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[I] Documento que acredita la existencia y represantación legal cuando el solicitante sea persona juridica
Poderes, al fuere el caso. Protocolo No. 19358

LI Documento de cesión del inventor al solicitante o a su causante.
LI oeciaraciones
Copia de la solicitud intemacional. (Resumen, descpcion, reMndicaciones, dibujos)
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El Traducción del examen preliminar efectuado por la IPEA,
[I De sec el caso, copia del contrato de acceso.
LI De sec el caso, documento que acredite la licencia o autorizacion de uso de conocimientos tradicionales de las comuni-dades indigenas.
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[ii] Arte final l2xl2.
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NOMBRE RAM1RO CASTRLDUQUE

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(54) Title: HMG-CoA REDUCTASE INHIBITORS AND MHOD

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(57) Abstract Compounds ofthe following structure are HMG CoA reductase inhibitors and thus are active in inhibiting cholesterol biosynthesis, modulating blood serum lipids, for example, lowering LDL cholesterol and/orincreasing HDL cholesterol, and treating -. hyperlipidemia, dyslipidemia, hormone replacement therapy, hypercholesterolemia, hypertriglyceridemia and atherosclerosis as well as Alzheimer’s disease and osteoporosis (Formula (1)) and pharmaceutically acceptable salts thereof, Z is Formula (a) or Formula (b); nisOor 1; xis0, 1,2,3 or 4; yis 0, 1,2,3 or 4, provided that at least one ofx and y is other than O; and optionally one or more carbons of(CH and/or (Cl!2), together with additional carbons form a 3 to 7 membered spirocydic ring; R1 and R2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl orcycloheteroalkyl; R3 is H or lower alkyl; R4 and R7 are as defined herein.

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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 lipids
15 employing such pharmaceutical compositions.

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

20 wherein:
Am is a binding domain sidechain;
X is a linker;
R’ and R2 are the same or different and are each independently selected from
25 (i) hydrogen,
(ii) alkyl,
(iii) aryl,

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(iv) cycloalkyl,
(v) aralkyl,
(vi) aralkoxy,
5 (vii) alkenyl,
(viii) cycloalkenyl, and
(ix) heterocyclo (e.g., thienyl, benzodioxolyl);

R3 is selected from
10 (i) hydrogen,
(ii) lower alkyl,
(iii) aryl,
(iv) cycloalkyl,
(v) alkoxy,
15 (vi) aralkyl,
(vii) aralkoxy,
(viii) alkenyl,
(ix) cycloalkenyl,
Cx) halo-substituted alkyl,
20 (xi) adamantyl, and
(xii) heterocyclo (e.g., thienyl, benzodioxolyl);

R4 is selected from
(i) hydrogen,
25 (ii) lower alkyl,
(iii) aryl,
(iv) cycloalkyl,
(v) alkoxy,
(vi) aralkyl,
30 (vii) aralkoxy,
(viii) alkenyl,
(ix) cycloalkenyl,
(x) adamantyl,
(xi) halogen,
35 (xii) halo-substituted alkyl (e.g.,
trifluoromethyl), and

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(xiii) heterocyclo (e.g., thienyl, benzodioxolyl);
or R3 and R4 taken together can be

- (CH2),

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U
but when Am is

R6

or a 6 lactone thereof, R3 and R4 cannot be (CH=CH)2;
R6 is hydrogen or lower alkyl;
V R8 is hydrogen, lower alkyl, alkali metal, or

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

The phosphinic (or phosphonic when X is CH2-O-)
acid HMG-binding domain sidechain (A1) is

FTC
0 R6

II I
R50yCH2CH2CO2R
OR

wherein R5 and R7 are independently selected from
hydrogen, lower alkyl, alkali metal ion and alkaline
earth metal ion; and R6 is hydrogen or lower alkyl.
25 The dihydroxy acid binding domain sidechain (A2 is

0

wherein R6 is hydrogen or lower alkyl, R8 is hydrogen or lower alkyl in free acid form or in the form of a

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physiologically acceptable and hydrolyzable ester or 8 lactone thereof (i.e., when Am is

DO

5 In addition, R8 can be alkali metal ion or alkaline earth
metal ion.
A suitable linker (X) is (CH2)a, CHCH, CC,
- CH20-, wherein 0 is linked to the phosphorous atom or
the aromatic anchor when Am is A1, and wherein 0 is
10 linked to the aromatic anchor when Am is A2, and wherein
"a" is 1, 2, or 3.

In accordance with the present invention, there are
provided certain pyridine-containing compounds that are
15 potent inhibitors of cholesterol biosynthesis by virtue
of their ability to inhibit the enzyme 3-methyl-glutaryl-coenzyme A reductase (HMG-00A reductase).
In particular, in its broadest chemical compound
aspect, the present invention provides compounds of the
20 formula
I

wherein

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n is 0 or 1;
x is 0, 1, 2, 3 or 4;
y is 0, 1, 2, 3 or 4, provided that at least one of
5 x and y is other then 0;
and optionally one or more carbons of (CH2) and/or
(CH2) may form part of a 3 to 7 membered spirocyclic
ring;
R1 and R2 are the same or different and are
10 independently selected from alkyl, arylalkyl, cycloalkyl,
alkenyl, cycloalkenyl, aryl, heteroaryl or
cycloheteroalkyl;
R3 is H or lower alkyl;
Rg is H, halogen, CF3, hydroxy, alkyl, alkoxy,
15 alkanoylamino, aroylamino or cyano;
R, is H or lower alkyl;

and represents a single bond or a double bond
(which may be cis or trans);
and including pharmaceutically acceptable salts
20 thereof when R3 is H. esters thereof, prodrug esters
thereof, and all stereoisomers thereof.

SPreferably, the Z group will be in form of a free
acid, a physiologically acceptable and hydrolyzable ester
or 8 lactone thereof, or an alkali metal salt, alkaline
25 earth metal salt or an amino acid salt.
Preferred are compounds of formula I of the
invention wherein

R1 and R2 are independently selected from alkyl, cycloalkyl and aryl;
30 R4 is H, alkyl, or halogen;
x is 2 or 3;
yiso;and
n is o.

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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;
x is 3;
Y is 0;
n is 0; and
is a double bond.
Still more preferred are compounds of formula I of the invention wherein
R1 is substituted aryl, preferably 4-fluorophenyl, 4-fluoro-3-methylphenyl or 3, 5-dimethylphenyl;
R2 is alkyl or cycloalkyl, preferably isopropyl, t-butyl or cyclopropyl;
R4 is H;
x is 3;
Y is 0;
n is 0;

is a double bond, preferably "trans"; and

Z is or

O*

;

or an alkali metal salt thereof, alkaline earth metal salt or an amino acid salt.
Most preferred compounds of formula I of the invention will have the structure IA
IA

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or an alkali or alkaline earth metal (such as Na, K or
Ca) salt thereof, or amino acid salt (such as arginine), wherein R5 and R6 are the same or different and independently selected from H, halogen and/or alkyl
5 (preferably 4-fluoro, 4-fluoro-3-methyl or 3,5-dimethyl);
and

R2 is alkyl or cycloalkyl, preferably isopropyl, t-
butyl or cyclopropyl.
In another aspect, the present invention provides
10 pharmaceutical compositions, useful as hypolipidemic or
hypocholesterolemic agents, or hypotriglyceridemic
agents, or anti-Alzheimer’s agents, or anti-osteoporosis agents as well as other uses as described herein,
comprising a hypolipidemic or hypocholesterolemic or
15 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.
20 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
25 dyslipidemia, mixed dyslipidemia, hyperlipidemia,
hypercholesterolemia, hypo a-lipoproteinemia, LDL Pattern
B, LDL Pattern A, hyperlipoproteinemia or
hypertriglyceridemia, and other aberrations of apolipoprotein B metabolism, or reducing levels of Lp(a),
30 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
35 markers such as C-reactive protein, or preventing or
treating low grade vascular inflammation, or preventing
or treating stroke, or preventing or treating dementia,

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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
5 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
10 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
15 in accordance with the present invention as defined
above.

In addition, in accordance with the present
invention, a method is provided for preventing or
treating diabetes, especially Type 2 diabetes, and
20 related diseases such as insulin resistance,
hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, Syndrome X, diabetic complications, dysmetabolic syndrome, and related
diseases, and sexual dysfunction, wherein a
25 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 preventing and
30 treating malignant lesions (such as ductal carcinoma in
situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions (such as fibroadenoma of
the breast and prostatic intraepithelial neoplasia (PIN), gastrointestinal malignencies, liposarcomas and various
35 other epithelial tumors (including breast, prostate,
colon, ovarian, gastric and lung), cancer-induced
asthenia (fatigue), irritable bowel syndrome, Crohn’s

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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
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 plasminogen activating
inhibitor (PAI)-1 activity, reducing 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
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 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 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.

In accordance with the present invention, there is provided compounds useful in inhibiting the enzyme HMG-
35 C0A reductase, which inhibitors are useful as hypocholesterolemic agents, dyslipidemic agents,

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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
5 refers to myocardial infarction, myocardial
revascularization procedures, angina, cardiovascular
death and acute coronary syndrome.
The term "cardiovascular diseases or events" as
employed herein refers to atherosclerosis of the coronary
10 arteries, myocardial infarction, including primary MI and
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
15 employed herein refers to cerebral infarction or stroke
(caused by vessel blockage or hernmorage), or transient ischemia attack (TIA), syncope, atherosclerosis of the intracranial and/or extracranial arteries, and the like.
The term "cholesterol-related diseases" as

20 employed herein refers to- diseases involving elevated
levels of LDL cholesterol, diseases involving regulation
of LDL receptors, diseases involving reduced levels of
HDL cholesterol, dyslipideinia, hyperlipidemia, elevated
LDL Pattern B, elevated LDL Pattern A.
25 hypercholesterolemia, hypo a-lipoproteineinia (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)
30 forms of primary hypercholesterolemia (including
Frederickson Types ha and lib), cholesterol ester
storage disease, and cholesterol ester transfer protein disease, and related diseases.
The conditions, diseases, and maladies
35 collectively referenced to as "Syndrome X" or
Dysmetabolic Syndrome (as detailed in Johanson, J. Clin. Endc5crinol. Metab., 1997, 82, 727-734, and other

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publications) include hyperglycemia and/or prediabetic insulin resistance syndrome, and is characterized by an initial insulin resistant state generating hyperinsulinemia, dyslipidemia, and impaired glucose
5 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
10 tolerance, obesity, hyperglycemia, Syndrome X,
dysmetabolic syndrome, diabetic complications and hyperinsulinemia.
The conditions, diseases and maladies collectively

referred to as "diabetic complications" include 40 15 retinopathy, neuropathy and nephropathy, and other known
complications of diabetes.
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-
20 obesity agents, and/or one or more lipid-lowering agents,
one or more lipid modulating agents (including anti-atherosclerosis agents), other types of anti-atherosclerosis agents, and/or one or more antiplatelet agents, one or more agents for treating hypertension, one
25 or more anti-cancer drugs, one or more agents for
treating arthritis, one or more anti-osteoporosis agents,
one or more agents for treating immunomodulatory
diseases.

The term "lipid-modulating" agent as employed
30 herein refers to agents which lower LDL and/or raise HDL
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
35 agents" as employed herein refers to conventional anti-
atherosclerosis agents including lipoxygenase inhibitors, ACAT inhibitors, antioxidants, PP2R agonists,

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phospholipase inhibitors (including PLA-2 inhibitors), and/or other known anti-atherosclerosis agents.
The terms pharmaceutically acceptable "salt" and
"salts" refer to basic salts formed with inorganic and
5 organic bases. Such salts include ammonium salts; alkali
metal salts, such as lithium, sodium and potassium salts (which are preferred); alkaline earth metal salts, such
as calcium and magnesium salts; salts with organic bases, such as amine like salts (e.g., dicyclohexylamine salt,
10 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
15 isolating or purifying the product.
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
20 or a bydrohalic acid such as HC1 or HBr, with strong
organic carboxylic acids, such as alkaneca.rboxylic acids of]. to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic
acid, such as saturated or unsaturated dicarboxylic
25 acids, for example oxalic, malonic, succinic, maleic,
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
30 or arginine), or benzoic acid, or with organic sulfonic
acids, such as (Cl-C4) alkyl or
arylsulfonic acids which are unsubstituted or
substituted, for example by halogen, for example methanesulfonic acid or p-toluenesulfonic acid.
35 The term "spirocyclic ring" as used in reference to
(cH2) and/or (cH2) refers to a 3 to 7 membered
spirocyclic ring formed from one or more of the carbons

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in (cH2) and/or one or more carbons in (CH2), together
with additional carbons to make up a 3 to 7 membered
ring.
Unless otherwise indicated, the term "lower alkyl",
5 "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, propyl, isopropyl, butyl,
10 t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2, 4-triinethyl-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 as halo, for example
15 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,
20 heteroarylalkoxy, ary]oxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylaniido, alkanoy].amino,
arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or zilkylthio.
Unless otherwise indicated, the term "cycloalkyl"
25 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, inc1ucing monocyclic alkyl, bicyclic alky].
(or bicycloalkyl) and tricyclic alkyl, containing a total
30 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, cyclohepty]., cyclooctyl, cyclodecyl and cyclododecyl,
35 cyclohexenyl,

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any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy,
5 hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl,
alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, heteroaryl, cycloheteroalkyl, amino, alkylainino, nitro,
cyano, thiol and/or alkylthio and/or any of the
substituents for alkyl.
10 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. Exeuplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl,
15 cyclooctenyl, cyclohexadienyl, and cycloheptadienyl,
which may be optionally substituted as defined for cycloalkyl.
The term "alkanoyl" as used herein alone or as
part of another group refers to alkyl linked to a
20 carbonyl group.
Unless otherwise indicated, the term "lower
alkenyl" or "alkenyl" as used herein by itself or as part
of another group refers to straigh: or branched chain radicals of 2 to 20 carbons, prefeiably 2 to 12 carbons,
25 and more preferably 1 to 8 carbons in the normal chain,
which include one to six double bonds in the normal
chain, such as vinyl, 2-propenyl, 3-,utenyl, 2-butenyl,
4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl,
30 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1

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to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl,
alkanoylamino, alkylamido, arylcarbonyl-amino, nitro,
5 cyano, thiol, alkylthio and/or any of the alkyl
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
10 radicals of 2 to 20 carbons, preferably 2 to 12 carbons
and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such

40

as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2 -heptynyl, 3-heptynyl,
15 4 -heptynyl, 3 -octynyl, 3-nonynyl, 4 -decynyl, 3 -undecynyl,
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,
20 cycloheteroalkyl, hydroxy, alkanoylataino, 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
25 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
30 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
35 for attachment at two different carbon atoms, they are

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termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted with 1 or 2 substituents as defined above for 11alkenyl" and "alkynyl".
(CH2)x or (cH2)y includes alkylene groups as
defined herein, which may optionally include 1, 2, or 3 substituents which include alkyl, alkenyl, halogen, aryl,
hydroxy, alkoxy, or C3 -C6 cycloalkyl.
Examples of (cH2) X or (CH2), alkylene groups
include -cH2-,

, ’ (2)4 ’
CE3

_ CH2?H_, cH2cjHcE, r’2
C2H5 CE3 C2H5

 cHcHcH2, cH2--cH2,

CH3

ci
 cH2cE2, (cE3)2H

F

 (cE3)2cE3
F

_cH2_?H_?HcH2_, _cH2_?R.CH2_?H_
ç H3 CE3 CE3 CE3

 CHcE2CH2 (CE2) 3CF3

CE3

03
 cB0O2c02

The term "halogen" or "halo" as used herein alone
or as part of another group refers to chlorine, bromine,

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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
5 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
10 to 10 carbons in the ring portion (such as phenyl or
naphthyl including l-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
15 for example

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(X> 0XX)-), and may be optionally substituted through available

carbon atoms with 1, 2, or 3 groups selected from
20 hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, halophenyl, benzoyloxy, haloalkoxy, alkenyl,
trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy,
25 arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroaryiheteroaryl, 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

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definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl,
arylcarbonyl, alkyl-aminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, axn.inocarbonyl, alkylcarbonyloxy,
5 arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfon-aminocarbonyl and/or any of the alkyl substituents set out herein.
Unless otherwise indicated, the term "lower
10 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
15 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,
20 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
25 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
30 substituted with alkyl, alkoxy, alkylthió, halo,
trifluoromethyl or hydroxy.
Unless otherwise indicated, the term "lower
alkylthio", alkylthio", "arylthio" or "ara].kylthio" as employed herein alone or as part of another group
35 includes any of the above alkyl, aralkyl or aryl groups
linked to a sulfur atom.

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Unless otherwise indicated, the term "lower alkylainino", "alkylamino", "arylainino", or
"arylalkylainino" as employed herein alone or as part of
another group includes any of the above alkyl, aryl or
5 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

(R) carbonyl C group; examples of acyl groups include
10 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
15 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 (CH2)r (where r is 1,
20 2 or 3), such as

091

O

OO9LN9;

s"/o 06)Z0

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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

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

O,OMoQ ONOL&<3

NN NN NN N NN

51$, 51), RN

N-

and the like.

The term "cycioheteroalkylalkyl" as used herein
alone or as part of another gorup refers to cycloheteroalkyl groups as defined above linked through a
C atom or heteroatom to a (CH2)r chain.
The term "heteroarylalkyl" or "heteroarylalkenyl"
as used herein alone or as part of another group refers

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to a heteroaryl group as defined above linked through a C atom or heteroatom to a chain, alkylene or alkenylene as defined above.
The term "polyhaloalkyl" as used herein refers to
5 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 CF3CH2, CF3 or CF3CF2CH2.
The term "polyhaloalkoxy" as used herein refers to
an "alkoxy" or "alkyloxy" group as defined above which
10 includes from 2 to 9, preferably from 2 to 5, halo
substituents, such as F or Cl, preferably F, such as
CF3cH20, CF30 or CF3CF2cH20.
All stereoisomers of the compounds of -the instant
invention are contemplated, either in admixture or in
15- 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
20 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
25 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
30 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.

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Examples of such prodrug esters include

CH3CO2CH2, CH3CO2cH2 t-C4H9CO2CR2, or

CH

0

(H3)2

II

C2}150C0CE2

Other examples of suitable prodrug esters include
0 o o 0 oko

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5
. n j

Ra CH2
b&)n,,CO2Ra

RQAOJ%IIX ’

IIL

wherein Ra can be H, alkyl (such as methyl or t-butyl), arylalkyl (such as benzyl) or aryl (such as phenyl); Rd
10 is H, alkyl, halogen or alkoxy, Re is alkyl, aryl,
arylalkyl or alkoxyl, and niis 0, 1 or 2.
Compounds of the invention may be prepared by the following method.
Referring to Reaction Scheme 1, Knovenagel
15 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 or NaHDMS in THF or
20 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
25 (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 (LiA1H4, DIBAL, LiBH4) to give alcohol 7 which can
30 subsequently be converted to the corresponding halide B

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(e.g. PBr3 in cH2C121 CBr4/PPh3 in CH3cN, or Pod3).
Conversion of halide 8 to the phosphorus compound 9 where
W is Ph or alkyl is effected by treatment of 8 with W2POE’C in toluene. Conversion of halide 8 to compound 9 where W
5 is OR (R is lower alkyl) may be effected by the reaction
of 8 with HOP(OR)2/base/THF or by Arbuzov reaction with P(OR)3. Witting reaction between 9 and aldehyde 10
(aldehyde 10 has been previously described in US patent 5,686,433) may be effected under standard conditions with
10 base (n-BuLi, LiN(TMS)2, LDA) in an appropriate solvent
(THF, Et201 toluene, DMPU) to afford the adduct 11.
Treatment of 11 under acidic conditions (e.g. TFA, HCl) effects the conversion of 11 to lactone Ia.
Saponification of Ia to lb (where R3 is alkali metal, or
15 alkaline earth metal) can be effected by treatment of Ia
with aqueous base or subsequently acidified to give lb where R3 is H. Additionally, Ia can be treated with an alcohol of the type R30H under basic conditions to form
the corresponding esters of lb.
20 As seen in Reaction Scheme 2, the saturated

derivatives of compound I (where loeis cH2-0-12) are obtained by catalytic (Pd/C, Pt/C, Pd(OH)2) hydrogenation
of 11, Ia, or lb to afford 12, Ic, or Id, respectively. Compound 12 may be converted to Ic and Id following the
25 earlier described methods for the conversion of compound
11 to Ia and lb.

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Scheme I

o o
ii U +

Knovenagel
condensation
R2’OR R1-CHO
R1YR13

OR

1 2

CO2R

NH3 R1 LR2

solvent II oxidant,
,xI I
6

halide III R2
formationii I. N
YClorBr 8
rr

R4

acid

11

wW

(o RR2

I B

R4

base
Where x is 04 and Is 04
but and cannot both
be 0

OH

R1 R2

reduce)),N

I

O??O
H13 JCOralkyI 10

iqeuous base

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IN
base

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S H2

catalyst

Scheme 2

OH

R1

CH2)fM la
(CH,JJ

H2 1H2

catalyst catalyst

aqeuous base

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The synthesis of compounds I wherein is CH=CH
and n is 1, is described in Scheme 3. Bis-silylation of compound lb’ with a bulky silyichioride (e.g., C1Si(t-butyl) Ph2, C1Si (t-butyl)Me2, C1SiPh3) in the presence of a
5 suitable base (e.g., TEA, imidazole, pyridine) and solvent (e.g., CH2C12, THF) provides compound lb2.
Treatment of lb2 with oxidants such as m-CPBA or CF3CO3H
in an appropriate solvent such as CH2C12 or HOAc affords N-oxide lb3. Desilylation of lb3 (TBAF/HOAc/THF or
10 HF/CH3CN) gives lb4 which may be saponified to lb5 using aqueous solutions of a metal hydroxide in an appropriate solvent (e.g., MeOH, dioxaKxe).

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SCHEME 3

CO2aIkyI
- öSIR

R1%J.#(R2

R7SICI

00 R1,L1.,R2 Oxidant ,. N (R9(t-butyl)Ph2,
lb1 Ph3)

(t-butyl)Me2, or
(CH2)
lb2

’(%)y(5K

COgalkyl HO

119SIQ R4

I]yL(

CO2aIkyISlR OH
R .R2

R1 R2
j
(c2

lb4

MOH, H20
ONSolvent

(M=alkaH metal)

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Additionally, compound Id’ 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
SCHENE 4

Oxidant R1

Id1

OH

LMOH,

H20
Solvent
Id2

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As

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Referring to Scheme 5, the arginine salt of the
compounds of formula I of the invention may be prepared
by treating alkali metal salt (preferably sodium) lb with acid (TFA, HC1) to form the acid lb6 which is treated
with arginine in the presence of suitable solvents such
as ethyl alcohol and H20, ethyl acetate, acetonitrile and the like, to form arginine salt lb7.

Scheme 5

HO
OH

lb

acid
arginine

R. IV

MH
H2N.._JLNH
CO2H

Scheme 6 depicts a preferred method for preparing
the HMG C0A reductase inhibitor of formula I of the invention using the Julia-Kocienski olefination reaction 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).

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Referring to Scheme 6, treatment of commercially
available chiral alcohol (12) with triflic anhydride and triethylamine in dichioromethane at low temperature (for example 0 to -30°C) affords triflate (13). Other
5 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)
10 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 NaHNDS to a mixture of
15 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).
20 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 lb9 of
the invention is prepared in a one pot procedure starting from (19) without isolating any intermediates. Removal
25 of acetonide under acidic condition provides diol (20)
which upon further treatment with sodium hydroxide gives
the sodium salt of the acid (21). Subsequent treatment
of 21 with acid followed by the addition of arginine produces crystalline arginine salt of the invention lb9.
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Thus, the intermediates of the invention can have the following structures:

CO2R (Ralkyl) OH
RI,L.R2 R1..,J.R2

(CHf B (CH2)f N

5- (CH)

(CHJRd

(pref. t-butyl)

Halide (prof. Br) V
Rl((R2

Po
RI RI

(CH2)

cAC8

(CH2)L
H2)y

1

K4 &N,

(W=aryl or alkoxy)

(pref. t-butyl)

Compounds containing dihydroxy acid HMG-CoA binding domain side chains may be prepared in homochiral form, which is preferred, or may be prepared as raceinic
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-00A) 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) (A;tra 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.

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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
5 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
10 compound per dosage, for use in the treatment. The dose
to be administered depends on the unitary dose, the symptoms, and the age and the body weight of the patient. The compounds of the present invention can be
administered in a similar manner as known compounds
15 suggested for use in inhibiting c.riolesterol biosynthesis,
such as pravastatin, lovastatin, simvastatin, visastatin
(or rosuvastatin), atorvastatin, cerivastatin,
fluvastatin, itavastatin (or pitavastatin), and the like,
...n mammalian species such as humans, dogs, cats and the
20 like. Thus, the compounds of the invention may be
administered in an amount from about 0.1 to 500 mg in a single dose or in the form of individual doses from 1 to
4 times per day, preferably 0.2 to 100 mg daily or in sustained release form.
25 The HMG C0A reductase inhibitors of formula I may be employed in combination with all therapeutic agents
which are useful in combination with HMG C0A reductase inhibitors.

Thus, where desired, the compounds of structure I
30 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, anti-obesity agents, antihypertensive agents, platelet
35 aggregation inhibitors, anti -Alzheimer’s agents, anti-
dementia agents, anti-osteoporosis agents, and/or hormone replacement therapeutic agents, and/or other therape.itic

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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
5 agents, anti -infective agents, hormone replacement
agents, growth hormone secretagogiies, selective androgen
receptor modulators, and/or other therapeutic agents
which may be administered orally in the same dosage form
or in a separate oral dosage form, or by injection.
10 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 formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG C0A reductase inhibitors, squalene
15 synthetase inhibitors, PP.AR a agonists, PPR dual a/’y
agonists, PPAR 6 agonists, fibric acid derivatives, ACAT
inhibitors, lipoxygenase inhibitors, cholesterol
absorption inhibitors, heal Na’/bile acid cotransporter
inhibitors, upregulators of LDL receptor activity,
20 cholesteryl ester transfer protein inhibitors, bile acid
sequestrants, and/or nicotinic acid and derivatives
thereof.

MTP inhibitors employed herein include MTP
inhibitors disclosed in U.S. Patent No. 5,595,872, U.S.
25 Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S.
Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S.
Patent No. 5,885,983 and U.S. Application Serial No.
09/175,180 filed October 20, 1998, now U.S. Patent No.
5,962,440. Preferred are each of the preferred MTP
30 inhibitors disclosed in each of the above patents and
applications.
All of the above U.S. Patents and applications are incorporated herein by reference.
Most preferred MTP inhibitors to be employed in
35 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.

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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 C0A
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
10 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
15 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,
20 pitavastatin (Nissan/Saxikyo’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,
25 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- t2- (substituted-pyrrol-1-y].) - alkyl)pyran-2-ones and derivatives thereof as disclosed
30 in U.S. Patent No. 4,647,576, Searle’s SC-45355 (a 3-

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substituted pentanedioic acid derivative)
dichioroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hyciroxy-propane--phosphonic acid derivatives as disclosed
5 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
10 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
15 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, a-phosphono-
sulfonates disclosed in U.S. Patent No. 5,712,396, those
20 disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31,
No. 10, pp 1869-1871, including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A.,
25 Neuenachwander, K., Ponpipoin, M.M., and Poulter, C.D.,
Current Pharmaceutical Design, 2, 1-40 (996).
In addition, other squalene synthetase inhibitors
suitable for use herein include the terpenoid
pyrophosphates disclosed by P. Ortiz de Montellano et al,
30 J. Med. Chem., 1977, 211, 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, phosphinyiphosphonates
reported by McClard, R.W. et al, J.A.C.S., 1987, 1Q..,
35 5544 and cyclopropanes reported by Capon, T. L., PhD
dissertation, June, 1987, Dept. Med. Chem. U of Utah,

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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,
5 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 geinfibrozil being
preferred, bile acid sequestrants such as cholestyramine,
10 colestipol and DEAE-Sephadex (Secholexfi, Policexidefi) and
cholestagel (Sarikyo/Geltex), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted
ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphos-
15 phorylcholine (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,
20 neomycin, p-aminosalicylic acid, aspirin,
poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylatntnonium chloride) and ionenes such
as disclosed in U.S. Patent No. 4,027,009, and other
25 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), (Avasjmibe); "The ACAT inhibitor, Cl-1011 is
30 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
35 selective suppression of the hepatic secretion of
ApoBlOO-containing lipoprotein", Ghiselli, Giancarlo,
Cardiovasc. Drug Rev. (1998), 16(1), 16-30; ’RP 73163: a

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bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(l), 47-50; "ACAT inhibitors: physiologic
mechanisms for hypolipidemic and anti -atherosclerotic
5 activities in experimental animals", Krause et al,
Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred
A., Inflammation: Mediators Pathways (1995), 173-98,
Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors:
potential anti -atherosclerotic agents", Sliskovic et al,
10 Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of
acyl-CoA:cholesterol 0-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble
ACAT inhibitor with lipid-regulating activity. Inhibitors
of acyl-CoA:cholesterol acyltransferase (ACAT). 7.
15 Development of a series of substituted N-phenyl-N’-E(l-
phenylcyclopentyl) methyl] ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts:
Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho
Pharmaceutical Co.. Ltd), as well as F-1394, CS-505,
20 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).
The hypolipidemic agent may be a cholesterol
25 absorption inhibitor preferably Schering-Plough’s
SCR48461 (ezetimibe) as well as those disclosed in Atherosclerosis 115, 45-63 (1995) and L Med. Chem. 41,
973 (1998).
The other lipid agent or lipid-modulating agent
30 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
JTT-705.

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

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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 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;
an HDL upregulator such as an LXR agonist, a PPR
a-agonist and/or an FXR agonist;
an a-glucosidase inhibitor, an aldose reductase
inhibitor and/or an LDL catabolism promoter such as disclosed in EP 1022272;
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;
an anti -oxidant such as beta-carotene, ascorbic
acid, cz-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;
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 PP.PR 3 agonist for treating dyslipidemia;
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.

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Preferred hypolipidemic agents are pravastatin,
lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, pitavastatin and rosuvastatin, as well as niacin and/or cholestagel.
5 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.

10 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
15 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
20 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
25 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
30 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
35 about 400 mg, and more preferably from about 5 to about
250 mg, one to four times daily.

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For oral administration, a satisfactory result may
be obtained employing an HMG C0A 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 C0A 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
lipoxygenase inhibitor including a 15-lipoxygenase (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-lipoxygenase inhibitor lacking significant antioxidant properties," Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxygenase 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.

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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 dose
5 combination and work up gradually to a high dose
combination.
The antidiabetic agent which may be optionally
employed in combination with the HMG-00A reductase inhibitor of formula I may be 1,2,3 or more antidiabetic
10 agents or antihyperglycemic agents including insulin
secretagog-ues or insulin sensitizers, which may include biguanides, sulfonyl ureas, glucosidase inhibitors,
aldose reductase inhibitors, PPPR y agonists such as thiazolidinediones, PP.AR. a agonists (such as fibric acid
15 derivatives), PPR 8 antagonists or agonists, aP2
inhibitors, PP.AR a/y 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
20 PTP-1B inhibitor (protein tyrosine phosphatase-lB
inhibitor).
The antidiabetic agent may be an oral
antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably
25 metformin HC1.
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.
30 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
35 agents which act on the ATP-dependent channel of the 3 -
cells, with glyburide and glipizide being preferred,

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which may be administered in the same or in separate oral dosage forms.
The compounds of structure I will be employed in a
weight ratio to the sulfonyl urea in the range from about
5 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.
10 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
15 about 0.05:1 to about 10:1.
The compounds of structure’I may be employed in
combination with a PP.AR y agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity
20 effect in NIDDM patients) such as troglitazone (Warner-
Lambert’s Rezulinfi, 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-
25 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.
30 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 101.
The sulfonyl urea and PP.AR y agonists in amounts of
35 less that about 150 mg oral antidiabetic agent may be
incorporated in a single tablet with the compounds of

structure I.

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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-l) or
5 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
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,
10 intranasal, inhalation or by transdermal or buccal
devices.

Where present, metformin, the sulfonyl ureas, such
as glyburide, glimepiride, glipyride, glipizide, 41chiorpropamide and gliclazide and the glucosidase
15 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
20 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 PP.R anti-diabetic agent may be
employed in amounts within the range from about 0.01 to
25 about 2000 mg/day which may be administered in single or
divided doses one to four times per day.

Ok 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
30 Reference.

Where present GLP-1 peptides or mimetics may be
administered in oral buccal formulations, by nasal
administration or parentera].ly as described in U.S.
Patent Nos. 5,346,701 (TheraTech), 5,614,492 and
35 5,631,224 which are incorporated herein by reference.

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The antidiabetic agent or other lipid agent may
also be a PPAR modulator such as a PP.AR a/y dual agonist such as AR-H039242 (Astra/Zeneca), GW-409544 (Glaxo-
Weilcome), KRP297 (Kyorin Merck) as well as those
5 disclosed by Murakami et al, "A Novel Insulin Sensitizer
Acts As a Coligand for Peroxisome Proliferation -
Activated Receptor Alpha (PP.AR alpha) and PP.AR gamma. Effect on PP1R alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47,
10 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
15 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
20 compounds designated as preferred in the above
application.
The antidiabetic agent may be an aP2 inhibitor
such as disclosed in U.S. application Serial No.
09/391,053, filed September 7, 1999, and in U.S.
25 application Serial No. 09/519,079, filed March 6, 2000

(attorney file LA27), employing dosages as set out A6
herein. Preferred are the compounds designated as
preferred in the above application.
The antidiabetic agent may be a DP4 inhibitor such
30 as disclosed in application Serial No. 09/788,173, filed
February 16, 2001 (attorney file LA50)., W099/38501,
W099/46272, W099/67279 (PROBIODRUG), W099/67278 (PROBIODRUG), W099/61431 (PROBIODRUG), NVP-.DPP728A (1-
[[[2- [(5-cyanopyridin-2-yl) amino] ethyl] amino] acetyl) -2-
35 cyano- (S) -pyrrolidine) (Novartis) (preferred) as
disclosed by Hughes et al, Biochemistry, 38(36), 11597-

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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
5 Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No.
221 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
10 invention may be repaglinide or Starlixfi (Novartis),
nateglinide (Novartis) or K2D1229 (PF/Kissei), with repaglinide being preferred.
The antidiabetic compound may be a melanocortin
receptor agonist such as a spiropiperidine as disclosed
15 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 y agonist, PPAR a agonist, PPAR 8 agonits or antagonist, PPAR a/y dual agonist, aP2
20 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
optionally employed with the HMG CoA reductase inhibitor
25 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 FTP-1B
inhibitor, an anorectic agent, a PPAR modulator including
30 PPAR y antagonists, PPAR a agonists, PPAR 6 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 oxidation upregulator or inducer (such as Famoxin(D
35 Genset).

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The beta 3 adrenergic agonist which may be
optionally employed in combination with a compound of formula I may be AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3
5 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.
The neuropeptide Y antagonists which may be
optionally employed in combination with a compound of
10 formula I include those described in WO 0113917 (EMS) 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
15 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
20 (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
25 in W097/21993 (U. Cal SF), W099/00353 (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.
30 The anorectic agent which may be optionally employed in combination with a compound of formula I may
be dexamphetamine, phentermine, phenyipropanolamine or mazinclol, with dexamphetainine being preferred.

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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
5 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
10 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. Theantihypertensive agents which may be employed
in combination with the HMG C0A reductase inhibitors of
15 the invention include ACE inhibitors, angiotensin II
receptor antagonists,NEP inhibitors such as candoxatril, NEP/ACE inhibitors, as well as calcium channel blockers (such as verapaxnil and amlodipine besylate), T-channel calcium antagonists (such as mibefradil), -adrenergic
20 blockers, diuretics, a-adrenergic blockers (such as
doxazosin mesylate and terazosin HC1), dual action
receptor antagonists (DARA), heart failure drugs such as digoxin, and other types of antihypertensive agents.
The angiotensin converting enzyme inhibitor which
25 may be employed herein includes those containing a
mercapto (-S-) moiety such as substituted proline derivatives,. such as any of those disclosed in U.S. Pat.
No. 4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-
30 methylpropionyll-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 zofenopril being preferred.

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Other examples of mercapto containing ACE
inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in din. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril and YS980.
5 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
10 the phosphonate substituted amino or imino acids or salts
disclosed in U.S. Pat. No. 4,452,790 with (S)-1-E6-amino-

2- ([hydroxy- (4-phenylbutyl) phosphinyl] oxy] -1-oxohexyl] -L-proline or (ceronapril) being preferred,
phosphinylalkanoyl prolines disclosed in U.S. Pat. No.
15 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 phosphonaxnidates disclosed in U.S. Pat. No. 4,432,971 discussed above.

20 Other examples of ACE inhibitors that may be
employed herein include Beecharn’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-
25 ethoxycarbonyl-3-phenyl- (iS) -propyl] amino) -2,3,4,5-
tetrahydro-2-oxo-1- (3S) -benzazepine-1 acetic acid HC1) disclosed in U.K. Patent No. 2103614 and CGS 16,617

(3(S) - [[(iS) -5-axnino-1-carboxypentyl]aIfliflO] -2,3,4,5-tetrahydro-2-oxo-1H-1-benzazePiflelethaflOic acid)
30 disclosed in U.S. Pat. No. 4,473,575; cetapril
(alacepril, Dainippon) disclosed in Eur. Therap. Res.
39:671 (1986); 40:543 (1986); ramipril (Hoechsst)
disclosed in Euro. Patent No. 79-022 and Curr. Ther. Res.
40:74 (1986); Ru 44570 (Hoechst) disclosed in
35 Arzneimittelforschurig 34:1254 (1985), cilazapril

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(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;
5 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. din. Pharmacol. 31:519 (1987); quinapril (Warner-Lambert)
10 disclosed in U.S. Pat. No. 4,344,949 and C1925 (Warner-
Lambert) ([3S_(2[R(*)R(*)]]3R()]-2-[2-[[1-(ethoxy-carbonyl) -3-phenyipropyl] amino) -1-oxopropyl] -1,2,3,4-tetrahydro-6, 7-dimethoxy-3-isoquinolinecarboxylic acid HC1)disclosed in Pharmacologist 26:243, 266 (1984), WY-
15 44221 (Wyeth) disclosed in J. Med. Chem. 26:394 (1983).
Preferred ACE inhibitors are captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril and mbexipril.
NEP/ACE inhibitors may also be employed herein in
20 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,
25 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
30 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,
35 gemopatrilat ([S [(R*, R*)] -hexahydro-6- t (2-rnercapto-1-oxo-

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The HMG CoA reductase compound of the invention may
also be employed in combination with a tyrosine kinase inhibitor such as disclosed in sO 2000/053605;
the selective androgen rec-ptor modulator suitable
5 for use herein may be LGD-2226 (ligand);
the antiarrhythmic agents s..iitable for use herein
include 13-blockers as set out herein including sotalol
and amioderome, calcium channel blDckers as set out
herein including verapamil, nifedi’ine, amlodipine-
10 besylate, and diltiazem, which may also be used in
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;
15 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 (PSGILG), glucosamine, chondroitin
sulfate (CS), hyaluronic acid (HA), pentosan polysulfate
20 (PPS), doxycycline or minocycline, such as disclosed in
EP 970694;
a cyclooxygenase (COX) -2 inhibitor, such as
celecoxib (Celebrexfi (Searle)) or rofecoxib (Vioxxfi
(Merck)) or a glycoprotein Ila/Ilib receptor antagonist
25 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
30 example, isosorbide dinitrate, or nitroglycerin;
a growth hormone secretagogue such as discloseC. in
U.S. applications Serial No. 09/662,448, filed Septetrer
14, 2000, and U.S. Provisional application 60/203,335,
filed May 11, 2000, and MK-677 (Merck), Pfizer’s CP-
35 424391 and Lilly’s LY 444,711;

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anti -atherosclerosis agents such as ACT inhibitors
and lipoxygenase inhibitors as described herein and phospholipase A-2 inhibitors such as S-3013 and
SB-435,495 (which are also anti-inflammatory agents);
5 anti-infective agents such as quinolones, for
example, ciprofloxacin, ofloxacin, and Tequinfi (Bristol-
Myers Squibb), tnacrolides such as erythromycin and clarithromycin (Biaxinfi (Abbott)), and azithromycin (Zithromax (Pfizer)); or
10 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
15 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
20 suitable for use in combinations of this invention
include, but are not limited to, tnicrotuble-stabilizing
agents such as the taxanes, for example, paclitaxel (also
known as Taxolfi), docetaxel (also known as Taxoterefi), 7-
0-metbylthio- methylpaclitaxel (disclosed in U.S.
25 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
30 epothilone, such as epothilone A, epothilone B,
epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B,
[1R*,3R*(E),7R*,1OS*,11R*,12R*,16S*])_7,11_dihydrOXy_ 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-
35 thiazolyl) ethenyli -4-aza-17-oxabicyclo [14.1. 0]hepta-
decane-5,9-dione (disclosed in WO 99/02514), (iS-
[1R*,3R*(E),7R*,1OS*,11R*,12R*,168*1]_3_E2_E2_

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(aminomethyl) -4-thiazolyl] -1-methylethenyl] -7, 11-di-hydroxy-8, 8,10,12, 16-pentamethyl-4, 17-dioxabi-
cyclo [14.1.01 -heptadecane-5, 9-dione (disclosed in USSN 09/506,481 filed on February 17, 2000, and examples 7 and
8 herein), and derivatives thereof; microtuble-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 ymca 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, dichioro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, meiphalan, vinbiastine, vincristine, leurosidine, vindesine,
leurosine, and the like. Other useful antineoplastic
agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosfamide,
meiphalan, 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

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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 hypercholesteroleinia, hyperlipidem.ia,
5 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
10 without other cholesterol lowering agents, osteoporosis
agents, Alzheimer’s agents, antidiabetic agent(s) and/or antihyperlipidemic agent(s) and/or other type therapeutic agents in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be
15 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
20 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
25 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
30 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
35 use, the contents of the vial are mixed with 2 inL of
physiological saline, to produce an injectable
preparation.

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

5 Ph = phenyl
Bn = benzyl
i-Bu = iso-butyl
Me = methyl
Et ethyl
10 TMS = trimethylsilyl
FMOC = fluorenylmethoxycarbonyl
Boc = tert-butoxycarbonyl
Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl DIPEA = diisopropyl ethylamine
15 PTSH = N-phenylthiotetrazOle
PPh3 = triphenyiphosphine
NMO = methylmorpholine N-oxide
TPAP = tetrapropylainmonium perruthenate
DEAD = diethyl azodicarboxylate
20 HOAc or AcOH = acetic acid
TFA = trifluoroacetic acids
Et2NH = diethylamine
NMM = N-methyl morpholine
n-BuLi = n-butyllithium
25 Pd/C = palladium on carbon
Pt02 = platinum oxide
MTBE = methyl t-butyl ether
DI water = dionized water
TEA = triethylamine
30 EDAC = 3 -ethyl-3’ - (dimethylamino) propyl-carbodilmide
hydrochloride (or 1- [(3- (dimethyl) amino) propyl]) -3-ethylcarbodiimide hydrochloride)
HOBT or HOBT.H20 = l-hydroxybenzotriazole hydrate
HOAT = 1-hydroxy-7-azabenzotriazOle
35 PyBOP reagent = benzotriazol-1-yloXy-triPYrrOlidiflO
phosphonium hexafluorophosphate
LiN (TMS)2 = Libis (trimethylsilyl) amide

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DIBAL = diisobutylaluininum hydride
LDA = lithium diisopropylamide
DMPU = 1, 3-dimethyl-3, 4,5, 6-tetrahydro-2 (1H) -pyrimidinone AcCN acetonitrile
5 LIHMDS = lithium bis(trixnethylsilyl)amide
NaHMDS = sodium bis(trimethylsilyl)amide
Red-2L = sodium bis (2-methoxyethoxy) aluminum hydride
mCPBA = m-chloro-p-benzoic acid
min = minute(s)
10 h or hr = hour(s)
L = liter
mL = milliliter
gL = microliter
g = gram(s)
15 mg = milligram(s)
mol = moles
rnmol = millimole(s)
meq = milliequivalent
RT, rt = room temperature
20 sat or sat’d = saturated
aq. = aqueous

TLC = thin layer chromatography
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass
25 spectrometry
MS or Mass Spec = mass spectrometry
NMR = nuclear magnetic resonance
mp = melting point
Bp = boiling point

30

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

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I.

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Example 1

A.

To a slurry of NaB (19.20 g, 480 mtnol) 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 tnmol) in Et20 (30 mL).
10 Approximately 10% of the solution was added, and then
025 niL 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
15 vigorous H2 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 4k ceased and the reaction mixture was stirred at room
temperature for 2h. The reaction mixture was cooled in
20 an ice-bath, diluted with Et20 (200 niL), and treated with
1 N HCl with some ice to adjust to around pH 3. The
reaction mixture was extracted with Et20 (3 x 150 niL).
The Et20 extracts were combined, washed with saturated
aqueous NaHCO3 (200 niL), H20 (200 niL) and brine (200 mL),
25 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.

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B.

To a stirred solution of Part A compound (28.24 g,
181 mmol) in benzene (128 mL) was added 4-fluorobenz-
5 aldehyde (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 Et20 (250 niL), washed with
10 aqueous 0.5 N HC1, saturated aqueous NaHC031 H20 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.
15
C.

* To a solution of 1-benzosuberone (7.35 g, 45.9 mmol) in THF (3 mL) at -78°C under N2 was added a solution
20 of lithium bis(trimethylsilyl)amide (1 M in THF, 40.5 mL,
40.5 mmol). The reaction mixture was stirred at -78°C
for 1 h, then a solution of Part B compound (7.07 g,
26.95 mmol) in THF (3 mL) was added dropwise. The
reaction mixture was stirred at -78°C for 1 h, then at 0°C
25 for 30 mm. The reaction mixture was quenched with HOAc
(8 mL) and poured into saturated aqueous NH4C1 (250 mL),
then extracted with Et20 (3 x 60 niL). The combined Et20 extracts were washed with H20 and brine, then dried

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(Na2SO4), filtered and concentrated in vacuo to give the title compound as a light yellow oil. The resulting
crude product was used in the next step without further purification.

To a stirred solution of crude Part C compound
(26.9 mmol) in HOAc (128 mL) was added ammonium acetate
10 (9.14 g, 118.6 mmol) and copper (II) acetate monohydrate
(19.7 g, 99.7 mmol). The reaction mixture was heated at reflux under argon overnight. After cooling to room temperature, the reaction mixture was poured into a
mixture of NH40H (150 mL) and ice (300 g), then extracted
15 with Et20 (3 x 100 mL). The combined Et20 extracts were
washed with H20 and brine, then dried (Na2SO4)1 filtered
and concentrated in vacuo. Purification by flash chromatography (2:20: 80-EtOAc/CH2C12/hexane) gave the
title compound as a white foam, 7.7 g, 71% yield (from
20 Part B compound).

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E.

To a stirred solution of Part D compound (7.7 g,
19.2 mmol) in THF (30 mL) at 0°C under argon was added a
5 solution of lithium aluminum hydride (1 M in THF, 60 mL,
60 mmol) at a rate to maintain the temperature below
10°C. After addition, the reaction mixture was stirred
at room temperature for 1.5 h and cooled to 0°C, then carefully quenched with H20 (15mL), 10% aqueous NaOH (15
10 mL) and H20 (15mL). The reaction mixture was stirred at
room temperature for 15 minutes and filtered. The solid was washed with Et20 and EtOAc. The combined organic extracts/washings were washed with H20 and brine, then
dried (Na2SO4), filtered and concentrated in vacuo.
15 Recrystallization from EtOAc-hexane gave the title
compound as a white solid, 5.25 g, 76% yield.

F.

Ir

20 To a slurry of Part E compound (5.2 g, 14.5 mmol)
in cH2C12 (40 mL) at 0°C under argon was added a solution
of PBr3 (29 mL, 29 mmol) in CH2C12 dropwise, maintaining
the temperature between 0 to 10°C. After addition, the reaction mixture was stirred at 0°C for 1 ii, then
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quehched with saturated aqueous NaHCO3 (100 tnL) and extracted with EtOAc (3 x 80 niL). The combined organic extracts were washed with H20 and brine, then dried
(Na2SO4), filtered and concentrated in vacuo.
5 Purification by flash chromatography (1:3 cH2C12/hexane)
gave the title compound as a white powder, 3.85 g, 63% yield.

G.

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A solution of diethyl phosphite (1.50 g, 10.9
mmol) in THF (10 niL) was cooled to -10°C under argon and then a solution of sodium bis (trimethylsilyl)amide (1 M
15 in THF,10.7 niL, 10.7 mmol) was added, dropwise. The
reaction mixture was stirred at -10°C for 30 min, and
then a solution of Part F compound (3.82 g, 9.05 mmol) in THF (15 niL) was added maintaining temperature around -10
to 0°C. The reaction mixture was stirred at -10°C for 1
20 h. The reaction mixture was quenched with saturated
aqueous 1’IH4C1 (150 niL), then extracted with EtOAc (3 x 100 niL). Combined EtOAc extracts were washed with saturated aqueous NH4C1 (150 niL), H20 and brine, then dried (Na2804)1 filtered and concentrated in vacua. Purification by
25 flash chromatography (1:2-EtOAc:bxane) gave the title
compound as a white foam, 4.1 g, 94% yield.

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H.

A flame-dried 200 mL round bottom flask was
charged with Part G compound (2.062 g, 4.3 mmol) and
5 chased with anhydrous toluene (2 x 10 mL), then dried on
high vacuum and purged with argon. The residue was
dissolved in THF (15 mL) and cooled to -78°C under argon.
A solution of nBuLi (2.4 M in hexanes, 1.90 mL, 4.52
mmol) was added dropwise, maintaining the temperature
10 around -78 to -74°C. A solution of the Example 2 Part G
aldehyde compound (1.332 g, 5.16 mmole) in THF (10 mL)
was added dropwise. The reaction mixture was stirred at
- 78°C for 40 mm, at -10°C for lh, and at room temperature for lh. The reaction mixture was quenched with saturated
15 aqueous NH4C1 (100 mL), then extracted with EtOAc (2 x 100
mL). Combined EtOAc layers were washed with H20 and
brine, then dried (Na2SO4), filtered and concentrated in vcuo. Purification by flash chromatography (27:973-EtOAc:cH2Cl2) gave the title compound as a white foam, 804
20 mg, 34s yield.

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To a solution of part H compound (804 mg, 1.38
muiol) inCI-W12 (18 mL) at 0°C under argon was added trifluoroacetic acid (1.59 mL, 20.7 mmol). The reaction mixture was stirred at room temperature for Sh, diluted
5 with EtOAc (100 mL) and washed with saturated aqueous
NaHCO3 (60 mL x 2), H20 and brine, then dried (Na2SO4)1 filtered and concentrated in vacuo. Purification by

10

flash chromatography (45:55-EtOAc:hexane) gave the title compound as a white foam, 540 mg, 83% yield.

J.

To a solution of Part I compound (515 mg, 1.1
mmol) in THF (10 mL) was added IN aqueous NaOH (1.37 mL,
15 1.37 mmol) and stirred at room temperature for 10 mm.
The reaction mixture was concentrated in vacuo and
purified by SP207 (Na form) resin, eluting with 3:7-
H3cN:H20. The desired fractions were pooled and
lyophilized to give the title compound as a white powder,

20 506 mg, 91% yield. LRMS gave the correct molecular ion 41
[(M - Na + 2H) = 4881 for the desired compound.

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Example 1A

Alternate Procedure for Example 1 Part B compound

Ph
Ph

To a stirred solution of Example 1 Part E compound
(13.07 g, 31.0 mmol) in toluene (300 mL) was added 0-
ethy]. diphenyiphosphinate (8.65 mL, 40.0 mmol) in one
10 portion. The reaction was heated to reflux, using a
Dean-Stark trap to remove the 15 mL of solvent. After
- 2h, the solution was cooled and evaporated to nearly
remove all of the solvent. The residue was triturated in hexanes (100 mL), the resulting solids were collected
15 and dried in vacuo at 60°C to give Part (1) compound as a
white solid, 15.25 g, 91% yield, mp 201-203°C.

(2).

20 A 1 L 3 -necked round bottom flask was flame-dried and then fitted with a mechanical stirrer, an argon-
filled balloon, vacuum take-off and a thermocouple. To a stirred slurry of Part (1) compound (7.00 g, 12.9 mmol)
in THF (200 mL) at 0°C was added n-butyllithiuni solution
25 (5.4 mL, 2.5 M in hexanes, 13.5 mmol) over 20 mm. A

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deep red-orange solution formed. After 30 mm, a
solution of zinc chloride-N, N, N’, -tetramethylethylene-diamine complex (dried in vacuo at 60°C for 2h, 3.42 g,
13.5 mmol) in THF (100 mL) was added via cannula and
5 stirred 30 mm. After 30 mm, the resulting solution was
canriulated into a solution of Example 2 Part G aldehyde
(4.30 g, 16.6 mmol) in THF (20 mL)’ at room temperature
over 20 mm. A light orange solution soon formed,
followed by a precipitate. After 3 h, the reaction was
10 quenched with brine (50 mL) and water (50 mL) and
extracted three times with ethyl acetate (100 mL). The organic extracts were combined, dried (MgSO4) and evaporated. LCMS of the crude material indicated
unreacted Part (1) compound and an 89/11 mixture of the
15 desired (E) isomer/undesired (Z) isomer.
The reaction was repeated and the combined crude
product (28g) was purified by flash chromatography on silica gel in two identical batches (12 x 22 cm column,
1.5 L 1:99 EtOAc/CH2C12, 2 L 1:39 EtOAC/cH2C12 and then 1.5
20 L 3:7 EtOAc/hexanes). Partially pure E/Z mixtures were
pooled and repurified to give the title Part (2) compound (which is the same as Example 1 Part H compound) (99.2%
(E) isomer) as a crystalline solid (after evaporation
from toluene), mp 146-147°C, 7.14 g (68% yield, based on
25 recovered Part (1) compound).

Example 2

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A.

To a solution of 4-fluoro-benzaldehyde (5g, 40.3
5 mmol) and ethyl isobutyryl acetate (6.5 mL, 40.3 mmol) in
benzene (50 mL) was added piperidine (400 p1, 4.04 mmol), followed by acetic acid (100 p1, 1.66 mmol). The
reaction was refluxed for 16 hours and partitioned
between aqueous HCl (iN, 20 mL) and ethyl acetate (50 mL
10 x 2). The combined organic layers were washed with
saturated NaHCO3 (20 mL), brine (10 ml), and dried over sodium sulfate (Na2SO4). The solvent was removed in
vacuo. Distillation at 140°C at 300 mm Hg afford 9.06 g
(85% yield) of compound A as a yellow oil. ESI-LC/MS
15 (M+H) =264.

B.

20 To a 1M lithium hexamethyldisazide solution (50

t mL, 50 mmol) at -78°C under N2 was added a THF (3 mL)

solution of benzosuborone (9 g, 56.1 mmol). The reaction
temperature was maintained below -75°C during the
addition. The reaction was then stirred at -78°C for 1
25 hour and compound A (9 g, 34.1 mmol, in 3 mL THF) was
slowly added to the reaction. After the addition was
complete, the reaction was stirred for 1 hour at -74°C
then warmed to 0°C and stirred for 20 minutes. The
reaction was quenched with HOAc (9 mL) and poured into
30 saturated ammonium chloride solution (NH4C1, 20 mL). The
aqueous layer was extracted with ethyl ether (100 mL x

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3). The combined organic layers were washed with water
(30 mL) and brine (30 mL), then dried over sodium sulfate (Na2804). The solvent was removed in vacuo and stripped
with toluene twice to afford crude compound B. The crude
5 compound B was used directly in the next step. ESI-LC/MS
(M+H) =425.

C.

10

To a solution of the crude compound B (12 g) in
aqueous HOAc (100 mL) was added ammonium acetate (9.5g,
123.2 mmol), followed by cupric acetate monohydrate
(20.7g, 113.9 mmol). The reaction was reflux for 20
15 hours, cooled 10 room temperature, then poured into a
solution of ammonium hydroxide in ice (1 to 1; v/v). The aqueous layer was extracted with ethyl ether (200 mL x
3). The combined organic layers were washed with water
(50 mL) and brine (50 mL). Flash chromatography (10%
20 ethyl acetate in hexane) afforded 10.2 g (88% yield) of
compound C as white powder. ESI-LC/MS (M+H)+ =404; m.p.
138-140°C.

D.

25

I

To a solution of compound C (10 g, 24.78 mmol) in
anhydrous THF (240 mL) at 0°C was added 1.0 M lithium aluminum hydride in THP (74 mL, 74 mmol). The reaction
30 was stirred at 0°C for 1 hour and then warmed to room
temperature and stirred for 16 hours. The reaction was

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then cooled to 0°C and quenched slowly with ice, then
sodium hydroxide (10% NaOH, 20 mL). The mixture was extracted with diethyl ether (50 mL x 2) and filtered.
The filter cake was then washed with more ethyl ether (10
mL) and ethyl acetate (10 mL). The combined organic
layers were washed with water (10 mL) and brine (10 mL),
then dried over sodium sulfate (Na2SO4). Flash
chromatography (20% ethyl acetate in hexane) afforded 6.5 g (7391; yield) of compound D. ESI-LC/MS (M+H)+ =362; m.p.

170-171°C.

E.

To a solution of compound D (8.5 g, 23.54 tnmol) in anhydrous CH2C12 (100 mL) at 0°C was slowly added 1.0 M phosphorous tribromide in cH2C12 (47 mL, 47.1 tnmol) while maintaining the temperature below 10°C. After the addition was complete, the reaction was stirred at 0°C for 1 hour and then poured into saturated cold NaHCO3 Solution (200mL) with stirring. The aqueous layer was extracted with cH2c12 (50m1 x 2) and the combined organic layer was washed with water (10 mL) and brine (10 mL), then dried over sodium sulfate (Na2SO4). Flash chromatography (10% ethyl acetate in hexane) gave 8.6 g (86% yield) of compound E as a white solid. ESI-LC/MS (M+H)+ =424; m.p. 157-159°C.

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F.

To a solution of diethyl phosphite (785 iL, 6.09
5 mmol) in anhydrous THF (25 mL) at -10°C under argon was
added a 1.0 M THF solution of sodium hexamethyldisazide
(6 mL, 6.09 mmol). The reaction mixture was stirred at
- 10°C for 30 minutes. A solution of compound E (2.15g,
5.08 mmol) in THF was added to the reaction while
10 maintaining the temperature at -10°C. After the addition
was complete, the reaction was stirred for 1 hour and quenched with water (20mL). The aqueous layer was
extracted with ethyl acetate (30tnL x 2) and the combined organic layers were washed with iN HC1 solution (5mL).
15 The organic solvent was removed in vacuo. Flash
chromatography using 20% to 30% ethyl acetate in hexane
as eluting afforded 2.29 g (94% yield) of compound F as a white solid. ESI-LC/MS (M+H)"=482; m.p. 102-105°C.

20 G.

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.An oven-dried 3 -neck 1-L flask equipped with
temperature sensor probe, 125-mL constant pressure
addition funnel and septum was charged with dry 0H2C12
25 (300 mL) and dry DMSO (20.9 mL, 0.2944 mol, 2.5 equiv)
under argon atmosphere; cooled to -7°C. Added neat oxalyl chloride (13.6 mL, 0.156 mol, 1.32 equiv) via syringe dropwise over 15 mm (temperature rose to -660C), then let stir additional 15 mm. A solution of the starting
30 alcohol 2- E (4R, 6S) -6- (hydroxymethyl) -2, 2-dimethyl-1, 3-
dioxan-4-yl] acetic acid t -butyl ester (30.66 g, 0.1178

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mol, 1 equiv) in dry CH2C12 (80 mL) was added dropwise
from the addition funnel over 30 mm (temperature rose to
- 68°C). The resulting white mixture was stirred for 70
min at -76°C, then added triethylamine (82 mL, 0.5889 mol,
5 5 equiv) dropwise from addition funnel over 35 mm
(temperature rose to -65°C), then stirred the light
yellow mixture vigorously at -76°C. TLC (SiO2, 20%
EtOAc/CH2C12, Rf=0.52). After 30 mm, removed the cooling
bath and quenched the reaction by slowly adding cold 20%
10 aq KH2PO4 (35 mL), followed by cold H20 (300 mL); let stir
15 mm (temperature rose to -70C). Poured into 2 -Li
separatory funnel and extracted with hexanes (500 mL).
Washed the organic extract with cold 10% aq KH2PO4 (3x300

9 mL) and saturated aqueous NaCl (300 mL). Dried the
15 organic over anhydrous Na2S041 filtered and concentrated
in vacuo to give yellow oil. Purification by Si02 flash chromatography (10cm x 20 cm column) with 35:65
EtOAc/Hexanea afforded the title compound as a white
solid (22.2 g, 0.0859 mol, 73%):

’H NMR (CDC13) 8 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, 3=1.3 Hz, 1H).

25 H.

To a cooled (-78°C) solution of compound F (2.02 g,
4.19 mtnol) in anhydrous THF (30 mL) under argon was
30 slowly added a 2.5 M THF solution of n-butyllithium (2.1
mL) over a period of 40 minutes. The temperature was maintained below -75°C during the addition. After the

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addition was complete, the reaction mixture was stirred
for another 40 minutes at -78°C. A solution of compound G
(2.2 g, 8.52 mmol) in THF under a:-gon was cannulated into
the phosphonate mixture at -78C. After the addition was
5 complete, the reaction was stirred for 1 hour at -78°C.
The reaction was then warmed to -10°C and stirred for 1
hour and then stirred at room temperature for an
additional hour. The mixture was quenched with saturated
ammonium chloride solution (5mL) and extracted with ethyl
10 acetate (60 mL x 3). The combined organic layers were
washed with water (lOmL) and brine (lOmL), then dried
over sodium sulfate (Na2SO4) and filtered. The filtrate
was concentrated in vacuo. Flash chromatography using 50-.
to 10% ethyl acetate in hexane as eluent afforded 1.48 g
15 (60% yield) of compound H as a white solid. ESI-LC/MS
(M+H)+ =586; m.p. 148-149°C.

I.

20

To a cooled (0°C) solution of compound H (500 mg,
0.854 mmol) in anhydrous CH2C12 (12mL) under argon was
slowly added trifluroacetic acid (987 mL, 12.82 mmol).
After the addition was complete, the reaction mixture was
25 allowed to stirred at 0°C for 10 minutes and at room
temperature for 3 hours and then the solvent was removed
In vacuo. The reaction mixture was quenched with
phosphate solution (pH 7.5, 12 mL) and extracted with
cH2Cl2 (20 mL x 2). The combined organic layers were
30 washed with brine (lOmL), dried over sodium sulfate
(Na2SO4), and filtered. The solvent was removed in vacuo. Flash silica gel chromatography using 30% to 50% ethyl

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acetate in hexane as an eluent afforded 331mg (80% yield)
of compound I as a white powder. ESI-LC/MS (M+H)+=588,
m.p. = 199-200°C.

5 J.

To a solution of compound I (316 mg, 0.671 mmol)
in anhydrous THF (6tnL) at room temperature was added an
10 aqueous solution of sodium hydroxide (IN NaOH, 839l,
0.839 mmol). The reaction was stirred at room
temperature for 10 minutes. The solvent was removed in
vacuo and taken up in water (5tnL). The solution was chromatographed on SP-207 resin eluting with water,
15 followed by 25%-40% acetonitrile in water. The desired
fractions were stripped, redissolved in water and lyophilized to give title compound (308 mg, 94% yield) as
a white solid. ESI-LC/MS (M+H)=490; ESI-MS (M+H)+ = 490;

20 ’H NNR (DMSO-D6; 400mHz) 6 0.97-1.01 (m, 1H), 1.24-1.46

it(m, 7H), 1.73-1.78 (m, 1H), 1.93-2.05 (m, 5H), 2.49-2.52

(m, 2H), 3.40-3.53 (m, 2H), 4.03-4.08 (m, 1H), 5.34 (dd,
1H, 1Y = 5.72, 10.56 Hz), 6.29 (d, 1H, J= 16.24 Hz),
7.21-7.19 (m, 5H), 7.32-7.42 (m, 2H), 7.71 (d, 1H, J =
25 7.48Hz);

13C 1NR (DMSO-D6, 400mHz) 6 175.6, 162.5, 161.3, 160.1,
154.2, 147.8, 140.5, 138.8, 134.5, 130.7, 130.5, 129.6,
128.5, 128.1, 126.3, 115.1, 114.9, 68.2, 66.6, 43.7,
30 43.3, 38.4, 32.3, 30.6, 30.1, 26.4, 24.8, 22.8, 22.7.
Anal. Calcd for C30H32NO4FNa 0.9 H20: C, 68.14; H, 6.44;

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N, 2.65; F, 3.59; Na, 4.35. Found: C, 67.79; H, 5.97; N, 2.51; F, 3.86; Na, 4.83.

Example 2A
5 Alternate Procedure for Example 2 Part H Compound
H(1).

To a stirred solution of Example 2 Part E compound
10 (3.34 g, 7.9 mmol) in ’toluene (40 mL) was added 0-ethyl diphenyiphosphinate (2.65 g, 11.5 mmol) in one portion.
The reaction was heated to reflux for 2h, then cooled to
room temperature. The white precipitate was collected
via filtration and washed with heptane. The residue was
15 dried in vacuo overnight to give title compound as a white solid, 4.3 g, 99’s yield, mp 264-265°C.

20

25

H(2).

To part H(1) compound (109 mg, 0.2 mmol) in 25 mL
2 -necked round bottom flask (flame-dried and fitted with
an argon-filled balloon, vacuum take-off and a
thermocouple) was added 0.5 mL of DMPU (distilled over
CaH2 under reduced pressure, stored with 4A molecular
sieves). The resulting slurry was warmed while stirring until becoming a clear solution, which was diluted with
THF (1.5 mL). The reaction mixture was evacuated and
purged three times with argon, then cooled to -78°C. To

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the cooled reaction mixture was added dropwise 0.42 mL of
a 0.5 M solution of LDA in THF’ (0.21 mmol)..An amber
colored solution formed. After stirring at -78°C for 30
minutes, a solution of Example 2 Part G aldehyde (67 mg,
5 0.26 mmol) in THF (0.5 mL) was added via a syringe.
After addition, the resulting yellow solution was stirred
at -78°C for 30 minutes, then at 0°C for 1 hour before quenched with an aqueous solution of ammonium chloride.
The reaction mixture was extracted three times with ethyl
10 acetate (10 mL). The organic extracts were combined,
washed with water and brine, dried (MgSO4) and evaporated. The crude product was purified using flash chromatography
on silica gel eluting with 5% EtOAc/hexane. The desired fractions were pooled and concentrated, and the collected
15 residue dried in vacuo overnight to give Part H(2)
compound as a white foam, 80 mg (68% yield).

1A stock solution of 0.5 M LDA in THF was prepared from diisopropylamine (redistilled, Aldrich) and 2.5 M of BuLi
20 in hexane (Aldrich) following the usual procedures and

stored at -20°C.

25

Example 3

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A.

To a solution of Example 2 Part H compound (500 mg,
5 0.854 mmol) in a mixture of MeOH and EtOH (10 mL) was
added 10% Palladium/C (100 mg) and purged with hydrogen (H3). The reaction mixture was then stirred at 55 psi under hydrogen for 2 hours. Upon the completion of the reaction, the catalyst was filtered and the solvent was
10 removed to afford 500mg (99% yield) of the
product as a white foam. ESI-LC/MS (M+H)=588.

B.

15

To a cooled (0°C) solution of Part A compound
(450mg, 0.766 mmol) in anhydrous CH2C12 (9mL) under argon
was slowly added trifluroacetic acid (886 mL, 12.5
mmol). After the addition was complete, the reaction
20 mixture was allowed to stirred at 0°C for 10 minutes and
at room temperature for 3 hours and then the solvent was removed The reaction mixture was quenched with phosphate solution (pH 7.5, 12 mL) and extracted with
H3c13 (20 mL x 2). The combined organic layer was washed
25 with brine (saturated NaCl solution, 10mL), dried over
sodium sulfate (Na2SO4) and filtered. The solvent was

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5

removed in vacuo. Flash silica gel chromatography using
30% to 50% ethyl acetate in hexane as an eluent afford
330mg (91% yield) part B compound as a white powder. ESI-
LC/MS (M+H)=474, MP (°C) = 253-254.

C.

To a solution of part B compound (330mg, 0.698
10 mmol) in anhydrous THF (8mL) at room temperature was
added an aqueous solution of sodium hydroxide (iN NaOH,
872j.]., 0.872 mmol). The reaction was stirred at room
temperature for 10 minutes. The solvent was removed in
vacuo and taken up in water (5mL). SP-207 resin bound
15 chromatography using water, followed by 20% to 40%
acetonitrile in water as the eluent afford 315 mg (92%
yield) of Part C compound as a white lyophillate. The
SP-207 resin was pre-washed with saturated sodium
bicarbonate solution (NaBC03, 50 mL) followed by saturated
20 sodium chloride solution (NaCl, 50 mL), and water (200
ML).

ESI-LC/MS (M+H)=492, ESI-MS (M+H)+ = 492;

25 ’HNMR (DMSO-D6; 400mHz) 81.05-1.09 (m, 1H), 1.23-1.29
Cm, 8H), 1.35-1.44 (tn, 2H), 1.70-1.78 (m, 1H), 1.90-1.98
(m, 6H), 2.25-2.35 (m, 1H), 2.45-2.55 (m, 1H), 3.36-3.40
(m, 1H), 3.62-3.65 (in, 1H,), 4.70 (s, 1H), 7.25-7.41 (m,
7H), 7.67 (d, 1H, J = 7.48Hz);

30

’C NMR (DMSO-D6, 400mHz) 8 175.8, 162.4, 160.6, 160.0,
155.0, 146.8, 141.0, 140.3, 138.9, 134.7, 131.2, 130.9,
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129.5, 128.8, 128.3, 126.3, 68.6, 65.6, 44.7, 44.3, 40.0, 32.6, 31.1, 30.6, 26.3, 22.2.

Following the procedure of Examples 1 to 3 the
5 following compounds may be prepared.

10

15

Example 4

Example 7

Examples 4 to 18

HO4

Y OB

where Y is as set out below

Example 5

Example 8

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Example 6

Example 9

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Example 10

5
Example 13

10 Example 16

F

F

Example 11

F

Example 14

Example 17

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Example 12

Example 15

Example 18

F

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5

Example 19

Example 22

Example 25

Example 20

Example 23

Example 26

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Example 22.

Example 24

Example 27

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Example 28

5
Example 31

Example 34

10

Example 29

Example 32

w

Example 30

Example 33

F

It will be appreciated that the compounds of
Examples 1 to 34 may also be converted to corresponding lactones and/or salts thereof.
15 With respect to Examples 35 to 38, please refer to Scheme 6.

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5

Example 35
Preparation of Pyridine Aldehyde (18) (Scheme 6)

A.

>io..CH3

Nk

To a mixture of 4-fluoro-benzaldehyde (935.8 g,
10 7.54 moles) and methyl isobutyry. acetate (1087 g, 7.54 moles) was added piperidine (64.: g, 0.75 mol), followed
by acetic acid (22.6 g, 0.38 mol). The mixture was
heated to 80 to 85° C for about 2 hours. 16 Liters (4 x
4L) of toluene was added and mixed with the reaction
15 mixture. The toluene was removed using a rotavapor (50-65° C/20-90 torr), leaving a yellow oil. The yellow oil
was dissolved in 5L MTBE and washed with:
1 x 3L HCJ. (0.5N)
1 x 3L NaHCO3 (saturated soln.)
20 lx3LDlwater
The MTBE was evaporated off. Thereafter, 1.5L of
MTBE was added and the mixture evaporated to remove water
to afford about 1780 g (yield 88%) of title compound as a yellow oil.

25

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B.

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5 To 7.35 L NaRMDS (7.35 moles, 1.05 eq) under N2
(cooled down between -72 to -65°C) was added a THF (6 L) solution of 1-benzosuborone (1177 g, 7.35 moles, 1.05
eq). The reaction temperature was maintained below -5 0°C during the addition. The reaction was then stirred at -
10 between -72 to -65°C for 1 hour and a solution of

compound A (1751.5g, 7.0 moles, in 6 L ThF) was slowly
added to the reaction while keeping the temperature below
- 50°C. After the addition was complete, the reaction was
stirred for 2-3 hours between -72 to -65°C. The reaction
15 was quenched with HOAc (1.4L) between -72 to -50°C. The
mixture was allowed to reach RT and saturated ammonium chloride solution (NH4C1,15L) was added plus 7L DI -water,
and the mixture agitated for 5-10 mm. The aqueous layer was extracted with 1 x 8L MTBE. The combined organic
20 layers were washed with water (2 x 9L) and brine (1 x
9L), then dried. The solvent was removed to afford crude compound B (3.08 kg). The crude compound B was used directly in the next step.

25 C.

To a solution of the crude compound B (3078 g) in
aqueous HOAc (16L) was added ammonium acetate (1446 g),
30 followed by cupric acetate monohydrate (1859 g). The
reaction was refluxed between 120 to 124°C for 12-15

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hours. Approximately 90% of the acetic acid was evaporated to produce a green slurry. The slurry was
then mixed with 14L MTBE.
The resulting solution was filtered through a
5 celite pad (177g celite in a 7" x 8", WH, funnel) and
the cake washed with 16L MTB. The organic phase was
washed with:
- 2 x 9 L DI -water, pH of combined wash=4.2
- 2 x 3 L NaHC031 pH of the combined wash=6.4
10 - 1 x 9 L DI -water, pH=6.0.
The solvent was evaporated to produce a black oil
(2883 g). 2.5 L of methanol was added and the mixture
agitated for approximately 2-3 h. The product was
filtered and washed with 2 L of cold methanol (-10 to
15 0°C). The product was dried at 40-50°C/20" of Hg to
produce an off-white solid, 793 g, HPIC AP=97.8. Yield =

27%.

I (18)

20

To a 500 rnL round bottom flask equipped with a
magnetic stirrer and a nitrogen inlet was charged Part C compound (17) (Scheme 6) (50.0g, 128.4 inmol) and toluene
25 (170 inL). The mixture was stirred at 20-25°C until a
clear solution was obtained. A solutin of 65% Red-Al in
toluene (57.8 inL, 192.6 mmol) was added and the reaction
mixture was heated to 80°C until complete as determined
by HPLC. The reaction mixture was cooled to -20°C and
30 quenched by pouring it into cold (0-5°C) 20% HC1 (495
teL). Phases were separated and the spent toluene phase
was discarded. The pH of the aqueous phase was adjusted

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from <0 to 4-5 with iON NaOH. Ethyl acetate (500 was
added and the pH adjustment continued to 7-8. The phases
were separated. The aqueous phase was extracted with
additional ethyl acetate (2 x 500 niL). The combined rich
5 ethyl acetate solution was washed with water (3 x 250 niL)
and concentrated under reduced pressure to -465 niL. This solution was carried through to the next oxidation step.
The rich ethyl acetate solution was charged from
above into a three neck l-L flask equipped with
10 mechanical stirring, temperature controller, and addition
funnel and cooled to 0-5°C. To the slurry, potassium
bromide (1.53 g, 12.8 nimol) and TEMPO (2,2,6,6-
tetraxnethyl-1-piperidinyloxy) (0.20 g, 1.28 nimol) were
added. The pH of NaOC1 (sodium hypochiorite) solution
15 (212.1 ml) was adjusted to -9.1 and added to the slurry
at a rate such that the temperature remained at 0-5°C. Stirring was continued at 0-5°C until the reaction was complete as determined by HPLC. The aqueous phase was extracted with EtOAc (2 x 200 niL). The combined rich
20 organic phase was washed with a 1:1 solution of sat. aq.
Na2S203 (sodium thiosulfate) (75 mL) and water (75 xnL)
followed by wash of the rich organic phase with iN NaOH
(250 niL). The rich organic phase was washed with water
(250 ml) and concentrated to -100 niL under reduced
25 pressure. Isopropanol (IPA) (400 niL) was added and the
resulting mixture was heated to reflux (80-85°C). The
solution was distilled to a volume of 250 niL. Water (50
niL) was added and the crystal slurry was stirred at 70-
80°C for 1 h then allowed to cool to 20-25°C over at least
30 1 h. The slurry was held at 20-25°C for at least 1 h
before collecting the solid by filtration on a Buchner
funnel. The cake was washed with cold (0°C) IPA/water
(4:1) (2 x 50 niL) and dried to a constant weight under
vacuum at 40°C to afford 41.5 g (90%) of title aldehyde
35 as a white crystalline solid.

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Example 36

(16) (Scheme 6)

5 A. Preparation of Sulfide (15)

9 0\>?O 0

INr

S,,_j,,?Ok (15) (Scheme 6)

VN

To a 250 niL flask was charged Kaneka alcohol
(12) (Scheme 6) (10.0 g, 38.41 inmol), methylene chloride
10 (100 niL), and triethylamine (11.75 niL, 84.51 mmol) and
cooled to -30°C. Triflic anhydride (7.11 niL, 42.25
zmnol) was added via a syringe at a rate to maintain the temperature at -35 to -25°C, -15 mm. The reaction
mixture was stirred at -30°C for -30 min and checked for
15 disappearance of Kaneka alcohol by TLC. A slurry of 1-
phenyl-1H-tetrazole-5-thiol (7.19 g, 40.34 inmol) in methylene chloride (50 niL) was added to the triflate solution. After the reaction was complete, water(100 niL)
was added and the mixture was stirred for -5 mm. The
20 phases were separated and the aqueous phase was
discarded. The rich orgnaic phase was washed with water
(100 niL) for -5 min and phases separated. The rich
organic phase was washed with saturated NaHCO3 (100 niL)
for -15 min and phases separated. The rich organic phase
25 was concentrated to -50 niL. The solution was taken to
the next step for further transformation.

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B. Preparation of Sulfone (16)

L1)
N
N’
N

IPA (150 xaL) 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) 6M07024.4H20 (ammonium heptamolybdate tetrahydrate)
(4.75 g, 3.84 mmol) in 30 H202 (hydrogen peroxide) was
added dropwise during 15 maintaining the
10 temperature of the solutin 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 InL 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 xnL) 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 37
Preparation of Olefin (19)

25

An N2 purged 250 xtL 3 -neck rb flask was charged with
* Example 35 pyridine derivative (18) (5.0 g, 13.9 Inmol),
Example 36 sulfone (16) (6.92 g, 15.3 mmol) and THF (75
rnL). The stirred solution was cooled to -74 to -78°C

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Slowly a 1M solution of LiHMDS (lithium bis(trimethylsilyl)amide) (15.3 ml, 15.3 mmol) in THF was charged at a rate such that the temperture remained
between -70 and -78°C. After addition of the base was
5 complete, the reaciton mixture was warmed to --45°C over
- 15 minutes. The stirred reaction was quenched at -70°C
by slow addition of sat. aq. NH4C1 (7.5 ml) solution and water (38 mL). The dry ice bath was removed and the solution was warmed to 20-25°C from the reaction mixture.
10 Ethyl acetate (50 mL) was added, the mixture agitated,
and layers separated. The organic layer was washed with
saturated sodium bicarbonate solution (2 x 38 ml)
followed by brine (25 mL) and concentrated to a volume of
50 ml. Acetonitrile (50 mL) was added and the solution
15 was concentrated to a volume of 50 ml. This step was
repeated. Water (-5-6 ml) was slowly added to the hot solution (60-70°C) until the cloud point was reached.
The thin slurry was held for 30 min at high temperature
and then slowly cooled over several hours with stirring.
20 The product was filtered, cake was washed with a 5:1
mixture of acetonitrile and water, and dried to afford
7.5 g (91%) of the title compound as a white crystalline material.

25 Example 38
Preparation of the final compound as arginine salt (1b9)

COOH
 H2N)Iy12

30 To a 3.0-liter round bottom flask equiped with a mechanical stirrer, a thermometer, and a septa was
charged Example 37 trans olefin (19) (92.0 g, 157 mmol)
and THF (600 mL) at ambient temperature. With stirring,

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5

10

15

to the resulting clear sight yellow solution was added 6N
HC1 (aq. 74.6 rnL, 447 inmol) at ambient temperature to
form (20)

(20)

The reaction mixture was stirred for 5.0-6.0 h followed
by addition of 2 N NaOH (aq. 389 mL, 777 nnuol) to form a light yellow suspension. Agitation was maintained at ambient until reaction (saponification of (20)) was judged complete by an in-process HPLC assay. THF was evaporated on a rotary evaporator at about 45°C. The white slurry residue was diluted With 1000 inL of water and was extracted with MTBE (methyl t-butyl ether) (230
inL x 2). After separating the NTBE layer, the aqueous
layer containing (21)

was transferred to a 5.0-liter round bottom flask
equipped with a mechanical stirrer, a thermometer, and a septa. While temperature was controlled at <29°C, 1 N HC1
20 (aq) was added to the above aqueous layer until the pH=6.94. Subsequently, 330 inL of ethyl acetate was added
to the aqueous layer followed by charging more 1 N HC1
(aq) until pH=2.82. After separating and saving the
ethyl acetate layer, the aqueous layer was extracted with

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ethyl acetate (330 InL x 3). The combined ethyl acetate layers containing acid lb8 of the invention

(10) (Scheme 6)

5 were washed with 50% brine (265 inL), brine (427 inL),
separated and mixed with a suspension of L-arginine (27.4
g, 157 inmol) in ethanol (276 niL) and water (138 niL). The
mixture was evaporated to dryness under reduced pressure
at ca 45-50°C. To the resulting white solid were added
10 ethyl acetate (450 niL), ethanol (316 rnL), and water (145
niL) followed by heating the white suspension to 50°C.
Another 36.7 niL of water was added to dissolve all solids
at 56°C; subsequently 1720 niL of ethy acetate was added
to the hot solution to initialize the crystallization.
15 The white suspension was stirred at 50°C for 1.5 h and at
ambient for 13 h. After filtration, the crystalline
solid was washed with 143 inL of a mixture of EtOAc (200
niL), EtOH (12 niL) and H20 (6 niL) and was dried in vacuo
at 40-50°C for 24 h. The title product obtained as a
20 white solid weighed 78.9 (g). Yield, 75.7%. [a]25D=+23.O
Cc 0.31, CH3CN:H20, 1:1, v/v).

1H NMR (CD30D): 8 7.74 (dd, J=2.5 Hz, J’=l.O Hz, 1H), 7.41 (dt, J=7.0 Hz, J’=6.1 Hz, 1H), 7.37 (dt, J=7.3 Hz, J’=1.4
25 Hz, 1H), 7.27 (d, J7.2 Hz, 1H), 7.22 (dd, J=15.4 Hz,
J’=7.OHz, 2H), 7.20 (d, J=7.0 Hz, 2H), 6.45 (d, J=16.5
Hz, 1H), 5.43 (dd, J=16.5 Hz, J’=6.5 Hz, 1H), 4.24 (q,
J=6.5 Hz, 1H), 3.79 (m, 1H), 3.55-3.50 (m, 2H), 3.23 (m,
2H), 2.62 (t, J=7.2 Hz, 2H), 2.31-2.21 (m, 2H), 2.16 (t,
30 J=6.8 Hz, 2H), 2.05 (m, 2H), 1.87 (q, J=7.0 Hz, 2H), 1.74

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(in, 2H), 1.57 (in, 1H), 1.34 (d, J=6.8 Hz, 6H), 1.31 (in, 1H).

13c NMR (CD30D): 8 180.1, 174.7, 164.5, 163.1, 162.5,
5 158.7, 157.8, 149.1, 141.91 141.01 140.8, 136.4, 132.6,
132.3, 131.6, 130.51 130.1, 129.7,129.2, 127.6, 126.6, 116.3, 116.0, 71.5, 68.0, 55.6, 45.0, 41.9,34.2, 33.1, 32.2, 29.6, 27.71 25.8, 22.5.

10 MS: calc’d for C36H46FN506 (M + H) 490 and 175, found

490 and 175.

IR (KBr): 3341, 3200, 3070, 2960, 2934, 2860, 1670,
1629, 1602, 1580, 1509, 1465, 1450, 1397, 1357, 1221,
15 842, 766, 740 cm1.

Anal. Calc’d for C36H46FN506: C, 65.14, H, 6.98, N, 10.55. Found C. 65.15, H, 6.97, N, 10.53.

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What is claimed is:
1. A compound having the structure

5 wherein

10

15

20

R4

Z is

Ws OR

A

or O*T_%%.J(::

n is 0 or 1;
x is 0, 1, 2, 3 or 4;
y is 0, 1, 2, 3 or 4, provided that at least one of
x and y is other than 0; and optionally one or more carbons of (CH2) and/or one or more carbons of (CH2) together with additional carbons form a 3 to 7 membered spirocyclic ring;
R1 and R2 are the same or different and are
independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;
R3 is H or lower alkyl;
R4 is H, halogen, CF3, hydroxy, alkyl, alkoxy, alkanoylainino, aroylainino or cyano;
R7 is H or lower alkyl;

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

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0

and pharmaceutically acceptable salts thereof (when
R3 Is H), esters thereof, prodrug esters thereof, and all stereoisomers thereof.

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

3. The compound as defined in Claim 1 wherein R1
is aryl,
10 R2 is alkyl or cycloalkyl or aryl;
R4 is H;
n is 0;
x is 3;
yis 0; and

15 0"’

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

4. The compound as defined in Claim 3 wherein R1
20 is 4-fluorophenyl, 4-fluoro-3-methylphenyl, or 3,5-dimethyiphenyl; and
R2 is isopropyl, t-butyl or cyclopropyl.

5.
25 structure

The compound as defined in Claim 1 having the

or an alkali metal salt, or an alkaline earth metal salt,
or an amino acid salt, or an acid addition salt via the pyridine of the corresponding 8 lactone,

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wherein R5 and R6 are the same or different and are independently selected from H, halogen or alkyl and
R2 is alkyl or cycloalkyl.

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

structure

10

15

or

wherein R3 is H or an alkali metal, alkaline earth metal, amino acid salt, or other pharmaceutically acceptable
salt, or the internal lactone thereof, in the form of its calcium salt, sodium salt or arginine salt.

7. A compound of the structure

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wherein R3 is H or an alkali or alkaline earth metal ion
or an amino acid, or the internal lactone thereof, in the
form of its sodium salt, calcium salt or arginine salt.

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

9. A pharmaceutical combination comprising the HMG
10 C0A 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 including antidiabetic agents, anti-obesity agents,
15 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 (including anti -anginal agents, anti-arrhythmic agents,
20 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 secretagogues, selective androgen receptor modulators,
25 and/or immunomodulatory agents.

10. The combination as defined in Claim 9 wherein
the hypolipidemic agent or lipid-lowering agent or other lipid agent or lipid modulating agent or anti-
30 atherosclerotic agent, which is employed comprises 1,2,3
or more MTP inhibitors, HMG C0A reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, PP.AR a agonists, PPAR dual a/7 agonists, PP.AR 8 agonists, ACAT inhibitors, lipoxygenase inhibitors, cholesterol
35 absorption inhibitors, ileal Na/bile acid cotransporter
inhibitors, upregulators of IJDL receptor activity, cholesteryl ester transfer protein inhibitors, bile acid

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seguestrants, or nicotinic acid and derivatives thereof,
ATP citrate lyase inhibitors, phytoestrogen compounds, an HDL upregulators, LDL catabolism promoters, antioxidants, PLA-2 inhibitors, antihomocysteine agents, HMG-00A
5 synthase inhibitors, lanosterol detnethylase 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
10 secretagogues or insulin sensitizers, which may include
biguanides, sulfonyl ureas, PTP-1B inhibitors, aldose
reductase inhibitors, glucosidase inhibitors, PPAR y agonists, PPAR a agonists, PPAR 8 antagonists or
agonists, aP2 inhibitors, PPAR a/y dual agonists,
15 dipeptidyl peptidase IV (DP4) inhibitors, SGLT2
inhibitors, glycogen phosphorylase inhibitors, and/or
meglitinides, insulin, and/or glucagon-like peptide-1
(GLP-1) ora mitnetics thereof;
wherein the other type of therapeutic agent which
20 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 aP2 inhibitor, a thyroid receptor beta
drug, an anorectic agent, a PTP-1B inhibitor, a CCKA
25 agonist, a neuropeptide Y antagonist, a melanocortin-4-
receptor agonist, a PPAR modulator which is a PPAR y
antagonist, PPAR a agonist, and/or PPAR 8 antagonist, a
leptin inhibitor such as a leptin receptor activator, a fatty acid oxidation upregulator or inducer;
30 wherein the lipid modulating agent is an MTP
inhibitor, an HMG C0A 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
35 is a cholesteryl ester transfer protein inhibitor;
wherein the antihypertensive agent employed is an
ACE inhibitor, angiotensin II receptor antagonist, NEP

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inhibitor, a NEP/ACE inhibitor, a calcium channel
blocker, a T-channel calcium antagonist, a 3-adrenergic blocker, a diuretic, a a-adrenergic blocker, a dual
action receptor antagonist (DARA), or a heart failure
5 drug.

11. The combination as defined in Claim 10 wherein
the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide,
10 chiorpropamide, gliclazide, acarbose, miglitol,
pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645,
YM-440, R-119702, AJ9677, repaglinide, nateglinide,
KD1129, AR-H039242, GW-409544, KRP297, AC2993, LY315902,
15 P32/98 and/or NVP-DPP-728A;
wherein the anti-obesity agent is orlistat, ATh-
962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine,
phenyipropanolamine, and/or mazindol, P57 or CP-644673
20 (Pfizer);
wherein the lipid modulating agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, pitavastatin, rosuvastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, ND-700,
25 cholestagel, niacin, and/or LY295427;
wherein the antihypertensive agent is an ACE
inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ram.ipril
or moexipril;
30 an NEP/ACE inhibitor which is omapatrilat, gemopatrilat, or CGS 30440;
an angiotensin II receptor antagonist which is
irbesartan, losartan or valsartan;
atniodipine besylate, prazosin HC1, verapamil,
35 nifedipine, nado].ol, propranolol, or clonidine HC1,
carvediol, atenolol, hydrochiorothiazide, torasemide, furosemide, spironolactone or indapamide;

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wherein the platelet aggregation inhibitor is
aspirin, clopidogrel, ticlopidine, dipyridamole, ifetroban, abciximab, tirofiban, eptifibatide, or anagrelide;
5 wherein the other therapeutic agent is an anti-
Alzheimer’s agent or anti-dementia agent, which is tacrine HC1 (Cognexfi), donepezil (Ariceptfi), a
secretase inhibtor, a f3-secretase inhibitor and/or antihypertensive agent;
10 an antiosteoporosis agent, which is parathyroid
hormone, a bisphosphonate, alendronate, a Ca receptor agonist or a progestin receptor agonist;
a hormone replacement therapeutic agent, which is a selective estrogen receptor modulator (SERM);
15 a tyrosine kinase inhibitor;
a selective androgen receptor modulator;
an antiarrhythmic agent, which is a n-blocker, or a
calcium channel blocker, or an a-adrenergic blocker;
coenzyme Q sub. 10;
20 an agent that upregulates type III endothelial cell
nitric acid syntase;
a chondroprotective compound which is polysulfated glycosaminoglycan (PSGAG), glucosaxaine, chondroitin
sulfate (CS), hyaluronic acid (HA), pentosan polysulfate
25 (PPS), doxycycline or minocycline;
a cyclooxygenase (COX) -2 inhibitor, which is
Celebrexfi (Searle) or Vioxxfi (Merck) or a glycoprotein Ila/Ilib receptor antagonist;
a 5 -HT reuptake inhibitor;
30 a growth hormone secretagogue;
an anti-atherosclerosis agent;
an anti-infective agent, or an ixnmunosuppressant
for use in transplantation, or an antineoplastic agent.

35 12. The combination as defined in Claim 10 wherein
the HMG C0A reductase inhibitor compound is in
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 C0A reductase inhibitor compound is in
combination with an ACE inhibitor which is rampipril;
5 wherein the HMG C0A redubtase 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,
20 LDL Pattern A, hyperlipidemia, hypercholesterolemia, hypo
a-lipoproteinemia, hyperlipoproteinemia or hypertriglyceridemia, and other aberrations of apolipoprotein B metabolism, or reducing levels of Lp(a),
or treating or preventing other cholesterol-related
25 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, reducing C-reactive protein, or preventing or
30 treating low grade vascular inflammation, or preventing
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
35 or primary prevention of coronary events, or secondary prevention of cardiovascular events, or
preventing or treating peripheral vascular disease,

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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
5 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
10 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
15 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
20 homeostasis, reducing PAl-i 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
25 defined in Claim 1.

16. A method for treating cholesterol related
diseases, diabetes and related diseases, cardiovascular
diseases, cerebrovascular diseases, which comprises
30 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,
35 and/or other type of therapeutic agent, which comprises
administering to a mammalian species in need of treatment
a therapeutically efective amount of such combinations.

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#1 1

17. A compound having the structure

R4

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

10

Halide

ICo2R (where R is alkyl),?CHPHF C

or

(where W is aryl, alkyl, or a].koxy),

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

CO2R (RaIkyi) OH

R1 R2 R, R2
(CHfN
6 (CH2)..rN
cACH2)v

Halide VW
R1
’ N

R1

(C

R2
H

(CHXN

R4 &N,
R4

(Wary, alkyl or alkoxy)

17

5

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HMG-00A 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 lipids
15 employing such pharmaceutical compositions.

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

structure

R2

20 wherein:

Am is a binding domain sidechain;
X is a linker;
R’ and R2 are the same or different and are each independently selected from
25 (i) hydrogen,
(ii) alkyl,
(iii) aryl,

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(iv) cycloalkyl,
(v) aralkyl,
(vi) aralkoxy,
5 (vii) alkenyl,
(viii) cycloalkenyl, and
(ix) heterocyclo (e.g., thienyl, benzodioxolyl);

R3 is selected from
10 (i) hydrogen,
(ii) lower alkyl,
(iii) aryl,
(iv) cycloalkyl,
, (v) alkoxy,
15 (vi) aralkyl,
(vii) aralkoxy,
(viii) alkenyl,
(ix) cycloalkenyl,
(x) halo-substituted alkyl,
20 (xi) adamantyl, and
(xii) heterocyclo (e.g., thienyl, benzodioxolyl);

R4 is selected from
(i) hydrogen,
25 (ii) lower alkyl,
(iii) aryl,
(iv) cycloalkyl,
(v) alkoxy,
(vi) aralkyl,
30 (vii) aralkoxy,
(viii) alkenyl,
(ix) cycloalkenyl,
(x) adamantyl,
(xi) halogen,
35 (xii) halo-substituted alkyl (e.g.,
trifluoromethyl), and

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(xiii) heterocyclo (e.g., thienyl, benzodioxolyl); or R3 and R4 taken together can be

(CH2), (CH2)q (cH2)r- or (CH=CH)2;

\/
5 but when Am is

R6

HO_CH_CH2_f_CH2_CO2R8
OH

or a 6 lactone thereof, R3 and R4 cannot be (CH=CH)2;
R6 is hydrogen or lower alkyl;
R8 is hydrogen, lower alkyl, alkali metal, or
10 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.
15 In preferred embodiments is an HMG-binding domain sidechain having a dihydroxy or a phosphinic acid function.

The phosphinic (or phosphonic when X is CH2-O-)
acid HMG-binding domain sidechain (A1) is

0 R6

5 II

%% %.

Un

wherein R5 and R’ are independently selected from
hydrogen, lower alkyl, alkali metal ion and alkaline earth metal ion; and R6 is hydrogen or lower alkyl.
25 The dihydroxy acid binding domain sidechain (A2 is

R6

HO_CH_CH2_?_cH2CO2R8
OH

wherein R6 is hydrogen or lower alkyl, R8 is hydrogen or lower alkyl in free acid form or in the form of a

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physiologically acceptable and hydrolyzable ester or & lactone thereof (i.e., when Am is

5 In addition, R8 can be alkali metal ion or alkaline earth
metal ion.
A suitable linker (X) is (CH2)a, -CH=CH-, CC,
- CH20-, wherein 0 is linked to the phosphorous atom or
the aromatic anchor when Am is A1, and wherein 0 is
10 linked to the aromatic anchor when Am is A2, and wherein
"a" is 1, 2, or 3.

In accordance with the present invention, there are
provided certain pyridine-containing compounds that are
15 potent inhibitors of cholesterol biosynthesis by virtue
of their ability to inhibit the enzyme 3-methyl-glutaryl-coenzyme A reductase (HMG-00A reductase).
In particular, in its broadest chemical compound
aspect, the present invention provides compounds of the
20 formula
I

wherein

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5

10

15

20

30

Z is

HO._..%.f/.....%..

or °içIIIIrz ; %^*" OH
n is 0 or 1;
x is 0, 1, 2, 3 or 4;
y is 0, 1, 2, 3 or 4, provided that at least one of
x and y is other then 0;
and optionally one or more carbons of (CH2) x and/or
(CH2) y may form part of a 3 to 7 membered spirocyclic ring;
R1 and R2 are the same or different and are
independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;
R3 is H or lower alkyl;
R4 is H, halogen, CF3, hydroxy, alkyl, alkoxy, alkanoylamino, aroylamino or cyano;
R7 is H or lower alkyl;

and 000erepresents a single bond or a double bond
(which may be cis or trans);
and including pharmaceutically acceptable salts
thereof when R3 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 or 8 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

R1 and R2 are independently selected from alkyl, cycloalkyl and aryl;
R4 is H, alkyl, or halogen;
x is 2 or 3;
y is 0; and
n is o.

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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;
5 R4isH;
x is 3;
Y is 0;
n is 0; and
is a double bond.
10 Still more preferred are compounds of formula I of
the invention wherein
R1 is substituted aryl, preferably 4-fluorophenyl, 4-fluoro-3-methylphenyl or 3, 5-dimethyiphenyl;
R2 is alkyl or cycloalkyl, preferably isopropyl, t-
15 butyl or cyclopropyl;
R4 is H;
x is 3;
y is 0;
n is 0;

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

Ho**f* ?!H 0]

z is CO2H or

0

)

%%

%%OH

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

25 Most preferred compounds of formula I of the
invention will have the structure IA
IA

H

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or an alkali or alkaline earth metal (such as Na, K or
Ca) salt thereof, or amino acid salt (such as arginine), wherein R5 and R6 are the same or different and independently selected from H, halogen and/or alkyl
5 (preferably 4-fluoro, 4-fluoro-3-methyl or 3,5-dimethyl);

and

R2 is alkyl or cycloalkyl, preferably isopropyl, t-
butyl or cyclopropyl.
In another aspect, the present invention provides
10 pharmaceutical compositions, useful as hypolipidemic or
hypocholesterolemic agents, or hypotriglyceridemic
agents, or anti-Alzheimer’s agents, or anti-osteoporosis agents as well as other uses as described herein,
comprising a hypolipidemic or hypocholesterolemic or
15 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.
20 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
25 dyslipidemia, mixed dyslipidemia, hyperlipidemia,
hypercholesterolemia, hypo ct-lipoproteinemia, LDL Pattern
B, LDL Pattern A, hyperlipoproteinemia or
hypertriglyceridemia, and other aberrations of
apolipoprotein B metabolism, or reducing levels of Lp(a),
30 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
35 markers such as C-reactive protein, or preventing or
treating low grade vascular inflammation, or preventing
or treating stroke, or preventing or treating dementia,

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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
5 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
10 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
15 in accordance with the present invention as defined
above.

In addition, in accordance with the present
invention, a method is provided for preventing or
treating diabetes, especially Type 2 diabetes, and
20 related diseases such as insulin resistance,
hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, Syndrome X, diabetic complications, dysmetabolic syndrome, and related
diseases, and sexual dysfunction, wherein a
25 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 preventing and
30 treating malignant lesions (such as ductal carcinoma in
situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions (such as fibroadenoma of
the breast and prostatic intraepithelial neoplasia (PIN), gastrointestinal malignencies, liposarcomas and various
35 other epithelial tumors (including breast, prostate,
colon, ovarian, gastric and lung), cancer-induced
asthenia (fatigue), irritable bowel syndrome, Crohn’s

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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
5 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 plasminogen activating
10 inhibitor (PAI)-1 activity, reducing 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.
15 In addition, in accordance with the present
invention, a method is provided for treating cholesterol
related diseases, diabetes and related diseases, cardiovascular diseases, cerebrovascular diseases as
defined above and hereinafter and other diseases as set
20 out above, wherein a therapeutically effective amount of
a combination of a compound of structure I 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
25 agent, is administered to a patient in need of treatment.
In the above methods of the invention wherein a
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)
30 within the range from about 0.01:1 to about 500:1,
preferably from about 0.5:1 to about 100:1.

In accordance with the present invention, there is provided compounds useful in inhibiting the enzyme HMG-
35 C0A reductase, which inhibitors are useful as
hypocholesterolemic agents, dyslipidemic agents,

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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
5 refers to myocardial infarction, myocardial
revascularization procedures, angina, cardiovascular
death and acute coronary syndrome.
The term "cardiovascular diseases or events" as
employed herein refers to atherosclerosis of the coronary
10 arteries, myocardial infarction, including primary MI and
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
15 employed herein refers to cerebral infarction or stroke
(caused by vessel blockage or hemmorage), or transient ischemia attack (TIA), syncope, atherosclerosis of the intracranial and/or extracranial arteries, and the like.
The term "cholesterol-related diseases" as

20 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,
25 hypercholesterolemia, hypo a-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)
30 forms of primary hypercholesterolemia (including
Frederickson Types ha and lib), cholesterol ester
storage disease, and cholesterol ester transfer protein disease, and related diseases.
The conditions, diseases, and maladies
35 collectively referenced to as "Syndrome X" or
Dysmetabolic Syndrome (as detailed in Johanson, J. Clin. Endocrinol. Metab., 1997, 82, 727-734, and other

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publications) include hyperglycemia and/or prediabetic
insulin resistance syndrome, and is characterized by an
initial insulin resistant state generating
hyperinsulinemia, dyslipidemia, and impaired glucose
5 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
10 tolerance, obesity, hyperglycemia, Syndrome X,
dysmetabolic syndrome, diabetic complications and hyperinsulinemia.
The conditions, diseases and maladies collectively
referred to as "diabetic complications" include
15 retinopathy, neuropathy and nephropathy, and other known
complications of diabetes.
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-
20 obesity agents, and/or one or more lipid-lowering agents,
one or more lipid modulating agents (including anti-atherosclerosis agents), other types of anti-
atherosclerosis agents, and/or one or more antiplatelet agents, one or more agents for treating hypertension, one
25 or more anti-cancer drugs, one or more agents for
treating arthritis, one or more anti-osteoporosis agents,
one or more agents for treating iinmunomodulatory
diseases.
The term "lipid-modulating" agent as employed
30 herein refers to agents which lower LDL and/or raise HDL
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
35 agents" as employed herein refers to conventional anti-
atherosclerosis agents including lipoxygenase inhibitors, ACAT inhibitors, antioxidants, PPAR agonists,