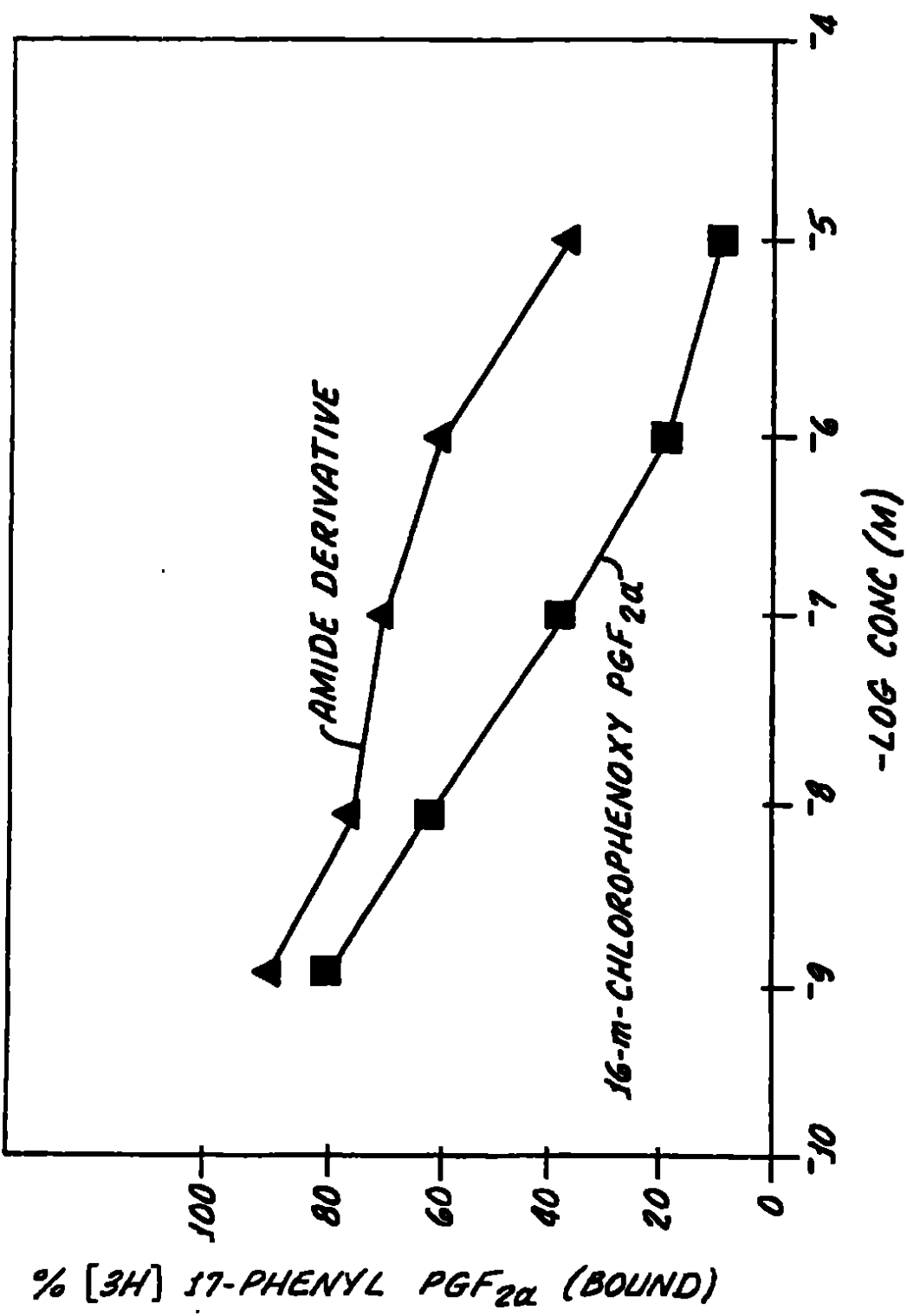
Name and mailing address of the ISA

 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

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FIG. 3.



INTERNATIONAL SEARCH REPORT

 Internat. Appl. No.
 PC1/US 97/02269

228

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K31/557

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)
 IPC 6 A61K

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)

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"A" document member of the same patent family

Date of the actual completion of the international search

30 May 1997

Date of mailing of the international search report

20.06.97

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 431 epo nl,
 Fax (+31-70) 340-3016

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Int'l application No.

PCT/US 97/02269

229

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

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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.

00094

INTERNATIONAL SEARCH REPORT

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International Application No.

PCT/US 97/02269

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INTERNATIONAL SEARCH REPORT

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00097

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/US 97/02269 231

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		SU 893130 A	23-12-81
		US 4244887 A	13-01-81
		ZA 7308554 A	25-09-74

PATENT COOPERATION TREATY

00098
232

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

To:

FISHER, Carlos A.
ALLERGAN, INC.
2525 Dupont Drive,
Irvine, CA 92612
ETATS-UNIS D'AMERIQUE

Date of mailing
(day/month/year)

21/01/2003

Applicant's or agent's file reference

17441PCTBAR

REPLY DUE

within 2 / 00 months/days
from the above date of mailing

International application No.

PCT/US 02/ 17291

International filing date (day/month/year)

30/05/2002

Priority date (day/month/year)

31/05/2001

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

A61K31/5575

Applicant

ALLERGAN, INC. et al.

RESPONSE DUE Feb 21, 2003

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4b1. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 30/09/2003

Name and mailing address of the IPEA:



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

Examiner

Formalities officer
(incl. extension of time limits)
Tel. (+49-89) 2399 2828



WRITTEN OPINION

International application No. PCT/US 02/17291

I. Basis of the opinion

The basis of this written opinion is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:
2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).
3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

PATENT COOPERATION TREATY

RECEIVED

00100

PCT

234

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FISHER, Carlos A.
ALLERGAN, INC.
2525 Dupont Drive,
Irvine, CA 92612
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

14/04/2003

Applicant's or agent's file reference
17441PCTBAR

IMPORTANT NOTIFICATION

International application No.

PCT/US 02/ 17291

International filing date (day/month/year)

30/05/2002

Priority date (day/month/year)

31/05/2001

Applicant

ALLERGAN, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/



European Patent Office
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Fax: (+49-89) 2399-4465

Authorized officer

LODOLO F
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 17441PCTBAR	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US 02/ 17291	International filing date (day/month/year) 30/05/2002	Priority date (day/month/year) 31/05/2001
International Patent Classification (IPC) or national classification and IPC A61K31/5575		
Applicant ALLERGAN, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 17/12/2002	Date of completion of this report 09/04/2003
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer F RSTER W K Tel. (+49-89) 2399 2828



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/US 02/17291

00102

236

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

PATENT COOPERATION TREATY

PCT/US02/17291

00183 237

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

FISHER, Carlos, A.
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
United States of America

Date of mailing (day/month/year)
17 July 2003 (17.07.03)

Applicant's or agent's file reference
17441PCTBAR

IMPORTANT INFORMATION

International application No.
PCT/US02/17291

International filing date (day/month/year)
30 May 2002 (30.05.02)

Priority date (day/month/year)
31 May 2001 (31.05.01)

Applicant
ALLERGAN, Inc. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
National : AU, BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SD, SE, SG, SI, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

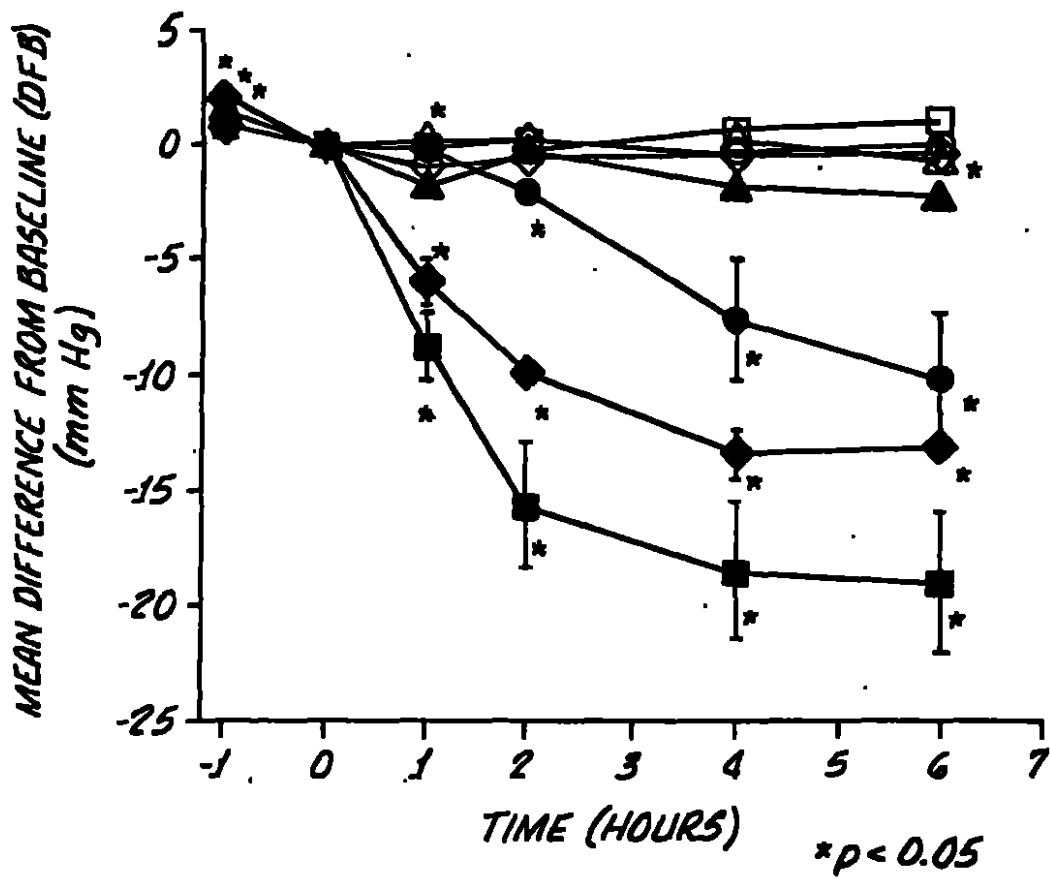
Olivia TEFY

Telephone No. (41-22) 338 8518

Form PCT/IB/332 (September 1997)

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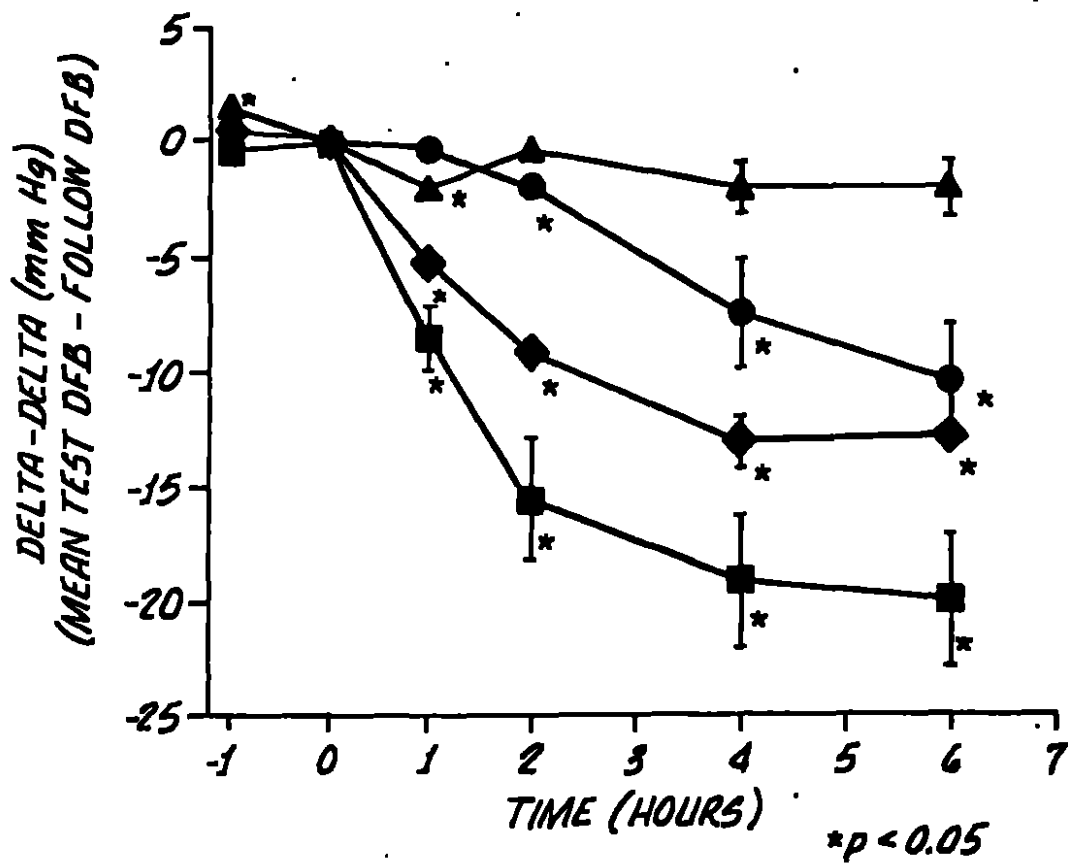
Fig. 1.



- ▲— VEHICLE (n=5)
- △— SALINE (VEHICLE GROUP, n=5)
- 0.001% HYPO LIP (n=5)
- SALINE (0.001% HYPO LIP GROUP, n=6)
- ◆— 0.05% TIMOLOL MALEATE (n=9)
- ◇— SALINE (0.05% TIMOLOL MALEATE GROUP, n=9)
- 0.001% HYPO LIP + 0.05% TIMOLOL MALEATE (n=8)
- SALINE (0.001% HYPO LIP + 0.05% TIMOLOL MALEATE GROUP, n=8)

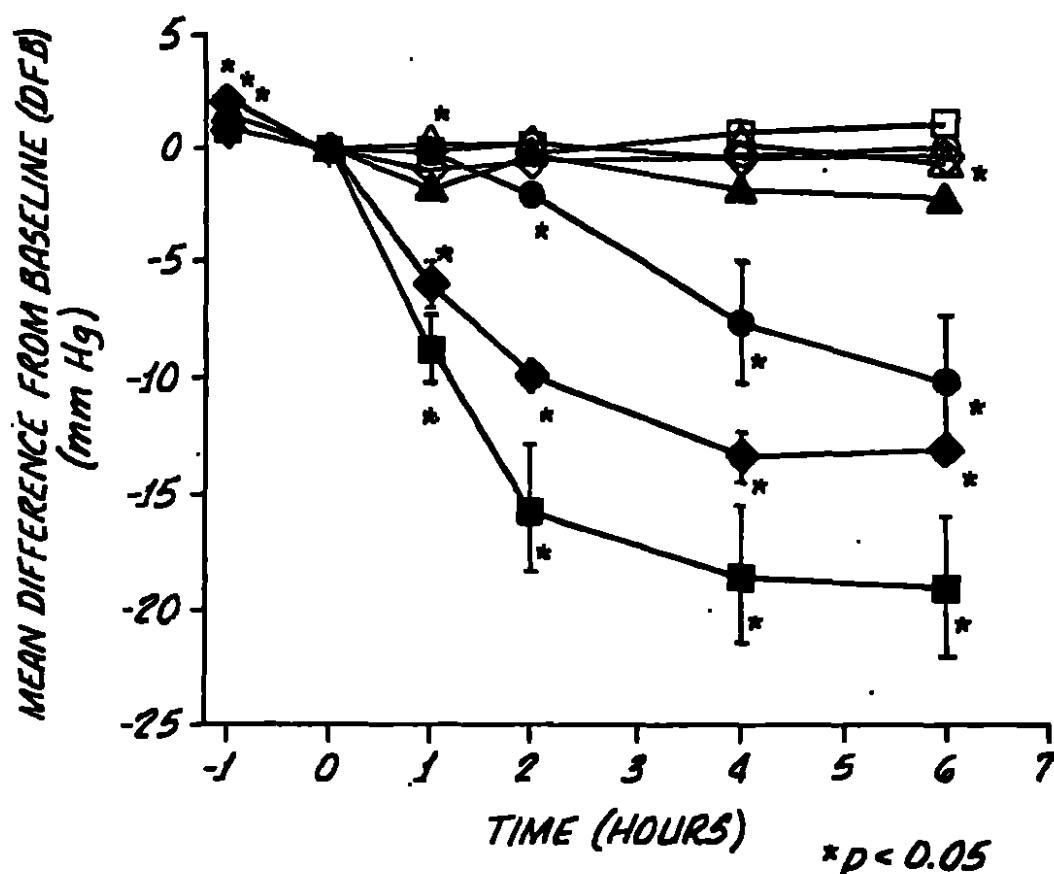
2/2

Fig. 2.



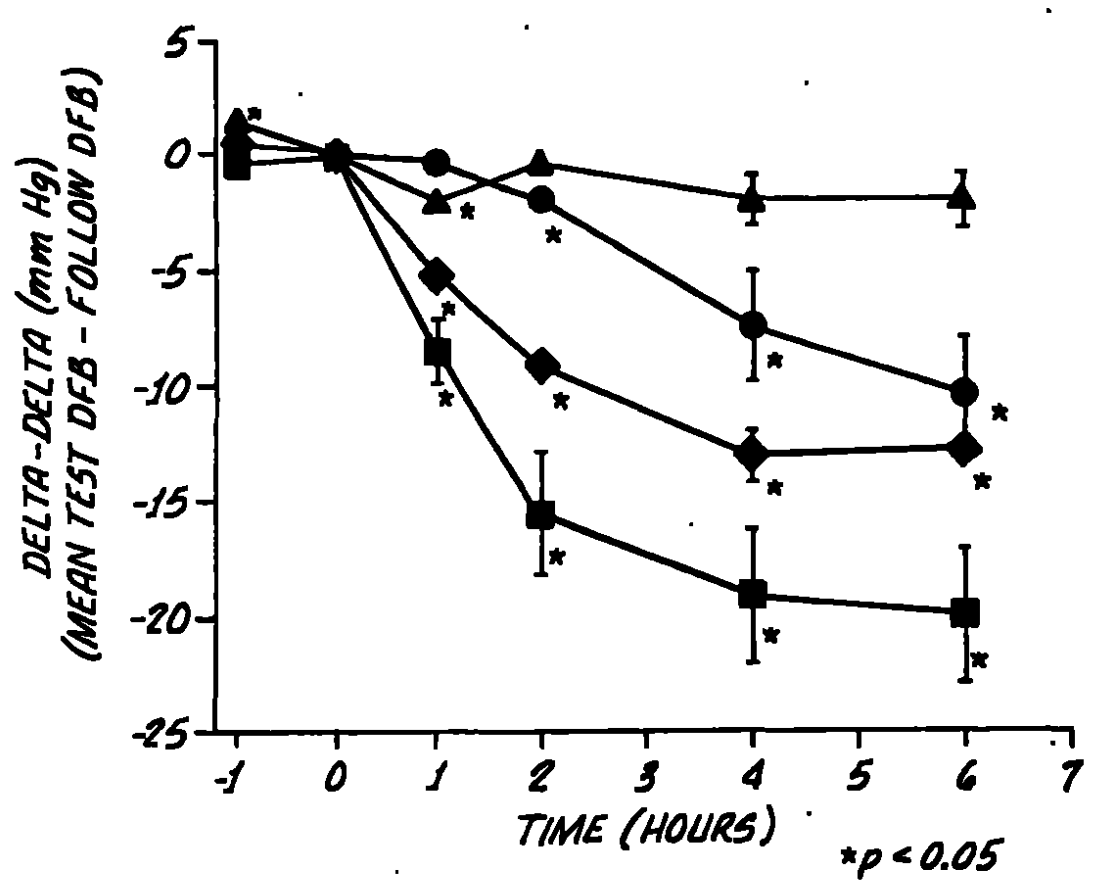
- ▲— VEHICLE (n=5)
- 0.001% HYPO LIPID (n=6)
- ◆— 0.05% TIMOLOL MALEATE (n=9)
- 0.001% HYPO LIPID + 0.05% TIMOLOL MALEATE (n=8)

1/2

FIG. 1.

- ▲— VEHICLE (n=5)
- △— SALINE (VEHICLE GROUP, n=5)
- 0.001% HYPO LIP (n=5)
- SALINE (0.001% HYPO LIP GROUP, n=6)
- ◆— 0.05% TIMOLOL MALEATE (n=9)
- ◇— SALINE (0.05% TIMOLOL MALEATE GROUP, n=9)
- 0.001% HYPO LIP + 0.05% TIMOLOL MALEATE (n=8)
- SALINE (0.001% HYPO LIP + 0.05% TIMOLOL MALEATE GROUP, n=8)

Fig. 2.



- ▲— VEHICLE (n=5)
- 0.001% HYPO LIPID (n=6)
- ◆— 0.05% TIMOLOL MALEATE (n=9)
- 0.001% HYPO LIPID + 0.05% TIMOLOL MALEATE (n=8)

③



Europäisches Patentamt
European Patent Office
Office européen des brevets

⑪ Publication number:

0 286 903
A1

⑫

EUROPEAN PATENT APPLICATION

⑰ Application number: 88104999.3

⑱ Int. Cl. 4: A61K 31/557 , //(A61K31/557,
31:535),(A61K31/557,31:135)

⑳ Date of filing: 28.03.88

㉑ Priority: 03.04.87 US 34484

㉒ Date of publication of application:
19.10.88 Bulletin 88/42

㉓ Designated Contracting States:
AT BE CH DE ES FR GB GR IT LJ LU NL SE

㉔ Applicant: The Trustees of Columbia
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Mühlstrasse 37
D-8000 München 80(DE)

㉗ Use of a prostaglandin in combination with an adrenergic blocking agent for reduction of
intraocular pressure.

㉘ This invention provides a method for treating
ocular hypertension or glaucoma in a subject's eye.
The method comprises contacting the surface of the
eye with an effective intraocular pressure reducing
amount of a mixture of an adrenergic blocking agent
and a prostaglandin or prostaglandin derivative in an
ophthalmically compatible carrier, so as to reduce
the intraocular pressure of the eye and maintain
such reduced intraocular pressure.

This invention also provides a composition for
topical treatment of ocular hypertension or glaucoma
in the eye of a subject. The composition comprises
an effective intraocular pressure reducing amount of
a mixture of an adrenergic blocking agent and a
prostaglandin or prostaglandin derivative in an oph-
thalmically compatible carrier.

EP 0 286 903 A1

USE OF A PROSTAGLANDIN IN COMBINATION WITH AN ADRENERGIC BLOCKING AGENT FOR REDUCTION OF INTRAOCULAR PRESSURE

Background of The Invention

The invention described herein was made with government support under grant number EY00333 from the National Eye Institute, National Institutes of Health, Department of Health and Human Services. The U.S. Government has certain rights in this invention.

Glaucoma, an eye disorder afflicting various mammals, including primates, is characterized by increased intraocular pressure (ocular hypertension). In man, such ocular hypertension results from an imbalance between the rate of secretion of aqueous humor by the ciliary epithellum into the posterior chamber of the eye and the resistance drainage of the aqueous humor from the anterior chamber, primarily via the canal of Schlemm. It is generally believed that increased outflow resistance due to obstruction of aqueous humor drainage routes is the primary cause of the imbalance.

Chronic glaucoma typically results in slow, progressive loss of visual fields and, if not controlled, ultimately in blindness. Initial treatment usually involves topical application of agonists or antagonists of autonomic neuroeffectors, particularly pilocarpine or timolol. If treatment with such topically applied drugs is not effective, systemic administration of carbonic anhydrase inhibitors may be employed. If such approaches are unsuccessful, the glaucoma may have to be treated by surgery or laser.

Eicosanoids and their derivatives include numerous biologically useful compounds. For example, the prostaglandin (PG) group, naturally occurring cyclic fatty acids, is known to possess diverse biological activities. Originally isolated as lipid-soluble extracts from sheep seminal vesicles and human seminal fluid, prostaglandins have been found to be produced by most mammalian tissues.

Activities of different prostaglandins include stimulation or relaxation of smooth muscle, dilation of small arteries, bronchial dilation, lowering of blood pressure, inhibition of gastric secretion, lipolysis and platelet aggregation, and induction of labor, abortion and menstruation.

It is becoming increasingly evident that PGs reduce intraocular pressure by increasing uveoscleral outflow. This is true for both the F type and A type of PGs and, hence presumably also for the E and B type PGs. See also, U.S. Patent No. 4,586,353, issued July 6, 1986, and co-pending, U.S. patent application, Serial No. 839,050, filed

March 13, 1986, the contents of which are hereby incorporated by reference into this application. Contraction of the ciliary muscle as induced by pilocarpine, for example, reduces or blocks uveoscleral outflow while uveoscleral outflow may be assumed to be increased by relaxation of the ciliary muscle. This is because the pathway of uveoscleral outflow is through the muscle part of the ciliary body, i.e., relaxation of the muscle increases the extracellular space between muscle fibers in this tissue, whereas contraction of the muscle decreases this space, thus decreasing or eliminating this flow pathway.

PGs could relax the ciliary muscle by one of two mechanisms: either by causing the release of catecholamines from adrenergic nerve endings contained within the ciliary muscle; or by acting on the ciliary muscle directly, causing relaxation by interaction with PG receptors of the muscle fiber surface. In the former case, adrenergic blocking agents, particularly beta blockers, would block the PG-induced increase in uveoscleral outflow. In the latter case, beta blockers would not block the beneficial intraocular pressure reducing effects of PGs.

Therefore, if topically applied, PGs would reduce intraocular pressure by relaxing the ciliary muscle through the release of catecholamines; combined therapy of an adrenergic blocking agent and PGs would be counterproductive since the adrenergic blocking agent would block the ocular hypotensive effect of the PG. However, if PGs acted directly on the ciliary muscle without the mediation of catecholamines, then adrenergic blocking agents would not interfere with the ocular hypotensive effect of PGs.

The most effective way of reducing intraocular pressure is by affecting both sides of the pressure equation: $P = F \times R$; where R is the resistance to the outflow of aqueous humor, F is flow (which, in turn, equals the rate of secretion of aqueous humor) and P equals the effective pressure gradient across the site of resistance (namely, Intraocular pressure - episcleral venous pressure). According to currently accepted concepts, there are two sites of aqueous humor outflow from the eye; the conventional outflow through the trabecular meshwork and the above-mentioned uveoscleral flow through the ciliary muscles. Pilocarpine decreases the resistance in the conventional flow channels through the trabecular meshwork; therefore, it works effectively in combination with an adrenergic blocking agent. However, pilocarpine at the same time decreases uveoscleral outflow by contracting the ciliary mus-

cle. In some cases of glaucoma, when flow through the trabecular meshwork is reduced to the point when it cannot be effectively increased by pilocarpine, pilocarpine can have only a very small additional beneficial effect or may have an adverse rather than a beneficial effect by reducing the remaining outflow channels through the ciliary muscle. Therefore, a combination drug, or drug regimen, that acts by decreasing aqueous humor secretion, such as an adrenergic blocking agent and a PG would be ideal, provided that the adrenergic blocking agent can be shown not to block the ocular hypotensive effects of PGs.

In the medical treatment of glaucoma, combination therapy, therefore, is commonly required since in many cases effective intraocular pressure control cannot be maintained with a single drug. The experiments set forth herein establish that the use of a combination of an adrenergic blocking agent and a PG have a great advantage from a physiological point of view, since they show that adrenergic blocking agents do not block the ocular hypotensive effect of a PG and since these blocking agents act by reducing the secretion of aqueous humor whereas PGs, as stated above, act by increasing uveoscleral outflow. In addition, using a combination of an adrenergic blocking agent and a prostaglandin, each of them in a concentration lower than would be required if used separately in the treatment of ocular hypertension and glaucoma, would yield a significant reduction in the occurrence of such side effects as ocular discomfort, irritative responses, conjunctival hyperemia, and cardiovascular response.

Summary of The Invention

This invention provides a method for treating ocular hypertension or glaucoma in a subject's eye. The method comprises contacting the surface of the eye with a composition comprising an effective intraocular pressure reducing amount of a mixture of an adrenergic blocking agent and a prostaglandin or prostaglandin derivative in an ophthalmically compatible carrier, so as to reduce the intraocular pressure of the eye and maintain such reduced intraocular pressure.

The invention also provides a composition for topical treatment of ocular hypertension or glaucoma. The composition comprises an effective intraocular pressure reducing amount of a mixture of an adrenergic blocking agent and a prostaglandin or prostaglandin derivative in an ophthalmically compatible carrier.

Moreover, this invention provides a method for treating ocular hypertension or glaucoma in a primate subject's eye which comprises contacting the

surface of the eye with a composition comprising an effective intraocular pressure reducing amount of a mixture of levobunolol hydrochloride and PGF_{2α}-1-isopropyl ester dissolved in an ophthalmically compatible carrier, so as to reduce the intraocular pressure of the eye and maintain such reduced intraocular pressure.

This invention further provides a composition for the topical treatment of ocular hypertension or glaucoma which comprises an effective intraocular pressure reducing amount of a mixture of levobunolol hydrochloride and PGF_{2α}-1-isopropyl ester dissolved in an ophthalmically compatible carrier.

Brief Description Of The Figures

Figure 1 This figure shows the effect of a 2% timolol solution and a combination of a 2% timolol solution and 0.5 μg PGF_{2α}-1-isopropyl ester on the intraocular pressure in cat eyes. Application of 0.5 μg PGF_{2α}-1-isopropyl ester to eyes already treated with a 2% timolol solution caused a significant further drop in intraocular pressure within one hour.

Figure 2 This figure shows the ocular hypotensive effect of a solution containing both timolol (at a concentration of 2.0%) and PGF_{2α}-1-isopropyl ester (at a final concentration of 0.002%) on cat eyes as compared to the ocular hypotensive effect of timolol applied by itself.

Figure 3 This figure shows the ocular hypotensive effect of PGF_{2α}-1-isopropyl ester on cat eyes pretreated 2 hrs earlier with an 0.5% solution of betaxolol.

Figure 4 This figure shows the ocular hypotensive effect of PGF_{2α}-1-isopropyl ester on cat eyes pretreated 2 hrs earlier with an 0.5% solution of levobunolol.

Detailed Description Of The Invention

This invention provides a method for treating ocular hypertension or glaucoma in a subject's eye. The method comprises contacting the surface of the eye with a composition comprising an effective intraocular pressure reducing amount of a mixture of an adrenergic blocking agent and a prostaglandin or prostaglandin derivative in an ophthalmically compatible carrier, so as to reduce the intraocular pressure of the eye and maintain such reduced intraocular pressure. In the preferred embodiment, the subject is a primate, particularly a human being.

Although any adrenergic blocking agent may be employed in the practice of this invention, the

preferred adrenergic blocking agent is a beta blocker. The presently preferred beta blockers are timolol maleate, betaxolol hydrochloride, and levobunolol hydrochloride. Furthermore, while any prostaglandin or prostaglandin derivative may be employed in the practice of this invention, the presently preferred prostaglandin or prostaglandin derivative is of one of the A, E or F type. Of these types, $\text{PGF}_{2\alpha}$ or a $\text{PGF}_{2\alpha}$ derivative are particularly useful, specifically $\text{PGF}_{2\alpha}$ -1-isopropyl ester.

Additionally, a range of concentrations of adrenergic blocking agents may be employed in the practice of the invention. However, the preferred amount present in the mixture is from about 0.01 μg to about 1,000 μg , specifically from about 5 μg to about 500 μg .

The presently preferred effective amount of prostaglandin or prostaglandin derivative present in the mixture is from about 0.01 μg to about 1,000 μg , specifically from about 0.1 μg to about 50 μg .

The ophthalmically compatible carrier may be any well known carrier. Presently preferred for use in the practice of this invention are aqueous solutions, such as a saline solution containing an ophthalmically compatible preservative a surfactant, and an agent, such as a soluble polymer, to increase the viscosity of the solution. In a preferred embodiment, the mixture is dissolved in the ophthalmically compatible carrier.

Various regimens may be employed for treating ocular hypertension or glaucoma in the subject's eye. In the preferred embodiment, the treatment comprises contacting the surface of the eye, i.e., the cornea, periodically, preferably at least daily, with an effective amount of a mixture of an adrenergic blocking agent and a prostaglandin or prostaglandin derivative to reduce intraocular pressure.

This invention further provides composition for topical treatment of ocular hypertension or glaucoma in a subject's eye. The composition comprises an effective intra-ocular pressure reducing amount of a mixture of an adrenergic blocking agent and a prostaglandin or a prostaglandin derivative in an ophthalmically compatible carrier.

In a preferred embodiment, the adrenergic blocking agent present in the composition is a beta blocker and the prostaglandin or prostaglandin derivative present in the composition is of the A, E or F type. The presently preferred beta blockers are timolol maleate, betaxolol hydrochloride, and levobunolol hydrochloride. The presently preferred prostaglandin or prostaglandin derivative is $\text{PGF}_{2\alpha}$ or a $\text{PGF}_{2\alpha}$ derivative, specifically $\text{PGF}_{2\alpha}$ -1-isopropyl ester.

The presently preferred effective amount of adrenergic blocking agent present in the composition is from about 0.01 μg to about 1,000 μg ,

specifically from about 5 μg to about 500 μg .

The presently preferred effective amount of prostaglandin or prostaglandin derivative present in the composition is from about 0.01 μg to about 1,000 μg , specifically from about 0.1 μg to about 50 μg .

The ophthalmically compatible carrier may be any well known carrier. Presently preferred for use in the practice of this invention are aqueous solutions, such as a saline solution containing an ophthalmically compatible preservative, a surfactant and an agent, such as a soluble polymer, to increase the viscosity of the solution. In a preferred embodiment, the mixture is dissolved in the ophthalmically compatible carrier.

This invention also provides a method for treating ocular hypertension or glaucoma in a primate subject's eye. The method comprises contacting the surface of the eye with a composition comprising an effective intraocular pressure reducing amount of a mixture of levobunolol and $\text{PGF}_{2\alpha}$ -1-isopropyl ester dissolved in an ophthalmically compatible carrier, so as to reduce the intraocular pressure of the eye and maintain such reduced intraocular pressure.

This invention further provides a composition for the topical treatment of ocular hypertension or glaucoma comprising an effective intraocular pressure reducing amount of a mixture of levobunolol hydrochloride and $\text{PGF}_{2\alpha}$ -1-isopropyl ester dissolved in an ophthalmically compatible carrier.

Finally, this invention provides a method for treating ocular hypertension or glaucoma in a subject's eye. The method comprises separately contacting the surface of the eye with an intraocular pressure reducing amount of an adrenergic blocking agent and of a prostaglandin or prostaglandin derivative, each in an ophthalmically compatible carrier, so as to reduce the intraocular pressure of the eye and maintain such reduced intraocular pressure.

EXPERIMENTAL RESULTS

Materials

The following materials used in the practice of this invention may be obtained from commercial sources: timolol maleate, (as TimopticTM from Merck Sharp & Dohme Division of Merck & Co. Inc., West Point, PA), betaxolol hydrochloride (as Betoptic from Alcon Laboratories, Fort Worth, Texas), and levobunolol HCl (as BetaganTM from Allergan America, Hiramigueros, Puerto Rico).

Method

Trained, unanesthetized cats (1.5 to 3.0 kg) which showed on biomicroscopical evidence of ocular inflammation such as anterior chamber flare or cellular invasion were used in all experiments. Eight cats were used in each set of experiments. Intraocular pressures (IOP) were measured using an Alcon floating tip Applanation Pneumatograph. The horizontal width of the pupil was measured using a millimeter pupil gauge. IOP and pupil diameters were measured before and several times after drug applications. Biomicroscopical examination of the anterior chamber was performed before and at 3, 8 and 24 hours after PG application.

PGF_{2α}-1-isopropyl ester (PGF_{2α}-IE) was supplied by Pharmacia AG (Uppsala, Sweden) already dissolved in 0.5% polysorbate 80 in normal saline containing 0.01% benzalkonium chloride; all dilutions were made up in this vehicle solution.

Timolol maleate powder was from Merck, Sharp and Dohme (West Point, PA) and was dissolved in 0.5% polysorbate 80 in normal saline with 0.01% benzalkonium chloride (40 mg/ml, and 20 mg/ml, respectively). Betaxolol hydrochloride (Betoptic; Alcon, Fort Worth, TX) at a concentration of 0.5% (5 mg/ml) and levobunolol hydrochloride (Betagan; Allergan, Irvine, CA) at a concentration of 0.5% (5 mg/ml), were obtained from the pharmacy.

In most experiments (those shown in Figures 1, 3 and 4), one beta-adrenergic blocking agents (500 μg Betoptic, or 125 μg Betagan) in a volume of 25 μl was applied first to both eyes of each cat immediately after baseline IOP and pupil diameter measurements. After 2 hours, immediately following another IOP and pupil diameter measurement, 0.5 μg (0.2%) of PGF_{2α}-IE in a volume of 25 μl was applied to one eye of each cat while the contralateral eye received 25 μl of the vehicle solution. IOP and pupil diameter measurements along with biomicroscopic examination of the anterior chamber were performed as described above.

In one group of 8 cats (results shown in Figure 2), a 25 μl-aliquot of a mixture of equal volumes of 4% timolol and 0.4% PGF_{2α}-IE yielding a dose of 500 μg of timolol and 0.5 μg of PGF_{2α}-IE in each 25 μl of 2% timolol (500 μg). IOP and pupil diameter measurements were taken as above.

Discussion

The beta blocker, timolol maleate, did not block the ocular hypotensive effect of PGF_{2α}-1-isopropyl ester. As shown in Figure 1, when a 2% timolol solution made up in an appropriate aqueous vehicle, was applied to both eyes of cats, there was some intraocular pressure reduction in both eyes at

2 hours. However, in the eyes which were then treated with 0.5 μg of PGF_{2α}-1-isopropyl ester (which is a threshold ocular hypotensive dose of PGF_{2α} in this species), a highly significant further drop in intraocular pressure occurred within one hour. In the contralateral eyes that received only timolol 2 hours earlier, the intraocular pressure only showed a very small, further decrease as compared to the pressure decrease observed during the first 2 hours.

Furthermore, as shown in Figure 2, there was a significant pressure reduction in cat eyes that were treated with 25 μl of the vehicle solution containing both timolol maleate (at a final concentration of 2.0%) and PGF_{2α}-1-isopropyl ester (at a final concentration of 0.002%) as compared to eyes that were treated with an identical volume of solution containing only timolol maleate. It should be noted that adrenergic receptors in cats have the same characteristics as other species, and, therefore, timolol maleate must be regarded as an adrenergic blocking agent in that species. Timolol maleate, however, is well-known to be a less effective pressure-reducing agent in cats than in humans. Therefore, in the human, the combination of timolol and a PG must have a greater effect than in cats. Since timolol maleate in the human, as in cats, acts by reducing the rate of aqueous humor production, while PG acts by increasing uveoscleral outflow, as long as timolol does not block the relaxing effect of PGs on the ciliary muscle, the effects of these two drugs must be at least additive.

Betaxolol hydrochloride and levobunolol hydrochloride also were employed in the practice of this invention, using 25 μl of the 0.5% clinically used solutions of Betoptic® and Betagan®, respectively. As is shown in Figure 3 and Figure 4, neither betaxolol hydrochloride nor levobunolol hydrochloride blocked the ocular hypotensive effect of PGF_{2α}-1-isopropyl ester. This suggests that levobunolol hydrochloride may be a very good candidate for combined therapy, since there was a more pronounced reduction of intraocular pressure within one hour after the topical application of 0.5 μg of PGF_{2α}-1-isopropyl ester in eyes that were pretreated with this beta blocker than typically occurs with this dose of PGF_{2α}-1-isopropyl ester. See, for example, the much smaller ocular hypotensive response to this dose of PGF_{2α}-1-isopropyl ester in betaxolol hydrochloride pretreated eyes (Figure 3) as compared to levobunolol hydrochloride pretreated eyes (Figure 4).

The positive interaction between levobunolol hydrochloride and PGF_{2α}-1-isopropyl ester suggests that PGF_{2α}-1-isopropyl ester may yield an effective intraocular pressure reduction at PGF_{2α}-1-isopropyl ester doses even less than 0.5 μg. While 0.5 μg is already a very small dose of

PGF_{2α} -1-isopropyl ester, a further reduction in this dose may have important clinical significance, since studies of Alm and Villumsen (Proceeding of the International Society for Eye Research, Vol. IV, #18:15, Seventh International Congress of Eye Research, Nagoya, Japan 1988) on human eyes show that reduction of the PGF_{2α} -1-isopropyl ester dose from 2.5 μg to 0.5 μg is sufficient to cause a considerable reduction in side effects, primarily conjunctival hyperemia. Therefore, the reduction of the PGF_{2α} -1-isopropyl ester dose in a combined therapy with levobunolol, or some other beta blocker will yield a significant reduction of the undesirable side effects of PGF_{2α} -1-isopropyl ester.

Claims

1. A method for treating ocular hypertension or glaucoma in a subject's eye which comprises contacting the surface of the eye with a composition comprising an effective intraocular pressure reducing amount of a mixture of an adrenergic blocking agent and a prostaglandin or prostaglandin derivative in an ophthalmically compatible carrier, so as to reduce the intraocular pressure of the eye and maintain such reduced intraocular pressure.

2. The method of claim 1, wherein the adrenergic blocking agent is a beta blocker.

3. The method of claim 2, wherein the beta blocker is timolol maleate.

4. The method of claim 2, wherein the beta blocker is betaxolol hydrochloride.

5. The method of claim 2, wherein the beta blocker is levobunolol hydrochloride.

6. The method of claim 1, wherein the prostaglandin or prostaglandin derivative is of the A, E or F type.

7. The method of claim 6, wherein the prostaglandin or prostaglandin derivative is PGF_{2α} or a PGF_{2α} derivative.

8. The method of claim 7, wherein the PGF_{2α} derivative is PGF_{2α} -1-isopropyl ester.

9. A method of claim 1, wherein the adrenergic blocking agent is present in the mixture in an amount between about 0.01 μg and about 1,000 μg.

10. A method of claim 9, wherein the adrenergic blocking agent is present in the mixture in an amount between about 5 μg and about 500 μg.

11. A method of claim 1, wherein the prostaglandin or prostaglandin derivative is present in the mixture in an amount between about 0.01 μg and about 1,000 μg.

12. A method of claim 11, wherein the prostaglandin or prostaglandin derivative is present in the mixture in an amount between about 0.1 μg and about 50 μg.

13. A method of claim 1, wherein the ophthalmically compatible carrier comprises an aqueous solution.

14. A method of claim 13, wherein the aqueous solution is a saline solution containing an ophthalmically compatible preservative, a surfactant, and an agent, such as a soluble polymer, to increase the viscosity of the solution.

15. A method of claim 1, wherein the mixture is dissolved in the ophthalmically compatible carrier.

16. A method of claim 1, wherein the contacting is effected periodically.

17. A method of claim 1, wherein the periodic contacting is effected at least daily.

18. A method of claim 1, wherein the subject is a primate.

19. A composition for the topical treatment of ocular hypertension or glaucoma comprising an effective intraocular pressure reducing amount of a mixture of an adrenergic blocking agent and a prostaglandin or a prostaglandin derivative in an ophthalmically compatible carrier.

20. A composition of claim 19, wherein the adrenergic blocking agent is a beta blocker.

21. A composition of claim 20, wherein the beta blocker is timolol maleate.

22. A composition of claim 20, wherein the beta blocker is betaxolol hydrochloride.

23. A composition of claim 20, wherein the beta blocker is levobunolol hydrochloride.

24. A composition of claim 19, wherein the prostaglandin or prostaglandin derivative is of the A, E or F type.

25. A composition of claim 24, wherein the PGF_{2α} derivative is PGF_{2α} or a PGF_{2α} derivative.

26. A composition of claim 25, wherein the PGF_{2α} derivative is PGF_{2α} -1-isopropyl ester.

27. A composition of claim 19, wherein the adrenergic blocking agent is present in the mixture in an amount between 0.01 μg and about 1,000 μg.

28. A composition of claim 27, wherein the adrenergic blocking agent is present in the mixture in an amount between about 5 μg and about 500 μg.

29. A composition of claim 19, wherein the prostaglandin or prostaglandin derivative is present in the mixture in an amount between about 0.01 μg and about 1,000 μg.

30. A composition of claim 29, wherein the prostaglandin or prostaglandin derivative is present in the mixture in an amount between about 0.1 μg and about 50 μg.

31. A composition of claim 19, wherein the ophthalmically compatible carrier comprises an aqueous solution.

32. A composition of claim 31, wherein the aqueous solution is a saline solution containing an ophthalmically compatible preservative, a surfactant, and an agent, such as a soluble polymer, to increase the viscosity of the solution.

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33. A composition of claim 18, wherein the mixture is dissolved in the ophthalmically compatible carrier.

34. A method for treating ocular hypertension or glaucoma in a primate subject's eye which comprises contacting the surface of the eye with a composition comprising an effective intraocular pressure reducing amount of a mixture of levobunolol hydro chloride and $\text{PGF}_{2\alpha}$ -1-isopropyl ester dissolved in an ophthalmically compatible carrier, so as to reduce the intraocular pressure of the eye and maintain such reduced intraocular pressure.

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35. A composition for the topical treatment of ocular hypertension or glaucoma comprising an effective intraocular pressure reducing amount of a mixture of levobunolol hydrochloride and $\text{PGF}_{2\alpha}$ -1-isopropyl ester dissolved in an ophthalmically compatible carrier.

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36. A method for treating ocular hypertension or glaucoma in a subject's eye which comprises separately contacting the surface of the eye with an intraocular pressure reducing amount of an adrenergic blocking agent and of a prostaglandin or prostaglandin derivative, each in an ophthalmically compatible carrier, so as to reduce the intraocular pressure of the eye and maintain such reduced intraocular pressure.

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Figure 1

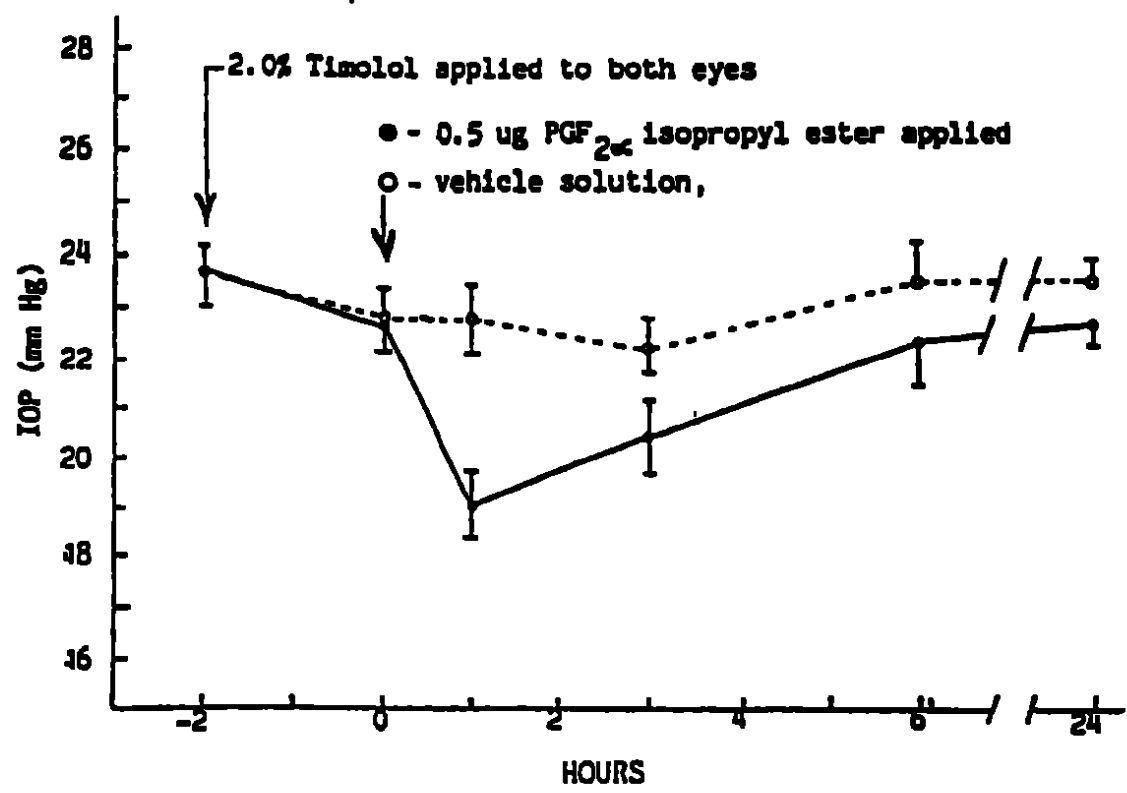


Figure 2

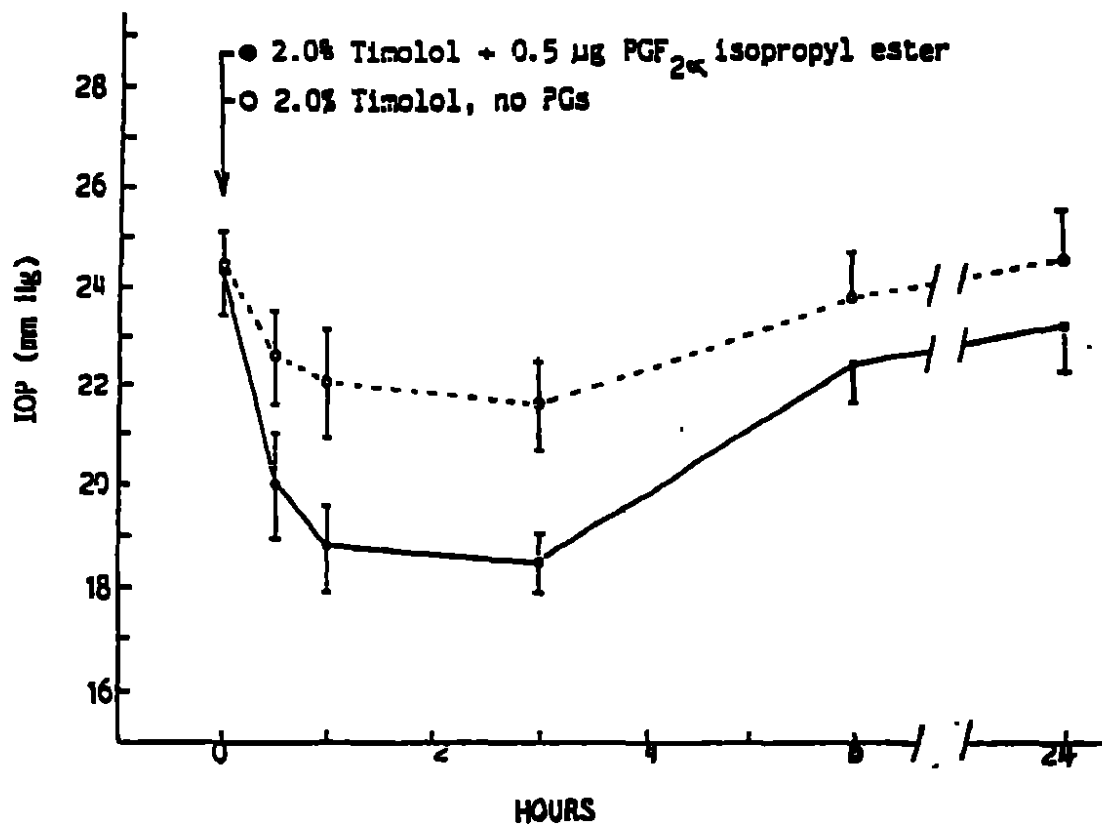


Figure 3

The ocular hypotensive effect of $\text{PGF}_{2\alpha}$ isopropyl ester ($\text{PGF}_{2\alpha}\text{-IE}$) on eyes of cats that were pretreated with 0.5% betaxolol (Betoptic)

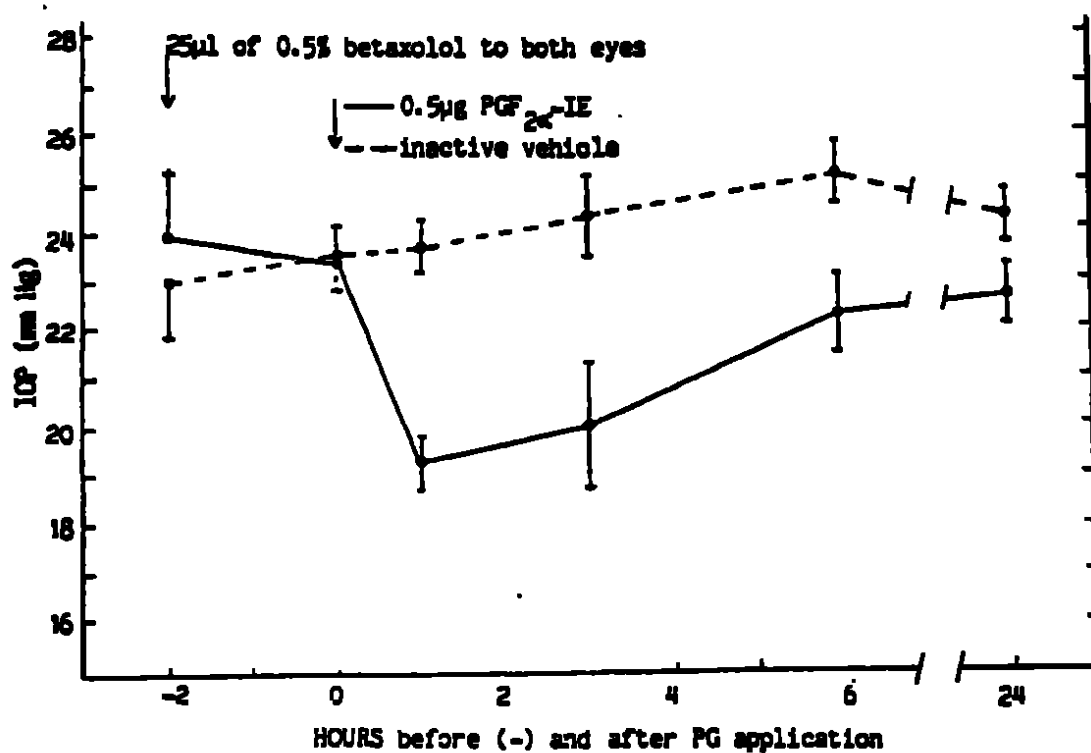
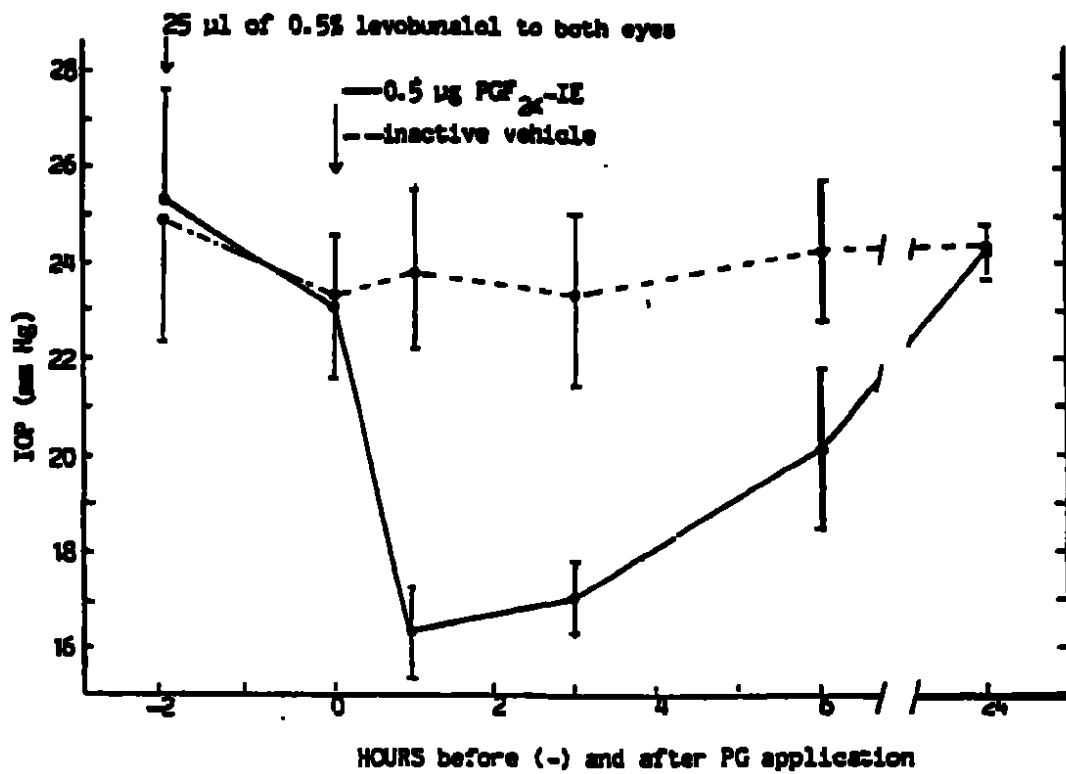


Figure 4

The ocular hypotensive effect of $\text{PGF}_{2\alpha}$ isopropyl ester ($\text{PGF}_{2\alpha}\text{-IE}$) on eyes of cats that were pretreated with 0.5% levobunolol (Betagan)





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PARTIAL EUROPEAN SEARCH REPORT
which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

Application number

EP 88 10 4999

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (INT. CL.4)
D, A	US-A-4 599 353 (L.Z. BITO) * Whole document * & EP-A-0 093 380	19-33, 35	A 61 K 31/557/ (A 61 K 31/557 31:535) (A 61 K 31/557 31:135)
P, A	EP-A-0 242 580 (TRUSTERS OF COLUMBIA UNIV.) * Whole document *	19-33, 35	
A	CHEMICAL ABSTRACTS, vol. 87, no. 11, September 12, 1977, page 52, ref. no. 78552x; Columbus, Ohio, US; T.J. ZIMMERMAN et al.: "Timolol. Dose response and duration of action" & ARCH. OPHTHALMOL. 1977, 95(4), 605-7. * Whole abstract *	19-33, 35	TECHNICAL FIELDS SEARCHED (INT. CL.4) A 61 K
INCOMPLETE SEARCH The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims. Claims searched completely: 19-33, 35 Claims searched incompletely: 1-18, 34 Claims not searched: 1-18, 34 Reason for the limitation of the search: Method for treatment of the human or animal body by surgery or therapy (see art. 52(4) of the European Patent Convention).			
Place of search The Hague.		Date of completion of the search 13-07-1988	Examiner BRINKMANN
CATEGORY OF CITED DOCUMENTS K: particularly relevant if taken alone C: particularly relevant if combined with another document of the same category A: technological background O: non-patent disclosure P: international document		T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons & : member of the same patent family, corresponding document	