DESCRIPTION

An Alzheimer's Disease Progression Inhibitor containing heterocyclic compound having specific structure

FIELD OF THE INVENTION

[0001]
The present invention is in the filed of medicinal chemistry and relates to an Alzheimer's disease progression inhibitor containing a heterocyclic compound having a specific structure.

BACKGROUND OF THE INVENTION

[0002]
Alzheimer' diseases is dementing neurodegenarative disorder for which there is no effective treatment at present. Genetic and biological studies provide evidence that the production and deposition of amyloid-β(Aβ) contribute to the etiology of Alzheimer' disease (for example, see Drug News & Perspectives. Vol.17, No.5, June 2004, Trends Neurosci., 20. 154-159(1997), and Science, 297, 353-356(2002)). Therefore an amyloid β deposition inhibitor will be useful agent as Alzheimer's disease progression inhibitor

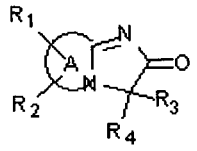
[0003]
γ-Secretase inihibitors are developing for inhibiting the production of amyloid β, but these compounds will have adverse side effects because of their inhibitory activity of Notch gene or N-Cadherin (for example, see J. Biol. Chem., 276, 45394-45402(2001)). Curcumin is a component of *Curcuma longa* contained in curry in a large amount and has antiinflammatory and antioxidative activity equivalent to prescribed nonsteroidal antiinflammatory drugs (NSAIDs). Studies have shown that curcumin inhibits amyloid-related pathologies. However, curcumin does not inhibit β amyloid deposition at satisfactory levels (for example, see *Pharmacia*, Japanese Pharmacology Association, Vol.38, No.9, 891-892, 2002). Therefore there is a strong demand for development of effective drugs having an sufficient effect and fewer side effects.

[0004]
Booklet of International Publication No. WO01/009131; and Booklet of International Publication No.WO02/060907 disclose brain function improvers containing heterocyclic compounds having specific structures. The heterocyclic compounds are disclosed as brain function improvers leading to treatment for memory loss and memory acquisition/retention disorder in senile dementia, Alzheimer's disease and related disorders. But the inhibitory activity of amyloid β deposition and the inhibitory activity of progression of Alzheimer's disease are not disclosed (for example, see Booklet of International Publication No. 01/009131; and Booklet of International Publication No.2002/060907).

SUMMARY OF THE INVENTION

[0005]

The present invention provides an Alzheimer's disease progression inhibitor from their inhibitory activity of Amyloid β deposition containing a heterocyclic compound having the general Formula (I):



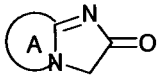
.....(I)

[0006]

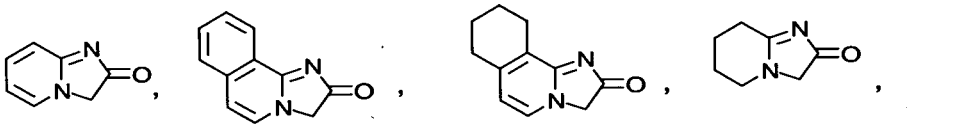
or a pharmaceutically acceptable salt or hydrate thereof.

[0007]

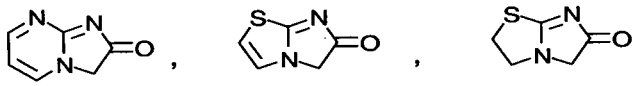
In the general Formula (I), the structural unit having the general formula (II) is one or more structural units selected from multiple types of structural units having the general Formula (III).



.....(II)



.....(III)



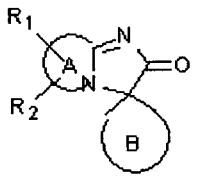
[0008]

In the general Formula (I), R_1 and R_2 each are one or more functional groups independently selected from the group consisting of a hydrogen atom, halogen atom, hydroxy group, amino group, acetylamino group, benzylamino group, trifluoromethyl group, C_1-C_6 alkyl group, C_1-C_6 alkoxy group, and -O-(CH_2)n-R_5, wherein R_5 is a vinyl group, C_3-C_6 cycloalkyl group, or phenyl group, and n is 0 or 1.

[0009]

Furthermore, in the general Formula (I), R_3 and R_4 each are one or more functional groups independently selected from the group consisting of a hydrogen atom , C_1-C_6 alkyl group, C_3-C_8

cycloalkyl group, and -CH(R_7)-R_6; alternatively, R_3 and R_4 together form a spiro ring having the general Formula (IV):



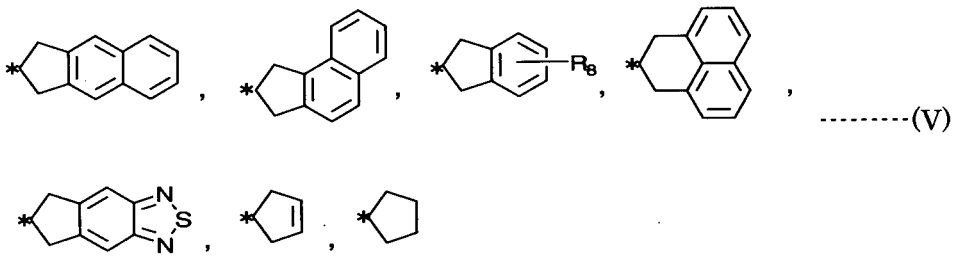
.....(IV)

[0010]

R_6 is one or more functional groups selected from the group consisting of a vinyl group; ethinyl group; phenyl optionally substituted by a C_1-C_6 alkyl group, C_1-C_6 alkoxy group, hydroxy group, 1 or 2 halogen atoms, di C_1-C_6 alkylamino group, cyano group, nitro group, carboxy group, or phenyl group; phenethyl group; pyridyl group; thienyl group; and furyl group. The above R_7 is a hydrogen atom or C_1-C_6 alkyl group.

[0011]

Furthermore, in the general Formula (IV), the structural unit B is one or more structural units selected from multiple types of structural units having the general Formula (V). The structural unit B binds at a position marked by * in the general Formula (V) to form a spiro ring.



.....(V)

[0012]

R_8 is one or more functional groups selected from the group consisting of a hydrogen atom, halogen atom, hydroxy group, C_1-C_6 alkoxy group, cyano group, and trifluoromethyl group.

[0013]

The compounds of Formula (I) may be used as an a delayer of the progression of Alzheimer's disease..

[0014]

The invention also relates to the inhibitor of progression of Alzheimer's disease in a human in need thereof, comprising administering to the human an effective amount of a compound having the general Formula (I).

Brief explanation of the drawings

[0015]

Fig.1 contains photographs for explaining the effect of Compound 1 on the number of amyloid β-immunoreactive cells in senescene accelerated mice (SAMP8).

Fig.2 depicts a graphical representation for explaining the effect of Compound 1 on the number of amyloid β-immunoreactive cells in senescene accelerated mice (SAMP8).

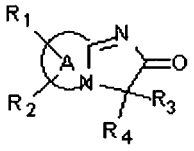
BEST MODES FOR CARRYING OUT THE INVENTION

[0016]

Embodiments of the present invention are described hereafter. Embodiments below relate to an Alzheimer's disease progression inhibitor composition containing a heterocyclic compound having the above described specific structure (azaindolizinone derivatives) and pharmaceutically acceptable carriers or diluents.

[0017]

The Alzheimer's disease progression inhibitor contain a heterocyclic compound having the general Formula (I):

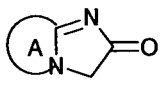


---------(I)

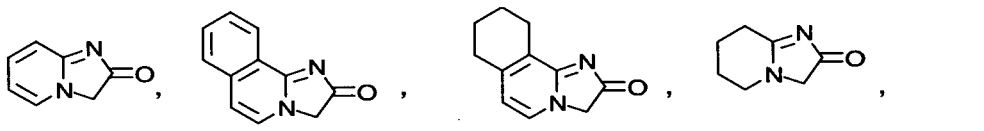
[0018]

or a pharmaceutically acceptable salt or hydrate thereof.

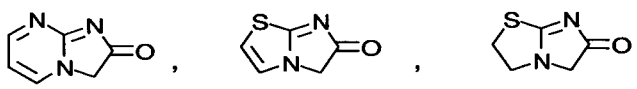
In the general Formula (I), the structural unit having the general Formula (II) is one or more structural units selected from multiple types of structural units having the general Formula (III).



---------(II)



---------(III)



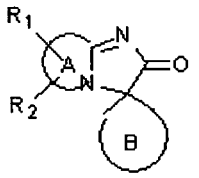
[0019]

Furthermore, in the general formula (I), R_1 and R_2 each are one or more functional groups independently selected from the group consisting of a hydrogen atom, halogen atom, hydroxy group, amino group, acetylamino group, benzylamino group, trifluoromethyl group, C_1-C_6 alkyl group, C_1-C_6 alkoxy group, and -O-(CH_2)n-R_5, wherein R_5 is a vinyl group, C_3-C_6

cycloalkyl group, or phenyl group, and n is 0 or 1.

[0020]

Furthermore, in the general Formula (I), R_3 and R_4 each are one or more functional groups independently selected from the group consisting of a hydrogen atom, C_1-C_6 alkyl group, C_3-C_8 cycloalkyl group, and -CH(R_7)-R_6; alternatively, R_3 and R_4 together form a spiro ring having the general formula (IV):



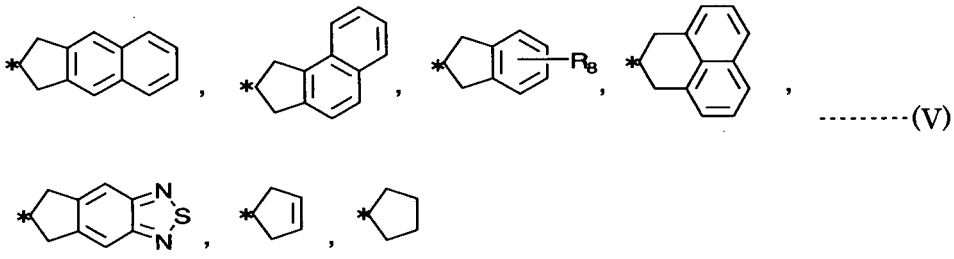
.....(IV)

[0021]

The above R_6 is one or more functional groups selected from the group consisting of a vinyl group; ethinyl group; phenyl optionally substituted by a C_1-C_6 alkyl group, C_1-C_6 alkoxy group, hydroxy group, 1 or 2 halogen atoms, di C_1-C_6 alkylamino group, cyano group, nitro group, carboxy group, or phenyl group), phenethyl group, pyridyl group, thienyl group, and furyl group. The above R_7 is a hydrogen atom or C_1-C_6 alkyl group.

[0022]

In the general Formula (IV), the structural unit B is one or more structural units selected from multiple types of structural units having the general Formula (V). The structural unit B binds at a position marked by * in the general Formula (V) to form a spiro ring.



.....(V)

[0023]

Here, R_8 is one or more functional groups selected from the group consisting of a hydrogen atom, halogen atom, hydroxy group, C_1-C_6 alkoxy group, cyano group, and trifluoromethyl group.

[0024]

When the heterocyclic compound having the general Formula (I) has asymmetric carbon atoms in the structure, its isomer from asymmetric carbon atoms and their mixture (racemic modification) is present. In such cases, all of them are included in the heterocyclic compound used in the embodiments described later.

[0025]

The heterocyclic compound has the general Formula (I). In the general Formula (I), the following terms have the meanings specified below along with their examples.

[0026]

The term "C_1-C_6" refers to 1 to 6 carbon atoms unless otherwise defined. The term "C_3-C_8" refers to 3 to 8 carbon atoms unless otherwise defined. The term "C_1-C_6 alkyl" includes linear or branched alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, sec-butyl, n-pentyl, and n-hexyl. The term "C_1-C_6 alkoxy" includes linear or branched alkoxy groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentyloxy, and n-hexyloxy. The term "C_3-C_8 cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "halogen atom" includes fluorine, chlorine, bromine, and iodine.

[0027]

The heterocyclic compound useful in the practice of the present invention is not particularly restricted as long as it has the above described specific structure. For example, the following compounds can be used.

3,3-dimethylimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dipropylimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibutylimidazo[1,2-a]pyridin-2(3H)-one,
3,3-diallylimidazo[1,2-a]pyridin-2(3H)-one,
3,3-diallyl-8-benzyloxyimidazo[1,2-a]pyridin-2(3H)-one,
3,3-di(2-propinyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzylimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-8-methylimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-5,7-dimethylimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-8-hydroxyimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-8-methoxyimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-8-ethoxyimidazo[1,2-a]pyridin-2(3H)-one,
8-allyloxy-3,3-dibenzylimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-8-isopropoxyimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-8-cyclopropylmethyloxyimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-8-cycloheptyloxyimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-6-chloroimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-6,8-dichloroimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-8-chloro-6-trifluoromethylimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-8-benzyloxyimidazo[1,2-a]pyridin-2(3H)-one,
8-amino-3,3-dibenzylimidazo[1,2-a]pyridin-2(3H)-one,
8-acetylamino-3,3-dibenzylimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibenzyl-8-benzylaminoimidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(3-chlorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(3-fluorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(4-fluorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(2,4-dichlorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(4-dimethylaminobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,

3,3-bis(4-methoxybenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(4-biphenylmethyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(4-cyanobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(4-hydroxy-benzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(3-phenyl-1-propyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(2,4-difluorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(4-nitrobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(4-carboxybenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
8-benzyloxy-3,3-bis(1-phenylethyl)imidazo[1,2-a]pyridin-2(3H)-one,
8-benzyloxy-3,3-bis(3-methylbenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
8-benzyloxy-3,3-bis(4-methylbenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3-benzyl-3-(4-fluorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
3-ethyl-3(4-fluorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,
8-methyl-3,3-bis(3-pyridylmethyl)imidazo[1,2-a]pyridin-2(3H)-one,
8-methyl-3,3-bis(4-pyridylmethyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(2-thienylmethyl)imidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(2-furilmethyl)imidazo[1,2-a]pyridin-2(3H)-one,
spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2′-indan],
spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2′-[2,3]dihydrophenarene],
spiro[imidazo[2,1-b]thiazol-6(5H)-one-5,2′-benzo[f]indan],
spiro[imidazo[1,2-b]thiazol-6(5H)-one-5,2′-indan],
spiro[2-methylimidazo[1,2-b]thiazol-6(5H)-one-5,2′-benzo[f]indan],
5,5-bis(4-fluorobenzyl)imidazo[2,1-b]thiazol-6(5H)-one,
5,5-dibenzylimidazo[2,1-b]thiazol-6(5H)-one,
5,5-bis(4-methylbenzyl)imidazo[2,1-b]thiazol-6(5H)-one,
5,5-bis(4-cyanobenzyl)imidazo[2,1-b]thiazol-6(5H)-one,
5,5-dibenzyl-2-methylimidazo[2,1-b]thiazol-6(5H)-one,
5,5-bis(4-fluorobenzyl)-2-methylimidazo[2,1-b]thiazol-6(5H)-one,
5,5-dicyclohexyl-2-methylimidazo[2,1-b]thiazol-6(5H)-one,
5,5-bis(4-cyanobenzyl)-2-methylimidazo[2,1-b]thiazol-6(5H)-one,
5,5-di(2-butenyl)imidazo[2,1-b]thiazol-6(5H)-one, 5,5-dibutylimidazo[2,1-b]thiazol-6(5H)-one,
5,5-dicyclohexylimidazo[2,1-b]thiazol-6(5H)-one,
5,5-bis(2-thienylmethyl)imidazo[2,1-b]thiazol-6(5H)-one,
spiro[2,3-dihydroimidazo[2,1-b]thiazol-6(5H)-one-5,2′-benzo[f]indan],
5,5-dibutyl-2,3-dihydroimidazo[2,1-b]thiazol-6(5H)-one,
5,5-di(2-butenyl)-2,3-dihydroimidazo[2,1-b]thiazol-6(5H)-one,
5,5-bis(4-methylbenzyl)-2,3-dihydroimidazo[2,1-b]thiazol-6(5H)-one,
5,5-bis(2-thienylmethyl)-2,3-dihydroimidazo[2,1-b]thiazol-6(5H)-one,
5,5-bis(4-fluorobenzyl)-2,3-dihydroimidazo[2,1-b]thiazol-6(5H)-one,
5,5-dibenzyl-2,3-dihydroimidazo[2,1-b]thiazol-6(5H)-one,

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-benzo[f]indan],
2-hydroxy-3-(2-naphthylmethyl)-imidazo[1,2-a]pyridine,
3-benzylimidazo[1,2-a]pyridin-2(3H)-one,
spiro[5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one-3,2'-benzo[f]indan],
3,3-dicyclohexyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one,
3,3-bis(2-thienylmethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dibutyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one,
3,3-dipropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one,
spiro[imidazo[1,2-a]pyrimidin-2(3H)-one-3,2'-benzo[f]indan],
3,3-di(2-butenyl)imidazo[1,2-a]pyrimidin-2(3H)-one,
3,3-bis(2-thienylmethyl)imidazo[1,2-a]pyrimidin-2(3H)-one,
3,3-bis(4-fluorobenzyl)imidazo[1,2-a]pyrimidin-2(3H)-one,
3,3-dicyclohexylimidazo[1,2-a]pyrimidin-2(3H)-one,
3,3-bis(4-cyanobenzyl)imidazo[1,2-a]pyrimidin-2(3H)-one,
3,3-bis(4-methylbenzyl)imidazo[1,2-a]pyrimidin-2(3H)-one,
4,4-dibenzyl-1-methyl-5-oxo-4,5-dihydroimidazole,
spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(4'-fluoroindan)],
spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(5'-methoxyindan)],
spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(5'-iodoindan)],
spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(4'-cyanoindan)],
spiro[imidazo[2,1-a]isoquinolin-2(3H)-one-3,2'-indan],
spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-((1,2,5-thiadiazo)[4,5-c]indan)],
spiro[imidazo[2,1-a]isoquinolin-2(3H)-one-3,2'-((1,2,5-thiadiazo)[4,5-c]indan)],
spiro[imidazo[1,2-a]pyrimidin-2(3H)-one-3,4'-(1'-cyclopentene)],
spiro[imidazo[1,2-a]pyrimidin-2(3H)-one-3,2'-indan],
spiro[imidazo[1,2-a]pyrimidin-2(3H)-one-3,2'-((1,2,5-thiadiazo)[4,5-c]indan)],
spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(5'-trifluoromethylindan)],
spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-benzo[e]indan],
spiro[imidazo[2,1-a]isoquinolin-2(3H)-one-3,1'-(3'-cyclopentene)],
spiro[8-benzyloxyimidazo[1,2-a]pyridin-2(3H)-one-3,1'-(3'-cyclopentene)],
spiro[7,8,9,10-tetrahydroimidazo[2,1-a]isoquinolin-2(3H)-one-3,1'-cyclopentane],
spiro[imidazo[2,1-a]isoquinolin-2(3H)-one-3,1'-cyclopentane],and
spiro[5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one-3,2'-indan]

[0028]

The heterocyclic compound of Formula (I) can be in the form of hydrate or acid addition salts as a pharmaceutically acceptable salt. Possible acid addition salts include inorganic acid salts such as the hydrochloride, sulfate, hydrobromide, nitrate, and phosphate salts and organic acid salts such as acetate, oxalate, propionate, glycolate, lactate, pyruvate, malonate, succinate, maleate, fumarate, malate, tartrate, citrate, benzoate, cinnamate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, and salicylate salts.

[0029]

The administration method, formulation, and dosage of the heterocyclic compound in mammals, particularly in human, are described hereafter. The heterocyclic compound can be administrated orally or parenterally. Formulations for oral administration include tablets, coated tablets, powder, granules, capsules, microcapsules, and syrups. Formulations for parenteral administration include injectable solutions (including those freeze-dried and dissolved for use), adhesive skin patches, and suppositories.

[0030]

These formulations can be prepared using pharmaceutically acceptable fillers, binders, lubricants, disintegrators, suspending agents, emulsifiers, antiseptic agents, stabilizing agents, and dispersing agents such as lactoses, saccharoses, starches, dextrines, crystalline celluloses, kaolins, calcium carbonate, talc, magnesium stearate, and distilled water or saline. Particular pharmaceutically acceptable components include mannitol, mircocrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. The dosage varies according to the symptom, age, and body weight of patients. An adult can take 0.1 to 60 mg per day in one to three doses.

[0031]

The inventors found that the heterocyclic compound having the above specific structure, exhibits inhibitory activity of amyloid β deposition in the hippocampus by amyloid β immunohistochemistry as described later in the examples. Screening of derivatives of the compound for amyloid β deposition inhibitory activity showed that azaindolizinone derivatives in which an indan ring forms a spiro ring have potent amyloid β deposition inhibitory activity. The above compound exhibits amyloid β deposition inhibitory activity based on a novel mechanism different from antioxidative activity. The compound has also been shown to be highly safe in the preclinical study as the Alzheimer's disease progression inhibitor

[0032]

The Alzheimer's disease progression inhibitor of the heterocyclic compound having the above specific structure is effective at lower dosages based on a mechanism which is different from curcumin, a component of *Curcuma longa* contained in curry in a large amount and which has antioxidative activity. Therefore, it is a new Alzheimer's disease progression inhibitorhaving a mechanism of action different from curcumin.

[0033]

The Alzheimer's disease progression inhibitor of this embodiment is preferably spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-indan] as this compound was shown to have excellent inhibitory activity of amyloid β deposition in the hippocampus amyloid β immunohistochemistry, which is a typical animal model test for inhibitory activity of amyloid β deposition, as described later in the examples.

[0034]

The Alzheimer's disease progression inhibitor may be administered by any means which

acheives reduction in amyloid β deposition in a mammal. Preferably, Alzheimer's disease progression inhibitor of this embodiment is orally administered. In another embodiment, the Alzheimer's disease progression inhibitorcompound may be administered as part of an adhesive skin patch. Alternatively, the Alzheimer's disease progression inhibitorcompound may be formulated into tablets, coated tablets, powder, granules, capsules, microcapsules, and syrups, as the amyloid β deposition inhibitor in the form of oral formulations is easily administered in mammals, including human beings.

[0035]

The Alzheimer's disease progression inhibitor compoundof this embodiment is preferably administered at an effective oral dosage of 0.0005 mg per kilogram of body weight or higher. In one embodiment, the compound is administered as part of a unitary pharmceutical dosage form containing 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 mg. When the inhibitor of progression of Alzheimer' disease is administered at an effective oral dosage of this lower limit or higher, the amyloid β deposition inhibitory activity in mammals including human beings is improved compared to when lower doses are administered.

[0036]

As discussed above, Alzheimer's disease progression inhibitor of the heterocyclic compound having the above specific structure exhibits excellent inhibitory activity of amyloid β deposition. Since amyloid β is neurotoxic and associated with the etiology of Alzheimer's disease, it is expected that administration of a compound of Formula (I) to a human patient in need thereof will slow or inhibit the progression of Alzheimer's disease. Such a human patient may exhibit the very early to late stages of Alzheimer's disease. For example, the human patient may exhibit very mild cognitive decline (stage 2), mild cognitive decline (early Alzheimer's disease, stage 3), moderate cognitive decline (mild or early-stage Alzheimer's disease, stage 4), moderately severe cognitive decline (moderate or mid-stage Alzheimer's disease, stage 5), severe cognitive decline (moderately severe or mid-stage Alzheimer's disease, stage 6), or very severe cognitive decline (severe or late-stage Alzheimer's disease, stage 7).

[0037]

The Alzheimer's disease progression inhibitor compound may be administered by any means which acheives the slowing or inhibiting of the progression of Alzheimer's disease. Preferably, the Alzheimer's disease progression inhibitor compound of this embodiment is orally administered. In another embodiment, the Alzheimer's disease progression inhibitor compound may be administered as part of an adhesive skin patch. Alternatively, the Alzheimer's disease progression inhibitor compound may be formulated into tablets, coated tablets, powder, granules, capsules, microcapsules, and syrups, as the amyloid β deposition inhibitor in the form of oral formulations is easily administered in mammals, including human beings.

[0038]

The Alzheimer's disease progression inhibitor compound of this embodiment is preferably

administered at an effective oral dosage of 0.0005 mg per kilogram of body weight or higher. In one embodiment, the compound is administered as part of a unitary pharmceutical dosage form containing 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 mg.

[0039]

Embodiments of the present invention are described above. These embodiments are given by way of example. The present invention can be realized in many other ways as the invention is not so limted.

[0040]

For example, some preferable ranges of effective oral dosages are defined in the above embodiments. However, other ranges of effective dosages can be determined for other administration forms. For example, a preferable range of effective dosages for administration by injection can be determined as appropriate. Furthermore, preferable ranges of administration intervals can be determined for particular administration forms in addition to the effective dosages with no more than routine experimentation.

EXAMPLES

[0041]

The present invention is further described using examples. However, the present invention is not restricted thereto.

0073]

[0042]

Example 1: Amyloid β deposition inhibitory activity

In order to show that compounds having Formula (I) have amyloid β deposition inhibitory activity, the activity of Compound 1 on amyloid β deposition was examined.

[0043]

Senescene accelerated mice (SAMP8) (male, 8 months old at the beginning of the study) were used for experiment. Approximately 0.1 mg/kg/day of Compound 1 was given in drinking water. Eight weeks after the dosing, the mouse brain was removed, Methacarn-fixed (methanol : chloroform : acetic acid = 6 : 3 : 1), and paraffin-embedded. Then, sections of 8 μm in thickness were prepared using a microtome.

[0044]

The sections were immunostained with streptavidin-biotin using a VECTASTATIN ABC kit. After one hour of incubation in 10% normal goat serum, the anti-amyloid β (Aβ) antibody was diluted with PBS to ten fold and incubated at 4 °C overnight. The following day, PBS rinsing, 1.5 hours of incubation with biotinylated anti-rabbit

secondary antibody, PBS rinsing, and 1.5 hours of incubation with peroxidase-labeled streptavidin were conducted. The immunoreaction was visualized with DAB and specimens were prepared.

[0045]

Immunoreactive Aβ–like granules in the hippocampus were counted under the microscope. The Aβ-like immunoreactive granule was observed as brown deposits in the hippocampus. The count was made for one section per individual.

[0046]

Fig.1 contains photographs showing the influence of Compound 1 on the number of amyloid β-immunoreactive cells in senescene accelerated mice (SAMP8). The photographs at the top show stained images of amyloid β-like granules in the hippocampus of senescene accelerated mice (SAMP8) given tap water as drinking water for 2 months from age of 8 months. The photographs at the bottom show stained images of amyloid β-like immunoreactivity in the hippocampus of senescene accelerated mice (SAMP8) given Compound 1 in drinking water at an effective oral dosage of 0.1 mg per kilogram of body weight for 2 months.

[0047]

Fig.2 is a graphical representation showing the influence of Compound 1 on the number of amyloid β-immunoreactive cells in senescene accelerated mice (SAMP8). The effective oral dosage of Compound 1 is plotted as abscissa and the number of amyloid β-immunoreactive granules is plotted as ordinate. Nine senescene accelerated mice (SAMP8) were given no Compound 1. Five, eitht and seven senescene accelerated mice (SAMP8) were given Compound 1 at oral dosage of 0.002mg, 0.01mg and 0.1mg per kilogram of body weight respectively.

[0048]

As shown in Figs. 1 and 2, an amyloid β-like immunoreactivity in the hippocampus was observed in senescene accelerated mice (SAMP8) given tap water as drinking water for 2 months from age of 8 months. On the other hand, the amyloid β-like immunoreactivity was reduced in senescene accelerated mice (SAMP8) given Compound 1 in drinking water at oral dosage of 0.002mg/kg/day, 0.01mg/kg/day and 0.1mg/kg/day for 2 months. The number of amyloid β-immunoreactive granules was significantly (*) decreased as a result of dosing of Compound 1.

[0049]

As described above, Compound 1 inhibits amyloid β deposition. Amyloid-related pathologies for which Compound 1 may be used the method for inhibiting of the progression of Alzheimer's disease in which amyloid β is considered to be a factor of the disorder.

[0050]

As described above, a compound having Formula (I) was shown to have inhibitory activity of amyloid β deposition in an amyloid β immunohistochemistry.

[0051]

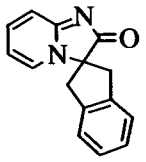
Preparation of compounds referred to in the embodiments

Some of the heterocyclic compound having the general Formula (I) and prepared by the method in examples of Booklet of International Publication No. 01/09131 are described hereafter by way of example. More specifically, they were synthesized with reference to Booklet of International Publication No. 01/09131 and Booklet of International Publication No. 2002/060907 Brochure.

[0052]

Exemplary Preparation 1

An exemplary preparation of spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-indan] (Compound 1) having the general formula below is described hereafter.



[0053]

An amount of 56.1g(1.04 mol) of sodium methoxide was dissolved in 15L of methanol, and an amount of 90.0g(0.0345 mol) of 2-amino-1-(ethoxycarbonylmethyl)pyridinium bromide and 60.0g(0.0342 mol) of ・,・'-dichloro-*o*-xylene were added successively at room temperature. The reaction mixture was stirred at room temperature over night and then the solvent was removed under reduced pressure. Dichloromethane was adde to the residue and insoluble matters were filtered off. The filtrate was concentrated under reduced pressure and the residue was chromatographed over silica gel column (ethyl acetate : methanol = 15 : 1) to give crude product. The crude product was washed by using ethyl acetate and then recrystallized from methanol to give an amount of 36g (40%) of the title compound in the form of white crystals. Results of analysis of the obtained compound are given below. The results show that the obtained compound was the targeted compound

[0054]

Melting Point: 206 °C (decomposition);

NMR ($CDCl_3$) δ: 3.16 (2H, d, J=16Hz), 3.89 (2H, d, J=16Hz), 6.49 (1H, t, J=7Hz), 7.1-7.2 (2H, m), 7.2-7.3 (4H, m), 7.61 (1H, t, J=7Hz);

MS m/z: 236 (M^+).

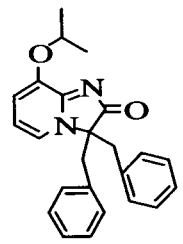
[0055]

Exemplary Preparation 2

Compounds 2 to 40 of Formulae (I) were each prepared from the respective starting materials in the same manner as in Exemplary Preparation 1. Results of analysis of the obtained compounds are given for each compound. The results show that the obtained compounds were the targeted Compounds 2 to 40.

[0056]

3,3-dibenzyl-8-isopropoxyimidazo[1,2-a]pyridin-2(3H)-one (Compound 2)



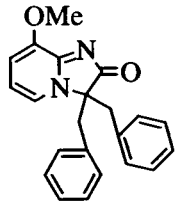
Melting Point: 247-248 °C;

NMR ($CDCl_3$) δ: 1.03 (6H, d, J=6Hz), 3.15 (2H, d, J=14Hz), 3.56 (2H, d, J=14Hz), 4.60 (1H, sept., J=6Hz), 6.48 (1H, t, J=7Hz), 6.79 (1H, d, J=8Hz), 6.9-7.2 (11H, m);

MS m/z: 372 (M^+)

[0057]

3,3-dibenzyl-8-methoxyimidazo[1,2-a]pyridin-2(3H)-one (Compound 3)



[0058]

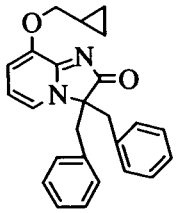
Melting Point: 274-275 °C;

NMR ($CDCl_3$) δ: 3.17 (2H, d, J=14Hz), 3.56 (2H, d, J=14Hz), 3.69 (3H, s), 6.49 (1H, t, J=7Hz), 6.67 (1H, d, J=8Hz), 6.9-7.2 (11H, m);

MS m/z: 344 (M^+).

[0059]

3,3-dibenzyl-8-cyclopropylmethyloxy-imidazo[1,2-a]pyridin-2(3H)-one (Compound 4)



[0060]

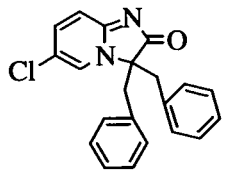
Melting Point: 236-237 °C;

NMR ($CDCl_3$) δ: 0.12 (2H, q, J=5Hz), 0.45 (2H, q, J=6Hz), 0.99 (1H, m), 3.16 (2H, d, J=14Hz), 3.55 (2H, d, J=14Hz), 3.73 (2H, d, J=7Hz), 6.47 (1H, t, J=7Hz), 6.76 (1H, d, J=8Hz), 7.0-7.2 (11H, m);

MS m/z: 384 (M^+).

[0061]

3,3-dibenzyl-6-chloroimidazo[1,2-a]pyridin-2(3H)-one (Compound 5)



[0062]

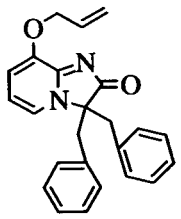
Melting Point: 246-248 °C;

NMR ($CDCl_3$) δ: 3.16 (2H, d, J=14Hz), 3.55 (2H, d, J=14Hz), 6.70 (1H, d, J=10Hz), 7.0-7.2 (12H,m);

MS m/z: 348 (M^+).

[0063]

8-allyloxy-3,3-dibenzylimidazo[1,2-a]pyridin-2(3H)-one (Compound 6)



[0064]

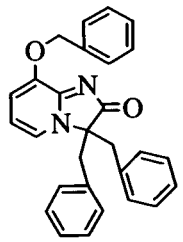
Melting Point: 214-215 °C;

NMR ($CDCl_3$) δ: 3.16 (2H, d, J=14Hz), 3.56 (2H, d, J=14Hz), 4.4-4.5 (2H, m), 5.0-5.2 (2H, m), 5.7-5.9 (1H, m), 6.47 (1H, t, J=7Hz), 6.74 (1H, d, J=8Hz), 6.9-7.2 (11H, m);

MS m/z: 370 (M^+).

[0065]

3,3-dibenzyl-8-benzyloxyimidazo[1,2-a]pyridin-2(3H)-one (Compound 7)



[0066]

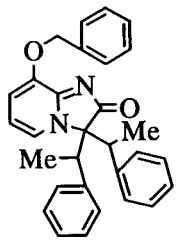
Melting Point: 240-241 °C;

NMR ($CDCl_3$) δ: 3.17 (2H, d, J=14Hz), 3.57 (2H, d, J=14Hz), 5.03 (2H, s), 6.39 (1H, t, J=8Hz), 6.65 (1H, d, J=8Hz), 7.0-7.2 (16H, m);

MS m/z: 420 (M^+).

[0067]

8-benzyloxy-3,3-bis(1-phenylethyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 8)



[0068]

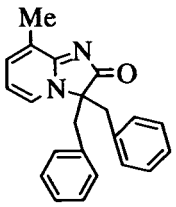
Melting Point: 234-235 °C;

NMR ($CDCl_3$) δ: 1.52 (6H, d, J=7Hz), 3.51 (2H, q, J=7Hz), 5.11 (2H, s), 6.14 (1H, t, J=7Hz), 6.41 (1H, d, J=7Hz), 6.63 (1H, d,J=8Hz), 7.0-7.2 (15H, m);

MS m/z: 448 (M^+).

[0069]

3,3-dibenzyl-8-methylimidazo[1,2-a]pyridin-2(3H)-one (Compound 9)



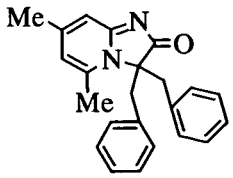
[0070]

Melting Point: 262-263 °C;

NMR ($CDCl_3$) δ: 2.05 (3H, s), 3.31 (2H, d, J=14Hz), 3.56 (2H, d, J=14Hz), 6.60 (1H, t, J=7Hz), 6.9-7.2 (12H, m);

MS m/z: 328 (M^+).

3,3-dibenzyl-5,7-dimethylimidazo[1,2-a]pyridin-2(3H)-one (Compound 10)



[0071]

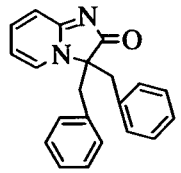
Melting Point: 237-238 °C;

NMR ($CDCl_3$) δ: 2.07 (3H, s), 2.80 (3H, s), 3.40 (2H, d, J=15Hz), 3.71 (2H, d, J=15Hz), 6.11 (1H, s), 6.34 (1H, s), 7.0-7.2 (10H, m);

MS m/z: 342 (M^+).

[0072]

3,3-dibenzylimidazo[1,2-a]pyridin-2(3H)-one (Compound 11)



[0073]

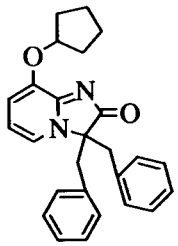
Melting Point: >300 °C;

NMR (DMSO-D_6) δ: 3.39 (4H, s), 6.60 (1H, d, J=9Hz), 6.8-7.2 (11H, m), 7.56 (1H, t, J=7Hz), 8.75 (1H, d, J=7Hz);

MS m/z: 314 (M^+).

[0074]

3,3-dibenzyl-8-cyclopentyloxyimidazo[1,2-a]pyridin-2(3H)-one (Compound 12)



[0075]

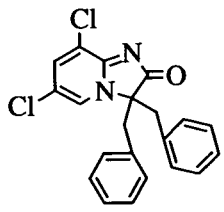
Melting Point: 268-269 °C;

NMR ($CDCl_3$) δ: 1.4-1.7 (8H, m), 3.15 (2H, d, J=14Hz), 3.55 (1H, d, J=14Hz), 4.7-4.9 (1H, m), 6.47 (1H, t, J=7Hz), 6.72 (1H, d, J=8Hz), 6.9-7.2 (11H, m);

MS m/z: 398 (M^+).

[0076]

3,3-dibenzyl-6,8-dichloroimidazo[1,2-a]pyridin-2(3H)-one (Compound 13)



[0077]

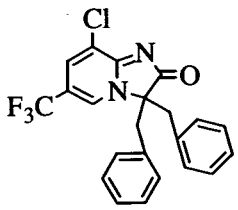
Melting Point: 260-261 °C;

NMR ($CDCl_3$) δ: 3.17 (2H, d, J=14Hz), 3.55 (2H, d, J=14Hz), 6.9-7.3 (11H, m), 7.41 (1H, d, J=2Hz);

MS m/z: 382 (M^+).

[0078]

3,3-dibenzyl-8-chloro-6-trifluoromethylimidazo[1,2-a]pyridin-2(3H)-one (Compound 14)



[0079]

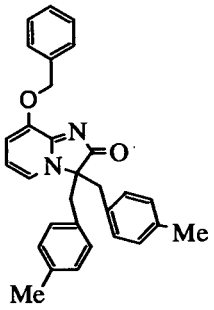
Melting Point: 234-236 °C;

NMR ($CDCl_3$) δ: 3.22 (2H, d, J=14Hz), 3.55 (2H, d, J=14Hz), 6.9-7.0 (4H, m), 7.1-7.4 (7H, m), 7.51 (1H, d, J=2Hz);

MS m/z: 416 (M^+).

[0080]

8-benzyloxy-3,3-bis(3-methylbenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 15)



[0081]

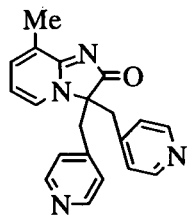
Melting Point: 233-235 °C;

NMR ($CDCl_3$) δ: 2.20 (6H, s), 3.14 (2H, d, J=14Hz), 3.48 (2H, d, J=14Hz), 5.05 (2H, s), 6.38 (1H, t, J=7Hz), 6.68 (1H, d, J=8Hz), 6.7-7.3 (14H, m);

MS m/z: 448 (M^+).

[0082]

8-methyl-3,3-bis(4-pyridylmethyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 16)



[0083]

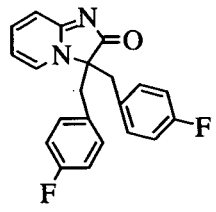
Melting Point: 228-230 °C;

NMR ($CDCl_3$) δ: 2.01 (3H, s), 3.13 (2H, d, J=14Hz), 3.60 (2H, d, J=14Hz), 6.60 (1H, t, J=7Hz), 6.95 (4H, d, J=6Hz), 7.22 (1H, d, J=7Hz), 7.46 (1H, d, J=7Hz), 8.40 (4H, d, J=6Hz);

MS m/z: 330 (M^+).

[0084]

3,3-bis (4-fluorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 17)



[0085]

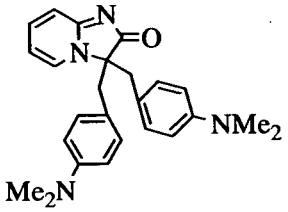
Melting Point: 290-292 °C;

NMR ($CDCl_3$) δ: 3.13 (2H, d, J=14Hz), 3.56 (2H, d, J=14Hz), 6.62 (1H, t, J=7Hz), 6.7-6.9 (5H, m), 6.9-7.1 (4H, m), 7.39 (1H, t, J=7Hz), 7.52 (1H, brd, J=7Hz);

MS m/z: 350 (M^+).

[0086]

3,3-bis(4-dimethylaminobenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 18)



[0087]

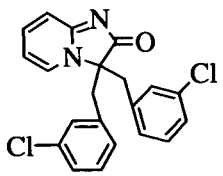
Melting Point: >300 °C;

NMR ($CDCl_3$) δ: 2.86 (12H, s), 3.09 (2H, d, J=14Hz), 3.37 (2H, d, J=14Hz), 6.4-6.6 (5H, m), 6.7-6.9 (5H, m), 7.2-7.3 (1H, m), 7.37 (1H, t, J=7Hz);

MS m/z: 400 (M^+).

[0088]

3,3-bis(3-chlorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 19)



[0089]

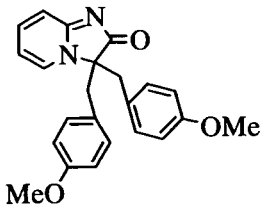
Melting Point: 271-272 °C;

NMR ($CDCl_3$) δ: 3.14 (2H, d, J=14Hz), 3.53 (2H, d, J=14Hz), 6.66 (1H, t, J=7Hz), 6.80 (1H, d, J=7Hz), 6.9-7.2 (8H, m), 7.43 (1H, t, J=7Hz), 7.51 (1H, brd, J=7Hz);

MS m/z: 382 (M^+).

[0090]

3,3-bis(4-methoxybenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 20)



[0091]

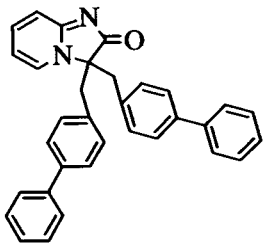
Melting Point: 248-251 °C;

NMR ($CDCl_3$) δ: 3.66 (6H, s), 3.67 (2H, d, J=15Hz), 4.00 (2H, d, J=15Hz), 6.59 (4H, d, J=9Hz), 6.93 (4H, d, J=9Hz), 7.50 (1H, t, J=7Hz), 6.71 (1H, d, J=7Hz), 7.91 (1H, t, J=7Hz), 9.78 (1H, d, J=7Hz);

MS m/z: 374 (M^+).

[0092]

3,3-bis(4-biphenylmethyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 21)



[0093]

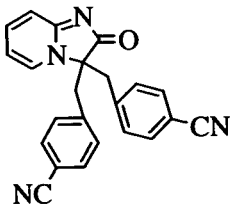
Melting Point: >300 °C;

NMR ($CDCl_3$) δ: 3.25 (2H, d, J=14Hz), 3.62 (2H, d, J=14Hz), 6.58 (1H, t, J=7Hz), 6.77 (1H, d, J=7Hz), 7.11 (4H, d, J=7Hz), 7.3-7.6 (16H, m);

MS m/z: 466 (M^+).

[0094]

3,3-bis(4-cyanobenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 22)



[0095]

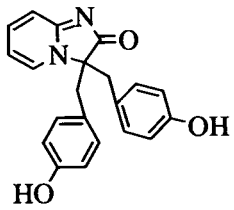
Melting Point: 294 °C (decomposition);

NMR ($CDCl_3$) δ: 3.19 (2H, d, J=14Hz), 3.70 (2H, d, J=14Hz), 6.6-6.8 (2H, m), 7.13 (4H, d, J=7Hz), 7.43 (1H, t, J=7Hz), 7.45 (4H, d, J=7Hz), 7.62 (1H, brd, J=7Hz);

MS m/z: 364 (M^+).

[0096]

3,3-bis(4-hydroxybenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 23)



[0097]

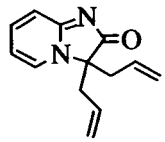
Melting Point: 276.5-277.5 °C;

NMR (CD_3OD-$CDCl_3$(1:1)) δ: 3.62 (2H, d, J=14Hz), 3.66 (2H, d, J=14Hz), 6.58 (4H, d, J=9Hz), 6.78 (4H, d, J=9Hz), 7.17 (1H, d, J=7Hz), 7.63 (1H, t, J=7Hz), 8.12 (1H, t, J=7Hz), 9.25 (1H, d, J=7Hz);

MS m/z: 346 (M^+).

[0098]

3,3-diallylimidazo[1,2-a]pyridin-2(3H)-one (Compound 24)



[0099]

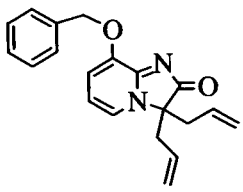
Melting Point: 64-66 °C;

NMR ($CDCl_3$) δ: 2.56 (2H, dd, J=9Hz, J=14Hz), 2.86 (2H, dd, J=6Hz, J=14Hz), 4.99 (2H, dd, J=1Hz, J=7Hz), 5.04 (2H, d, J=1Hz), 5.4-5.6 (2H, m), 6.67 (1H, t, J=7Hz), 7.17 (1H, d, J=7Hz), 7.52 (1H, d, J=7Hz), 7.59 (1H, d, J=7Hz);

MS m/z: 214 (M^+).

[0100]

3,3-diallyl-8-benzyloxyimidazo[1,2-a]pyridin-2(3H)-one (Compound 25)



[0101]

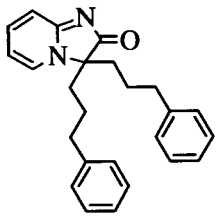
Melting Point: 160-162 °C;

NMR ($CDCl_3$) δ: 2.54 (2H, dd, J=8Hz, J=14Hz), 2.86 (2H, dd, J=6Hz, J=14Hz), 4.96 (2H, dd, J=1Hz, J=5Hz), 5.01 (2H, d, J=1Hz), 5.29 (2H, s), 5.4-5.6 (2H, m), 6.53 (1H, dd, J=7Hz, J=8Hz), 6.94 (1H, d, J=7Hz), 7.16 (1H, d, J=8Hz), 7.3-7.5 (5H, m);

MS m/z: 320 (M^+).

[0102]

3,3-bis(3-phenyl-1-propyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 26)



[0103]

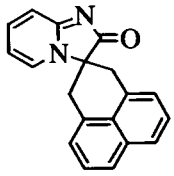
Melting Point: 227-228 °C;

NMR ($CDCl_3$) δ: 0.9-1.1 (2H, m), 1.4-1.6 (2H, m), 1.6-1.8 (2H, m), 2.0-2.2 (2H, m), 2.3-2.5 (2H, m), 2.5-2.7 (2H, m), 6.61 (1H, t, J=7Hz), 7.0-7.1 (4H, m), 7.1-7.3 (8H, m), 7.58 (1H, t, J=7Hz);

MS m/z: 370 (M^+).

[0104]

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-[2,3]dihydrophenarene] (Compound 27)



[0105]

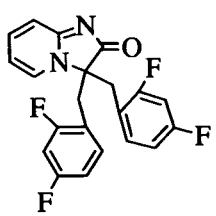
Melting Point: 262 °C (decomposition);

NMR ($CDCl_3$): 3.12 (2H, d, J=17Hz), 3.98 (2H, d, J=17Hz), 6.18(1H, t, J=7Hz), 6.48 (1H, d, J=7Hz), 7.24 (1H, d, J=7Hz), 7.34 (2H, d, J=7Hz), 7.4-7.6 (3H, m), 7.86 (2H, d, J=7Hz);

MS m/z: 286 (M^+).

[0106]

3,3-bis(2,4-difluorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 28)



[0107]

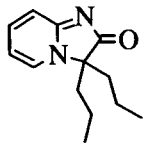
Melting Point: 269-271 °C;

NMR ($CDCl_3$) δ: 3.38 (2H, d, J=14Hz), 3.47 (2H, d, J=14Hz), 6.5-6.7 (3H, m), 6.7-6.8 (3H, m), 7.2-7.5 (3H, m), 7.6-7.7 (1H, m);

MS m/z: 368 (M^+).

[0108]

3,3-dipropylimidazo[1,2-a]pyridin-2(3H)-one (Compound 29)



[0109]

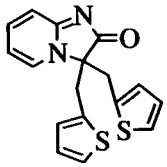
Melting Point: 73-75 °C;

NMR ($CDCl_3$) δ: 0.7-0.9 (8H, m), 1.1-1.3 (2H, m), 1.6-1.8 (2H, m), 2.0-2.2 (2H, m), 6.73 (1H, t, J=7Hz), 7.19 (1H, d, J=7Hz), 7.50 (1H, d, J=7Hz), 7.63 (1H, t, J=7Hz);

MS m/z: 218 (M^+).

[0110]

3,3-bis (2-thienylmethyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 30)



[0111]

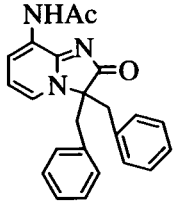
Melting Point: 289.5 °C (decomposition);

NMR ($CDCl_3$) δ: 3.41 (2H, d, J=15Hz), 3.70 (2H, d, J=15Hz), 6.64 (1H, t, J=7Hz), 6.7-7.0 (5H, m), 7.07 (2H, dd, J=1Hz, J=5Hz), 7.38 (1H, d, J=7Hz), 7.48 (1H, t, J=7Hz);

MS m/z: 326 (M^+).

[0112]

8-acetylamino-3,3-dibenzylimidazo[1,2-a]pyridin-2(3H)-one (Compound 31)



[0113]

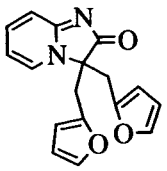
Melting Point: 235-237 °C;

NMR ($CDCl_3$) δ: 2.05 (3H, s), 3.20 (2H, d, J=14Hz), 3.55 (2H, d, J=14Hz), 6.61 (1H, t, J=7Hz), 6.9-7.1 (4H, m), 7.1-7.2 (7H, m), 7.78 (1H, brs), 8.39 (1H, d, J=7Hz);

MS m/z: 371 (M^+).

[0114]

3,3-bis(2-furylmethyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 32)



[0115]

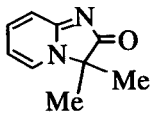
Melting Point: 205 °C (decomposition);

NMR ($CDCl_3$) δ: 3.37 (4H, s), 6.11 (2H, d, J=3Hz), 6.23 (2H, dd, J=2Hz, J=3Hz), 6.56 (1H, t, J=7Hz), 6.97 (1H, d, J=7Hz), 7.20 (2H, d, J=2Hz), 7.22 (1H, d, J=7Hz), 7.51 (1H, t, J=7Hz);

MS m/z: 294 (M^+).

[0116]

3,3-dimethylimidazo[1,2-a]pyridin-2(3H)-one (Compound 33)



[0117]

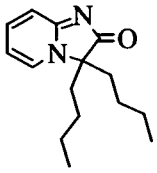
Melting Point: 200-202 °C;

NMR (CD_3OD-$CDCl_3$(1:1)) δ: 1.93 (6H, s), 7.72 (1H, t, J=7Hz), 7.78 (1H, d, J=7Hz), 8.50 (1H, t, J=7Hz), 9.01 (1H, d, J=7Hz);

MS m/z: 162 (M^+).

[0118]

3,3-dibutylimidazo[1,2-a]pyridin-2(3H)-one (Compound 34)



[0119]

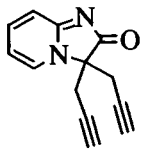
Melting Point: 100.5-102 °C;

NMR ($CDCl_3$) δ: 0.6-0.9 (8H, m), 1.0-1.3 (6H, m), 1.6-1.8 (2H, m), 2.0-2.2 (2H, m), 6.71 (1H, t, J=7Hz), 7.19 (1H, d, J=7Hz), 7.50 (1H, d, J=7Hz), 7.62 (1H, t, J=7Hz);

MS m/z: 246 (M^+).

[0120]

3,3-di(2-propinyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 35)



[0121]

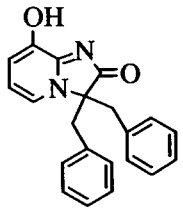
Melting Point: 172-175 °C;

NMR ($CDCl_3$) δ: 2.07 (2H, t, J=3Hz), 2.80 (2H, dd, J=3Hz, J=17Hz), 3.08 (2H, dd, J=2.6Hz, J=17Hz), 6.75 (1H, t, J=7Hz), 7.24 (1H, d, J=7Hz), 7.69 (1H, t, J=7Hz), 8.02 (1H, d, J=7Hz);

MS m/z: 210 (M^+).

[0122]

3,3-dibenzyl-8-hydroxyimidazo[1,2-a]pyridin-2(3H)-one (Compound 36)



[0123]

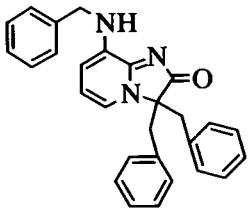
Melting Point: 283-285 °C;

NMR ($CDCl_3$) δ: 3.20 (2H, d, J=14Hz), 3.55 (2H, d, J=14Hz), 6.58 (1H, t, J=7Hz), 6.87 (1H, d, J=7Hz), 6.9-7.0 (4H, m), 7.07 (1H, d, J=7Hz), 7.1-7.2 (6H, m);

MS m/z: 330 (M^+).

[0124]

3,3-dibenzyl-8-benzylaminoimidazo[1,2-a]pyridin-2(3H)-one (Compound 37)



[0125]

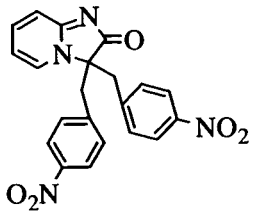
Melting Point: 250 °C;

NMR ($CDCl_3$) δ: 3.42 (2H, d, J=14Hz), 3.70 (2H, d, J=14Hz), 4.35 (2H, d, J=6Hz), 6.93 (1H, d, J=7Hz), 7.0-7.3 (16H, m), 7.48 (1H, d, J=7Hz), 8.66 (1H, brs);

MS m/z: 419 (M^+).

[0126]

3,3-bis(4-nitrobenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 38)



[0127]

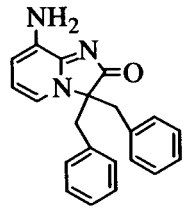
Melting Point: >300 °C;

NMR (CD_3OD-$CDCl_3$(1:1)) δ: 3.21 (2H, d, J=14Hz), 3.67 (2H, d, J=14Hz), 6.66 (1H, t, J=7Hz), 6.75 (1H, d, J=7Hz), 7.15 (4H, d, J=9Hz), 7.39 (1H, t, J=7Hz), 7.42 (4H, d, J=9Hz), 7.56 (1H, d,J=7Hz);

MS m/z: 404 (M^+).

[0128]

8-amino-3,3-dibenzylimidazo[1,2-a]pyridin-2(3H)-one (Compound 39)



[0129]

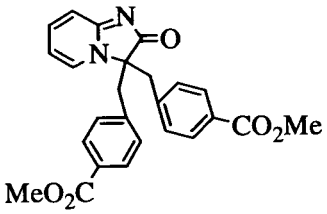
Melting Point: 283-285 °C;

NMR ($CDCl_3$) δ: 3.17 (2H, d, J=14Hz), 3.53 (2H, d, J=14Hz), 4.06 (2H, brs), 6.4-6.5 (2H, m), 6.94 (1H, t, J=7Hz), 7.0-7.1 (4H, m), 7.1-7.2 (6H, m);

MS m/z: 330 (M^+).

[0130]

3,3-bis(4-methoxycarbonylbenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 40)



[0131]

Melting Point: 289-290 °C;

NMR ($CDCl_3$) δ: 3.22 (2H, d, J=14Hz), 3.66 (2H, d, J=14Hz), 3.86 (6H, s), 6.60 (1H, t, J=7Hz), 6.70 (1H, d, J=7Hz), 7.0-7.1 (4H, m), 7.35 (1H, t, J=7Hz), 7.50 (1H, d, J=7Hz), 7.8-7.9 (4H, m);

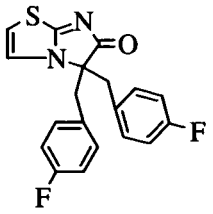
MS m/z: 430 (M^+).

[0132]

Exemplary Preparation 3

An exemplary preparation of 5,5-bis(4-fluorobenzyl)imidazo[2,1-b]thiazol-6(5H)-one (Compound 43) having the general formula below is described hereafter.

[0133]



[0134]

First, 300 mg (1.4 mmol) of 2-amino-3-ethoxycarbonylmethylthiazolium bromide and then 1.15 ml (9.0 mmol) of p-fluorobenzyl bromide were added to an ethanol solution (10ml) of sodium ethoxide prepared from 210 mg (9.0 mmol) of metallic sodium while cooling over ice and stirred at room temperature overnight. The solvent was removed by distillation under reduced pressure and water was added to the residue. The resultant mixture was extracted several times using ethyl acetate, rinsed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure and the residue was chromatographed over silica gel column (ethyl acetate : methanol = 10 : 1). An amount of 852 mg (80.0·) of the title compound was obtained in the form of crystals. Recrystallization from ethanol yielded white crystals having a melting point of higher than 300 °C.

[0135]

Results of analysis of the obtained compound are given below. The results show that the obtained compound was the targeted compound.

[0136]

NMR (CD_3OD-$CDCl_3$(1:1)) δ: 3.23 (2H, d, J=14Hz), 3.43 (2H, d, J=14Hz), 6.66 (1H, d, J=4Hz), 6.8-6.9 (4H, m), 6.9-7.1 (4H, m), 7.28 (1H, d, J=4Hz);

MS m/z: 356 (M^+).

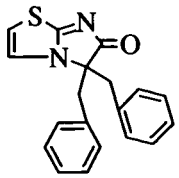
[0137]

Exemplary Preparation 4

Compounds 44 to 68 having the general formulae corresponding to starting materials were each prepared in the same manner as in Exemplary Preparation 3. Results of analysis of the obtained compounds are given below. The results show the obtained compounds were the targeted compounds.

[0138]

5,5-dibenzylimidazo[2,1-b]thiazol-6(5H)-one (Compound 44)



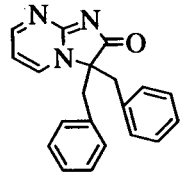
[0139]

Melting Point: >300 °C;

NMR (DMSO-d_6) δ: 3.69 (2H, d, J=15Hz), 3.74 (2H, d, J=15Hz), 7.27 (1H, d, J=4Hz), 7.3-7.4 (4H, m), 7.5-7.6 (6H, m), 8.44 (1H, d, J=4Hz);
MS m/z: 320 (M^+).

[0140]

3,3-dibenzylimidazo[1,2-a]pyrimidin-2(3H)-one (Compound 45)

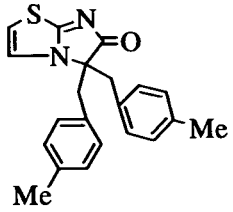


[0141]

Melting Point: >300 °C;
NMR (DMSO-d_6) δ: 3.42 (4H, dd, J=14Hz, J=16Hz), 6.9-7.0 (5H, m), 7.1-7.2 (6H, m), 8.46 (1H, dd, J=3Hz, J=5Hz), 9.07 (1H, dd, J=2Hz, J=6Hz);
MS m/z: 315 (M^+).

[0142]

5,5-bis(4-methylbenzyl)imidazo[2,1-b]thiazol-6(5H)-one (Compound 46)

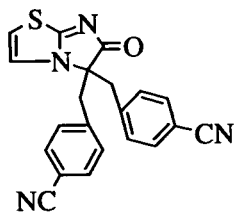


[0143]

Melting Point: >300 °C;
NMR (DMSO-d_6) δ: 2.20 (6H, s), 3.24 (2H, d, J=14Hz), 3.36 (2H, d, J=14Hz), 6.84 (4H, d, J=8Hz), 6.89 (1H, d, J=4Hz), 6.97 (4H, d, J=8Hz), 8.03 (4H, d, J=4Hz);
MS m/z: 348 (M^+).

[0144]

5,5-bis(4-cyanobenzyl)imidazo[2,1-b]thiazol-6(5H)-one (Compound 47)



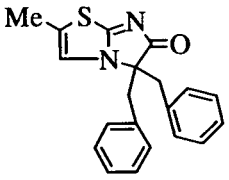
[0145]

Melting Point: 264-267 °C;
NMR ($CDCl_3$) δ: 3.23 (2H, d, J=14Hz), 3.56 (2H, d, J=14Hz), 6.54 (1H, d, J=6Hz), 7.02 (1H, d, J=6Hz), 7.15 (4H, d, J=9Hz), 7.51 (4H, d, J=9Hz);

MS m/z: 370 (M^+).

[0146]

5,5-dibenzyl-2-methylimidazo[2,1-b]thiazol-6(5H)-one (Compound 48)



[0147]

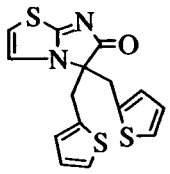
Melting Point: >300 °C;

NMR (CD_3OD-$CDCl_3$ (1:1)) δ: 2.34 (3H, d, J=1Hz), 3.28 (2H, d, J=13Hz), 3.43 (2H, d, J=13Hz), 7.0-7.1 (4H, m), 7.1-7.3 (7H, m);

MS m/z: 334 (M^+).

[0148]

5,5-bis(2-thienylmethyl)imidazo[2,1-b]thiazol-6(5H)-one (Compound 49)



[0149]

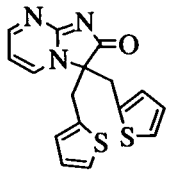
Melting Point: 286 °C (decomposition);

NMR ($CDCl_3$) δ: 3.43 (2H, d, J=15Hz), 3.60 (2H, d, J=15Hz), 6.49 (1H, d, J=5Hz), 6.7-7.0 (5H, m), 7.12 (2H, dd, J=1Hz, J=6Hz);

MS m/z: 332 (M^+).

[0150]

3,3-bis(2-thienylmethyl)imidazo[1,2-a]pyrimidin-2(3H)-one (Compound 50)



[0151]

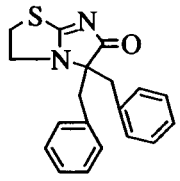
Melting Point: 192 °C (decomposition);

NMR (CD_3OD-$CDCl_3$(1:1)) δ: 3.54 (2H, d, J=15Hz), 3.76 (2H, d, J=15Hz), 6.7-6.9 (5H, m), 7.11 (2H, dd, J=1Hz, J=5Hz), 8.23 (1H, dd, J=2Hz, J=6Hz), 8.62 (1H, dd, J=2Hz, J=4Hz);

MS m/z: 327 (M^+).

[0152]

5,5-dibenzyl-2,3-dihydroimidazo[2,1-b]thiazol-6(5H)-one (Compound 51)



[0153]

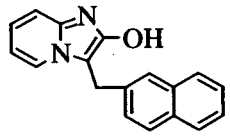
Melting Point: 233-236 °C;

NMR ($CDCl_3$) δ: 3.03 (2H, d, J=14Hz), 3.23 (2H, t, J=7Hz), 3.41 (2H, d, J=14Hz), 3.63 (2H, t, J=7Hz), 7.1-7.2 (4H, m), 7.2-7.3 (6H, m);

MS m/z: 322 (M^+).

[0154]

2-hydroxy-3-(2-naphthylmethyl)imidazo[1,2-a]pyridine (Compound 52)



[0155]

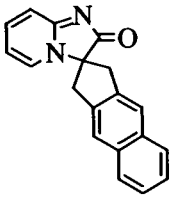
Melting Point: 205 °C (decomposition);

NMR (CD_3OD-$CDCl_3$(1:1)) δ: 3.41 (1H, d, J=15Hz), 3.76 (1H, d, J=15Hz), 6.72 (1H, t, J=7Hz), 7.02 (1H, d, J=9Hz), 7.29 (1H, d, J=9Hz), 7.4-7.5 (2H, m), 7.58 (2H, brs), 7.6-7.9 (4H, m);

MS m/z: 274 (M^+).

[0156]

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-benzo[f]indan] (Compound 53)



[0157]

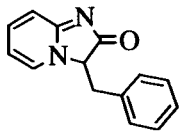
Melting Point: 214 °C (decomposition);

NMR (CD_3OD-$CDCl_3$(1:1)) δ: 3.33 (2H, d, J=16Hz), 4.02 (2H, d, J=16Hz), 6.58 (1H, t, J=7Hz), 7.16 (1H, d, J=7Hz), 7.24 (1H, d, J=9Hz), 7.5-7.6 (2H, m), 7.74 (1H, t, J=8Hz), 7.8-7.9 (4H, m);

MS m/z: 286 (M^+).

[0158]

3-benzylimidazo[1,2-a]pyridin-2(3H)-one (Compound 54)



[0159]

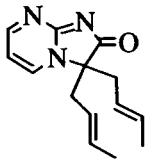
Melting Point: 182 °C (decomposition);

NMR ($CDCl_3$) δ: 3.09 (1H, dd, J=8Hz, J=15Hz), 3.64 (1H, dd, J=4Hz, J=15Hz), 4.58 (1H, dd, J=4Hz, J=8Hz), 6.47 (1H, t, J=7Hz), 7.0-7.1 (2H, m), 7.1-7.2 (2H, m), 7.3-7.4 (3H, m), 7.54 (1H, t, J=7Hz);

MS m/z: 224 (M^+).

[0160]

3,3-di(2-butenyl)imidazo[1,2-a]pyrimidin-2(3H)-one (Compound 55)



[0161]

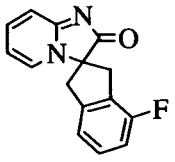
Melting Point: 149.5 °C (decomposition);

NMR ($CDCl_3$) δ: 1.55 (6H, d, J=6Hz), 2.51 (2H, dd, J=8Hz, J=15Hz), 2.76 (2H, dd, J=8Hz, J=15Hz), 5.1-5.3 (2H, m), 5.4-5.7 (2H, m), 6.69 (1H, dd, J=5Hz, J=6Hz), 7.75 (1H, dd, J=2Hz, J=6Hz), 8.7 (1H, dd, J=2Hz, J=5Hz);

MS m/z: 243 (M^+).

[0162]

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(4'-fluoroindan)] (Compound 56)



[0163]

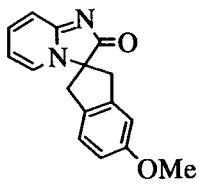
Melting Point: 148.0 °C (decomposition);

NMR ($CDCl_3$) δ: 3.24 (2H, dd, J=18Hz, J=22Hz), 3.88 (2H, t, J=18Hz), 6.55 (1H, t, J=7Hz), 7.01 (1H, t, J=9Hz), 7.10 (1H, d, J=7Hz), 7.2-7.3 (3H, m), 7.63 (1H, t, J=8Hz);

MS m/z: 254 (M^+).

[0164]

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(5'-methoxyindan)] (Compound 57)



[0165]

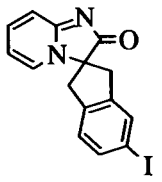
Melting Point: 150.0-152.0 °C;

NMR ($CDCl_3$) δ: 3.08(2H, dd, J=6Hz, J=17Hz), 3.8-4.0 (5H, m), 6.49 (1H, t, J=7Hz), 6.8-6.9 (2H, m), 7.1-7.3 (3H, m), 7.60 (1H, t, J=7Hz);

MS m/z: 266 (M^+).

[0166]

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(5'-iodoindan)] (Compound 58)



[0167]

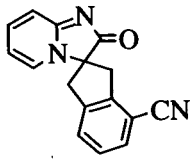
Melting Point: 167-171 °C;

NMR ($CDCl_3$) δ: 3.14 (2H, dd, J=6Hz, J=17Hz), 3.82 (2H, dd, J=17Hz, J=18Hz), 6.57 (1H, t, J=7Hz), 7.08 (1H, d, J=8Hz), 7.1-7.3 (2H, m), 7.6-7.7 (3H, m);

MS m/z: 362 (M^+).

[0168]

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(4'-cyanoindan)] (Compound 59)



[0169]

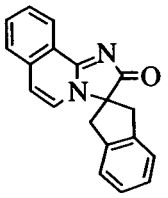
Melting Point: 247.7 °C (decomposition);

NMR ($CDCl_3$) δ: 3.26 (2H, dd, J=3Hz, J=18Hz), 3.93 (2H, dd, J=6Hz, J=18Hz), 6.56 (1H, t, J=7Hz), 7.15 (1H, d, J=7Hz), 7.23 (1H, d, J=9Hz), 7.44 (1H, d, J=8Hz), 7.6-7.7 (3H, m);

MS m/z: 261 (M^+).

[0225]

spiro[imidazo[2,1-a]isoquinolin-2(3H)-one-3,2'-indan] (Compound 60)



[0170]

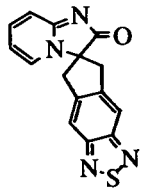
Melting Point: 201-203 °C;

NMR ($CDCl_3$) δ: 3.22 (2H, d, J=17Hz), 3.91 (2H, d, J=17Hz), 6.74 (1H, d, J=7Hz), 6.89 (1H, d, J=7Hz), 7.32 (4H, s), 7.6-7.7 (2H, m), 7.79 (1H, t, J=7Hz), 8.63 (1H, d, J=8Hz);

MS m/z: 286 (M^+).

[0171]

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-((1,2,5-thiadiazo)[4,5-c]indan)] (Compound 61)



[0172]

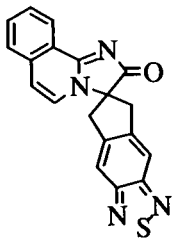
Melting Point: 86-88 °C;

NMR ($CDCl_3$-CD_3OD(1:1)) δ: 3.44 (2H, d, J=18Hz), 4.00 (2H, d, J=18Hz), 6.71 (1H, t, J=7Hz), 7.2-7.4 (2H, m), 7.81 (1H, t, J=7Hz), 7.97 (2H, s);

MS m/z: 294 (M^+).

[0173]

spiro[imidazo[2,1-a]isoquinolin-2(3H)-one-3,2'-((1,2,5-thiadiazo)[4,5-c]indan)] (Compound 62)



[0174]

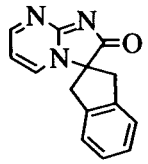
Melting Point: 271.5 °C (decomposition);

NMR ($CDCl_3$) δ: 3.39 (2H, d, J=16Hz), 4.04 (2H, brd, J=16Hz), 6.77 (1H, d, J=7Hz), 6.81 (1H, d, J=7Hz), 7.6-7.8 (2H, m), 7.82 (1H, brs, J=8Hz), 7.95 (2H, brs), 8.65 (1H, d, J=8Hz);

MS m/z: 344 (M^+).

[0175]

spiro[imidazo[1,2-a]pyrimidin-2(3H)-one-3,2'-indan] (Compound 63)



[0176]

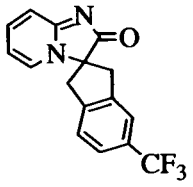
Melting Point: 195.5 °C (decomposition);

NMR ($CDCl_3$) δ: 3.17 (2H, d, J=17Hz), 3.92 (2H, d, J=17Hz), 6.53 (1H, dd, J=5Hz, J=6Hz), 7.44 (1H, dd, J=2Hz, J=6Hz), 7.32 (4H, s), 8.72 (1H, dd, J=2Hz, J=5Hz);

MS m/z: 237 (M^+).

[0177]

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(5'-trifluoromethylindan)] (Compound 64)



[0178]

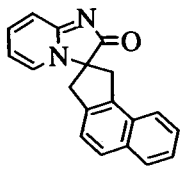
Melting Point: 176.5-179.5 °C;

NMR ($CDCl_3$) δ: 3.25 (2H, d, J=17Hz), 3.92 (2H, d, J=17Hz), 6.57 (1H, t, J=7Hz), 7.1-7.2 (2H, m), 7.44 (1H, d, J=8Hz), 8.5-8.7 (3H, m);

MS m/z: 304 (M^+).

[0179]

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-benzo[e]indan] (Compound 65)



[0180]

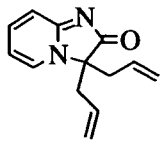
Melting Point: 256.0 °C (decomposition);

NMR ($CDCl_3$) δ: 3.33 (1H, d, J=17Hz), 3.56 (1H, d, J=17Hz), 4.09 (2H, t, J=17Hz), 6.50 (1H, t, J=7Hz), 7.22 (1H, d, J=9Hz), 7.29 (1H, d, J=7Hz), 7.42 (1H, d, J=8Hz), 7.5-7.7 (4H, m), 7.83 (1H, d, J=8Hz), 7.92 (1H, d, J=6Hz);

MS m/z: 286 (M^+).

[0181]

3,3-diallylimidazo[1,2-a]pyridin-2(3H)-one (Compound 66)



[0182]

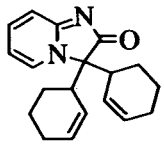
Melting Point: 64-66 °C;

NMR ($CDCl_3$) δ: 2.56 (2H, dd, J=9Hz, J=14Hz), 2.86 (2H, dd, J=6Hz, J=14Hz), 4.99 (2H, dd, J=1Hz, J=7Hz), 5.40 (2H, d, J=1Hz), 5.4-5.6 (2H, m), 6.67 (1H, t, J=7Hz), 7.17 (1H, d, J=7Hz), 7.52 (1H, d, J=7Hz), 7.59 (1H, d, J=7Hz);

MS m/z: 214 (M^+).

[0183]

3,3-bis(2-cyclohexenyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 67)



[0184]

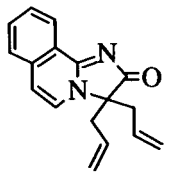
Melting Point: 245-247 °C;

NMR ($CDCl_3$) δ: 1.4-2.0 (12H, m), 2.9-3.1 (2H, m), 5.29 (1H, brd, J=10Hz), 5.8-6.0 (3H, m), 6.62 (1H, t, J=7Hz), 7.17 (1H, d, J=9Hz), 7.5-7.7 (2H, m);

MS m/z: 294 (M^+).

[0185]

3,3-diallylimidazo[2,1-a]isoquinolin-2(3H)-one (Compound 68)



[0186]

Melting Point: 108-110 °C;

NMR ($CDCl_3$) δ: 2.62 (2H, dd, J=8Hz, J=14Hz), 2.89 (2H, dd, J=6Hz, J=14Hz), 4.9-5.1 (4H, m), 5.4-5.6 (2H, m), 6.91 (1H, d, J=7Hz), 7.25 (1H, d, J=7Hz), 7.6-7.7 (2H, m), 7.80 (1H, t, J=8Hz), 8.57 (1H, d,J=8Hz);

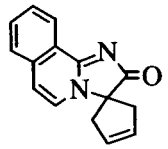
MS m/z: 264 (M^+).

[0187]

Exemplary Preparation 5

An exemplary preparation of spiro[imidazo[2,1-a]isoquinolin-2(3H)-one-3,4'-(1'-cyclopentene)]

(Compound 69) having the general formula below is described hereafter.



[0188]

An amount of 80 mg of Grubbs reagent (0.24 mmol) was added to a chloroform solution (80 ml) of 1.0 g (3.8 mmol) of 3,3-diallylimidazo[2,1-a]isoquinolin-2(3H)-one obtained in the same manner as in Exemplary Preparation 1 under an argon atmosphere and heated under flux for 14 hours. The reaction mixture was allowed to stand for cooling and the solvent was removed by distillation under reduced pressure. Water was added to the residue and the mixture was extracted with dichloromethane several times. The extracted layers were rinsed together with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure and the residue was chromatographed over silica gel column for purification (ethyl acetate : methanol = 10 : 1) to obtain 748 mg (83.5 %) of the title compound in the form of light brown crystals.

[0189]

Results of analysis of the obtained compound are given below. The results show that the obtained compound was the targeted compound.

[0190]

Melting Point: 173.5 °C (decomposition);

NMR ($CDCl_3$) δ: 2.70 (2H, d, J=17Hz), 3.30 (2H, d, J=17Hz), 5.92 (2H, s), 6.89 (1H, d, J=7Hz), 7.33 (1H, d, J=7Hz), 7.6-7.8 (2H, m), 7.79 (1H, t, J=7Hz), 8.60 (1H, d, J=7Hz);

MS m/z: 236 (M^+).

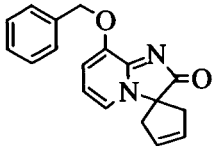
[0191]

Exemplary Preparation 6

Compound 70 having the general formula below corresponding to starting materials was prepared in the same manner as in Exemplary Preparation 5. Results of analysis of the obtained compound are given below for each compound. The results show that the obtained compound was the targeted Compound 70.

[0192]

spiro[8-benzyloxyimidazo[1,2-a]pyridin-2(3H)-one-3,4'-(1'-cyclopentene)] (Compound 70)



[0193]

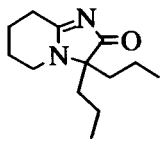
Melting Point: 178.5-180.5 °C;
NMR ($CDCl_3$) δ: 2.64 (2H, d, J=16Hz), 3.29 (2H, d, J=16Hz), 5.30 (2H, s), 5.88 (2H, s), 6.49 (1H, dd, J=6Hz, J=8Hz), 6.94 (1H, dd, J=6Hz, J=8Hz), 6.94 (1H, d, J=8Hz), 7.2-7.5 (5H, m);
MS m/z: 292 (M^+).

[0194]

Exemplary Preparation 7

An exemplary preparation of 3,3-dipropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one (Compound 71) having the general formula below is described hereafter.

[0195]



[0196]

An amount of 100mg of 10 % palladium on carbon was added to an ethanol solution (30 ml) of 300 mg (1.4 mmol) of 3,3-diallylimidazo[1,2-a]pyridin-2(3H)-one obtained in the same manner as in Exemplary Preparation 5 and the mixture was subject to catalytic reduction at room temperature under a hydrogen atmosphere overnight. The insoluble substances were filtered off and the solvent was removed from the filtrate by distillation under reduced pressure. The residue was chromatographed over silica gel column (hexane : ethyl acetate = 10 : 1) to obtain 281 mg (90.3%) of the title compound in the form of crystals. Recrystallization from hexane-ethyl acetate (10:1) yielded white crystals having a melting point of 98.5-101 °C.

[0197]

Results of analysis of the obtained compound are given below. The results show that the obtained compound was the targeted compound.

[0198]

NMR ($CDCl_3$) δ: 0.86 (6H, t, J=7Hz), 0.9-1.1 (2H, m), 1.1-1.2 (2H, m), 1.4-1.6 (2H, m), 1.7-2.0 (6H, m), 2.79 (2H, t, J=6Hz), 3.19 (2H, t, J=6Hz);
MS m/z: 222 (M^+).

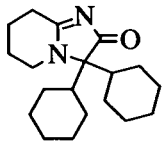
[0199]

Exemplary Preparation 8

Compounds 72 to 77 having the general formulae corresponding to starting materials were prepared in the same manner as in Exemplary Preparation 7.
Results of analysis of the obtained compounds are given below for each compound. The results show that the obtained compounds were the targeted Compounds 72 to 77.

[0200]

3,3-dicyclohexyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one (Compound 72)



[0201]

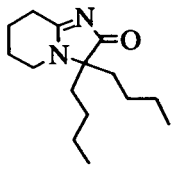
Melting Point: 218-220 °C;

NMR ($CDCl_3$) δ: 0.9-1.4 (8H, m), 1.5-2.0 (18H, m), 2.79 (2H, t, J=6Hz), 3.30 (2H, t, J=6Hz);

MS m/z: 302 (M^+).

[0202]

3,3-dibutyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one (Compound 73)



[0203]

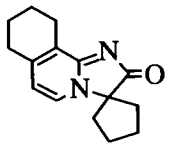
Melting Point: 35-40 °C;

NMR ($CDCl_3$) δ: 0.88 (6H, t, J=7Hz), 0.9-1.4 (8H, m), 1.6-2.2 (8H, m), 3.2-3.4 (4H, m);

MS m/z: 250 (M^+).

[0204]

spiro[7,8,9,10-tetrahydroimidazo[2,1-a]isoquinolin-2(3H)-one-3,1'-cyclopentane] (Compound 74)



[0205]

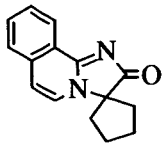
Melting Point: 270.5 °C (decomposition);

NMR ($CDCl_3$) δ: 1.8-2.2 (10H, m), 2.3-2.5 (2H, m), 2.6-2.8 (4H, m), 6.44 (1H, d, J=7Hz), 7.35 (1H, d, J=7Hz);

MS m/z: 242 (M^+).

[0206]

spiro[imidazo[2,1-a]isoquinolin-2(3H)-one-3,1'-cyclopentane] (Compound 75)



[0207]

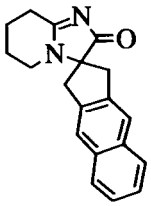
Melting Point: 164.5-167.5 °C;

NMR ($CDCl_3$) δ: 1.8-2.3 (6H, m), 2.4-2.6 (2H, m), 6.94 (1H, d, J=7Hz), 7.33 (1H, d, J=7Hz), 7.6-7.7 (2H, m), 7.79 (1H, t, J=6Hz), 8.60 (1H, d, J=8Hz);

MS m/z: 238 (M^+).

[0208]

spiro[5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one-3,2'-benzo[f]indan] (Compound 76)



[0209]

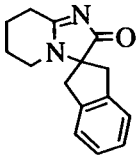
Melting Point: 252.5 °C (decomposition);

NMR ($CDCl_3$-CD_3OD(1:1)) δ: 1.9-2.1 (4H, m), 3.0-3.2 (4H, m), 3.50 (2H, d, J=18Hz), 3.79 (2H, d, J=18Hz), 7.4-7.5 (2H, m), 7.75 (2H, s), 7.8-7.9 (2H, m);

MS m/z: 290 (M^+).

[0210]

spiro[5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2(3H)-one-3,2'-indan] (Compound 77)



[0211]

Melting Point: 276.5 °C (decomposition);

NMR ($CDCl_3$-CD_3OD (1:1)) δ: 1.9-2.1 (4H, m), 3.0-3.3 (4H, m), 3.45 (2H, d, J=17Hz), 3.66 (2H, d, J=17Hz), 7.30 (4H, s);

MS m/z: 240 (M^+).

[0212]

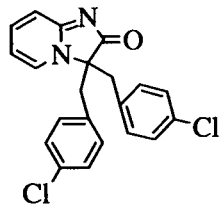
Exemplary Preparation 9

Compounds 78 to 81 having the general formulae corresponding to starting materials were each prepared in the same manner as in Exemplary Preparation 1. Results of analysis of the obtained compounds are given below for each compound. The results

show that the obtained compounds were the targeted Compounds 78 to 81.

[0213]

3,3-bis(4-chlorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one (Compound 78)



[0214]

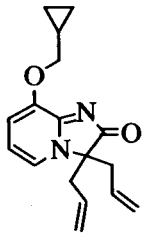
Melting Point: 293.0-296.0 (°C).

1H-NMR ($CDCl_3$) δ: 3.11 (2H, d, J=14Hz), 3.55 (2H, d, J= 14Hz), 6.62 (1H, t, J=7Hz), 6.78 (1H, d, J=8Hz), 6.94 (4H, d, J=8Hz), 7.12 (4H, d, J=8Hz), 7.40 (1H, t, J=7Hz), 7.47 (1H, d, J=7Hz);

MS m/z: 382 (M^+)

[0215]

8-cyclopropylmethyloxy-3,3-diallylimidazo[1,2-a]pyridin-2(3H)-one (Compound 79)



[0216]

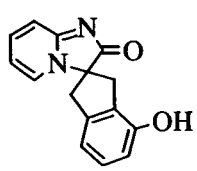
Melting Point: 139.0-142.0 (°C);

1H-NMR ($CDCl_3$) δ: 0.35-0.40 (2H, m), 0.60-0.65 (2H, m), 1.30-1.40 (1H, m), 2.50-2.60 (2H, m), 2.80-2.90 (2H, m), 3.94 (2H, d, J=7Hz), 4.96 (2H, brs), 5.02 (2H, brs), 5.40-5.65 (2H, m), 6.57 (1H, t, J=7Hz, J=8Hz), 6.91 (1H, d, J=8Hz), 7.16 (1H, d, J=7Hz);

MS m/z: 284 (M^+).

[0217]

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(4'-hydroxy-indan)] (Compound 80)



[0218]

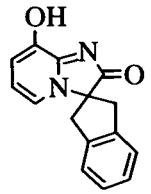
Melting Point: 240.0 °C (dec.);

1H-NMR (CD_3OD) δ: 3.17 (1H, d, J=17Hz), 3.19 (1H, d, J=17Hz), 3.50 (1H, d, J=17Hz),

3.61 (1H, d, J=17Hz), 6.63 (1H, d, J=8Hz), 6.70-6.80 (2H, m), 7.07 (1H, d, J=8Hz), 7.12 (1H, d, J=9Hz), 7.51 (1H, d, J=7Hz), 7.81 (1H, d, J=8Hz);
MS m/z: 352 (M^+).

[0219]

spiro[8-hydroxy-imidazo[1,2-a]pyridin-2(3H)-one-3,2'-indan] (Compound 81)



[0220]

Melting Point: 285.0-290.0 °C;
1H-NMR ($CDCl_3$) δ: 3.22 (2H, d, J=17Hz), 3.91 (2H, d, J=17Hz), 6.57 (1H, dd, J=6Hz, J=7Hz), 6.82 (1H, d, J=6Hz), 7.27 (1H, d, J=7Hz), 7.31 (4H, s);
MS m/z: 352 (M^+).

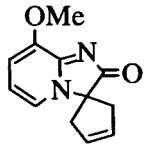
[0221]

Exemplary Preparation 10

Compounds 82 to 83 having the general formulae corresponding to starting materials were each prepared in the same manner as in Exemplary Preparation 5. Results of analysis of the obtained compounds are given below for each compound. The results show that the obtained compounds were the targeted Compounds 82 to 83.

[0222]

spiro[8-methoxyimidazo[1,2-a]pyridin-2(3H)-one-3,4'-(1'-cyclopentene)] (Compound 82)

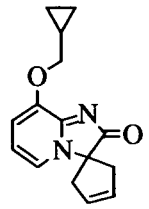


[0223]

Melting Point: 200.0-202.0 °C;
1H-NMR ($CDCl_3$): 2.64 (2H, d, J=17Hz), 3.29 (2H, d, J=17Hz), 3.96 (3H, s), 5.88 (2H, s), 6.57 (1H, dd, J=7Hz, J=8Hz), 6.91 (1H, d, J=8Hz), 7.29 (1H, d, J=7Hz);
MS m/z: 216 (M^+).

[0224]

spiro[8-cyclopropylmethyloxyimidazo[1,2-a]pyridin-2(3H)-one-3,4'-(1'-cyclopentene)] (Compound 83)



[0225]

Melting Point: 134.0-137.0 °C;

1H-NMR ($CDCl_3$) δ: 0.35-0.40 (2H, m), 0.60-0.70 (2H, m), 1.30-1.40 (1H, m), 2.64 (2H, d, J=16Hz), 3.28 (2H, d, J=16Hz), 3.98 (2H, d, J=7Hz), 5.88 (2H, s), 6.54 (1H, dd, J=7Hz, J=8Hz), 6.92 (1H, d, J=8Hz), 7.28 (1H, d, J=7Hz);

MS m/z: 256 (M^+).

[0226]

Exemplary Pharmaceutical Formulation

The following table shows a typical pharmaceutical composition that may be administered according to the invention.

[0227]

Component	Quantity per 10 mg tablet	Quantity per 60 mg tablet
Compound 1	10 mg	60 mg
Mannitol	95.9 mg	45.9 mg
Microcrystalline cellulose	19.3 mg	19.3 mg
Low-substituted hydroxypropyl cellulose	7.0 mg	7.0 mg
Hydroxypropyl cellulose	5.0 mg	5.0 mg
Magnesium stearate	2.8 mg	2.8 mg
Total	140.0 mg	140.0 mg

[0228]

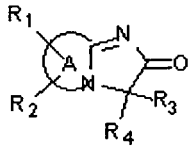
The present invention is described above using examples. The examples are given by way of example. It is understood by a person in the art that various modifications are available and those modifications are included in the scope of the present invention.

[0229]

For example, the above examples used mice as a mammal. However, other mammals including human can be used. Even in such cases, the above Compounds 1 to 83 exhibit antidepressant, neuroprotection, amyloid β deposition inhibitory, or age retardant activity in other mammals including human.

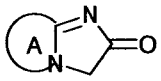
CLAIMS

1. An Alzheimer's disease progression inhibitor comprising a heterocyclic compound having the general formula (I):



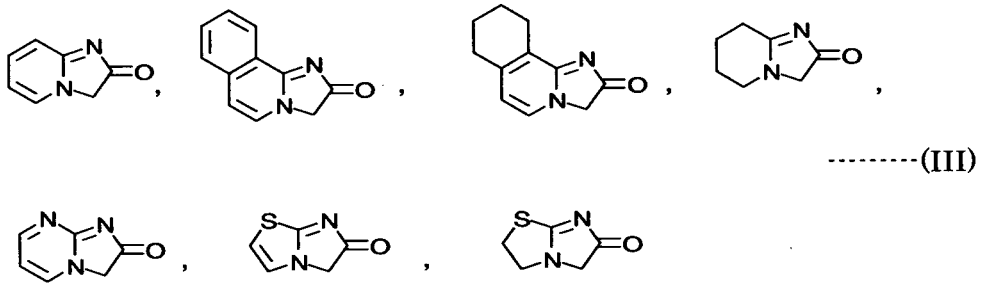
.....(I)

in the general formula (I), the structural unit having the general formula (II):



.....(II)

is one or more structural units selected from multiple types of structural units having the general formula (III):



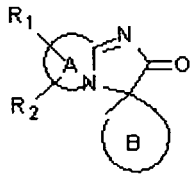
.....(III)

in the general formula (I),

R_1 and R_2 each are one or more functional groups independently selected from the group consisting of a hydrogen atom, halogen atom, hydroxy group, amino group, acetylamino group, benzylamino group, trifluoromethyl group, C_1-C_6 alkyl group, C_1-C_6 alkoxy group, and -O-(CH_2)n-R_5 (R_5 is a vinyl group, C_3-C_6 cycloalkyl group, or phenyl group, and n is 0 or 1);

R_3 and R_4 each are one or more functional groups independently selected from the group consisting of a hydrogen atom, C_1-C_6 alkyl group, C_3-C_8 cycloalkyl group, and -CH(R_7)-R_6;

alternatively, R_3 and R_4 together form a spiro ring having the general formula (IV):



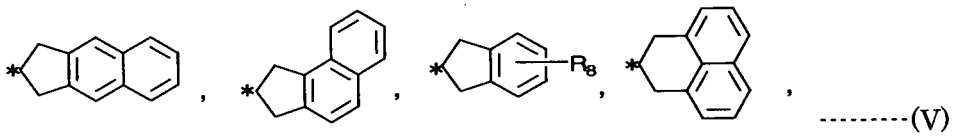
.....(IV)

said R_6 is one or more functional groups selected from the group consisting of a vinyl group, ethinyl group, phenyl (which may be substituted by a C_1-C_6 alkyl group, C_1-C_6 alkoxy group, hydroxy group , 1 or 2 halogen atoms, di C_1-C_6 alkylamino group, cyano group, nitro group,

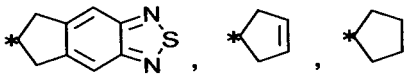
carboxy group, or phenyl group), phenethyl group, pyridyl group, thienyl group, and furil group;

said R_7 is a hydrogen atom or C_1-C_6 alkyl group;

in the general formula (IV), the structural unit B is one or more structural units selected from multiple types of structural units having the general formula (V):



.....(V)



said structural unit B binds at a position marked by * in the general formula (V) to form a spiro ring; and

R_8 is one or more functional groups selected from the group consisting of a hydrogen atom, halogen atom, hydroxy group, C_1-C_6 alkoxy group, cyano group, and trifluoromethyl group.

2. The Alzheimer's disease progression inhibitor according to Claim 1 wherein said heterocyclic compound is one or more heterocyclic compounds selected from the group consisting of:

3,3-dibenzylimidazo[1,2-a]pyridin-2(3H)-one,

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-indan],

3,3-dipropylimidazo[1,2-a]pyridin-2(3H)-one,

3,3-dibutylimidazo[1,2-a]pyridin-2(3H)-one,

5,5-dibenzylimidazo[2,1-b]thiazol-6(5H)-one,

3,3-dibenzylimidazo[1,2-a]pyrimidin-2(3H)-one,

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(4'-fluoroindan)],

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(5'-methoxyindan)],

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(4'-cyanoindan)],

spiro[imidazo[2,1-a]isoquinolin-2(3H)-one-3,2'-indan],

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-((1,2,5-thiadiazo)[4,5-c]indan)],

spiro[imidazo[1,2-a]pyrimidin-2(3H)-one-3,2'-indan],

spiro[imidazo[2,1-a]isoquinolin-2(3H)-one-3,4'-(1'-cyclopentene)],

3,3-bis(4-chlorobenzyl)imidazo[1,2-a]pyridin-2(3H)-one,

8-cyclopropylmethyloxy-3,3-diallylimidazo[1,2-a]pyridin-2(3H)-one,

spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-(4'-hydroxyindan)],

spiro[8-hydroxy-imidazo[1,2-a]pyridin-2(3H)-one-3,2'-indan],

spiro[8-methoxyimidazo[1,2-a]pyridin-2(3H)-one-3,4'-(1'-cyclopentene)], and

spiro[8-cyclopropylmethyloxyimidazo[1,2-a]pyridin-2(3H)-one-3,4'-(1'-cyclopentene)].

3. The Alzheimer's disease progression inhibitor according to Claim 1 or 2 wherein said heterocyclic compound is spiro[imidazo[1,2-a]pyridin-2(3H)-one-3,2'-indan].

4. The Alzheimer's disease progression inhibitor according to Claim 1 to 3 wherein said inhibitor of progression of Alzheimer's disease is orally administered.