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(54) **THERAPEUTIC AGENT FOR SENILE DEMENTIA**

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Jun. 23, 2003 (JP) 2003-178386

(51) **Int. Cl.**
A61K 31/497 (2006.01)

(52) **U.S. Cl.**
USPC **514/254.02**

(58) **Field of Classification Search**
None
See application file for complete search history.

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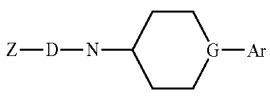
(57) **ABSTRACT**

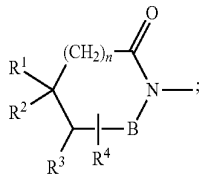
A therapeutic/preventive agent for cognitive dysfunctions, which comprises as an active ingredient an imide derivative of the following formula [1]:

[1]



wherein Z is a group of the formula [2]:

[2]



D is a group of —$(CH_2)_p$-A-$(CH_2)_q$—; G is =N—, —CH—, etc.; and Ar is an aromatic heterocyclic group, etc.

11 Claims, 2 Drawing Sheets

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FIG. 1

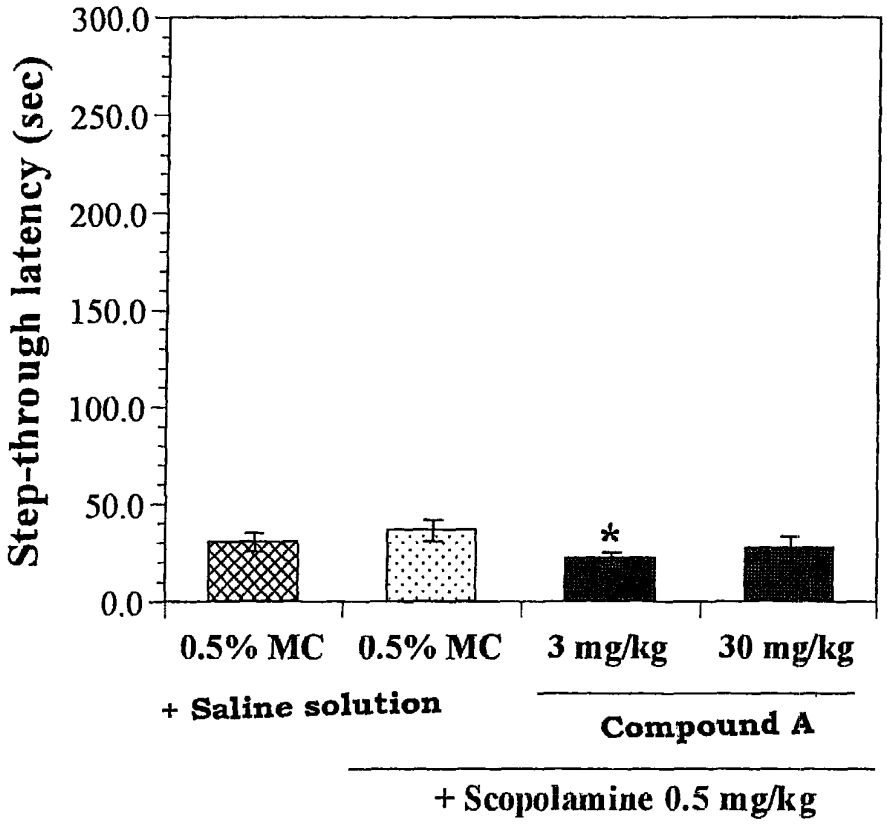
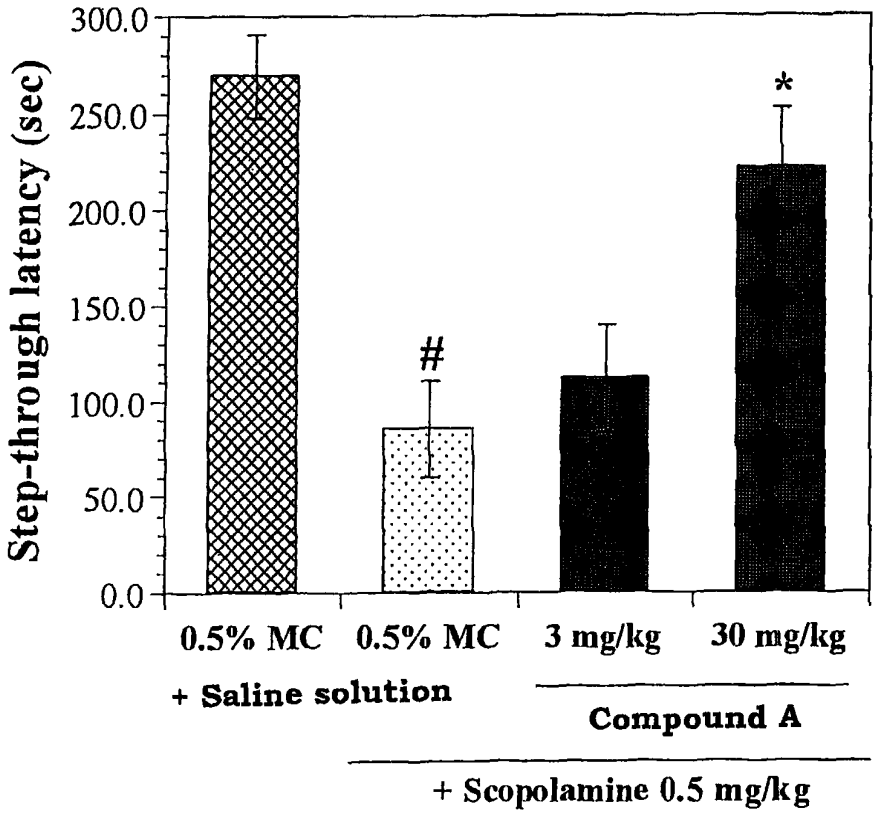

Step-through latency (sec)
300.0
250.0
200.0
150.0
100.0
50.0
0.0
*
0.5% MC
0.5% MC
3 mg/kg
30 mg/kg
+ Saline solution
Compound A
+ Scopolamine 0.5 mg/kg

FIG. 2


Step-through latency (sec)
300.0
250.0
200.0
150.0
100.0
50.0
0.0
#
*
0.5% MC
0.5% MC
3 mg/kg
30 mg/kg
+ Saline solution
Compound A
+ Scopolamine 0.5 mg/kg

THERAPEUTIC AGENT FOR SENILE DEMENTIA

This application is a division of application Ser. No. 12/140,927, filed Jun. 17, 2008, now U.S. Pat. No. 8,148,379, which is a divisional of application Ser. No. 10/562,039, filed Dec. 22, 2005 now abandoned which is a national phase application of International Application No. PCT/JP2004/009095 filed on Jun. 22, 2004, which claims priority to JP 2003/178386 filed in Japan on Jun. 23, 2003 under 35 U.S.C. §119; the entire contents of all are hereby incorporated by reference.

TECHNICAL FIELD

The present invention relates to a therapeutic agent for dementia, more particularly, a therapeutic agent for dementia, which comprises as an active ingredient an imide derivative.

BACKGROUND ART

Senile dementia is divided broadly into the Alzheimer type dementia and the cerebrovascular dementia, and about 80% of the patients of senile dementia can be classified into these categories. As the population rapidly ages, the number of the patients of senile dementia demonstrates an upward trend in these days. In Japan, it is speculated that about 7% of the people 65 years old or over show the symptoms of dementia, and hence, it is an urgent need to develop an excellent therapeutic agent for dementia. The Alzheimer type dementia is accompanied by senile plaque and neurofibrillary tangle, and it is pathologically characterized by encephalatrophy caused by significant neuronal death. In familial Alzheimer's disease, several gene mutations have been identified, whereby a leading hypothesis for neuronal pathogenetic mechanism thereof has been speculated, but the most of cases are sporadic, and hence, it may be said that Alzheimer's disease is still a disease of unknown cause. Accordingly, at the present, there is no radical therapeutic method for inhibiting neurodegeneration. The Alzheimer type dementia shows as core symptoms cognition dysfunctions such as disorders of memory, faculty of orientation, attention, etc., and it is also accompanied by peripheral symptoms such as psychotic manifestations or abnormal behavior problems (e.g., depression, aggressive attack, delusion, etc.). In the symptomatic treatment of these symptoms, only an acetylcholine esterase inhibitor has been clinically used, and it has been reported that acetylcholine esterase inhibitors are also effective to not only core symptoms but also peripheral symptoms. In the treatment with acetylcholine esterase inhibitors, neurotransmitter acetylcholine is supplemented by inhibiting acetylcholine-degrading enzyme, while acetylcholine neuronal cells, which are closely-linked with cognitive function, are especially disturbed in Alzheimer's disease and neurotransmitter acetylcholine is reduced.

On the other hand, the cerebrovascular dementia is a disease which develops owing to cerebrovascular disorders, and at the moment, there is no cure for core symptoms thereof. However, recently, the clinical trial of acetylcholine esterase inhibitors has been done, and it has become apparent that these medicaments are also effective to cerebrovascular dementia. Accordingly, there is a possibility that a therapeutic agent having a similar therapeutic mechanism to the Alzheimer's disease such as acetylcholine esterase inhibitors may be effective even to cerebrovascular dementia (e.g., Rinsho-Seishinigaku (i.e., Clinical Psychiatry), 31 (10): 1189-1193 (2002)).

On the other hand, there has not been known any therapeutic agent which shows no acetylcholine esterase inhibitory activity but is effective to senile dementia such as the Alzheimer type dementia and the cerebrovascular dementia. Moreover, JP Patent No. 2800953 discloses imide derivatives showing an excellent antipsychotic activity and anxiety reducing activity, but it has never indicated whether or not those derivatives show effects on senile dementia.

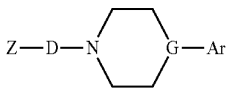
DISCLOSURE OF INVENTION

The present invention provides a therapeutic agent for senile dementia. More particularly, the present invention provides a therapeutic agent effective to both of the core symptoms and the peripheral symptoms of senile dementia.

The present inventors have intensively studied in order to solve the above problems, and found that the imide compound of the present invention exhibits a therapeutic effect in cognitive/memory disturbance models produced by acetylcholine receptor blocker, which are representative animal models for senile dementia, and finally they have accomplished the present invention.

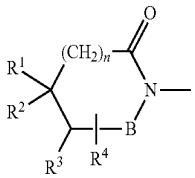
Namely, the present invention relates to the following:

(1) A therapeutic/preventive agent for cognitive dysfunctions, which comprises as an active ingredient an imide derivative of the formula [1]:



[1]

(wherein Z is a group of the formula [2]:



[2]

(in which B is a carbonyl or a sulfonyl; R^1R^2, R^3 and R^4 are independently a hydrogen atom or a lower alkyl, provided that R^1 and R^2, or R^1 and R^3 may combine each other to form a hydrocarbon ring, or R^1 and R^3 may combine each other to form an aromatic hydrocarbon ring; said hydrocarbon ring may optionally be cross-linked with a lower alkylene or an oxygen atom; said lower alkylene and hydrocarbon ring may optionally be substituted by at least one alkyl; and n is 0 or 1), D is a group of the formula [3]:

$$—(CH_2)_p\text{-}A\text{-}(CH_2)_q— \quad [3]$$

(in which A is a hydrocarbon ring optionally be cross-linked with a lower alkylene or an oxygen atom; said lower alkylene and hydrocarbon ring may optionally be substituted by at least one alkyl; and p and q are independently 0, 1 or 2),

G is N, CH or COH, and —Ar is an aromatic heterocyclic group, an aromatic hydrocarbon group, benzoyl, phenoxy, or phenylthio, or

G is a carbon atom, and —Ar is biphenylmethylidene,

where said aromatic heterocyclic group, aromatic hydrocarbon group, benzoyl, phenoxy or phenylthio, and biphenylm-

ethylidene may optionally be substituted by at least one group selected from a lower alkyl, a lower alkoxy and a halogen atom},

or an acid addition salt thereof.

(2) The therapeutic/preventive agent for cognitive dysfunctions according to the above (1), which is a therapeutic agent for senile dementia.

(3) A therapeutic/preventive agent for cognitive dysfunctions, which comprises as an active ingredient an imide derivative of the above formula [1], wherein —Ar is an aromatic heterobicyclic group, naphthyl, benzoyl, phenoxy or phenylthio and G is N, CH or COH, or —Ar is biphenyl-methylidene and G is a carbon atom (said aromatic heterobicyclic group, naphthyl, benzoyl, phenoxy, phenylthio and biphenylmethylidene may optionally be substituted by at least one group selected from a lower alkyl, a lower alkoxy and a halogen atom), or an acid addition salt thereof.

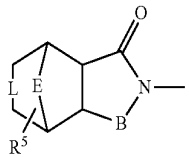
(4) The therapeutic/preventive agent for cognitive dysfunctions according to the above (3), which is a therapeutic agent for senile dementia.

(5) A therapeutic/preventive agent for cognitive dysfunctions, which comprises as an active ingredient an imide derivative of the above formula [1], wherein —Ar is an aromatic heterocyclic group condensed with a benzene ring, or naphthyl, benzoyl, phenoxy or phenylthio (said aromatic heterocyclic group condensed with a benzene ring, naphthyl, benzoyl, phenoxy, and phenylthio may optionally be substituted by at least one group selected from a lower alkyl, a lower alkoxy and a halogen atom), and G is N, CH or COH, or an acid addition salt thereof.

(6) The therapeutic/preventive agent for cognitive dysfunctions according to the above (5), which is a therapeutic agent for senile dementia.

(7) A therapeutic/preventive agent for cognitive dysfunctions, which comprises as an active ingredient an imide derivative of the above formula [1], wherein Z is a group of the formula [4]:

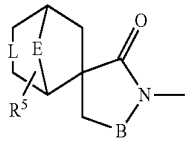
[4]



in which -L- is a single bond or a double bond, E is a lower alkylene optionally substituted by a lower alkyl, or an oxygen atom, R^5 is a hydrogen atom or a lower alkyl, and B is the same as defined in the above (1);

a group of the formula [5]:

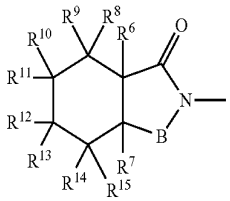
[5]



in which -L-, E, R^5 and B are as defined above;

a group of the formula [6]:

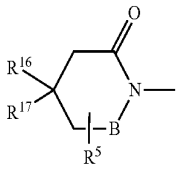
[6]



in which R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} are independently a hydrogen atom or a lower alkyl, or the adjacent two groups of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} may combine each other to form a double bond, and B is as defined above;

a group of the formula [7]:

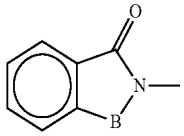
[7]



in which R^{16} and R^{17} are independently a hydrogen atom or a lower alkyl, or R^{16} and R^{17} may combine each other to form a saturated hydrocarbon ring, and R^5 and B are as defined above; or

a group of the formula [8]:

[8]



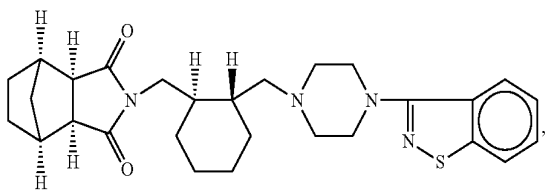
in which B is as defined above,

or an acid addition salt thereof.

(8) The therapeutic/preventive agent for cognitive dysfunctions according to the above (7), which is a therapeutic agent for senile dementia.

(9) A therapeutic/preventive agent for cognitive dysfunctions, which comprises as an active ingredient an imide derivative of the formula [9]:

[9]



or an acid addition salt thereof.

(10) The therapeutic/preventive agent for cognitive dysfunctions according to the above (9), which is a therapeutic agent for senile dementia.

(11) The therapeutic/preventive agent for cognitive dysfunctions according to the above (2), (4), (6), (8) or (10), which is a therapeutic agent for the Alzheimer type dementia.

(12) The therapeutic/preventive agent for cognitive dysfunctions according to the above (2), (4), (6), (8) or (10), which is a therapeutic agent for the cerebrovascular dementia.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** shows the effects of the imide derivative on rats in one step-through passive avoidance test where the acetylcholine receptor blocker scopolamine was used for inducing amnesia, and indicates the step-through latency during the training (*: P<0.05 vs the group treated with 0.5% MC+scopolamine (Steel's test)).

FIG. **2** shows the effects of the imide derivatives on rats in one step-through passive avoidance test where the acetylcholine receptor blocker scopolamine was used for inducing amnesia, and indicates the step-through latency during the test (*: P<0.05 vs the group treated with 0.5% MC+scopolamine (Steel's test), #: •<0.01 vs the group treated with 0.5% MC+saline solution (Mann-Whitney test)).

BEST MODE FOR CARRYING OUT THE INVENTION

Each group of the imide derivative of the formula [1] of the present invention are explained in detail.

The lower alkylene for Z and A includes, for example, ones having not more than 3 carbon atoms such as methylene, ethylene, trimethylene, etc.

The hydrocarbon ring for Z and A includes, for example, a cycloalkane or cycloalkene having not more than 7 carbon atoms. The cycloalkane having not more than 7 carbon atoms includes, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, etc. The cycloalkene having not more than 7 carbon atoms includes, for example, cyclopentene, cyclohexene, cycloheptene, etc.

The hydrocarbon ring being cross-linked with a lower alkylene or an oxygen atom for Z and A includes, for example, rings having not more than 10 carbon atoms such as bicyclo[1.1.1]pentane, bicyclo[2.1.1]hexane, bicyclo[2.1.1]hex-2-ene, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-2-ene, bicyclo[2.2.2]octane, bicyclo[2.2.2]oct-2-ene, bicyclo[4.1.1]octane, bicyclo-[4.1.1]oct-2-ene, bicyclo[4.1.1]oct-3-ene, bicyclo[3.2.1]octane, bicyclo-[3.2.1]oct-2-ene, bicyclo[3.2.1]oct-3-ene, bicyclo[3.2.1]oct-6-ene, bicyclo-[3.2.2]nonane, bicyclo[3.2.2]non-2-ene, bicyclo[3.2.2]non-3-ene, bicyclo-[3.2.2]non-6-ene, 2-oxabicyclo[1.1.1]butane, 2-oxabicyclo[2.1.1]pentane, 2-oxabicyclo[2.1.1]pent-4-ene, 7-oxabicyclo[2.2.1]hexane, 7-oxabicyclo-[2.2.1]hex-2-ene, 7-oxabicyclo[4.1.1]heptane, 7-oxabicyclo[4.1.1]hept-2-ene, 7-oxabicyclo[4.1.1]hept-3-ene, 8-oxabicyclo[3.2.1]heptane, 8-oxabicyclo[3.2.1]hept-2-ene, 8-oxabicyclo[3.2.1]hept-3-ene, 8-oxabicyclo-[3.2.1]hept-6-ene, etc.

The aromatic hydrocarbon ring for Z includes, for example, ones having not more than 10 carbon atoms such as phenyl ring, naphthyl ring, etc.

The binding position of the hydrocarbon ring for A includes, for example, -1,1-, -1,2-, -1,3-, -1,4-, etc.

The aromatic hydrocarbon group for —Ar includes, for example, ones having not more than 10 carbon atoms such as phenyl, naphthyl, etc. The aromatic heterocyclic group for —Ar includes, for example, an aromatic heteromonocyclic group and an aromatic heterobicyclic group.

The aromatic heteromonocyclic group includes, for example, ones having not more than 6 carbon atoms, and further having the same or different 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, such as pyridyl, pyrimidinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, furyl, imidazolyl, etc.

The aromatic heterobicyclic group includes, for example, ones having not more than 10 carbon atoms, and further having the same or different 1 to 5 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, such as benzolog-fused rings (e.g., benziso-thiazolyl, benzisoxazolyl, benzofuryl, quinolyl, isoquinolyl, indolyl, indazolyl, benzimidazolyl, benzoxazolyl, etc.), naphthyridinyl, puteridinyl, thienofuranyl, imidazothiophen-yl, imidazofuranyl, etc.

The alkyl includes, for example, ones having not more than 6 carbon atoms, and preferably lower alkyl groups having not more than 4 carbon atoms, such as methyl, ethyl, propyl, 2-propyl, butyl, etc. The lower alkyl includes, for example, ones having not more than 4 carbon atoms, such as methyl, ethyl, propyl, 2-propyl, butyl, etc.

The lower alkoxy includes, for example, ones having not more than 4 carbon atoms, such as methoxy, ethoxy, propoxy, 2-propoxy, butoxy, etc.

The halogen atom is fluorine, chlorine, bromine, iodine.

The present compound [1] may have stereoisomers and/or an optical isomer. The present invention also includes a mixture of these isomers or each isolated isomer.

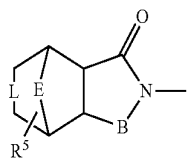
The preferable group for —Ar is an aromatic heterobicyclic group, or naphthyl, benzoyl, phenoxy or phenylthio (in these cases, G is N, CH, or COH), or biphenylmethylidene (in this case, G is a carbon atom), where said aromatic heterobicyclic group, naphthyl, benzoyl, phenoxy, phenylthio and biphenylmethylidene may optionally be substituted by at least one group selected from a lower alkyl, a lower alkoxy and a halogen atom.

The more preferable group for —Ar is a benzolog-fused ring, naphthyl, benzoyl, phenoxy, or phenyl (said benzolog-fused ring, naphthyl, benzoyl, phenoxy, and phenylthio may optionally be substituted by at least one group selected from a lower alkyl, a lower alkoxy and a halogen atom), and in this case, G is N, CH or COH.

The further preferable group for —Ar is benzisothiazolyl, benzisoxazolyl, isoquinolyl, benzofuranyl, indazolyl or indolyl (said benzisothiazolyl, benzisoxazolyl, isoquinolyl, benzofuranyl, indazolyl and indolyl may optionally be substituted by at least one group selected from a lower alkyl, a lower alkoxy and a halogen atom), and in this case, G is N, CH or COH.

The preferable group for Z is, for example, a group of the formula [4]:

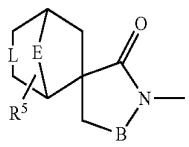
[4]



(in which -L- is a single bond or a double bond, E is a lower alkylene optionally substituted by a lower alkyl, or an oxygen atom, R^5 is a hydrogen atom or a lower alkyl, and B is a carbonyl or a sulfonyl);

a group of the formula [5]:

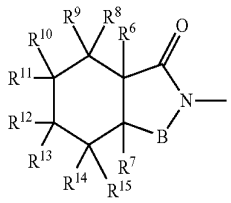
[5]



(in which -L-, E, R^5 and B are as defined above);

a group of the formula [6]:

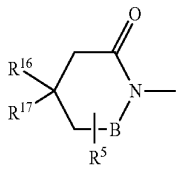
[6]



(in which R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} are independently a hydrogen atom or a lower alkyl, or the adjacent two groups of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} may combine each other to form a double bond, and B is as defined above);

a group of the formula [7]:

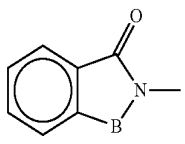
[7]



(in which R^{16}, R^{17} are independently a hydrogen atom or a lower alkyl, or R^{16} and R^{17} may combine each other to form a saturated hydrocarbon ring, and R^5 and B are as defined above); or

a group of the formula [8]:

[8]

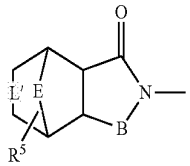


(in which B is as defined above), etc.

Then, the saturated hydrocarbon ring formed by combining R^{16} and R^{17} includes, for example, a cycloalkane having not more than 7 carbon atoms, such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, etc.

The preferable group for Z is, for example, a group of the formula [10]:

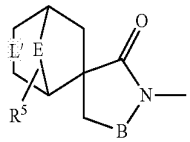
[10]



(in which -L'- is a single bond, E is a lower alkylene optionally substituted by a lower alkyl, or an oxygen atom, R^5 is a hydrogen atom or a lower alkyl, and B is a carbonyl or a sulfonyl);

a group of the formula [11]:

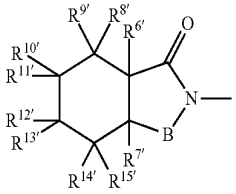
[11]



(in which -L'-, E, R^5 and B are as defined above);

a group of the formula [12]:

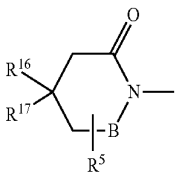
[12]



(in which $R^{6'}$, $R^{7'}$, $R^{8'}$, $R^{9'}$, $R^{10'}$, $R^{11'}$, $R^{12'}$, $R^{13'}$, $R^{14'}$, $R^{15'}$ are independently a hydrogen atom or a lower alkyl, and B is as defined above);

a group of the formula [7]:

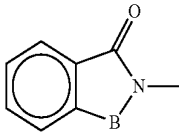
[7]



(in which R^{16}, R^{17}, R^5 and B are as defined above); or

a group of the formula [8]:

[8]



(B is as defined above).

The imide derivative of the present invention or an acid addition salt thereof may be prepared, for example, by the method disclosed in JP Patent No. 2800953 1 as mentioned above.

The imide derivative of the present invention may be used in the form of a pharmaceutically acceptable acid addition salt thereof. Inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, etc. or organic acids such as fumaric acid, citric acid, tartaric acid, succinic acid, etc. may be exemplified as an acid for forming addition salts.

The imide derivative or a pharmaceutically acceptable acid addition salt thereof, which is the active compound of the present invention, may be administered at a dose suitable for necessity of each case in a conventional dosage form. For example, it can be administered orally in the form of tablets, capsules, syrups, suspension, etc. or parenterally in the form of injection preparation such as liquid preparations (e.g., solutions, emulsions, suspension, patches, etc.).

In addition, the above-mentioned suitable dosage forms may be prepared by mixing an active compound with a conventional pharmaceutically acceptable carriers, excipients, binders, stabilizers, etc. When used in the form of injection, it may additionally contain buffering agents, solublizers, isotonic agents, etc.

The dose and the frequency of the administration of the present therapeutic agent may vary according to the dosage forms, or the severity of the diseases to be treated. For example, the imide derivative is orally administered at a dose of 1 to 200 mg per day in an adult, which is administered once a day or divided into several dosage units.

The diseases to which the therapeutic agent of the present invention is effective are the Alzheimer type and the cerebrovascular dementia, more particularly, various senile dementias (e.g., dementia with Lewy bodies, dementia from Pick's disease, dementia from Creutzfeldt-Jakob disease, dementia from Huntington's chorea, dementia from Parkinson's disease, etc.) including multiple infarct dementia, dementia caused by cerebral infarction, Binswanger disease, dementia caused by stroke, amyloid angiopathy, ischemic dementia. Further, the therapeutic agent of the present invention shows the improving activity of cognitive dysfunctions accompanied by acetylcholine neuronal dysfunctions, and hence, it may be used in the treatment of traumatic cognitive dysfunctions, dementia in Down syndrome, schizophrenial cognitive dysfunctions, or cognitive dysfunctions accompanied by acetylcholine neuronal dysfunctions from any cause, in addition to the treatment of senile dementia.

EXAMPLES

The present invention is illustrated in more detail by Examples, but the present invention should not be construed to be limited thereto.

Example 1

Method

Male Wistar rats (7 weeks old) were used. As a test medicament, (1R,2S,3R,4S)—N-[(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl-methyl]-1-cyclohexylmethyl]-2,3-bicycl[2.2.1]heptanedicarboxylmide (Compound A) was suspended in 0.5% methyl cellulose (MC) solution. As an agent for inducing amnesia, scopolamine (manufactured by Wako Pure Chemical Industries, Ltd., product No. 198-07901), which is an acethylcoline receptor blocker, was dissolved in saline solution (manufactured by TERUMO CORPORATION). Compound A at a dose of 3 mg/kg or 30 mg/kg, or 0.5% MC as a control was orally administered to the animals one hour prior to the training step in the one step-through passive avoidance test, and then, scopolamine at a dose of 0.5 mg/kg or a saline solution as a control was subcutaneously administered to the animals 30 minutes prior to the training step. The volume of each solution to be administered was 5 ml/kg each.

The one step-through passive avoidance test in rats was carried out in the following manners with using an apparatus consisting of a light-dark box and an electric stimulator (manufactured by O'hara & Co., Ltd., product no. PA-2030A) as an experimental apparatus. Namely, on Day 1, after the medicament and the agent for inducing amnesia were administered, the rats were put into the light box of the experimental apparatus where the back of each rat was directed to the dark box. Then, 10 seconds later, a guillotine door set at the border between the dark box and the light box was opened. Due to the habits of the rats, once the rats entered into the dark box, the guillotine door was quickly closed. At three seconds after the entering into the dark box, an electroconvulsive shock (0.5 mA, for 3 seconds) was given to the rats. Again, the guillotine door was opened, and after the rats spontaneously returned to the light box, the animals were transferred into the home cage. The period between the time just after the guillotine door was opened and the time at which the rats entered into the dark box was measured as a step-through latency. As to the animals which did not enter into the dark room even after 300 seconds, the training was terminated, and those animals were dropped in the following experiment for the reasons of training failure.

On Day 2 of the experiment, a test was carried out about 24 hours after the training. The procedures of the test were carried out in the same manner to the training step except that an electroconvulsive shock was not given. The step-through latency in the test was measured up to 300 seconds, and the step-through latency over 300 seconds was regarded as 300 seconds. FIG. **1** and FIG. **2** show the effects of Compound A on the scopolamine-induced cognitive/memory dysfunction models in the one step-through passive avoidance test when it was orally administered at a dosage of 3 mg/kg or 30 mg/kg. FIG. **1** shows the step-through latency during the training step, and FIG. **2** shows the step-through latency during the test. The number of the animals was 15 per group, and the data was expressed in mean±SEM.

(Results)

The agent for inducing amnesia, scopolamine did not affect on the step-through latency during the training. Compound A slightly shortened the step-through latency during the training step at a dose of 3 mg/kg. During the test, the animals treated with scopolamine showed a significantly shorter step-through latency as compared to the animals treated with saline solution (cognitive/memory dysfunction inducing effect). In the group treated with both of Compound A at a dose of 30 mg/kg and scopolamine, the step-through latency was significantly extended. That is, it was observed that Compound A exhibited an improving effect of scopolamine-induced cognitive/memory dysfunctions. Thus, it was found that the imide derivatives may exhibit an improving activity of scopolamine-induced cognitive/memory dysfunctions, and as a result, it may become apparent that the present invention may provide a therapeutic method for senile dementia and a therapeutic agent for said method.

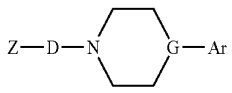
INDUSTRIAL APPLICABILITY

According to the present invention, it was found that the imide derivatives may exhibit an improving activity of sco-

polamine-induced cognitive/memory dysfunctions, and as a result, it has become apparent that the present invention may provide a therapeutic method for senile dementia and a therapeutic agent for said method.

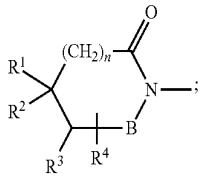
The invention claimed is:

1. A method for treatment of senile dementia, which comprises administering an effective amount of an imide derivative of the formula [1]:



[1]

wherein Z is a group of the formula [2]:



[2]

in which B is a carbonyl or a sulfonyl; R^1, R^2, R^3 and R^4 are independently a hydrogen atom or a lower alkyl, provided that R^1 and R^2, or R^1 and R^3 may combine each other to form a hydrocarbon ring, or R^1 and R^3 may combine each other to form an aromatic hydrocarbon ring; said hydrocarbon ring may optionally be cross-linked with a lower alkylene or an oxygen atom; said lower alkylene and hydrocarbon ring may optionally be substituted by at least one alkyl; and n is 0 or 1,

D is a group of the formula [3]:

$$—(CH_2)_p\text{-}A\text{-}(CH_2)_q—$$ [3]

in which A is a hydrocarbon ring optionally be cross-linked with a lower alkylene or an oxygen atom; said lower alkylene or said hydrocarbon ring may optionally be substituted by at least one alkyl; and p and q are independently 0, 1 or 2,

G is N, CH or COH, and —Ar is an aromatic heterocyclic group, an aromatic hydrocarbon group, benzoyl, phenoxy, or phenylthio, or

G is a carbon atom, and —Ar is biphenylmethylidene,

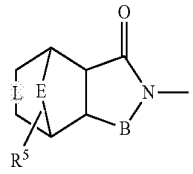
where said aromatic heterocyclic group aromatic hydrocarbon group, benzoyl, phenoxy, phenylthio, and biphenylmethylidene may optionally be substituted by at least one group selected from a lower alkyl, a lower alkoxy and a halogen atom,

or an acid addition salt thereof.

2. The method according to claim **1**, wherein —Ar is an aromatic heterobicyclic group, naphthyl, benzoyl, phenoxy or phenylthio, and G is N, CH or COH, or —Ar is biphenylmethylidene, and G is a carbon atom, wherein said aromatic heterobicyclic group, naphthyl, benzoyl, phenoxy, phenylthio and biphenylmethylidene may optionally be substituted by at least one group selected from a lower alkyl, a lower alkoxy and a halogen atom.

3. The method according to claim **1**, wherein —Ar is an aromatic heterocyclic group condensed with a benzene ring, or naphthyl, benzoyl, phenoxy or phenylthio, wherein said aromatic heterocyclic group condensed with a benzene ring, naphthyl, benzoyl, phenoxy, and phenylthio may optionally be substituted by at least one group selected from a lower alkyl, a lower alkoxy and a halogen atom, and G is N, CH or COH.

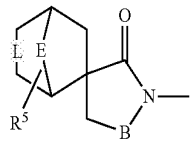
4. The method according to claim **1**, wherein Z is a group of the formula [4];



[4]

in which -L- is a single bond or a double bond, E is a lower alkylene optionally substituted by a lower alkyl, or an oxygen atom, R^5 is a hydrogen atom or a lower alkyl, and B is a carbonyl or a sulfonyl;

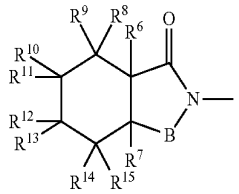
a group of the formula [5]:



[5]

in which -L is a single bond or a double bond, E is a lower alkylene optionally substituted by a lower alkyl, or an oxygen atom, R^5 is a hydrogen atom or a lower alkyl, and B is carbonyl or a sulfonyl;

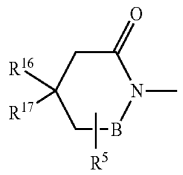
a group of the formula [6]:



[6]

in which R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} are independently a hydrogen atom or a lower alkyl, or the adjacent two groups of R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} may combine each other to form a double bond, and B is a carbonyl or a sulfonyl;

a group of the formula [7]:

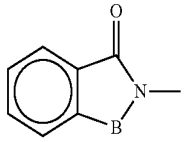


[7]

in which R^{16} and R^{17} are independently a hydrogen atom or a lower alkyl, or R^{16} and R^{17} may combine each other to form a saturated hydrocarbon ring, R^5 is a hydrogen atom or a lower alkyl, and B is a carbonyl or a sulfonyl; or

a group of the formula [8]:

[8]



in which B is a carbonyl or a sulfonyl.

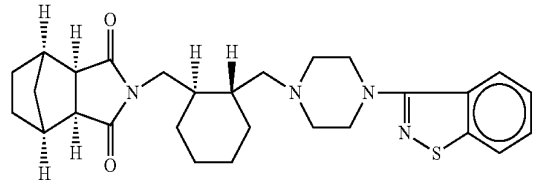
5. The method according to claim **1**, wherein the senile dementia is selected from the group consisting of Alzheimer type dementia, cerebrovascular dementia, dementia with Lewy bodies, dementia from Pick's disease, dementia from Creutzfeldt-Jakob disease, dementia from Huntington's chorea and dementia from Parkinson's disease.

6. The method according to claim **1**, wherein the senile dementia is Alzheimer type dementia.

7. The method according to claim **1**, wherein the senile dementia is selected from the group consisting of cerebrovascular dementia and dementia with Lewy bodies.

8. A method for treatment of senile dementia, which comprises administering an effective amount of an imide compound of the formula [9]:

[9]



or an acid addition salt thereof, and

wherein the senile dementia is selected from the group consisting of cerebrovascular dementia, dementia with Lewy bodies, dementia from Pick's disease, dementia from Creutzfeldt-Jakob disease and dementia from Huntington's chorea.

9. The method according to claim **8**, wherein the senile dementia is selected from the group consisting of cerebrovascular dementia and dementia with Lewy bodies.

10. The method according to claim **8**, wherein the senile dementia is cerebrovascular dementia.

11. The method according to claim **8**, wherein the senile dementia is dementia with Lewy bodies.

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