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(54) Titre : DERIVES DE 2-PYRIDINYL-6,7,8,9-TETRAHYDROPYRIMIDO[1,2-A]PYRIMIDIN-4-ONE ET DE 7-PYRIDINYL-2,3-DIHYDROIMIDAZO[1,2-A]PYRIMIDIN-5(1H)ONE

(54) Title: 2-PYRIDINYL-6,7,8,9-TETRAHYDROPYRIMIDO[1,2-A]PYRIMIDIN-4-ONE AND 7-PYRIDINYL-2,3-DIHYDROIMIDAZO[1,2-A]PYRIMIDIN-5(1H)ONE DERIVATI VES

(57) Abrégé/Abstract:
The invention relates to pyrimidone derivative represented by formula (I) or a salt thereof wherein X represents hydrogen atoms, a sulfur atom, an oxygen atom or a C_{1-2} alkyl group and a hydrogen atom; Y represents a bond, an ethenylene group, an ethynylene group, a 1,2-cyclopropylene, an oxygen atom, a sulfur atom, a sulfonyl group, a sulfoxyde group, a carbonyl group, a nitrogen atom being optionally substituted; or a methylene group optionally substituted; R1 represent a 2,3 or 4-pyridyl group optionally substituted by a C_{3-6}cycloalkyl group a C_{1-4}alkyl group, a C_{1-4}alkoxy group, a benzyl group or a halogen atom; when Y represents a bond , a methylene group optionally substituted or a carbonyl group then R2 represent a C_{1-16}alkyl group, a C_{3-6} cycloalkyl group, a C_{1-4}alkylthio group, a C_{1-4}alkoxy group, a C_{1-2}perhalogenated alkyl group, a C 1-3halogenated alkyl group, a 5,6,7,8-tetrahydronaphthyl ring, a naphthyl ring, a phenylthio group, a benzyl group, a phenyl ring, a pyridyl ring, an indole ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring; when Y represents an ethenylene group, an ethynylene group, an oxygen atom, a sulfur atom, a sulfonyl group, a sulfoxyde group or a nitrogen atom being optionally substituted then R2 represents a C_{1-6}alkyl group, a C_{3-6}cycloalkyl group, a C_{1-2}perhalogenated alkyl group, a C_{1-3}halogenated alkyl group, a naphthyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a benzyl group, a phenyl ring, a pyridyl ring, an indole ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring. And a medicament comprising the said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative diseases caused by abnormal activity of GSK3β such as Alzheimer's disease.

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(54) Title: 2-PYRIDINYL-6,7,8,9-TETRAHYDROPYRIMIDO[1,2-a]PYRIMIDIN-4-ONE AND 7-PYRIDINYL-2,3-DIHYDROIMIDAZO[1,2-a]PYRIMIDIN-5(1H)ONE DERIVATI VES

(57) Abstract: The invention relates to pyrimidone derivative represented by formula (I) or a salt thereof wherein X represents hydrogen atoms, a sulfur atom, an oxygen atom or a C_{1-2} alkyl group and a hydrogen atom; Y represents a bond, an ethenylene group, an ethynylene group, a 1,2-cyclopropylene, an oxygen atom, a sulfur atom, a sulfonyl group, a sulfoxyde group, a carbonyl group, a nitrogen atom being optionally substituted; or a methylene group optionally substituted; R1 represent a 2,3 or 4-pyridyl group optionally substituted by a C_{3-6}cycloalkyl group a C_{1-4}alkyl group, a C_{1-4}alkoxy group, a benzyl group or a halogen atom; when Y represents a bond , a methylene group optionally substituted or a carbonyl group then R2 represent a C_{1-16}alkyl group, a C_{3-6}cycloalkyl group, a C_{1-4}alkylthio group, a C_{1-4}alkoxy group, a C_{1-2}perhalogenated alkyl group, a C 1-3halogenated alkyl group, a 5,6,7,8-tetrahydronaphthyl ring, a naphthyl ring, a phenylthio group, a benzyl group, a phenyl ring, a pyridyl ring, an indole ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring; when Y represents an ethenylene group, an ethynylene group, an oxygen atom, a sulfur atom, a sulfonyl group, a sulfoxyde group or a nitrogen atom being optionally substituted then R2 represents a C_{1-6}alkyl group, a C_{3-6}cycloalkyl group, a C_{1-2}perhalogenated alkyl group, a C_{1-3}halogenated alkyl group, a naphthyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a benzyl group, a phenyl ring, a pyridyl ring, an indole ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring. And a medicament comprising the said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative diseases caused by abnormal activity of GSK3β such as Alzheimer's disease.

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SPECIFICATION

2-PYRIDINYL-6,7,8,9-TETRAHYDROPYRIMIDO[1,2-*a*] PYRIMIDIN-4-ONE AND 7-PYRIDINYL-2,3-DIHYDROIMIDAZO[1,2-*a*] PYRIMIDIN-5(1*H*)ONE DERIVATIVES

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal activity of GSK3β.

Background Art

GSK3β (glycogen synthase kinase 3β) is a proline directed serine, threonine kinase that plays an important role in the control of metabolism, differentiation and survival. It was initially identified as an enzyme able to phosphorylate and hence inhibit glycogen synthase. It was later recognized that GSK3β was identical to tau protein kinase 1 (TPK1), an enzyme that phosphorylates tau protein in epitopes that are also found to be hyperphosphorylated in Alzheimer's disease and in several tauopathies.

Interestingly, protein kinase B (AKT) phosphorylation of GSK3β results in a loss of its kinase activity, and it has been hypothesized that this inhibition may mediate some of the effects of neurotrophic factors. Moreover, phosphorylation by GSK3β of β-catenin, a protein involved in cell survival, results in its degradation by an ubiquitinilation dependent proteasome pathway.

Thus, it appears that inhibition of GSK3β activity may result in neurotrophic activity. Indeed there is evidence that lithium, an uncompetitive inhibitor of GSK3β, enhances neuritogenesis in some models and also increases neuronal survival, through the induction of survival factors such as Bcl-2 and the inhibition of the expression of proapoptotic factors such as P53 and Bax.

Recent studies have demonstrated that β-amyloid increases the GSK3β activity and tau protein phosphorylation. Moreover, this hyperphosphorylation as well as the neurotoxic effects of β-amyloid are blocked by lithium chloride and by a GSK3β antisense mRNA. These observations strongly suggest that GSK3β may be the link between the two major pathological processes in Alzheimer's disease: abnormal APP (Amyloid Precursor Protein) processing and tau protein hyperphosphorylation.

Although tau hyperphosphorylation results in a destabilization of the neuronal cytoskeleton, the pathological consequences of abnormal GSK3β activity are, most likely, not only due to a pathological phosphorylation of tau protein because, as mentioned above, an excessive activity of this kinase may affect survival through the modulation of the expression of apoptotic and antiapoptotic factors. Moreover, it has been shown that β-amyloid-induced increase in GSK3β activity results in the phosphorylation and, hence the inhibition of pyruvate dehydrogenase, a pivotal enzyme in energy production and acetylcholine synthesis.

Altogether these experimental observations indicate that GSK3β may find application in the treatment of the neuropathological consequences and the cognitive and attention deficits associated with Alzheimer's disease, as well as other acute and chronic neurodegenerative diseases. These include, in a non-limiting manner, Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma.

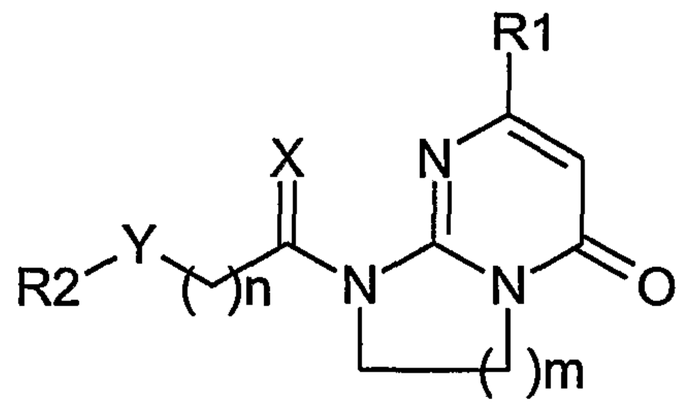
In addition GSK3β may find application in the treatment of other diseases such as: Non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors

Disclosure of the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of a disease caused by abnormal GSK3β activity, more particularly of neurodegenerative diseases. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables prevention and/or treatment of neurodegenerative diseases such as Alzheimer's disease.

Thus, the inventors of the present invention have identified compounds possessing inhibitory activity against GSK3β. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases.

The present invention thus provides pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof:



(I)

wherein:

X represents hydrogen atoms, a sulphur atom, an oxygen atom or a C_{1-2} alkyl group and a hydrogen atom;

Y represents a bond, an ethenylene group, an ethynylene group, a 1,2-cyclopropylene, an oxygen atom, a sulphur atom, a sulfonyl group, a sulfinyl group, a carbonyl group, a nitrogen atom being optionally substituted by a C_{1-6} alkyl group, a phenyl or a benzyl group; or a methylene group optionally substituted by one or two groups chosen from a C_{1-6} alkyl group, a phenyl group, a hydroxyl group or a C_{1-4} alkoxy group;

R1 represents a 2, 3 or 4-pyridyl group optionally substituted by a C_{3-6} cycloalkyl group a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a benzyl group or a halogen atom;

when Y represents a bond, a 1,2-cyclopropylene, a methylene group optionally substituted or a carbonyl group then R2 represents a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group, a C_{1-4} alkylthio group, a C_{1-4} alkoxy group, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a 5,6,7,8-tetrahydronaphthyl ring, a naphthyl ring, a phenylthio group, a benzyl group, a phenyl ring, a pyridyl ring, an indole ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring ; the benzyl group or the rings being optionally substituted by 1 to 4 substituents selected from a C_{1-6} alkyl group, a methylendioxy group, a halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a hydroxyl group, a C_{1-4} alkoxy group, a nitro, a cyano, an amino, a C_{1-5} monoalkylamino group, a C_{2-10} dialkylamino group, a C_{1-6} alkylcarbonylamino group, a $C_{6,10}$ arylcarbonylamino group, a C_{1-4} alkylsulfonyl group, C_{1-4} alkylsulfonyloxy group or a phenyl group;

when Y represents an ethenylene group, an ethynylene group, an oxygen atom, a sulphur atom, a sulfonyl group, a sulfoxyde group or a nitrogen atom being optionally substituted then R2 represents a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a naphthyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a benzyl group, a phenyl ring, a pyridyl ring, an indole ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring; the benzyl group or the rings being optionally substituted by 1 to 4 substituents selected from a C_{1-6} alkyl group, a methylendioxy group, a halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a hydroxyl group, a C_{1-4} alkoxy group, a nitro, a cyano, an amino, a C_{1-5} monoalkylamino group, a C_{2-10} dialkylamino group, a C_{1-6} alkylcarbonylamino group, a $C_{6,10}$ arylcarbonylamino group, a C_{1-4} alkylsulfonyl group, C_{1-4} alkylsulfonyloxy group or a phenyl group;

m represents 1 or 2;
and n represents 0 to 3.

According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by abnormal GSK3β activity, and the aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases and in addition other diseases such as: Non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are neurodegenerative diseases and are selected from the group consisting of Alzheimer's disease, Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain

and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma, and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives.

The present invention further provides an inhibitor of GSK3β activity comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

According to further aspects of the present invention, there is provided a method for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal GSK3β activity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

As used herein, the C_{1-6} alkyl group represents a straight or branched alkyl group having 1 to 6 carbon atoms, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, and the like;

The C_{3-6} cycloalkyl group represents a cyclic alkyl group having from 3 to 6 carbon atoms;

The C_{1-4} alkoxy group represents an alkyloxy group having 1 to 4 carbon atoms for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, and the like;

The C_{1-4} alkylthio group represents an alkylthio group having 1 to 4 carbon atoms for example, methylthio group, ethylthio group, propylthio group, isopropylthio group, butylthio group, isobutylthio group, sec-butylthio group, tert-butylthio group, and the like;

The C_{1-4} alkylsulfonyl group represents an alkylsulfonyl group having 1 to 4 carbon atoms for example, methylsulfonyl group, ethylsulfonyl group,

propylsulfonyl group, isopropylsulfonyl group, butylsulfonyl group, isobutylsulfonyl group, sec-butylsulfonyl group, tert-butylsulfonyl group, and the like;

The halogen atom represents a fluorine, chlorine, bromine or iodine atom;

The C_{1-2} perhalogenated alkyl group represents an alkyl group wherein all the hydrogen have been substituted by halogen atoms, for example a CF_3 or C_2F_5;

The C_{1-3} halogenated alkyl group represents an alkyl group wherein at least one hydrogen has not been substituted by a halogen atom;

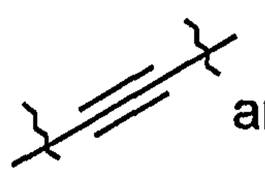
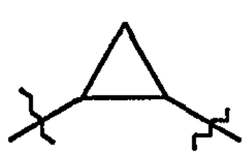
The C_{1-5} monoalkylamino group represents an amino group substituted by one C_{1-5} alkyl group, for example, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group and isopentylamino group;

The C_{2-10} dialkylamino group represents an amino group substituted by two C_{1-5} alkyl groups, for example, dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group and diisopropylamino group;

The C_{1-6} alkylcarbonylamino group represents an amino group substituted by a C_{1-6} acyl group, for example, formyl group, acetyl group, propionyl group, pivaloyl group, butyryl group, isobutyryl group, pentanoyl group, 3-methylbutyryl group and hexanoyl group;

The $C_{6,10}$ arylcarbonylamino group represents an amino group substituted by a benzoyl group and a naphthoyl group;

The ethenylene, ethynylene and the 1,2-cyclopropylene group represents respectively the following groups:

;  and 

The leaving group represents a group which could be easily cleaved and substituted, such a group may be for example a tosyl, a mesyl, a bromide and the like.

The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, *N,N*-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, *N*-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine,

δ-hydroxylysine, and arginine. The base-addition salts of acidic compounds are prepared by standard procedures well known in the art.

When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

The acid-addition salts of the basic compounds are prepared by standard procedures well know in the art which include, but are not limited thereto, dissolving the free base in an aqueous alcohol solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and an acid in an organic solvent, in which case the salt separates directly, or is precipitated with a second organic solvent, or can be obtained by concentration of the solution. The acids which can be used to prepare the acid-addition salts include preferably those which produce, when combined with the free base, pharmaceutically-acceptable salts, that is, salts whose anions are relatively innocuous to the animal organism in pharmaceutical doses of the salts, so that the beneficial properties inherent in the free base are not compromised by side effects ascribable to the anions. Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the present invention.

In addition to the pyrimidinone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The pyrimidinone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidinone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers in pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention.

Examples of preferred compounds of the present invention are shown in table 1 hereinafter. However, the scope of the present invention is not limited by these compounds.

Preferred compounds of the present invention represented by formula (I) include also:

(1) Compounds wherein R1 represents a 3- or 4-pyridyl group and more preferably 4-pyridyl group, which may be substituted by a C_{1-2} alkyl group, C_{1-2} alkoxy group or a halogen atom; and/or

(2) Compounds wherein X represents hydrogen atoms, an oxygen atom or a methyl group and a hydrogen atom; and/or

(3) Compounds wherein Y represents a bond, an ethenylene group, an ethynylene group, an oxygen atom, a sulphur atom, a sulfinyl group, a carbonyl group, a methylene group optionally substituted or a nitrogen atom being optionally substituted by one or two benzyl group; and/or

(4) R2 represents a C_{1-4} alkyl group, C_{1-2} alkylthio group, C_{1-2} alkoxy group, a trifluoromethyl group, a C_{5-6} cycloalkyl group, a naphthyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a phenylthio group, a benzyl group, a phenyl ring, a pyridyl ring, an indole ring, a thiophene ring; the rings being optionally substituted by 1 to 4 substituents.

More preferred compounds of the present invention represented by formula (I) include also:

(1) Compounds wherein R1 represents an unsubstituted 4-pyridyl group; and/or

(2) Compounds wherein R2 represents a C_{1-4} alkyl group, C_{1-2} alkylthio group, C_{1-2} alkoxy group, a trifluoromethyl group, a C_{5-6} cycloalkyl group, a naphthyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a phenyl ring, a pyridyl ring, an indole ring, a thiophene ring; the rings being optionally substituted by 1 to 4 substituents; and/or

(3) Compounds wherein X represents hydrogen atoms, an oxygen atom or a methyl group and a hydrogen atom; and/or

(4) Compounds wherein Y represents a bond, a ethenylene, a ethynylene, a sulphur atom, an oxygen atom, a carbonyl group, a sulfinyl group, a methylene group optionally substituted by a C_{1-4} alkyl group and/or a hydroxy group, or a nitrogen atom optionally substituted by one or two benzyl group; and/or

(5) n is 0, 1 or 2.

Particularly preferred compounds of the present invention represented by formula (I) include the compounds of table 1 :

1 : 9-[2-(1*H*-indol-3-yl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
2 : 9-(3-phenylpropyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
3 : 9-(2-phenylethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
4 : 9-[3-(1*H*-indol-3-yl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
5 : 9-(2-phenoxyethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
6 : 9-[3-(3,4-methylenedioxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
7 : 9-[2-(2-methoxyphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
8 : 9-[2-(4-fluorophenoxyethyl)]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
9 : 9-[3-(2-chlorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
10 : 9-[3-(4-methylphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
11 : 9-[3-(4-trifluoromethylphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
12 : 9-(4-phenylbutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
13 : 9-[3-(2-methylphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
14 : 9-[2-(2,5-dimethoxyphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
15 : 9-[2-(2-methoxyphenoxy)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
16 : 9-[3-(2-methoxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;
17 : 9-[2-(4-chlorophenoxy)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

18 : 9-[3-(3-methoxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

19 : 9-(2-methoxyphenylmethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

20 : 9-[2-phenylthioethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

21 : 9-[3-(3,4-dimethoxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

22 : 9-[3-(3,4,5-trimethoxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

23 : 9-[2-(phenylsulfonyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

24 : 9-[3-(3,4-fluorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

25 : 9-[3-phenylpropanoyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

26 : 9-[3-(4-fluorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

27 : 9-[3-(2,5-dimethoxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

28 : 9-[3-(2,4-dichlorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

29 : 9-[3-(3-fluorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

30 : 9-[3-(4-chlorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

31 : 9-(3,3-dimethylbutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

32 : 9-(2-cyclohexylethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

33 : 9-[3-(pyridin-3-yl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

34 : 9-[2-(4-methylsulfonyloxyphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

35 : 9-(3-methylbutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

36 : 9-(3,3-diphenylpropyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

37 : 9-[4-(4-methoxyphenyl)butyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

38 : 9-[4-(4-nitrophenyl)butyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

39 : 9-[3-(2-fluorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

40 : 9-(3-phenylprop-2-ynyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

41 : 9-(3-phenylbutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

42 : 9-[2-(2-chloro-4-fluorophenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

43 : 9-(2-phenyl-2-oxo-ethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

44 : 9-(3-benzyloxypropyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

45 : 9-(3-methylthioethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

46 : 9-[2-(1-naphthyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

47 : 9-[2-(thiophen-2-yl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

48 : 9-[2-(3-trifluoromethylphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

49 : 9-[(2-(thiophen-3-yl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

50 : 9-[2-(2-bromophenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

51 : 9-(4-cyclohexylbutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

52 : 9-[2-(3-bromophenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

53 : 9-[2-(4-*tert*-butylphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

54 : 9-[2-(2,4,6-trimethylphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

55 : 9-[2-(4-ethoxyphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

56 : 9-[2-(2-chloro-6-fluorophenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

57 : 9-[2-(3-chlorophenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

58 : 9-[2-(3-methylphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

59 : 9-(3-methoxybutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

60 : 9-(3-cyclohexylpropyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

61 : 9-[3-[di(phenylmethyl)amino]propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

62 : 9-(2-phenyl-cyclopropylmethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

63 : 9-(3-phenylprop-2-enyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

64 : 9-(2-phenyl-2-hydroxypropyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

65 : 9-[3-(4-fluorophenyl)-3-oxo-propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

66 : 9-(4,4,4-trifluorobutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

67 : 9-[3-phenyl-3-oxo-propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

68 : 9-[3-phenyl-3-hydroxypropyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

69 : 9-[3,3,3-trifluoro-2-hydroxypropyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

70 : (R)-9-[2-phenyl-2-hydroxyethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

71 : (S)-9-[2-phenyl-2-hydroxyethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

72 : 9-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

73 : 9-[1-methyl-2-oxo-2-phenyl-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

74 : 9-[1-methyl-2-hydroxy-2-phenyl-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

75 : 9-[2-(4-methylphenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

76 : 9-[2-(4-chlorophenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

77 : 9-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

78 : 9-[2-(4-phenylphenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

79 : 9-[2-(3-methoxyphenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

80 : 9-[2-(2-naphthyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

81 : 9-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

82 : 9-[2-(3-methoxy-4,5-methylendioxyphenyl)-2-oxo-1-methylethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

83 : 9-[2-(4-methylphenyl)-2-hydroxy-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

84 : 9-[2-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-6-yl)-2-hydroxy-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

85 : 9-[2-(phenylamino)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

86 : 9-[2-(3-chlorophenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

87 : 9-[2-(3-chlorophenyl)-2-hydroxy-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

88 : 9-[2-(3-fluorophenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

89 : 9-[2-(3-fluorophenyl)-2-hydroxy-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

And the compounds of table 2 :

1 : 1-[2-(1*H*-Indol-3-yl)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

2 : 1-[3-(phenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

3 : 1-[3-(1*H*-indol-3-yl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

4 : 1-[2-(phenyl)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

5 : 1-[3-(2-methylphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

6 : 1-[3-(2-methoxyphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

7 : 1-(4-phenylbutyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

8 : 1-[3-(2-chlorophenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

9 : 1-[3-(2,5-dimethoxyphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

10 : 1-[3-(4-methylphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

11 : 1-[3-(3-methoxyphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

12 : 1-[3-(3,4,5-trimethoxyphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

13 : 1-[2-(4-fluorophenoxy)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

14 : 1-[2-(4-chlorophenoxy)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

15 : 1-[3-(2,4-dichlorophenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

16 : 1-[2-(phenylthio)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

17 : 1-(3-phenylpropanoyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

18 : 1-[3-(4-fluorophenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

19 : 1-[3-(3,4-difluorophenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

20 : 1-(2-cyclohexylethyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

21 : 1-(3,3-dimethylbutyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one.

22 : 1-(2-phenyl-2-oxo-ethyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one, and

23 : (S)-1-(4,4,4-trifluoro-3-hydroxybutyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-

a]pyrimidin-5(1*H*)-one.

24 : 1-(4,4,4-trifluoro-but-2-en-1-yl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

25 : 1-[3-(4-trifluoromethylphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

26 : (R)-1-(4,4,4-trifluoro-3-hydroxybutyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

27 : 1-[3-(2-fluorophenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

28 : 1-[2-(2,5-dimethoxy-phenyl)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

29 : 1-[2-(phenylsulfonyl)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

30 : 1-(4,4,4-trifluorobutyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

31 : 1-[3-(pyridin-3-yl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

32 : 1-[2-(2-methoxy)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

33 : 1-[2-(4-chloro-phenyl)-2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

34 : 1-[2-(naphth-2-yl)-2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

35 : 1-[2-(3-methoxy-4,5-methylendioxy-phenyl)-2-oxo-1-methyl-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

36 : 1-[2-(4-phenyl-phenyl)-2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

37 : 1-[2-(4-methylphenyl)2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

38 : 1-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

39 : 1-[2-(4-fluorophenyl)-2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

40 : 1-[2-(3-methoxyphenyl)-2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one.

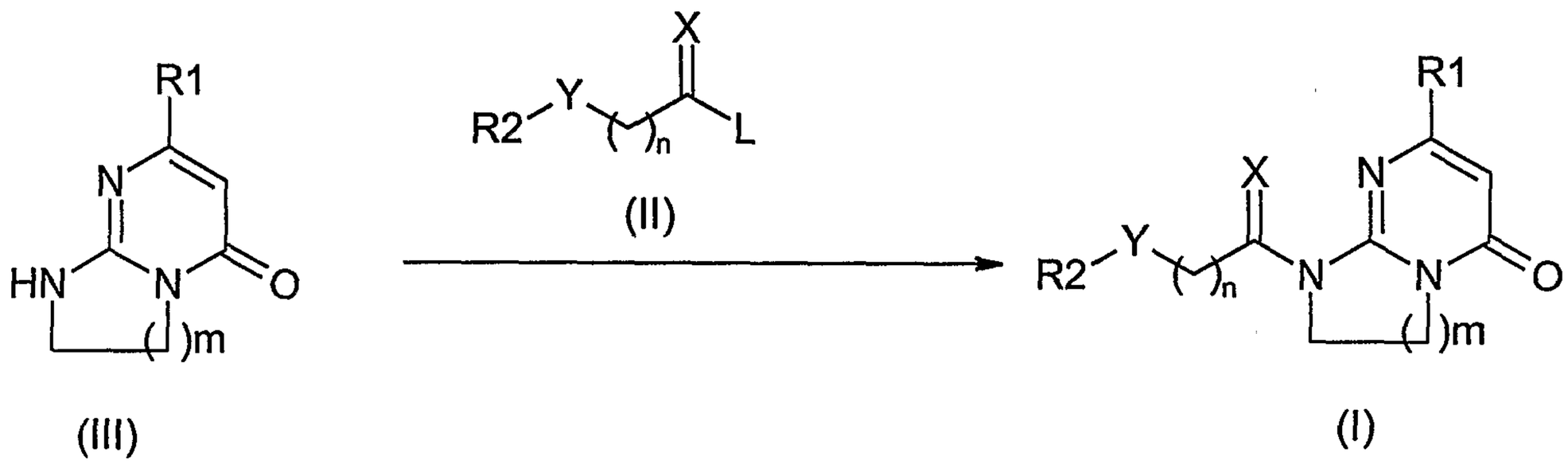
As a further object, the present invention concerns also methods for preparing the pyrimidin-4-onecompounds represented by the aforementioned formula (I).

These compounds can be prepared, for example, according to methods explained below.

Preparation method

2-[1,2-*a*]pyrimidin-4-one compounds represented by the aforementioned formula (I) may be prepared according to scheme 1.

Scheme 1



(In the above scheme the definition of R1, R2, X, Y and n are the same as those already described for compound of formula (I)).

The [1,2-*a*]pyrimidin-4-one derivative represented by the above formula (III), wherein R1 is as defined for compound of formula (I), is allowed to react with a base such as sodium hydride, sodium carbonate or potassium carbonate, in a solvent such as *N,N*-dimethylformamide, *N*-methylpyrrolidine, *N,N*-dimethylacetamide or chloroform, at a suitable temperature ranging from 0 to 130°C under ordinary air, and then with a compound of formula (II), wherein R2, Y and n are as defined for compound of formula (I) and L represents a leaving group, to obtain the compound of the aforementioned formula (I).

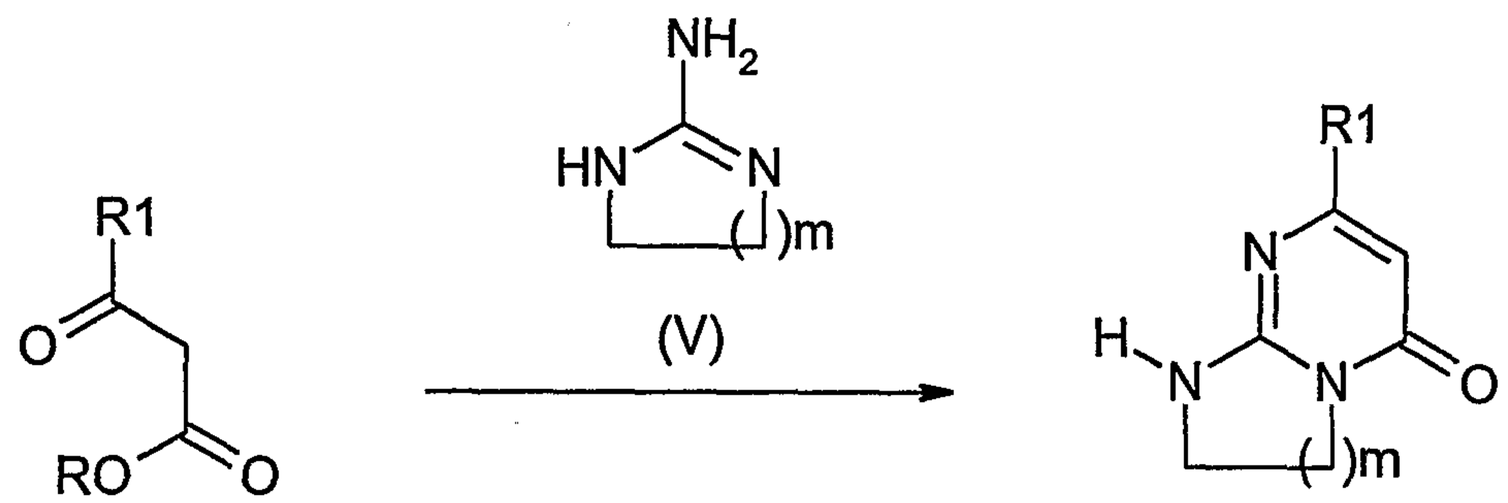
Preferably when X represents hydrogen atoms, L represents a bromide or mesyl group and the reaction is carried out with sodium hydride in *N,N*-dimethylformamide at a suitable temperature ranging from 70 to 130 °C.

Preferably when X represents oxygen atom, L represents a chloride and the reaction is carried out with sodium hydride in chloroform at a suitable temperature ranging from 0 to 70 °C.

Compound of formula (II) is commercially available or may be synthesized according to well-known methods of one skilled in the art.

The compound of formula (III) may be prepared according to the method defined in scheme 2.

Scheme 2



(IV) (III)

(In the above scheme the definition of R1 is the same as already described.)

According to this method, the 3-ketoester of formula (IV) is allowed to react with a compound 2 of formula (V). The reaction may be carried out in an alcoholic solvent such as ethanol, propanol or isopropanol, in presence of a base such as sodium hydride, sodium carbonate or potassium carbonate, at a suitable temperature ranging from 25°-100°C under ordinary air.

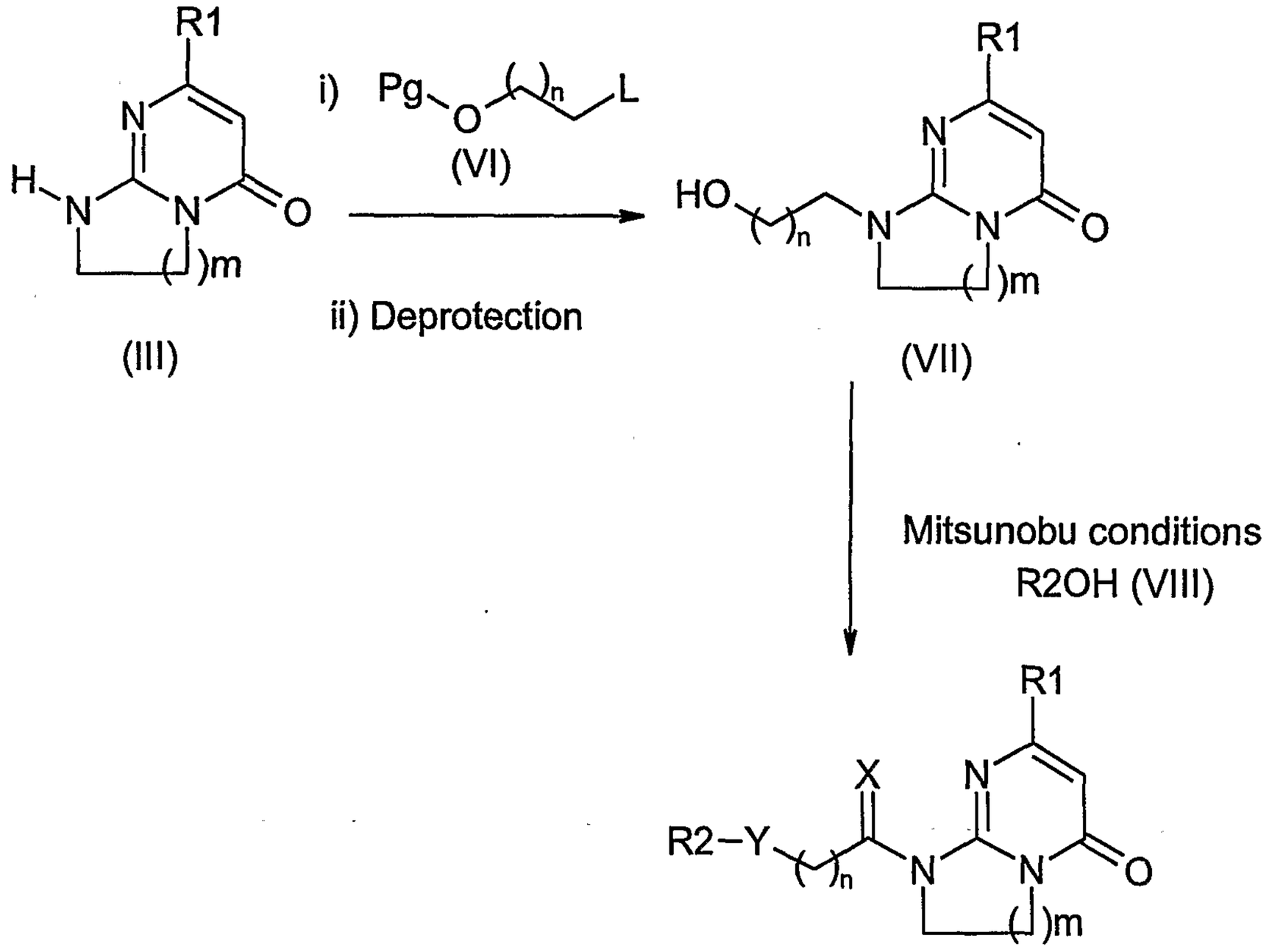
Compound of formula (IV) is commercially available or may be synthesised according to well-known methods of one skilled in the art.

For example compounds of formula (IV), wherein R1 represent a pyridyl group optionally substituted by a C $_{1-4}$ alkyl group, C_{1-4} alkoxy group or a halogen atom, can be prepared by reacting a nicotinic acid optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or an halogen, with a malonic acid monoester. The reaction can be carried out using methods well known to one skilled in the art, such as for example in presence of a coupling agent such as 1,1'-carbonylbis-1*H*-imidazole in a solvent such as tetrahydrofuran at a temperature ranging from 20 to 70°C.

Compound of formula (V) may be synthesised according to the method described by Smith and Christensen (J. Org. Chem. 1955, 20, 829).

Alternatively and when Y represents an oxygen atom, X represents hydrogen atoms and R2 represents an aryl or heteroaryl group, compounds of the aforementioned formula (I) may be prepared according to scheme 3.

Scheme 3



(In the above scheme the definition of R1 is the same as already described.)

According to this method, compounds of formula (III), are allowed to react with a base such as sodium hydride or potassium carbonate in a solvent such as *N,N*-dimethylformamide at a suitable temperature ranging from 70° to 130 °C under ordinary air, then followed by addition compounds of formula (VI), wherein Pg represents a protecting group, preferably a tetrahydropyran, and L represents a leaving group, preferably a bromide. The deprotection is then carried out using methods well known to one skilled in the art, such as for example when the protecting group is a tetrahydropyran group, the deprotection is then carried out in presence of ammonium chloride in a solvent such as methanol at a temperature ranging from 20° to 70°C to give compound of formula (VII). Compounds of formula (I), as defined hereabove, can then be prepared by reacting the compound of formula (VII) with a compound of formula (VIII) using methods well known to one skilled in the art, such as for example in presence of triphenylphosphine and diethylazodicarboxylate as coupling agent in a solvent such tetrahydrofuran at room temperature.

Compounds of formula (VI) and (VIII) are commercially available or may be synthesised according to well-known methods of one skilled in the art.

In the above reactions, protection or deprotection of a functional group may sometimes be necessary. A suitable protecting group Pg can be chosen depending on the type of a functional group, and a method described in the literature may be applied. Examples of protecting groups, of protection and deprotection methods are given for example in *Protective groups in Organic Synthesis* Greene et al., 2nd Ed. (John Wiley & Sons, Inc., New York).

The compounds of the present invention have inhibitory activity against GSK3β.

Accordingly, the compounds of the present invention are useful as an active ingredient for the preparation of a medicament, which enables preventive and/or therapeutic treatment of a disease caused by abnormal GSK3β activity and more particularly of neurodegenerative diseases such as Alzheimer's disease. In addition, the compounds of the present invention are also useful as an active ingredient for the preparation of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases such as Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular

accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma; and other diseases such as non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

The present invention further relates to a method for treating neurodegenerative diseases caused by abnormal activity of GSK3β and of the aforementioned diseases which comprises administering to a mammalian organism in need thereof an effective amount of a compound of the formula (I).

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substances may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of another medicament for the treatment of the above mentioned diseases. The type of pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content ratios of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

The dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Chemical Examples

The present invention will be explained more specifically with reference to the following general examples, however, the scope of the present invention is not limited to these examples.

Example 1 (Compound N° 7 of table 1)

9-[2-(2-Methoxyphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one (Z)-but-2-enedioate (1:1)

1.1. 2-Pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

A mixture of 8.98g (46.5 mmol) of ethyl 3-(4-pyridyl)-3-oxopropionate and 8.0g (46.5 mmol) of 2-amino tetrahydropyrimidine dihydrochloride (prepared according to J. Org. Chem. 1955, 20, 829.) and 19.3g (139.5 mmol) of potassium carbonate in 60ml of ethanol was heated at reflux temperature during 18 h. The cooled solution was evaporated to removed solvent and the residue was treated with water and extracted with dichloromethane. The extracts were dried and evaporated to give 8.0g (75%) of product as a white powder. Mp : 219 °C.

1.2. 9-[2-(2-Methoxyphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one (Z)-but-2-enedioate (1:1)

A suspension of 0.25g (1.09 mmol) of 2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one in 3ml of anhydrous dimethylformamide was treated with 57mg (1.42 mmol) of sodium hydride (60% suspension in mineral oil) and the resulting mixture was heated at 70 °C for 30 min. 0.327g (1.42 mmol) of 1-[2-(methylsulfonyloxy)ethyl]-2-methoxybenzene (prepared according to J. Med. Chem. 1983, 26(1), 42) was added and the reaction mixture was heated at 130 °C during 1h. The cooled solution was treated with water and extracted with ethyl acetate. The organic phase was dried and evaporated to give crude product, which was purified by silica gel chromatography, eluting with dichloromethane/methanol in the proportions 100/0 to 95/5. The 0.338g of pure product obtained in the form of free base was dissolved in hot ethanol and treated with 1 equivalent of (Z)-but-2-enedioïc acid . The cooled solution was filtered to afford 0.325 g (62%) of white solid. Mp : 157-160°C.

Example 2 (Compound N° 4 of table 1)
9-[3-(1*H*-Indol-3-yl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

2.1. 3-(1*H*-Indol-3-yl)propanol (J. Med. Chem. (1995), 38(11), 1998)

To a suspension of 4.8g (126.8 mmol) of lithium aluminium hydride in 240ml of diethylether at 0°C was added dropwise 10g (52.8 mmol) of 3-(1*H*-indol-3-yl)propanoic acid dissolved in 430ml of diethylether and the resulting mixture stirred at room temperature for 1h.
The reaction mixture was diluted with 100ml of diethylether at 0°C and treated with excess of a saturated aqueous solution of sodium sulfate. Further solid sodium sulfate was added and the organic phase was filtered to remove salts. The solvent was evaporated to dryness to give 9g (98%) of product as an oil.

2.2. 3-(1*H*-Indol-3-yl)propyl bromide (Chem. Pharm. Bull. (1988), 36(8), 2853)

To a solution of 2g (11.41 mmol) of 3-(1*H*-indol-3-yl)propanol in 40 ml of dioxane was added at room temperature 5.3g (12.55 mmol) of dibromotriphenylphosphorane and the resulting solution was stirred during 18h. An excess of cyclohexane was added and the resulting precipitate was filtered and discarded. The solvent was evaporated to dryness to give 2.7g (99%) of product as an oil which was used in the subsequent step without further purification.

2.3. 9-[3-(1*H*-Indol-3-yl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
A suspension of 0.30g (1.31 mmol) of 2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one in 8ml of anhydrous dimethylformamide was treated with 68mg (1.44 mmol) of sodium hydride (60% suspension in mineral oil) and the resulting mixture was heated at 70°C for 30 min. 0.407g (1.71 mmol) of 3-(1*H*-indol-3-yl)propyl bromide was added and the reaction mixture was heated at 130 °C during 18h.
The cooled solution was treated with water and extracted with ethyl acetate. The organic phase was dried and evaporated to give crude product which was purified by silica gel chromatography, eluting with dichloromethane/methanol/ammonia in the proportions 98/2/0.2 to 90/10/1 to afford 0.3g (59%) of pure product.
Mp : 230-232°C.

Example 3 (Compound N° 15 of table 1)
9-(2-(2-Methoxyphenoxyethyl))-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one (Z)-but-2-enedioate (1:1)

3.1. 9-(2-Hydroxyethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

A suspension of 0.30g (1.31 mmol) of 2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one in 6ml of anhydrous dimethylformamide was treated with 63mg (1.58 mmol) of sodium hydride (60% suspension in mineral oil) and the resulting mixture was heated at 70 °C for 30 min. 0.329g (1.58 mmol) of 2-(2-bromoethoxy)tetrahydro-2*H*-pyran was added and the reaction mixture was heated at 130°C during 1h.
The cooled solution was treated with water and extracted with ethyl acetate. The organic phase was dried and evaporated to give an oil, which was dissolved in 2ml of methanol and treated with 0.127g of ammonium chloride. The resulting mixture was heated for 18h at reflux temperature.
The cooled solution was evaporated to dryness and the residue treated with water and solid potassium carbonate and extracted with dichloromethane. The organic phase was evaporated to give 0.158g (49%) of product as an oil which was used without further purification.

3.2. 9-(2-(2-Methoxyphenoxyethyl))-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one (Z)-but-2-enedioate (1:1)

To a solution of 0.146g (0.536 mmol) of 9-(2-hydroxyethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one in 4ml of tetrahydrofuran under argon atmosphere, was added 0.197g (0.75 mmol) of triphenylphosphine, 0.080g (0.643 mmol) 2-methoxyphenol and 0.131g (0.75 mmol) of diethylazodicarboxylate. The reaction mixture was stirred for 1h.
The solvent was evaporated and the residue was treated with water and dilute aqueous hydrochloric acid and washed with diethylether. The aqueous phase was neutralised with solid potassium carbonate and extracted with dichloromethane. Evaporation of the organic phase gave crude product, which was purified by chromatography on silica gel, eluting with dichloromethane/methanol/ammonia in the proportions 95/5/0.5 to give 0.080g of product in the form of a free base.
Treatment with 1 equivalent of (Z)-but-2-enedioïc acid in ethanol afforded 0.060g (23%) of product.
Mp : 140-142°C.

Example 4 (Compound N° 25 of table 1) 9-[3-Phenylpropanoyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

A suspension of 0.2g (0.87 mmol) of 2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one in 5ml of chloroform was treated with 26mg (1.14 mmol) of sodium hydride (60% suspension in mineral oil) and the resulting mixture was stirred at room temperature for 15min and then cooled to 0°C. 0.148g (0.964 mmol) of 3-phenylpropionyl chloride was added and the reaction mixture was stirred at room temperature during 18h.
The reaction mixture was washed with a saturated aqueous solution of ammonium chloride and dried and evaporated. The residue was purified by chromatography on silica gel eluting with dichloromethane/methanol in the proportion 100/0 to 95/5 to afford give 0.120mg (38%) of pure product as a white solid.
Mp : 137-140°C.

A list of chemical structures and physical data for compounds of the aforementioned formula (I) illustrating the present invention is given in table 1 and 2. The compounds have been prepared according to the methods of the example.

Example 5 (Compound N° 3 of table 2)
1-[3-(1*H*-Indol-3-yl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one

5.1. 7-Pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one

A mixture containing 8g (41.4 mmol) of ethyl 3-(4-pyridyl)-3-oxopropionate and 14g (164 mmol) of 4,5-dihydro-1*H*-imidazol-2-ylamine in 75 ml of ethanol was heated at reflux temperature during 18 h.
The solvent was evaporated and the crude product was purified by chromatography on silica gel eluting with a mixture of dichloromethane/methanol in the proportions 100/0 to 90/10 to obtain 6.3g of 7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one as free base.
Mp : 318-320°C

5.2. 3-(1*H*-Indol-3-yl)propanol (J. Med. Chem. (1995), 38(11), 1998)

To a suspension of 4.8g (126.8 mmol) of lithium aluminium hydride in 240ml of diethylether at 0°C was added dropwise 10g (52.8 mmol) of 3-(1*H*-indol-3-yl)propanoic acid dissolved in 430ml of diethylether and the resulting mixture stirred at room temperature for 1h.
The reaction mixture was diluted with 100ml of diethylether at 0°C and treated with excess of a saturated aqueous solution of sodium sulfate. Further solid sodium sulfate was added and the organic phase was filtered to remove salts. The solvent was evaporated to dryness to give 9g (98%) of product as an oil.

5.3. 3-(1*H*-Indol-3-yl)propyl bromide (Chem. Pharm. Bull. (1988), 36(8), 2853)

To a solution of 2g (11.41 mmol) of 3-(1*H*-indol-3-yl)propanol in 40 ml of dioxane was added at room temperature 5.3g (12.55 mmol) of dibromotriphenylphosphorane and the resulting solution was stirred during 18h. An excess of cyclohexane was added and the resulting precipitate was filtered and discarded. The solvent was evaporated to dryness to give 2.7g (99%) of product as an oil which was used in the subsequent step without further purification.

5.4. 1-[3-(1*H*-Indol-3-yl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one

To a suspension of 0.19g (0.89 mmol) of 7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one in 10 ml of anhydrous *N,N*-dimethylformamide was added 0.135g (0.97 mmol) of potassium carbonate and the resulting mixture was heated at 130°C during 10min. There is added 0.232g (0.97 mmol) of 3-(1*H*-indol-3-yl)propyl bromide and heating is continued for 3 h.
The cooled suspension is treated with water, extracted with ethyl acetate and the organic extracts dried over sodium sulfate. The crude product was purified by chromatography on silica gel eluting with a mixture dichloromethane/methanol/ammonia in the ratio 90/10/1 to afford 0.18g of pure product.
Mp : 218-220°C.

Example 6 (Compound N°16 of table 2)
1-[2-(Phenylthio)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one hydrochloride (1:1)

To a suspension of 0.2g (0.93 mmol) of 7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one in ml of anhydrous *N,N*-dimethylformamide was added 48.5mg (1.21 mmol) of sodium hydride (60% suspension in mineral oil) and the resulting mixture was heated at 70°C during 30min. There was added 0.32g (1.49 mmol) of 2-bromoethyl phenyl sulphide and heating was continued at 130°C during 1 h.
Water was added to the cooled mixture and the resulting solution extracted with ethyl acetate. The combined extracts were washed with water and evaporated. The crude product was purified by chromatography on silica gel eluting with a mixture of dichloromethane/methanol/diethylamine in the proportions 98/2/0.2 to obtain pure compound as free base. The compound was converted to the hydrochloride salt by addition of hydrochloric acid to an isopropylic solution of the free base. There is obtained 0.11g of product as a yellow solid.
Mp : 199-202°C

Example 7 (Compound N°14 of table 2)
1-[2-(4-Chlorophenoxy)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one hydrochloride (1:1)

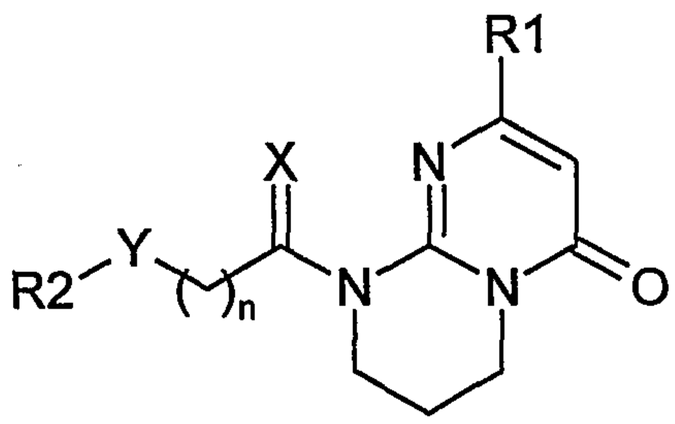
To a suspension of 0.2 g (0.93 mmol) of 7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a]*pyrimidin-5(1*H*)-one in 5 ml of anhydrous *N,N*-dimethylformamide was added 48.5mg (1.21 mmol) of sodium hydride (60% suspension in mineral oil) and the resulting mixture was heated at 70°C for 30 min. 0.351g (1.49 mmol) of 2-(4-chlorophenoxy)ethyl bromide was added and the reaction mixture was heated at 130 °C during 18h.
Water was added to the cooled mixture and the resulting solution extracted with ethyl acetate. The combined extracts were washed with water and evaporated. The crude product was purified by chromatography on silica gel eluting with a mixture of dichloromethane/methanol in the proportions 100/0 to 96/4 to obtain pure compound as free base. The compound was converted to the hydrochloride salt by addition of hydrochloric acid to an ethanolic solution of the free base. There is obtained 0.24g of product as a yellow solid.
Mp : 211-213°C

Example 8 (Compound N°17 of table 2)
1-[-(3-Phenyl)propanoyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one

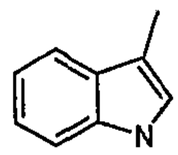
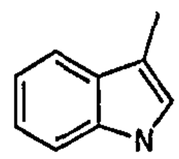
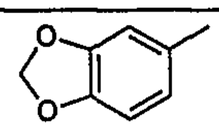
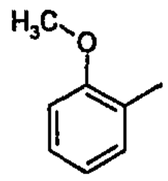
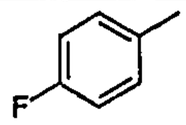
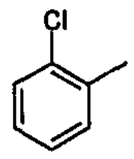
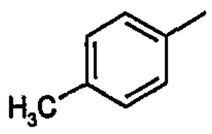
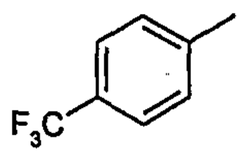
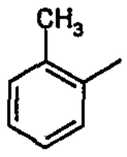
A suspension of 0.2g (0.93 mmol) of 7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one in 5ml of *N,N*-dimethylformamide was treated with 48mg (1.20 mmol) of sodium hydride (60% suspension in mineral oil) and the resulting mixture was stirred at room temperature for 15min and then cooled to 0°C. 0.251g (1.49 mmol) of 3-phenylpropionyl chloride was added and the reaction mixture was stirred at room temperature during 18h.
The reaction mixture was washed with a saturated aqueous solution of ammonium chloride and dried and evaporated. The residue was purified by chromatography on silica gel eluting with dichloromethane/methanol in the proportion 100/0 to 95/5 to afford give 0.2g of pure product as a white solid.
Mp : 171-172°C.

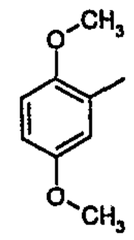
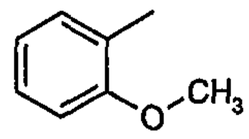
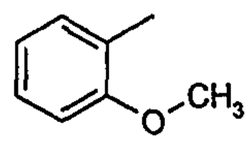
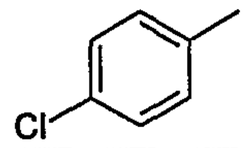
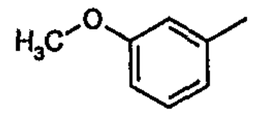
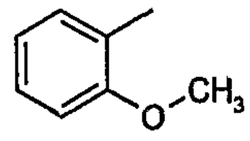
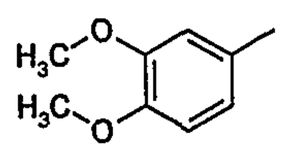
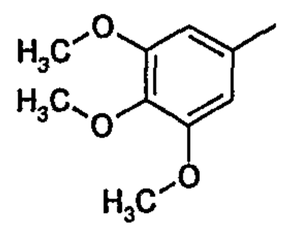
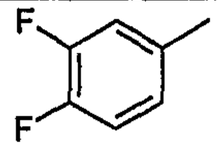
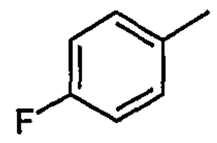
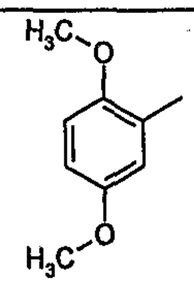
In the table, R1 is an unsubstituted 4-pyridyl group, Ph represents a phenyl group, in the column "X", when X represents two hydrogen atoms, only "H" is indicated, and in the column R2 , "___" indicates the bond attached to the Y group.

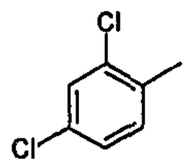
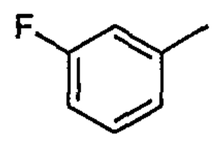
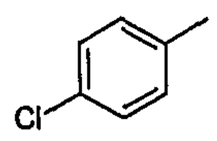
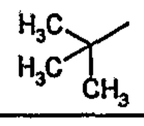
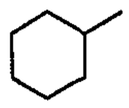
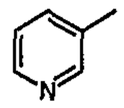
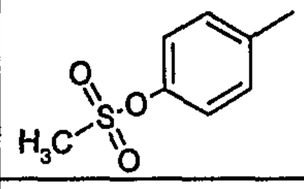
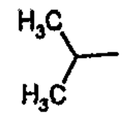
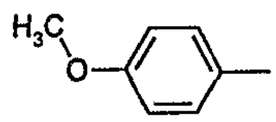
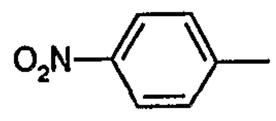
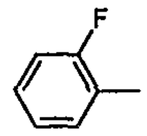
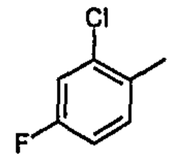
Table 1

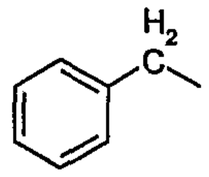
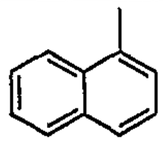
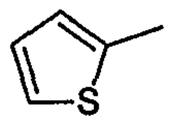
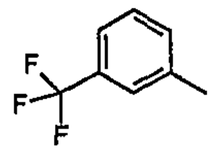
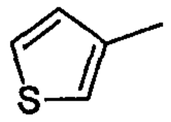
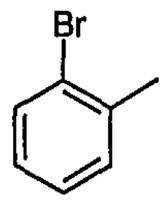
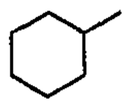
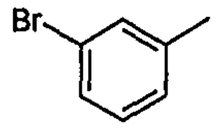
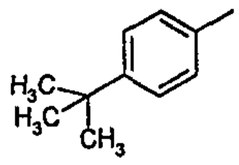
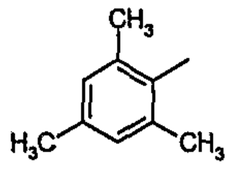
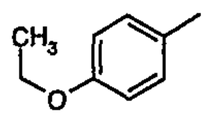
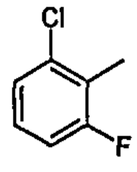


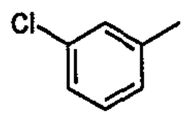
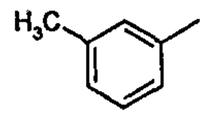
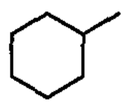
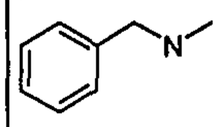
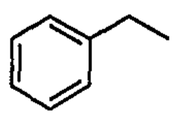
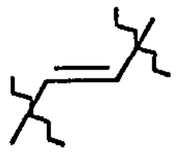
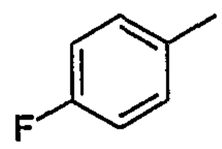
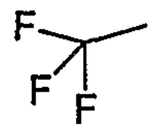
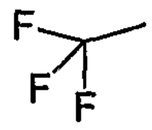
(I)

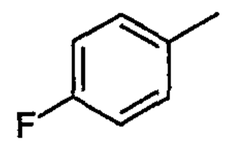
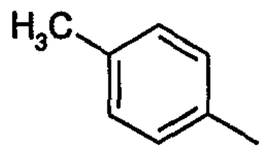
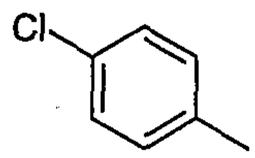
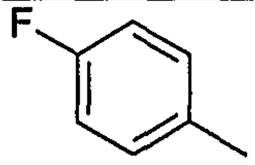
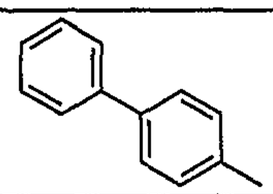
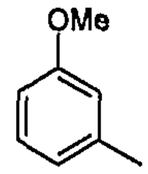
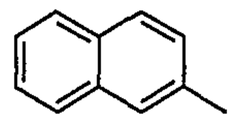
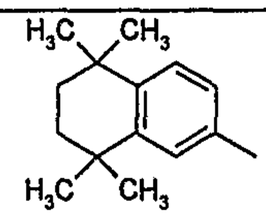
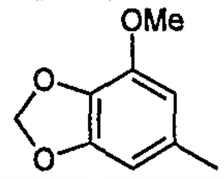
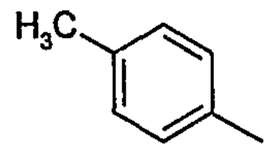
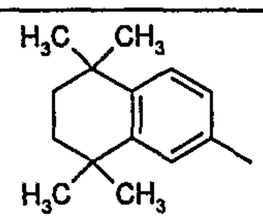
N°	X	Y	R2	n	Mp °C	salt
1	H	CH_2		0	217-219	(1:1) (+/-) 2,3-dihydroxy butanedioate
2	H	CH_2	Ph	1	130-132	(1:1) (Z)-but-2-enedioate
3	H	CH_2	Ph	0	141-143	(1:1) (Z)-but-2-enedioate
4	H	CH_2		1	230-232	base
5	H	O	Ph	1	190-192	(1:1) (Z)-but-2-enedioate
6	H	CH_2		1	150-152	(1:1) (Z)-but-2-enedioate
7	H	CH_2		0	157-160	(1:1) (Z)-but-2-enedioate
8	H	O		1	161-163	(1:1) (Z)-but-2-enedioate
9	H	CH_2		1	128-130	(1:1) (Z)-but-2-enedioate
10	H	CH_2		1	157-159	(1:1) (Z)-but-2-enedioate
11	H	CH_2		1	160-162	(1:1) (Z)-but-2-enedioate
12	H	CH_2	Ph	2	156-158	(1:1) (Z)-but-2-enedioate
13	H	CH_2		1	160-162	(1:1) (Z)-but-2-enedioate

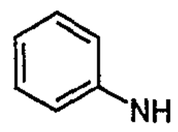
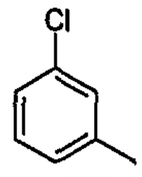
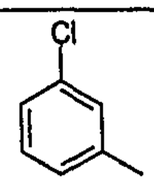
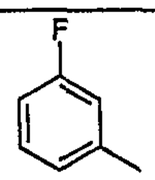
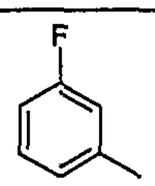
N°	X	Y	R2	n	Mp °C	salt
14	H	CH_2		0	160-162	(1:1) (Z)-but-2-enedioate
15	H	O		1	140-142	(1:1) (Z)-but-2-enedioate
16	H	CH_2		1	153-155	(1:1) (Z)-but-2-enedioate
17	H	O		1	223-225	(1:1) hydrochloride
18	H	CH_2		1	238-240	(1:1) hydrochloride
19	H	bond		0	258-260	(1:1) hydrochloride
20	H	S	Ph	1	215-217	(1:1) hydrochloride
21	H	CH_2		1	176-178	(1:1) hydrochloride
22	H	CH_2		1	225-227	(1:1) hydrochloride
23	H	SO_2	Ph	1	254-256	(1:1) hydrochloride
24	H	CH_2		1	215-217	(1:1) hydrochloride
25	O	CH_2	Ph	1	137-140	base
26	H	CH_2		1	245-247	(1:1) hydrochloride
27	H	CH_2		1	245-247	(1:1) hydrochloride

N°	X	Y	R2	n	Mp °C	salt
28	H	CH_2		1	208-210	(1:1) hydrochloride
29	H	CH_2		1	221-223	(1:1) hydrochloride
30	H	CH_2		1	222-224	(1:1) hydrochloride
31	H	CH_2		0	166-167	base
32	H	CH_2		0	134-135	base
33	H	CH_2		1	81.5	base
34	H	CH_2		0	148.8	base
35	H	CH_2		0	137.4	base
36	H	PhCH	Ph	1	154.3	base
37	H	CH_2		2	89.3	base
38	H	CH_2		2	140.4	base
39	H	CH_2		1	243-245	(1:1) hydrochloride
40	H	≡	Ph	0	235-237	(1:1) hydrochloride
41	H	$CHCH_3$	Ph	1	222-224	(1:1) hydrochloride
42	H	CH_2		0	268-272	(1:1) hydrochloride
43	H	CO	Ph	0	284-286	(1:1) hydrochoride

N°	X	Y	R2	n	$[M+H]^+$ Observed	salt
44	H	O		2	391	base
45	H	CH_2	SMe	2	331	base
46	H	CH_2		0	383	base
47	H	CH_2		0	339	base
48	H	CH_2		0	401	base
49	H	CH_2		0	339	base
50	H	CH_2		0	412	base
51	H	CH_2		2	367	base
52	H	CH_2		0	412	base
53	H	CH_2		0	389	base
54	H	CH_2		0	375	base
55	H	CH_2		0	377	base
56	H	CH_2		0	385	base

N°	X	Y	R2	n	$[M+H]^+$ Observed	salt
57	H	CH_2		0	367	base
58	H	CH_2		0	347	base
59	H	$CHCH_3$	OCH_3	1	315	base
60	H	CH_2		1	353	base
61	H			2	466	Base
62	H	racemate	Ph	0	213-216	Hydrochloride
63	H		Ph	0	264-266	Hydrochloride
64	H	$C(OH)(CH_3)$ racemate	Ph	0	126-129	(Z)-but-enedioate
65	H	CO		1	226-229	hydrochloride
66	H	CH_2		1	254-256	hydrochloride
67	H	CO	Ph	1	136-138	(Z)-but-enedioate
68	H	CH(OH) racemate	Ph	1	147-149	base
69	H	CH(OH) racemate		0	248-250	hydrochloride
70	H	CH(OH) (+)-(R)	Ph	0	232-234	hydrochloride
71	H	CH(OH) (-)-(S)	Ph	0	220-222	hydrochloride

N°	X	Y	R2	n	$[M+H]^+$ Observed	salt
72	H	CH(OH) racemate		1	145-147	base
73*	H, CH_3 (rac)	CO	Ph	0	194-196	hydrochloride
74*	H, CH_3 (rac)	CH(OH) racemate	Ph	0	232-234	base
75	H	CO		0	263-264	hydrochloride
76	H	CO		0	247	hydrochloride
77	H	CO		0	245	hydrochloride
78	H	CO		0	140-141	hydrochloride
79	H	CO		0	204-205	hydrochloride
80	H	CO		0	217-218	hydrochloride
81	H	CO		0	209-210	Hydrochloride
82*	H, CH_3 (rac)	CO		0	233-234	hydrochloride
83	H	CH(OH) racemate		0	157-158	base
84	H	CH(OH) racemate		0	248-249	Base

N°	X	Y	R2	n	[M+H]+ Observed	salt
85	H	CO		0	220-222	Base
86	H	CO		0	263-265	hydrochloride
87	H	CH(OH) racemate		0	172-174	base
88	H	CO		0	273-275	hydrochloride
89	H	CH(OH) racemate		0	96-98	base

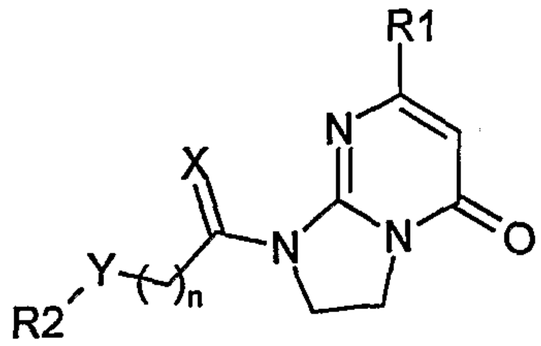
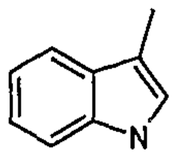
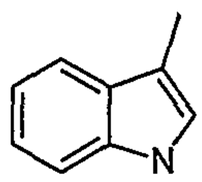
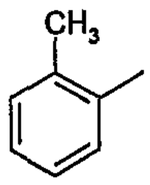
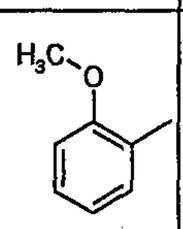
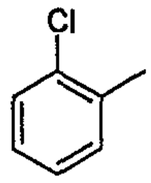
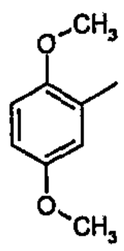
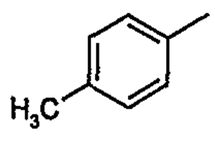
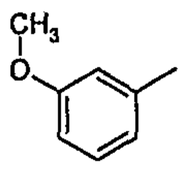
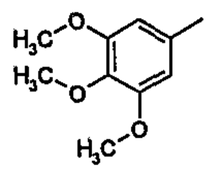
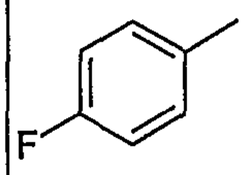
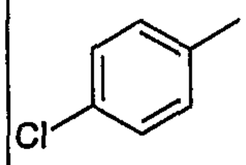
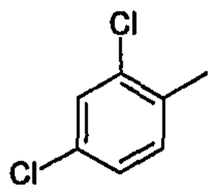
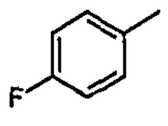
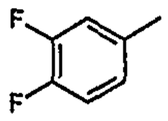
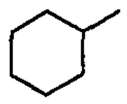
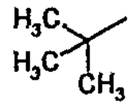
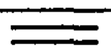
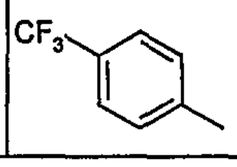
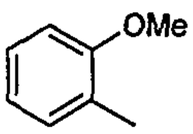
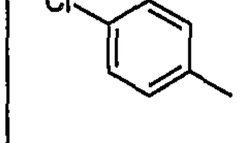
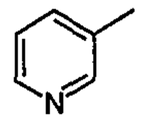
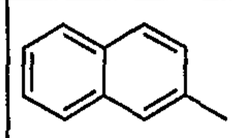
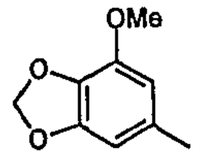
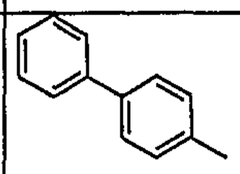
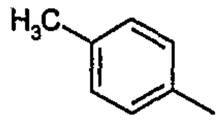
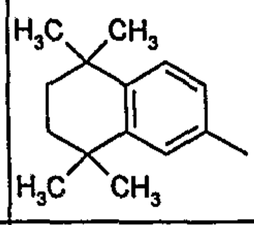
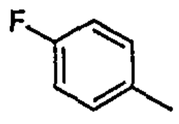
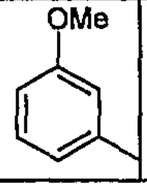


Table 2

N°	R1	Y	X	R2	n	Mp °C	salt
1	4-py	CH_2	H		0	205-207	(Z)-but-enedioate
2	4-py	CH_2	H	Ph	1	258-260	(Z)-but-enedioate
3	4-py	CH_2	H		1	218-220	base
4	4-py	CH_2	H	Ph	0	158-160	(Z)-but-enedioate
5	4-py	CH_2	H		1	224-225	hydrochloride
6	4-py	CH_2	H		1	228-229	hydrochloride
7	4-py	CH_2	H	Ph	2	238.5-240	hydrochloride
8	4-py	CH_2	H		1	222-223	hydrochloride
9	4-py	CH_2	H		1	208-209	hydrochloride
10	4-py	CH_2	H		1	227-228	hydrochloride
11	4-py	CH_2	H		1	190-191	hydrochloride

N°	R1	Y	X	R2	n	Mp °C	Salt
12	4-py	CH_2	H		1	197-201	hydrochloride
13	4-py	O	H		1	205-207	hydrochloride
14	4-py	O	H		1	211-213	Hydrochloride
15	4-py	CH_2	H		1	207-208	hydrochloride
16	4-py	S	H	Ph	1	199-202	hydrochloride
17	4-py	CH_2	O	Ph	1	170	base
18	4-py	CH_2	H		1	251-252	hydrochloride
19	4-py	CH_2	H		1	187-188	hydrochloride
20	4-py	CH_2	H		0	117-118	base
21	4-py	CH_2	H		0	142-143	base
22	4-py	CO	H	Ph	0	252-256	hydrochloride
23	4-py	CH(OH) (S)	H	CF_3	1	191-192	base
24	4-py	 (trans)	H	CF_3	0	136-138	base
25	4-py	CH_2	H		1	136-137	base

N°	R1	Y	X	R2	n	Mp °C	Salt
26	4-py	CH(OH) (R)	H	CF_3	1	187-189	base
27	4-py	CH_2	H		1	201-203	hydrochloride
28	4-py	CH_2	H		0	221-223	hydrochloride
29	4-py	SO_2	H	Ph	1	261-264	base
30	4-py	CH_2	H	CF_3	1	261-263	hydrochloride
31	4-py	CH_2	H		1	186-187	hydrochloride
32	4-py	CH_2	H		0	240-242	hydrochloride
33	4-py	CO	H		0	241-242	hydrochloride
34	4-py	CO	H		0	284-285	hydrochloride
35	4-py	CO	CH_3 (Rac)		0	252-253	hydrochloride
36	4-py	CO	H		0	238-239	hydrochloride
37	4-py	CO	H		0	226-227	hydrochloride
38	4-py	CO	H		0	233-234	Hydrochloride
39	4-py	CO	H		0	250-251	Hydrochloride
40	4-py	CO	H		0	238-239	hydrochloride

Test Example: Inhibitory activity of the medicament of the present invention against GSK3β:

Two different protocols can be used.

In a first protocol : 7.5 µM of prephosphorylated GS1 peptide and 10 µM ATP (containing 300,000 cpm of 33P-ATP) were incubated in 25 mM Tris-HCl, pH 7.5, 0.6 mM DTT, 6 mM $MgCl_2$, 0.6 mM EGTA, 0.05 mg/ml BSA buffer for 1 hour at room temperature in the presence of GSK3beta (total reaction volume : 100 microliters).

In a second protocol : 4.1 µM of prephosphorylated GS1 peptide and 42 µM ATP (containing 260,000 cpm 33P-ATP) were incubated in 80 mM Mes-NaOH, pH 6.5, 1 mM Mg acetate, 0.5 mM EGTA, 5 mM 2-mercaptoethanol, 0.02% Tween 20, 10% glycerol buffer for 2 hours at room temperature in the presence of GSK3beta.
Inhibitors were solubilised in DMSO (final solvent concentration in the reaction medium, 1%).

The reaction was stopped with 100 microliters of a solution made of 25 g polyphosphoric acid (85% P_2O_5), 126 ml 85% H_3PO_4, H_2O to 500 ml and then diluted to 1:100 before use. An aliquot of the reaction mixture was then transferred to Whatman P81 cation exchange filters and rinsed with the solution described above. Incorporated 33P radioactivity was determined by liquid scintillation spectrometry.
The phosphorylated GS-1 peptide had the following sequence :
NH2-YRRAAVPPSPSLSRHSSPHQS(P)EDEE-COOH.

The GSK3β inhibitory activity of the compounds of the present invention are expressed in IC_{50}, and as an illustration the range of IC_{50}'s of the compounds in table 1 is between 2 nanomolar to 1 micromolar concentrations.

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

(1) Parenteral preparations

The ingredients below were mixed by an ordinary method to prepare injections contained in a 1 ml ampoule.

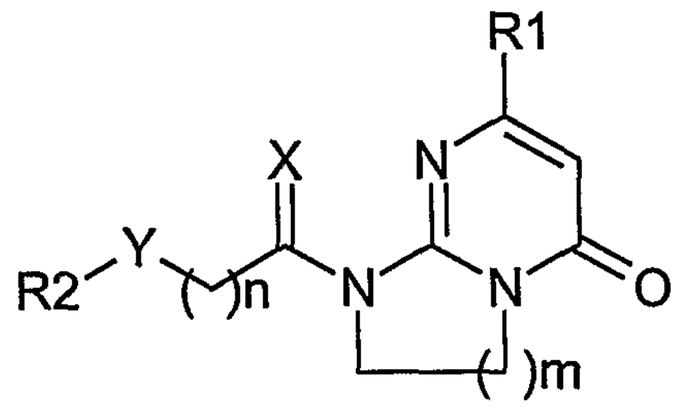
Compound of Example 1	3 mg
Sodium chloride	4 mg
Distilled water for injection	1 ml

Industrial Applicability

The compounds of the present invention have GSK3β inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal activity of GSK3β .

What is claimed is:

1. A pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



(I)

wherein:

X represents hydrogen atoms, a sulphur atom, an oxygen atom or a C_{1-2} alkyl group and a hydrogen atom;

Y represents a bond, an ethenylene group, an ethynylene group, a 1,2-cyclopropylene, an oxygen atom, a sulphur atom, a sulfonyl group, a sulfinyl group, a carbonyl group, a nitrogen atom being optionally substituted by a C_{1-6} alkyl group, a phenyl or a benzyl group; or a methylene group optionally substituted by one or two groups chosen from a C_{1-6} alkyl group, a phenyl group, a hydroxyl group or a C_{1-4} alkoxy group;

R1 represents a 2, 3 or 4-pyridyl group optionally substituted by a C_{3-6} cycloalkyl group a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a benzyl group or a halogen atom;

when Y represents a bond, a methylene group optionally substituted or a carbonyl group then R2 represents a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group, a C_{1-4} alkylthio group, a C_{1-4} alkoxy group, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a 5,6,7,8-tetrahydronaphthyl ring, a naphthyl ring, a phenylthio group, a benzyl group, a phenyl ring, a pyridyl ring, an indole ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring ; the benzyl group or the rings being optionally substituted by 1 to 4 substituents selected from a C_{1-6} alkyl group, a methylendioxy group, a halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a hydroxyl group, a C_{1-4} alkoxy group, a nitro, a cyano, an amino, a C_{1-5} monoalkylamino group, a C_{2-10} dialkylamino group, a C_{1-6} alkylcarbonylamino group, a $C_{6,10}$ arylcarbonylamino group, a C_{1-4} alkylsulfonyl group, C_{1-4} alkylsulfonyloxy group or a phenyl group;

when Y represents an ethenylene group, an ethynylene group, an oxygen atom, a sulphur atom, a sulfonyl group, a sulfoxyde group or a nitrogen atom being optionally substituted then R2 represents a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a naphthyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a benzyl group, a phenyl ring, a pyridyl ring, an indole ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring; the benzyl group or the rings being optionally substituted by 1 to 4 substituents selected from a C_{1-6} alkyl group, a methylendioxy group, a halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a hydroxyl group, a C_{1-4} alkoxy group, a nitro, a cyano, an amino, a C_{1-5} monoalkylamino group, a C_{2-10} dialkylamino group, a C_{1-6} alkylcarbonylamino group, a $C_{6,10}$ arylcarbonylamino group, a C_{1-4} alkylsulfonyl group, C_{1-4} alkylsulfonyloxy group or a phenyl group;

m represents 1 or 2;

and n represents 0 to 3.

2. A pyrimidone derivative or a salt thereof or a solvate thereof or a hydrate thereof according to claim 1, wherein R1 represents an unsubstituted 4-pyridyl group.

3. A pyrimidone derivative or a salt thereof or a solvate thereof or a hydrate thereof according to claim 1 or 2, wherein R2 represents a C_{1-4} alkyl group, C_{1-2} alkylthio group, C_{1-2} alkoxy group, a trifluoromethyl group, a C_{5-6} cycloalkyl group, a naphthyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a phenyl ring, a pyridyl ring, an indole ring, a thiophene ring; the rings being optionally substituted by 1 to 4 substituents.

4. A pyrimidone derivative which is selected from the group consisting of :

1 : 9-[2-(1*H*-indol-3-yl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

2 : 9-(3-phenylpropyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

3 : 9-(2-phenylethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

4 : 9-[3-(1*H*-indol-3-yl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

5 : 9-(2-phenoxyethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

6 : 9-[3-(3,4-methylenedioxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

7 : 9-[2-(2-methoxyphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

8 : 9-[2-(4-fluorophenoxyethyl)]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

9 : 9-[3-(2-chlorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

10 : 9-[3-(4-methylphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

11 : 9-[3-(4-trifluoromethylphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

12 : 9-(4-phenylbutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

13 : 9-[3-(2-methylphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

14 : 9-[2-(2,5-dimethoxyphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

15 : 9-[2-(2-methoxyphenoxy)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

16 : 9-[3-(2-methoxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

17 : 9-[2-(4-chlorophenoxy)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

18 : 9-[3-(3-methoxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

19 : 9-(2-methoxyphenylmethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

20 : 9-[2-phenylthioethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

21 : 9-[3-(3,4-dimethoxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

22 : 9-[3-(3,4,5-trimethoxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

23 : 9-[2-(phenylsulfonyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

24 : 9-[3-(3,4-fluorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

25 : 9-[3-phenylpropanoyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

26 : 9-[3-(4-fluorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

27 : 9-[3-(2,5-dimethoxyphenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

28 : 9-[3-(2,4-dichlorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

29 : 9-[3-(3-fluorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

30 : 9-[3-(4-chlorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

31 : 9-(3,3-dimethylbutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

32 : 9-(2-cyclohexylethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

33 : 9-[3-(pyridin-3-yl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

34 : 9-[2-(4-methylsulfonyloxyphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

35 : 9-(3-methylbutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

36 : 9-(3,3-diphenylpropyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

37 : 9-[4-(4-methoxyphenyl)butyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

38 : 9-[4-(4-nitrophenyl)butyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

39 : 9-[3-(2-fluorophenyl)propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

40 : 9-(3-phenylprop-2-ynyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

41 : 9-(3-phenylbutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

42 : 9-[2-(2-chloro-4-fluorophenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

43 : 9-(2-phenyl-2-oxo-ethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

44 : 9-(3-benzyloxypropyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

45 : 9-(3-methylthioethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

46 : 9-[2-(1-naphthyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

47 : 9-[2-(thiophen-2-yl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

48 : 9-[2-(3-trifluoromethylphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

49 : 9-[(2-(thiophen-3-yl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

50 : 9-[2-(2-bromophenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

51 : 9-(4-cyclohexylbutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

52 : 9-[2-(3-bromophenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

53 : 9-[2-(4-*ter*-butylphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

54 : 9-[2-(2,4,6-trimethylphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

55 : 9-[2-(4-ethoxyphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

56 : 9-[2-(2-chloro-6-fluorophenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

57 : 9-[2-(3-chlorophenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

58 : 9-[2-(3-methylphenyl)ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

59 : 9-(3-methoxybutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

60 : 9-(3-cyclohexylpropyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

61 : 9-[3-[di(phenylmethyl)amino]propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

62 : 9-(2-phenyl-cyclopropylmethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

63 : 9-(3-phenylprop-2-enyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

64 : 9-(2-phenyl-2-hydroxypropyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

65 : 9-[3-(4-fluorophenyl)-3-oxo-propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

66 : 9-(4,4,4-trifluorobutyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

67 : 9-[3-phenyl-3-oxo-propyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

68 : 9-[3-phenyl-3-hydroxypropyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

69 : 9-[3,3,3-trifluoro-2-hydroxypropyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

70 : (R)-9-[2-phenyl-2-hydroxyethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

71 : (S)-9-[2-phenyl-2-hydroxyethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

72 : 9-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

73 : 9-[1-methyl-2-oxo-2-phenyl-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

74 : 9-[1-methyl-2-hydroxy-2-phenyl-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

75 : 9-[2-(4-methylphenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

76 : 9-[2-(4-chlorophenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

77 : 9-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

78 : 9-[2-(4-phenylphenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

79 : 9-[2-(3-methoxyphenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

80 : 9-[2-(2-naphthyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

81 : 9-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronapht-2-yl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

82 : 9-[2-(3-methoxy-4,5-methylendioxyphenyl)-2-oxo-1-methylethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

83 : 9-[2-(4-methylphenyl)-2-hydroxy-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

84 : 9-[2-(1,1,4,4,-tetramethyl-1,2,3,4-tetrahydronapht-6-yl)-2-hydroxy-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

85 : 9-[2-(phenylamino)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

86 : 9-[2-(3-chlorophenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

87 : 9-[2-(3-chlorophenyl)-2-hydroxy-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

88 : 9-[2-(3-fluorophenyl)-2-oxo-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one; and

89 : 9-[2-(3-fluorophenyl)-2-hydroxy-ethyl]-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one;

or a salt thereof or a solvate thereof or a hydrate thereof.

5. A pyrimidone derivative which is selective from the group consisting of :

1 : 1-[2-(1*H*-Indol-3-yl)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

2 : 1-[3-(phenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

3 : 1-[3-(1*H*-indol-3-yl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

4 : 1-[2-(phenyl)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

5 : 1-[3-(2-methylphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

6 : 1-[3-(2-methoxyphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

7 : 1-(4-phenylbutyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

8 : 1-[3-(2-chlorophenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

9 : 1-[3-(2,5-dimethoxyphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

10 : 1-[3-(4-methylphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

11 : 1-[3-(3-methoxyphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

12 : 1-[3-(3,4,5-trimethoxyphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

13 : 1-[2-(4-fluorophenoxy)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

14 : 1-[2-(4-chlorophenoxy)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

15 : 1-[3-(2,4-dichlorophenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

16 : 1-[2-(phenylthio)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

17 : 1-(3-phenylpropanoyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

18 : 1-[3-(4-fluorophenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

19 : 1-[3-(3,4-difluorophenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

20 : 1-(2-cyclohexylethyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

21 : 1-(3,3-dimethylbutyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one.

22 : 1-(2-phenyl-2-oxo-ethyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one, and

23 : (S)-1-(4,4,4-trifluoro-3-hydroxybutyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one.

24 : 1-(4,4,4-trifluoro-but-2-en-1-yl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

25 : 1-[3-(4-trifluoromethylphenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

26 : (R)-1-(4,4,4-trifluoro-3-hydroxybutyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

27 : 1-[3-(2-fluorophenyl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

28 : 1-[2-(2,5-dimethoxy-phenyl)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,

29 : 1-[2-(phenylsulfonyl)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,
30 : 1-(4,4,4-trifluorobutyl)-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,
31 : 1-[3-(pyridin-3-yl)propyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,
32 : 1-[2-(2-methoxy)ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,
33 : 1-[2-(4-chloro-phenyl)-2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,
34 : 1-[2-(napht-2-yl)-2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,
35 : 1-[2-(3-methoxy-4,5-methylendioxy-phenyl)-2-oxo-1-methyl-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,
36 : 1-[2-(4-phenyl-phenyl)-2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,
37 : 1-[2-(4-methylphenyl)2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,
38 : 1-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronapht-2-yl)2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one,
39 : 1-[2-(4-fluorophenyl)-2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one, and
40 : 1-[2-(3-methoxyphenyl)-2-oxo-ethyl]-7-pyridin-4-yl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one;

or a salt thereof or a solvate thereof or a hydrate thereof.

6. A medicament comprising as an active ingredient a substance selected from the group consisting of a pyrimidone derivative according to claim 1.

7. A GSK3β inhibitor selected from the group of a pyrimidone derivative represented by formula (I) or a salt thereof or a solvate thereof or a hydrate thereof according to claim 1.

8. Use of a pyrimidone derivative according to any one of claims 1 to 5 for the preparation of a medicament for preventive and/or therapeutic treatment of a disease caused by abnormal GSK3β activity.

9. Use of a pyrimidone derivative according to any one of claims 1 to 5 for the preparation of a medicament for preventive and/or therapeutic treatment of a neurodegenerative disease.

10. Use of a compound according to claim 9, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, tauopathies, vascular dementia; acute stroke, traumatic injuries; cerebrovascular accidents, brain cord trauma, spinal cord trauma; peripheral neuropathies; retinopathies or glaucoma.

11. Use of a compound according to any one of claims 1 to 5 for the preparation of a medicament for preventive and/or therapeutic treatment of non-insulin dependent diabetes; obesity; manic depressive illness; schizophrenia; alopecia; or cancers.

12. Use according to claim 11 wherein cancer is breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia or virus-induced tumors.