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Industria y Comercio
SUPERINTENDENCIA

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Trámite: 011 PCT-PATENT 378 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☒ Capítulo I.

☒ Capítulo II.

2

SOLICITANTE
(71)

Nombre: BRISTOL - MYERS SQUIBB COMPANY

Dirección: P.O. Box 4000, Princeton, NJ 08543-4000, Estados Unidos de América

Nacionalidad o Domicilio: Estados Unidos

Lugar de Constitución: Estados Unidos

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IDENTIFICACION

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: RAMIRO CASTRO DUQUE

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IDENTIFICACION

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C.E. ☐ Otro ☐

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Número 170.322 TP 1003

4

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Publicación Internacional No. WO 01/96347 A1 Fecha 20-12-2001

7 Título (54): INHIBIDORES DE HMG-CoA REDUCTASA Y MÉTODO

7 Clasificación Internacional (51) C07D 311/04, 457/04, 471/04, A61K 31/55

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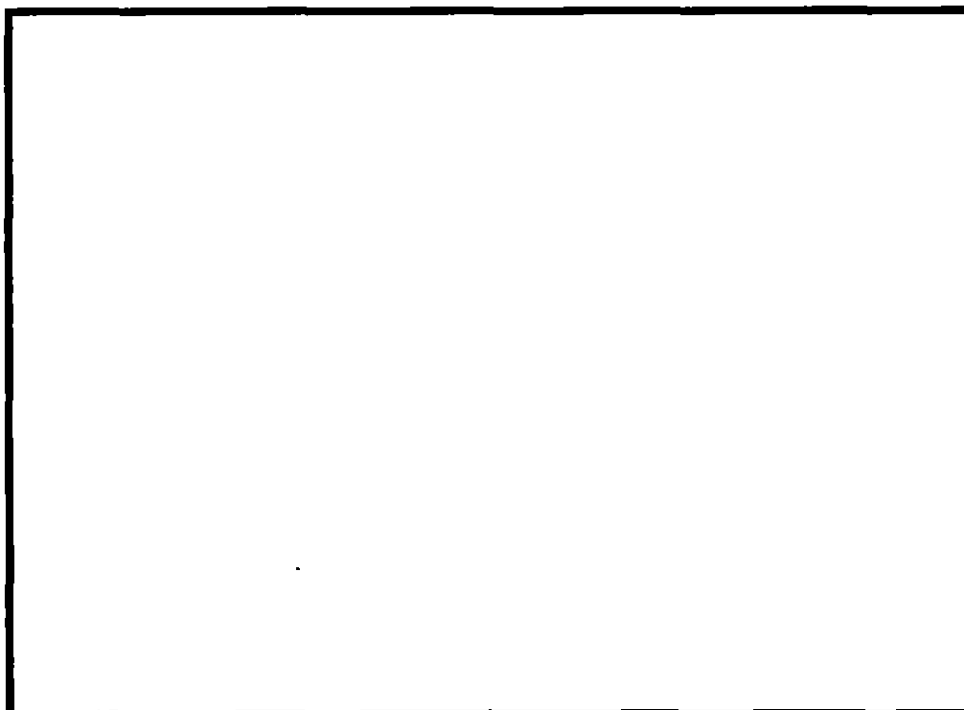
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$378.000
- ☒ Comprobante de pago por reivindicación de prioridad. \$106.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Protocolo No. 19358
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11 FIGURA CARACTERÍSTICA:



12. Sujeito la concesión de la patente:

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA

C.G. 170.322 de Bogotá T.P. 1003 del C.S.F.

Instrucciones para la presentación de los anexos, ver reverso de esta página.



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Industria y Comercio

SUPERINTENDENCIA

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WIGAND & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	030-00110-6	1326257	16/10/2002	12,000,000.00

***** CONCEPTO *****

WT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50003-01-01 SOLICITUDES	02 INVOCACION DE UNA PRIORIDAD EN NU	106,000.00
	TOTAL :	\$ 106,000.00

EN: CIENTO SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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RC 34

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BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	1325192	10/10/2002	2,184,000.00

***** C O N C E P T O *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	378,000.00
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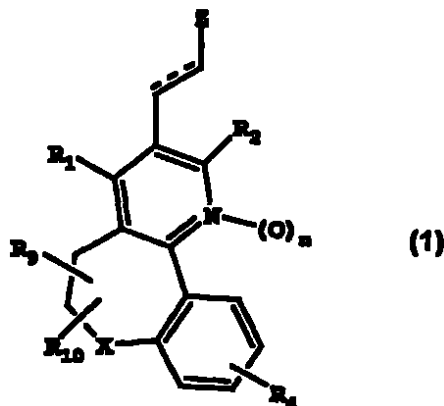
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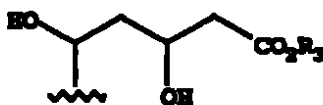
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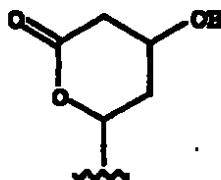
(54) Title: HMG-CoA REDUCTASE INHIBITORS AND METHOD



(57) Abstract: Compounds of structure (1) are
HMG CoA 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
atherosclerosis and pharmaceutically acceptable
salts thereof, wherein X is O or S; Z is (2) or (3);
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; and R₃ to R₉ are as defined herein.



(2)



(3)

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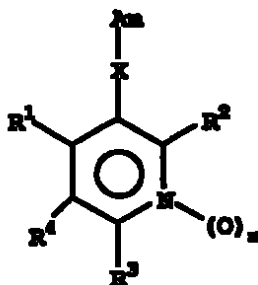
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

HMG-CoA REDUCTASE INHIBITORS AND METHOD

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
 10 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA
 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.

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



20 wherein:

Am is a binding domain sidechain;

X is a linker;

R¹ and R² are the same or different and are each
 independently selected from

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

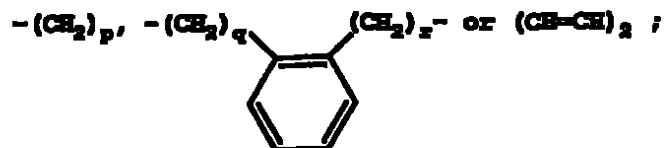
(ix) heterocyclo (e.g., thienyl, benzodioxolyl);

R³ is selected from

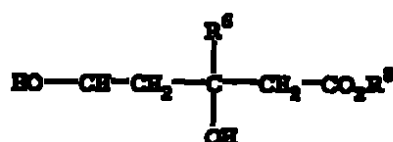
- 5 (i) hydrogen,
 (ii) lower alkyl,
 (iii) aryl,
 (iv) cycloalkyl,
 (v) alkoxy,
 (vi) aralkyl,
 10 (vii) aralkoxy,
 (viii) alkenyl,
 (ix) cycloalkenyl,
 (x) halo-substituted alkyl,
 (xi) adamantyl, and
 15 (xii) heterocyclo (e.g., thienyl, benzodioxolyl);

R⁴ is selected from

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



35 but when A_m is



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

R^6 is hydrogen or lower alkyl;

R^8 is hydrogen, lower alkyl, alkali metal, or
5 alkaline earth metal;

n is 0 or 1;

p is 3, 4 or 5;

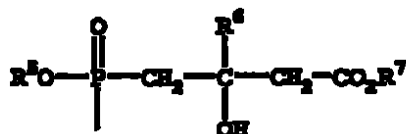
q is 0, 1, 2, or 3; and

r is 0, 1, 2, or 3.

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

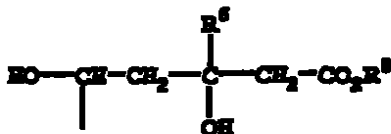
The phosphinic (or phosphonic when X is $\text{CH}_2\text{-O-}$) acid HMG-binding domain sidechain (A_1) is

15

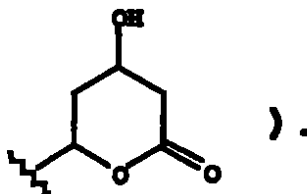


wherein R^5 and R^7 are independently selected from hydrogen, lower alkyl, alkali metal ion and alkaline earth metal ion; and R^6 is hydrogen or lower alkyl.

20 The dihydroxy acid binding domain sidechain (A_2) is



wherein R^6 is hydrogen or lower alkyl, R^8 is hydrogen or lower alkyl in free acid form or in the form of a
25 physiologically acceptable and hydrolyzable ester or δ lactone thereof (i.e., when Am is



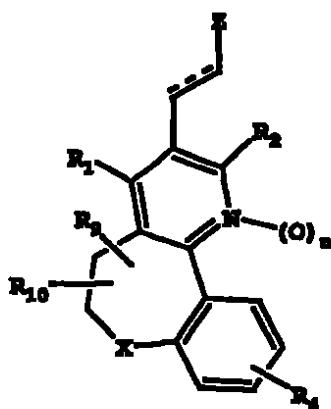
In addition, R^8 can be alkali metal ion or alkaline earth metal ion.

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.

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).

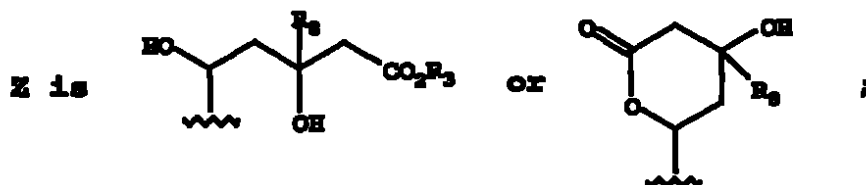
In particular, in its broadest chemical compound aspect, the present invention provides compounds of the formula

I



wherein X is O, S or NR_7 ;

20



n is 0 or 1;

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, or lower alkyl;

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

R_7 is H, alkyl, aryl, alkanoyl, aroyl, or
5 alkoxy carbonyl;

R_8 is H or lower alkyl;

R_9 and R_{10} are the same or different and are independently selected from H or alkyl, or where at least one of R_9 and R_{10} is alkyl, R_9 and R_{10} may be taken
10 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);

15 and including pharmaceutically acceptable salts thereof where R_3 is H, 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
20 or δ lactone thereof, or an alkali metal salt, alkaline earth metal salt or an amino acid salt.

Preferred are compounds of formula I of the invention wherein

R_1 and R_2 are independently selected from alkyl,
25 cycloalkyl and aryl;

R_4 is H, alkyl or halogen;

X is O; and

n is 0.

More preferred are compounds of formula I of the
30 invention wherein R_1 is aryl (especially substituted aryl as defined hereinafter);

R_2 is alkyl or cycloalkyl;

R_4 is H;

R_9 and R_{10} are H;

35 X is O;

n is 0; and

~~==~~ 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;

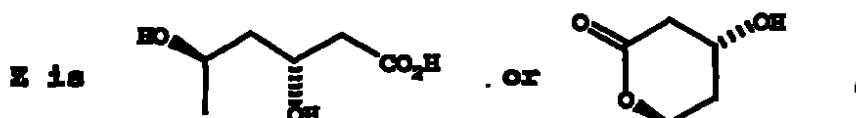
5 R_2 is alkyl or cycloalkyl, preferably isopropyl, t-butyl or cyclopropyl;

R_4 is H;

X is O;

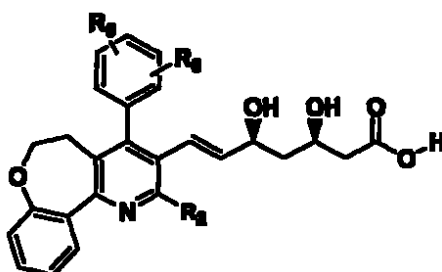
n is 0;

10 $\text{---}\text{=}\text{---}$ is a double bond, preferably "trans"; and



or an alkali or alkaline earth metal salt thereof or an amino acid salt.

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



or an alkali or alkaline earth metal (such as Na, K or
20 Ca) salt thereof, or an amino acid salt (such as arginine), wherein R_5 and R_6 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

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

In another aspect, the present invention provides pharmaceutical compositions, useful as hypolipidemic or hypocholesterolemic agents, or hypotriglyceridemic
30 agents, or anti-Alzheimer's agents, or anti-osteoporosis

agents as well as other uses as described herein,
comprising a hypolipidemic or hypocholesterolemic or
hypotriglyceridemic or anti-Alzheimer's disease or anti-
osteoporosis amount, or other therapeutically effective
5 amount (depending upon use) 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
10 blood serum cholesterol levels and/or modulating blood
serum cholesterol levels such as lowering LDL cholesterol
and/or increasing HDL cholesterol, or treating
dyslipidemia, mixed dyslipidemia, hyperlipidemia,
hypercholesterolemia, hypo α -lipoproteinemia, LDL Pattern
15 B, LDL Pattern A, hyperlipoproteinemia or
hypertriglyceridemia, and other aberrations of
apolipoprotein B metabolism, or reducing levels of Lp(a),
or treating or preventing other cholesterol-related
diseases, or treating or preventing or reversing
20 progression of atherosclerosis, or preventing or treating
Alzheimer's disease, or preventing or treating
osteoporosis and/or osteopenia, or reducing inflammatory
markers such as C-reactive protein, or preventing or
treating low grade vascular inflammation, or preventing
25 or treating stroke, or preventing or treating dementia,
or preventing and treating coronary heart disease
(including primary and secondary prevention of myocardial
infarction), or preventing or treating stable and
unstable angina, or primary prevention of coronary
30 events, or secondary prevention of cardiovascular events,
or preventing or treating peripheral vascular disease,
preventing or treating peripheral arterial disease, or
preventing or treating acute vascular syndromes, or
preventing or reducing the risk of undergoing myocardial
35 revascularization procedures, or preventing or treating
microvascular diseases such as nephropathy, neuropathy,
retinopathy and nephrotic syndrome or preventing or

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treating hypertension in a patient in need of such treatment by administering a pharmaceutical composition in accordance with the present invention as defined above.

5 In addition, in accordance with the present invention, a method is provided for preventing or treating diabetes, especially Type 2 diabetes, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of
10 fatty acids or glycerol, obesity, Syndrome X, diabetic complications, dysmetabolic syndrome, and related diseases, and sexual dysfunction, wherein a therapeutically effective amount of a compound of structure I is administered to a patient in need of
15 treatment.

 In addition, in accordance with the present invention, a method is provided for preventing and treating malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the
20 breast), premalignant lesions (such as fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), gastrointestinal malignencies, liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), cancer-induced
25 asthenia (fatigue), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and gallstones, and HIV infection, other infectious diseases, drug-induced lipodystrophy, and proliferative diseases such as psoriasis, wherein a therapeutically effective amount of
30 a compound of structure I is administered to a human patient in need of treatment.

 In addition, in accordance with the present invention, a method is provided for improving coagulation homeostasis including reducing PAI-1 activity, reducing
35 fibrinogen, and/or reducing platelet aggregation, and/or improving endothelial function, wherein a therapeutically

effective amount of a compound of structure I is administered to a patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating cholesterol
5 related diseases, diabetes and related diseases, cardiovascular diseases, cerebrovascular diseases as defined above and hereinafter and other diseases as set out above, wherein a therapeutically effective amount of a combination of a compound of structure I and a
10 hypolipidemic agent, and/or lipid modulating agent and/or antidiabetic agent and/or cardiovascular agent, cerebrovascular agent, and/or other type of therapeutic agent, is administered to a patient in need of treatment.

In the above methods of the invention wherein a
15 combination is administered, the compound of structure I will be employed in a weight ratio to the other therapeutic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 500:1, preferably from about 0.5:1 to about 100:1.

20

In accordance with the present invention, there is provided compounds useful in inhibiting the enzyme HMG-CoA reductase, which inhibitors are useful as
hypocholesterolemic agents, dyslipidemic agents,
25 hypolipidemic agents, hypotriglyceridemic agents, anti-Alzheimer's disease agents, and antiosteoporosis agents as well as other uses as described herein.

The term "coronary events" as employed herein refers to myocardial infarction, myocardial
30 revascularization procedures, angina, cardiovascular death and acute coronary syndrome.

The term "cardiovascular diseases or events" as employed herein refers to atherosclerosis of the coronary arteries, myocardial infarction, including primary MI and
35 secondary MI, recurrent myocardial infarction, angina pectoris (including stable and unstable angina), congestive heart failure, and sudden cardiac death.

The term "cerebrovascular diseases or events" as employed herein refers to cerebral infarction or stroke (caused by vessel blockage or hemorrhage), or transient ischemia attack (TIA), syncope, atherosclerosis of the intracranial and/or extracranial arteries, and the like.

The term "cholesterol-related diseases" as employed herein refers to diseases involving elevated levels of LDL cholesterol, diseases involving regulation of LDL receptors, diseases involving reduced levels of HDL cholesterol, dyslipidemia, hyperlipidemia, elevated LDL Pattern B, elevated LDL Pattern A, hypercholesterolemia, hypo α -lipoproteinemia (low HDL cholesterol syndrome), hyperlipoproteinemia, elevated Lp(a) levels, hypertriglyceridemia, other aberrations of apolipoprotein B metabolism, heterozygous familial, presumed familial combined and non-familial (non-FH) forms of primary hypercholesterolemia (including Frederickson Types IIa and IIb), cholesterol ester storage disease, and cholesterol ester transfer protein disease, and related diseases.

The conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Dysmetabolic Syndrome (as detailed in Johanson, *J. Clin. Endocrinol. Metab.*, 1997, 82, 727-734, and other publications) include hyperglycemia and/or prediabetic insulin resistance syndrome, and is characterized by an initial insulin resistant state generating hyperinsulinemia, dyslipidemia, and impaired glucose tolerance, which can progress to Type II diabetes, characterized by hyperglycemia, which can progress to diabetic complications.

The term "diabetes and related diseases" refers to Type II diabetes, Type I diabetes, impaired glucose tolerance, obesity, hyperglycemia, Syndrome X, dysmetabolic syndrome, diabetic complications and hyperinsulinemia.

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The conditions, diseases and maladies collectively referred to as "diabetic complications" include retinopathy, neuropathy and nephropathy, and other known complications of diabetes.

5 The term "other type(s) of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than compounds of formula I), one or more anti-obesity agents, and/or one or more lipid-lowering agents, one or more lipid modulating agents (including anti-
10 atherosclerosis agents), other types of anti-atherosclerosis agents, and/or one or more antiplatelet agents, one or more agents for treating hypertension, one or more anti-cancer drugs, one or more agents for treating arthritis, one or more anti-osteoporosis agents,
15 one or more anti-obesity agents, one or more agents for treating immunomodulatory diseases, and/or one or more agents for treating anorexia nervosa.

The term "lipid-modulating" agent as employed herein refers to agents which lower LDL and/or raise HDL
20 and/or lower triglycerides and/or lower total cholesterol and/or other known mechanisms for therapeutically treating lipid disorders.

The term "other types of anti-atherosclerosis agents" as employed herein refers to conventional anti-
25 atherosclerosis agents including lipoxxygenase inhibitors, ACAT inhibitors, antioxidants, PPAR δ agonists, phospholipase inhibitors including PLA-2 inhibitors and/or other known anti-atherosclerotic agents.

The terms pharmaceutically acceptable "salt" and
30 "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,
35 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

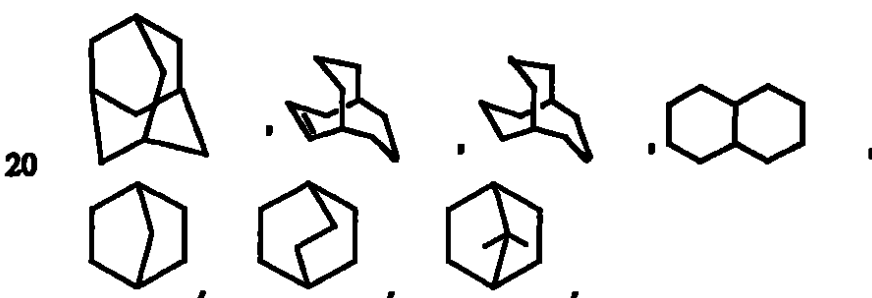
like; and zwitterions, the so-called "inner salts".
Nontoxic, pharmaceutically acceptable salts are preferred, although other salts are also useful, e.g., in isolating or purifying the product.

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,

cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl, cycloheteroalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, 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 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 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, 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.

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-butylnyl, 2-butylnyl, 4-pentylnyl, 3-pentylnyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonylnyl, 4-decynyl, 3-undecynyl,
35 4-dodecynyl and the like, and which may be optionally

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 "arylalkenyl" and "arylalkynyl" 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".

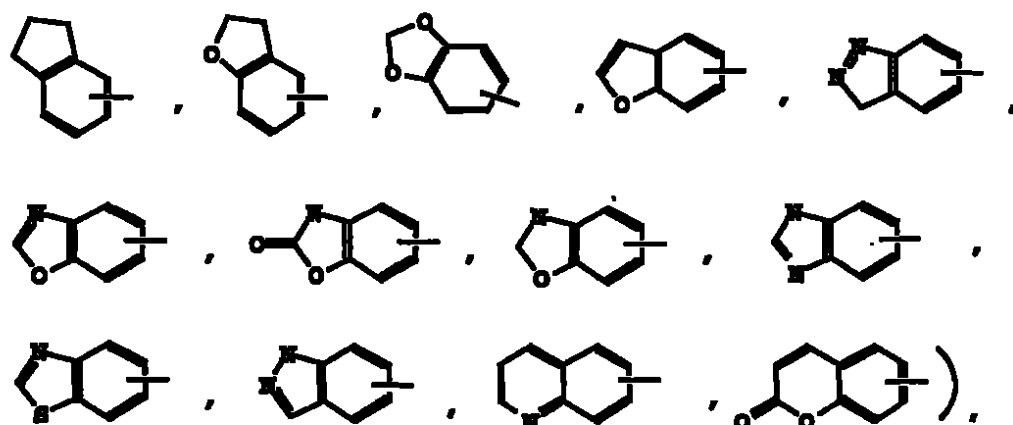
The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3 , with chlorine or fluorine being preferred.

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
5 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, alkylaminocarbonyl, arylaminocarbonyl, alkoxy carbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino,
25 arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl and/or any of the alkyl substituents set out herein.

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

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.

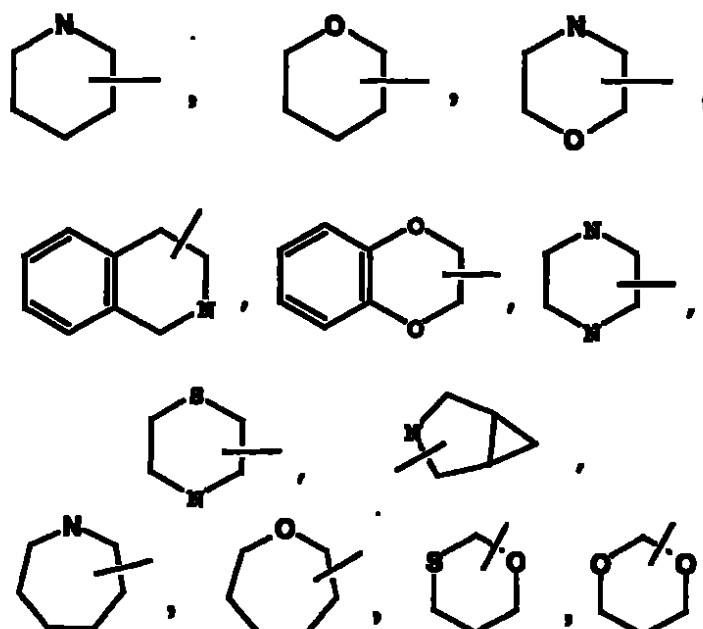
Unless otherwise indicated, the term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

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 $\left(\overset{\text{O}}{\underset{\text{C}}{\parallel}} \right)$ group; examples of acyl groups include any of the R¹ 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



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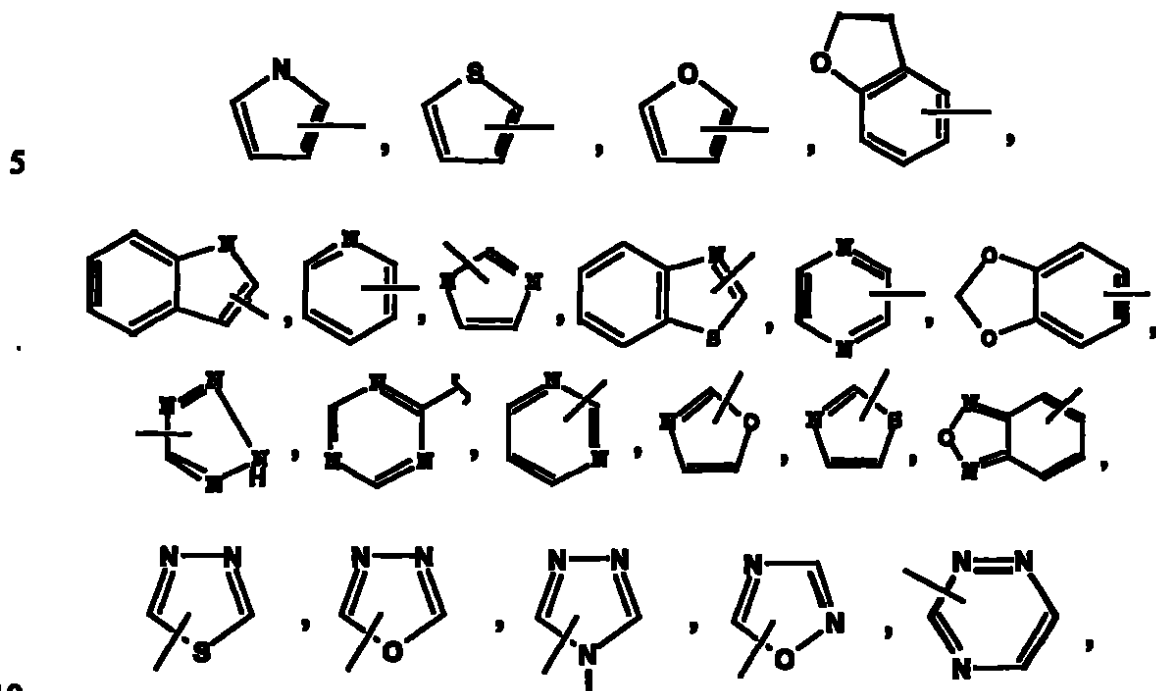
and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the alkyl substituents set out herein. In addition, any of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

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 $(CH_2)_r$ chain.

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 $-(CH_2)_r-$ chain, alkylene or alkenylene as defined above.

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 $CF_3CF_2CH_2$.

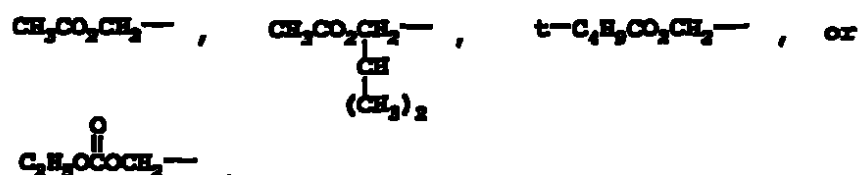
The term "polyhaloalkoxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo

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

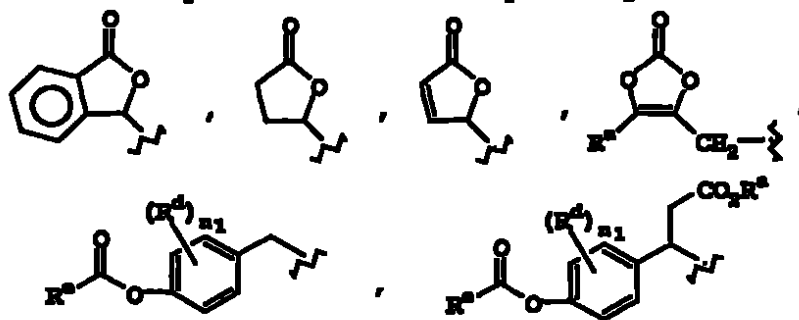
All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one or the R substituents. Consequently, compounds of formula 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, 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 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.

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 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.

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 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 CH₂CN or POCl₃).

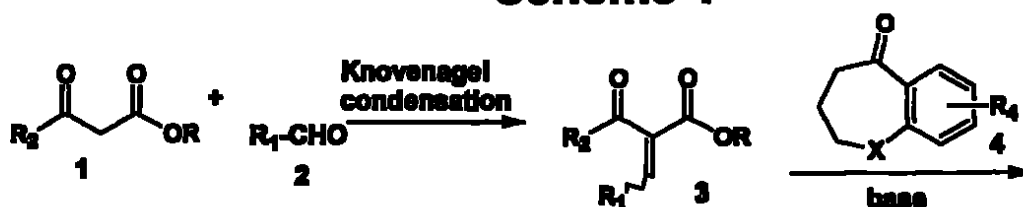
Conversion of halide 8 to the phosphorus compound 9 where W is Ph or alkyl is effected by treatment of 8 with W₂POEt in toluene. Conversion of halide 8 to compound 9 where W

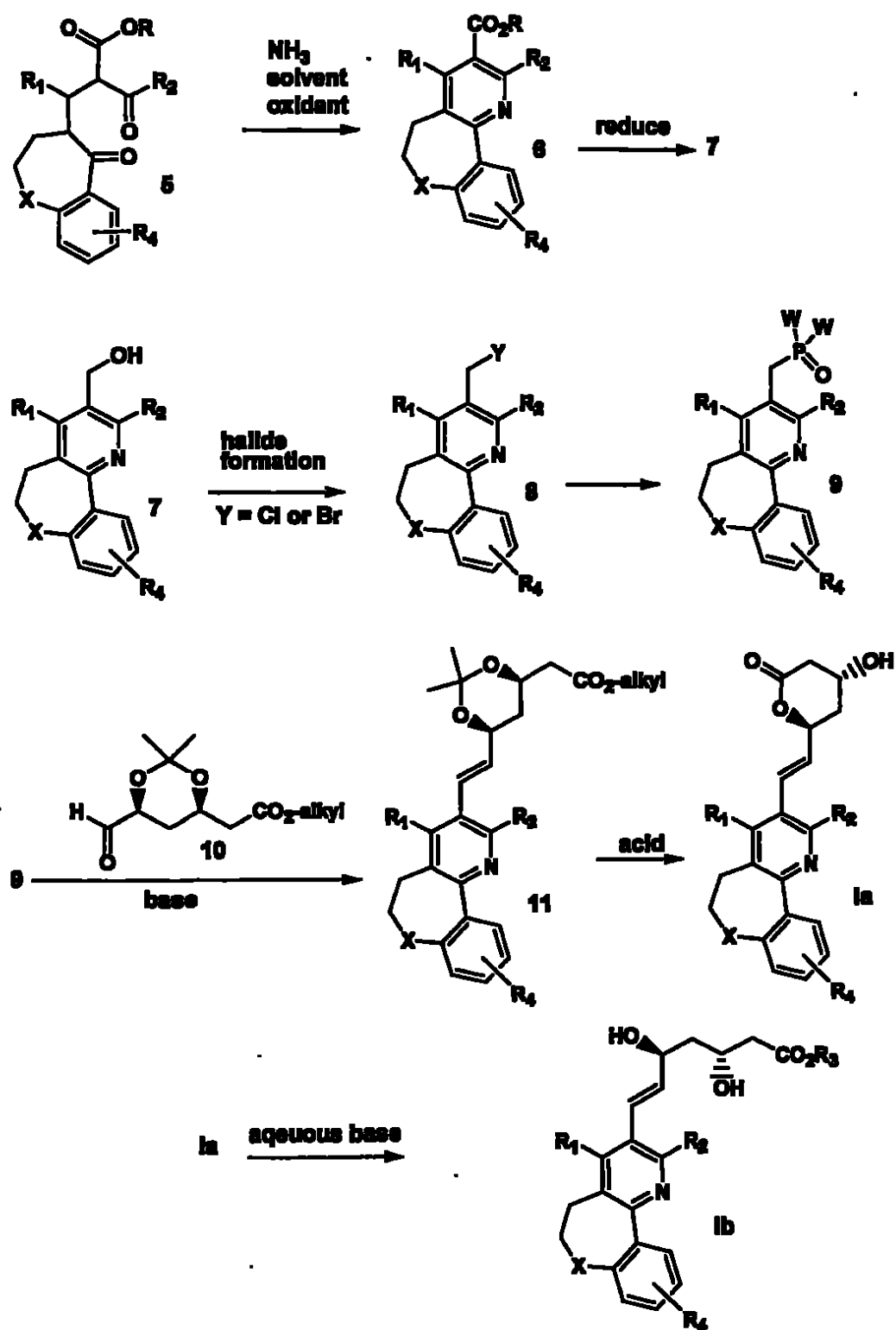
- is OR (R is lower alkyl) may be effected by the reaction of 8 with HOP(OR)_2 /base/THF or by Arbuzov reaction with P(OR)_3 . Wittig reaction between 9 and aldehyde 10 (aldehyde 10 has been previously described in US patent 5,686,433) may be effected under standard conditions with base (n-BuLi, LiN(TMS)_2 , LDA) in an appropriate solvent (THF, Et_2O , 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.
- 10 Saponification of Ia to Ib (where R_2 is alkali metal, or alkaline earth metal) can be effected by treatment of Ia with aqueous base or subsequently acidified to give Ib where R_2 is H. Additionally, Ia can be treated with an alcohol of the type R_2OH under basic conditions to form
- 15 the corresponding esters of Ib.

- As seen in Reaction Scheme 2, the saturated derivatives of compound I (where ~~2,2,2~~ is $\text{CH}_2\text{-CH}_2$) are obtained by catalytic (Pd/C, Pt/C, Pd(OH)_2) hydrogenation of 11, Ia, or Ib to afford 12, Ic, or Id, respectively.
- 20 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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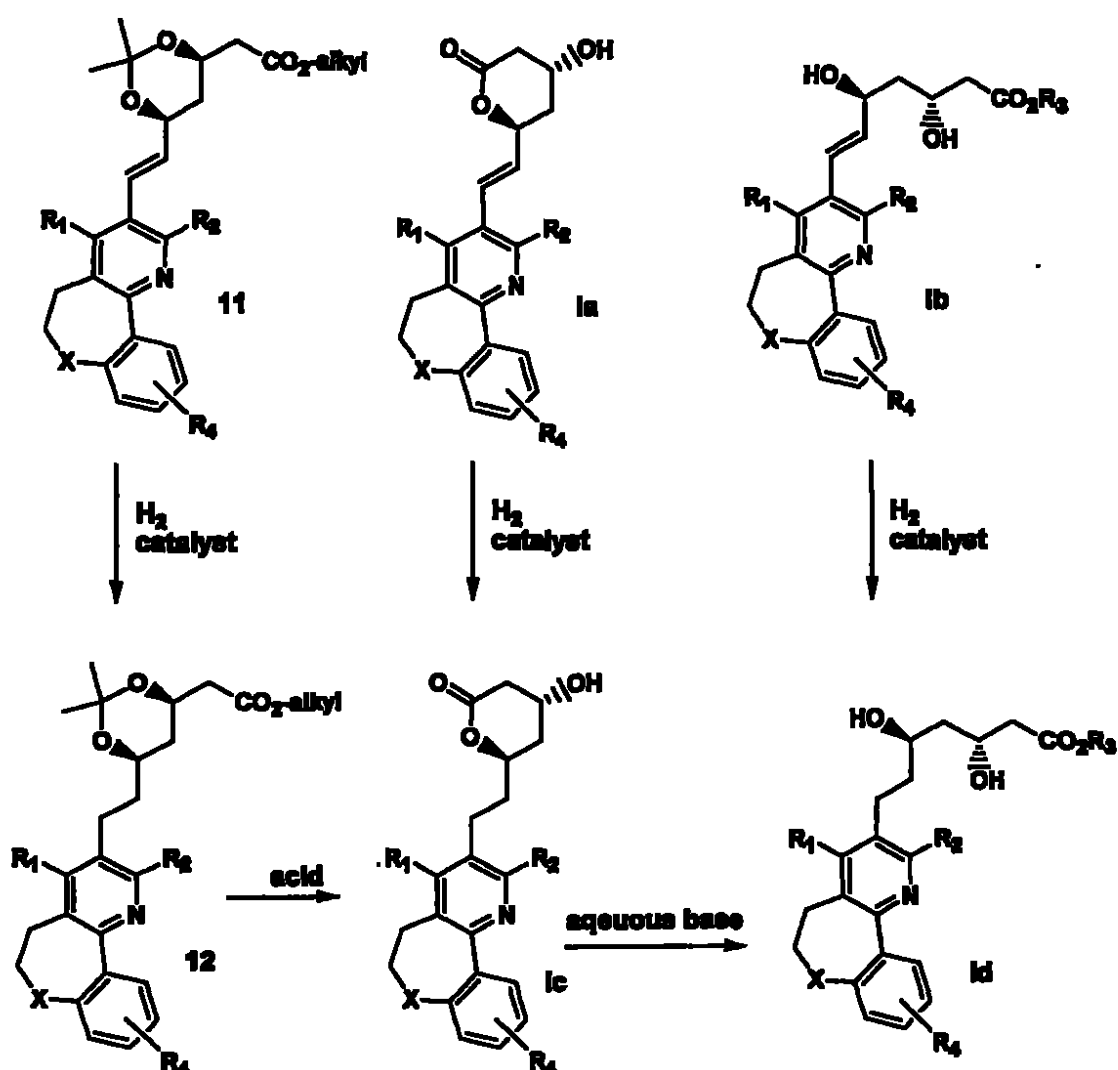
Scheme 1





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Scheme 2

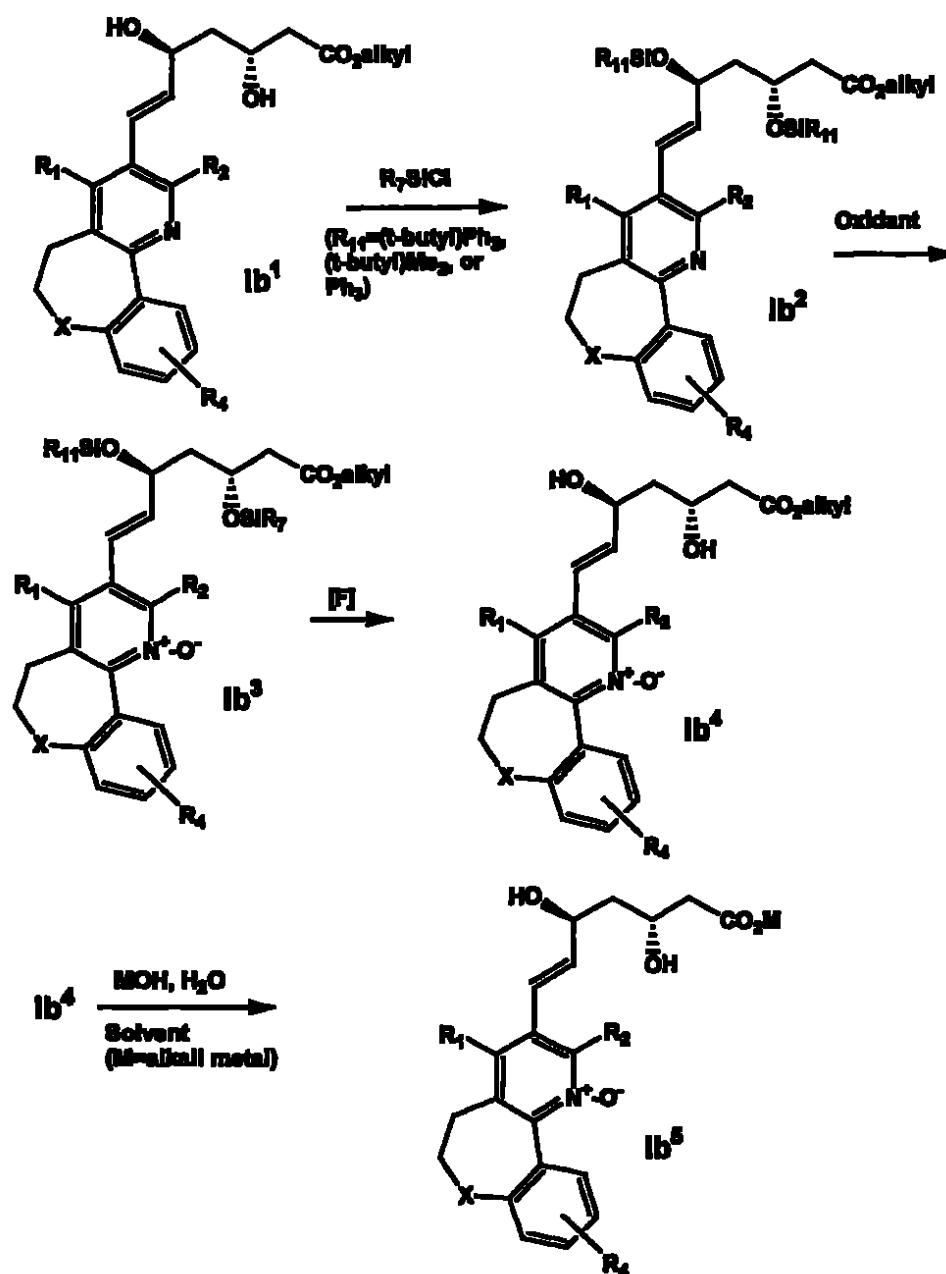


The synthesis of compounds I wherein ~~CH=CH~~ is CH=CH and n is 1, is described in Scheme 3. Bis-silylation of compound Ib¹ with a bulky silylchloride (e.g., ClSi(t-butyl)Ph₂, ClSi(t-butyl)Me₂, ClSiPh₃) in the presence of a suitable base (e.g., TEA, imidazole, pyridine) and solvent (e.g., CH₂Cl₂, THF) provides compound Ib². Treatment of Ib² with oxidants such as m-CPBA or CF₃CO₃H in an appropriate solvent such as CH₂Cl₂ or HOAc affords N-oxide Ib³. Desilylation of Ib³ (TBAF/HOAc/THF or 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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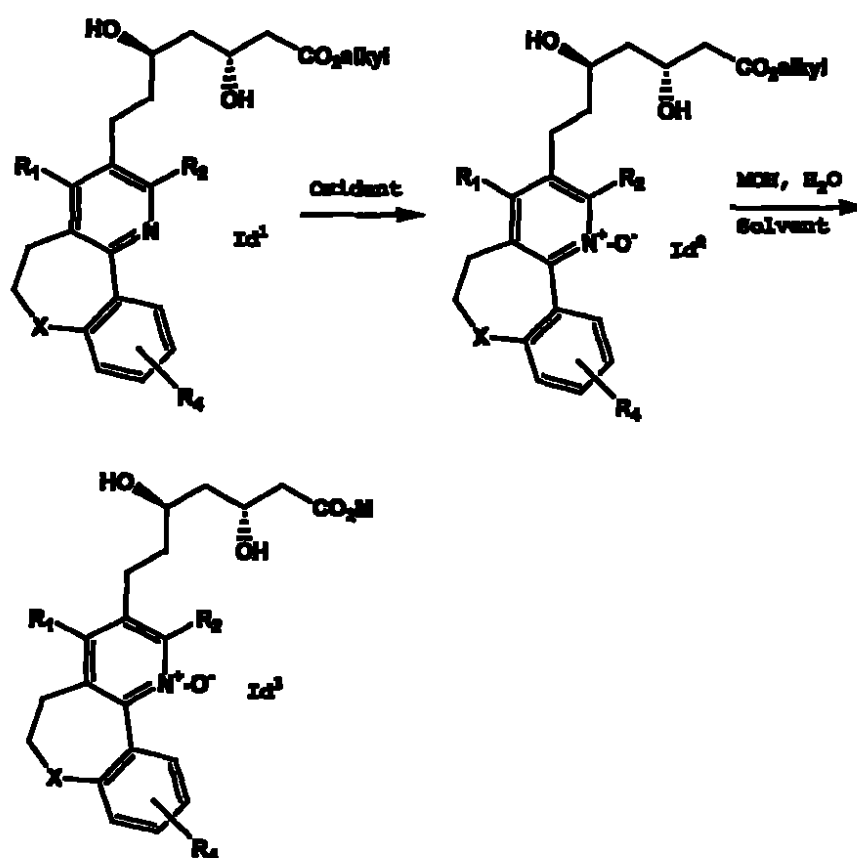
SCHEME 3



Additionally, compound Id¹ may be oxidized and saponified, as described above, to provide compounds I wherein ~~is~~ 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.

Scheme 5 depicts a preferred method for preparing the HMG CoA reductase inhibitor of formula I of the invention using the Julia-Kocienski olefination reaction
20 employing 4-pyridyl carboxylaldehyde (18) and chiral

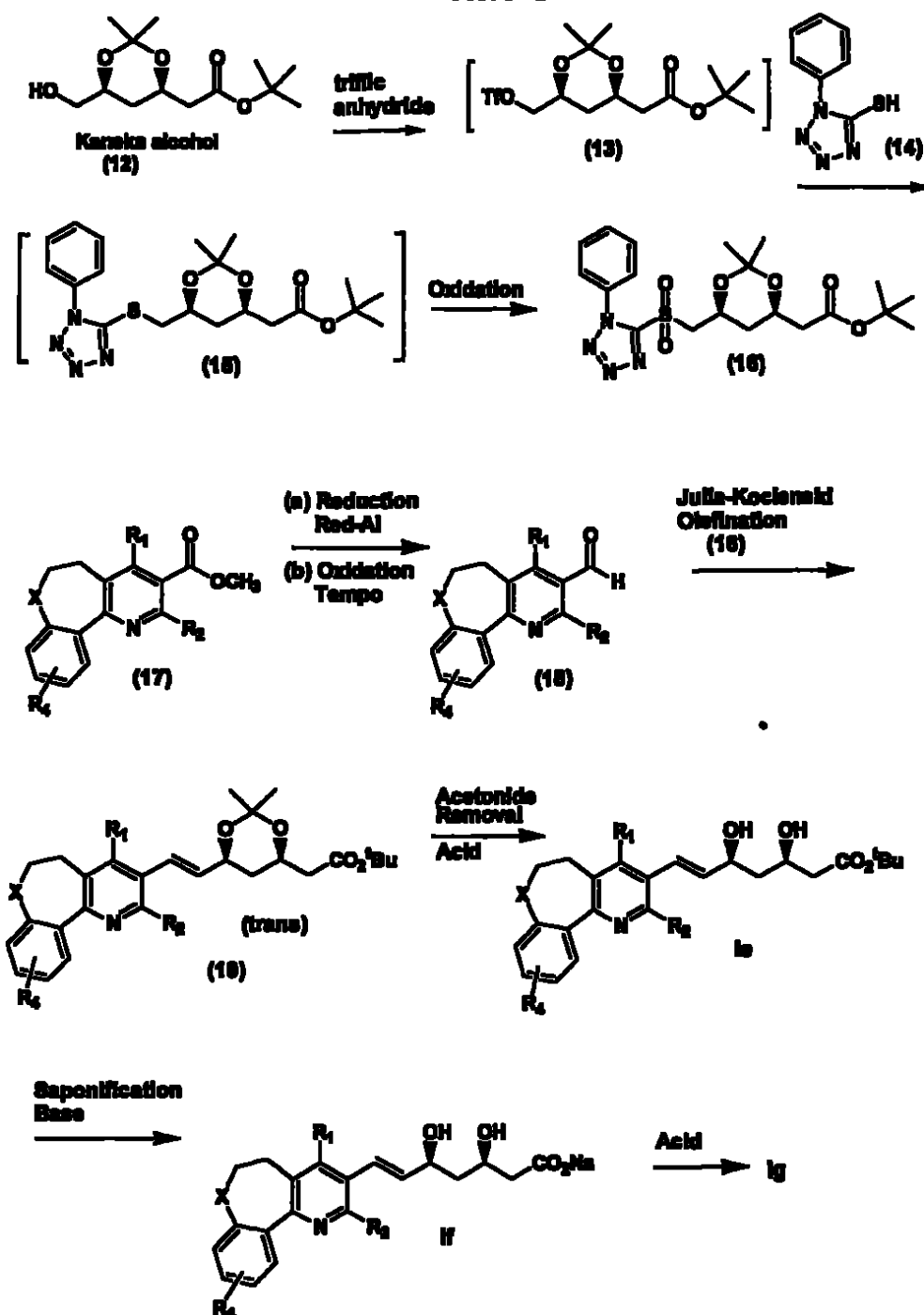
sulfone (16). The desired *trans* intermediate (19) is isolated in high yield and optical purity which is converted to the final product of the invention. As will be seen, the chiral sulfone (16), a key intermediate in the Julia-Kocienski step, is prepared in three steps starting from the commercially available Kaneka alcohol (12) via triflate (13) and sulfide intermediate (15).

Referring to Scheme 5, treatment of commercially available chiral alcohol (12) with triflic anhydride and triethylamine in dichloromethane at low temperature (for example 0 to -30°C) affords triflate (13). Other pyridine or amine bases may be employed. Triflate (13) (without being isolated) is carried onto the next step without further purification. A methylene chloride solution of triflate (13) is treated with 1-phenyl-1H-tetrazole-5-thiol (14) to provide the chiral sulfide (15) which is oxidized with hydrogen peroxide in the presence of catalytic ammonium heptamolybdate tetrahydrate to give crystalline sulfone (16). Other oxidant, such as *m*-chloro-*p*-benzoic acid (mCPBA) may be employed.

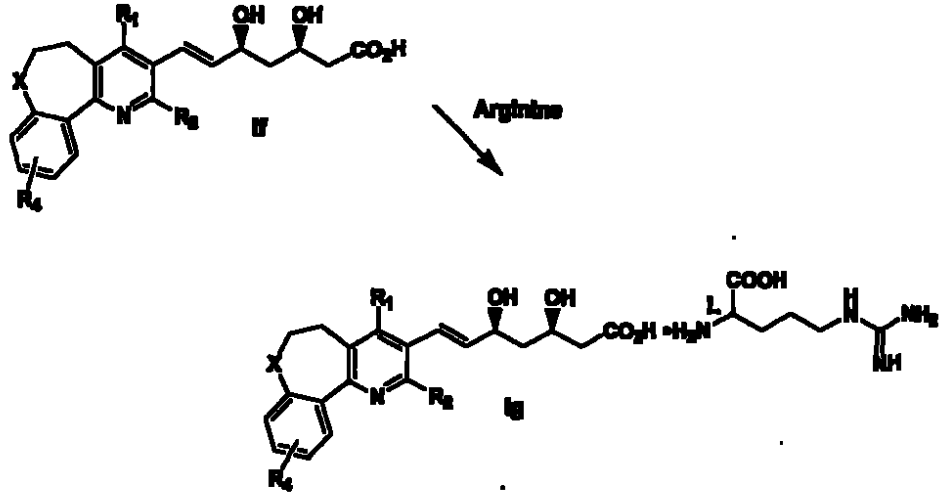
Addition of LiHMDS or NaHMDS to a mixture of sulfone (16) and pyridine carboxylaldehyde (18) in THF at low temperature (-78 to -35°C) provides *trans* olefin (19) in high diastereoselectivity (>99%).

The pyridine aldehyde (18) is obtained as a crystalline solid from the corresponding ester (17). Reduction of ester (17) with Red-Al followed by oxidation with Tempo (2,2,6,6-tetramethyl-1-piperidinyloxy) gives aldehyde (18) in high yield. The final compound 1e of the invention is prepared in a one pot procedure starting from (19) without isolating any intermediates. Removal of acetonide under acidic condition provides diol 1e of the invention which upon further treatment with sodium hydroxide gives the sodium salt of the acid 1f of the invention. Subsequent treatment of 1f with acid followed by the addition of arginine produces crystalline arginine salt of the invention 1g.

Scheme 5

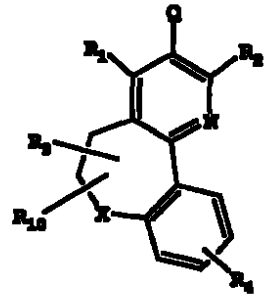


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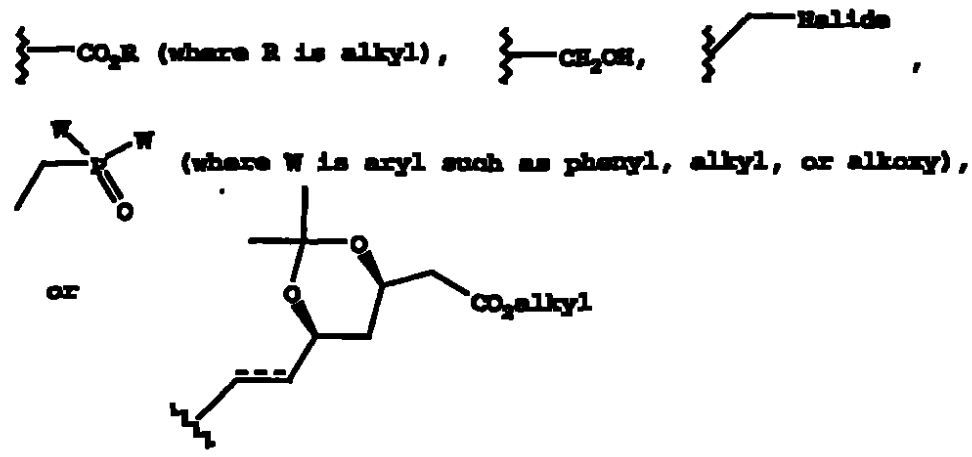


In addition, in accordance with the present invention, intermediates 6, 7, 8, 9, 11 and 12 are novel compounds and form part of the present invention. These compounds have the general structure

II

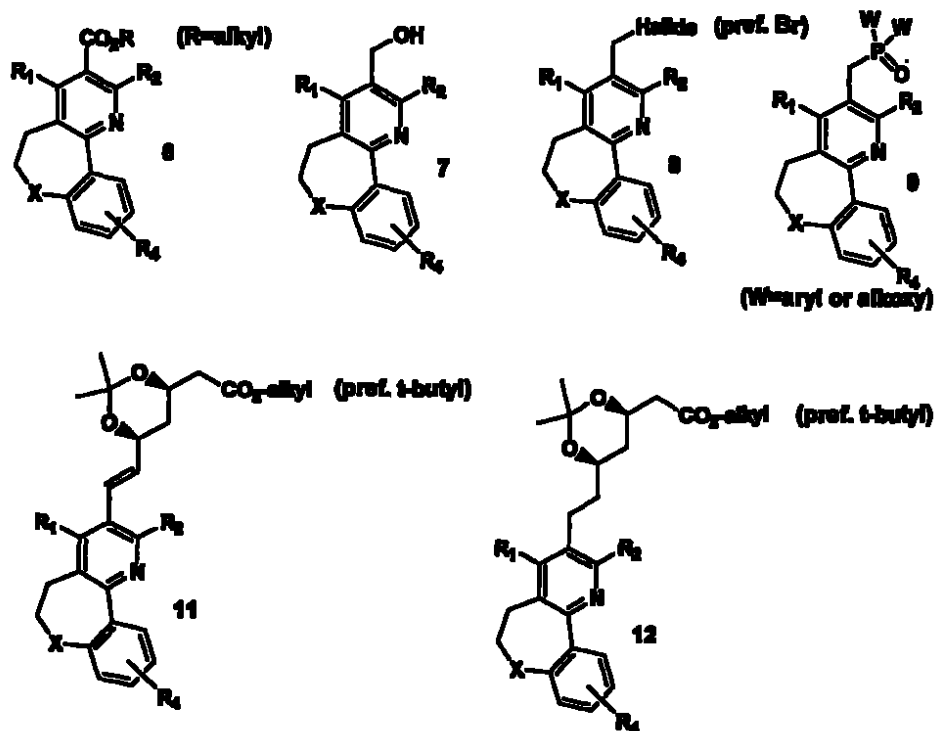


10 wherein X is O, S or NR_7 , R_1 , R_2 , R_4 , R_7 , R_9 and R_{10} as are as defined above, Q is



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



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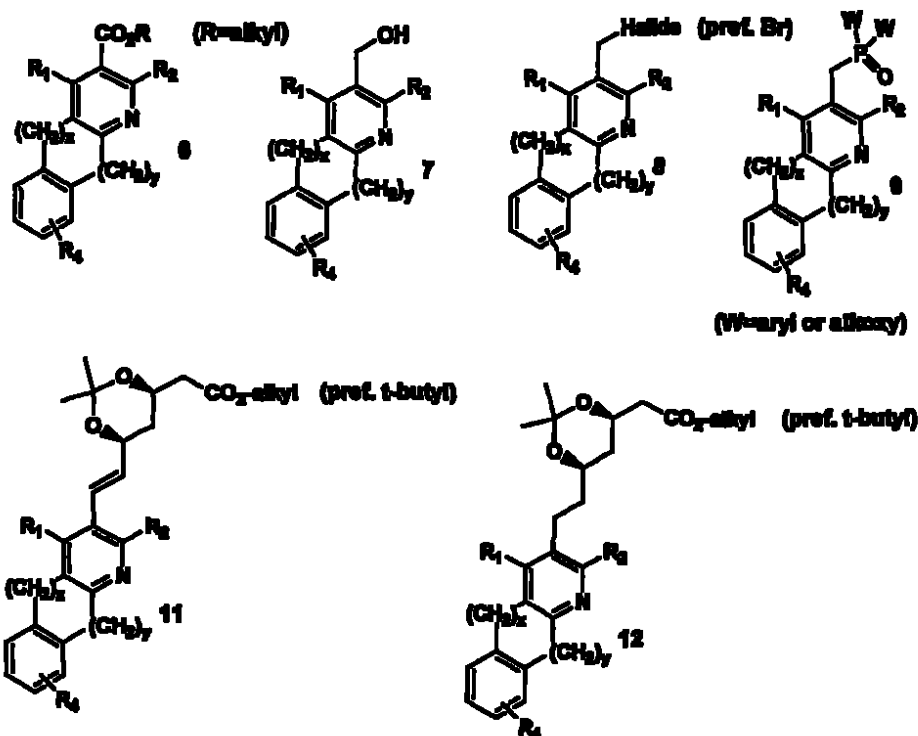
Compounds 6, 7, 8, 9, 11 and/or 12 may include R_9 and R_{10} substituents.

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.

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

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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.

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, lovastatin, cerivastatin, visastatin (or rosuvastatin) (Astra Zeneca ZD4522), fluvastatin, itavastatin (or pitavastatin) 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 association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles of 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.

10 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 (or rosuvastatin), atorvastatin, cerivastatin, 15 fluvastatin, itavastatin (or pitavastatin), 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 20 4 times per day, preferably 0.2 to 100 mg daily or in sustained release form.

The HMG CoA reductase inhibitors of formula I may be employed in combination with all therapeutic agents which are useful in combination with HMG CoA reductase inhibitors. 25

Thus, where desired, the compounds of structure I may be used in combination with one or more hypolipidemic agents or lipid-lowering agents, or lipid agents, or lipid modulating agents, and/or one or more other types of therapeutic agents including antidiabetic agents, 30 anti-obesity agents, antihypertensive agents, platelet aggregation inhibitors, anti-Alzheimer's agents, anti-dementia agents, anti-osteoporosis agents, and/or hormone replacement therapeutic agents, and/or other therapeutic agents, and/or other cardiovascular agents (including 35 anti-anginal agents, anti-arrhythmic agents, anti-atherosclerosis agents, anti-inflammatory agents, anti-

platelet agents, anti-heart failure agents), anti-cancer agents, anti-infective agents, hormone replacement agents, growth hormone secretagogues, selective androgen receptor modulators, and/or other therapeutic agents
5 which may be administered orally in the same dosage form or in a separate oral dosage form, or by injection.

The hypolipidemic agent or lipid-lowering agent or other lipid agent or lipid modulating agent which may be optionally employed in combination with the compounds of
10 formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, PPAR α agonists, PPAR dual α/γ agonists, PPAR δ agonists, fibric acid derivatives, ACAT inhibitors, lipoxxygenase inhibitors, cholesterol
15 absorption inhibitors, ileal Na⁺/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, cholesteryl ester transfer protein inhibitors, bile acid sequestrants, and/or nicotinic acid and derivatives thereof.

20 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.
25 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
30 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.

35 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

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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 -phosphonosulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)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 (Rhône-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 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.

The other hypolipidemic agent may be an ACAT inhibitor (which also has anti-atherosclerosis activity) 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, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCK 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfanyl-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

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activities in experimental animals", Krause et al,
Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Manfred
A., Inflammation: Mediators Pathways (1995), 173-98,
Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors:
5 potential anti-atherosclerotic agents", Sliskovic et al,
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
10 of acyl-CoA:cholesterol acyltransferase (ACAT). 7.
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
15 Pharmaceutical Co. Ltd), as well as F-1394, CS-505,
F-12511, HL-004, K-10085 and YIC-CS-434.

The hypolipidemic agent may be an upregulator of
LDL receptor activity such as MD-700 (Taisho
Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

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

25 The other lipid agent or lipid-modulating agent
may be a cholesteryl transfer protein inhibitor (CETP)
such as Pfizer's CP-529,414 as well as those disclosed in
WO/0038722 and in EP 818448 (Bayer) and EP 992496, and
Pharmacia's SC-744 and SC-795 as well as CETi-1 and
30 JTT-705.

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

35 The ATP citrate lyase inhibitor which may be
employed in the combination of the invention may include,
for example, those disclosed in U.S. Patent No.
5,447,954.

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The other lipid agent also includes a phytoestrogen compound such as disclosed in WO 00/30665 including isolated soy bean protein, soy protein concentrate or soy flour as well as an isoflavone such as genistein, daidzein, glycitein or equol, or phytosterols, phytostanol or tocotrienol as disclosed in WO 2000/015201;

- a beta-lactam cholesterol absorption inhibitor such as disclosed in EP 675714;
- 10 an HDL upregulator such as an LXR agonist, a PPAR α -agonist and/or an FXR agonist;
- an α -glucosidase inhibitor, an aldose reductase inhibitor and/or an LDL catabolism promoter such as disclosed in EP 1022272;
- 15 a sodium-proton exchange inhibitor such as disclosed in DE 19622222;
- an LDL-receptor inducer or a steroidal glycoside such as disclosed in U.S. Patent No. 5,698,527 and GB 2304106;
- 20 an anti-oxidant such as beta-carotene, ascorbic acid, α -tocopherol or retinol as disclosed in WO 94/15592 as well as Vitamin C and an antihomocysteine agent such as folic acid, a folate, Vitamin B6, Vitamin B12 and Vitamin E;
- 25 isoniazid as disclosed in WO 97/35576;
- a cholesterol absorption inhibitor, an HMG-CoA synthase inhibitor, or a lanosterol demethylase inhibitor as disclosed in WO 97/48701;
- a PPAR δ agonist for treating dyslipidemia;
- 30 or a sterol regulating element binding protein-I (SREBP-1) as disclosed in WO 2000/050574, for example, a sphingolipid, such as ceramide, or neutral sphingomyelinase (N-SMase) or fragment thereof.

Preferred hypolipidemic agents are pravastatin, 35 lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, pitavastatin and rosuvastatin, as well as niacin and/or cholestagel.

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 or as otherwise known in the art.

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.

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.

The dosages and formulations for the hypolipidemic agent or other lipid agent or lipid modulating agent will be as disclosed in the various patents and applications discussed above.

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

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.

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 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,

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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
5 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
10 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
15 from about 25 to about 200 mg.

The anti-atherosclerotic agent includes 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
20 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
25 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
30 agent may be employed together in the same oral dosage 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
35 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 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, aldose reductase inhibitors, PPAR γ agonists such as thiazolidinediones, PPAR α agonists (such as fibric acid derivatives), PPAR δ antagonists or agonists, α P2 inhibitors, PPAR α/γ dual agonists, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, glycogen phosphorylase inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1), and/or a PTP-1B inhibitor (protein tyrosine phosphatase-1B inhibitor).

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, 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 0.05:1 to about 10:1.

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

The compounds of structure I may also be employed in combination with a antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) or mimetic such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 t

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Habener, the disclosure of which is incorporated herein by reference), as well as AC2993 (Amylen) and LY-315902 (Lilly), which may be administered via injection, intranasal, inhalation or by transdermal or buccal devices.

Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyrider, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference (PDR).

Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

Where present, the PPAR anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present insulin and other anti-diabetic agents as set out above may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides or mimetics may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

The antidiabetic agent or other lipid agent may also be a PPAR modulator such as a PPAR α/γ dual agonist such as AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid

5 Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998), and in U.S. application Serial No. 09/664,598, filed September 18, 2000, (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. application Serial No. 09/679,027, filed October 4, 2000 (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 α P2 inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. application Serial No. 09/519,079, filed March 6, 2000 (attorney file LA27), employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

20 The antidiabetic agent may be a DP4 inhibitor such as disclosed in application Serial No. 09/788,173, filed February 16, 2001 (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-(S)-pyrrolidine) (Novartis) (preferred) as 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 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.

35 The meglitinide which may optionally be employed in combination with the compound of formula I of the

invention may be repaglinide or Starlix® (Novartis), nateglinide (Novartis) or KAD1229 (PF/Kissei), with repaglinide being preferred.

5 The antidiabetic compound may be a melanocortin receptor agonist such as a spiropiperidine as disclosed in WO 99/64002.

The HMG CoA reductase inhibitor of formula I will be employed in a weight ratio to the meglitinide, PPAR modulator such as a PPAR γ agonist, PPAR α agonist, PPAR δ 10 agonists or antagonist, PPAR α/γ dual agonist, aP2 inhibitor, DP4 inhibitor or SGLT2 inhibitor or other antidiabetic agent within the range from about 0.01:1 to about 100:1, preferably from about 0.05:1 to about 10:1.

The other type of therapeutic agent which may be 15 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 inhibitor, a serotonin (and dopamine) reuptake inhibitor, an aP2 inhibitor, a thyroid receptor beta drug, a PTP-1B 20 inhibitor, an anorectic agent, a PPAR modulator including PPAR γ antagonists, PPAR α agonists, PPAR δ antagonists, a CCKA agonist, a leptin inhibitor such as a leptin receptor activator, a neuropeptide Y antagonist, a melanocortin-4-receptor (MC4R) agonist, a fatty acid 25 oxidation upregulator or inducer (such as Famoxin® Genset).

The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of formula I may be AJ9677 (Takeda/Dainippon), L750355 30 (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.

5 The neuropeptide Y antagonists which may be optionally employed in combination with a compound of formula I include those described in WO 0113917 (BMS) or in U.S. Patent No. 6,218,408 (Synaptic) and in WO 0114376 (Banyu).

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.

10 The serotonin (and dopamine) reuptake inhibitor 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.

15 The thyroid receptor beta compound which may be 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), GB98/284425 (KaroBio), and U.S. Provisional Application
20 60/183,223 filed February 17, 2000, with compounds of the KaroBio applications and the above U.S. provisional application being preferred.

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

The CCKA agonists which may be employed herein include Glaxo-SmithKline's GI-181,771 and Sanofi's SR146,131.

30 The PTP-1B inhibitor which may be an anti-obesity and/or an antidiabetic agent include those disclosed in WO 99/585,521, WO 99/58518, WO 99/58522 and WO 99/61435.

The anti-obesity agent employed may also be Pfizer's P57 or CP-644,673 (licensed from Phytopharm).

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.

5 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 inhibitors such as candoxatril, NEP/ACE inhibitors, as well as calcium channel blockers
10 (such as verapamil and amlodipine besylate), T-channel calcium antagonists (such as mibefradil), β -adrenergic blockers, diuretics, α -adrenergic blockers (such as doxazosin mesylate and terazosin HCl), dual action receptor antagonists (DARA), heart failure drugs such as
15 digoxin, and other types of antihypertensive agents.

 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.
20 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 mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U.S. Pat. No. 4,316,906 with
25 zofenopril being preferred.

 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.

30 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), indalapril (delapril) disclosed in U.S. Pat. No. 4,385,051; indolapril (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)

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disclosed in U.S. Pat. No. 4,344,949 and CI925 (Warner-Lambert) ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(ethoxycarbonyl)-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).

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.

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, gemopatrilat ([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.

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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
5 more preferably from about 10 to about 150 mg.

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
10 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.

15 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).

Dual action receptor antagonists (DARA) suitable
20 for use herein include those disclosed in U.S. applications Serial No. 09/513,779, filed February 25, 2000, and Serial No. 09/604,322, filed June 26, 2000.

Other examples of preferred antihypertensive agents suitable for use herein include omapatrilat (Vanlev®),
25 gemopatrilat, amlodipine besylate (Norvasc®), prazosin HCl (Minipress®), verapamil, nifedipine, diltiazem, felodipine, nisoldipine, isradipine, nicardipine, beta blockers such as nadolol, atenolol (Tenormin®), sotalol, terazosin, doxazosin, carvedilol, and propranolol, and
30 clonidine HCl (Catapres®).

Diuretics which may be employed in combination with compounds of formula I include hydrochlorothiazide, torasemide, furosemide, spironolactone, and indapamide.

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Antiplaquet agents which may be employed in combination with compounds of formula I of the invention include aspirin, clopidogrel, ticlopidine, dipyridamole, abciximab, tirofiban, eptifibatide, anagrelide, and
5 ifetroban, with clopidogrel and aspirin being preferred.

The antihypertensive agents, diuretics and 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.

10 Anti-Alzheimer's agents or anti-dementia agents suitable for use herein with the HMG CoA reductase inhibitors of the invention include tacrine HCl (Cognex) and donepezil (Aricept®), as well as γ -secretase inhibitors, β -secretase inhibitors and/or
15 antihypertensive agents. Dosages employed will be as set out in the PDR.

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

The hormone replacement therapeutic agents, where present, will be employed in dosages as set out in the
25 latest edition of the PDR. Examples of such agents include selective estrogen receptor modulators (SERMs) such as raloxifen, tamoxifen or lasoxifen.

The HMG CoA reductase compound of the invention may also be employed in combination with a tyrosine kinase
30 inhibitor such as disclosed in WO 2000/053605;

the selective androgen receptor modulator suitable for use herein may be LGD-2226 (Ligand);

the antiarrhythmic agents suitable for use herein include β -blockers as set out herein including sotalol
35 and amioderome, calcium channel blockers as set out herein including verapamil, nifedipine, amlodipine-besylate, and diltiazem, which may also be used in

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combination with a debrillator device such as a pace maker;

coenzyme Q sub. 10 such as disclosed in U.S. Patent No. 5,316,765, 4,933,165, 4,929,437;

5 an agent that upregulates type III endothelial cell nitric acid syntase such as disclosed in WO 2000/003746;

a chondroprotective compound such as a polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate
10 (PPS), doxycycline or minocycline, such as disclosed in EP 970694;

a cyclooxygenase (COX)-2 inhibitor, such as celecoxib (Celebrex® (Searle)) or rofecoxib (Vioxx® (Merck)) or a glycoprotein IIa/IIIb receptor antagonist
15 such as disclosed in WO 99/45913 and tirofiban or abciximab;

a 5-HT reuptake inhibitor such as disclosed in WO 99/44609;

anti-anginal agents such as vasodilators, for
20 example, isosorbide dinitrate, or nitroglycerin;

a growth hormone secretagogue such as disclosed in U.S. applications Serial No. 09/662,448, filed September 14, 2000, and U.S. Provisional application 60/203,335, filed May 11, 2000, and MK-677 (Merck), Pfizer's CP-
25 424391 and Lilly's LY 444,711;

anti-atherosclerosis agents such as ACAT inhibitors and lipoxxygenase inhibitors as described herein and phospholipase A-2 inhibitors such as S-3013 and SB-435,495 (which are also anti-inflammatory agents);

30 anti-infective agents such as quinolones, for example, ciprofloxacin, ofloxacin, and Tequin® (Bristol-Myers Squibb), macrolides such as erythromycin and clarithromycin (Biaxin® (Abbott)), and azithromycin (Zithromax (Pfizer)); or

35 an immunosuppressant (for use in transplantations) such as cyclosporine, mycophenolate mofetil, azathioprine and the like.

As used herein, the phrase "antineoplastic agent" refers to compounds which prevent cancer cells from multiplying. In general, the antineoplastic agents used herein prevent cancer cells from multiplying by: (1) interfering with the cell's ability to replicate DNA, or (2) inducing apoptosis in the cancerous cells.

Examples of antineoplastic agents which are suitable for use in combinations of this invention include, but are not limited to, microtubule-stabilizing agents such as the taxanes, for example, paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), 7-O-methylthio-methylpaclitaxel (disclosed in U.S. 5,646,176), 3'-tert-butyl-3'-N-tert-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel (disclosed in USSN 60/179,965 filed on February 3, 2000, and example 17 herein), C-4 methyl carbonate paclitaxel (disclosed in WO 94/14787), the epothilone, such as epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione (disclosed in WO 99/02514), [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]-heptadecane-5,9-dione (disclosed in USSN 09/506,481 filed on February 17, 2000, and examples 7 and 8 herein), and derivatives thereof; microtubule-disruptor agents; alkylating agents; anti-metabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers; growth inhibitors; hormonal/antihormonal therapeutic agents; and haematopoietic growth factors.



Other classes of antineoplastic agents suitable for use in the method of the present invention include, but are not limited to, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the
5 cytotoxic nucleosides, discodermolide, the pteridine family of drugs, diynenes, aromatase inhibitors, and the podophyllotoxins. Particularly useful members of those classes not previously mentioned include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin,
10 methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan,
15 vinblastine, vincristine, leurosidine, vindesine, leurosine, and the like. Other useful antineoplastic agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosfamide, melphalan, hexamethyl melamine, thiotepa, cytarabin,
20 idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, and interleukins.

It will be appreciated that unless otherwise
25 specified the dosage regiment for therapeutic agents used in combination with the compounds of the invention will be as specified in the PDR.

In carrying out the method of the invention for treating hypercholesterolemia, hyperlipidemia,
30 hyperlipoproteinemia, hypertriglyceridemia, or atherosclerosis, and related diseases, or Alzheimer's disease or osteoporosis, or other disclosures as set out hereinbefore, a pharmaceutical composition will be employed containing the compounds of structure I, with or
35 without other cholesterol lowering agents, osteoporosis agents, Alzheimer's agents, antidiabetic agent(s) and/or antihyperlipidemic agent(s) and/or other type therapeutic

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agents in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be 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 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 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 individual doses from 1-4 times per day and also single dose once weekly (5 to 1000 mg).

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 physiological saline, to produce an injectable preparation.

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

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

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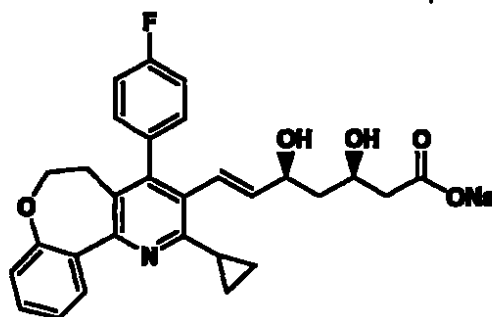
- Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
DIPEA = diisopropyl ethylamine
PTSH = N-phenylthiotetrazole
PPh₃ = triphenylphosphine
5 NMO = methylmorpholine N-oxide
TPAP = tetrapropylammonium perruthenate
DEAD = diethyl azodicarboxylate
HOAc or AcOH = acetic acid
TFA = trifluoroacetic acid
10 Et₂NH = diethylamine
NMM = N-methyl morpholine
n-BuLi = n-butyllithium
Pd/C = palladium on carbon
PtO₂ = platinum oxide
15 MTBE = methyl t-butyl ether
DI water = dionized water
TEA = triethylamine
EDAC = 3-ethyl-3'-(dimethylamino)propyl-carbodiimide
hydrochloride (or 1-[(3-(dimethylamino)propyl)]-3-
20 ethylcarbodiimide hydrochloride)
HOBT or HOBT.H₂O = 1-hydroxybenzotriazole hydrate
HOAT = 1-hydroxy-7-azabenzotriazole
PyBOP reagent = benzotriazol-1-yloxy-tripyrrolidino
phosphonium hexafluorophosphate
25 LiN(TMS)₂ = Libis(trimethylsilyl)amide
DIBAL = diisobutylaluminum hydride
LDA = lithium diisopropylamide
DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
AcCN = acetonitrile
30 LiHMDS = lithium bis(trimethylsilyl)amide
NaHMDS = sodium bis(trimethylsilyl)amide
Red-AL = sodium bis(2-methoxyethoxy)aluminum hydride
mCPBA = m-chloro-p-benzoic acid
min = minute(s)
35 h or hr = hour(s)
L = liter
mL = milliliter

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- μL = microliter
g = gram(s)
mg = milligram(s)
mol = moles.
5 mmol = millimole(s)
meq = milliequivalent
RT, rt = room temperature
sat or sat'd = saturated
aq. = aqueous
10 TLC = thin layer chromatography
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass spectrometry
MS or Mass Spec = mass spectrometry
15 NMR = nuclear magnetic resonance
mp = melting point
Bp = boiling point

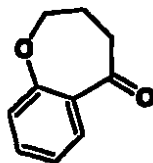
- The following Examples represent preferred
20 embodiments of the invention. Unless otherwise indicated, all temperatures are in degrees Centigrade.

Example 1



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A.

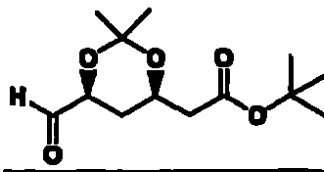


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A mixture of polyphosphoric acid (82.9 g) and dry
-xylene (30 ml) was heated to 105-110°C in an oil bath,
treated with a solution of 4-phenoxybutyric acid (25 g,
0.137 mole) in dry o-xylene (110 ml) and stirred at 105-
5 110°C for 2 hours. The reaction 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
with water (2 x 80 ml) and brine (80 ml), dried
10 (anhydrous Na_2SO_4), 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
(27.19 g) which was divided into two portions,
chromatographing each portion on a silica gel column,
15 (KM, 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).

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A(1).



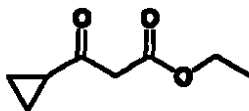
An oven-dried 3-neck 1-L flask equipped with
temperature sensor probe, 125-mL constant pressure
25 addition funnel and septum was charged with dry CH_2Cl_2 ,
(300 mL) and dry DMSO (20.9 mL, 0.2944 mol, 2.5 equiv)
under argon atmosphere; cooled to -75°C. Oxalyl chloride
(13.6 mL, 0.156 mol, 1.32 equiv) was added neat via
syringe dropwise over 15 min (temperature rose to -66°C),
30 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
35 -68°C). The resulting white mixture was stirred for 70

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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 , $R_f=0.52$). 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 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).

A(2).



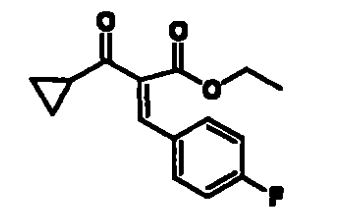
To a slurry of NaH (19.20 g, 480 mmol) and diethyl carbonate (80 mL) in a 3-neck 1L round bottom flask at room temperature was added a solution of cyclopropyl methylketone (23.5 mL, 238 mmol) in Et_2O (30 mL). Approximately 10% of the solution was added, and then 0.25 mL of EtOH was added to the reaction 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

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ceased and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was cooled in an ice-bath, diluted with Et₂O (200 mL), and treated with 1 N HCl with some ice to adjust to around pH 3. The
5 reaction mixture was extracted with Et₂O (3 x 150 mL). The Et₂O extracts were combined, washed with saturated aqueous NaHCO₃ (200 mL), H₂O (200 mL) and brine (200 mL), and dried (Na₂SO₄), filtered and concentrated under reduced pressure to give a yellow oil. The oil was
10 distilled under vacuum to give the title compound as a colorless oil, 28.5 g, 77%. B.p. = 94-96°C/8 mmHg.

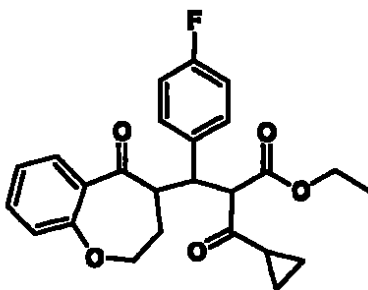
A(3).



15 To a stirred solution of part A(2) compound (28.24 g, 181 mmol) in benzene (128 mL) was added 4-fluorobenzaldehyde (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
20 with a Dean-Stark trap. After 16 h, the reaction was cooled to room temperature, diluted with Et₂O (250 mL), 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
25 flash chromatography (1:10 EtOAc/hexane) gave the title compound as a light yellow oil, 29 g, 61% yield.

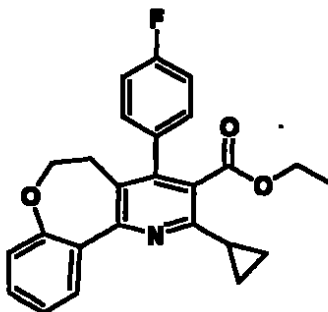
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B:



A solution of compound of Part A (7.21 g, 40.9 mmol) in dry THF (5.0 ml) was added to a -78°C solution of lithium bis(trimethylsilyl)amide (1.0 M in THF; 49 ml, 49 mmol) in dry THF (25 ml) and stirred at -78°C under argon for 1 hour. The reaction mixture was treated with a solution of Example 1 Part A(3) compound (7.15 g, 27.3 mmol), in dry THF, stirred at -78°C for 30 minutes then at 0°C for 30 minutes. The reaction mixture was quenched at 0°C by the dropwise addition of glacial acetic acid (5 ml) and the resulting slurry was stirred at room temperature for another 5 minutes then poured 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.

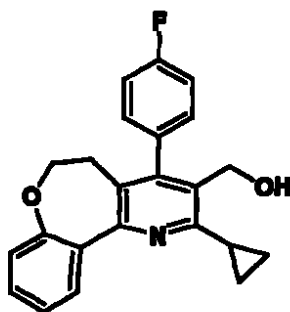


A mixture of crude Part B compound (17.0 g, 27.3 mmol), ammonium acetate (9.34 g, 120 mmol) and copper

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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 Na_2SO_4), 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).
Rf 0.53 (Silica gel; EtOAc:Hexane-1:4; UV)

D.

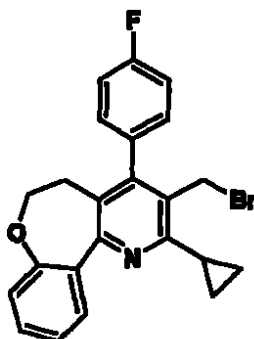


A solution of Part C compound (2.515 g, 6.23 mmol) in dry THF (30 ml) was cooled to 0°C (ice-water bath), treated dropwise with lithium aluminum hydride (1.0 M in THF; 12.5 ml, 12.5 mmol), stirred at 0°C for 30 minutes then at room temperature for 3 hours. The reaction mixture was cooled to 0°C, treated successively with water (0.5 ml), 15% NaOH (0.5 ml) and water (1.5 ml), 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.

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Yield: 2.386 g, white foam (100 %). Rf 0.15 (Silica gel; EtOAc:Hexane-1:4; UV).

E.



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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 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).

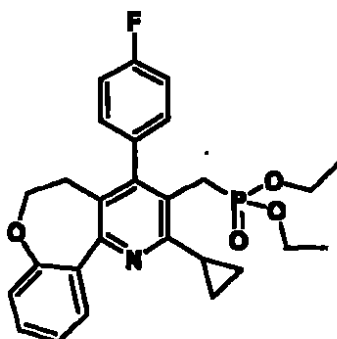
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p

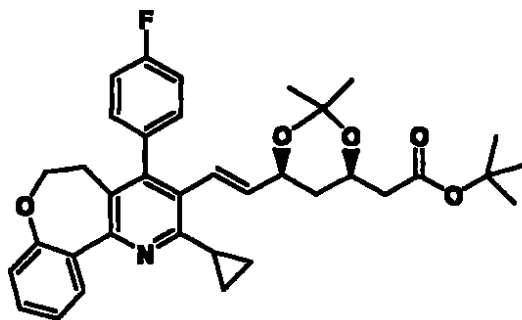
F.



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

20.

G.



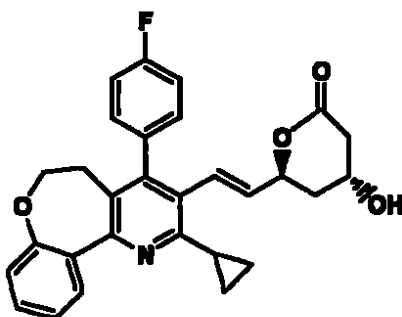
A solution of Part F compound (2.29 g, 4.756 mmol) in dry THF (20 ml) was cooled to -78°C, treated with 2.37

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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).

H.



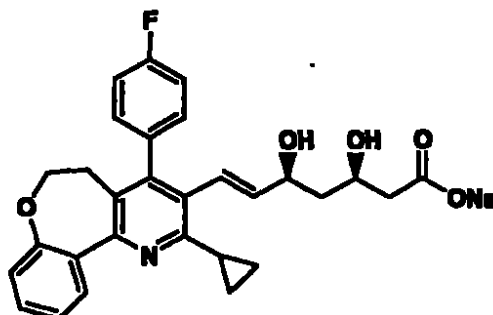
A solution of Part G compound (850 mg, 1.45 mmol) in dry dichloromethane (20 ml) was cooled to 0°C, treated with trifluoroacetic acid (1.85 ml, 24 mmol), stirred at 0°C for 5 minutes, then at room temperature for 4.5 hours. The reaction mixture was poured slowly into a 1 L flask containing ethyl acetate (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

72

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)

5

I.



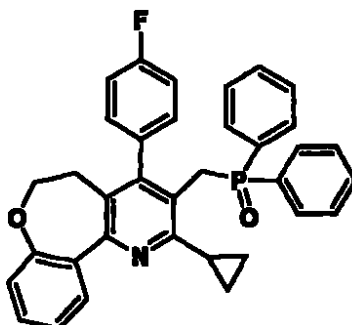
A solution of Part H compound (550 mg, 1.17 mmol) in dry THF (10 ml) was treated with 1.0 N NaOH (1.46 ml; 1.46 mmol) and stirred at room temperature for 10 minutes. The reaction mixture was evaporated to dryness and the residual solid was dissolved in a mixture of water (8.7 ml) and 1.0 N sodium hydroxide (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%) Rf 0.48 (Silica gel; CH₂Cl₂:MeOH:HOAc-18:1:1; UV).

Analysis for C₂₇H₂₆FO₄Na • 0.8 H₂O (MW = 525.94):

25 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).



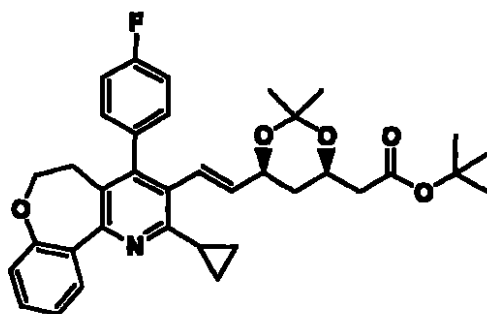
5

The Example 1 Part E bromide (13.03 g, 0.027 mol, 1 equiv) and Ph_2POEt (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
10 stirrable white mixture after about 10 min. The reaction was complete after 1 hr by tlc (SiO_2 , 30% EtOAc/ CH_2Cl_2 , 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
15 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/ H_2O + 0.2% H_3PO_4 , B=90:10 MeOH/ H_2O + 0.2% H_3PO_4) R.T.=3.70 min (100%);

20 ^1H NMR (CDCl_3) 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
25 (m, 9 H), 7.469-7.521 (m, 2 H), 7.822 (d, $J=7.5$ Hz, 1 H); MS m/z 546 ($M+H$) $^+$.

74

G(2).



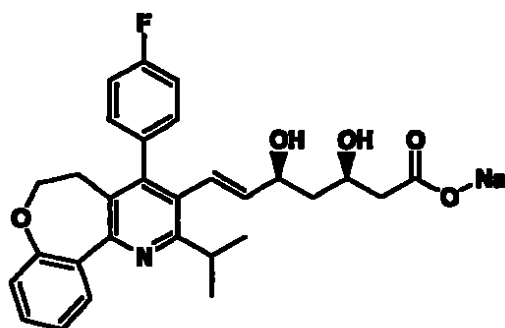
A flame-dried 250-mL flask was charged with Part
5 G(1) compound (14.82 g, 27.2 mmol, 1 equiv), chased with
anhydrous toluene (2x50 mL), dried over high-vacuum and
filled with argon. THF (150 mL) was added and the partial
slurry was cooled to 0°C. A 2.5 M solution of n-BuLi in
hexanes (11.4 mL, 0.0285 mol, 1.05 equiv) was added
10 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
15 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
20 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 quenched
with half-saturated aqueous NaCl (200 mL) and extracted
25 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
chromatography (10 cm x 25 cm) with 2% EtOAc/CH₂Cl₂ (2 L),
30 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

75

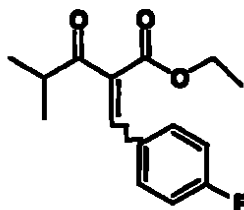
compound) as a white solid (11.13 g, 0.019 mol, 70%):
 HPLC (Shimadzu, YMC S-5 C18 4.6x50 mm column, 4 min
 gradient @ 4 mL/min, UV detection 220 nm, start %B=70,
 final %B=100; A=10:90 MeOH/H₂O + 0.2% H₃PO₄, B=90:10
 5 MeOH/H₂O + 0.2% H₃PO₄) R.T.=4.36 min (100%);

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),
 10 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
 (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)⁺.

15

Example 2

A.



20

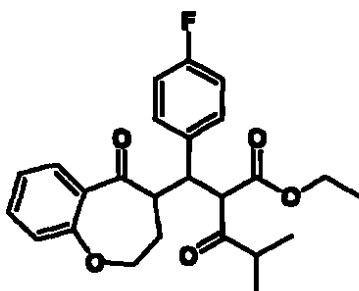
A mixture of p-fluorobenzaldehyde (4.939 g, 0.039
 mol, 1 equiv), ethyl isobutyrylacetate (6.495 g, 0.039
 mol, 1 equiv), piperidine (0.395 mL, 3.91 mmol, 0.1
 25 equiv), and glacial acetic acid (0.070 mL, 1.22 mmol,
 0.03 equiv) in anhydrous benzene (30 mL) was heated at
 reflux with a Dean-Stark trap to collect H₂O. After 20
 hrs, the reaction was cooled to rt. The yellow reaction
 mixture was diluted with Et₂O (50mL) and washed with 0.5N

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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
5 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),
10 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)⁺.

B.

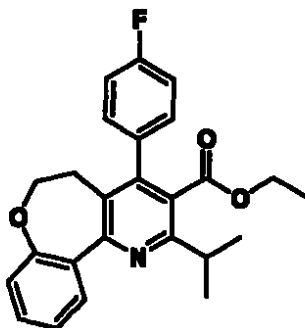


An oven-dried 250-mL 3-neck flask purged with argon was charged with anhydrous THF (30 mL) and lithium bis(trimethylsilyl)amide (1M in THF, 57.9 mL, 0.058 mol, 1.8 equiv), then cooled to -78°C in a dry ice-acetone
20 bath. A solution of Example 1 Part A compound (7.824 g, 0.0482 mol, 1.5 equiv) in dry THF (6 mL) was added via 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
25 mol, 1 equiv) in dry THF (6 mL) was added via 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 NH₄Cl. The mixture was extracted with Et₂O (100 mL) and
30 the ethereal extract was washed with H₂O (2x30 mL) and satd aq NaCl. The organic was dried over anhydrous Na₂SO₄, vacuum filtered and concentrated by rotary

ff

evaporation in vacuo to a yellow oil (17.19 g): MS (FAB) m/z 427 (M+H)⁺.

C.



5

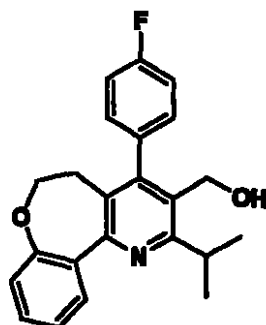
The crude Part B compound (17.19 g), NH₄OAc (11.0g, 0.142 mol, 4.4 equiv), and Cu(OAc)₂ monohydrate (24.2 g, 0.119 mol, 3.7 equiv) were dissolved in glacial HOAc (120 mL) under argon and heated at gentle reflux for 20 hrs. The reaction was cooled to rt, then poured into an ice cold solution of conc NH₄OH (100 mL) in H₂O (200 mL). The mixture was extracted with Et₂O (200 mL+2x100 mL), then the combined ethereal extracts was washed with H₂O (2x100 mL) and satd aq NaCl. The extract was dried over anhydrous Na₂SO₄, vacuum filtered and concentrated by rotary evaporation in vacuo. The resulting brown oil was chased with hexanes to remove HOAc, followed by drying in 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):

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)⁺.

25

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D.

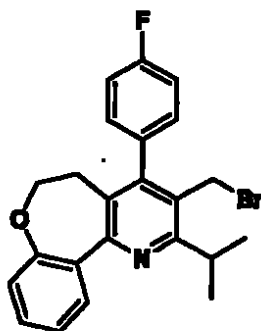


- Part C compound (5.78 g, 0.0143 mol, 1 equiv) was dissolved in dry THF (70 mL) under argon and cooled to 0°C. A solution of LiAlH₄ in THF (1M, 28.5 mL, 0.0285 mol, 2 equiv) was added slowly. The reaction was stirred at rt for 2 hrs, followed by 25 min at reflux. TLC (SiO₂, 5% EtOAc/CH₂Cl₂, R_f=0.24). 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 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%):

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), 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)⁺.

79

E.

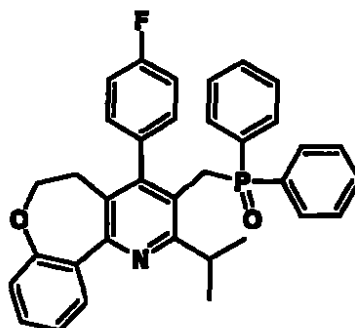


The Part D alcohol (3.066g, 8.437 mmol, 1 equiv),
5 dissolved in dry CH_2Cl_2 (60 mL) under argon at 0°C , was
treated by dropwise addition of a 1M solution of PBr_3 in
 CH_2Cl_2 (16.9 mL, 16.9 mmol, 2 equiv). The reaction was
stirred at rt for 30 min, at which time the reaction was
recooled to 0°C and treated with satd aq NaHCO_3 (90 mL).
10 The mixture was diluted with CH_2Cl_2 (50 mL), the layers
were separated, and the organic washed with H_2O (2x50 mL)
and satd aq NaCl (50 mL). The organic was dried over
anhydrous Na_2SO_4 , filtered and concentrated in vacuo. TLC
(SiO_2 , 5% EtOAc/ CH_2Cl_2 , $R_f=0.69$). The residue was
15 purified by SiO_2 flash chromatography (3.8cm x 15cm
column) with CH_2Cl_2 to obtain product as white solid (2.97
g, 6.97 mmol, 83%):

^1H NMR (CDCl_3) δ 1.403 (d, $J=6.6$ Hz, 6H), 2.430 (t, $J=6.2$
20 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.

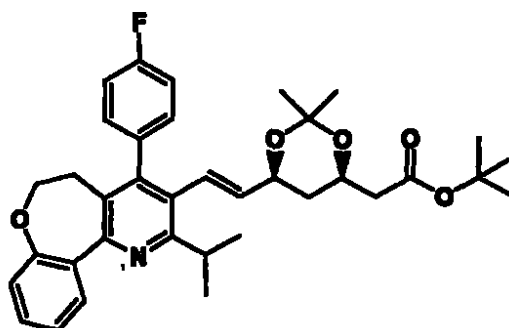


The Part E bromide (2.97 g, 6.967 mmol, 1 equiv)
5 and ethyl diphenylphosphinite (1.7 mL, 7.663 mmol, 1.1
equiv) were heated at reflux under argon for 1.5 hrs.
TLC (SiO₂, 30% EtOAc/CH₂Cl₂, product Rf=0.47). The
reaction was cooled in an ice bath, then the solid
collected by vacuum filtration in Buchner funnel; the
10 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
15 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

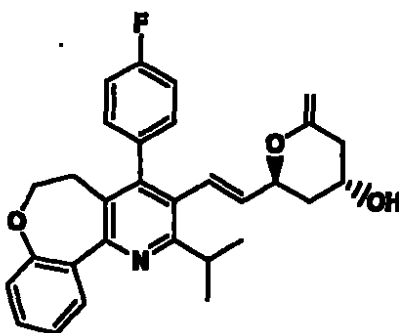
21

chased with anhydrous toluene (3x5 mL), dried on high 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 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 (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-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), 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, 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), 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)⁺.

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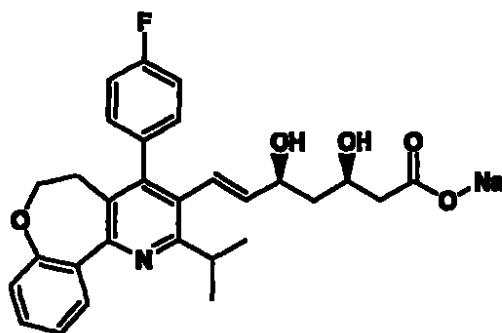
H.



The Part G compound (0.230 g, 0.391 mmol) was
5 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
10 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
15 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),
20 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 ($M+H$) $^+$.

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)⁺;

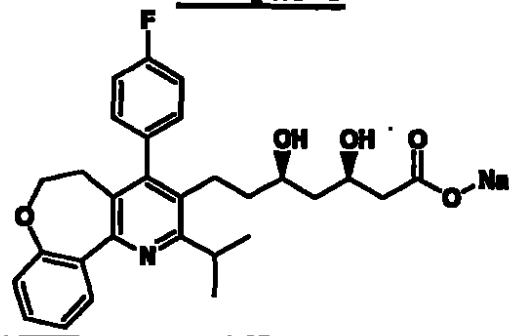
Anal. Calcd for $C_{22}H_{22}FNO_3Na \cdot H_2O$:

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

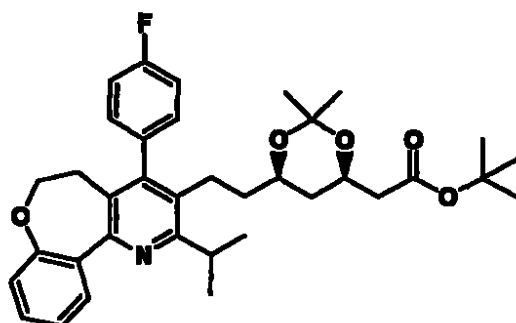
Found: C, 65.46; H, 5.70; N, 2.52.

5

Example 3



A.



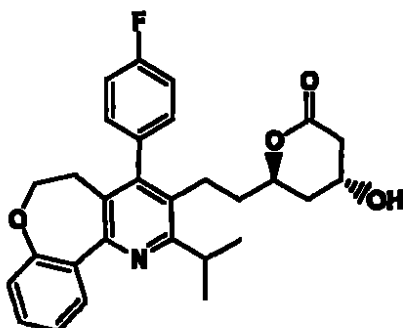
- 10 The Example 2 Part G compound (200 mg, 0.3403 mmol, 1 equiv) was hydrogenated at 45 psi H_2 in anhydrous MeOH (30 mL) with 10% Pd-C (40 mg, 20 wt %) for 2 hrs. The catalyst was washed with small portions of MeOH and the filtrate was concentrated by rotary evaporation in vacuo.
- 15 The residue was 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, $J=7.9$ Hz, 1 H), 7.1416 (d, $J=6.6$ Hz, 4 H), 7.265 (t,

85

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)⁺.

B.



5

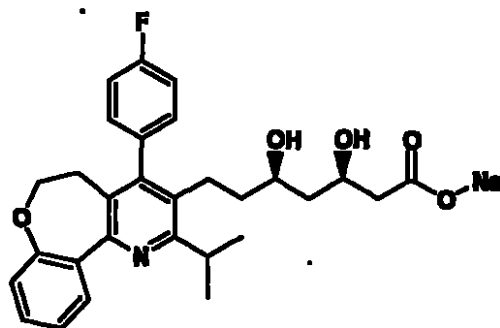
Part A compound (258 mg, 0.4375 mmol) was dissolved in dry CH₂Cl₂ (5 mL) under argon, cooled to 0°C and treated with trifluoroacetic acid (0.5 mL). Stirring was continued at room temperature for 7 hrs, at which time the reaction was complete by HPLC. Saturated aqueous NaHCO₃ (25 mL) was added to the 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)⁺.

30

96

C.



Part B compound (149 mg, 0.3133 mmol, 1 equiv) was dissolved in THF (3 mL) and 1N aqueous NaOH (0.392 mL, 0.3916 mmol, 1.25 equiv) and stirred at room temperature for 30 min. The solvent was removed by rotary evaporation in vacuo and the residue was dried under high-vacuum. An SP207 resin column (1.9 cm x 10 cm) was prepared as follows: resin was poured into a glass chromatography column equipped with fritted disc support and the resin was washed sequentially with saturated aqueous NaHCO₃ (15 mL), saturated aqueous NaCl (15 mL), and Milli-Q H₂O (100 mL). The dried residue was taken up in Milli-Q H₂O (8 mL) and carefully applied to top of the column. The column was eluted with Milli-Q H₂O (100 mL), 10% AcCN/ H₂O (60 mL), 20% AcCN/ H₂O (60 mL), and 25% AcCN/ H₂O (100 mL). Product-containing fractions were combined and concentrated by rotary evaporation to a small volume, and transferred to a 40-mL lyophilization jar. The contents were frozen in acetone-dry ice bath and lyophilized. This afforded the product as a white lyophilate (149 mg, 0.289 mmol, 92%): 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=10:90 MeOH/H₂O + 0.2% H₃PO₄) R.T.=3.58 min (92.9%);

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.

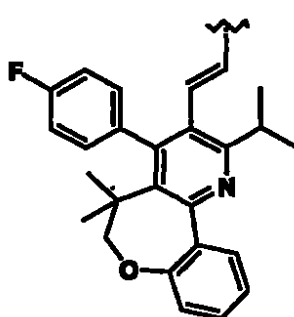
Examples 4 to 26

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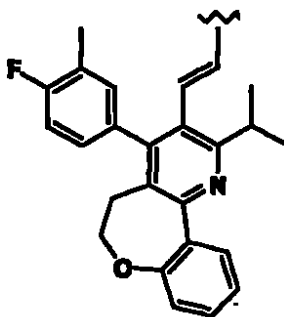
where Y is as set out below

Example 4

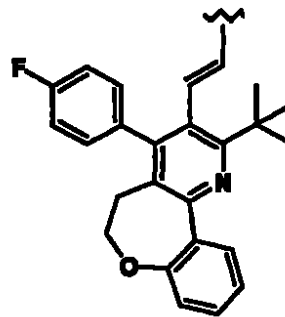


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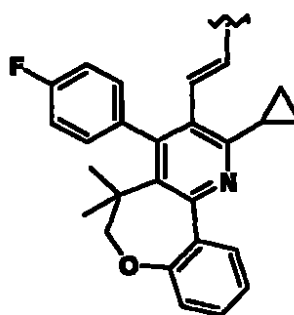
Example 5



Example 6

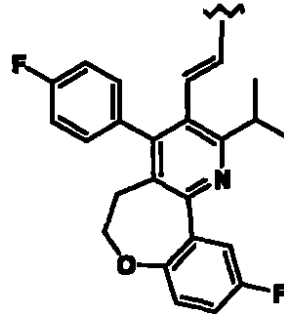


Example 7

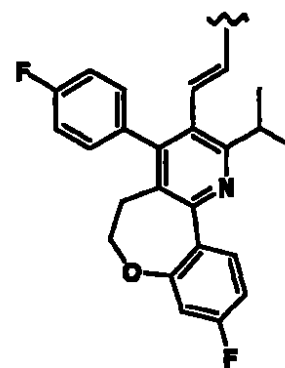


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Example 8

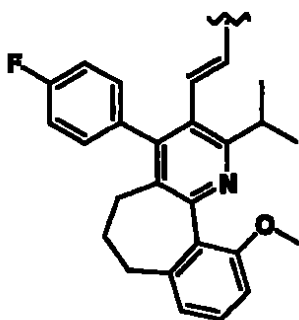


Example 9

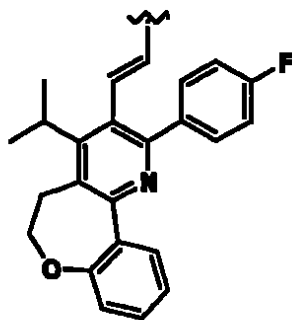


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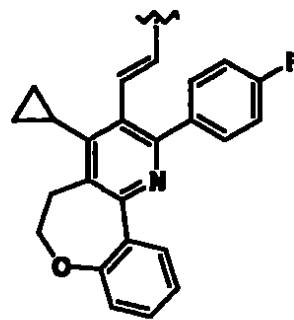
Example 10



Example 11

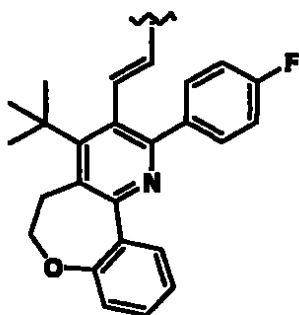


Example 12

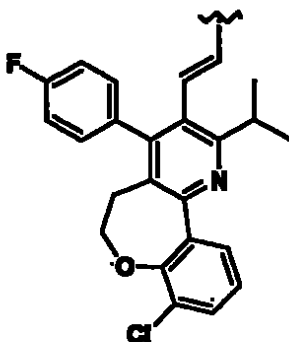


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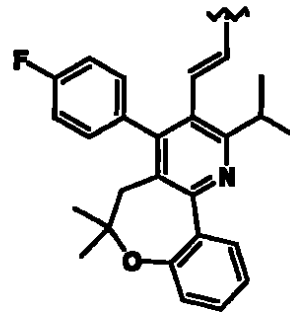
Example 13



Example 14

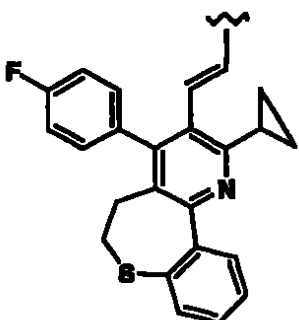


Example 15

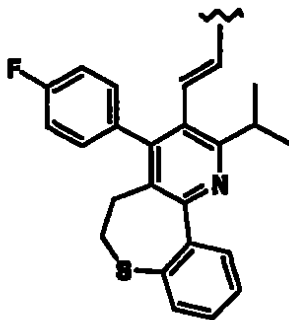


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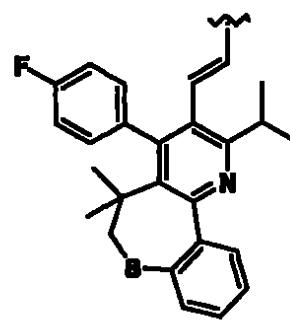
Example 16

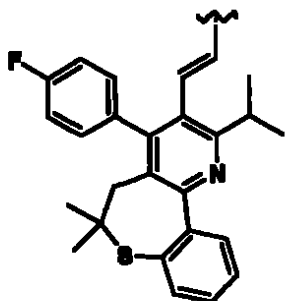
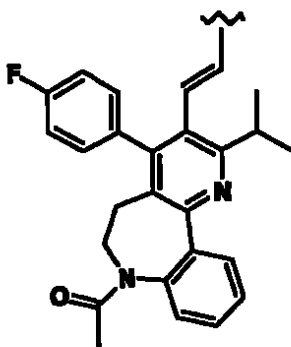
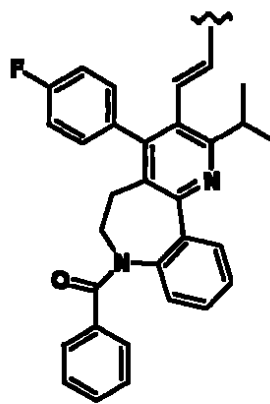


Example 17

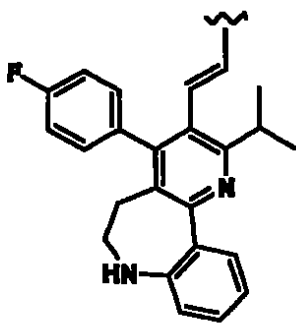
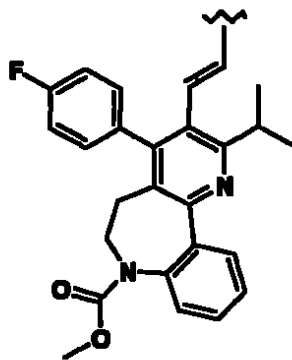
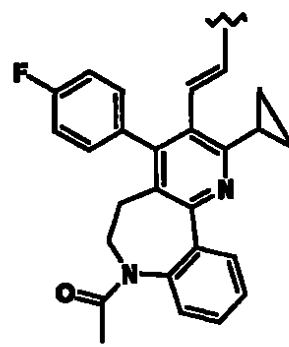


Example 18

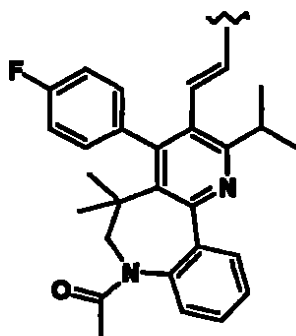
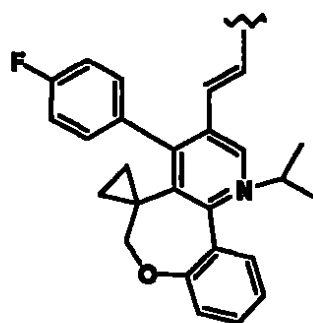


Example 19Example 20Example 21

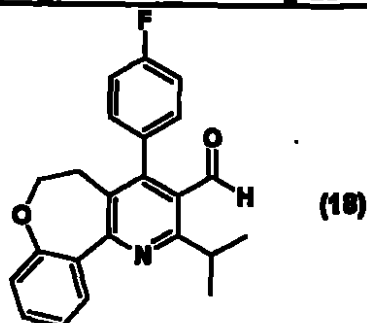
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Example 22Example 23Example 24

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Example 25Example 26

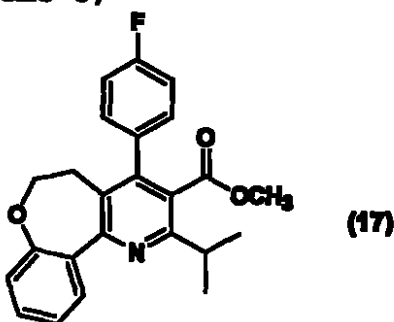
90

Example 27Preparation of Pyridine Aldehyde (18) (Scheme 5)

5 Following the procedure outlined in reaction Scheme 5 and the description thereof, the Example 27 aldehyde is obtained.

 An example of a typical preparation of the aldehyde is set out below.

10 To a 500 mL round bottom flask equipped with a magnetic stirrer and a nitrogen inlet was charged compound (17) (Scheme 5)



(50 g, 128.4 mmol)

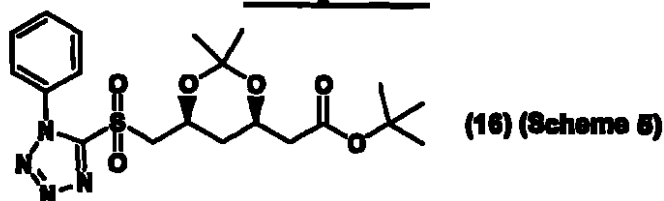
15 (prepared as described in Example 2 Parts A, B and C except methyl isobutyryl acetate is substituted for ethyl isobutyryl acetate) and toluene (170 mL). The mixture is stirred at 20-25°C until a clear solution is obtained. A solution of 65% Red-Al in toluene (57.8 mL, 192.6 mmol) is
20 added and the reaction mixture is heated to 80°C until complete as determined by HPLC. The reaction mixture is cooled to ~20°C and quenched by pouring it into cold (0-5°C) 20% HCl (495 mL). Phases are separated and the spent toluene phase is discarded. The pH of the aqueous
25 phase is adjusted from <0 to 4-5 with 10N NaOH. Ethyl acetate (500 mL) is added and the pH adjustment continued

M

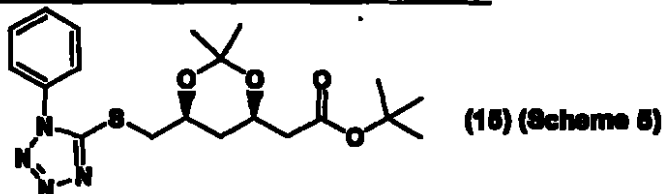
to 7-8. The phases are separated. The aqueous phase is extracted with additional ethyl acetate (2 x 500 mL). The combined rich ethyl acetate solution is washed with water (3 x 250 mL) and concentrated under reduced
5 pressure to ~465 mL. This solution is carried through to the next oxidation step.

The rich ethyl acetate solution is charged from above into a three neck 1-L flask equipped with mechanical stirring, temperature controller, and addition
10 funnel and cooled to 0-5°C. To the slurry, potassium bromide (1.53 g, 12.8 mmol) and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) (0.20 g, 1.28 mmol) are added. The pH of NaOCl (sodium hypochlorite) solution (212.1 mL) is adjusted to ~9.1 and added to the slurry at
15 a rate such that the temperature remained at 0-5°C. Stirring is continued at 0-5°C until the reaction is complete as determined by HPLC. The aqueous phase is extracted with EtOAc (2 x 200 mL). The combined rich organic phase is washed with a 1:1 solution of sat. aq.
20 Na₂S₂O₃ (sodium thiosulfate) (75 mL) and water (75 mL) followed by wash of the rich organic phase with 1N NaOH (250 mL). The rich organic phase is washed with water (250 mL) and concentrated to ~100 mL under reduced pressure. Isopropanol (IPA) (400 mL) is added and the
25 resulting mixture is heated to reflux (80-85°C). The solution is distilled to a volume of ~250 mL. Water (50 mL) is added and the crystal slurry is stirred at 70-80°C for 1 h then allowed to cool to 20-25°C over at least 1 h. The slurry is held at 20-25°C for at least 1 h before
30 collecting the solid by filtration on a Buchner funnel. The cake is washed with cold (0°C) IPA/water (4:1) (2 x 50 mL) and dried to a constant weight under vacuum at 40°C to afford title aldehyde.

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Example 28

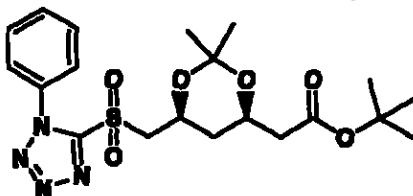
5

A. Preparation of Sulfide (15)

To a 250 mL flask was charged Kaneka alcohol (12) (Scheme 6) (10.0 g, 38.41 mmol), methylene chloride (100 mL), and triethylamine (11.75 mL, 84.51 mmol) and cooled to -30°C. Triflic anhydride (7.11 mL, 42.25 mmol) was added via a syringe at a rate to maintain the temperature at -35 to -25°C, ~15 min. The reaction mixture was stirred at -30°C for ~30 min and checked for disappearance of Kaneka alcohol by TLC. A slurry of 1-phenyl-1H-tetrazole-5-thiol (7.19 g, 40.34 mmol) in methylene chloride (50 mL) was added to the triflate solution. After the reaction was complete, water (100 mL) was added and the mixture was stirred for ~5 min. The phases were separated and the aqueous phase was discarded. The rich organic phase was washed with water (100 mL) for ~5 min and phases separated. The rich organic phase was washed with saturated NaHCO₃ (100 mL) for ~15 min and phases separated. The rich organic phase was concentrated to ~50 mL. The solution was taken to the next step for further transformation.

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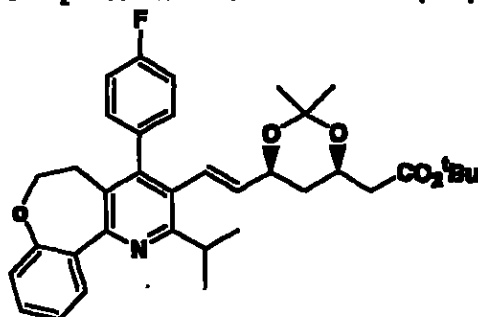
B. Preparation of Sulfone (16)



IPA (150 mL) was added to the Part A sulfide
 5 solution from the above step. The solution was cooled to
 0-5°C. To the stirred solution of sulfide, a solution of
 (NH₄)₇MO₇O₂₄•4H₂O (ammonium heptamolybdate tetrahydrate)
 (4.75 g, 3.84 mmol) in 30% H₂O₂ (hydrogen peroxide) was
 added dropwise during ~15 min, maintaining the
 10 temperature of the solution at 0-5°C. The conversion of
 sulfide to sulfone was monitored by HPLC ~24 h. After
 completion of the reaction, methylene chloride was
 distilled out. The pot temperature was maintained at not
 more than 25°C. The crystal slurry was distilled to a
 15 volume of ~230 mL with IPA and the resulting slurry was
 stirred for at least 1 h at 20-22°C. The solid was
 collected by vacuum filtration, the cake washed with
 IPA/water (4:1, 25 mL) followed by drying under vacuum at
 40°C to constant weight affording 12.8 g (74%) of the
 20 title sulfone as a white crystalline solid.

Example 29

Preparation of Olefin (19)



25

Following the procedure set out in reaction Scheme
 5 and the description thereof, the Example 27 pyridine
 derivative and the Example 28 sulfone are employed to
 prepare the title compound.

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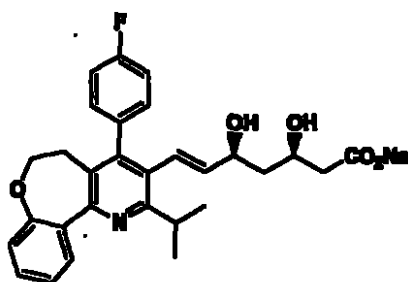
An example of a typical preparation of the Example 29 compound is set out below.

- 5 A, N₂ purged 250 mL 3-neck rb flask is charged with Example 27 pyridine derivative (18) (5 g, 13.9 mmol), Example 28 sulfone (16) (6.9 g, 15.3 mmol) and THF (75 mL). The stirred solution is cooled to -74 to -78°C. Slowly a 1M solution of LiHMDS (lithium bis(trimethylsilyl)amide) (15.3 mL, 15.3 mmol) in THF is charged at a rate such that the temperture remained
- 10 between -70 and -78°C. After addition of the base is complete, the reaciton mixture is warmed to --45°C over ~15 minutes. The stirred reaction is quenched at -70°C by slow addition of sat. aq. NH₄Cl (7.5 mL) solution and water (38 mL). The dry ice bath is removed and the
- 15 solution is warmed to 20-25°C from the reaction mixture. Ethyl acetate (50 mL) is added, the mixture agitated, and layers separated. The organic layer is washed with saturated sodium bicarbonate solution (2 x 38 mL) followed by brine (25 mL) and concentrated to a volume of
- 20 50 mL. Acetonitrile (50 mL) is added and the solution is concentrated to a volume of 50 mL. This step is repeated. Water (~5-6 mL) is slowly added to the hot solution (60-70°C) until the cloud point is reached. The thin slurry is held for 30 min at high temperature and
- 25 then slowly cooled over several hours with stirring. The product is filtered, cake is washed with a 5:1 mixture of acetonitrile and water, and dried to afford the title compound.

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Example 30

Preparation of the final compound



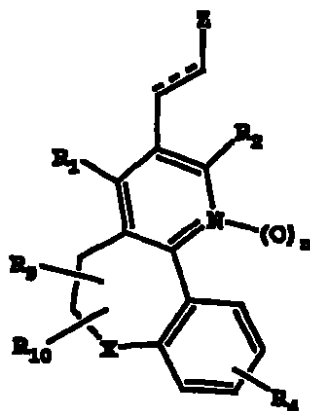
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Following the procedure of Example 3 Parts B and C, the Example 29 compound is employed to prepare the title compound in the form of the sodium salt.

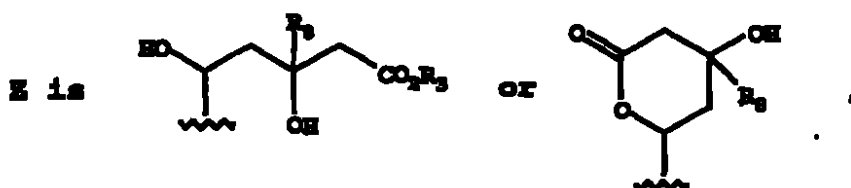
10

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 or lower alkyl;

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

R_7 is H, alkyl, aryl, alkanoyl, aroyl or alkoxycarbonyl;

R_8 is H or lower alkyl;

20 R_9 and R_{10} are the same or different and are independently selected from H or alkyl, or R_9 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 (where R₃ is H), 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 R₁ is aryl,

10 R_2 is alkyl or cycloalkyl or aryl;

R₄ is H;

n is 0;

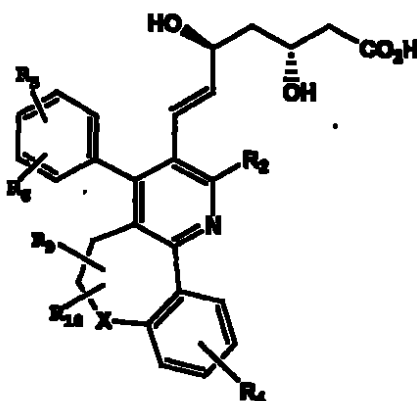
X is 0; and

~~22~~ is a trans double bond, in the form of a free
15 acid or an alkali or alkaline earth metal salt or an
amino acid salt.

4. The compound as defined in Claim 3 wherein R₁ is 4-fluorophenyl, 4-fluoro-3-methylphenyl, or 3,5-dimethylphenyl; and

R₂ is isopropyl, t-butyl or cyclopropyl.

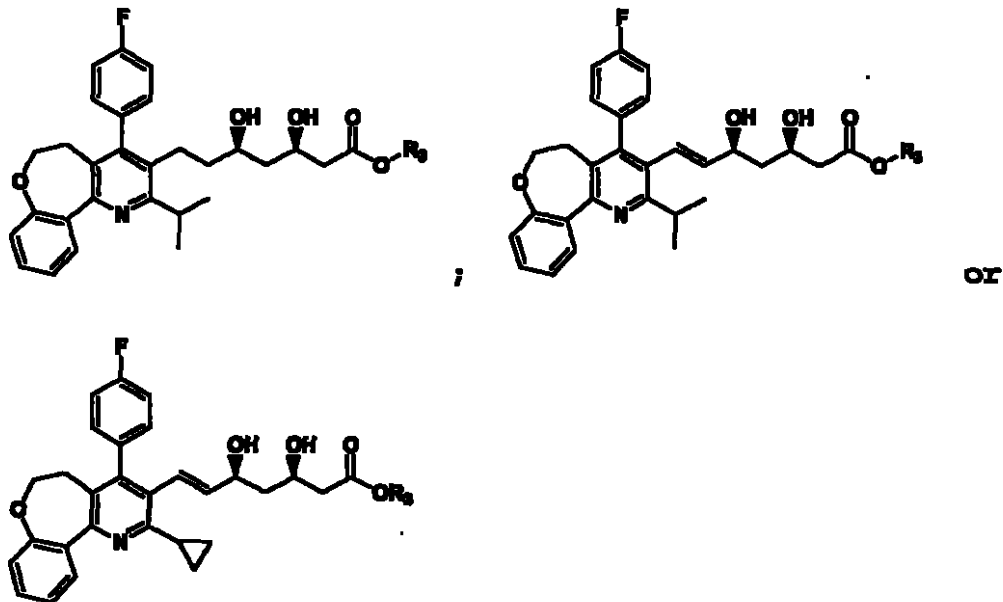
5. The compound as defined in Claim 1 having the structure



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

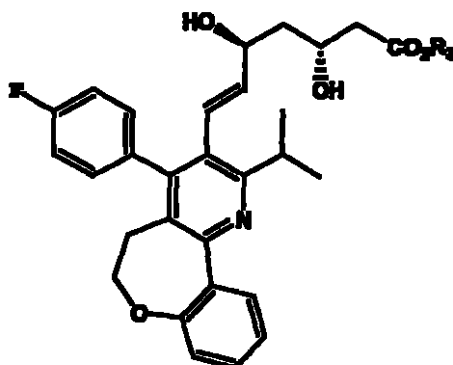
wherein R_5 and R_6 are the same or different and are independently selected from H, halogen or alkyl and R_2 is alkyl or cycloalkyl.

- 5 6. The compound as defined in Claim 1 having the structure



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

- 15 7. A compound of the structure



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

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

5 9. A pharmaceutical combination comprising the HMG
CoA reductase inhibitor compound as defined in Claim 1
and one or more hypolipidemic agents or lipid-lowering
agents, or lipid agents, or lipid modulating agents,
and/or one or more other types of therapeutic agents
10 including antidiabetic agents, anti-obesity agents,
antihypertensive agents, platelet aggregation inhibitors,
anti-dementia agents, anti-Alzheimer's agents, anti-
osteoporosis agents, and/or hormone replacement
therapeutic agents, and/or other cardiovascular agents
15 (including anti-anginal agents, anti-arrhythmic agents,
anti-atherosclerosis agents, anti-inflammatory agents,
anti-arthritis agents, anti-platelet agents, anti-heart
failure agents), anti-cancer agents, anti-infective
agents, hormone replacement agents, growth hormone
20 secretagogues, selective androgen receptor modulators,
and/or immunomodulatory agents.

10. The combination as defined in Claim 9 wherein
the hypolipidemic agent or lipid-lowering agent or other
25 lipid agent or lipid modulating agent or anti-
atherosclerotic agent, which is employed comprises 1,2,3
or more MTP inhibitors, HMG CoA reductase inhibitors,
squalene synthetase inhibitors, fibric acid derivatives,
PPAR α agonists, PPAR dual α/γ agonists, PPAR δ agonists,
30 ACAT inhibitors, lipoxxygenase inhibitors, cholesterol
absorption inhibitors, ileal Na⁺/bile acid cotransporter
inhibitors, upregulators of LDL receptor activity,
cholesteryl ester transfer protein inhibitors, bile acid
sequestrants, or nicotinic acid and derivatives thereof,
35 ATP citrate lyase inhibitors, phytoestrogen compounds, an
HDL upregulators, LDL catabolism promoters, antioxidants,
PLA-2 inhibitors, antihomocysteine agents, HMG-CoA

synthase inhibitors, lanosterol demethylase inhibitors, or sterol regulating element binding protein-I agents;

wherein the antidiabetic agent which may be optionally employed is 1,2,3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, which may include biguanides, sulfonyl ureas, PTP-1B inhibitors, aldose reductase inhibitors, glucosidase inhibitors, PPAR γ agonists, PPAR α agonists, PPAR δ antagonists or agonists, α P2 inhibitors, PPAR α/γ dual agonists, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, glycogen phosphorylase inhibitors, and/or meglitinides, insulin, and/or glucagon-like peptide-1 (GLP-1) or a mimetics thereof;

wherein the other type of therapeutic agent which may be optionally employed is 1, 2, 3 or more of an anti-obesity agent which is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, an α P2 inhibitor, a thyroid receptor beta drug, an anorectic agent, a PTP-1B inhibitor, a CCKA agonist, a neuropeptide Y antagonist, a melanocortin-4-receptor agonist, a PPAR modulator which is a PPAR γ antagonist, PPAR α agonist, and/or PPAR δ antagonist, a leptin inhibitor such as a leptin receptor activator, a fatty acid oxidation upregulator or inducer;

wherein the lipid modulating 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 lipoxygenase inhibitor, or an ACAT inhibitor and the other lipid agent is a cholesteryl ester transfer protein inhibitor;

wherein the antihypertensive agent employed is an ACE inhibitor, angiotensin II receptor antagonist, NEP inhibitor, a NEP/ACE inhibitor, a calcium channel blocker, a T-channel calcium antagonist, a β -adrenergic blocker, a diuretic, a α -adrenergic blocker, a dual

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action receptor antagonist (DARA), or a heart failure drug.

11. The combination as defined in Claim 10 wherein
5 the antidiabetic agent is 1, 2, 3 or more of metformin,
glyburide, glimepiride, glipyrider, glipizide,
chlorpropamide, gliclazide, acarbose, miglitol,
pioglitazone, troglitazone, rosiglitazone, insulin,
G1-262570, isaglitazone, JTT-501, NN-2344, L895645,
10 YM-440, R-119702, AJ9677, repaglinide, nateglinide,
KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902,
P32/98 and/or NVP-DPP-728A;

wherein the anti-obesity agent is orlistat, ATL-
962, AJ9677, L750355, CP331648, sibutramine, topiramate,
15 axokine, dexamphetamine, phentermine,
phenylpropanolamine, and/or mazindol, P57 or CP-644673
(Pfizer);

wherein the lipid modulating agent is pravastatin,
lovastatin, simvastatin, atorvastatin, cerivastatin,
20 fluvastatin, pitavastatin, rosuvastatin, fenofibrate,
gemfibrozil, clofibrate, avasimibe, TS-962, MD-700,
cholestagel, niacin, and/or LY295427;

wherein the antihypertensive agent is an ACE
inhibitor which is captopril, fosinopril, enalapril,
25 lisinopril, quinapril, benazepril, fentiapril, ramipril
or moexipril;

an NEP/ACE inhibitor which is omapatrilat,
gemopatrilat, or CGS 30440;

an angiotensin II receptor antagonist which is
30 irbesartan, losartan or valsartan;

amlodipine besylate, prazosin HCl, verapamil,
nifedipine, nadolol, propranolol, or clonidine HCl,
carvediol, atenolol, hydrochlorothiazide, torasemide,
furosemide, spironolactone or indapamide;

35 wherein the platelet aggregation inhibitor is
aspirin, clopidogrel, ticlopidine, dipyridamole,

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ifetroban, abciximab, tirofiban, eptifibatide, or anagrelide;

wherein the other therapeutic agent is an anti-Alzheimer's agent or anti-dementia agent, which is
5 tacrine HCl (Cognex®), donepezil (Aricept®), a γ -secretase inhibitor, a β -secretase inhibitor and/or antihypertensive agent;

an antiosteoporosis agent, which is parathyroid hormone, a bisphosphonate, alendronate, a Ca receptor
10 agonist or a progestin receptor agonist;

a hormone replacement therapeutic agent, which is a selective estrogen receptor modulator (SERM);

a tyrosine kinase inhibitor;

a selective androgen receptor modulator;

15 an antiarrhythmic agent, which is a β -blocker, or a calcium channel blocker, or an α -adrenergic blocker;

coenzyme Q sub. 10;

an agent that upregulates type III endothelial cell nitric acid syntase;

20 a chondroprotective compound which is polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (PPS), doxycycline or minocycline;

a cyclooxygenase (COX)-2 inhibitor, which is
25 Celebrex® (Searle) or Vioxx® (Merck) or a glycoprotein IIa/IIIb receptor antagonist;

a 5-HT reuptake inhibitor;

a growth hormone secretagogue;

an anti-atherosclerosis agent;

30 an anti-infective agent, or an immunosuppressant for use in transplantation, or an antineoplastic agent.

12. The combination as defined in Claim 10 wherein the HMG CoA reductase inhibitor compound is in
35 combination with an ACE inhibitor or a NEP/ACE inhibitor.

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13. The combination as defined in Claim 12 wherein the HMG CoA reductase inhibitor compound is in combination with an ACE inhibitor which is ramipril;

5 wherein the HMG CoA reductase inhibitor is in combination with a NEP/ACE inhibitor which is omapatrilat or gemopatrilat;

wherein the HMG CoA reductase inhibitor is in combination with a platelet aggregation inhibitor.

10 14. The combination as defined in Claim 13 wherein the platelet inhibitor is clopidogrel, or aspirin or a combination of clopidogrel and aspirin.

15 15. A method of inhibiting cholesterol biosynthesis or lowering blood serum cholesterol levels and/or modulating blood serum cholesterol levels, lowering LDL cholesterol and/or increasing HDL cholesterol, or treating dyslipidemia, mixed dyslipidemia, LDL Pattern B, LDL Pattern A, hyperlipidemia, hypercholesterolemia, hypo
20 α -lipoproteinemia, hyperlipoproteinemia or hypertriglyceridemia, and other aberrations of apolipoprotein B metabolism, or reducing levels of Lp(a), or treating or preventing other cholesterol-related diseases, or treating or preventing or reversing
25 progression of atherosclerosis, or preventing or treating Alzheimer's disease, or preventing or treating osteoporosis and/or osteopenia, or reducing inflammatory markers, reducing C-reactive protein, or preventing or treating low grade vascular inflammation, or preventing
30 or treating stroke, or preventing or treating dementia, or preventing and treating coronary heart disease, and primary and secondary prevention of myocardial infarction, or preventing or treating stable and unstable angina, or primary prevention of coronary events, or
35 secondary prevention of cardiovascular events, or preventing or treating peripheral vascular disease, preventing or treating peripheral arterial disease, or

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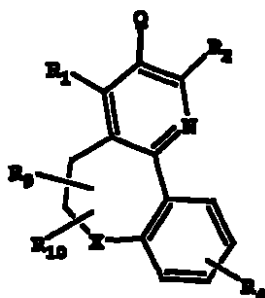
preventing or treating acute vascular syndromes, or preventing or reducing the risk of undergoing myocardial revascularization procedures, or preventing or treating microvascular diseases such as nephropathy, neuropathy, retinopathy and nephrotic syndrome, or preventing or treating hypertension, preventing or treating Type I diabetes, Type 2 diabetes, and related diseases, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, LDL Pattern B, LDL Pattern A, Syndrome X, diabetic complications, dysmetabolic syndrome, and related diseases, and sexual dysfunction, preventing and treating malignant lesions, premalignant lesions, gastrointestinal malignancies, liposarcomas and epithelial tumors, cancer-induced asthenia (fatigue), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and gallstones, and HIV infection, drug-induced lipodystrophy, and proliferative diseases, improving coagulation homeostasis, reducing PAI-1 activity, reducing fibrinogen, and/or reducing platelet aggregation, and/or improving endothelial function, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

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16. A method for treating cholesterol related diseases, diabetes and related diseases, cardiovascular diseases, cerebrovascular diseases, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a combination of a compound as defined in Claim 1 and a hypolipidemic agent, and/or lipid modulating agent and/or antidiabetic agent and/or cardiovascular agent, cerebrovascular agent, and/or other type of therapeutic agent, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of such combinations.

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17. A compound having the structure



wherein X is O, S or NR₇ where R₇ is H, alkyl, aryl,
 5 alkanoyl, aroyl or alkoxycarbonyl; R₁ and R₂ are the same
 or different and are independently selected from alkyl,
 arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl,
 heteroaryl or cycloheteroalkyl;

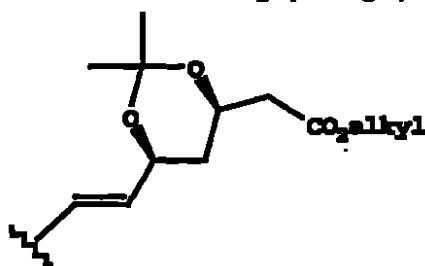
R₉ and R₁₀ are the same or different and are
 10 independently selected from H or alkyl, or R₉ and R₁₀ may
 be taken together with the carbon or carbons to which
 they are attached to form a 3 to 7 membered carbocyclic
 ring;

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



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

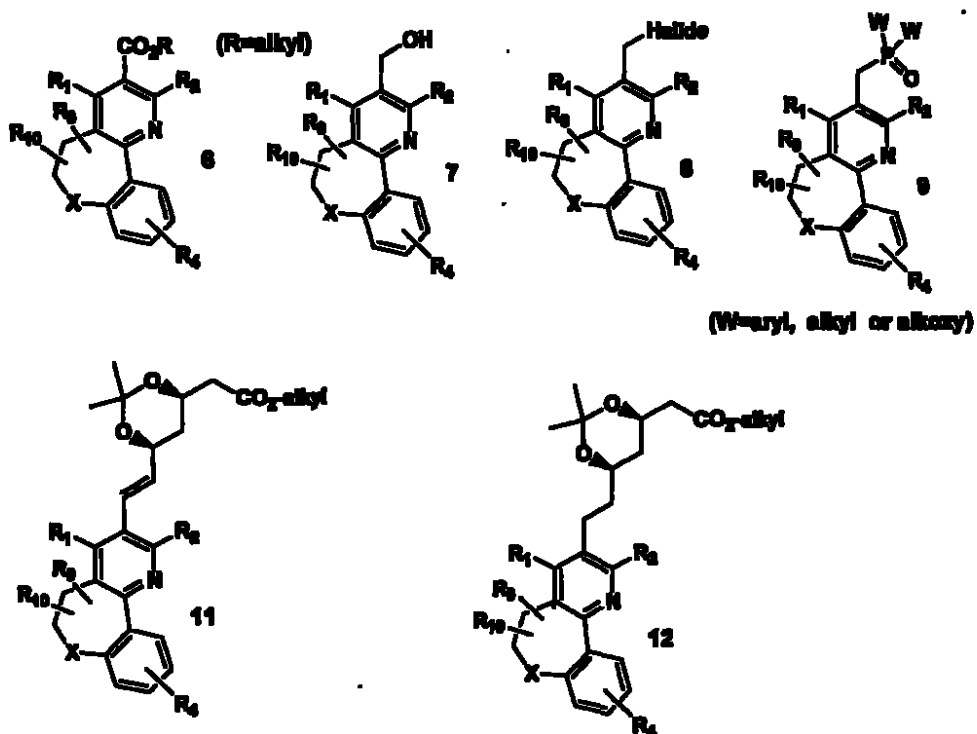
or



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18. The compound as defined in Claim 17 having the following structures:



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/18864

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D491/04 C07D495/04 C07D471/04 A61K31/55
 //(C07D491/04, 313:00, 221:00), (C07D495/04, 337:00, 221:00),
 (C07D471/04, 223:00, 221:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 444 533 A (SQUIBB & SONS INC) 4 September 1991 (1991-09-04) examples 3,9,10	1-18
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	-/-	

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

* Special categories of cited documents:

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

E earlier document but published on or after the international filing date

L document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document relating to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

25 October 2001

Date of mailing of the international search report

06/11/2001

Name and mailing address of the ISA

European Patent Office, P.O. Box 5010 Paternoster
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 Fax: (+31-70) 340-8016

Authorized officer

Frelon, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/18864

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 753 675 A (WATTANASIN SOMPONG) 19 May 1998 (1998-05-19) cited in the application abstract; claims	1-18
A	EP 0 491 226 A (BAYER AG) 24 June 1992 (1992-06-24) the whole document	1-18
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/18864

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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TRANSMITTAL LETTER TO THE
UNITED STATES RECEIVING OFFICE

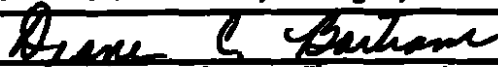
Date	12 June 2001
International Application No.	TBA
Attorney Docket No.	HX116

I. Certification under 37 CFR 1.10 (If applicable)

EL600710569US
Express Mail mailing number

12 June 2001
Date of Deposit

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


Signature of person mailing correspondence

Diane C. Bartram
Typed or printed name of person mailing correspondence

II. ☒ New International Application

TITLE	HMG-CoA REDUCTASE INHIBITORS AND METHOD
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Earliest priority date (Day/Month/Year)
15 JUNE 2000 (15.06.00)

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

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

application no.	60/211,565	filed on	15 JUNE 2000 (15.06.00)
application no.		filed on	

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

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

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

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

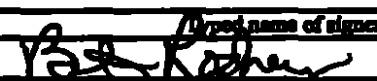
- D. ☐ Submission of Priority Documents

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

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

V. ☐ Other (please specify):

The person signing this form is the:	☐ Applicant	BRISTOL-MYERS SQUIBB COMPANY BURTON RODNEY
	☒ Attorney/Agent (Reg. No.) 22,078	
	☐ Common Representative	Signature

Boat # 867

112

12 June 2001

EL600710559US

PCT/US 01/18864

2,749.00

Int'l Patent Law

JUN 27 2001

BR

Docked Item Use Date

JG17 Rec'd PCT/PTO 12 JUN 2001

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11439	☐ 1st Day ☐ 2nd Day	
11439	Int'l Alpha Country Code	ODD Fee
11439	Acceptance Mark	Total Fee & Post \$ 76.00

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FROM: MARLA MAYFIAS (B. Rodney HX115 PCT)
BRISTOL-MYERS SQUIBB CO
PO BOX 4000
PRINCETON NJ 08543-4000

TO: ASSISTANT COMMISSIONER
FOR PATENTS
BOX PCT APPLICATION
WASHINGTON DC 20231-9999

REQUEST

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

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) HX115

Box No. I TITLE OF INVENTION
HMG-CoA REDUCTASE INHIBITORS AND METHOD

Box No. II APPLICANT

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

BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000
UNITED STATES OF AMERICA

☐ This person is also inventor.

Telephone No.
(800) 252-4336

Facsimile No.
(800) 252-4526

Teleprinter No.

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

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

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

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

ROBL, Jeffrey A.
7 Tulp Drive
Newtown, PA 18940
UNITED STATES OF AMERICA

This person is:

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

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

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

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

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

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

☒ agent ☐ common representative

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

BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000
SEE SUPPLEMENTAL SHEET NO. 4

Telephone No.
(800) 252-4336

Facsimile No.
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Teleprinter No.

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

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

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

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) CHEN, Bang-Chi 28 Marion Drive Plainsboro, NJ 08940 UNITED STATES OF AMERICA		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (that is, country) of nationality: PEOPLE'S REPUBLIC OF CHINA	State (that is, country) of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) SUN, Chong-Qing 527 Dutch Neck Road East Windsor, NJ 08520 UNITED STATES OF AMERICA		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (that is, country) of nationality: PEOPLE'S REPUBLIC OF CHINA	State (that is, country) of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (that is, country) of nationality:	State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (that is, country) of nationality:	State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (that is, country) of nationality:	State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box		
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.		

Box No.V DESIGNATION OF STATES

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

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

Regional Patent

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

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

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

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

- ☒ .. ECUADOR
- ☐ ☐

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

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) If more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
- (ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
- (iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
- (iv) If, in addition to the agent(s) indicated in Box IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
- (v) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
- (vi) If, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
- (vii) If, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

CONTINUED FROM PAGE 1 BOX IV (AGENT. OR COMMON REPRESENTATIVE)

BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000
UNITED STATES OF AMERICA

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BUCHHOLZ, Briana;
D'AMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; HERMENAUE, Ronald;
KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LOPEZ, Gabriel;
MAKUJINA, Shah; MATHIAS, Marla; McNEIL, Scott; MORSE, David; O'BRIEN,
Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton;
RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie;
WINSLOW, Anastasia

Box No. VI PRIORITY CLAIM					☐ Further priority claims are indicated in the Supplemental Box.	
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:				
		national application: country	regional application: regional Office	international application: receiving Office		
item (1) 15 JUNE 2000 (15.06.00)	60/211,595	US				
item (2)						
item (3)						

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(h)(ii)). See Supplemental Box.

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

Box No. VIII CHECK LIST: LANGUAGE OF FILING	
This international application contains the following number of sheets: request : 5 description (excluding sequence listing part) : 89 claims : 11 abstract : 1 drawings : sequence listing part of description : Total number of sheets : 116	This international application is accompanied by the item(s) marked below: 1. ☒ fee calculation sheet 2. ☒ separate signed power of attorney 3. ☐ copy of general power of attorney; reference number, if any: 4. ☐ statement explaining lack of signature 5. ☐ priority document(s) identified in Box No. VI as item(s): 6. ☐ translation of international application into (language): 7. ☐ separate indications concerning deposited microorganism or other biological material 8. ☐ nucleotide and/or amino acid sequence listing in computer readable form 9. ☒ other (specify): TRANSMITTAL LETTER, GENERAL POWER OF Attorney's
Figure of the drawings which should accompany the abstract:	Language of filing of the international application:

Box No. IX SIGNATURE OF APPLICANT OR AGENT	
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request). Burton Rodney	

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

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's
file reference

HX115

Applicant

BRISTOL-MYERS SQUIBB COMPANY

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE

240.00

T

2. SEARCH FEE

846.00

S

International search to be carried out by

ISA/EP

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

3. INTERNATIONAL FEE

Basic Fee

The international application contains 116 sheets.

first 30 sheets

382.00

b1

86

x 9.00

=

774.00

b2

remaining sheets additional amount

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

1,156.00

B

Designation Fees

The international application contains 88 designations.

492.00

6

x 82.00

=

number of designation fees
payable (maximum)

amount of designation fee

D

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

1,648.00

I

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

4. FEE FOR PRIORITY DOCUMENT (if applicable)

15.00

P

5. TOTAL FEES PAYABLE

2,749.00

TOTAL

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

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☒ authorization to charge
deposit account (see below)☐ bank draft☐ coupons☐ cheque☐ cash☐ other (specify):☐ postal money order☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ US ☒ is hereby authorized to charge the total fees indicated above to my deposit account.☒ (this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.☒ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

19-3880

Deposit Account No.

30/05/01

Date (day/month/year)

Burton Rodney

Signature

120
PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):

BRISTOL-MYERS SQUIBB COMPANY

hereby appoints (appoint) the following person as:



agent



common representative

Name and address

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

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BUCHHOLZ, Briana;
D'AMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; HERMENA, Ronald;
KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LOPEZ, Gabriel;
MAKUJINA, Shah; MATHIAS, Maria; McNEIL, Scott; MORSE, David; O'BRIEN,
Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton;
RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie;
WINSLOW, Anastasia

BRISTOL-MYERS SQUIBB COMPANY

P.O. Box 4000

Princeton, NJ 08543-4000, UNITED STATES OF AMERICA

to represent the undersigned before



all the competent International Authorities



the International Searching Authority only



the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: HMG-CoA REDUCTASE INHIBITORS AND METHOD

Applicant's or agent's file reference: HX115

International application number (if already available):

filed with the following Office THE UNITED STATES PATENT AND TRADEMARK as receiving Office
and to make or receive payments on behalf of the undersigned.

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

BRISTOL-MYERS SQUIBB COMPANY


Stephen B. Davis
Patent Counsel

Date:

30/05/01

CERTIFICATION

121

The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

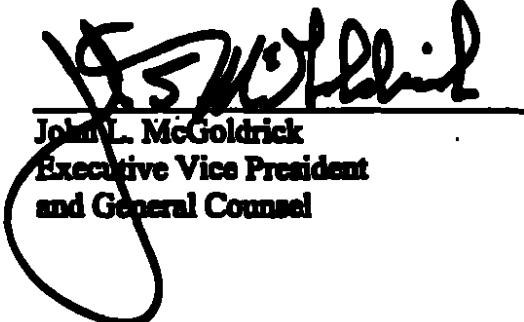
Marla J. Mathias

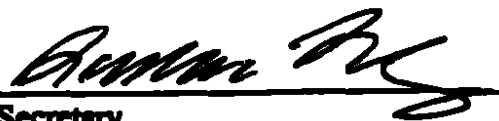
Stephen B. Davis

David M. Morse

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and requests in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights: (b) to initiate and prosecute oppositions and appeals: (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerks' Offices and Commissions or Commissioners that may be necessary: (d) to sign and approve on behalf of this corporation all documents and powers of attorney which in the judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred: (e) to request all proceedings: (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge: (g) to withdraw applications and all documents relating thereto: (h) to commence proceedings against infringers and assure the defense in infringement actions: and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure the granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 9th day of Dec. 2000.


John L. McGoldrick
Executive Vice President
and General Counsel


Secretary

GENERAL POWER OF ATTORNEY

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

(PCT Rule 90.5)

The undersigned person(s):

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

ROBL, Jeffrey A.
7 Tulip Drive
Newtown, PA 18940
UNITED STATES OF AMERICA

hereby appoint(s) the following person as:



Name and address

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

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; DAVIS, Stephen; DUBOFF, Samuel; HERMENA, Ronald S.; KILCOYNE, John; KLEIN, Christopher; LOPEZ, Gabriel; MAKUJINA, Shah; MATHIAS, Maria; MORSE, David; O'BRIEN, Maureen; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; BUCHHOLZ, Briana; DAMICO, Stephen; LANGE, Keith; PATEL, Rena; PEIST, Kenneth; MCNEIL, Scott; PROVOOST, Jonathan
BRISTOL-MYERS SQUIBB COMPANY
P.O. Box 4000
Lawrenceville-Princeton Road
Princeton, New Jersey UNITED STATES OF AMERICA

to represent the undersigned before



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

THE UNITED STATES PATENT AND TRADEMARK OFFICE

as receiving Office

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

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



Jeffrey A. Robl

Date:

March 29, 2001

GENERAL POWER OF ATTORNEY

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

(PCT Rule 90.5)

The undersigned person(s):

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

CHEN, Bang-Chi
28 Marion Drive
Plainsboro, NJ 08536
UNITED STATES OF AMERICA

hereby appoint(s) the following person as:



Name and address

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

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; DAVIS, Stephen; DOBOFF, Samuel; HERMENA, Ronald S.; KILCOYNE, John; KLEIN, Christopher; LOPEZ, Gabriel; MAKUJINA, Shah; MATHIAS, Maria; MORSE, David; O'BRIEN, Maureen; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; BUCHHOLZ, Briana; DAMICO, Stephen; LANGE, Keith; PATEL, Rena; PEIST, Kenneth; MCNEIL, Scott; PROVOOST, Jonathan
BRISTOL-MYERS SQUIBB COMPANY
P.O. Box 4000
Lawrenceville-Princeton Road
Princeton, New Jersey UNITED STATES OF AMERICA

to represent the undersigned before



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

THE UNITED STATES PATENT AND TRADEMARK OFFICE

as receiving Office

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

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

B-L: Chen

Bang-Chi Chen

Date:

6/2/01

GENERAL POWER OF ATTORNEY

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

(PCT Rule 90.5)

The undersigned person(s):

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

SUN, Chong-Qing
527 Dutch Neck Road
East Windsor, NJ 08520
UNITED STATES OF AMERICA

hereby appoint(s) the following person as:

☒ agent☐ common representative

Name and address

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

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; DAVIS, Stephen; DUBOFF, Samuel; HERMENA, Ronald S.; KILCOYNE, John; KLEIN, Christopher; LOPEZ, Gabriel; MAKUJINA, Shah; MATHIAS, Maria; MORSE, David; O'BRIEN, Maureen; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; BUCHHOLZ, Briana; DAMICO, Stephen; LANGE, Keith; PATEL, Rena; PEIST, Kenneth, MCNEIL, Scott; PROVOOST, Jonathan
BRISTOL-MYERS SQUIBB COMPANY
P.O. Box 4000
Lawrenceville-Princeton Road
Princeton, New Jersey UNITED STATES OF AMERICA

to represent the undersigned before

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

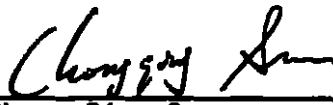
in connection with any and all international applications filed by the undersigned with the following Office

THE UNITED STATES PATENT AND TRADEMARK OFFICE

as receiving Office

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

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


Chong-Qing Sun

Date:

03/28/01

PATENT COOPERATION TREATY

125

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

RODNEY, Burton
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 18 September 2001 (18.09.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference HX115	
International application No. PCT/US01/18864	International filing date (day/month/year) 12 June 2001 (12.06.01)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 15 June 2000 (15.06.00)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

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

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
15 June 2000 (15.06.00)	60/211,595	US	08 Augu 2001 (06.08.01)

RECEIVED
Int'l Patent Law

10/14
OCT 02 2001
Docketed Item Due Date

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

Facsimile No. (41-22) 740.14.35

Authorized officer

Mougamadou ABIDINE (Fax 338.87.40)

Telephone No. (41-22) 338.83.38

The demand must be filed directly in the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

126

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference HX116	
International application No. PCT/US01/18864	International filing date (day/month/year) 12 June 2001 (12.06.01)	(Earliest) Priority date (day/month/year) 15 JUNE 2000 (15.06.00)	
Title of invention HMG-CoA REDUCTASE INHIBITORS AND METHOD			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) BRISTOL-MYERS SQUIBB COMPANY P. O. BOX 4000 PRINCETON, NEW JERSEY 08543-4000 UNITED STATES OF AMERICA		Telephone No.: (609) 252-4336	
		Facsimile No.: (609) 252-4526	
		Teleprinter No.:	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ROBL, Jeffrey A. 7 Tulip Drive Newtown, PA 18940 UNITED STATES OF AMERICA			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) CHEN, Bang-Chi 28 Marion Drive Plainsboro, NJ 08536 UNITED STATES OF AMERICA			
State (that is, country) of nationality: PEOPLE'S REPUBLIC OF CHINA		State (that is, country) of residence: US	
☒ Further applicants are indicated on a continuation sheet.			

Case No.: HX: 15

Application No.: PCT/US01/18864

127

Mailing Date:

January 9, 2002

Express Mail No.:

EL600710576US

The patent and Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below for PCT filing: DEMAND

☐ Appln. Filing Papers

☐ Transmittal Fee:

☐ Search Fee:

JAN 05 Rec'd PCT/PTO 0 9 JAN 2002

☐ Basic Fee:

☐ Designation Fee:

☐ Priority Document Fee:

X Preliminary Exam. Fee

750.00

X Handling Fee

146.00

Total

896.00

2002-01-09 10:00

Continuation of Box No. II APPLICANT(S)

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

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
SUN, Chong-Qing
527 Dutch Neck Road
East Windsor, NJ 08520
UNITED STATES OF AMERICA

State (that is, country) of nationality: PEOPLE'S REPUBLIC OF CHINA	State (that is, country) of residence: US
--	--

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

State (that is, country) of nationality:	State (that is, country) of residence:
--	--

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

State (that is, country) of nationality:	State (that is, country) of residence:
--	--

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

State (that is, country) of nationality:	State (that is, country) of residence:
--	--

☐ Further applicants are indicated on another continuation sheet.

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

The following person is ☒ agent ☐ common representative
and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☒ is hereby appointed and any earlier appointment of (an) agent(s) /common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

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

BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000
UNITED STATES OF AMERICA

SEE CONTINUATION SHEET NO. 5

Telephone No.:
(609) 252-4336

Facsimile No.:
(609) 252-4526

Teleprinter No.:

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

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:

1. The applicant wishes the international preliminary examination to start on the basis of:

- ☒ the international application as originally filed
- the description ☐ as originally filed
☐ as amended under Article 34
- the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34
- the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

- ☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received not received

- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 4. ☐ statement explaining lack of signature |
| 2. ☒ separate signed power of attorney | 5. ☐ nucleotide and/or amino acid sequence listing in computer readable form |
| 3. ☐ copy of general power of attorney; reference number, if any: | 6. ☐ other (specify): |

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

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


Burton Rodney

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPRA on:

131

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

1. *If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

- (i) *If more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*
- (ii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
- (iii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*
- (iv) *If, in addition to the agent(s) indicated in Box IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
- (v) *If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
- (vi) *If, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*
- (vii) *If, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.*

2. *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

3. *If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

Continued from Page 3, Box III
DEMAND-PCT/US01/18864

ALGIERI, Aldo; BABAIKO, Suzanne; BABCOCK, Timothy; BOUDREAUX, Gerald; BUCHHOLZ, Brian; BELFIELD, Jing; DAMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; DOLAN, Peter; FERGUSON, Blair; FURMAN, Theodore; GIBBONS, MAUREEN; HERMENAUE, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rene; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Bur ton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; VANATTEN, Mary; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia

BRISTOL-MYERS SQUIBB COMPANY

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

<table border="1" style="width: 100%; border-collapse: collapse;"><tr><td style="width: 50%;">International application No. PCT/US01/18884</td><td style="width: 50%;"></td></tr><tr><td>Applicant's or agent's file reference HX118</td><td></td></tr></table>	International application No. PCT/US01/18884		Applicant's or agent's file reference HX118		<table border="1" style="width: 100%; border-collapse: collapse;"><tr><td style="height: 40px; vertical-align: top;">For International Preliminary Examining Authority use only</td></tr><tr><td style="height: 40px; vertical-align: top;">Date stamp of the IPEA</td></tr></table>	For International Preliminary Examining Authority use only	Date stamp of the IPEA												
International application No. PCT/US01/18884																			
Applicant's or agent's file reference HX118																			
For International Preliminary Examining Authority use only																			
Date stamp of the IPEA																			
Applicant BRISTOL-MYERS SQUIBB COMPANY, ET AL																			
Calculation of prescribed fees <table style="width: 100%;"><tr><td style="width: 60%;">1. Preliminary examination fee</td><td style="width: 20%; text-align: right;">780.00</td><td style="width: 20%; text-align: center;">P</td></tr><tr><td colspan="3"> </td></tr><tr><td>2. Handling fee <i>(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)</i></td><td style="text-align: right;">148.00</td><td style="text-align: center;">H</td></tr><tr><td colspan="3"> </td></tr><tr><td>3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box</td><td style="text-align: right;">898.00</td><td></td></tr><tr><td></td><td style="text-align: right;">TOTAL</td><td></td></tr></table>		1. Preliminary examination fee	780.00	P				2. Handling fee <i>(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)</i>	148.00	H				3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	898.00			TOTAL	
1. Preliminary examination fee	780.00	P																	
2. Handling fee <i>(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)</i>	148.00	H																	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	898.00																		
	TOTAL																		
Mode of Payment <table style="width: 100%;"><tr><td>☒ authorization to charge deposit account with the IPEA (see below)</td><td>☐ cash</td></tr><tr><td>☐ cheque</td><td>☐ revenue stamps</td></tr><tr><td>☐ postal money order</td><td>☐ coupons</td></tr><tr><td>☐ bank draft</td><td>☐ other (specify):</td></tr></table>		☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):										
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash																		
☐ cheque	☐ revenue stamps																		
☐ postal money order	☐ coupons																		
☐ bank draft	☐ other (specify):																		
Deposit Account Authorization <i>(this mode of payment may not be available at all IPEAs)</i> The IPEA/ <u>US</u> ☒ is hereby authorized to charge the total fees indicated above to my deposit account. ☒ <i>(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)</i> is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.																			
<table style="width: 100%;"><tr><td style="width: 30%;">18-3880</td><td style="width: 30%; text-align: center;">9 / 1 / 02</td><td style="width: 40%; text-align: center;"> Signature Burton Rodney</td></tr><tr><td>Deposit Account Number</td><td>Date (day/month/year)</td><td></td></tr></table>		18-3880	9 / 1 / 02	 Signature Burton Rodney	Deposit Account Number	Date (day/month/year)													
18-3880	9 / 1 / 02	 Signature Burton Rodney																	
Deposit Account Number	Date (day/month/year)																		

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):

BRISTOL-MYERS SQUIBB COMPANY

hereby appoints (appoint) the following person as:



agent



common representative

Name and address

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

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BOUDREAU, Gerald; BUCHHOLZ, Brian; BELFIELD, Jing; DAMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; DOLAN, Peter; FERGUSON, Blair; FURMAN, Theodore; GIBBONS, MAUREEN; HERMENAU, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rene; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; VANATTEN, Mary; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia

to represent the undersigned before



all the competent International Authorities



the International Searching Authority only



the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention:

HMG-CoAREDUCTASE INHIBITORS AND METHOD

Applicant's or agent's file reference:

HX115

International application number (if already available):

PCT/US01/18864

filed with the following Office UNITED STATES PATENT AND TRADEMARK OFFICE as receiving Office
and to make or receive payments on behalf of the undersigned.

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

Stephen B. Davis
Stephen B. Davis

Date:

January 9, 2002

CERTIFICATION

134

The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

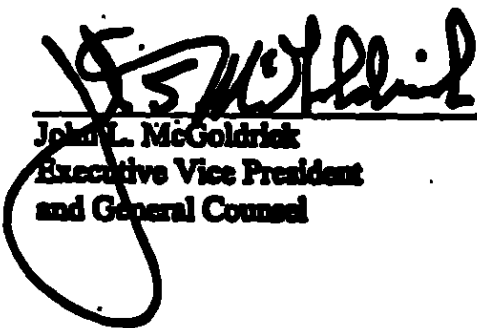
Maria J. Mathias

Stephen B. Davis

David M. Morne

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and requests in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights: (b) to initiate and prosecute oppositions and appeals: (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerks' Offices and Commissions or Commissioners that may be necessary: (d) to sign and approve on behalf of this corporation all documents and powers of attorney which in the judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred: (e) to request all proceedings: (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge: (g) to withdraw applications and all documents relating thereto: (h) to commence proceedings against infringers and assure the defense in infringement actions: and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure the granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 3rd day of Dec. 2000.


John L. McGoldrick
Executive Vice President
and General Counsel


Secretary

MAIL13

Case No.:

Application No.: **PO# US01/18864**

Mailing Date: **January 9, 2002**

Express Mail No.: **EL600710576US**

The patent and Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below for PCT filing: **DEMAND**

- ☐ Appln. Filing Papers
- ☐ Transmittal Fee:
- ☐ Search Fee:
- ☐ Basic Fee:
- ☐ Designation Fee:
- ☐ Priority Document Fee:
- ☒ Preliminary Exam. Fee **750.00**
- ☒ Handling Fee **146.00**
- Total 896.00**

135

END-PO 8008



**POST OFFICE
TO ADDRESSEE**



EL600710576US

FOR POSTAL USE ONLY				DELIVERY (POSTAL USE ONLY)			
PO ZIP Code	Day of Delivery ☐ Mon ☐ Tues	Flat Rate Envelope ☐		Delivery Attempt	Time ☐ AM ☐ PM	Employee Signature	
Date In	☐ 11 AM ☐ 3 PM	Postage	\$	Delivery Attempt	Time ☐ AM ☐ PM	Employee Signature	
Weight	☐ 1st Day ☐ 2nd Day	Return Receipt Fee		Delivery Date	Time ☐ AM ☐ PM	Employee Signature	
Weight	Int'l Alpha Country Code	ODD Fee	Insurance Fee	Signature of Addressee or Agent			
No Delivery ☐ Weekend ☐ Holiday	Acceptance Clerk Initials	Total Postage & Fees		Name - Please Print			
METHOD OF PAYMENT Express Mail Corporate Acct. No. X085205				☐ SIGNATURE OF DESTINATARY (Domestic Only: Additional merchandise insurance is void if signature is requested. I wish delivery to be made without obtaining signature of addressee or addressee's agent if delivery employee judges that article can be left in secure location) and I authorize that delivery employee's signature constitutes valid proof of delivery.			
FROM: (PLEASE PRINT) MARLA MATHIAS (Demand HX115) BRISTOL-MYERS SQUIBB CO PO BOX 4000 PRINCETON NJ 08543-4000				TO: (PLEASE PRINT) ASSISTANT COMMISSIONER FOR PATENTS BOX PCT APPLICATION WASHINGTON DC 20231-9999			

Mailing Label

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

BRISTOL-MYERS SQUIBB Company
P.O. Box 4000
PRINCETON, NJ 08543-4000
UNITED STATES OF AMERICANOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

RECEIVED
Int'l Patent Law

NOV 15 2001

Docketed Item

Due Date

Date of mailing
(day/month/year)

06/11/2001

Applicant's or agent's file reference

HX115

US 105 2/6/01

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 01/18864

International filing date
(day/month/year)

12/06/2001

Applicant

BRISTOL-MYERS SQUIBB COMPANY

- 1.
- ☒
- The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 18:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

- 2.
- ☐
- The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

- 3.
- ☐
- With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for International publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Chantal Meyer

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

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

What parts of the international application may be amended?

Under Article 18, only the claims may be amended.

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

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

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

Where not to file the amendments?

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

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

How?

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

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

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

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

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference HX115	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 01/18864	International filing date (day/month/year) 12/06/2001	(Earliest) Priority Date (day/month/year) 15/06/2000
Applicant BRISTOL-MYERS SQUIBB COMPANY		

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

This International Search Report consists of a total of 4 sheets.

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

1. Basis of the report

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

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

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

☐ contained in the international application in written form.

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

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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

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

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

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

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

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

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

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

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

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/18864 140

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D491/04 C07D495/04 C07D471/04 A61K31/55
//(C07D491/04,313:00,221:00),(C07D495/04,337:00,221:00),
(C07D471/04,223:00,221:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 444 533 A (SQUIBB & SONS INC) 4 September 1991 (1991-09-04) examples 3,9,10	1-18
Y	US 5 686 433 A (ROBL JEFFREY ADAM) 11 November 1997 (1997-11-11) cited in the application examples 63,75,76,99	1-18
Y	EP 0 325 130 A (BAYER AG) 26 July 1989 (1989-07-26) claims	1-18
Y	EP 0 818 197 A (BAYER AG) 14 January 1998 (1998-01-14) page 16; table 5	1-18
	-/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

25 October 2001

Date of mailing of the international search report

06/11/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentien 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Frelon, D

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 753 675 A (WATTANASIN SOMPONG) 19 May 1998 (1998-05-19) cited in the application abstract; claims	1-18
A	EP 0 491 226 A (BAYER AG) 24 June 1992 (1992-06-24) the whole document	1-18
A	ROBL J A ET AL: "PHOSPHORUS-CONTAINING INHIBITORS OF HMG-COA REDUCTASE. 2. SYNTHESIS AND BIOLOGICAL ACTIVITIES OF A SERIES OF SUBSTITUTED PYRIDINES CONTAINING A HYDROXYPHOSPHINYL" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 34, no. 9, 1991, pages 2804-2815, XP002922111 ISSN: 0022-2623 the whole document	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/18864

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

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 15 and 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/18864

143

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0444533	A	04-09-1991	AU 645287 B2	13-01-1994
			AU 7101691 A	29-08-1991
			CA 2036417 A1	27-08-1991
			EP 0444533 A2	04-09-1991
			HU 56574 A2	30-09-1991
			IE 910543 A1	28-08-1991
			JP 4211660 A	03-08-1992
			NZ 237097 A	23-12-1993
			PT 96874 A	31-10-1991
			US 5506219 A	09-04-1996
			US 5686433 A	11-11-1997
			US 5691322 A	25-11-1997
			ZA 9101046 A	28-10-1992
US 5686433	A	11-11-1997	US 5506219 A	09-04-1996
			US 5691322 A	25-11-1997
			AU 645287 B2	13-01-1994
			AU 7101691 A	29-08-1991
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			NZ 237097 A	23-12-1993
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			AU 637321 B2	27-05-1993
			AU 3941389 A	21-06-1990
			DK 422989 A	01-03-1990
			EP 0356788 A2	07-03-1990
			HU 52479 A2	28-07-1990
			JP 2108665 A	20-04-1990
			NZ 230121 A	26-08-1993
			ZA 8905869 A	30-05-1990
EP 0325130	A	26-07-1989	DE 3801406 A1	27-07-1989
			AU 642127 B2	14-10-1993
			AU 2861789 A	20-07-1989
			CN 1274719 A	29-11-2000
			CN 1034364 A ,B	02-08-1989
			DD 283400 A5	10-10-1990
			DK 23389 A	21-07-1989
			EP 1123924 A1	16-08-2001
			EP 1123925 A1	16-08-2001
			EP 0325130 A2	26-07-1989
			FI 890258 A ,B,	21-07-1989
			HU 50776 A2	28-03-1990
			JP 1216974 A	30-08-1989
			JP 2558344 B2	27-11-1996
			KR 132432 B1	17-04-1998
			NO 177005 B	27-03-1995
			NZ 227637 A	25-02-1993
			PT 89477 A ,B	08-02-1990
			US 5006530 A	09-04-1991
			US 5169857 A	08-12-1992
			US 5401746 A	28-03-1995
			ZA 8900429 A	28-02-1990

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/18864

144

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0818197	A	14-01-1998	DE 19627431 A1 15-01-1998
		AU 715101 B2 13-01-2000	
		BG 101748 A 30-04-1998	
		BR 9703890 A 03-11-1998	
		CA 2209825 A1 08-01-1998	
		CN 1174196 A 25-02-1998	
		CZ 9702144 A3 14-01-1998	
		EE 9700153 A 16-02-1998	
		EP 0818197 A1 14-01-1998	
		HR 970333 A1 30-04-1998	
		HU 9701157 A2 30-03-1998	
		IL 121234 A 06-12-2000	
		JP 10167967 A 23-06-1998	
		NO 973143 A 09-01-1998	
		PL 320953 A1 19-01-1998	
		SG 46781 A1 20-02-1998	
		SK 92597 A3 06-05-1998	
		TR 9700584 A2 21-01-1998	
		TW 382631 B 21-02-2000	
		US 5932587 A 03-08-1999	
US 5753675	A	19-05-1998	NONE
EP 0491226	A	24-06-1992	DE 4040026 A1 17-06-1992
		AT 141261 T 15-08-1996	
		AU 652977 B2 15-09-1994	
		AU 8961591 A 18-06-1992	
		CA 2057444 A1 15-06-1992	
		CN 1062350 A ,B 01-07-1992	
		CN 1113485 A 20-12-1995	
		CS 9103602 A3 17-06-1992	
		DE 59108081 D1 19-09-1996	
		DK 491226 T3 06-01-1997	
		EP 0491226 A1 24-06-1992	
		ES 2091852 T3 16-11-1996	
		FI 915854 A 15-06-1992	
		GR 3020826 T3 30-11-1996	
		HK 1004552 A1 27-11-1998	
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		KR 192625 B1 15-06-1999	
		LU 90230 A9 18-05-1998	
		NO 177140 B 18-04-1995	
		NZ 240946 A 27-09-1993	
		PL 169757 B1 30-08-1996	
		PT 99776 A ,B 30-11-1992	
		SK 280115 B6 06-08-1999	
		RU 2026290 C1 09-01-1995	
		US 5177080 A 05-01-1993	
		ZA 9109833 A 30-09-1992	

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: BURTON RODNEY BRISTOL-MYERS SQUIBB COMPANY P.O. BOX 4000 PRINCETON, NJ 08542-4000		PCT AUG 20 2002 WRITTEN OPINION
Docketed Item <u>04</u> (PCT Rule 66) Due Date <u>8/19/02</u> Attorney <u>BE</u>		Date of Mailing (day/month/year) 19 JUL 2002
Applicant's or agent's file reference HX115		REPLY DUE within <u>ONE</u> months from the above date of mailing
International application No. PCT/US01/18864	International filing date (day/month/year) 12 JUNE 2001	Priority date (day/month/year) 15 JUNE 2000
International Patent Classification (IPC) or both national classification and IPC IPC(7): A61K 31/075 and US Cl.: 514/80		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

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

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 60.9(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

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

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 60.9(4).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 60.8. For the form and the language of the amendments, see Rules 60.8 and 60.9.

Also For an additional opportunity to submit amendments, see Rule 60.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 60.4 bis.
For an informal communication with the examiner, see Rule 60.6.

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

4. The final date by which the international preliminary examination report must be established according to Rule 60.8 is: 15 OCTOBER 2002

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20531	Authorized officer <i>David Lukton</i> DAVID LUKTON Telephone No. (703) 305-0196
Facsimile No. (703) 305-3330	

I. Basis of the opinion**1. With regard to the elements of the international application:***☒ the international application as originally filed☒ the description:pages 1-89 , as originally filedpages NONE , filed with the demandpages NONE , filed with the letter of _____☒ the claims:pages 90-100 , as originally filedpages NONE , as amended (together with any statement) under Article 19pages NONE , filed with the demandpages NONE , filed with the letter of _____☒ the drawings:pages NONE , as originally filedpages NONE , filed with the demandpages NONE , filed with the letter of _____☒ the sequence listing part of the description:pages NONE , as originally filedpages NONE , filed with the demandpages 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 48.3(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 sequences disclosed in the international application, the written opinion was drawn 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 opinion has been drawn 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 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".

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	<u>1-18</u>	YES
	Claims	<u>NONE</u>	NO
Inventive Step (IS)	Claims	<u>1-18</u>	YES
	Claims	<u>NONE</u>	NO
Industrial Applicability (IA)	Claims	<u>1-18</u>	YES
	Claims	<u>NONE</u>	NO

2. citations and explanations

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

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

NEW CITATIONS
NONE

VIII. Certain observations on the international application

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

The compounds of claims 1-7 are asserted to be inhibitors of *3*-methyl-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 therefrom 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 8, 15 and 16.

Claims 1-8, 15, 16 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 3.1(a) for the reasons set forth in the immediately preceding paragraph.

WRITTEN OPINION

International application No.

PCT/US01/18804

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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

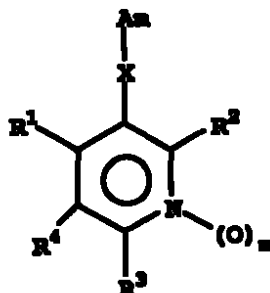
TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

HMG-CoA REDUCTASE INHIBITORS AND METHOD

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.

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



20 wherein:

Am is a binding domain sidechain;

X is a linker;

R¹ and R² are the same or different and are each independently selected from

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

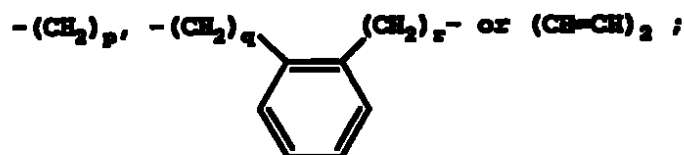
(ix) heterocyclo (e.g., thienyl, benzodioxolyl);

R^3 is selected from

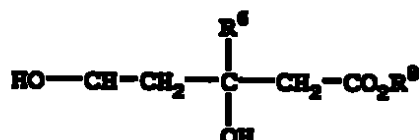
- 5 (i) hydrogen,
 (ii) lower alkyl,
 (iii) aryl,
 (iv) cycloalkyl,
 (v) alkoxy,
 (vi) aralkyl,
 10 (vii) aralkoxy,
 (viii) alkenyl,
 (ix) cycloalkenyl,
 (x) halo-substituted alkyl,
 (xi) adamantyl, and
 15 (xii) heterocyclo (e.g., thienyl, benzodioxolyl);

R^4 is selected from

- (i) hydrogen,
 (ii) lower alkyl,
 20 (iii) aryl,
 (iv) cycloalkyl,
 (v) alkoxy,
 (vi) aralkyl,
 (vii) aralkoxy,
 25 (viii) alkenyl,
 (ix) cycloalkenyl,
 (x) adamantyl,
 (xi) halogen,
 (xii) halo-substituted alkyl (e.g.,
 30 trifluoromethyl), and
 (xiii) heterocyclo (e.g., thienyl, benzodioxolyl);
 or R^3 and R^4 taken together can be



35 but when A_n is



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

R^6 is hydrogen or lower alkyl;

R^8 is hydrogen, lower alkyl, alkali metal, or
5 alkaline earth metal;

n is 0 or 1;

p is 3, 4 or 5;

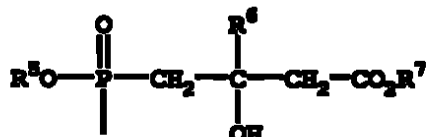
q is 0, 1, 2, or 3; and

r is 0, 1, 2, or 3.

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

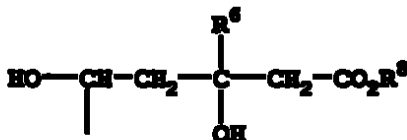
The phosphinic (or phosphonic when X is $\text{CH}_2\text{-O-}$) acid HMG-binding domain sidechain (A_1) is

15

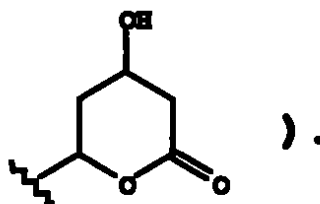


wherein R^5 and R^7 are independently selected from hydrogen, lower alkyl, alkali metal ion and alkaline earth metal ion; and R^6 is hydrogen or lower alkyl.

20 The dihydroxy acid binding domain sidechain (A_2 is



wherein R^6 is hydrogen or lower alkyl, R^8 is hydrogen or lower alkyl in free acid form or in the form of a
25 physiologically acceptable and hydrolyzable ester or δ lactone thereof (i.e., when Am is



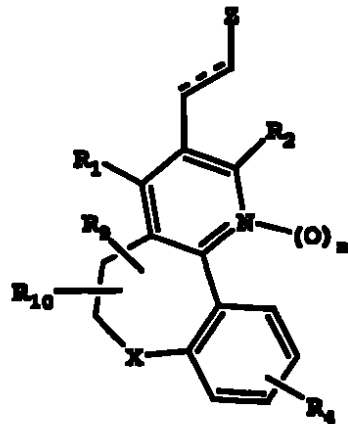
In addition, R^8 can be alkali metal ion or alkaline earth metal ion.

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.

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).

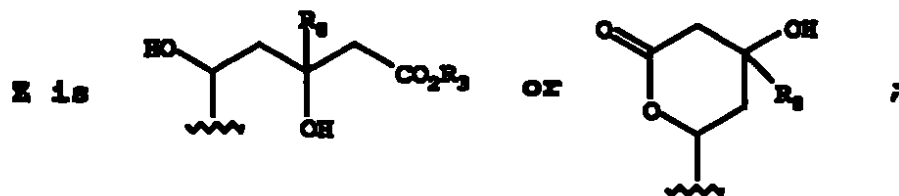
In particular, in its broadest chemical compound aspect, the present invention provides compounds of the formula

I



wherein X is O, S or NR_7 ;

20



n is 0 or 1;

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

R₃ is H, or lower alkyl;

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

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

R₈ is H or lower alkyl;

10 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);

15 and including pharmaceutically acceptable salts thereof where R₃ is H, esters thereof, prodrug esters thereof, and all stereoisomers thereof.

20 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, alkaline earth metal salt or an amino acid salt.

Preferred are compounds of formula I of the invention wherein

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

R₄ is H, alkyl or halogen;

X is O; and

n is 0.

30 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;

R₄ is H;

R₉ and R₁₀ are H;

35 X is O;

n is 0; and

 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;

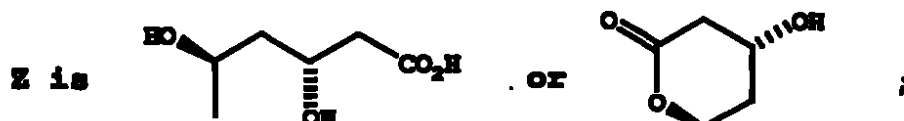
5 R_2 is alkyl or cycloalkyl, preferably isopropyl, t-butyl or cyclopropyl;

R_4 is H;

X is O;

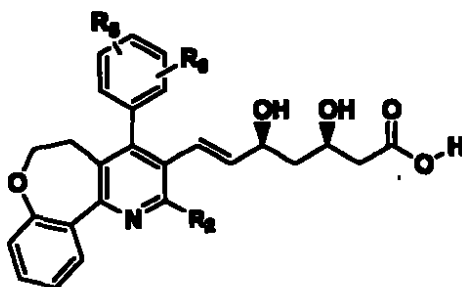
n is 0;

10  is a double bond, preferably "trans"; and



or an alkali or alkaline earth metal salt thereof or an amino acid salt.

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



or an alkali or alkaline earth metal (such as Na, K or
20 Ca) salt thereof, or an amino acid salt (such as arginine), 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

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

In another aspect, the present invention provides pharmaceutical compositions, useful as hypolipidemic or hypocholesterolemic agents, or hypotriglyceridemic
30 agents, or anti-Alzheimer's agents, or anti-osteoporosis

agents as well as other uses as described herein, comprising a hypolipidemic or hypocholesterolemic or hypotriglyceridemic or anti-Alzheimer's disease or anti-osteoporosis amount, or other therapeutically effective amount (depending upon use) 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 cholesterol levels such as lowering LDL cholesterol and/or increasing HDL cholesterol, or treating dyslipidemia, mixed dyslipidemia, hyperlipidemia, hypercholesterolemia, hypo α -lipoproteinemia, LDL Pattern B, LDL Pattern A, hyperlipoproteinemia or hypertriglyceridemia, and other aberrations of apolipoprotein B metabolism, or reducing levels of Lp(a), or treating or preventing other cholesterol-related diseases, or treating or preventing or reversing progression of atherosclerosis, or preventing or treating Alzheimer's disease, or preventing or treating osteoporosis and/or osteopenia, or reducing inflammatory markers such as C-reactive protein, or preventing or treating low grade vascular inflammation, or preventing or treating stroke, or preventing or treating dementia, or preventing and treating coronary heart disease (including primary and secondary prevention of myocardial infarction), or preventing or treating stable and unstable angina, or primary prevention of coronary events, or secondary prevention of cardiovascular events, or preventing or treating peripheral vascular disease, preventing or treating peripheral arterial disease, or preventing or treating acute vascular syndromes, or preventing or reducing the risk of undergoing myocardial revascularization procedures, or preventing or treating microvascular diseases such as nephropathy, neuropathy, retinopathy and nephrotic syndrome or preventing or

treating hypertension in a patient in need of such treatment by administering a pharmaceutical composition in accordance with the present invention as defined above.

5 In addition, in accordance with the present invention, a method is provided for preventing or treating diabetes, especially Type 2 diabetes, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of
10 fatty acids or glycerol, obesity, Syndrome X, diabetic complications, dysmetabolic syndrome, and related diseases, and sexual dysfunction, wherein a therapeutically effective amount of a compound of structure I is administered to a patient in need of
15 treatment.

 In addition, in accordance with the present invention, a method is provided for preventing and treating malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the
20 breast), premalignant lesions (such as fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), gastrointestinal malignencies, liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), cancer-induced
25 asthenia (fatigue), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and gallstones, and HIV infection, other infectious diseases, drug-induced lipodystrophy, and proliferative diseases such as psoriasis, wherein a therapeutically effective amount of
30 a compound of structure I is administered to a human patient in need of treatment.

 In addition, in accordance with the present invention, a method is provided for improving coagulation homeostasis including reducing PAI-1 activity, reducing
35 fibrinogen, and/or reducing platelet aggregation, and/or improving endothelial function, wherein a therapeutically

effective amount of a compound of structure I is administered to a patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating cholesterol
5 related diseases, diabetes and related diseases, cardiovascular diseases, cerebrovascular diseases as defined above and hereinafter and other diseases as set out above, wherein a therapeutically effective amount of a combination of a compound of structure I and a
10 hypolipidemic agent, and/or lipid modulating agent and/or antidiabetic agent and/or cardiovascular agent, cerebrovascular agent, and/or other type of therapeutic agent, is administered to a patient in need of treatment.

In the above methods of the invention wherein a
15 combination is administered, the compound of structure I will be employed in a weight ratio to the other therapeutic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 500:1, preferably from about 0.5:1 to about 100:1.

20

In accordance with the present invention, there is provided compounds useful in inhibiting the enzyme HMG-CoA reductase, which inhibitors are useful as
hypocholesterolemic agents, dyslipidemic agents,
25 hypolipidemic agents, hypotriglyceridemic agents, anti-Alzheimer's disease agents, and antiosteoporosis agents as well as other uses as described herein.

The term "coronary events" as employed herein refers to myocardial infarction, myocardial
30 revascularization procedures, angina, cardiovascular death and acute coronary syndrome.

The term "cardiovascular diseases or events" as employed herein refers to atherosclerosis of the coronary arteries, myocardial infarction, including primary MI and
35 secondary MI, recurrent myocardial infarction, angina pectoris (including stable and unstable angina), congestive heart failure, and sudden cardiac death.

The term "cerebrovascular diseases or events" as employed herein refers to cerebral infarction or stroke (caused by vessel blockage or hemorrhage), or transient ischemia attack (TIA), syncope, atherosclerosis of the intracranial and/or extracranial arteries, and the like.

The term "cholesterol-related diseases" as employed herein refers to diseases involving elevated levels of LDL cholesterol, diseases involving regulation of LDL receptors, diseases involving reduced levels of HDL cholesterol, dyslipidemia, hyperlipidemia, elevated LDL Pattern B, elevated LDL Pattern A, hypercholesterolemia, hypo α -lipoproteinemia (low HDL cholesterol syndrome), hyperlipoproteinemia, elevated Lp(a) levels, hypertriglyceridemia, other aberrations of apolipoprotein B metabolism, heterozygous familial, presumed familial combined and non-familial (non-FH) forms of primary hypercholesterolemia (including Frederickson Types IIa and IIb), cholesterol ester storage disease, and cholesterol ester transfer protein disease, and related diseases.

The conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Dysmetabolic Syndrome (as detailed in Johanson, *J. Clin. Endocrinol. Metab.*, 1997, 82, 727-734, and other publications) include hyperglycemia and/or prediabetic insulin resistance syndrome, and is characterized by an initial insulin resistant state generating hyperinsulinemia, dyslipidemia, and impaired glucose tolerance, which can progress to Type II diabetes, characterized by hyperglycemia, which can progress to diabetic complications.

The term "diabetes and related diseases" refers to Type II diabetes, Type I diabetes, impaired glucose tolerance, obesity, hyperglycemia, Syndrome X, dysmetabolic syndrome, diabetic complications and hyperinsulinemia.

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The conditions, diseases and maladies collectively referred to as "diabetic complications" include retinopathy, neuropathy and nephropathy, and other known complications of diabetes.

5 The term "other type(s) of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than compounds of formula I), one or more anti-obesity agents, and/or one or more lipid-lowering agents, one or more lipid modulating agents (including anti-
10 atherosclerosis agents), other types of anti-atherosclerosis agents, and/or one or more antiplatelet agents, one or more agents for treating hypertension, one or more anti-cancer drugs, one or more agents for treating arthritis, one or more anti-osteoporosis agents,
15 one or more anti-obesity agents, one or more agents for treating immunomodulatory diseases, and/or one or more agents for treating anorexia nervosa.

 The term "lipid-modulating" agent as employed herein refers to agents which lower LDL and/or raise HDL
20 and/or lower triglycerides and/or lower total cholesterol and/or other known mechanisms for therapeutically treating lipid disorders.

 The term "other types of anti-atherosclerosis agents" as employed herein refers to conventional anti-
25 atherosclerosis agents including lipoxxygenase inhibitors, ACAT inhibitors, antioxidants, PPAR δ agonists, phospholipase inhibitors including PLA-2 inhibitors and/or other known anti-atherosclerotic agents.

 The terms pharmaceutically acceptable "salt" and
30 "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,
35 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

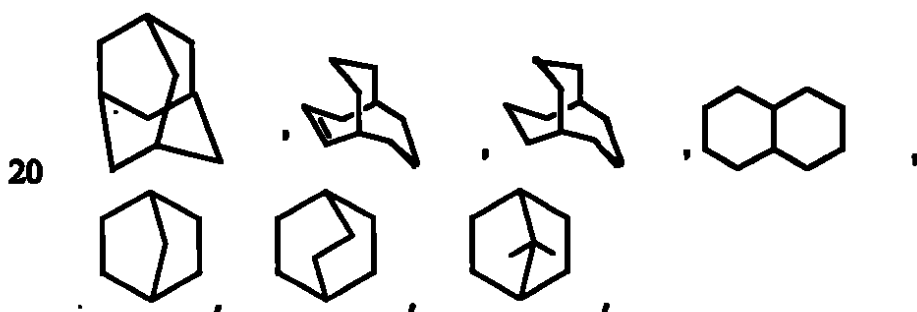
like; and zwitterions, the so-called "inner salts". Nontoxic, pharmaceutically acceptable salts are preferred, although other salts are also useful, e.g., in isolating or purifying the product.

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,

cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl, cycloheteroalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, 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 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 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, 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.

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

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-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonyl, 4-decynyl, 3-undecynyl,
35 4-dodecynyl and the like, and which may be optionally

substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, 5 arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the alkyl substituents set out herein.

The terms "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkenyl and alkynyl groups as described above having an aryl 10 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 15 defined above for "alkyl", such as, for example, alkyl, halo, hydroxy, alkoxy and/or cycloalkyl.

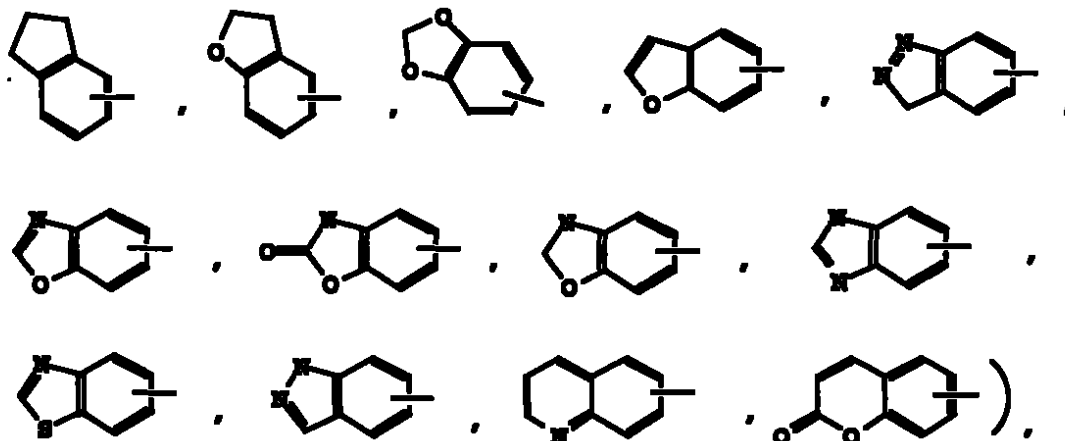
Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are 20 termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted with 1 or 2 substituents as defined above for "alkenyl" and "alkynyl".

The term "halogen" or "halo" as used herein alone 25 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 30 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 35 to 10 carbons in the ring portion (such as phenyl or

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, alkylaminocarbonyl, arylaminocarbonyl, alkoxy carbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino,

25 arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl and/or any of the alkyl substituents set out herein.

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

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.

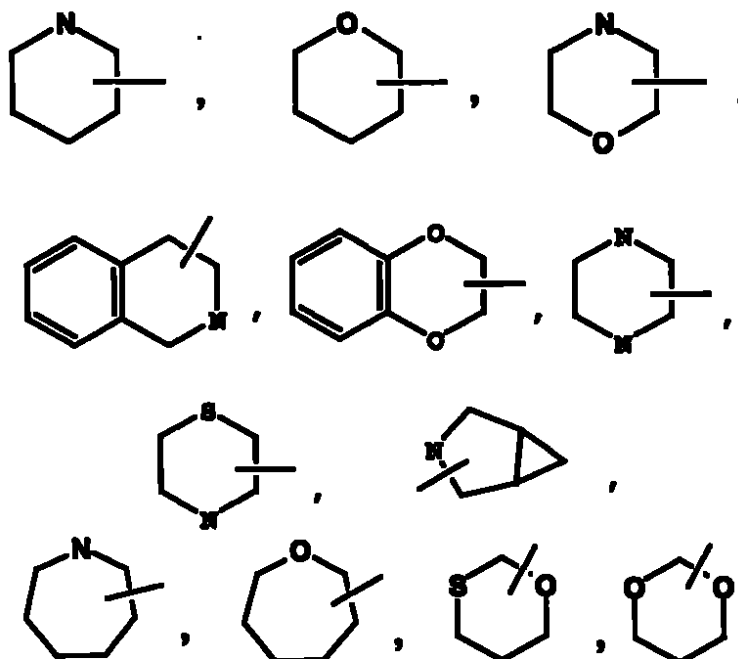
Unless otherwise indicated, the term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

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 $\left(\begin{smallmatrix} \text{O} \\ \parallel \\ \text{C} \end{smallmatrix} \right)$ group; examples of acyl groups include any of the R¹ groups attached to a carbonyl, such as

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



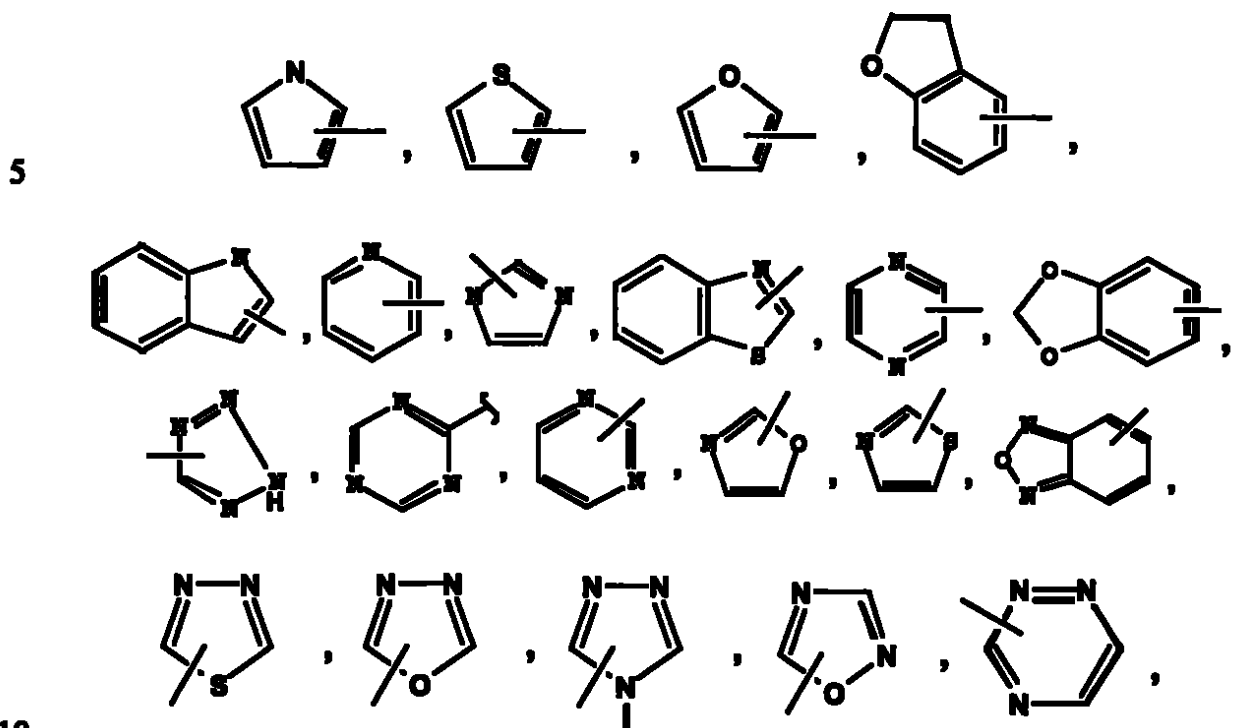
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and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the alkyl substituents set out herein. In addition, any of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl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

25

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.

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.

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 $CF_3CF_2CH_2$.

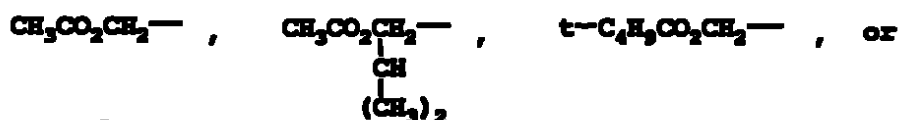
The term "polyhaloalkoxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo

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

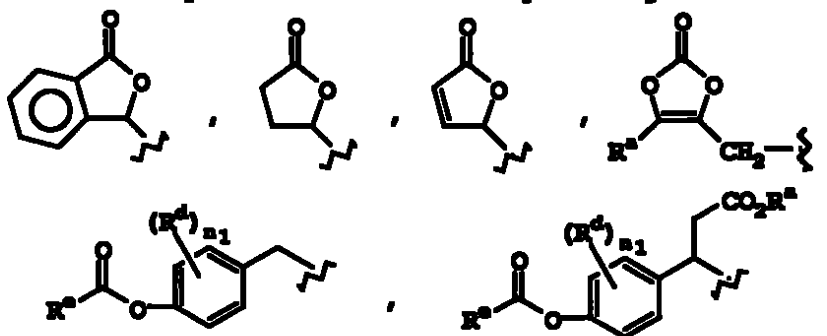
All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one or the R substituents. Consequently, compounds of formula 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



30

(70)

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 alkoxyl, 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.

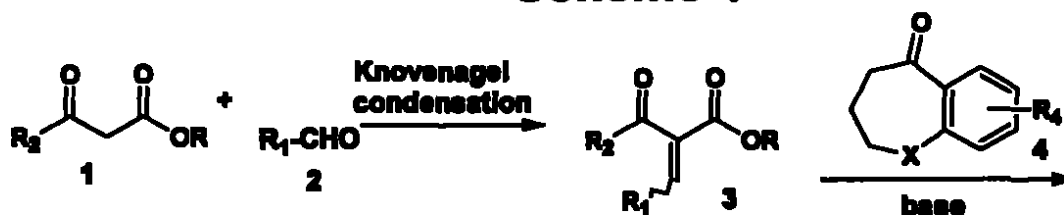
25 Conversion of the 1,5-diketone 5 to the pyridyl
ester 6 may be effected by treatment with an ammonia
source (such as NH₄OAc) in the presence of an oxidant
(such as Cu(OAc)₂ or oxygen) in a suitable solvent (such
as refluxing HOAc), or by reaction of 5 with
30 hydroxylamine hydrochloride in HOAc with 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 CH₂CN 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 where W

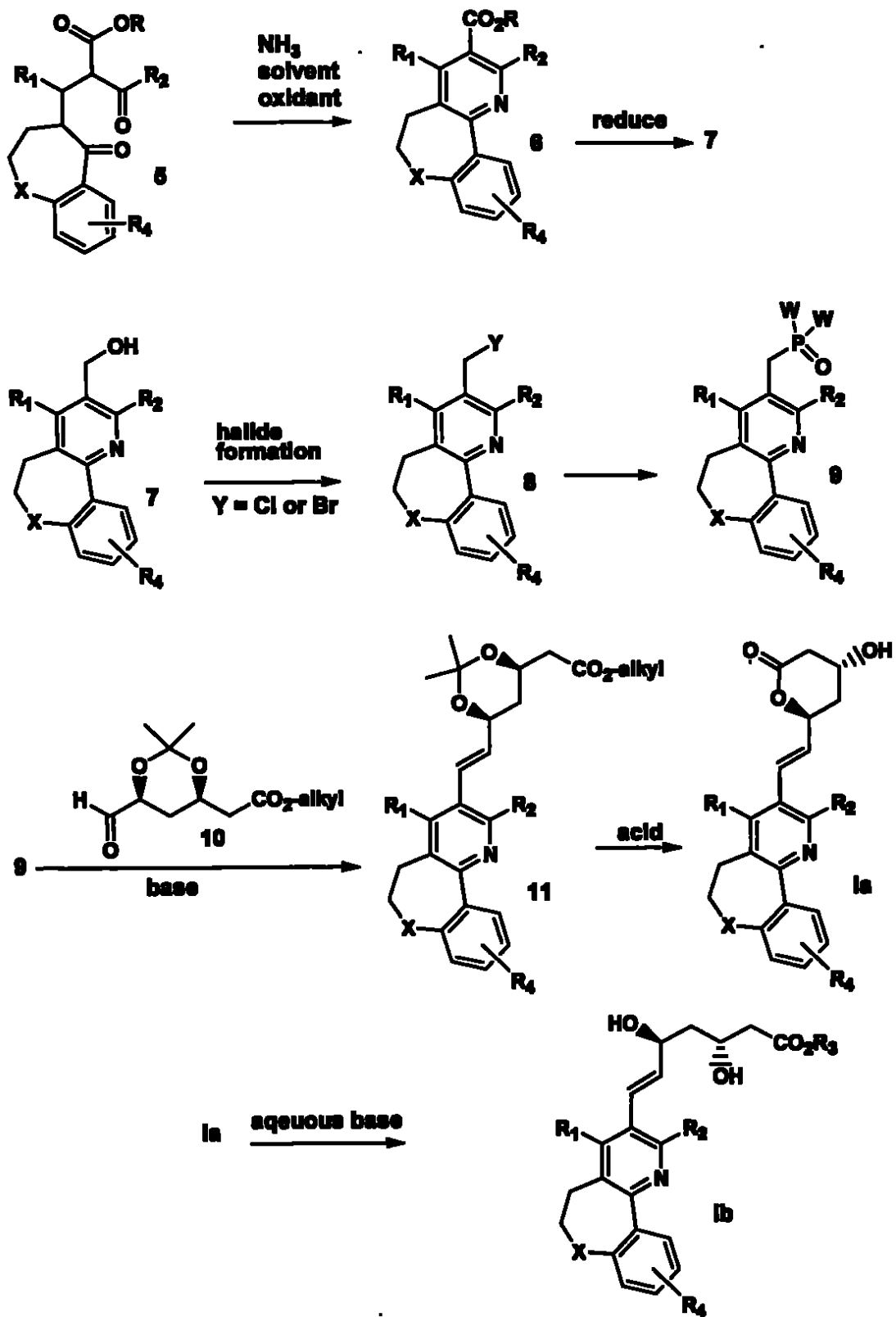
- is OR (R is lower alkyl) may be effected by the reaction of 8 with $\text{HOP(OR)}_2/\text{base/THF}$ or by Arbuzov reaction with P(OR)_3 . Wittig reaction between 9 and aldehyde 10 (aldehyde 10 has been previously described in US patent 5,686,433) may be effected under standard conditions with base (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.
- 10 Saponification of Ia to Ib (where R₃ is alkali metal, or alkaline earth metal) can be effected by treatment of Ia with aqueous base or subsequently acidified to give Ib where R₃ is H. Additionally, Ia can be treated with an alcohol of the type R₂OH under basic conditions to form
- 15 the corresponding esters of Ib.

- As seen in Reaction Scheme 2, the saturated derivatives of compound I (where ~~is~~ is $\text{CH}_2\text{-CH}_2$) are obtained by catalytic (Pd/C, Pt/C, Pd(OH)_2) hydrogenation of 11, Ia, or Ib to afford 12, Ic, or Id, respectively.
- 20 Compound 12 may be converted to Ic and Id following the earlier described methods for the conversion of compound 11 to Ia and Ib.

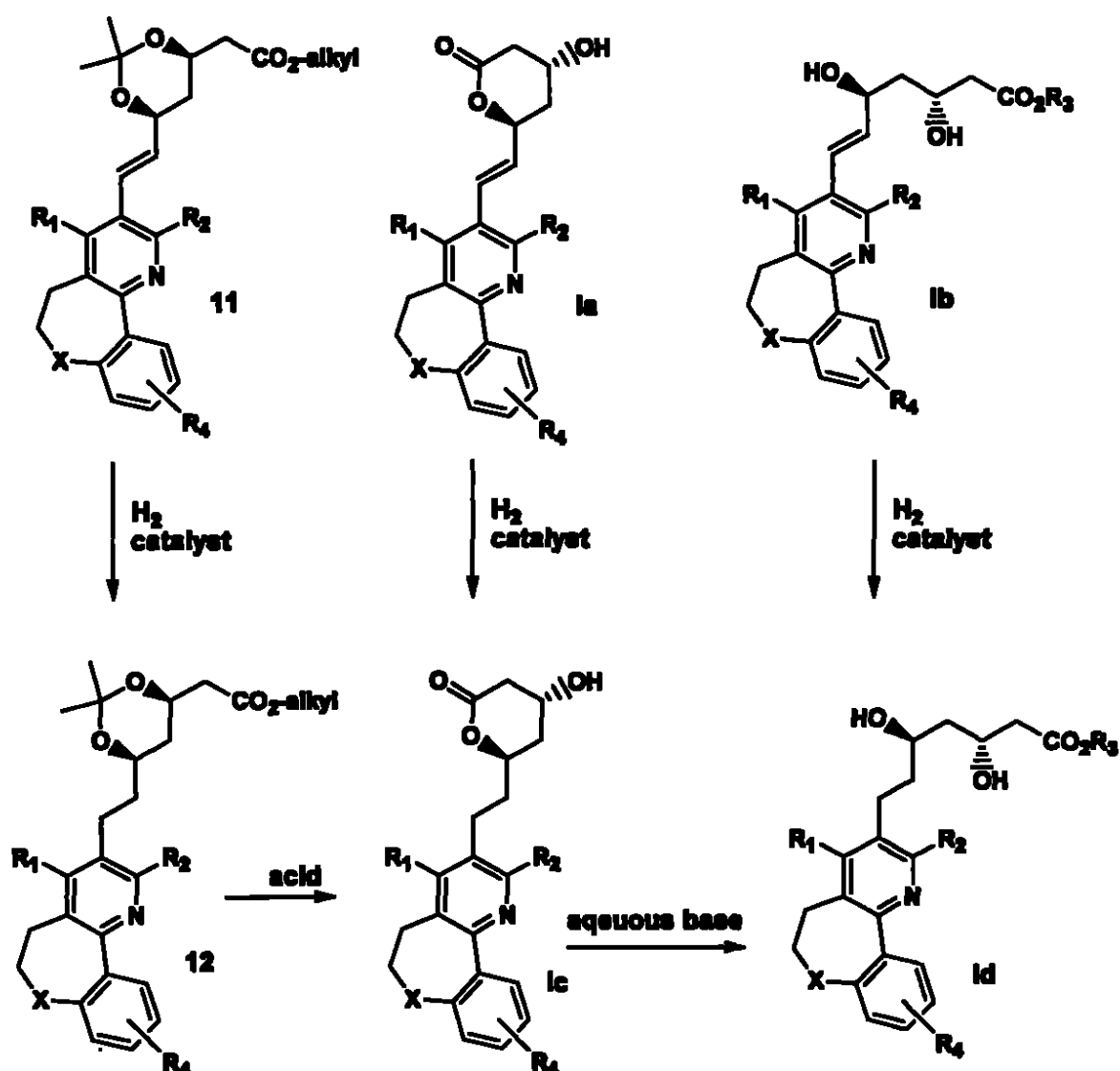
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Scheme 1





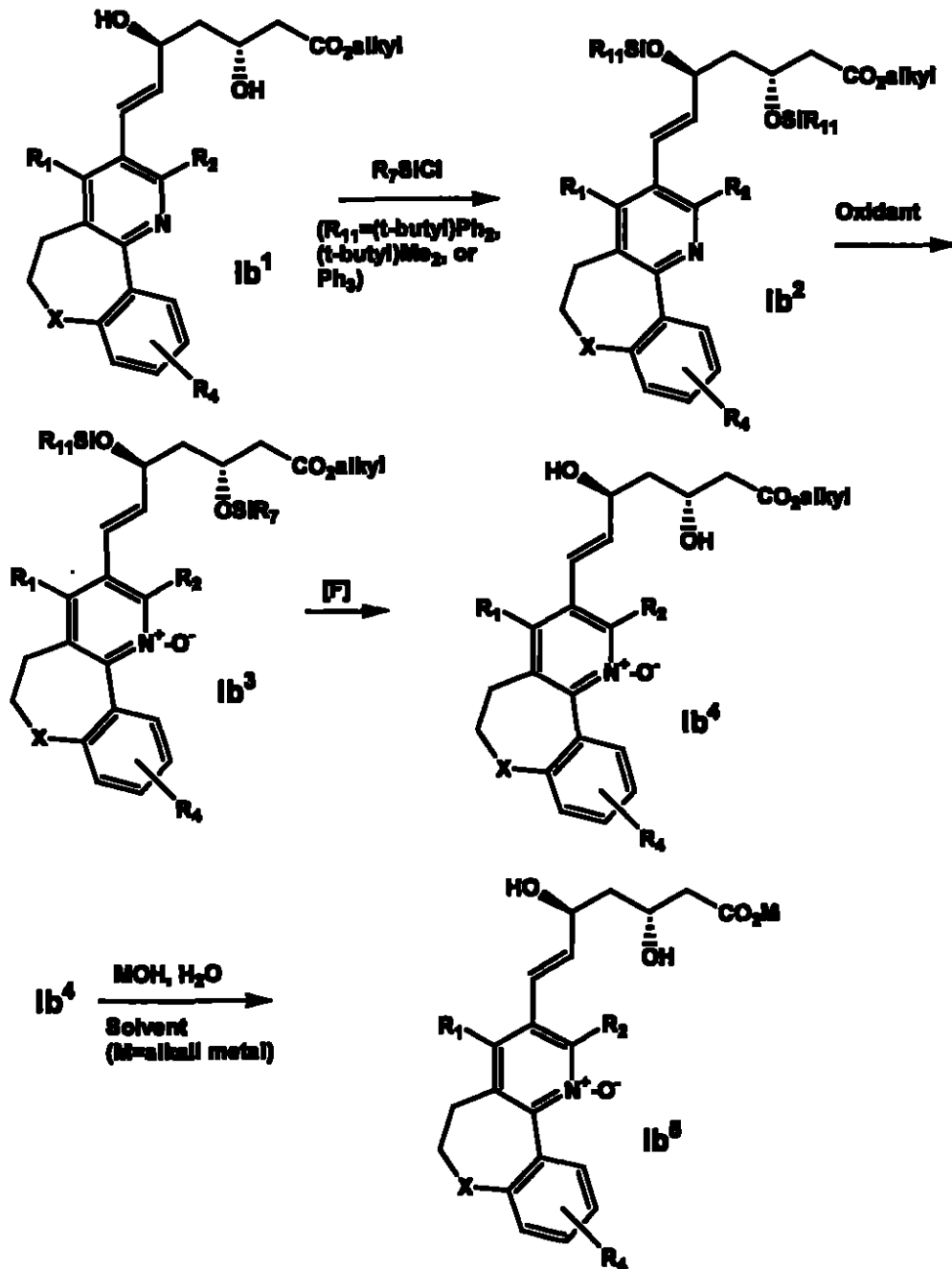
Scheme 2



The synthesis of compounds I wherein $\text{---} \text{CH}=\text{CH} \text{---}$ is $\text{CH}=\text{CH}$ and n is 1, is described in Scheme 3. Bis-silylation of compound Ib¹ with a bulky silylchloride (e.g., $\text{ClSi}(\text{t-butyl})\text{Ph}_2$, $\text{ClSi}(\text{t-butyl})\text{Me}_2$, ClSiPh_3) in the presence of a suitable base (e.g., TEA, imidazole, pyridine) and solvent (e.g., CH_2Cl_2 , THF) provides compound Ib². Treatment of Ib² with oxidants such as $m\text{-CPBA}$ or $\text{CF}_3\text{CO}_3\text{H}$ in an appropriate solvent such as CH_2Cl_2 or HOAc affords N-oxide Ib³. Desilylation of Ib³ (TBAF/HOAc/THF or HF/ CH_3CN) gives Ib⁴ which may be saponified to Ib⁵ using

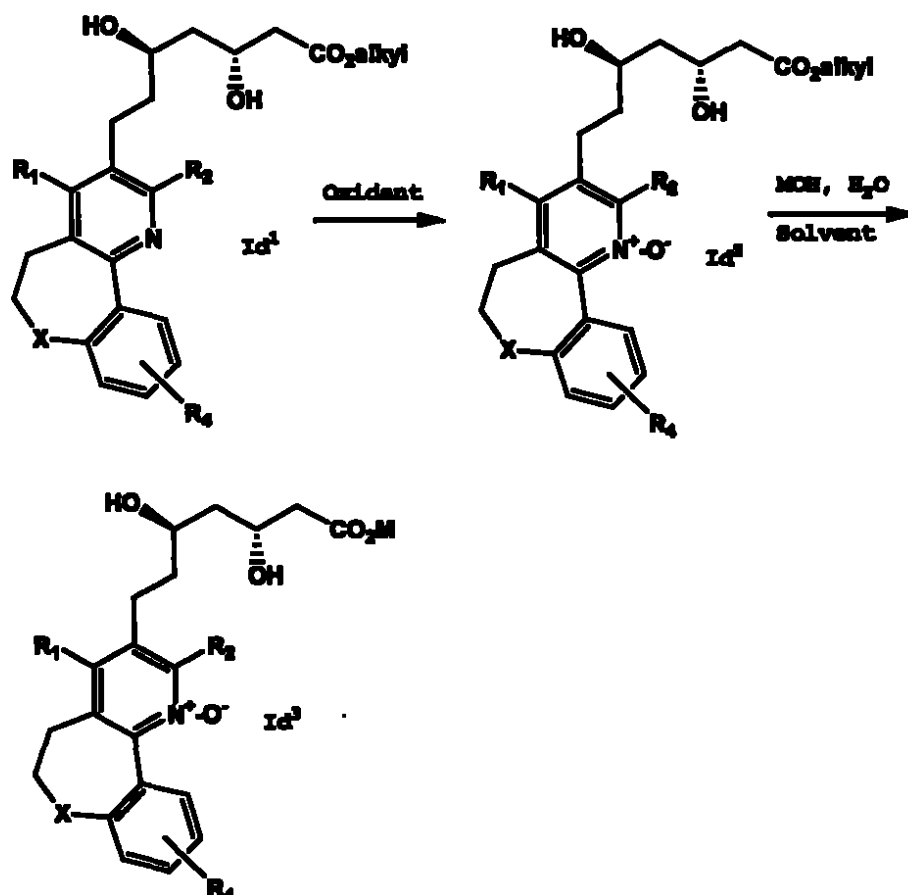
aqueous solutions of a metal hydroxide in an appropriate solvent (e.g., MeOH, dioxane).

5

SCHEME 3

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.

5

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.

Scheme 5 depicts a preferred method for preparing the HMG CoA reductase inhibitor of formula I of the invention using the Julia-Kocienski olefination reaction
20 employing 4-pyridyl carboxylaldehyde (18) and chiral

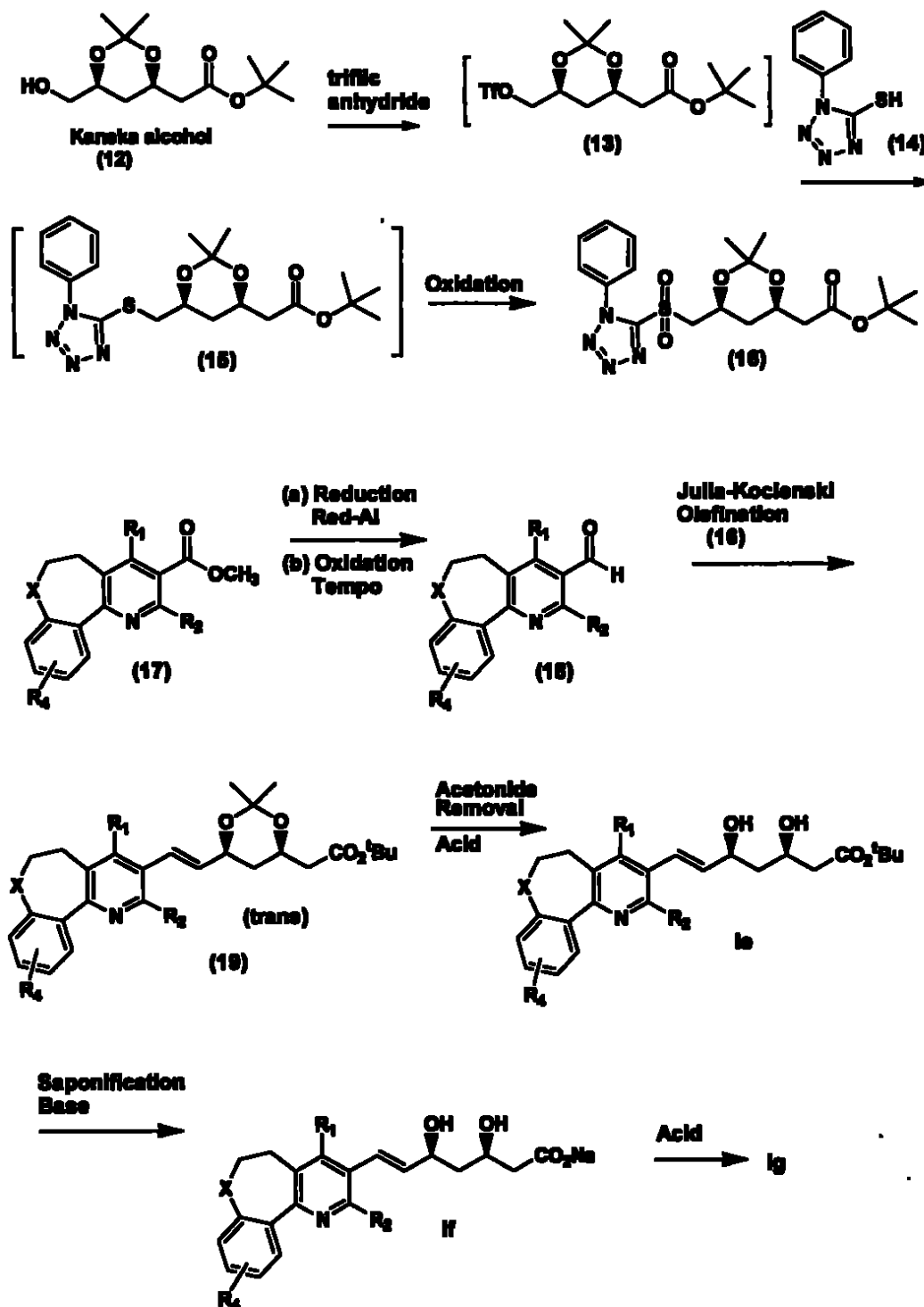
sulfone (16). The desired trans intermediate (19) is isolated in high yield and optical purity which is converted to the final product of the invention. As will be seen, the chiral sulfone (16), a key intermediate in the Julia-Kocienski step, is prepared in three steps starting from the commercially available Kaneka alcohol (12) via triflate (13) and sulfide intermediate (15).

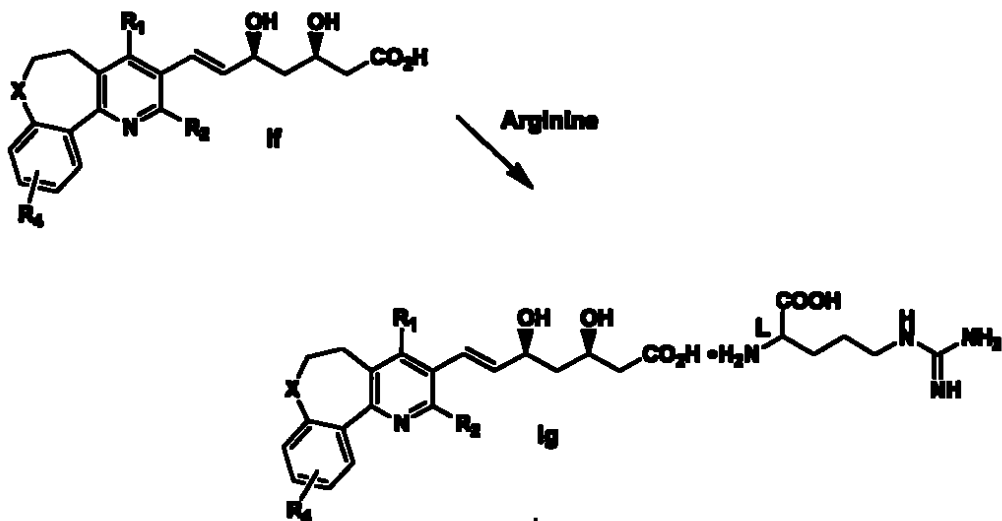
Referring to Scheme 5, treatment of commercially available chiral alcohol (12) with triflic anhydride and triethylamine in dichloromethane at low temperature (for example 0 to -30°C) affords triflate (13). Other pyridine or amine bases may be employed. Triflate (13) (without being isolated) is carried onto the next step without further purification. A methylene chloride solution of triflate (13) is treated with 1-phenyl-1H-tetrazole-5-thiol (14) to provide the chiral sulfide (15) which is oxidized with hydrogen peroxide in the presence of catalytic ammonium heptamolybdate tetrahydrate to give crystalline sulfone (16). Other oxidant, such as m-chloro-p-benzoic acid (mCPBA) may be employed.

Addition of LiHMDS or NaHMDS to a mixture of sulfone (16) and pyridine carboxylaldehyde (18) in THF at low temperature (-78 to -35°C) provides trans olefin (19) in high diastereoselectivity (>99%).

The pyridine aldehyde (18) is obtained as a crystalline solid form the corresponding ester (17). Reduction of ester (17) with Red-Al followed by oxidation with Tempo (2,2,6,6-tetramethyl-1-piperidinyloxy) gives aldehyde (18) in high yield. The final compound Ie of the invention is prepared in a one pot procedure starting from (19) without isolating any intermediates. Removal of acetonide under acidic condition provides diol Ie of the invention which upon further treatment with sodium hydroxide gives the sodium salt of the acid If of the invention. Subsequent treatment of If with acid followed by the addition of arginine produces crystalline arginine salt of the invention Ig.

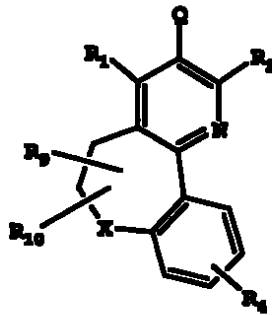
Sch m 5



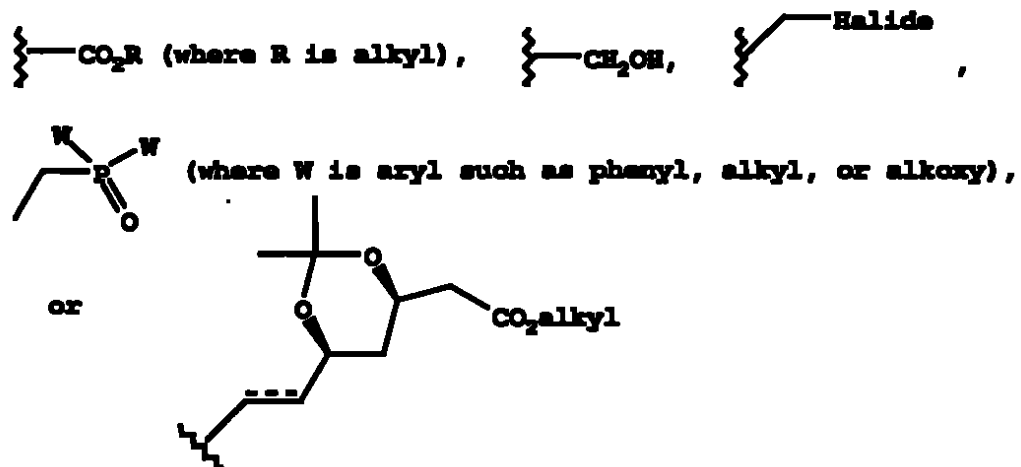


In addition, in accordance with the present invention, intermediates 6, 7, 8, 9, 11 and 12 are novel compounds and form part of the present invention. These compounds have the general structure

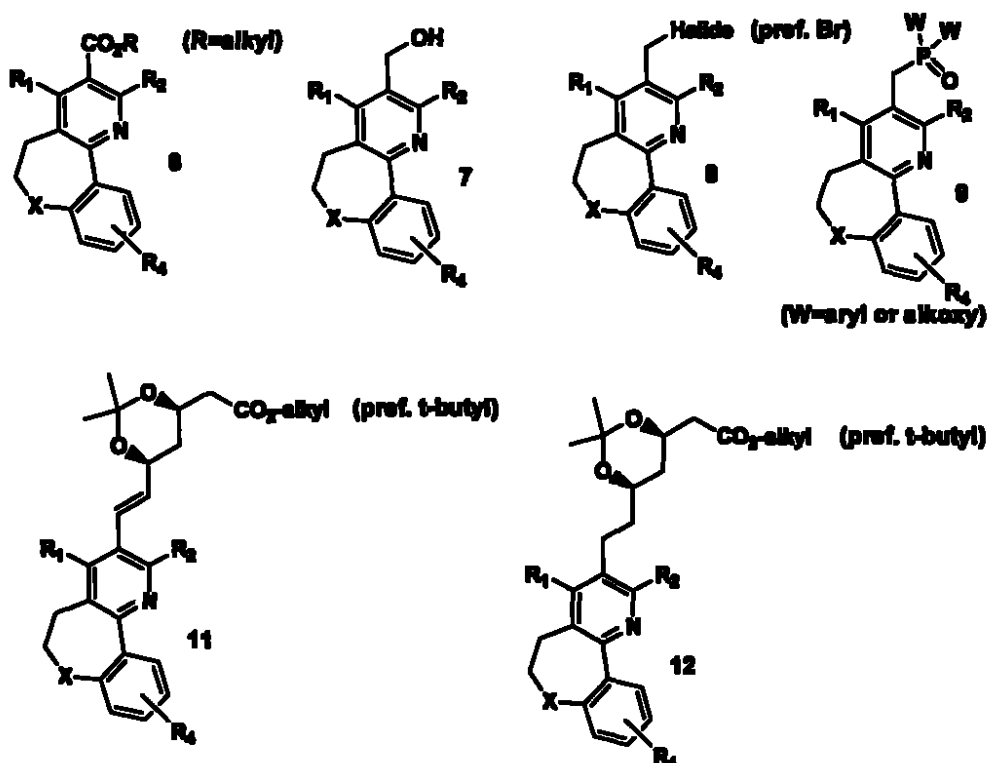
II



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



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



5

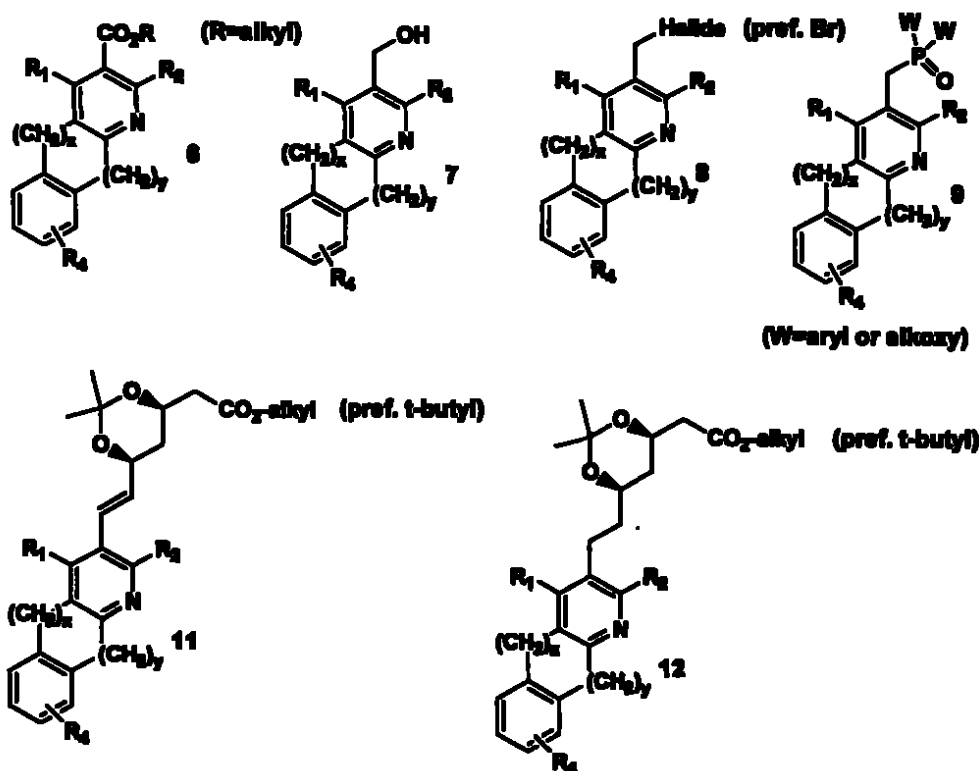
Compounds 6, 7, 8, 9, 11 and/or 12 may include R_9 and R_{10} substituents.

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.

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

15

170



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.

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, lovastatin, cerivastatin, visastatin (or rosuvastatin) (Astra Zeneca ZD4522), fluvastatin, itavastatin (or pitavastatin) 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 association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles of diluents and pharmaceutical additives of a type

A

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.

10 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 (or rosuvastatin), atorvastatin, cerivastatin, 15 fluvastatin, itavastatin (or pitavastatin), 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 20 4 times per day, preferably 0.2 to 100 mg daily or in sustained release form.

The HMG CoA reductase inhibitors of formula I may be employed in combination with all therapeutic agents which are useful in combination with HMG CoA reductase 25 inhibitors.

Thus, where desired, the compounds of structure I may be used in combination with one or more hypolipidemic agents or lipid-lowering agents, or lipid agents, or lipid modulating agents, and/or one or more other types 30 of therapeutic agents including antidiabetic agents, anti-obesity agents, antihypertensive agents, platelet aggregation inhibitors, anti-Alzheimer's agents, anti-dementia agents, anti-osteoporosis agents, and/or hormone replacement therapeutic agents, and/or other therapeutic 35 agents, and/or other cardiovascular agents (including anti-anginal agents, anti-arrhythmic agents, anti-atherosclerosis agents, anti-inflammatory agents, anti-

platelet agents, anti-heart failure agents), anti-cancer agents, anti-infective agents, hormone replacement agents, growth hormone secretagogues, selective androgen receptor modulators, and/or other therapeutic agents
5 which may be administered orally in the same dosage form or in a separate oral dosage form, or by injection.

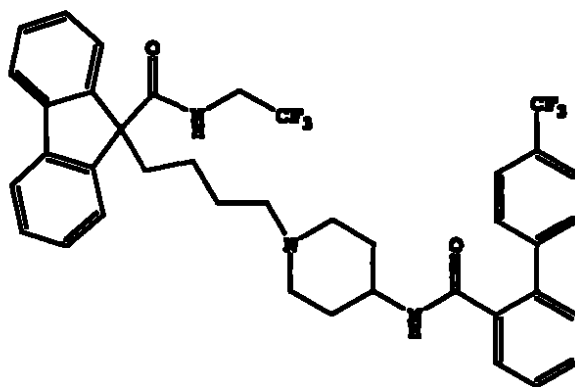
The hypolipidemic agent or lipid-lowering agent or other lipid agent or lipid modulating agent which may be optionally employed in combination with the compounds of
10 formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, PPAR α agonists, PPAR dual α/γ agonists, PPAR δ agonists, fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol
15 absorption inhibitors, ileal Na⁺/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, cholesteryl ester transfer protein inhibitors, bile acid sequestrants, and/or nicotinic acid and derivatives thereof.

20 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.
25 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.

30 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.

35 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 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, pitavastatin (Nissan/Sankyo's nisvastatin (NK-104) or itavastatin), disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca rosuvastatin (visastatin (ZD-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 mevastatin (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 -phosphonosulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)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., Ponpipom, 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 fen fibrate, gemfibrozil, cl fibrate, bezafibrate, ciprofibrate, clin fibrate 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 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.

The other hypolipidemic agent may be an ACAT inhibitor (which also has anti-atherosclerosis activity) 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, 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, 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,
Editor(s): Ruffell, Robert R., Jr.; Hllinger, Manfred
A., Inflammation: Mediators Pathways (1995), 173-98,
Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors:
5 potential anti-atherosclerotic agents", Sliskovic et al,
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
10 of acyl-CoA:cholesterol acyltransferase (ACAT). 7.
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
15 Pharmaceutical Co. Ltd), as well as F-1394, CS-505,
F-12511, HL-004, K-10085 and YIC-C8-434.

The hypolipidemic agent may be an upregulator of
LDL receptor activity such as MD-700 (Taisho
Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

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

25 The other lipid agent or lipid-modulating agent
may be a cholesteryl transfer protein inhibitor (CETP)
such as Pfizer's CP-529,414 as well as those disclosed in
WO/0038722 and in EP 818448 (Bayer) and EP 992496, and
Pharmacia's SC-744 and SC-795 as well as CETi-1 and
30 JTT-705.

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

35 The ATP citrate lyase inhibitor which may be
employed in the combination of the invention may include,
for example, those disclosed in U.S. Patent No.
5,447,954.

The ther lipid agent als includes a
phyt estrogen compound such as discl sed in WO 00/30665
including isolated soy bean protein, soy protein
concentrate or soy flour as well as an isoflavone such as
5 genistein, daidzein, glycitein or equol, or phytosterols,
phytostanol or tocotrienol as disclosed in WO
2000/015201;

a beta-lactam cholesterol absorption inhibitor
such as disclosed in EP 675714;

10 an HDL upregulator such as an LXR agonist, a PPAR
 α -agonist and/or an FXR agonist;

an α -glucosidase inhibitor, an aldose reductase
inhibitor and/or an LDL catabolism promoter such as
disclosed in EP 1022272;

15 a sodium-proton exchange inhibitor such as
disclosed in DE 19622222;

an LDL-receptor inducer or a steroidal glycoside
such as disclosed in U.S. Patent No. 5,698,527 and
GB 2304106;

20 an anti-oxidant such as beta-carotene, ascorbic
acid, α -tocopherol or retinol as disclosed in WO 94/15592
as well as Vitamin C and an antihomocysteine agent such
as folic acid, a folate, Vitamin B6, Vitamin B12 and
Vitamin E;

25 isoniazid as disclosed in WO 97/35576;

a cholesterol absorption inhibitor, an HMG-CoA
synthase inhibitor, or a lanosterol demethylase inhibitor
as disclosed in WO 97/48701;

a PPAR δ agonist for treating dyslipidemia;
30 or a sterol regulating element binding protein-I
(SREBP-1) as disclosed in WO 2000/050574, for example, a
sphingolipid, such as ceramide, or neutral
sphingomyelenase (N-SMase) or fragment thereof.

Preferred hypolipidemic agents are pravastatin,
35 lovastatin, simvastatin, atorvastatin, fluvastatin,
cerivastatin, pitavastatin and rosuvastatin, as well as
niacin and/or cholestagel.

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 or as otherwise known in the art.

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.

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.

The dosages and formulations for the hypolipidemic agent or other lipid agent or lipid modulating agent will be as disclosed in the various patents and applications discussed above.

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

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.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount from about 1 to about 500 mg, preferably from about 2 to 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 anti-atherosclerotic agent includes a lipooxygenase inhibitor including a 15-lipooxygenase (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-lipooxygenase inhibitor lacking significant antioxidant properties," Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipooxygenase 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 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

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combination and work up gradually to a high dose combination.

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, aldose reductase inhibitors, PPAR γ agonists such as thiazolidinediones, PPAR α agonists (such as fibric acid derivatives), PPAR δ antagonists or agonists, α P2 inhibitors, PPAR α/γ dual agonists, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, glycogen phosphorylase inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1), and/or a PTP-1B inhibitor (protein tyrosine phosphatase-1B inhibitor).

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 N . 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, 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

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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-Wellcome'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 0.05:1 to about 10:1.

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

The compounds of structure I may also be employed in combination with an antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) or mimetic such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to

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Habener, the disclosure of which is incorporated herein by reference), as well as AC2993 (Amylen) and LY-315902 (Lilly), which may be administered via injection, intranasal, inhalation or by transdermal or buccal devices.

Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyrizide, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference (PDR).

Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

Where present, the PPAR anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present insulin and other anti-diabetic agents as set out above may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides or mimetics may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

The antidiabetic agent or other lipid agent may also be a PPAR modulator such as a PPAR α/γ dual agonist such as AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a Ligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid

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Metabolism in Liver f Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998), and in U.S. application Serial N . 09/664,598, filed September 18, 2000, (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.

The antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. application Serial No. 09/679,027, filed October 4, 2000 (attorney file LA49), employing dosages as set out therein. Preferred are the compounds designated as preferred in the above application.

The antidiabetic agent may be an α P2 inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. application Serial No. 09/519,079, filed March 6, 2000 (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 application Serial No. 09/788,173, filed February 16, 2001 (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 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 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.

The meglitinide which may optionally be employed in combination with the compound of formula I of the

inventi n may be repaglinide r Starlix (Novartis),
nateglinide (Novartis) r KAD1229 (PF/Kissei), with
repaglinide being preferred.

5 The antidiabetic compound may be a melanocortin
receptor agonist such as a spiroperidine as disclosed
in WO 99/64002.

The HMG CoA reductase inhibitor of formula I will
be employed in a weight ratio to the meglitinide, PPAR
modulator such as a PPAR γ agonist, PPAR α agonist, PPAR δ
10 agonists or antagonist, PPAR α/γ dual agonist, aP2
inhibitor, DP4 inhibitor or SGLT2 inhibitor or other
antidiabetic agent within the range from about 0.01:1 to
about 100:1, preferably from about 0.05:1 to about 10:1.

The other type of therapeutic agent which may be
15 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
inhibitor, a serotonin (and dopamine) reuptake inhibitor,
an aP2 inhibitor, a thyroid receptor beta drug, a PTP-1B
20 inhibitor, an anorectic agent, a PPAR modulator including
PPAR γ antagonists, PPAR α agonists, PPAR δ antagonists, a
CCKA agonist, a leptin inhibitor such as a leptin
receptor activator, a neuropeptide Y antagonist, a
melanocortin-4-receptor (MC4R) agonist, a fatty acid
25 oxidation upregulator or inducer (such as Famoxin®
Genset).

The beta 3 adrenergic agonist which may be
optionally employed in combination with a compound of
formula I may be AJ9677 (Takeda/Dainippon), L750355
30 (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.

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The neuropeptide Y antagonists which may be optionally employed in combination with a compound of formula I include those described in WO 0113917 (BMS) or in U.S. Patent No. 6,218,408 (Synaptic) and in WO 0114376 (Banyu).

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 dopoamine) reuptake inhibitor 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 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), 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.

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.

The CCKA agonists which may be employed herein include Glaxo-SmithKline's GI-181,771 and Sanofi's SR146,131.

The PTP-1B inhibitor which may be an anti-oesity and/or an antidiabetic agent include those disclosed in WO 99/585,521, WO 99/58518, WO 99/58522 and WO 99/61435.

The anti-obesity agent employed may also be Pfizer's P57 or CP-644,673 (licensed from Phytopharm).

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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.

5 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 inhibitors such as candoxatril, NEP/ACE inhibitors, as well as calcium channel blockers
10 (such as verapamil and amlodipine besylate), T-channel calcium antagonists (such as mibefradil), β -adrenergic blockers, diuretics, α -adrenergic blockers (such as doxazosin mesylate and terazosin HCl), dual action receptor antagonists (DARA), heart failure drugs such as
15 digoxin, and other types of antihypertensive agents.

 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.
20 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 mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U.S. Pat. No. 4,316,906 with
25 zofenopril being preferred.

 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.

30 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)

20 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

25 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;

30 indolapril (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)

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disclosed in U.S. Pat. No. 4,344,949 and CI925 (Warner-Lambert) ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(ethoxycarbonyl)-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).

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.

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, gemopatrilat ([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.

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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.

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).

Dual action receptor antagonists (DARA) suitable for use herein include those disclosed in U.S. applications Serial No. 09/513,779, filed February 25, 2000, and Serial No. 09/604,322, filed June 26, 2000.

Other examples of preferred antihypertensive agents suitable for use herein include omapatrilat (Vanlev®), gemopatrilat, amlodipine besylate (Norvasc®), prazosin HCl (Minipress®), verapamil, nifedipine, diltiazem, felodipine, nisoldipine, isradipine, nicardipine, beta blockers such as nadolol, atenolol (Tenormin®), sotalol, terazosin, doxazosin, carvedilol, and propranolol, and clonidine HCl (Catapres®).

Diuretics which may be employed in combination with compounds of formula I include hydrochlorothiazide, torasemide, furosemide, spironolactone, and indapamide.

Antiplaquet agents which may be employed in combination with compounds of formula I of the invention include aspirin, clopidogrel, ticlopidine, dipyridamole, abciximab, tirofiban, eptifibatide, anagrelide, and ifetroban, with clopidogrel and aspirin being preferred.

The antihypertensive agents, diuretics and 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.

Anti-Alzheimer's agents or anti-dementia agents suitable for use herein with the HMG CoA reductase inhibitors of the invention include tacrine HCl (Cognex) and donepezil (Aricept®), as well as γ -secretase inhibitors, β -secretase inhibitors and/or antihypertensive agents. Dosages employed will be as set out in the PDR.

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®) as well as Ca receptor agonists and progestin receptor agonists. Dosages employed will be as set out in the PDR.

The hormone replacement therapeutic agents, where present, will be employed in dosages as set out in the latest edition of the PDR. Examples of such agents include selective estrogen receptor modulators (SERMs) such as raloxifen, tamoxifen or lasoxifen.

The HMG CoA reductase compound of the invention may also be employed in combination with a tyrosine kinase inhibitor such as disclosed in WO 2000/053605;

the selective androgen receptor modulator suitable for use herein may be LGD-2226 (Ligand);

the antiarrhythmic agents suitable for use herein include β -blockers as set out herein including sotalol and amioderome, calcium channel blockers as set out herein including verapamil, nifedipine, amlodipine-besylate, and diltiazem, which may also be used in

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combination with a debrillator device such as a pace maker;

coenzyme Q sub. 10 such as disclosed in U.S. Patent No. 5,316,765, 4,933,165, 4,929,437;

5 an agent that upregulates type III endothelial cell nitric acid syntase such as disclosed in WO 2000/003746;

a chondroprotective compound such as a polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (PPS), doxycycline or minocycline, such as disclosed in 10 EP 970694;

a cyclooxygenase (COX)-2 inhibitor, such as celecoxib (Celebrex® (Searle)) or rofecoxib (Vioxx® (Merck)) or a glycoprotein IIa/IIIb receptor antagonist 15 such as disclosed in WO 99/45913 and tirofiban or abciximab;

a 5-HT reuptake inhibitor such as disclosed in WO 99/44609;

20 anti-anginal agents such as vasodilators, for example, isosorbide dinitrate, or nitroglycerin;

a growth hormone secretagogue such as disclosed in U.S. applications Serial No. 09/662,448, filed September 14, 2000, and U.S. Provisional application 60/203,335, filed May 11, 2000, and MK-677 (Merck), Pfizer's CP- 25 424391 and Lilly's LY 444,711;

anti-atherosclerosis agents such as ACAT inhibitors and lipoxxygenase inhibitors as described herein and phospholipase A-2 inhibitors such as S-3013 and SB-435,495 (which are also anti-inflammatory agents);

30 anti-infective agents such as quinolones, for example, ciprofloxacin, ofloxacin, and Tequin® (Bristol-Myers Squibb), macrolides such as erythromycin and clarithromycin (Biaxin® (Abbott)), and azithromycin (Zithromax (Pfizer)); or

35 an immunosuppressant (for use in transplantations) such as cyclosporine, mycophenolate mofetil, azathioprine and the like.

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As used herein, the phrase "antineoplastic agent" refers to compounds which prevent cancer cells from multiplying. In general, the antineoplastic agents used herein prevent cancer cells from multiplying by: (1) interfering with the cell's ability to replicate DNA, or (2) inducing apoptosis in the cancerous cells.

Examples of antineoplastic agents which are suitable for use in combinations of this invention include, but are not limited to, microtubule-stabilizing agents such as the taxanes, for example, paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), 7-O-methylthio-methylpaclitaxel (disclosed in U.S. 5,646,176), 3'-tert-butyl-3'-N-tert-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel (disclosed in USSN 60/179,965 filed on February 3, 2000, and example 17 herein), C-4 methyl carbonate paclitaxel (disclosed in WO 94/14787), the epothilone, such as epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione (disclosed in WO 99/02514), [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]-heptadecane-5,9-dione (disclosed in USSN 09/506,481 filed on February 17, 2000, and examples 7 and 8 herein), and derivatives thereof; microtubule-disruptor agents; alkylating agents; anti-metabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers; growth inhibitors; hormonal/antihormonal therapeutic agents; and haematopoietic growth factors.

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Other classes of antineoplastic agents suitable for use in the method of the present invention include, but are not limited to, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, discodermolide, the pteridine family of drugs, diynenes, aromatase inhibitors, and the podophyllotoxins. Particularly useful members of those classes not previously mentioned include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptapurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, and the like. Other useful antineoplastic agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosfamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, and interleukins.

It will be appreciated that unless otherwise specified the dosage regiment for therapeutic agents used in combination with the compounds of the invention will be as specified in the PDR.

In carrying out the method of the invention for treating hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, or atherosclerosis, and related diseases, or Alzheimer's disease or osteoporosis, or other disclosures as set out hereinbefore, a pharmaceutical composition will be employed containing the compounds of structure I, with or without other cholesterol lowering agents, osteoporosis agents, Alzheimer's agents, antidiabetic agent(s) and/or antihyperlipidemic agent(s) and/or other type therapeutic

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agents in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be 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 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 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 individual doses from 1-4 times per day and also single dose once weekly (5 to 1000 mg).

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 physiological saline, to produce an injectable preparation.

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

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

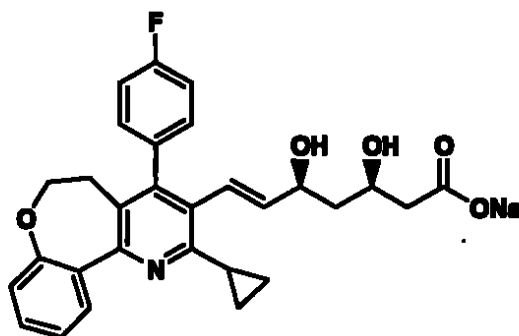
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- Cbz = carbobenzyloxy or carbobenzoxo or benzyloxycarbonyl
DIPEA = diisopropyl ethylamine
PTSH = N-phenylthiotetrazole
PPh₃ = triphenylphosphine
- 5 NMO = methyldmorpholine N-oxide
TPAP = tetrapropylammonium perruthenate
DEAD = diethyl azodicarboxylate
HOAc or AcOH = acetic acid
TFA = trifluoroacetic acid
- 10 Et₂NH = diethylamine
NMM = N-methyl morpholine
n-BuLi = n-butyllithium
Pd/C = palladium on carbon
PtO₂ = platinum oxide
- 15 MTBE = methyl t-butyl ether
DI water = deionized water
TEA = triethylamine
EDAC = 3-ethyl-3'-(dimethylamino)propyl-carbodiimide
hydrochloride (or 1-[(3-(dimethylamino)propyl)]-3-
20 ethylcarbodiimide hydrochloride)
HOBT or HOBT.H₂O = 1-hydroxybenzotriazole hydrate
HOAT = 1-hydroxy-7-azabenzotriazole
PyBOP reagent = benzotriazol-1-yloxy-tripyrrolidino
phosphonium hexafluorophosphate
- 25 LiN(TMS)₂ = Lithium bis(trimethylsilyl)amide
DIBAL = diisobutylaluminum hydride
LDA = lithium diisopropylamide
DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
AcCN = acetonitrile
- 30 LiHMDS = lithium bis(trimethylsilyl)amide
NaHMDS = sodium bis(trimethylsilyl)amide
Red-AL = sodium bis(2-methoxyethoxy)aluminum hydride
mCPBA = m-chloro-p-benzoic acid
min = minute(s)
- 35 h or hr = hour(s)
L = liter
mL = milliliter

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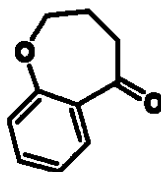
- μL = microliter
g = gram(s)
mg = milligram(s)
mol = moles
5 mmol = millimole(s)
meq = milliequivalent
RT, rt = room temperature
sat or sat'd = saturated
aq. = aqueous
10 TLC = thin layer chromatography
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass spectrometry
MS or Mass Spec = mass spectrometry
15 NMR = nuclear magnetic resonance
mp = melting point
Bp = boiling point

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

Example 1

25

A.

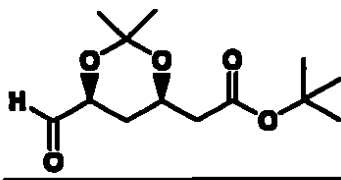


72X

A mixture of polyphosphoric acid (82.9 g) and dry
 -xylene (30 ml) was heated to 105-110°C in an oil bath,
 treated with a solution of 4-phenoxybutyric acid (25 g,
 0.137 mole) in dry o-xylene (110 ml) and stirred at 105-
 5 110°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
 with water (2 x 80 ml) and brine (80 ml), dried
 10 (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
 (27.19 g) which was divided into two portions,
 chromatographing each portion on a silica gel column,
 15 (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).

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A(1).



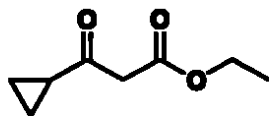
An oven-dried 3-neck 1-L flask equipped with
 temperature sensor probe, 125-mL constant pressure
 25 addition funnel and septum was charged with dry CH₂Cl₂,
 (300 mL) and dry DMSO (20.9 mL, 0.2944 mol, 2.5 equiv)
 under argon atmosphere; cooled to -75°C. Oxalyl chloride
 (13.6 mL, 0.156 mol, 1.32 equiv) was added neat via
 syringe dropwise over 15 min (temperature rose to -66°C),
 30 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 CH₂Cl₂ (80 mL) was added dropwise
 from the addition funnel over 30 min (temperature rose to
 35 -68°C). The resulting white mixture was stirred for 70

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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 , $R_f=0.52$). 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 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).

A(2).



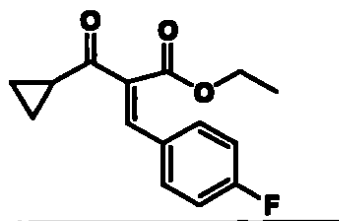
To a slurry of NaH (19.20 g, 480 mmol) and diethyl carbonate (80 mL) in a 3-neck 1L round bottom flask at room temperature was added a solution of cyclopropyl methylketone (23.5 mL, 238 mmol) in Et_2O (30 mL). Approximately 10% of the solution was added, and then 0.25 mL of EtOH was added to the reaction 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

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ceased and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was cooled in an ice-bath, diluted with Et₂O (200 mL), and treated with 1 N HCl with some ice to adjust to around pH 3. The reaction mixture was extracted with Et₂O (3 x 150 mL). The Et₂O extracts were combined, washed with saturated aqueous NaHCO₃ (200 mL), H₂O (200 mL) and brine (200 mL), and dried (Na₂SO₄), 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.

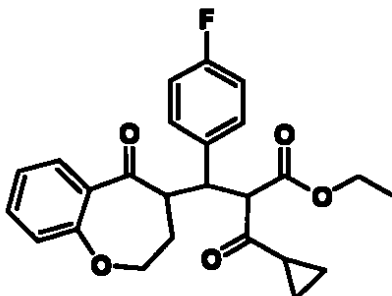
A(3).



To a stirred solution of part A(2) compound (28.24 g, 181 mmol) in benzene (128 mL) was added 4-fluorobenzaldehyde (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), 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.

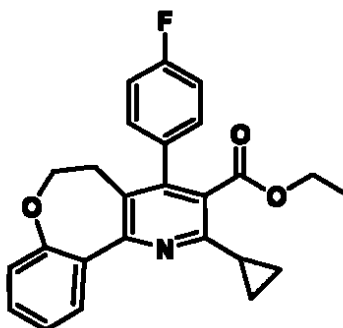
210

B:



A solution of compound of Part A (7.21 g, 40.9 mmol) in dry THF (5.0 ml) was added to a -78°C solution of lithium bis(trimethylsilyl)amide (1.0 M in THF; 49 ml, 49 mmol) in dry THF (25 ml) and stirred at -78°C under argon for 1 hour. The reaction mixture was treated with a solution of Example 1 Part A(3) compound (7.15 g, 27.3 mmol), in dry THF, stirred at -78°C for 30 minutes then at 0°C for 30 minutes. The reaction mixture was quenched at 0°C by the dropwise addition of glacial acetic acid (5 ml) and the resulting slurry was stirred at room temperature for another 5 minutes then poured 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.

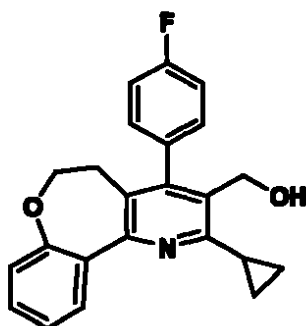


A mixture of crude Part B compound (17.0 g, 27.3 mmol), ammonium acetate (9.34 g, 120 mmol) and copper

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acetate mon hydrate (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 Na_2SO_4), 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).
Rf 0.53 (Silica gel; EtOAc:Hexane-1:4; UV)

D.

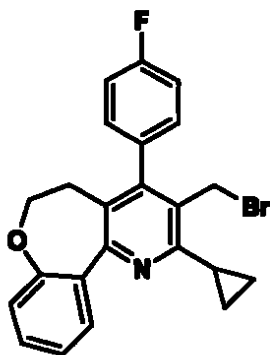


A solution of Part C compound (2.515 g, 6.23 mmol) in dry THF (30 ml) was cooled to 0°C (ice-water bath), treated dropwise with lithium aluminum hydride (1.0 M in THF; 12.5 ml, 12.5 mmol), stirred at 0°C for 30 minutes then at room temperature for 3 hours. The reaction mixture was cooled to 0°C, treated successively with water (0.5 ml), 15% NaOH (0.5 ml) and water (1.5 ml), 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.

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Yield: 2.386 g, white f am (100 %). Rf 0.15 (Silica gel; EtOAc:Hexane-1:4; UV).

E.

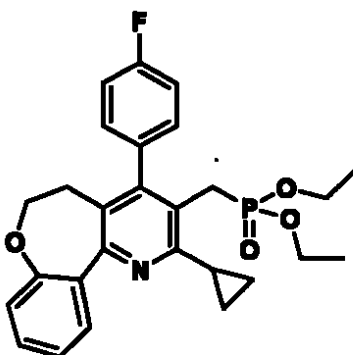


5

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 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).

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213

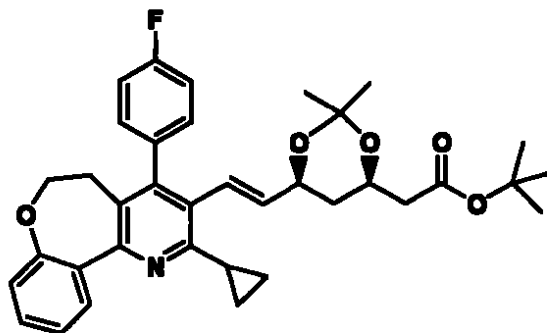
F.



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

20.

G.



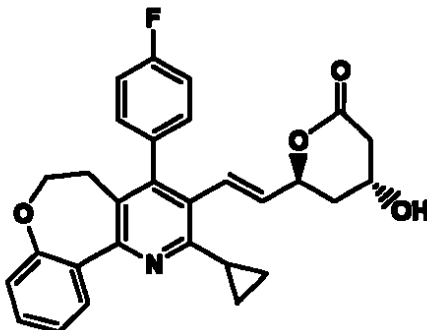
A solution of Part F compound (2.29 g, 4.756 mmol) in dry THF (20 ml) was cooled to -78°C , treated with 2.37

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M n-butyllitium (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).

H.



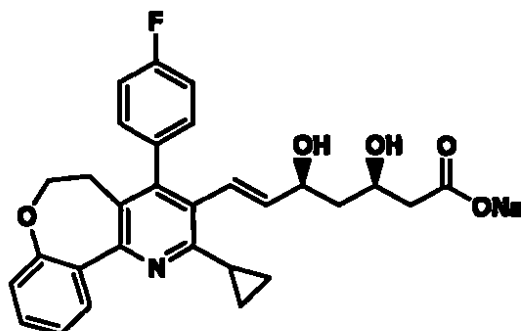
A solution of Part G compound (850 mg, 1.45 mmol) in dry dichloromethane (20 ml) was cooled to 0°C, treated with trifluoroacetic acid (1.85 ml, 24 mmol), stirred at 0°C for 5 minutes, then at room temperature for 4.5 hours. The reaction mixture was poured slowly into a 1 L flask containing ethyl acetate (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

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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)

5

I.



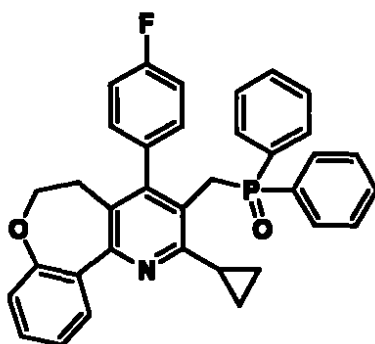
A solution of Part H compound (550 mg, 1.17 mmol) in dry THF (10 ml) was treated with 1.0 N NaOH (1.46 ml; 1.46 mmol) and stirred at room temperature for 10 minutes. The reaction mixture was evaporated to dryness and the residual solid was dissolved in a mixture of water (8.7 ml) and 1.0 N sodium hydroxide (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%) Rf 0.48 (Silica gel; CH₂Cl₂:MeOH:HOAc-18:1:1; UV).

Analysis for C₂₈H₂₆FNO₄Na • 0.8 H₂O (MW = 525.94):

25 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).

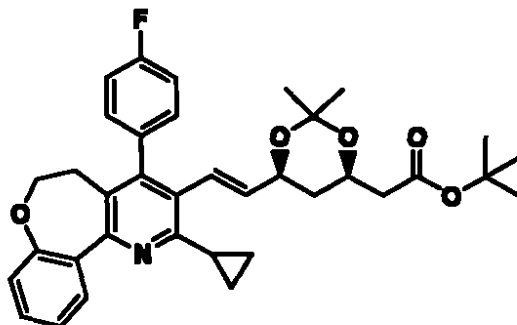


5

The Example 1 Part E bromide (13.03 g, 0.027 mol, 1 equiv) and Ph_2POEt (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
10 stirrable white mixture after about 10 min. The reaction was complete after 1 hr by tlc (SiO_2 , 30% EtOAc/ CH_2Cl_2 , 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
15 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/ H_2O + 0.2% H_3PO_4 , B=90:10 MeOH/ H_2O + 0.2% H_3PO_4) R.T.=3.70 min (100%);

20 ^1H NMR (CDCl_3) 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
25 (m, 9 H), 7.469-7.521 (m, 2 H), 7.822 (d, $J=7.5$ Hz, 1 H); MS m/z 546 ($\text{M}+\text{H}$) $^+$.

G(2).



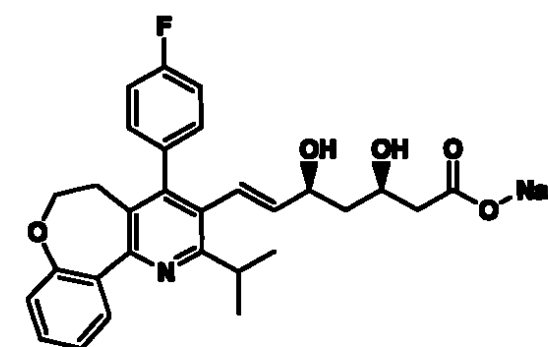
A flame-dried 250-mL flask was charged with Part
5 G(1) compound (14.82 g, 27.2 mmol, 1 equiv), chased with
anhydrous toluene (2x50 mL), dried over high-vacuum and
filled with argon. THF (150 mL) was added and the partial
slurry was cooled to 0°C. A 2.5 M solution of n-BuLi in
hexanes (11.4 mL, 0.0285 mol, 1.05 equiv) was added
10 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
15 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
20 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 quenched
with half-saturated aqueous NaCl (200 mL) and extracted
25 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
chromatography (10 cm x 25 cm) with 2% EtOAc/CH₂Cl₂ (2 L),
30 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

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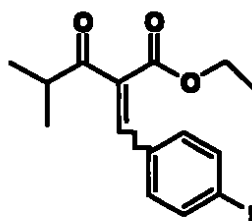
compound) as a white solid (11.13 g, 0.019 mol, 70%):
 HPLC (Shimadzu, YMC S-5 C18 4.6x50 mm column, 4 min
 gradient @ 4 mL/min, UV detection 220 nm; start %B=70,
 final %B=100; A=10:90 MeOH/H₂O + 0.2% H₃PO₄, B=90:10
 5 MeOH/H₂O + 0.2% H₃PO₄) R.T.=4.36 min (100%);

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),
 10 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
 (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)⁺.

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Example 2

A.



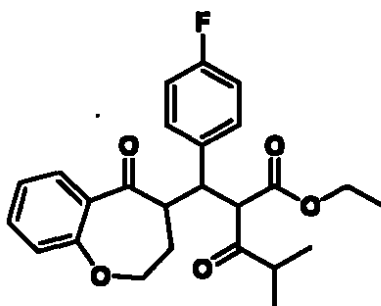
20

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
 25 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 (50mL) 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)⁺.

B.



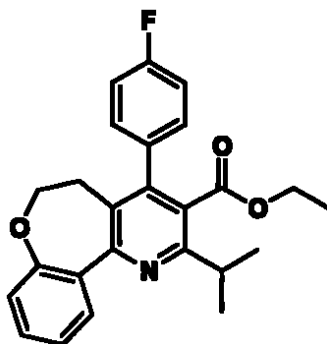
15

An oven-dried 250-mL 3-neck flask purged with argon was charged with anhydrous THF (30 mL) and lithium 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 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 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 NH₄Cl. The mixture was extracted with Et₂O (100 mL) and the ethereal extract was washed with H₂O (2x30 mL) and satd aq NaCl. The organic was dried over anhydrous Na₂SO₄, vacuum filtered and concentrated by rotary

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evaporati n in vacuo t a yellow oil (17.19 g): MS (FAB)
m/z 427 (M+H)⁺.

C.



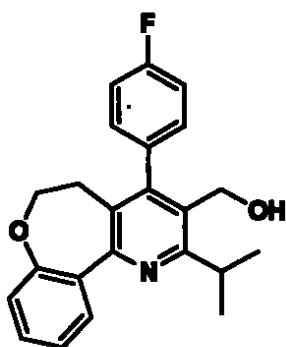
5

The crude Part B compound (17.19 g), NH₄OAc (11.0g, 0.142 mol, 4.4 equiv), and Cu(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. The reaction was cooled to rt, then poured into an ice cold solution of conc NH₄OH (100 mL) in H₂O (200 mL). The mixture was extracted with Et₂O (200 mL+2x100 mL), then the combined ethereal extracts was washed with H₂O (2x100 mL) and satd aq NaCl. The extract was dried over anhydrous Na₂SO₄, vacuum filtered and concentrated by rotary evaporation in vacuo. The resulting brown oil was chased with hexanes to remove HOAc, followed by drying in 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):

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)⁺.

221

D.

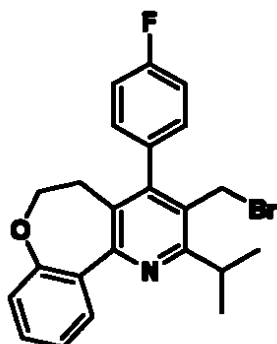


Part C compound (5.78 g, 0.0143 mol, 1 equiv) was
5 dissolved in dry THF (70 mL) under argon and cooled to
0°C. A solution of LiAlH₄ in THF (1M, 28.5 mL, 0.0285
mol, 2 equiv) was added slowly. The reaction was stirred
at rt for 2 hrs, followed by 25 min at reflux. TLC (SiO₂,
5% EtOAc/CH₂Cl₂, Rf=0.24). The reaction was cooled to
10 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
by rotary evaporation in vacuo to a yellow oil.
15 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%):

¹H NMR (CDCl₃) δ 1.402 (d, J=6.6 Hz, 6H), 2.463 (t, J=6.2
20 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),
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)⁺.

22

E.

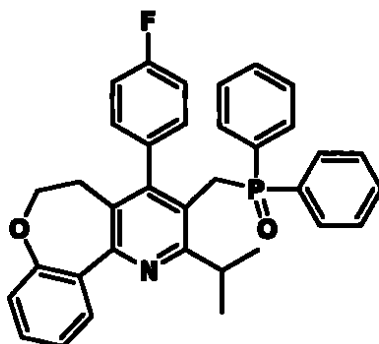


The Part D alcohol (3.066g, 8.437 mmol, 1 equiv),
5 dissolved in dry CH_2Cl_2 (60 mL) under argon at 0°C , was
treated by dropwise addition of a 1M solution of PBr_3 in
 CH_2Cl_2 (16.9 mL, 16.9 mmol, 2 equiv). The reaction was
stirred at rt for 30 min, at which time the reaction was
recooled to 0°C and treated with satd aq NaHCO_3 (90 mL).
10 The mixture was diluted with CH_2Cl_2 (50 mL), the layers
were separated, and the organic washed with H_2O (2x50 mL)
and satd aq NaCl (50 mL). The organic was dried over
anhydrous Na_2SO_4 , filtered and concentrated in vacuo. TLC
(SiO_2 , 5% $\text{EtOAc}/\text{CH}_2\text{Cl}_2$, $R_f=0.69$). The residue was
15 purified by SiO_2 flash chromatography (3.8cm x 15cm
column) with CH_2Cl_2 to obtain product as white solid (2.97
g, 6.97 mmol, 83%):

^1H NMR (CDCl_3) δ 1.403 (d, $J=6.6$ Hz, 6H), 2.430 (t, $J=6.2$
20 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 ($\text{M}+\text{H}$) $^+$.

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F.

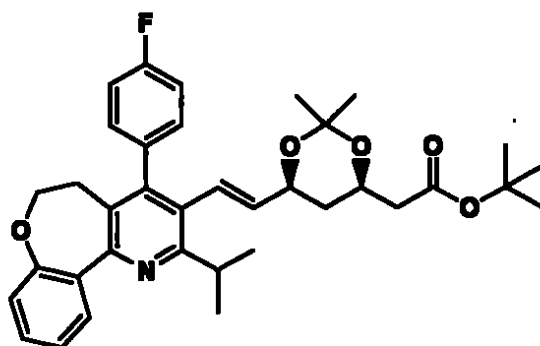


The Part E bromide (2.97 g, 6.967 mmol, 1 equiv)
5 and ethyl diphenylphosphinite (1.7 mL, 7.663 mmol, 1.1 equiv) were heated at reflux under argon for 1.5 hrs. TLC (SiO₂, 30% EtOAc/CH₂Cl₂, product R_f=0.47). The reaction was cooled in an ice bath, then the solid collected by vacuum filtration in Buchner funnel; the
10 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.



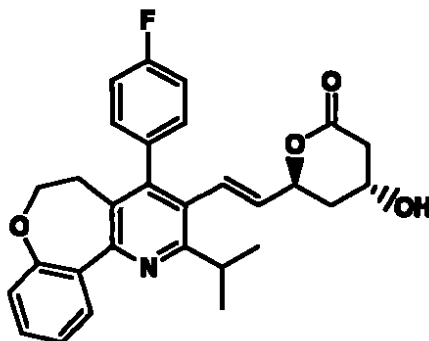
25 An oven-dried 50-mL flask charged with the Part F diphenylphosphine oxide (1.00 g, 1.826 mmol, 1 equiv) was

chased with anhydrous toluene (3x5 mL), dried *in vacuo*, 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 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 (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-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), 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, 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), 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)⁺.

225

H.

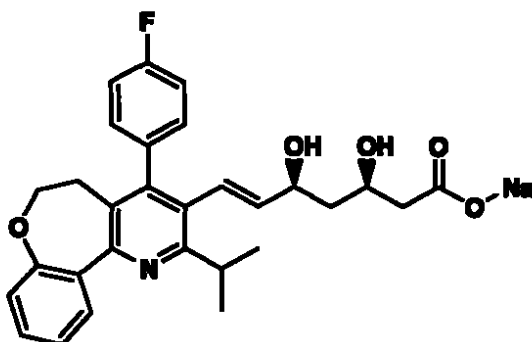


The Part G compound (0.230 g, 0.391 mmol) was dissolved in dry CH_2Cl_2 (5 mL) under an argon atmosphere and cooled to 0°C . Trifluoroacetic acid (0.5 mL) was added and the mixture was stirred at rt for 6 hrs. TLC (SiO_2 , 20% EtOAc/ CH_2Cl_2 , $R_f=0.31$). The reaction solution was transferred to a 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.



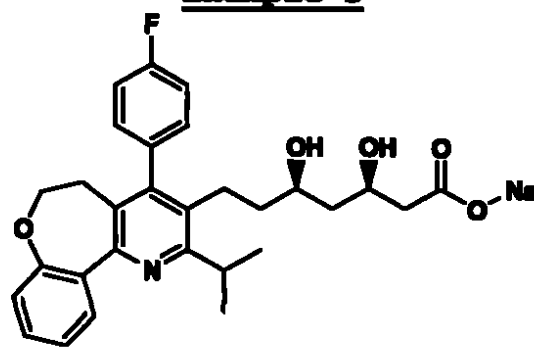
- The Part H lactone (148 mg, 0.3125 mmol, 1 equiv) was dissolved in THF (3 mL), treated with 1N aq NaOH (0.391 mL, 0.3907 mmol, 1.25 equiv), and stirred at rt. TLC (SiO₂, 0.5:0.5:9 HOAc/MeOH/CH₂Cl₂, R_f=0.25). After 30 min, the solvents were removed by rotary evaporation in vacuo and the residue dried 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)⁺;

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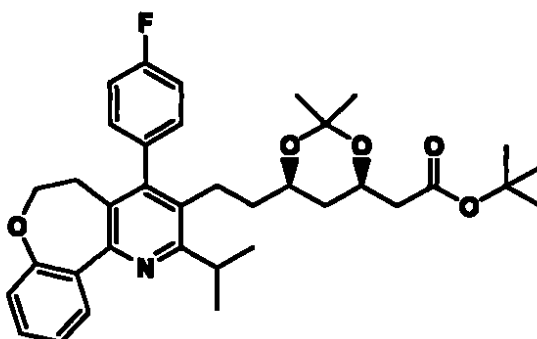
Anal. Calcd for $C_{23}H_{22}FNO_3Na \cdot H_2O$:
 C, 65.53; H, 5.88; N, 2.64.
 Found: C, 65.46; H, 5.70; N, 2.52.

5

Example 3



A.



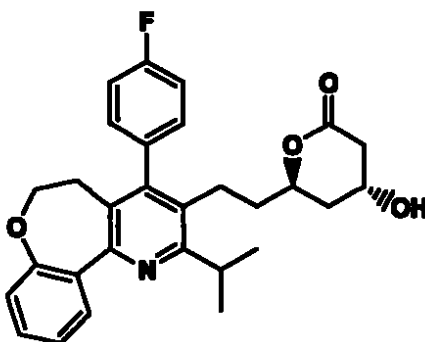
- 10 The Example 2 Part G compound (200 mg, 0.3403 mmol, 1 equiv) was hydrogenated at 45 psi H_2 in anhydrous MeOH (30 mL) with 10% Pd-C (40 mg, 20 wt %) for 2 hrs. The catalyst was washed with small portions of MeOH and the filtrate was concentrated by rotary evaporation in vacu .
- 15 The residue was 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, $J=7.9$ Hz, 1 H), 7.1416 (d, $J=6.6$ Hz, 4 H), 7.265 (t,

228

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)⁺.

B.



5

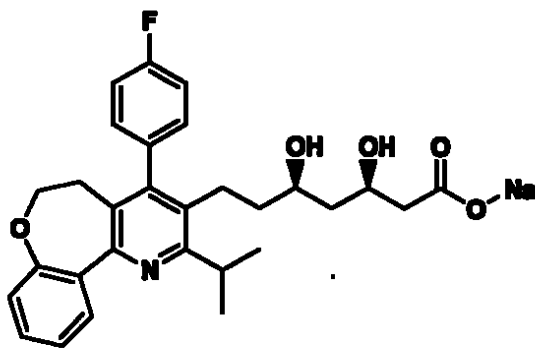
Part A compound (258 mg, 0.4375 mmol) was dissolved in dry CH₂Cl₂ (5 mL) under argon, cooled to 0°C and treated with trifluoroacetic acid (0.5 mL). Stirring was continued at room temperature for 7 hrs, at which time the reaction was complete by HPLC. Saturated aqueous NaHCO₃ (25 mL) was added to the 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)⁺.

30

27A
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C.



Part B compound (149 mg, 0.3133 mmol, 1 equiv) was dissolved in THF (3 mL) and 1N aqueous NaOH (0.392 mL, 0.3916 mmol, 1.25 equiv) and stirred at room temperature for 30 min. The solvent was removed by rotary evaporation in vacuo and the residue was dried under high-vacuum. An SP207 resin column (1.9 cm x 10 cm) was prepared as follows: resin was poured into a glass chromatography column equipped with fritted disc support and the resin was washed sequentially with saturated aqueous NaHCO₃ (15 mL), saturated aqueous NaCl (15 mL), and Milli-Q H₂O (100 mL). The dried residue was taken up in Milli-Q H₂O (8 mL) and carefully applied to top of the column. The column was eluted with Milli-Q H₂O (100 mL), 10% AcCN/ H₂O (60 mL), 20% AcCN/ H₂O (60 mL), and 25% AcCN/ H₂O (100 mL). Product-containing fractions were combined and concentrated by rotary evaporation to a small volume, and transferred to a 40-mL lyophilization jar. The contents were frozen in acetone-dry ice bath and lyophilized. This afforded the product as a white lyophilate (149 mg, 0.289 mmol, 92%): 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=10:90 MeOH/H₂O + 0.2% H₃PO₄) R.T.=3.58 min (92.9%);

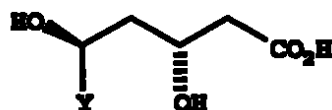
¹H NMR (DMSO-d₆) δ 1.048-1.105 (m, 1 H), 1.232-1.50 (m, 9 H), 1.750 (dd, J=14.9 Hz, 8.3 Hz, 1 H), 1.966 (dd, J=14.9 Hz, 4.0 Hz, 1 H), 2.298-2.356 (m, 3 H), 3.335-3.424 (m, 2 H), 3.616-3.656 (m, 1 H), 4.3166 (t, J=6.2 Hz, 2 H),

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

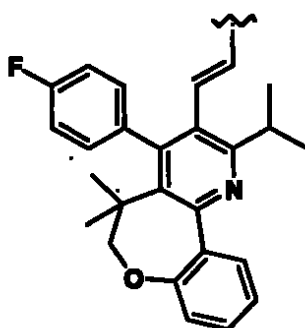
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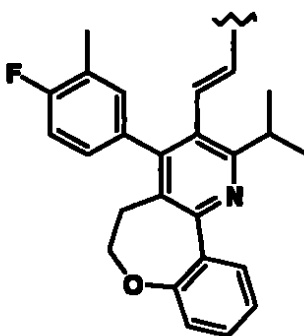
where Y is as set out below

15

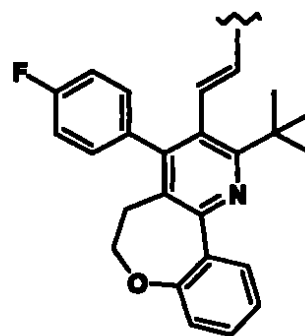
Example 4



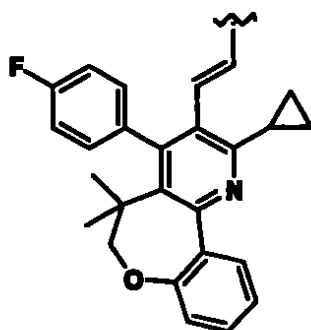
Example 5



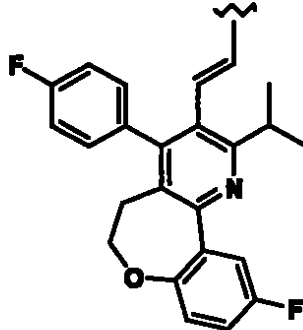
Example 6



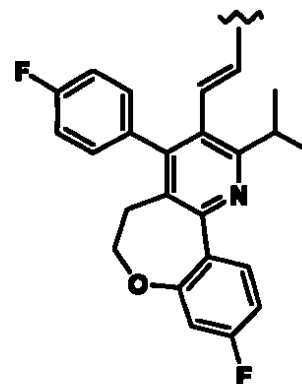
Example 7



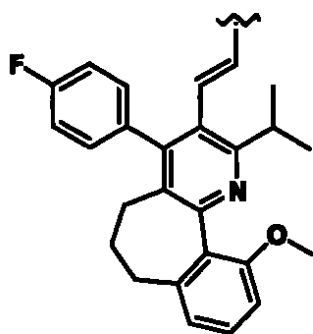
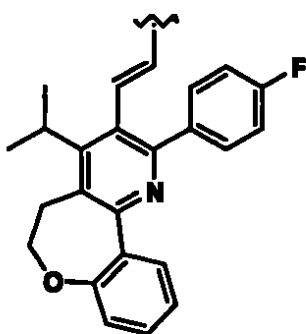
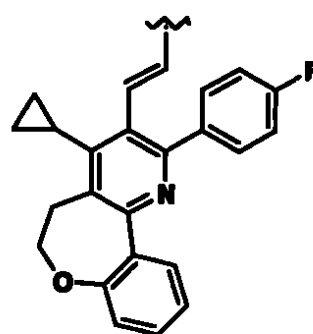
Example 8



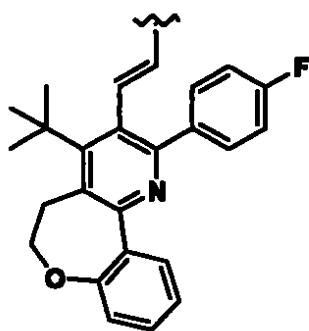
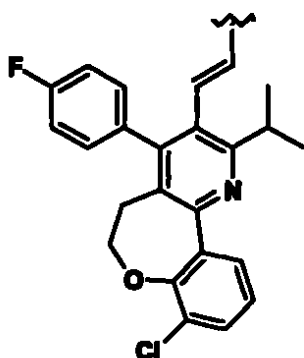
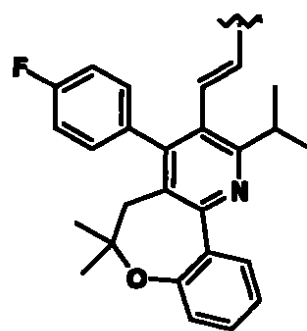
Example 9



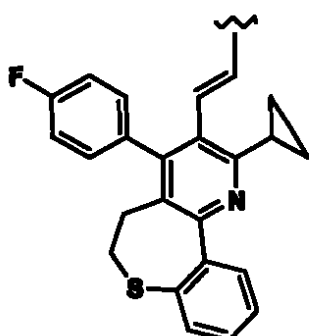
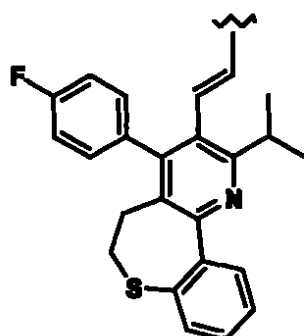
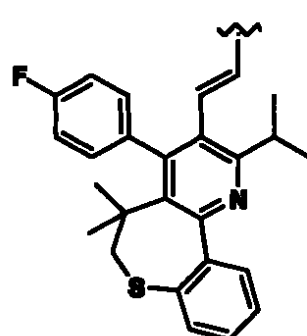
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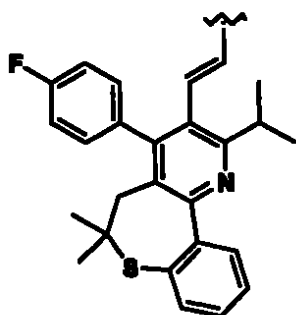
Example 10Example 11Example 12

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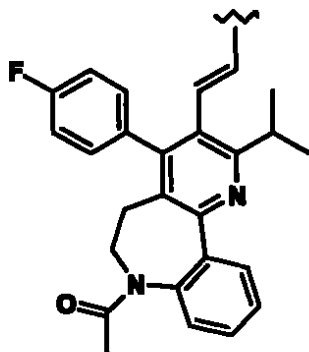
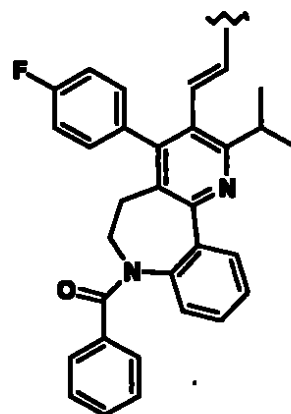
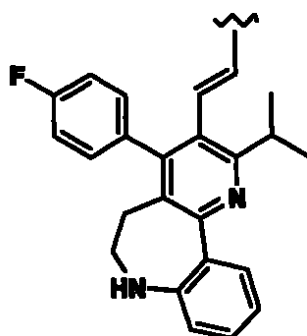
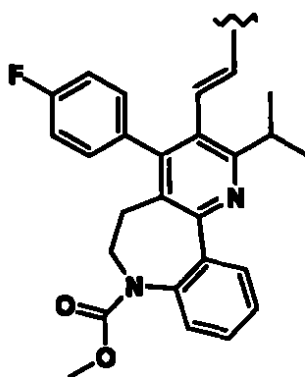
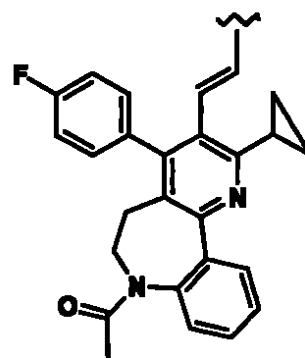
Example 13Example 14Example 15

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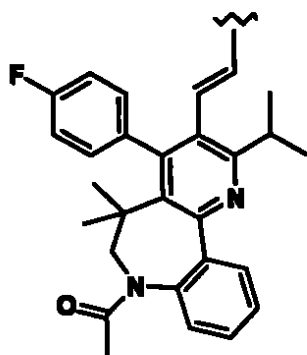
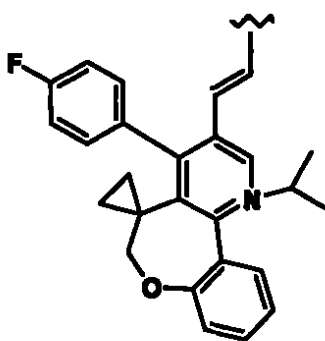
Example 16Example 17Example 18

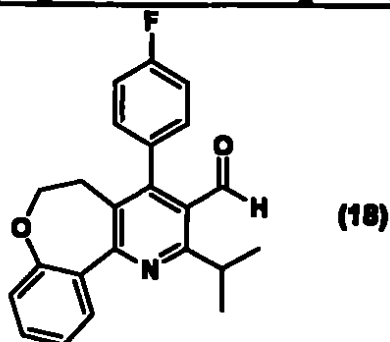
Example 19

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Example 20Example 21Example 22Example 23Example 24

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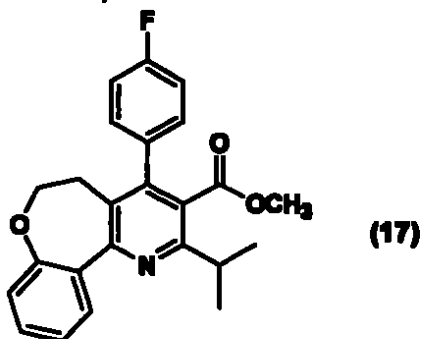
Example 25Example 26

Example 27Preparation of Pyridine Aldehyde (18) (Scheme 5)

5 Following the procedure outlined in reaction Scheme 5 and the description thereof, the Example 27 aldehyde is obtained.

 An example of a typical preparation of the aldehyde is set out below.

10 To a 500 mL round bottom flask equipped with a magnetic stirrer and a nitrogen inlet was charged compound (17) (Scheme 5)



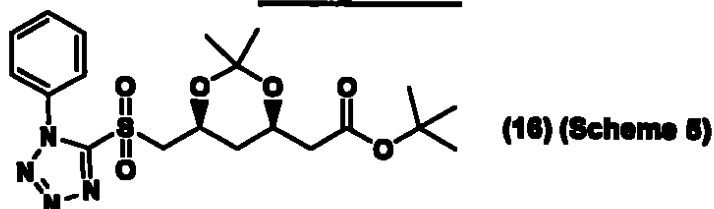
(50 g, 128.4 mmol)

15 (prepared as described in Example 2 Parts A, B and C except methyl isobutyryl acetate is substituted for ethyl isobutyryl acetate) and toluene (170 mL). The mixture is stirred at 20-25°C until a clear solution is obtained. A solution of 65% Red-Al in toluene (57.8 mL, 192.6 mmol) is
20 added and the reaction mixture is heated to 80°C until complete as determined by HPLC. The reaction mixture is cooled to ~20°C and quenched by pouring it into cold (0-5°C) 20% HCl (495 mL). Phases are separated and the spent toluene phase is discarded. The pH of the aqueous
25 phase is adjusted from <0 to 4-5 with 10N NaOH. Ethyl acetate (500 mL) is added and the pH adjustment continued

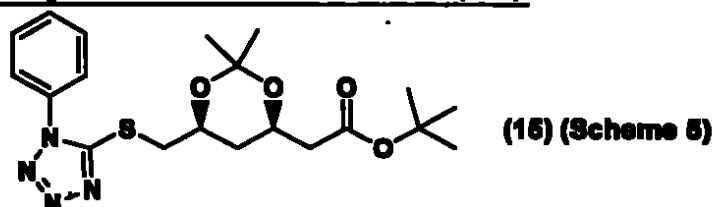
to 7-8. The phases are separated. The aqueous phase is extracted with additional ethyl acetate (2 x 500 mL). The combined rich ethyl acetate solution is washed with water (3 x 250 mL) and concentrated under reduced pressure to ~465 mL. This solution is carried through to the next oxidation step.

The rich ethyl acetate solution is charged from above into a three neck 1-L flask equipped with mechanical stirring, temperature controller, and addition funnel and cooled to 0-5°C. To the slurry, potassium bromide (1.53 g, 12.8 mmol) and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) (0.20 g, 1.28 mmol) are added. The pH of NaOCl (sodium hypochlorite) solution (212.1 mL) is adjusted to ~9.1 and added to the slurry at a rate such that the temperature remained at 0-5°C. Stirring is continued at 0-5°C until the reaction is complete as determined by HPLC. The aqueous phase is extracted with EtOAc (2 x 200 mL). The combined rich organic phase is washed with a 1:1 solution of sat. aq. Na₂S₂O₃ (sodium thiosulfate) (75 mL) and water (75 mL) followed by wash of the rich organic phase with 1N NaOH (250 mL). The rich organic phase is washed with water (250 mL) and concentrated to ~100 mL under reduced pressure. Isopropanol (IPA) (400 mL) is added and the resulting mixture is heated to reflux (80-85°C). The solution is distilled to a volume of ~250 mL. Water (50 mL) is added and the crystal slurry is stirred at 70-80°C for 1 h then allowed to cool to 20-25°C over at least 1 h. The slurry is held at 20-25°C for at least 1 h before collecting the solid by filtration on a Buchner funnel. The cake is washed with cold (0°C) IPA/water (4:1) (2 x 50 mL) and dried to a constant weight under vacuum at 40°C to afford title aldehyde.

25

Example 28

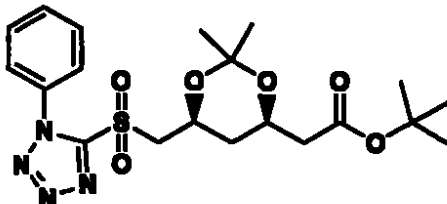
5

A. Preparation of Sulfide (15)

To a 250 mL flask was charged Kaneka alcohol (12) (Scheme 6) (10.0 g, 38.41 mmol), methylene chloride (100 mL), and triethylamine (11.75 mL, 84.51 mmol) and cooled to -30°C. Triflic anhydride (7.11 mL, 42.25 mmol) was added via a syringe at a rate to maintain the temperature at -35 to -25°C, ~15 min. The reaction mixture was stirred at -30°C for ~30 min and checked for disappearance of Kaneka alcohol by TLC. A slurry of 1-phenyl-1H-tetrazole-5-thiol (7.19 g, 40.34 mmol) in methylene chloride (50 mL) was added to the triflate solution. After the reaction was complete, water (100 mL) was added and the mixture was stirred for ~5 min. The phases were separated and the aqueous phase was discarded. The rich organic phase was washed with water (100 mL) for ~5 min and phases separated. The rich organic phase was washed with saturated NaHCO₃ (100 mL) for ~15 min and phases separated. The rich organic phase was concentrated to ~50 mL. The solution was taken to the next step for further transformation.

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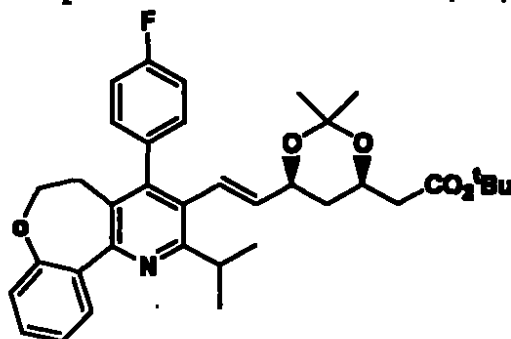
B. Preparation of Sulfone (16)



IPA (150 mL) was added to the Part A sulfide
5 solution from the above step. The solution was cooled to 0-5°C. To the stirred solution of sulfide, a solution of (NH₄)₆Mo₇O₂₄·4H₂O (ammonium heptamolybdate tetrahydrate) (4.75 g, 3.84 mmol) in 30% H₂O₂ (hydrogen peroxide) was added dropwise during ~15 min, maintaining the
10 temperature of the solution at 0-5°C. The conversion of sulfide to sulfone was monitored by HPLC ~24 h. After completion of the reaction, methylene chloride was distilled out. The pot temperature was maintained at not more than 25°C. The crystal slurry was distilled to a
15 volume of ~230 mL with IPA and the resulting slurry was stirred for at least 1 h at 20-22°C. The solid was collected by vacuum filtration, the cake washed with IPA/water (4:1, 25 mL) followed by drying under vacuum at 40°C to constant weight affording 12.8 g (74%) of the
20 title sulfone as a white crystalline solid.

Example 29

Preparation of Olefin (19)



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Following the procedure set out in reaction Scheme 5 and the description thereof, the Example 27 pyridine derivative and the Example 28 sulfone are employed to prepare the title compound.

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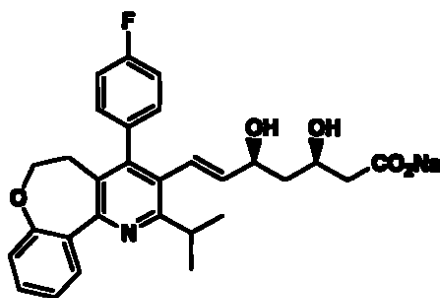
An example of a typical preparation of the Example 29 compound is set out below.

A_n N₂ purged 250 mL 3-neck rb flask is charged with Example 27 pyridine derivative (18) (5 g, 13.9 mmol),
5 Example 28 sulfone (16) (6.9 g, 15.3 mmol) and THF (75 mL). The stirred solution is cooled to -74 to -78°C . Slowly a 1M solution of LiHMDS (lithium bis(trimethylsilyl)amide) (15.3 mL, 15.3 mmol) in THF is charged at a rate such that the temperture remained
10 between -70 and -78°C. After addition of the base is complete, the reaciton mixture is warmed to ~-45°C over ~15 minutes. The stirred reaction is quenched at -70°C by slow addition of sat. aq. NH₄Cl (7.5 mL) solution and water (38 mL). The dry ice bath is removed and the
15 solution is warmed to 20-25°C from the reaction mixture. Ethyl acetate (50 mL) is added, the mixture agitated, and layers separated. The organic layer is washed with saturated sodium bicarbonate solution (2 x 38 mL) followed by brine (25 mL) and concentrated to a volume of
20 50 mL. Acetonitrile (50 mL) is added and the solution is concentrated to a volume of 50 mL. This step is repeated. Water (~5-6 mL) is slowly added to the hot solution (60-70°C) until the cloud point is reached. The thin slurry is held for 30 min at high temperature and
25 then slowly cooled over several hours with stirring. The product is filtered, cake is washed with a 5:1 mixture of acetonitrile and water, and dried to afford the title compound.

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Example 30

Preparation of the final compound



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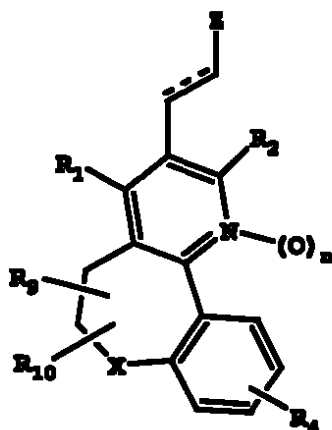
Following the procedure of Example 3 Parts B and C, the Example 29 compound is employed to prepare the title compound in the form of the sodium salt.

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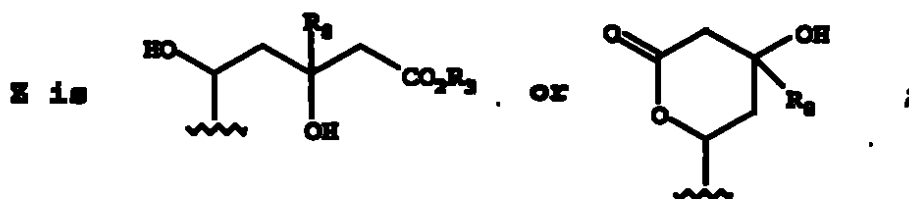
239

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 or lower alkyl;

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

R_7 is H, alkyl, aryl, alkanoyl, aroyl or alkoxycarbonyl;

R_8 is H or lower alkyl;

- 20 R_9 and R_{10} are the same or different and are independently selected from H or alkyl, or R_9 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);

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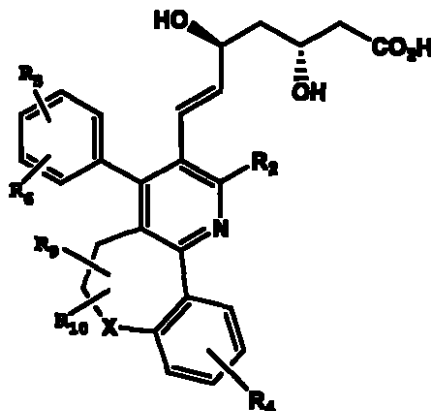
and including pharmaceutically acceptable salts thereof (where R_3 is H), esters thereof, prodrug esters thereof, and all stereoisomers thereof.

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 R_1 is aryl,
10 R_2 is alkyl or cycloalkyl or aryl;
 R_4 is H;
 n is 0;
 X is O; and
 ~~is~~ is a trans double bond, in the form of a free
15 acid or an alkali or alkaline earth metal salt or an amino acid salt.

 4. The compound as defined in Claim 3 wherein R_1 is 4-fluorophenyl, 4-fluoro-3-methylphenyl, or 3,5-
20 dimethylphenyl; and
 R_2 is isopropyl, t-butyl or cyclopropyl.

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

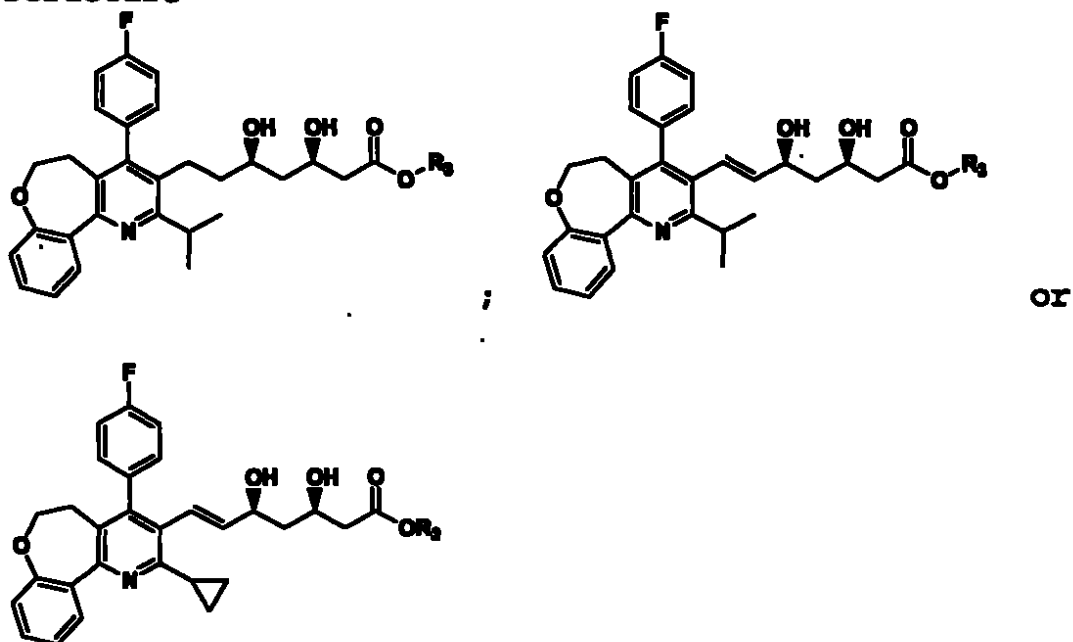


25 or an alkali or alkaline earth metal salt thereof or an amino acid salt or an acid addition salt via the pyridine of the corresponding δ lactone,

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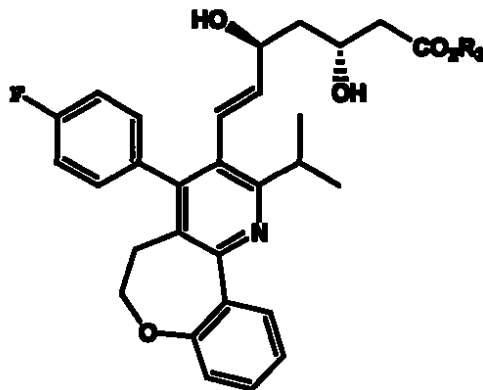
wherein R_5 and R_6 are the same or different and are independently selected from H, halogen or alkyl and R_2 is alkyl or cycloalkyl.

- 5 6. The compound as defined in Claim 1 having the structure



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

- 15 7. A compound of the structure



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

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

5 9. A pharmaceutical combination comprising the HMG
CoA reductase inhibitor compound as defined in Claim 1
and one or more hypolipidemic agents or lipid-lowering
agents, or lipid agents, or lipid modulating agents,
and/or one or more other types of therapeutic agents
10 including antidiabetic agents, anti-obesity agents,
antihypertensive agents, platelet aggregation inhibitors,
anti-dementia agents, anti-Alzheimer's agents, anti-
osteoporosis agents, and/or hormone replacement
therapeutic agents, and/or other cardiovascular agents
15 (including anti-anginal agents, anti-arrhythmic agents,
anti-atherosclerosis agents, anti-inflammatory agents,
anti-arthritis agents, anti-platelet agents, anti-heart
failure agents), anti-cancer agents, anti-infective
agents, hormone replacement agents, growth hormone
20 secretagogues, selective androgen receptor modulators,
and/or immunomodulatory agents.

 10. The combination as defined in Claim 9 wherein
the hypolipidemic agent or lipid-lowering agent or other
25 lipid agent or lipid modulating agent or anti-
atherosclerotic agent, which is employed comprises 1,2,3
or more MTP inhibitors, HMG CoA reductase inhibitors,
squalene synthetase inhibitors, fibric acid derivatives,
PPAR α agonists, PPAR dual α/γ agonists, PPAR δ agonists,
30 ACAT inhibitors, lipoxxygenase inhibitors, cholesterol
absorption inhibitors, ileal Na⁺/bile acid cotransporter
inhibitors, upregulators of LDL receptor activity,
cholesteryl ester transfer protein inhibitors, bile acid
sequestrants, or nicotinic acid and derivatives thereof,
35 ATP citrate lyase inhibitors, phytoestrogen compounds, an
HDL upregulators, LDL catabolism promoters, antioxidants,
PLA-2 inhibitors, antihomocysteine agents, HMG-CoA

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synthase inhibitors, lanosterol demethylase inhibitors, or sterol regulating element binding protein-1 agents;

wherein the antidiabetic agent which may be optionally employed is 1, 2, 3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, which may include biguanides, sulfonyl ureas, PTP-1B inhibitors, aldose reductase inhibitors, glucosidase inhibitors, PPAR γ agonists, PPAR α agonists, PPAR δ antagonists or agonists, α P2 inhibitors, PPAR α/γ dual agonists, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, glycogen phosphorylase inhibitors, and/or meglitinides, insulin, and/or glucagon-like peptide-1 (GLP-1) or a mimetics thereof;

wherein the other type of therapeutic agent which may be optionally employed is 1, 2, 3 or more of an anti-obesity agent which is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, an α P2 inhibitor, a thyroid receptor beta drug, an anorectic agent, a PTP-1B inhibitor, a CCKA agonist, a neuropeptide Y antagonist, a melanocortin-4-receptor agonist, a PPAR modulator which is a PPAR γ antagonist, PPAR α agonist, and/or PPAR δ antagonist, a leptin inhibitor such as a leptin receptor activator, a fatty acid oxidation upregulator or inducer;

wherein the lipid modulating 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 and the other lipid agent is a cholesteryl ester transfer protein inhibitor;

wherein the antihypertensive agent employed is an ACE inhibitor, angiotensin II receptor antagonist, NEP inhibitor, a NEP/ACE inhibitor, a calcium channel blocker, a T-channel calcium antagonist, a β -adrenergic blocker, a diuretic, a α -adrenergic blocker, a dual

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action receptor antagonist (DARA), or a heart failure drug.

11. The combination as defined in Claim 10 wherein
5 the antidiabetic agent is 1, 2, 3 or more of metformin,
glyburide, glimepiride, glipyrizide, glipizide,
chlorpropamide, gliclazide, acarbose, miglitol,
pioglitazone, troglitazone, rosiglitazone, insulin,
G1-262570, isaglitazone, JTT-501, NN-2344, L895645,
10 YM-440, R-119702, AJ9677, repaglinide, nateglinide,
KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902,
P32/98 and/or NVP-DPP-728A;

wherein the anti-obesity agent is orlistat, ATL-
962, AJ9677, L750355, CP331648, sibutramine, topiramate,
15 axokine, dexamphetamine, phentermine,
phenylpropanolamine, and/or mazindol, P57 or CP-644673
(Pfizer);

wherein the lipid modulating agent is pravastatin,
lovastatin, simvastatin, atorvastatin, cerivastatin,
20 fluvastatin, pitavastatin, rosuvastatin, fenofibrate,
gemfibrozil, clofibrate, avasimibe, TS-962, MD-700,
cholestagel, niacin, and/or LY295427;

wherein the antihypertensive agent is an ACE
inhibitor which is captopril, fosinopril, enalapril,
25 lisinopril, quinapril, benazepril, fentiapril, ramipril
or moexipril;

an NEP/ACE inhibitor which is omapatrilat,
gemopatrilat, or CGS 30440;

an angiotensin II receptor antagonist which is
30 irbesartan, losartan or valsartan;

amlodipine besylate, prazosin HCl, verapamil,
nifedipine, nadolol, propranolol, or clonidine HCl,
carvediol, atenolol, hydrochlorothiazide, torasemide,
furosemide, spironolactone or indapamide;

35 wherein the platelet aggregation inhibitor is
aspirin, clopidogrel, ticlopidine, dipyridamole,

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ifetroban, abciximab, tirofiban, eptifibatide, or anagrelide;

wherein the other therapeutic agent is an anti-Alzheimer's agent or anti-dementia agent, which is
5 tacrine HCl (Cognex®), donepezil (Aricept®), a γ -secretase inhibitor, a β -secretase inhibitor and/or antihypertensive agent;

an antiosteoporosis agent, which is parathyroid hormone, a bisphosphonate, alendronate, a Ca receptor
10 agonist or a progestin receptor agonist;

a hormone replacement therapeutic agent, which is a selective estrogen receptor modulator (SERM);

a tyrosine kinase inhibitor;

a selective androgen receptor modulator;

15 an antiarrhythmic agent, which is a β -blocker, or a calcium channel blocker, or an α -adrenergic blocker;

coenzyme Q sub. 10;

an agent that upregulates type III endothelial cell nitric acid syntase;

20 a chondroprotective compound which is polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (PPS), doxycycline or minocycline;

a cyclooxygenase (COX)-2 inhibitor, which is
25 Celebrex® (Searle) or Vioxx® (Merck) or a glycoprotein IIa/IIIb receptor antagonist;

a 5-HT reuptake inhibitor;

a growth hormone secretagogue;

an anti-atherosclerosis agent;

30 an anti-infective agent, or an immunosuppressant for use in transplantation, or an antineoplastic agent.

12. The combination as defined in Claim 10 wherein the HMG CoA reductase inhibitor compound is in
35 combination with an ACE inhibitor or a NEP/ACE inhibitor.

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13. The combination as defined in Claim 12 wherein the HMG CoA reductase inhibitor compound is in combination with an ACE inhibitor which is ramipril;

5 wherein the HMG CoA reductase inhibitor is in combination with a NEP/ACE inhibitor which is omapatrilat or gemopatrilat;

wherein the HMG CoA reductase inhibitor is in combination with a platelet aggregation inhibitor.

10 14. The combination as defined in Claim 13 wherein the platelet inhibitor is clopidogrel, or aspirin or a combination of clopidogrel and aspirin.

15 15. A method of inhibiting cholesterol biosynthesis or lowering blood serum cholesterol levels and/or modulating blood serum cholesterol levels, lowering LDL cholesterol and/or increasing HDL cholesterol, or treating dyslipidemia, mixed dyslipidemia, LDL Pattern B, LDL Pattern A, hyperlipidemia, hypercholesterolemia, hypo
20 α -lipoproteinemia, hyperlipoproteinemia or hypertriglyceridemia, and other aberrations of apolipoprotein B metabolism, or reducing levels of Lp(a), or treating or preventing other cholesterol-related diseases, or treating or preventing or reversing
25 progression of atherosclerosis, or preventing or treating Alzheimer's disease, or preventing or treating osteoporosis and/or osteopenia, or reducing inflammatory markers, reducing C-reactive protein, or preventing or treating low grade vascular inflammation, or preventing
30 or treating stroke, or preventing or treating dementia, or preventing and treating coronary heart disease, and primary and secondary prevention of myocardial infarction, or preventing or treating stable and unstable angina, or primary prevention of coronary events, or
35 secondary prevention of cardiovascular events, or preventing or treating peripheral vascular disease, preventing or treating peripheral arterial disease, or

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preventing or treating acute vascular syndromes, or preventing or reducing the risk of undergoing myocardial revascularization procedures, or preventing or treating microvascular diseases such as nephropathy, neuropathy, retinopathy and nephrotic syndrome, or preventing or treating hypertension, preventing or treating Type I diabetes, Type 2 diabetes, and related diseases, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, LDL Pattern B, LDL Pattern A, Syndrome X, diabetic complications, dysmetabolic syndrome, and related diseases, and sexual dysfunction, preventing and treating malignant lesions, premalignant lesions, gastrointestinal malignancies, liposarcomas and epithelial tumors, cancer-induced asthenia (fatigue), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and gallstones, and HIV infection, drug-induced lipodystrophy, and proliferative diseases, improving coagulation homeostasis, reducing PAI-1 activity, reducing fibrinogen, and/or reducing platelet aggregation, and/or improving endothelial function, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

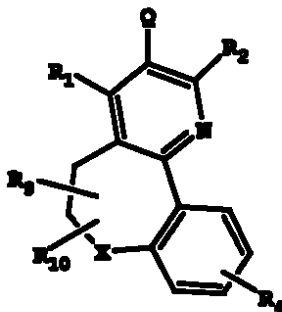
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16. A method for treating cholesterol related diseases, diabetes and related diseases, cardiovascular diseases, cerebrovascular diseases, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a combination of a compound as defined in Claim 1 and a hypolipidemic agent, and/or lipid modulating agent and/or antidiabetic agent and/or cardiovascular agent, cerebrovascular agent, and/or other type of therapeutic agent, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of such combinations.

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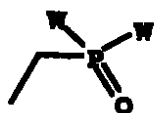
17. A compound having the structure



wherein X is O, S or NR₇, where R₇ is H, alkyl, aryl,
 5 alkanoyl, aroyl or alkoxy carbonyl; R₁ and R₂ are the same
 or different and are independently selected from alkyl,
 arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl,
 heteroaryl or cycloheteroalkyl;

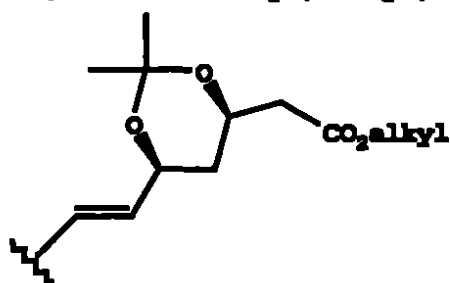
R₉ and R₁₀ are the same or different and are
 10 independently selected from H or alkyl, or R₉ and R₁₀ may
 be taken together with the carbon or carbons to which
 they are attached to form a 3 to 7 membered carbocyclic
 ring;

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



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

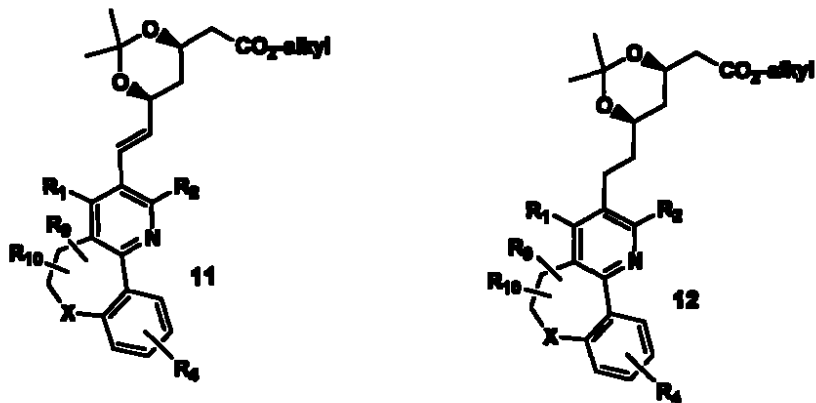
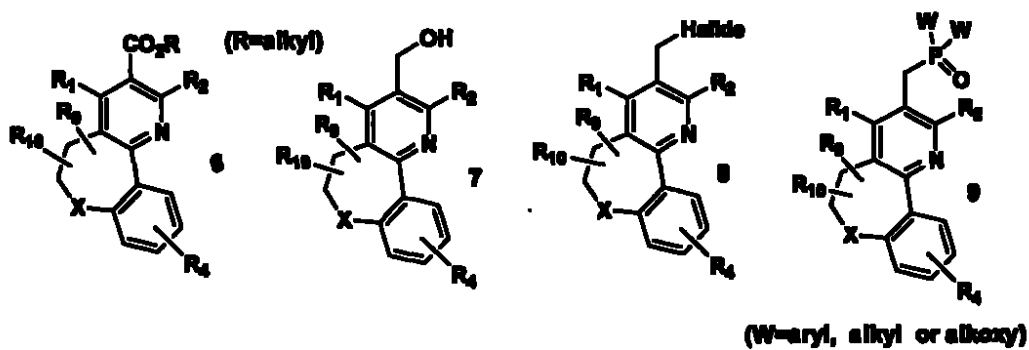
or



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18. The compound as defined in Claim 17 having the following structures:

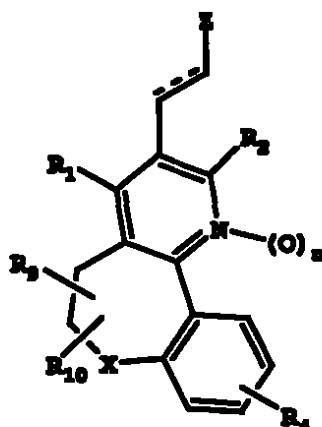


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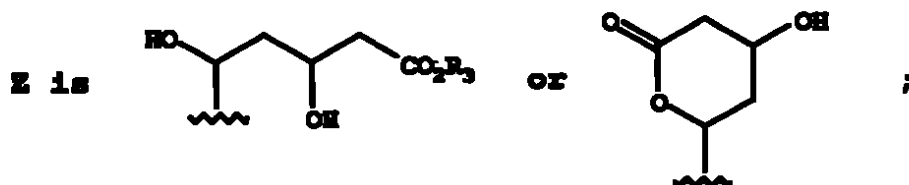
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HMG-CoA REDUCTASE INHIBITORS AND METHODAbstract of the Disclosure

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



and pharmaceutically acceptable salts thereof,
 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
 20 cycloheteroalkyl; and

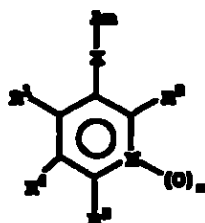
R₃ to R₉ are as defined herein.

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INHIBIDORES DE HMG-CoA REDUCTASA Y MÉTODO

La presente invención se relaciona con compuestos y composiciones farmacéuticas útiles como agentes hipocolesterolémicos e hipolipidémicos. Más particularmente, esta invención tiene que ver con (1) ciertos inhibidores de la enzima 3-hidroxi-3-metilglutaril-coenzima A reductasa (HMG-CoA reductasa) que incluyen una piridina que contiene núcleo unido por medio de un enlazador a una cadena lateral de dominio de enlace de HMG, (2) composiciones farmacéuticas que contienen dichos compuestos y (3) un método de disminuir los niveles de colesterol del suero sanguíneo y modular niveles de lípidos del suero sanguíneo empleando dichas composiciones farmacéuticas.

La patente estadounidense No. 5,686,433 a Robl divulga la estructura



en donde:

Am es una cadena lateral de dominio de enlace;

X es un enlazante;

R¹ y R² son los mismos o diferentes y cada uno se selecciona independientemente de

- (i) hidrógeno,
- (ii) alquilo,
- (iii) arilo,
- (iv) cicloalquilo,
- (v) aralquilo,
- (vi) aralcoxi,
- (vii) alquenilo,
- (viii) cicloalquenilo, y

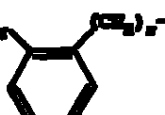
(ix) heterocicl (por ejemplo, tienilo, benzodioxolilo);

R^3 se selecciona de

- (i) hidrógeno,
- (ii) alquilo inferior,
- (iii) arilo,
- (iv) cicloalquilo,
- (v) alcoxi,
- (vi) aralquilo,
- (vii) aralcoxi,
- (viii) alquenilo,
- (ix) cicloalquenilo,
- (x) alquilo halo-sustituido,
- (xi) adamantilo, y
- (xii) heterociclo (por ejemplo, tienilo, benzodioxolilo);

R^4 se selecciona de

- (i) hidrógeno,
- (ii) alquilo inferior,
- (iii) arilo,
- (iv) cicloalquilo,
- (v) alcoxi,
- (vi) aralquilo,
- (vii) aralcoxi,
- (viii) alquenilo,
- (ix) cicloalquenilo,
- (x) adamantilo,
- (xi) halógeno,
- (xii) alquilo halo-sustituido (por ejemplo, trifluorometilo), y
- (xiii) heterociclo (por ejemplo, tienilo, benzodioxolilo); o R^3 y R^4 tomados conjuntamente pueden ser

pero cuando A_m  es



o una δ lactona del mismo, R^3 y R^4 no pueden ser $(\text{CH}=\text{CH})_2$;

R^6 es hidrógeno o alquilo inferior,

R^8 es hidrógeno, alquilo inferior, metal alcalino, o metal alcalinotérreo;

n es 0 ó 1;

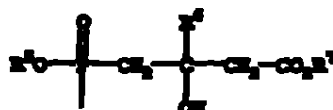
p es 3, 4 ó 5;

q es 0, 1, 2, ó 3; y

r es 0, 1, 2, ó 3.

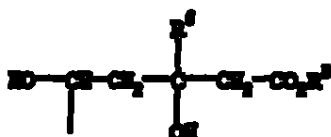
En incorporaciones preferidas (A_m) es una cadena lateral de dominio de enlace de HMG que tiene una función dihidroxi ácido o ácido fosfinico.

La cadena (A_1) lateral de dominio de enlace de HMG de ácido fosfinico (o fosfónico cuando X es $\text{CH}_2\text{-O-}$) es

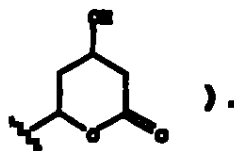


en donde R^5 y R^7 se seleccionan independientemente de hidrógeno, alquilo inferior, ión de metal alcalino y ión de metal alcalinotérreo; y R^6 es hidrógeno o alquilo inferior.

La cadena (A_2) lateral de dominio de enlace de dihidroxi ácido es



en donde R^6 es hidrógeno o alquilo inferior, R^8 es hidrógeno o alquilo inferior en forma de ácido libre o en la forma de un éster hidrolizable y fisiológicamente aceptable o δ lactona del mismo (es decir, cuando Am es



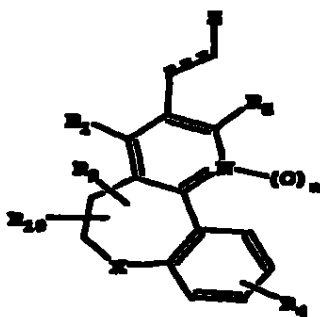
Además, R^8 puede ser un ión de metal alcalino o ión de metal alcalinotérreo.

Un enlazante apropiado (X) es $-(CH_2)_a-$, $-CH=CH-$, $-C\equiv C-$, $-CH_2O-$, en donde O está enlazado al átomo de fósforo o el ancla aromática cuando Am es A_1 , y en donde O está enlazado al ancla aromática cuando Am es A_2 , y en donde "a" es 1, 2, ó 3.

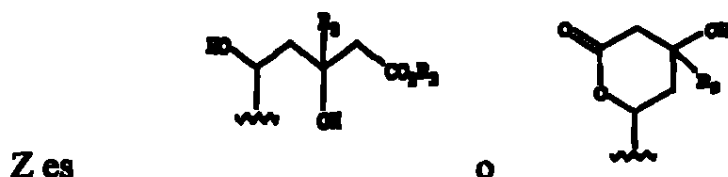
De acuerdo con la presente invención, se proveen ciertos compuestos con contenidos de piridina que son potentes inhibidores de biosíntesis de colesterol en virtud de su capacidad de inhibir la enzima 3-metil-glutaril-coenzima A reductasa (HMG-CoA reductasa).

En particular, en su aspecto más amplio de compuesto químico, la presente invención proporciona compuestos de la fórmula

I



en donde X es O, S o NR_7 ;



n es 0 ó 1;

R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente de alquilo, arilalquilo, cicloalquilo, alquenilo, cicloalquenilo, arilo, heteroarilo o cicloheteroalquilo;

R₃ es H, o alquilo inferior;

R₄ es H, halógeno, CF₃, hydroxi, alquilo, alcoxi, alcanoilamin, aroilamino o ciano;

R₇ es H, alquilo, arilo, alcanoilo, aroilo, o alcóxicarbonilo;

R₈ es H o alquilo inferior;

R₉ y R₁₀ son los mismos o diferentes y se seleccionan independientemente de H o alquilo, o donde por lo menos uno de R₉ y R₁₀ es alquilo, R₉ y R₁₀ pueden tomarse juntos con el carbono o carbonos a los cuales se unen para formar un anillo carboxílico de 3 a 7 miembros, los que pueden incluir un anillo espirocíclico;

y  representa un enlace único o un doble enlace (que puede ser cis o trans);

e incluyendo sus sales farmacéuticamente aceptables en donde R₃ es H, sus ésteres, sus ésteres de profármaco, y todos sus estereoisómeros.

Preferiblemente, el grupo Z será en forma de un ácido libre, un éster hidrolizable y fisiológicamente aceptable o δ lactona del mismo, o una sal de metal alcalino, sal de metal alcalinotérreo o una sal de aminoácido.

Se prefieren los compuestos de fórmula I de la invención en donde

R₁ y R₂ se seleccionan independientemente de alquilo, cicloalquilo y arilo;

R₄ es H, alquilo, o halógeno;

x es 0; y

n es 0.

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Más preferidos son los compuestos de fórmula I de la invención en donde R_1 es arilo (especialmente arilo sustituido como se define más adelante);

R_2 es alquilo o cicloalquilo;

R_4 es H;

R_9 y R_{10} son H;

X es O;

n es 0; y



es un enlace doble.

Aún más preferidos son compuestos de fórmula I de la invención en donde

R_1 es arilo sustituido, preferiblemente 4-fluorofenilo, 4-fluoro-3-metilfenilo o 3,5-dimetilfenilo;

R_2 es alquilo o cicloalquilo, preferiblemente isopropilo, t-butilo ciclopropilo;

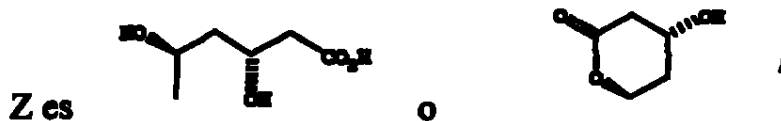
R_4 es H;

X es O;

n es 0;



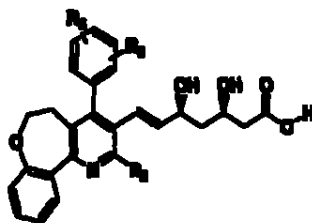
es un enlace doble, preferiblemente "trans"; y



o una sal de metal alcalino del mismo, sal de metal alcalinotérreo o una sal de aminoácido.

Los compuestos más preferidos de fórmula I de la invención tendrán la estructura

✓✓



o una sal de metal alcalino o alcalinotérreo (tal como Na, K o Ca), o sal de aminoácido (tal como arginina), en donde R₅ y R₆ son los mismos o diferentes y seleccionados independientemente de H, halógeno y/o alquilo (preferiblemente 4-fluoro, 4-fluoro-3-metil o 3,5-dimetil); y

R₂ es alquilo o cicloalquilo, preferiblemente isopropilo, t-butilo o ciclopropilo.

En otro aspecto, la presente invención provee composiciones farmacéuticas, útiles como agentes hipocolesterolémicos e hipolipidémicos, o agentes hipotrigliceridémicos, o agentes anti-Alzheimer, o agentes anti-osteoporosis así como otros usos como se describe aquí, que comprenden una cantidad hipolipidémica o hipocolesterolémica o hipotrigliceridémica o enfermedad anti-Alzheimer o anti-osteoporosis, u otra cantidad terapéuticamente efectiva (dependiendo del empleo) de un compuesto de fórmula I de acuerdo con esta invención, en combinación con un portador farmacéuticamente aceptable.

En otro aspecto, la presente invención provee un método de inhibir biosíntesis R₁ y R₂ se de colesterol o de disminuir los niveles de colesterol del suero sanguíneo y/o modular niveles de colesterol del suero sanguíneo tal como reducir colesterol LDL y/o aumentar colesterol HDL, o tratando dislipidemia, dislipidemia mixta, hiperlipidemia, hipercolesterolemia, hipo α -lipoproteinemia, Patrón B LDL, Patrón A LDL, hiperlipoproteinemia o hipertrigliceridemia, y otras aberraciones de metabolismo de apolipoproteína B, o reducir los niveles de Lp(a), o tratar o prevenir otras enfermedades relacionadas con el colesterol, o tratar o prevenir o revertir la progresión de aterosclerosis, o prevenir o tratar la enfermedad de Alzheimer, o prevenir o tratar osteoporosis y/o osteopenia, o reduciendo los marcadores inflamatorios tales como proteína C-reactiva, o prevenir o tratar



inflamación vascular de grado bajo, prevenir o tratar apoplejía, o prevenir o tratar demencia, o prevenir y tratar aterosclerosis de las arterias coronarias (inclusive prevención primaria y secundaria de infarto del miocardio), o prevenir o tratar angina estable e inestable, o prevención primaria de eventos coronarios, o prevención secundaria de eventos cardiovasculares, o prevenir o tratar enfermedad vascular periférica, prevenir o tratar enfermedad arterial periférica, o prevenir o tratar síndromes vasculares agudos, o prevenir o reducir el riesgo de someterse a intervenciones de revascularización del miocardio, o prevenir o tratar enfermedades microvasculares tales como nefropatía, neuropatía, retinopatía y síndrome nefrótico o prevenir o tratar hipertensión en un paciente necesitado de dicho tratamiento administrando una composición farmacéutica de acuerdo con la presente invención como se define más arriba.

Adicionalmente, de acuerdo con la presente invención, se provee un método para prevenir o tratar diabetes, especialmente diabetes Tipo 2, y enfermedades relacionadas tales como resistencia a la insulina, hiperglicemia, hiperinsulinemia, niveles elevados en la sangre de ácidos grasos o glicerol, obesidad, Síndrome X, complicaciones diabéticas, síndrome dismetabólico, y enfermedades relacionadas, y disfunción sexual, en donde una cantidad terapéuticamente efectiva de un compuesto de estructura I se administra a un paciente necesitado de tratamiento.

Además, de acuerdo con la presente invención, se provee un método para prevenir y tratar lesiones malignas (tales como carcinoma ductal in situ de la mama y carcinoma lobular in situ de la mama), lesiones pre-malignas (tales como fibroadenoma mamario y neoplasia intra-epitelial prostática (PIN), malignidades gastrointestinales, liposarcomas y varios otros tumores epiteliales (inclusive de mama, próstata, colon, ovarios, gástrico y pulmón), astenia inducida por cáncer (fatiga), síndrome de intestino irritable, enfermedad de Crohn, ulceritis gástrica, y cálculos biliares, e infección HIV, otras enfermedades infecciosas, lipodistrofia inducida por fármacos, y enfermedades proliferativas tales como psoriasis, en donde una cantidad

terapéuticamente efectiva de un compuesto de estructura I se administra a un paciente humano necesitado de tratamiento.

Adicionalmente, de acuerdo con la presente invención, se provee un método para mejorar la homeostasis de coagulación inclusive reducir la actividad PAI-1, disminuir el fibrinógeno, y/o reducir la agregación de plaquetas, y/o mejorar la función endotelial, en donde una cantidad terapéuticamente efectiva de un compuesto de estructura I se administra a un paciente necesitado de tratamiento.

Además, de acuerdo con la presente invención, se provee un método para tratar enfermedades relacionadas con colesterol, diabetes y enfermedades relacionadas, enfermedades cardiovasculares, enfermedades cerebrovasculares como se definen más arriba y más adelante y otras enfermedades tal como se expuso anteriormente, en donde una cantidad terapéuticamente efectiva de una combinación de un compuesto de estructura I y un agente hipolipidémico, y/o agente modulador de lípidos y/o agente antidiabético y/o agente cardiovascular, agente cerebrovascular, y/o otro tipo de agente terapéutico, se administra a un paciente necesitado de tratamiento.

En los métodos anteriores de la invención en donde se administra una combinación, el compuesto de estructura I se empleará en una proporción de peso al otro agente terapéutico (dependiendo de su modo de operación) en el rango desde alrededor de 0.01:1 hasta alrededor de 500:1, preferiblemente desde alrededor de 0.5:1 hasta alrededor de 100:1.

De acuerdo con la presente invención, se proveen compuestos útiles en inhibir la enzima HMG-CoA reductasa, inhibidores que son útiles como agentes hipocolesterolémicos, agentes dislipidémicos, agentes hipolipidémicos, agentes hipotrigliceridémicos, agentes de enfermedad de anti-Alzheimer, y agentes antiosteoporosis así como otros usos como se describe aquí.

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El término "eventos coronarios" como se emplea aquí se refiere al infarto del miocardio, procedimientos de revascularización del miocardio, angina, muerte cardiovascular y síndrome coronario agudo.

El término "enfermedades o eventos cardiovasculares" como se emplea aquí se refiere a aterosclerosis de las arterias coronarias, infarto del miocardio, inclusive MI primario y MI secundario, infarto recurrente del miocardio, angina pectoris (inclusive angina estable e inestable), falla cardíaca congestiva, y muerte súbita cardíaca.

El término "enfermedades o eventos cerebrovasculares" como se emplea aquí se refiere infarto cerebral o apoplejía (causada por bloqueo de los vasos o hemorragia), o ataque isquémico transitorio (TIA), síncope, aterosclerosis de las arterias intracraneales y/o extracraneales, y similares.

El término "enfermedades relacionadas con el colesterol" como se emplea aquí se refiere a enfermedades que implican niveles elevados de colesterol LDL, enfermedades que implican la regulación de receptores LDL, enfermedades que implican niveles reducidos de colesterol HDL, dislipidemia, hiperlipidemia, Patrón B LDL elevado, Patrón A LDL elevado, hipercolesterolemia, hipo α -lipoproteinemia (síndrome de colesterol HDL bajo), hiperlipoproteinemia, niveles Lp(a) elevados, hipertrigliceridemia, otras aberraciones de metabolismo de apolipoproteína B, formas heterócigas familiares, presumidas familiares combinadas y no familiares (no FH) de hipercolesterolemia primaria (inclusive Tipos Frederickson IIa y IIb), enfermedad de almacenamiento de éster de colesterol, y enfermedades de proteína de transferencia de éster de colesterol, y enfermedades relacionadas.

Los trastornos, enfermedades y dolencias, referenciadas colectivamente como "Síndrome X" o Síndrome Dismetabólico (tal como se detalla en Johanson, *J. Clin. Endocrinol. Metab.*, 1997, 82, 727-734, y otras publicaciones) incluyen hiperglicemia y/o síntoma pre-diabético de resistencia a la insulina, y se caracteriza por un estado inicial resistente a la insulina que genera hiperinsulinemia, dislipidemia, y tolerancia deteriorada

a la glucosa, que puede desarrollarse en diabetes Tipo II, caracterizada por hiperglicemia, la cual puede desarrollarse a complicaciones diabéticas.

El término "diabetes y enfermedades relacionadas" se refiere a diabetes Tipo II, diabetes Tipo I, tolerancia deteriorada a la glucosa, obesidad, hiperglicemia, Síndrome X, síndrome dismetabólico, complicaciones diabéticas e hiperinsulinemia.

Los trastornos, enfermedades y dolencias referenciadas colectivamente como "complicaciones diabéticas" incluyen retinopatía, neuropatía y nefropatía, y otras complicaciones conocidas de diabetes.

El término "otro tipo (s) de agentes terapéuticos" como se emplea aquí se refiere a uno o más agentes antidiabéticos (distintos de los compuestos de fórmula I), uno o más agentes anti-obesidad, y/o uno más agentes reductores de lípido, uno más agentes moduladores de lípido (inclusive agentes anti-aterosclerosis), otros tipos de agentes anti-aterosclerosis, y/o uno más agentes antiplaquetas, uno más agentes para tratar la hipertensión, uno más fármacos anti-cáncer, uno más agentes para tratar la artritis, uno más agentes anti-osteoporosis, uno más agentes anti-obesidad, uno más agentes para tratar enfermedades inmunomodulatorias y uno más agentes para tratar anorexia nervosa.

El término "agente modulador de lípido" tal como se emplea aquí se refiere a agentes que disminuyen LDL y/o aumentan HDL y/o disminuyen triglicéridos y/o reducen el colesterol total y/o otros mecanismos conocidos para tratar terapéuticamente disfunciones de lípido.

El término "otros tipos de agentes anti-aterosclerosis" como se emplea aquí se refiere a agentes anti-aterosclerosis convencionales inclusive inhibidores de lipoxigenasa, inhibidores ACAT, antioxidantes, δ agonistas PPAR, inhibidores de fosfolipasa (inclusive inhibidores PLA-2), y/o otros agentes anti-ateroscleróticos conocidos.

Los términos "sal" farmacéuticamente aceptable y "sales" se refieren a sales básicas formadas con bases orgánicas e inorgánicas. Dichas sales incluyen sales de amonio; sales de metal alcalino, tales como sales de litio,

sodio y potasio (que son preferidas); sales de metal alcalinotérreo, tales como sales de calcio y magnesio ; sales con bases orgánicas, tales como sales parecidas a amina (por ejemplo, sal de dicitclohexilamina, benztatina, N-metil-D-glucamina, y sales de hidrabamina); y sales con aminoácidos tales como arginina, lisina y similares; y los dobles iones bipolo, las denominadas "sales internas".

Se prefieren sales sales farmacéuticamente aceptables, no tóxicas, aunque también son útiles otras sales, por ejemplo, en aislar o purificar el producto.

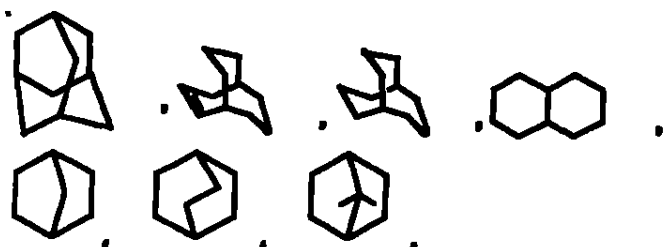
El término "sal" farmacéuticamente aceptable y "sales" incluye asimismo sales de adición de ácido. Éstas se forman, por ejemplo, con ácidos inorgánicos fuertes, tales como ácidos minerales, por ejemplo, ácido sulfúrico, ácido fosfórico o un ácido hidrohálico tal como HCl o HBr, con ácidos carboxílicos orgánicos fuertes, tales como ácidos alcancarboxílicos de 1 a 4 átomos de carbono los cuales son sustituidos o no sustituidos, por ejemplo, por halógeno, por ejemplo ácido acético, tales como ácidos dicarboxílicos saturados o insaturados, por ejemplo, ácido oxálico, malónico, succínico, maleico, fumárico, ftálico o tereftálico, tales como ácidos hidroxicarboxílicos, por ejemplo ácido ascórbico, glicólico, láctico, málico, tartárico o cítrico, tales como aminoácidos, (por ejemplo ácido aspártico o glutámico o lisina o arginina), o ácido benzoico, o con ácidos sulfónicos orgánicos, tales como ácidos (C₁.C₄) alquílicos o arilsulfónicos los cuales son sustituidos o no sustituidos, por ejemplo por halógeno, por ejemplo, ácido metansulfónico o ácido p-toluensulfónico.

A menos que se indique lo contrario, el término "alquilo inferior", "alquilo" o "alqu" como se emplea aquí solo o como parte de otro grupo incluye hidrocarburos de cadena recta y ramificada, que contienen 1 a 20 carbonos, preferiblemente 1 a 10 carbonos, más preferiblemente 1 a 8 carbonos, en la cadena normal, tales como metilo, etilo, propilo, isopropilo, butilo, t-butilo, isobutilo, pentilo, hexilo, isohexilo, heptilo, 4,4-dimetilpentilo, octilo, 2,2,4-trimetil-pentilo, nonilo, decilo, undecilo,

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dodecilo, sus diferentes isómeros de cadena ramificada, y similares así como tales grupos que incluyen 1 a 4 sustituyentes tales como halo, por ejemplo, F, Br, Cl o I o CF₃, alquilo, alcoxi, arilo, ariloxi, aril(arilo) o diarilo, arilalquilo, arilalquiloxi, alquenilo, cicloalquilo, cicloalquilalquilo, cicloalquilalquiloxi, amino, hidroxilo, hidroxialquilo, acilo, cicloheteroalquilo, heteroarilo, heteroariloxi, heteroarilalquilo, heteroarilalcoxi, ariloxialquilo, alquiltio, arilalquiltio, ariloxiarilo, alquilamido, alcanoilamino, arilcarbonilamino, nitro, ciano, tiol, haloalquilo, trihaloalquilo y/o alquiltio.

A menos que se indique lo contrario, el término "cicloalquilo" como se emplea aquí, solo o como parte de otro grupo, incluye grupos hidrocarburo cíclicos saturados o parcialmente insaturados (que contienen 1 ó 2 enlaces dobles) que comprenden 1 a 3 anillos, inclusive alquilo monocíclico, alquilo bicíclico (o bicicloalquilo) y alquilo tricíclico, que contienen un total de 3 a 20 carbonos que forman el anillo, preferiblemente 3 a 10 carbonos, que forman el anillo y que pueden fusionarse a 1 ó 2 anillos aromáticos como se describe para arilo, el cual incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclodecilo y ciclododecilo, ciclohexenilo,



cualquiera de cuyos grupos puede sustituirse opcionalmente con 1 a 4 sustituyentes tales como halógeno, alquilo, alcoxi, hidroxilo, arilo, ariloxi, arilalquilo, cicloalquilo, alquilamido, alcanoilamino, oxo, acilo, arilcarbonilamino, heteroarilo, cicloheteroalquilo, amino, alquilamino, nitro, ciano, tiol y/o alquiltio y/o cualquiera de los sustituyentes de alquilo.

El término "cicloalquenilo" como se emplea aquí solo o como parte de otro grupo se refiere a hidrocarburos cíclicos que comprenden 3 a 12 carbonos, preferiblemente 5 a 10 carbonos y 1 ó 2 enlaces dobles. Grupos

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ejemplares cicloalquenilo incluyen ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclohexadienilo, y cicloheptadienilo, los cuales pueden sustituirse opcionalmente como se definen para cicloalquilo.

El término "alcanoilo" tal como se emplea aquí solo o como parte de otro grupo se refiere a alquilo enlazado a un grupo carbonilo.

A menos que se indique lo contrario, el término "alquenilo inferior" o "alquenilo" tal como se emplea aquí, por sí mismo o como parte de otro grupo, se refiere a radicales de cadena recta o ramificada de 2 a 20 carbonos, preferiblemente 2 a 12 carbonos, y más preferiblemente 1 a 8 carbonos en la cadena normal, los cuales incluyen uno a seis enlaces dobles en la cadena normal, tales como vinilo, 2-propenilo, 3-butenilo, 2-butenilo, 4-pentenilo, 3-pentenilo, 2-hexenilo, 3-hexenilo, 2-heptenilo, 3-heptenilo, 4-heptenilo, 3-octenilo, 3-nonenilo, 4-decenilo, 3-undecenilo, 4-dodecenilo, 4,8,12-tetradecatrienilo, y similares, y los cuales pueden sustituirse opcionalmente con 1 a 4 sustituyentes, a saber, halógeno, haloalquilo, alquilo, alcoxi, alquenilo, alquinilo, arilo, arilalquilo, cicloalquilo, amino, hidroxilo, heteroarilo, cicloheteroalquilo, alcanoilamino, alquilamido, arilcarbonil-amino, nitro, ciano, tiol, alquiltio y/o cualquiera de los sustituyentes alquilo expuestos aquí.

A menos que se indique lo contrario, el término "alquinilo inferior" o "alquinilo" tal como se emplea aquí, por sí mismo o como parte de otro grupo, se refiere a radicales de cadena recta o ramificada de 2 a 20 carbonos, preferiblemente 2 a 12 carbonos y más preferiblemente 2 a 8 carbonos en la cadena normal, los cuales incluyen un triple enlace en la cadena normal, tal como 2-propinilo, 3-butinilo, 2-butinilo, 4-pentinilo, 3-pentinilo, 2-hexinilo, 3-hexinilo, 2-heptinilo, 3-heptinilo, 4-heptinilo, 3-octinilo, 3-noninilo, 4-decinilo, 3-undecinilo, 4-dodecinilo y similares, y los cuales pueden sustituirse opcionalmente con 1 a 4 sustituyentes, a saber, halógeno, haloalquilo, alquilo, alcoxi, alquenilo, alquinilo, arilo, arilalquilo, cicloalquilo, amino, heteroarilo, cicloheteroalquilo, hidroxilo, alcanoilamino,

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alquilamido, arilcarbonilamino, nitro, ciano, tiol, y/o alquiltio, y/o cualquiera de los sustituyentes alquilo expuestos aquí.

Los términos "arilalquenilo" y "arilalquinilo", tal como se usan solos o como parte de otro grupo, se refieren a grupos alquenilo y alquinilo tal como se describen más arriba teniendo un sustituyente arilo.

Donde grupos alquilo como los definidos anteriormente tienen enlaces simples para unión a otros grupos en dos átomos diferentes de carbono, se los designa grupos "alquileno" y pueden sustituirse opcionalmente con 1 ó 2 sustituyentes como se definieron más arriba para "alquilo", tales como, por ejemplo, alquilo, halo, hidroxilo, alcoxi y/o cicloalquilo.

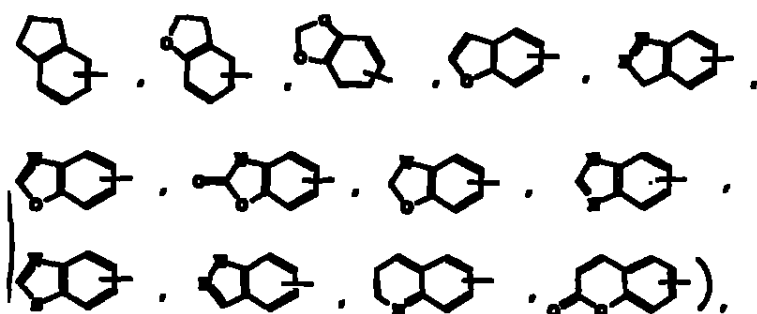
Donde grupos alquenilo como los definidos anteriormente y grupos alquinilo como los definidos más arriba, respectivamente, tienen enlaces simples para unión a dos átomos de carbono diferentes, pueden designarse "grupos alquenileno" y "grupos alquinileno", respectivamente, y pueden sustituirse opcionalmente con 1 ó 2 sustituyentes como los definidos arriba para "alquenilo" y "alquinilo".

El término "halógeno" o "halo" tal como se emplea aquí, solo o como parte de otro grupo, se refiere a cloro, bromo, flúor, y yodo así como CF₃, prefiriéndose cloro o flúor.

El término "ión metálico" se refiere a iones de metal alcalino tales como sodio, potasio o litio y iones de metal alcalinotérreo tales como magnesio y calcio, así como cinc y aluminio.

A menos que se indique lo contrario, el término "arilo" tal como se emplea aquí, solo o como parte de otro grupo, se refiere a grupos aromáticos monocíclicos y bicíclicos que contienen 6 a 10 carbonos en la porción del anillo (tal como fenilo o naftilo inclusive 1-naftilo y 2-naftilo) y pueden incluir opcionalmente uno a tres anillos adicionales fusionados a un anillo carbocíclico o un anillo heterocíclico (tales como anillos arilo, cicloalquilo, heteroarilo o cicloheteroalquilo, por ejemplo

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y pueden sustituirse opcionalmente por átomos de carbono disponibles con 1, 2, ó 3 grupos seleccionados de hidrógeno, halo, haloalquilo, alquilo, haloalquilo, alcoxi, halofenilo, benzoiloxi, haloalcoxi, alquenil, trifluorometilo, trifluorometoxi, alquinilo, cicloalquilalquil, cicloheteroalquilo, cicloheteroalquilalquilo, arilo, heteroarilo, arilalquil, ariloxi, ariloxialquilo, arilalcoxi, ariltio, arilazo, heteroarilalquilo, heteroarilalquenilo, heteroarilheteroarilo, heteroariloxi, hidroxil, nitro, ciano, amino, amino sustituido en donde el amino incluye 1 ó 2 sustituyentes (los cuales son alquilo, alcanoilo, arilo o cualquiera de los demás compuestos arilo mencionados en las definiciones), tiol, alquiltio, ariltio, heteroariltio, ariltioalquilo, alcoxiariltio, alquilcarbonilo, arilcarbonilo, alquilaminocarbonilo, arilaminocarbonilo, alcoxicarbonilo, aminocarbonilo, alquilcarboniloxi, arilcarboniloxi, alquilcarbonilamino, arilcarbonilamino, arilsulfinilo, arilsulfinilalquilo, arilsulfonilamino o arilsulfonaminocarbonilo y/o cualquiera de los sustituyentes alquil expuestos aquí.

A menos que se indique lo contrario, el término "alcoxi inferior", "alcoxi", "ariloxi" o "aralcoxi" como se emplea aquí, solo o como parte de otro grupo, incluye cualquiera de los grupos alquilo, aralquilo o arilo, de arriba, enlazados a un átomo de oxígeno.

A menos que se indique lo contrario, el término "amino sustituido" como se emplea aquí, solo o como parte de otro grupo, se refiere a amino sustituido con uno o dos sustituyentes, los cuales pueden ser los mismos diferentes, tales como alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, cicloheteroalquilo, cicloheteroalquilalquilo, cicloalquilo, cicloalquilalquil,

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haloalquil, hidroalquilo, alcohalquilo, tioalquilo. Estos sustituyentes pueden sustituirse además con un ácido carboxílico y/o cualquiera de los sustituyentes de alquilo como se expuso arriba. Adicionalmente, los sustituyentes amino pueden tomarse juntos con el átomo de nitrógeno al cual se unen para formar 1-pirrolidinilo, 1-piperidinilo, 1-azepinilo, 4-morfolinilo, 4-tiamorfolinilo, 1-piperazinilo, 4-alquil-1-piperazinilo, 4-arilalquil-1-piperazinilo, 4-diarilalquil-1-piperazinilo, 1-pirrolidinilo, 1-piperidinilo, o 1-azepinilo, opcionalmente sustituidos con alquilo, alcoxi, alquiltio, halo, trifluorometilo o hidroxilo.

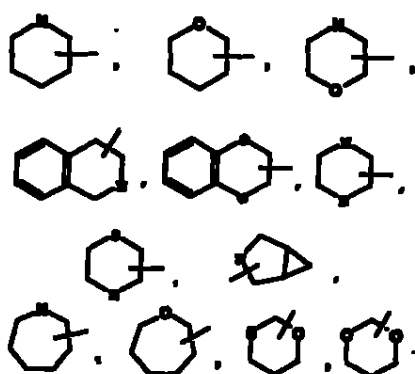
A menos que se indique lo contrario, el término "alquiltio inferior", "alquiltio", "ariltio" o "aralquiltio" como se emplea aquí, solo o como parte de otro grupo, incluye cualquiera de los grupos alquilo, aralquilo o arilo enlazados a un átomo de azufre.

A menos que se indique lo contrario, el término "alquilamino inferior", "alquilamino", "arilamino", or "arilalquilamino" como se emplea aquí, solo o como parte de otro grupo, incluye cualquiera de los grupos alquilo, arilo o arilalquilo, de arriba, enlazado a un átomo de nitrógeno.

A menos que se indique lo contrario, el término "acilo" como se emplea aquí por sí mismo o parte de otro grupo, según se define aquí, se

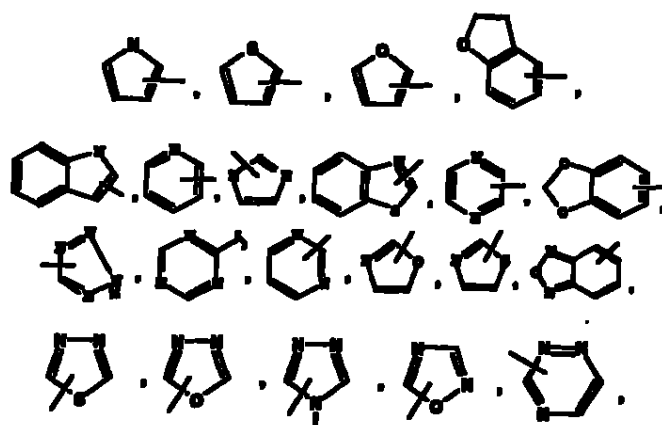
refiere a un radical orgánico enlazado a un grupo carbonilo $\left(\begin{smallmatrix} \text{O} \\ \parallel \\ \text{C} \end{smallmatrix} \right)$; ejemplos de grupos acilo incluyen cualquiera de los grupos R¹ unidos a un carbonilo, tal como alcanilo, alquenoilo, aroilo, aralcanilo, heteroarilo, cicloalcanilo, cicloheteroalcanilo y similares.

A menos que se indique lo contrario, el término "cicloheteroalquilo" tal como se emplea aquí, solo o como parte de otro grupo, se refiere a un anillo saturado o parcialmente insaturado de 5-, 6- ó 7 miembros el cual incluye 1 a 2 heteroátomos tales como nitrógeno, oxígeno y/o azufre, enlazado a través de un átomo de carbono o un heteroátomo, donde posible, opcionalmente mediante el enlazante (CH₂)_r (donde r es 1, 2 ó 3), tal como



y similares. Los grupos de arriba pueden incluir 1 a 4 sustituyentes tales como as alquilo, halo, oxo y/o cualquiera de los sustituyentes alquilo expuestos aquí. Además, cualquiera de los anillos cicloheteroalquilo puede fusionarse a un anillo cicloalquilo, arilo, heteroarilo o cicloheteroalquilo.

A menos que se indique lo contrario, el término "heteroarilo" tal como se emplea aquí, solo o como parte de otro grupo, se refiere a un anillo aromático de 5 ó 6 miembros el cual incluye 1, 2, 3 ó 4 heteroátomos tales como nitrógeno, oxígeno o azufre, y dichos anillos fusionados a un anillo arilo, cicloalquilo, heteroarilo o cicloheteroalquilo (por ejemplo, benzotiofenilo, indolilo), e incluye posibles N-óxidos. El grupo heteroarilo puede incluir opcionalmente 1 a 4 sustituyentes tales como cualquiera de los sustituyentes expuestos más arriba para alquilo. Ejemplos de grupos heteroarilo incluyen los siguientes:



y similares.

El término "cicloheteroalquilalquilo" tal como se emplea aquí, solo o como parte de otro grupo, se refiere a grupos cicloheteroalquilo según se definieron más arriba enlazados a través de un átomo C o heteroátomo a una cadena (CH₂)_r.

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El término "heteroarilalquilo" o "heteroarilalquenilo" tal como se emplea aquí, solo o como parte de otro grupo, se refiere a un grupo heteroarilo, como se definió arriba, enlazado a través de un átomo C o heteroátomo a una cadena $-(CH_2)_r-$, alquilenos o alquenilenos, como se definió más arriba.

El término "polihaloalquilo" tal como se emplea aquí se refiere a un grupo "alquilo", según se define arriba, el cual incluye desde 2 a 9, preferiblemente desde 2 a 5, sustituyentes halo, tal como F o Cl, preferiblemente F, tal como CF_3CH_2 , CF_3 o $CF_3CF_2CH_2$. El término "polihaloalcoxi" tal como se emplea aquí se refiere a un grupo "alcoxi" o "alquiloxi" según se definió más arriba el cual incluye desde 2 a 9, preferiblemente desde 2 a 5, sustituyentes halo, tal como F o Cl, preferiblemente F, tal como CF_3CH_2O , CF_3O o $CF_3CF_2CH_2O$.

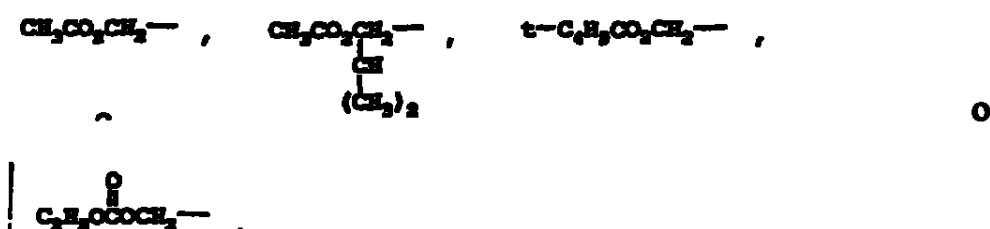
Todos los estereoisómeros de los compuestos de la presente invención están contemplados, bien en mezcla o bien en forma pura o sustancialmente pura. Los compuestos de la presente invención pueden tener centros asimétricos en cualquiera de los átomos de carbono, inclusive uno cualquiera o los sustituyentes R. Por consiguiente, los compuestos de fórmula I pueden existir en formas enantioméricas o diastereoméricas o en sus mezclas. Los procesos para preparación pueden utilizar racematos, enantiómeros o diastereómeros como materiales iniciales. Cuando se preparan productos diastereoméricos o enantioméricos, pueden separarse mediante métodos convencionales, por ejemplo, cristalización cromatográfica o fraccionaria.

El término "ésteres de profármaco" como se emplea aquí incluye ésteres y carbonatos formados haciendo reaccionar uno o más hidroxilos de compuestos de fórmula I con agentes acilantes alquilo, alcoxi, o arilo sustituido que emplean procedimientos conocidos por aquellas personas con habilidades en el arte para generar acetatos, pivalatos, metilcarbonatos, benzoatos y similares. Además, ésteres de profármaco que son conocidos

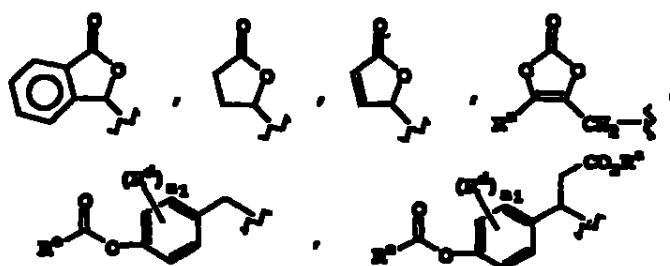
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en el arte para ésteres de ácido carboxílico y de fósforo tales como metilo, etilo, bencilo y similares.

Ejemplos de dichos ésters de profármaco incluyen



Otros ejemplos de ésteres de profármaco apropiados incluyen



en donde R^a puede ser H, alquilo (tal como metilo o t-butilo), arilalquilo (tal como bencilo) o arilo (tal como fenilo); R^d es H, alquilo, halógeno o alcoxi, R^e es alquilo, arilo, arilalquilo alcoxi, and n_1 es 0, 1 ó 2.

Donde los compuestos de estructura I están en forma de ácido, éstos pueden formar una sal farmacéuticamente aceptable, tal como sales de metal alcalino tales como litio, sodio o potasio; sales de metal alcalinotérreo tales como calcio o magnesio, así como zinc o aluminio y otros cationes tales como amonio, colina, dietanolamina, lisina (D o L), etilendiamina, t-butilamina, t-octilamina, tris-(hidroximetil)aminometano (TRIS), N-metil glucosamina (NMG), trietanolamina y dehidroabietilamina.

Compuestos de la invención pueden prepararse por el siguiente método.

Refiriéndose al Esquema de Reacción 1, la condensación de Knoevenagel de beta-ceto éster 1 de fácil obtención, donde R es alquilo inferior, con aldehído 2 bajo condiciones estándar (por ejemplo HOAc, piperidina, tolueno, reflujo) proporciona el correspondiente aducto 3. La 1,4-adición inducida por base de cetona 4 (por ejemplo, $\text{LiN}(\text{TMS})_2$ en THF

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o EtONa en EtOH) suministra el aducto 5, usualmente como una mezcla de diastereómeros.

La conversión de la 1,5-dicetona 5 en el ester de piridilo 6 puede efectuarse mediante tratamiento con una fuente de amoníaco (tal como NH_4OAc) en la presencia de un oxidante (tal como $\text{Cu}(\text{OAc})_2$ u oxígeno) en un solvente apropiado (tal como un haciendo refluir HOAc), o mediante reacción de 5 con hidrocloreuro de hidroxilamina en HOAc con calor. La funcionalidad éster de 6 puede reducirse por métodos estándar (LiAlH_4 , DIBAL, LiBH_4) para producir alcohol 7 el cual, subsiguientemente, puede convertirse en el haluro correspondiente 8 (por ejemplo, PBr_3 en CH_2Cl_2 , $\text{CBr}_4/\text{PPh}_3$ en CH_3CN , o POCl_3).

La conversión de haluro 8 en el compuesto de fósforo 9 donde W es Ph o alquilo se efectúa por tratamiento de 8 con W_2POEt en tolueno. La conversión de haluro 8 en el compuesto 9 donde W es OR (R es alquilo inferior) puede efectuarse por la reacción de 8 con $\text{HOP}(\text{OR})_2/\text{base}/\text{THF}$ o por reacción de Arbuzov con $\text{P}(\text{OR})_3$. La reacción de Witting entre 9 y aldehído 10 (aldehído 10 se ha descrito previamente en la patente estadounidense 5,686,433) puede efectuarse bajo condiciones estándar con base ($n\text{-BuLi}$, $\text{LiN}(\text{TMS})_2$, LDA) en un solvente apropiado (THF, Et_2O , tolueno, DMPU) para proporcionar el aducto 11.

El tratamiento de 11 bajo condiciones ácidas (por ejemplo, TFA, HCl) efectúa la conversión de 11 en lactona Ia.

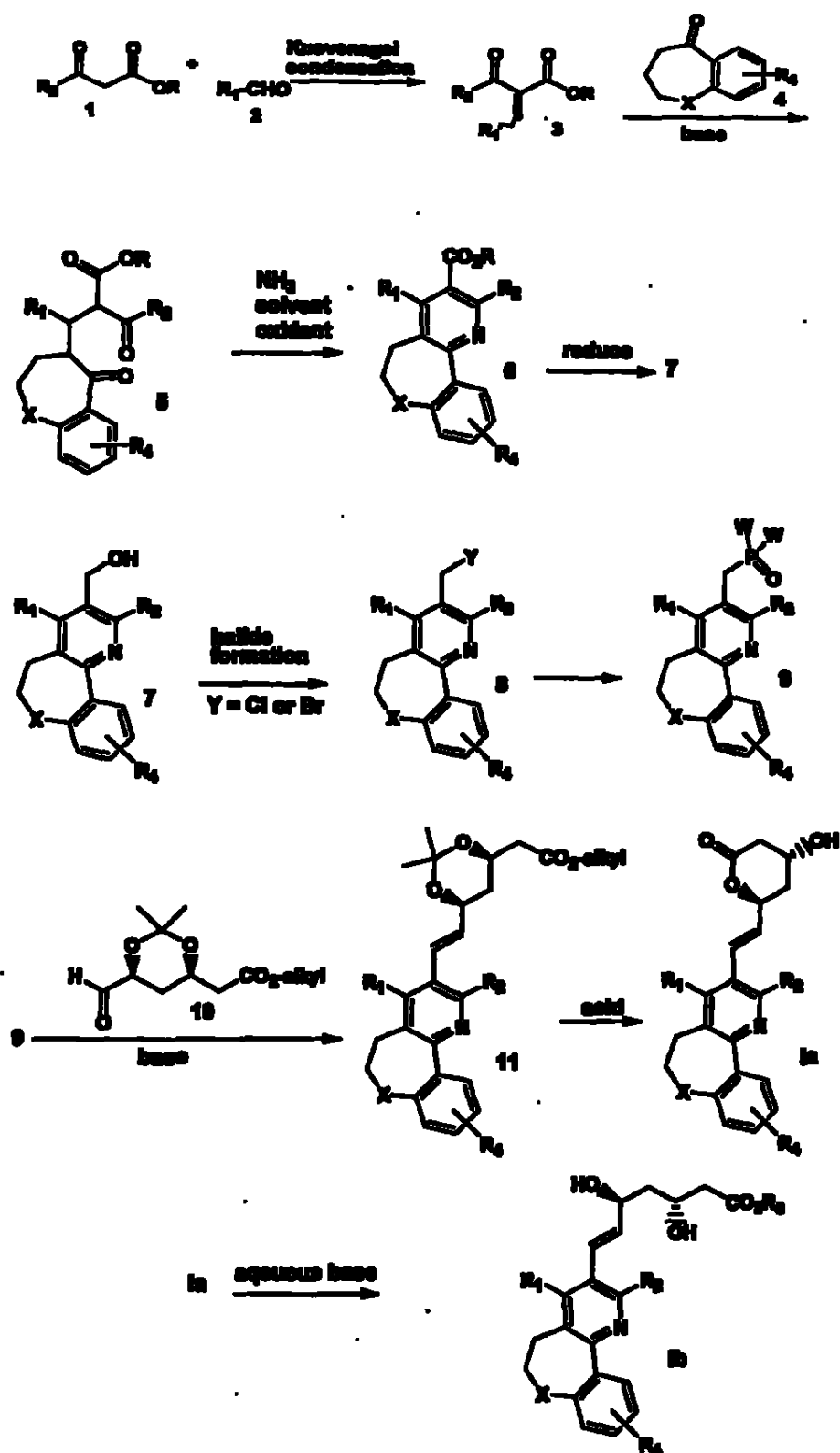
La saponificación de Ia en Ib (donde R_3 es metal alcalino, o metal alcalinotérreo) puede efectuarse por tratamiento de Ia con base acuosa o acidificarse subsiguientemente para producir Ib donde R_3 es H. Adicionalmente, Ia puede tratarse con un alcohol del tipo R_3OH bajo condiciones básicas para formar los ésteres correspondientes de Ib.

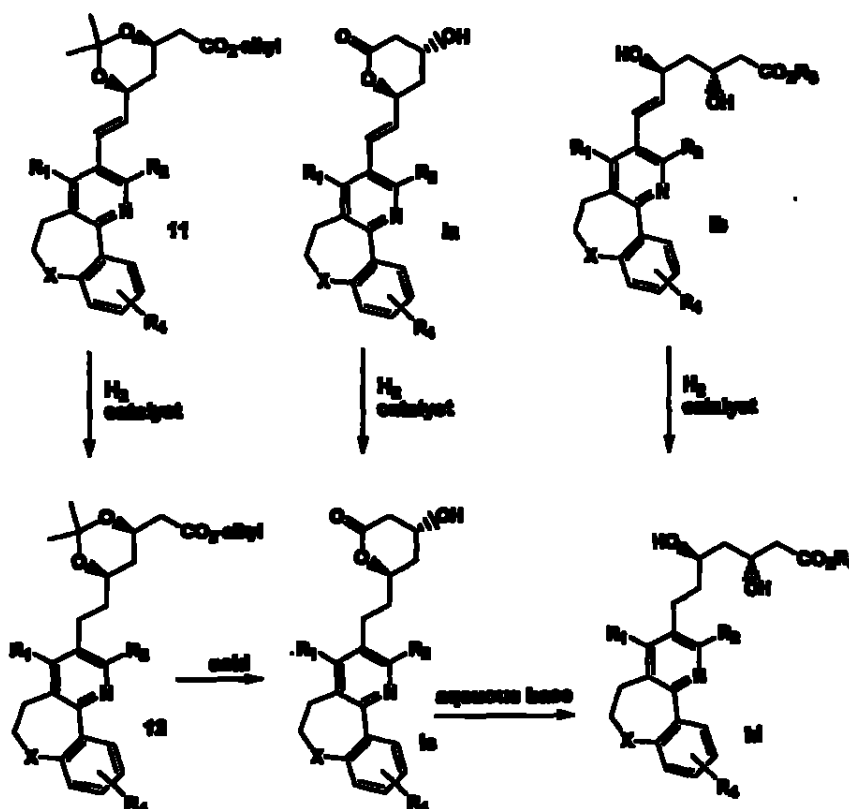
Tal como se observa en el Esquema de Reacción 2, los derivados saturados del compuesto I (donde --- es $\text{CH}_2\text{---CH}_2$) se obtienen por hidrogenación catalítica (Pd/C , Pt/C , $\text{Pd}(\text{OH})_2$) de 11, Ia, o Ib para proporcionar 12, Ic, o Id, respectivamente. El compuesto 12 puede

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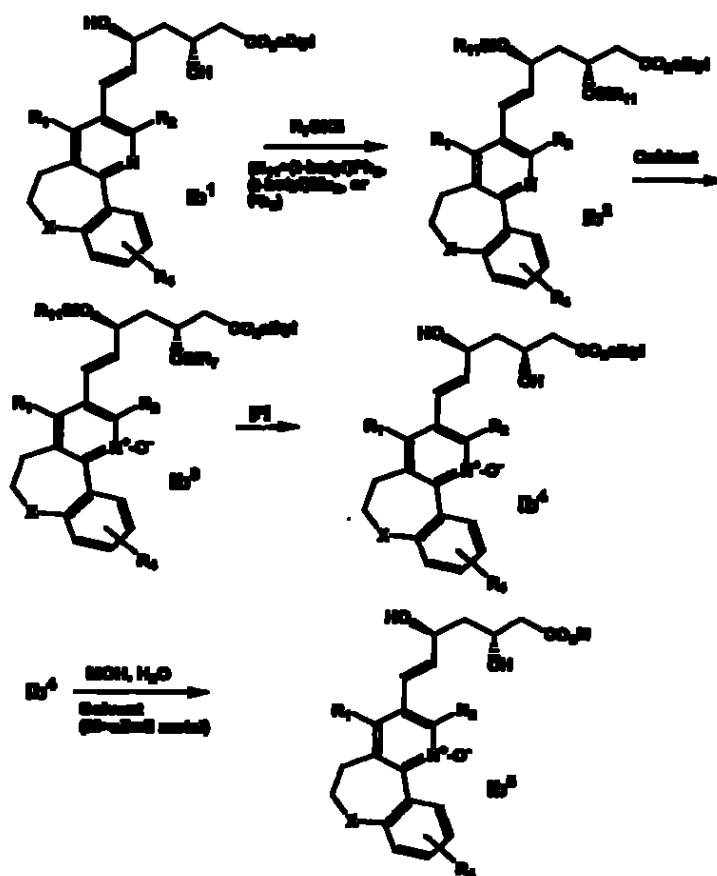
convertirse en Ic y Id siguiendo los métodos anteriormente descritos para la conversión del compuesto 11 en Ia y Ib.

ESQUEMA 1



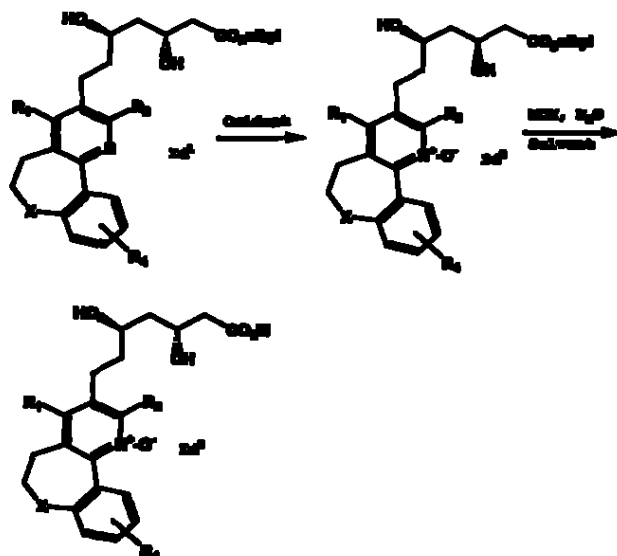
ESQUEMA 2

La síntesis de compuestos I en donde $\text{---}\text{CH}=\text{CH}\text{---}$ es $\text{CH}=\text{CH}$ y n es 1, se describe en Esquema 3. Bis-sililación de compuesto Ib¹ con un cloruro de sililo voluminoso (por ejemplo, ClSi(t-butil)Ph₂, ClSi(t-butil)Me₂, ClSiPh₃) en la presencia de una base apropiada (por ejemplo, TEA, imidazol, piridina) y solvente (por ejemplo, CH₂Cl₂, THF) proporciona el compuesto Ib². El tratamiento de Ib² con oxidantes tales como m-CPBA o CF₃CO₃H en un solvente apropiado tal como CH₂Cl₂ o HOAc proporciona N-óxido Ib³. Desililación de Ib³ (TBAF/HOAc/THF o HF/CH₃CN) produce Ib⁴ que puede saponificarse en Ib⁵ usando soluciones acuosas de un metal hidróxido en un solvente apropiado (por ejemplo, MeOH, dioxano).

ESQUEMA 3

Adicionalmente, el compuesto Id¹ puede oxidarse y saponificarse, como se define más arriba, para proporcionar compuestos I, en donde CH_2CH_2 es CH_2CH_2 y n es 1 (por ejemplo, compuestos Id² e Id³) como se muestra en Esquema 4.

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ESQUEMA 4

Se apreciará que en los Esquemas 1 a 4, con respecto a los compuestos 4, 5, 6, 7, 8, 9, 11, Ia, Ib, 12, Ic, Id, Ib¹, Ib², Ib³, Ib⁴, Ib⁵, Id¹, Id² e Id³, aunque los sustituyentes R₉ y R₁₀, como se definieron más arriba, no se incluyen en estos compuestos, los Esquemas 1 a 4 pueden llevarse a cabo donde dichos compuestos incluyen los sustituyentes R₉ y R₁₀.

Esquema 5 representa un método preferido para preparar el inhibidor de HMG CoA reductasa de fórmula I de la invención utilizando la reacción de olefinación Julia-Kocienski que emplea 4-piridil carboxilaldehído (18) y sulfona quiral (16). El intermediario *trans* deseado (19) se aísla en alto rendimiento y pureza óptica, el cual se convierte en el producto final de la invención. Como se apreciará, la sulfona quiral (16) un intermediario clave en el paso Julia-Kocienski, se prepara en tres pasos a partir del alcohol Kaneka (12), disponible en el comercio, mediante triflato (13) e intermediario sulfuro (15).

Refiriéndose al esquema 5, el tratamiento de alcohol quiral disponible en el comercio (12) con anhídrido triflico y trietilamina en diclorometano a baja temperatura (por ejemplo, 0 a -30°C) produce triflato (13). Pueden emplearse otras bases de amina o piridina. Triflato (13) (sin estar aislado) se lleva al siguiente paso sin más purificación. Una solución de cloruro de

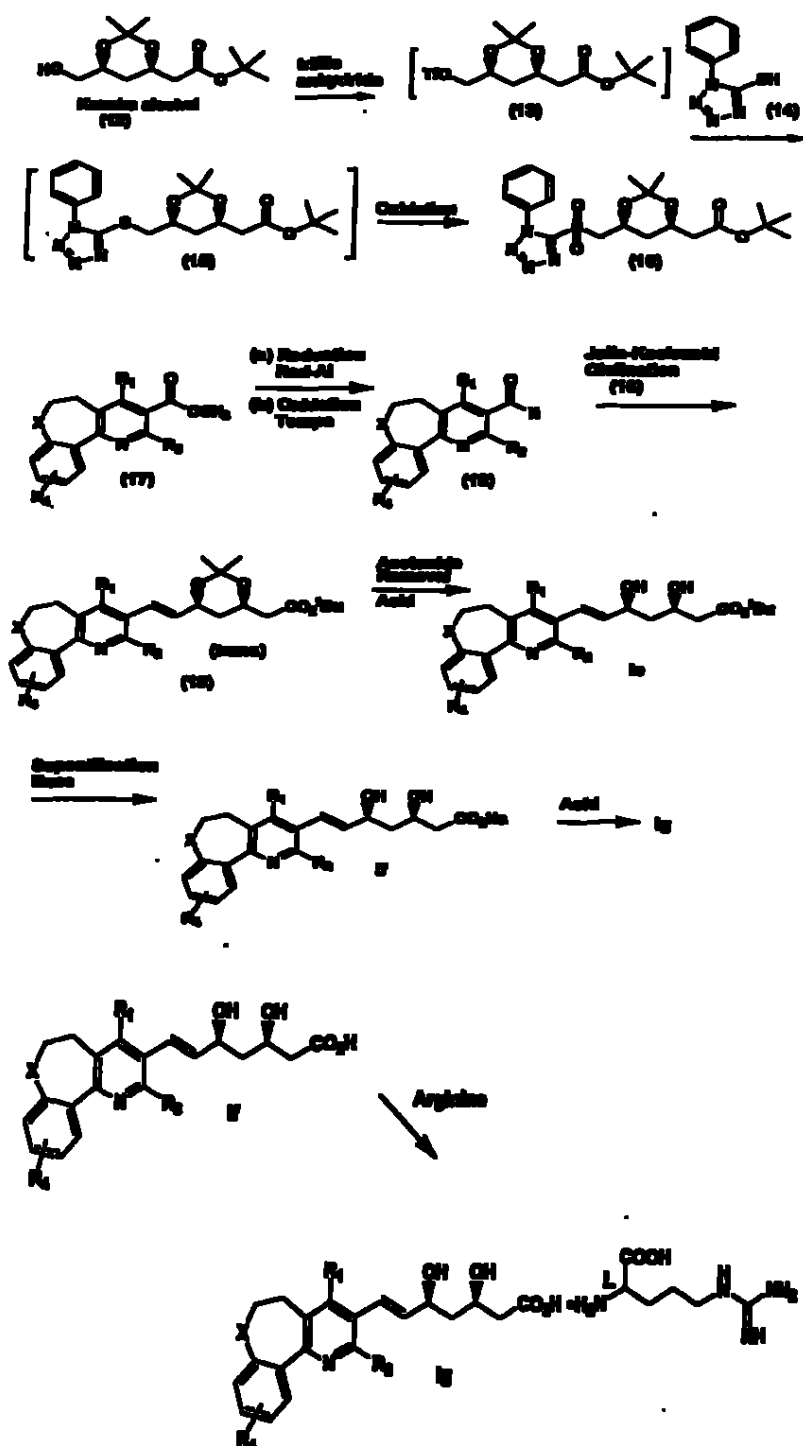
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metileno de triflato (13) se trata con 1-fenil-1H-tetrazol-5-tiol (14) para proporcionar el sulfuro quiral (15), el cual se oxida con peróxido de hidrógeno en la presencia de tetrahidrato heptamolibdato de amoni catalítico para producir sulfona cristalina (16). Puede emplearse otro oxidante, tal como ácido m-cloro-p-benzoico (mCPBA).

La adición de LiHMDS o NaHMDS a una mezcla de sulfona (16) y carboxilaldehído de piridina (18) en THF a baja temperatura (−78 a −35°C) proporciona olefina *trans* (19) en alta diastereoselectividad (>99%).

El aldehído de piridina (18) se obtiene como una forma de sólido cristalino del éster correspondiente (17). La reducción del éster (17) con Red-Al seguida por oxidación con tempo (2,2,6,6-tetrametil-1-piperidiniloxi) proporciona el aldehído (18) en alto rendimiento. El compuesto final Ie de la invención se prepara en un procedimiento en marmita partiendo de (19) sin aislar intermedios de ninguna clase. El retiro de acetonido bajo condición ácida proporciona diol Ie de la invención el cual, luego de tratamiento adicional con hidróxido de sodio, produce la sal de sodio del ácido If de la invención. El tratamiento subsiguiente de If con ácido, seguido por la adición de arginina, produce sal de arginina cristalina de la invención Ig.

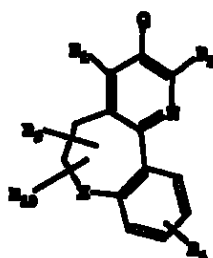
ESQUEMA 5



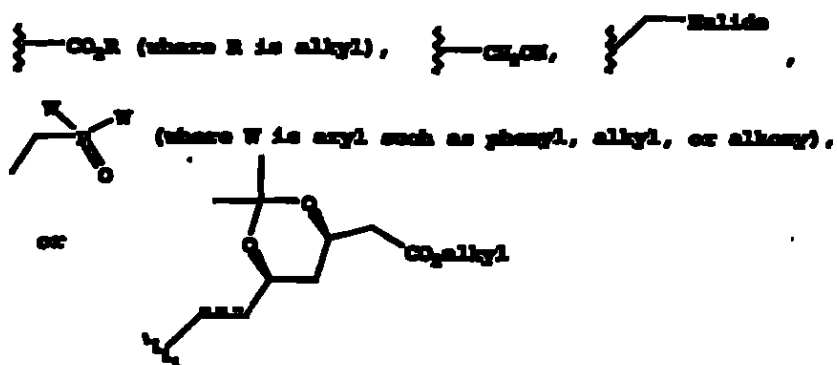
Además, de acuerdo con la presente invención, los intermedios 6, 7, 8, 9, 11 y 12 son compuestos novedosos y forman parte de la presente invención. Estos compuestos tienen la estructura general

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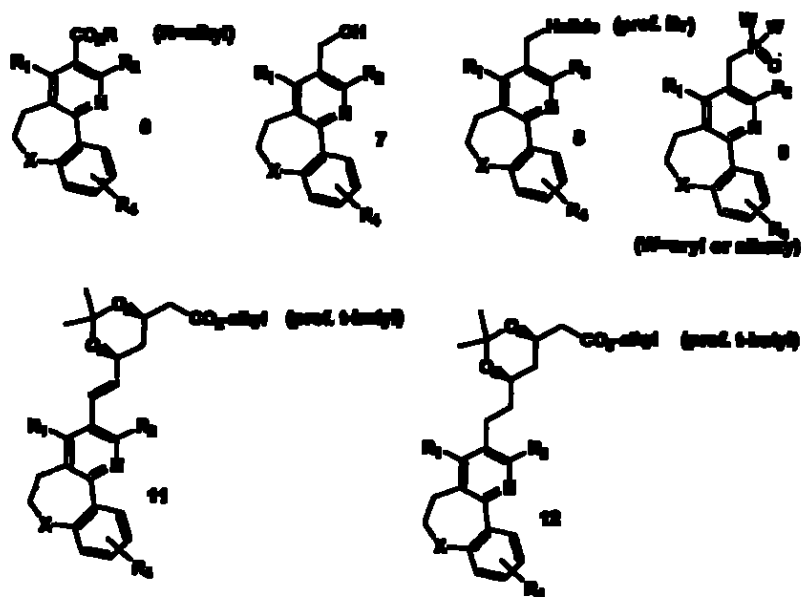
II



en donde X es O, S o NR₇, R₁, R₂, R₄, R₇, R₉ y R₁₀ son como se definieron más arriba, Q es



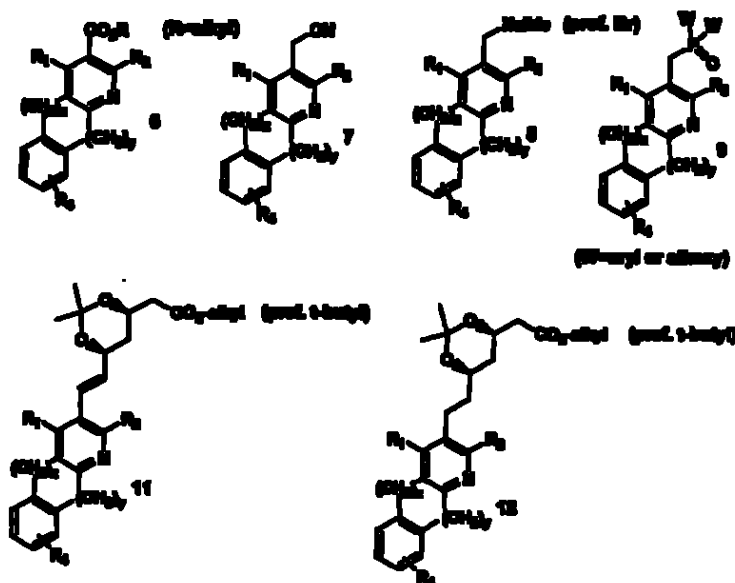
Por lo tanto, los intermedios de la invención pueden tener las siguientes estructuras:



Compuestos 6, 7, 8, 9, 11 y/o 12 pueden incluir sustituyentes R₉ y R₁₀.

Compuestos que contienen cadenas laterales de dominio de enlace HMG-CoA de dihidroxi ácido pueden prepararse en forma homoquiral, la cual se prefiere, o pueden prepararse como mezclas racémicas (3S*, 5R*) y pueden resolverse posteriormente para obtener el isómero 3S, 5R.

Por lo tanto, los intermedios de la invención pueden tener las siguientes estructuras:



Compuestos que contienen cadenas laterales de dominio de enlace HMG-CoA de dihidroxi ácido pueden prepararse en forma homoquiral, la cual se prefiere, o pueden prepararse como mezclas racémicas (3S*, 5R*) y pueden resolverse posteriormente para obtener el isómero 3S, 5R.

Los compuestos de la invención son inhibidores de 3- hidroxil-3- metil-glutaril coenzima A (HMG-CoA) reductasa y, en consecuencia, son útiles en inhibir la biosíntesis de colesterol y/o en reducir triglicéridos, en una manera similar a atorvastatina, pravastatina, simvastatina, lovastatina, cerivastatina, visastatina (o rosuvastatina) (Astra Zeneca ZD4522), fluvastatina, itavastatina (o pitavastatina) y similares.

Un aspecto más de la presente invención es una composición farmacéutica que contiene por lo menos uno de los compuestos de fórmula I de la presente invención en asociación con un vehículo farmacéutico o diluyente. La composición farmacéutica puede formularse empleando

AD

vehículos sólidos convencionales de diluyentes y aditivos farmacéuticos de un tipo apropiado al modo de administración deseada. Los compuestos pueden administrarse por una vía oral, por ejemplo, en la forma de tabletas, cápsulas, gránulos o polvos, o pueden administrarse por una vía parenteral en la forma de preparaciones inyectables. Dichas formas de dosificación contienen desde 0.1 a 1500 mg de compuesto activo por dosificación, para uso en el tratamiento. La dosis a administrarse depende de la dosis unitaria, los síntomas, y la edad y el peso corporal del paciente.

Los compuestos de la presente invención pueden administrarse en una manera similar como compuestos conocidos sugeridos para uso en inhibir la biosíntesis de colesterol, tales como pravastatina, lovastatina, simvastatina, visastatina (o rosuvastatina), atorvastatina, cerivastatina, fluvastatina, itavastatina (o pitavastatina), y similares, en especies mamíferas tales como humanos, perros, gatos y similares. En consecuencia, los compuestos de la invención pueden administrarse en una cantidad desde alrededor de 0.1 to 500 mg en una dosis única o en la forma de dosis individuales desde 1 a 4 veces al día, preferiblemente 0.2 a 100 mg diariamente o en forma de liberación sostenida.

Los inhibidores de HMG CoA reductasa de fórmula I pueden emplearse en combinación con todos los agentes terapéuticos que son útiles en combinación con inhibidores de HMG CoA reductasa.

Por lo tanto, donde se desee, los compuestos de estructura I pueden emplearse en combinación con uno o más agentes hipolipidémicos o agentes reductores de lípido, o agentes de lípidos, o agentes moduladores de lípido, y/o uno o más otros tipos de agentes terapéuticos inclusive agentes antidiabéticos, agentes anti-obesidad, agentes antihipertensivos, inhibidores de agregación de plaquetas, agentes anti-Alzheimer, agentes anti-demencia, agentes anti-osteoporosis, y/o agentes terapéuticos de reemplazo de hormonas, y/o otros agentes terapéuticos, y/o otros agentes cardiovasculares (inclusive agentes anti-anginales, agentes anti-arrítmicos, agentes anti-aterosclerosis, agentes anti-inflamatorios, agentes anti-plaquetas, agentes anti-falla cardíaca), agentes anti-cáncer, agentes anti-infecciosos, agentes

de reemplazo de hormonas, secretagogos hormonales de crecimiento, moduladores selectivos de receptor andrógeno, y/o otros agentes terapéuticos que pueden administrarse oralmente en la misma forma de dosificación o en una forma separada de dosificación oral, o por inyección.

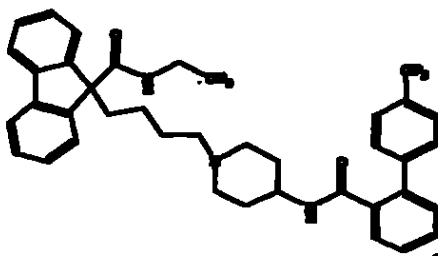
El agente hipolipidémico o agente reductor de lípido u otro agente de lípidos o agente modulador de lípido que pueden emplearse opcionalmente en combinación con los compuestos de fórmula I de la invención pueden incluir 1, 2, 3 o más inhibidores MTP, inhibidores de HMG CoA reductasa, inhibidores de escualeno sintetasa, α agonistas PPAR, α/γ agonistas duales PPAR, agonistas δ PPAR, derivados de ácido fibríco, inhibidores ACAT, inhibidores de lipoxigenasa, inhibidores de absorción de colesterol, inhibidores de co-transportador de ácido biliar/ Na^+ ileal, reguladores ascendentes de actividad de receptor LDL, inhibidores de proteína de transferencia de éster colesterílico, secuestrantes de ácido biliar, y/o ácido nicotínico y sus derivados.

Los inhibidores MTP empleados aquí incluyen los inhibidores MTP divulgados en la Patente estadounidense No. 5,595,872, Patente estadounidense No. 5,739,135, Patente estadounidense No. 5,712,279, Patente estadounidense No. 5,760,246, Patente estadounidense No. 5,827,875, Patente estadounidense No. 5,885,983 y Solicitud estadounidense Serial No. 09/175,180 radicada el 20 de octubre de 1998, ahora Patente estadounidense No. 5,962,440. Se prefieren cada uno de los inhibidores MTP divulgados en cada una de las patentes y solicitudes mencionadas arriba.

Todas las patentes y solicitudes estadounidenses anteriores se incorporan aquí por referencia.

Los inhibidores MTP más preferidos a emplearse de acuerdo con la presente invención incluyen de inhibidores MTP preferidos como los que se exponen en las Patentes estadounidenses Nos. 5,739,135 y 5,712,279, y Patente estadounidense No. 5,760,246.

El inhibidor MTP más preferido es 9-[4-[4-[[2-(2,2,2-trifluoroetoxi)benzoil]amino]-1-piperidinil]butil]-N-(2,2,2-trifluoroetil)-9H-fluoren-9-carboxamida.



El agente hipolipidémico puede ser un inhibidor de HMG CoA reductasa que incluye, pero no se limita a, mevastatina y compuestos relacionados como se divulgan en la Patente estadounidense No. 3,983,140, lovastatina (mevinolina) y compuestos relacionados como se divulgan en la Patente estadounidense No. 4,231,938, pravastatina y compuestos relacionados como se divulgan en la Patente estadounidense No. 4,346,227, simvastatina y compuestos relacionados como se divulgan en las Patentes estadounidenses Nos. 4,448,784 y 4,450,171. Otros inhibidores de HMG CoA reductasa que pueden emplearse aquí incluyen, pero no se limitan a, fluvastatina, divulgada en la Patente estadounidense No. 5,354,772, cerivastatina divulgada en las Patentes estadounidenses Nos. 5,006,530 y 5,177,080, atorvastatina divulgada en las Patentes estadounidenses Nos. 4,681,893, 5,273,995, 5,385,929 y 5,686,104, pitavastatina (nisvastatina de Nissan/Sankyo (NK-104) o itavastatina), divulgado en la Patente estadounidense No. 5,011,930, Shionogi-Astra/Zeneca rosuvastatin (visastatin (ZD-4522)) divulgado en la Patente estadounidense No. 5,260,440, y compuestos relacionados de estatina divulgados en la Patente estadounidense No. 5,753,675, análogos de pirazol de derivados de mevalonolactona como se divulgan en la Patente estadounidense No. 4,613,610, análogos de indeno de derivados de mevalonolactona como se divulgan en la solicitud PCT WO 86/03488, 6-[2-(sustituido-pirrol-1-il)-alquil]piran-2-onas y sus derivados como se divulga en la Patente estadounidense N . 4,647,576, SC-45355 de Searle (un derivado de ácido



pentandiólico 3-sustituido) dicloroacetato, análogos de imidazol de mevalonolactona como se divulgan en la solicitud PCT WO 86/07054, derivados de ácido 3-carboxi-2-hidroxi-propan-fosfónico como se divulgan en la Patente francesa No. 2,596,393, pirrol 2,3-disustituido, derivados de furano y tiofeno como se divulgan en la solicitud de Patente europea No. 0221025, análogos de naftilo de mevalonolactona como se divulgan en la Patente estadounidense No. 4,686,237, octahidronaftalenos tales como los divulgados en la Patente estadounidense No. 4,499,289, ceto análogos de mevinolina (lovastatina) como se divulgan en la solicitud de Patente europea No. 0,142,146 A2, y derivados de quinolina y piridina divulgados en las Patentes estadounidenses Nos. 5,506,219 y 5,691,322.

Además, en GB 2205837 se divulgan compuestos de ácido fosfinico útiles en inhibir HMG CoA reductasa apropiados para uso aquí.

Los inhibidores de escualeno sintetasa adecuados para uso aquí incluyen, pero no se limitan a, α -fosfono-sulfonatos divulgados en la Patente estadounidense No. 5,712,396, los divulgados por Biller y colaboradores, J. Med. Chem., 1988, vol. 31, No. 10, páginas 1869-1871, inclusive (fosfinil-metil)fosfonatos isoprenoides así como otros inhibidores conocidos de escualeno sintetasa, por ejemplo, como se divulgan en la Patente estadounidense No. 4,871,721 y 4,924,024 y en Biller, S.A., Neuenschwander, K., Ponpipom, M.M., y Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

Adicionalmente, otros inhibidores de escualeno sintetasa apropiados para uso aquí incluyen los pirofosfatos terpenoides divulgados por P. Ortiz de Montellano y colaboradores, J. Med. Chem., 1977, 20, 243-249, el análogo A de farnesil difosfato y análogos de presqualeno pirofosfato (PSQ-PP) como se divulgan por Carey y Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, fosfinil fosfonatos reportados por McClard, R.W. y colaboradores, J.A.C.S., 1987, 109 5544 y ciclopropanos reportados por Capson, T.L., PhD dissertation, junio, 1987, Dept. Med. Chem. U de Utah, Extracto, Tabla de Contenido, página 16, 17, 40-43, 48-51, Sumario.

Otros agentes hipolipidémicos adecuados para uso aquí incluyen, pero no se limitan a, derivados de ácido fibríco, tales como fenofibrato, gemfibrozil, clofibrato, bezafibrato, ciprofibrato, clinofibrato y similares, probucol, y compuestos relacionados como se divulgan en la Patente estadounidense No. 3,674,836, prefiriéndose probucol y gemfibrozil, secuestrantes de ácido biliar tales como colestiramina, colestipol y DEAE-Sephadex (Secholex®, Policexide®) y cholestagel (Sankyo/Geltex), así como lipostabil (Rhone-Poulenc), Eisai E-5050 (un derivado de etanolamina N-sustituido), imanixil (HOE-402), tetrahidrolipstatina (THL), istigmastanilfosforilcolina (SPC, Roche), aminociclodextrina (Tanabe Seiyoku), Ajinomoto AJ-814 (derivado de azuleno), melinamida (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 y CL-283,546 (derivados de urea disustituidos), ácidos nicotínicos (niacina), acipimox, acifran, neomicina, ácido p-aminosalicílico, aspirina, derivados de poli(dialilmetilamina) tales como se divulgan en la Patente estadounidense No. 4,759,923, cloruro de poli(dialildimetilamonio) de amina cuaternaria y ionenos tal como se divulgan en la Patente estadounidense No. 4,027,009, y otros agentes reductores conocidos de colesterol del suero.

El otro agente hipolipidémico puede ser un inhibidor ACAT (que tiene también actividad anti-aterosclerosis) tal como se divulga en *Drugs of the Future* 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, CI-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters ", Nicolosi y colaboradores, *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, *Cardiovasc. Drug Rev.* (1998), 16 (1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., y colaboradores, *Bioorg. Med. Chem. Lett.* (1996), 6 (1), 47-50; " ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause y colaboradores,

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 y colaboradores, Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of acyl-CoA: cholesterol acyltransferase (ACAT) as hypocholesterolemic agents". 6. El primer inhibidor ACAT soluble en agua con actividad reguladora de lípido. Inhibidores de acil-CoA: colesterol aciltransferasa (ACAT). 7. "Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout y colaboradores, Chemtracts: Org. Chem. (1995), 8(6), 359-62, o TS-962 (Taisho Pharmaceutical Co. Ltd), así como F-1394, CS-505, F-12511, HL-004, K-10085 y YIC-C8-434.

El agente hipolipidémico puede ser un regulador ascendente de actividad de receptor LDL tal como MD-700 (Taisho Pharmaceutical Co. Ltd) y LY295427 (Eli Lilly).

El agente hipolipidémico puede ser un inhibidor de absorción de colesterol preferiblemente SCH48461 de Schering-Plough (ezetimibe) así como los divulgados en Atherosclerosis 115, 45-63 (1995) y J. Med. Chem. 41, 973 (1998).

El otro agente de lípido o agente modulador de lípido puede ser un inhibidor de proteína de transferencia de colesterol (CETP) tal como CP-529,414 de Pfizer así como los divulgados en WO/0038722 y en EP 818448 (Bayer) y EP 992496, y SC-744 y SC-795 de Pharmacia, así como CETi-1 y JTT-705.

El agente hipolipidémico puede ser un inhibidor de cotransportador de ácido biliar/ Na^+ ileal tal como el divulgado en Drugs of the Future, 24, 425-430 (1999).

El inhibidor de liasa de citrato ATP que puede emplearse en la combinación de la invención puede incluir, por ejemplo, los divulgados en la Patente estadounidense No. 5,447,954.

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El otro agente de lípido comprende además un compuesto de fitoestrógeno como se divulga en WO 00/30665, inclusive proteína aislada de soya, concentrado de proteína de soya o harina de soya, así como un isoflavone tal como genisteína, daidzeína, gliciteína o equol, o fitosteroles, fitostanol o tocotrienol como se divulgan en WO 2000/015201;

un inhibidor de absorción de beta-lactama colesterol tal como se divulga en EP 675714;

un regulador ascendente HDL tal como un agonista LXR, un α -agonista PPAR y/o un agonista FXR;

un inhibidor de α -glucosidasa, un inhibidor de aldosa reductasa y/o un promotor de catabolismo LDL tal como se divulga en EP 1022272;

un inhibidor de intercambio de protón de sodio tal como se divulga en DE 19622222;

un inductor de receptor LDL o un glicósido esteroide tal como el divulgado en la Patente estadounidense No. 5,698,527 y GB 2304106;

un anti-oxidante tal como beta-caroteno, ácido ascórbico, α -tocoferol o retinol como se divulga en WO 94/15592 así como vitamina C y un agente antihomocisteína tal como ácido fólico, un folato, vitamina B6, vitamina B12 y vitamina E;

isoniacida como se divulga en WO 97/35576;

un inhibidor de absorción de colesterol, un inhibidor de HMG-CoA sintasa, o un inhibidor de lanosterol demetilasa como se divulga en WO 97/48701;

un δ agonista PPAR para tratar dislipidemia;

o una proteína-I (SREBP-1) de enlace de elemento regulador de esterol como se revela en WO 2000/050574, por ejemplo, un esfingolípido, tal como ceramida, o esfingomielenasa neutral (N-SMase) o su fragmento.

Agentes hipolipidémicos preferidos son pravastatina, lovastatina, simvastatina, atorvastatina, fluvastatina, cerivastatina, pitavastatina y rosuvastatina, así como niacina y/o cholestagel.

La patentes estadounidenses menci nadas más arriba se incorporan aquí por referencia. Las cantidades y dosificaciones empleadas serán como se indican la Physician's Desk Reference y/o en las patentes expuestas más arriba o, de lo contrario, como se conozca en el arte.

Los compuestos de fórmula I de la invención se emplearán en una proporción de peso al agente hipolipidémico (donde presente), en el rango desde alrededor de 500:1 hasta alrededor de 1:500, preferiblemente desde alrededor de 100:1 hasta alrededor de 1:100.

La dosis administrada tiene que ajustarse cuidadosamente de acuerdo con la edad, peso y trastorno del paciente, así como la vía de administración, forma de dosificación y régimen y el resultado deseado.

Las dosificaciones y formulaciones para el agente hipolipidémico u otro agente de lípido o agente modulador de lípido serán como se divulgan en las diferentes patentes y solicitudes comentadas más arriba.

Las dosificaciones y formulaciones para el otro agente hipolipidémico u otro agente de lípido o agente modulador de lípido a emplearse, donde sea pertinente, serán como se expone en la última edición de la Physicians' Desk Reference.

Para administración oral, un resultado satisfactorio puede obtenerse empleando un inhibidor MTP en una cantidad en el rango de desde alrededor de 0.01 mg hasta alrededor de 500 mg y preferiblemente desde alrededor de 0.1 mg hasta alrededor de 100 mg, una o dos veces diarias.

Una forma de dosis oral preferida, tal como tabletas o cápsulas, contendrá el inhibidor MTP en una cantidad de desde alrededor de 1 hasta alrededor de 500 mg, preferiblemente desde alrededor de 2 a 400 mg, y más preferiblemente desde alrededor de 5 hasta alrededor de 250 mg, una o dos veces diarias.

Para administración oral, un resultado satisfactorio puede obtenerse empleando un inhibidor de HMG CoA reductasa, por ejemplo, pravastatina, lovastatina, simvastatina, atorvastatina, fluvastatina o cerivastatina en dosificaciones empleadas como se indica en la Physician's Desk Reference,

tal como en una cantidad en el rango de desde alrededor de 1 a 2000 mg, y preferiblemente desde alrededor de 4 hasta alrededor de 200 mg.

El inhibidor de escualeno sintetasa puede emplearse en dosificaciones en una cantidad en el rango de desde alrededor de 10 mg hasta alrededor de 2000 mg y preferiblemente desde alrededor de 25 mg hasta alrededor de 200 mg.

Una forma de dosificación oral preferida, tal como tabletas o cápsulas, contendrá el inhibidor de HMG CoA reductasa en una cantidad desde alrededor de 0.1 hasta alrededor de 100 mg, preferiblemente desde alrededor de 0.5 hasta alrededor de 80 mg, y más preferiblemente desde alrededor de 1 hasta alrededor de 40 mg.

Una forma de dosificación oral preferida, tal como tabletas o cápsulas, contendrá el inhibidor de escualeno sintetasa en una cantidad de desde alrededor de 10 hasta alrededor de 500 mg, preferiblemente desde alrededor de 25 hasta alrededor de 200 mg.

El agente anti-aterosclerótico incluye un inhibidor de lipoxigenasa que comprende un inhibidor de lipoxigenasa inclusive un inhibidor de lipoxigenasa 15 (15- LO), tal como derivados de benzimidazol como se divulgan en WO 97/12615, inhibidores de 15-LO como se divulgan en WO 97/12613, isotiazolonas como se divulgan en WO 96/38144, e inhibidores de 15-LO como se divulgan por Sendobry y colaboradores "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective, 15-lipoxygenase inhibitor lacking significant antioxidant properties" Brit. J. Pharmacology (1997) 120, 1199-1206, y Cornicelli y colaboradores, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11-20.

Los compuestos de fórmula I y el agente hipolipidémico pueden emplearse juntos en la misma forma de dosificación oral o en formas de dosificación oral separadas tomadas al mismo tiempo.

Las composiciones descritas arriba pueden administrarse en las formas de dosificación, ya descritas, en dosis únicas o divididas de una a



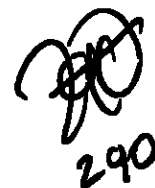
cuatro veces diarias. Puede ser aconsejable iniciar a un paciente sobre la base de una combinación de dosis bajas y subir gradualmente a una combinación de dosis altas.

El agente antidiabético que puede emplearse opcionalmente en combinación con el inhibidor de HMG-CoA reductasa de fórmula I puede ser 1, 2, 3 ó más agentes antidiabéticos o agentes antihiperglicémicos inclusive secretagogos de insulina o sensibilizadores de insulina, los cuales pueden incluir biguanidas, sulfonilureas, inhibidores de glucosidasa, inhibidores de aldosa reductasa, γ agonistas PPAR tales como tiazolidindionas, α agonistas PPAR (tales como derivados de ácido fibríco), δ antagonistas o agonistas PPAR, inhibidores α P2, α/γ agonistas duales PPAR, inhibidores de dipeptidil peptidasa IV (DP4), inhibidores SGLT2, inhibidores de glicógeno fosforilasa, y/o meglitinidas, así como insulina, y/o inhibidor de péptido-1 (GLP-1) similar del glucagón, y/o un inhibidor PTP-1B (inhibidor de proteína tirosina fosfatasa-1B).

El agente antidiabético puede ser un agente antihiperglicémico oral preferiblemente una biguanida tal como metformina o fenformina o sus sales, preferiblemente metformina HCl.

Donde el agente antidiabético es una biguanida, los compuestos de estructura I se emplearán en una proporción de peso a biguanida en el rango desde alrededor de 0.001:1 hasta alrededor de 10:1, preferiblemente desde alrededor de 0.01:1 hasta alrededor de 5:1.

Igualmente, el agente antidiabético puede ser preferiblemente una sulfonilurea tal como glyburida (también conocida como glibenclamida), glimepirida (divulgada en la Patente estadounidense No. 4,379,785), glipizida, gliclazida o clorpropamida, otras sulfonilureas conocidas u otros agentes antihiperglicémicos que actúan en el canal ATP-dependiente de las células β , prefiriéndose gliburida y glipizida, que pueden administrarse en las mismas formas o en formas de dosificación oral separadas.



Los compuestos de la estructura I se emplearán en una proporción de peso a la sulfonilurea en el rango desde alrededor de 0.01:1 hasta alrededor de 100:1, preferiblemente desde alrededor de 0.02:1 hasta alrededor de 5:1.

El agente antidiabético oral puede ser igualmente un inhibidor de glucosidasa tal como acarbosa (divulgado en la Patente estadounidense No. 4,904,769) o miglitol (divulgado en la Patente estadounidense N. 4,639,436), que puede administrarse en las mismas formas o en formas de dosificación oral separadas.

Los compuestos de estructura I se emplearán en una proporción de peso al inhibidor de glucosidasa en el rango desde alrededor de 0.01:1 hasta alrededor de 100:1, preferiblemente desde alrededor de 0.05:1 hasta alrededor de 10:1.

Los compuestos de estructura I pueden emplearse en combinación con un γ agonista PPAR tal como un agente anti-diabético oral de tiazolidindiona u otros sensibilizadores de insulina (que tiene un efecto de sensibilidad a la insulina en pacientes NIDDM) tal como troglitazona (Warner- Lambert's Rezulin®, divulgado en la Patente estadounidense No. 4,572,912), rosiglitazona (SKB), pioglitazona (Takeda), Mitsubishi's MCC-555 (divulgado en la Patente estadounidense No. 5,594,016), Glaxo-Welcome's GL-262570, englitazona (CP-68722, Pfizer) o darglitazona (CP-86325, Pfizer, isaglitazona (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), o YM-440 (Yamanouchi), preferiblemente rosiglitazona y pioglitazona.

Los compuestos de estructura I se emplearán en una proporción de peso a la tiazolidindiona en una cantidad en el rango desde alrededor de 0.01:1 hasta alrededor de 100:1, preferiblemente desde alrededor de 0.05:1 hasta alrededor de 10:1.

La sulfonilurea y los γ agonistas en cantidades de menos de alrededor de 150 mg de agente antidiabético oral pueden incorporarse en una tableta única con los compuestos de estructura I.



Los compuestos de la estructura I pueden emplearse asimismo en combinación con un agente antihiperlipémico tal como insulina o con el péptido-I (GLP-I) similar del glucagón o mimético tal como GLP-I(1-36) amida, GLP-I(7-36) amida, GLP-I(7-37) (como se divulgan en la Patente estadounidense No. 5,614,492 a Habener, cuya divulgación se incorpora aquí por referencia), así como AC2993 (Amileno) y LY-315902 (Lilly), que pueden administrarse mediante inyección, intranasal, inhalación o mediante dispositivos transcutáneos o bucales.

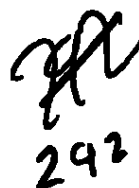
Donde presentes, metformina, las sulfonilureas, tales como glyburida, glimepirida, glipirida, glipizida, clorpropamida y gliclazida y los inhibidores de glucosidasa acarbosa o miglitol o insulina (inyectable, pulmonar, bucal, u oral) pueden emplearse en formulaciones como las descritas arriba y en cantidades y dosificación como se indica en la Physician's Desk Reference (PDR).

Donde presentes, metformina o su sal puede emplearse en cantidades en el rango desde alrededor de 500 hasta alrededor de 2000 mg/día los cuales pueden administrarse en dosis únicas o divididas una a cuatro veces diarias.

Donde presentes, el agente anti-diabético PPAR puede emplearse en cantidades en el rango desde alrededor de 0.01 hasta alrededor de 2000 mg/día los cuales pueden administrarse en dosis únicas o divididas una a cuatro veces diarias.

Donde presentes, la insulina y otros agentes anti-diabéticos, tal como se exponen arriba, pueden emplearse en formulaciones, cantidades y dosificación como se indica por la Physician's Desk Reference.

Donde presentes, los péptidos GLP-I o miméticos pueden administrarse en formulaciones buco-orales, por administración nasal o parenteralmente como se describe en las Patentes estadounidenses Nos. 5,346,701 (TheraTech), 5,614,492 y 5,631,224 que se incorporan aquí por referencia.



El agente anti-diabético u otro agente lipídico puede ser igualmente un modulador PPAR tal como α/γ agonista dual PPAR como AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo- Wellcome), KRP297 (Kyorin Merck) así como los divulgados por Murakami y colaboradores, "A Novel Insulin Sensitizer Acts As a Coligand for peroxisome Proliferation - 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), y en la Solicitud estadounidense Serial No. 09/664,598, radicada el 18 de september de 2000, (archivo de apoderado LA29) cuya divulgación se incorpora aquí por referencia, empleando dosificaciones como las expuestas allí, los cuales compuestos designados como preferidos se prefieren para uso aquí.

El agente anti-diabético puede ser un inhibidor SGLT2 tal como se divulga en la Solicitud estadounidense Serial No. 09/679,027, radicada el 4 de octubre de 2000 (archivo de apoderado LA49), que emplea dosificaciones como las expuestas allí. Se prefieren los compuestos designados como preferidos en la solicitud en mención.

El agente anti-diabético puede ser un inhibidor $\alpha P2$ como se divulga en la Solicitud estadounidense Serial No. 09/391,053, radicada el 7 de septiembre de 1999, y en la Solicitud estadounidense Serial No. 09/519,079, radicada el 6 de marzo de 2000 (archivo de apoderado LA27), emplenado dosificaciones como se expone aquí. Se prefieren los compuestos designados como preferidos en la solicitud en mención.

El agente anti-diabético puede ser un inhibidor DP4 tal como se divulga en la Solicitud Serial No. 09/788,173, radicada el 16 de febrero de 2001 (archivo de apoderado LA50), WO99/38501, WO99/46272, WO99/67279 (PROBIOFÁRMACO), WO99/67278 (PROBIOFÁRMACO), WO99/61431 (PROBIOFÁRMACO), NVP-DPP728A (1-[[[2-[(5-cianopiridin-2-il)amino]etil]amino]acetil]-2-ciano-(S)-pirrolidina) (Novartis) (preferida) como se divulga por Hughes y colaboradores, Biochemistry, 38(36), 11597- 11603, 1999, TSL-225 ácido (triptofil-1,2,3,4-tetrahidro-isoquinolin-3-carboxílico (divulgado por

Yamada y colaboradores, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540, 2-cianopirrolididas y 4-cianopirrolididas como se divulgan por Ashworth y colaboradores, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, páginas 1163-1166 y 2745-2748 (1996) empleando dosificaciones como las expuestas en las referencias de arriba.

La meglitinida que puede emplearse opcionalmente en combinación con el compuesto de fórmula I de la invención puede ser repaglinida Starlix® (Novartis), nateglinida (Novartis) o KAD1229 (PF/Kissei), prefiriéndose la repaglinida.

El compuesto antidiabético puede ser un agonista de receptor de melanocortina tal como una espiropiperidina como se divulga en WO 99/64002.

El inhibidor de HMG CoA reductasa de fórmula I se empleará en una proporción de peso a la meglitinida, modulador PPAR tal como γ agonista PPAR, α agonista PPAR, δ agonista PPAR o antagonista, α/γ agonista dual PPAR, inhibidor $\alpha P2$, inhibidor DP4 o inhibidor SGLT2 u otro agente antidiabético en el rango desde alrededor de 0.01:1 hasta alrededor de 100:1, preferiblemente desde alrededor de 0.05:1 hasta alrededor de 10:1.

El otro tipo of agente terapéutico que puede emplearse opcionalmente con el inhibidor de HMG CoA reductasa de fórmula I puede ser 1, 2, 3 o más de un agente anti-obesidad inclusive un agonista beta 3 adrenérgico, un inhibidor de lipasa, un inhibidor de reabsorción de serotonina (y dopamina) un inhibidor $\alpha P2$, un fármaco beta receptor tiroideo, un inhibidor PTP-1B, un agente anoréxico, un modulador PPAR inclusive γ antagonistas PPAR, α agonistas PPAR, δ antagonistas PPAR, un agonista CCKA, un inhibidor de leptina tal como un activador de receptor de leptina, un Y antagonista de neuropéptido, un agonista de melanocortin-4-receptor (MC4R), un regulador ascendente de oxidación de ácido graso o inductor (tal como Famoxin® Genset).

El agonista beta-3-adrenérgico que puede emplearse opcionalmente en combinación con compuesto de fórmula I puede ser AJ9677



(Takeda/Dainippon), L750355 (Merck), o CP331648 (Pfizer) u otros agonistas beta-3 conocidos como se divulgan en las Patentes estadounidenses Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 y 5,488,064, siendo preferidas AJ9677, L750,355 y CP331648.

Los antagonistas de neuropéptido Y que pueden emplearse opcionalmente en combinación con un compuesto de fórmula I incluyen los descritos WO 0113917 (BMS) o en la Patente estadounidense No. 6,218,408 (Synaptic) y en WO 0114376 (Banyu).

El inhibidor de lipasa que puede emplearse opcionalmente en combinación con un compuesto de fórmula I puede ser orlistat o ATL-962 (Alizyme), prefiriéndose orlistat.

El inhibidor de reabsorción de serotonina (y dopoamina) que puede emplearse opcionalmente en combinación con un compuesto de fórmula I puede ser sibutramina, topiramato (Johnson & Johnson) o axokine (Regeneron), prefiriéndose sibutramina y topiramato.

El compuesto beta receptor tiroideo que puede emplearse opcionalmente en combinación con un compuesto de fórmula I puede ser un ligando de receptor tiroideo como se divulga en WO97/21993 (U. Cal SF), WO99/00353 (KaroBio), GB98/284425 (KaroBio), y la Solicitud Provisional estadounidense 60/183,223 radicada el 17 de febrero de 2000, prefiriéndose los compuestos de las solicitudes de KaroBio y la solicitud provisional estadounidense ya mencionada.

El agente anoréxico que puede emplearse opcionalmente en combinación con un compuesto de fórmula I puede ser dexamfetamina, fentermina, fenilpropanolamina o mazindol, prefiriéndose dexamfetamina.

Los agonistas CCKA que pueden emplearse aquí incluyen GI-181,771 de Glaxo-SmithKline y SR146,131 de Sanofi.

El inhibidor PTP-1B que puede ser un agente anti-obesidad y/o antidiabético incluye los divulgados en WO 99/585,521, WO 99/58518, WO 99/58522 y WO 99/61435.



El agente anti-obesidad empleado puede ser igualmente P57 o CP-644,673 de Pfizer (licenciado de Phytopharm).

Los diferentes agentes anti-obesidad descritos más arriba pueden emplearse en la misma forma de dosificación con el compuesto de fórmula I o en diistintas formas de dosificación, en dosificaciones y regímenes como se conocen generalmente en el arte o en la PDR.

Los agentes antihipertensivos que pueden emplearse en combinación con los inhibidores de HMG CoA reductasa de la invención incluyen inhibidores ACE, antagonistas de receptor de angiotensina II, inhibidores NEP tales como candoxatril, inhibidores NEP/ACE, así como bloqueadores de canal del calcio (tales como verapamil y amlodipina besilato), antagonistas de calcio de canal T (tales como mibefradil), bloqueadores β -adrenérgicos, diuréticos, bloqueadores α -adrenérgicos (tales como doxazosina mesilato y terazosina HCl), antagonistas de receptor de acción dual (DARA), fármacos para falla cardíaca tales como digoxina, y otros tipos de agentes antihipertensivos.

El inhibidor de la enzima de conversión de la angiotensina que puede emplearse aquí incluye aquellos que comprenden una mitad mercapto (-S-) tales como derivados de prolina sustituidos, tales como cualquiera de los divulgados en la Patente estadounidense No. 4,046,889 a Ondetti y colaboradores mencionada más arriba, prefiriéndose captopril, es decir, 1-[(2S)-3-mercapto-2-metilpropionil]-L-prolina, y prefiriéndose derivados de mercaptoacilo de prolinas sustituidas tales como cualquiera de las divulgadas en la Patente estadounidense No. 4,316,906, prefiriéndose zofenopril.

Otros ejemplos de inhibidores de ACE que contienen mercapto que pueden emplearse aquí incluyen rentiapril (fentiapril, Santen) divulgados en Clin. Exp. Pharmacol. Physiol. 10:131 (1983); así como pivopril y YS980.

Otros ejemplos de inhibidores de enzima de conversión de angiotensina que pueden emplearse aquí incluyen cualquiera de los divulgados en la Patente estadounidense No. 4,374,829 mencionados más arriba, prefiriéndose N-(1-etoxycarbonil-3-fenilpropil)-1-alanil-L-prolina,

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es decir, enalapril, cualquiera de amino- o iminoácidos fosfonato sustituidos o sales divulgadas en la Patente estadounidense No. 4,452,790, prefiriéndose (S)-1-[6-amino-2-[[hidroxi-(4-fenilbutil)fosfinil]oxi]-1-oxohexil]-L-prolina o (ceronapril), fosfinilalcanoil prolinas divulgadas en la Patente estadounidense No. 4,168,267 mencionados más arriba, prefiriéndose fosinopril, cualquiera de las prolinas fosfinilalcanoil sustituidas divulgadas en la Patente estadounidense No. 4,337,201, y los fosfonamidatos divulgados en la Patente estadounidense No. 4,432,971 comentadas más arriba.

Otros ejemplos de inhibidores ACE que pueden emplearse aquí incluyen BRL 36,378 de Beecham como se divulga en las Solicitudes de Patente Europeas Nos. 80822 y 60668; MC-838 de Chugai divulgado en C.A. 102:72588v y Jap. J. Pharmacol. 40:373 (1986); CGS 14824 HCl de ácido (3-([1-etoxicarbonil-3-fenil-(1S)-propil]amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepin-1-acético) de Ciba-Geigy divulgado en la Patente del Reino Unido No. 2103614 y CGS 16,617 ácido (3(S)-[[[(1S)-5-amino-1-carboxipentil]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-etanóico) divulgado en la Patente estadounidense No. 4,473,575; cetapril (alacepril, Dainippon) divulgado en Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) divulgado en la Patente Europea No. 79-022 y Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) divulgado en Arzneimittelforschung 34:1254 (1985), cilazapril (Hoffman-LaRoche) divulgado en J. Cardiovasc. Pharmacol. 9: 39 (1987); R 31-2201 (Hoffman-LaRoche) divulgado en FEBS Lett. 165: 201 (1984); lisinopril (Merck), indalapril (delapril) divulgado en la Patente estadounidense No. 4,385,051; indolapril (Schering) divulgado en J. Cardiovasc. Pharmacol. 5:643, 655 (1983), spirapril (Schering) divulgado en Acta. Pharmacol. Toxicol. 59 (Supp. 5): 173 (1986); perindopril (Servier) divulgado en Eur. J. clin. Pharmacol. 31:519 (1987); quinapril (Warner-Lambert) divulgado en la Patente estadounidense No. 4,344,949 y CI925 (Warner-Lambert) HCl de ácido ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(etoxi-carbonil)-3-fenilpropil]amino]-1-oxopropil]-1,2,3,4-tetrahydro-6,7-dimetoxi-3-

isoquinolincarboxílico) divulgado en *Pharmacologist* 26:243, 266 (1984), WY- 44221 (Wyeth) divulgado en *J. Med. Chem.* 26:394 (1983).

Inhibidores ACE preferidos son captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril y moexipril.

Inhibidores NEP/ACE pueden emplearse también aquí porque poseen actividad inhibitoria de endopeptidasa neutral (NEP) y actividad inhibitoria de la enzima de conversión de la angiotensina (ACE). Ejemplos inhibidores NEP/ACE adecuados para uso aquí incluyen los divulgados en las Patentes estadounidenses Nos. 5,362,727, 5,366,973, 5,225,401, 4,722,810, 5,223,516, 4,749,688, Patente estadounidense No. 5,552,397, U.S. Pat. No. 5,504,080, Patente estadounidense No. 5,612,359, Patente estadounidense No. 5,525,723, Solicitudes de Patente Europeas 0599,444, 0481,522, 0599,444, 0595,610, Solicitud de Patente Europea 0534363A2, 534,396 y 534,492, y Solicitud de Patente Europea 0629627A2.

Se prefieren aquellos inhibidores NEP/ACE y sus dosificaciones que se designan como preferidos en las patentes/solicitudes de arriba, patentes estadounidenses que se incorporan aquí por referencia; los más preferidos son omapatrilat, gemopatrilat ácido ([S[(R*,R*)]-hexahidro-6-[(2-mercapto-1-oxo-3-fenilpropil) amino]-2,2-dimetil-7-oxo-1H-azepin-1-acético) y CGS 30440.

El antagonista de receptor de angiotensina II (también referido aquí como antagonista de angiotensina II o antagonista AII) apropiado para uso aquí incluye, pero no se limita a, irbesartan, losartan, valsartan, candesartan, tasosartan o eprosartan, prefiriéndose irbesartan, losartan o valsartan.

Una forma de dosificación oral preferida, tal como tabletas o cápsulas, contendrá el inhibidor ACE o antagonista AII en una cantidad en el rango desde alrededor 0.1 hasta alrededor de 500 mg, preferiblemente desde alrededor de 5 hasta alrededor de 200 mg y más preferiblemente desde alrededor de 10 hasta alrededor de 150 mg.

Para administración parenteral, el inhibidor ACE, antagonista de angiotensina II o inhibidor NEP/ACE se empleará en una cantidad en el

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rango desde alrededor de 0.005 mg/kg hasta alrededor de 10 mg/kg y preferiblemente desde alrededor de 0.01 mg/kg hasta alrededor de 1 mg/kg.

Donde un fármaco tiene que administrarse por vía intravenosa, se formulará en vehículos convencionales, tales como agua destilada, salina, solución de Ringer u otros portadores convencionales.

Podrá apreciarse que dosificaciones preferidas de inhibidor ACE y antagonista AII serán como se exponen en la última edición de la Physician's Desk Reference (PDR).

Antagonistas de receptor de acción dual (DARA) apropiados para uso aquí incluyen los divulgados en las Solicitudes estadounidenses Serial No. 09/513,779, radicada el 25 de febrero de 2000, y Serial No. 09/604,322, radicada el 26 de junio de 2000.

Otros ejemplos de agentes antihipertensivos apropiados para uso aquí incluyen omapatrilat (Vanlev®), gemopatrilat, amlodipina besilato (Norvasc®), HCl de prazosina HCl (Minipress®), verapamil, nifedipina, diltiazem, felodipina, nisoldipina, isradipina, nicardipina, beta bloqueadores tales como nadolol, atenolol (Tenormin®), sotalol, terazosina, doxazosina, carvedilol, y propranolol, y HCl de clonidina (Catapres®).

Diuréticos que pueden emplearse en combinación con compuestos de fórmula I incluyen hidroclorotiazida, torasemida, furosemida, espironolactona, e indapamida.

Agentes antiplaquetas que pueden emplearse en combinación con compuestos de fórmula I de la invención incluyen aspirina, clopidogrel, ticlopidina, dipiridamol, abciximab, tirofiban, eptifibatide, anagrelide, e ifetroban, prefiriéndose clopidogrel y aspirina.

Los agentes antihipertensivos, diuréticos y fármacos antiplaquetas pueden emplearse en cantidades como se indica en la PDR. Ifetroban puede emplearse en cantidades como las expuestas en la Patente estadounidense No. 5,100,889.

Agentes anti-Alzheimer o agentes anti-demencia apropiados para uso aquí con los inhibidores de la HMG CoA reductasa de la invención incluyen HCl de tacrina (Cognex®) y donepezil (Aricept®), así como inhibidores de

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γ -secretasa, inhibidores de β -secretasa y/ agentes antihipertensivos. Las dosificaciones empleadas serán como se expone en la PDR.

Agentes antiosteoporosis apropiados para uso aquí en combinación con los inhibidores de la HMG CoA reductasa de la invención incluyen hormona paratiroide o bisfosfonatos, tales como MK-217 (alendronato) (Fosamax®) así como agonistas de receptor de Ca y agonistas de receptor de progestina. Las dosificaciones empleadas serán como se expone en la PDR.

Los agentes terapéuticos de reemplazo de hormonas, donde presentes, se emplearán en dosis como las expuestas en la última edición de la PDR. Ejemplos de dichos agentes incluyen moduladores selectivos del receptor del estrógeno (SERMs) tales como raloxifen, tamoxifen o lasoxifen.

El compuesto de HMG CoA reductasa de la invención puede emplearse asimismo en combinación con un inhibidor de tirosina cinasa tal como se divulga en WO 2000/053605;

El modulador selectivo de receptor de andrógeno apropiado para uso aquí puede ser LGD-2226 (ligando);

Los agentes antiarrítmicos apropiados para uso aquí incluyen β -bloqueadores como se expone aquí inclusive sotalol y amioderome, bloqueadores de canal de calcio como se exponen aquí inclusive verapamil, nifedipina, amlodipina-besilato, y diltiazem, los cuales pueden usarse igualmente en combinación con un dispositivo desfibrilador, tal como un marcapasos;

coenzima Q sub. 10 tal como se divulga en las Patentes estadounidenses Nos. 5,316,765, 4,933,165, 4,929,437;

un agente que regula en forma ascendente la sintasa de ácido nítrico de célula endotelial tipo III tal como se divulga en WO 2000/003746;

un compuesto condroprotector tal como un glicosaminoglicano polisulfatado (PSGAG), glucosamina, sulfato de condroitina (CS), ácido hialurónico (HA), polisulfato de pentosana (PPS), doxiciclina o minociclina, tal como se divulga en EP 970694;

un inhibidor de ciclooxigenasa (COX)-2, tal como celecoxib (Celebrex® (Searle)) o rofecoxib (Vioxx® (Merck)) o un antagonista de receptor de glicoproteína IIa/IIIb tal como se divulga en WO 99/45913 y tirofiban o abciximab;

un inhibidor de reabsorción de 5-HT tal como se divulga en WO 99/44609;

agentes anti-anginales tales como vasodilatadores, por ejemplo, dinitrato de isosorbide, o nitroglicerina;

un secretagogo de la hormona del crecimiento tal como se divulga en las Solicitudes estadounidenses Serial No. 09/662,448, radicada el 14 de septiembre de 2000, y la Solicitud provisional estadounidense 60/203,335, radicada el 11 de mayo de 2000, y MK-677 (Merck), CP- 424391 de Pfizer y LY 444,711 de Lilly;

agentes anti-aterosclerosis tales como inhibidores ACAT e inhibidores de lipoxigenasa como se describen aquí e inhibidores de fosfolipasa A-2 tales como S-3013 y SB-435,495 (los cuales son también agentes anti-inflamatorios);

agentes anti-infecciosos tales como quinolonas, por ejemplo, ciprofloxacina, ofloxacina, y Tequin® (Bristol- Myers Squibb), macrólidos tales como eritromicina y claritromicina (Biaxin® (Abbott)), y azitromicina (Zithromax (Pfizer)); o

un inmunosupresor (para uso en transplantes) tales como ciclosporina, micofenolato mofetil, azatioprina y similares.

Tal como se emplea aquí, la expresión "agente antineoplástico " se refiere a compuestos que impiden la multiplicación de las células cancerígenas. En general, los agentes antineoplásticos usados aquí impiden la multiplicación de las células cancerígenas: (1) interfiriendo la capacidad de la célula de replicar el ADN, o (2) induciendo apoptosis (muerte celular programada) en las células cancerosas.

Ejemplos de agentes antineoplásticos que son apropiados para uso en combinaciones de esta invención incluyen, pero no se limitan a, agentes estabilizadores de microtúbulos tales como los taxanos, por ejemplo,

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paclitaxel (también conocido como Taxol®), docetaxel (también conocido como Taxotere®), 7-O-metiltio- metilpaclitaxel (divulgado en la Patente estadounidense No. 5,646,176), 3'-tert-butil-3'-N-tert-butiloxicarbonil-4-deacetil-3'-defenil-3'-N-debenzoil-4-O-methoxycarbonil-paclitaxel (divulgado en USSN 60/179,965 radicada el 3 de febrero de 2000, y ejemplo 17 aquí), C-4 metil carbonato paclitaxel (divulgado en WO 94/14787), la epotilona, tal como epotilona A, epotilona B, epotilona C, epotilona D, desoxiepotilona A, desoxiepotilona B, [1S- [1R*, 3R*(E), 7R*, 10S*, 11R*, 12R*, 16S*]]-7,11-dihidroxi-8,8,10,12,16-pentametil-3-[1-metil-2-(2-metil-4-tiazolil)etenil]-4-aza-17-oxabicyclo[14.1.0]hepta-decan-5,9-diona (divulgada en WO 99/02514), [1S- [1R*, 3R* (E) , 7R*, 10S*, 11R* ,12R*, 16S*]] -3-[2-[2-aminometil)-4-tiazolil]-1-metiletenil]-7,11-dihidroxi-8, 8, 10, 12, 16-pentametil-4,17-dioxabicyclo[14.1.0]-heptadecan-5,9-diona (divulgada en USSN 09/506,481 radicada el 17 de febrero de 2000, y ejemplos 7 y 8 aquí), y sus derivados; agentes de disruptor de microtúbulos; agentes alquilantes; anti-metabolitos; epidofilotoxina; una enzima antineoplástica; un inhibidor de topoisomerasa; procarbazona; mitoxantrona; complejos de coordinación de platino; modificadores de respuesta biológica; inhibidores de crecimiento; agentes terapéuticos hormonales/antihormonales; y factores de crecimiento hematopoiético.

Otras clases de agentes antineoplásticos apropiados para uso en el método de la presente invención incluyen, pero no se limitan a, la familia antraciclina de fármacos, los fármacos vinca, las mitomicinas, las bleomicinas, los nucleósidos citotóxicos, discodermolida, la familia pteridina de fármacos, diinenos, inhibidores de aromatasa, y las podofilotoxinas. Miembros particularmente útiles de aquellas clases no mencionadas previamente incluyen, por ejemplo, doxorubicina, carminomicina, daunorubicina, aminopterina, metotrexato, metopterina, dicloro-metotrexato, mitomicina C, porfiromicina, 5-fluorouracil, 6-mercaptopurina, gemcitabina, citosina arabinosida, podofilotoxina o derivados de podofilotoxina tales como etoposida, fosfato de etoposida o teniposida, melphalan, vinblastina, vincristina, leurosina, vindesina,

leurosina, y similares. Otros agentes antineoplásticos útiles incluyen estramustina, cisplatino, carboplatino, ciclofosfamida, bleomicina, tamoxifén, ifosfamida, melphalan, hexametil melamina, tiotepa, citarabina, idatrexato, trimetrexato, dacarbazina, L-asparaginasa, camptotecina, CPT-11, topotecan, ara-C, bicalutamida, flutamida, leuprolide, derivados de piridobenzoindol, interferones, e interleucinas.

Se apreciará que, a menos que se especifique lo contrario, el régimen de dosificación para agentes terapéuticos usados en combinación con los compuestos de la invención será como se especifican en la PDR.

En la realización del método de la invención para tratar hipercolesterolemia, hiperlipidemia, hiperlipoproteinemia, hipertrigliceridemia, o aterosclerosis, y enfermedades relacionadas, o enfermedad de Alzheimer u osteoporosis, u otras divulgaciones como se expuso anteriormente, se empleará una composición farmacéutica que contiene los compuestos de la estructura I, con o sin otros agentes reductores de colesterol, agentes osteoporosis, agentes de Alzheimer, agente(s) antidiabéticos y/o agente(s) antihiperlipidémicos y/o otros agentes terapéuticos en asociación con un vehículo farmacéutico o diluyente. La composición farmacéutica puede formularse empleando vehículos o diluyentes sólidos o líquidos y aditivos farmacéuticos de un tipo apropiado al modo de administración deseada, tal como portadores farmacéuticamente aceptables, excipientes, aglutinantes y similares. Los compuestos pueden administrarse a especies mamíferas inclusive humanos, monos, perros, etc., por una vía oral, por ejemplo, en la forma de tabletas, cápsulas, perlas, gránulos o polvos, o pueden administrarse por vía parenteral en la forma de preparaciones inyectables, o pueden administrarse intranasalmente o en parches transcutáneos. Formulaciones sólidas típicas contendrán desde alrededor de 0.1 a alrededor de 500 mg de un compuesto de fórmula I. La dosis para adultos es preferiblemente entre 0.5 y 1.000 mg al día, los cuales pueden administrarse en una dosis única o en la forma de dosis individuales desde 1-4 veces al día e incluso dosis única una vez a la semana (5 a 1.000 mg).

Una preparación inyectable típica se produce poniendo asépticamente 250 mg de compuestos de la estructura I en un frasco, secando asépticamente por congelamiento y sellando. Para empleo, los contenidos de la ampolleta se mezclan con 2 mL de salina fisiológica, para producir una preparación inyectable.

Las siguientes abreviaturas se emplean en los Ejemplos y en otras partes aquí:

Ph = fenilo

Bn = bencilo

i-Bu = iso-butilo

Me = metilo

Et = etilo

TMS = trimetilsililo

Fmoc = fluorenilmetoxycarbonilo

Boc = tert-butoxycarbonilo

Cbz = carbobenciloxi o carbobenzoxi o benciloxycarbonilo

DIPEA = diisopropil etilamina

PTSH = N-feniltetrazol

PPh₃ = trifenilfosfina

NMO = metilmorfolina N-Óxido

TPAP = tetrapropilamonio perrutenato

DEAD = dietil azodicarboxilato

HOAc o AcOH = ácido acético

TFA = ácido trifluoroacético

Et₂NH = dietilamina

NMM = N-metil morfolina

n-BuLi = n-butil-litio

Pd/C = paladio sobre carbono

PtO₂ = óxido de platino

MTBE = metil t-butil éter

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DI agua = agua deionizada

TEA = trietilamina

EDAC = 3-etil-3'-(dimetilamin)propil-carbodiimida

hidrocloruro (ó 1- [(3-(dimetil)amino)propil])-3-etilcarbodiimida
hidrocloruro)

HOBT o HOBT. H₂O = 1-hidroxibenzotriazol hidrato

HOAT = 1-hidroxi-7-azabenzotriazol

Reactivo PyBOP = benzotriazol-1-iloxi-tripirrolidino fosfonio
hexafluorofosfato

LiN(TMS)₂ = bis(trimetilsilil)amida de litio

DIBAL = hidruro de diisobutilaluminio

LDA = diisopropilamida de litio

DMPU = 1, 3-dimetil-3,4,5,6-tetrahidro-2(1H)-pirimidinona

AcCN = acetonitrilo

LiHMDS = bis (trimetilsilil)amida de litio

NaHMDS = bis (trimetilsilil)amida de sodio

Red-AL = bis (2-metoxietoxi)aluminio hidruro de sodio

mCPBA = ácido m-cloro-p-benzoico

min = minuto(s)

h ó hr = hora(s)

L = litro

mL = mililitro

μL = microlitro

g = gramo(s)

mg = miligramo (s)

mol = moles

mmol = milimol (es)

meq = miliequivalente

RT, rt = temperatura ambiente

sat o sat' d = saturado

aq. = acuoso

TLC = cromatografía de capa delgada

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HPLC = cromatografía líquida de alto rendimiento

LC/MS = cromatografía líquida de alto rendimiento /espectrometría de masa

MS o Mass Spec = espectrometría de masa

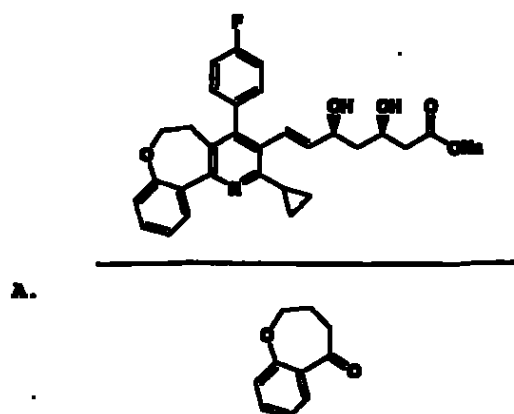
NMR = resonancia magnética nuclear

mp = punto de fusión

Bp = punto de ebullición

Los siguientes ejemplos representan incorporaciones preferidas de la invención. A menos que se indique lo contrario, todas las temperaturas son en grados centígrados.

Ejemplo 1

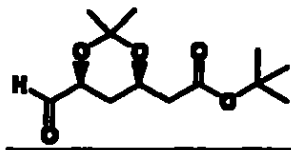


Una mezcla de ácido polifosfórico (82.9 g) y o-xileno seco (30 ml) se calentó a 105-110°C en un baño de aceite, se trató con una solución de ácido 4-fenoxibutírico (25 g, 0.137 moles) en o-xileno seco (110 ml) y se agitó a 105-110°C durante 2 horas. La mezcla de la reacción se enfrió a temperatura ambiente durante un período de 2 horas, se vertió en agua helada (180 ml), luego se extrajo con éter (3 x 150 ml). Los extractos orgánicos combinados (color óxido) se lavaron con agua (2 x 80 ml) y salmuera (80 ml), se secó (Na₂SO₄ anhidro), se filtró, se evaporó a sequedad y se evaporó una vez a partir de hexanos (500 ml). El residuo se secó in vacuo durante 48 horas para producir un jarabe rojizo-marrón (27.19 g) que se dividió en dos fracciones, cromatografiando cada porción en un columna de gel de sílice, (EM, 2-1/4" x 10") para producir un jarabe color ambarino

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claro (10.792 g). La trituración de una fracción impure con éter (3 x 25 ml) produjo 1.98 g adicionales de producto. Rendimiento: 12.77 g, jarabe ambarino; 58 %. Rf 0.38 (gel de sílice; EtOAc: Hexano 1 : 4; UV).

A(l) .



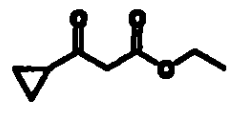
Un matraz de 1-L, de 3 cuellos, secado al horno, equipado con una sonda de sensor de temperatura, embudo de adición de 125 mL a presión constante y tabique, se cargó con CH₂Cl₂ seco (300 mL) y DMSO seco (20.9 mL, 0.2944 mol, 2.5 equiv) bajo atmósfera de argón, se enfrió a 75°C. Se agregó cloruro de oxalilo (13.6 mL, 0.156 mol, 1.32 equiv) puro mediante una jeringa gota a gota durante 15 minutos (la temperatura subió a -66°C), y luego se dejó agitar durante 15 minutos más. Se añadió gota a gota una solución del alcohol ácido 2-[(4R, 6S)-6-(hidroximetil)-2,2-dimetil-1,3-dioxan-4-il]acético t-butil éster (30.66 g, 0.1178 mol, 1 equiv) en CH₂Cl₂ seco (80 mL) desde el embudo de adición durante 30 minutos (la temperatura aumentó a -68°C). La mezcla blanca resultante se agitó durante 70 minutos a -76°C, luego se agregó gota a gota trietilamina (82 mL, 0.5889 mol, 5 equiv) desde el embudo de adición durante 35 minutos (la temperatura aumentó a -65°C), seguidamente la mezcla amarillo claro se agitó vigorosamente a -76°C. TLC (SiO₂, 20% EtOAc/CH₂Cl₂, Rf=0.52). Luego de 30 minutos, el baño de enfriamiento se retiró y la mezcla de la reacción se extinguió agregando lentamente KH₂PO₄ acuoso al 20% frío (35 mL), seguido por H₂O fría (300 mL); y luego se dejó agitar 15 minutos (la temperatura aumentó a -7°C). La mezcla de la reacción se vertió en un embudo separador de 2L y se extrajo con hexanos (500 mL). El extracto orgánico se lavó con KH₂PO₄ acuoso al 10% frío (3x300 mL) y NaCl acuoso saturado (300 mL). Se secó el orgánico sobre Na₂SO₄ anhidro, se filtró y concentró in vacuo para producir un aceite amarillo. La purificación mediante cromatografía de destello SiO₂ (columna 10cm x 20

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cm) con 35:65 EtOAc/Hexanos produjo el compuesto del título con un sólido blanco (22.2 g, 0.0859 mol, 73%):

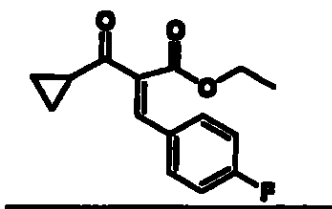
^1H NMR (CDCl_3): δ 1.267-1.465 (m, 16H), 1.802 (dd, $J=12.7$ Hz, 2.2 Hz, 1H), 2.290-2.464 (m, 2H), 4.314 (d, $J=18.4$ Hz, 2H), 9.555 (d, $J=1.3$ Hz, 1H).

A(2).



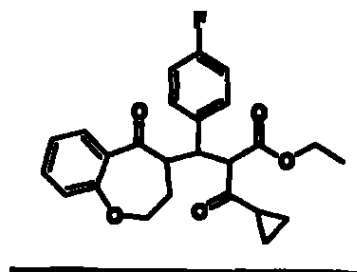
A una lechada de NaH (19.20 g, 480 mmol) y dietil carbonato (80 mL) en un matraz de base redonda de 1L con tres cuellos a temperatura ambiente se agregó una solución de ciclopropil metilcetona (23.5 mL, 238 mmol) en Et_2O (30 mL). Se añadió aproximadamente 10% de la solución, y luego 0.25 mL de EtOH se adicionaron a la lechada de reacción. Continuó la adición de la cetona restante con leve evolución de gas liviano. Luego de la adición de toda la solución de cetona, la reacción se tornó completamente exotérmica con una vigorosa evolución de H_2 . La mezcla de la reacción se enfrió periódicamente con un baño de hielo para mantener la temperatura alrededor de 35°C a 50°C . Después de una hora, la evolución de gas había cesado y la mezcla de la reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de la reacción se secó en un baño de hielo, se diluyó Et_2O (200 mL), y se trató con 1 N HCl con algo de hielo para ajustar a alrededor de pH 3. Se extrajo la mezcla de la reacción con Et_2O (3 x 150 mL). Los extractos de Et_2O se combinaron, se lavaron con NaHCO_3 (200 mL) acuoso saturado, H_2O (200 mL) y salmuera (200 mL), y se secó (Na_2SO_4), se filtró y concentró bajo presión reducida para producir un aceite amarillo. El aceite se destiló bajo vacío para producir el compuesto del título como un aceite incoloro, 28.5 g, 77%. B.p. = $94-96^\circ\text{C}/8$ mmHg.

A(3)



A una solución agitada del compuesto Parte A (2) (28.24 g, 181 mmol) en benceno (128 mL) se agregó 4-fluorobencen-aldehído (19.4 mL, 181 mmol), HOAc (0.31 mL, 5.4 mmol) y piperidina (1.8 mL, 18.2 mL). La mezcla de la reacción se calentó a reflujo y se recogió azeotropo con una trampa Dean-Stark. Luego de 16 horas, la mezcla de la reacción se enfrió a temperatura ambiente, se diluyó con Et₂O (250 mL), se lavó con 0.5 N HCl acuoso, NaHCO₃ acuoso saturado, H₂O y salmuera, y después se secó (Na₂SO₄), se filtró y concentró bajo presión reducida. La purificación por cromatografía de destello (1:10 Et₂OAc/hexano) produjo el compuesto del título como un aceite amarillo, rendimiento 29 g, 61%.

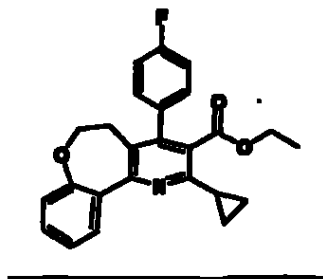
B.



Una solución de compuesto de Parte A (7.21 g, 40.9 mmol) en THF seco (5.0 ml) se añadió a una solución de bis (trimetilsilil)amida de litio a -78°C (1.0 M en THF; 49 ml, 49 mmol) en THF seco (25 ml) y se agitó a -78°C bajo argón durante 1 hora. Se trató la mezcla de la reacción con una solución del compuesto Parte A(3) del Ejemplo 1 (7.15 g, 27.3 mmoles), en THF seco, se agitó a -78°C durante 30 minutos, luego a 0°C durante 30 minutos. La mezcla de la reacción se extinguió a 0°C mediante adición gota a gota de ácido acético glacial (5 ml) y la lechada resultante se agitó a temperatura ambiente durante otros 5 minutos, luego se vertió lentamente en una solución de cloruro de amonio (25%, 140 ml). La solución amarillo brillante se extrajo con éter (2 x 100 ml) y los extractos orgánicos combinados se lavaron con agua (2 x 25 ml) y salmuera (25 ml), se secaron (Na₂SO₄ anhidro), se filtraron y se evaporaron a sequedad in vacuo para producir una mezcla de producto crudo como un aceite amarillo (17.16 g).

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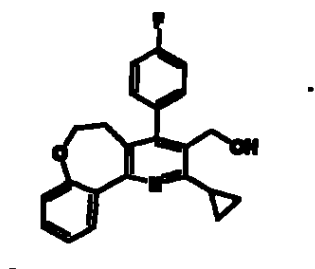
C.



Una mezcla de compuesto crudo Parte B (17.0 g, 27.3 mmol), acetato de amonio (9.34 g, 120 mmol) y monohidrato de acetato de cobre (20.54 g, 101 mmol) en ácido acético glacial (100 ml) se hizo refluir bajo argón durante 19 horas. La mezcla se vertió en una solución helada de hidróxido de amonio concentrado (85 ml) en agua (170 ml) y se extrajo la solución azul brillante con éter (3 X 200 ml). Los extractos orgánicos combinados se lavaron con agua (2 x 80 ml) y salmuera (80 ml), se secaron (Na_2SO_4 anhidro), se filtraron, se evaporaron a sequedad y se secaron in vacuo. El producto crudo (14 g, jarabe marrón) se cromatografió en dos lotes, cada uno en una columna de gel de sílice (EM, 2-1/4" x 10") para producir el producto deseado como un sólido blancuzco (4.161 g). Se obtuvieron 931 mg adicionales de producto de la cromatografía de las fracciones mixtas. Rendimiento: 5.092 g, 46 % de compuesto A).

Rf 0.53 (gel de sílice; EtOAc:Hexano-1:4; UV)

D.

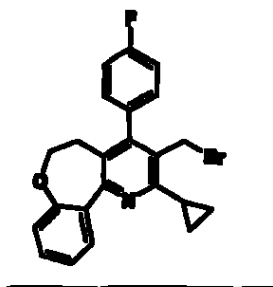


Una solución compuesto Parte C (2.515 g, 6.23 mmol) en THF seco (30 ml) se enfrió a 0°C (baño de agua helada), se trató gota a gota con hidruro de aluminio de litio (1.0 M en THF; 12.5 ml, 12.5 mmol), se agitó a 0°C durante 30 minutos, seguidamente a temperatura ambiente durante 3 horas. La mezcla de la reacción se enfrió a 0°C, se trató sucesivamente con agua (0.5 ml), 15% NaOH (0.5 ml) y agua (1.5 ml), se agitó a temperatura ambiente durante 5 minutos, luego se diluyó

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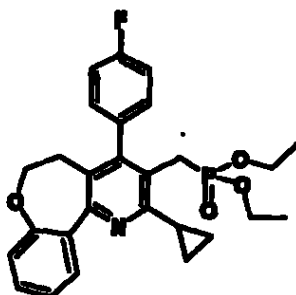
con acetato de etilo (50 ml). La lechada se filtró a través de una almohadilla de Celite®, lavando la almohadilla con acetato de etilo (3 x 25 ml). El filtrado claro se evaporó a sequedad y se secó in vacuo para producir el producto del título. Rendimiento: 2.386 g, espuma blanca (100 %). Rf 0.15 (gel de sílice; EtOAc:Hexano-1:4; UV).

E.



Una solución de compuesto Parte D (2.27 g, 6.23 mmol) en diclorometano seco (45 ml) se enfrió a 0°C (baño de agua helada) y se trató gota a gota con tribromuro de fósforo (1.0 M en diclorometano; 12.5 ml, 12.5 mmol). Se retiró el baño helado y la mezcla de la reacción se agitó a temperatura ambiente durante 30 minutos luego de lo cual se volvió a enfriar a 0°C y se trató gota a gota con bicarbonato de sodio saturado (70 ml). La mezcla se calentó luego a temperatura ambiente y se extrajo con acetato de etilo (2 x 100 ml). Los extractos orgánicos combinados se lavaron con agua (2 x 50 ml) y salmuera (50 ml), re-extrayendo cada lavado acuoso con diclorometano (100 ml). Los extractos orgánicos se secaron (sulfato de sodio anhidro), se filtraron, evaporaron a sequedad y se secaron in vacuo para producir el producto del título como un sólido blanco. Rendimiento: 2.503 g, (94 %). m.p. = 169-171°C. Rf 0.58 (gel de sílice; EtOAc:Hexano - 1:4; UV).

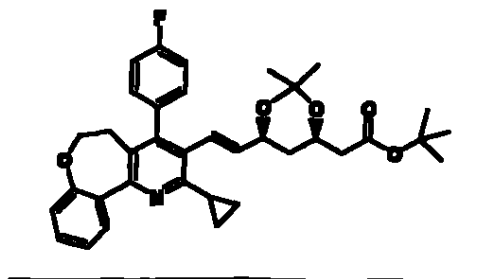
F.



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Una solución de dietil fosfito (0.88 ml, 6.83 mmoles) en THF seco (10 ml) se enfrió a -10°C (acetónitrilo – baño de hielo seco), se trató con (bistrimetilsilil)amida de sodio (1.0 M en THF; 6.7 ml, 6.7 mmol) y se agitó a -10°C durante 30 minutos. La solución enfriada se trató con una solución de compuesto Parte E (2.41 g, 5.68 mmol) en THF seco (20 ml), se agitó a -10°C durante 1.0 hora y luego se extinguió a -10°C con agua (14 ml). La solución se extrajo con acetato de etilo (2 x 75 ml) y los extractos orgánicos combinados se lavaron con 1.0 M de ácido clorhídrico (8.0 ml) y salmuera (10 ml), se secaron (sulfato de sodio anhidro), filtraron, evaporaron a sequedad y se secaron in vacuo. El producto crudo (3.12 g, jarabe) se cromatografió en una columna de gel de sílice (EM, 5.5 cm x 12.5 cm) para producir el compuesto del título como un jarabe. Rendimiento: 2.34 g (85.5%). Rf 0.33 (gel de sílice; EtOAc – Hexano - 1:1; UV).

G.

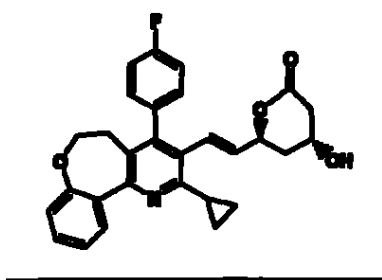


Una solución compuesto Parte F (2.29 g, 4.756 mmol) en THF seco (20 ml) se enfrió a -78°C , se trató con 2.37 M de n-butil litio (2.41 ml, 5.71 mmol) y se agitó a -78°C durante 40 minutos. La solución se trató gota a gota mediante una cánula con una solución de compuesto Parte A(1) a -78°C (2.36 g, 9.15 mmol) en THF seco (10 ml), manteniendo ambas soluciones a -78°C todas las veces. La mezcla de la reacción se agitó a -78°C durante 1.0 hora, -10°C durante 1.0 hora y a temperatura ambiente durante 5 horas, se extinguió con 25% de solución de cloruro de amonio (12 ml), luego se extrajo con acetato de etilo (2 x 1.00 ml). Los extractos orgánicos combinados se lavaron con 25% de solución de cloruro de amonio (12 ml) y salmuera (12 ml), se secaron (sulfato de sodio anhidro), se filtraron, evaporaron a sequedad y se secaron in vacuo. El jarabe

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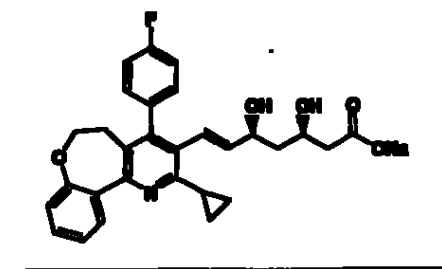
amarillo de producto crudo se cromatografió en una columna de gel de sílice (EM, 2- 1/4" x 10") para producir el compuesto del título como un jarabe. Rendimiento: 878 mg (32 %). Rf 0.37 (gel de sílice; EtOAc:Hexano - 1: 4; UV).

H.



Una solución de compuesto Parte G (850 mg, 1.45 mmol) en diclorometano seco (20 ml) se enfrió a 0°C, se trató con ácido trifluoroacético (1.85 ml, 24 mmol), se agitó at 0°C durante 5 minutos, luego a temperatura ambiente durante 4.5 horas. La mezcla de la reacción se vertió lentamente en un matraz de 1 L que contenía acetato de etilo (300 ml) y bicarbonato de sodio saturado (40 ml), enjuagando el matraz con acetato de etilo (50 ml). La mezcla se agitó bien y se separaron las fases, lavando la fase orgánica con bicarbonato de sodio saturado (25 ml) y salmuera (25 ml). La fase orgánica se secó sobre sulfato de sodio anhidro, se filtró, evaporó a sequedad y se secó in vacuo. La mezcla de producto crudo se cromatografió en en una columna de gel de sílice (EM, 1.51" x 12") para producir el compuesto como un jarabe. Rendimiento: 570 mg (83 %). Rf 0.23 (gel de sílice; EtOAc:Hexano - 1:1; UV)

I.



Una solución de compuesto Parte H (550 mg, 1.17 mmol) en THF seco (10 ml) se trató con 1.0 N NaOH (1.46 ml; 1.46 mmol) y se agitó a temperatura ambiente durante 10 minutos. La mezcla de la reacción se

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evaporó a sequedad y el sólido residual se disolvió en una mezcla de agua (8.7 ml) y 1.0 N de hidróxido de sodio (70 ul). La solución se eluyó en una columna SP207 (Na⁺ form; 1.5" x 4"), eluyendo la columna con agua (200 ml), 10% CH₃CN/H₂O (200 ml), 20% CH₃CN/H₂O (100 ml) y 50% CH₃CN/H₂O (200 ml). Las fracciones deseadas se combinaron y evaporaron a sequedad. El semi-sólido obtenido se disolvió en agua (300 ml) y se liofilizó para producir los compuestos del título como un sólido blanco. Rendimiento: 583 mg (95%) R_f 0.48 (gel de sílice; CH₂Cl₂:MeOH:HOAc-18:1:1; UV).

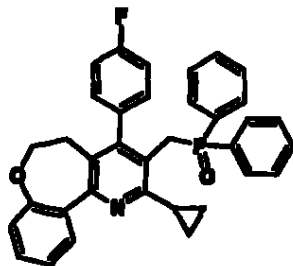
Análisis para C₂₉H₂₆FNO₄Na • 0.8 H₂O (MW = 525.94):

Calculado: C, 66.23; H, 5.29; N, 2.66; F, 3.61

Hallado: C, 66.37; H, 5.30; N, 2.62; F, 3.91

Procedimiento Alternativo para Compuesto Parte G Ejemplo 1

G(I).



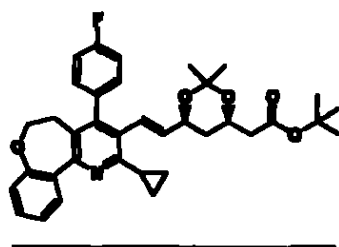
El bromuro Parte E Ejemplo 1 (13.03 g, 0.027 mol, 1equiv) y Ph₂POEt (6.5 mL, 0.0297 mol, 1.1 equiv) se calentaron a reflujo en tolueno anhidro (200 ml) bajo una atmósfera de argón. La reacción se volvió una mezcla blanca espesa pero agitable después de cerca de 10 minutos. La reacción se completó luego de de 1 hora por TLC (SiO₂, 30% EtOAc/CH₂Cl₂, producto R_f=0.34). La mezcla se enfrió a 0°, y el precipitado blanco se recolectó mediante filtración por vacío, se lavó con hexanos (2x50 ml), y se secó in vacuo (14.8 g, 0.027 mol, 100%): HPLC (columna Shimadzu, YMC S-5 C18 4.6x50 mm, gradiente 4min. @

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4mL/min., detección UV 220 nM; inicial %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%);

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)⁺.

G (2).



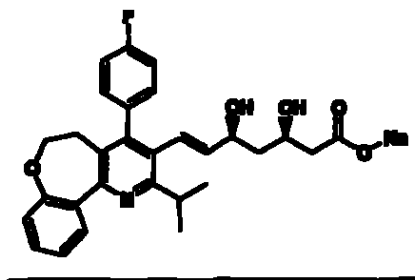
Un matraz de 250-mL secado a la llama se cargó con compuesto Parte G(1) (14.82 g, 27.2 mmol, 1 equiv); se combinó con tolueno anhidro (2x50 mL), se secó sobre alto vacío y se llenó con argón. Se agregó THF (150 ml) y la lechada parcial se enfrió a 0°C. Se añadió una solución 2.5 M de n-BuLi en hexanos (11.4 mL, 0.0285 mol, 1.05 equiv) gota a gota a la mezcla vigorosamente agitada durante un período de 40 minutos. La solución resultante de color verde se agitó entonces durante 1 hora a 0°C. El compuesto aldehído Ejemplo A(1) (8.42 g, 0.0326 mol, 1.2 equiv) en un matraz secado a la llama de 500-mL (material previamente combinado con tolueno anhidro, 3x20 ml) bajo una atmósfera de argón se disolvió en THF seco (75 ml) y se enfrió a -78°C. La solución de anión de fosfina se añadió gota a gota al aldehído mediante la cánula durante un período de 45 min, luego se agitó la solución color azul oscuro a -78°C durante 1.5 horas. La mezcla se dejó entonces calentar a temperatura ambiente durante un período de 2 horas; la solución inicialmente azul se volvió de color rojo ladrillo y, finalmente, de color anaranjado claro. TLC (SiO₂, 5% EtOAc/CH₂Cl₂, producto R_f=0.37). La reacción se extinguió con NaCl acuoso semi-

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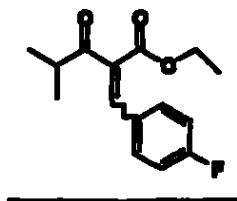
saturado (200 ml) y se extrajo con Et₂O (300 ml); la orgánica se lavó con H₂O (2x100 ml) y NaCl (100 mL) acuoso saturado. La capa orgánica se secó sobre Na₂SO₄ anhidro, se filtró y concentró in vacuo. Purificación por cromatografía de destello SiO₂ (10 cm x 25 cm) con 2% EtOAc/ CH₂Cl₂ (2 L), 3% EtOAc/ CH₂Cl₂ (2 L), 5% EtOAc/ CH₂Cl₂ (1 L), 7% EtOAc/ CH₂Cl₂ (1 L), y 10% EtOAc/ CH₂Cl₂ (1 L) produjo el compuesto del título Parte G(2) compuesto (el mismo compuesto que Parte G Ejemplo 1) como un sólido blanco (11.13 g, 0.019 mol, 70%): HPLC (columna Shimadzu, YMC S-5 C18 4.6x50 mm, 4 min. gradiente @ 4 mL/min., detección UV 220 nM; inicial %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%);

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 (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)⁺.

Ejemplo 2



A.

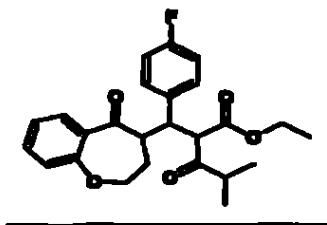


31b

Una mezcla de p-fluorobenzaldehído (4.939 g, 0.039 mol, 1 equiv), etil isobutirilacetato (6.495 g, 0.039 mol, 1 equiv), piperidina (0.395 mL, 3.91 mmol, 0.1 equiv), y ácido acético glacial (0.070 mL, 1.22 mmol, 0.03 equiv) en benceno anhidro (30 mL) se calentó a reflujo con una trampa Dean-Stark para recoger H₂O. Luego de 20 horas, la reacción se enfrió a temperatura ambiente. La mezcla amarilla de la reacción se diluyó con Et₂O (50 mL) y se lavó 0.5N HCl acuoso, NaHCO₃ acuoso saturado, H₂O, y NaCl acuoso saturado. El extracto orgánico se secó sobre Na₂SO₄ anhidro, se filtró al vacío y el filtrado se concentró por evaporación rotatoria in vacuo a un aceite amarillo. La destilación al vacío generó el producto deseado como un aceite amarillo claro (8.575 g, 0.0324 mol, 83%): bp 107-115°C (0.225 mm Hg);

¹H NMR (CDCl₃) δ 1.047 y 1.160 (d's, J=6.6 Hz, 6H, proporción 1.4:1), 1.260 y 1.296 (t's, J=7.1 Hz, 3H, proporción 1:1.4), 2.674 y 3.140 (m's, J=7 Hz, 1H, proporción 1.4:1), 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)⁺.

B.

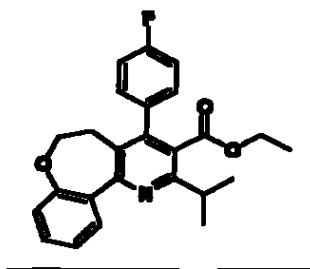


Un matraz de 3 cuellos, de 250 ml, secado al horno, purgado con argón se cargó con THF anhidro (30 ml) y bis(trimetilsilil)amida de litio (1M en THF, 57.9 ml, 0.058 mol, 1.8 equiv), luego se enfrió a -78°C en un baño hielo seco - acetona. Una solución del compuesto Parte A de Ejemplo 1 (7.824 g, 0.0482 mol, 1.5 equiv) en THF seco (6 ml) se agregó mediante la cánula y el enolato se dejó generar durante 1 hora a -78°C. Luego se añadió una solución de compuesto Parte A (8.50 g, 0.0322 mol, 1 equiv) en THF seco (6 ml) mediante la cánula y la solución ámbar resultante se agitó a -78°C durante 30 minutos, luego a 0°C durante 30 minutos. La reacción

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se extinguió con ácido acético glacial (6 ml), luego se vertió en NH_4Cl acuoso saturado. La mezcla se extrajo con Et_2O (100 ml) y el extracto etéreo se lavó con H_2O (2x30 mL) y NaCl acuoso saturado. La orgánica se secó sobre Na_2SO_4 anhidro, se filtró al vacío y se concentró por evaporación rotatoria in vacuo a un aceite amarillo (17.19 g): MS (FAB) m/z 427 ($\text{M}+\text{H}$)⁺.

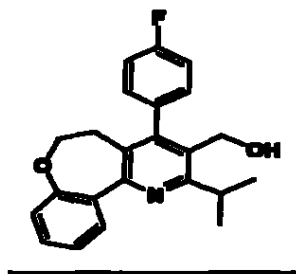
C.



El compuesto crudo Parte B (17.19 g), NH_4OAc (11.0 g, 0.142 mol, 4.4 equiv), y monohidrato $\text{Cu}(\text{OAc})_2$ (24.2 g, 0.119 mol, 3.7 equiv) se disolvieron en HOAc glacial (120 ml) bajo argón y se calentaron a reflujo suave durante 20 horas. La reacción se enfrió a temperatura ambiente, luego se vertió en una solución congelada de NH_4OH concentrado (100 mL) en H_2O (200 ml). La mezcla se extrajo con Et_2O (200 mL+2x100 ml), luego los extractos etéreos combinados se lavaron con H_2O (2x100 mL) y NaCl acuoso saturado. El extracto se secó sobre Na_2SO_4 anhidro, se filtró con vacío y se concentró por evaporación rotatoria in vacuo. El aceite marrón resultante se combinó con hexanos para retirar HOAc , seguido por secamiento in vacuo. La purificación en dos lotes de dos columnas de destello SiO_2 (5cm x 22 cm) con 5% EtOAc /Hexanos generó el producto como un aceite amarillo que cristalizó luego de reposar (5.98 g, 0.0148 mol, 46% para dos pasos):

^1H NMR (CDCl_3) δ 0.959 (t, $J=7$ Hz, 3H), 1.164 y 1.359 (d's, $J=7$ Hz, 6H, proporción 1:4), 2.557 (t, $J=6.2$ Hz, 2H), 2.897 y 3.146 (m's, $J=7$ Hz, 1H, proporción 1:4), 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 ($\text{M}+\text{H}$)⁺.

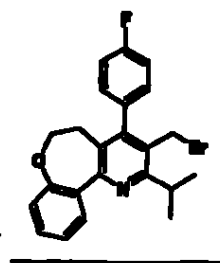
D.



Compuesto Parte C (5.78 g, 0.0143 mol, 1 equiv) se disolvió en THF seco (70 ml) bajo argón y se enfrió a 0°C. Una solución LiAlH₄ en THF (1M, 28.5 mL, 0.0285 mol, 2 equiv) se agregó lentamente. La reacción se agitó a temperatura ambiente durante 2 horas, seguida por 25 minutos a reflujo. TLC (SiO₂, 5% EtOAc/CH₂Cl₂, R_f=0.24). La reacción se enfrió a 0°C, luego se extinguió cuidadosamente con H₂O (2.3 mL), 15% NaOH acuoso (2.3 mL), H₂O (4.7 mL). La mezcla blanca se agitó a temperatura ambiente durante 10 minutos, luego se filtró con vacío y el sólido se lavó con EtOAc. El filtrado se concentró por evaporación rotatoria in vacuo en un aceite amarillo. La purificación en una columna de destello SiO₂ (5cm x 20 cm) con un gradiente de 4% a 8% EtOAc/ CH₂Cl₂ generó el producto como un sólido blanco (4.082 g, 0.0112 mol, 79%):

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), 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.



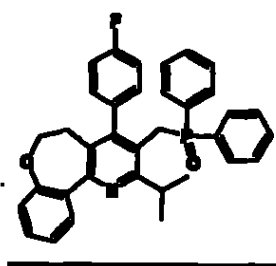
El alcohol Parte D (3.066 g, 8.437 mmol, 1 equiv), disuelto en CH₂Cl₂ seco (60 mL) bajo argón a 0°C, se añadió mediante adición gota a gota de 1M solución de PBr₃ en CH₂Cl₂ (16.9 mL, 16.9 mmol, 2 equiv). La

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reacción se agitó a temperatura ambiente durante 30 minutos, tiempo en el cual la reacción se volvió a enfriar 0°C y se trató NaHCO₃ acuoso saturado (90 mL). La mezcla se diluyó con CH₂Cl₂ (50 mL), se separaron las capas, y la orgánica se lavó con H₂O (2x50 mL) y NaCl acuoso saturado (50 mL). La capa orgánica se secó sobre Na₂SO₄ anhidro, se filtró y se concentró in vacuo. TLC (SiO₂, 5% EtOAc/ CH₂Cl₂, R_f=0.69). El residuo se purificó por cromatografía de destello SiO₂ (columna 3.8cm x 15cm) con CH₂Cl₂ para obtener el producto como un sólido blanco (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)⁺.

F.

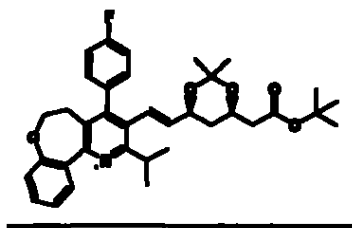


El bromuro Parte E (2.97 g, 6.967 mmol, 1 equiv) y etil difenilfosfinita (1.7 mL, 7.663 mmol, 1.1 equiv) se calentaron a reflujo bajo argón durante 1.5 horas. TLC (SiO₂, 30% EtOAc/CH₂Cl₂, producto R_f=0.47). La reacción se enfrió en un baño de hielo, luego se recogió el sólido por filtración con vacío en un embudo de Buchner; el sólido se lavó con pequeños volúmenes de tolueno, seguido por hexanos. Esto generó el producto como un sólido blanco (3.48 g, 6.35 mmol, 91 %):

¹H NMR (CDCl₃) δ 1.256 (d, J=6.6 Hz, 6H), 2.334 (t, J=6.15 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)⁺.

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G.



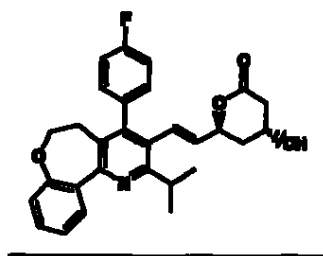
Un matraz de 50-mL, secado al horno, cargado con el óxido de difenilfosfina Parte F (1.00 g, 1.826 mmol, 1 equiv) se combinó con tolueno anhidro (3x5 mL), se secó a alto vacío, y se llenó con argón. El sólido seco se disolvió en THF seco (10 mL) y la suspensión resultante se enfrió a 0°C. Lentamente se agregó un solución de nBuLi (Aldrich, titulada con ácido difenilacético: 2.4 M en hexanos; 0.80 ml, 1.92 mmol, 1.05 equiv) gota a gota durante 20 minutos. La solución color ámbar oscuro resultante se dejó agitando a 0°C durante 1 hora. El aldehído A(1) (0.566 g, 2.192 mmol, 1.2 equiv) en un matraz de 100 mL secado al horno (material previamente combinado con tolueno anhidro (3x5 ml) y secado in vacuo) bajo atmósfera de argón se disolvió en THF seco (5 mL) y se enfrió a -78°C. La solución aniónica se agregó mediante cánula a la solución de aldehído durante un período de 25 minutos, seguidamente la solución color verde oscuro se agitó a -78°C durante 1.5 horas. El baño acetona/hielo seco se retiró entonces y la reacción se dejó calentar lentamente a temperatura ambiente; la solución inicialmente verde se volvió una mezcla anaranjada. Después de 2 horas, la reacción se extinguió con NaCl acuoso semi-saturado (60 mL), se extrajo con Et₂O (100 mL), se lavó a continuación la orgánica con H₂O y NaCl acuoso saturado. La purificación por cromatografía de destello SiO₂ (columna 3.8 cm x 15cm) proporcionó el producto como una espuma blanca (556 mg, 0.946 mmol, 52 %). También se recuperó óxido de difenilfosfina sin reaccionar (445 mg, 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), 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),

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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)⁺.

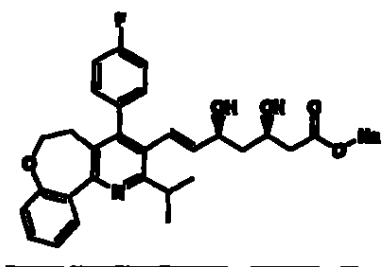
H.



El compuesto Parte G (0.230 g, 0.391 mmol) se disolvió en CH₂Cl₂ seco (5 mL) bajo una atmósfera de argón y se enfrió a 0°C. Se agregó ácido trifluoroacético (0.5 mL) y la mezcla se agitó a temperatura ambiente durante 6 horas. TLC (SiO₂, 20% EtOAc/CH₂Cl₂, R_f=0.31). La solución de la reacción se transfirió a un embudo separador y se trató con NaHCO₃ acuoso saturado (25 mL), se extrajo con EtOAc (100 mL), y la orgánica se lavó con NaHCO₃ acuoso saturado y NaCl acuoso saturado. La orgánica se secó sobre Na₂SO₄ anhidro, se filtró y concentró por evaporación rotatoria in vacuo. El residuo se purificó por cromatografía de destello SiO₂ (columna 1.9 cm x 15 cm) para suministrar el producto como un sólido blanco (160 mg, 0.338 mmol, 86%):

¹H NMR (CDCl₃) 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)⁺.

I.



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La lactona Parte H (148 mg, 0.3125 mmol, 1 equiv) se disolvió en THF (3 mL), se trató con 1N NaOH acuoso (0.391 mL, 0.3907 mmol, 1.25 equiv), y se agitó a temperatura ambiente. TLC (SiO_2 , 0.5:0.5:9 HOAc/MeOH/ CH_2Cl_2 , $R_f=0.25$). Después de 30 minutos, se retiraron los solventes por evaporación rotatoria *in vacuo* y el residuo se secó en alto vacío. Se preparó una columna de resina SP207 Na-form (lecho 1.9cm x 10cm) en la siguiente forma: la resina se vertió en una columna de cromatografía de vidrio equipada con soporte de disco de fritas, se lavó la resina con NaHCO_3 acuoso saturado (15 mL), NaCl acuoso saturado (15 mL), y H_2O deionizada (100 mL, Milli-Q). El residuo se absorbió en Milli-Q DI H_2O (5 mL), se aplicó a la columna, y se eluyó con Milli-Q DI H_2O (100 mL), 10% AcCN/ H_2O (60 mL), y 25% AcCN/ H_2O (125 mL). Las fracciones que contenían el producto se combinaron y concentraron por evaporación rotatoria in vacuo en un pequeño volumen, luego se transfirieron a una jarra de liofilización de 40-mL, empleando H_2O adicional para enjuagar el matraz. El contenido de la jarra se congeló en un baño acetona/hielo seco y se liofilizó para proporcionar el producto como un liofilizado blanco (148 mg, 0.288 mmol, 92%):

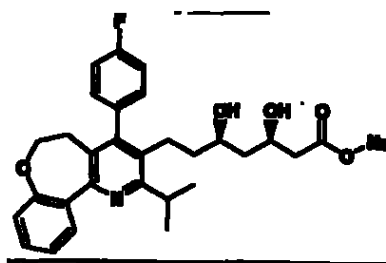
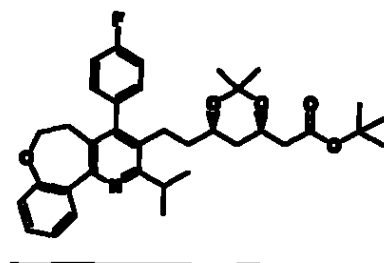
^1H NMR ($\text{DMSO}-d_6$) δ 0.90-1.00 (m, 1H), 1.20-1.35 (m, 7H), 1.727 (dd, $J=14.9$ Hz, 7.9 Hz, 1H), 1.955 (dd, $J=14.9$ Hz, 4 Hz, 1H), 2.399 (t, $J=6.2$ Hz, 2H), 3.424-3.490 (m, 2H), 4.00-4.10 (m, 1H), 4.386 (t, $J=6.2$ Hz, 2H), 4.954 (br s, 1H), 5.354 (dd, $J=16.2$ Hz, 5.3 Hz, 1H), 6.297 (d, $J=16.2$ 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 ($\text{M}+\text{H}$) $^+$;

Análisis. Calculado para $\text{C}_{29}\text{H}_{29}\text{FNO}_5\text{Na} \cdot \text{H}_2\text{O}$:

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

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

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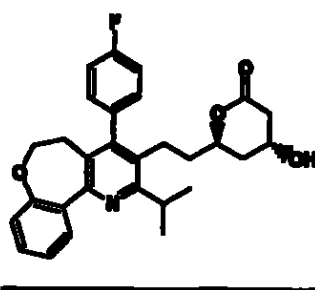
Ejemplo 3**A.**

El compuesto Parte G Ejemplo 2 (200 mg, 0.3403 mmol, 1 equiv) se hidrogenó a 45 psi H_2 en MeOH anhidro (30 ml) con 10% Pd-C (40 mg, 20 % en peso) durante 2 horas. El catalizador se lavó con pequeñas porciones de MeOH y el filtrado se concentró por evaporación rotatoria in vacuo. El residuo se purificó por cromatografía de destello SiO_2 (2.5cm x 13 cm) con 3% EtOAc/ CH_2Cl_2 para suministrar el producto como una espuma blanca (193 mg, 0.3273 mmol, 96%): HPLC (columna Shimadzu YMC S-5 C18 4.6x50 mm, gradiente 4 minutos @ 4mL/min, detección UV 220 nm; inicial %B=60, final %B=100; 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), 4.10-4.20 (m, 1 H), 4.328 (t, $J=6.2$ Hz, 2 H), 7.067 (d, $J=7.9$ 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 ($M+H$) $^+$.

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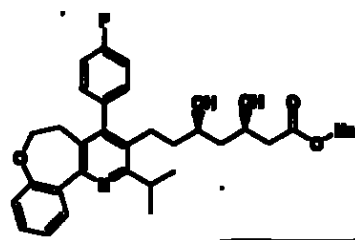
B.



Compuesto Parte A (258 mg, 0.4375 mmol) se disolvió en CH_2Cl_2 seco (5 mL) bajo argón, se enfrió a 0°C y se trató con ácido trifluoroacético (0.5 mL). Se continuó agitando a temperatura ambiente durante 7 horas, tiempo en el cual la reacción se concluyó por HPLC. Se añadió NaHCO_3 acuoso saturado (25 mL) a la reacción, la reacción se diluyó con EtOAc (100 mL), y las capas se separaron. La orgánica se lavó con NaHCO_3 acuoso saturado y NaCl acuoso saturado, luego se secó sobre Na_2SO_4 anhidro, se filtró y concentró in vacuo. La purificación por cromatografía de destello SiO_2 (1.9 cm x 15 cm) con 20% EtOAc/ CH_2Cl_2 proporcionó una espuma blanca (163 mg, 0.343 mmol, 78%): HPLC (columna Shimadzu, YMC S-5 C18 4.6x50 mm, gradiente 4 minutos @ 4mL/minuto, detección UV 220 nM; inicial %B=0, final %B=100; A=10:90 MeOH/ H_2O + 0.2% H_3PO_4 , B=90:10 MeOH/ H_2O + 0.2% H_3PO_4) R.T.=3.81 minutos (94.6%);

^1H NMR (CDCl_3) δ 1.37 (d, $J=6.6$ Hz, 6 H), 1.45-1.85 (m, 4 25 H) I 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 ($\text{M}+\text{H}$) $^+$.

C.



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Compuesto Parte B (149 mg, 0.3133 mmol, 1 equiv) se disolvió en THF (3 mL) y 1N NaOH 1N acuoso (0.392 mL, 0.3916 mmol, 1.25 equiv) y se agitó a temperatura ambiente durante 30 minutos. El solvente se retiró por evaporación rotatoria in vacuo y el residuo se secó bajo alto vacío. Se preparó una columna de resina SP207 (1.9 cm x 10 cm) en la siguiente forma: se vertió resina en una columna de cromatografía de vidrio equipada con un soporte de disco de fritas y la resina se lavó secuencialmente con NaHCO₃ acuoso saturado (15 mL), NaCl acuoso saturado (15 mL), y Milli-Q H₂O (100 mL). El residuo seco se absorbió en Milli-Q H₂O (8 mL) y se aplicó cuidadosamente a la parte superior de la columna. La columna se eluyó con Milli-Q H₂O (100 mL), 10% AcCN/H₂O (60 mL), 20% AcCN/H₂O (60 mL), y 25% AcCN/H₂O (100 mL). Se combinaron y concentraron las fracciones que contenían el producto por evaporación rotatoria en un pequeño volumen, y se transfirieron a una jarra de liofilización de 40-mL. El contenido se congeló en un baño de acetona/hielo seco y se liofilizó. Esto proporcionó el producto como un liofilizado blanco (149 mg, 0.289 mmol, 92%): HPLC (columna Shimadzu, YMC S-5 C18 4.6x50 mm, gradiente 4 minutos @ 4mL/minuto, detección UV detection 220 nm: inicial %B=0, final %B=100; A=10:90 MeOH/H₂O + 0.2% H₃PO₄, B=10:90 MeOH/H₂O + 0.2% H₃PO₄) R. T. =3.58 min (92.9%);

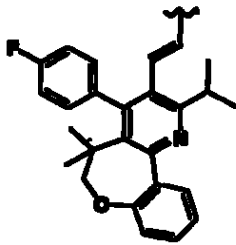
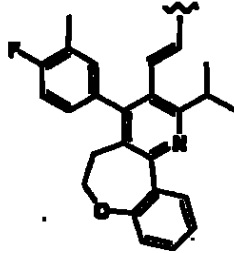
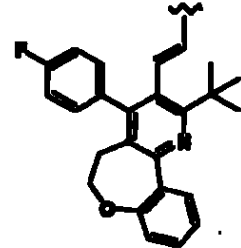
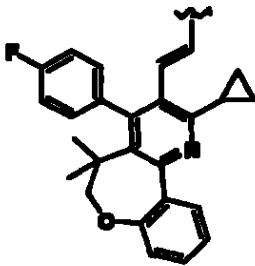
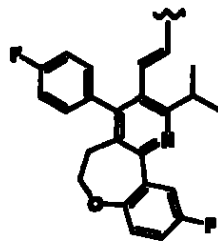
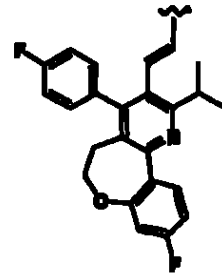
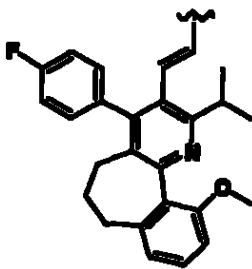
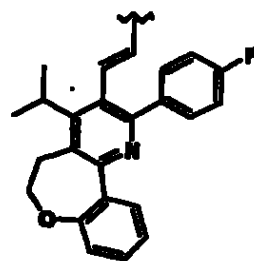
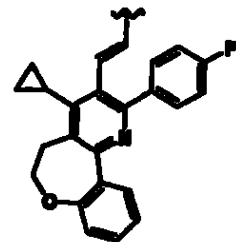
¹H NMR (DMSO-d₆) 4 min 1.048-1.105 (m, 1 H), 1.232-1.50 (m, 9 H), 1.750 (dd, J=14.9 Hz, 8.3 Hz, 1 H), 1.966 (dd, J=14.9 30 Hz, 4.0 Hz, 1 H), 2.298-2.356 (m, 3 H), 3.335-3.424 (m, 2 H), 3.616-3.656 (m, 1 H), 4.3166 (t, J=6.2 Hz, 2 H), 4.711 (br s, 1 H), 7.098 (d, J=7.9 Hz, 1 H), 7.276-7.43 (m, 6 H), 7.773 (d, J=7.5 Hz, 1 H); MS (ESI +Q) m/z 494 (M+H)⁺ para formar ácido.

Los siguiente Ejemplos pueden prepararse empleando procedimientos expuestos aquí y en los Ejemplos de trabajo.

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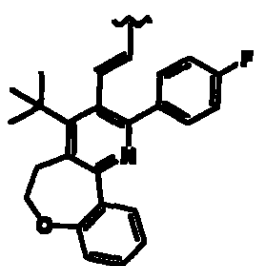
Ejemplo 4 a 26

donde Y es como se expone a continuación

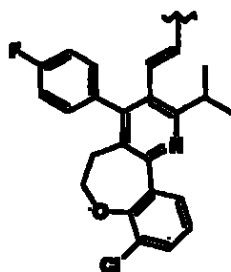
Ejemplo 4**Ejemplo 5****Ejemplo 6****Ejemplo 7****Ejemplo 8****Ejemplo 9****Ejemplo 10****Ejemplo 11****Ejemplo 12**

32X

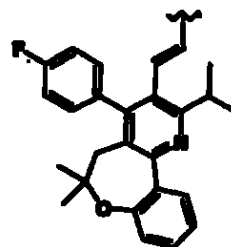
Ejemplo 13



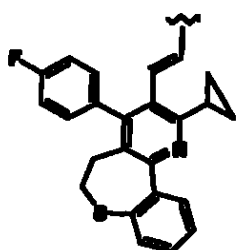
Ejemplo 14



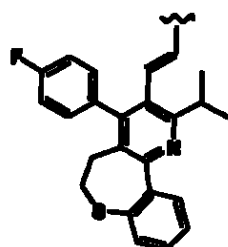
Ejemplo 15



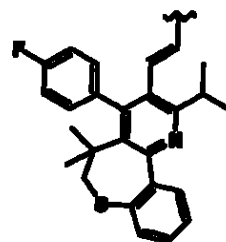
Ejemplo 16



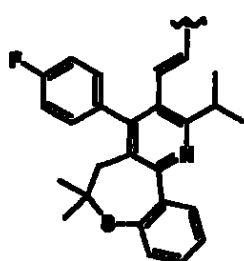
Ejemplo 17



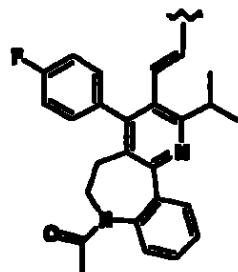
Ejemplo 18



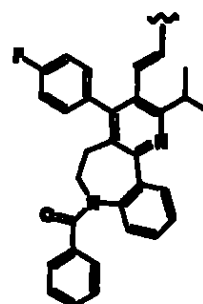
Ejemplo 19



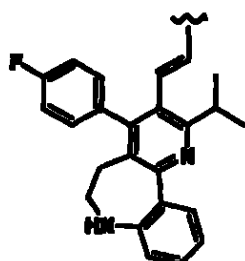
Ejemplo 20



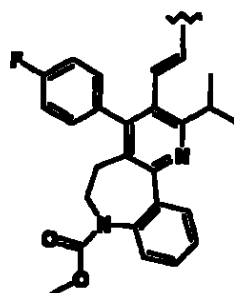
Ejemplo 21



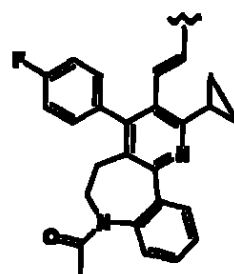
Ejemplo 22



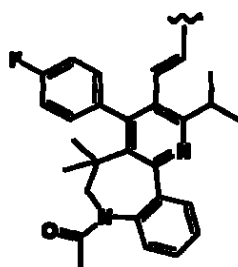
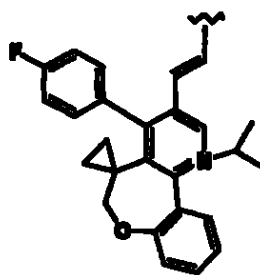
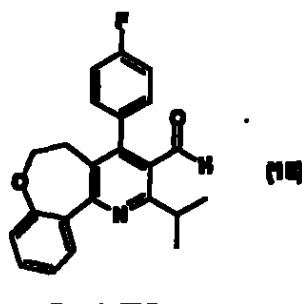
Ejemplo 23



Ejemplo 24



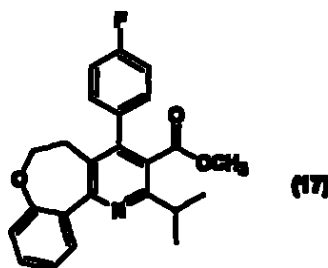
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Ejemplo 25**Ejemplo 26****Ejemplo 27****Preparación de Aldehído de Piridina (18) (Esquema 5)**

Siguiendo el procedimiento descrito en la reacción Esquema 5 y su descripción, se obtiene el aldehído Ejemplo 27.

Un ejemplo de una preparación típica del aldehído se expone a continuación.

En un matraz de base redonda de 500 mL equipado con un agitador magnético y una boca de entrada de nitrógeno se cargó el compuesto (17) (Esquema 5)



(50 g, 128.4 mmol)

(preparado como se describe en Ejemplo 2 Partes A, B y C salvo que metil isobutiril acetato se sustituye por etil isobutiril acetato) y tolueno (170 mL). La mezcla se agitó a 20-25°C hasta obtener una solución transparente. Se agregó una solución de 65% Red-Al en tolueno (57.8 mL, 192.6 mmol) y la mezcla de la reacción se calentó a 80°C hasta que se concluyó según 1

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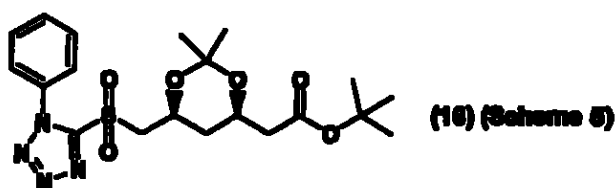
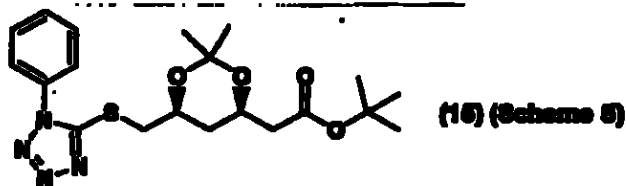
determinado por HPLC. La mezcla de la reacción se enfrió a $\sim 20^{\circ}\text{C}$ y se extinguió vertiéndola en 20% HCl (495 mL) frío ($0 - 5^{\circ}\text{C}$). Se separaron las fases y se descartó la fase de tolueno gastado. Se ajustó el pH de la fase acuosa de <0 a 4-5 con 10N NaOH. Se añadió acetato de etilo (500 mL) y se continuó el ajuste del pH a 7-8. Se separaron las fases. La fase acuosa se extrajo con acetato de etilo adicional (2×500 mL).

La rica solución de acetato de etilo combinado se lavó con agua (3×250 mL) y se concentró bajo presión reducida a ~ 465 mL. Esta solución se llevó al siguiente paso de oxidación.

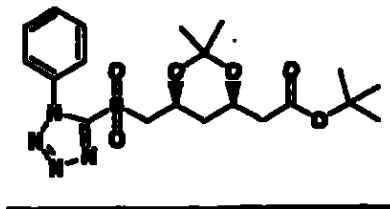
La rica solución de acetato de etilo se cargó de arriba en un matraz de 1 L, de tres cuellos, equipado con agitación mecánica, controlador de temperatura y embudo de adición y se enfrió a $0-5^{\circ}\text{C}$. A la lechada se añadieron bromuro de potasio (1.53 g, 12.8 mmol) y TEMPO (2,2,6,6-tetrametil-1-piperidiniloxi) (0.20 g, 1.28 mmol). El pH de la solución de NaOCl (hipoclorito de sodio) (212.1 mL) se ajustó a ~ 9.1 y se agregó a la lechada a una velocidad tal que la temperatura permaneciera a $0-5^{\circ}\text{C}$. Se continuó agitando a $0-5^{\circ}\text{C}$ hasta que la reacción se concluyó según se determinó por HPLC. La fase acuosa se extrajo con EtOAc (2×200 mL). La fase orgánica rica combinada se lavó con una solución 1:1 de $\text{Na}_2\text{S}_2\text{O}_3$ acuoso saturado (tiosulfato de sodio) (75 mL) y agua (75 mL) seguida por lavado de la fase orgánica rica con 1N NaOH (250 mL). La fase orgánica rica se lavó con agua (250 mL) y se concentró a ~ 100 ml bajo presión reducida. Se agregó isopropanol (IPA) (400 mL) y la mezcla resultante se calentó a reflujo ($80-85^{\circ}\text{C}$). La solución se destiló a un volumen de ~ 250 ml. Se añadió agua (50 mL) y la lechada cristalina se agitó a $70-80^{\circ}\text{C}$ durante 1 hora, luego se dejó enfriar a $20-25^{\circ}\text{C}$ durante por lo menos 1 hora. La lechada se mantuvo a $20-25^{\circ}\text{C}$ durante al menos 1 hora antes de recoger el sólido por filtración en un embudo de Buchner.

La torta se lavó con IPA/agua fría (0°C) (4:1) (2×50 mL) y se secó a un peso constante bajo vacío a 40°C para producir el aldehído del título.

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Ejemplo 28**A. Preparación de Sulfuro (15)**

En un matraz de 250 mL se cargó alcohol Kaneka (12) (Esquema 6) (10.0 g, 38.41 mmol), cloruro de metileno (100 mL), y trietilamina (11.75 mL, 84.51 mmol) y se enfrió a -30°C . Se añadió anhídrido triflico (7.11 mL, 42.25 mmol) a través de una jeringa a una velocidad para mantener la temperatura entre -35 a -25°C , ~15 minutos. La mezcla de la reacción se agitó a -30°C durante ~30 minutos y se comprobó la desaparición de alcohol Kaneka mediante TLC. A la solución de triflato se agregó una lechada 1-fenil-1H-tetrazol-5-tiol (7.19 g, 40.34 mmol) en cloruro de metileno (50 mL). Una vez concluida la reacción, se agregó agua (100 mL) y la mezcla se agitó durante ~5 minutos. Se separaron las fases y se descargó la fase acuosa. La fase orgánica rica se lavó con agua (100 mL) durante ~5 minutos y las fases se separaron. La fase orgánica rica se lavó con NaHCO_3 saturado (100 mL) durante ~15 minutos y las fases se separaron. La rica fase orgánica se concentró a ~50 mL. La solución se tomó en el siguiente paso para su posterior transformación

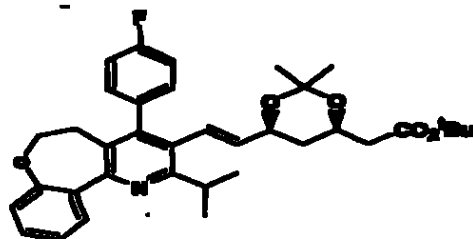
B. Preparación de Sulfona (16)

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IPA (150 mL) se agregó a la solución de sulfuro Parte A del paso de arriba. La solución se enfrió a 0-5°C. A la solución agitada de sulfuro se añadió una solución de $(\text{NH}_4)_6\text{MO}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$ (tetrahidrato heptamolibdato de amonio) (4.75 g, 3.84 mmol) en 30% H_2O_2 (peróxido de hidrógeno) gota a gota durante ~15 minutos manteniendo la temperatura de la solución a 0-5°C. La conversión de sulfuro a sulfona se monitoreó por HPLC ~24 horas. Una vez concluida la reacción, se extrajo mediante destilación cloruro de metileno. La temperatura de marmita se mantuvo a no más de 25°C. La lechada cristalina se destiló a un volumen de ~230 mL con IPA y la lechada resultante se agitó durante al menos 1 hora a 20-22°C. Se recogió el sólido por filtración de vacío, la torta se lavó con IPA/agua (4:1, 25 ml) seguida por secamiento bajo vacío a 40°C a peso constante proporcionando 12.8 g (74%) de la sulfona del título como un sólido blanco cristalino.

Ejemplo 29

Preparación de Olefina (19)



Siguiendo el procedimiento expuesto en el Esquema de reacción 5 y su descripción, el derivado de piridina Ejemplo 27 y la sulfona Ejemplo 28 se emplean para preparar el compuesto del título.

Un ejemplo de una preparación típica del compuesto Ejemplo 29 se expone a continuación.

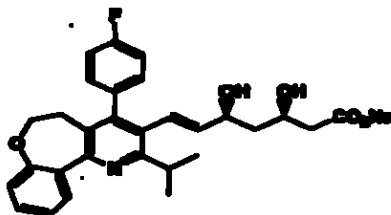
Un matraz de base redonda, de 3 cuellos, 250 mL, purgado con N_2 se cargó con el derivado de piridina de Ejemplo 27 (18) (5 g, 13.9 mmol), sulfona Ejemplo 28 (16) (6.9 g, 15.3 mmol) y THF (75 mL). La solución agitada se enfrió -74 a -78°C. Lentamente 1M de solución de LiHMDS (bis(trimetilsilil)amida de litio) (15.3 ml, 15.3 mmol) en THF se cargó a una velocidad tal que la temperatura permaneciera entre -70 y -78°C. Una

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vez concluida la adición de la base, la mezcla de la reacción se calentó a -45°C durante ~15 minutos. La reacción agitada se extinguió a -70°C. Mediante lenta adición de solución de NH_4Cl acuoso saturado (7.5 mL) y agua (38 mL). El baño helado se retiró y la solución se calentó a 20-25°C a partir de la mezcla de la reacción. Se añadió acetato de etilo (50 mL), la mezcla se agitó, y las capas se separaron. La capa orgánica se lavó con solución de bicarbonato de sodio saturado (2 x 38 mL) seguida por salmuera (25 mL) y se concentró en un volumen de 50 mL. Se agregó acetonitrilo (50 mL) y la solución se concentró en un volumen de 50 mL. Este paso se repitió. Se añadió agua (~5-6 mL) lentamente a la solución caliente (60-70°C) hasta que se obtuvo el punto de separación de fases. La lechada delgada se mantuvo durante 30 minutos a alta temperatura y luego se enfrió varias hora agitando. El producto se filtró, la torta se lavó con una mezcla 5:1 de acetonitrilo y agua, y se secó para producir el compuesto del título.

Example 30

Preparación del compuesto final

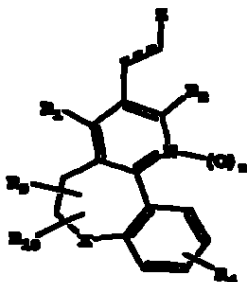


Siguiendo el procedimiento de Ejemplo 3 Partes B y C, el compuesto Ejemplo 29 se empleó para preparar el compuesto del título en la forma de sal de sodio.

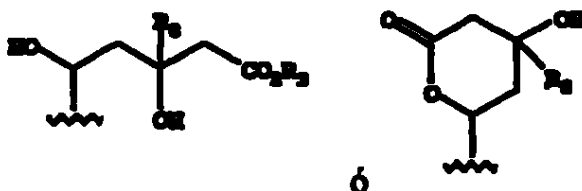
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Lo que se reivindica es:

1. Un compuesto que tiene la estructura



en donde X es O, S o NR;



z es

ó

n es 0 ó 1;

R_1 y R_2 son los mismos o diferentes y se seleccionan independientemente de alquilo, arilalquilo, cicloalquilo, alquenilo, cicloalquenilo, arilo, heteroarilo o cicloheteroalquilo;

R_3 es H o alquilo inferior;

R_4 es H, halógeno, CF_3 , hidroxilo, alquilo, alcoxi, alcanoilamino, aroilamino, o ciano;

R_7 es H, alquilo, arilo, alcanoilo, aroilo o alcoxicarbonilo;

R_8 es H o alquilo inferior;

R_9 y R_{10} son los mismos o diferentes y se seleccionan independientemente de H o alquilo, o R_9 y R_{10} pueden tomarse juntos con el carbono o carbonos a los cuales se unen para formar un anillo carbocíclico de 3 a 7 miembros,

y  representa un enlace simple o un enlace doble (que puede ser cis o trans);

e inclusive sus sales farmacéuticamente aceptables (donde R_3 es H), sus ésteres, sus ésteres de profármaco, y todos sus estereoisómeros.

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2. El compuesto como se define en la reivindicación 1 en donde



es un doble enlace que es trans.

3. El compuesto como se define en la reivindicación 1 en donde

R_1 es arilo,

R_2 es alquilo o cicloalquilo o arilo;

R_4 es H;

n es 0;

X es O; y



es un enlace doble trans, en la forma de un ácido libre o sal de metal alcalino o alcalinotérreo o una sal de aminoácido.

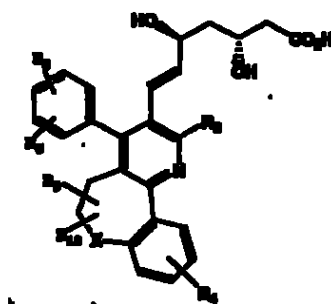
4. El compuesto como se define en la reivindicación 3 en donde

R_1 es 4-fluorofenilo, 4-fluoro-3-metilfenilo, ó 3,5-dimetilfenilo; y

R_2 es isopropilo, t-butilo o ciclopropilo.

5. El compuesto como se define en la reivindicación 1 que tiene

la estructura



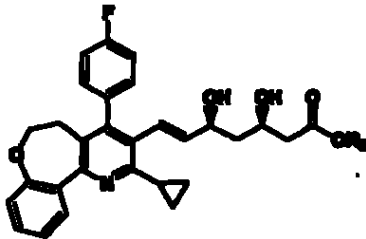
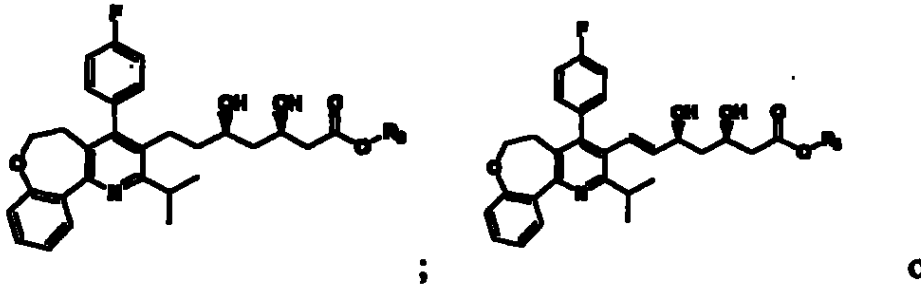
o su sal de un metal alcalino o alcalinotérreo o una sal de aminoácido o una sal de adición de ácido mediante la piridina de la δ lactona correspondiente,

donde R_3 y R_6 son los mismos o diferentes y se seleccionan independientemente de H, halógeno o alquilo y

R_2 es alquilo o cicloalquilo.

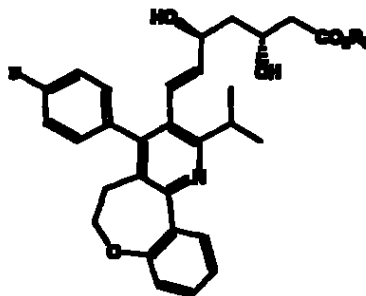
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6. El compuesto como se define en la reivindicación 1 que tiene la estructura



en donde R_3 es H o una sal de metal alcalino o alcalinotérreo o de aminoácido u otra sal farmacéuticamente aceptable, o su lactona interna.

7. Un compuesto de la estructura



en donde R_3 es H o un ión de metal alcalino o alcalinotérreo o un aminoácido, o su lactona interna.

8. Una composición farmacéutica que comprende un compuesto como se define en la reivindicación 1 y un portador farmacéuticamente aceptable para el mismo.

9. Una combinación farmacéutica que comprende el compuesto inhibidor de la HMG CoA reductasa como se define en la reivindicación 1 y uno o más agentes hipolipémicos agentes reductores de lípido, o agentes

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de lípido, o agentes moduladores de lípido, y/o uno o más otros tipos de agentes terapéuticos inclusive agentes antidiabéticos, agentes anti-obesidad, agentes antihipertensivos, inhibidores de agregación de plaquetas, agentes anti-demencia, agentes anti-Alzheimer, agentes anti-osteoporosis, y/ agentes terapéuticos de reemplazo de hormonas, y/o otros agentes cardiovasculares (inclusive agentes anti-anginales, agentes anti-arritmicos, agentes anti-aterosclerosis, agentes anti-inflamatorios, agentes anti-artritis, agentes anti-plaquetas, agentes anti-falla cardíaca), agentes anti-cáncer, agentes anti-infecciosos, agentes de reemplazo de hormonas, secretagogos hormonales de crecimiento, moduladores de receptor andrógeno selectivo, y/o agentes inmunomoduladores.

10. La combinación como se define en la reivindicación 9 en donde el agente hipolipidémico o agente reductor de lípido u otro agente de lípido o agente modulador de lípido o agente anti-aterosclerótico, que se emplea comprende 1, 2, 3 o más inhibidores MTP, inhibidores de HMG CoA reductasa, inhibidores de escualeno sintetasa, derivados de ácido fibrico, α agonistas PPAR, α/γ agonistas duales PPAR, δ agonistas PPAR, inhibidores ACAT, inhibidores de lipoxigenasa, inhibidores de absorción de colesterol, inhibidores de co-transportador de ácido biliar/ Na^+ ileal, reguladores ascendentes de actividad de receptor LDL, inhibidores de proteína de transferencia de éster colesterílico, secuestrantes de ácido biliar, o ácido nicotínico y sus derivados, inhibidores de citrato liasa ATP, compuestos de fitoestrógeno, reguladores ascendentes HDL, promotores de catabolismo LDL, antioxidantes, inhibidores de PLA-2, agentes antihomocisteína, inhibidores de HMG-CoA sintasa, inhibidores de lanosterol demetilasa, o agentes proteína-I de enlace de elemento regulador de esterol;

en donde el agente antidiabético que puede emplearse opcionalmente es 1,2,3 ó más agentes antidiabéticos o agentes antihiper glucémicos inclusive secretagogos de insulina o sensibilizadores de insulina, los cuales pueden incluir biguanidas, sulfonilureas, inhibidores PTP-1B, inhibidores

de aldosa reductasa, inhibidores de glucosidasa, γ agonistas PPAR, α agonistas PPAR, δ antagonistas PPAR o agonistas, inhibidores $\alpha P2$, α/γ agonistas duales PPAR, inhibidores de dipeptidil peptidasa IV (DP4), inhibidores SGLT2, inhibidores de glicógeno fosforilasa, y/o meglitinidas, insulina, y/o péptido-1 (GLP-1) similar del glucagón, o sus miméticos; en donde el otro tipo de agente terapéutico que puede emplearse opcionalmente es 1, 2, 3 o más de un agente anti-obesidad que es un agonista beta 3 adrenérgico, un inhibidor de lipasa, un inhibidor de reabsorción de serotonina (y dopamina), un inhibidor $\alpha P2$, un fármaco beta receptor tiroideo, un agente anoréxico, un inhibidor PTP-1B, un agonista CCKA, un antagonista de neuropéptido Y, un agonista de receptor melanocortina-4, un modulador PPAR que es un γ antagonista PPAR, α agonistas PPAR, y/o δ antagonistas PPAR, un inhibidor de leptina tal com un activador de receptor de leptina, un regulador ascendente de oxidación de ácido graso o inductor;

en donde el agente modulador de lípido es un inhibidor de MTP, un inhibidor de HMG CoA reductasa, un inhibidor de escualeno sintetasa, un derivado de ácido fibríco, un regulador ascendente de actividad de receptor LDL, un inhibidor de lipoxigenasa, o un inhibidor de ACAT y el otro agente de lípido es un inhibidor de proteína de transferencia de éster colesterfílico;

en donde el agente antihipertensivo empleado es un inhibidor ACE, antagonista de receptor de angiotensina II, inhibidor NEP, un inhibidor NEP/ACE, un bloqueador de canal del calcio, un antagonista de calcio de canal T, un bloqueador β -adrenérgico, un diurético, un bloqueador α -adrenérgico, un antagonista de receptor de acción dual (DARA), o un fármaco para falla cardíaca .

11. La combinación como se define en la reivindicación 10 en donde el agente antidiabético es 1, 2, 3 ó más de metformina, glyburida, glimepirida, glipirida, glipizida, clorpropamida, gliclazida, acarbosa, miglitol, pioglitazona, troglitazona, rosiglitazona, insulina, Gl-262570,

isaglitazona, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinida, nateglinida, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 y/o NvP-DPP-728A;

en donde el agente anti-obesidad es orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramina, topiramato, axokine, dexamfetamina, fentermina,

fenilpropanolamina, y/o mazindol, P57 o CP-644673 (Pfizer);

en donde el agente modulador de lípido es pravastatina, lovastatina, simvastatina, atorvastatina, cerivastatina, fluvastatina, pitavastatina, rosuvastatina, fenofibrato, gemfibrozil, clofibrato, avasimibe, TS-962, MD-700, cholestagel, niacina, y/o LY295427;

en donde el agente antihipertensivo es un inhibidor ACE el cual es captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril o moexipril;

un inhibidor de NEP/ACE el cual es omapatrilat, gemopatrilat, o CGS 30440;

un antagonista de receptor de angiotensina II el cual es irbesartan, losartan o valsartan;

amlodipina besilato, prazosina HCl, verapamil, nifedipina, nadolol, propranolol, o clonidina HCl, carvediol, atenolol, hidroclorotiazida, torasemida, furosemida, espironolactona o indapamida;

en donde el inhibidor de agregación de plaquetas es aspirina, clopidogrel, ticlopidina, dipyridamol, ifetroban, abciximab, tirofiban, eptifibatide, o anagrelide;

en donde el otro agente terapéutico es un agente Alzheimer's o agente anti-demencia, el cual es tacrina HCl (Cognex®), donepezil (Aricept®), un inhibidor de Γ -secretasa, un inhibidor de β -secretasa y/o agente antihipertensivo;

un agente antiosteoporosis, el cual es una hormona paratiroide, un bisfosfonato, alendronato, un agonista de receptor Ca o un agonista de receptor de progestina;



un agente terapéutico de reemplazo hormonal, el cual es un modulador de receptor de estrógeno selectivo (SERM);

un inhibidor de tirosina cinasa;

un modulador de receptor de andrógeno selectivo;

un agente antiarrítmico, el cual es un bloqueador β , o un bloqueador de canal de calcio, o un bloqueador α -adrenérgico;

coenzima Q sub. 10;

un agente que regula ascendentemente la sintasa de ácido nítrico de célula endotelial tipo III;

un compuesto condroprotector que es glicosaminoglicana polisulfatada (PSGAG), glucosamina, condroitina sulfato (CS), ácido hialurónico (HA), polisulfato de pentosana (PPS), doxiciclina minociclina;

un inhibidor de ciclooxigenasa (COX)-2, el cual es Celebrex® (Searle) o Vioxx® (Merck) o un antagonista de receptor de glicoproteína IIa/IIIb;

un inhibidor de reabsorción de 5-HT;

un secretagogo hormonal de crecimiento; un agente anti-aterosclerosis;

un agente anti-infeccioso, o un inmunosupresor para uso en transplante, o un agente antineoplástico.

12. La combinación como se define en la reivindicación 10 en donde el compuesto inhibidor de HMG CoA reductasa está en combinación con un inhibidor de ACE o un inhibidor de NEP/ACE.

13. La combinación como se define en la reivindicación 12 en donde el compuesto inhibidor de HMG CoA reductasa está en combinación con un inhibidor de ACE el cual es ramipril;

en donde el inhibidor de HMG CoA reductasa está en combinación con un inhibidor de NEP/ACE el cual es omapatrilat o gemopatrilat;

en donde el inhibidor de HMG CoA reductasa está en combinación con un inhibidor de agregación de plaquetas.

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14. La combinación como se define en la reivindicación 13 en donde el inhibidor de plaquetas es clopidogrel, o aspirina o una combinación de clopidogrel y aspirina.

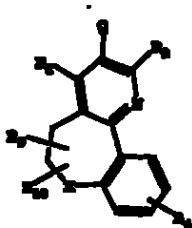
15. Un método de inhibir biosíntesis de colesterol o de disminuir los niveles de colesterol del suero sanguíneo y/o modular niveles de colesterol del suero sanguíneo reducir colesterol LDL y/o aumentar colesterol HDL, o tratar dislipidemia, dislipidemia mixta, Patrón B LDL, Patrón A LDL, hiperlipidemia, hipercolesterolemia, hipo α -lipoproteinemia, hiperlipoproteinemia o hipertrigliceridemia, y otras aberraciones de metabolismo de apolipoproteína B, o reducir niveles de Lp(a), o tratar prevenir otras enfermedades relacionadas con el colesterol, o tratar o prevenir o revertir la progresión de aterosclerosis, o prevenir o tratar la enfermedad de Alzheimer, o prevenir o tratar osteoporosis y/o osteopenia, reducir marcadores inflamatorios, reducir proteína C-reactiva, o prevenir o tratar inflamación vascular de grado bajo, o prevenir o tratar apoplejía, o prevenir o tratar demencia, o prevenir y tratar enfermedad cardíaca coronaria, y prevención primaria y secundaria de infarto del miocardio, prevenir o tratar angina estable e inestable, o prevención primaria de eventos coronarios, o prevención secundaria de eventos cardiovasculares, o prevenir o tratar enfermedad vascular periférica, prevenir o tratar enfermedad arterial periférica, o prevenir o tratar síndromes vasculares agudos, o prevenir o reducir el riesgo de someterse a intervenciones de revascularización del miocardio, o prevenir o tratar enfermedades microvasculares tales como nefropatía, neuropatía, retinopatía y síndrome nefrótico o prevenir o tratar hipertensión, prevenir o tratar diabetes Tipo 1, diabetes Tipo 2, y enfermedades relacionadas, resistencia a la insulina, hiperglicemia, hiperinsulinemia, niveles elevados en la sangre de ácidos grasos o glicerol, obesidad, Patrón B LDL, Patrón A LDL, Síndrome X, complicaciones diabéticas, síndrome dismetabólico, y enfermedades relacionadas, y disfunción sexual, prevenir y tratar lesiones malignas,

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lesiones pre-malignas, malignidades gastrointestinales, liposarcomas y tumores epiteliales, astenia inducida por cáncer (fatiga), síndrome de intestino irritable, enfermedad de Crohn, ulceritis gástrica, y cálculos biliares, e infección HIV, lipodistrofia inducida por fármacos, y enfermedades proliferativas, mejorar la homeostasis de coagulación, reducir la actividad PAI-1, disminuir el fibrinógeno, y/o reducir la agregación de plaquetas, y/o mejorar la función endotelial, que comprende administrar a una especie mamífera necesitada de tratamiento una cantidad terapéuticamente efectiva de un compuesto como se define en la reivindicación 1.

16. Un método para tratar enfermedades relacionadas con colesterol, diabetes y enfermedades relacionadas, enfermedades cardiovasculares, enfermedades cerebrovasculares que comprende administrar a una especie mamífera necesitada de tratamiento una cantidad terapéuticamente efectiva de una combinación de un compuesto como se define en la reivindicación 1 y un agente hipolipidémico, y/o agente modulador de lípido y/o agente antidiabético y/o agente cardiovascular, agente cerebrovascular, y/o otro tipo de agente terapéutico, que comprende administrar a una especie mamífera necesitada de tratamiento una cantidad terapéuticamente efectiva de dichas combinaciones.

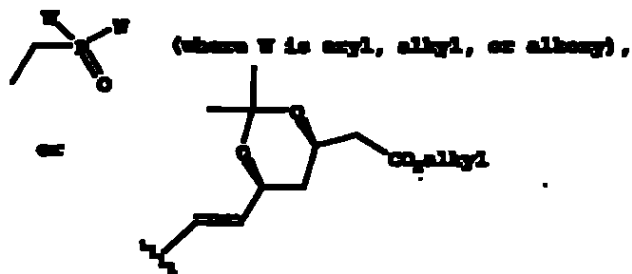
17. Un compuesto que tiene la estructura



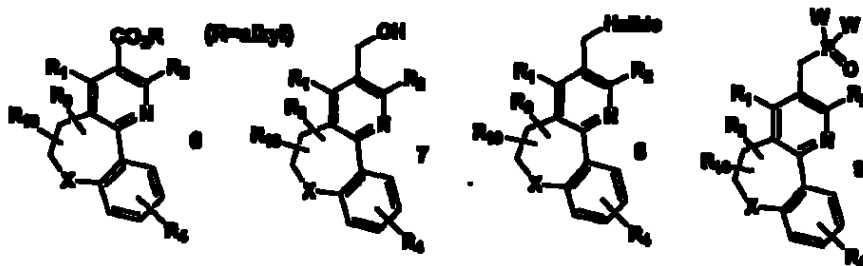
en donde X es O, S o NR₇ en donde R₇ es H, alquilo, arilo, alcanilo, aroilo o alcoxicarbonilo; R₁ y R₂ son los mismos o diferentes y se seleccionan independientemente de alquilo, arilalquilo, cicloalquilo, alquenilo, cicloalquenilo, arilo, heteroaril o cicloheteroalquilo;

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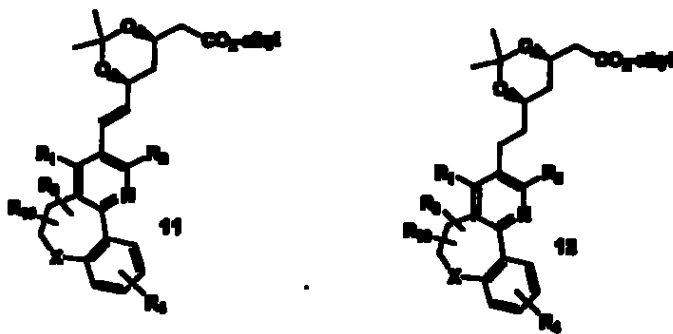
R_9 y R_{10} son los mismos o diferentes y se seleccionan independientemente de H o alquilo, o R_9 y R_{10} pueden tomarse juntos con el carbono o carbonos a los cuales se unen para formar un anillo carbocíclico de 3 a 7 miembros;



18. El compuesto como se define en la reivindicación 17 que tiene las siguientes estructuras:



(W=arilo, alquilo o alcoxi)



INFORME INTERNACIONAL DE BÚSQUEDA

Solicitud Internacional No.
PTC/US 01/18884

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD IPC 7 C07D491/04 C07D495/04 C07D471/04 A61K31/55 // (C07D491/04, 313:00, 221:00), (C07D495/04, 337:00, 221:00), (C07D471/04, 223:00, 221:00)		
De acuerdo con la Clasificación Internacional de Patentes (IPC) o con ambas, la Clasificación Nacional e IPC		
B. CAMPOS BUSCADOS Documentación mínima buscada (sistema de clasificación seguido y símbolos de clasificación) IPC 7 C07D A61K A61P Documentación buscada distinta de la documentación mínima siempre que dichos documentos se incluyan en los campos buscados Base electrónica de datos consultada durante la búsqueda Internacional (nombre de la base de datos y, eventualmente, términos de búsqueda empleados) EPO-Interna, Datos WPI, PAJ, BIOSIS		
C. DOCUMENTOS CONSIDERADOS RELEVANTES		
Categoría	Designación del documento, con indicación, si se considera apropiado, de los pasajes relevantes	Relevante para la Reivindicación No.
Y	EP 0 444 533 A (SQUIBB & SONS INC.) 4 de septiembre de 1991 (1991-09-04) ejemplos 3, 9, 10	1-18
Y	US 5 686 433 A (ROBL JEFFREY ADAM) 11 de noviembre de 1997 (1997-11-11) citada en la solicitud ejemplos 63, 75, 76, 99	1-18
Y	EP 0 325 130 A (BAYER AG) 26 de julio de 1989 (1989-07-26) reivindicaciones	1-18
Y	EP 0 818 187 A (BAYER AG) 14 de enero de 1998 (1998-01-14) página 16; tabla 5	1-18
— — — — —		
☒	Otros documentos se enumeran en la continuación de cuadro C.	☒
Miembros de la familia de patente se enumeran en el anexo.		
"A" documento que define el estado general del arte pero que no se considera que sea de relevancia particular "E" documento anterior pero publicado en la fecha de presentación internacional o después "L" documento que puede arrojar dudas con respecto a la reivindicación (reivindicaciones) de prioridad o que se cita para establecer la fecha de publicación de otra designación u otra razón especial (como se especifica) "O" documento referente a una revelación verbal, uso, exhibición u otros medios "P" documento publicado con anterioridad a la fecha de presentación internacional, pero con posterioridad a la fecha de prioridad reclamada	"T" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la aplicación pero citado para entender el principio o teoría subyacente a la invención. "X" documento de particular relevancia; la invención reivindicada no puede considerarse nueva o no puede considerarse que implica un paso innovador si el documento se toma solo. "Y" documento de particular relevancia; la invención reivindicada no puede considerarse que implica un paso innovador si el documento se combina con uno o más de dichos documentos, siendo obvia dicha combinación a una persona con habilidades en el arte. "&" documento miembro de la misma familia de patente	
Fecha de la conclusión actual de la búsqueda Internacional 25 de octubre de 2001		Fecha de envío por correo del informe de búsqueda Internacional 06/11/2001
Nombre y dirección postal de la Oficina de Búsqueda Internacional (ISA) European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 851 epo nl, Fax: (+31-70) 340-3016		Funcionario autorizado Frelon, D

INFORME INTERNACIONAL DE BÚSQUEDA

Solicitud Internacional No.
PTC/US 01/18864

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C. (Continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría ^o	Designación del documento, con indicación, si se considera apropiado, de los pasajes relevantes	Relevante para la Reivindicación No.
A	US 5 753 875 A (WATTANASIN SOMPONG) 19 de mayo de 1998 (1998-05-19) citada en la solicitud extracto; reivindicaciones —	1-18
A	EP 0 491 226 A (BAYER AG) 24 de junio de 1992 (1992-06-24) todo el documento —	1-18
A	ROBL J A Y COLABORADORES: "INHIBIDORES CON CONTENIDO DE FÓSFORO DE HMG-COA REDUCTASA. 2. SÍNTESIS Y ACTIVIDADES BIOLÓGICAS DE UNA SERIE DE PIRIDINAS SUSTITUIDAS QUE CONTIENEN UN HIDROXIFOSFINILO" DIARIO DE QUÍMICA MEDICA, SOCIEDAD QUÍMICA NORTEAMERICANA. WASHINGTON, US, vol. 34, no. 9, 1991, páginas 2804-2815, XP002922111 ISSN: 0022-2623 Todo el documento —	

INFORME INTERNACIONAL DE BÚSQUEDA
**Solicitud Internacional No.
PTC/US 01/18864**

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Documento de patente citado en el Informe de búsqueda	Fecha de Publicación	Miembro (s) de familia de patente	Fecha de publicación
EP 0444533 A	04-09-1991	AU 645287 B2 AU 7101691 A CA 2036417 A1 EP 0444533 A2 HU 56574 A2 IE 910543 A1 JP 4211680 A NZ 237097 A PT 96874 A US 5506219 A US 5686433 A US 5691322 A ZA 9101046 A	13-01-1994 29-08-1991 27-08-1991 04-09-1991 30-09-1991 28-08-1991 03-08-1992 23-12-1993 31-10-1991 09-04-1996 11-11-1997 25-11-1997 28-10-1992
US 5686433 A	11-11-1997	US 5506219 A US 5691322 A AU 645287 B2 AU 7101691 A CA 2036417 A1 EP 0444533 A2 HU 56574 A2 IE 910543 A1 JP 4211680 A NZ 237097 A PT 96874 A ZA 9101046 A AU 637321 B2 AU 3941389 A DK 422989 A EP 0356788 A2 HU 52479 A2 JP 2108665 A NZ 230121 A ZA 8905889 A	09-04-1996 25-11-1997 13-01-1994 29-08-1991 27-08-1991 04-09-1991 30-09-1991 28-08-1991 03-08-1992 23-12-1993 31-10-1991 28-10-1992 27-05-1993 21-06-1990 01-03-1990 07-03-1990 28-07-1990 20-04-1990 28-08-1993 30-05-1990
EP 0325130 A	28-07-1989	DE 3801406 A1 AU 642127 B2 AU 2861789 A CN 1274719 A CN 1034364 A, B DD 283400 A5 DK 23389 A EP 1123924 A1 EP 1123925 A1 EP 0325130 A2 FI 890258 A, B HU 50776 A2 JP 1216974 A JP 2558344 B2 KR 132432 B1 NO 177005 B NZ 227637 A PT 89477 A, B US 5006530 A US 5169857 A US 5401746 A ZA 8900429 A	27-07-1989 14-10-1993 20-07-1989 29-11-2000 02-08-1989 10-10-1990 21-07-1989 16-08-2001 16-08-2001 28-07-1989 21-07-1989 28-03-1990 30-08-1989 27-11-1996 17-04-1998 27-03-1995 25-02-1993 08-02-1990 09-04-1991 08-12-1992 28-03-1995 28-02-1990

INFORME INTERNACIONAL DE BÚSQUEDA

Solicitud Internacional No.
PTC/US 01/18864

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Documento de patente citado en el informe de BÚSQUEDA	Fecha de Publicación	Miembro (s) de familia de patente	Fecha de publicación
EP 0818197 A	14-01-1998	DE 19827431 A1 AU 715101 B2 BG 101748 A BR 9703890 A CA 2209825 A1 CN 1174196 A CZ 9702144 A3 EE 9700153 A EP 0818197 A1 HR 970333 A1 HU 9701157 A2 IL 121234 A JP 10167867 A NO 973143 A PL 320953 A1 SG 46781 A1 SK 92597 A3 TR 9700584 A2 TW 382631 B US 5932587 A	15-01-1998 13-01-2000 30-04-1998 03-11-1998 08-01-1998 25-02-1998 14-01-1998 16-02-1998 14-01-1998 30-04-1998 30-03-1998 06-12-2000 23-06-1998 09-01-1998 19-01-1998 20-02-1998 06-05-1998 21-01-1998 21-02-2000 03-08-1999
US 5753675 A	19-05-1998	NINGUNO	
EP 0491226 A	24-06-1992	DE 4040026 A1 AT 141261 T AU 852977 B2 AU 8961591 A CA 2057444 A1 CN 1062350 A, B CN 1113485 A CS 9103802 A3 DE 59108081 D1 DK 491226 T3 EP 0491226 A1 ES 2091852 T3 FI 915854 A GR 3020826 T3 HK 1004552 A1 HU 81282 A2 HU 9500173 A3 IE 914350 A1 IL 100327 A JP 2786363 B2 JP 4308573 A KR 192625 B1 LU 90230 A9 NO 177140 B NZ 240946 A PL 169757 B1 PT 99776 A, B SK 280115 B6 RU 2026290 C1 US 5177080 A ZA 9109833 A	17-06-1992 15-08-1996 15-09-1994 18-06-1992 15-08-1992 01-07-1992 20-12-1995 17-06-1992 19-09-1996 06-01-1997 24-06-1992 16-11-1996 15-06-1992 30-11-1996 27-11-1996 28-12-1992 28-07-1995 17-06-1992 08-12-1995 13-08-1998 30-10-1992 15-06-1999 18-05-1996 18-04-1995 27-09-1993 30-08-1996 30-11-1992 06-08-1999 09-01-1995 05-01-1993 30-08-1992

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCION	MODELO DE UTILIDAD	()	(x)
- Indicación de que se solicita la concesión de una patente.		()	(x)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	(x)
- Descripción de la invención.		()	()
- Dibujos de ser estos pertinentes.		()	(x)
- Comprobante de Pago de las tasas establecidas.			
COMPLETA	(x)	INCOMPLETA	()
DISEÑO INDUSTRIAL ()			
- Indicación de que se solicita el registro de Diseño Industrial		()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.		()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.		()	()
- Comprobante de pago de las tasas establecidas		()	()
COMPLETA	()	INCOMPLETA	()
ESQUEMA DE TRAZADO ()			
- Indicación de que solicita el registro de un Esquema de trazado.		()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.		()	()
- Representación gráfica del esquema de trazado		()	()
- Comprobante de pago de las tasas establecidas.		()	()
COMPLETA	()	INCOMPLETA	()

Eduin Nuño
 Firma Responsable:

13-12-2002

Fecha:

INFORME DE PROTOCOLO

SUPERINDUSTRIA Y COMERCIO		SISTEMA DE REGISTRO	
		Fecha 26/08/2003	
MANTENIMIENTO DE PROTOCOLOS			
Numero : 19358			
Fecha : 07/05/1999			
Conferido: BRISTOL-MYERS SQUIBB COMPANY			
País : US ESTADOS UNIDOS DE AMERICA			
Ciudad : 02 PRINCETON, NEW JERSEY			
Represent: S Sustituir : S Desistir : S			
No. Radicacion : 99 28346 Clase: 8 Secv: 0 Seac: 0			
Presencia	Codigo	Ctr	Nombre
1	340	A	CASTRO DUQUE RAMIRO
2	3002		GOMEZ MEJIA HECTOR
Encontrados (1/1) registro(s)			

2020
Bogotá, D.C.,

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
BRISTOL MYERS SQUIBB COMPANY

Oficio N° **07051**

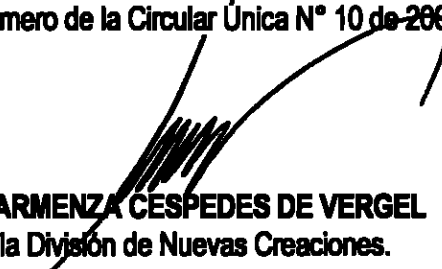
ASUNTO:	Radicación N°	02-113275
	Solicitud internacional	PCT/US01/18864
	Fecha inicio fase nacional	15-01-2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el artículo 38 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 Superintendencia de Industria y Comercio, se le comunica que:

- El solicitante debe aclarar si la solicitud corresponde al capítulo I o II del PCT, ya que en el formulario petitorio no resulta claro este hecho; según sea el caso, deben adjuntarse todos los documentos y/o traducciones que correspondan.
- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

29 AGO. 2003

El anterior requerimiento fue notificado por fijación en lista de fecha _____.

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