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OLARTE RAISBECK MOURE & CASTRO LTDA.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES
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Ref: Expediente No. 06-117.272

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Solicitud de Patente de Invención titulada: "COMPUESTOS Y COMPOSICIONES COMO MODULADORES DEL RECEPTOR ACTIVADO POR PROLIFERADOR
DE PEROXISOMA (PPAR)"
Solicitante: IRM LLC.
Nuestra Ref.: P2006/000228

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGUN EL ARTICULO 44 DE LA DECISION 486, GACETA No. 597

CARLOS R. OLARTE, mayor de edad y vecino de Bogota, D.C., identificado tat como aparece at pie de mi firma, en mi condición de apoderado, respetuosamente me permito solicitar que se examine si la invención reüne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a to establecido en el articulo 44 de la Decision 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de $210.000 pesos para cubrir la tasa correspondiente, segin la Resolución 44372 del aflo 2007.

Aten

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Anexo: Recibo por $210.000 pesos

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SUPERINTENDENCIA BE INDUSTRIA V COMERCIO

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(12) United States Patent (10) Patent No.: US 6,5069757 Bi
Tajima et al. - (45) Date of Patent: Jan. 14, 2003

(54) CARBOXYLIC ACID DERIVATIVES AND
DRUGS CONTAINING THE SAME AS THE
ACTIVE INGREDIENT

(75) Inventors: Hisao Trjima, Osaka (JP); Yoshisuke
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(JP)

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patent is extended or adjusted under 35
U.S.C. 154(h) by 0 days.

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(2), (4) Date: Sep. 11, 2000

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C07D 277/24; A61K 31/42; A61K 31/215
(52) U.S. Cl................... 514/254.02; 514/340; 514/361;
514/365; 514/374; 544/369; 546/271.4;
548/127; 548/204; 548/236
(58) Field of Search.................................548/204, 236,
548/127; 546/271.4; 544/369; 514/365,
374, 361, 254.02, 340

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(57) ABSTRACT

A peroxisome proliferator activated receptor regulator con-taining a carboxylic acid derivative of formula (1)

Cr)
(R1) R2

2 R4
ºyc1A1A
R3

(wherein(wherein all symbols are as defined in the specification), a non-toxic acid thereof or a hydrate thereof as active ingre-dient. Because of having an effect of regulating PPAR, a compound of formula (I) is useful as a hypoglycemic agent, a hypolipidemic agent, a preventive and/or a remedy for diseases associating metabolic disorders (diabetes, obesity, syndrome X, hypercholesterolemia, hyperlipoproteinemia, etc.), hyperlipemia, atherosclerosis, hypertension, circula-tory diseases, overeating, coronary heart diseases, etc., an HDL cholesterol-elevating agent, an LDL cholesterol and/or VLDL cholesterol-lowering agent and a drug for relief from risk factors of diseases or syndrome X.

10 Claims, No Drawings

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0 R’° R1"

R12F or (Cn2011)R12F,

R8 R9

wherein

Rk, R7k, R, R9-F, R10’ and RlF are independently selected from hydrogen, C1-8 alkyl, etc.,
RF is selected from hydroxy, C1-8 alkyloxy, etc.) and a pharmaceutically acceptable salt have fibrinogen receptor antagonist activity (necessary part is extracted
in the explanation of the group).

DISCLOSURE OF THE INVENTION

As a result of energetic investigations in order to find compounds which possess PPAR regulating activity, the present inventors have found that the purpose is accom-plished by the compound of formula (I).
Part of the compounds of formula (I) is known by the said specifications of JP Kokai Hei 1-143856 and JP Kohyo Hei 8-504194. The effects of these compounds, that is to say, lipoxygenase inhibitory activity, leucotriene competitive activity and fibrinogen receptor antagonist activity are also known, but PPAR regulating effect of these compounds is not easily expected from these facts.
The other part of the compounds of formula (I) is novel which has never been known so far.

The present invention relates to
1) a peroxisorne proliferator activated receptor regulator containing a carboxylic acid derivative of formula (I)

(R R2

CN.C2 cycl A’A2r

R4

(iii) halogen or
(iv) trihalomethyl,
Cyc1 is

10
S or

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15

Cyc2 is
20 (i) carbocyclic ring or
(ii) hetero ring,
R’ is

(1) hydrogen,
(ii) Cl-S alkyl,
25 (iii) halogen,
(iv) C1-4 alkoxy,
(v) nitro,
(vi) trihalomethyl,
(vii) trihalomethoxy,
30 (viii) trihalomethylthio,
(ix) cyano or
(x) C1.-4 alkylthio,
R4 is -

35 (1) Ra R9
\/
A4CCOOR7 or

(wherein
A1 is Cl-4 alkylene or C2-4 alkenylene, A2 is 07- or 8--,
A3 is CII or N,
nis1-5,
R1 is

(1) hydrogen,
(ii) C1-8 alkyl,
(iii) halogen,
(iv) C1-4 alkoxy,
(v) nitro,
(vi) trihalomethyl,
(vii) trihalomethoxy,
(viii) trihalomethylthio,
(ix) cyano,
(x) C1-4 alkylthio,
(xi) NR5R1 (wherein R5 and Ra are each independently, hydrogen or C1-4 alkyl),
(xii) carbocyclic ring or
(xiii) hetero ring,
R’ is

(i) hydrogen,
(ii) C1-4 alkyl,

40 (ii) 2,4-thiazolidindion-5-yl,
A4 is

(1) bond,
(ii) C1-4 alkylene,
(iii) C1---4 alkylene-O or
45 (iv) C1--4 alkylene-S----,
R7, R8 and R9 are each independently hydrogen or C1-4 alkyl, with the proviso that
(1) R4 is attached to 2- or 3-position and
(2) when R4 is attached to 3-position, A4 is bond or
50 methylene, A3 is CH and Cyc1 is benzene, then A is methylene, ethylene or vinylene.), its non-toxic salt
or hydrate thereof as active ingredient,
2) a carboxylic acid derivative of formula (I)

55

(R1) R2

(I)

60 (t) cycl A’A2r

R3

(wherein

65 A’ is C1-.4 alkylene or C2-4 alkenylene, A2 is 0----- or 8,
A3 is CH or N,

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9 n is 1.-5,
R is

(i) hydrogen,
(ii) C1-8 alkyl,
(iii) halogen,
(iv) C1-.4 alkoxy,
(v) nitro,
(Vi) trihalomethyl,
trihalomethoxy,
(viii) trihalomethylthio,
(ix) cyano,
(x) C1-4 alkylthio,
(Xi) NR5R6 (wherein R5 and Ro are each independently hydrogen or C1-4 alkyl),
(xii) carbocyclic ring or
(xiii) hetero ring,
R2 is

(i) hydrogen,

. (ii) C1-.4 alkyl,

(iii) halogen or
trihalomethyl,
Cyc1 is

Cyc2 is
(i) a carbocyclic ring or
(ii) a hetero ring,
R‘ is

(i) hydrogen,
(ii) C1-8 alkyl,
(iii) halogen,
(iv) C1.-4 alkoxy,
(v) nitro,
(vi) trihalomethyl,
(vii) trihalomethoxy,
(viii) trihalomethylthio,
(ix) cyano or
(x) (1-4 alkylthio,
R4 is

(i)
R8 R9

A4

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 COOR7 or

(ii) 2,4-thiazolidindion-5-yl,
A4 is

(i) bond,
(ii) C1-4 alkylene,
(iii) C1--4 alkylene-O or
(iv) C1--4 alkylene-S,
R7, R8 and R9 are each independently hydrogen or C1-4 alkyl, with the proviso that

10

(1) R4 is attached to 2- or 3-position and
(2) when R4 is attached to 3-position, A4 is a bond or methylene, A3 is CH and Cyc1 is benzene, A1 is methylene, ethylnene or vinylene.), a non-toxic acid
5 thereof or a hydrate thereof and
3) a method for the preparation of a compound of formula (I).

DETAILED EXPLANATION OF THE

10 INVENTION

Unless otherwise specified, all isomers are included in the present invention. For example, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylene, alkenylene and alkynylene include straight-chain and branched-chain ones. Moreover,
15 the isomers in the structure of double bond, ring, fused ring
(E, Z, cis, trans), the isomers generated by the presence of asymmetric carbon atom(s) etc. (R, S isomers, ct, 3 isomers, enantiomers, diastereomers) optically active isomers having optical rotation (D, L, d, 1 isomers), isomers separated by
20 chromatography (more polar or less polar isomers), equilib-
rium compounds, compounds of arbitrary ratio of these compounds.
In the present invention, C1--4 alkyl is methyl, ethyl, propyl, butyl and isomers thereof.
25 C1-8 alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl,
heptyl, octyl and isomers thereof.
C1-4 alkoxy is methoxy, ethoxy, propoxy, butoxy and isomers thereof.

30 C1-4 alkylthio is methylthio, ethylthio, propylthio,
butylthio and isomers thereof.
C1-4 alkylene is methylene, ethylene, trimethylene, tet-ramethylene and isomers thereof.
C2-4 alkenylene is ethenylene, propenylene, butenylene
35 and isomers thereof.

Halogen is iodine, bromine, fluorine and chlorine. Trihalomethyl is methyl group which is tn-substituted by iodine, bromine, fluorine or chlorine.

40 Trihalomethoxy is methoxy group which is tn-substituted
by iodine, bromine, fluorine or chlorine.
Trihalomethylthio is methylthio group which is tn-substituted by iodine, bromine, fluorine or chlorine. Carbocyclic ring represents C3.45 mono-, bi-, or tn-
45 cyclic carbon ring and bridged carbocyclic ring. C3-15 mono-, bi-, or tn-cyclic carbon ring and bridged carbocyclic ring contains, for example, cyclopropane, cyclohutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cyclopentene, cyclohexene, 50 cyclopentadiene, cyclohexadiene, benzene, pentalene, indene, naphthalene, azulene, fluorene, phenanthrene, anthracene, acenaphthylene, hiphenylene, penhydronaphthalene, indane (dihydroindene), p e r h y d r 0 in d e n e, d i h yd ron a p h t h ale n e,
55 tetnahydronaphthalene, penhydronaphthalene,
perhycinoazulene, perhydrofluorene, perhydrophenanthrene, perhydroanthracene, perhydroacenaphthylene, penhydrophenylene, bicyclopentane, bicyclohexane, bicy-cloheptane ([2.2.1]bicycloheptane), bicyclooctane,
o bicyclononane, bicyclodecane, adamantane, etc.
Hetero ring includes a 4-48 membered mono-, di- or tn-cyclic hetero aryl, or partially or completely saturated one containing 1-4 of nitrogen, 1-2 of oxygen and/or 1 ofsulfur. Said 4-18 membered mono-, di- or tn-cyclic hetero aryl
65 containing 1-4 of nitrogen, 1-2 of oxygen and/or 1 of sulfur
includes pynrole, innidazole, tniazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine,

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diazepine, furan, pyran, oxepin, oxazepin, thiophene, thiain (thiopyran), thiepin, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, oxazine, ozadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, isoindole, benzofuran, isobenzofuran, henzothiophene, isabenzothiophene, indazole, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, henzoirnidazole, carbazole, acridine, etc.
Said 4-18 membered mono-, di- or tn-cyclic hetero aryl or partially or completely saturated one containing 1-4 of nitrogen, 1-2 of oxygen and/or 1 of sulfur includes pyrroline, pyrrolidine, imidazoline, imidazolidine, tniazoline, triazolidine, tetrazoline, tetrazolidine, dihydropynidine, dihydropyrazine, dihydropyrimidine, dihydropyridazinc, pipenidine, piperazine, tetrahydropyrimidine, tetrahydropynidazine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrothiophene, tetrahydrothiophene, dihydrothiaine (dihydrothiopyran), tetrahydrotbiaine (tetrahydrothiopyran), dihydroxazole, tetrahydroxazole, dihydroisoxazole, tetrahydroisoxazole, dihydrothiazole, tetrahydrothiazole, dihydroisothiazole, tetrahydroisothiazole, morpholine, thiomorpholine, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhvdroisobenzofuran, dihydrohenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisohenzothiophene, diliydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, p e r ii y d r o q u in olin e, di h y d r o iso q u in olin e, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perk ydrophthalazine, dihydronaphthynidine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, per hydroquinoxaline, dihydroquinazoline, tetra hydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, dihydrobcnzoxazolc, perhydrohenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrohenzimidazolc, perhyd robe nzimidazole, benzoxazepine, benzoxadiazepine, benzothiazepine, henzothiadiazepine, henzazepine, henzodiazepine, indoloxazepine, indolotetrabydroxazepine, indoloxadiazepine, indolotetrahydroxadiazepine, indolothiazepine, indolotetrahydrothiazepine, indolothiadiazepine, indolotetrahydrothiadiazepine, indolazepine, indolotetrahydroazepine, indolodiazepine, indolotetrahydrodiazepine, benzofurazane, henzothiadiazolc, henzotriazole, camphor, imidazothiazole, dihydrocarbazole, tetrahydrocarbazole, perhydrocarbazole, d ihydroacridinc, tetrahydroacnidine, perhydroacridine, 1,3-dioxaindane, 1,4-dioxaindane ring, etc.
In the formula (I), R’ is preferably C1-4 alkyl, more preferably methyl and ethyl.
In the formula (I), Cyc’ is preferably,

- 0--
(wherein the bond in the right hand is attached to A1), more preferably

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0 5

(wherein the bond in the right hand is attached to A’.).

In the formula (I), A’ is preferably C1-4 alkylene, more

10 preferably C1-2 alkylene (CH2, (CH2)2),
In the formula (I), A2 is preferably 0.
In the formula (I), A3 is preferably CH.
In the formula (I), R4 is preferably attached to 3 -position.

In the formula (I), R4 is preferably

R8 it

A4

\/
 CCOOR7.

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In the formula (I), A4 is preferably a bond, C1-4 alkylene-O or C1--.4 alkylene-S---, more preferably a bond or CH,S. In the formula (I), R8 and R are preferably hydrogen or methyl, more preferably hydrogen. 25 In the formula (I), R’ is preferably hydrogen, Cl-Sailcyl, halogen, trihalomethoxy or tnihalomethylthio, more prefer-ably hydrogen, halogen or trihalomethoxy.

In the formula (I), a carbocyclic ring represented by Cyc2

30 is, preferably C3-10 mono- or hi-cyclic carbon ring, more
preferably cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclo nonane, cyclodecane or benzene, particularly preferably, cyclopropane, cyclopentane, cyclohexane or benzene.
35 In the formula (I), a hetero ring represented by Cyc’ is preferably 3-40 membered mono- or bi-cyclic hetero aryl containing 1-2 of nitrogen, 1-2 of oxygen and/or 1 ofsulfur or partly or totally saturated one, more preferably furan, thiophene, pyridine, quinoline, thiadiazole (1,2,3-40 thiadiazole), piperazine or dioxaindane (1,3-dioxaindane), particularly preferably dioxaindane (1,3-dioxaindane).
In the formula (I), a carbocyclic ring represented by R’ is preferably C3-10 mono- or hi-cyclic carbon ring, more preferably cyclopropane, cyclobutane, cyclopentane, 45 cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane or benzene, particularly preferably cyclopropane, cyclopentane, cyclohexane or benzene.
In the formula (I), a hetero ring represented by R1 is preferably a 5-10 membered mono- or bi-cyclic hetero aryl
50 or partially or completely saturated one containing 1-2 of
nitrogen, 1-2 of oxygen and/or 1 of sulfur, more preferably furan, thiophene, pyridine, thiadiazole (1,2,3-thiazole), pip-erazine or dioxaindane (1,3-dioxaindane), particularly pref-

55 erably thiadiazole (1,2,3-thiadiazole).
In the present invention, PPAR regulator includes all the regulators of PPAR a, y, ö, u+y, a+ö, y+ô and u+y+& Preferable regulatory fashion is, PPAR a regulator, PPAR regulator, PPAR a+y regulator, PPAR cL+6 regulator, more

Q preferably PPAR a+y regulator or PPAR 6 regulator.
PPAR regulator also includes PPAR agonist and PPAR antagonist, preferably PPAR agonist, more preferably PPAR a agonist, PPAR agonist, PPAR a+y agonist or PPAR a+y agonist or PPAR agonist, particularly preferably PPAR
65 a+y agonist or PPAR agonist.
Among the..compounds of formula (I), preferable ones are, a compound of formula (I-a)

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Scheme 4

H0

CHO

1)

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D_R3
(CycZ j Cyci A1-0H (XVIII-1)
PhP, ADDP
(It)

Halogenation (RI-i)n R2

or mesylation TMSCN,

(XIX)

HO

CHO

(R°’) R2

A1_R10 ()

(R1 -I (P1) R2

e: ’_ccIA1_A2
CN

SOd2 A1A2
::N

(XX) (VI)

The starting materials in the reaction schemes are known per se or may he prepared by known methods.
The reactions of the reaction schemes may be carried out by known methods.
The other starting materials and reagents in the present invention are known per se or may be prepared by known methods.

In each reaction described in the present specification, reaction products may be purified by conventional tech-niques. For example, purification may he carried out by distillation at atmospheric or reduced pressure, by high performance liquid chromatography, thin layer chromatog-raphy or column chromatography using silica gel or mag-nesium silicate, by washing or by recrystallization, etc. Purification may tic carried out after each reaction, or after a series of reactions.
The compounds described in the present specification may he converted to corresponding salts by known methods. Non-toxic and water-soluble salts are preferable. Suitable salts include a salt of alkali metal (potassium, sodium, etc.), a salt of alkali earth metal (calcium, magnesium, etc.), an ammonium salt, a pharmaceutically acceptable salt of organic amine (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, heozylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl) am inomethane, lysine, arginine, N-methyl-D-glucamine, etc.)
The compounds of formula (I) may be converted to corresponding acid addition salts by known methods. Non-toxic and water-soluble acid addition salts are preferable. Suitable acid addition salts include salts of inorganic acid

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(e.g. salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid) and salts of organic acid (e.g. salts of acetic acid, trifluoroacetic acid, lactic acid, tartaric acid, oxalic acid, fumarie acid, maleic acid, citric 40 acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid,, toluenesulfonic acid, isethionic acid, glucuronic acid and gluconic acid), etc.
The compounds of the present invention described in the

present specification or salts thereof may be converted to 45 hydrates by a known method.
PHARMACOLOGICAL ACTIVITY

It was confirmed that a compound of the present invention

of formula (I) has PPAR regulating activities by the follow- 50 ing experiments.
Measurement of PPAR a, PPAR y and PPAR 6
Agonist Activities
1) Preparation of Materials Using Human PPAR a, ’ or 6 in
55 Luciferase Assay
The whole operation was based on basic gene engineering techniques, and in the operation conventional methods in yeast One-hybrid or Two -hybrid system were used.
As a luciferase gene expression vector under the control
to of thymidine kinase (1K) promotor, luciferase structural gene was excised from PicaGene Basic Vector 2 (A Brand Name, Toyo Ink Inc., catalogue No. 309-04821), to prepare luciferase gene expression vector pTK-Luc. under the con-

trol of TK promotor (-105/+51) as a minimum essential 65 promotor activity from pTK3 having 1K promotor

(Chrontech Inc., catalogue No.6179-9). In the upper stream of TK promotor, four times repeated UAS sequence was

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inserted, which is the response element of Ga14 protein, a basic transcription factor in yeast, to construct 4xLJAS-TK-Luc. as reporter gene. The following is the enhancer sequence used (Sequence No. 1).
Sequence No. 1: Enhancer sequence repeating Ga14 response element four-times tandemly
5-T(cGAcGGAG’rAcTGTCcTCCG)x4 AGCT-3’
A vector was prepared as described hereafter which expresses chimeric receptor protein wherein in carboxyl terminus of yeast Ga14 protein DNA binding domain was fused to ligand binding domain of human PPAR a, ’ or ö. That is to say, PicaGene Basic Vector 2 (a Brand Name; Toyo Ink Inc., catalogue No. 309-04821) was used as a basic expression vector, the structural gene was exchanged for that of chimeric receptor protein, while promotor and enhancer domains were kept as they were.
DNA encoding a fused protein composed of Ga14 DNA binding domain, amino acids 1-147 linked to the ligand binding domain of human PPAR a, y or 1 in frame was inserted to the downstream of promotor/enhancer in PicaGene Basic Vector 2 (a Brand Name). Here the DNA was aligned as follows; in the amino terminus of human PPAR a,,’ or 6 ligand binding domain, nuclear translocation signal originated from SV-40 T-antigen, Ala Pro Lys Lys Lys Arg Lys Val Gly (sequence No. 2) was added to make fusion protein localizing intranuclearly. On the other hand, in the carhoxy terminus of them, influenza hemagglutinin epitope, Tyr Pro Tyr Asp Val Pro Asp Tyr Ala (sequence No. 3) and stop codon for translation was added in this order, to detect an expressed fused protein tagged epitope sequence.
The portion of structural gene used as ligand binding domain of human PPAR (x, y or 8 is as follows: human PPAR a ligand binding domain: Serbo7Tyr4as human PPAR ligand binding domain: Ser175-Tyr478 human PPAR ligand binding domain: Ser1-Tyr"’ in comparison with human PPAR y 1 and human PPAR y 2, Ser204-Tyr50 in human y 2 is corresponding and identical to Ser176-Tyr478 in human PPAR ’ 1), according to the comparison of human PPAR structures described in the literatures by R. Mukherjee at al. (See I. Steroid Biochem. Molec, Biol., 51, 157 (1994)), M. E. Green et al., (See Gene Expression., 4, 281 (1995)), A. Elhrecht et al. (See Biochem Biophys. Res, Commun,, 224, 431 (1996)) or A. Schmidt et at. (See Mol. Endocrinology., 6, 1634 (1992)). In order to measure basal level of transcription, an expression vector containing DNA binding domain of Ga14 protein lacking in PPAR ligand binding domain, which is exclusively encoding the amino acids of No. 1No. 147 in Ga14 protein was also prepared.
2) Luciferase Assay Using Human PPAR a, y or
CV-1 cells used as host cells were cultured by a conven-tional technique. That is to say, Dulbecco’s modified Eagle medium (DMEM) supplemented 10% bovine fetal serum (GIBCO BRL Inc., catalogue No. 26140-061) and 50 U/mI of penicillin G and 50jig/ml of streptomycin sulfate were used to culture CV-1 cells under the atmosphere of 5% carbon dioxide gas at 37° C.
2x105 cells were seeded in a 10 cm dish, and once washed with the medium without serum, followed by addition of the medium (10 ml) thereto. Reporter gene (10 gig), Gal4-PPAR expression vector (0.5
BRL

and 50 il of LipofectAMlNE (a
Brand Name, GIBRO BRL Inc., catalogue No. 18324-012) were well mixed and added to the culture to introduce these DNAS into the cells. They were cultured at 37° C. for 5-6 hours, and thereto was added 10 ml of medium containing 20% of dialyzed bovine fetal serum (GIBRO BRL Inc., catalogue No, 26300-061), and then cultured at 37° C. overnight. The cells were dispersed by trypsin, and they

EIE were again seeded in 96-well plates in a density of 8000

cells/100 til of DMEM-10% dialyzed serum/well. Several hours after the cultivation, cells were attached to the plastic ware, then 100uIofDMEM-10% dialyzed serum containing the compounds of the present invention, whose concentra-tion is twice as high as the final concentration of them. The culture was settled at 37° C. for 42 hours and the cells were dissolved, to measure luciferase activity according to manu-facturer’s instruction.

10 As to PPAR a agonist activity, the relative activity of the compounds of the present invention (0.3 M) was shown in table 21, under the condition that luciferase activity was defined as 1.0 when a positive control compound carbap-rostacyclin made a final concentration of 10 uM, which apparently activated PPAR a (See Eur. J. Biochem., 233, 242 (1996); Genes & Development., 10, 974 (1996)).
As to PPAR y agonist activity, the relative activity of the compounds of the present invention (1.0 M) was shown in table 22, under the condition that luciferase activity was
20 defined as 1.0 when a positive control compound troglita-
zone made a final concentration of 10 M, which signifi-cantly activated PPAR ’ (See Cell., 83, 863 (1995); Endocrinology., 137, 4189 (1996) and J. Med. Chem., 39, 665 (1996)) and has already launched.
25 As to PPAR 8 agonist activity, the relative activity of the compounds of the present invention was shown in table 23, under the condition that luciferase activity was defined as 1.0 when solvent containing no compound was added. Furthermore, the reproducibility was very good in each
30 point examined in triplicate. And dose dependent activation
of PPARs thereof was also confirmed.

TABLE 21

PPAR a agonist activit
35

Compound No. Relative Activity

Example 2 2.1
Example 2 (5) 0.8
Example 2 (11) 3.2
40 Example 2 (12) 1.7

TABLE 22

45 PPAR agonist activity

Compound No. Relative Activity

Example 2 (12) 1.4

50

TABLE 23

PPAR t agonist activit

55 Concentration (aM)

Compound No. 0 1.0 10.0

Example 2 (22) 1.0 9.3 66.7
Example 2 (93) 1.0 36.1 54.7

60 Example 5 1.0 11.0 61.6

Hypoglycemic and Hypolipidemic Effects in KKAy Mice Male, 7-weeks old KKAy/Ta mice weighed from 35 to 40
g (seven mice per group) were pre-breaded for approxi-
65 mately one week and acclimatized for three days on milled
diet. On the first day of the experiment (Day 0), mice were divided into some groups by weight, plasma glucose and

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triglyceride (TG) levels to minimize the differences among groups. From the next day for two days they were given compounds by food mixture containing 0.03% (w/w) of the compound of the present invention or by milled diet only. At 13:00 of the third day, blood samples were collected and glucose and TG were measured. These results are shown in table 24. Additionally, there was no significant difference in the food intake between control group (milled diet only) and compounds-treated group (milled diet containing 0.03% compounds).

TABLE 24

glycemic value (mg/dl) TO value (mg/dl)
Compound No. 3 days 3 days

control 495 a 35 558 a 107
food containing compound 214 – 19’ 221 a 66’
or Example 2 (12)
38.9 rngkg/day
(converted)

’p < 0.01 v.a. control (seven mice per group)

Hypocholesterolemic and Hypolipidemic Effects in Normal Rats

Male, six-weeks old SD rats (seven rats per group) were left to take milled diet and water ad libitum and were acclimatized for I week.
At 9:00 on the first day of the experiment (Day 0) blood sampling was (lone from tail vein. The rats were divided into some groups by body weight, trigiyceride(TG), non-esterified fatty acid (NEFA), total cholesterol (TC) values to minimize differences of the parameters among the groups. At 17:00 of the day the compound of the present invention suspended in 0.5%,aqueous solution of carboxymethylcel-lulose (CMC) was orally administered at a dose of 10 mg/kg, and thereafter, with hypercholesterolemic food (5.5% peanut oil, 1.5% cholesterol and 0.5% cholic acid were mixed with milled CRF-1 diet, Charles River Inc.) was given to the rats. At 9:00 of the next day, blood sampling was done from tail vein, The lipid values in blood (TG, NEFA and TC values) were measured. The results are shown in table 25, ’l’here was no significant difference of the food intake between the control group (provided only 0.5% CMC) and the group treated with the compounds of the present inven-tion.

TABLE 25

TC value TO value NEFA value

Compound No. (mg/dl) (mgldt) (uEq/1)

control 188 5 147 a 9 489 a 66
Example 2 (12) 70 5" 100 a 14’ 178 a 14"

’p a 0.05 vs control (seven rats per group)
’’p < 0.01 vs control (sever rats per group)

The hypoglycemic or hypolipidemic effects observed in KKAy mice imply the possibility of preventives and/or remedies for diabetes and hyperlipidemia, etc. Cholesterol-lowering and free fatty acid-lowering effects observed in high cholesterol diet-fed rats imply that the compounds of the present invention are useful as preventives and/or rem-edies of atherosclerosis etc.

INDUSTRIAL APPLICABILITY
[Effect]
ThC compounds of formula (I), non-toxic salts thereof and hydrates thereof have PPAR regulating effect, and therefore are expected to he applied as hypoglycemic agents, hypo-

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lipidemic agents, preventives and/or remedies for diseases associated with metabolic disorders (diabetes, obesity, syn-drome X, hypercholesterolemia, hyperlipoproteinemia, etc.), hyperlipidemia, atherosclerosis, hypertension, eircula-tory diseases, overeating, coronary heart diseases, etc., IIDL cholesterol-elevating agents, LDL cholesterol and/or VLDL cholesterol-lowering agents and agents for relieving risk factors of diabetes or syndrome X.
The compounds of formula (I), non-toxic salts thereof and
10 hydrates thereof have particularly PPAR a agonist and/or
PPAR ’y agonist effect, and therefore are thought to be useful as hypoglycemic agents, hypolipidemic agents, preventives and/or remedies for diseases associated with metabolic disorders (diabetes, obesity, syndrome X, hypercholesterolemia, hyperlipoproteinernia, etc.), Is hyperlipidemia, atherosclerosis, hypertension, circulatory diseases, overeating, etc. coronary heart diseases, etc. Since they are expected to have HDL cholesterol-elevating effect, LDL cholesterol and/or VLDL cholesterol-lowering effect, inhibition of progress of atherosclerosis and its treatment,
20 and inhibitory effect against obesity, they are also expected
to be useful for the treatment and/or prevention of diabetes as hypoglycemic agents, for the amelioration of hypertension, for the relief from risk factors of syndrome X, and as preventives against occurrence of coronary heart
25 diseases,
Since the compounds of formula (I), non-toxic salts thereof and hydrates thereof also have PPAR 6 agonist activity, they are expected to have HDL cholesterol-elevating effect, and therefore, they are expected to be useful
30 as agents for the inhibition of progress of atherosclerosis and
its treatment, hypolipidemic agents and/or hypoglycemic agents. Furthermore, they are also expected to he useful for the treatment of hyperglycemia, as hypoglycemic agents, for the treatment of diabetes, for the relief from risk factors of 35 syndrome X, and as preventives against occurrence of coronary heart diseases.
[Toxicity]
The toxicity of the compounds of the present invention
are very low and the compounds are safe enough for
40 pharmaceutical use.
[Application to Pharmaceuticals]
For the purpose above described, the compounds of the present invention of formula (I), non-toxic salts, acid addi-tion salts or hydrates thereof may normally be administered
45 usually systemically or topically, orally or parenterally.
The doses to be administered are determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the dura-tion of the treatment. In the human adult, the doses per person are generally in the range of from 1 mg to 1000 mg, by oral administration, up to several times per day, and in the range of from 0.1 mg to 100 mg, by parenteral administra-tion (preferably intravenous administration), up to several times per day, or continuous administration from 1 to 24
55 hours per day from vein.
As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may he used.

60 The compounds of the present invention may be admin-istered in the form of, for example, solid forms for oral administration, liquid forms for oral administration, injections, liniments or suppositories for parenteral admin-istration.

85 Solid forms for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules, etc. Capsules include hard capsules and soft capsules.

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30 minutes. To the reaction mixture was added a saturated aqueous solution of sodium bicarbonate and was extracted with dichioromethane. The extract was washed with a satu-

rated aqueous solution of sodium chloride, dried over anhy-drous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate5:1) to give the tittle compound (4.41 g) having the following physical data.

TLC: Rf 0.71 (hexane:ethyl acetate-2:1);

NMR (CDCI1): 67.25 (t, J-7.5 Hz, 111), 7.10-6.95 (m, 3H), 5.20 (s, 2H), 4.45 (s, 2H), 3.50 (s, 311).

REFERENCE EXAMPLE 4

2-(3-methoxymethoxyphenylmethylthio)acetic acid.methyl ester

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A suspension of the compound prepared in Reference Example 3 (4.41 g), methyl thioglycolate (1.5 ml), potas-sium carbonate (2.45 g) and potassium iodide (250 mg) in acetonitrile (50 ml) was refluxed for 3 hours. The reaction mixture was filtered. The filtrate was concentrated. The

residue was purified by column chromatography on silica gel (hexane:ethyl acetate-5:1) to give the title compound (2.81 g) having the following physical data.

TLC: Rf 0.57 (hexanc:ethyl acetate-2:1);

NMR (CDCI.3): 67.25 (t, J7.5 Hz, IH), 7.05-6.90 (m, 311), 5.20 (s, 211), 3.80 (s, 211), 3.75 (s, 311), 3.50 (s, 3H), 3.10 (s, 2H).

REFERENCE EXAMPLE 5

2-(3-hydroxyphenylmethylthio)acetic acid methyl
ester

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CH3

To a solution of the compound prepared in Reference Example 4 (2.81 g) in methanol (20 ml), was added 4N solution of hydrogen chloride in dioxane (11 ml) and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate=5:1) to give the title compound (2.16 g)having the following physical data.

TLC: Rf 0.45 (hexane:ethyl acetate-2:1);

NMR (CDC13): 67220 (t, 1-7.5 Hz, IH), 6.90 (d, J7.5 Hz, 1H), 6.85 (d, 1-2 Hz, 1H), 6.75 (dd, 3-7.5, 2 Hz, 1H), 5.05
(s, 1H), 3.80 (s, 2H), 3.75 (s, 3H), 3.10 (s, 2H).

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EXAMPLE 1

2-(-(4-(4-methylphenyl)thiazol-2-ylmethoxy) phenylrnethylthio)acetic acid.methyl ester

HC

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The compound prepared in Reference Example 5 (0.30 g) was dissolved in dichioromethane (10 ml) and thereto were added 2-hydroxymethyl-4-(4-rnethylphenyl)thiazole (0.34

20 g) and triphenyiphosphine (0.44 g) and the mixture was
stirred at room temperature for 5 minutes. To the reaction mixture was added 1,1-azodicarhonyldipiperidine (0.56 g) and the mixture was stirred at room temperature overnight. To the reaction mixture was added diethyl ether and the
25 mixture was filtered. The filtrate was washed with a satu-
rated aqueous solution of sodium bicarbonate, water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on
30 silica gel (hexane:ethyl acetate -10:1) to give the compound
of the present invention (0.51 g) having the following physical data.

TLC: Rf 0.56 (hexane:ethyl acetate-3:1);

35 NMR (CDC13): 87.79 (d, 1-8.2 Hz, 2H), 7.44 (s, 1H), 7.22-7.30 (m, 3H), 6.91-7.05 (m, 311), 5.42 (s, 211), 3.81 (s, 2H), 3.72 (s, 3H), 3.08 (s, 2H), 2.39 (s, 3H).

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EXAMPLE 1(1)EXAMPLE 1(137)

The following, compounds were obtained by the same procedure as shown in Example 1, using the compound prepared in Reference Example 5 or corresponding 45 derivatives, and 2-hydroxymethyl-4-(4-methylphenyl) thiazole or corresponding derivatives.

EXAMPLE 1(1)

50 6-(3-(4-(4-methylphenyl)thiazol-2-ylmethoxy) phenyl)hexanoic acid.methyl ester

50

TLC: Rf 0.75 (hexane ethyl acetate=2:1);

NMR (CDC13): 87.48-7.66 (2H, m), 7.43 (1H, s),
c 7.28-7.10 (3H, m), 6.88-6.72 (314, m), 5.41 (2H, s), 3.66
(311, s), 2.59 (2H, t, 3-8.0 Hz), 2.39 (3H, s), 2.30 (2H, t, J=7.5 Hz), 1.74-1.46 (41, m), 1.45-1.16 (2H, m).

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EXAMPLE 1(2) EXAMPLE 1(5)

4-(3-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy) 5-(3-(biphenyl-4-ylmethoxy)phenyl)pentanoic phenyl)butanoic acid.methyl ester
acid.methyl ester 5

: C? 0

CHI): D?

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TLC: Rf 0.39 (hexane:ethyl acetate 3:1);
NMR (CDC13): 67.98 (m, 2H), 7.38-7.46 (m, 3H), 7.17
(m, 1H), 6.72-6.77 (m, 311), 4.23 (t, J7.0 Hz, 2H), 3.66 (s,
15 3H), 2.98 (t, J-7.0 Hz, 2H), 2.60 (t, 3-7.5 Hz, 211), 2,38 (s,

TLC: Rf 0.57 (hcxane:ethyl acetate-4:1); 3H), 2.32 (t, J7.5 Hz, 2H), 1.93 (tt, J=7.5, 7.5 Hz, 2H).
NMR (CDCI,): 67.30-7.62 (m, 9H), 7.20 (m, 1H),

EXAMPLE 1(6)

6.77-6.83 (m, 3H), 5.08 (s, 2H), 3.64 (s, 3H), 2.60 (t, J6.8 20 6(3-(2-(5-methyl.2-phenyoxazo1-4-y1)ethoxy)
Hz, 2H), 2.32 (t, J6.8 Hz, 2H), 1.59-1.66 (m, 4H). phenyl)hexanoic acid.methyl ester

EXAMPLE 1(3)

4-(3-(biphenyl-4-ylmethoxy)phenyl)butanoic
acid.methyl ester

TLC: Rf 0.65 (hexane:ethyl acetate-3:1);

NMR (CDCI3): 67.57-7.64 (m, 4H), 7.31-7.53 (m, SH),
7.22 (m, 1H), 6.78-6.87 (m, 3H), 5.09 (s, 2H), 3.66 (s, 3H), 2.64 O i=7,5 Hz, 2H), 2.33 (t, J7.5 Hz, 2H), 1,96 (U, 3=7.5, 7.5 Hz, 2H).

EXAMPLE 1(4)

4-(3-(4-(4-methylphenyl)thiazol-2-ylmethoxy) phenyl)butanoic acid.methyl ester

FI3C

0 CH

TLC: RI 0.59 (hexane:ethyl acetate 3:1);

NMR (CDC1): 67,79 (d, J=8.0 Hz, 2H), 7.44 (s, 1H), 7,18-7.26 (m, 311), 6,81-6.87 (m, 31-1), 5.41 (s, 2H), 3.66 (s, 3H), 2.64 (t, J=7.5 Hz, 2H), 2.39 (s, 3H, 2.33 (t, J=7.5 Hz, 2H), 1.95 (U, 3-7.5, 7.5 Hz, 2H).

2 5 140

TLC: Rf 0.51 (hexane:ethyl acetate=3:1);
30 NMR (CDC13): 68.04-7.92 (2H, m), 7,50-7.36 (311, m), 7.16 (1H, t, 3-8.0 Hz), 6,80-6,60 (3H, m), 4.23 (211, t, 3-7.0 Hz), 3.65 (3H, s), 2.98 (211, t, J=7.0 Hz), 2.56 (211, t, 3=7.5 Hz), 2.38 (3H, s), 2.29 (2H, t, J7.0 Hz), 1.75-1.52 (4H, m), 1.44-1.26 (211, m).
35

EXAMPLE 1(7)

5-(3-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy) phenyl)pentarioic acid.methyl ester
40

TLC: Rf 0.28 (hexane:ethyl acetate-5:1);
NMR (CDC13): 68.03-7.94 (2H, m), 7.49-7.36 (3H, m),
50 7,23-7.12 (1H, m), 6.78-6,68 (311, m), 4.23 (2H, t, 3=7.0
Hz), 3.65 (3H, s), 2.98 (21-1, t, 3=7.0 Hz), 2.64-2.52 (211, m), 2,38 (3H, s), 2.38-2.26 (2H, m), 1.75-1,58 (411, m).

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EXAMPLE 1(8)

2-(3-(3-(biphenyl-4-ylmetboxy)phenyl)propylthio)
acetic acid.methyl ester

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TLC: Rf 0.73 (hexane ethyl acetate-2 1); EXAMPLE 1(12)
NMR (CDCI,): 7.57-7.64 (m, 41-1), 7.31-7.53 (m, 511),
7,22 (dd, J9.0, 7.6 Hz, 1H), 679-6.86 (m, 3H), 5.10 (s, 2-(3-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy) 21-1), 3.72 (s, 3H), 3.23 (s, 211), 2.71 (t, J7.4 Hz, 21-1), 2.65 phenylmethylthio)acetic acid.methyl ester (t, J7.4 Hz, 214), 1.93 (tt, J7.4, 7.4 Hz, 214).

EXAMPLE 1(9)

2-3-(3-(4-(4-methy1pheny1)thiazo1-2-y1methoxy)
phenyl)prapylthio)acetic acid.methyl ester

L,JLN

Sf0"’CH3
lc? - 0

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0
rk’7’? S

0
’?CH3

CHO CH,110

0

TLC: Rf 0.36 (hexane ethyl acetate3:1);

NMR (CDCI3): 87.95-8.00 (rn, 211), 7.37-7.44 (in, 311),
15 7.20 (dd, J=8.0, 8.0 Hz, 11-1), 6,87-6.90 (in, 2H), 6.80 (dd,
J8.0, 2.5 Hz, 111), 4.24 (t, J6.7 Hz, 211), 3.77 (s, 214), 3.70
(s, 311), 3.07 (s, 21-1), 2.98 (t, J6.7 Hz, 2H), 2.37 (s, 311).

20 EXAMPLE 1(13)
.  TLC: Rf 0.68 (hexane:ethyl acetate2 1);

NMR (CDCI,): 67.79 (d, J8.0 Hz, 211), 7.44 (s, 114), 5.(2-(2-(5.methyl-2-phenyloxazol-4-yl)ethoxy) 7,18-7,26 (m, 311), 6.82-6.88 (m, 311), 5.41 (s, 211), 3.72(s, phenyl)pentarioic acid.methyl ester
311), 3.22 (s, 21-1), 2.71 (t, J7.5 Hz, 211), 2.64 (t, J7.5 Hz,
2H), 2.39 (s, 311), 1.92 (tt, J=7.5, 7.5 Hz, 2H). 25

EXAMPLE 1(10) /Th

6-(2-(2-(5methy1-2-phenyloxazo1-4-y1)ethoxy)
phenyl)hexanoic acid.methyl ester 30 CH

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0

"CHI TLC: Rf 0.59 (hexane:ethyl acetate 2:1);

35 NMR (CDCI,): 68.05-7.95 (m, 2H), 7.45-7.35 (in, 3H),
7.20-7,05 (in, 211), 6.90-6.80 (m, 2H);, 4.25 (t, J6.5 Hz,
\ _J. 2H), 3.65 (s, 31-1), 3.00 (t, J6.5 Hz, 2H), 2.60 (t, J=7 Hz,
CH, 2H), 2.40 (s, 314), 2.25 (t, S7 Hz, 211), 1.80-1.45 (in, 4H).

TLC: Rf 0.51 (hexane:ethyl acetate 5:1);
NMR (CDCI,): 87,954,00 (in, 214), 7.40-7.45 (m, 311),

S 7,02-7,17 (m, 2H), 6.81-6.89 (in, 211), 4,25 (t, J6.4 Hz,

21-1), 3.65 (s, 31-1), 2.99 (t, J6.4 Hz, 2H), 2.56 (t, J7.8 Hz,
211), 2.38 (s, 311), 2.26 (t, J7,8 Hz, 2H), 1.46-1.76 (rn, 41-1),
1.22-1.45 (in, 2H).

EXAMPLE 1(11)

2-(3-(biphenyl-4-yhnethoxy)phenyhnethylthio)acetic
acid.methyl ester

40 EXAMPLE 1(14)

6-(2-(4-(4-rnethylphenyl)thiazol-2-ylrnethoxy) phenyl)hexanoic acid.methyl ester
45
H3C

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TLC: Rf 0,55 (hexane:ethyl acetate-5:1);

NMR (CDCI,): 67.79 (d, J-8.0 Hz, 214), 7.44 (s, 11-1), 7,24
(cI, J8.0 Hz, 2H), 7.15-7.22 (in, 211), 6.91-6.98 (in, 211),
1 5.42 (s, 211), 3.65 (s, 31-1), 2.73 (t, J7.6 Hz, 214), 2.39 (s,
0 3H), 2.32 (t, 17.4 Hz, 21-1), 1.61-1.77 (in, 41-1), 1.38-1.50
(in, 21-1).

TLC: Rf 0.56 (hexane ethyl acetate-3:1);
NMR ((i)(’13): 87.57-7.63 (in, 411), 7.34-7.52 (in, 51-1), 7.24 (dd, J=8.1, 7.7 Hz, 1H), 6.87-7.00 (rn, 311’), 5.10 (s, 211), 3.80 (s, 211), 3.71 (s, 3H), 3.07 (s, 2H).

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EXAMPLE 1(15)

2-(3-(3-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy) phenyl)propylthio)acetic acid.methyl ester

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EXAMPLE 1(96)

2-(3-(2-(5..inethy1-2-(2, 2-difluoro-1,3-dioxaindan-5-yl)oxazol-4-yl)ethoxy)phenyl)acetic acid.methyl
ester

TLC: Rf 0.52 (hexane:ethyl acetate-2:1);
NMR (CDC1): 67,75 (dd, J’-8.4, 1.8 Hz, IH), 7.68 (d, J1.8 Hz, 114), 7.21 (m, 1H), 7.10 (d, J8.4 Hz, 1H), 6.89-6.76 (m, 311), 4.23 (t, J6.6 Hz, 2H), 3.68 (s, 311), 3.58 (s, 2H), 2.96 (t, J6,6 Hz, 214), 2.37 (s, 314).

EXAMPLE 1(9 7)

2-(3-(2-(5-methyl-2-(4-tritluoromethylthiophenyl) oxazol-4-yl)ethoxy)phenylmethylthio)acetic
acid.methyl ester

TLC: Rf 0.45 (hexane:ethyl acetate3:1);
NMR (CDC’.): 68.02 (d, J8.4 Hz, 2H), 7.70 (d, J8.4 lIz, 211), 7.21 (t, J=7,8 Hz; 114), 6.91-6.73 (m, 311), 4.24 (t, J6.6 Hz, 214), 3.78 (s, 214), 3.71 (s, 311), 3.08 (s, 2H), 2,98 (t, J6.6 Hz, 211), 2.40 (s, 3H).

EXAMPLE 1(98)

2-(3-(2-(5’methy1-2(4-cyanopheny1)oxazo1-4-y1) ethoxy)pheriylrnethylthio)acetic acid.methyl ester

\===z/ .:(17? 0

TLC: Rf 0.35 (hexane:ethyl acetate2:1);
NMR (CDC13) 68.08 (d, J8.4 Hz, 214), 7.71 (d,.J8.4 Hz, 2H), 7.21 (m, 114), 6.75-6.94 (m, 3H), 4.24 (t, J=6.6 Hz, 2H), 3.78 (s, 2H), 3,72 (s, 3H), 3.09 (s, 2H), 2.99 (t, J6.6 Hz, 214), 2.41 (s, 3H).

EXAMPLE 1(99)

2-(3-(2-(5-methyl-2-(furari-2-yl)oxazol-4-yl)ethoxy) phenyln’iethylthio)acetic acid.methyl ester

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3.78 (s, 211), 3,72 (s, 31-1), 3.08 (s, 211), 2.97 (t, J-6,6 Hz, 214), 2.37 (s, 3H).

5 EXAMPLE 1(100)

2-(3-(5- methyl-2-phenyloxazol-4-ylmethoxy)
pheiiyl)acetic acid.methyl ester

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C’-’3

Is

20 TLC: Rf 0.69 (hexane:ethyl acetate2:1);

NMR (CDC13): 67.984.10 (m, 2H), 7.40-7.54 (m, 3H), 7.26 (m, 1H), 6.86-7.00 (m, 3H), 4.99 (s, 2H), 3.68 (s, 3H), 3.61 (s, 2H), 2.44 (s, 3H).

EXAMPLE 1(101)

35 2-3.(2-5-methyl-2-pheny1thiazo1-4-y1)ethoxy) pheriyl)acetic acid.methyl ester

40

TLC: Rf 0.56 (hexane:ethyl acetate-2:1);

45 NMR (CDC13): 67.90-7.81 (m, 2H), 7.46-7.35 (m, 3H), 7,25-7.16 (m, 1H), 6.87-6.78 (m, 3H), 4.32 (t, J6.8 Hz, 214), 3.68 (s, 314), 3.58 (s, 2H), 3.19 (t, J-6.8 Hz, 2H), 2.46
(s, 3H).

50 EXAMPLE 1(102)

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TLC: Rf 0.42 (hexane:ethyl acetate2:1);
NMR (CDC13): 67.94-8.04 (m, 2H), 7.36-7.50 (m, 3H),
TLC: Rf 0.32 (hexane:ethyl acetate-2:1); 65 7.22 (m, 1H), 6.76-6.90 (m, 3H), 3.98 (t, J=6.2 Hz, 2H), NMR (CDC1): 67.52 (in, 1H), 7.21 (in, 114), 6,86-6.96 3.69 (s, 3H), 3.59 (s, 2H), 2.70 (t, J7,0 Hz, 211), 2.28 (s, (m, 311), 6.79 (in, 111), 6.51 (m, 1H), 4.24(t, J6.6 Hz, 211), 311), 2.15 (m, 211).

2-(3-(3-(5-methyl-2-phcnyloxazol-4-yl)propoxy)
phenyl)acetic acid.methyl ester

0,,,, ,jV’’i{r"S’)r10"NCH

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EXAMPLE 1(132)

2-(3-(2(5-methy1-2(4-aitropheny1)oxazol-4-y1) ethoxy)pheriyl)acetic acid.methyl ester

:Cic?,-, a 0

I’LC: Rf 0,57 (hexane:ethyl acetate-4:3);
NMR (CDC13): 88.29 (d, J=9.0 Hz, 2H), 8.13 (Cl, J9.0 Hz, 211), 7.22 (in, 1H), 6.77-687 (in, 3H), 4.25 (t, J-6.6 Hz, 2H), 3.86 (s, 3H), 3.58 (s, 2H), 3.00 (t, J6.6 Hz, 2H), 2.42 (s, 3H).

EXAMPLE 1(133)

2-(3(2-(S-methy1-2-(quino1in-2-yl)oxazol-4-y1) ethoxy)phenyl)acetic acid.methyl ester

134

OCF3

"NCH3

TLC: Rf 0.43 (hexane:ethyl acetate=2:1);
10 NMR (CDC13): 88.114.04 (m, 111), 7.49-7.31 (in, 311),
7.27-7.16 (in, 1H), 6.88-6.76 (in, 3H), 4.25 (t, J=6.6 Hz, 2H), 3.68 (s, 3H), 3.58 (s, 2H), 2.99 (t, J6.6 Hz, 2H), 2.39 (s, 3H).
EXAMPLE 1(136)
15 2-(-(2-(4-methyl-2-pheny1oxazo1-5-yl)ethoxy) phenyl)acetic acid.methyl ester

O: (01:??O 0

20
CFI3

CH3 TLC: Rf 0.37 (hexane:ethyl acetate-2:1);

25 7.28_7J8(in,1H),60_77(fl1,3H),LL22(LJ8Hz,
2H), 3.68 (s, 3H), 3.58 (s, 2H), 3.16 (t, J6.8 Hz, 2H), 2.22
(s, 3H).
TLC: RI 0.38 (hexane:ethyl acetate4:3); EXAMPLE 1(137)
NMR (CDC13): 8.17-8.29 (in, 3H), 7.83 (m, 111), 7.75 2-(3-(2-(5-inethyl-2-(1,3-dioxaindan-5-yl)oxazol-4-
(rn, IH), 7.57 (m, 1H), 7.22 (m, IH), 6.78-6,86 (in, 311), yl)ethoxy)phenylmethoxy)acetic acid.t-butyl ester

40

4,29 (t, J=6.6 Hz, 211), 3.68 (s, 3H), 3.58 (s, 214), 3.05 (1, TLC: Rf 0.83 (hexane:ethyl acetate=1:1);
J6.6 Hz, 2H), 2.49 (s, 311). NMR (CDC11): 87.51 (dd, J8.0, 1.8 Hz, 1H), 7.43 (d,
J=1.8 Hz, 1H), 7.24 (t, J-7.8 Hz, 1H), 6,97-6.79 (in, 4H),
EXAMPLE 1(134) 6.01 (s, 211), 4.58 (s, 2H), 4,23 (t, J-6.8 Hz, 2H), 3.96 (s,
45 2H), 2.95 (t, J6.8 Hz, 2H), 2.35 (s, 3H), 1.48 (s, 9H).

2-(3-(2-(5-methyl-2-(3-trifiuoroinethoxyphenyl)
oxazo1-4-yl)ethoxy)phenyl)acetic acid.methyl ester

TLC: Rf 0.46 (hexane:ethyl acetate2:1);

NMR (CDC13): 67.91 (dt, J=7.8, 1.2 Hz, in), 7.85-7.82 (m, 1H), 7.45 (t, J7.8 Hz, 111), 7.28-7.17 (in, 2H), 6,88-6.77 (in, 311), 4.24 (t, J6.6 Hz, 214), 3.68 (s, 3H), 3.58 (s, 211), 2,97 (t, J=6.6 Hz, 2H), 2.39 (s, 3H).

EXAMPLE 1(135)

2-(3-(2-(5-methyl-2-(2-trifiuoromethoxyphenyl) oxazol-4-yl)ethoxy)phenyl)acetic acid.methyl ester

EXAMPLE 2

2-(3-(4-(4-methylphenyl)thiazol-2-ylmethoxy) phenylinethylthio)acetic acid
50

55

H3C

(OH s

0

60

The compound prepared in Example 1 (0.51 g) was dissolved in a mixture of methanol-tetrahydrofuran (8 ml, 1:1), and thereto was added 2N aqueous solution of sodium hydroxide (3.2 ml) and the mixture was stirred at room
65 temperature for 3 hours. The reaction mixture was acidified
by adding hydrochloric acid and the solution was extracted with ethyl acetate. The extract was washed with water and

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135 a saturated aqueous solution of sodium chloride,
successively, dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from hexane-ethyl acetate to give the compound of the present invention (0.39 g) having the following physical data.

TLC: Rf 0.37 (ethyl acetate);

NMR (CDC13+4 drop of CD30D): 67.77 (2H, d, J8.0 Hz), 7.45 (11-1, s), 7.23-7,31 (3H, m), 6.91-7.05 (3H, m), 10 5.42 (21-1, s), 3.83 (2H, s), 3.08 (211, s), 2.39 (3H, s).

EXAMPLE 2(1)EXAMPLE 2(137)

The following compounds of the present invention were obtained by the same procedure as shown in Example 2, using the compounds prepared in Example 1(1)Example 1(137) in place of the compound prepared in Example 1, optionally followed by converting them to the corresponding salts by known methods.

EXAMPLE 2(1)

6-(3-(4-(4-methylphenyl)thiazol-2-ylmethoxy) phenyl)hexanoic acid

H3(’

N

0 liz-1

C ’ O O H
Oil

TLC: Rf 0.41 (hexane:ethyl acetate-1:1);

NMR (CDCI3): 67,78 (2H, d, J=8.0 Hz), 7.43 (1H, s), 7.28-7.16 (3H, m), 6.90-6.78 (31-1, m), 5.42 (2H, s), 2.60 (211, t,.T7.5 Hz), 2.39 (311, s), 2.34 (211, t, J7.5 Hz), .1.76-1.54 (4H, m), 1.46-1.24 (21-1, m).

EXAMPLE 2(2)

5-(3-(biphenyl-4-ylmethoxy)phenyl)pentanoic acid

I’LC: Rf 0.49 (ethyl acetate);

NMR (CDCU): 67.58-7.64 (411, m), 7.35-7.53 (SH, m), 7.21 (1H, m), 6.78-6,84 (3H, m), 5.09 (2H, s), 2.62 (2H, t, J=7.0 lIz), 2,38 (2H, t, J=7.0 Hz), 1.64-1.72 (4H, m).

15

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EXAMPLE 2(3)

4-(3-(biphenyl-4-ylmethoxy)phenyl)butanoic acid

TLC: Rf 0.67 (ethyl acetate);

OH

NMR (daDMSO): 67.62-7.66 (4H, m), 7.31-7.51 (511,
20 m), 7.14 (1H, dd, J=7.5, 7.5 Hz), 6.71-6.82 (311, rn), 5.07 (2H, s), 2.52 (2H, t, J7.0 Hz), 2.06 (2H, t, J=7.0 Hz), 1.74 (2H, tt, J=7.0, 7,0 Hz).

25 EXAMPLE 2(4)

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4-(3-(4-(-methylphenyl)thiazol-2-ylmethoxy) phenyl)butanoic acid

TLC: Rf 0.63 (ethyl acetate);

NMR (CDC13): 67.78 (2H, d, J=8.0 Hz), 7.43 (1H, s), 7.23 (2H, d, J8.0 Hz), 7.22 (111, m), 6.81-6.88 (3H, m), 5.41 41 (211, s), 2.66 (214, t, J7.5 l-Iz), 2.38 (3H, s), 2.36 (21-1, 1, J7.5 Hz), 1.96 (2H, tt, J7.5, 7.5 Hz).

EXAMPLE 2(5) 50

4-(3-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy) phenyl)butanoic acid

55 0 OH

60

TLC: Rf 0.47 (ethyl acetate);

NMR (CDC11): 67.94-8.02 (2H, m), 7,39-7.48 (3H, m),
65 7.18 (111, m), 6.72-6.78 (31-1, m), 4.23 (21-1, t, 3=6.6 Hz), 2.98 (2H, t, J=6.6 Hz), 2.64 (21-I, t, J7.2 Hz), 2.38 (3H, s), 2.35 (211, t, J=7.2 Hz), 1.95 (2H, tt, J=7.2, 7.2 Hz.).

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EXAMPLE 2(6) EXAMPLE 2(9)

6-(3-(2-(5-methyl-2.phenyloxazol-4-yl)ethoxy) 2-(3.(3-(4(4-niethy1phenyI)thiazol-2-y1methoxy) phenyl)hexanoic acid 5 phenyl)propylthio)acetic acid

H OR C

\

CH, 10 OH

TLC: Rf 0.41. (ch1oroform:methano1 15:1);

NMR (CDC13): 88.02-7.91 (21’1, m), 7,49-7.36 (3H, m), 7.16 (1H, t, J8,0 Hz), 6.78-6.69 (3H, m), 4.24 (2H, t, 3=7.0 Hz), 2.98 (214, t, J7.0 Hz), 2.58 (2H, t, J7.5 Hz), 2.38 (3H, s), 2.34(2H, t, J7.5 Hz), i.75-1.54(4H, m), 1.45-1.25 (2H, M).

EXAMPLE 2(7)

5-(3-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy) phenyl)peritanoic acid

15

TLC: Rf 0.41 (ch1oroform: methanol= 10:1);

NMR (CDC13): 87.75 (2H, d, J8.0 Hz), 7.43 (1H, s), 7.18-7.26 (3H, m), 6.80-6.91 (3H, m), 5.44 (21-I, s), 3.23 20 (2}l, s), 2.71 (2H, t, J-7.4 Hz), 2.65 (2H, t, J7.4 Hz), 2.38 (3H, s), 1.93 (211, tt, J=7.4, 7.4 liz).

EXAMPLE 2(10)

25

6-(2-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy) phenyl)hexanoic acid

0
OH

30

IIC)

’T’LC: Rf 0.36 (ch1oroform:methanol= 15: 1);

NMR (CDC1): 88.04-7.92 (214, m), 7.49-7.36 (3H, m), 7.17(1,1, J8.0 Hz), 6.78-6.68 (314, m), 4.24 (2H, 1, J7.0 Hz), 2.98 (ZH, t, J7.0 Hz), 2,68-2.53 (211, m), 2.45-2.30 (51-1, rn), 1.79-1.56 (4H, in).

EXAMPLE 2(8)

2-(3-(3-(biphenyl-4-ylrnethoxy)pbenyl)propylthio)
acetic acid

?10, I

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TLC: Rf 0.38 (ch1oroform:methanol= 10:1);

NMR (CDCl): 87,35-7.64 (9H, m), 7.22 (114, m), 6.78-6.86 (311, rn), 5.09 (211, s), 3.25 (21-1, s), 2.70 (2Ff, t, J7.5 Hz), 2.67 (214, t, J7.5 Hz), 1.94 (2H, tt, J7.5, 7.5 1L’.).

35

40

TLC: R1 0.50 (chloroform:methanol= 10: 1);

NMR (CDC13): 87.95-8.00 (2H, m), 7,39-7.44 (3H, m), 7.07-7.17 (2H, m), 6,81-6,88 (2H, m), 4.23 (214, t, J6.7 Hz), 3.00 (2H, t, J=6.7 Hz), 2.57(2H, t, J-7.3 Hz), 2.37(3H, s), 2.30 (2H, t,J7.4 Hz), 1.46-4.69 (411, m), 1,22-1.40(2H, 45 m).

EXAMPLE 2(11)

50 2-(3-(biphenyl-4-ylniethoxy)phenylmethylthio)acetic acid

55

60

65

TLC: Rf 0.39 (ethyl acetate);

NMR (CDCI3): 57.60-7.64 (414, m), 7.22-7.53 (6H, m), 6.89-7,02 (3H, in), 5.11 (211, s), 3.83 (21-1, s), 3.10 (211, s).

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EXAMPLE 2(12) EXAMPLE 2(15)

2-(3-(2-(5-methyl.2-phenyloxazol-4-yl)ethoxy) 2-(3-(3-(2-5-methyl-2-phenyloxazo1-4-yI)ethoxy) phenylmethylthio)acetic acid 5 phenyl)propylthio)acetic acid
OH OH

0
10

TLC: RI 0.33 (ethyl acetate);

NMR (CDC1): 67.95-8.00 (2H, m), 7.40-7.47 (311, m),
7.21 (114, dd, 1-8.0, 8,0 Hz), 7,03 (1H, dd, 1-2.0, 1.0 Hz), 6.88 (III, ddd, J=8.0,3.0, 2 lIz), 6.81 (114, ddd, J8.0, 3,0, 1.0 Hz), 4.28 (2H, t, 1-7.5 Hz), 3.86 (2H, s), 3.16 (2H, s), 2.98 (2(1, t, J7.5 lIz), 2.39 (311, s).

EXAMPLE 2(13)

5-(2-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy) phenyl)pentanoic acid

TLC: Rf 0.5,8 (ch1oroform:methano19: 1);

TLC: Rf 0,42 (chloroform:methanol=10: 1);
15

NMR (CDCL,): 7.94-7.98 (m, 211), 7.41-7.44 (m, 311), 7.16 (dd, J7.7, 7.7 Hz, 1H), 6.89 (m, 1H), 6.72-6.76 (m, 2H), 4.29 (t, 3-7.2 Hz, 211), 3,23 (s, 2H), 3.01 (t, 3-7.2 Hz,
20 211), 2.72 (t, J-6.7 Hz, 2H), 2.66 (t, J-6,7 Hz, 2H), 2.40 (s,
311), 1.94 (tt, J-6.7, 6.7 Hz, 2H).

EXAMPLE 2(16)
25

2-(3.(2-biphenyl-4-yl)etboxy)pheny1methylthio)
OH acetic acid

30 " ", OH

35

NMR (CDCI3): 68.00-7.95 (2H, m), 7.50-7.35 (311, rn), 7.20-7.05 (2H, m), 6.90-6.80 (2H, m), 4.25 (2H, t, 3-7 Hz), 3.05 (214, t, J-7 Hz), 2.60 (2H, t, 3-7 Hz), 2,40 (31-1, s), 2,35 (211, t, 3-6 Hz), 1.80-1.50 (411, m).

EXAMPLE 2(14)

6-(2-(4-(4-methylphenyl)thiazol-2-ylmethoxy) phenyl)hexanoic acid

TLC: Rf 0.76 (ethyl acetate);

NMR (CDC1.): 87.79 (214, d, 3-8.4 Hz), 7.44 (111, s), 7.15-7.26 (411, m), 6.91-6.98 (211, m), 5.41 (21-1, s), 2.73 (211, t, J-7.4 Hz), 2.38 (3H, s), 2.36 (2H, t, J-7.3 Hz), 1.62-1.78 (411, m), 1.37-1.52 (2J-1, m).

40

TLC: Rf 0.43 (chloroform:methanol- 10: 1);

NMR (CDC13): 67.52-7.61 (m, 4H), 7.34-7.47 (in, 5H), 7.23 (dd, 3-8.0, 8.0 Hz, 1H), 6.80-6.92 (m, 311), 4,21 (t, J-6.8 Hz, 2H), 3.81 (s, 2H), 3.14 (t, 1-6.8 Hz, 2H), 3.11 (s,
45 211).

50

EXAMPLE 2(17)

2-(4-chloro-3-(2-(5-methyl-2-phenyloxazo1-4-yI) ethoxy)phenylmethylthio)acetic acid

0::,

51 TOH O-CJCC
60

TLC: Rf 0.38 (water:methano1:ch1oroform1:10:100);

NMR (CDCI3): 87.99 (in, 21-1), 7.50-7.40 (in. 314), 7.28
65 (d, J-8.0 Hz, 1H), 7.15 (d, J-2.0 Hz, IH), 6.82 (dd, J-8.0,
2.0 Hz, 1H), 6.30 (br., 1H), 4,38 (t, J-6.5 Hz, 2H), 3.85 (s, 2H), 3.18 (s, 2H), 3.03 (t, J-6.5 Hz, 2H), 2.42 (s, 3H).

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[Continued on next page]

(54) Title: PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR MODULATORS

(57) Abstract: The present
R3 invention is directed to

R8 /

OXA compounds represented by the
R9 RIO following structural formula, and
R40 R30 (I) pharmaceutically acceptable salts

thereof, Formula I: (Formula I);
wherein: (a) R5 is selected from

R6 c’ W R4 the group consisting of (C1 -C6)
R5 alkyl, (C: -C6) alkenyl, aryl

(C0-C4) alkyl, aryloxy (C0 -C4)
alkyl, arylthio (C.0 -C4) alkyl, and further wherein when R5 is alkyl, R5 can optionally combine with W to form a 6 membered cycloheteroalkyl ring that is fused with the oxazole or thiazole ring to which the R5 group is attached; (b) R9 is selected from the group consisting of C1-05 alkyl, C1-05 alkenyl, and arylC0-C3alkyl; (c) T1 is selected from the group consisting of C and N; (d) W is selected from the group consisting of CH2, C(0)N(R21), N(R21), N(R21)CH2, 0, OCH2, 5, and SO2; and(e) X is selected from the group consisting of C, CHZC, and CCH2

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PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR MODULATORS

BACKGROUND OF THE INVENTION

Peroxisome Proliferator Activated Receptors (PPARs) are
5 members of the nuclear hormone receptor super family, which
are ligand-activated transcription factors regulating gene expression. Various subtypes of PPARs have been discovered. These include PPARa, NTJC1, PPAR7 and PPARö.

. The PPARa receptor subtypes are reported to be
10 activated by medium and long -chain fatty acids. They are
involved in stimulating beta -oxidation of fatty acids and
with the activity of fibrates reportedly producing a
substantial reduction in plasma triglycerides and moderate reduction in low density lipoprotein (LDL) cholesterol.
15 PPARo, PPAR? and PPAR6 receptors have been implicated in
diabetes mellitus, cardiovascular disease, obesity, Syndrome
X and gastrointestinal disease, such as, inflammatory bowel disease. Syndrome X is the combination of symptoms
including hyperinsulemia combined with hypertension,
20 elevated body weight, elevated triglycerides and elevated

LDL.

Current PPAR agonist treatment for Syndrome X relates
to the use of thiazolidinediones (TZDs) or other insulin sensitivity enhancers (ISEs). TZDs are a class of PPAR
25 gamma agonists which have been shown to increase the
sensitivity of insulin sensitive cells. Increasing insulin sensitivity rather than the amount of insulin in the blood reduces the likelihood of hypoglycemic coma. However, TZDs
and ISEs typically have little effect in preventing the
30 cardiovascular part of Syndrome X in that their
administration usually dose not result in the lowering of triglycerides and LDL-cholesterol while raising HDL-cholesterol. Furthermore, side effects commonly associated with treatment with TZDs can include significant weight
35 gain, and, for troglitazone, can include liver toxicity.
Therefore, a need exists for new pharmaceutical agents which

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affect treat or prevent cardiovascular disease, particularly that associated with Syndrome X, while preventing or
minimizing weight gain, and more preferably while improving insulin sensitivity. It may be especially desirable when
5 the active pharmaceutical agent selectively modulates a PPAR receptor subtype to provide an especially desirable pharmacological profile.

SUMMARY OF THE INVENTION

10 The present invention is directed to compounds
represented by the following structural Formula I:
R3
R
R7

B

R9 R10
R30

R6 T1 ’ Z
R5

and pharmaceutically acceptable salts thereof, wherein:

15 (a) R3 and R4 are each independently selected from the
group consisting of hydrogen, (C, -C,) alkyl, halo,
and (C1 -C6) alkoxy;
(b) R30 and R40 are each independently selected form
the group consisting of hydrogen, (C1 -C4) alkyl,
20 and (C -C6) alkoxy;
(c) R5 is selected from the group consisting of (01-C6)
alkyl, (C1 -C6) alkenyl, aryl(C0-C4)alkyl,
aryloxy(C-C4)alkyl, arylthio(C0-C4)alkyl, wherein
said aryl(C0-C4)alkyl, aryloxy(C0-C4)alkyl, and
25 arylthio (C0 -C4) alkyl are each independently
optionally substituted with from one to three
substituents each independently selected from R51,
and further wherein when R5 is alkyl, R5 can
optionally combine with W to form a 6 membered
30 cycloheteroalkyl ring that is fused with the
oxazole or thiazole ring to which the R5 group is
attached;

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(d) P.5’ are each independently selected from the group
consisting of halo, -(0)-(C1-05)alkylCOOH, C, -C,
alkyl, C. -C, alkyl000H, and CF,,
(e) P.6 is selected from the group consisting of
5 trihalomethyl, trihalomethoxy, hydroxy(C0-C3)a1kyl,
(C1 -C4) alkyl, (C1 -C6) alkyiNC (0) -,
tetramethyldioxaborolanyl, halo, -C(0) (C1-C4)alkyl,
- 0-(C -c,)alkyl-CO,H, aryloxy/ arylthio, -C(0)N(C1-
06) alkyl, (C -C4) alkoxy, tetrahydropyranyloxy,
10 morpholinyl, (C5 -C6) cycloalkyloxy, (C5 -C6)
heterocyclo-oxy, pyridinyl, pyramidiny’l, pyrazinyAl
and aryl (C0-C4)alkyl, wherein said pyridinyl,
pyrimidinyl, pyrazinyl, aryl (C0-C4)alkyl, aryloxy,
(C5-C6)heterocyclo-oxy, and arylthio are each
15 optionally substituted with from one to three
substituents independently selected from R61;
(f) P.6’ and R9’ are each independently selected from
the group consisting of CF., C -C4 alkyl, halo, hydroxy(C-C3)alkyl, C1 -C3 alkoxy, and -C(0)CH3;
20 (g) R7 and R8 are each independently selected from the
group consisting of hydrogen, CF,, and (C,-
CJ alkyl;
(1-i) P.9 is selected from the group consisting of C1-05
alkyl, C1-05alkenyl, and arylC0-C3alkyl, wherein
25 said arylalkyl is optionally substituted with from
one to three substituents each independently
selected from P.9’;
(i) P.10 is selected from the group consisting of
hydrogen, and Cl-05 alkyl;
30 (j) Q is selected from the group consisting of 0, a
single bond, and C;
(k) T is selected from the group consisting of C and
N;
(1) Wis selected from the group consisting of CH21
35 C(0)N(R21), N(P.21), N(R21)CH2, 0, OCH2, S, and SO2;
(m) R21 is selected from the group consisting of
hydrogen and C1 -C2 alkyl;

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(n) X is selected from the group consisting of C,
CH2C, and CCH2;
(a) Y and Z are each independently selected from the
group consisting of 0, N and S, wherein at least
one of Y and Z is selected from the group
consisting of 0 and S;
(p) A is an functional group selected from the group
consisting of carboxyl, C1-C,alkylnitrile, carboxamide, and (CH2) COOR19;
(q) n is 0, 1, 2 or 3; and
(r) R19 is selected from the group consisting of
hydrogen, and C -C3 alkyl.
Another embodiment of the present invention is a
compound. of Formula I’:

R8 R9,,R1

R6
R5

and pharmaceutically acceptable salts thereof, wherein:

(a) R3 and R4 are each independently selected from the
group consisting of hydrogen, (C1 -C4) alkyl, halo,
and (C1 -C6) alkoxy;
(b) R5 is selected from the group consisting of (C’ -C,)
alkyl, (C1 -C6) alkenyl, substituted aryl(C0-
C4)alkyl, substituted aryloxy(C0-C4)alkyl,
substituted arylth–o(c0-C4) alkyl, unsubstituted
aryl (C0-C4)alkyl, unsubstituted aryloxy(C0-C4)alkyl,
and unsubstituted arylthio (C0 -C4) alkyl;
(c) R6 is selected from the group consisting of
trihalomethyl, halo, hydroxy, hydroxy(C1.-C3) alkyl,
(C1-C4)alkyl, -C(o) (C-C4)alkyl, -C(0)N(C1-C6)alkyl,
- 0-(C1-C2)alkyl-CO2H, (C1-C4)alkyloxy, (C5 -C6)
cycloalkyloxy, (C, heterocyclic, (C5 -C,)

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heterocyclo-oxy, substituted (C5 -C6) heterocyclo-
oxy, aryl (C0 -C4) alkyl, substituted aryl (C, -C,) alkyl;
(d) R7 and R8 are each independently selected from the
group consisting of hydrogen, CF., and (Ci-
5 C,) alkyl;
(e) R9 is selected from the group consisting of Cl-05
alkenyl, unsubtituted arylC0-C3alkyl, subtituted
arylC0-C3alkyl, substituted arylthioC1-c2alkyl,
unsubstituted arylthioC-C2alkyl, substituted
10 aryloxyC-C2alkyl, unsubstituted aryloxyC1-C2alkyl
and Cl-05 alkyl;
(f) RiO is hydrogen or methyl;
(g) Q is selected from the group consisting of 0 and
C;
15 (h) W is selected from the group consisting of 0, S,
and SOS;
(i) X is selected from the group consisting of CH,
CH2CH, and CHCH2;

(j) Y and Z are each independently selected from the
20 group consisting of 0, N and S;
(k) A is an functional group selected from the group
consisting of carboxyl, C1-C3alkylnitrile,
carboxamide, and (CH2)
(1) n is 0, 1, 2 or 3; and
25 (m) R19 is selected from the group consisting of
hydrogen, optionally substituted C1-C4alkyl and
optionally substituted arylmethyl.
In one embodiment, the present invention also
relates to pharmaceutical compositions which comprising at
30 least one compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
In another embodiment, the present invention relates to
a method of selectively modulating a PPAR delta receptor by
35 contacting the receptor with at least one compound

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represented by Structural Formula I, and pharmaceutically acceptable salts thereof.
In another embodiment, the present invention relates to
a method of modulating one or more of the PPAR alpha, beta,
5 gamma, and/or delta receptors.
In a further embodiment, the present invention relates
to a method of making a compound represented by Structural Formula I.
The compounds of the present invention are believed to
10 be effective in treating and preventing Syndrome X, Type II
diabetes, hyperglycemia, hyperlipidemia, obesity,
coagaulopathy, hypertension, atherosclerosis, and other disorders related to Syndrome X and cardiovascular diseases.
In addition, the compounds can be associated with fewer
15 clinical side effects than compounds currently used to treat
these conditions. Further, compounds of this invention can
be useful for lowering fibrinogen, increasing HDL levels, treating renal disease, controlling desirable weight,
treating dernyelinating diseases, treating certain viral
20 infections, and treating liver disease.

DETAILED DESCRIPTION OF THE INVENTION
The terms used to describe the instant invention have
the following meanings herein.
25 As used herein, alkyl groups include straight chained
and branched hydrocarbons, which are completely saturated. Cycloalkyl groups, as used herein, include cyclic
hydrocarbons, which are completely saturated.
As used herein, the term "halo" means Cl, F, or Br.
30 Especially preferred halo groups are Cl and F.
An especially preferred trihalomethyl group is -CF,.
As used herein, when Q is a single bond means that Q is
absent and the -C(R30) (R40) group is directly bonded to the phenyl.
35 As used herein, when arylalkyl is arylC0alkyl, then the
aryl group is bonded directly to the group to which the

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increases serum HDL levels in a patient. It is especially
preferred that HDL levels will be increased by about 30% or more. In adition, a therapeutically effective amount of a
compound, used to prevent or treat NIDDM, typically reduces
5 serum glucose levels, or more specifically HbAlc, of a
patient by about 0.7% or more.
Advantageously, compositions containing the compound of Structural Formula I or the salts thereof may be provided in dosage unit form, preferably each dosage unit containing
10 from about 1 to about 500 mg be administered although it
will, of course, readily be understood that the amount of
the compound or compounds of Structural-Formula I actually
to be administered will be determined by a physician, in the light of all the relevant circumstances.
15 When used herein Syndrome X includes pre -diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy,
hypertension and other complications associated with
20 diabetes. The methods and treatments mentioned herein
include the above and encompass the treatment and/or
prophylaxis of any one of or any combination of the
following pre -diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II
25 or non-insulin dependent diabetes, dyslipidemia,
hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially atherosclerosis.

The compositions are formulated and administered in the
30 same general manner as detailed herein. The compounds of
the instant invention may be used effectively alone or in combination with one or more additional active agents
depending on the desired target therapy. Combination
therapy includes administration of a single pharmaceutical
35 dosage composition which contains a compound of Structural
Formula I and one or more additional active agents, as well
as administration of a compound of Structural Formula I and

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each active agent in its own separate pharmaceutical dosage formulation. For example, a compound of Structural Formula
I or salt thereof and an insulin secretogogue such as biguanides, thiazolidinediones, sulforiylureas, insulin, or
5 Y.-glucosidose inhibitors can be administered to the patient
together in a single oral dosage composition such as a
tablet or capsule, or each agent administered in separate
oral dosage formulations. Where separate dosage
formulations are used, a compound of Structural Formula I
10 and one or more additional active agents can be administered
at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.
An example of combination treatment or prevention of
15 atherosclerosis may be wherein a compound of Structural
Formula I or salts thereof is administered in combination
with one or more of the following active agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins,
20 aspirin, and the like. As noted above, the compounds of
Structural Formula I can be administered in combination with more than one additional active agent.
Another example of combination therapy can be seen in
treating diabetes and related disorders wherein the
25 compounds of Structural Formula I, salts thereof can be
effectively used in combination with, for example,
sulfonylureas, biguanides, thiazolidined–ones, a-glucosidase inhibitors, other insulin secretogogues, insulin as well as
the active agents discussed above for treating
30 atherosclerosis.

The compounds of the present invention, and the pharmaceutically acceptable salts, have valuable
pharmacological properties and can be used in pharmaceutical compositions containing a therapeutically effective amount
35 of a compound of the present invention, or pharmaceutically
acceptable salts thereof, in combination with one or more

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pharmaceutically acceptable excipients. Excipients are
inert substances such as, without limitation, carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders,
5 disintegrating agents, encapsulating material and other
conventional adjuvants. Proper formulation is dependent
upon the route of administration chosen. Pharmaceutical compositions typically contain from about 1 to about 99
weight percent of the active ingredient that is a compound
10 of the present invention.
Preferably, the pharmaceutical formulation is in unit
dosage form. A ’unit dosage form" is a physically discrete
unit containing a unit dose, suitable for administration in human subjects or other mammals. For example, a unit dosage
15 form can be a capsule or tablet, or a number of capsules or
tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to
produce the desired therapeutic effect, in association with
one or more pharmaceutically-acceptable excipients. The
20 quantity of active ingredient in a unit dose may be varied
or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.
The dosage regimen utilizing the compounds of the
present invention is selected by one of ordinary skill in
25 the medical or veterinary arts, in view of a variety of
factors, including, without limitation, the species, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory
30 function of the recipient, the dbsage form employed, the
particular compound and salt thereof employed, and the like. Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more
35 times per day. Where delivery is via transdermal forms, of
course, administration is continuous.

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0

CH3

MS (ES): 526.2 (M+1), the structure is also confirmed by proton NMR.

5 Example 4
i4-{1- [4- 12- (2-Chloro-6-fluoro--phenvl) -ethyl] -2- (4-trifluoromethyl-phenyl) -thiazol-5-yl] -ethoxy} -2-methyl-phenoxy) -acetic acid.

10

15

?OZCH3

O\AOH

MS (ES): 594.2 (M4+1, 35C1), 596.2 (M+l, 37C1), the structure
is also confirmed by proton NMR.

Example 5
3- (4-1- [4- [2- (2-Chloro-6-fluoro-IDhenvl) -ethyll -2- (4-trifluoromethyl-phenyl)-th–azol-5-yl] -ethoxy}-2
- methyl -pheny1) -propioriic acid

9H3 rl""?O\?-AOH

F H3

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F

MS (ES): 526.2
proton NMR.

99

CH

(M+1), the structure is also confirmed by

5 Example 4 J4 -{l- [4- 12- (2-Chloro-6-fluoro-phenyl) -ethyl] -2- (4-tjfluoromethyl-phenyl)-thjazol-5-y1] -ethoxy}-2-rnethyl-phenoxy) -acetic acid

10

15

30j:::?CH3

F ’

MS (ES): 594.2 (M+l, "Cl), 596.2 (M4+1, "Cl), the structure
is also confirmed by proton NMR.

Example 5
3- (4-{l- [4- [2- (2-Ch1oro-6-f1uoro-heny1) -ethvll -2- (4-trifluoromethyl-phenyl) -th–azol-5-yl] -ethoxy}-2
- methyl -phenyl) -propionic acid

ç H OH

F+J\ H3

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F

101

0

0 CH

CH3

MS (Es) 540.2 (M+1), the structure is also confirmed by
. proton NMR. Example 9
5 C2 -Methyl --4-{2- [4 -phenyl -2- (4-trifluoromethyl-phenyl) -
thiazol-5-yll -ethylsulfanyl}--phenoxy) -acetic acid
0

F->--I S’’"CH3
F

0/
S

CH3

MS (Es): 530.2 (M+1), the structure is also confirmed by proton NMR.
10

Example 10
3 (2 -Methyl -4 -{i- [4 -phenyl -2-- (4-trifluoromethyl-phenyl) - thiazol-5-yl] -ethoxy}-phenyl)-propionic acid

F40’
CH3

15 MS (ES): 512.2 (M4+l), the structure is also confirmed by
proton NMR.

Example 11
Li-{i- [4 -Isopropyl -2- (4-trifluoromethyl-phenyl)-thiazol-5-
20 vii -ethylsulfanyl}-2-methyl-phenoxy) -acetic acid

SUPERINTENDENCIA DE INDUSTRIA V COMERCIO DIRECCION DE NUEVAS CREACIONES

2020
Bogota, D.C.

Abogado
I CARLOS R. OLARTE

ASUNTO RadicaciOn 06-117272
TrÆmite 011
Evento 379
ActuaciOn 41’kt

OficioQ 485 Folios 035

Patente de Invención FX1Patente de Modelo de Utilidad

Via Nacional 7 -

Via PCT (fase nacional) Fx1Cap.IF-1 Cap. II 7X

No. Sol. Internacional PCT/US2005/01 8167
Fecha de PresentaciOn Internal. 24-05-2005

Como resultado del examen de fondo, realizado con fundamento en el articulo 45 de la DecisiOn 486 de la ComisiOn de la Comunidad Andina, se le comunica:

1. Documentos estudiados

DescripciOn: Folios 190-461 y 475 como se radicO inicialmente
Reivindicaciones: Folios 462-474 como se radicO inicialmente
Prioridad: Folio 1 60/574.137, 24-05-2004
US, 60/648.985, 31-01-2005

2. Objeto de la invención

TItulo de la solicitud: COMPUESTOS Y COMPOSICIONES COMO MODULADORES DEL RECEPTOR ACTIVADO POR PROLIFERADOR DE PEROXISOMA (PPAR) (folio 1).

El problema tØcnico planteado en la sollcitüd estÆ relacionado con la necesidad de obtener compuestos que modulen la actividad del receptor activado por proliferador de peroxisoma (PPAR), que sean ütiles para tratar trastornos asociados con las tales receptores como dislipidemia, hiperlipidemia, hepercolesterolemia, enfermedades vasculares y cardiovasculares, entre otras (folio 190-191; pÆg. 1-2).

Para solucionar este problema tØcnico la solicitud en estudio proporciona en:

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Reivindicaciones 1-5 y 13 (en parte): un compuesto de formula I y las sales farmacØuticamente aceptables, hidratos, solvatos, isómeros y profÆrmacos del mismo.

R15

14 T L2

R

- - </ X
(R13)’ I

Reivindicaciones 6-8: relacionadas con mØtodos de tratamientos.

Reivindicaciôn 9 y 14: el uso de un compuesto y composiciones farmacØuticas.

Reivindicaciones 10, y 12-13 (en parte): una composicion farmacØutica que comprende un compuesto de formula I en combinación con uno o mas excipientes farmacØuticamente aceptables.

Reivindicaciones 11 y 12-13 (en parte): una combinaciOn farmacØutica, en especial una composición farmacØutica que comprende:

1) un compuesto de formula I o una sal farmacØuticamente aceptable del mismo y
2) cuando menos un ingrediente activo 6 una sal farmacØuticamente aceptable del mismo seleccionado a partir del grupo que consiste en:
a) agentes antidiabØticos seleccionados de compuestos una lista de diversos grupos farmacolOgicos
nombrados,
b) agentes hipolipidØmicos seleccionados compuestos de varios grupos farmacolOgicos dados de compuestos como colestiramina, fibratos, acido nicotinico aspirina,
c) un agente contra la obesidad un agente regulador del apetito seleccionado de 23 compuestos
seæalados de compuestos antagonistas del receptor de canabinoide,
d) agentes anti-hipertensivos por ejemplo seleccionados de una lista de grupos farmacologicos seæalados.
e) un compuesto incremeritador de lipoproteinas de alta densidad (HDL),
f) un modulador de absorciOn de colesterol como Zetia KT&-971,
g) anÆlogos mimØticos de Apo-Al
h) inhibidores de trombina coma Ximelagatran,
I) inhibidores de aldosterona como anastrazol, fadrazol eplerona,
j) inhibidores de acumulación de plaquetas como aspirina, bisulfato de clopidogrel,
k) estrôgeno, testosterona, un modulador del receptor estrogeno selectivo, un modulador del receptor de
androgeno selectivo
1) un agente quimioterapØutico como compuestos seleccionados de varios grupos farmacologicos
senalados,
m) un agente que interactuØ con un receptor 5-HT3 y/o un agente que interactuØ con un receptor 5-HT-4 coma tegaserod, maleato de tegaserod, cisaprida, cilansetron;

opcionalmente un vehIculo farmacØuticamente aceptable.

Clasificaciôn lnternacional de Patentes ((PC): A611<31/421, C07D277/24, C07D41 3/04.

3. De la solicitud de Patente

3.1. Reivindicaciones (artIculo 30 D 486)

> Se solicita en las reivindicaciones 1-5 y 13 (en parte): un compuesto de formula I con radicales R13 a R16 y variables L2 y p, y las sales farmacØuticamente aceptables, hidratos, solvatos, isómeros y profÆrmacosdel mismo; pero, existe falta de claridad, concision y sustento de la materia solicitada, dado que:

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551 ’) - Se solicitan solvatos del compuesto de formula I, pero no se encuentra soporte
de ningün solvato en los compuestos ejemplificados en la descripciôn, por lo que
tal tØrmino debe ser eliminado.

- El tØrmino general "profÆrmacos"no define a que compuestos especIficos se
hace referencia; es necesario eliminarlo o cambiarlo por tØrminos concretos acorde a lo soportado.

- Se seæalansustituyentes con tØrminos generales y ambiguos como "ariloC610,
heteroariloC510, heterocicloalquiloC3..8, R15 y R16 forman un heteroariloC514 bicIclico o tricIclico fusionado"; es necesario que dichos tØrminos se defina de forma especIfica en cada caso y acorde con los compuestos que se ejemplifican
y que evidencian la actividad seæalada.

- Expresiones generales ambiguas como "en donde cualguier arilo, heteroarilo,
cicloalquilo, heterocicloalquilo, y la combinaciOn de R15 y R16, estÆn opcionalmente sustituidos por... (sustituyentes seleccionados de una lista dada)", no permiten definir con claridad la materia solicitada; por lo que es necesario que el termino en donde cualciuier sea eliminado y que las sustituciones concretas para cada tipo de anillo se definan de manera acorde a los soportado por los compuestos que evidencian actividad.

- Se caracteriza inadecuadamente un compuesto por su uso como medicamento
(reivindicación 13), ya que un compuesto debe ser caracterizado por su formula o estructura quimica.

- No existe soporte para la materia solicitada, ya que solo se ejemplican las
opciones cuando:

L2: generalmente -OCH2-
ocasionalmente -SCH2-, -CH2S-, -S- -0-aIquilC2.4-S-

(R13): p es 0 1 yR13 es Cl,Br, alquiloC1,36 alcoxiloC1

R14: -0-alquilC23-COOH 6 -alquiICi2-COOH

R15 y R16 independiente son generalmente fenilo

opcionalmente sustituidos por uno dos de Br, Cl, F, -0-alquiloCi,34,-O-CF3, CN, NO2,-CF3, alquiloC1, -S-alquiloCi,3, -N(alquil0C1..3)2, -CH2-OH, -CON(alquiloC1..3)2,
- CONH-ciclopropilo,-NHSO2CH3, -S02alquiloC2 -NHCOaIquiIoC1, fenilo, morfolinilo, piperidinilo 6 pirrolidinilo.

Se solicita en las reivindicaciones 11-12 y 13 (en parte) una combinaciôn en especial una composiciOn farmac(,-utica que comprende:

1. un compuesto de formula I o una sal farmacØuticamente aceptable del mismo y
2. cuando menos otro ingrediente activo 6 una sal farmacØuticamente aceptable del mismo, seleccionado de un compuesto perteneciente a uno de los 13 tipos de diversos grupos farmacologicos indicados en los numerales a) a m).

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Pero, dicha materia no es clara ni concisa puesto que el segundo componente es otro agente activo que puede ser seleccionado de 13 grupos de compuestos definidos por diversos grupos farmacológicos.

Adicionalmente, no existe soporte para tat materia puesto que en la descripciOn no existe evidencia de alguna composición concreta, que tenga un compuesto de formula I y otro activo especifico de los numerosos grupos farmacologicos senalados y que presente resultados de una ventaja o efecto tØcnico inesperado.

Por otra parte, se caracteriza inadecuadamente una composición por ser para tratamiento de diversas condiciones y por su uso como medicamento (reivindicaciones 12 y 13), ya que una composiciôn debe ser caracterizada por lo elementos que la comprenden.

Por lo anterior, el capitulo reivindicatorio no cumple con el requisito de tener claridad, concision y sustento de acuerdo con las exigencias del articulo 30 de la Decision 486.

4. Excepción a la patentabilidad (artIculo 20 D486 literal d)

Las reivindicaciones 6-8, relacionadas con un mØtodo de tratamiento, estÆn exceptuadas de patentabilidad de acuerdo con el artIculo anterior; por Ic que es necesario eliminarlas del alcance de la solicitud.

5. Reivindicaciones relativas a un uso o a un segundo uso (artIculos 14 y21 D
486)

De acuerdo con los artIculos anteriores, las reivindicaciones 9y 14, relacionadas con el uso de compuestos y composiciones, no se consideran objeto de protecciOn porque el uso no es un producto o un procedimiento tecnolagico; per 10 que es necesario eliminarlas del alcance de la invenciôn.

6. Determinación del Estado de la TØcnica

Considerando que la fecha de presentación de la primera solicitud de patente de la que se reivindica prioridad es 24-05-2004, se buscaron documentos del estado de la tØcnica relacionados, con fecha de publicaciOn anterior a Østa.

No Documento Titulo Fecha de

Publicación
Carboxylic acid derivatives and drugs
DI US6506757 containing the same as the active 10-01-2001
ingredient

02 W003072100 Peroxisome proliferator activated 04-09-2003 receptor modulators

Anterioridad Dl en folios 521-535 Y D2 en folios 536-548.

7. AnÆlisisde patentabilidad (artIculo 14 D486)

7.1 Nivel inventive (artIculo18D486)

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Se solicita en las reivindicaciones 1-5 y 13 (en parte): un compuesto de formula I con radicales R13 a R16 y variables L2 y p, y las sales farmacØuticamente aceptables, hidratos, solvatos, isómeros y profÆrmacosdel mismo; en las 10, y 12-13 (en parte) una composiciOn que lo comprende.

SOLICITUD I Dl D2
Un compuesto de Un compuesto de formula (I) Un compuesto de formula (I)
formula (I) (folio 522; col. 7-8) (folios 538-540; pÆg. 1-4)

Con radicales R13 a R16 y
variables L2 y p, segin
capitulo reivindicatorio.

(As R2

1A2 2 R4

(I)

C ci:

R: H, aiquilo, halageno o trihalometilo

Cyc2: anillo carbociclilo a un hetero
anillo
R1: H, halageno, alquiloC18, NO2,
aIcoxiCi, triahalometilo, trihalometoxi, CN, alquiltioalquilCl-4tio, -NH2, -

NH(alquiloC14, N(alquiloC42, anillo
carbociclico 0 wi hetero anillo.

n: 1-5

A1: alquilenoCi_41 alquenilenoCi
A2: 0 o S
A3: CH

R3: H, alquiloCi8, halôgeno, aIoxiC1,
triahalometilo, trihalometoxi

R4:

A4: enlace, alquileneC, -alquileneCi. 40

R7, R8 y R9: independientemente son H o alquiloCi.

Obteniendo por ej. los compuestos:

Ej. 1(4) oII

Ej. 2(4)

Ej. 1(101)

los 528, 531, 533; col.87, 124, 1

R3 ?A

R6 TF

R5 (I)

Z y Y: seleccionados de 0, N O S

X: C, CH2, CCH2 W:O, OCH2, S a SO2 R9: alquiloC15 RIO: H, alquiloC15

T: Co N
R6: triahalometilo, trihalometoxi,
hidroxialquiloCi, alquiloCi, alcoxiC1_4,
-CONHalquiloCi, -COaIquiloC1.,
halogeno, morfolinilo, cicloalquilC5soxi
o heterocicloC5oxi, piridinilo,
primidinilo, pirazinilo, arilalquiloCo,
ariloxi opcionalmente sustituidos por - CF3, aIquiloC1, halageno a hidroxialquiloC13.
R7 y R8: H, -CF3 a alquiloCi

R3 y R4: H, alquiloC1, alqoxiCi a halOgeno

Q: enlace, 0 a C
R40 y R30: H, alqUilOC1A 6 aIqoxiCi
A: carboxilo a -(CH)nCOOR19
n: 1 a 3

R19; H 0 alquiloCl3

Obteniendo por ej. los compuestos:

Ej. 8

OjOH

Ej. 9 CH,

FQOeN,
Ej. 10 CH,

(folios 548; pÆg. 10 1)

Tanto Dl como D2 divulgan compuestos moduladores de receptores PPAR derivados de tiazol de formula (I) en cada caso, tal como se enseæaen el cuadro comparativo; ütiles para tratar trastornos asociados con las tales receptores como dislipidemia, hiperlipidemia, hipercolesterolemia, enfermedades vasculares y card iovascu lares, entre otras.

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La solicitud se diferencia de Dl en que el tiazol tiene dos (R15 y R16) sustituyentes de tipo arilo opcionalmente sustituido o arilalquilo (donde arilo es fenilo generalmente en los ej.) mientras que en DI tiene solo uno de tipo arilo ya que el otro corresponde a R2 que es H, aiquilo, halogeno o trihalometilo.

El Efecto TØcnico que logra dicha diferencia es que los compuestos presentan actividad como moduladores de receptores PPAR.

Ast, el Problema TØcnico Objetivo de esta solicitud esta relacionado con necesidad de obtener otros compuestos derivados de tiazol que modulen la actividad de receptores PPAR, que sean ttiles para tratar trastornos asociados con las tales receptores como dislipidemia, hiperlipidemia, hipercolesterolemia, enfermedades vasculares y card iovasculares, entre otras (folio 190-191; pÆg. 1-2).

No obstante, D2 ya enseæaque el tiazol puede tener dos sustituyentes de tipo arilo opcionalmente sustituido o arilalquilo (donde arilo es fenilo como en los ej. 8-10) y mantener la actividad moduladora sobre receptores PPAR.

En consecuencia, acorde con las ensenanzas de Dl y D2, el experto en la materia cambia el radical R2 (H, alquilo, halOgeno o trihalometilo) por otro de tipo arilo 0 arilalquilo como lo sugiere D2 para obtener los derivados de tiazol con dos sustituyentes de tipo arilo o arilalquilo solicitados, por lo que la materia reclamada no tiene nivel inventivo.

> Se solicita en las reivindicaciones 11-12 y 13 (en parte) una combinaciOn en especial una composiciOn farmacØutica que comprende:

1. un compuesto de formula I o una sal farmacØuticamente aceptable del mismo

2. cuando menos otro ingrediente activo 6 una sal farmacØuticamente aceptable del mismo, seleccionado de un compuesto perteneciente a uno de los 13 tipos de diversos grupos farmacologicos indicados en los nunierales a) a m).

El documento D2 divulga composiciones farmacØuticas que contienen un compuesto derivado de tiazol de formula (I) modulador de receptores PPAR en combinaciôn con uno o mas agentes activos como secretagogos de insulina (sulfonilureas, biguanidas, tiazolidinonas, entre otros), inhibidores a-glucosidasa, agentes hiperlipidØmicos, agentes antihipercolesterolØmicos, fibratos, aspirina, vitaminas, entre otros; para alcanzar efectos terapØuticos combinados (543-544; pag.11-12).

Por lo anterior y dado que en la descripciOn no existe evidencia de alguna composiciôn concreta, que tenga un compuesto de formula I y otro activo especifico de los numerosos grupos farmacolOgicos sŁnalados,y que presente resultados de una ventaja o efecto tØcnico inesperado, la materia reivindicada no tiene nivel I nventivo.

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8. Conclusion

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Los requisitos de patentabilidad de la presente socitud se encuentran afectados as!

No Documento No Reivindicaciones Afectadas Requisito que

Afecta

Dl US6506757 1-5, 10 12-13 (en parte) Nivel inventivo
02 W003072100 11-12 13 (en parte) Nivel inventivo

En cumplimiento del artIculo 45 de la Decision 486 de la Comisiôn de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de sesenta dIas contados a partir de la fecha de notificaciOn de la presente comunicaciOn. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesiOn, se denegarÆ (a patente.

NotifIquese el presente ofi nforme a to dispuesto en el artIculo 8 de (a resolución reglameraria W. 00 10 del 15 de enero de 2001, advirtiendo que contra Øl no procede recufso a uno en la via gubernativa.

ALIX CARMENJZA CESPEDES DE VERGEL

Directora de evas Creaciones (C)

El anterior requerimiento fue notificado por fijación en (ista, de fecha

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