and an opioid receptor modulator (PTL 1). However, there is not known a medicine, containing a vitamin D derivative and used in combination with an immunosuppressant, for promoting remyelination.

[Citation List]

[Patent Literature]

[0011]

[PTL 1] JP-T-2014-506583

[Non Patent Literature]

[0012]

[NPL 1] A. G. de la Fuente et al., Journal of Cell Biology, 2015, 211(5), 975-985

[NPL 2] H. A. Shirazi et al., Experimental and Molecular Pathology, 2015, 98(2), 240-245

[NPL 3] M. A. Zmijewski et al., Experimental Dermatology, 2020, 29, 876-884

[NPL 4] M. R. Durk et al., The Journal of Neuroscience, 2014, 34(21), 7091-7101

[NPL 5] E. C. Y. Chow et al., The American Journal of Physiology: Endocrinology and Metabolism, 2013, 304(9), E977-989

[Summary]

[Technical Problem]

[0013]

An object of the present disclosureis to provide a vitamin D derivative or a pharmaceutically acceptable salt or solvate thereof, having excellent central nervous system penetration and used in combination with an immunosuppressant, as a medicine

for promoting induction of differentiation of oligodendrocyte progenitor cells into oligodendrocytes and a medicine for promoting remyelination.

[Solution to Problem]

[0014]

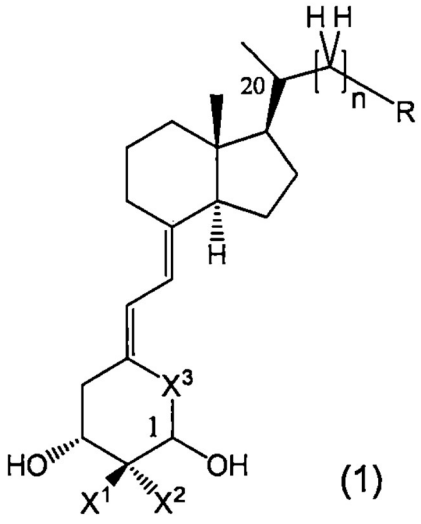
As a result of diligent research for the above purpose, the present inventors reached the following.

[0015]

That is, the present disclosure is a medicine for promoting induction of differentiation of oligodendrocyte progenitor cells into oligodendrocytes, and a medicine for promoting remyelination, both used in combination with an immunosuppressant and containing a vitamin D derivative represented by the following formula (1) or a pharmaceutically acceptable salt or solvate thereof.

[0016]

[Chem. 1]



(1)

[0017]

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 C-2 of the pyrrolidine ring (Rb) represents (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 (However, when X^1 and X^2 together form a methylidene group, X^3 is not a C=CH_2 group.).

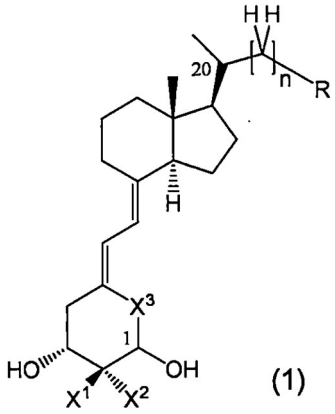
n represents an integer of 1 to 3.

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

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

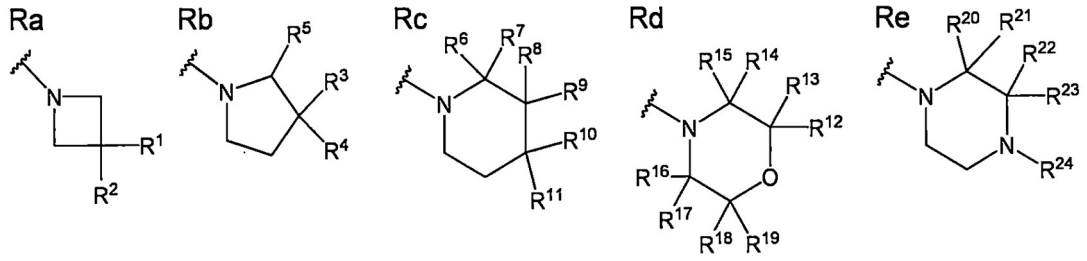
In one aspect, the present disclosure relates to a medicine in combination with an immunosuppressant, comprising: a vitamin D derivative represented by formula (1) or a pharmaceutically acceptable salt or solvate thereof.

[Chem. 1]



wherein R represents any one of the structures Ra, Rb, Rc, Rd, and Re in the following formulas

[Chem. 2]



wherein

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, provided that 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 C-2 of the pyrrolidine ring (Rb) represents (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 -$(CH_2)_m$- where m is an integer of 2 to 5;

X^3 represents a CH_2 group or a C=CH_2 group, provided that when X^1 and X^2 together form a methylidene group, X^3 is not a C=CH_2 group;

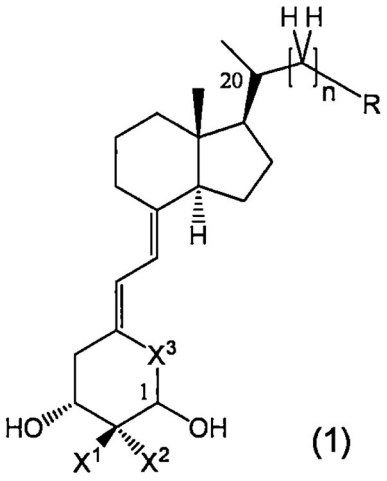
n represents an integer of 1 to 3;

the stereochemistry of the hydroxy group at C-1 represents (R) configuration or (S) configuration; and

the stereochemistry of the methyl group at C-20 represents (R) configuration or (S) configuration.]

In another aspect, the present disclosure relates to a medicine comprising: a vitamin D derivative represented by formula (1) or a pharmaceutically acceptable salt or solvate thereof and an immunosuppressant.

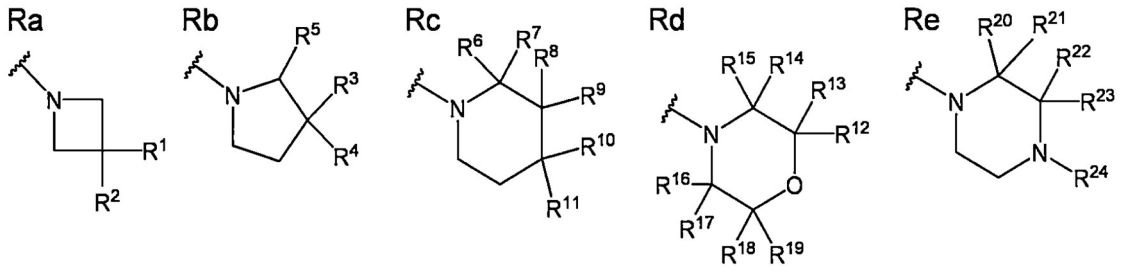
[Chem. 7]



(1)

wherein R represents any one of the structures Ra, Rb, Rc, Rd, and Re in the following formulas

[Chem. 8]



wherein

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, provided that 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 C-2 of the pyrrolidine ring (Rb) represents (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, provided that 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 C-1 represents (R) configuration or (S) configuration; and

the stereochemistry of the methyl group at C-20 represents (R) configuration or (S) configuration.]

Further, the present disclosure is a medicine for promoting induction of differentiation of oligodendrocyte progenitor cells into oligodendrocytes and a medicine for promoting remyelination, both containing a vitamin D derivative represented by the above formula (1) or a pharmaceutically acceptable salt or solvate thereof and an immunosuppressant.

In another aspect, the present disclosure relates to a medicine as disclosed herein for use in therapy.

In another aspect, the present disclosure relates to use of a medicine as disclosed herein in the manufacture of a medicament for promoting induction of differentiation of oligodendrocyte progenitor cells into oligodendrocytes, for promoting remyelination, and for treating one or more diseases selected from the group consisting of multiple sclerosis, neuromyelitis optica, progressive multifocal leukoencephalopathy, multiple system atrophy, acute disseminated encephalomyelitis, atopic myelitis, HTLV-1-associated myelopathy, HIV-associated leukoencephalopathy, Krabbe's disease, Guillain-Barre syndrome, Fisher's syndrome, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth disease, Parkinson's disease, schizophrenia, bipolar disorder, major depressive disorder, autistic spectrum disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, drug-dependent depression, autism, Alzheimer-type dementia, and ischemic stroke.

[Advantageous Effects of Invention]

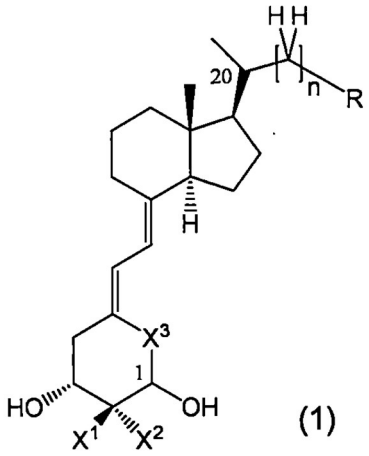
[0020]

[CLAIMS]

[Claim 1]

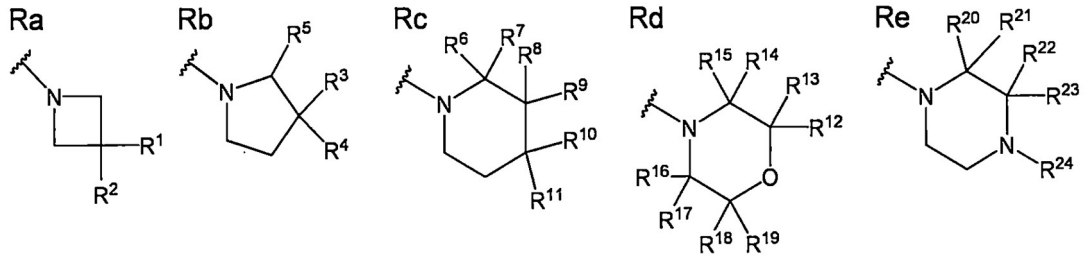
A medicine in combination with an immunosuppressant, comprising: a vitamin D derivative represented by formula (1) or a pharmaceutically acceptable salt or solvate thereof

[Chem. 1]



wherein R represents any one of the structures Ra, Rb, Rc, Rd, and Re in the following formulas

[Chem. 2]



wherein

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, provided that 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 C-2 of the pyrrolidine ring (Rb) represents (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 -$(CH_2)_m$- where m is an integer of 2 to 5;

X^3 represents a CH_2 group or a C=CH_2 group, provided that 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;

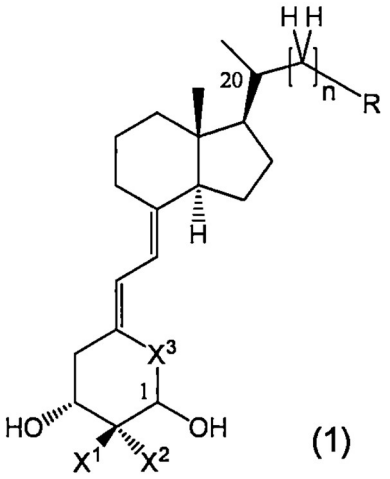
the stereochemistry of the hydroxy group at C-1 represents (R) configuration or (S) configuration; and

the stereochemistry of the methyl group at C-20 represents (R) configuration or (S) configuration.]

[Claim 2]

A medicine comprising: a vitamin D derivative represented by formula (1) or a pharmaceutically acceptable salt or solvate thereof and an immunosuppressant.

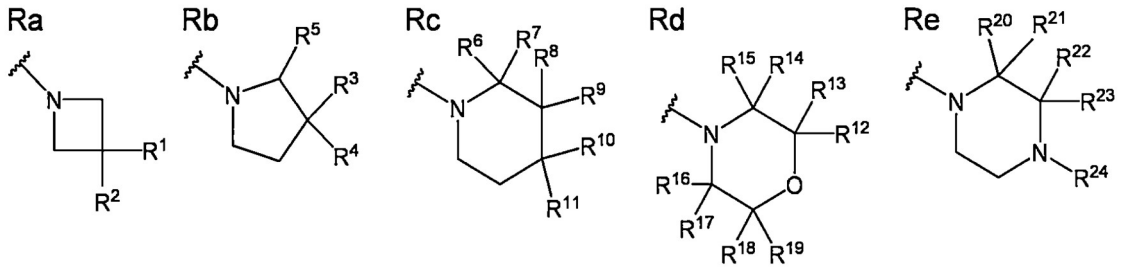
[Chem. 7]



(1)

wherein R represents any one of the structures Ra, Rb, Rc, Rd, and Re in the following formulas

[Chem. 8]



wherein

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, provided that 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 C-2 of the pyrrolidine ring (Rb) represents (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, provided that 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 C-1 represents (R) configuration or (S) configuration; and

the stereochemistry of the methyl group at C-20 represents (R) configuration or (S) configuration.]

[Claim 3]

The medicine according to claim 1 or 2, wherein formula (1) is as follows:

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 fluorine atoms, a C_3-C_6 cycloalkyl group, a C_1-C_6 alkoxy group optionally substituted with 1 to 3 fluorine atoms, a fluorine 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_3 alkyl group optionally substituted with 1 to 3 fluorine atoms, provided that when R^1, R^3, R^5, and R^7 each independently represent a C_1-C_6 alkoxy group optionally substituted with 1 to 3 fluorine atoms, or a fluorine 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^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22}, and R^{23} each independently represent 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;

each pair of R^1 and R^2, R^3 and R^4, 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}, and R^{22} and R^{23} can be bonded with each other to form a 3- to 5-membered ring structure;

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

X^1 and X^2 each independently represent a hydrogen atom or a methyl group, or X^1 and X^2 together form a methylidene group;

X^3 represents a CH_2 group or a $C{=}CH_2$ group, provided that 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; and

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

[Claim 4]

The medicine according to any one of claims 1 to 3, wherein R represents Rb.

[Claim 5]

The medicine according to any one of claims 1 to 3, wherein R represents Rd.

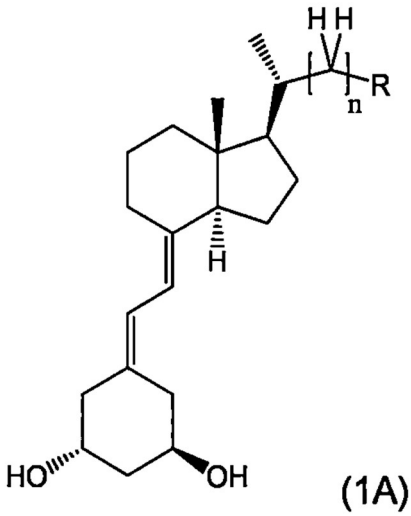
[Claim 6]

The medicine according to any one of claims 1 to 5, wherein X^1 and X^2 represent a hydrogen atom and X^3 represents a CH_2 group.

[Claim 7]

The medicine according to claim 1 or 2, wherein the vitamin D derivative represented by formula (1) is represented by the following formula (1A)

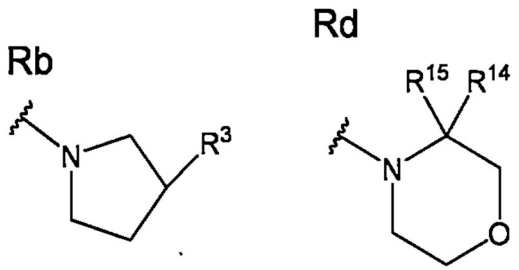
[Chem. 13]



(1A)

wherein R represents the structure of Rb or Rd in the following formula

[Chem. 14]



wherein

R^3 represents a C_1-C_6 alkyl group substituted with two fluorine atoms;

the stereochemistry of R^3 represents (R) configuration or (S) configuration;

R^{14} and R^{15} each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

the stereochemistry of R^{14} and R^{15} each independently represents (R) configuration or (S) configuration; and

n represents an integer of 1 or 2.

[Claim 8]

The medicine according to claim 1 or 2, 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-(difluoromethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B022)

(2) (1R,3R)-5-(2-((1R,3aS,7aR,E)-1-((S)-1-((R)-3-(difluoromethyl)pyrrolidin-1-yl)propan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)cyclohexane-1,3-diol (Compound B026)

(3) (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)

(4) (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)

(5) (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)

(6) (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 9]

The medicine according to any one of claims 1 to 8, wherein the immunosuppressant is fingolimod (FTY720), interferon β-1a, interferon β-1b, glatiramer acetate, mitoxantrone, natalizumab, siponimod, ozanimod, ponesimod, dimethyl fumarate, diroximel fumarate, cladribine, ocrelizumab, rituximab, ofatumumab, ublituximab, alemtuzumab, divozilimab, evobrutinib, orelabrutinib, tolebrutinib, remibrutinib, or fenebrutinib.

[Claim 10]

The medicine according to any one of claims 1 to 9, wherein each of the vitamin D derivative represented by formula (1) and the immunosuppressant is contained at a therapeutically effective dose or is used at a therapeutically effective dose.

[Claim 11]

The medicine according to any one of claims 1 to 9, wherein the vitamin D derivative represented by formula (1) is contained at a therapeutically effective dose, and

the immunosuppressant is used at a subtherapeutic dose or is contained at a subtherapeutic dose.

[Claim 12]

The medicine according to any one of claims 1 to 9, wherein each of the vitamin D derivative represented by formula (1) and the immunosuppressant is contained at a subtherapeutic dose or is used at a therapeutically effective dose.

[Claim 13]

The medicine according to any one of claims 1 to 12, wherein the medicine is formulated for systemic administration.

[Claim 14]

The medicine according to any one of claims 1 to 13, wherein the vitamin D derivative represented by formula (1) and the immunosuppressant are to be administered sequentially.

[Claim 15]

The medicine according to any one of claims 1 to 13, wherein the vitamin D derivative represented by formula (1) and the immunosuppressant are to be administered simultaneously.

[Claim 16]

A medicine according to any one of claims 1 to 15 for use in therapy.

[Claim 17]

Use of a medicine according to any one of claims 1 to 15 in the manufacture of a medicament for promoting induction of differentiation of oligodendrocyte progenitor cells into oligodendrocytes, for promoting remyelination, and for treating one or more diseases selected from the group consisting of multiple sclerosis, neuromyelitis optica,

progressive multifocal leukoencephalopathy, multiple system atrophy, acute disseminated encephalomyelitis, atopic myelitis, HTLV-1-associated myelopathy, HIV-associated leukoencephalopathy, Krabbe's disease, Guillain-Barre syndrome, Fisher's syndrome, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth disease, Parkinson's disease, schizophrenia, bipolar disorder, major depressive disorder, autistic spectrum disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, drug-dependent depression, autism, Alzheimer-type dementia, and ischemic stroke.

[Claim 18]

The use according to claim 17, wherein the medicament is formulated for systemic administration.

[Claim 19]

The use according to claim 18 or 19, wherein the vitamin D derivative represented by formula (1) and the immunosuppressant are to be administered sequentially.

[Claim 20]

The use according to any one of claims 17 to 19, wherein the vitamin D derivative represented by formula (1) and the immunosuppressant are to be administered simultaneously.