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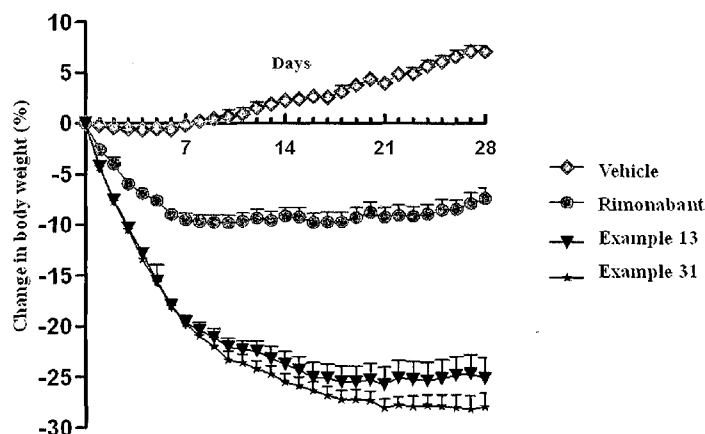
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(54) Title: 1,5-DIARYL-4,5-DIHYDRO-1H-PYRAZOLE-3-CARBOXAMIDINE DERIVATIVES AS CANNABINOID CB1 RECEPTOR ANTAGONIST, METHOD FOR PREPARING SAME, AND PHARMACEUTICAL COMPOSITION COMPRISING SAME

FIG. 1



(57) Abstract: The present invention relates to a novel 1,5-diaryl-4,5-dihydro-1H-pyrazole-3-carboxamidine compound or a pharmaceutically acceptable salt thereof having inverse agonist activity or antagonistic activity against a cannabinoid CB1 receptor, a method for preparing the same, and a pharmaceutical composition comprising the same. The inventive compound shows cannabinoid CB1 receptor antagonistic activity with a high selectivity for the peripheral tissues, thereby exhibiting anti-obesity effects, and thus is useful in the prevention or treatment of obesity or obesity-related metabolic diseases.

DESCRIPTION

1,5-DIARYL-4,5-DIHYDRO-1H-PYRAZOLE-3-CARBOXAMIDINE DERIVATIVES AS CANNABINOID CB1 RECEPTOR ANTAGONIST, METHOD FOR PREPARING SAME, AND PHARMACEUTICAL COMPOSITION COMPRISING SAME

FIELD OF THE INVENTION

The present invention relates to a novel 1,5-diaryl-4,5-dihydro-1H-pyrazole-3-carboxamidine compound or a pharmaceutically acceptable salt thereof having inverse agonist activity or antagonistic activity against a cannabinoid CB1 receptor, a method for preparing the same, and a pharmaceutical composition comprising the same.

BACKGROUND OF THE INVENTION

Previous *in vitro* and *in vivo* studies have indicated that antagonists with inverse agonist activity or antagonist activity against a cannabinoid CB1 receptor can affect energy homeostasis via central and peripheral mechanisms of action.

Based on clinical trials, it was proven that rimonabant (SR141716A, Pfizer), a selective CB1 receptor antagonist, was effectively in reducing the weights of obese patients and thereby alleviating conditions such as metabolic syndromes including obesity-related cardiovascular disorders, diabetes, etc. Since then CB1 receptors have become a topic of interest for the treatment of obesity and obesity-related metabolic diseases.

Besides rimonabant, a number of CB1 receptors including otenabant (CP-945598, Pfizer), surinabant (Sanofi-Aventis), ibipinabant (SLV 319, Solvay Pharmaceuticals), Taranabant (MK-0364, Merck), drinabant (AVE1625, Aventis Pharmaceuticals), and the like were tested on clinical trials or available on the market. However, these drugs were accompanied by CNS-related adverse side effects such as depression, anxiety, dizziness, insomnia, and the

like, as well as other adverse effects related to gastrointestinal disorders including nausea, diarrhea, and the like, and thus, these drugs were withdrawn from the market and their development have been discontinued. The main cause for such psychiatric side effects caused by the administration of the conventional CB1 receptor antagonists is due to the fact that these drugs are distributed largely in the brain tissue.

Considering the fact that there is a lack of effective drugs for the treatment of obesity as for its severity, a development of an effective CB1 receptor antagonist having its preexisting problems fixed has become a topic of interest.

Accordingly, the present inventors have endeavored to manufacture a CB1 receptor antagonist which are selective for the peripheral tissues, rather than the brain tissue, so as to reduce the adverse side effects of conventional drugs, and have accomplished the present invention by discovering a novel 1,5-diaryl-4,5-dihydro-1*H*-pyrazole-3-carboxamidine derivative having antagonistic activity against a CB1 receptor with a high selectivity for the peripheral tissues.

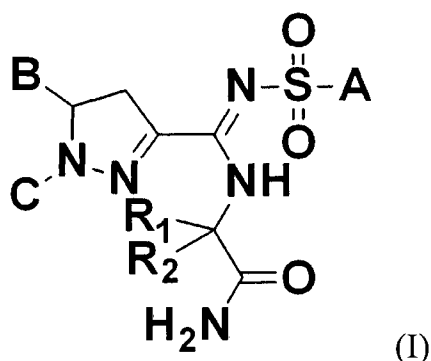
SUMMARY OF THE INVENTION

Therefore, it is an object of the present invention to provide a novel 1,5-diaryl-4,5-dihydro-1*H*-pyrazole-3-carboxamidine derivative compound having cannabinoid receptor antagonistic activity with a high selectivity for the peripheral tissues.

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

It is another object of the present invention to provide a pharmaceutical composition comprising the compound.

In accordance with one object of the present invention, there is provided a compound represented by formula (I) or a pharmaceutically acceptable salt thereof:



wherein A is selected from the group consisting of C₁₋₇alkyl, C₆₋₁₀aryl, C₄₋₁₀heteroaryl, C₃₋₆cycloalkyl, and C₃₋₆heterocycloalkyl, and optionally, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, linear or branched C₁₋₆alkyl, linear or branched C₁₋₆alkoxy, halo, CN, OH, NO₂, -(C=O)-R', SH, SR', SOR', SO₂R', NH₂, NHR', NR'R'', -(C=O)-NH₂, -(C=O)-NHR', and -(C=O)-NR'R'';

B and C are each independently C₆₋₁₀aryl or C₄₋₁₀heteroaryl, and optionally, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, linear or branched C₁₋₆alkyl, linear or branched C₁₋₆alkoxy, halo, dihalo, trihalo, CN, OH, NO₂, -(C=O)-R', SH, SR', SOR', SO₂R', NH₂, NHR', NR'R'', -(C=O)-NH₂, -(C=O)-NHR', and -(C=O)-NR'R'';

R' and R'' are each independently linear or branched C₁₋₆alkyl; and

R₁ and R₂ are each independently hydrogen or C₁₋₆alkyl, and optionally, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, linear or branched C₁₋₆alkyl, linear or branched C₁₋₆alkoxy, halo, CN, OH, NO₂, and SH.

In accordance with another object of the present invention, there is provided a method for preparing the compound or a pharmaceutically acceptable salt thereof.

In accordance with another object of the present invention, there is provided a pharmaceutical composition for the prevention or treatment of obesity or an obesity-related metabolic disease, comprising the compound or a pharmaceutically acceptable salt thereof as an active ingredient.

The compound in accordance with the present invention having inverse agonist activity or antagonistic activity against a cannabinoid CB1 receptor with a high selectivity for the peripheral tissues exhibits anti-obesity effects, and thus can be useful in the prevention or treatment of obesity or obesity-related metabolic diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing a weight reduction effect resulting from administration of the compounds prepared in Examples 13 and 31 of the present invention in diet-induced obesity (DIO) mice.

Fig. 2 is a graph showing a food intake suppression effect resulting from administration of the compounds prepared in Examples 13 and 31 of the present invention in DIO mice.

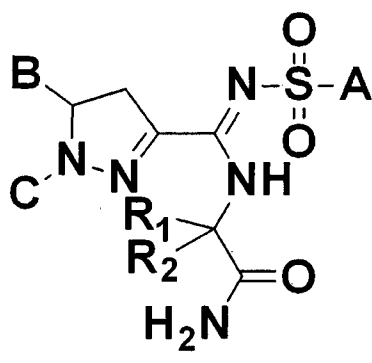
Fig. 3 is a graph demonstrating improved insulin and leptin resistance resulting from administration of the compounds prepared in Examples 13 and 31 of the present invention.

Fig. 4 is a graph showing reduced translocation of the drug into the brain tissue resulting from administration of the compounds prepared in Examples 13 and 31 of the present invention.

Fig. 5 is a graph showing the time spent at open arms and the total distance travelled resulting from administration of the compounds prepared in Examples 13 and 31 of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound represented by formula (I) or a pharmaceutically acceptable salt thereof:



wherein A is selected from the group consisting of C₁₋₇alkyl, C₆₋₁₀aryl, C₄₋₁₀heteroaryl, C₃₋₆cycloalkyl, and C₃₋₆heterocycloalkyl, and optionally, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, linear or branched C₁₋₆alkyl, linear or branched C₁₋₆alkoxy, halo, CN, OH, NO₂, -(C=O)-R', SH, SR', SOR', SO₂R', NH₂, NHR', NR'R'', -(C=O)-NH₂, -(C=O)-NHR', and -(C=O)-NR'R'';

B and C are each independently C₆₋₁₀aryl or C₄₋₁₀heteroaryl, and optionally, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, linear or branched C₁₋₆alkyl, linear or branched C₁₋₆alkoxy, halo, dihalo, trihalo, CN, OH, NO₂, -(C=O)-R', SH, SR', SOR', SO₂R', NH₂, NHR', NR'R'', -(C=O)-NH₂, -(C=O)-NHR', and -(C=O)-NR'R'';

R' and R'' are each independently linear or branched C₁₋₆alkyl; and

R₁ and R₂ are each independently hydrogen or C₁₋₆alkyl, and optionally, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, linear or branched C₁₋₆alkyl, linear or branched C₁₋₆alkoxy, halo, CN, OH, NO₂, and SH.

Preferably, A is C₆₋₁₀aryl or C₄₋₁₀heteroaryl, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, halo, dihalo, and C₁₋₆alkyl; B is C₆₋₁₀aryl or C₄₋₁₀heteroaryl, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen and CN; C is C₆₋₁₀aryl which is optionally substituted with halo; and R₁ and R₂ are each independently hydrogen, linear or branched C₁₋₆alkyl, or linear or branched C₁₋₆alkyl substituted with OH.

In substituents A to C, the C₆₋₁₀aryl and C₄₋₁₀heteroaryl is selected from the group consisting of phenyl, furanyl, benzofuranyl, thienyl, benzothienyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridiziny.

More preferably, A is 4-chlorophenyl, 4,4-difluoropiperidinyl or 4-methylpiperazinyl; B is phenyl, 4-cyanophenyl or 2-thiophenyl; C is 4-chlorophenyl; R₁ is hydrogen or methyl; R₂ is methyl, hydroxymethyl, isopropyl or isobutyl.

More preferable compounds according to the compound of formula (I) of the present invention are listed below:

1) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

2) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-methylpiperazin-1-yl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

3) (2*S*)-2-(*N'*-((4-chlorophenyl)-1-(4-methoxyphenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

4) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4,4-difluoropiperidin-1-yl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

5) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-cyanophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

6) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(4-cyanophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

7) (2*S*)-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-thiophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

8) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)acetamide;

9) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)propanamide;

10) (R,Z)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-2-methylpropanamide;

11) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-4-methylpentanamide;

12) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-hydroxypropanamide;

5 13) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

14) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3,3-dimethylbutanamide;

10 15) (2*S*)-2-((*Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(2,4-difluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

16) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((6-chloropyridin-3-yl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

15 17) (*S*)-2-((*R,Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(2,4-difluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

18) (*S*)-2-((*R,Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

19) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-fluorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

20 20) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((6-chloropyridin-3-yl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

21) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-furanyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

22) 2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-thiophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

23) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(5-methyl-2-furanyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

30 24) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(5-methyl-2-furanyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

25) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(5-

methyl-2-thiophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide

26) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-pyridinyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

27) 2-(*R,Z*)-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

28) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

29) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(furan-2-yl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3,3-dimethylbutanamide;

30) (2*S*)-2-((*Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(2,4-dichlorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

31) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

32) (*S*)-2-((*R,Z*)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide; and

33) (*S*)-2-((*Z*)-1-(4-chlorophenyl)-*N'*-((6-chloropyridin-3-yl)sulfonyl)-5-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide.

The term “halo,” as used herein, refers to fluoro, bromo, chloro or iodo.

The term “alkyl,” as used herein, refers to linear or branched saturated hydrocarbon chain radicals having 1 to 7 carbon atoms. Particular examples thereof may include, but not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, *n*-pentyl, isopentyl, and hexyl.

The term “alkoxy,” as used herein, refers to -OR_a groups, wherein R_a is an alkyl as defined above. Particular examples thereof may include, but not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, and *t*-butoxy.

The term "aryl," as used herein, refers not only to fused groups such as naphthyl and phenanthrenyl, but also to monocyclic or bicyclic aromatic rings such as phenyl, substituted phenyl, etc. The said aryl group is optionally substituted with one or more substituents, *i.e.*, halogen, alkyl, alkoxy, hydroxyl, 5 carboxy, carbamoyl, alkyloxycarbonyl, nitro, trifluoromethyl, amino, cycloalkyl, cyano, alkyl S(O)_n (*n* = 1, 2, 3) or thiol, but not limited thereto.

The term "heteroaryl," as used herein, refers to 5- to 10-membered monocyclic heteroaryl groups such as furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isooxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 10 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, cinnolinyl, phtheridinyl, purinyl, and 6,7-dihydro-5*H*-[1]pyridinyl; or bicyclic heteroaryl groups such as 5,6,7,8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzo[*b*]thiophenyl, 15 benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofurayl, isobenzofuranyl, isoindolyl, indolyl, indolizynyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalynyl, quinazolinyl, pyrazolo[3,4-*b*]pyridinyl, and benzoxazinyl.

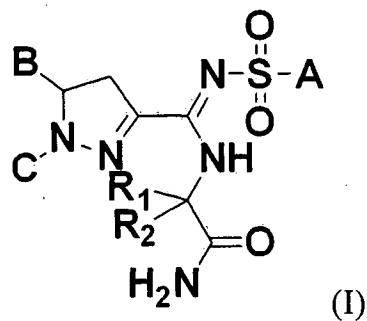
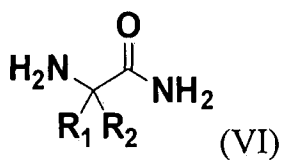
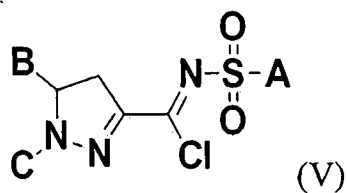
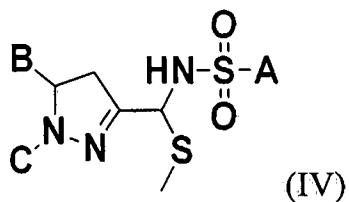
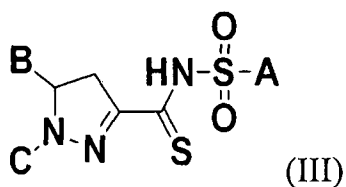
A "pharmaceutically acceptable salt" of the compound of formula (I) 20 may be prepared by conventional methods well-known in the art, for example, an acid-addition salt of inorganic acid such as hydrochloric acid, bromic acid, sulfuric acid, sodium bisulfate, phosphoric acid, nitric acid, carbonic acid, and the like; organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, succinic acid, benzoic acid, citric acid, maleic acid, malonic acid, tartaric acid, 25 gluconic acid, lactic acid, gestisic acid, fumaric acid, lactobionic acid, salicylic acid, acetylsalicylic acid (aspirin) and the like; amino acid such as glycine, alanine, vanillin, isoleucine, serine, cysteine, cystine, aspartic acid, glutamine, lysine, arginine, tyrosine, proline, and the like; and sulfonic acid such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, 30 toluenesulfonic acid, and the like; or a metallic salt formed by the reaction with an alkali metal such as sodium, potassium, and the like; or a salt formed with an ammonium ion.

Further, the present invention provides a method for preparing the compound of formula (I).

The compound of formula (I) according to the present invention may be prepared by a method comprising the steps of: 1) allowing a compound of formula (II) to react with phosphorus pentasulfide (P_2S_5) or Lawesson's reagent in a solvent selected from the group consisting of toluene, xylene, benzene, chlorobenzene, and a mixture thereof to obtain a compound of formula (III); 2) allowing the compound of formula (III) to react with methyl iodide in a solvent selected from the group consisting of acetone, acetonitrile, tetrahydrofuran, dichloromethane, chloroform, and a mixture thereof in the presence of a base such as triethylamine to obtain a compound of formula (IV); and 3) allowing the compound of formula (IV) to react with a compound of formula (VI) in a solvent selected from the group consisting of acetone, acetonitrile, tetrahydrofuran, dichloromethane, chloroform, and a mixture thereof in the presence of a base to obtain the compound of formula (I).

Alternatively, the compound of formula (I) according to the present invention may be prepared by a method comprising the steps of: a step of allowing the compound of formula (II) to react with chloride such as phosphorus pentachloride (PCl_5) in a solvent selected from toluene, xylene, benzene, chlorobenzene, and a mixture thereof to obtain a compound of formula (V); and a step of allowing the compound of formula (V) thus obtained to react with a compound of formula (VI) in a solvent selected from the group consisting of acetone, acetonitrile, tetrahydrofuran, dichloromethane, chloroform, and a mixture thereof in the presence of a base to obtain the compound of formula (I).

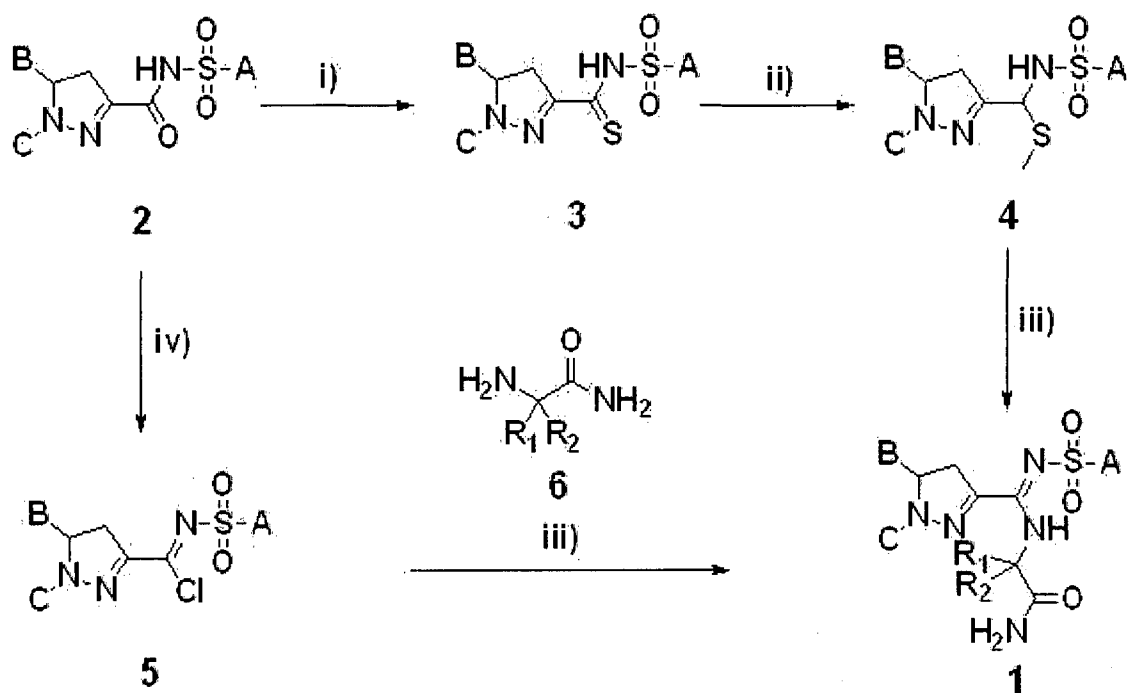




wherein A, B, C, R₁ and R₂ have the same meanings as defined in the compound of formula (I) above.

The method for preparing the compound of formula (I) may be prepared according to the procedure shown in Reaction Scheme 1 below:

[Reaction Scheme 1]



wherein A, B, C, R_1 and R_2 have the same meanings as defined in the compound of formula (I) above.

In accordance with an embodiment of the present invention, the above reaction processes are exemplified as below.

The compound of formula (II) which is used as a starting material may be prepared by halogenating 4,5-dihydro-1H-pyrazole-3-carboxylate and then reacting with a sulfonamide compound in the presence of a base, using the method disclosed in References [*J. Med. Chem.* 2007, 50, p5951-5966; *Bioorganic & Medicinal Chemistry Letters*, 2010, 20(5), p1752-1757; and WO 2005074920] or any similar method thereof. According to one embodiment of the present invention, the sulfonamide compound is, for example, 4-chlorobenzenesulfonamide, 4,4-difluoropiperidin-1-sulfonamide, 4-methylpiperazine-1-sulfonamide, and the like.

The reaction processes are explained in more detail with reference to Reaction Scheme 1. In step 1), the compound of formula (III) is obtained by introducing sulfur to the compound of formula (II). The compound of formula (II) is subjected to a reaction with P_2S_5 or Lawesson's reagent in an organic

solvent, for example, such as toluene by heating or heating under reflux conditions for 6 to 12 hours.

In step 2), the compound of formula (IV) is obtained by introducing methyl reaction group to the compound of formula (III). The compound of formula (III) is subjected to a reaction with methyl iodide in an organic solvent, for example, such as acetone in the presence of a base such as triethylamine or potassium carbonate under room temperature or heating conditions for 1 to 5 hours.

In step 3), the compound of formula (I) is obtained by allowing the compound of formula (IV) with an amide derivative such as the compound of formula (VI) in an organic solvent, for example, such as tetrahydrofuran in the presence of a base such as triethylamine or potassium carbonate under room temperature or heating conditions for 3 to 12 hours.

Alternatively, the compound of formula (I) may be prepared by the following method. The compound of formula (II) is subjected to a reaction in an organic solvent, for example, such as chlorobenzene in the presence of PCl_5 by heating or heating under reflux conditions for 1 to 3 hours to obtain the compound of formula (V), changing the reaction temperature to a lower or room temperature, and then subjecting the compound thus formed to a reaction with an amide derivative such as the compound of formula (VI) in an organic solvent, for example, such as dichloromethane in the presence of a base such as triethylamine or potassium carbonate at a room temperature or heating conditions for 1 to 3 hours.

Meanwhile, the present invention also provides a pharmaceutical composition for the prevention or treatment of obesity and an obesity-related metabolic disease, comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

The obesity-related metabolic disease may be selected from the group consisting of Type 2 Diabetes, chronic hepatic diseases, angina, hypertension, congestive heart failure, and hyperlipidemia, but not limited thereto.

The pharmaceutical composition comprising the compound of the

present invention or a pharmaceutically acceptable salt thereof may be formulated in the form of oral or parenteral formulations according to conventional methods, and may contain a filler, an extender, a binder, a wetting agent, a disintegrant, a diluent such as a surfactant, or an excipient.

5 A solid formulation for oral administration may be prepared by mixing at least one benzamide derivative of the present invention with at least one excipient, for example, starch, calcium carbonate, sucrose, lactose or gelatin. Also, besides a simple excipient, a lubricant such as magnesium stearate or talc may be used.

10 A liquid formulation for oral administration may be prepared in the form of a suspension, a liquid preparation, an emulsion or a syrup. A simple diluent such as water, liquid paraffin, and the like, as well as other excipients including a wetting agent, a sweetening agent, a flavoring agent or a preservative, may be employed.

15 A formulation for parenteral administration may be prepared in the form of a sterilized aqueous solution, a non-aqueous solvent, a solvent suspension, an emulsion, a lyophilized formulation or a suppository. The non-aqueous solvent or solvent suspension may contain propylene glycol, polyethylene glycol or vegetable oil such as olive oil, injectable ester such as ethylolate. In the
20 suppository, a base material may include Witepsol, macrogol, Tween 61, cacao butter, laurin butter, glycerol or gelatin.

Additionally, a proposed daily dose of the pharmaceutical composition of the present invention to a human (of approximately 70 kg body weight) may be in the range of 0.1 to 1,000 mg/day, preferably 1 to 500 mg/day, in a single
25 dose or in divided doses per day. It is understood that the daily dose should be determined in light of various relevant factors including the condition, age, body weight and sex of the subject to be treated, administration route, and disease severity.

30 Further, the present invention provides a use of the compound of formula (I) for the manufacture of a medicament for preventing or treating obesity or an obesity-related metabolic disease.

Furthermore, the present invention provides a method for preventing or

treating obesity or an obesity-related metabolic disease, comprising administering to a mammal an effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

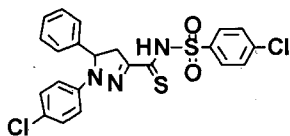
[Examples]

The following Examples are provided to illustrate preferred embodiments of the present invention, and are not intended to limit the scope of the present invention.

Example 1: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide

<Example 1A>

Step 1) Preparation of 1-(4-chlorophenyl)-*N*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carbothioamide



The compound of formula (II), 1-(4-chlorophenyl)-*N*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboxamide, was prepared according to the method disclosed in References [*J. Med. Chem.* 2007, 50, p5951-5966; *Bioorganic & Medicinal Chemistry Letters*, 2010, 20(5), p1752-1757; and WO 2005/074920] or a similar method thereto. The compound of formula (II) (1.0 g, 2.1 mmol) and phosphorus pentasulfide (P₂S₅, 0.94 g, 4.2 mmol) were added to toluene (20 mL), and stirred at 120°C for 6 hours. Substances which were undissolved in the organic solvent were filtered out using a Celite. The resulting filtrate was washed with ethyl acetate, and the organic layer was concentrated under reduced pressure. The concentrated residues were dissolved in ethyl acetate, and washed with a saturated aqueous solution of sodium hydrogen carbonate and brine. The solid residue thus

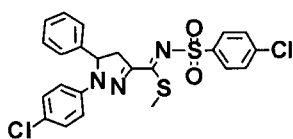
obtained was crystallized by using ethanol to obtain the title compound (0.7 g).

¹H-NMR (300 MHz, CDCl₃) δ 8.05 (d, 2H), 7.50 (d, 2H), 7.4-7.1 (m, 5H) 7.02 (d, 2H), 5.40 (dd, 1H), 3.77 (dd, 1H), 3.24 (dd, 1H).

MS (ESI⁺): *m/z* = 490.0 [M+H]⁺.

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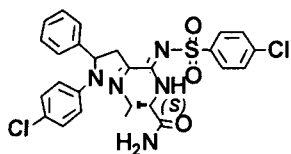
Step 2): Preparation of methyl 1-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carbimidothiolate



10 The compound obtained in Step 1) (240 mg, 0.5 mmol) was dissolved in acetone, and added with methyl iodide (70 mg, 0.5 mmol) and triethylamine (100 mg, 1.0 mmol). The mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure. The concentrated residue thus obtained was dissolved in ethyl acetate, and washed with 1 N aqueous
15 hydrochloric acid solution and brine. The solid residue thus obtained was crystallized by using methanol to obtain the title compound (150 mg).

¹H-NMR (300 MHz, CDCl₃) δ 7.93 (d, 2H), 7.47 (d, 2H), 7.4-7.1 (m, 5H) 7.05 (d, 2H), 5.50 (dd, 1H), 4.16 (dd, 1H), 3.44 (dd, 1H), 2.38 (s, 3H).

20 Step 3): Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide



25 The compound obtained in Step 2) (100 mg, 0.2 mmol) was dissolved in tetrahydrofuran (2 mL), and then *L*-valinamide (34 mg, 0.22 mmol) and triethylamine (44 mg, 0.44 mmol) were sequentially added thereto. The

reaction mixture was heated to 80°C and stirred for 6 hours. The organic layer thus formed was washed with water, 1 N aqueous hydrochloric acid solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue thus obtained was purified by preparative layer chromatography (silica gel 60 F₂₅₄, 1mm) to obtain the title compound as a yellow compound (30 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 9.10 (d, 1H), 7.85 (d, 2H), 7.77 (d, 2H), 7.4~7.1 (m, 7H) 6.86 (d, 1H), 5.44 (dd, 1H), 4.33 (m, 1H). 4.0 (dd, 1H), 3.13 (dd, 1H), 2.09 (m, 1H), 1.04~0.88 (m, 6H).

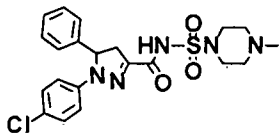
MS (ESI⁺): *m/z* = 572.1 [M+H]⁺.

<Example 1B>

(*R*)-1-(4-Chlorophenyl)-*N*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboxamide was prepared according to the method disclosed in References [*J. Med. Chem.* 2007, 50, p5951-5966; *Bioorganic & Medicinal Chemistry Letters*, 2010, 20(5), p1752-1757; and WO 2005/074920] or a similar method thereto. The compound thus prepared (189 mg, 0.4 mmol) and phosphorus pentachloride (214 mg, 0.45 mmol) were added to chlorobenzene, and stirred at 130°C for 1 hour. Upon completion of the reaction, the reaction solution was concentrated.

The concentrated compound was added with a solvent, dichloromethane, and then cooled down to 0°C under an atmosphere of nitrogen. Subsequently, *L*-valinamide (62.9 mg, 0.54 mmol) and triethylamine (114 mg, 1.13 mmol) were sequentially added thereto. The reaction mixture was slowly heated to room temperature while stirring for 1.5 hours. Upon completion of the reaction, the mixture was extracted using dichloromethane and water, and the organic layer was dried over anhydrous sodium sulfate and concentrated. The compound thus obtained was purified by preparative layer chromatography (silica gel 60 F₂₅₄, 1mm) to obtain the title compound as a yellow compound (18 mg).

Example 2: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N*'-((4-methylpiperazin-1-yl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-

carboximidamido)-3-methylbutanamideStep 1) Preparation of 1-(4-chlorophenyl)-N-((4-methylpiperazin-1-yl)sulfonyl)-5-phenyl-4,5-dihydro-1H-pyrazole-3-carboxamide

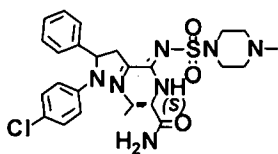
1-(4-chlorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid was prepared according to the method disclosed in References [*J. Med. Chem.* 2007, 50, p5951-5966; *Bioorganic & Medicinal Chemistry Letters*, 2010, 20(5), p1752-1757; and WO 2005/074920] or a similar method thereto. The compound thus prepared (1.0 g, 3.3 mmol) was added to toluene (20 mL) and added with thionyl chloride (1.6 g, 13.3 mmol). The mixture was heated to 120°C and it was refluxed for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue thus obtained was dissolved in acetonitrile (20 mL) to obtain a solution (Solution A).

Sodium hydroxide (0.33 g, 8.3 mmol) was dissolved in water (0.33 mL), which was added to acetonitrile (20 mL). Then 4-methylpiperazine sulfonamide (0.71 g, 4.0 mmol) was added thereto. The mixture thus obtained was slowly added with Solution A (20 mL), followed by stirring for 1 hour. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure. The concentrated residue thus obtained was added with ethyl acetate, and then washed with 1 N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate, and brine. The solid residue thus obtained was crystallized by using ethanol to obtain the title compound (0.52 g).

¹H-NMR (300 MHz, CDCl₃) δ 7.4~7.3 (m, 4H), 7.20-7.16 (m, 3H), 7.01 (d, 2H), 5.41 (dd, 1H), 3.73 (dd, 1H), 3.1 (m, 9H), 2.86 (s, 3H).

MS (ESI⁺): *m/z* = 462.1 [M+H]⁺.

Step 2) Preparation of (2S)-2-(1-(4-chlorophenyl)-N'-((4-methylpiperazin-1-yl)sulfonyl)-5-phenyl-4,5-dihydro-1H-pyrazole-3-

carboximidamido)-3-methylbutanamide

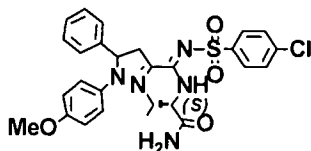
The compound obtained in Step 1) (0.52 g, 1.1 mmol) and phosphorus pentachloride (0.46 g) were added to chlorobenzene (5.0 mL) and stirred at 130°C for 1 hour. Upon completion of the reaction, the reaction solution was concentrated. The concentrated compound was added with dichloromethane (5.0 mL), and then cooled down to 0°C under an atmosphere of nitrogen.

Subsequently, *L*-valinamide (0.15 g, 1.1 mmol) and triethylamine (0.16 g, 1.65 mmol) were sequentially added thereto. The reaction mixture was slowly heated to room temperature while stirring for 1.5 hours. The organic layer was washed with water, 1 N aqueous hydrochloric acid solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue thus obtained was purified by preparative layer chromatography (silica gel 60 F₂₅₄, 1mm) to obtain the title compound as a yellow compound (56 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 8.49 (dd, 1H), 7.56 (m, 1H), 7.4~7.1 (m, 9H) 6.90 (d, 1H), 5.48 (dd, 1H), 4.37 (m, 1H), 4.0 (dd, 1H), 4.0~3.6 (m, 1H), 3.07 (m, 4H), 2.36 (m, 4H), 0.96~0.93 (m, 6H).

MS (ESI⁺): *m/z* = 560.2 [M+H]⁺.

Example 3: Preparation of (2*S*)-2-(*N'*-((4-chlorophenyl)sulfonyl)-1-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide



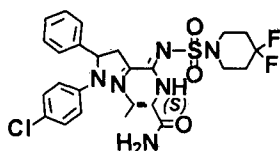
The same method as that in Example 1 or a similar method thereto was conducted to obtain the title compound as a yellow compound (60 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 8.6 (m, 1H), 7.85~7.78 (m, 2H),

7.75~7.54 (m, 2H) 7.41~7.21 (m, 5H), 6.85~6.7 (m, 3H), 5.48 (dd, 1H), 4.27 (m, 1H), 4.0 (dd, 1H), 3.65 (s, 3H), 3.13 (dd, 1H), 2.07 (m, 1H), 0.95~0.85 (m, 6H).

MS (ESI⁺): $m/z = 568.2$ [M+H]⁺.

5 **Example 4: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4,4-difluoropiperidin-1-yl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide**



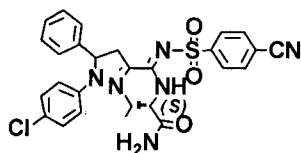
The same method as that in Example 1 or a similar method thereto was
10 conducted to obtain the title compound as a yellow compound (4.4 mg).

¹H-NMR (300 MHz, DMSO-*d*₆) δ 8.49 (dd, 1H), 7.56 (m, 1H), 7.4~7.1 (m, 9H), 6.90 (d, 1H), 5.48 (dd, 1H), 4.37 (m, 1H), 4.0 (dd, 1H), 4.0~3.6 (m, 1H), 3.8~3.6 (m, 4H), 3.1~3.0 (m, 4H), 0.96~0.93 (m, 6H).

MS (ESI⁺): $m/z = 581.2$ [M+H]⁺.

15

Example 5: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-cyanophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide



20 The same method as that in Example 1 or a similar method thereto was conducted to obtain the title compound as a yellow compound (24 mg).

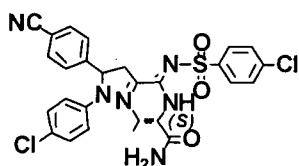
¹H-NMR (300 MHz, DMSO-*d*₆) δ 9.10 (m, 1H), 7.91~7.7 (m, 4H), 7.4~7.1 (m, 9H), 6.8 (m, 2H), 5.5 (dd, 1H), 4.4 (m, 1H), 4.1 (dd, 1H), 3.2 (dd, 1H), 2.1 (m, 1H), 1.0~0.9 (m, 6H).

25

MS (ESI⁺): $m/z = 563.2$ [M+H]⁺.

Example 6: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(4-cyanophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide

5

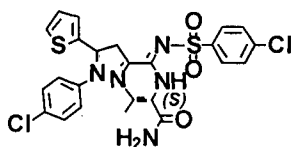


The same method as that in Example 1 or a similar method thereto was conducted to obtain the title compound as a yellow compound (50 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 9.16 (d, 1H), 7.85 (d, 2H), 7.95 (m, 2H), 7.80 (m, 3H), 7.21 (m, 2H), 6.77 (d, 2H), 5.56 (dd, 1H), 4.28 (m, 1H), 4.0~3.8 (m, 1H), 3.2~3.1 (m, 1H), 2.0 (m, 1H), 0.9~0.8 (m, 6H).

MS (ESI⁺): *m/z* = 597.1 [M+H]⁺.

Example 7: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-thiophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide

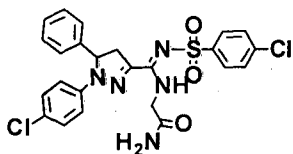


The same method as that in Example 1 or a similar method thereto was conducted to obtain the title compound as a yellow compound (80 mg).

¹H-NMR (300 MHz, CDCl₃) δ 8.63 (s, 1H), 7.85~7.90 (m, 2H), 7.45~7.48 (m, 2H), 7.17~7.20 (m, 3H), 6.98~7.04 (m, 2H), 6.89~6.91 (m, 2H), 6.11 (s, 1H), 5.90 (s, 1H), 5.73 (m, 1H), 5.55~5.61 (m, 2H), 4.85~4.89 (m, 1H), 4.40 (m, 1H), 4.10~4.13 (m, 1H), 3.49~3.79 (m, 2H), 3.17~3.30 (m, 1H), 2.52 (s, 1H), 2.15 (s, 1H), 1.12~1.14 (d, 6H).

MS (ESI⁺): *m/z* = 578.1 [M+H]⁺.

Example 8: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)acetamide

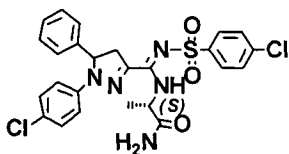


The same method as that in Example 1 or a similar method thereto was conducted to obtain the title compound as a yellow compound (34 mg).

¹H-NMR (300MHz, CDCl₃) δ 7.87 (d, 2H), 7.44 (d, 2H), 7.41~7.12 (m, 7H), 6.96 (d, 2H), 5.84 (m, 1H), 5.57 (m, 1H) 5.35 (m, 1H), 4.42 (m, 2H), 3.87 (m, 1H), 3.20 (m, 1H).

MS (ESI⁺): *m/z* = 530.1 [M+H]⁺.

Example 9: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)propanamide

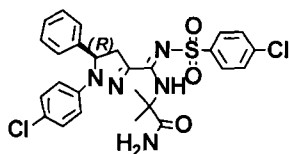


The same method as that in Example 1 or a similar method thereto was conducted to obtain the title compound as a yellow compound (36 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 9.10 (m, 1H), 7.8~7.77 (m, 4H), 7.4~7.1 (m, 9H), 6.75 (m, 2H), 5.44 (dd, 1H), 4.33 (m, 1H), 4.0 (dd, 1H), 3.13 (dd, 1H), 1.4 (m, 3H).

MS (ESI⁺): *m/z* = 544.1[M+H]⁺.

Example 10: Preparation of (*R,Z*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-2-methylpropanamide

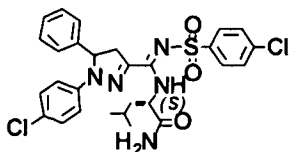


The same method as that in Example 1 or a similar method thereto was conducted to obtain the title compound as a yellow compound (24 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 9.10 (m, 1H), 7.8~7.77 (m, 4H),
 5 7.4~7.1 (m, 9H), 6.75 (m, 2H), 5.44 (dd, 1H), 4.33 (m, 1H), 4.0 (dd, 1H), 3.13 (dd, 1H), 1.3 (m, 6H).

MS (ESI⁺): *m/z* = 558.1 [M+H]⁺.

Example 11: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-4-methylpentanamide

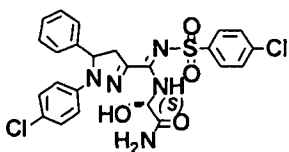


The same method as that in Example 1 or a similar method thereto was conducted to obtain the title compound as a yellow compound (54 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 9.15 (m, 1H), 7.83 (m, 2H), 7.58 (m,
 15 2H), 7.4~7.1 (m, 9H), 6.86 (m, 2H), 5.54 (m, 1H), 4.4 (m, 1H), 4.0 (m, 1H), 3.2 (m, 1H), 2.3(m, 1H), 1.68 (m, 1H), 0.9~0.7 (m, 6H).

MS (ESI⁺): *m/z* = 586.1 [M+H]⁺.

Example 12: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-hydroxypropanamide



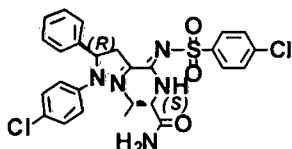
The same method as that in Example 1 or a similar method thereto was
 25 conducted to obtain the title compound as a yellow compound (25 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 8.9 (m, 1H), 8.06 (m, 2H), 7.85 (m,

2H), 7.77 (m, 2H), 7.4~7.1 (m, 7H), 6.86 (m, 2H), 5.6 (dd, 1H), 4.3 (m, 1H), 4.0 (dd, 1H), 3.7 (m, 2H), 3.13 (dd, 1H).

MS (ESI⁺): m/z = 560.1 [M+H]⁺.

5 **Example 13: Preparation of (S)-2-((R,Z)-1-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3-methylbutanamide**



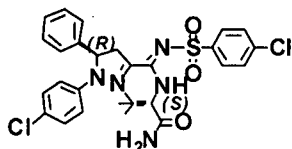
The same method as that in Example 1 or a similar method thereto was conducted to obtain the title compound as a yellow compound (816 mg).

¹H-NMR (300MHz, DMSO-d₆) δ 9.05 (d, H), 7.77 (d, 2H), 7.56 (d, 2H), 7.43~7.18 (m, 7H), 6.85 (d, 1H), 5.47 (dd, 1H), 4.30 (t, 1H), 3.90 (dd, 1H), 3.23 (dd, 1H), 2.12~2.05 (m, 1H), 0.95~0.88 (m, 6H).

MS (ESI⁺): m/z = 572.1 [M+H]⁺.

15

Example 14: Preparation of (S)-2-((R,Z)-1-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3,3-dimethylbutanamide



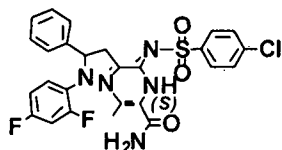
20

The same method as that in Example 1 or a similar method thereto was conducted to obtain the title compound as a yellow compound (66 mg).

¹H-NMR (300MHz, DMSO-d₆) δ 8.98 (d, 1H), 7.76 (d, 2H), 7.55 (d, 2H), 7.47~7.18 (m, 7H), 6.80 (d, 2H), 5.40 (dd, 1H), 4.44 (d, 1H), 3.86 (dd, 1H), 3.21 (dd, 1H), 0.94 (s, 9H).

MS(ESI⁺): m/z = 586.1 [M+H]⁺.

Example 15: Preparation of (2*S*)-2-((*Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(2,4-difluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide

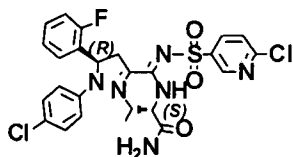


The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (66 mg).

¹H-NMR (300MHz, DMSO-d₆) δ 9.06 (bs, H), 7.92~6.88 (m, 12H), 5.53 (dd, 1H), 4.28 (t, 1H), 3.94 (dd, 1H), 3.23 (dd, 1H), 2.18~1.99 (m, 1H), 0.93~0.72 (m, 6H).

MS (ESI⁺): *m/z* = 574.1 [M+H]⁺.

Example 16: Preparation of (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((6-chloropyridin-3-yl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide

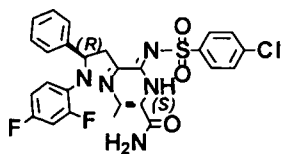


The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (124 mg).

¹H-NMR (300MHz, DMSO-d₆) δ 9.13 (d, 1H), 8.76 (bs, 1H), 8.16 (dd, 1H), 7.71 (d, 1H), 7.43~7.05 (m, 7H), 6.85 (d, 2H) 5.74 (dd, 1H), 4.27 (t, 1H), 3.94 (dd, 1H), 3.25 (dd, 1H), 2.17~2.00 (m, 1H), 0.95~0.76 (m, 6H).

MS(ESI⁺): *m/z* = 591.1 [M+H]⁺.

Example 17: Preparation of (*S*)-2-((*R,Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(2,4-difluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide

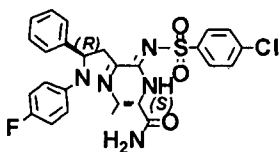


The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (46.7 mg).

¹H-NMR (300MHz, DMSO-d₆) δ 9.06 (d, H), 7.92~6.88 (m, 12H), 5.53 (dd, 1H), 4.28 (t, 1H), 3.94 (dd, 1H), 3.23 (dd, 1H), 2.18~1.99 (m, 1H), 0.93~0.72 (m, 6H).

MS (ESI⁺): *m/z* = 574.1 [M+H]⁺.

Example 18: Preparation of (S)-2-((R,Z)-N'-((4-chlorophenyl)sulfonyl)-1-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3-methylbutanamide

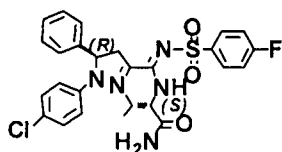


The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (42.3 mg).

¹H-NMR (300MHz, DMSO-d₆) δ 8.99 (d, 1H), 7.77 (d, 2H), 7.56 (d, 2H), 7.51~6.95 (d, 7H), 6.93~6.80 (m, 2H), 5.45 (dd, 1H), 4.29 (t, 1H), 3.88 (dd, 1H), 3.25 (dd, 1H), 0.99~0.78 (m, 6H).

MS(ESI⁺): *m/z* = 556.2 [M+H]⁺.

Example 19: Preparation of (S)-2-((R,Z)-1-(4-chlorophenyl)-N'-((4-fluorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3-methylbutanamide

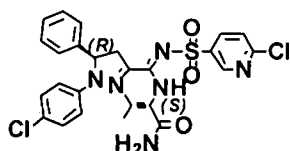


The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (46.5 mg).

¹H-NMR (300MHz, DMSO-d₆) δ 8.99 (d, 1H), 7.82 (d, 2H), 7.49~7.16 (m, 9H), 6.87 (d, 2H), 6.91~6.88 (d, 2H), 5.47 (dd, 1H), 4.30 (t, 1H), 3.90 (dd, 1H), 3.23 (dd, 1H), 2.18~2.01 (m, 1H), 0.95~0.79 (m, 6H).

MS(ESI⁺): *m/z* = 556.2 [M+H]⁺.

Example 20: Preparation of (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((6-chloropyridin-3-yl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide

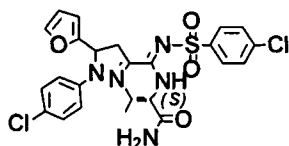


The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (198 mg).

¹H-NMR (300MHz, DMSO-d₆) δ 9.14 (bs, 1H), 8.75 (bs, 1H), 8.15 (dd, 1H), 7.66 (d, 1H), 7.45~7.03 (m, 7H), 6.84 (d, 2H), 5.54 (dd, 1H), 4.26 (t, 1H), 3.90 (dd, 1H), 3.24 (dd, 1H), 2.15~1.98 (m, 1H), 0.97~0.73 (m, 6H).

MS(ESI⁺): *m/z* = 573.1 [M+H]⁺.

Example 21: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-furanyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide



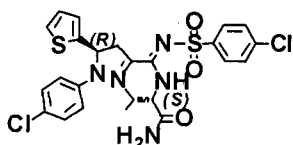
The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (80 mg).

¹H-NMR (300MHz, CDCl₃) δ 8.63 (s, 1H), 7.87~7.92 (m, 2H),

7.46~7.48 (m, 1H), 7.32~7.35 (m, 2H), 7.19~7.22 (m, 2H), 7.03~7.08 (m, 2H), 6.15 (s, 1H), 5.85 (s, 1H), 5.45 (m, 1H), 5.29 (m, 2H), 4.84 (m, 1H), 4.40 (m, 1H), 4.10~4.15 (m, 1H), 3.49~3.79 (m, 2H), 3.17~3.30 (m, 1H), 2.23 (s, 1H), 2.17 (s, 3H), 2.15 (s, 1H), 1.12~1.14 (d, 6H).

5 MS (ESI⁺): m/z = 562.1 [M+H]⁺.

Example 22: Preparation of 2-(*R,Z*)-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-thiophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide



10

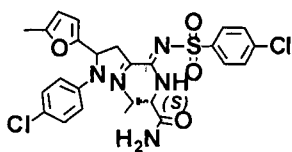
The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (50 mg).

¹H-NMR (300MHz, CDCl₃) δ 8.65 (s, 1H), 7.85~7.90 (m, 2H), 7.44~7.47 (m, 1H), 7.26~7.33 (m, 2H), 7.17~7.19 (m, 2H), 6.98~7.05 (m, 1H), 6.85~6.90 (m, 2H), 6.15 (s, 1H), 5.85 (s, 1H), 5.45 (m, 1H), 5.29 (m, 2H), 4.84 (m, 1H), 4.40 (m, 1H), 4.10~4.15 (m, 1H), 3.49~3.79 (m, 2H), 3.17~3.30 (m, 1H), 2.23 (s, 1H), 2.17 (s, 3H), 2.15 (s, 1H), 1.12~1.14 (d, 6H).

15

MS (ESI⁺): m/z = 578.1 [M+H]⁺.

Example 23: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(5-methyl-2-furanyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide



The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (50 mg).

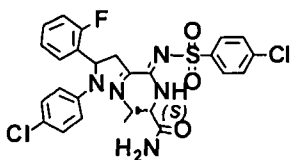
25

¹H-NMR (300MHz, CDCl₃) δ 8.61 (s, 1H), 7.89~7.92 (m, 2H),

7.45~7.48 (m, 1H), 7.26~7.32 (m, 2H), 7.20~7.22 (m, 2H), 7.08 (m, 2H), 6.15 (s, 1H), 5.85 (s, 1H), 5.45 (m, 1H), 5.29 (m, 2H), 4.84 (m, 1H), 4.40 (m, 1H), 4.10~4.15 (m, 1H), 3.49~3.79 (m, 2H), 3.17~3.30 (m, 1H), 2.23 (s, 1H), 2.17 (s, 3H), 2.15 (s, 1H), 1.12~1.14 (d, 6H).

5 MS (ESI⁺): $m/z = 576.1$ [M+H]⁺.

Example 24: Preparation of (2S)-2-(1-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3-methylbutanamide



10

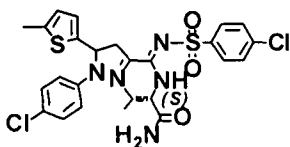
The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (40 mg).

¹H-NMR (300MHz, CDCl₃) δ 8.61 (s, 1H), 7.85~7.88 (m, 2H), 7.42~7.45 (m, 3H), 7.14~7.17 (m, 2H), 7.08 (m, 2H), 6.92~6.95 (m, 2H), 6.32 (s, 1H), 6.15 (s, 1H), 5.85 (m, 1H), 5.55 (m, 2H), 4.84 (m, 1H), 4.40 (m, 1H), 4.10~4.15 (m, 1H), 3.49~3.79 (m, 2H), 3.17~3.30 (m, 1H), 2.53 (s, 1H), 2.23 (s, 1H), 1.12~1.14 (d, 6H).

15

MS (ESI⁺): $m/z = 590.1$ [M+H]⁺.

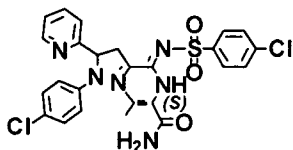
Example 25: Preparation of (2S)-2-(1-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-5-(5-methyl-2-thiophenyl)-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3-methylbutanamide



25

The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (40 mg).

Example 26: Preparation of (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-pyridinyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide



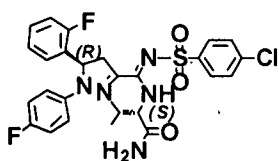
5

The same method as that in Example 1B or a similar method thereof was conducted to obtain the title compound as a yellow compound (30 mg).

¹H-NMR (300MHz, CDCl₃) δ 8.67 (s, 1H), 7.85~7.90 (m, 2H), 7.62~7.65 (m, 1H), 7.45~7.48 (m, 2H), 7.19~7.22 (m, 2H), 7.16 (m, 2H), 7.05~7.09 (m, 2H), 6.08~6.15 (m, 1H), 5.60 (m, 1H), 5.55 (m, 2H), 4.90 (m, 1H), 4.43 (m, 1H), 4.10~4.29 (m, 1H), 3.67~3.81 (m, 2H), 3.22~3.31 (m, 2H), 2.53 (s, 1H), 2.23 (s, 1H), 1.12~1.14 (d, 6H).

MS (ESI⁺): *m/z* = 573.1 [M+H]⁺.

Example 27: Preparation of 2-(*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide

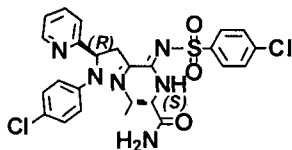


The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (250 mg).

¹H-NMR (300MHz, CDCl₃) δ 8.61 (s, 1H), 7.85~7.88 (m, 2H), 7.42~7.45 (m, 3H), 7.14~7.17 (m, 2H), 7.08 (m, 2H), 6.92~6.95 (m, 2H), 6.32 (s, 1H), 6.15 (s, 1H), 5.85 (m, 1H), 5.55 (m, 2H), 4.84 (m, 1H), 4.40 (m, 1H), 4.10~4.15 (m, 1H), 3.49~3.79 (m, 2H), 3.17~3.30 (m, 1H), 2.53 (s, 1H), 2.23 (s, 1H), 1.12~1.14 (d, 6H).

MS (ESI⁺): *m/z* = 590.1 [M+H]⁺.

Example 28: Preparation of (S)-2-((R,Z)-1-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl-5-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3-methylbutanamide



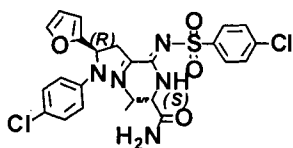
5

The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (68 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 9.02(d, 1H), 8.56~8.52 (m, 1H), 7.88~7.12 (m, 9H), 6.86~6.83 (d,2H), 5.54~5.50 (dd, 1H), 4.30 (t, 1H), 3.97~3.88 (dd, 1H), 3.28~3.07 (m, 1H), 2.12~2.05 (m, 1H) 0.89~0.83 (m, 6H).

MS (ESI⁺): m/z = 572.1 [M+H]⁺.

Example 29: Preparation of (S)-2-((R,Z)-1-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-5-(furan-2-yl)-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3,3-dimethylbutanamide

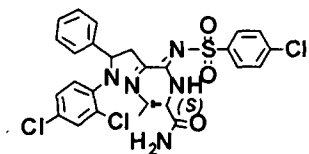


The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (35 mg).

¹H-NMR (300MHz, DMSO-d₆) δ 8.97 (d, H), 7.77 (d, 2H), 7.58 (d, 2H), 7.45~7.18 (m, 7H), 6.84 (d, 1H), 5.49 (dd, 1H), 4.80 (t, 1H), 3.88 (dd, 1H), 3.77 (bs, 1H), 3.59~3.42 (m, 2H), 3.23 (dd, 1H), 1.98~1.80 (m, 1H), 0.90~0.74 (m, 6H).

MS (ESI⁺): m/z = 561.1 [M+H]⁺.

25 **Example 30: Preparation of (2*S*)-2-((*Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(2,4-dichlorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-**

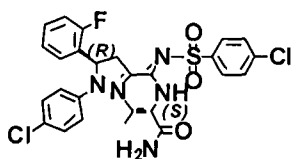
carboximidamido)-3-methylbutanamide

The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (26 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 9.22~9.08 (m, 1H), 7.89~7.79 (m, 2H), 7.62~7.55 (m, 2H), 7.49~7.21 (m, 8H), 5.82~5.80 (m, 1H), 4.29 (t, 1H), 3.63~3.58 (m, 1H), 3.32~3.28 (m, 1H), 2.09~2.07 (m, 1H), 0.89~0.83 (m, 6H).

MS(ESI⁺): *m/z* = 605.1 [M+H]⁺.

Example 31: Preparation of (S)-2-((R,Z)-1-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3-methylbutanamide

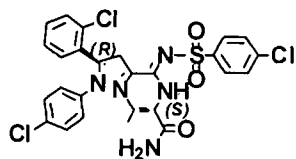


The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (20 mg).

¹H-NMR (300MHz, CDCl₃) δ 8.61 (s, 1H), 7.85~7.88 (m, 2H), 7.42~7.45 (m, 3H), 7.14~7.17 (m, 2H), 7.08 (m, 2H), 6.92~6.95 (m, 2H), 6.32 (s, 1H), 6.15 (s, 1H), 5.85 (m, 1H), 5.55 (m, 2H), 4.84 (m, 1H), 4.40 (m, 1H), 4.10~4.15 (m, 1H), 3.49~3.79 (m, 2H), 3.17~3.30 (m, 1H), 2.53 (s, 1H), 2.23 (s, 1H), 1.12~1.14 (d, 6H).

MS (ESI⁺): *m/z* = 574.1 [M+H]⁺.

Example 32: Preparation of (S)-2-((R,Z)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3-methylbutanamide

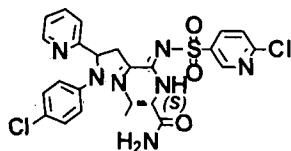


The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (150 mg).

¹H-NMR (300 MHz, DMSO-d₆) δ 9.06 (br, 1H), 7.88~7.02 (m, 10H),
 5 6.76~6.73 (d, 2H), 5.66~5.59 (m, 1H), 4.32 (t, 1H), 4.01~3.91 (m, 1H),
 3.31~3.11 (m, 1H), 2.10~2.04 (m, 1H), 0.89~0.83 (m, 6H).

MS(ESI⁺): *m/z* = 605.1 [M+H]⁺.

Example 33: Preparation of (S)-2-((Z)-1-(4-chlorophenyl)-N'-((6-chloropyridin-3-yl)sulfonyl)-5-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole-3-carboximidamido)-3-methylbutanamide



The same method as that in Example 1B or a similar method thereto was conducted to obtain the title compound as a yellow compound (150 mg).

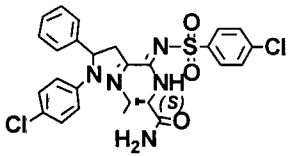
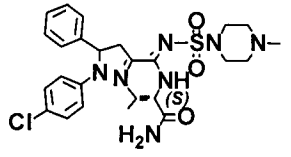
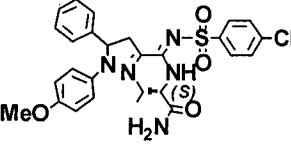
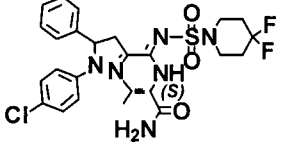
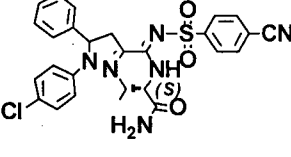
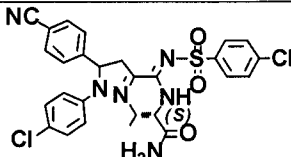
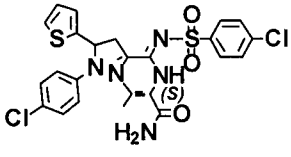
¹H-NMR (300 MHz, DMSO-d₆) δ 9.26~9.11 (br, 1H), 8.79~8.76 (dd,
 15 1H), 8.58~8.57 (dd, 1H), 8.17~8.16 (dd, 1H) 7.82~7.10 (m, 6H), 6.87~6.85 (d,
 2H), 5.60~5.54 (m, 1H), 4.27 (t, 1H), 4.03~3.92 (m, 1H), 3.31~3.13 (m, 1H),
 2.13~2.06 (m, 1H), 0.88~0.85 (m, 6H).

MS(ESI⁺): *m/z* = 573.1 [M+H]⁺.

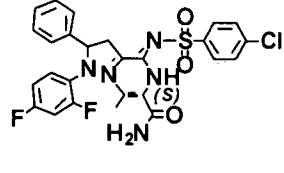
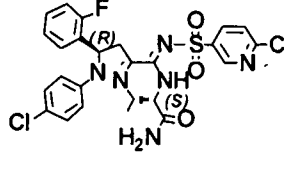
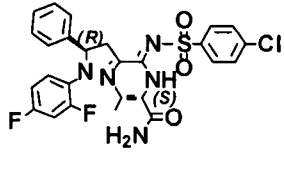
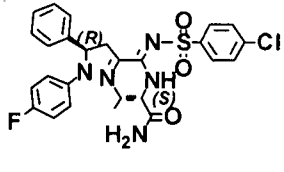
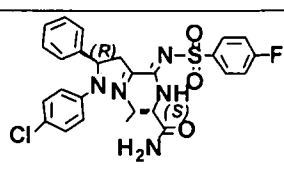
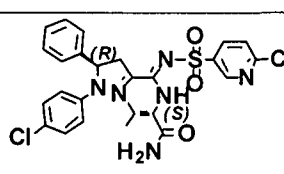
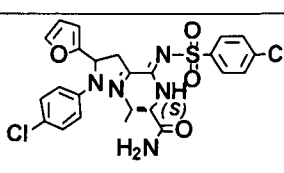
The chemical structures of the compounds according to Examples 1 to 33 are shown in Table 1 below.

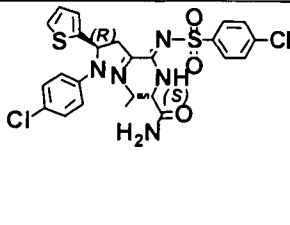
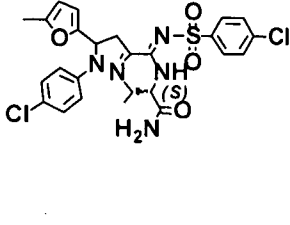
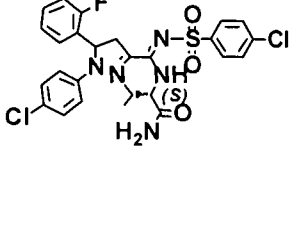
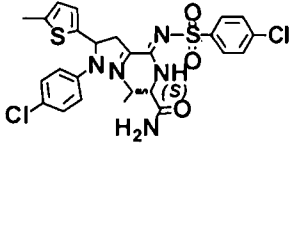
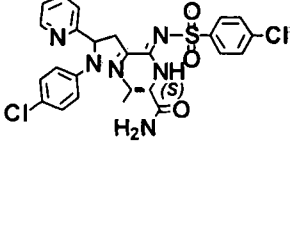
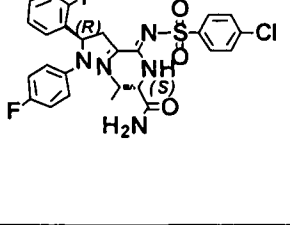
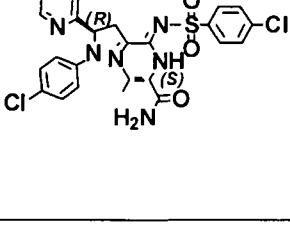
[Table 1]

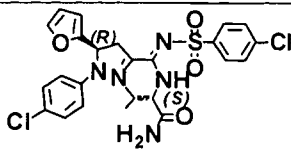
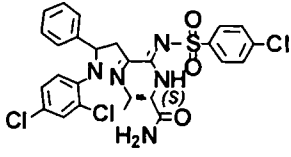
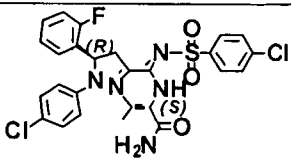
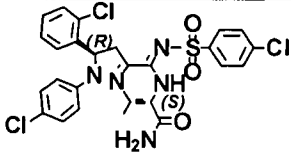
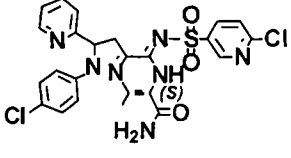
Ex.	Chemical name	
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1	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
2	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-methylpiperazin-1-yl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
3	(2 <i>S</i>)-2-(<i>N'</i> -((4-chlorophenyl)sulfonyl)-1-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
4	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4,4-difluoropiperidin-1-yl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
5	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-cyanophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
6	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(4-cyanophenyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
7	(2 <i>S</i>)-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(2-thiophenyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	

8	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)acetamide	
9	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)propanamide	
10	(<i>R,Z</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-2-methylpropanamide	
11	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-4-methylpentanamide	
12	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-hydroxypropanamide	
13	(<i>S</i>)-2-((<i>R,Z</i>)-1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
14	(<i>S</i>)-2-((<i>R,Z</i>)-1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3,3-dimethylbutanamide	

15	(2 <i>S</i>)-2-((<i>Z</i>)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-1-(2,4-difluorophenyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
16	(<i>S</i>)-2-((<i>R,Z</i>)-1-(4-chlorophenyl)- <i>N'</i> -((6-chloropyridin-3-yl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
17	(<i>S</i>)-2-((<i>R,Z</i>)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-1-(2,4-difluorophenyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
18	(<i>S</i>)-2-((<i>R,Z</i>)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-1-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
19	(<i>S</i>)-2-((<i>R,Z</i>)-1-(4-chlorophenyl)- <i>N'</i> -((4-fluorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
20	(<i>S</i>)-2-((<i>R,Z</i>)-1-(4-chlorophenyl)- <i>N'</i> -((6-chloropyridin-3-yl)sulfonyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
21	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(2-furanyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	

22	2-(<i>R,Z</i>)-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(2-thiophenyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
23	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(5-methyl-2-furanyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
24	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
25	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(5-methyl-2-thiophenyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
26	(2 <i>S</i>)-2-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(2-pyridinyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
27	2-(<i>R,Z</i>)-(1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
28	(<i>S</i>)-2-((<i>R,Z</i>)-1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(pyridin-2-yl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	

29	(<i>S</i>)-2-((<i>R,Z</i>)-1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(furan-2-yl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3,3-dimethylbutanamide	
30	(2 <i>S</i>)-2-((<i>Z</i>)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-1-(2,4-dichlorophenyl)-5-phenyl-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
31	(<i>S</i>)-2-((<i>R,Z</i>)-1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
32	(<i>S</i>)-2-((<i>R,Z</i>)-5-(2-chlorophenyl)-1-(4-chlorophenyl)- <i>N'</i> -((4-chlorophenyl)sulfonyl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	
33	(<i>S</i>)-2-((<i>Z</i>)-1-(4-chlorophenyl)- <i>N'</i> -((6-chloropyridin-3-yl)sulfonyl)-5-(pyridin-2-yl)-4,5-dihydro-1 <i>H</i> -pyrazole-3-carboximidamido)-3-methylbutanamide	

Experimental Example 1: [³⁵S]GTPγS Binding Assay

A binding assay was conducted to evaluate the antagonistic activity of Gi protein-coupled receptor, *i.e.*, cannabinoid receptor 1, as follows.

The assay is based upon the principle that agonists bind to G-protein coupled receptors to stimulate GDP-GTP exchange at the G-protein. A non-hydrolyzable form of GTP, *i.e.*, GTPγS, a radiochemical [³⁵S]-1250Ci/mmol, 12.5mCi/mmol, 1 mCi (Perkin Elmer, cat. NEG030H001MC), and WGA-coated SPA beads (Cat. RPNQ0210) were used for the assay. Each of the compounds

prepared in Examples 1 to 5 was placed in an 1x assay buffer (20 mM HEPES, 100 mM NaCl, 25 mM MgCl₂, 1 mM EDTA, pH 7.4), and diluted to produce samples with various concentrations including 10 μ M, 1 μ M, 100 nM, 10 nM, 1 nM, and 0.1 nM. A CB1 receptor membrane (Cat. HTS019M, Millipore) was diluted with a saponin solution, and mixed with 3 μ M GDP at the ratio of 1:1 (v/v) to form a mixture.

The mixture of the CB1 receptor membrane and GDP thus prepared (100 μ L) was added with diluted samples, further added with a mixture prepared by adding WGA-coated SPA beads and the [³⁵S]GTP γ S mixture at the ratio of 1:1 (v/v). The reaction mixture was allowed to react for 50 minutes at room temperature, and then [³⁵S]GTP γ S activity was measured by using a β -scintillation counter. In this test, a basal well excluded only the compounds, and a background well excluded the compounds, membrane and GDP for the reaction. IC₅₀ values were calculated for each compound by using GraphPad Prism 4.0 software.

As a result, compounds of Examples 1, 2, 3, 4, 5, 7, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25, 26, 27, 28, 29, 30, 31, 32, and 33 exhibited IC₅₀ values of 10 nM, 8 nM, 14 nM, 16 nM, 10 nM, 3 nM, 4 nM, 10 nM, 13 nM, 5 nM, 11 nM, 7 nM, 9 nM, 6 nM, 10 nM, 5 nM, 7 nM, 17 nM, 8 nM, 5 nM, 8 nM, 6 nM, 17 nM, 10 nM, 16 nM, and 16 nM, respectively. These values indicate that the compounds according to the Examples of the present invention show excellent antagonistic activity against the CB1 receptors.

Experimental Example 2: Assay for Anti-Obesity Effects (*in vivo*)

2-1: Change in Feeding Amount and Body Weight

Diet induced obesity (DIO) mice were used to evaluate the suppressive effect of the inventive compounds on feeding amount and body weight gain.

5-week-old C57BL/6 mice (OrientBio, Korea) were fed with a high fat diet for 2 to 5 months to make DIO mice. All DIO mice were housed in a 12:12 hour light:dark cycle room (11:00 light-out, 23:00 light-on) with controlled conditions of temperature and humidity, and had free access to food and water.

One week before each test, each mouse was individually housed, and a baseline of its feeding amount and body weight was determined by conducting a habituation to a treatment. Mice were randomly grouped into treatment groups, based on their initial body weights and feeding amounts. A vehicle and a commonly known antagonist (rimonabant), as a positive control, were each administered to DIO mice so as to evaluate the suppressive effect of the compounds of Examples 13 and 31 according to the present invention on feeding amount. One hour before the start of dark cycle, DIO mice were treated with the test compound at 3 mg/kg. The body weight and feeding amount were measured every 24 hours from day 0 (before the treatment) until day 28 using an electronic scale. The effectiveness of the test compounds was evaluated by comparing the data (changes in body weight and feeding amount) obtained from the vehicle-treated group, the standard positive control-treated group, and the test compound-treated groups.

As shown in Fig. 1, body weights were gradually reduced in mice which were treated with the compounds of Examples 13 and 31 according to the present invention, and this weight reduction effect was observed during the 4-week treatment period, and lasted for a certain period of time even after the treatment.

Additionally, as shown in Fig. 2, feeding amount was decreased owing to the administration of the inventive compounds. The feeding amount slowly returned to the normal level, and was maintained constantly at the normal level after the body weight had been reduced. Thus, it can be concluded that the compounds of Examples 13 and 31 according to the present invention exhibit anti-obesity effects.

2-2: Changes in Leptin and Insulin levels

Blood samples were taken from the DIO mice used in Experimental Example 2-1, and changes in leptin and insulin levels were measured.

Plasma was separated from the blood sampled from the DIO mice when Experimental Example 2-1 was completed, and plasma leptin and insulin levels were measured using an ELISA (Enzyme linked immunosorbent assay) kit (insulin: Crystal Chem, cat #90060, leptin: ALPCO), and quantified so as to

evaluate the changes due to the administration of the test compounds.

As shown in Fig. 3, the compounds of Examples 13 and 31 according to the present invention effectively reduced the levels of insulin and leptin that are closely related to obesity-related metabolic diseases and obesity.

5

2-3: Brain-to-Plasma Exposure ratio

Brain exposure rates of the compounds of the present invention were examined after oral administration of the compounds to the DIO mice and normal ICR mice.

10 The compounds of Examples 13 and 31 according to the present invention and rimonabant, a comparative compound, were orally administered to the mice at a dose of 3 mg/kg body weight. At 0.5 hour after the administration, which is expected to be the T_{max} of the compounds, blood and brain tissue samples were taken from the mice. The blood samples were
15 placed in heparin-treated eppendorf tubes (1000 IU/mL, heparin, 3 μ L), and immediately centrifuged (12,000 rpm, 2 minutes) to separate the plasma. Brain samples were diluted 10 times using a 4% bovine serum albumin (BSA) solution, and pulverized.

The concentrations of the test compounds in the blood and brain tissue
20 samples were analyzed by (LC-MS/MS), and the results are shown in Fig. 4.

As can be seen in Fig. 4, the brain exposure rates of the compounds of Examples 13 and 31 according to the present invention (about 7%, and 9%, respectively) was superior to that of rimonabant (about 59%) in DIO mice. In normal ICR mice, the brain exposure rates of the compounds of Examples 13
25 and 31 according to the present invention (about 3% and 0.4%, respectively) was also superior to that of rimonabant (about 42%).

Considering the close relationship between the brain exposure rate and adverse side effects, this result demonstrates that the compounds according to the present invention are excellent drugs which have the possibilities of
30 overcoming preexisting problems of conventional drugs.

Experimental Example 3: Evaluation of Depression and Anxiety via Behavioral Test

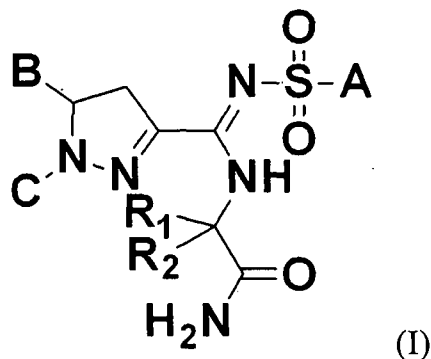
The incidence of central nervous system adverse effects, *i.e.*, depression and anxiety caused by the compounds of the present invention was evaluated as follows.

5 In order to evaluate the incidence of anxiety due to the drug, an elevated plus maze (EPM) test was carried out as follows, wherein an elevated plus maze was installed 50 cm above the ground. The maze for EPM test consisted of two open arms and two closed arms which were crossed over. The compounds of Examples 13 and 31, and rimonabant, as a positive control, were each orally
10 administered to ICR mice at 3 mg/kg, and the test was conducted at 30 minutes post-dose. The mice were placed on a center zone where the open arms and the closed arms were crossed, and their behavior was observed for 6 minutes. The behavior of mice was recorded using a camera installed on the ceiling, and the time spent at the open arms and the total distance travelled were analyzed
15 using a tracking software Ethovision XT 7 program (Noldus). Also, the same test was conducted using ICR mice administered with a vehicle only (vehicle group). The result is shown in Fig. 5.

After measuring the behavior of the animals, it was discovered that, like the vehicle group, the mice administered with the compounds of Examples 13
20 and 31 showed movements in both the open and closed arms, whereas the mice treated with rimonabant exhibited movements in the closed arms only.

What is claimed is:

1. A compound represented by formula (I) or a pharmaceutically acceptable salt thereof:



wherein A is selected from the group consisting of C₁₋₇alkyl, C₆₋₁₀aryl, C₄₋₁₀heteroaryl, C₃₋₆cycloalkyl, and C₃₋₆heterocycloalkyl, and optionally, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, linear or branched C₁₋₆alkyl, linear or branched C₁₋₆alkoxy, halo, CN, OH, NO₂, -(C=O)-R', SH, SR', SOR', SO₂R', NH₂, NHR', NR'R'', -(C=O)-NH₂, -(C=O)-NHR', and -(C=O)-NR'R'';

B and C are each independently C₆₋₁₀aryl or C₄₋₁₀heteroaryl, and optionally, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, linear or branched C₁₋₆alkyl, linear or branched C₁₋₆alkoxy, halo, dihalo, trihalo, CN, OH, NO₂, -(C=O)-R', SH, SR', SOR', SO₂R', NH₂, NHR', NR'R'', -(C=O)-NH₂, -(C=O)-NHR', and -(C=O)-NR'R'';

R' and R'' are each independently linear or branched C₁₋₆alkyl; and

R₁ and R₂ are each independently hydrogen or C₁₋₆alkyl, and optionally, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, linear or branched C₁₋₆alkyl, linear or branched C₁₋₆alkoxy, halo, CN, OH, NO₂, and SH.

2. The compound of claim 1, wherein

A is C₆₋₁₀aryl or C₄₋₁₀heteroaryl, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen, halo, dihalo, and C₁₋₆alkyl;

B is C₆₋₁₀aryl or C₄₋₁₀heteroaryl, each of which is independently substituted with at least one substituent selected from the group consisting of hydrogen and CN;

C is C₆₋₁₀aryl which is optionally substituted with halo; and

R₁ and R₂ are each independently hydrogen, linear or branched C₁₋₆alkyl, or linear or branched C₁₋₆alkyl substituted with OH.

3. The compound of claim 1, wherein the compound is selected from the group consisting of:

1) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

2) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-methylpiperazin-1-yl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

3) (2*S*)-2-(*N'*-((4-chlorophenyl)-1-(4-methoxyphenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

4) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4,4-difluoropiperidin-1-yl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

5) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-cyanophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

6) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(4-cyanophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

7) (2*S*)-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-thiophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;

8) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)acetamide;

9) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)propanamide;

10) (R,*Z*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-2-methylpropanamide;

11) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-4-methylpentanamide;

- 12) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-hydroxypropanamide;
- 13) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 14) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3,3-dimethylbutanamide;
- 15) (2*S*)-2-((*Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(2,4-difluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 16) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((6-chloropyridin-3-yl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 17) (*S*)-2-((*R,Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(2,4-difluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 18) (*S*)-2-((*R,Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 19) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-fluorophenyl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 20) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((6-chloropyridin-3-yl)sulfonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 21) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-furanyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 22) 2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-thiophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 23) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(5-methyl-2-furanyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 24) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(5-methyl-2-furanyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 25) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(5-methyl-2-thiophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide

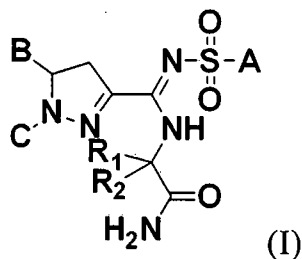
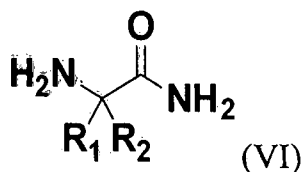
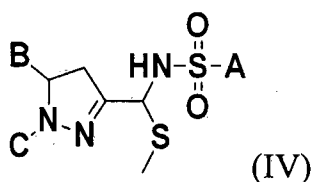
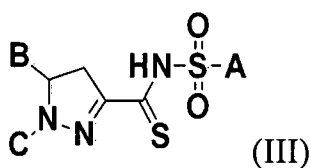
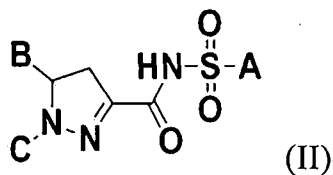
- 26) (2*S*)-2-(1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-pyridinyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 27) 2-(*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 28) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 29) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(furan-2-yl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3,3-dimethylbutanamide;
- 30) (2*S*)-2-((*Z*)-*N'*-((4-chlorophenyl)sulfonyl)-1-(2,4-dichlorophenyl)-5-phenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 31) (*S*)-2-((*R,Z*)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-5-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide;
- 32) (*S*)-2-((*R,Z*)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-*N'*-((4-chlorophenyl)sulfonyl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide; and
- 33) (*S*)-2-((*Z*)-1-(4-chlorophenyl)-*N'*-((6-chloropyridin-3-yl)sulfonyl)-5-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole-3-carboximidamido)-3-methylbutanamide.

4. A method for preparing a compound of formula (I), which comprises the steps of:

1) allowing a compound of formula (II) to react with phosphorus pentasulfide (P₂S₅) or Lawesson's reagent in a solvent selected from the group consisting of toluene, xylene, benzene, chlorobenzene, and a mixture thereof to obtain a compound of formula (III);

2) allowing the compound of formula (III) to react with methyl iodide in a solvent selected from the group consisting of acetone, acetonitrile, tetrahydrofuran, dichloromethane, chloroform, and a mixture thereof under a basic condition to obtain a compound of formula (IV); and

3) allowing the compound of formula (IV) to react with a compound of formula (VI) in a solvent selected from the group consisting of acetone, acetonitrile, tetrahydrofuran, dichloromethane, chloroform, and a mixture thereof in the presence of a base to obtain the compound of formula (I):

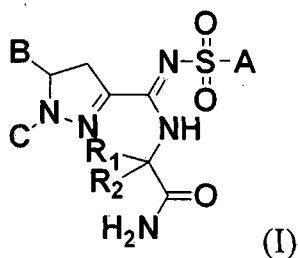
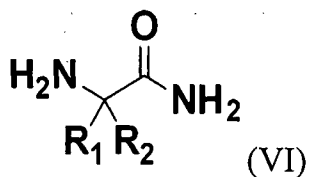
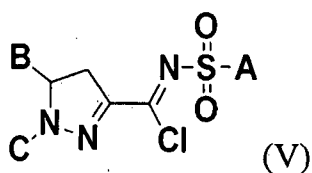
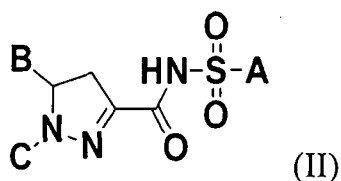


wherein A, B, C, R₁ and R₂ have the same meanings as defined in claim 1.

5. A method for preparing a compound of formula (I), which comprises the steps of:

1) allowing the compound of formula (II) to react with chloride in a solvent selected from toluene, xylene, benzene, chlorobenzene, and a mixture thereof to obtain a compound of formula (V); and

2) allowing the compound of formula (V) thus obtained to react with a compound of formula (VI) in a solvent selected from the group consisting of acetone, acetonitrile, tetrahydrofuran, dichloromethane, chloroform, and a mixture thereof in the presence of a base to obtain the compound of formula (I):



wherein A, B, C, R₁ and R₂ have the same meanings as defined in claim

1.

6. A pharmaceutical composition for the prevention or treatment of obesity or an obesity-related metabolic disease, comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof as an active ingredient.

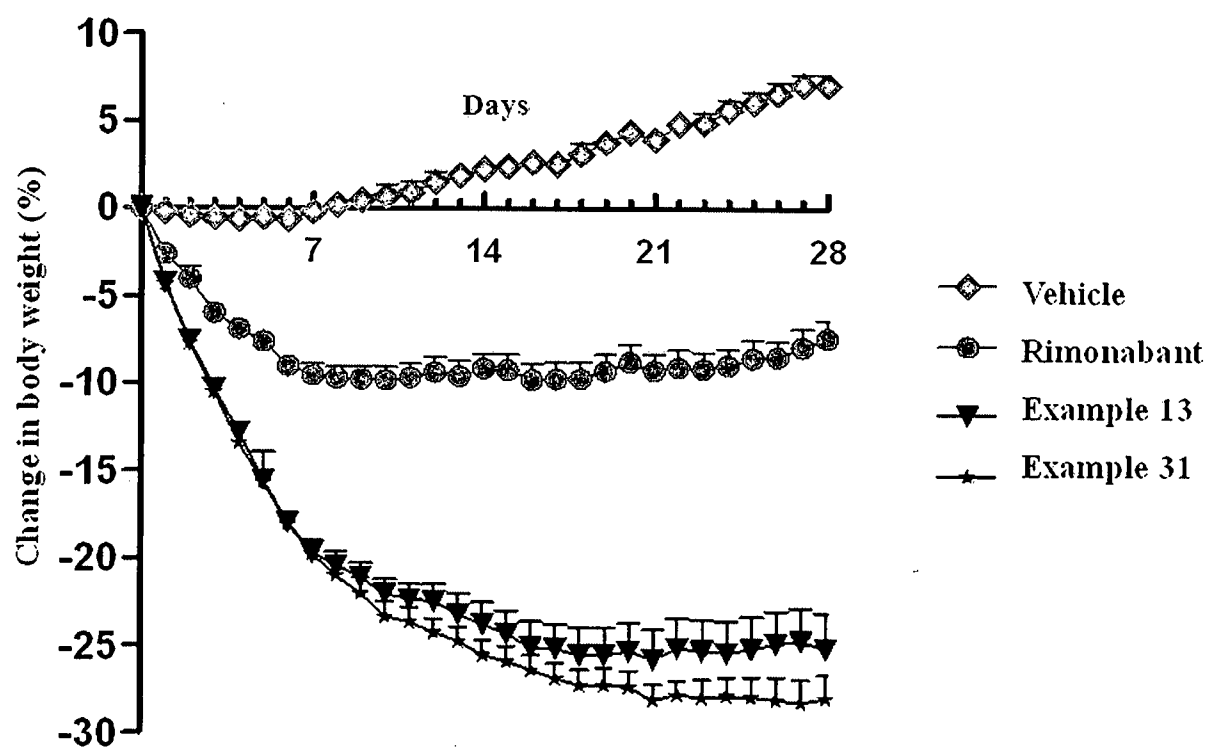
7. The pharmaceutical composition of claim 6, wherein the obesity-related metabolic disease is Type 2 Diabetes, chronic hepatic diseases, angina, hypertension, congestive heart failure or hyperlipidemia.

8. A use of the compound of claim 1 for the manufacture of a medicament for preventing or treating obesity or an obesity-related metabolic disease.

9. A method for preventing or treating obesity or an obesity-related metabolic disease, comprising administering to a mammal the compound of formula (I) of claim 1 or a pharmaceutically acceptable salt thereof.

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FIG. 1



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FIG. 2

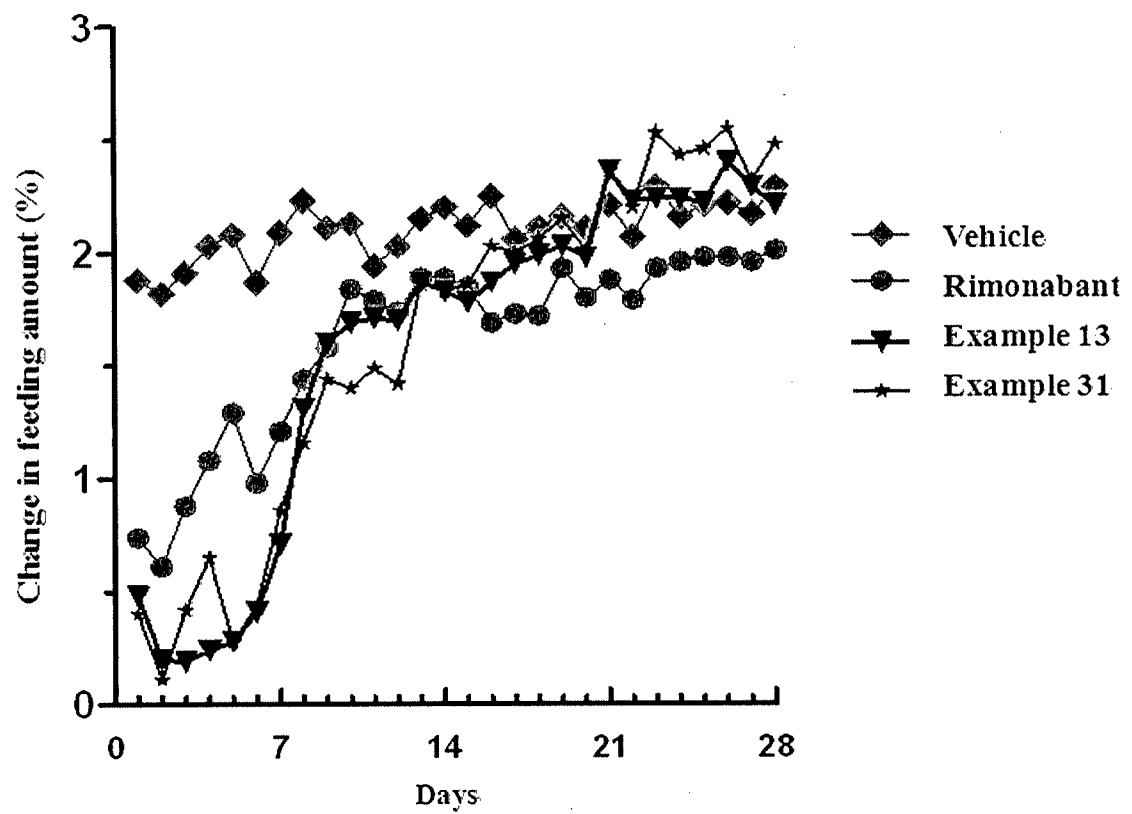


FIG. 3

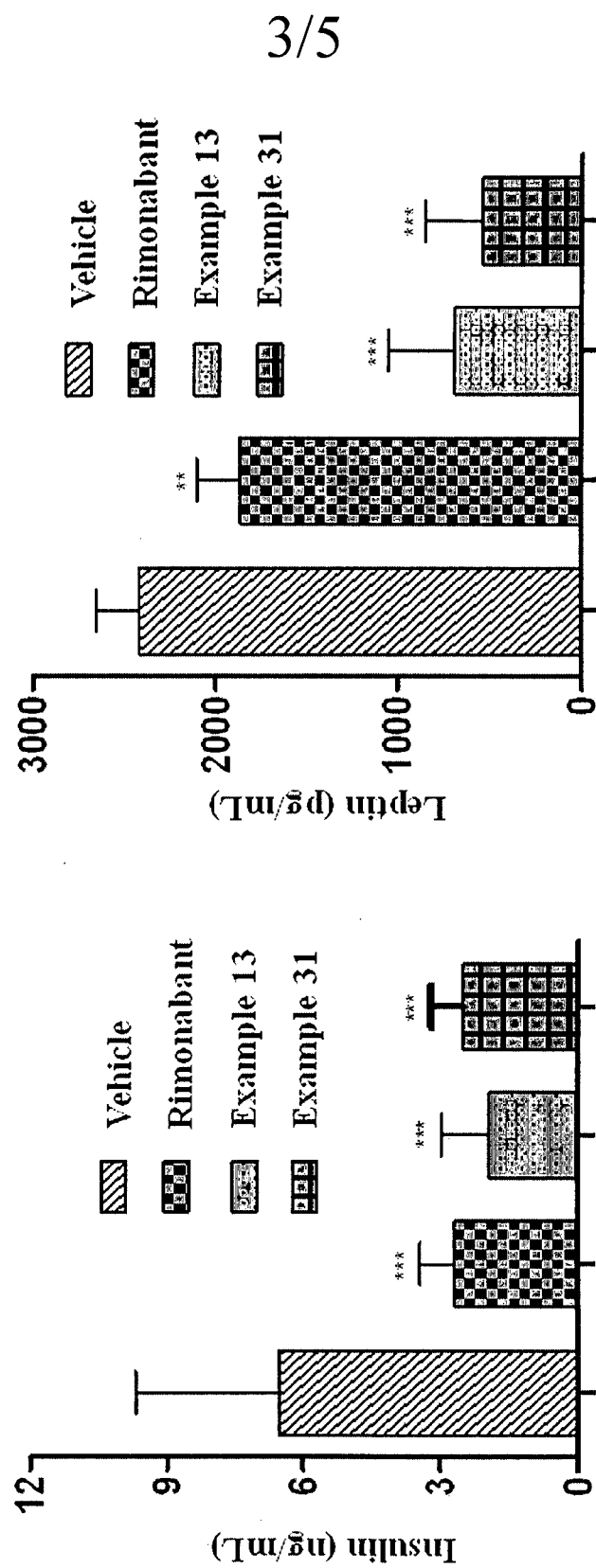


FIG. 4

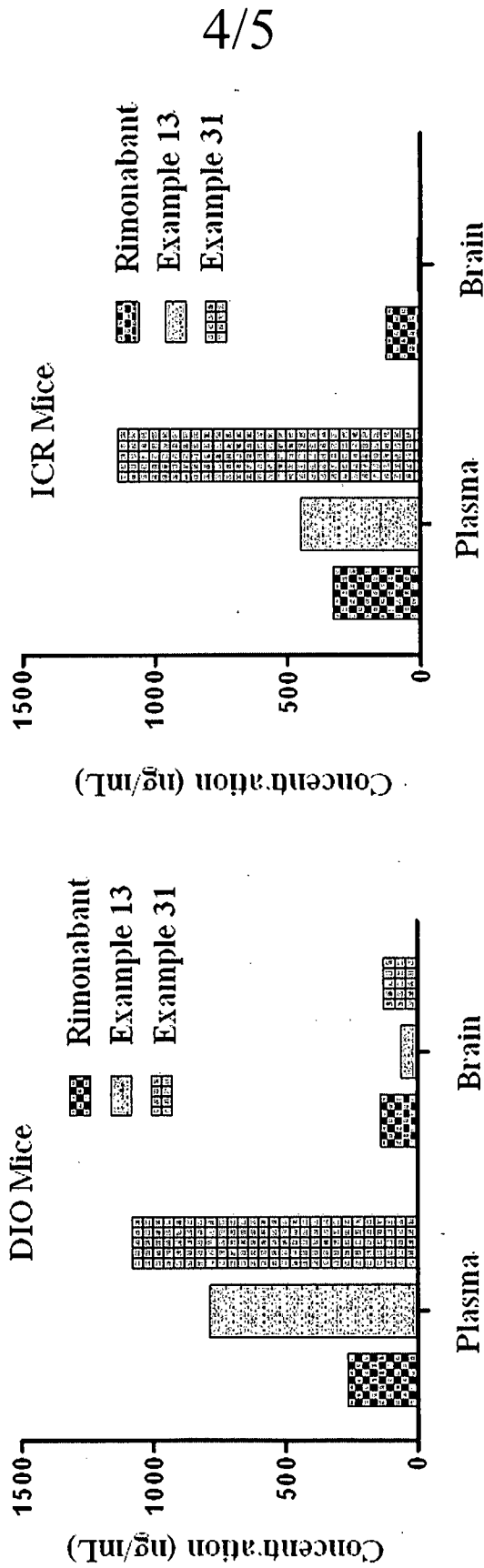
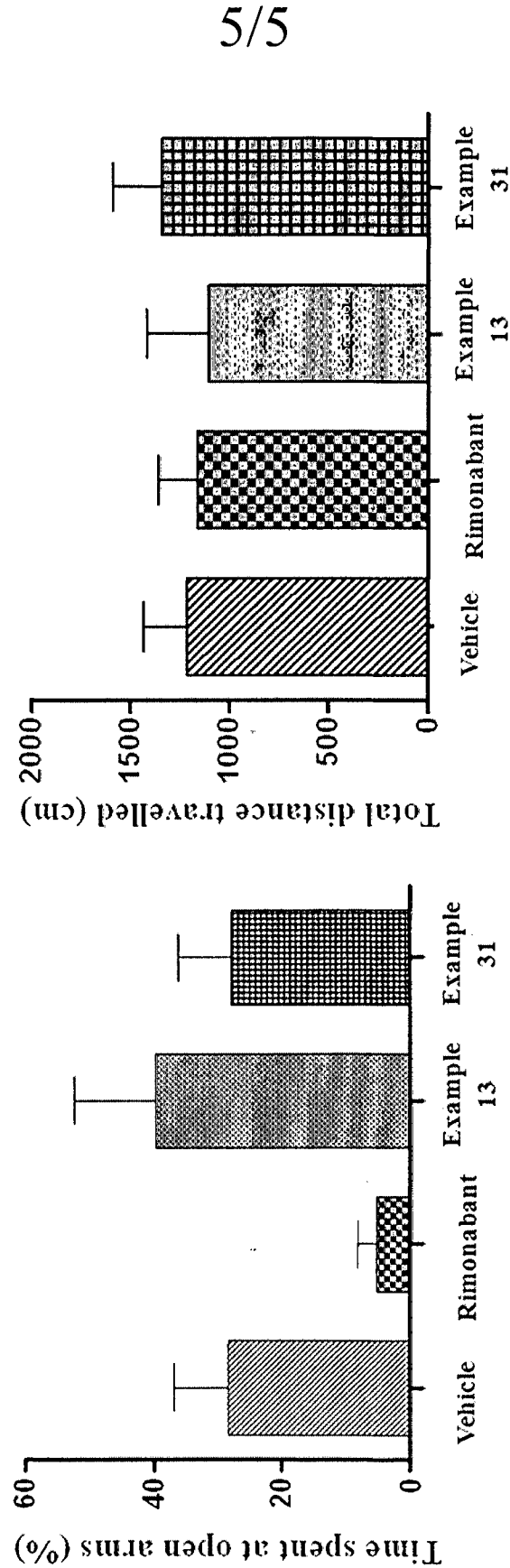


FIG. 5



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2014/005479**A. CLASSIFICATION OF SUBJECT MATTER****C07D 487/04(2006.01)i, C07D 231/06(2006.01)i, A61K 31/4985(2006.01)i, A61P 3/00(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)

C07D 487/04; C07D 231/06; A61K 31/4155; A01N 43/56; A61K 31/415; C07D 403/12; C07D 401/12; A61K 31/4985; A61P 3/00

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

Google, eKOMPASS(KIPO internal) & Keywords: 1,5-diaryl-4,5-dihydro-1H-pyrazole-3-carboxamide, sulfonyl, CB1, obesity related metabolic disease, Type 2 diabetes

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005-074920 A1 (SOLVAY PHARMACEUTICALS B.V.) 18 August 2005 See Formula (I)	1-8
A	WO 2009-130234 A1 (SOLVAY PHARMACEUTICALS B.V.) 29 October 2009 See Formula (I)	1-8
A	WO 2011-044370 A1 (JENRIN DISCOVERY) 14 April 2011 See Formula I, Ic, Id	1-8
A	Jos H. M. Lange et al. 'Synthesis, SAR and intramolecular hydrogen bonding pattern of 1,3,5-trisubstituted 4,5-dihydropyrazoles as potent cannabinoid CB1 receptor antagonists', Bioorganic & Medicinal Chemistry Letters, 2010, vol. 20, No. 5, pp. 1752-1757 See Compound 1-4	1-8
A	WO 2007-125048 A1 (SOLVAY PHARMACEUTICALS GMBH) 08 November 2007 See Table 1	1-8



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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

29 October 2014 (29.10.2014)

Date of mailing of the international search report

30 October 2014 (30.10.2014)

Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2014/005479**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 9 pertains to a method for treatment of the human body by therapy and thus related to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2014/005479

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

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