

Non Patent Literature 16: Azhary et al. American Family Physician, 2010, Vol. 81, p. 887-892

Non Patent Literature 17: McMahon et al. Current Opinion in Neurobiology, 1995, Vol. 5, p. 616-624

Non Patent Literature 18: Argypriou et al. Critical Reviews in Oncology/Hematology, 2012, Vol. 82, p. 51-77

Non Patent Literature 19: Apfel et al. JAMA, 2000, Vol. 284, p. 2215-2221

SUMMARY ~~OF INVENTION~~

TECHNICAL PROBLEM

[0020]

An object of the present ~~invention~~disclosure is to provide a therapeutic or prophylactic agent for peripheral neuropathies.

SOLUTION TO PROBLEM

[0021]

As a result of intensive studies to achieve the above object, the present inventors have discovered that a specific cyclic amine derivative or a pharmacologically acceptable salt thereof has a significant effect of suppressing peripheral neuropathies.

[0022]

Specifically, the present ~~invention~~disclosure provides a therapeutic agent or a prophylactic agent for peripheral neuropathies, comprising as an active ingredient, a cyclic amine derivative represented by the following general formula (I) or a pharmacologically acceptable salt thereof.

[Chemical Formula 1]

optionally substituted with a fluorine atom, and further preferably a methyl group, an ethyl group, a difluoromethyl group or a 2,2,2-trifluoroethyl group.

[0025]

In the above cyclic amine derivative, it is preferable that A is the group represented by general formula (IIa) and that the stereochemical configuration of the asymmetric carbon marked with * is preferably S, in which R¹ is more preferably a methyl group or an ethyl group optionally substituted with a fluorine atom, and further preferably a methyl group, an ethyl group, a difluoromethyl group or a 2,2,2-trifluoroethyl group.

[0026]

The present [inventiondisclosure](#) also provides a pharmaceutical composition for treating or preventing peripheral neuropathies, containing a cyclic amine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof, and a pharmacologically acceptable excipient, and the like.

[0027]

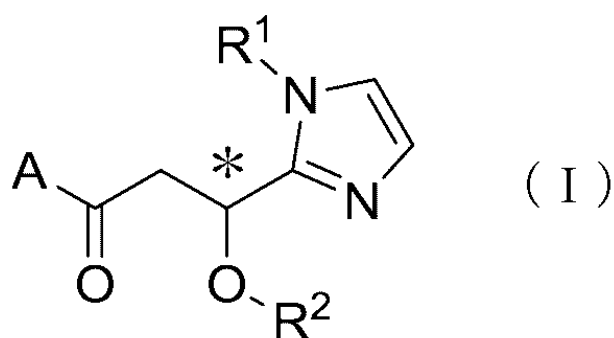
The present [inventiondisclosure](#) also provides a cyclic amine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof for use in treatment or prevention of peripheral neuropathies.

[0028]

The present [inventiondisclosure](#) also provides use of a cyclic amine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof in treatment or prevention of peripheral neuropathies.

[0029]

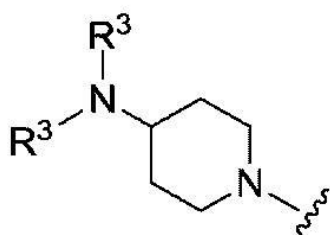
The present [inventiondisclosure](#) also provides use of a cyclic amine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof in producing a medicine for treatment or prevention of peripheral neuropathies. [In one aspect, the present disclosure provides use of a cyclic amine derivative represented by general formula \(I\) or a pharmacologically acceptable salt thereof in the manufacture of a medicament for treating or preventing peripheral neuropathies.](#)



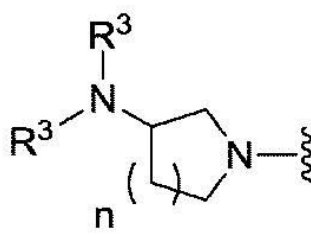
wherein,

carbon marked with * is asymmetric carbon; and

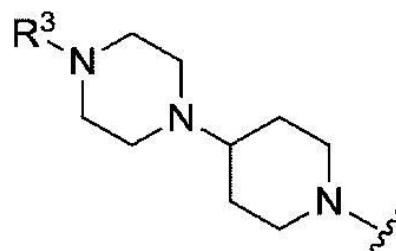
A represents a group represented by general formulae (IIa), (IIb) or (IIc):



(I I a)



(I I b)



(I I c)

wherein R¹ represents a methyl group or an ethyl group optionally substituted with one or more halogen atoms,

R² represents a hydrogen atom or an alkylcarbonyl group having 2 to 5 carbon atoms,

each R³ independently represents a methyl group or an ethyl group, and

n represents 1 or 2.

[0030]

The present ~~invention~~disclosure also provides a method for treating or preventing peripheral neuropathies, which includes administering a therapeutically effective amount of a cyclic

amine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof to a patient who needs treatment.

[0031]

In each ~~embodiment~~example of the present ~~invention~~disclosure, the above peripheral neuropathies are preferably drug-induced peripheral neuropathies, autoimmune peripheral neuropathies, metabolic peripheral neuropathies, hereditary peripheral neuropathies, vasculitic peripheral neuropathies, toxic peripheral neuropathies, infectious peripheral neuropathies, or peripheral neuropathies associated with malignant tumor, more preferably drug-induced peripheral neuropathies, autoimmune peripheral neuropathies, metabolic peripheral neuropathies, or hereditary peripheral neuropathies, and further preferably drug-induced peripheral neuropathies, autoimmune peripheral neuropathies, or metabolic peripheral neuropathies. The above drug-induced peripheral neuropathies are preferably anticancer agent-induced peripheral neuropathies. The above autoimmune peripheral neuropathies are preferably at least one type selected from Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), and paraproteinemic neuropathy (PPN). The above metabolic peripheral neuropathies are preferably diabetic peripheral neuropathy. The above hereditary peripheral neuropathy is preferably Charcot-Marie-Tooth disease.

ADVANTAGEOUS EFFECTS OF ~~INVENTION~~DISCLOSURE

[0032]

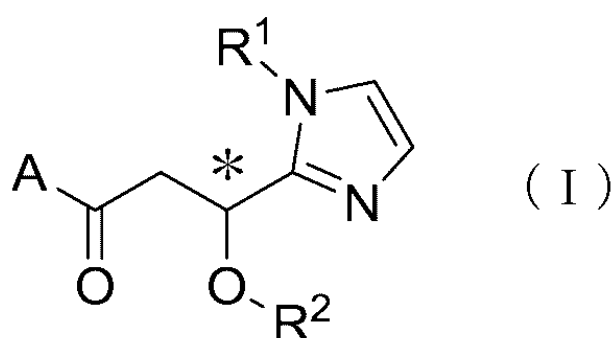
With the cyclic amine derivative or the pharmacologically acceptable salt thereof of the present ~~invention~~disclosure, peripheral neuropathies can be treated or prevented. The above peripheral neuropathies are for example, drug-induced peripheral neuropathies, autoimmune peripheral neuropathies, or metabolic peripheral neuropathies. The above drug-induced peripheral neuropathies are particularly anticancer agent-induced peripheral neuropathies. The above autoimmune peripheral neuropathies are particularly at least one type selected from Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), and paraproteinemic neuropathy (PPN). The

CLAIMS

[Claim 1]

Use of a cyclic amine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof [in the manufacture of a medicament for treating or preventing peripheral neuropathies.](#)

~~[Chemical Formula 1]~~

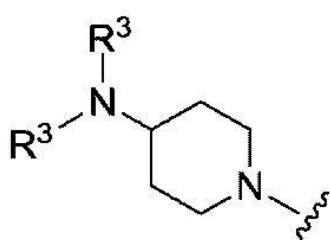


~~[wherein,~~

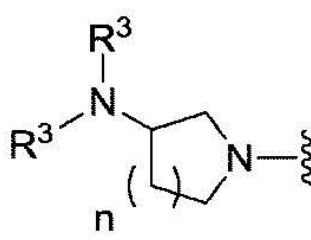
carbon marked with * is asymmetric carbon; and

A represents a group represented by general formulae (IIa), (IIb) or (IIc):

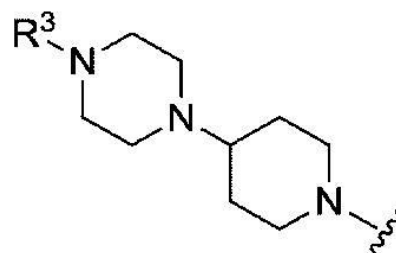
~~[Chemical Formula 2]~~



(I I a)



(I I b)



(I I c)

wherein R¹ represents a methyl group or an ethyl group optionally substituted with [a-one or more](#) halogen atoms,

R² represents a hydrogen atom or an alkylcarbonyl group having 2 to 5 carbon atoms,

each R³ independently represents a methyl group or an ethyl group, and

n represents 1 or 2.

~~in producing a medicine for treatment or prevention of peripheral neuropathies.~~

[Claim 2]

The use according to claim 1, wherein A is the group represented by general formula (IIa).

[Claim 3]

The use according to claim 1, wherein A is the group represented by general formulae (IIb) or (IIc).

[Claim 4]

The use according to claim 1, wherein A is the group represented by general formula (IIa) and the stereochemical configuration of the asymmetric carbon marked with * is S.

[Claim 5]

The use according to any one of claims 1 to 4, wherein R¹ represents a methyl group or an ethyl group optionally substituted with [a one or more](#) fluorine atoms.

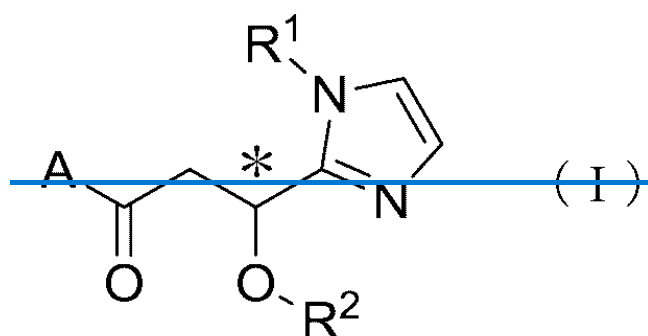
[Claim 6]

The use according to any one of claims 1 to 4, wherein R¹ is a methyl group, an ethyl group, a difluoromethyl group or a 2,2,2-trifluoroethyl group.

[Claim 7]

~~Use of a cyclic amine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof~~

~~{Chemical Formula 3}~~

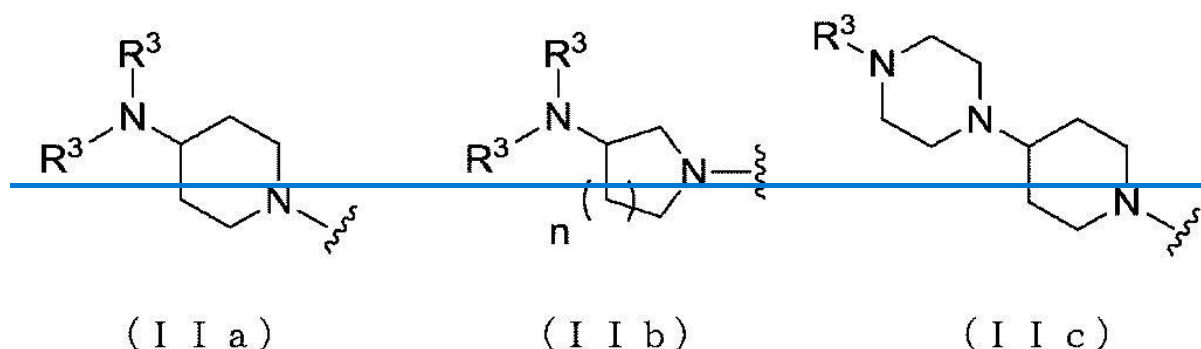


~~{wherein,~~

carbon marked with * is asymmetric carbon; and

A represents a group represented by general formulae (IIa), (IIb) or (IIc):

[Chemical Formula 4]



wherein R¹ represents a methyl group or an ethyl group optionally substituted with a halogen atom,

R² represents a hydrogen atom or an alkylcarbonyl group having 2 to 5 carbon atoms,

each R³ independently represents a methyl group or an ethyl group, and

n represents 1 or 2,]

The use according to any one of claims 1 to 6, wherein the peripheral neuropathies are drug-induced peripheral neuropathies.

[Claim 8]

The use according to claim 7, wherein A is the group represented by general formula (IIa).

[Claim 9]

The use according to claim 7, wherein A is the group represented by general formulae (IIb) or (IIc).

[Claim 10]

The use according to claim 7, wherein A is the group represented by general formula (IIa), and the stereochemical configuration of the asymmetric carbon marked with * is S.

[Claim 11]

The use according to any one of claims 7 to 10, wherein R¹ represents a methyl group or an ethyl group optionally substituted with a fluorine atom.

[Claim 12]

~~The use according to any one of claims 7 to 10, wherein R¹ is a methyl group, an ethyl group, a difluoromethyl group or a 2,2,2-trifluoroethyl group.~~

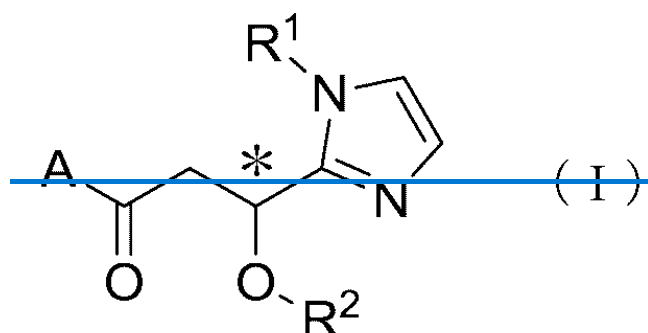
[Claim ~~138~~]

The use according to ~~any one of claims 7 to 12~~claim 7, wherein the drug-induced peripheral neuropathies are at least one type selected from anticancer agent-induced peripheral neuropathy, antiviral agent-induced peripheral neuropathy, antimicrobial agent-induced peripheral neuropathy, antitubercular agent-induced peripheral neuropathy, antiarrhythmic agent-induced peripheral neuropathy, lipid-lowering drug-induced peripheral neuropathy, immunosuppressive drug-induced peripheral neuropathy, gout therapeutic agent-induced peripheral neuropathy and peripheral neuropathies induced by other drugs.

[Claim ~~149~~]

~~Use of a cyclic amine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof~~

~~[Chemical Formula 5]~~

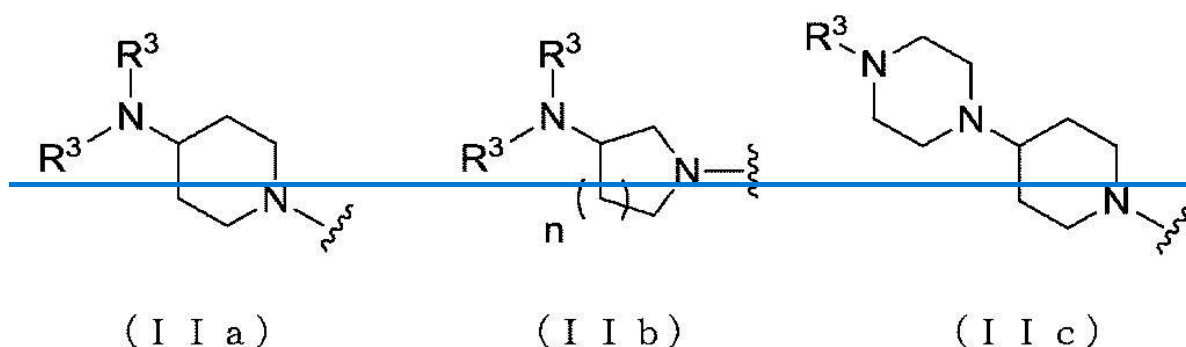


~~[wherein,~~

~~carbon marked with * is asymmetric carbon; and~~

~~A represents a group represented by general formulae (IIa), (IIb) or (IIc):~~

~~[Chemical Formula 6]~~



—wherein R^1 represents a methyl group or an ethyl group optionally substituted with a halogen atom,

— R^2 represents a hydrogen atom or an alkylcarbonyl group having 2 to 5 carbon atoms,

—each R^3 independently represents a methyl group or an ethyl group, and

—n represents 1 or 2.],

in producing a medicine for treatment or prevention of The use according to any one of claims 1 to 6, wherein the peripheral neuropathies are autoimmune peripheral neuropathies.

{Claim 15}

—The use according to claim 14, wherein A is the group represented by general formula (IIa).

{Claim 16}

—The use according to claim 14, wherein A is the group represented by general formulae (IIb) or (IIc).

{Claim 17}

—The use according to claim 14, wherein A is the group represented by general formula (IIa), and the stereochemical configuration of the asymmetric carbon marked with * is S.

{Claim 18}

—The use according to any one of claims 14 to 17, wherein R^1 represents a methyl group or an ethyl group optionally substituted with a fluorine atom.

{Claim 19}

—The use according to any one of claims 14 to 17, wherein R^1 is a methyl group, an ethyl group, a difluoromethyl group or a 2,2,2-trifluoroethyl group.

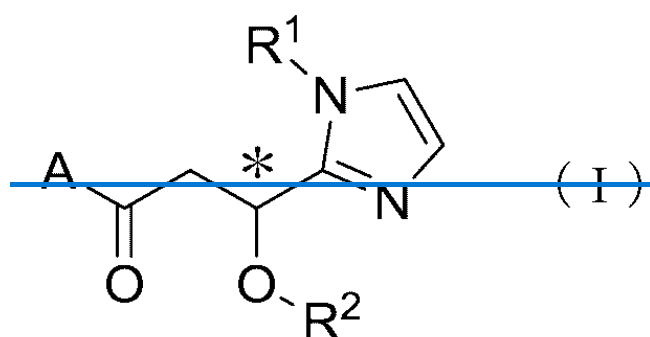
[Claim 2010]

The use according to ~~any one of claims 14 to 19~~claim 9, wherein the autoimmune peripheral neuropathies are at least one type selected from Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy and paraproteinemic neuropathy.

[Claim 211]

~~Use of a cyclic amine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof~~

~~{Chemical Formula 7}~~

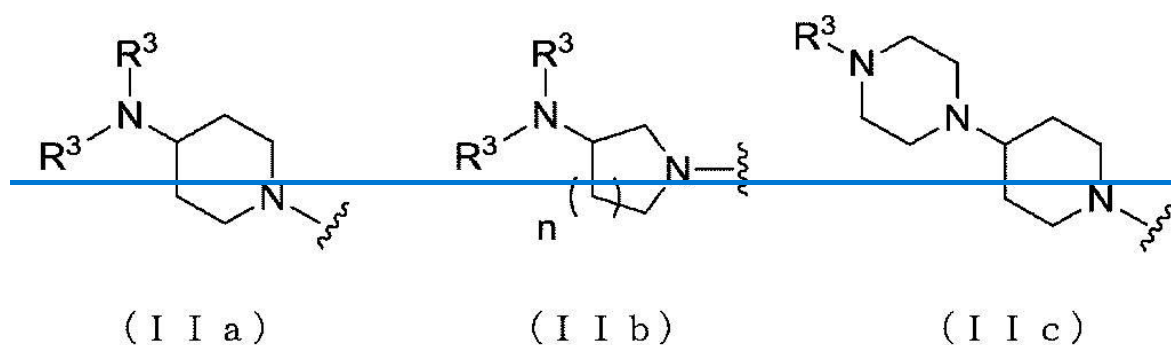


~~{wherein,~~

~~—— carbon marked with * is asymmetric carbon; and~~

~~—— A represents a group represented by general formulae (IIa), (IIb) or (IIc):~~

~~{Chemical Formula 8}~~



~~—— wherein R¹ represents a methyl group or an ethyl group optionally substituted with a halogen atom,~~

~~— R² represents a hydrogen atom or an alkylcarbonyl group having 2 to 5 carbon atoms,
— each R³ independently represents a methyl group or an ethyl group, and
— n represents 1 or 2.],~~

~~in producing a medicine for treatment or prevention of~~The use according to any one of claims 1 to 6, wherein the peripheral neuropathies are metabolic peripheral neuropathies.

~~{Claim 22}~~

~~— The use according to claim 21, wherein A is the group represented by general formula (IIa).~~

~~{Claim 23}~~

~~— The use according to claim 21, wherein A is the group represented by general formulae (IIb) or (IIc).~~

~~{Claim 24}~~

~~— The use according to claim 21, wherein A is the group represented by general formula (IIa), and the stereochemical configuration of the asymmetric carbon marked with * is S.~~

~~{Claim 25}~~

~~— The use according to any one of claims 21 to 24, wherein R¹ represents a methyl group or an ethyl group optionally substituted with a fluorine atom.~~

~~{Claim 26}~~

~~— The use according to any one of claims 21 to 24, wherein R¹ is a methyl group, an ethyl group, a difluoromethyl group or a 2,2,2-trifluoroethyl group.~~

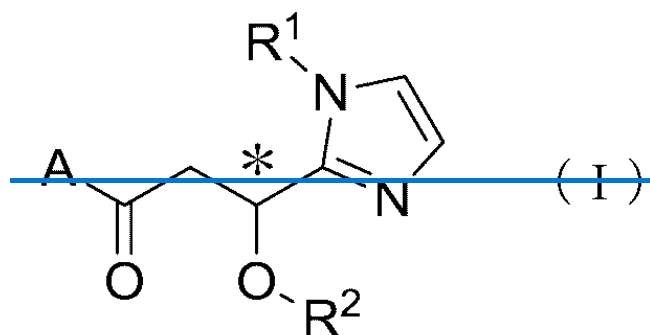
~~[Claim 27]~~12]

The use according to ~~any one of claims 21 to 26~~claim 11, wherein the metabolic peripheral neuropathies are at least one type selected from diabetic peripheral neuropathy, uremic peripheral neuropathy, collagen-peripheral neuropathy and vitamin deficiency peripheral neuropathy.

~~[Claim 28]~~13]

~~Use of a cyclic amine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof~~

~~{Chemical Formula 9}~~

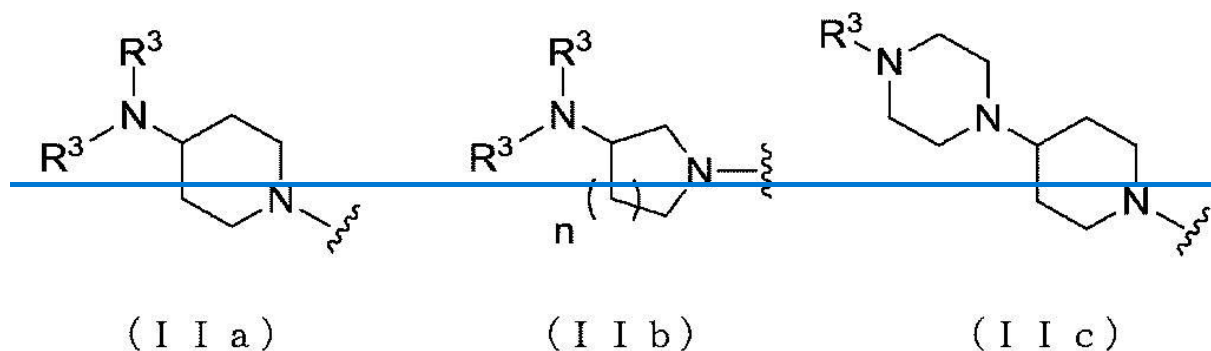


~~{wherein,~~

~~—— carbon marked with * is asymmetric carbon; and~~

~~—— A represents a group represented by general formulae (IIa), (IIb) or (IIc):~~

~~{Chemical Formula 10}~~



~~—— wherein R¹ represents a methyl group or an ethyl group optionally substituted with a halogen atoms,~~

~~—— R² represents a hydrogen atom or an alkylcarbonyl group having 2 to 5 carbon atoms,~~

~~—— each R³ independently represents a methyl group or an ethyl group, and~~

~~—— n represents 1 or 2.];~~

~~in producing a medicine for treatment or prevention of~~The use according to any one of claims 1 to 6, wherein the peripheral neuropathies are hereditary peripheral neuropathies.

~~{Claim 29}~~

~~— The use according to claim 28, wherein A is the group represented by general formula (IIa).~~

~~{Claim 30}~~

~~— The use according to claim 28, wherein A is the group represented by general formulae (IIb) or (IIc).~~

~~{Claim 31}~~

~~— The use according to claim 28, wherein A is the group represented by general formula (IIa), and the stereochemical configuration of the asymmetric carbon marked with * is S.~~

~~{Claim 32}~~

~~— The use according to any one of claims 28 to 31, wherein R¹ represents a methyl group or an ethyl group optionally substituted with a fluorine atom.~~

~~{Claim 33}~~

~~— The use according to any one of claims 28 to 31, wherein R¹ is a methyl group, an ethyl group, a difluoromethyl group or a 2,2,2-trifluoroethyl group.~~

~~[Claim 34]~~

The use according to ~~any one of claims 28 to 33~~claim 13, wherein the hereditary peripheral neuropathies are at least one type selected from Charcot-Marie-Tooth disease, familial amyloid polyneuropathy, hereditary neuropathy to pressure palsies (HNPP) and hereditary neuralgic amyotrophy.