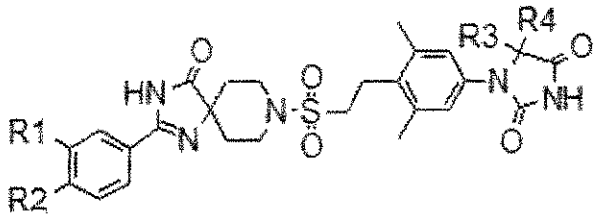
therapeutic target range of 7.6-8.8 mg/dL. Results obtained from these model animals suggest that the compounds represented by formula (1), which show a strong effect on human PTH1R and high stability in human liver microsomes, are useful as therapeutic agents for hypoparathyroidism.

In one aspect the present invention refers to a compound or pharmacologically acceptable salt, a hydrate, or a solvate thereof, wherein the compound is selected from the group consisting of:
1-(4-(2-((2-(4-fluoro-3-(trifluoromethoxy)phenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(4-(2-((2-(3-bromophenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(4-(2-((2-(4-fluoro-3-(trifluoromethyl)phenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(4-(2-((2-(3-fluoro-4-(trifluoromethoxy)phenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(4-(2-((2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(3,5-dimethyl-4-(2-((4-oxo-2-(3-(trifluoromethyl)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione);
1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione;
1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-8-methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione;
5-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-2-oxa-5,7-diazaspiro[3.4]octane-6,8-dione; and
4-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-4,6-diazaspiro[2.4]heptane-5,7-dione. In another aspect, the present invention refers to a pharmaceutical composition, which comprises the compound or pharmacologically acceptable salt, a hydrate, or a solvate thereof of the present invention as an active ingredient. In another aspect, the present invention refers to a compound or pharmaceutically acceptable salt, a hydrate, or a solvate thereof of the present invention for use as an agent for oral administration.

In yet another aspect, the present invention refers to the use of the compound or pharmacologically acceptable salt, a hydrate, or a solvate thereof of of the present invention for the production of an agent for preventing or treating osteoporosis, fracture, adynamic bone disease, achondroplasia, hypochondroplasia, osteomalacia, osteoarthritis, arthritis, thrombocytopenia, hypoparathyroidism, hyperphosphatemia, or tumoral calcinosis.

Furthermore, ~~T~~the present ~~invention~~ disclosure relates to the following:

[1] A compound represented by general formula (1) below or a pharmacologically acceptable salt thereof:



(1)

(wherein,

when R1 and R2 are not both hydrogen atoms, R1 and R2 are independently:

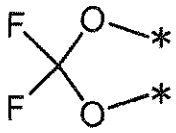
1) hydrogen atom;

2) halogen atom;

3) an alkyl group comprising one or two carbons that may be substituted with one to five fluorine atoms; or

4) an alkoxy group comprising one or two carbons that may be substituted with one to five fluorine atoms; or

R1 and R2 bond with each other to form a group represented by the formula below:



(wherein each * indicates the position of bonding with the phenyl portion); and

R3 and R4 are independently a methyl group that may be substituted with one to three fluorine atoms; or

R3 and R4, together with a bound carbon atom, form a three- to six-membered carbocyclic ring (wherein, one of the carbon atoms forming the ring may be replaced with an oxygen atom, a sulfur atom, or a methyl-substituted or unsubstituted nitrogen atom).

In the present invention, a compound in which the combination of R1 and R2 is a trifluoromethyl group and a hydrogen atom, and where R3 and R4, together with a bound carbon atom, form a cyclopentyl ring, can be excluded from the above-mentioned compounds represented by formula (1).

treatment or prevention of osteoporosis, fracture, adynamic bone disease, achondronplasia, hypochondroplasia, osteomalacia, osteoarthritis, arthritis, thrombocytopenia, hypoparathyroidism, hyperphosphatemia, or tumoral calcinosis, or stem cell mobilization.

Furthermore the present ~~invention~~ disclosure provides methods for treating pathological conditions that may be treated by PTH-like actions, such as hypoparathyroidism, by administering a compound of formula (1) or a salt thereof.

[Effects of the Invention]

The present invention provides hydantoin derivatives with strong PTH-like effects and high metabolic stability. Use of the hydantoin derivatives enables treatment of pathological conditions caused by PTH-like actions, such as hypoparathyroidism.

Brief Description of the Drawings

Fig. 1 depicts a graph showing the average change of level in serum Ca concentration for each compound up to 24 hours after administration, when the compound is orally administered at a dose of 30 mg/kg to a TPTX rat model.

[Mode for Carrying Out the Invention]

The present invention relates to hydantoin derivatives and use thereof. The present inventors have synthesized a compound represented by the above formula (1) or a pharmacologically acceptable salt thereof for the first time and have found that the compound or a salt thereof is a compound having a strong parathyroid hormone (PTH)-like effect and high metabolic stability.

The "alkyl" herein refers to a monovalent group derived by removing any one hydrogen atom from an aliphatic hydrocarbon, and covers a subset of hydrocarbyl or hydrocarbon group structures not containing a heteroatom or an unsaturated carbon-carbon bond and containing hydrogen and carbon atoms in the backbone. Examples of the alkyl group include those of linear or branched structures. The alkyl group is preferably an alkyl group comprising one or two carbon atoms. The alkyl group is specifically, for example, a methyl group or an ethyl group, and is preferably a methyl group.

The term "alkoxy" as used herein refers to an oxy group to which the above-defined "alkyl" is bound, and preferably refers to an alkoxy group comprising one or two carbon atoms. Specific examples include methoxy and ethoxy groups, and a preferred example is methoxy group.

The "B optionally substituted with A" herein denotes that any hydrogen atom(s) in B may be substituted with any number of As.

CLAIMS

1. A compound or pharmacologically acceptable salt, a hydrate, or a solvate thereof, wherein the compound is selected from the group consisting of:

1-(4-(2-((2-(4-fluoro-3-(trifluoromethoxy)phenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;

1-(4-(2-((2-(3-bromophenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;

1-(4-(2-((2-(4-fluoro-3-(trifluoromethyl)phenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;

1-(4-(2-((2-(3-fluoro-4-(trifluoromethoxy)phenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;

1-(4-(2-((2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;

1-(3,5-dimethyl-4-(2-((4-oxo-2-(3-(trifluoromethyl)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione;

1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione);

1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione;

1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-8-methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione;

5-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-2-oxa-5,7-diazaspiro[3.4]octane-6,8-dione; and

4-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-4,6-diazaspiro[2.4]heptane-5,7-dione.

2. The compound or pharmacologically acceptable salt, a hydrate, or a solvate thereof of claim 1, wherein the compound is 1-(3,5-dimethyl-4-(2-((4-oxo-2-(3-(trifluoromethyl)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione

3. The compound or pharmacologically acceptable salt, a hydrate, or a solvate thereof of claim 1, wherein the compound is 1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione.

4. The compound or pharmacologically acceptable salt, a hydrate, or a solvate thereof of claim 1, wherein the compound is 1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione.

5. The compound or pharmacologically acceptable salt, a hydrate, or a solvate thereof of any one of claims 1-4, which is a hydrate or a solvate.

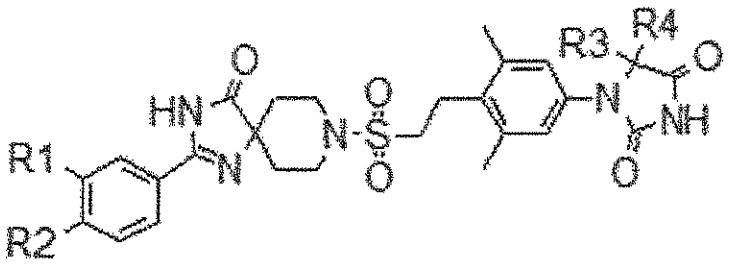
6. A pharmaceutical composition, which comprises the compound or pharmacologically acceptable salt, a hydrate, or a solvate thereof of any one of claims 1 to 5 as an active ingredient.

7. A compound or pharmaceutically acceptable salt, a hydrate, or a solvate thereof of any one of claims 1 to 5 for use as an agent for oral administration.

8. Use of the compound or pharmacologically acceptable salt, a hydrate, or a solvate thereof of any one of claims 1 to 5 for the production of an agent for preventing or treating osteoporosis, fracture, adynamic bone disease, achondroplasia, hypochondroplasia, osteomalacia, osteoarthritis, arthritis, thrombocytopenia, hypoparathyroidism, hyperphosphatemia, or tumoral calcinosis.

CLAIMS

1. A compound represented by general formula (1) below or a pharmacologically acceptable salt thereof:



(1)

(wherein,

when R1 and R2 are not both hydrogens, R1 and R2 are independently:

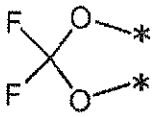
1) hydrogen;

2) halogen atom;

3) an alkyl group comprising one or two carbons that may be substituted with one to five fluorine atoms; or

4) an alkoxy group comprising one or two carbons that may be substituted with one to five fluorine atoms; or

R1 and R2 bond with each other to form a group represented by the formula below:



(wherein each * indicates the position of bonding with the phenyl portion); and

R3 and R4 are independently a methyl group that may be substituted with one to three fluorine atoms; or

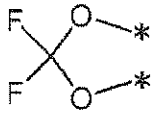
R3 and R4, together with a bound carbon atom, form a three- to six-membered carbocyclic ring (wherein, one of the carbon atoms forming the ring may be replaced with an oxygen atom, a sulfur atom, or a methyl-substituted or unsubstituted nitrogen atom).

2. The compound or pharmacologically acceptable salt thereof of claim 1, wherein R1 and R2 are selected from the combinations below:

1) R1 is a hydrogen atom or a halogen atom, and R2 is a hydrogen atom, a trifluoromethyl group, or a trifluoromethoxy group (provided that R1 and R2 are not both hydrogen atoms);

2) R1 is a trifluoromethyl group or a trifluoromethoxy group, and R2 is a hydrogen atom or a halogen atom;

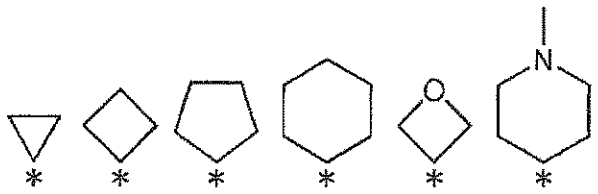
3) R1 and R2 bond with each other to form a group represented by the formula below:



(wherein, each * indicates the position of bonding with the phenyl portion); and

R3 and R4 are methyl groups; or

R3 and R4, together with a bound carbon atom, form a ring selected from below:



(wherein * indicates the position of bonding with the imidazolidine-2,4-dione portion).

3. The compound or pharmacologically acceptable salt thereof of claim 1, wherein R1 and R2 are selected from the combinations below:

1) R1 is a trifuloromethoxy group and R2 is a fluorine atom;

2) R1 is a bromine atom and R2 is a hydrogen atom;

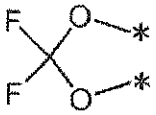
3) R1 is a trifuloromethoxy group and R2 is a fluorine atom;

4) R1 is a fluorine atom and R2 is a trifluoromethoxy group;

5) R1 is a trifluoromethyl group and R2 is a hydrogen atom;

6) R1 is a hydrogen atom and R2 is a trifluoromethoxy group;

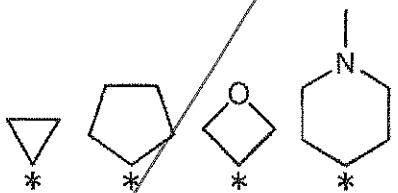
7) R1 and R2 bond with each other to form a group represented by the formula below:



(wherein each * indicates the position of bonding with the phenyl portion); and

R3 and R4 are methyl groups; or

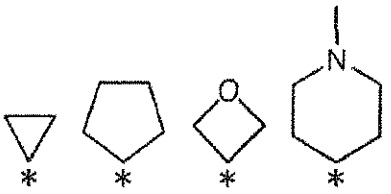
R3 and R4, together with a bound carbon atom, form a ring selected from below:



(wherein * indicates the position of bonding with the imidazolidine-2,4-dione portion).

4. The compound or pharmacologically acceptable salt thereof of claim 1, wherein R3 and R4 are methyl groups.

5. The compound or pharmacologically acceptable salt thereof of claim 1, wherein R3 and R4, together with a bound carbon atom, form a ring selected from below:



(wherein * indicates the position of bonding with the imidazolidine-2,4-dione portion).

6. The compound or pharmacologically acceptable salt thereof of claim 1, wherein the compound is selected from the group consisting of:
1-(4-(2-((2-(4-fluoro-3-(trifluoromethoxy)phenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(4-(2-((2-(3-bromophenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(4-(2-((2-(4-fluoro-3-(trifluoromethyl)phenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(4-(2-((2-(3-fluoro-4-(trifluoromethoxy)phenyl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(4-(2-((2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-4-oxo-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)-3,5-dimethylphenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(3,5-dimethyl-4-(2-((4-oxo-2-(3-(trifluoromethyl)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione;
1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione);
1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione;
1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-8-methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione;
5-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-2-oxa-5,7-diazaspiro[3.4]octane-6,8-dione; and
4-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-4,6-diazaspiro[2.4]heptane-5,7-dione.

7. The compound or pharmacologically acceptable salt thereof of claim 1, wherein the compound is

1-(3,5-dimethyl-4-(2-((4-oxo-2-(3-(trifluoromethyl)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl) sulfonyl)ethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione

8. The compound or pharmacologically acceptable salt thereof of claim 1, wherein the compound is
1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione.

9. The compound or pharmacologically acceptable salt thereof of claim 1, wherein the compound is
1-(3,5-dimethyl-4-(2-((4-oxo-2-(4-(trifluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]deca-1-en-8-yl)sulfonyl)ethyl)phenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione.

10. A pharmaceutical composition, which comprises the compound or pharmacologically acceptable salt thereof of any one of claims 1 to 9 as an active ingredient.

11. The pharmaceutical composition of claim 10, which is for use in oral administration.

12. A pharmaceutical composition for activating intracellular cAMP response, which comprises the compound or pharmacologically acceptable salt thereof of any one of claims 1 to 9 as an active ingredient.

13. A stem cell-mobilizing agent, or an agent for preventing or treating osteoporosis, fracture, adynamic bone disease, achondroplasia, hypochondroplasia, osteomalacia, osteoarthritis, arthritis, thrombocytopenia, hypoparathyroidism, hyperphosphatemia or tumoral calcinosis, which comprises the compound or pharmacologically acceptable salt thereof of any one of claims 1 to 9 as an active ingredient.

14. Use of the compound or pharmacologically acceptable salt thereof of any one of claims 1 to 9 for the production of a stem cell-mobilizing agent or an agent for preventing or treating osteoporosis, fracture, adynamic bone disease, achondroplasia, hypochondroplasia, osteomalacia, osteoarthritis, arthritis, thrombocytopenia, hypoparathyroidism, hyperphosphatemia, or tumoral calcinosis.

15. The compound or pharmacologically acceptable salt thereof of any of claims 1 to 9 for treatment or prevention of osteoporosis, fracture, adynamic bone disease, achondronplasia, hypochondroplasia, osteomalacia, osteoarthritis, arthritis, thrombocytopenia, hypoparathyroidism, hyperphosphatemia, or tumoral calcinosis, or stem cell mobilization.