[DESCRIPTION]

[Title of Invention]

SCHWANN CELL DIFFERENTIATION PROMOTER AND/OR DEDIFFERENTIATION INHIBITOR

[Technical Field]

[0001]

The present invention is a therapeutic agent or ameliorative agent containing a vitamin D derivative, and specifically relates to a therapeutic agent or ameliorative agent for a disease whose symptoms are ameliorated or alleviated by differentiation-promoting effect on immature Schwann cells, dedifferentiation-inhibiting effect on mature Schwann cells, and/or differentiation-promoting effect on dedifferentiated Schwann cells. More specifically, the vitamin D derivative used in the present invention is a vitamin D derivative having a cyclic tertiary amine in the side chain and includes pharmaceutically acceptable salts and solvates thereof. Examples of pharmaceuticals that can be clinically applied as therapeutic agents or ameliorative agents for diseases whose symptoms are ameliorated or alleviated by differentiation-promoting effect or dedifferentiation-inhibiting effect on Schwann cells include therapeutic agents or ameliorative agents used for Chemotherapy Induced peripheral neuropathy (CIPN), Diabetic Neuropathy (DN), Myasthenia gravis (MG), and Amyotrophic lateral sclerosis (ALS).

[Background Art]

[0002]

Schwann cells are glial cells that form myelin sheaths (myelin) in peripheral

nerves. When myelin in peripheral nerves is damaged by hyperglycemia, anticancer drugs, etc., Schwann cells dedifferentiate and demyelinate, leading to various neuropathies. Although such peripheral neuropathy can occur in various pathological conditions, there is no effective treatment currently, which necessitate the development of a fundamental treatment based on inhibiting dedifferentiation and promoting differentiation of Schwann cells.

[0003]

PTLs 1 to 3 disclose compounds having neuroprotective and/or neuroreparative effects. All of these are based on their effects on Schwann cells, and PTL 1 shows the promotion of Schwann cell differentiation, neurite elongation, and increase in neuromuscular junctions. PTLs 2 and 3 show the suppression of dedifferentiation.

[0004]

In contrast, although the vitamin D derivatives of the present invention are disclosed in PTLs 4 and 5, these vitamin D derivatives are not known to have differentiation-promoting effect or dedifferentiation-inhibiting effect on Schwann cells.

[Citation List]

[Patent Literature]

[0005]

[PTL 1] WO2021/241504

[PTL 2] WO2020/027150

[PTL 3] WO2021/15369

[PTL 4] WO2022/059684

[PTL 5] WO2023/171736

[Summary of Invention]

[Technical Problem]

[0006]

The problem to be solved by the present invention is to provide a therapeutic agent or ameliorative agent for diseases whose symptoms are ameliorated or alleviated by differentiation-promoting effect on immature Schwann cells, dedifferentiation-inhibiting effect on mature Schwann cells, and/or differentiation-promoting effect on dedifferentiated Schwann cells (hereinafter may be abbreviated as "Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect").

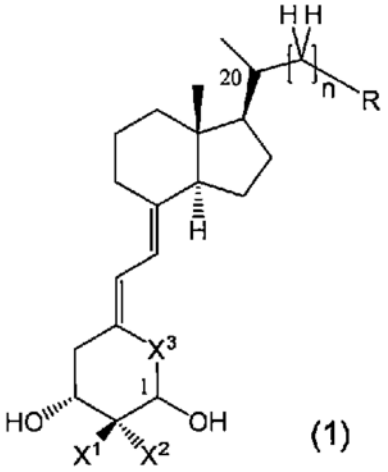
[Solution to Problem]

[0007]

As a result of diligent research, the inventors have found out that a vitamin D derivative represented by the following formula (1), or a pharmaceutically acceptable salt or solvate thereof has a Schwann cell differentiation-promoting effect and/or dedifferentiation-inhibiting effect, and has completed the present invention.

[0008]

[Chem. 1]



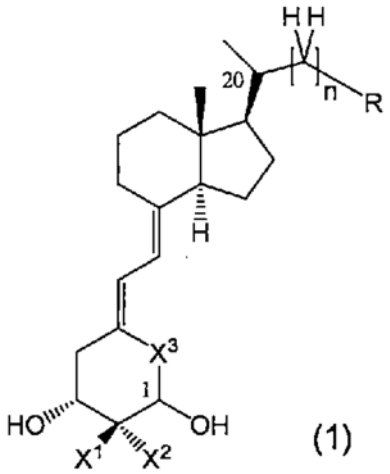
[0009]

That is, the purpose of the present invention relates, for example, to the following:

[0010]

[Clause 1] A therapeutic agent or ameliorative agent for a disease whose symptoms are ameliorated or alleviated by Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect, comprising a vitamin D derivative represented by formula (1), or a pharmaceutically acceptable salt or solvate thereof.

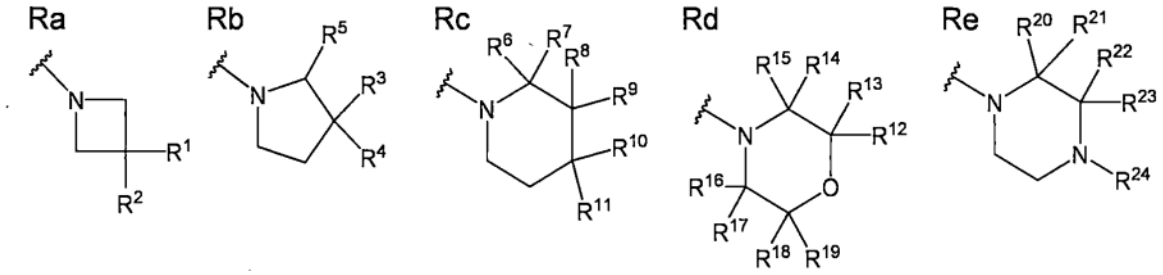
[Chem. 2]



(In the formula, R represents any one of the structures Ra, Rb, Rc, Rd, and Re in the

following formulas.

[Chem. 3]



[0011]

R^1, R^3, R^8, and R^{10} each independently represent a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, a C_3-C_6 cycloalkyl group, a C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms, a halogen atom, or a hydrogen atom.

R^2, R^4, R^9, and R^{11} each independently represent a hydrogen atom, a hydroxy group, or a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms. (wherein, when R^1, R^3, R^8, and R^{10} each independently represent a C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms, or a halogen atom, R^2, R^4, R^9, and R^{11} substituting on the same carbon atom as R^1, R^3, R^8, and R^{10} are not hydroxy groups, respectively.)

R^6, R^7, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, and R^{23} each independently represent a hydrogen atom, a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, or a C_3-C_6 cycloalkyl group.

Each pair of R^1 and R^2, R^3 and R^4, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{14} and R^{15}, R^{16} and R^{17}, R^{18} and R^{19}, R^{20} and R^{21}, and R^{22} and R^{23} can be bonded with each other to form a 3- to 5-membered ring structure.

R^5 represents a hydrogen atom, a C_1-C_6 alkyl group optionally substituted with one -OR^{501} group, or a C_3-C_6 cycloalkyl group optionally substituted with one -OR^{501} group, and R^{501}

represents a hydrogen atom, or a C_1-C_6 alkyl group.

R^{24} represents a hydrogen atom, a C_1-C_3 alkyl group, or a C_1-C_3 alkylsulfonyl group.

The stereochemistry at 2-position of the pyrrolidine ring (Rb) represents either (R) configuration or (S) configuration.

X^1 and X^2 each independently represent a hydrogen atom or a C_1-C_3 alkyl group, or X^1 and X^2 together form a methylidene group, or $-(CH_2)_m-$ (wherein m is an integer of 2 to 5).

X^3 represents a CH_2 group or a $C=CH_2$ group (wherein, when X^1 and X^2 together form a methylidene group, X^3 is not a $C=CH_2$ group).

n represents an integer of 1 to 3.

The stereochemistry of the hydroxy group at 1-position represents either (R) configuration or (S) configuration.

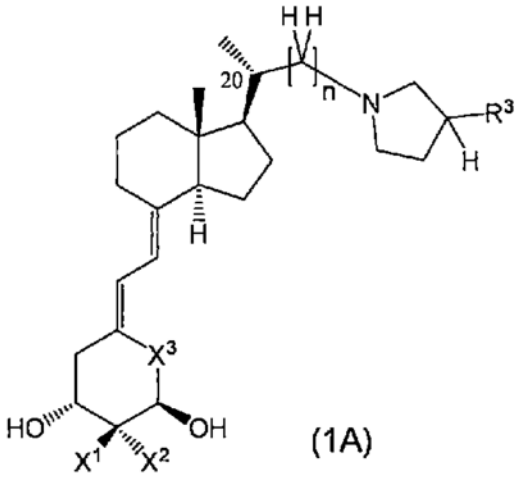
The stereochemistry of the methyl group at 20-position represents either (R) configuration or (S) configuration.)

[0012]

[Clause 2] The therapeutic agent or ameliorative agent according to clause 1,

wherein the vitamin D derivative of formula (1) is represented by the following formula (1A).

[Chem. 4]



(1A)

(n represents an integer of 1 to 3.

R^3 represents a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, a C_3-C_6 cycloalkyl group, a C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms.

X^1 and X^2 each independently represent a hydrogen atom or a C_1-C_3 alkyl group, or X^1 and X^2 together form a methylidene group, or $-(CH_2)_m-$ (wherein m is an integer of 2 to 5).

X^3 represents a CH_2 group or a $C=CH_2$ group (wherein, when X^1 and X^2 together form a methylidene group, X^3 is not a $C=CH_2$ group).)

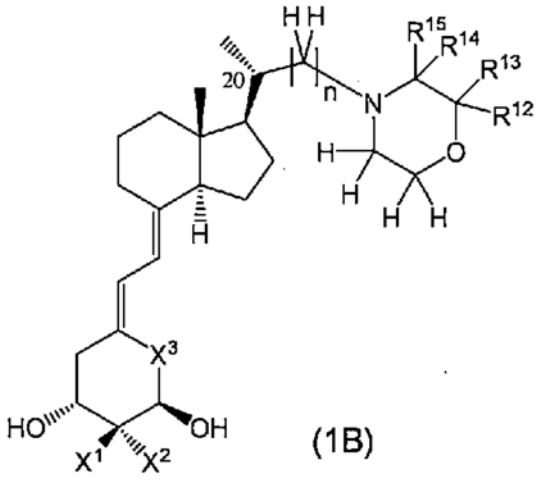
[0013]

[Clause 3] The therapeutic agent or ameliorative agent according to clause 2, wherein n represents 1, R^3 represents a C_2-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, or a C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms.

[0014]

[Clause 4] The therapeutic agent or ameliorative agent according to clause 1, wherein the vitamin D derivative of formula (1) is represented by the following formula (1B).

[Chem. 5]



(1B)

(n represents an integer of 1 to 3.

R^{12}, R^{13}, R^{14}, and R^{15} each independently represent a hydrogen atom, a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, or a C_3-C_6 cycloalkyl group.

Each pair of R^{12} and R^{13}, and R^{14} and R^{15} can be bonded with each other to form a 3- to 5-membered ring structure.

X^1 and X^2 each independently represent a hydrogen atom or a C_1-C_3 alkyl group, or X^1 and X^2 together form a methylidene group, or $-(CH_2)_m-$ (wherein m is an integer of 2 to 5).

X^3 represents a CH_2 group or a $C=CH_2$ group (wherein, when X^1 and X^2 together form a methylidene group, X^3 is not a $C=CH_2$ group).)

[0015]

[Clause 5] The therapeutic agent or ameliorative agent according to clause 4, wherein n represents 1, R^{12} and R^{13} are bonded with each other to represent a cyclopropyl group, or R^{14} and R^{15} simultaneously represent a methyl group.

[Clause 6] The therapeutic agent or ameliorative agent according to any one of clauses 1 to 5, wherein X^1 and X^2 are hydrogen atoms and X^3 is a CH_2 group.

[Clause 7] The therapeutic agent or ameliorative agent according to any one of clauses 1

to 5, wherein X^1 and X^2 are hydrogen atoms and X^3 is a $C=CH_2$ group.

[Clause 8] The therapeutic agent or ameliorative agent according to any one of clauses 1 to 5, wherein X^1 and X^2 together form a methylidene group and X^3 is a CH_2 group.

[Clause 9] The therapeutic agent or ameliorative agent according to any of clauses 1, 2, 4, or 6 to 8, wherein n represents 2.

[Clause 10] The therapeutic agent or ameliorative agent according to any one of clauses 1 to 9, wherein the vitamin D derivative represented by formula (1) is any one of the following vitamin D derivatives, or a pharmaceutically acceptable salt or solvate thereof:

(1) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-ethylpyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol (Compound B005)

(2) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-ethylpyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol (Compound B006)

(3) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(1,1-difluoroethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B030)

(4) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(1,1-difluoroethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B034)

(5) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(2,2-difluoroethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B042)

(6) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(2,2-difluoroethyl)pyrrolidin-1-

yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B043)

(7) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(difluoromethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B051)

(8) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(difluoromethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B052)

(9) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(2,2-difluoroethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B057)

(10) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(2,2-difluoroethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B058)

(11) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(3,3-difluoropropyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B063)

(12) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(3,3-difluoropropyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B064)

(13) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-3-(difluoromethyl)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B080)

(14) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((R)-3-(difluoromethyl)pyrrolidin-1-

yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B081)

(15) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((R)-3-(2,2-difluoroethyl)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B082)

(16) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-3-(1,1-difluoroethyl)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B083)

(17) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-3-(difluoromethoxy)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B086)

(18) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((R)-3-(difluoromethoxy)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B087)

(19) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-(4-oxa-7-azaspiro[2.5]octan-7-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D019)

(20) (1R,3S,Z)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-morpholinobutan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (Compound D022)

(21) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-morpholinobutan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D023)

(22) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-morpholinobutan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol

(Compound D024)

(23) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((S)-2-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol (Compound D025)

(24) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-(4-oxa-7-azaspiro[2.5]octan-7-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D030)

(25) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-2-(difluoromethyl)morpholino)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D034)

(26) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((S)-2-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D041)

(27) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((R)-3-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D042)

(28) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((S)-3-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D043)

(29) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-5-morpholinopentan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D044)

(30) (1R,3S,Z)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-(3,3-dimethylmorpholino)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (Compound F006)

(31) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-(3,3-dimethylmorpholino)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound G006).

[0016]

[Clause 11] The therapeutic agent or ameliorative agent according to any one of clauses 1 to 10, wherein a disease whose symptoms are ameliorated or alleviated by Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect is Chemotherapy Induced peripheral neuropathy (CIPN).

[Clause 12] The therapeutic agent or ameliorative agent according to any one of clauses 1 to 10, wherein a disease whose symptoms are ameliorated or alleviated by Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect is Diabetic Neuropathy (DN).

[Clause 13] The therapeutic agent or ameliorative agent according to any one of clauses 1 to 10, wherein a disease whose symptoms are ameliorated or alleviated by Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect is Myasthenia gravis (MG).

[Clause 14] The therapeutic agent or ameliorative agent according to any one of clauses 1 to 10, wherein a disease whose symptoms are ameliorated or alleviated by Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect is Amyotrophic lateral sclerosis (ALS).

[Advantageous Effects of Invention]

[0017]

The present invention provides a therapeutic agent or ameliorative agent for a

disease whose symptoms are ameliorated or alleviated by differentiation-promoting effect on immature Schwann cells, dedifferentiation-inhibiting effect on mature Schwann cells, and/or differentiation-promoting effect on dedifferentiated Schwann cells.

[Brief Description of Drawings]

[0018]

Fig. 1 shows the differentiation-promoting effect by the vitamin D derivative of the present invention on immature Schwann cells.

Fig. 2 shows the dedifferentiation-inhibiting effect and differentiation-promoting effect by the vitamin D derivative of the present invention on paclitaxel-induced Schwann cell dedifferentiation.

Fig. 3 shows the dedifferentiation-inhibiting effect and differentiation-promoting effect by the vitamin D derivative of the present invention on paclitaxel-induced Schwann cell dedifferentiation.

Fig. 4 shows the dedifferentiation-inhibiting effect and differentiation-promoting effect by the vitamin D derivative of the present invention on high glucose-induced Schwann cell dedifferentiation.

Fig. 5 shows the comparation result of the dedifferentiation-inhibiting effect and differentiation-promoting effect among the vitamin D derivative D023 of the present invention, Eldecalcitol, and 1α,25-dihydroxyvitamin D_3 on high glucose-induced Schwann cell dedifferentiation.

Fig. 6 shows the pain inhibitory effect by the vitamin D derivative of the present invention on Streptozotocin (STZ)-induced diabetic rats.

[Description of Embodiments]

[0019]

Terms used alone or in combination in the present description will be explained below. Unless otherwise stated, the explanation of each substituent shall be common to each part. When a variable exists in each of any components, the variable is defined independently from other components. In addition, combinations of substituents and variables are permissible only if such combinations result in chemically stable compounds. When the substituent itself is substituted with two or more groups, these many groups can exist on the same or different carbon atom as long as a stable structure is formed.

[0020]

In the present invention, "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom.

[0021]

In the present invention, "C_1-C_6 alkyl group" means a monovalent saturated linear or branched aliphatic hydrocarbon group having 1 to 6 carbon atoms, and includes methyl group, ethyl group, n-propyl group, n-butyl group, n-pentyl group, n-hexyl group, isopropyl group, isobutyl group, s-butyl group, t-butyl group, isopentyl group, 2-methylbutyl group, neopentyl group, 1-ethylpropyl group, 4-methylpentyl group, 3-methylpentyl group, 2-methylpentyl group, 1-methylpentyl group, 3,3-dimethylbutyl group, 2,2-dimethylbutyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group, 1,3-dimethylbutyl group, 2,3-dimethylbutyl group, 1-ethylbutyl group, 2-ethylbutyl group, t-pentyl group, and isohexyl group.

[0022]

In the present invention, "methylidene group" refers to a $=CH_2$ group.

[0023]

In the present invention, "C_3-C_6 cycloalkyl group" means a cycloalkyl group having 3 to 6 carbon atoms. Examples of those cyclic alkyl groups include, though not limited to these, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

[0024]

In the present invention, "C_1-C_6 alkoxy group" means a group composed of an alkyl group having 1 to 6 carbon atoms among the above "C_1-C_6 alkyl group" and an oxy group. Examples of these include methoxy group, ethoxy group, n-propyloxy group, isopropyloxy group, n-butoxy group, s-butoxy group, 2-methylpropoxy group, n-pentyloxy group, isopentyloxy group, 2-methylbutoxy group, 1-ethylpropoxy group, 2,2-dimethylpropoxy group, n-hexyloxy group, 4-methylpentoxy group, 3-methylpentoxy group, 2-methylpentoxy group, 3,3-dimethylbutoxy group, 2,2-dimethylbutoxy group, 1,1-dimethylbutoxy group, and t-butoxy group.

[0025]

In the present invention, "C_1-C_6 alkylsulfonyl group" means a group composed of the above "C_1-C_6 alkyl group" and a sulfonyl group. Examples of these include methylsulfonyl group, ethylsulfonyl group, and isopropylsulfonyl group.

[0026]

In the above definition, for example, "C" in such as "C_1" represents a carbon atom, and the numeral following "C" represents the number of carbon atoms. For example, "C_1-C_6" represents a range from 1 to 6 carbon atoms. Of course, in the present invention, if the numeral for carbon atoms is changed, it means the same group having

the changed number of carbon atoms. For example, "C_1-C_3 alkyl group" means those having 1 to 3 carbon atoms among the alkyl groups defined by "C_{1-6} alkyl group". The rule of the numeral for carbon atoms is the same in other groups.

[0027]

In the present invention, "C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms" means a C_1-C_6 alkyl group which may have 1 to 3 halogen atoms at the substitutable positions. When a C_1-C_6 alkyl group is substituted with a plurality of halogen atoms, the C_1-C_6 alkyl group may be substituted with halogen atoms of the same kind or different kind. “C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms” and the like also obey the same rule.

[0028]

In the present invention, "vitamin D derivative" means a compound having a secosteroid structure (i.e., 4-(2-cyclohexylideneethylidene)octahydro-1H-indene).

[0029]

In the formula (1) above, X^1 and X^2 each independently represent a hydrogen atom or a C_1-C_3 alkyl group, or X^1 and X^2 together form a methylidene group, or $-(CH_2)_m-$ (wherein m is an integer of 2 to 5). Preferably, X^1 and X^2 each independently represent a hydrogen atom, or X^1 and X^2 together form a methylidene group.

[0030]

In the formula (1) above, X^3 represents a CH_2 group or a $C=CH_2$ group (wherein, when X^1 and X^2 together form a methylidene group, X^3 is not a $C=CH_2$ group).

[0031]

Preferred combinations of X^1 , X^2 , and X^3 include the following cases: (i) X^1 and X^2 represent hydrogen atoms and X^3 represents a CH_2 group, (ii) X^1 and X^2 represent

hydrogen atoms and X^3 represents a C= CH_2 group, and (iii) X^1 and X^2 together form a methylidene group and X^3 represents a CH_2 group.

[0032]

In the formula (1) above, n represents an integer of 1 to 3.

The stereochemistry of the methyl group at 20-position in the above formula (1) may be either (R) configuration or (S) configuration.

The stereochemistry of hydroxy group at 1-position in the above formula (1) may be either (R) configuration or (S) configuration.

In the formula (1) above, R represents the structure of Ra to Re described above. Of these, the pyrrolidine ring (Rb) and the morpholine ring (Rd) are particularly preferred structures. The stereochemistry at 2-position of the pyrrolidine ring (Rb) represents either (R) configuration or (S) configuration.

[0033]

R^1, R^3, R^8, and R^{10} each independently represent a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, a C_3-C_6 cycloalkyl group, a C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms, a halogen atom, or a hydrogen atom. Preferred groups for R^1, R^3, R^8, and R^{10} include a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, a C_3-C_6 cycloalkyl group, a C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms, a fluorine atom, or a hydrogen atom, more preferably a methyl group, an ethyl group, a methoxy group, an ethoxy group, a difluoromethyl group, a 1,1-difluoroethyl group, a 2,2-difluoroethyl group, a difluoromethoxy group, a 2,2-difluoroethoxy group, a 3,3-difluoropropyl group, and a 2,2-difluoropropyl group.

[0034]

R^2, R^4, R^9, and R^{11} each independently represent a hydrogen atom, a hydroxy group, or a C_1-C_3 alkyl group optionally substituted with 1 to 3 halogen atoms. A hydrogen atom, a hydroxy group, or a C_1-C_3 alkyl group optionally substituted with 1 to 3 fluorine atoms is preferable, and a hydrogen atom or a hydroxy group is more preferable. When R^1, R^3, R^8, and R^{10} each independently represent a C_1-C_3 alkoxy group optionally substituted with 1 to 3 halogen atoms or a halogen atom, R^2, R^4, R^9, and R^{11} substituting on the same carbon atom as R^1, R^3, R^8, and R^{10} are preferably not hydroxy groups but hydrogen atoms, respectively.

[0035]

R^6, R^7, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, and R^{23} each independently represent a hydrogen atom, a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, or a C_3-C_6 cycloalkyl group. Among these, a hydrogen atom, a C_1-C_6 alkyl group optionally substituted with 1 to 3 fluorine atoms, or a C_3-C_6 cycloalkyl group is preferable, and a hydrogen atom, a methyl group, or a difluoromethyl group is more preferable.

[0036]

Each pair of R^1 and R^2, R^3 and R^4, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{14} and R^{15}, R^{16} and R^{17}, R^{18} and R^{19}, R^{20} and R^{21}, and R^{22} and R^{23} can be bonded with each other to form a 3- to 5-membered ring structure. Here, the 3- to 5-membered ring structure is a hydrocarbon ring, and each pair of R^1 and R^2, R^3 and R^4, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{14} and R^{15}, R^{16} and R^{17}, R^{18} and R^{19}, R^{20} and R^{21}, and R^{22} and R^{23} together with the carbon atom substituted with each pair can form a cyclopropyl ring, a cyclobutyl ring, or a cyclopentyl ring.

[0037]

R^5 represents a hydrogen atom, a C_1-C_6 alkyl group optionally substituted with one -OR^{501} group, or a C_3-C_6 cycloalkyl group optionally substituted with one -OR^{501} group, and R^{501} represents a hydrogen atom, or a C_1-C_6 alkyl group. R^5 is preferably a hydrogen atom or -$C(CH_3)_2$-OR^{501}.

[0038]

R^{24} represents a hydrogen atom, a C_1-C_3 alkyl group, or a C_1-C_3 alkylsulfonyl group. Methylsulfonyl is particularly preferable.

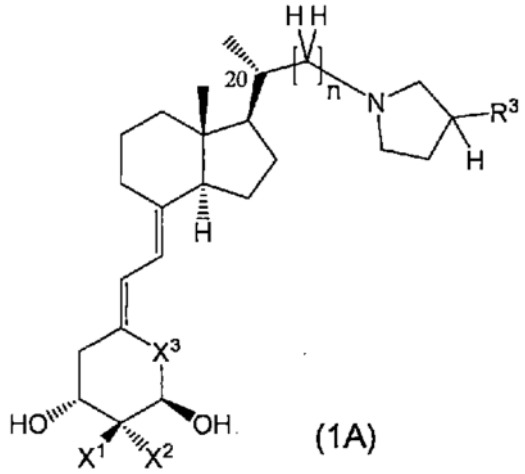
[0039]

Further, among the vitamin D derivatives represented by formula (1) or pharmaceutically acceptable salts or solvates thereof, specific preferred examples of the present invention include vitamin D derivatives represented by formulas (1A) and (1B) or pharmaceutically acceptable salts or solvates thereof.

[0040]

A vitamin D derivative represented by formula (1A) or a pharmaceutically acceptable salt or solvate thereof

[Chem. 6]



(1A)

(n represents an integer of 1 to 3.

R^3 represents a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, a C_3-C_6 cycloalkyl group, or a C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms.

X^1 and X^2 each independently represent a hydrogen atom or a C_1-C_3 alkyl group, or X^1 and X^2 together form a methylidene group, or $-(CH_2)_m-$ (wherein m is an integer of 2 to 5).

X^3 represents a CH_2 group or a $C=CH_2$ group (wherein, when X^1 and X^2 together form a methylidene group, X^3 is not a $C=CH_2$ group).)

[0041]

In formula (1A), n preferably represents 1 or 2. When n represents 1, R^3 preferably represents a C_2-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, or a C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms.

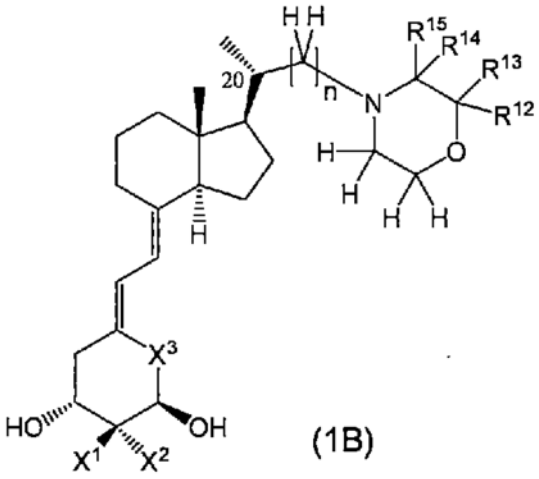
[0042]

In formula (1A), preferred combinations of X^1, X^2, and X^3 include the following cases: (i) X^1 and X^2 represent hydrogen atoms and X^3 represents a CH_2 group, (ii) X^1 and X^2 represent hydrogen atoms and X^3 represents a $C= CH_2$ group, and (iii) X^1 and X^2 together form a methylidene group and X^3 represents a CH_2 group.

[0043]

A vitamin D derivative represented by formula (1B) or a pharmaceutically acceptable salt or solvate thereof

[Chem. 7]



(1B)

(n represents an integer of 1 to 3.

R^{12}, R^{13}, R^{14}, and R^{15} each independently represent a hydrogen atom, a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, or a C_3-C_6 cycloalkyl group.

Each pair of R^{12} and R^{13}, and R^{14} and R^{15} can be bonded with each other to form a 3- to 5-membered ring structure. Here, the 3- to 5-membered ring structure is a hydrocarbon ring, and each pair of R^{12} and R^{13} and R^{14} and R^{15} together with the carbon atom substituted with each pair can form a cyclopropyl ring, a cyclobutyl ring, or a cyclopentyl ring.

X^1 and X^2 each independently represent a hydrogen atom or a C_1-C_3 alkyl group, or X^1 and X^2 together form a methylidene group, or $-(CH_2)_m-$ (wherein m is an integer of 2 to 5).

X^3 represents a CH_2 group or a $C=CH_2$ group (wherein, when X^1 and X^2 together form a methylidene group, X^3 is not a $C=CH_2$ group).)

[0044]

In formula (1B), n preferably represents 1 or 2. When n represents 1, it is preferable that R^{12} and R^{13} are bonded with each other to represent a cyclopropyl group, or that R^{14} and R^{15} simultaneously represent methyl groups.

[0045]

In formula (1B), preferred combinations of X^1, X^2, and X^3 include the following cases: (i) X^1 and X^2 represent hydrogen atoms and X^3 represents a CH_2 group, (ii) X^1 and X^2 represent hydrogen atoms and X^3 represents a C= CH_2 group, and (iii) X^1 and X^2 together form a methylidene group and X^3 represents a CH_2 group.

[0046]

Specific preferred examples of the vitamin D derivative of the present invention represented by formula (1) include the following compounds.

(1) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-ethylpyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol (Compound B005)

(2) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-ethylpyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol (Compound B006)

(3) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(1,1-difluoroethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B030)

(4) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(1,1-difluoroethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B034)

(5) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(2,2-difluoroethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B042)

(6) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(2,2-difluoroethyl)pyrrolidin-1-

yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B043)

(7) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(difluoromethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B051)

(8) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(difluoromethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B052)

(9) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(2,2-difluoroethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B057)

(10) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(2,2-difluoroethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B058)

(11) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(3,3-difluoropropyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B063)

(12) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(3,3-difluoropropyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B064)

(13) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-3-(difluoromethyl)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B080)

(14) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((R)-3-(difluoromethyl)pyrrolidin-1-

yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B081)

(15) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((R)-3-(2,2-difluoroethyl)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B082)

(16) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-3-(1,1-difluoroethyl)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B083)

(17) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-3-(difluoromethoxy)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B086)

(18) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((R)-3-(difluoromethoxy)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B087)

(19) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-(4-oxa-7-azaspiro[2.5]octan-7-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D019)

(20) (1R,3S,Z)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-morpholinobutan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (Compound D022)

(21) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-morpholinobutan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D023)

(22) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-morpholinobutan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol

(Compound D024)

(23) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((S)-2-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol (Compound D025)

(24) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-(4-oxa-7-azaspiro[2.5]octan-7-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D030)

(25) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-2-(difluoromethyl)morpholino)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D034)

(26) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((S)-2-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D041)

(27) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((R)-3-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D042)

(28) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((S)-3-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D043)

(29) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-5-morpholinopentan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D044)

(30) (1R,3S,Z)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-(3,3-dimethylmorpholino)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (Compound F006)

(31) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-(3,3-dimethylmorpholino)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound G006).

[0047]

The vitamin D derivative of the present invention can be converted into a pharmaceutically acceptable salt thereof, as necessary. Examples of such a salt include hydrochloride, hydrobromide, methanesulfonate, para-toluenesulfonate, acetate, trifluoroacetate, fumarate, maleate, malate, succinate, oxalate, citrate, and benzoate. Particularly preferred salts include hydrochloride, acetate, fumarate, maleate, malate, and succinate.

[0048]

In addition, the vitamin D derivative of the present invention can be converted into a pharmaceutically acceptable solvate thereof, as necessary. Examples of such a solvent include water, methanol, ethanol, 1-propanol, 2-propanol, butanol, acetonitrile, acetone, methyl ethyl ketone, methyl acetate, and ethyl acetate. Particularly preferred are water, methanol, ethanol, and acetonitrile.

[0049]

Vitamin D derivatives represented by formula (1), or pharmaceutically acceptable salts or solvates thereof, have excellent effects in promoting differentiation on immature Schwann cells, inhibiting dedifferentiation on mature Schwann cells, and/or promoting differentiation on dedifferentiated Schwann cells. The excellent effects in promoting differentiation on immature Schwann cells, inhibiting dedifferentiation on mature Schwann cells, and/or promoting differentiation on dedifferentiated Schwann cells are useful for a therapeutic agent or ameliorative agent for diseases whose symptoms

are ameliorated or alleviated by the effects in promoting differentiation on immature Schwann cells, inhibiting dedifferentiation on mature Schwann cells, or promoting differentiation on dedifferentiated Schwann cells. More specifically, the vitamin D derivatives or pharmaceutically acceptable salts or solvates thereof can be clinically applied as therapeutic agents or ameliorative agents for Chemotherapy Induced peripheral neuropathy (CIPN), Diabetic Neuropathy (DN), Myasthenia gravis (MG), and Amyotrophic lateral sclerosis (ALS).

[0050]

The therapeutic agent or ameliorative agent for a disease whose symptoms are ameliorated or alleviated by Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect, containing a vitamin D derivative represented by formula(1), or a pharmaceutically acceptable salt or solvate thereof, is prepared into a pharmaceutical composition using those commonly used in formulation such as, carriers, bases, excipients, and other additives. The carrier, base and excipient used in pharmaceutical compositions may be solid or liquid, and examples thereof include lactose, magnesium stearate starch, talc, gelatin, agar, pectin, gum arabic, olive oil, sesame oil, cocoa butter, ethylene glycol, and medium chain fatty acid triglycerides, as well as others commonly used. Administration may be in any form such as oral administration by tablet, pill, capsule, soft capsule, granule, powder, liquid, etc., or parenteral administration by injection such as intravenous injection, intramuscular injection, etc., suppository, transdermal and nasal administration, etc.

[0051]

The therapeutically effective dose of the active ingredient in the therapeutic agent of the present invention varies depending on the administration route, the age and

sex of the patient, and the severity of the disease, but is usually about 0.1 to 10000 μg/day, and the frequency of administration is usually 1 to 3 times/day to 1 to 3 times/week, and the formulation is preferably prepared to satisfy such conditions. However, since the dose varies depending on various conditions, a dose smaller than the above dose sometimes may be sufficient, and a dose exceeding the above range sometimes may be required.

[Examples]

[0052]

The present invention will be specifically described based on the following examples, but the present invention is not limited to these examples. Furthermore, the vitamin D derivative of the present invention can be obtained by the method described in WO2022/059684.

[0053]

[Example 1]

Evaluation of the differentiation-promoting effect by the vitamin D derivatives of the present invention on immature Schwann cells.

1) Preparation of rat Schwann cells

Primary rat Schwann cells were prepared as follows. Sciatic nerves were collected from Wistar/ST rats (1-day-old, Japan SLC) and treated for 2 hours at 37°C in a medium (2 mM GlutaMAX (Gibco #35050-061) / 1% Penicillin-Streptomycin (Gibco #15140-122) / Serum-free Advanced DMEM/F-12 (Gibco #12634-010)), containing 250 U/mL hyaluronidase type I-S (Sigma-Aldrich #H3506) and 160 U/mL collagenase type I (Merck Millipore #SCR103).. After pipetting, the sample was centrifuged (300×g, 5 minutes, room temperature) and the pellet was resuspended in maintenance medium (2 μM forskolin (Sigma-Aldrich #6886) / 20 ng/mL heregulin β-1 (Sigma-Aldrich #H7660)

in 5% D-(+)-trehalose Dihydrate (Nacalai Tesque #11667-34) / 2 mM GlutaMAX (Gibco #35050-061) / 1% Penicillin-Streptomycin (Gibco #15140-122) / Serum-free Advanced DMEM/F-12 (Gibco #12634-010)), and the entire cell suspension was seeded onto a 6-well plate coated with poly-L-lysine (SIGMA-ALDRICH #P4707). The plate was then incubated in a CO_2 incubator under 5% CO_2 at 37°C. After 4 days of culture, the culture medium was replaced with maintenance medium containing 10% heat inactivated fetal bovine serum. Four days after replacing the culture medium, the cells were harvested and resuspended in removing fibroblast medium (0.1% mouse anti-CD90/Thy1 antibody (BIO-RAD #MCA04GT) / 3% bovine serum albumin (SIGMA-ALDRICH #A7906-50G) / 2 mM GlutaMAX (Gibco #35050-061) / 1% Penicillin-Streptomycin (Gibco #15140-122) / Serum-free Advanced DMEM/F-12 (Gibco #12634-010)), and incubated on ice for 2 hours. After centrifugation (300×g, 5 minutes, room temperature), the pellet was treated for 1 hour at 37°C with rabbit complement medium (20% rabbit complement (CEDARLANE #CL3441-S50-R) / 3% bovine serum albumin (SIGMA-ALDRICH #A7906-50G) / 2 mM GlutaMAX (Gibco #35050-061) / 1% Penicillin-Streptomycin (Gibco #15140-122) / Serum-free Advanced DMEM/F-12 (Gibco #12634-010)) to remove fibroblasts. After centrifugation (300×g, 5 minutes, room temperature), the pellet was resuspended in maintenance medium and seeded at a density of 5.0×10^5 cells/10 mL/dish onto a 10 cm dish coated with poly-L-lysine (SIGMA-ALDRICH #P4707). Subsequently, cells obtained through expansion culture were defined as primary rat Schwann cells and used in the experiments.

2) Evaluation of the vitamin D derivatives of the present invention

The vitamin D derivatives of the present invention were evaluated according to the following procedure. The obtained primary rat Schwann cells were suspended in

maintenance medium, seeded onto a 10-cm dish coated with poly-L-lysine (SIGMA-ALDRICH #P4707), and cultured under the condition of 5.0% CO_2 at 37°C. Subconfluent cells were washed with PBS, detached with 0.05% Trypsin/EDTA (Gibco #25300-054), and then centrifuged (300×g, 5 minutes, room temperature). After removing the supernatant, the cells were suspended in maintenance medium to prepare a cell suspension. The cell suspension was seeded at a density of 2.0×10^4 cells/100 μL/well onto a Poly-D-lysine 96-well Black Clear plate (CORNING, 254640), and cultured under the condition of 5.0% CO_2 at 37°C. After confirming cell adhesion, 100 μL/well of maintenance medium containing vitamin D derivatives prepared at each concentration or 0.1% DMSO was added to each well to give a final volume of 200 μL/well, and then the cells were cultured for 2 days. After culturing, immunostaining and image analysis for MAG were performed as follows. After removing all the supernatant and washing with PBS, 4% paraformaldehyde (FUJIFILM Wako Pure Chemical Corporation #163-20145) was added thereto, and the cells were fixed by incubation at room temperature for 15 minutes. After removing the supernatant, a 0.1% Tween-20-containing skim milk solution was added thereto, and the cells were incubated at room temperature for 30 minutes. After washing three times with PBS, a PBS solution containing 2.5 μg/mL anti-MAG antibody (Millipore #MAB1567) was added thereto, and the cells were incubated overnight at 4°C. After washing three times with PBS, a PBS solution containing 5 μg/mL Alexa fluor 488 anti-mouse IgG (Invitrogen, A11029) was added thereto, and the cells were incubated at room temperature for 60 minutes. After washing three times with PBS, a PBS solution containing 1 μg/mL Hoechst33342 (DOJINDO #NU043) was added thereto, and the cells were incubated for 15 minutes at room temperature in the dark. Subsequently, fluorescence images of six fields of view per well were acquired using a

fluorescence microscope (KEYENCE #BZ-X800). The acquired fluorescence images were analyzed using an image analysis application (KEYENCE #BZ-X800 Analyzer) to measure the MAG-positive area, and the sum of the six fields of view in each well was calculated.

3) Results

Fig. 1 shows the differentiation-promoting effect of the vitamin D derivatives of the present invention on immature Schwann cells. The vitamin D derivatives of the present invention significantly promoted the differentiation of immature Schwann cells compared to the DMSO group.

[0054]

[Example 2]

Evaluation of the dedifferentiation-inhibiting effect and the differentiation-promoting effect of the vitamin D derivatives of the present invention in paclitaxel-induced Schwann cell dedifferentiation

In the present example, the dedifferentiation-inhibiting effect and differentiation-promoting effect of the vitamin D derivatives of the present invention in paclitaxel-induced Schwann cell dedifferentiation were evaluated.

1) Methods

Primary rat Schwann cells were prepared in the same manner as in Example 1, and vitamin D derivatives were evaluated according to the following procedure. The obtained primary rat Schwann cells were suspended in maintenance medium, seeded on a 10-cm dish coated with poly-L-lysine (SIGMA-ALDRICH #P4707), and cultured under the condition of 5.0% CO_2 at 37°C. Subconfluent cells were washed with PBS, detached with 0.05% Trypsin/EDTA (Gibco #25300-054), and then centrifuged (300×g, 5 minutes,

room temperature). After removing the supernatant, the cells were suspended in differentiation medium (20 μM forskolin (Sigma-Aldrich #6886) / 20 ng/mL heregulin β-1 (Sigma-Aldrich #H7660) in 5% D-(+)-trehalose Dihydrate (Nacalai Tesque #11667-34) / 2 mM GlutaMAX (Gibco #35050-061) / 1% Penicillin-Streptomycin (Gibco #15140-122) / Serum-free Advanced DMEM/F-12 (Gibco #12634-010)) to prepare a cell suspension. The cell suspension was seeded at a density of 1.0×10^4 cells/100 μL/well onto a Poly-D-lysine 96-well Black Clear plate (CORNING #354640). Immature Schwann cells require two days or more of differentiation culture for maturation, and thus were cultured for three days under 5.0% CO_2 at 37°C. Subsequently, 100 μL/well of each sample was added to each well to give a final volume of 200 μL/well, and the cells were cultured for 2 days. The samples were as follows: Pac(-) group, in which DMSO was added to the differentiation medium to a concentration of 0.2%; DMSO group, in which 2 μM paclitaxel (DMSO solution) was added to differentiation medium to a concentration of 0.1% and DMSO was added to a concentration of 0.2%; Amorolfine group, in which 2 μM paclitaxel (DMSO solution) was added to differentiation medium to a concentration of 0.1%, and 2 mM Amorolfine (DMSO solution) was added to a concentration of 0.1%; and vitamin D derivative group, in which 2 μM paclitaxel (DMSO solution) was added to differentiation medium to a concentration of 0.1%, and 2 mM vitamin D derivative (DMSO solution) was added to a concentration of 0.1%. After culturing, immunostaining and image analysis for MAG were performed as follows. After removing all the supernatant and washing with PBS, 4% paraformaldehyde (FUJIFILM Wako Pure Chemical Corporation #163-20145) was added thereto, and the cells were fixed by incubation at room temperature for 15 minutes. After removing the supernatant, a 0.1% Tween-20-containing skim milk solution was added thereto, and the cells were

incubated at room temperature for 30 minutes. After washing three times with PBS, a PBS solution containing 2.5 μg/mL anti-MAG antibody (Millipore #MAB1567) was added thereto, and the cells were incubated overnight at 4°C. After washing three times with PBS, a PBS solution containing 5 μg/mL Alexa fluor 488 anti-mouse IgG (Invitrogen, A11029) was added thereto, and the cells were incubated at room temperature for 60 minutes. After washing three times with PBS, a PBS solution containing 1 μg/mL Hoechst33342 (DOJINDO #NU043) was added thereto, and the cells were incubated for 15 minutes at room temperature in the dark. Subsequently, fluorescence images of six fields of view per well were acquired using a fluorescence microscope (KEYENCE #BZ-X800). The acquired fluorescence images were analyzed using an image analysis application (KEYENCE #BZ-X800 Analyzer) to measure the MAG-positive area, and the sum of the six fields of view in each well was calculated.

2) Results

Figs. 2 and 3 show the dedifferentiation-inhibiting effect and differentiation-promoting effect of the vitamin D derivatives of the present invention in paclitaxel-induced Schwann cell dedifferentiation. In the present experiment, mature Schwann cells were dedifferentiated by paclitaxel (anticancer drug) treatment (comparison between the DMSO group and the paclitaxel-untreated group (Pac(-) group)). The vitamin D derivative group of the present invention exhibited dedifferentiation-inhibiting and differentiation-promoting effects to a similar extent as Amorolfin, a positive control compound.

[0055]

[Example 3]

Evaluation of the dedifferentiation-inhibiting effect and differentiation-promoting effect

of the vitamin D derivatives of the present invention in high glucose-induced Schwann cell dedifferentiation

In the present example, the dedifferentiation-inhibiting and differentiation-promoting effects of the vitamin D derivatives of the present invention in high glucose-induced Schwann cell dedifferentiation were evaluated, and a comparison was made between the vitamin D derivative D023 of the present invention and known vitamin D derivatives, eldecalcitol and 1α,25-dihydroxyvitamin D_3 (1α,25-$(OH)_2D_3$).

1) Methods

Primary rat Schwann cells were prepared in the same manner as in Example 1, and vitamin D derivatives were evaluated according to the following procedure. The obtained primary rat Schwann cells were suspended in maintenance medium (2 μM forskolin (Sigma-Aldrich #6886) / 20 ng/mL heregulin β-1 (Sigma-Aldrich #H7660) in 5% D-(+)-trehalose dihydrate (Nacalai Tesque #11667-34) / 2 mM GlutaMAX (Gibco #35050-061) / 1% Penicillin-Streptomycin (Gibco #15140-122) / Serum-free Advanced DMEM/F-12 (Gibco #12634-010)), then seeded on a 10-cm dish coated with poly-L-lysine (SIGMA-ALDRICH #P4707) and cultured under the condition of 5.0% CO_2 at 37°C. Subconfluent cells were washed with PBS, detached with 0.05% Trypsin/EDTA (Gibco #25300-054), and then centrifuged (300×g, 5 minutes, room temperature). After removing the supernatant, the cells were suspended in differentiation medium (20 μM forskolin (Sigma-Aldrich #6886) / 20 ng/mL heregulin β-1 (Sigma-Aldrich #H7660) in 5% D-(+)-trehalose Dihydrate (Nacalai Tesque #11667-34) / 2 mM GlutaMAX (Gibco #35050-061) / 1% Penicillin-Streptomycin (Gibco #15140-122) / Serum-free Advanced DMEM/F-12 (Gibco #12634-010)) to prepare a cell suspension. The cell suspension was seeded at a density of 1.0×10^4 cells/100 μL/well onto a Poly-D-lysine 96-well Black Clear

plate (CORNING #354640). Immature Schwann cells require two days or more of differentiation culture for maturation, and thus were cultured under the condition of 5.0% CO_2 at 37°C for four days. Subsequently, 100 μL/well of the sample was added to each well to give a final volume of 200 μL/well, and the cells were cultured for 4 days. The samples were as follows: Glucose(-) group, in which distilled water (Invitrogen #10977015) was added to the differentiation medium to a concentration of 2% and DMSO was added to a concentration of 0.1%; DMSO group, in which 2.5M glucose solution (Sigma-Aldrich #G8769-100ML) was added to the differentiation medium to a concentration of 2% and DMSO was added to a concentration of 0.1%; Amorolfine group, in which 2.5M glucose solution (Sigma-Aldrich #G8769-100ML) was added to the differentiation medium to a concentration of 2% and 2 mM Amorolfine (DMSO solution) was added to a concentration of 0.1%; Vitamin D derivative group, in which 2.5M glucose solution (Sigma-Aldrich #G8769-100ML) was added to the differentiation medium to a concentration of 2% and vitamin D derivative (prepared at 2000 times the final concentration, DMSO solution) was added to a concentration of 0.1%; Eldecalcitol group, in which 2.5M glucose solution (Sigma-Aldrich #G8769-100ML) was added to the differentiation medium to a concentration of 2% and 2 mM eldecalcitol (DMSO solution) was added to a concentration of 0.1%; and 1α,25-dihydroxyvitamin D_3 group, in which 2.5M glucose solution (Sigma-Aldrich #G8769-100ML) was added to the differentiation medium to a concentration of 2% and 2 mM 1α,25-dihydroxyvitamin D_3 (DMSO solution) was added to a concentration of 0.1%. After culturing, MAG immunostaining and image analysis were performed in the same manner as in Example 1.

2) Results

Figs. 4 and 5 show the dedifferentiation-inhibiting effect and differentiation-

promoting effect of the vitamin D derivatives of the present invention on mature Schwann cells under high glucose-induced dedifferentiation conditions. The vitamin D derivatives of the present invention exhibited, even under high glucose load condition, dedifferentiation-inhibiting and differentiation-promoting effects on mature Schwann cells to a similar extent as Amorolfin, a positive control compound. Compound D023, a vitamin D derivative, inhibited high glucose-induced dedifferentiation of Schwann cells in a concentration-dependent manner and promoted differentiation. Furthermore, the effect was significant at 100 nM and 1000 nM. In contrast, eldecalcitol and 1α,25-dihydroxyvitamin D_3, which are vitamin D derivatives, exhibited neither a dedifferentiation-inhibiting effect nor a differentiation-promoting effect in the present experiment. These results also confirmed that the vitamin D derivative of the present invention is superior to known vitamin D derivatives.

[0056]

[Example 4]

Evaluation of the effect on allodynia using streptozotocin (STZ)-induced diabetic rats

1) Methods

STZ dissolved in citrate buffer (pH 4.5) was administered to SD rats (7 weeks old, male) intravenously via the tail vein at a dose of 55 mg/kg to induce the pathological condition. Two, three, and four weeks after disease induction, the 50% paw withdrawal threshold was measured in both hind limbs using the von Frey test, and the sum of the measured values (maximum 30g) was defined as the pain threshold. Four weeks after disease induction, rats were divided into groups based on their pain threshold (four weeks after disease induction), the mean pain threshold (mean value at 2, 3, and 4 weeks after disease induction), and body weight. On the day following group assignment,

administration of a vitamin D derivative (20 μg/kg), duloxetine (30 mg/kg), or vehicle was initiated. As dosing solutions, suspensions of vitamin D derivative or duloxetine in a 0.5 w/v% methylcellulose (MC) solution, or a 0.5 w/v% MC solution were used. The 0.5 w/v% MC solution was prepared by dissolving MC 400 (Fujifilm Wako Pure Chemical Corporation #132-05055) in sterile water for injection (Fuso Pharmaceutical Industries, Ltd.). The dosing solutions were administered orally once a day for a total of seven times. Two hours after the final administration, the 50% paw withdrawal threshold was measured in both hind limbs using the von Frey test. The sham group refers to a non-disease-induced group that received only citrate buffer (pH 4.5) instead of STZ.

2) Results

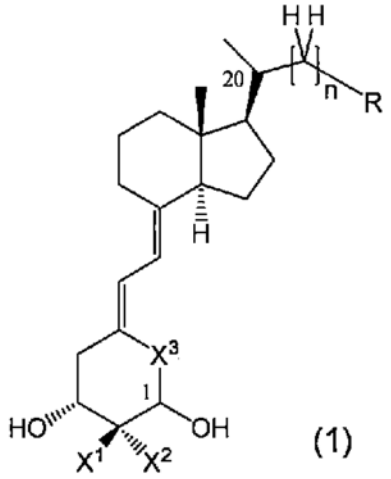
Fig. 6 shows the effect of the vitamin D derivative of the present invention on allodynia in STZ-induced diabetic rats. The vitamin D derivative D023 of the present invention exhibited, at a low dose of 20 μg/kg, the effect on allodynia equivalent to or greater than that of duloxetine (30 mg/kg) used for the treatment of diabetic peripheral neuropathy.

[CLAIMS]

[Claim 1]

A therapeutic agent or ameliorative agent for a disease whose symptoms are ameliorated or alleviated by Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect, comprising a vitamin D derivative represented by formula (1), or a pharmaceutically acceptable salt or solvate thereof.

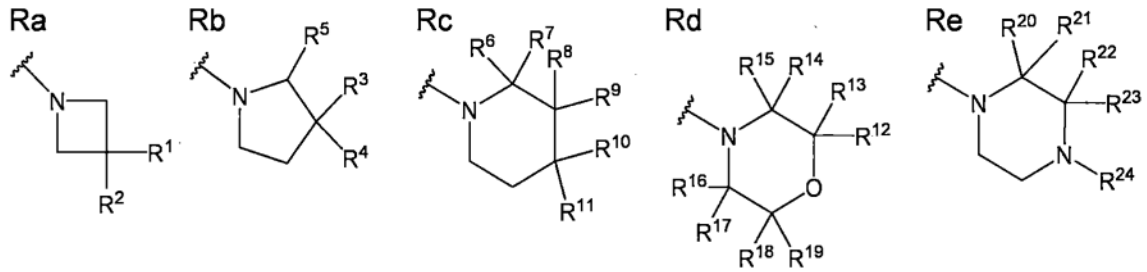
[Chem. 1]



(1)

(In the formula, R represents any one of the structures Ra, Rb, Rc, Rd, and Re in the following formulas.

[Chem. 2]



R^1, R^3, R^8, and R^{10} each independently represent a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, a C_3-C_6 cycloalkyl group, a C_1-C_6 alkoxy group

optionally substituted with 1 to 3 halogen atoms, a halogen atom, or a hydrogen atom.

R^2, R^4, R^9, and R^{11} each independently represent a hydrogen atom, a hydroxy group, or a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms. (wherein, when R^1, R^3, R^8, and R^{10} each independently represent a C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms, or a halogen atom, R^2, R^4, R^9, and R^{11} substituting on the same carbon atom as R^1, R^3, R^8, and R^{10} are not hydroxy groups, respectively.)

R^6, R^7, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, and R^{23} each independently represent a hydrogen atom, a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, or a C_3-C_6 cycloalkyl group.

Each pair of R^1 and R^2, R^3 and R^4, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{14} and R^{15}, R^{16} and R^{17}, R^{18} and R^{19}, R^{20} and R^{21}, and R^{22} and R^{23} can be bonded with each other to form a 3- to 5-membered ring structure.

R^5 represents a hydrogen atom, a C_1-C_6 alkyl group optionally substituted with one -OR^{501} group, or a C_3-C_6 cycloalkyl group optionally substituted with one -OR^{501} group, and R^{501} represents a hydrogen atom, or a C_1-C_6 alkyl group.

R^{24} represents a hydrogen atom, a C_1-C_3 alkyl group, or a C_1-C_3 alkylsulfonyl group.

The stereochemistry at 2-position of the pyrrolidine ring (Rb) represents either (R) configuration or (S) configuration.

X^1 and X^2 each independently represent a hydrogen atom or a C_1-C_3 alkyl group, or X^1 and X^2 together form a methylidene group, or -$(CH_2)_m$- (wherein m is an integer of 2 to 5).

X^3 represents a CH_2 group or a C=CH_2 group (wherein, when X^1 and X^2 together form a methylidene group, X^3 is not a C=CH_2 group).

n represents an integer of 1 to 3.

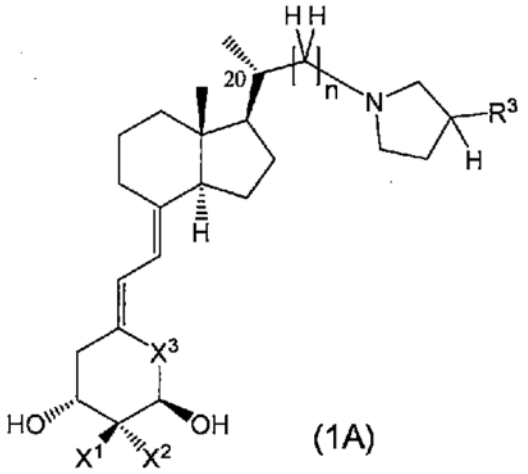
The stereochemistry of the hydroxy group at 1-position represents either (R) configuration or (S) configuration.

The stereochemistry of the methyl group at 20-position represents either (R) configuration or (S) configuration.)

[Claim 2]

The therapeutic agent or ameliorative agent according to claim 1, wherein the vitamin D derivative of formula (1) is represented by the following formula (1A).

[Chem. 3]



(1A)

(n represents an integer of 1 to 3.

R^3 represents a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, a C_3-C_6 cycloalkyl group, a C_1-C_6 alkoxy group optionally substituted with 1 to 3 halogen atoms.

X^1 and X^2 each independently represent a hydrogen atom or a C_1-C_3 alkyl group, or X^1 and X^2 together form a methylidene group, or $-(CH_2)_m-$ (wherein m is an integer of 2 to 5).

X^3 represents a CH_2 group or a $C=CH_2$ group (wherein, when X^1 and X^2 together form a methylidene group, X^3 is not a $C=CH_2$ group).)

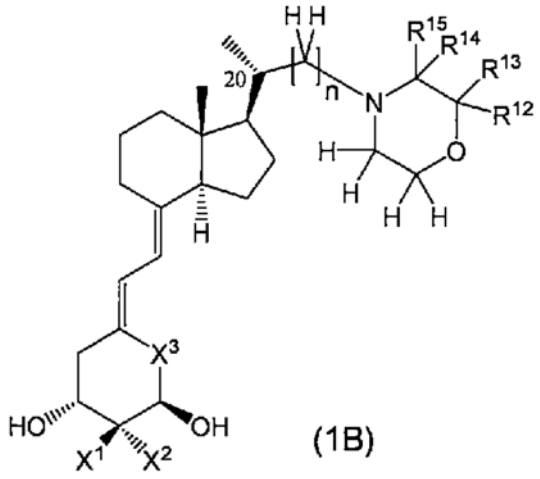
[Claim 3]

The therapeutic agent or ameliorative agent according to claim 2, wherein n represents 1, R^3 represents a C_2-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, or a C1-C6 alkoxy group optionally substituted with 1 to 3 halogen atoms.

[Claim 4]

The therapeutic agent or ameliorative agent according to claim 1, wherein the vitamin D derivative of formula (1) is represented by the following formula (1B).

[Chem. 4]



(1B)

(n represents an integer of 1 to 3.

R^{12}, R^{13}, R^{14}, and R^{15} each independently represent a hydrogen atom, a C_1-C_6 alkyl group optionally substituted with 1 to 3 halogen atoms, or a C_3-C_6 cycloalkyl group.

Each pair of R^{12} and R^{13}, and R^{14} and R^{15} can be bonded with each other to form a 3- to 5-membered ring structure.

X^1 and X^2 each independently represent a hydrogen atom or a C_1-C_3 alkyl group, or X^1 and X^2 together form a methylidene group, or $-(CH_2)_m-$ (wherein m is an integer of 2 to 5).

X^3 represents a CH_2 group or a $C=CH_2$ group (wherein, when X^1 and X^2 together form a

methylidene group, X^3 is not a $C=CH_2$ group).)

[Claim 5]

The therapeutic agent or ameliorative agent according to claim 4, wherein n represents 1, R^{12} and R^{13} are bonded with each other to represent a cyclopropyl group, or R^{14} and R^{15} simultaneously represent a methyl group.

[Claim 6]

The therapeutic agent or ameliorative agent according to any one of claims 1 to 5, wherein X^1 and X^2 are hydrogen atoms and X^3 is a CH_2 group.

[Claim 7]

The therapeutic agent or ameliorative agent according to any one of claims 1 to 5, wherein X^1 and X^2 are hydrogen atoms and X^3 is a $C=CH_2$ group.

[Claim 8]

The therapeutic agent or ameliorative agent according to any one of claims 1 to 5, wherein X^1 and X^2 together form a methylidene group and X^3 is a CH_2 group.

[Claim 9]

The therapeutic agent or ameliorative agent according to any of claims 1, 2, 4, or 6 to 8, wherein n represents 2.

[Claim 10]

The therapeutic agent or ameliorative agent according to any one of claims 1 to 9, wherein the vitamin D derivative represented by formula (1) is any one of the following vitamin D derivatives, or a pharmaceutically acceptable salt or solvate thereof:

(1) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-ethylpyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol (Compound B005)

(2) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-ethylpyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol (Compound B006)

(3) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(1,1-difluoroethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B030)

(4) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(1,1-difluoroethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B034)

(5) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(2,2-difluoroethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B042)

(6) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(2,2-difluoroethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B043)

(7) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(difluoromethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B051)

(8) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(difluoromethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B052)

(9) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(2,2-difluoroethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B057)

(10) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(2,2-difluoroethoxy)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B058)

(11) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((S)-3-(3,3-difluoropropyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B063)

(12) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(3,3-difluoropropyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B064)

(13) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-3-(difluoromethyl)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B080)

(14) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((R)-3-(difluoromethyl)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B081)

(15) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((R)-3-(2,2-difluoroethyl)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B082)

(16) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-3-(1,1-difluoroethyl)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B083)

(17) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-3-(difluoromethoxy)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B086)

(18) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((R)-3-(difluoromethoxy)pyrrolidin-1-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B087)

(19) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-(4-oxa-7-azaspiro[2.5]octan-7-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D019)

(20) (1R,3S,Z)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-morpholinobutan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (Compound D022)

(21) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-morpholinobutan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D023)

(22) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-morpholinobutan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol (Compound D024)

(23) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((S)-2-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol (Compound D025)

(24) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-(4-oxa-7-azaspiro[2.5]octan-7-yl)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D030)

(25) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((R)-4-((S)-2-(difluoromethyl)morpholino)butan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D034)

(26) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((S)-2-

methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D041)

(27) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((R)-3-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D042)

(28) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-4-((S)-3-methylmorpholino)butan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D043)

(29) (1R,3R)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-5-morpholinopentan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound D044)

(30) (1R,3S,Z)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-(3,3-dimethylmorpholino)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (Compound F006)

(31) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-(3,3-dimethylmorpholino)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound G006).

[Claim 11]

The therapeutic agent or ameliorative agent according to any one of claims 1 to 10, wherein a disease whose symptoms are ameliorated or alleviated by Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect is Chemotherapy Induced peripheral neuropathy (CIPN).

[Claim 12]

The therapeutic agent or ameliorative agent according to any one of claims 1 to 10, wherein a disease whose symptoms are ameliorated or alleviated by Schwann cell

differentiation-promoting effect or dedifferentiation-inhibiting effect is Diabetic Neuropathy (DN).

[Claim 13]

The therapeutic agent or ameliorative agent according to any one of claims 1 to 10, wherein a disease whose symptoms are ameliorated or alleviated by Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect is Myasthenia gravis (MG).

[Claim 14]

The therapeutic agent or ameliorative agent according to any one of claims 1 to 10, wherein a disease whose symptoms are ameliorated or alleviated by Schwann cell differentiation-promoting effect or dedifferentiation-inhibiting effect is Amyotrophic lateral sclerosis (ALS).