(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 February 2008 (07.02.2008)

PCT

(10) International Publication Number
WO 2008/016278 A1

(51) International Patent Classification:
C07D 307/68 (2006.01)

(21) International Application Number:
PCT/KR2007/003744

(22) International Filing Date: 3 August 2007 (03.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2006-0073717 4 August 2006 (04.08.2006) KR

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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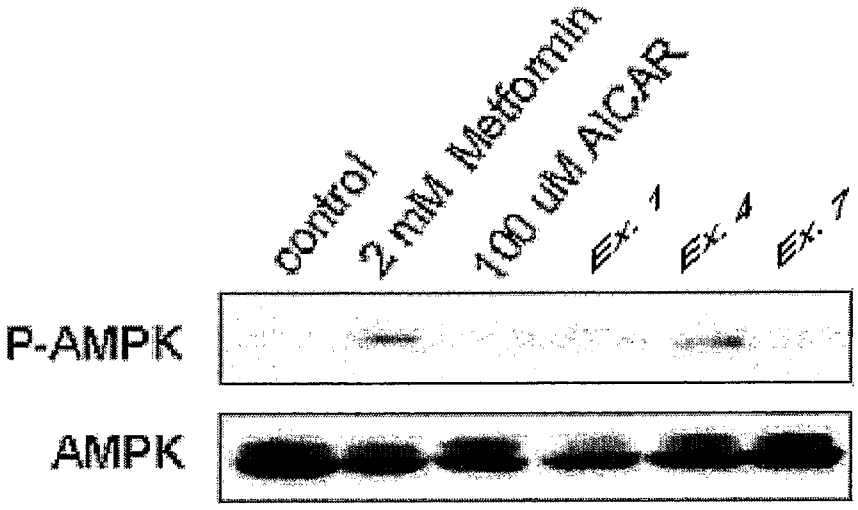
(54) Title: FURAN-2-CARBOXYLIC ACID DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF



(57) Abstract: This invention relates to a furan-2-carboxylic acid derivative capable of activating AMP-activated protein kinase (AMPK), which is useful for the prevention and treatment of metabolic syndromes including diabete, obesity, hyperlipidemia, hypercholesterolemia, fatty liver and steatohepatitis factors.

WO 2008/016278 A1

Published:
— *with international search report*

FURAN-2-CARBOXYLIC ACID DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF

Field of the Invention

The present invention relates to a novel furan-2-carboxylic acid derivative capable of activating AMP-activated protein kinase (AMPK), which is useful for the prevention and treatment of metabolic syndromes.

Background of the Invention

Metabolic syndrome refers to a cluster of conditions including diabete (e.g., Type 2 diabete), obesity, hyperlipidemia, hypercholesterolemia, fatty liver and steatohepatitis factors, which raises patients' risk of being afflicted by coronary atherosclerosis, myocardial infarction and stroke 3 times or higher than normal people. The occurrence of metabolic syndromes has gradually increased.

Metabolic syndromes are associated with AMPK, a metabolic regulator. AMPK is an energy sensor found in all eukaryotic cells, which is involved in metabolism regulation: it is activated in response to an increase in the ratio of AMP/ATP in cells due to cellular or body energy depletion and the phosphorylation of threonine 172 of AMPK.

The activated AMPK regulates glucose absorption in muscle and fat cells. It is reported that AMPK is activated by the treatment of an AMPK activator, e.g., AICAR (5-aminoimidazol-4-carboxamide-1-D-ribofuranoside) in muscle cells to increase the translocation of a glucose transport protein GLUT 4 to the cell membrane, thereby raising glucose absorption in the cells (*See* Edward O. Ojuka et al., *J Appl Physiol.*, 88(3), 1072-1075, 2000; and Honghai Zheng, *J Appl Physiol.*, 91, 1073-1083, 2001).

AMPK reduces fat synthesis through lowering the expression of a sterol regulatory element binding protein-1c (SREBP-1c) which controls the synthesis of acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), and it also inhibits the activity of ACC by directly phosphorylating ACC.

Thus, the activated AMPK reduces the formation of fat such as triglyceride or cholesterol in cells (*See Trends in Pharmacological Science*, 26, 69-76, 2005), which is beneficial in regulating much conditions as obesity and glucose metabolic disturbance of metabolic syndromes (*See* Neil et al., *Nature Drug discovery*, 3, 340, 2004).

As an AMPK-activating drug, metformin has been used for treating Type 2 diabete (*See Current drug targets*, 4, 685-696, 2005), but, it causes gastric-related side effects such as diarrhea.

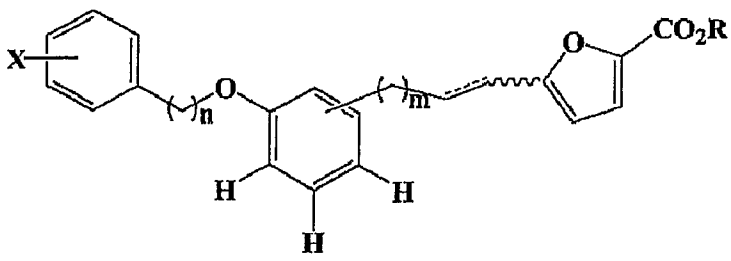
Summary of the Invention

Accordingly, it is a primary object of the present invention to provide a novel compound, which is capable of activating AMPK to inhibit the formation of fatty acid and glucose and facilitate glucose absorption in cells, with no side effects.

It is another object of the present application to provide a method for preparing said compound.

It is a further object of the present application to provide a pharmaceutical composition comprising said compound as an active ingredient, for preventing or treating metabolic syndromes such as insulin-independent diabetes mellitus, obesity and atherosclerosis.

In accordance with one aspect of the present invention, there is provided a furan-2-carboxylic acid derivative of formula (I) or a pharmaceutically acceptable salt or isomer thereof:



(I)

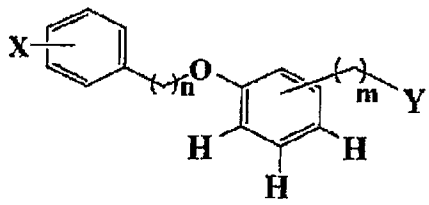
wherein,

X is hydrogen or halogen;

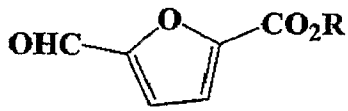
R is hydrogen or C_{1-4} alkyl;

n is an integer in the range of 1 to 3; and
m is an integer in the range of 0 to 2.

The present invention also provides a method for preparing the compound of formula (I), comprising bringing a compound of formula (II) to react with a compound of formula (III) in a solvent in the presence of a base:



(II)



(III)

wherein,

Y is triphenylphosphonium bromide, triphenylphosphonium iodide or benzothiazol-2-sulfonyl; and

X, R, n and m are the same as defined in formula (I).

The present invention further provides a pharmaceutical composition for preventing or treating metabolic syndromes, comprising the compound of formula (I), a pharmaceutically acceptable salt or isomer thereof as an active ingredient.

Brief Description of the Drawings

The above and other objects and features of the present invention will become apparent from the following description of the invention taken in conjunction with the accompanying FIG. 1 which shows Western blot analyze results obtained for the activation of AMPK by the inventive furan-2-carboxylic acid derivative.

Detailed Description of the Invention

The present invention provides a novel compound of formula (I), a pharmaceutically acceptable salt or isomer thereof as an AMPK activator.

Among the compounds of formula (I) of the present invention, preferred are those wherein R is hydrogen or methyl.

The pharmaceutically acceptable salt of the inventive compound of formula (I) includes a salt formed with an inorganic base such as an alkali metal (e.g., lithium, sodium and potassium), an alkaline earth metal (e.g., calcium and magnesium) or chromium, or an organic base such as amines (e.g., quaternary ammonium, dicyclohexyl amine and N-methyl-D-glucamine) or amino acids (e.g., arginine and lycine).

Also, the inventive compound of formula (I) may exist in an E- or Z-isomer due to the existence of a double-bond therein. Accordingly, the present invention includes an E- or Z-isomer of the compound of formula (I) and a racemic mixture thereof.

Exemplary compounds of formula (I) according to the present invention are as follows:

1) 5-(2-{3-[2-(4-fluorophenyl)ethoxy]phenyl}ethyl)furan-2-carboxylic acid;

2) (E)/(Z)-5-{3-[3-(4-fluorobenzyloxy)phenyl]propenyl}furan-2- carboxylic acid;

3) 5-{3-[3-(4-fluorobenzyloxy)phenyl]propyl}furan-2-carboxylic acid;

4) 5-(3-{3-[2-(4-fluorophenyl)ethoxy]phenyl}propyl)furan-2-carboxylic acid;

5) 5-{2-[3-(4-fluorobenzyloxy)phenyl]ethyl}furan-2-carboxylic acid;

6) 5-{2-[2-(4-fluorobenzyloxy)phenyl]ethyl}furan-2-carboxylic acid;

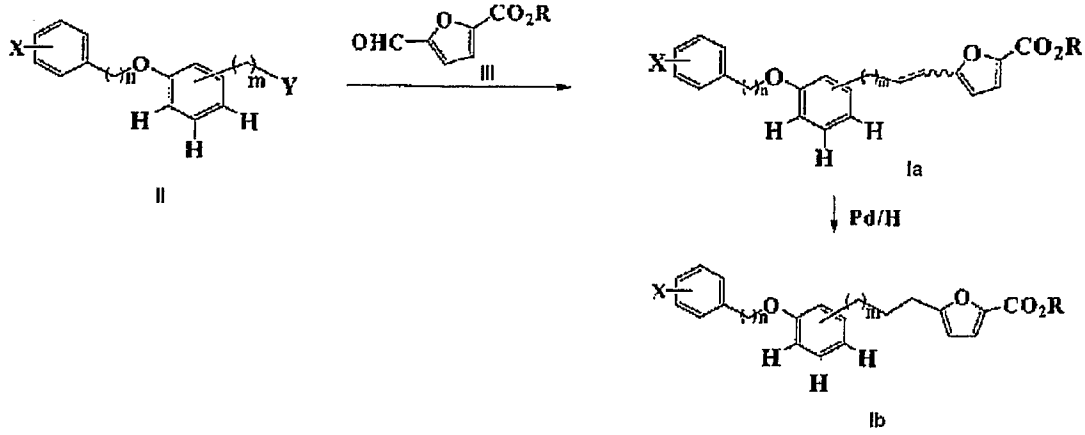
7) 5-(2-{2-[2-(4-fluorophenyl)ethoxy]phenyl}ethyl)furan-2-carboxylic acid;

8) (E)/(Z)-5-(2-{2-[2-(4-fluorophenyl)ethoxy]phenyl}vinyl)furan-2-carboxylic acid; and

9) (E)/(Z)-5-{2-[2-(4-fluorobenzyloxy)phenyl]vinyl}furan-2-carboxylic acid.

The inventive compound of formula (I) can be prepared by bringing a compound of formula (II) to react with a compound of formula (III) in a solvent in the presence of a base, as shown in Reaction Scheme 1.

Reaction Scheme 1



wherein, Y is triphenylphosphonium bromide, triphenylphosphonium iodide or benzothiazol-2-sulfonyl; and X, R, n and m are the same as defined in formula (I).

In Reaction Scheme 1, the compound of formula (Ia) containing one double bond may be prepared by conducting a conventional olefination reaction such as Wittig reaction and Julia olefination.

For the Wittig reaction, the compound of formula (II) and the compound of formula (III) are preferably used in an equivalent ratio of 1.0:0.8 to 1.0:1.5 in a solvent in the presence of a base.

Examples of the base which may be used in the Wittig reaction include, but are not limited to, potassium *t*-butoxide, sodium *t*-butoxide, sodium methoxide, sodium ethoxide, sodium hydride, *n*-butyl lithium, *t*-butyl lithium and a mixture thereof, preferably potassium *t*-butoxide. The base is suitably used in 1.0 to 3.0 equivalents based on the compound of formula (II).

For the Julia olefination, it is preferred that the compound of formula (II) wherein Y is benzothiazol-2-sulfonyl is allowed to react with the compound of formula (III) in an equivalent ratio of 1.0:0.8 to 1.0:1.5 in a solvent in the presence of a base.

Examples of the base which may be used in the Julia olefination reaction include, but are not limited to, sodium (bis-trimethylsilyl)amide, lithium (bis-trimethylsilyl)amide, potassium (bis-trimethylsilyl)amide, potassium *t*-butoxide, sodium *t*-butoxide, sodium methoxide, sodium ethoxide and a mixture thereof, preferably lithium (bis-trimethylsilyl)amide.

The base is suitably used in 1.0 to 3.0 equivalents based on the compound of formula (II).

The solvent which may be used in the Wittig or Julia olefination reaction is dimethyl formamide (DMF), tetrahydrofuran (THF), diethyl ether (Et_2O), dimethoxyethane (DME) or a mixture thereof, preferably dimethyl formamide.

The solvent is suitably used in an amount of 1.0 to 4.0 ㎖, preferably 2.5 to 3.0 ㎖ based on 1 mmol of the reactant, and the reaction is preferably conducted at a temperature ranging from -78℃ to the boiling point of the solvent used.

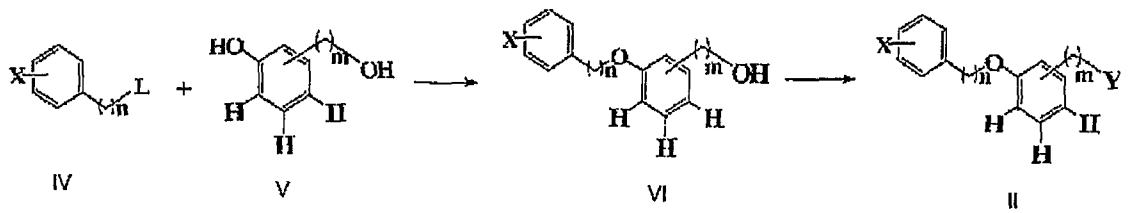
The compound of formula (Ia) thus prepared is a racemic mixture, whose isomer mix ratio can be confirmed by an H-NMR analysis, and if necessary, each isomer may be isolated therefrom according to a conventional separation method such as chromatography.

Further, the compound of formula (Ia) may be subjected to hydrogenation using a palladium/charcoal catalyst to obtain the compound of formula (Ib).

The furan carbaldehyde of formula (III) used as a starting material in Reaction Scheme 1 is preferably 5-formyl-furan-2-carboxylic acid or methyl 5-formyl-furan-2-carboxylate. The former is commercially available and the latter can be easily obtained from methylation of 5-formyl-furan-2-carboxylic acid.

The compound of formula (II) used as another starting material in Reaction Scheme 1 may be prepared as shown in Reaction Scheme 2.

Reaction Scheme 2



IV V VI II

wherein, X, R, n and m are the same as defined in formula (I), Y is the same as defined in Reaction Scheme 1, and L is hydroxyl group or a conventional leaving group such as halogen, alkylsulfonyl and arylsulfonyl.

In Reaction Scheme 2, the compound of formula (IV) is commercially

available or may be easily prepared by substituting a hydroxyl group-containing compound with a conventional leaving group in accordance with a conventional method. The compound of formula (V) is also commercially available or may be easily prepared by reducing an aldehyde or carboxylic acid group-containing compound in accordance with a conventional method. The compound of formula (IV) and the compound of formula (V) are preferable used in a molar ratio ranging from 1.0:1.0 to 1.5:1.0 in a solvent in the presence of a base for the alkylation or Mitsunobu reaction of phenoxy group, to obtain the compound of formula (VI). The solvent useful in said reaction is DMF, acetone or acetonitrile. The base useful in said reaction is potassium carbonate or cesium carbonate.

The compound of formula (VI) may be subjected to a substitution reaction with triphenylphosphonium bromide, triphenylphosphonium iodide or benzothiazol-2-sulfonyl, to obtain the compound of formula (II).

The compound of formula (II) wherein Y is triphenylphosphonium bromide or triphenylphosphonium iodide may be prepared by dissolving the compound of formula (VI) in dichloromethane or diethyl ether, adding 30% hydrogen bromide/acetic acid solution or N-iodosuccinimide thereto, mixing the resulting bromide or iodide compound with triphenylphosphine in dimethyl formamide and stirring the mixture at room temperature for 1 to 3 hours. The 30% hydrogen bromide/acetic acid solution is used in an amount of 1 to 10 equivalents (HBr base) relative to the compound of formula (VI); the N-iodosuccinimide, 1 to 5 equivalents; and triphenylphosphine, 1 to 3 equivalents.

Also, the compound of formula (II) wherein Y is benzothiazol-2-sulfonyl may be prepared by mixing the compound of formula (VI) with benzo[di]thiazol-2-thiol (1 to 3 equivalents), triphenylphosphine (1 to 3 equivalents) and diethyl azodicarboxylate (DEAD) (1 to 3 equivalents) in a solvent such as THF or DMF, followed by stirring at room temperature for 1 to 3 hours to substitute the hydroxyl group of the compound of formula (VI) with benzo[di]thiazol-2-thiol, and oxidizing the resultant using m-chloroperbenzoic acid (3 to 5 equivalents) and sodium bicarbonate (5 to 10 equivalents). The oxidation is suitably conducted at a temperature ranging from room temperature to the boiling point of the solvent used for 2

to 4 hours.

Furthermore, the present invention provides a pharmaceutical composition for preventing or treating metabolic syndromes, comprising the inventive compound of formula (I), a pharmaceutically acceptable salt or isomer thereof as an active ingredient.

The pharmaceutical composition of the present invention may be formulated in a form suitable for a desired use or purpose using conventional pharmaceutically acceptable additives such as excipient, filler, binder, lubricant, disintegrant, coating agent, emulsifier, suspending agent, solvent, stabilizing agent, penetration enhancer, and ointment.

The pharmaceutical composition may be orally administered in the form of tablets, coated tablets, capsules, powders, granules, solutions, emulsions or suspensions. Also, the pharmaceutical composition may be rectally administered in the form of suppositorys, topically or transdermally in the form of ointments, creams, gels or solutions, or parenterally in the form of an injection solutions.

The amount of the inventive compound of formula (I) actually administered will be determined depending on various factors including the age and condition of the patient and the chosen route of administration. The suitable daily dosage for oral administration of the compound of formula (I) is about 100 to 500 mg for an adult patient.

The present invention will be described in further detail with reference to Examples. However, it should be understood that the present is not restricted by the specific Examples.

Example 1: Preparation of 5-(2-{3-[2-(4-fluorophenyl)ethoxy]phenyl} ethyl)furan-2-carboxylic acid

(1-1) Preparation of 2-(4-fluorophenyl)-ethyl methanesulfonate

2-(4-Fluorophenyl)-ethanol (7.13 mmol) was dissolved in dichloromethane (10 ㎖), to which methanesulfonyl chloride (7.84 mmol) and triethylamine (10.7 mmol) were added. The mixture was slowly to

react at room temperature for 1 hour, the reaction mixture was washed with 1N hydrochloric acid, and water was added thereto. The resultant was extracted with dichloromethane and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under a reduced pressure, to obtain the title compound.

(1-2) Preparation of {3-[2-(4-fluorophenyl)-ethoxy]phenyl}methanol

The compound (1.76 mmol) obtained in Step (1-1) and 3-hydroxybenzyl alcohol (1.94 mmol) were dissolved in acetonitrile (10 mℓ), to which potassium carbonate (K_2CO_3) (3.62 mmol) was added. The mixture was refluxed for 12 hours, filtered, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1), to obtain the title compound (Yield 80%).

(1-3) Preparation of {3-[2-(4-fluorophenyl)-ethoxy]phenyl}bromomethane

The compound (1.22 mmol) obtained in Step (1-2) was dissolved in 2 mℓ of a 9:1 (v/v) mixture of hydrogen bromide (30% in AcOH) and dichloromethane, stirred at room temperature for 2 hours, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1), to obtain the title compound (Yield 59%).

(1-4) Preparation of (E)/(Z)-5(2-{3-[2-(4-fluorophenyl)-ethoxy]phenyl}vinyl)furan-2-carboxylic acid

The compound (1.30 mmol) obtained in Step (1-3) was dissolved in a solution of triphenyl phosphine (1.46 mmol) in DMF (10 mℓ) and the resulting solution was vigorously stirred at room temperature for 2 hours. 5-Formyl-furan-2-carboxylic acid (0.76 mmol) and potassium *t*-butoxide (5.49 mmol) was added thereto and stirred at room temperature for 5 hours. 10% hydrochloric acid solution was added to the resultant, followed by extracting with ethyl acetate. The organic layer was dried over Na_2SO_4 and

concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (2% dichloromethane/methanol), to obtain the title compound (Yield 45%).

(1-5) Preparation of 5(2-{3-[2-(4-fluorophenyl)-ethoxy]phenyl}ethyl)furan-2-carboxylic acid

The compound (0.17 mmol) obtained in Step (1-4) was dissolved in a 1:9 (v/v) mixture of methanol and dichloromethane, and 5% palladium/charcoal (Pd/C) catalyst was added thereto. The resulting mixture was saturated with hydrogen (hydrogen gas balloon), stirred for 3 hours, filtered, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (2% dichloromethane/methanol), to obtain the title compound (Yield 80%).

^{1}H-NMR (300MHz, $CDCl_3$) d 2.94 (m, 4H, CH_2CH_2), 3.05 (t, J = 6.9 Hz, 2H, $\underline{CH_2}CH_2O$), 4.14 (t, J = 6.9 Hz, 2H, $CH_2\underline{CH_2}O$), 6.12 (d, J = 3.3 Hz, 1H, fur), 6.75 (m, 4H, Ph), 7.00 (m, 2H, Ph), 7.21 (m, 3H, Ph).

Example 2: Preparation of (E)/(Z)-5-{3-[3-(4-fluorobenzyloxy)phenyl] propenyl}furan-2-carboxylic acid

(2-1) Preparation of 3-(2-hydroxyethyl)phenol

Boron trifluoride-diethyletherate (BF_3Et_2O) (4.27 mmol) was slowly added dropwise in a mixture of sodium borohydride (9.87 mmol) and 3-hydroxyphenyl acetic acid (6.58 mmol) dissolved in tetrahydrofuran (20 mℓ). The mixture was refluxed for 3 hours, and water was added thereto. The resultant was extracted with ethyl acetate, dried over anhydrous Mg_2SO_4, filtered, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography, to obtain the title compound (Yield 85%).

(2-2) Preparation of 2-[3-(4-fluorobenzyloxy)phenyl]ethanol

3-(2-Hydroxyethyl)phenol (8.06 mmol) obtained in Step (2-1) and potassium carbonate (8.70 mmol) were dissolved in DMF, and 1-(bromomethyl)-4-fluorobenzene (8.06 mmol) was added thereto, followed by stirring at room temperature for 12 hours. Water was added to the resultant, which was extracted with ethyl acetate, dried over anhydrous Mg_2SO_4, filtered, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography, to obtain the title compound (Yield 85%).

(2-3) Preparation of 2-[3-(4-fluorobenzyloxy)phenethylsulfonyl] benzo[d]thiazol

The compound (800 mg, 3.07 mmol) obtained in Step (2-2), benzo[di]thiazol-2-thiol (771 mg, 4.61 mmol) and triphenylphosphine (1.45mg, 553 mmol) were dissolved in THF (8 mℓ), to which diethylazodicarboxylic acid (DEAD) (0.68 mℓ, 4.61 mmol) was added. The mixture was stirred at room temperature for 1 hour, and water (26 mℓ) was added thereto. The resultant was extracted with ethyl acetate (80 mℓ X 2), washed with brine, dried over anhydrous Mg_2SO_4, filtered, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 20:1), to obtain 2-[3-(4-fluorobenzyloxy)phenethylthio]benzo[d]thiazol.

2-[3-(4-fluorobenzyloxy)phenethylthio]benzo[d]thiazol (1.7g, 4.15 mmol) obtained above, sodium bicarbonate (1.55g, 18.4 mmol) and *m*-chloroperoxybenzoic acid were dissolved in dichloromethane (20 mℓ), followed by stirring at room temperature for 4 hours. Sodium thiosulfite ($Na_2S_2O_4$) was added to the solution, which was extracted with ethyl acetate (170 mℓ X 2). The extract was washed with brine, dried over anhydrous Mg_2SO_4, filtered, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:1), to obtain 1.1 g of the title compound (Yield 85%).

(2-4) Preparation of methyl (E)/(Z)-5-{3-[3-(4-fluorobenzyloxy)phenyl]

propenyl}furan-2-carboxylate

The compound (1.03 mmol) obtained in Step (2-3) and methyl 5-formylfuran-2-carboxylic acid (0.97 mmol) were dissolved in DMF (10 mℓ), to which lithium (bis-trimethylsilyl)amide ($LiN(TMS)_2$) (1.24 mmol) was slowly added dropwise at -78℃. The mixture was warmed to room temperature and stirred for 2 hours. A saturated aqueous solution (3 mℓ) of ammonium chloride (NH_4Cl) was added thereto, and the resultant was extracted with water and ethyl acetate (2/1, 30 mℓ). The organic layer was washed with brine, dried over anhydrous Mg_2SO_4, filtered, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 20:1), to obtain 170 mg of the title compound (Yield 48%).

(2-5) Preparation of (E)/(Z)-5-{3-[3-(4-fluorobenzyloxy)phenyl]propenyl}furan-2-carboxylic acid

The compound (0.164 mmol) obtained in Step (2-4) was dissolved in water/THF (1/1, 2 mℓ), and lithium hydroxide (LiOH) (0.49 mmol) was added thereto, followed by stirring for 12 hours. The mixture was neutralized with 1N hydrochloric acid and extracted with water and ethyl acetate (1:1, 2 mℓ). The organic layer was washed with brine, dried over anhydrous Mg_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 20:1), to obtain 50 mg of the title compound (Yield 87%).

^{1}H-NMR (300MHz, $CDCl_3$) d (E) 3.63 (d, J = 8.4 Hz, 2H, allylic), 5.01 (s, 2H, CH_2), 6.26 (d, J = 15.9 Hz, 1H, CH), 6.31 (d, J = 3.5 Hz, 1H, fur), 6.62 (d, J = 15.9 Hz, 1H, CH), 7.03-7.42 (m, 9H, Ph, fur); MS *m/z* 352 (M+, 0.3), 185 (14), 109 (100).

Example 3: 5-{3-[3-(4-fluorobenzyloxy)phenyl]propyl}furan-2-carboxylic acid

(E)/(Z)-5-{3-[3-(4-fluorobenzyloxy)phenyl]propenyl}furan-2-carboxylic acid (0.16 mmol) obtained in Example 2 was hydrogenated according to the procedure of Step (1-5) of Example 1, to obtain the title compound (Yield 59%).

^{1}H-NMR (300MHz, $CDCl_3$) d 1.93(m, 2H , propyl) , 2.60(m, 4H , propyl), 4.96(s, 2H, CH_2), 6.03 (m, 1H, fur), 6.72-7.39 (m, 9H, Ph, fur) MS *m/z* 354 (M+, 2), 227 (4), 109 (100).

M.P.: 58.7℃ ~ 81.1℃

Example 4: 5-(3-{3-[2-(4-fluorophenyl)ethoxy]phenyl}propyl)furan-2-carboxylic acid

2-(4-Fluorophenyl)-ethyl methanesulfonate obtained in Step (1-1) of Example 1 and 3-hydroxyphenyl acetic acid were used as starting materials for conducting the procedures of Step (1-2) of Example 1, Step (2-3) (Yield 62%) and Step (2-4) (Yield 36%) of Example 2, Step (1-5) of Example 1 and Step (2-5) (Yield 62%) of Example 2, successively, to obtain the title compound.

^{1}H-NMR (300MHz, $CDCl_3$) d 1.94 (m, 2H, $CH_2\underline{CH_2}CH_3$), 2.61 (t, J = 7.4Hz, 2H, $\underline{CH_2}CH_2\underline{CH_2}$), 7.21 (t, J = 7.4Hz, 2H, $\underline{CH_2}CH_2\underline{CH_2}$), 3.05 (t, J = 6.9Hz, 2H, $OCH_2\underline{CH_2}$), 6.17 (m, 1H, fur), 6.80-7.26 (m, 9H, fur, Ph); MS *m/z* 368 (M+, 100), 229 (34), 103 (80)
M.P.: 131.6℃ ~ 132.5℃

Example 5: Preparation of 5-{2-[3-(4-fluorobenzyloxy)phenyl]ethyl} furan-2-carboxylic acid

(5-1) Preparation of [3-(4-fluorobenzyloxy)phenyl]methanol

The procedure of Step (2-2) of Example 2 was repeated except for using 3-hydroxybenzyl alcohol as a starting material, to obtain the title

compound.

(5-2) Preparation of [3-(4-fluorobenzyloxy)phenyl]iodomethane

Triphenylphosphine (9.52 mmol) was dissolved in 7 mℓ of dichloromethane, and N-iodosuccinimide (10.0 mmol) was slowly added dropwise thereto. The mixture was stirred for 5 minutes, to which a solution of the compound (3.40 mmol) obtained in Step (5-1) dissolved in dichloromethane (10 mℓ) was slowly added dropwise. After stirring for 3 hours, 5 mℓ of a saturated sodium hydrogen carbonate ($NaHCO_3$) solution was added to the resulting solution, which was extracted with water and dichloromethane (3:1, 20 mℓ), and washed with brine. The organic was dried over anhydrous Mg_2SO_4, filtered, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 20:1), to obtain the title compound (Yield 39%).

(5-3) Preparation of (E)/(Z)-5-{2-[3-(4-fluorobenzyloxy)phenyl]vinyl} furan-2-carboxylic acid

The procedure of Step (1-4) of Example 1 was repeated except for using the compound (0.28 mmol) obtained in Step (5-2), to obtain the title compound (Yield 52%).

(5-4) Preparation of 5-{2-[3-(4-fluorobenzyloxy)phenyl]ethyl}furan-2-carboxylic acid

The procedure of Step (1-5) of Example 1 was repeated except for using the compound (0.12 mmol) obtained in Step (5-3), to obtain the title compound (Yield 50%).

^{1}H-NMR (300MHz, $CDCl_3$) d 2.97 (m, 4H, CH_2CH_2), 4.99 (s, 2H, CH_2), 6.12 (d, J = 2.7 Hz, 1H, fur), 6.78-7.48 (m, 9H, fur, Ph); MS *m/z* 340 (M+, 2), 123 (22), 109 (100).

Example 6: Preparation of 5-{2-[2-(4-fluorobenzyloxy)phenyl]ethyl} furan-2-carboxylic acid

2-Hydroxybenzyl alcohol was used as a starting material for conducting the procedures of Step (2-2) of Example 2 and then Step (1-3) (Yield 62%), Step (1-4) (Yield 34%) and Step (1-5) (Yield 90%) of Example 1, successively, to obtain the title compound.

^{1}H-NMR (300MHz, $CDCl_3$) d 3.03 (s, 4H, CH_2CH_2), 5.04 (s, 2H, CH_2), 6.05 (m, 1H, fur), 6.90-7.40 (m, 9H, Ph, fur) MS *m/z* 340 (M+, 2), 109 (92), 59(100).

Example 7: Preparation of 5-(2-{2-[2-(4-fluorophenyl)ethoxy]phenyl} ethyl)furan-2-carboxylic acid

2-Hydroxybenzyl alcohol and 2-(4-fluorophenyl)-ethyl methanesulfonate obtained in Step (1-1) of Example 1 were used as starting materials for conducting the procedures of Step (1-2), Step (1-3) (Yield 89%), Step (1-4) (Yield 50%) and Step (1-5) (Yield 90%) of Example 1, successively, to obtain the title compound.

^{1}H-NMR (300MHz, $CDCl_3$) d 2.91 (m, 4H, CH_2CH_2), 3.08 (t, J = 6.3 Hz, 2H, CH2CH2O), 4.16 (t, J = 6.3 Hz, 2H, CH_2CH_2O), 6.06 (d, J = 3.3 Hz, 1H, fur), 6.81-7.27 (m, 9H, Ph, fur) MS *m/z* 354 (M+, 3), 72 (74), 59 (100).
M.P.: 58.9℃ ~ 81.1℃

Example 8: Preparation of (E/Z)-5-(2-{2-[2-(4-fluorophenyl)ethoxy] phenyl}vinyl)furan-2-carboxylic acid

2-Hydroxybenzyl alcohol and 2-(4-fluorophenyl)-ethyl methane sulfonate obtained in Step (1-1) of Example 1 were used as starting materials for conducting the procedures of Step (1-2), Step (1-3) (Yield 89%) and Step (1-4) (Yield 50%) of Example 1, successively, to obtain the title compound.

^{1}H-NMR (300MHz, $CDCl_3$) d 3.14 (t, J = 6.6 Hz, 2H, $\underline{CH_2}CH_2O$), 4.23 (t, J = 6.6 Hz, 2H, $CH_2\underline{CH_2}O$), 6.43 (d, J = 3.6 Hz, 1H, fur), 6.86-7.58 (m, 11H, CH, fur, Ph) MS *m/z* 352 (M+, 12), 123 (100), 103 (26).
M.P.: 168.4℃ ~ 169.0℃.

Example 9: Preparation of (E/Z)-5-{2-[2-(4-fluorobenzyloxy)phenyl] vinyl}furan-2-carboxylic acid

2-Hydroxybenzyl alcohol was used as a starting material for conducting the procedures of Step (2-2) of Example 2, Step (1-3) (Yield 62%) and Step (1-4) (Yield 34%) of Example 1, successively, to obtain the title compound.

^{1}H-NMR (300MHz, $CDCl_3$) d 4.99 (s, 0.9H, CH_2), 5.13 (s, 1.1H, CH2), 6.22 (m, 0.45H, fur), 6.45 (d, J = 18.9Hz, 0.5H, CH), 6.51 (m, 0.55H, fur), 6.65(d, J = 18.9 Hz, 0.5H, CH), 6.8-7.7 (m, 10H, Ph, CH, fur) MS *m/z* 338 (M+, 3), 229 (10), 109 (100).
M.P.: 80℃ ~ 83℃.

Experimental Example 1: AMPK activation Test

Hepatoma HepG2 cells obtained from the Korean Cell Line Bank were cultured in DMEM (Dulbecco's Modified Eagle Medium) at a concentration of 1×10^4 cells/well. The cells were treated with each of the test compounds of the present invention (100 μM), metformin (2 mM) (Sigma) and AICAR (100 μM) (Sigma) as comparative compounds, and the control group without test compound, which were incubated in a humidified atmosphere of 5% CO_2 at 37℃ for 24 hours. Then, the cells were treated with a Pro-Prep protein extract solution (INtRON Biotechnology). For Western blotting assay, the extracted protein was separated in SDS-PAGE and electrophoretically transferred to protein-fixing membranes, followed by incubation with the anti-AMPK antibody (Cell signaling) or anti-phospho-AMPK (pAMPK) antibody (Cell signaling). A light-sensitive film was used to detect immunoreactive bands and the intensity of bands was quantified. The AMPK

activity increase brought about by the test compound treatment was measured by dividing the intensity of pAMPK with the intensity of AMPK. The results are shown in Table 1, in the form of the extent of increase of the AMPK activity relative to AICAR (The measurement for AICAR is assigned to "1").

Table 1

Compound (100 μM)	Increase Extent
Ex. 1	2.6 times
Ex. 4	2.8 times
Ex. 7	1.9 times

Experimental Example 2: Effectiveness in inhibiting cholesterol synthesis

The effectiveness in inhibiting cholesterol synthesis of AMPK activated by the inventive compound was evaluated using Hepatoma HepG2 cells according to the following procedure (*See* Drake M. Amundson and Mingjie Zhou, *J Biochem Biophys Methods. Jan* 13; 38(1):43-52, 1999).

Hepatoma HepG2 cells obtained from the Korean Cell Line Bank were cultured in DMEM at a concentration of 1×10^4 cells /well. The cells were treated with each of the test compounds of the present invention (50 μM), and the control group without test compound, which were incubated in an atmosphere of 5% CO_2 at 37℃ for 24 hours. Then, the cells were treated with a cell lysis solution (0.1 M potassium phosphate, pH 7.4, 0.05 M NaCl, 5 mM cholic acid, 0.1% Triton® X-100) and reacted on ice for 10 minutes. The cell lysates were treated with 50 μℓ of a 2 times-concentrated reagent (300 μM Amplex Red reagent (Invitorgen), 2 U/mℓ HRP (Invitorgen), 2 U/mℓ cholesterol oxidase (Invitorgen), 0.2 U/mℓ cholesterol esterase (Invitorgen)) and reacted for 30 minutes at 37 ℃. The content of cholesterol formed in the cell lysates was measured using a fluorscence microscope and quantified. The results are shown in Table 2, in the form of the cholesterol content (%) relative to the control group (The measurement for control group is assigned to "100%").

Table 2

Compound (50 μM)	Cholesterol Content (%)	Compound (50 μM)	Cholesterol Content (%)
Ex. 1	80.6	Ex. 6	92.8
Ex. 2	76.7	Ex. 7	91.5
Ex. 3	50.3	Ex. 8	69.3
Ex. 4	57.2	Ex. 9	84.5
Ex. 5	83.8		

Experimental Example 3: Effectiveness in inhibiting triglyceride formation

Hepatoma HepG2 cells obtained from the Korean Cell Line Bank were cultured in DMEM at a concentration of 2×10^4 cells /well. The cells were treated with each of the test compounds of the present invention (50 μM), and the control group without test compound, which were incubated in an atmosphere of 5% CO_2 at 37℃ for 24 hours. Then, the cells were treated with a cell lysis solution (0.1 M potassium phosphate, pH 7.4, 0.05 M NaCl, 5 mM cholic acid, 0.1% Triton® X-100) and reacted on ice for 10 minutes. The cell lysates were treated with 50 ㎕ of a 2 times-concentrated reagent (300 μM Amplex Red reagent (Invitorgen), 2 U/㎖ lipase (ASAN Pharmaceutical Co., Ltd.), 0.75 U/㎖ glycerol kinase (ASAN Pharmaceutical Co., Ltd.), 151333 U/㎖ peroxidase (ASAN Pharmaceutical Co., Ltd.), 22.2 U/㎖ glyceric oxidase (ASAN Pharmaceutical Co., Ltd.) and reacted for 30 minutes at 37 ℃. The content of the triglyceride formed in the cell lysates was measured using a fluorscence microscope and quantified. The results are shown in Table 3, in the form of the triglyceride content (%) relative to the control group (The measurement for control group is assigned to "100%").

Table 3

Compound (50 μM)	Triglyceride Content (%)	Compound (50 μM)	Triglyceride Content (%)
Ex. 1	97.6	Ex. 6	95.7
Ex. 2	77.4	Ex. 7	83.2
Ex. 3	74.0	Ex. 8	56.8
Ex. 4	29.1	Ex. 9	84.7
Ex. 5	95.5		

Experimental Example 4: Effectiveness in inhibiting hepatic gluconeogenesis

Hepatoma HepG2 cells were cultured in DMEM at a concentration of 5×10^4 cells/well. The cells were treated with each of the test compounds of the present invention (50 μM), and the control group without test compound, which were incubated in an atmosphere of 5% CO_2 at 37℃ for 24 hours.

Then, 0.5 uCi 14C-lactate (Amersham Bioscience) and 10 mM L-lactate (Sigma) were treated in the incubation media, and the cells were incubated for 4 hours, followed by removing the media. The cells were washed with PBS, to which 0.1N sodium hydroxide was added and then placed at room temperature for 1 hour. After neutralizing with 1N hydrochloric acid, the content of glucose formed in the cells was measured using a liquid scintillation counter (Beckman counter) and quantified. The results are shown in Table 4, in the form of the glucose content (%) relative to the control group (The measurement for control group is assigned to "100%").

Table 4

Compound (50 μM)	Glucose Content (%)	Compound (50 μM)	Glucose Content (%)
Ex. 1	67.3	Ex. 6	74.8
Ex. 2	96.4	Ex. 7	49.0
Ex. 3	32.8	Ex. 8	42.9
Ex. 4	48.5	Ex. 9	66.8

Experimental Example 5: Effectiveness in muscular glucose utilization

C2C12 muscle myoblast cells obtained from the Korean Cell Line Bank were cultured in DMEM containing 10% bovine calf serum. When the cell density was 90%, the culture medium was replaced with DMEM containing 2% bovine calf serum and the cells were cultured for 3 days therein, followed by culturing in the same medium for 2 days, to induce muscle cell differentiation. The cells of 3×10^5/well were treated with each of the test compounds of the present invention (50 μM), and the control group without test compound, which were then treated with 1 μM insulin (Sigma) and incubated in an atmosphere of 5% CO_2 at 37℃.

Then, 1 uCi ^{3}H-didoxy-glucose (Amersham Bioscience) and 10 μM didoxy-glucose (Sigma) were treated in the incubation media at 37 ℃ for 15 minutes, followed by removing the media. The cells were washed with PBS, to which 0.1N sodium hydroxide was added. After neutralizing with 1N hydrochloric acid, the content of glucose absorbed in the cells was measured using a liquid scintillation counter (Beckman counter) and quantified. The results are shown in Table 5, in the form of glucose content (%) utilized in the muscular cell relative to the control group (The measurement for control group is assigned to "100%").

Table 5

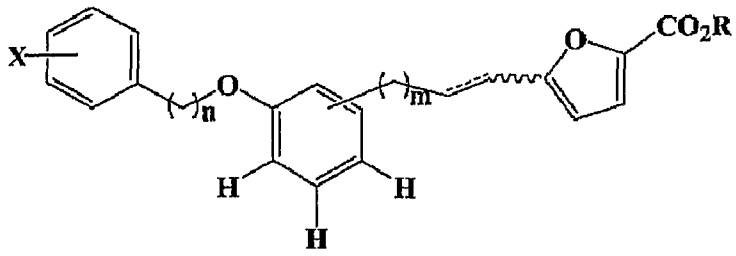
Compound (50 μM)	Glucose Content (%)	Compound (50 μM)	Glucose Content (%)
Ex. 1	187.2	Ex. 6	104.8
Ex. 4	314.7	Ex. 7	124.6

As shown in Tables 1 to 5, the inventive compound is effective in the activation of AMPK, which is useful for preventing or treating metabolic syndromes including diabete (e.g., Type 2 diabete), obesity, hyperlipidemia, hypercholesterolemia, fatty liver and steatohepatitis factors.

While the invention has been described with respect to the specific embodiments, it should be recognized that various modifications and changes may be made by those skilled in the art to the invention which also fall within the scope of the invention as defined as the appended claims.

What is claimed is:

1. A compound of formula (I) or a pharmaceutically acceptable salt or isomer thereof:

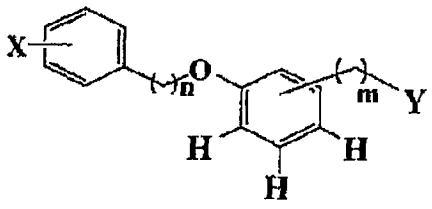


(I)

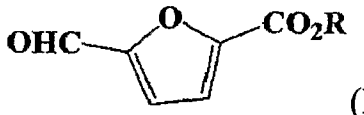
wherein,
X is hydrogen or halogen;
R is hydrogen or C_{1-4} alkyl;
n is an integer in the range of 1 to 3; and
m is an integer in the range of 0 to 2.

2. The compound of claim 1, which is selected from the group consisting of:
1) 5-(2-{3-[2-(4-fluorophenyl)ethoxy]phenyl}ethyl)furan-2-carboxylic acid;
2) (E)/(Z)-5-{3-[3-(4-fluorobenzyloxy)phenyl]propenyl}furan-2-carboxylic acid;
3) 5-{3-[3-(4-fluorobenzyloxy)phenyl]propyl}furan-2-carboxylic acid;
4) 5-(3-{3-[2-(4-fluorophenyl)ethoxy]phenyl}propyl)furan-2-carboxylic acid;
5) 5-{2-[3-(4-fluorobenzyloxy)phenyl]ethyl}furan-2-carboxylic acid;
6) 5-{2-[2-(4-fluorobenzyloxy)phenyl]ethyl}furan-2-carboxylic acid;
7) 5-(2-{2-[2-(4-fluorophenyl)ethoxy]phenyl}ethyl)furan-2-carboxylic acid;
8) (E)/(Z)-5-(2-{2-[2-(4-fluorophenyl)ethoxy]phenyl}vinyl)furan-2-carboxylic acid;
9) (E)/(Z)-5-{2-[2-(4-fluorobenzyloxy)phenyl]vinyl}furan-2-carboxylic acid; and
a pharmaceutically acceptable salt or isomer thereof.

3. A method for preparing the compound of formula (I) of claim 1, comprising bringing a compound of formula (II) to react with a compound of formula (III) in a solvent in the presence of a base:



(II)



(III)

wherein,

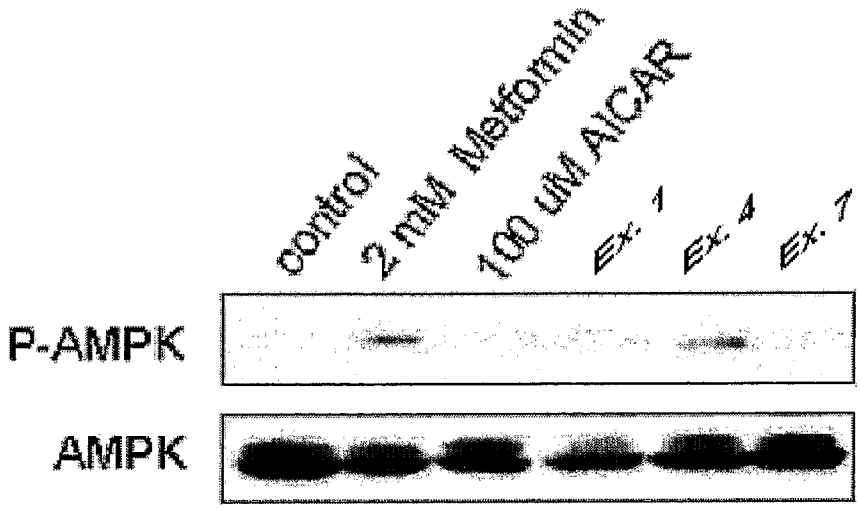
Y is triphenylphosphonium bromide, triphenylphosphonium iodide or benzothiazol-2-sulfonyl; and

X, R, n and m are the same as defined in claim 1.

4. A pharmaceutical composition for preventing or treating metabolic syndromes, comprising the compound of claim 1, a pharmaceutically acceptable salt or isomer thereof as an active ingredient.

5. The pharmaceutical composition of claim 4, wherein the metabolic syndrome is Type 2 diabete, obesity, hyperlipidemia, hypercholesterolemia, fatty liver or steatohepatitis factors.

FIG. 1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2007/003744

A. CLASSIFICATION OF SUBJECT MATTER

C07D 307/68(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 : as above

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

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

PUB MED

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/051937 A2 (ARENA Pharmaceutical, INC.) 09.06.2005 See abstract, claims 1-48	1-5
A	OJUKA, EDWARD O. et al, Increased expression of GULT-4 and hexokinase in rat epitrochlearis muscle exposed to AICAR in vitro, J. Appl. Physiol., 2000, 88(3), p 1072-1075 See abstract, discussion	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search	Date of mailing of the international search report
09 NOVEMBER 2007 (09.11.2007)	**09 NOVEMBER 2007 (09.11.2007)**
Name and mailing address of the ISA/KR Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer CHOI, Won Chul Telephone No. 82-42-481-5608

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2007/003744

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO2005051937 A2	09.06.2005	EP1701947 A2	20.09.2006
		US20070093545 A1	26.04.2007