

AS: 89.220

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

RESPUESTA A OFICIO 07051 DE AGOSTO 29, 2003

REF: Expediente No. 02 113.275 - Solicitud de Patente FASE NACIONAL
Corresp. a la Solicitud Internacional PCT/US01/18884
a favor de BRISTOL - MYERS SQUIBB COMPANY
Titulada: INHIBIDORES DE HMG-CoA REDUCTASA Y MÉTODO

RAMIRO CASTRO DUQUE, vecino de Bogotá, portador de la tarjeta profesional No. 1003, obrando como apoderado de la Sociedad BRISTOL - MYERS SQUIBB COMPANY, según lo acredita el documento de Poder presentado en esa División bajo el No. 19358, para dar cumplimiento al requerimiento notificado por fijación en lista el 29 de Agosto de 2003 y de acuerdo con los Artículos 38 y 39 de la Decisión 486 de la Comisión de la Comunidad Andina, Artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la SIC, me permito anexar al presente escrito los siguientes documentos:

1. Nos permitimos aclarar que de conformidad con los documentos allegados al expediente la presente solicitud corresponde al capítulo II del PCT.
2. Copia del examen preliminar efectuado por la IPEA, junto con su correspondiente traducción al castellano.
3. Documento donde consta la cesión del derecho a la Patente otorgado por los inventores al solicitante, debidamente apostillado.
4. Copia certificada por la Oficina de Patentes de Estados Unidos, de la primera solicitud presentada para la misma invención, de la cual REIVINDICAMOS PRIORIDAD.
5. Extracto para publicación y Tarjeta de Archivo Temático.
6. Artes finales (2 de 12 cm X 12 cm y 1 de 6 cm X 6 cm).

De la señora jefe atentamente,


RAMIRO CASTRO DUQUE
C.C. No. 170.322 de Bogotá
Código 340
Cra 7a. No. 16-56 Piso 9

Bogotá, Septiembre 15, 2003
CHP/MEV/hr

Brigard & Castro
Abogados

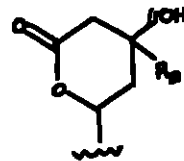
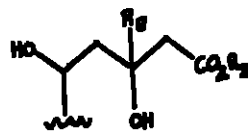
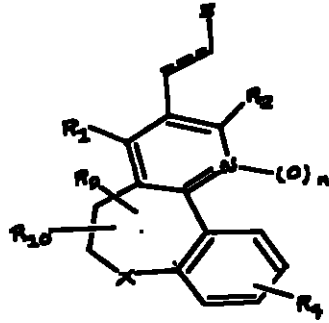
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FIL 353: TRABAJO TEMATICO
FIL 354: EXTRACTOS PUBLICACIONES

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference EX115	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No PCT/US01/18864	International filing date (day/month/year) 12 June 2001 (12.06.2001)	Priority date (day/month/year) 15 June 2000 (15.06.2000)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/675 and US Cl.: 514/90		
Applicant BRISTOL-MYERS SQUIBB COMPANY		
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 <u>4</u> 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 70.15 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of <u>0</u> sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☐ Non-establishment of report 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 09 January 2002 (09.01.2002)	Date of completion of this report 12 November 2002 (12.11.2002)	
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Lukton Davis Telephone No. 703-308-0196	

Form PCT/IPEA/409 (cover sheet) July 1998

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US01/13364

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed.
- ☒ the description:
 pages 1-89 as originally filed
 pages NONE filed with the demand
 pages NONE filed with the letter of _____
- ☒ the claims:
 pages 90-100 as originally filed
 pages NONE as amended (together with any statement) under Article 19
 pages NONE filed with the demand
 pages NONE filed with the letter of _____
- ☒ the drawings:
 pages NONE as originally filed
 pages NONE filed with the demand
 pages NONE filed with the letter of _____
- ☐ the sequence listing part of the description:
 pages NONE as originally filed
 pages NONE filed with the demand
 pages NONE filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 43.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

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

- ☐ contained in the international application in printed 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.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.3(a)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/18864

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-18	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-18	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-18	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-18 meet the criteria set out in PCT Article 33(2)-(3), because the prior art of record does not teach or fairly suggest the claimed compounds, compositions or methods of using the compounds or composition:

Claims 1-18 meet the criteria set out in PCT Article 33(4) for industrial applicability.

----- NEW CITATIONS -----

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

W. PCT/US01/14004

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-8, 15, 16 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art.

The compounds of claims 1-7 are asserted to be inhibitors of 3-hydroxy-glutaryl-coenzyme A reductase (HMG-CoA reductase). However, no evidence is presented that shows this to be the case. Structure/activity relationships of enzyme inhibitors are unpredictable, and so "undue experimentation" would be required to determine which of the claimed compounds will inhibit HMG-CoA reductase, and under what conditions. In addition, claim 8 is drawn to a "pharmaceutical composition"; this term implies an assertion of therapeutic efficacy. If it were to turn out that the claimed compounds exhibit some inhibition of HMG-CoA reductase in vitro, it would not necessarily follow that from that the compounds will be effective in vivo to reduce serum cholesterol levels. Inhibition is a question of degree, and it is not established what degree of inhibition is sufficient to achieve a reduction of serum cholesterol. Moreover, issues of pharmacokinetics and bioavailability remain to be determined. Accordingly, if it turns out that the claimed compounds exhibit some inhibition of HMG-CoA reductase in vitro, it will remain the case that "undue experimentation" would be required to practice the invention of claims 1, 15 and 16.

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 PCT)

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No. de Expediente del Solicitante o Apoderado HX115	PROCEDIMIENTO POSTERIOR Véase comunicación sobre el envío del Informe de Examen Preliminar Internacional (Formulario PCT/IPEA/416)	
No. Solicitud Internacional PCT / US01/ 18864	Fecha Internacional de Presentación (día/mes/año) 12 de Junio de 2001 (12.06.2001)	Fecha de Prioridad (día/mes/año) 15 de Junio de 2000 (15.06.2000)
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC IPC(7): A61K 31/675 y US Cl.: 514/80		
Solicitante BRISTOL-MYERS SQUIBB COMPANY		

- Este Informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 36.
- Este INFORME comprende un total de 4 hojas, inclusive esta portada

☐ Además se adjuntan ANEXOS al Informe; en este caso se trata de hojas con descripciones, reivindicaciones y/o dibujos, que se modificaron y que sirven de base a este Informe, y/o hojas con correcciones efectuadas por esta oficina (véase Regla 70.16 y Sección 607 de las Instrucciones administrativas al PCT).

Estos anexos comprenden en total de 0 hojas.
- Este Informe contiene datos con respecto a los siguientes puntos:
 - ☒ Base del Informe
 - ☐ Prioridad
 - ☐ Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación Industrial
 - ☐ Uniformidad deficiente de la invención
 - ☒ Declaración motivada bajo Regla 68.2(a)(ii) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación Industrial; citas y explicaciones que sustentan esta declaración
 - ☐ Ciertos documentos enumerados
 - ☐ Ciertas deficiencias del registro internacional
 - ☒ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición 09 de Enero de 2002 (09.01.2002)	Fecha de la preparación de este Informe 12 de Noviembre de 2002 (12.11.2002)
Nombre y dirección postal de la Oficina Encargada del Examen Preliminar internacional (IPEA/US) Comisionado de Patentes y Marcas Box PCT Washington D.C., 20231	Empleado Autorizado Lukton David Teléfono No. 703-308-0196

Fax No. (703) 305 - 3230

Formulario PCT/IPEA/409 (portada) (Julio 1998)

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL	Solicitud Internacional No. PCT/US01/18884
I. Base del Informe	
1. Con respecto a los elementos de la solicitud internacional:** ☒ la solicitud internacional tal como se radicó originalmente ☒ la descripción: páginas <u>1-89</u> como se radicaron originalmente páginas <u>NINGUNA</u> radicadas con la petición páginas <u>NINGUNA</u> radicadas con la carta de _____ ☒ las reivindicaciones: Páginas <u>90-100</u> como se radicaron originalmente páginas <u>NINGUNA</u> como se modificaron (junto con cualquier declaración) bajo artículo 19 páginas <u>NINGUNA</u> radicadas con la petición páginas <u>NINGUNA</u> radicadas con la carta de _____ ☒ los dibujos: páginas <u>NINGUNA</u> como se radicaron originalmente páginas <u>NINGUNA</u> radicadas con la petición páginas <u>NINGUNA</u> radicadas con la carta de _____ ☐ la parte del listado de secuencias de la descripción: páginas <u>NINGUNA</u> como se radicaron originalmente páginas <u>NINGUNA</u> radicadas con la petición páginas <u>NINGUNA</u> radicadas con la carta de _____	
2. En lo concerniente al idioma, todos los elementos indicados más arriba estuvieron a disposición de la administración o le fueron enviados en el idioma en el cual se radicó la solicitud internacional, salvo indicación en contrario consignada bajo este punto. Estos elementos estuvieron a disposición de la administración o le fueron enviados en el idioma siguiente _____ que es: ☐ el idioma de una traducción enviada para efectos de la búsqueda internacional (según la regla 23.1 (b)). ☐ el idioma de publicación de la solicitud internacional (según la regla 48.3 (b)). ☐ el idioma de la traducción enviada para efectos del examen preliminar internacional (según la regla 55.2 y/o 55.3).	
3. En lo que concierne a la secuencia de nucleótidos y/o aminoácidos divulgados en la solicitud internacional (en caso dado), el examen preliminar internacional se llevó a cabo sobre la base del listado de secuencias: ☐ contenido en la solicitud internacional, por escrito. ☐ radicado con la solicitud internacional, en formato de lectura por computador. ☐ remitido posteriormente a la administración, por escrito. ☐ remitido posteriormente a la administración, en formato de lectura por computador. ☐ se ha rendido la declaración, según la cual el listado de secuencias por escrito y suministrado posteriormente no va más allá de la divulgación hecha en la solicitud tal como se radicó. ☐ se ha rendido la declaración, según la cual las informaciones registradas en formato de lectura por computador son idénticas a las de los listados de secuencias, presentados por escrito.	
4. ☒ Las modificaciones han acarreado la anulación: ☒ de la descripción, páginas <u>NINGUNA</u> ☒ de las reivindicaciones, Nos. <u>NINGUNA</u> ☒ de los dibujos, hojas/fig. <u>NINGUNA</u>	
5. ☐ El presente informe se preparó sin tener en cuenta (algunas de) las modificaciones, que se consideraron que van más allá de la exposición de la invención tal como se radicó según se indica a continuación en el Cuadro Suplementario (regla 70.2 (c)).**	
* Hojas intercambiables, que se presentaron a la Oficina de Radicación con base en una solicitud según Artículo 14, se consideran en el marco de este informe como "presentadas inicialmente" y no se le adjuntan porque no contienen ningún tipo de modificaciones (Reglas 70.16 y 70.17). ** Toda hoja intercambiable que incluya modificaciones de esta índole debe indicarse en el punto 1 y anexarse al presente informe.	

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No.

PCT/US01/18884

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V. Declaración motivada bajo Regla 88.2(a)(II) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; citas y explicaciones que sustentan esta declaración

1. DECLARACIÓN

Novedad (N)	Reivindicaciones <u>1-18</u>	SI
	Reivindicaciones <u>NINGUNA</u>	NO
Actividad Inventiva (IS)	Reivindicaciones <u>1-18</u>	SI
	Reivindicaciones <u>NINGUNA</u>	NO
Posibilidad de Aplicación Industrial (IA)	Reivindicaciones <u>1-18</u>	SI
	Reivindicaciones <u>NINGUNA</u>	NO

2. CITAS Y EXPLICACIONES

Reivindicaciones 1-18 satisfacen los criterios expuestos en Artículo 33(2)-3 PCT porque el arte previo no enseña o medianamente sugiere los compuestos reivindicados, composiciones o métodos de usar los compuestos o composiciones.

Reivindicaciones 1-18 satisfacen los criterios expuestos en Artículo 33(4) PCT para posibilidad de aplicación industrial

NUEVAS CITAS

VIII. Ciertas observaciones sobre la solicitud internacional

Se hacen las siguientes observaciones sobre la claridad de las reivindicaciones, descripción, y dibujos o la cuestión de si las reivindicaciones están completamente sustentadas por la descripción:

Reivindicaciones 1-8, 15, 16 se objetan como carentes de claridad bajo Regla 68.2(a)(v) PCT porque las reivindicaciones no están completamente sustentadas por la descripción. La descripción no divulga la invención reivindicada en una forma suficientemente clara y completa para que la invención reivindicada sea llevada a cabo por una persona experta en el arte.

Se sostiene que los compuestos de reivindicaciones 1-7 son inhibidores de 3-metil-glutaril-coenzima A reductasa (HMG-CoA reductasa). No obstante, no se presenta evidencia que muestre que éste sea el caso. Las relaciones estructura/actividad de inhibidores de enzimas son impredecibles y, por lo tanto, se requeriría una "experimentación excesiva" para determinar cuál de los compuestos reivindicados inhibirán HMG CoA reductasa, y bajo qué condiciones. Adicionalmente, reivindicación 8 se relaciona con una "composición farmacéutica"; este término implica una afirmación de eficacia. Si resultara que los compuestos reivindicados exhiben alguna inhibición de HMG-CoA reductasa *in vitro*, de ahí no se seguiría necesariamente que los compuestos sean efectivos *in vivo* para reducir los niveles de colesterol en el suero. La inhibición es una cuestión de grado, y no se establece qué grado de inhibición es suficiente para lograr una reducción del colesterol en el suero. Más aún, quedan por determinar problemas de farmacocinética y bio-disponibilidad. Por consiguiente, el resulta que los compuestos reivindicados exhiben alguna inhibición de HMG-CoA reductasa *in vitro*, subsistirá el caso de que se requeriría "experimentación excesiva" para poner en práctica la invención de reivindicaciones 8, 15 y 16.

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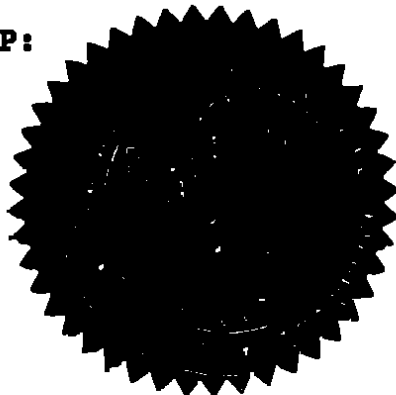
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. **COUNTRY: UNITED STATES OF AMERICA**
2. **THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MARIA CASTALDO**
3. **ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY**
4. **BEARS THE SEAL/STAMP OF:
MARIA CASTALDO, NOTARY**

CERTIFIED

5. **AT TRENTON, NEW JERSEY**
6. **THE 7TH DAY OF NOVEMBER 2002**
7. **BY: John E McCormac, CPA, NEW JERSEY TREASURER**
8. **NO. A161118**
9. **SEAL/STAMP:**
10. **SIGNATURE**



John E McCormac

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AFFIDAVIT

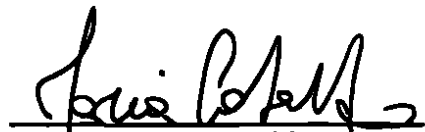
**I, Stephen B. Davis, Patent Counsel, Patent Department,
BRISTOL-MYERS SQUIBB COMPANY, do hereby certify that this is a
notarized true copy of the original assignment signed by the inventors,
JEFFREY A. ROBL, BANG-CHI CHEN, CHONG-QUING SUN.**

The original document is in the possession of BRISTOL-MYERS SQUIBB COMPANY.


Stephen B. Davis
Patent Counsel

STATE OF NEW JERSEY)
)
COUNTY OF MERCER)

Subscribed and sworn to before me this
18th day of October, 2002


Maria Castaldo
Notary Public of New Jersey
My commission expires October 6, 2003

SEAL



UNITED STATES DEPARTMENT OF COMMERCE
Patents and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

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MARCH 23, 2001

PTAS

BRISTOL-MYERS SQUIBB COMPANY
MARIA J. MATHIAS
P.O. BOX 4000
PATENT DEPARTMENT
PRINCETON, NJ 08543-4000

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UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 03/20/2001

REEL/FRAME: 011414/0954
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

ROBL, JEFFREY A.

DOC DATE: 07/17/2000

ASSIGNOR:

CHEN, BANG-CHI

DOC DATE: 07/17/2000

ASSIGNOR:

SUN, CHONG-QUING

DOC DATE: 07/17/2000

ASSIGNEE:

BRISTOL-MYERS SQUIBB COMPANY
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000

SERIAL NUMBER: 60211595

FILING DATE: 06/15/2000

PATENT NUMBER:

ISSUE DATE:

011414/0954 PAGE 2

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MARCUS KIRK, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Jeffrey A. Robl, Bang-Chi Chen,
Chong-Qing Sun

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

- ☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____

Execution Date: 07/17/00

2. Name and address of receiving party(ies)

364

Name: Bristol-Myers Squibb Company

Internal Address: _____

Street Address: Lawrenceville-Princeton Road

City: Princeton State: NJ ZIP: 08543-4000

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)

60/211,595

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Maria J. Mathias

Internal Address: Bristol-Myers Squibb Company

Patent Department

Street Address: P.O. Box 4000

City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 4

7. Total fee (37 CFR 3.41) \$ 40

☐ Enclosed

☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:

19-3880 (in the name of Bristol-Myers Squibb Company)

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Burton Rodney

Name of Person Signing
Reg. No. 22,076

Signature

Date

☐ Certificate of mailing on reverse side

Total number of pages including cover sheet, attachments, and document: 2

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

12
365

Please return to: Burton Rodney
Patent Department
Bristol-Myers Squibb Company
Post Office Box 4000
Princeton, New Jersey 08543-4000

ASSIGNMENT

Pursuant to contractual obligations heretofore assumed by us and/or for other good and valuable consideration, receipt of which is hereby acknowledged, we,

Jeffrey A. Robl
7 Tulip Drive
Newtown, PA 18940

Bang-Chi Chen
28 Marion Drive
Plainsboro, NJ 08536

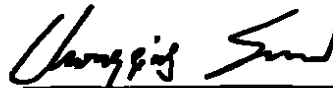
Chong-Qing Sun
527 Dutch Neck Road
East Windsor, NJ 08520

having made a certain invention for which a United States provisional patent application entitled HMG-CoA REDUCTASE INHIBITORS AND METHOD has been prepared, do hereby assign to Bristol-Myers Squibb Company, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, New Jersey 08543-4000, its successors and assigns, the entire right, title, and interest in and to said invention, said provisional application, any application claiming priority from said provisional application, filed in any country, and any patents to be granted thereon, and all divisions, continuations, reissues, and extensions thereof in all countries; and we hereby authorize and request the Commissioner of Patents and Trademarks to issue any such United States patent to Bristol-Myers Squibb Company, its successors and assigns, and we agree to communicate to Bristol-Myers Squibb Company or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, sign all lawful papers, execute all divisional, continuing, and reissue applications, make all rightful declarations and oaths, and in general to do everything possible to aid Bristol-Myers Squibb Company, its successors, assigns and nominees to obtain and enforce proper protection for said invention in all countries.

IN WITNESS WHEREOF, we have hereto set our hands and seals


Jeffrey A. Robl


Bang-Chi Chen


Chong-Qing Sun

Continued on page 2

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STATE OF NEW JERSEY)
COUNTY OF MERCER) ss.

On the 17th day of July, 2000, before me came Jeffrey A. Robl, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Maria Zulla
Notary Public

[SEAL]

MARIA ZULLA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires June 8, 2004

STATE OF NEW JERSEY)
COUNTY OF MERCER) ss.

On the 17th day of July, 2000, before me came Sang-Chi Chen, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Maria Zulla
Notary Public

[SEAL]

MARIA ZULLA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires June 8, 2004

STATE OF NEW JERSEY)
COUNTY OF MERCER) ss.

On the 17th day of July, 2000, before me came Chong-Qing Sun, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

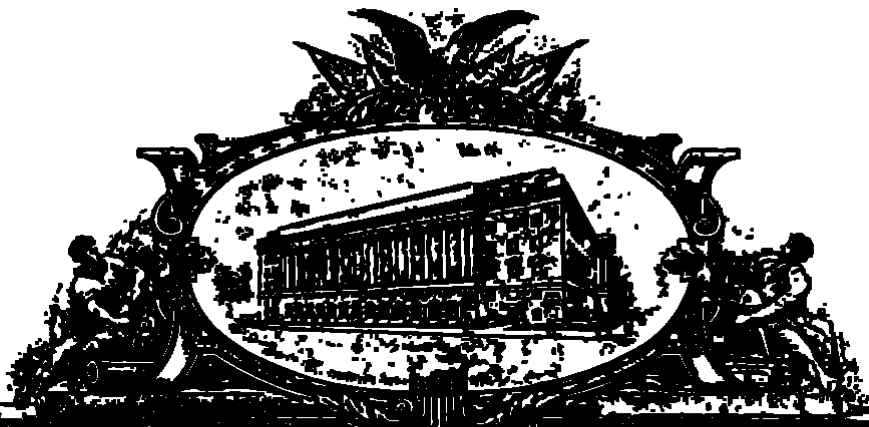
Maria Zulla
Notary Public

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PA 286130



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 20, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/211,595

FILING DATE: June 15, 2000



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. Williams
N. WILLIAMS

Certifying Officer

06/15/00

10682 U.S. PTO

Docket Number H00116(P&P)

FILED BY "EXPRESS MAIL" UNDER 37 CFR 1.10

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60/211595

06/15/00

Address to: Assistant Commissioner for Patents
Box Provisional Patent Application
Washington, DC 20231

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Transmitted herewith for filing under 37 CFR §1.63(c) is the PROVISIONAL APPLICATION for patent of

INVENTOR(S)		
Given Name (last and middle (if any))	Family Name or Surname	Residence (City and either State or Foreign Country)
Jeffrey A. Bang-Chi Chong-Qing	Robi Chen Sun	Newtown, Pennsylvania Plainboro, New Jersey East Windsor, New Jersey
TITLE OF THE INVENTION (250 characters max) HMG-CoA REDUCTASE INHIBITORS AND METHOD		
CORRESPONDENCE ADDRESS Direct all correspondence to the address associated with Customer No. 23014, which is currently: Marie J. Mathias Bristol-Myers Squibb Company Patent Department P.O. Box 4000 Princeton, NJ 08542-4000		
ENCLOSED APPLICATION PARTS (check all that apply) ☒ Specification (including Any Claims and Abstract) - 80 pages ☐ Drawings - sheets ☐ Other (specify):		
METHOD OF PAYMENT The Commissioner is hereby authorized to charge filing fee and any additional fees required to Deposit Account Number: 19-3680 in the name of Bristol-Myers Squibb Company. PROVISIONAL FILING FEE AMOUNT: \$ 100		

☐ U.S. Government agency and contract number: (If the invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.)

Date: June 15, 2000

Respectfully submitted,

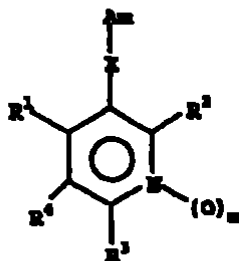

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369HMG-CoA REDUCTASE INHIBITORS AND METHODField of the Invention

5 The present invention relates to compounds and pharmaceutical compositions useful as hypocholesterolemic and hypolipidemic agents. More particularly, this invention concerns (1) certain inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA
10 reductase) that include a pyridine containing nucleus attached by means of a linker to an HMG-binding domain sidechain, (2) pharmaceutical compositions containing such compounds and (3) a method of lowering blood serum cholesterol levels and modulating blood serum lipid
15 levels employing such pharmaceutical compositions.

Background of the Invention

U.S. Patent No. 5,686,433 to Robl discloses the structure



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wherein:

Am is a binding domain sidechain;

X is a linker;

R¹ and R² are the same or different and are each

25 independently selected from

- (i) hydrogen,
- (ii) alkyl,
- (iii) aryl,
- (iv) cycloalkyl,
- 30 (v) aralkyl,
- (vi) aralkoxy,
- (vii) alkenyl,

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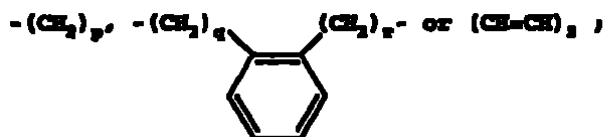
- (viii) cycloalkenyl, and
(ix) heterocyclo (e.g., thienyl, benzodioxolyl);

R³ is selected from

- 5 (i) hydrogen,
(ii) lower alkyl,
(iii) aryl,
(iv) cycloalkyl,
(v) alkoxy,
10 (vi) aralkyl,
(vii) aralkoxy,
(viii) alkenyl,
(ix) cycloalkenyl,
(x) halo-substituted alkyl,
15 (xi) adamantyl, and
(xii) heterocyclo (e.g., thienyl, benzodioxolyl);

R⁴ is selected from

- 20 (i) hydrogen,
(ii) lower alkyl,
(iii) aryl,
(iv) cycloalkyl,
(v) alkoxy,
(vi) aralkyl,
25 (vii) aralkoxy,
(viii) alkenyl,
(ix) cycloalkenyl,
(x) adamantyl,
(xi) halogen,
30 (xii) halo-substituted alkyl (e.g.,
trifluoromethyl), and
(xiii) heterocyclo (e.g., thienyl, benzodioxolyl);
or R³ and R⁴ taken together can be

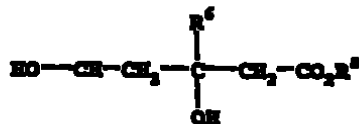


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but when A_n is



or a δ lactone thereof, R^3 and R^4 cannot be $(CH=CH)_2$;

R^6 is hydrogen or lower alkyl;

5 R^7 is hydrogen, lower alkyl, alkali metal, or alkaline earth metal;

n is 0 or 1;

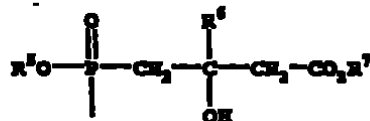
p is 3, 4 or 5;

q is 0, 1, 2, or 3; and

10 r is 0, 1, 2, or 3.

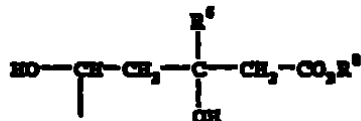
In preferred embodiments (Am) is an HMG-binding domain sidechain having a dihydroxy or a phosphinic acid function.

The phosphinic (or phosphonic when X is CH_2-O-)
15 acid HMG-binding domain sidechain (A_1) is



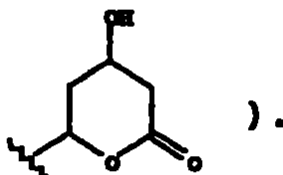
wherein R^5 and R^7 are independently selected from hydrogen, lower alkyl, alkali metal ion and alkaline
20 earth metal ion; and R^6 is hydrogen or lower alkyl.

The dihydroxy acid binding domain sidechain (A_2) is



wherein R^6 is hydrogen or lower alkyl, R^7 is hydrogen or
25 lower alkyl in free acid form or in the form of a physiologically acceptable and hydrolyzable ester or δ lactone thereof (i.e., when Am is

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In addition, R^1 can be alkali metal ion or alkaline earth metal ion.

- A suitable linker (X) is $-(CH_2)_a-$, $-CH=CH-$, $-C\equiv C-$, $-CH_2O-$, wherein O is linked to the phosphorous atom or the aromatic anchor when Am is A_1 , and wherein O is linked to the aromatic anchor when Am is A_2 , and wherein "a" is 1, 2, or 3.

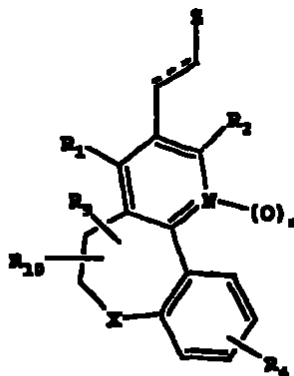
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Brief Description of the Invention

- In accordance with the present invention, there are provided certain pyridine-containing compounds that are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the enzyme 3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase).

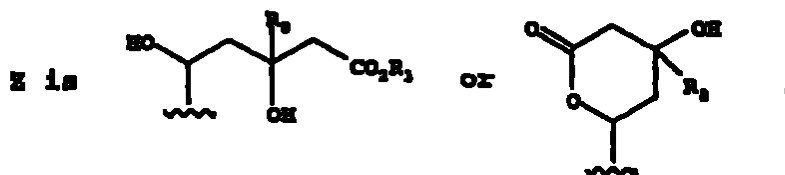
- In particular, in its broadest chemical compound aspect, the present invention provides compounds of the formula

I



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wherein X is O, S or NR_7 ;



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n is 0 or 1;

R₁ and R₂ are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

R₃ is H, lower alkyl or a metal ion such as an alkali metal ion or an alkaline earth metal ion;

R₄ is H, halogen, CF₃, hydroxy, alkyl, alkoxy, alkanoylamino, aroylamino, or cyano;

R₇ is H, alkyl, aryl, alkanoyl, aroyl, or alkoxy carbonyl;

R₈ is H or lower alkyl;

R₉ and R₁₀ are the same or different and are independently selected from H or alkyl, or where at least one of R₉ and R₁₀ is alkyl, R₉ and R₁₀ may be taken together with the carbon or carbons to which they are attached to form a 3 to 7 membered carbocyclic ring, which may include a spirocyclic ring;

and ~~---~~ represents a single bond or a double bond (which may be cis or trans);

and including pharmaceutically acceptable salts thereof, esters thereof, prodrug esters thereof, and all stereoisomers thereof.

Preferably, the Z group will be in form of a free acid, a physiologically acceptable and hydrolyzable ester or δ lactone thereof, or an alkali metal salt.

Preferred are compounds of formula I of the invention wherein

R₁ and R₂ are independently selected from alkyl, cycloalkyl and aryl;

R₄ is H, alkyl or halogen;

X is O, and

n is 0.

More preferred are compounds of formula I of the invention wherein R₁ is aryl (especially substituted aryl as defined hereinafter);

R₂ is alkyl or cycloalkyl;

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R_4 is H;
 R_3 and R_{10} are H;
 X is O;
 n is 0; and

5 ~~is~~ is a double bond.

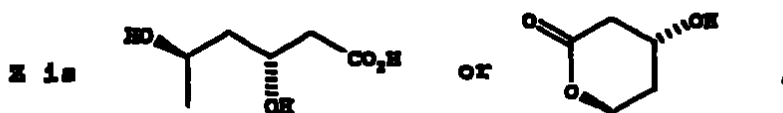
Still more preferred are compounds of formula I of the invention wherein

R_1 is substituted aryl, preferably 4-fluorophenyl, 4-fluoro-3-methylphenyl or 3,5-dimethylphenyl;

10 R_2 is alkyl or cycloalkyl, preferably isopropyl, t-butyl or cyclopropyl;

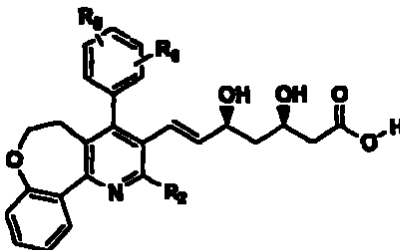
R_4 is H;
 X is O;
 n is 0;

15 ~~is~~ is a double bond, preferably "trans"; and



or an alkali or alkaline earth metal salt thereof.

20 Most preferred compounds of formula I of the invention will have the structure



25 or an alkali or alkaline earth metal (such as Na, K or Ca) salt thereof, wherein R_3 and R_4 are the same or different and independently selected from H, halogen and/or alkyl (preferably 4-fluoro, 4-fluoro-3-methyl or 3,5-dimethyl); and

R_2 is alkyl or cycloalkyl, preferably isopropyl, t-butyl or cyclopropyl.

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In another aspect, the present invention provides pharmaceutical compositions, useful as hypolipidemic or hypocholesterolemic agents, or hypotriglyceridemic agents, comprising a hypolipidemic or hypocholesterolemic or hypotriglyceridemic amount of a compound of formula I in accordance with this invention, in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of inhibiting cholesterol biosynthesis or lowering blood serum cholesterol levels and/or modulating blood serum lipids such as lowering LDL cholesterol levels and/or increasing HDL cholesterol levels or treating hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia or hypertriglyceridemia, or treating or preventing atherosclerosis in a patient in need of such treatment by administering a pharmaceutical composition in accordance with the present invention as defined above.

Detailed Description of the Invention

In accordance with the present invention, there is provided compounds useful in inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA reductase), which inhibitors are useful as hypocholesterolemic and hypolipidemic agents, hypotriglyceridemic agents and antiosteoporosis agents.

Definitions of Terms

The terms pharmaceutically acceptable "salt" and "salts" refer to basic salts formed with inorganic and organic bases. Such salts include ammonium salts, alkali metal salts, such as lithium, sodium and potassium salts (which are preferred); alkaline earth metal salts, such as calcium and magnesium salts; salts with organic bases, such as amine like salts (e.g., dicyclohexylamine salt, benzathine, N-methyl-D-glucamine, and hydrabamine salts); and salts with amino acids like arginine, lysine and the

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like; and zwitterions, the so-called "inner salts".
Nontoxic, pharmaceutically acceptable salts are preferred, although other salts are also useful, e.g., in isolating or purifying the product.

- 5 The term pharmaceutically acceptable "salt" and "salts" also includes acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid such as HCl or HBr, with strong
10 organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example, acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic,
15 fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic
20 acids, such as (C1-C4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methanesulfonic acid or p-toluenesulfonic acid.

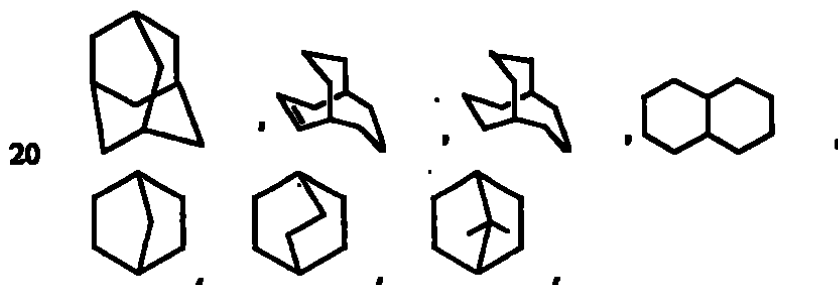
- Unless otherwise indicated, the term "lower
25 alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl,
30 propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethyl-pentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such
35 as halo, for example F, Br, Cl or I or CF₃, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl,

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- cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl, cycloheteroalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido,
- 5 alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio.

- Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1
- 10 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclic alkyl, bicyclic alkyl (or bicycloalkyl) and tricyclic alkyl, containing a total of 3 to 20 carbons forming the ring, preferably 3 to 10
- 15 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



- any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy,
- 25 hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, heteroaryl, cycloheteroalkyl, amino, alkylamino, nitro, cyano, thiol and/or alkylthio and/or any of the substituents for alkyl.
- 30 The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 3 to 12 carbons, preferably 5 to 10 carbons

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and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for

5 cycloalkyl.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower
10 alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal
15 chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1
20 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonyl-amino, nitro, cyano, thiol, alkylthio and/or any of the alkyl
25 substituents set out herein.

Unless otherwise indicated, the term "lower
alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons
30 and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butyne, 2-butyne, 4-pentyne, 3-pentyne, 2-hexynyl, 3-hexynyl, 2-heptyne, 3-heptyne, 4-heptyne, 3-octynyl, 3-nonyne, 4-decynyl, 3-undecynyl,
35 4-dodecynyl and the like, and which may be optionally

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substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the alkyl substituents set out herein.

The terms "arylaalkenyl" and "arylaalkynyl" as used alone or as part of another group refer to alkenyl and alkynyl groups as described above having an aryl substituent.

Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed "alkylene" groups and may optionally be substituted with 1 or 2 substituents as defined above for "alkyl", such as, for example, alkyl, halo, hydroxy, alkoxy and/or cycloalkyl.

Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted with 1 or 2 substituents as defined above for "alkenyl" and "alkynyl".

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF₃, with chlorine or fluorine being preferred.

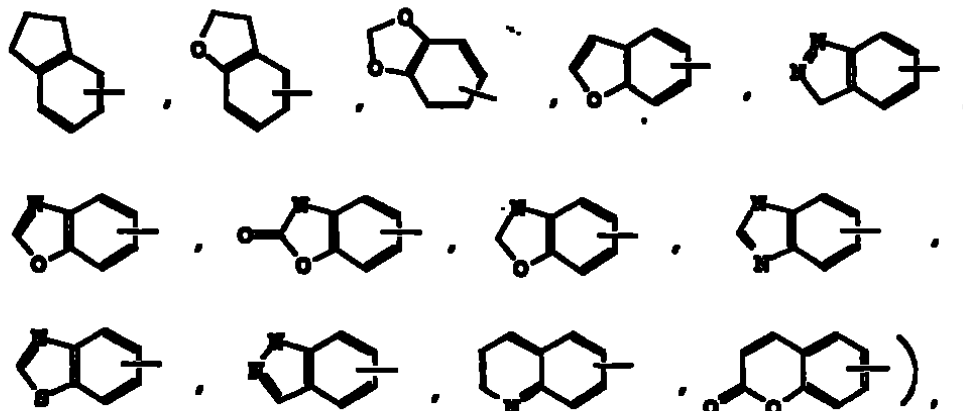
The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

Unless otherwise indicated, the term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or

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naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example



- and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from
- 10 hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, halophenyl, benzoyloxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy,
 - 15 arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, alkanoyl, aryl or any of the other aryl compounds mentioned in the
 - 20 definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkyl-aminocarbonyl, arylaminocarbonyl, alkoxy carbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino,
 - 25 arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfon-aminocarbonyl and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed

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herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

Unless otherwise indicated, the term "substituted amino" as employed herein alone or as part of another group refers to amino substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with a carboxylic acid and/or any of the substituents for alkyl as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

Unless otherwise indicated, the term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

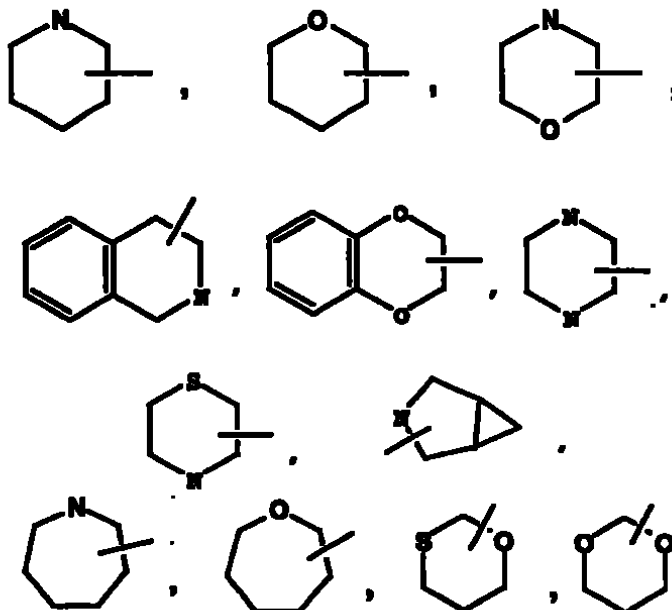
Unless otherwise indicated, the term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

Unless otherwise indicated, the term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\begin{smallmatrix} R \\ C \end{smallmatrix} \right)$ group; examples of acyl groups include any of the R^1 groups attached to a carbonyl, such as

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alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

Unless otherwise indicated, the term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_r$ (where r is 1, 2 or 3), such as

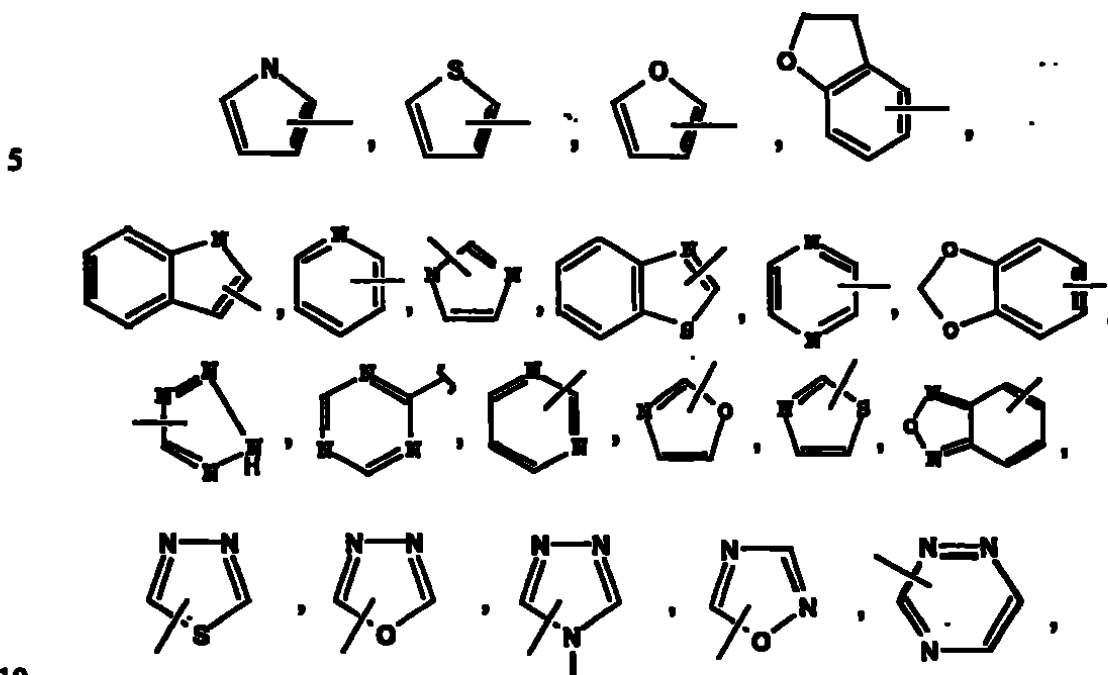


and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the alkyl substituents set out herein. In addition, any of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. The heteroaryl group may optionally include 1 to

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4 substituents such as any of the substituents set out above for alkyl. Examples of heteroaryl groups include the following:



and the like.

The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_x$ chain.

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The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_x-$ chain, alkylene or alkenylene as defined above.

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The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2 , CF_3 or $CF_3CF_2CH_2$.

25 The term "polyhaloalkoxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo

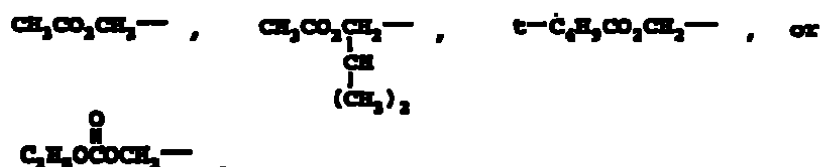
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substituents, such as F or Cl, preferably F, such as $\text{CF}_3\text{CH}_2\text{O}$, CF_3O or $\text{CF}_3\text{CF}_2\text{CH}_2\text{O}$.

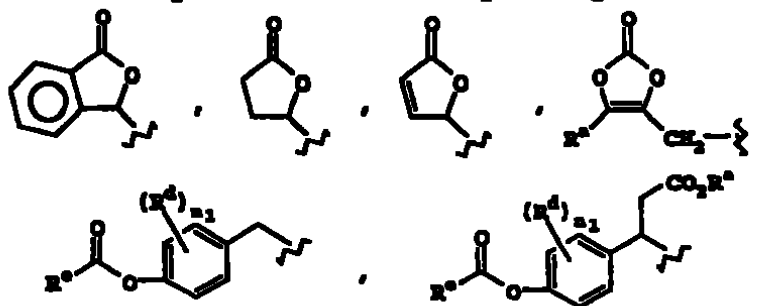
All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one or the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

The term "prodrug esters" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula I with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates and the like. In addition, prodrug esters which are known in the art for carboxylic and phosphorus acid esters such as methyl, ethyl, benzyl and the like.

Examples of such prodrug esters include



Other examples of suitable prodrug esters include



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wherein R^a can be H, alkyl (such as methyl or t-butyl),
arylalkyl (such as benzyl) or aryl (such as phenyl); R^d
is H, alkyl, halogen or alkoxy, R^e is alkyl, aryl,
5 arylalkyl or alkoxy, and n₁ is 0, 1 or 2.

Where the compounds of structure I are in acid
form they may form a pharmaceutically acceptable salt
such as alkali metal salts such as lithium, sodium or
potassium, alkaline earth metal salts such as calcium or
10 magnesium as well as zinc or aluminum and other cations
such as ammonium, choline, diethanolamine, lysine (D or
L), ethylenediamine, t-butylamine, t-octylamine, tris-
(hydroxymethyl)aminomethane (TRIS), N-methyl glucosamine
(NMG), triethanolamine and dehydroabietylamine.

15 Compounds of the invention may be prepared by the
following method.

Referring to Reaction Scheme 1, Knoevenagel
condensation of readily available beta-keto ester 1,
where R is lower alkyl, with aldehyde 2 under standard
20 conditions (e.g. HOAc, piperidine, toluene, reflux)
affords the corresponding adduct 3. Base induced 1,4-
addition of ketone 4 (e.g. LiN(TMS)₂ in THF or EtONa in
EtOH) provides the adduct 5, usually as a mixture of
diastereomers.

25 Conversion of the 1,5-diketone 5 to the pyridyl
ester 6 may be effected by treatment with an ammonia
source (such as NH₄OAc) in the presence of an oxidant
(such as Cu(OAc)₂ or oxygen) in a suitable solvent (such
as refluxing HOAc), or by reaction of 5 with
30 hydroxylamine hydrochloride in HOAc with heat. The ester
functionality of 6 can be reduced by standard methods
(LiAlH₄, DIBAL, LiBH₄) to give alcohol 7 which can
subsequently be converted to the corresponding halide 8
(e.g. PBr₃ in CH₂Cl₂, CBr₄/PPh₃ in CH₃CN or POCl₃).

35 Conversion of halide 8 to the phosphorus compound 9 where
W is Ph or alkyl is effected by treatment of 8 with
W₂POEt in toluene. Conversion of halide 8 to compound 9

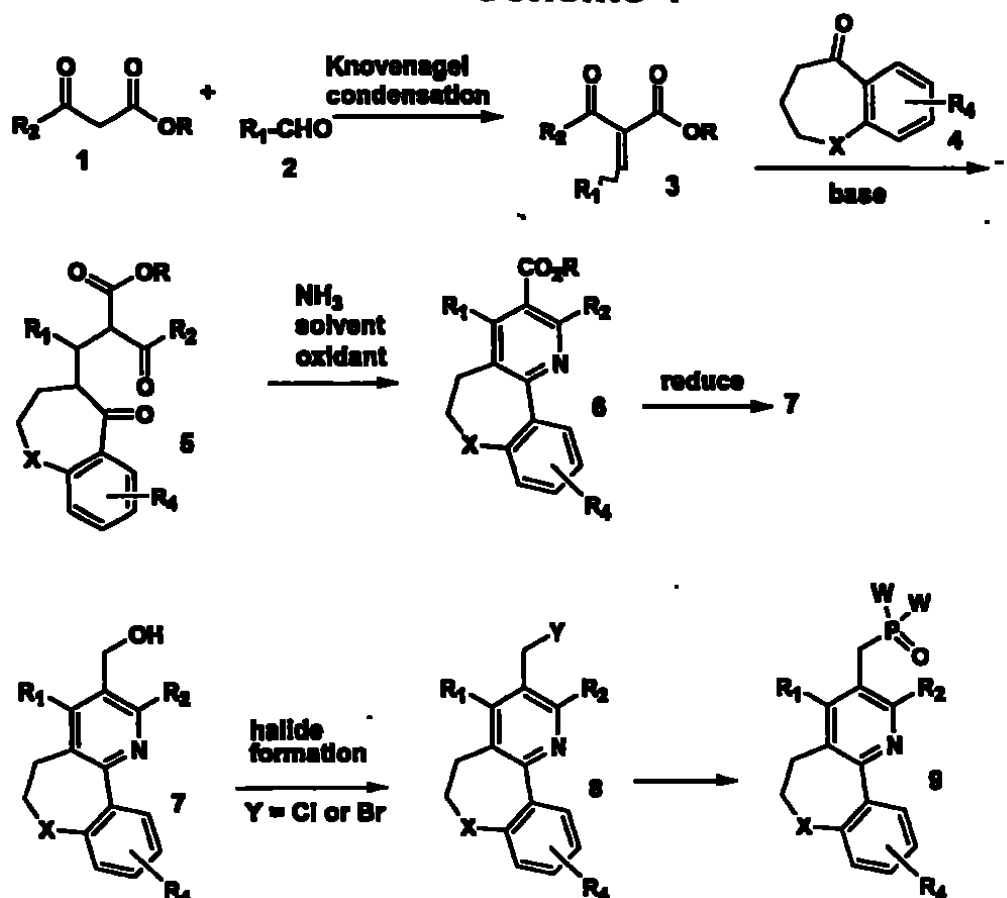
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- where W is OR (R is lower alkyl) may be effected by the reaction of 8 with HOP(OR)₂/base/THF or by Arbuzov reaction with P(OR)₃. Witting reaction between 9 and aldehyde 10 (aldehyde 10 has been previously described in US patent 5,686,433) may be effected under standard conditions with base (n-BuLi, LiN(TMS)₂, LDA) in an appropriate solvent (THF, Et₂O, toluene, DMPU) to afford the adduct 11. Treatment of 11 under acidic conditions (e.g. TFA, HCl) effects the conversion of 11 to lactone Ia. Saponification of Ia to Ib (where R₁ is alkali metal, or alkaline earth metal) can be effected by treatment of Ia with aqueous base or subsequently acidified to give Ib where R₁ is H. Additionally, Ia can be treated with an alcohol of the type R₂OH under basic conditions to form the corresponding esters of Ib.

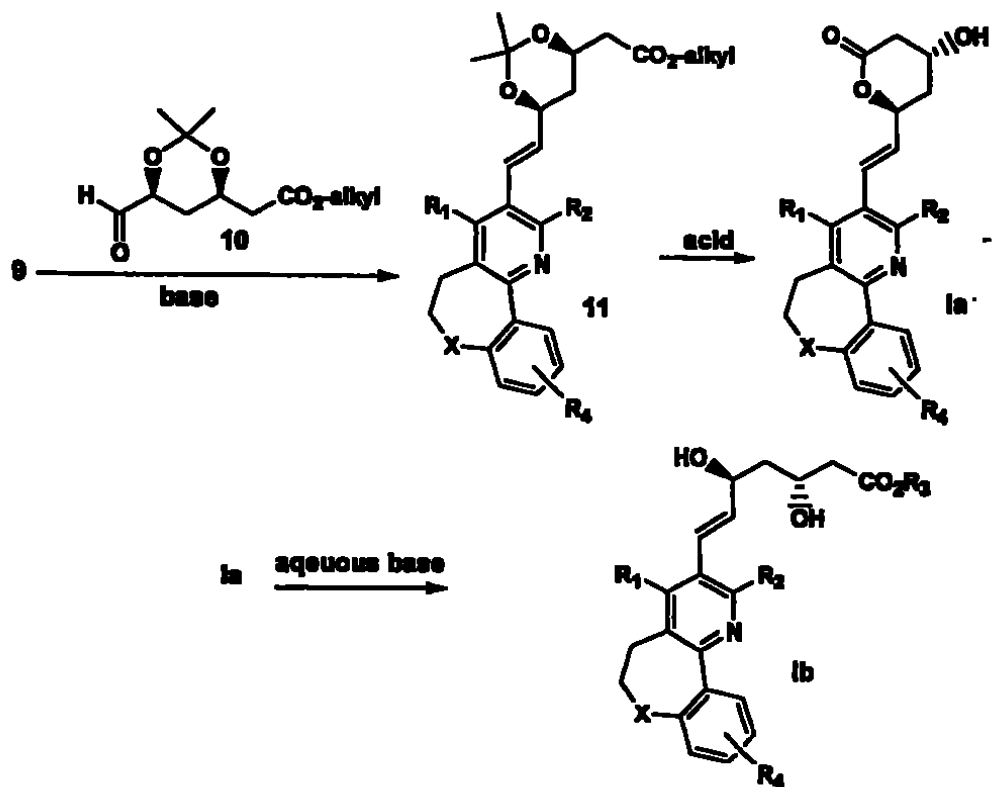
- As seen in Reaction Scheme 2, the saturated derivatives of compound I (where ~~is~~ is CH₂-CH₂) are obtained by catalytic (Pd/C, Pt/C, Pd(OH)₂) hydrogenation of 11, Ia, or Ib to afford 12, Ic, or Id, respectively. Compound 12 may be converted to Ic and Id following the earlier described methods for the conversion of compound 11 to Ia and Ib.

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Scheme 1



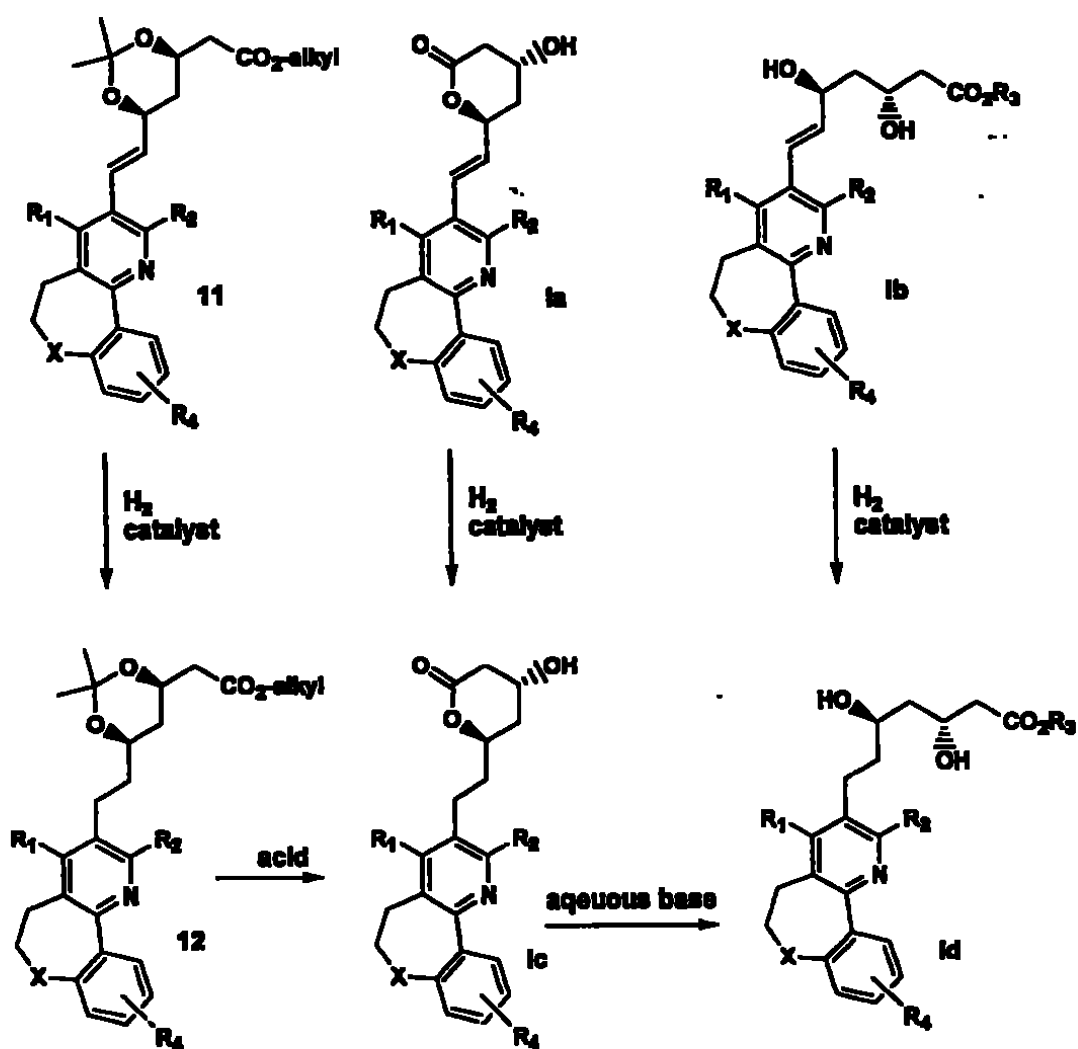
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Scheme 2

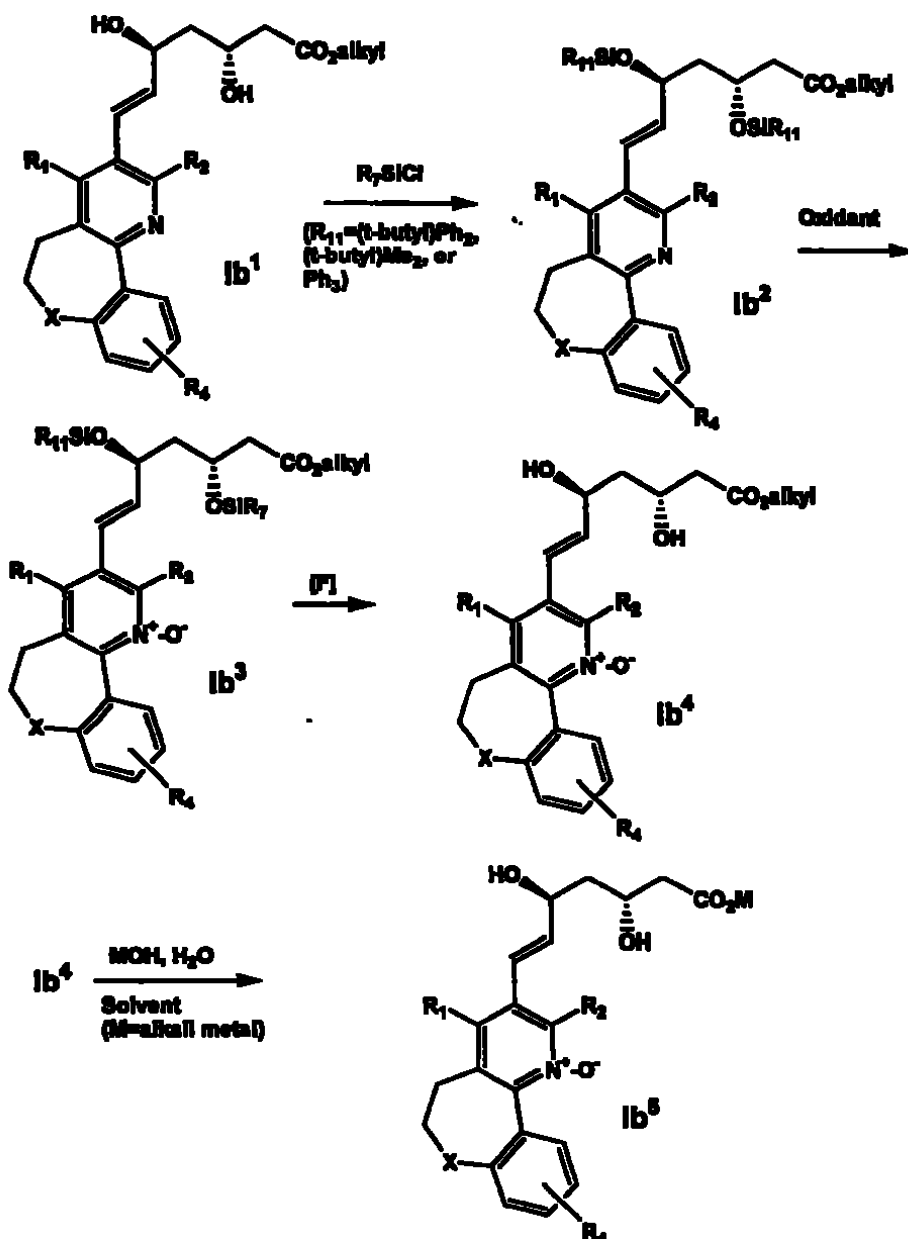


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- The synthesis of compounds I wherein ~~2-2~~ is CH=CH and n is 1, is described in Scheme 3. Bis-silylation of compound Ib¹ with a bulky silylchloride (e.g., ClSi(t-butyl)Ph₂, ClSi(t-butyl)Me₂, ClSiPh₃) in the presence of a
- 5 suitable base (e.g., TEA, imidazole, pyridine) and solvent (e.g., CH₂Cl₂, THF) provides compound Ib². Treatment of Ib² with oxidants such as m-CPBA or CF₃CO₂H in an appropriate solvent such as CH₂Cl₂ or HOAc affords N-oxide Ib³. Desilylation of Ib³ (TBAF/HOAc/THF or
- 10 HF/CH₃CN) gives Ib⁴ which may be saponified to Ib⁵ using aqueous solutions of a metal hydroxide in an appropriate solvent (e.g., MeOH, dioxane).

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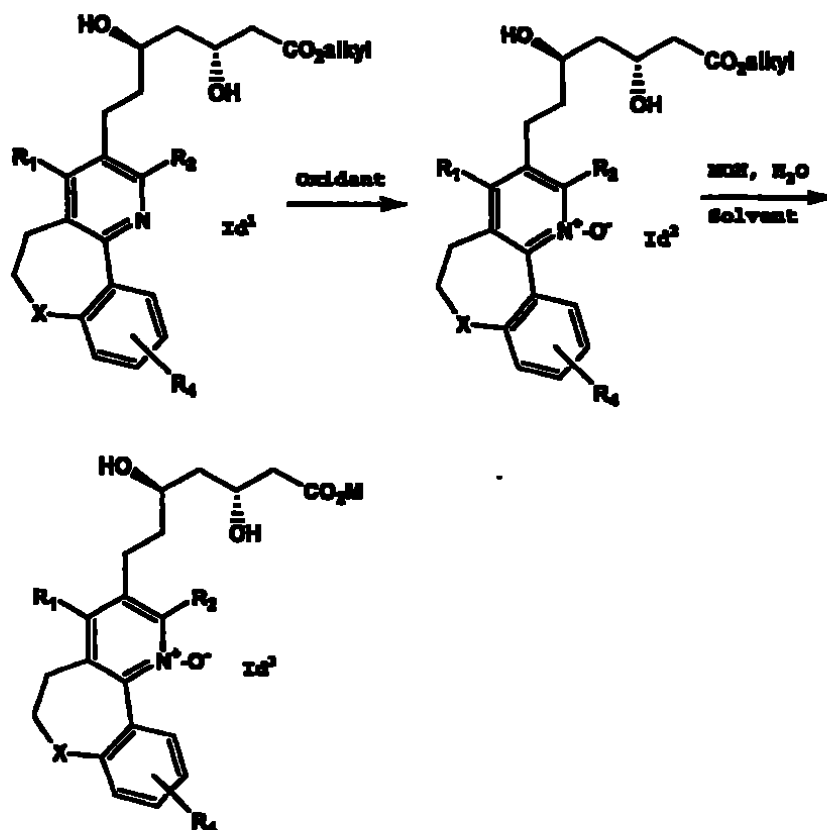
SCHEME 3



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Additionally, compound Id¹ may be oxidized and saponified, as described above, to provide compounds I wherein --- is CH₂CH₂ and n is 1 (e.g., compounds Id² and Id³) as shown in Scheme 4.

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SCHEME 4

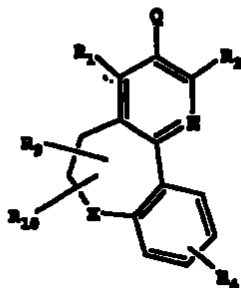
- 10 It will be appreciated that in Schemes 1 to 4, with respect to compounds 4, 5, 6, 7, 8, 9, 11, Ia, Ib, 12, Ic, Id, Ib¹, Ib², Ib³, Ib⁴, Ib⁵, Id¹, Id² and Id³, although substituents R₉ and R₁₀ as defined hereinbefore are not included in these compounds, Schemes 1 to 4 may be
- 15 carried out where such compounds include R₉ and R₁₀ substituents.

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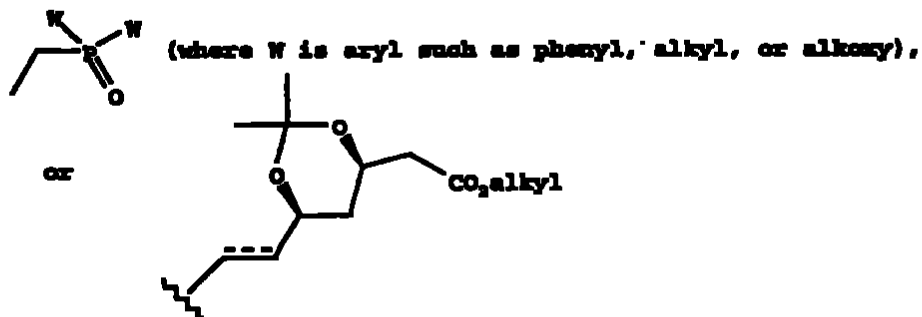
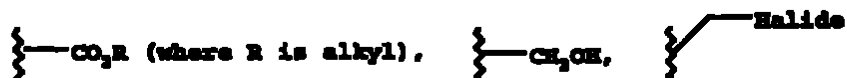
In addition, in accordance with the present invention, intermediates 6, 7, 8, 9, 11 and 12 are novel compounds and form part of the present invention. These compounds have the general structure

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II



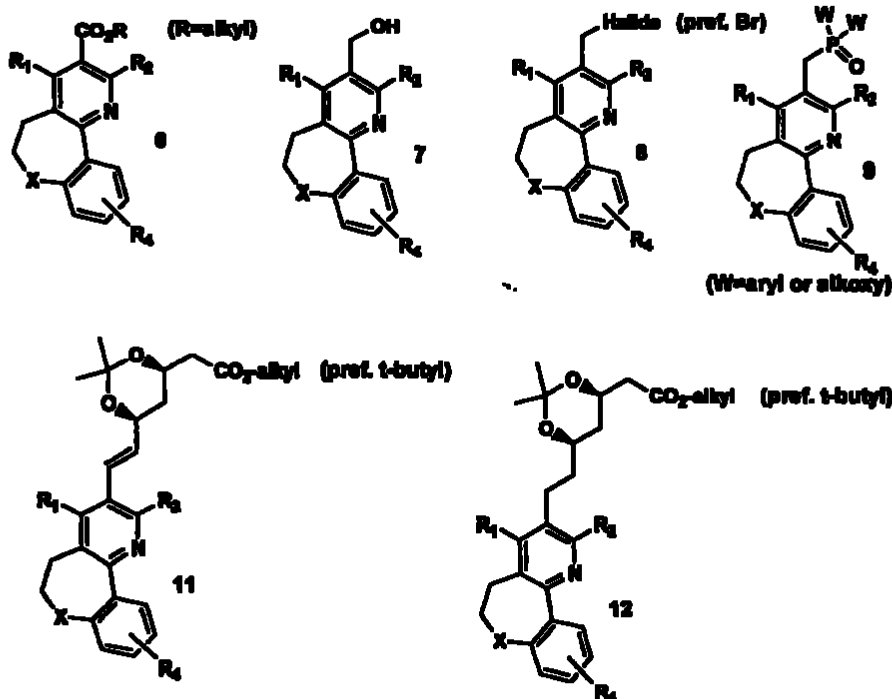
wherein X is O, S or NR₇, R₁, R₂, R₄, R₇, R₉ and R₁₀ as are as defined above, Q is



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Thus, the intermediates of the invention can have the following structures:

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Compounds 6, 7, 8, 9, 11 and/or 12 may include R_9 and R_{10} substituents.

5 Compounds containing dihydroxy acid HMG-CoA binding domain side chains may be prepared in homochiral form, which is preferred, or may be prepared as racemic mixtures (3S*, 5R*) and may later be resolved to obtain the 3S, 5R isomer.

10 The compounds of the invention are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and thus are useful in inhibiting cholesterol biosynthesis and/or in lowering triglycerides, in a manner similar to atorvastatin, pravastatin, simvastatin, 15 lovastatin, cerivastatin, visastatin (Astra Zeneca ZD4522), fluvastatin, itavastatin and the like.

A further aspect of the present invention is a pharmaceutical composition containing at least one of the compounds of formula I of the present invention in 20 association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles of

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diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations. Such dosage forms contain from 0.1 to 1500 mg of active compound per dosage, for use in the treatment. The dose to be administered depends on the unitary dose, the symptoms, and the age and the body weight of the patient.

The compounds of the present invention can be administered in a similar manner as known compounds suggested for use in inhibiting cholesterol biosynthesis, such as pravastatin, lovastatin, simvastatin, visastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, and the like, in mammalian species such as humans, dogs, cats and the like. Thus, the compounds of the invention may be administered in an amount from about 0.1 to 500 mg in a single dose or in the form of individual doses from 1 to 4 times per day, preferably 0.2 to 100 mg daily or in sustained release form.

Where desired, the compounds of structure I may be used in combination with one or more hypolipidemic agents or lipid-lowering agents and/or one or more other types of therapeutic agents including antidiabetic agents, anti-obesity agents, antihypertensive agents, platelet aggregation inhibitors, and/or anti-osteoporosis agents, which may be administered orally in the same dosage form, in a separate oral dosage form or by injection.

The hypolipidemic agent or lipid-lowering agent which may be optionally employed in combination with the compounds of formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxxygenase inhibitors, cholesterol absorption inhibitors, ileal Na⁺/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, bile

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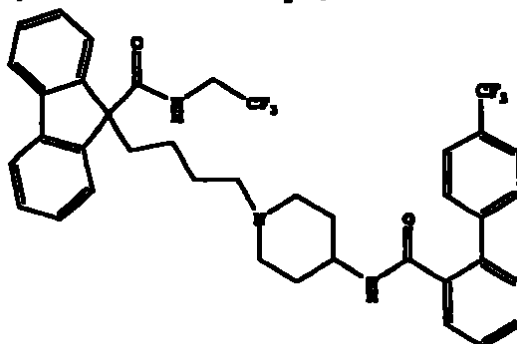
acid sequestrants, and/or nicotinic acid and derivatives thereof.

MTP inhibitors employed herein include MTP inhibitors disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Application Serial No. 09/175,180 filed October 20, 1998, now U.S. Patent No. 5,962,440. Preferred are each of the preferred MTP inhibitors disclosed in each of the above patents and applications.

All of the above U.S. Patents and applications are incorporated herein by reference.

Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Patent Nos. 5,739,135 and 5,712,279, and U.S. Patent No. 5,760,246.

The most preferred MTP inhibitor is 9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



The hypolipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and

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- 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, itavastatin (Nissan/Sankyo's nisvastatin (NK-104)) disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca visastatin (2D-4522) disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No. 0,142,146 A2, and quinoline and pyridine derivatives disclosed in U.S. Patent No. 5,506,219 and 5,691,322.

In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

- The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α -phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31,

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No. 10, pp 1869-1871, including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Pompipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary.

Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®) and cholestagel (Sankyo/Geltex), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid (niacin), acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in

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U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

- 5 The other hypolipidemic agent may be an ACAT inhibitor such as disclosed in, Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, 10 Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, 15 Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, 20 Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Manfred A., Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, 25 Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. 30 Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho Pharmaceutical Co. Ltd).
- 35 The hypolipidemic agent may be an upregulator of LD2 receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

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The hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's SCH48461 as well as those disclosed in Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

5 The hypolipidemic agent may be an ileal Na⁺/bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425-430 (1999).

10 Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, itavastatin and visastatin.

The above-mentioned U.S. patents are incorporated herein by reference. The amounts and dosages employed will be as indicated in the Physician's Desk Reference and/or in the patents set out above.

15 The compounds of formula I of the invention will be employed in a weight ratio to the hypolipidemic agent (were present), within the range from about 500:1 to about 1:500, preferably from about 100:1 to about 1:100.

20 The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

25 The dosages and formulations for the hypolipidemic agent will be as disclosed in the various patents and applications discussed above.

The dosages and formulations for the other hypolipidemic agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

30 For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg to about 500 mg and preferably from about 0.1 mg to about 100 mg, one to four times daily.

35 A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to

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about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

For oral administration, a satisfactory result may be obtained employing an HMG CoA reductase inhibitor, for example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin in dosages employed as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 0.5 to about 80 mg, and more preferably from about 1 to about 40 mg.

A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The other hypolipidemic agent may also be a lipoxxygenase inhibitor including a 15-lipoxxygenase (15-LO) inhibitor such as benzimidazole derivatives as disclosed in WO 97/12615, 15-LO inhibitors as disclosed in WO 97/12613, isothiazolones as disclosed in WO 96/38144, and 15-LO inhibitors as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxxygenase inhibitor lacking significant antioxidant properties, Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11-20.

The compounds of formula I and the hypolipidemic agent may be employed together in the same oral dosage

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form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

The preferred hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin as well as niacin and/or cholestagel.

The antidiabetic agent which may be optionally employed in combination with the HMG-CoA reductase inhibitor of formula I may be 1,2,3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, which may include biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR γ agonists, such as thiazolidinediones, α 2 inhibitors, PPAR α/γ dual agonists, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1).

The antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

Where the antidiabetic agent is a biguanide, the compounds of structure I will be employed in a weight ratio to biguanide within the range from about 0.001:1 to about 10:1, preferably from about 0.01:1 to about 5:1.

The antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the β -cells, with glyburide and glipizide being preferred,

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which may be administered in the same or in separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.02:1 to about 5:1.

The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the same or in a separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05:1 to about 10:1.

The compounds of structure I may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin[®], disclosed in U.S. Patent No. 4,572,912), rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Welcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

The compounds of structure I will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to about 10:1.

The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds of structure I.

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Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998), and in U.S. provisional application No. 60/155,400, filed September 22, 1999, (attorney file LA29) the disclosure of which is incorporated herein by reference, employing dosages as set out therein, which compounds designated as preferred are preferred for use herein.

10 The antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. provisional application No. 60/158,773, filed October 12, 1999 (attorney file LA49), employing dosages as set out therein. Preferred are the compounds designated as preferred in the above application.

15 The antidiabetic agent may be an aP2 inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. provisional application No. 60/127,745, filed April 5, 20 1999 (attorney file LA27*), employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The antidiabetic agent may be a DP4 inhibitor such as disclosed in Provisional Application 60/188,555 filed 25 March 10, 2000 (attorney file LA50), WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(8)-pyrrolidine) (Novartis) (preferred) as 30 disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999, TSL-225 (tryptophyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by 35 Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) employing dosages as set out in the above references.

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The meglitinide which may optionally be employed in combination with the compound of formula I of the invention may be repaglinide, nateglinide (Novartis) or KAD1229 (PF/Kissei), with repaglinide being preferred.

- 5 The HMG CoA reductase inhibitor of formula I will be employed in a weight ratio to the meglitinide, PPAR γ agonist, PPAR α/γ dual agonist, $\alpha P2$ inhibitor, DP4 inhibitor or SGLT2 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to
- 10 about 10:1.

- The other type of therapeutic agent which may be optionally employed with the HMG CoA reductase inhibitor of formula I may be 1, 2, 3 or more of an anti-obesity agent including a beta 3 adrenergic agonist, a lipase
- 15 inhibitor, a serotonin (and dopamine) reuptake inhibitor, an $\alpha P2$ inhibitor, a thyroid receptor beta drug and/or an anorectic agent.

- The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of
- 20 formula I may be AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, with AJ9677, L750,355 and CP331648 being preferred.

- 25 The lipase inhibitor which may be optionally employed in combination with a compound of formula I may be orlistat or ATL-962 (Alizyme), with orlistat being preferred.

- The serotonin (and dopamine) reuptake inhibitor
- 30 which may be optionally employed in combination with a compound of formula I may be sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), with sibutramine and topiramate being preferred.

- The thyroid receptor beta compound which may be
- 35 optionally employed in combination with a compound of formula I may be a thyroid receptor ligand as disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio),

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GB98/284425 (KaroBio), and U.S. Provisional Application 60/183,223 filed February 17, 2000, with compounds of the KaroBio applications and the above U.S. provisional application being preferred.

5 The anorectic agent which may be optionally employed in combination with a compound of formula I may be dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

10 The various anti-obesity agents described above may be employed in the same dosage form with the compound of formula I or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

15 The antihypertensive agents which may be employed in combination with the HMG CoA reductase inhibitors of the invention include ACE inhibitors, angiotensin II receptor antagonists, NEP/ACE inhibitors, as well as calcium channel blockers, β -adrenergic blockers and other types of antihypertensive agents.

20 The angiotensin converting enzyme inhibitor which may be employed herein includes those containing a mercapto (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in U.S. Pat. No. 4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, being preferred, and
25 mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U.S. Pat. No. 4,316,906 with zofenopril being preferred.

30 Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril and YS980.

35 Other examples of angiotensin converting enzyme inhibitors which may be employed herein include any of those disclosed in U.S. Pat. No. 4,374,829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred, any of

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the phosphonate substituted amino or imino acids or salts disclosed in U.S. Pat. No. 4,452,790 with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline or (ceronapril) being preferred,

- 5 phosphinylalkanoyl prolines disclosed in U.S. Pat. No. 4,168,267 mentioned above with fosinopril being preferred, any of the phosphinylalkanoyl substituted prolines disclosed in U.S. Pat. No. 4,337,201, and the phosphonamides disclosed in U.S. Pat. No. 4,432,971
10 discussed above.

- Other examples of ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as disclosed in European Patent Application Nos. 80822 and 60668; Chugai's MC-838 disclosed in C.A. 102:72588v and Jap. J. Pharmacol. 40:373 (1986); Ciba-Geigy's CGS 14824 (3-[[1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in U.S. Pat. No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in Euro. Patent No. 79-022 and Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) disclosed in Arzneimittelforschung 34:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987); R 31-2201 (Hoffman-LaRoche) disclosed in FEBS Lett. 165:201 (1984); lisinopril (Merck), indalaprill (delapril) disclosed in U.S. Pat. No. 4,385,051; indolaprill (Schering) disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983), spirapril (Schering) disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5):173 (1986); perindopril (Servier) disclosed in Eur. J. clin. Pharmacol. 31:519 (1987); quinapril (Warner-Lambert) disclosed in U.S. Pat. No. 4,344,949 and CI925 (Warner-Lambert) ([3S-[2[R(+)]R(+)]3R(+)]-2-[2-[1-(ethoxy-
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carbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid HCl) disclosed in Pharmacologist 26:243, 266 (1984), WY-44221 (Wyeth) disclosed in J. Med. Chem. 26:394 (1983).

5 Preferred ACE inhibitors are captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril and moexipril.

NEP/ACE inhibitors may also be employed herein in that they possess neutral endopeptidase (NEP) inhibitory activity and angiotensin converting enzyme (ACE) inhibitory activity. Examples of NEP/ACE inhibitors suitable for use herein include those disclosed in U.S. Pat. No.s. 5,362,727, 5,366,973, 5,225,401, 4,722,810, 5,223,516, 4,749,688, U.S. Patent. No. 5,552,397, U.S. Pat. No. 5,504,080, U.S. Patent No. 5,612,359, U.S. Pat. No. 5,525,723, European Patent Application 0599,444, 0481,522, 0599,444, 0595,610, European Patent Application 0534363A2, 534,396 and 534,492, and European Patent Application 0629627A2.

20 Preferred are those NEP/ACE inhibitors and dosages thereof which are designated as preferred in the above patents/applications which U.S. patents are incorporated herein by reference; most preferred are omapatrilat, BMS 189,921 ([S-(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid) and CGS 30440.

The angiotensin II receptor antagonist (also referred to herein as angiotensin II antagonist or AII antagonist) suitable for use herein includes, but is not limited to, irbesartan, losartan, valsartan, candesartan, tasosartan or eprosartan, with irbesartan, losartan or valsartan being preferred.

A preferred oral dosage form, such as tablets or capsules, will contain the ACE inhibitor or AII antagonist in an amount within the range from about 0.1 to about 500 mg, preferably from about 5 to about 200 mg and more preferably from about 10 to about 150 mg.

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For parenteral administration, the ACE inhibitor, angiotensin II antagonist or NEP/ACE inhibitor will be employed in an amount within the range from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.01 mg/kg to about 1 mg/kg.

Where a drug is to be administered intravenously, it will be formulated in conventional vehicles, such as distilled water, saline, Ringer's solution or other conventional carriers.

It will be appreciated that preferred dosages of ACE inhibitor and AII antagonist will be as set out in the latest edition of the Physician's Desk Reference (PDR).

Other examples of preferred antihypertensive agents suitable for use herein include omapatrilat (Vanlev®), amlodipine besylate (Norvasc®), prazosin HCl (Minipress®), verapamil, nifedipine, nadolol, propranolol, and clonidine HCl (Catapres®).

Antiplatelet agents which may be employed in combination with HMG CoA reductase inhibitors of the invention include aspirin, clopidogrel, ticlopidine, dipyridamole and ifetroban, with clopidogrel and aspirin being preferred.

The antiplatelet drugs may be employed in amounts as indicated in the PDR. Ifetroban may be employed in amounts as set out in U.S. Patent No. 5,100,889.

Antiosteoporosis agents suitable for use herein in combination with the HMG CoA reductase inhibitors of the invention include parathyroid hormone or bisphosphonates, such as MK-217 (alendronate) (Fosamax®). Dosages employed will be as set out in the PDR.

In carrying out the method of the invention for treating hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, atherosclerosis, and related diseases, a pharmaceutical composition will be employed containing the compounds of structure I, with or without other cholesterol lowering

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agents, osteoporosis agents, antidiabetic agent(s) and/or antihyperlipidemic agent(s) and/or other type therapeutic agents in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be

5 formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration, such as pharmaceutically acceptable carriers, excipients, binders and the like. The compounds can be administered

10 to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, beads, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations, or they can be administered

15 intranasally or in transdermal patches. Typical solid formulations will contain from about 0.1 to about 500 mg of a compound of formula I. The dose for adults is preferably between 0.5 and 1,000 mg per day, which can be administered in a single dose or in the form of

20 individual doses from 1-4 times per day.

A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of

25 physiological saline, to produce an injectable preparation.

The following abbreviations are employed in the Examples and elsewhere herein:

- 30 Ph = phenyl
 Bn = benzyl
 i-Bu = iso-butyl
 Me = methyl
 Et ethyl
- 35 TMS = trimethylsilyl
 FMOC = fluorenylmethoxycarbonyl
 Boc = tert-butoxycarbonyl

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Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl

HOAc or AcOH = acetic acid

TFA = trifluoroacetic acid

Et₂NH = diethylamine

5 DI = deionized

Bp = boiling point

NMM = N-methyl morpholine

n-BuLi = n-butyllithium

Pd/C = palladium on carbon

10 PtO₂ = platinum oxide

TEA = triethylamine

EDAC = 3-ethyl-3'-(dimethylamino)propyl-carbodiimide

hydrochloride (or 1-[(3-(dimethyl)amino)propyl]-3-ethylcarbodiimide hydrochloride)

15 HOBT or HOBT.H₂O = 1-hydroxybenzotriazole hydrate

HOAT = 1-hydroxy-7-azabenzotriazole

PyBOP reagent = benzotriazol-1-yloxy-tripyrrolidino phosphonium hexafluorophosphate

LiN(TMS)₂ = Libis(trimethylsilyl)amide

20 DIBAL = diisobutylaluminum hydride

LDA = lithium diisopropylamide

DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

AcCN = acetonitrile

min = minute(s)

25 h or hr = hour(s)

L = liter

mL = milliliter

μL = microliter

g = gram(s)

30 mg = milligram(s)

mol = moles

mmol = millimole(s)

meq = milliequivalent

RT, rt = room temperature

35 sat or sat'd = saturated

aq. = aqueous

TLC = thin layer chromatography

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HPLC = high performance liquid chromatography
 LC/MS = high performance liquid chromatography/mass spectrometry

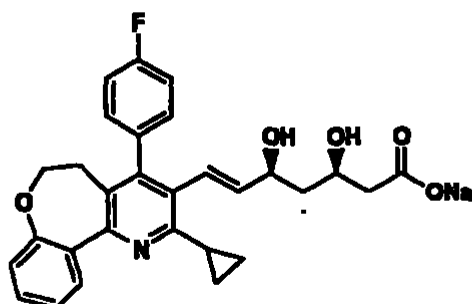
MS or Mass Spec = mass spectrometry

5 NMR = nuclear magnetic resonance

mp = melting point

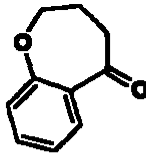
The following Examples represent preferred
 embodiments of the invention. Unless otherwise
 10 indicated, all temperatures are in degrees Centigrade.

Example 1



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A.

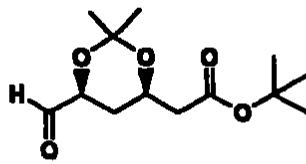


A mixture of polyphosphoric acid (82.9 g) and dry
 o-xylene (30 ml) was heated to 105-110°C in an oil bath,
 treated with a solution of 4-phenoxybutyric acid (25 g,
 20 0.137 mole) in dry o-xylene (110 ml) and stirred at 105-
 110°C for 2 hours. The reaction mixture was cooled to
 room temperature over a 2-hour period, poured into ice-
 water (180 ml), then extracted with ether (3 x 150 ml).
 The combined organic extracts (rust-colored) were washed
 25 with water (2 x 80 ml) and brine (80 ml), dried
 (anhydrous Na₂SO₄), filtered, evaporated to dryness and
 evaporated once from hexanes (500 ml). The residue was
 dried in vacuo for 48 hours to give a reddish-brown syrup

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(27.19 g) which was divided into two portions, chromatographing each portion on a silica gel column, (EM, 2-1/4" x 10") to give a light amber syrup (10.792 g). Trituration of an impure fraction with ether (3 x 25 mL) gave an additional 1.98 g of product. Yield : 12.77 g, amber syrup; 58 %. Rf 0.38 (Silica gel; EtOAc:Hexane-1:4; UV).

A(1).



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An oven-dried 3-neck 1-L flask equipped with temperature sensor probe, 125-mL constant pressure addition funnel and septum was charged with dry CH_2Cl_2 (300 mL) and dry DMSO (20.9 mL, 0.2944 mol, 2.5 equiv) under argon atmosphere; cooled to -75°C . Oxalyl chloride (13.6 mL, 0.156 mol, 1.32 equiv) was added neat via syringe dropwise over 15 min (temperature rose to -66°C), and then let stir additional 15 min. A solution of the alcohol 2-[(4R,6S)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetic acid t-butyl ester (30.66 g, 0.1178 mol, 1 equiv) in dry CH_2Cl_2 (80 mL) was added dropwise from the addition funnel over 30 min (temperature rose to -68°C). The resulting white mixture was stirred for 70 min at -76°C , then triethylamine (82 mL, 0.5889 mol, 5 equiv) was added dropwise from addition funnel over 35 min (temperature rose to -65°C), then the light yellow mixture was stirred vigorously at -76°C . TLC (SiO_2 , 20% EtOAc/ CH_2Cl_2 , Rf=0.52). After 30 min, the cooling bath was removed and the reaction was quenched by slowly adding cold 20% aq KH_2PO_4 (35 mL), followed by cold H_2O (300 mL); and then let stir 15 min (temperature rose to -7°C). The reaction was poured into a 2-L separatory funnel and extracted with hexanes (500 mL). The organic extract was washed with cold 10% aq KH_2PO_4 (3x300 mL) and saturated aqueous NaCl (300 mL). The organic was dried

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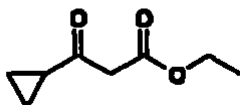
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over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give yellow oil. Purification by SiO_2 flash chromatography (10cm x 20 cm column) with 35:65 EtOAc/Hexanes afforded the title compound as a white solid (22.2 g, 0.0859 mol, 73%):

^1H NMR (CDCl_3) δ 1.267-1.465 (m, 16H), 1.802 (dd, $J=12.7$ Hz, 2.2 Hz, 1H), 2.290-2.464 (m, 2H), 4.314 (d, $J=18.4$ Hz, 2H), 9.555 (d, $J=1.3$ Hz, 1H).

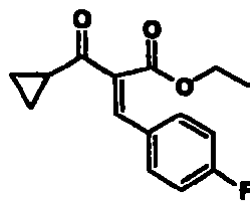
10 A(2).



To a slurry of NaH (19.20 g, 480 mmol) and diethyl carbonate (80 mL) in a 3-neck 1L round bottom flask at room temperature was added a solution of cyclopropyl methylketone (23.5 mL, 238 mmol) in Et_2O (30 mL). Approximately 10% of the solution was added, and then 0.25 mL of EtOH was added to the reaction slurry. Addition of the remaining ketone solution continued with light gas evolution. After addition of all of the ketone solution, the reaction became quite exothermic with vigorous H_2 evolution. The reaction mixture was cooled periodically with an ice-bath to keep the temperature around 35°C to 50°C. After one hour, gas evolution had ceased and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was cooled in an ice-bath, diluted with Et_2O (200 mL), and treated with 1 N HCl with some ice to adjust to around pH 3. The reaction mixture was extracted with Et_2O (3 x 150 mL). The Et_2O extracts were combined, washed with saturated aqueous NaHCO_3 (200 mL), H_2O (200 mL) and brine (200 mL), and dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow oil. The oil was distilled under vacuum to give the title compound as a colorless oil, 28.5 g, 77%. B.p. = 94-96°C/8 mmHg.

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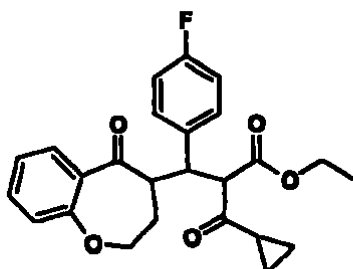
A(3).



To a stirred solution of part A(2) compound (28.24 g, 181 mmol) in benzene (128 mL) was added 4-fluoro-
 5 benzaldehyde (19.4 mL, 181 mmol), HOAc (0.31 mL, 5.4 mmol) and piperidine (1.8 mL, 18.2 mL). The reaction mixture was heated at reflux and azeotrope was collected with a Dean-Stark trap. After 16 h, the reaction was cooled to room temperature, diluted with Et₂O (250 mL),
 10 washed with aqueous 0.5 N HCl, saturated aqueous NaHCO₃, H₂O and brine, and then dried (Na₂SO₄), filtered and concentrated under reduced pressure. Purification by flash chromatography (1:10 EtOAc/hexane) gave the title compound as a light yellow oil, 29 g, 61% yield.

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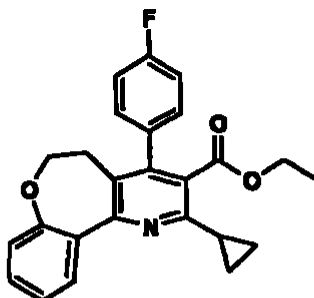
B:



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slowly into an ammonium chloride solution (25%, 140 ml). The bright yellow solution was extracted with ether (2 x 100 ml) and the combined organic extracts were washed with water (2 x 25 ml) and brine (25 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried in vacuo to give the crude product mixture as a yellow oil (17.16 g).

C.



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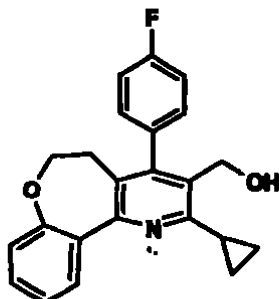
A mixture of crude Part B compound (17.0 g, 27.3 mmol), ammonium acetate (9.34 g, 120 mmol) and copper acetate monohydrate (20.54 g, 101 mmol) in glacial acetic acid (100 ml) was refluxed under argon for 19 hours. The mixture was poured into an ice-cold solution of concentrated ammonium hydroxide (85 ml) in water (170 ml) and the bright blue solution was extracted with ether (3 x 200 ml). The combined organic extracts were washed with water (2 x 80 ml) and brine (80 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness, and dried in vacuo. The crude product (14 g, brown syrup) was chromatographed in two batches, each on a silica gel column (EM, 2-1/4" x 10") to give the desired product as an off-white solid (4.161 g). An additional 931 mg of product was obtained from chromatography of mixed fractions. Yield: 5.092 g, 46 % from compound A). R_f 0.53 (Silica gel; EtOAc:Hexane-1:4; UV)

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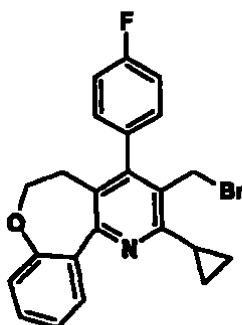
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D.



- A solution of Part C compound (2.515 g, 6.23 mmol) in dry THF (30 ml) was cooled to 0°C (ice-water bath),
5 treated dropwise with lithium aluminum hydride (1.0 M in THF; 12.5 ml, 12.5 mmol), stirred at 0°C for 30 minutes then at room temperature for 3 hours. The reaction mixture was cooled to 0°C, treated successively with water (0.5 ml), 15% NaOH (0.5 ml) and water (1.5 ml),
10 stirred at room temperature for 5 minutes then diluted with ethyl acetate (50 ml). The slurry was filtered through a Celite® pad, washing the pad well with ethyl acetate (3 x 25 ml). The clear filtrate was evaporated to dryness and dried in vacuo to give the title product.
15 Yield: 2.386 g, white foam (100 %). Rf 0.15 (Silica gel; EtOAc:Hexane-1:4; UV).

E.

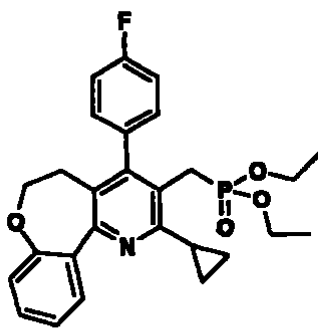


- 20 A solution of Part D compound (2.27 g, 6.23 mmol) in dry dichloromethane (45 ml) was cooled to 0°C (ice-water bath) and treated dropwise with phosphorus tribromide (1.0 M in dichloromethane; 12.5 ml, 12.5 mmol). The ice bath was removed and the reaction mixture

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was stirred at room temperature for 30 minutes after which it was re-cooled to 0°C and treated dropwise with saturated sodium bicarbonate (70 ml). The mixture was then warmed to room temperature and extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were washed with water (2 x 50 ml) and brine (50 ml), re-extracting each aqueous wash with dichloromethane (100 ml). The organic extracts were dried (anhydrous sodium sulfate), filtered, evaporated to dryness and dried in vacuo to give the title product as a white solid. Yield: 2.503 g, (94 %). m.p. = 169-171°C. Rf 0.58 (Silica gel; EtOAc:Hexane- 1:4; UV).

F.



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A solution of diethyl phosphite (0.88 ml, 6.83 mmoles) in dry THF (10 ml) was cooled to -10°C (acetonitrile-dry ice bath), treated with sodium (bistrimethylsilyl)amide (1.0 M in THF; 6.7 ml, 6.7 mmol) and stirred at -10°C for 30 minutes. The cooled solution was treated with a solution of Part E compound (2.41 g, 5.68 mmol) in dry THF (20 ml), stirred at -10°C for 1.0 hour then quenched at -10°C with water (14 ml). The solution was extracted with ethyl acetate (2 x 75 ml) and the combined organic extracts washed with 1.0 M hydrochloric acid (8.0 ml) and brine (10 ml), dried (anhydrous sodium sulfate), filtered, evaporated to dryness and dried in vacuo. The crude product (3.12 g, syrup) was chromatographed on a silica gel column (EM, 5.5 cm x 12.5 cm) to give the title compound as a syrup.

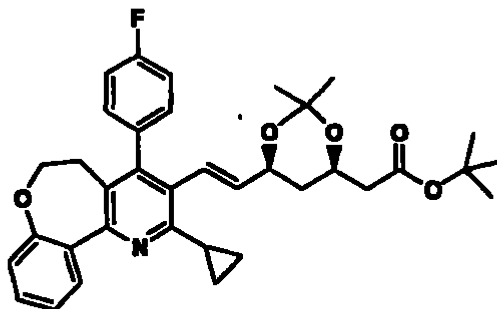
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Yield: 2.34 g (85.5%). Rf 0.33 (Silica gel; EtOAc-Hexane-1:1; UV).

G.

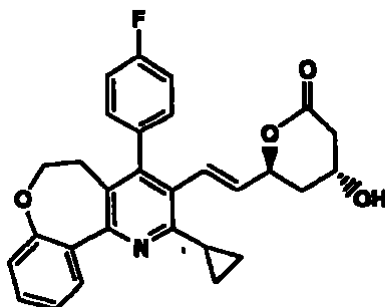


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A solution of Part F compound (2.29 g, 4.756 mmol) in dry THF (20 ml) was cooled to -78°C , treated with 2.37 M n-butyllithium (2.41 ml, 5.71 mmol) and stirred at -78°C for 40 minutes. The solution was treated dropwise via cannula with a -78°C solution of Part A(1) compound (2.36 g, 9.15 mmol) in dry THF (10 ml), keeping both solutions at -78°C at all times. The reaction mixture was stirred at -78°C for 1.0 hr, -10°C for 1.0 hr and at room temperature for 5 hr, quenched with 25% ammonium chloride solution (12 ml) then extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were washed with 25% ammonium chloride solution (12 ml) and brine (12 ml), dried (anhydrous sodium sulfate), filtered, evaporated to dryness and dried in vacuo. The crude product yellow syrup was chromatographed on a silica gel column (EM, 2-1/4" x 10") to afford the title compound as a syrup. Yield: 878 mg (32 %). Rf 0.37 (Silica gel; EtOAc:Hexane-1:4; UV).

421

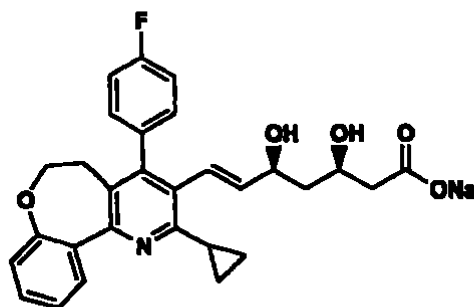
H.



5 A solution of Part G compound (850 mg, 1.45 mmol) in dry dichloromethane (20 ml) was cooled to 0°C, treated with trifluoroacetic acid (1.85 ml, 24 mmol), stirred at 0°C for 5 minutes, then at room temperature for 4.5 hours. The reaction mixture was poured slowly into a 1 L flask containing ethyl acetate (300 ml) and saturated sodium bicarbonate (40 ml), rinsing the flask with ethyl acetate (50 ml). The mixture was stirred well and the phases separated, washing the organic phase with saturated sodium bicarbonate (25 ml) and brine (25 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, evaporated to dryness and dried in 15 vacuo. The crude product mixture was chromatographed on a silica gel column (EM, 1.5" x 12") to give the desired compound as a syrup. Yield: 570 mg (83 %). Rf 0.23 (Silica gel; EtOAc:Hexane-1:1; UV)

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I.



A solution of Part H compound (550 mg, 1.17 mmol) in dry THF (10 ml) was treated with 1.0 N NaOH (1.46 ml; 1.46 mmol) and stirred at room temperature for 10

X 422

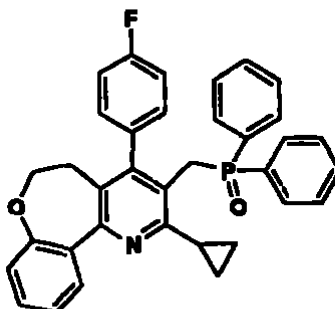
minutes. The reaction mixture was evaporated to dryness and the residual solid was dissolved in a mixture of water (8.7 ml) and 1.0 N sodium hydroxide (70 ul). The solution was eluted on an SP207 column (Na⁺ form; 1.5" x 4"), eluting the column with water (200 ml), 10% CH₃CN/H₂O (200 ml), 20% CH₃CN/H₂O (100 ml) and 50% CH₃CN/H₂O (200 ml). The desired fractions were combined and evaporated to dryness. The semi-solid obtained was dissolved in water (300 ml) and lyophilized to give the title compounds as a white solid. Yield: 583 mg (95%) R_f 0.48 (Silica gel, CH₂Cl₂:MeOH:HOAc-18:1:1; UV).

Analysis for C₂₃H₂₆FNO₄Na • 0.8 H₂O (MW = 525.94):

Calc'd: C, 66.23; H, 5.29; N, 2.66; F, 3.61
Found: C, 66.37; H, 5.30; N, 2.62; F, 3.91

Alternate Procedure for Example 1 Part G Compound

G(1).



The Example 1 Part E bromide (13.03 g, 0.027 mol, 1 equiv) and Ph₂POEt (6.5 mL, 0.0297 mol, 1.1 equiv) were heated at reflux in anhydrous toluene (200 mL) under an argon atmosphere. The reaction became a thick yet stirrable white mixture after about 10 min. The reaction was complete after 1 hr by tlc (SiO₂, 30% EtOAc/CH₂Cl₂, product R_f=0.34). The mixture was cooled to 0°, and the white precipitate was collected by vacuum filtration, washed with hexanes (2x50 mL), and dried in vacuo (14.8

423

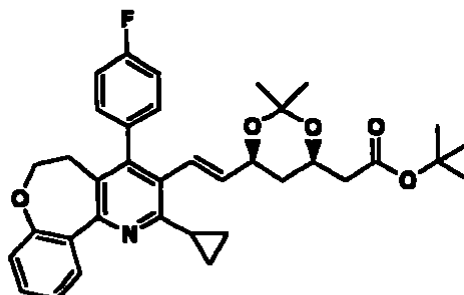
g, 0.027 mol, 100%): HPLC (Shimadzu, YMC S-5 C18 4.6x50 mm column, 4min gradient @ 4mL/min, UV detection 220 nm; start %B=50, final %B=100; A=10:90 MeOH/H₂O + 0.2% H₃PO₄, B=90:10 MeOH/H₂O + 0.2% H₃PO₄) R.T.=3.70 min (100%);

5

¹H NMR (CDCl₃) δ 0.712-0.760 (m, 2 H), 1.10-1.14 (m, 2 H), 2.163-2.228 (m, 1 H), 2.3211 (t, J=6.2 Hz, 2 H), 3.850 (d, J=14 Hz, 2 H), 4.2568 (t, J=6.2 Hz, 2 H), 6.779 (dd, J=8.3 Hz, 5.3 Hz, 2 H), 6.9542 (t, J=8.3 Hz, 2 H), 7.070 (d, J=7.9 Hz, 1 H), 7.257 (t, J=7.5 Hz, 1 H), 7.334-7.421 (m, 9 H), 7.469-7.521 (m, 2 H), 7.822 (d, J=7.5 Hz, 1 H); MS m/z 546 (M+H)⁺.

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G(2).



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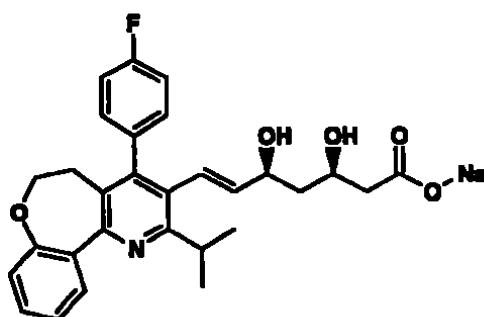
A flame-dried 250-mL flask was charged with Part G(1) compound (14.82 g, 27.2 mmol, 1 equiv), chased with anhydrous toluene (2x50 mL), dried over high-vacuum and filled with argon. THF (150 mL) was added and the partial slurry was cooled to 0°C. A 2.5 M solution of n-BuLi in hexanes (11.4 mL, 0.0285 mol, 1.05 equiv) was added dropwise to the vigorously stirred mixture over a period of 40 min. The resulting green colored solution was then stirred for 1 hr at 0°C. The aldehyde Example A(1) compound (8.42 g, 0.0326 mol, 1.2 equiv) in a flame-dried 500-mL flask (material previously chased with anhydrous toluene, 3x20 mL) under an argon atmosphere was dissolved in dry THF (75 mL) and cooled to -78°C. The phosphine anion solution was added dropwise to the aldehyde via cannula over a period of 45 min, then the dark blue colored solution was stirred at -78°C for 1.5 hr. The

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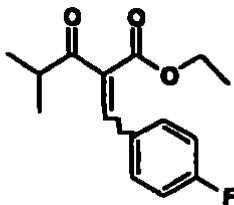
- mixture was let warm to room temperature over a 2 hr period; the initially blue solution became a dark brick-red color and finally a light orange color. TLC (SiO₂, 5% EtOAc/CH₂Cl₂, product R_f=0.37). The reaction was
- 5 quenched with half-saturated aqueous NaCl (200 mL) and extracted with Et₂O (300 mL); the organic was washed with H₂O (2x100 mL) and saturated aqueous NaCl (100 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. Purification by SiO₂ flash
- 10 chromatography (10 cm x 25 cm) with 2% EtOAc/CH₂Cl₂ (2 L), 3% EtOAc/CH₂Cl₂ (2 L), 5% EtOAc/CH₂Cl₂ (1 L), 7% EtOAc/CH₂Cl₂ (1 L), and 10% EtOAc/CH₂Cl₂ (1 L) afforded Part G(2) compound (the same as Example 1 Part G compound) as a white solid (11.13 g, 0.019 mol, 70%):
- 15 HPLC (Shimadzu, YMC S-5 C18 4.6x50 mm column, 4 min gradient @ 4 mL/min, UV detection 220 nm; start %B=70, final %B=100; A=10:90 MeOH/H₂O + 0.2% H₃PO₄, B=90:10 MeOH/H₂O + 0.2% H₃PO₄) R.T.=4.36 min (100%);
- 20 ¹H NMR (CDCl₃) δ 0.928-1.039 (m, 3 H), 1.191-1.368 (m, 6 H), 1.4384 (s, 3 H), 1.4483 (s, 9 H), 2.225-2.431 (m, 3 H), 2.4782 (t, J=6.2 Hz, 2 H), 4.188-4.334 (m, 2 H), 4.3667 (t, 2 H), 5.5846 (dd, J=16.2 Hz, 5.7 Hz, 1 H), 6.342 (d, J=16.2 Hz, 1 H), 7.0663-7.1356 (m, 5 H), 7.257
- 25 (t, J=7.5 Hz, 1 H), 7.3538 (t, J=7.5 Hz, 1 H), 7.828 (d, J=7.5 Hz, 1 H); MS (FAB) m/z 586 (M+H)⁺.

Example 2

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A.

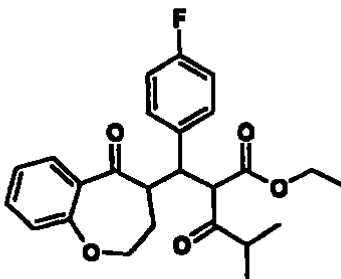


A mixture of p-fluorobenzaldehyde (4.939 g, 0.039 mol, 1 equiv), ethyl isobutyrylacetate (6.495 g, 0.039 mol, 1 equiv), piperidine (0.395 mL, 3.91 mmol, 0.1 equiv), and glacial acetic acid (0.070 mL, 1.22 mmol, 0.03 equiv) in anhydrous benzene (30 mL) was heated at reflux with a Dean-Stark trap to collect H₂O. After 20 hrs, the reaction was cooled to rt. The yellow reaction mixture was diluted with Et₂O (50 mL) and washed with 0.5N aq HCl, satd. aq NaHCO₃, H₂O, and satd. aq NaCl. The organic extract was dried over anhydrous Na₂SO₄, vacuum filtered and the filtrate concentrated by rotary evaporation in vacuo to yellow oil. Vacuum distillation afforded the desired product as a light yellow oil (8.575 g, 0.0324 mol, 83%): bp 107-115°C (0.225 mm Hg);

¹H NMR (CDCl₃) δ 1.047 and 1.160 (d's, J=6.6 Hz, 6H, 1.4:1 ratio), 1.260 and 1.296 (t's, J=7.1 Hz, 3H, 1:1.4 ratio), 2.674 and 3.140 (m's, J=7 Hz, 1H, 1.4:1 ratio), 4.245-4.324 (m, 2H), 7.010-7.074 (m, 2H), 7.346-7.448 (m, 2H), 7.701 (s, 1H). MS (FAB) m/z 265 (M+H)⁺, 287 (M+Na)⁺.

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B.

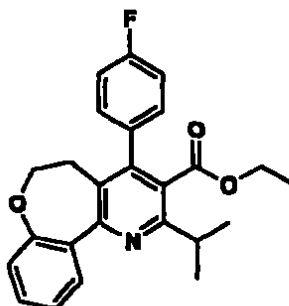


An oven-dried 250-mL 3-neck flask purged with argon was charged with anhydrous THF (30 mL) and lithium

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bis(trimethylsilyl)amide (1M in THF, 57.9 mL, 0.058 mol, 1.8 equiv), then cooled to -78°C in a dry ice-acetone bath. A solution of Example 1 Part A compound (7.824 g, 0.0482 mol, 1.5 equiv) in dry THF (6 mL) was added via
5 cannula and the enolate allowed to generate over 1 hr at -78°C . Then a solution of Part A compound (8.50 g, 0.0322 mol, 1 equiv) in dry THF (6 mL) was added via
10 cannula and the resulting amber solution stirred at -78°C for 30 min, then at 0°C for 30 min. The reaction was quenched with glacial acetic acid (6 mL), then poured into satd aq NH_4Cl . The mixture was extracted with Et_2O (100 mL) and the ethereal extract was washed with H_2O (2x30 mL) and satd aq NaCl . The organic was dried over anhydrous Na_2SO_4 , vacuum filtered and concentrated by
15 rotary evaporation in vacuo to a yellow oil (17.19 g):
MS (FAB) m/z 427 (M+H) $^{+}$.

C.



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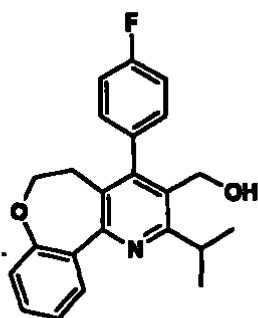
The crude Part B compound (17.19 g), NH_4OAc (11.0g, 0.142 mol, 4.4 equiv), and $\text{Cu}(\text{OAc})_2$ monohydrate (24.2 g, 0.119 mol, 3.7 equiv) were dissolved in glacial HOAc (120 mL) under argon and heated at gentle reflux for 20 hrs.
25 The reaction was cooled to rt, then poured into an ice cold solution of conc NH_4OH (100 mL) in H_2O (200 mL). The mixture was extracted with Et_2O (200 mL+2x100 mL), then the combined ethereal extracts was washed with H_2O (2x100 mL) and satd aq NaCl . The extract was dried over
30 anhydrous Na_2SO_4 , vacuum filtered and concentrated by rotary evaporation in vacuo. The resulting brown oil was chased with hexanes to remove HOAc, followed by drying in

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vacuo. Purification in two batches on two SiO₂ flash columns (5cm x 22 cm) with 5% EtOAc/Hexanes afforded the product as a yellow oil which crystallized upon sitting (5.98 g, 0.0148 mol, 46% for two steps):

5
¹H NMR (CDCl₃) δ 0.959 (t, J=7 Hz, 3H), 1.164 and 1.359 (d's, J=7 Hz, 6H, 1:4 ratio), 2.557 (t, J=6.2 Hz, 2H); 2.897 and 3.146 (m's, J=7 Hz, 1H, 1:4 ratio), 4.006 (q, J=7 Hz, 2H), 4.418 (t, J=6.2 Hz, 2H), 6.710-7.578 (m, 7H), 7.898 (d, J=7.5 Hz, 1H); MS (ESI +Q) m/z 406 (M+H)⁺.
10

D.



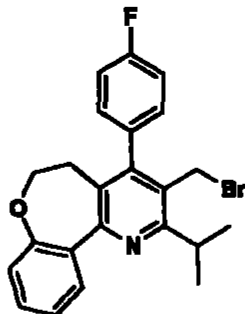
15 Part C compound (5.78 g, 0.0143 mol, 1 equiv) was dissolved in dry THF (70 mL) under argon and cooled to 0°C. A solution of LiAlH₄ in THF (1M, 28.5 mL, 0.0285 mol, 2 equiv) was added slowly. The reaction was stirred at rt for 2 hrs, followed by 25 min at reflux. TLC
20 (SiO₂, 5% EtOAc/CH₂Cl₂, R_f=0.24). The reaction was cooled to 0°C, then carefully quenched with H₂O (2.3 mL), 15% aq NaOH (2.3 mL), and H₂O (4.7 mL). The white mixture was stirred at rt for 10 min, then vacuum filtered and the solid washed with EtOAc. The filtrate was concentrated
25 by rotary evaporation in vacuo to a yellow oil. Purification on a SiO₂ flash column (5cm x 20 cm) with a gradient of 4% to 8% EtOAc/CH₂Cl₂ afforded the product as a white solid (4.082 g, 0.0112 mol, 79%):

30 ¹H NMR (CDCl₃) δ 1.402 (d, J=6.6 Hz, 6H), 2.463 (t, J=6.2 Hz, 2H), 3.532 (m, J=6.6 Hz, 1H), 4.382 (t, J=6.2 Hz, 2H), 4.461 (d, J=5.3 Hz, 2H), 7.097 (d, J=7.9 Hz, 1H),

Z

7.168 (t, J=8.8 Hz, 2H), 7.233-7.397 (m, 4H), 7.929 (d, J=7.5 Hz, 1H); MS (ESI +Q) m/z 364 (M+H)⁺.

E.



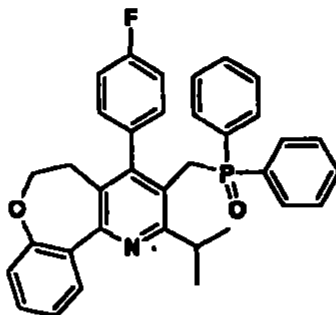
5

The Part D alcohol (3.066g, 8.437 mmol, 1 equiv), dissolved in dry CH₂Cl₂ (60 mL) under argon at 0°C, was treated by dropwise addition of a 1M solution of PBr₃ in CH₂Cl₂ (16.9 mL, 16.9 mmol, 2 equiv). The reaction was stirred at rt for 30 min, at which time the reaction was recooled to 0°C and treated with satd aq NaHCO₃ (90 mL). The mixture was diluted with CH₂Cl₂ (50 mL), the layers were separated, and the organic washed with H₂O (2x50 mL) and satd aq NaCl (50 mL). The organic was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. TLC (SiO₂, 5% EtOAc/ CH₂Cl₂, R_f=0.69). The residue was purified by SiO₂ flash chromatography (3.8cm x 15cm column) with CH₂Cl₂ to obtain product as white solid (2.97 g, 6.97 mmol, 83%):

¹H NMR (CDCl₃) δ 1.403 (d, J=6.6 Hz, 6H), 2.430 (t, J=6.2 Hz, 2H), 3.459 (m, J=6.6 Hz, 1H), 4.290 (s, 2H), 4.356 (t, J=6.2 Hz, 2H), 7.087 (d, J=7.9 Hz, 1H), 7.183 (t, J=7.5 Hz, 2H), 7.263-7.397 (m, 4H), 7.910 (d, J=7.5 Hz, 1H); MS (ESI +Q) m/z 426/428 (M+H)⁺.

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F.

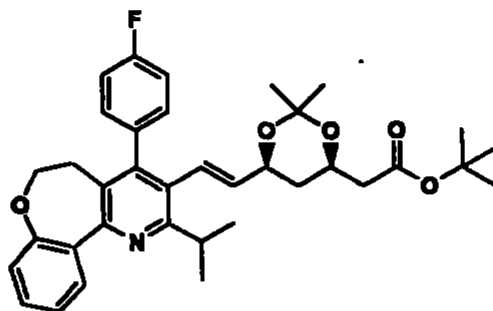


The Part E bromide (2.97 g, 6.967 mmol, 1 equiv) and ethyl diphenylphosphinite (1.7 mL, 7.663 mmol, 1.1 equiv) were heated at reflux under argon for 1.5 hrs. TLC (SiO₂, 30% EtOAc/CH₂Cl₂, product R_f=0.47). The reaction was cooled in an ice bath, then the solid collected by vacuum filtration in Buchner funnel; the solid was washed with small volumes of toluene, followed by hexanes. This afforded product as white solid (3.48 g, 6.35 mmol, 91%):

¹H NMR (CDCl₃) δ 1.256 (d, J=6.6 Hz, 6H), 2.334 (t, J=6 Hz, 2H), 3.33 (m, 1H), 3.716 (d, J=13.6 Hz, 2H), 4.252 (t, J=6 Hz, 2H), 6.767 (br t, J=5.3 Hz, 2H), 6.895 (t, J=8.5 Hz, 2H), 7.072 (d, J=7.9 Hz, 1H), 7.284 (t, J=7.4 Hz, 1H), 7.320-7.420 (m, 9H), 7.460-7.520 (m, 2H), 7.929 (d, J=7.4 Hz, 1H); MS (ESI +Q) m/z 548 (M+H)⁺.

20

G.



25

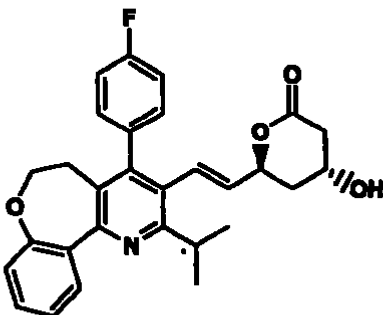
An oven-dried 50-mL flask charged with the Part F diphenylphosphine oxide (1.00 g, 1.826 mmol, 1 equiv) was

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chased with anhydrous toluene (3x5 mL), dried on hi-
vacuum, and filled with argon. The dry solid was
dissolved in dry THF (10 mL) and the resulting suspension
cooled to 0°C. nBuLi solution (Aldrich, titrated with
5 diphenylacetic acid: 2.4 M in hexanes; 0.80 mL, 1.92
mmol, 1.05 equiv) was added slowly dropwise over 20 min.
The resulting dark amber-colored solution was allowed to
stir at 0°C for 1 hr. The Example 1 A(1) aldehyde (0.566
g, 2.192 mmol, 1.2 equiv) in an oven-dried 100-mL flask
10 (material previously chased with anhydrous toluene (3x5
mL) and dried in vacuo) under argon atmosphere was
dissolved in dry THF (5 mL) and cooled to -78°C. The
anion solution was added via cannula to the aldehyde
solution over a period of 25 min, then the dark green-
15 colored solution was stirred at -78°C for 1.5 hrs. The
acetone/dry ice bath was then removed and the reaction
allowed to slowly warm to room temperature; the initially
green solution became an orange mixture. After 2 hrs,
the reaction was quenched with half-satd aq NaCl (60 mL),
20 extracted with Et₂O (100 mL), then washed the organic
with H₂O and satd aq NaCl. Purification by SiO₂ flash
chromatography (3.8cm x 15cm column) afforded the product
as a white foam (556 mg, 0.946 mmol, 52 %). Also
recovered unreacted diphenylphosphine oxide (445 mg,
25 0.8127 mmol):

¹H NMR (CDCl₃) δ 0.890 (q, 1H), 1.323-1.462 (m, 21H),
1.595 (d, 1H), 2.249 (dd, J=15.4 Hz, 6.2 Hz, 1H), 2.403
(dd, J=15.4 Hz, 7.0 Hz, 1H), 2.516 (t, J=6.2 Hz, 2H),
30 3.406 (m, 1H), 4.197-4.295 (m, 2H), 4.407 (m, 2H), 5.288
(dd, J=16.2 Hz, 5.7 Hz, 1H), 6.327 (dd, J=16.2 Hz, 1.3
Hz, 1H), 7.076-7.142 (m, 5H), 7.277-7.399 (m, 2H), 7.943
(d, J=7.5 Hz, 1H); MS (ESI +Q) m/z 588 (M+H)⁺.

H.

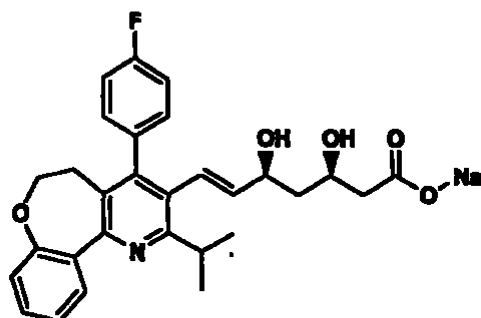


The Part G compound (0.230 g, 0.391 mmol) was dissolved in dry CH_2Cl_2 (5 mL) under an argon atmosphere and cooled to 0°C . Trifluoroacetic acid (0.5 mL) was added and the mixture was stirred at rt for 6 hrs. TLC (SiO_2 , 20% EtOAc/ CH_2Cl_2 , $R_f=0.31$). The reaction solution was transferred to a separatory funnel and treated with satd aq NaHCO_3 (25 mL), extracted with EtOAc (100 mL), and the organic washed with satd aq NaHCO_3 , and satd aq NaCl . The organic was dried over anhydrous Na_2SO_4 , filtered and concentrated by rotary evaporation in vacuo. The residue was purified by SiO_2 flash chromatography (1.9cm x 15cm column) to afford the product as a white solid (160 mg, 0.338 mmol, 86%):

^1H NMR (CDCl_3) δ 1.304 (d, $J=6.6$ Hz, 6H), 1.442-1.690 (m, 2H), 2.476-2.678 (m, 4H), 3.339 (m, 1H), 4.157 (m, 1H), 4.389 (t, $J=6.2$ Hz, 2H), 5.076 (m, 1H), 5.320 (dd, $J=16.2$ Hz, 10.1 Hz, 1H), 6.489 (d, $J=16.2$ Hz, 1H), 7.06-7.16 (m, 5H), 7.281 (t, 1H), 7.368 (t, 1H), 7.914 (d, $J=7.5$ Hz, 1H); MS (ESI +Q) m/z 474 ($M+H$) $^+$.

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I.



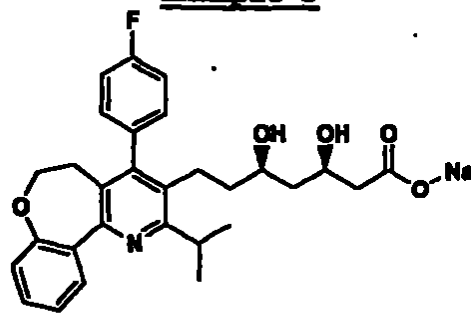
- The Part H lactone (148 mg, 0.3125 mmol, 1 equiv) was dissolved in THF (3 mL), treated with 1N aq NaOH (0.391 mL, 0.3907 mmol, 1.25 equiv), and stirred at rt. TLC (SiO₂, 0.5:0.5:9 HOAc/MeOH/CH₂Cl₂, R_f=0.25). After 30 min, the solvents were removed by rotary evaporation in vacuo and the residue dried on hi-vacuum. A SP207 Na-form resin column (1.9cm x 10cm bed) was prepared as follows: the resin was poured into a glass chromatography column equipped with fritted disc support, the resin was washed with satd aq NaHCO₃ (15 mL), satd aq NaCl (15 mL), and DI H₂O (100 mL, Milli-Q). The residue was taken up in Milli-Q DI H₂O (5 mL), applied to column, and eluted with Milli-Q DI H₂O (100 mL), 10% AcCN/H₂O (60 mL), and 25% AcCN/H₂O (125 mL). Product-containing fractions were combined and concentrated by rotary evaporation in vacuo to a small volume, then transferred to a 40-mL lyophilization jar, using additional H₂O to rinse out flask. The contents of the jar were frozen in an acetone-dry ice bath and lyophilized to afford the product as a white lyophilate (148 mg, 0.288 mmol, 92%):
- ¹H NMR (DMSO-d₆) δ 0.90-1.00 (m, 1H), 1.20-1.35 (m, 7H), 1.727 (dd, J=14.9 Hz, 7.9 Hz, 1H), 1.955 (dd, J=14.9 Hz, 4 Hz, 1H), 2.399 (t, J=6.2 Hz, 2H), 3.424-3.490 (m, 2H), 4.00-4.10 (m, 1H), 4.386 (t, J=6.2 Hz, 2H), 4.954 (br s, 1H), 5.354 (dd, J=16.2 Hz, 5.3 Hz, 1H), 6.297 (d, J=16.2 Hz, 1H), 7.12 (d, J=7.9 Hz, 1H), 7.20-7.46 (m, 7H), 7.802 (dd, J=7.9 Hz, 1.8 Hz, 1H); MS (ESI +Q) m/z 492 (M+H)⁺;

Anal. Calcd for $C_{29}H_{29}FNO_5Na \cdot H_2O$:

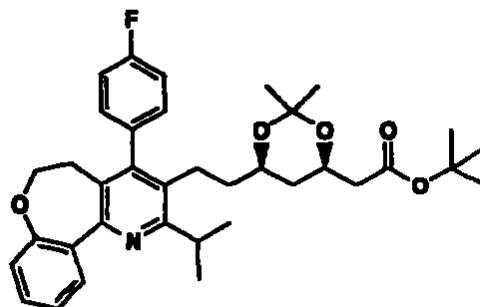
C, 65.53; H, 5.88; N, 2.64.

Found: C, 65.46; H, 5.70; N, 2.52.

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Example 3

A.



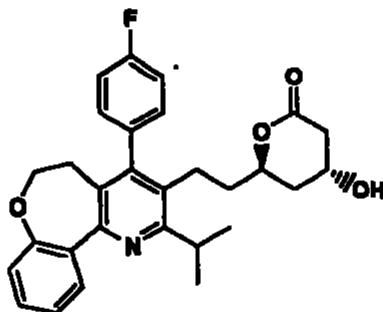
- 10 The Example 2 Part G compound (200 mg, 0.3403 mmol, 1 equiv) was hydrogenated at 45 psi H_2 in anhydrous MeOH (30 mL) with 10% Pd-C (40 mg, 20 wt %) for 2 hrs. The catalyst was washed with small portions of MeOH and the filtrate was concentrated by rotary evaporation in vacuo.
- 15 The residue was purified by SiO_2 flash chromatography (2.5cm x 13 cm) with 3% EtOAc/ CH_2Cl_2 to afford the product as a white foam (193 mg, 0.3273 mmol, 96%): HPLC (Shimadzu YMC S-5 C18 4.6x50 mm column, 4 min gradient @ 4mL/min, UV detection 220 nm; start %B=60, final %B=100; 20 A=10:90 MeOH/ H_2O + 0.2% H_3PO_4) R.T.=4.35 min (100%);

1H NMR ($CDCl_3$) δ 0.902 (q, $J=12.3$ Hz, 1H), 1.27-1.60 (m, 24 H), 2.212 (dd, $J=15.4$ Hz, 6.2 Hz, 1 H), 2.25-2.42 (m, 4 H), 2.50-2.60 (m, 1 H), 3.336 (m, 1 H), 3.599 (m, 1 H), 25 4.10-4.20 (m, 1 H), 4.328 (t, $J=6.2$ Hz, 2 H), 7.067 (d,

434

J=7.9 Hz, 1 H), 7.1416 (d, J=6.6 Hz, 4 H), 7.265 (t, J=7.5 Hz, 1 H), 7.340 (t, J=7.5 Hz, 1 H), 7.901 (d, J=7.5 Hz, 1 H); MS (ESI +Q) m/z 590 (M+H)⁺.

5 B.



Part A compound (258 mg, 0.4375 mmol) was dissolved in dry CH₂Cl₂ (5 mL) under argon, cooled to 0°C and treated with trifluoroacetic acid (0.5 mL). Stirring was continued at room temperature for 7 hrs, at which time the reaction was complete by HPLC. Saturated aqueous NaHCO₃ (25 mL) was added to the reaction, the reaction was diluted with EtOAc (100 mL), and the layers separated. The organic was washed with saturated aqueous NaHCO₃ and saturated aqueous NaCl, then dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. Purification by SiO₂ flash chromatography (1.9 cm x 15 cm) with 20% EtOAc/CH₂Cl₂ afforded a white foam (163 mg, 0.343 mmol, 78%): HPLC (Shimadzu, YMC S-5 C18 4.6x50 mm column, 4 min gradient @ 4mL/min, UV detection 220 nm; start %B=0, final %B=100; A=10:90 MeOH/H₂O + 0.2% H₃PO₄, B=90:10 MeOH/H₂O + 0.2% H₃PO₄) R.T.=3.81 min (94.6%);

¹H NMR (CDCl₃) δ 1.37 (d, J=6.6 Hz, 6 H), 1.45-1.85 (m, 4 H), 2.40-2.75 (m, 6 H), 3.327 (m, 1 H), 4.285 (br s, 1 H), 4.350 (t, J=6.2 Hz, 2 H), 4.49 (m, 1 H), 7.093 (d, J=7.9 Hz, 1 H), 7.181 (d, J=7.0 Hz, 4 H), 7.291 (t, J=7.5 Hz, 1 H), 7.3697 (t, J=7.5 Hz, 1 H), 7.912 (d, J=7.5 Hz, 1 H); MS (ESI +Q) m/z 476 (M+H)⁺.

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¹H NMR (DMSO-d₆) δ 1.048-1.105 (m, 1 H), 1.232-1.50 (m, 9 H), 1.750 (dd, J=14.9 Hz, 8.3 Hz, 1 H), 1.966 (dd, J=14.9 Hz, 4.0 Hz, 1 H), 2.298-2.356 (m, 3 H), 3.335-3.424 (m, 2 H), 3.616-3.656 (m, 1 H), 4.3166 (t, J=6.2 Hz, 2 H),

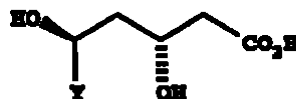
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4.711 (br s, 1 H), 7.098 (d, J=7.9 Hz, 1 H), 7.276-7.43 (m, 6 H), 7.773 (d, J=7.5 Hz, 1 H); MS (ESI +Q) m/z 494 (M+H)⁺ for acid form.

- 5 The following Examples may be prepared employing procedures set out herein and in the working Examples.

Examples 4 to 26

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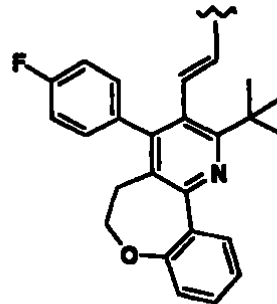
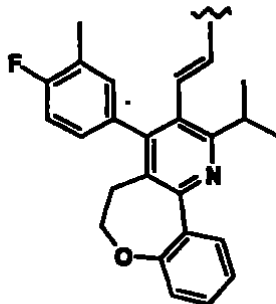
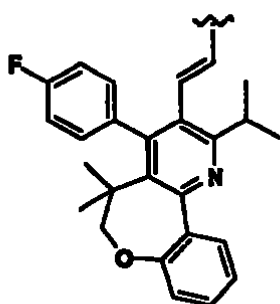
where Y is as set out below

Example 4

Example 5

Example 6

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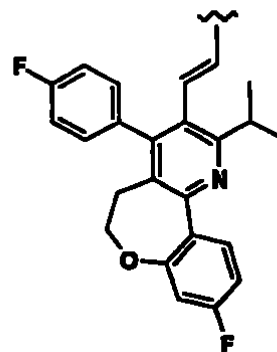
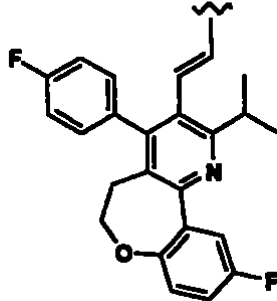
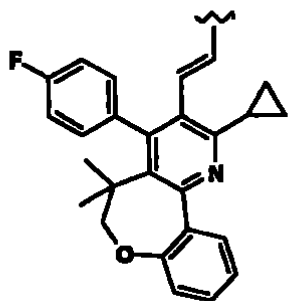


Example 7

Example 8

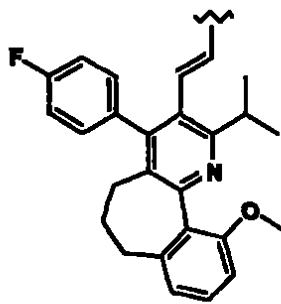
Example 9

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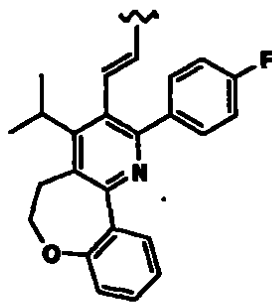


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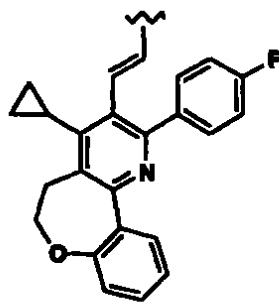
Example 10



Example 11

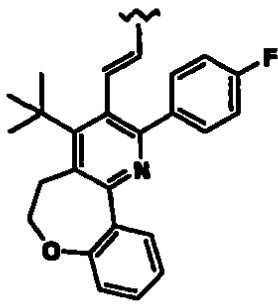


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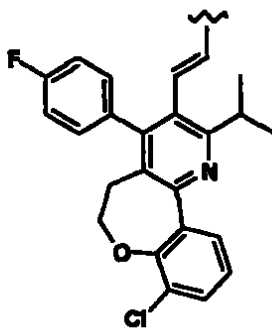


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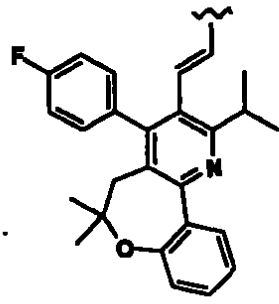
Example 13



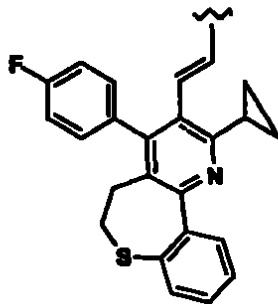
Example 14



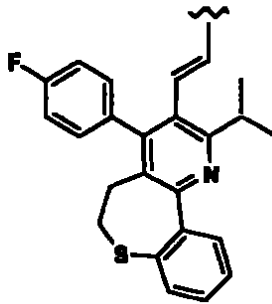
Example 15



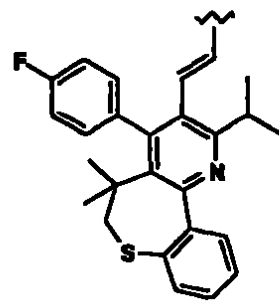
Example 16



Example 17



Example 18

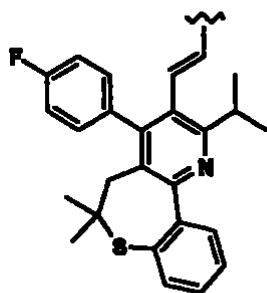


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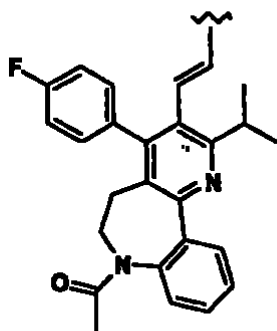
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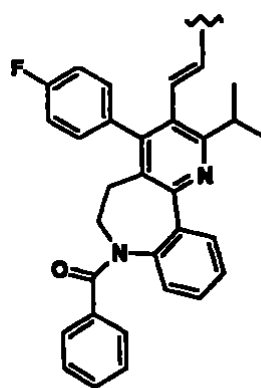
Example 19



Example 20

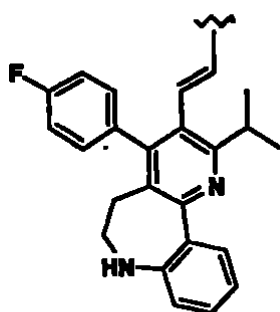


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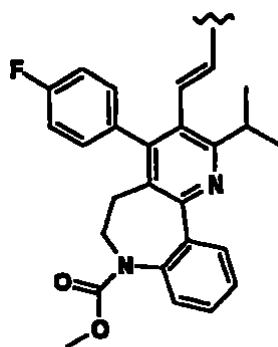


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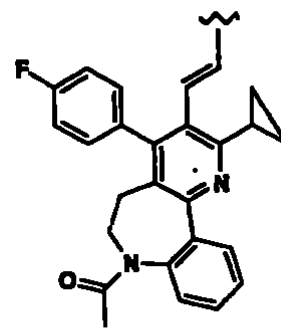
Example 22



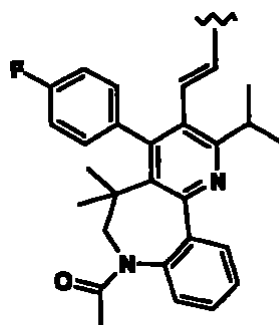
Example 23



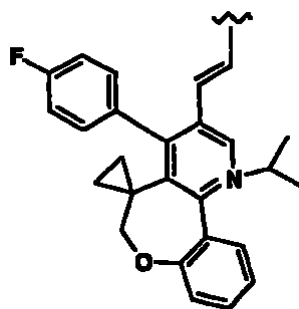
Example 24



Example 25



Example 26

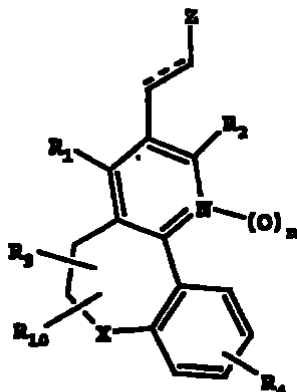


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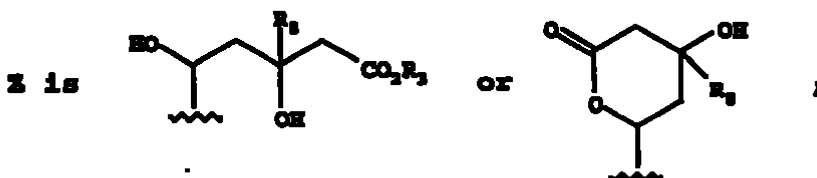
439

What is claimed is:

1. A compound having the structure



5 wherein X is O, S or NR;



n is 0 or 1;

10 R_1 and R_2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

 R_3 is H, lower alkyl or a metal ion;

15 R_4 is H, halogen, CF_3 , hydroxy, alkyl, alkoxy, alkanoylamino, aroylamino, or cyano;

R_5 is H, alkyl, aryl, alkanoyl, aroyl or alkoxycarbonyl;

 R_6 is H or lower alkyl;

20 R_7 and R_{10} are the same or different and are independently selected from H or alkyl, or R_7 and R_{10} may be taken together with the carbon or carbons to which they are attached to form a 3 to 7 membered carbocyclic ring;

25 and represents a single bond or a double bond (which may be cis or trans);

and including pharmaceutically acceptable salts thereof, esters thereof, prodrug esters thereof, and all stereoisomers thereof.

5 2. The compound as defined in Claim 1 wherein ~~is~~
is a double bond which is trans.

3. The compound as defined in Claim 1 wherein Z is in the form of a pharmaceutically acceptable basic salt.

4. The compound as defined in Claim 1 in the form of a pharmaceutically acceptable acid addition salt.

5. The compound as defined in Claim 1 wherein R₁
15 and R₂ are independently selected from alkyl, cycloalkyl
and aryl;

R₄ is H or halogen;

is 0:

and x is 0.

20

6. The compound as defined in Claim 1 wherein R₁ is aryl,

R₂ is alkyl or cycloalkyl;

R_4 is H ;

25 n is o;

X is 0; and

²⁻²⁻² is a trans double bond, in the form of a free acid or an alkali or alkaline earth metal salt.

30 7. The compound as defined in Claim 6 wherein R₁
is phenyl which contains 1 or 2 substituents,

R₂ is alkyl or cycloalkyl;

R₄ is H;

X is 0; and

35 ~~2-2~~ is a trans double bond, in the form of a free acid or an alkali or alkaline earth metal salt.

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8. The compound as defined in Claim 7 wherein R_1 is 4-fluorophenyl, 4-fluoro-3-methylphenyl, or 3,5-dimethylphenyl; and

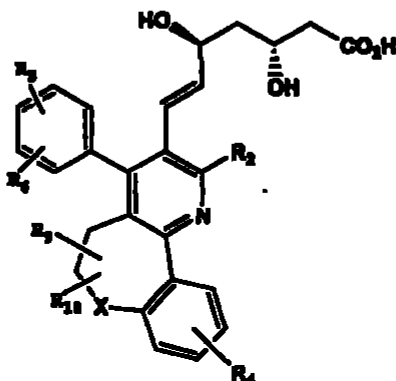
5 R_2 is isopropyl, t-butyl or cyclopropyl.

9. The compound as defined in Claim 1 wherein Z has the structure



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10. The compound as defined in Claim 1 having the structure



15 or an alkali or alkaline earth metal salt thereof or an acid addition salt via the pyridine of the corresponding δ lactone,

wherein R_3 and R_4 are the same or different and are independently selected from H, halogen or alkyl and R_5 is alkyl or cycloalkyl.

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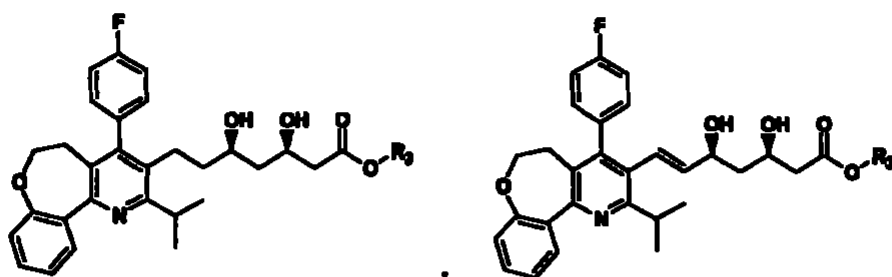
11. The compound as defined in Claim 10 wherein R_3 and R_4 are H and 4-fluoro;

H and 4-fluoro-3-methyl or 3,5-dimethyl; and

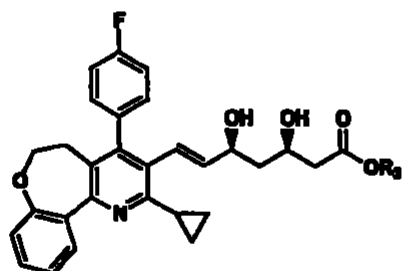
25 R_5 is isopropyl, t-butyl or cyclopropyl.

12. The compound as defined in Claim 1 having the structure

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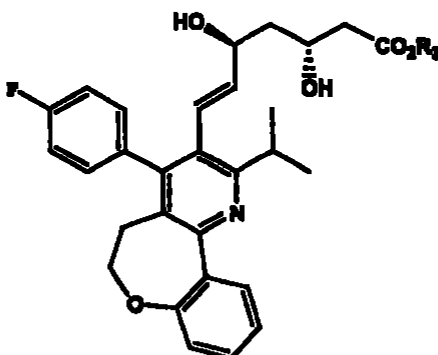


or



- 5 wherein R_3 is H or an alkali or alkaline earth metal or other pharmaceutically acceptable salt, or the internal lactone thereof.

13. A compound of the structure



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wherein R_3 is H or an alkali or alkaline earth metal ion or the internal lactone thereof.

14. The compound as defined in Claim 13 wherein R_3 is sodium.

15. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

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16. A pharmaceutical combination comprising an HMG CoA reductase inhibitor compound as defined in Claim 1 and another lipid-lowering agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an antiosteoporosis agent.

17. The pharmaceutical combination as defined in Claim 16 comprising said HMG CoA reductase inhibiting compound and an antidiabetic agent.

18. The combination as defined in Claim 17 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an α P2 inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin and/or a meglitinide.

19. The combination as defined in Claim 18 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyrider, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A.

20. The combination as defined in Claim 17 wherein the HMG CoA reductase inhibiting compound is present in a weight ratio to the antidiabetic agent within the range from about 0.001 to about 100:1.

21. The combination as defined in Claim 16 wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake

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inhibitor, a thyroid receptor beta compound, an $\alpha 2$ inhibitor and/or an anorectic agent.

22. The combination as defined in Claim 21 wherein
5 the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol.

10 23. The combination as defined in Claim 16 wherein the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxxygenase inhibitor, or an ACAT inhibitor.

15 24. The combination as defined in Claim 23 wherein the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil,
20 clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427.

25 25. The combination as defined in Claim 23 wherein the HMG CoA reductase inhibiting compound is present in a weight ratio to the lipid-lowering agent within the range from about 0.001:1 to about 100:1.

30 26. The combination as defined in Claim 16 wherein the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or β -adrenergic blocker.

35 27. The combination as defined in Claim 26 wherein the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril;

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amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, or clonidine HCl.

29. A method for treating hypercholesterolemia,
15 hyperlipidemia, hyperlipoproteinemia,
hypertriglyceridemia or atherosclerosis, which comprises
administering to a mammalian species in need of treatment
a therapeutically effective amount of a compound as
defined in Claim 1.

R₉ and R₁₀ are the same or different and are
30 independently selected from H or alkyl, or R₉ and R₁₀ may
be taken together with the carbon or carbons to which

[illegible]

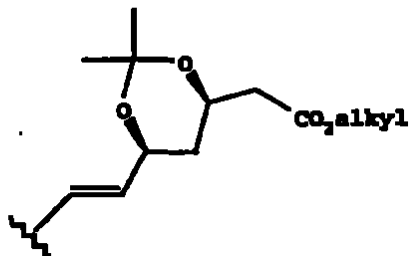
they are attached to form a 3 to 7 membered carbocyclic ring;

Q is $\text{---CO}_2\text{R}$ (where R is alkyl), $\text{---CH}_2\text{OH}$, ---Halide ,



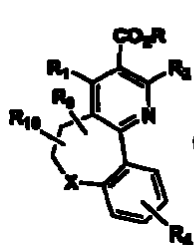
(where W is aryl, alkyl, or alkoxy),

or

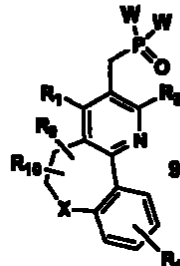
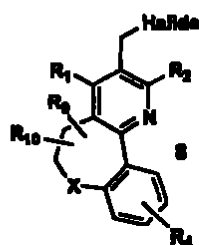
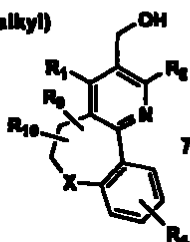


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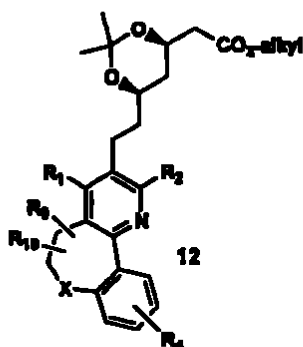
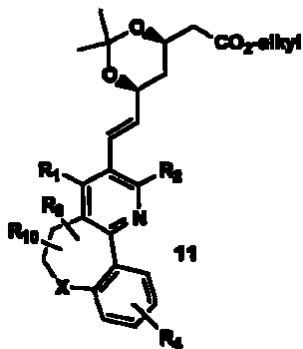
31. The compound as defined in Claim 30 having the following structures:



(R=alkyl)



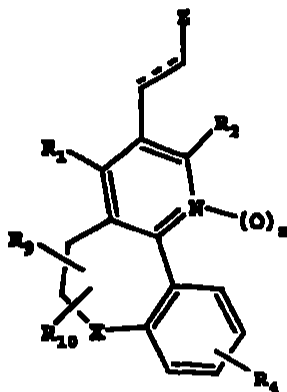
(W=aryl, alkyl or alkoxy)



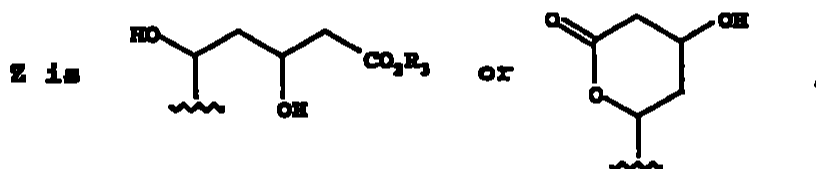
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447HMG-CoA REDUCTASE INHIBITORS AND METHODAbstract of the Disclosure

Compounds of the following structure are HMG CoA
 5 reductase inhibitors and thus are active in inhibiting
 cholesterol biosynthesis, modulating blood serum lipids
 such as lowering LDL cholesterol and/or increasing HDL
 cholesterol, and treating hyperlipidemia,
 hypercholesterolemia, hypertriglyceridemia and
 10 atherosclerosis



wherein X is O or S;



15 n is 0 or 1;

R₁ and R₂ are the same or different and are
 independently selected from alkyl, arylalkyl, cycloalkyl,
 alkenyl, cycloalkenyl, aryl, heteroaryl or
 cycloheteroalkyl;

20 R₃ is H, lower alkyl or a metal ion;

R₄ is H, halogen, CF₃, hydroxy, alkyl, alkoxy,
 alkanoylamino, aroylamino or cyano;

R₇ is H, alkyl, aryl, alkanoyl, aroyl or
 alkoxycarbonyl;

25 R₉ is H or lower alkyl;

R₉ and R₁₀ are independently H or alkyl, or R₉ and
 R₁₀ may be taken together with the carbon or carbons to

HX0115(PSP)

which they are attached to form a 3 to 7 membered carbocyclic ring;

and ~~==~~ represents a single bond or a double bond (which may be cis or trans);

- 5 and including pharmaceutically acceptable salts, thereof, esters thereof, prodrug esters thereof, and all stereoisomers thereof.

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Industria y Comercio
SUPERINTENDENCIA

2° EXAMEN DE FORMA SOLICITUD PCT, PATENTE DE INVENCION

Radicación N° **02-113275**

Folio 405

Concepto Técnico N° **283**

Clasificación Internacional de Patentes: **A61K 31/55**

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486, se determinó que esta solicitud de Patente:

- SI ☒ NO ☐ Contiene un resumen de la invención (Art. 26-e)
- SI ☒ NO ☐ Contiene el título o nombre de la invención (Art. 27-d)
- SI ☒ NO ☐ Contiene la descripción de la invención (Art. 26-b)
- SI ☒ NO ☐ NO ES APLICABLE ☐ Contiene los dibujos necesarios para comprender la invención (Art. 26-d)
- SI ☒ NO ☐ Contiene una o más reivindicaciones (Art. 26-c)
- SI ☐ NO ☐ NO ES APLICABLE ☒ Han sido desarrollados los productos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen (Art. 26-h)
- SI ☐ NO ☐ NO ES APLICABLE ☒ Los productos y o procedimientos han sido obtenidos o desarrollados a partir a partir de los conocimientos tradicionales de las comunidades indígenas, afro americanas, o locales de los Países Miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes (Art. 26-i)
- SI ☐ NO ☒ La invención se refiere a un producto relativo a un material biológico (Art. 26-j)
- SI ☒ NO ☐ NO ES APLICABLE ☐ La prioridad coincide con la materia reivindicada.
- SI ☒ NO ☐ **CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI ☐ NO ☐ Ver hoja(s) anexa(s)

EXAMINADOR TÉCNICO: 202051

Bogotá D C, febrero 27 de 2004.

2020
Bogotá D C

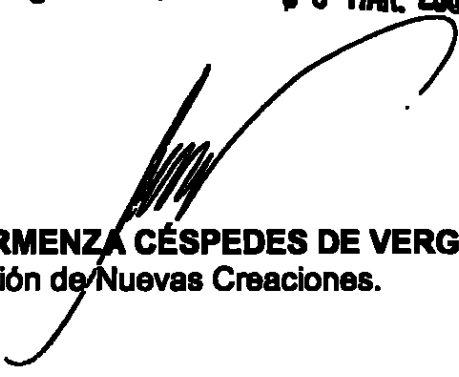
Doctor(a)
RAMIRO CASTRO DUQUE.
Apoderado(a)

REFERENCIA:	Radicación N°	02-113275
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	Fecha inicio fase nacional	15/01/2003
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	346
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486.

Cúmplase
Dado en Bogotá D C,

08 MAR. 2004


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones.

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