(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 May 2007 (10.05.2007)

PCT

(10) International Publication Number
WO 2007/052541 A1

(51) International Patent Classification:
C07D 211/22 (2006.01) *A61K 31/445* (2006.01)
C07D 211/94 (2006.01)

(21) International Application Number:
PCT/JP2006/321443

(22) International Filing Date: 20 October 2006 (20.10.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2005-319382 2 November 2005 (02.11.2005) JP

(71) Applicant *(for all designated States except US)*: **Eisai R & D Management Co., Ltd.** [JP/JP]; 6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo, 1128088 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **IIMURA, Yoichi** [JP/JP]; c/o Tsukuba Research Laboratories, Eisai Co., Ltd., 1-3, Tokodai 5-chome, Tsukuba-shi, Ibaraki, 3002635 (JP). **MATSUI, Kenji** [JP/JP]; c/o Tsukuba Research Laboratories, Eisai Co., Ltd., 1-3, Tokodai 5-chome, Tsukuba-shi, Ibaraki, 3002635 (JP).

(74) Agents: **ASAMURA, Kiyoshi** et al.; Room 331, New Ohtemachi Bldg., 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo, 1000004 (JP).

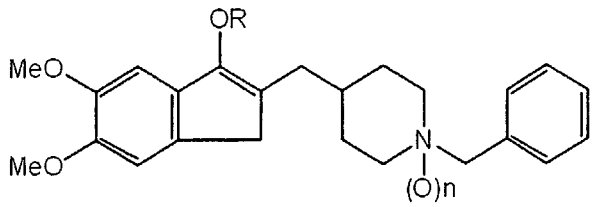
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PRODRUG OF DONEPEZIL HYDROCHLORIDE



(57) Abstract: A compound represented by the general formula: wherein R is an optionally substituted C1-6 alkyl group and the like, and n is an integer of 0 or 1, or a pharmaceutically acceptable salt thereof is expected to be effective in the remission and reduction of side effects (e.g. vomit, diarrhea and nightmare) observed in some cases after the administration of donepezil hydrochloride.

WO 2007/052541 A1

DESCRIPTION

PRODRUG OF DONEPEZIL HYDROCHLORIDE

Technical Field

The present invention relates to a novel prodrug of donepezil hydrochloride, which is a therapeutic agent for Alzheimer type dementia, a process for production thereof and a pharmaceutical composition containing them.

Background Art

In recent years, senile dementia represented by Alzheimer type dementia has become a serious problem with a growth of the aged population, and the development of an excellent therapeutic agent for senile dementia is eagerly desired.

It has been reported that in case of Alzheimer type dementia, the amounts of neurotransmitters such as acetylcholine, norepinephrine and serotonin are decreased with the accumulation of β-amyloids. The cholinesterase inhibitor that controlled the decomposition of the acetylcholine was developed by focusing attention on the close relation to the decrease in the cognitive function including the memory to the degeneration of cholinergic neuron. The cholinesterase inhibitors used as a therapeutic agent for Alzheimer type dementia includes donepezil

hydrochloride, rivastigmine and galantamine, etc.

Among these acetylcholine inhibitors, donepezil hydrochloride is an excellent therapeutic agent characterized by a few peripheral side effect based on the high selectivity of acetylcholinesterase to butyrylcholinesterase and by the long half-life in blood etc. (see Japanese Patent No. 2578475, Japanese Patent No. 2777159 and J of Med Chem (1995) 38, 4821). As a result of clinical tests, it has been confirmed that donepezil hydrochloride is effective against a mild or medium case of Alzheimer type dementia. The effect of donepezil hydrochloride is the suppression of the progress of dementia symptoms in a mild or medium case of Alzheimer type dementia. In addition, on the basis of the results of subsequent clinical tests, an additional application for launching donepezil hydrochloride with new efficacy and effect on a serious case of Alzheimer type dementia has been made.

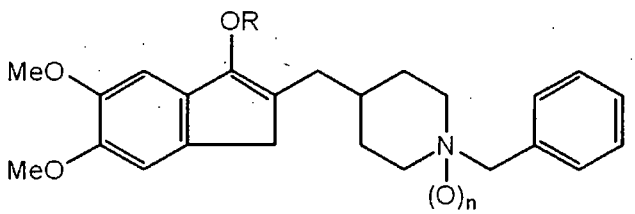
Disclosure of Invention

Donepezil hydrochloride is a very excellent therapeutic agent for Alzheimer type dementia from the viewpoint of efficacy, absorption, distribution, toxicity and the like and is most commonly used all over the world. Donepezil causes a rapid increase of its blood level after administration because of its satisfactory absorption and distribution, to exhibit its efficacy. On the other hand, it has been reported

that the side effects of donepezil hydrochloride, such as vomit, diarrhea and nightmare are observed which are considered to be due to the rapid increase of the blood level of donepezil caused soon after administration. The remission and reduction of the side effects (e.g. vomit, diarrhea and nightmare) caused in some cases are a problem to be solved for the present invention.

The present inventors earnestly made efforts in order to solve the above problem, and consequently could prevent the rapid increase of the blood level of donepezil by converting donepezil to a prodrug to retard the release of the pharmaceutical activity itself into blood. This prevention permits remission and reduction of the above-mentioned side effects (e.g. vomit, diarrhea and nightmare) observed in some cases, whereby the present invention has been accomplished.

That is, the present invention relates to a compound represented by the formula (I):

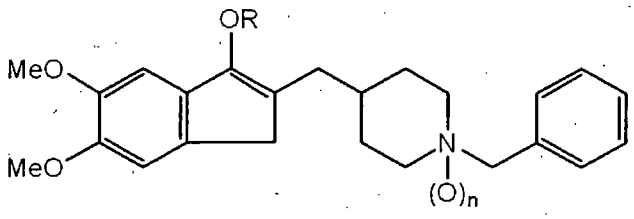


(I)

wherein R is a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent group α, a carbamoyl group optionally substituted by one or two C1-6 alkyl groups, a C6-14 aryloxycarbonyl group optionally substituted by one to

three substituents selected from the substituent group α, a C2-6 alkanoyl group optionally substituted by one to three substituents selected from the substituent group α, or a C6-14 arylcarbonyl group optionally substituted by one to three substituents selected from the substituent group α; and n is an integer of 0 or 1, or a pharmaceutically acceptable salt thereof; said substituent group α consisting of a C1-6 alkoxy group, a C2-6 alkenyl group, a C1-6 alkyl group, a C1-6 alkylthio group, a C2-6 alkynyl group, a C6-14 aryl group, a cyano group, a C3-8 cycloalkoxy group, a C3-8 cycloalkyl group, a C3-8 cycloalkylthio group, a halogen atom and a nitro group.

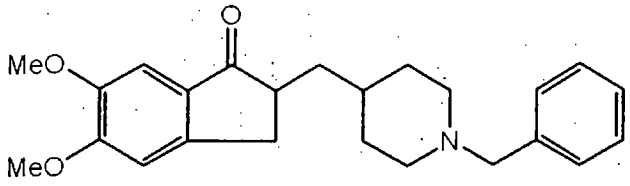
Further, the present invention also relates to a process for producing a compound represented by the formula (I):



(I)

wherein R and n are as defined above, or a pharmaceutically acceptable salt thereof, which comprises the steps of;

reacting a compound represented by the formula (III):



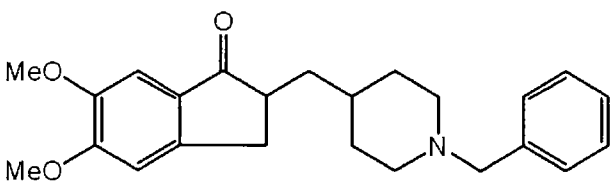
(III)

or a salt thereof with a compound represented by the formula (IV):

$$R^1COX \qquad (IV)$$

wherein R^1 is an amino group optionally substituted by one or two C1-6 alkyl groups, a C6-14 aryloxy group optionally substituted by one to three substituents selected from the substituent group α as defined above, a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent α as defined above, or a C6-14 aryl group optionally substituted by one to three substituents selected from the substituent group α as defined above; and X is a leaving group, or

reacting a compound represented by the formula (III):



(III)

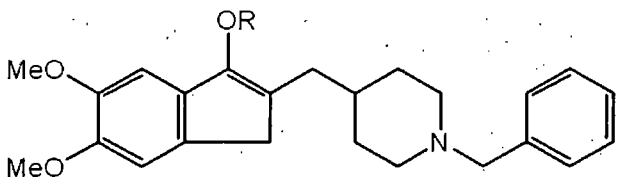
or a salt thereof with a compound represented by the

formula (V):

$$CH(OR^2)_3 \qquad (V)$$

wherein R^2 is a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent group α as defined above,

thereby obtaining a compound represented by the formula (II):



(II)

wherein R is a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent group α as defined above, a carbamoyl group optionally substituted by one or two C1-6 alkyl groups, a C6-14 aryloxycarbonyl group optionally substituted by one to three substituents selected from the substituent group α as defined above, a C2-6 alkanoyl group optionally substituted by one to three substituents selected from the substituent group α as defined above, or a C6-14 arylcarbonyl group optionally substituted by one to three substituents selected from the substituent group α as defined above, or a salt thereof, and

if necessary, subjecting the compound of the formula (II) or a salt thereof to salt forming reaction

and/or oxidation reaction.

Still further, the present invention relates to a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof as defined above, as an active ingredient.

The compound of the formula (I) of the present invention is expected to be effective in the treatment, prevention, remission, amelioration and the like of, for example, a cerebral accident (e.g. cerebral hemorrhage or cerebral infarction), cerebral arteriosclerosis, or a head injury; and aprosexia, lalopathy, hypobulia, emotional disturbance, memory disturbance, hallucinatory-paranoid syndrome, behavioral abnormality which are associated with, for example, encephalitis or cerebral palsy.

In addition, the remission and reduction of the side effects (e.g. vomit, diarrhea and nightmare) observed in some cases after the administration of donepezil hydrochloride are the expected advantages of the present invention.

Best Mode for Carrying Out the Invention

In the description in the present specification, the term "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom, an iodine atom or the like, preferably a chlorine atom or a bromine atom.

The term "C3-8 cycloalkyl group" means a

cyclic alkyl group of 3 to 8 carbon atoms. Preferable examples of this group are cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, etc.

The term "C1-6 alkyl group" means an alkyl group of 1 to 6 carbon atoms. Preferable examples of this group are linear or branched alkyl groups such as methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, t-butyl group, n-pentyl group, isopentyl group, neopentyl group, n-hexyl group, 1-methylpropyl group, 1,2-dimethylpropyl group, 1-ethylpropyl group, 1-methyl-2-ethylpropyl group, 1-ethyl-2-methylpropyl group, 1,1,2-trimethylpropyl group, 1-methylbutyl group, 2-methylbutyl group, 1,1-dimethylbutyl group, 2,2-dimethylbutyl group, 2-ethylbutyl group, 1,3-dimethylbutyl group, 2-methylpentyl group, 3-methylpentyl group, etc. More preferable examples thereof are methyl group, ethyl group and n-propyl group.

The term "C2-6 alkenyl group" means an alkenyl group of 2 to 6 carbon atoms. Preferable examples of this group are linear or branched alkenyl groups such as vinyl group, allyl group, 1-propenyl group, isopropenyl group, 1-buten-1-yl group, 1-buten-2-yl group, 1-buten-3-yl, 2-buten-1-yl group, 2-buten-2-yl group, etc.

The term "C2-6 alkynyl group" means an alkynyl group of 2 to 6 carbon atoms. Preferable

examples of this group are linear or branched alkynyl groups such as ethynyl group, 1-propynyl group, 2-propynyl group, butynyl group, pentynyl group, hexynyl group, etc.

The term "C1-6 alkoxy group" means a group formed by the replacement of a hydrogen atom of an alkyl group of 1 to 6 carbon atoms by an oxygen atom. This group includes, for example, methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, sec-butoxy group, t-butoxy group, n-pentyloxy group, isopentyloxy group, sec-pentyloxy group, t-pentyloxy group, n-hexyloxy group, isohexyloxy group, 1,2-dimethylpropoxy group, 2-ethylpropoxy group, 1-methyl-2-ethylpropoxy group, 1-ethyl-2-methylpropoxy group, 1,1,2-trimethylpropoxy group, 1,1-dimethylbutoxy group, 2,2-dimethylbutoxy group, 2-ethylbutoxy group, 1,3-dimethylbutoxy group, 2-methylpentyloxy group, 3-methylpentyloxy group and hexyloxy group.

The term "C3-8 cycloalkoxy group" means a group formed by the replacement of a hydrogen atom of a cyclic alkyl group of 3 to 8 carbon atoms by an oxygen atom. This group includes, for example, cyclopropoxy group, cyclobutoxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group and cyclooctyloxy group.

The term "C1-6 alkylthio group" means a group formed by the replacement of a hydrogen atom of an

alkyl group of 1 to 6 carbon atoms by a sulfur atom. This group includes, for example, methylthio group, ethylthio group, n-propylthio group, isopropylthio group, n-butylthio group, isobutylthio group, t-butylthio group, n-pentylthio group, isopentylthio group, neopentylthio group, n-hexylthio group and 1-methylpropylthio group.

The term "C3-8 cycloalkylthio group" means a group formed by the replacement of a hydrogen atom of a cyclic alkyl group of 3 to 8 carbon atoms by a sulfur atom. This group includes, for example, cyclopropylthio group, cyclobutylthio group, cyclopentylthio group, cyclohexylthio group, cycloheptylthio group and cyclooctylthio group.

The "C6-14 aryl group" includes, for example, phenyl group, naphthyl group and anthryl group. Of these, phenyl group is preferable.

The term "C6-14 aryloxycarbonyl group" means a group formed by bonding of a carbonyl group to the phenolic hydroxyl group of an aryloxy group of 6 to 14 carbon atoms. Preferable examples of this group are phenoxycarbonyl group, naphthyloxycarbonyl group, anthryloxycarbonyl group, etc. Phenoxycarbonyl group is more preferable.

The term "C6-14 arylcarbonyl group" means a group formed by bonding of a carbonyl group to an aromatic ring of 6 to 14 carbon atoms. Preferable examples of this group are benzoyl group, naphthoyl

group, etc. Benzoyl group is more preferable.

The term "C2-6 alkanoyl group" means an alkanoyl group of 2 to 6 carbon atoms. Preferable examples of this group are acetyl group, propanoyl group, butanoyl group, pentanoyl group and hexanoyl group.

The term "substituent group α" means the group consisting of a C1-6 alkoxy group, a C2-6 alkenyl group, a C1-6 alkyl group, a C1-6 alkylthio group, a C2-6 alkynyl group, a C6-14 aryl group, a cyano group, a C3-8 cycloalkoxy group, a C3-8 cycloalkyl group, a C3-8 cycloalkylthio group, a halogen atom and a nitro group.

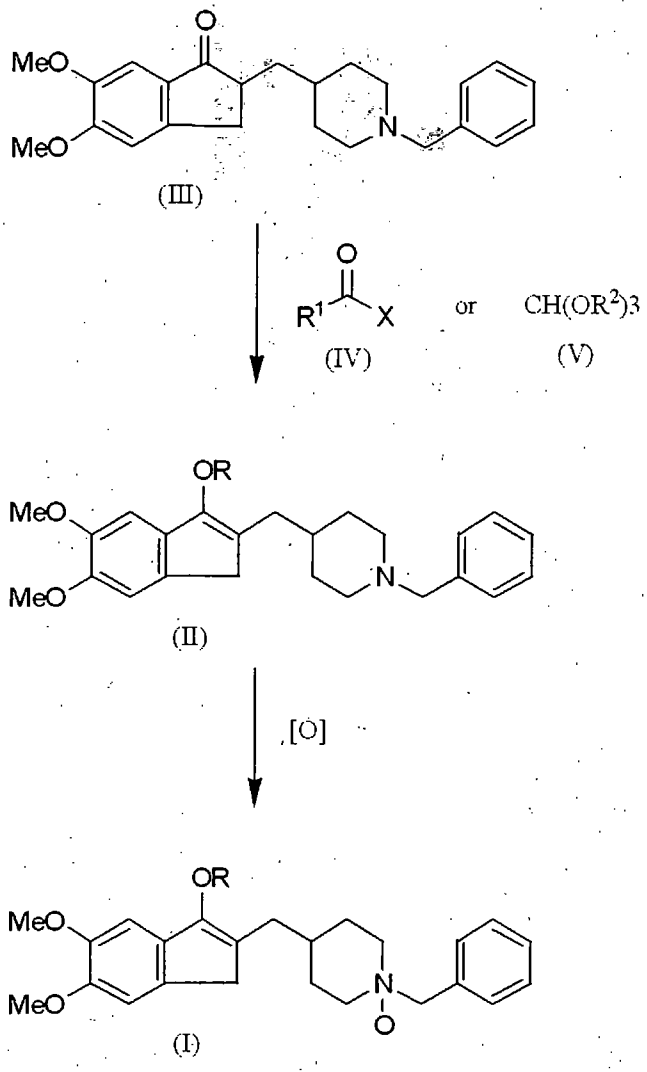
The term "pharmaceutically acceptable salt" means a salt of the compound (I) which can be used as an active agent of a pharmaceutical composition. Preferred examples of such a salt may include a mineral acid salt such as hydrochloride, hydrobromide, sulfate and nitrate; an inorganic acid salt such as perchlorate, phosphate, carbonate and bicarbonate; an organic carboxylate such as acetate, oxalate, maleate, tartarate, fumarate and citrate; an organic sulfonate such as methanesulfonate, trifluoromethanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate and camphorsulfonate; an amino acid salt such as aspartate and glutamate; a quaternary amine salt; an alkali metal salt such as sodium salt and potassium salt; and an alkali-earth metal salt such as magnesium salt and

calcium salt.

The term "salt" means the same meanings as those of the term "pharmaceutically acceptable salt" as mentioned above.

Next, a process for producing the compound of the formula (I) of the present invention (hereinafter referred to as the compound (I); the same abbreviation applied to compounds represented by other formulas) or a salt thereof is explained below.

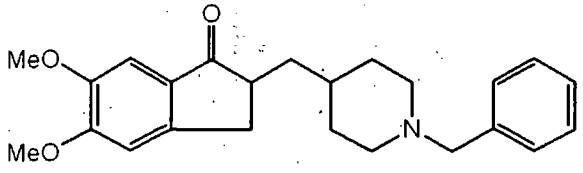
The compound (I) or a salt thereof is synthesized by the use of a compound (III) or a salt thereof, which is donepezil or donepezil salt, as a starting material as shown below.



That is, the synthesis is carried out by the following process 1 when R of the compound (I) is the carbamoyl group, the aryloxycarbonyl group, the alkanoyl group or the arylcarbonyl group.

Process 1

A compound (III)



(III)

or a salt thereof is reacted with a compound represented by the formula (IV):

$$R^1COX \quad (IV)$$

wherein R^1 is an amino group optionally substituted by one or two C1-6 alkyl groups, a C6-14 aryloxy group optionally substituted by one to three substituents selected from the substituent group α, a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent group α, or a C6-14 aryl group optionally substituted by one to three substituents selected from the substituent group α; and X is a leaving group.

More specifically, when R^1 is an amino group optionally substituted by one or two C1-6 alkyl groups, the reaction is carried out in pyridine solvent in a sealed tube at a temperature of 0 to 100°C, preferably 90°C. When R^1 is an C6-14 aryloxy group optionally substituted by one to three substituents selected from the substituent group α, or when R^1 is an C1-6 alkyl group optionally substituted by a substituent(s)

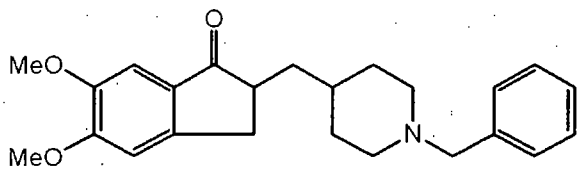
selected from the substituent group α, or a C6-14 aryl group optionally substituted by a substituent(s) selected from the substituent group α, the reaction is carried out at -60°C to room temperature in an inert solvent such as tetrahydrofuran or dimethylformamide by using lithium bistrimethylsilylamide or lithium diisopropylamide as a base.

As to the synthesis of the starting material (IV), when R^1 is an amino group optionally substituted by one or two C1-6 alkyl groups, R^1COX is generally synthesized by the use of a corresponding amine as a starting material according to methods as described in Tetrahedron Lett, 1994, 35, 839. When R^1 is a C6-14 aryloxy group optionally substituted by one to three substituents selected from the substituent group α, R^1COX is generally synthesized by the use of a corresponding phenol as a starting material according to methods as described in J of Med Chem (1983) 26, 264 and Synthesis (1993) 103. When R^1 is a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent group α, or a C6-14 aryl group optionally substituted by one to three substituents selected from the substituent group α, R^1COX is generally obtained in high yield by treating a corresponding carboxylic acid with thionyl chloride or oxalyl chloride according to methods as described in Jikken Kagaku Koza (Experimental Chemistry), 4th Edition, Vol. 22, 115, Maruzen Co., Ltd.

Oherwise, the compound (I) or a salt thereof is synthesized by the process 2 when R of the compound (I) is an optionally substituted C1-6 alkyl group.

Process 2

A compound (III)



(III)

or a salt thereof is reacted with a compound represented by the formula (V):

$$CH(OR^2)_3 \quad (V)$$

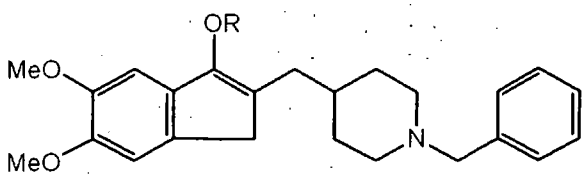
wherein R^2 is a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent group α.

More specifically, the compound (III) or salt thereof is reacted with the compound (V) in a sealed tube in the presence of an acid such as hydrochloric acid or p-toluenesulfonic acid at a temperature of 0 to 100°C, preferably 90 to 100°C. This reaction proceeds also on microwave irradiation.

The compound (V) may be generally synthesized in high yield by the use of a corresponding alcohol and ethyl orthoformate as starting materials according to methods as described in J. Am. Chem. Soc. 74, 554

(1952) and ibid. 77, 3801 (1955)

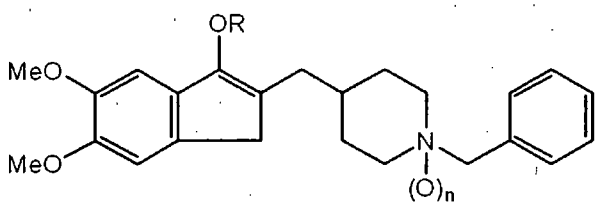
Thus, according to the process 1 and the process 2, the compound (II)



(II)

wherein R is as defined above, or a salt thereof is obtained.

If necessary, such a compound (II) may be converted to a salt with, for example hydrochloric acid, hydrobromic acid, p-toluenesulfonic acid or the like according to a conventional method. In addition, if necessary, the compound (II) or the salt thereof is converted to an N-oxide enol compound (I):



(I)

wherein R is as defined above, and n is an integer of 1, by oxidation with an oxidizing agent such as hydrogen peroxide, a hydroperoxide or perbenzoic acid or the like at a temperature of -20℃ to a room temperature in a solvent such as benzene, methanol, methylene chloride or chloroform for 1 hour to 3 days.

The compound of the formula (I) or a pharmaceutically acceptable salt thereof is useful as a

therapeutic agent for Alzheimer-type dementia and may be orally or parenterally administered for treatment. When used in the form of an oral preparation, the compound may be formulated into a solid preparation such as a powder, granules, capsules, tablets or the like or a liquid preparation such as a syrup, elixir or the like. When used in the form of a parenteral preparation, the compound may be formulated into an injection, an inhalation, a percutaneous preparation, a suppository or the like. These preparations are produced according to conventional methods by adding pharmacologically and pharmaceutically acceptable preparation adjuvants to the active ingredient. Although the dose is varied depending on the kind of a disease to be treated, the age, sex, body weight and symptom of a patient, and administration route, the compound is administered in a dose of, in general, approximately 1 to 10 mg in terms of donepezil per day in one portion or several portions.

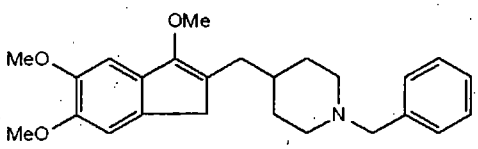
The present invention is illustrated in detail with the following examples, which should not be construed as limiting the scope of the invention. The abbreviations used in the examples are common abbreviations generally known to those skilled in the art. Some of the abbreviations are described below.

A proton nuclear magnetic resonance spectrum was measured at 400 MHz by the use of $CDCl_3$ as a solvent, and chemical shift is recorded in δ unit (ppm)

with respect to tetramethylsilane and coupling constants were recorded in hertz (Hz). In a spectral pattern, s; singlet, d; doublet, t; triplet, and b; broad. Analytical thin-layer chromatography (TLC) was carried out on a pre-coated silica gel plate (60F-254), followed by visualization and detection by the use of UV light and ethanolic phosphomolybdic acid.

Example 1

Synthesis of 1-benzyl-4-[(1,5,6-trimethoxy-3H-inden)-2-yl]methylpiperidine



To donepezil (200 mg, 0.527 mmol) were added 1 ml of trimethyl orthoformate and 2 ml of a 1.25 M solution of hydrogen chloride in methanol, and the reaction mixture was stirred in a sealed tube at 90°C for 5 days. The reaction mixture was allowed to cool to room temperature and was then concentrated under reduced pressure to remove the solvent. Methylene chloride was added to the residue, followed by washing with a saturated aqueous sodium hydrogencarbonate solution. The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure, and the resulting residue was purified by a silica gel column chromatography (NH-silica gel, n-hexane/ethyl acetate) to obtain the title compound (43.0 mg, yield: 21%).

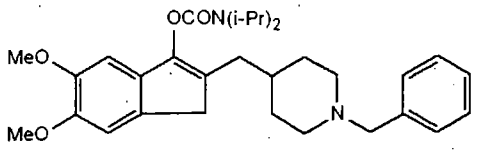
In another process, donepezil (250 mg, 0.659 mmol), 1 ml of trimethyl orthoformate and 3 ml of a 1.25 M solution of hydrogen chloride in methanol were placed in a sealed tube, and the reaction mixture was irradiated with a microwave at an output of 100 watts for 40 minutes at a reaction temperature of 90°C. The reaction mixture was allowed to cool to room temperature and was then concentrated under reduced pressure to remove the solvent. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, followed by extraction with methylene chloride. The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure, and the resulting residue was purified by a silica gel column chromatography (n-hexane/ethyl acetate) to obtain the title compound (69.3 mg, yield: 27%).

^{1}H-NMR($CDCl_3$)δ:1.19-1.31(2H,m),1.37-1.47(1H,m),1.55-1.62(2H,m),1.85(2H,dt,J=0.20,1.16Hz),2.31(2H,d,J=0.72Hz),2.80(2H,b-d,J=1.16Hz),3.06(2H,s),3.41(2H,s),3.80(3H,s),3.81(3H,s),3.84(3H,s),6.80(1H,s),6.88(1H,s,),7.13-7.25(5H,m).

ESI-MS:m/z=394($M+H^+$).

Example 2

Synthesis of 1-benzyl-4-[(1-N,N-diisopropylcarbamoyloxy-5,6-dimethoxy-3H-inden)-2-yl]methylpiperidine



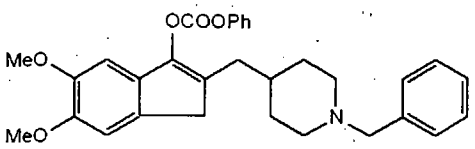
N,N-diisopropylcarbamoyl chloride (94.9 mg, 0.580 mmol) and 2 ml of pyridine were added to donepezil (200 mg, 0.527 mmol), and the reaction mixture was stirred in a sealed tube at 90°C for 5 days. The reaction mixture was allowed to cool to room temperature and was then concentrated under reduced pressure to remove the solvent. Ethyl acetate was added to the residue, followed by washing with a saturated aqueous sodium hydrogencarbonate solution and then a saturated aqueous sodium chloride solution. The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure, and the resulting residue was purified by a silica gel column chromatography (NH-silica gel, n-hexane/ethyl acetate). Then, the mixture thus obtained was purified by a preparative thin-layer chromatography (methylene chloride/methanol) to obtain the title compound (47.0 mg, yield: 18%).

^{1}H-NMR($CDCl_3$)δ:1.16-1.34(14H,m),1.37-1.48(1H,m),1.57-1.64(2H,m),1.84(2H,dt,J=0.20,1.16Hz),2.24(2H,d,J=0.71Hz),2.78(2H,b-d,J=1.16Hz),3.16(2H,s),3.40(2H,s),3.78(3H,s),3.79(3H,s),3.88-4.08(2H,m),6.56(1H,s),6.87(1H,s),7.15-7.25(5H,m).

ESI-MS:m/z=507($M+H^+$).

Example 3

Synthesis of 1-benzyl-4-[(1-phenoxycarbonyloxy-5,6-dimethoxy-3H-inden)-2-yl]methylpiperidine



Donepezil (100 mg, 0.264 mmol) was dissolved in tetrahydrofuran (THF, 3 ml) under a nitrogen atmosphere and the resulting solution was cooled to -60°C. Then, lithium bistrimethylsilylamide (1.0 M, a THF solution, 0.40 ml, 0.40 mmol) was poured into the reaction mixture. The resulting mixture was heated to -10°C from -60°C over a period of 1.5 hours and then cooled to -60°C, and a THF solution (1 ml) containing phenyl chloroformate (0.050 ml, 0.40 mmol) was poured into the reaction mixture. After slow heating to room temperature from -60°C, the reaction mixture was stirred overnight and a saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure, and the resulting residue was purified by a preparative thin-layer chromatography (methylene chloride/methanol) to obtain the title compound (43.4 mg, yield: 33%).

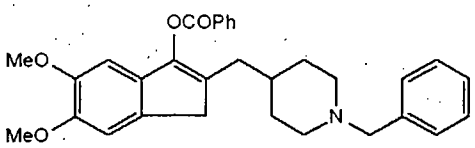
^{1}H-NMR($CDCl_3$)δ:1.24-1.38(2H,m),1.43-1.54(1H,m), 1.62(2H,b-d,J=1.24Hz),1.89(2H,b-t,J=1.07Hz),2.32(2H,d,

J=0.71Hz), 2.82(2H,b-d,J=1.07Hz),3.21(2H,s),3.44(2H,b-s),3.81(3H,s),3.83(3H,s),6.70(1H,s),6.91(1H,s),7.15-7.25(8H,m),7.32-7.37(2H,m).

ESI-MS:m/z=500($M+H^+$).

Example 4

Synthesis of 1-benzyl-4-[(1-benzoyloxy-5,6-dimethoxy-3H- inden)-2-yl]methylpiperidine



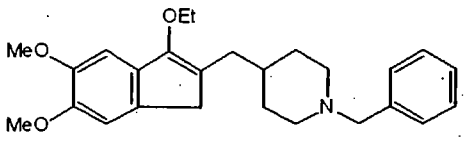
The title compound (40.3 mg, yield: 32%) was obtained according to the process described in Example 3, except for reacting benzoyl chloride (0.046 mL) in place of phenyl chloroformate with donepezil (100 mg, 0.264 mmol).

^{1}H-NMR($CDCl_3$)δ:1.20-1.32(3H,m),1.35-1.43(1H,m),1.47-1.55(1H,m)1.71-1.83(2H,m)2.06-2.12(2H,m),2.66-2.76(2H,m),2.99(1H,d,J=1.72Hz),3.38(2H,s),3.62(1H,d,J=1.72Hz),3.86(3H,s),3.92(3H,s),6.84(1H,s),7.14(1H,s),7.15-7.27(7H,m),7.38(1H,t,J=0.75Hz),7.62(2H,d,J=0.75Hz).

ESI-MS:m/z=484($M+H^+$).

Example 5

Synthesis of 1-benzyl-4-[(1-ethoxy-5,6-dimethoxy-3H-inden)-2- yl]methylpiperidine



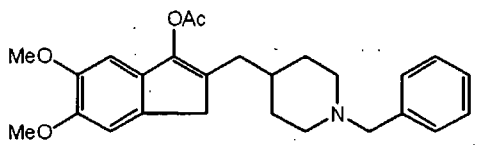
The title compound (50.2 mg, yield: 23%) was obtained according to the process described in Example 1, except for reacting triethyl orthoformate (1 mL) in place of trimethyl orthoformate with donepezil (200 mg, 0.528 mmol).

^{1}H-NMR($CDCl_3$)δ:1.23-1.35(2H,m),1.30(3H,t,J=0.70Hz),1.38-1.48(1H,m),1.56-1.63(2H,m),1.89(2H,b-t,J=1.10Hz),2.30(2H,d,J=0.71Hz),2.83(2H,b-d,J=1.10Hz),3.08(2H,s),3.47(2H,s),3.80(3H,s),3.83(3H,s),4.00(2H,q,J=0.70Hz),6.77(1H,s),6.88(1H,s),7.15-7.27(5H,m).

ESI-MS:m/z=408($M+H^+$).

Example 6

Synthesis of 1-benzyl-4-[(1-acetoxy-5,6-dimethoxy-3H-inden)- 2-yl]methylpiperidine



The title compound (71.2 mg, yield: 43%) was obtained according to the process described in Example 3, except for reacting acetyl chloride (0.042 mL) in place of phenyl chloroformate with donepezil (150 mg, 0.396 mmol).

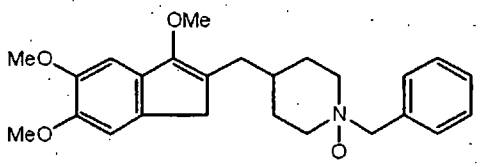
^{1}H-NMR($CDCl_3$)δ:1.20-1.34(3H,m),1.44-1.52(2H,m),1.72-

1.86(3H,m),2.18-2.23(1H,m),2.20(3H,s),2.69-2.76(2H,m),
2.74(1H,d,J=1.70Hz),3.67(2H,s),3.78(1H,d,J=1.70Hz),3.81
(3H,s),3.90(3H,s),6.81(1H,s),7.03(1H,s),
7.13-7.25(5H,m).

ESI-MS:m/z=423($M+H^+$).

Example 7

Synthesis of 1-benzyl-4-[(1,5,6-trimethoxy-3H-inden)-2-yl]methylpiperidine-1-oxide



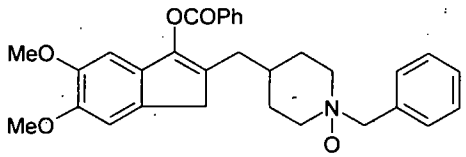
To 1-benzyl-4-[(1,5,6-trimethoxy-3H-inden)-2-yl]methylpiperidine (21.0 mg, 0.053 mmol) were added 2 mL of methanol and 0.5 mL of a 30% aqueous hydrogen peroxide solution, and the reaction mixture was stirred at room temperature for 2 days. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous sodium hydrogencarbonate solution was added to the residue, followed by extraction with methylene chloride. The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure, and the resulting residue was purified by a thin-layer chromatography to obtain the title compound (6.9 mg, yield: 32%).

^{1}H-NMR($CDCl_3$)δ:1.40-1.52(1H,m),1.53(2H,b-d,J=1.44Hz),
2.09-2.35(3H,m),2.38(2H,d,J=0.86Hz),2.96-3.16(3H,m),

3.04(2H,s),3.79(3H,s),3.80(3H,s),3.83(3H,s),4.34(2H,s),
6.80(1H,s),6.86(1H,s),7.30-7.45(5H,m).
ESI-MS:m/z=410($M+H^+$).

Example 8

Synthesis of 2-[(1-benzylpiperidine-1-oxid-4-yl)methyl]-5,6-dimethoxy-3H-inden-1-yl benzoate



The title compound (14.4 mg, yield: 29%) was obtained by the same process as in Example 7 except for reacting 1-benzyl-4-[(1-benzoyloxy-5,6-dimethoxy-3H-inden)- 2-yl]methylpiperidine (47.3 mg, 0.098 mmol) with 0.5 mL of a 30% aqueous hydrogen peroxide solution.
^{1}H-NMR($CDCl_3$)δ:1.33(1H,b-d,J=1.38Hz),1.43-1.53(1H,m),
1.43-1.53(1H,m),1.63(1H,b-d,J=1.38Hz),1.83(1H,dd,J=
0.55,1.44Hz),2.04(1H,dq,J=0.38,1.3Hz),2.15(1H,dq,J=
0.38,1.3Hz),2.25(1H,dd,J=0.55,1.44Hz),2.88-3.10(5H,m),
3.59(1H,d,J=1.73Hz),3.87(3H,s),3.93(3H,s),4.29(2H,s),
6.83(1H,s),7.14(1H,s),7.21-7.27(2H,m),7.28-7.35(3H,m),
7.36-7.42(3H,m),7.53-7.58(2H,m).
ESI-MS:m/z=500($M+H^+$).

Test Example 1

Evaluation of metabolism

In order to demonstrate the usefulness of the

compound of the present invention as a drug, the following drug metabolism test was carried out by choosing the compound of Example 1 as a representative compound.

The compound of Example 1 was administered to fasted male rats (aged 8 weeks, n= 2) in the form of a solution of the compound in 10% DMSO/10% Tween 20, and the blood levels of the original compound and donepezil produced in the living body were periodically measured. The area under the blood concentration-time curve (AUC) for each of them is shown in Table 1 below.

Table 1

Test compound	Administration route and dose	AUC infinite (ng•hr/mL)	
		Prodrug	Donepezil hydrochloride
Compound of Example 1	i.v., 1.0 mg/kg	181.3	172.0
	p.o., 3.0 mg/kg	2.8	517.3

The results of Table 1 indicate that the compound of Example 1 can prevent the rapid increase of the blood level more effectively than donepezil hydrochloride, thereby retarding the release of the pharmaceutical activity itself into blood.

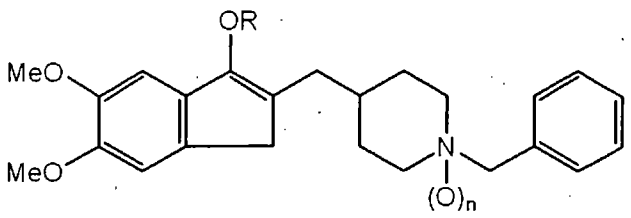
This prevention permits remission and reduction of the above-mentioned side effects (e.g. vomit, diarrhea and nightmare) observed in some cases, whereby the present invention has been accomplished.

Industrial Applicability

According to the present invention, the compound of the formula (I) or a salt thereof, which is a prodrug of donepezil hydrochloride, permits remission and reduction of effects of donepezil hydrochloride (e.g. vomit, diarrhea and nightmare) , and is therefore useful as a therapeutic agent for Alzheimer type dementia having smaller side effects.

CLAIMS

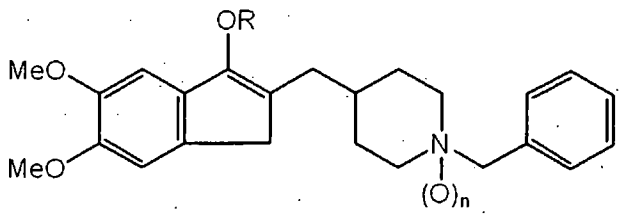
1. A compound represented by the formula (I):



(I)

wherein R is a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent group α, a carbamoyl group optionally substituted by one or two C1-6 alkyl groups, a C6-14 aryloxycarbonyl group optionally substituted by one to three substituents selected from the substituent group α, a C2-6 alkanoyl group optionally substituted by one to three substituents selected from the substituent group α, or a C6-14 arylcarbonyl group optionally substituted by one to three substituents selected from the substituent group α; and n is an integer of 0 or 1, or a pharmaceutically acceptable salt thereof; said substituent group α consisting of a C1-6 alkoxy group, a C2-6 alkenyl group, a C1-6 alkyl group, a C1-6 alkylthio group, a C2-6 alkynyl group, a C6-14 aryl group, a cyano group, a C3-8 cycloalkoxy group, a C3-8 cycloalkyl group, a C3-8 cycloalkylthio group, a halogen atom and a nitro group.

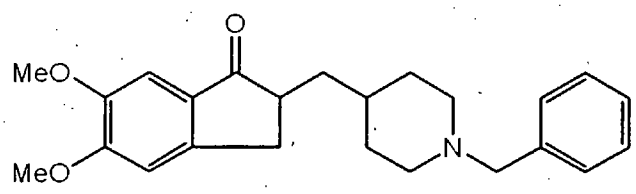
2. A process for producing a compound represented by the formula (I):



(I)

wherein R and n are as defined in claim 1, or a pharmaceutically acceptable salt thereof, which comprises the steps of;

reacting a compound represented by the formula (III):



(III)

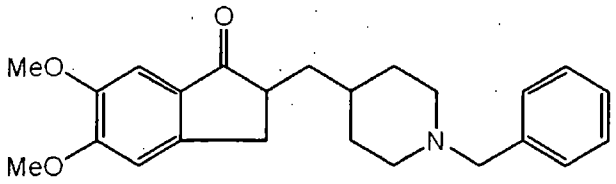
or a salt thereof with a compound represented by the formula (IV):

$$R^1COX \quad (IV)$$

wherein R^1 is an amino group optionally substituted by one or two C1-6 alkyl groups, a C6-14 aryloxy group optionally substituted by one to three substituents selected from the substituent group α as defined in claim 1, a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent α as defined in claim 1, or a C6-14 aryl group optionally substituted by one to three substituents selected from the substituent group α as defined in

claim 1; and X is a leaving group, or

reacting a compound represented by the formula (III):



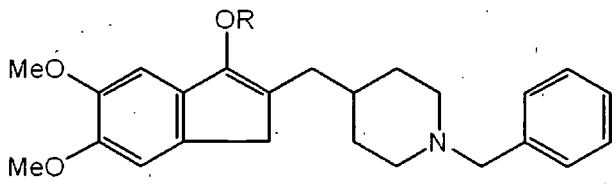
(III)

or a salt thereof with a compound represented by the formula (V):

$$CH(OR^2)_3 \qquad (V)$$

wherein R^2 is a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent group α as defined in claim 1,

thereby obtaining a compound represented by the formula (II):



(II)

wherein R is a C1-6 alkyl group optionally substituted by one to three substituents selected from the substituent group α as defined in claim 1, a carbamoyl group optionally substituted by one or two C1-6 alkyl groups, a C6-14 aryloxycarbonyl group optionally substituted by one to three substituents selected from

the substituent group α as defined in claim 1, a C2-6 alkanoyl group optionally substituted by one to three substituents selected from the substituent group α as defined in claim 1, or a C6-14 arylcarbonyl group optionally substituted by one to three substituents selected from the substituent group α as defined in claim 1, or a salt thereof, and

if necessary, subjecting the compound of the formula (II) or a salt thereof to salt forming reaction and/or oxidation reaction.

3. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to claim 1, as an active ingredient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2006/321443

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/22 C07D211/94 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 296 560 A2 (EISAI CO LTD [JP]) 28 December 1988 (1988-12-28) example 4	1-3
Y	EP 0 365 194 A2 (PFIZER [US]) 25 April 1990 (1990-04-25) page 2, line 7 - page 3, line 17	1-3
Y	WO 02/06236 A (HOFFMANN LA ROCHE [CH]) 24 January 2002 (2002-01-24) line 1 - page 2, line 11	1-3

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2007	05/02/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Usuelli, Ambrogio

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SINGH G ET AL: "PRODRUG APPROACH IN NEW DRUG DESIGN AND DEVELOPMENT" JOURNAL OF SCIENTIFIC & INDUSTRIAL RESEARCH, vol. 55, July 1996 (1996-07), pages 497-510, XP001029288 figure 4	1-3
Y	BURKHART J P ET AL: "Preparation of alpha-keto ester enol acetates as potential prodrugs of human neutrophil elastase inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 1-6, 6 January 1998 (1998-01-06), pages 63-64, XP004136623 ISSN: 0960-894X the whole document	1-3
Y	PATEL J P ET AL: "Enol Esters as Potential Prodrugs I. Stability and Enzyme-Mediated Hydrolysis of alpha-Acetoxystyrene" INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 5, 1980, pages 329-333, XP002415940 the whole document	1-3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2006/321443

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0296560 A2	28-12-1988	AT 134618 T	15-03-1996
		AT 171161 T	15-10-1998
		AT 205828 T	15-10-2001
		AT 204862 T	15-09-2001
		AU 627151 B2	20-08-1992
		AU 1821688 A	22-12-1988
		CA 1338808 C	24-12-1996
		CN 1030752 A	01-02-1989
		CY 2349 A	04-06-2004
		CY 2350 A	04-06-2004
		CY 1940 A	16-05-1997
		DD 283377 A5	10-10-1990
		DE 3855028 D1	04-04-1996
		DE 3856251 D1	22-10-1998
		DE 3856251 T2	18-03-1999
		DE 3856487 D1	04-10-2001
		DE 3856487 T2	08-05-2002
		DE 3856491 D1	25-10-2001
		DE 3856491 T2	23-05-2002
		DE 19775093 I1	04-09-2003
		DK 337988 A	23-12-1988
		ES 2083359 T3	16-04-1996
		ES 2121039 T3	16-11-1998
		ES 2164720 T3	01-03-2002
		ES 2160747 T3	16-11-2001
		FI 882716 A	23-12-1988
		GR 3019142 T3	31-05-1996
		HK 216396 A	27-12-1996
		HU 9500122 A3	28-07-1995
		HU 9500123 A3	28-06-1995
		LU 90221 A9	06-05-1998
		NO 882696 A	23-12-1988
		NZ 224970 A	25-09-1991
		PH 26315 A	29-04-1992
		PT 87783 A	01-07-1988
		SG 50439 A1	20-07-1998
		RU 2009128 C1	15-03-1994
		US 4895841 A	23-01-1990
		US 5100901 A	31-03-1992
		ZA 8804338 A	29-03-1989
EP 0365194 A2	25-04-1990	DE 68923673 D1	07-09-1995
		DE 68923673 T2	18-01-1996
		ES 2075055 T3	01-10-1995
		GR 3017565 T3	31-12-1995
		ZA 8907854 A	29-05-1991
WO 0206236 A	24-01-2002	AR 029717 A1	10-07-2003
		AU 7061901 A	30-01-2002
		BR 0112475 A	29-07-2003
		CA 2415890 A1	24-01-2002
		CN 1441782 A	10-09-2003
		EP 1303490 A1	23-04-2003
		HK 1058198 A1	13-05-2005
		HR 20030003 A2	28-02-2003
		HU 0301311 A2	28-08-2003
		JP 2004504301 T	12-02-2004
		MA 26929 A1	20-12-2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2006/321443

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0206236 A		MX PA03000366 A	27-05-2003
		NO 20030154 A	13-01-2003
		NZ 523273 A	27-08-2004
		PL 365684 A1	10-01-2005
		US 2002045642 A1	18-04-2002
		ZA 200210207 A	17-03-2004