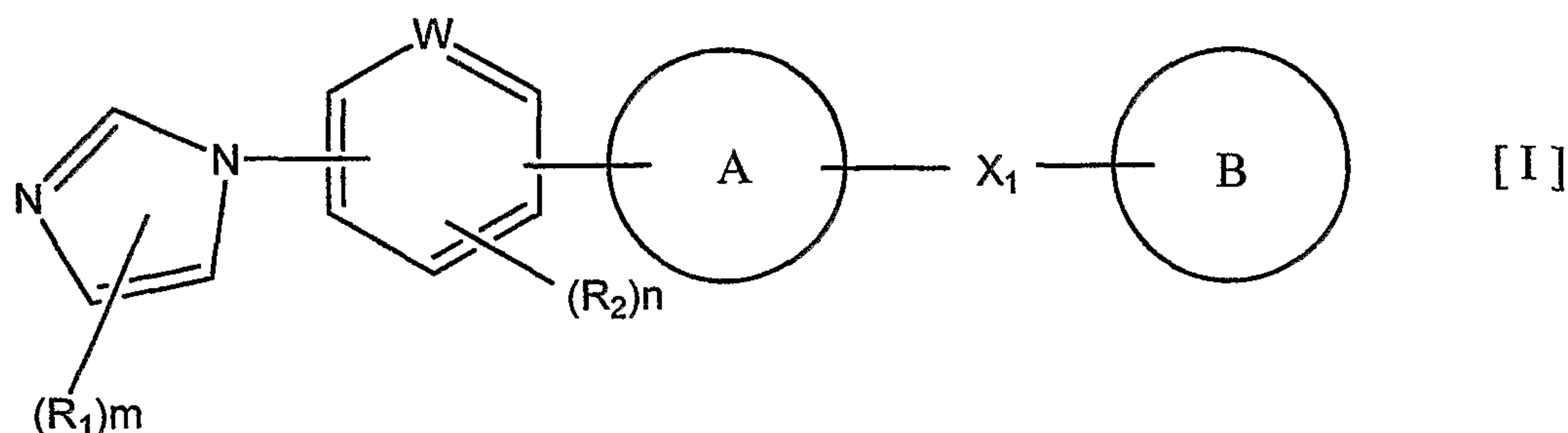




(86) Date de dépôt PCT/PCT Filing Date: 2010/02/24
(87) Date publication PCT/PCT Publication Date: 2010/09/02
(85) Entrée phase nationale/National Entry: 2011/08/25
(86) N° demande PCT/PCT Application No.: JP 2010/053368
(87) N° publication PCT/PCT Publication No.: 2010/098487
(30) Priorités/Priorities: 2009/02/26 (US61/155,697);
2009/02/26 (JP2009-043337)

(51) Cl.Int./Int.Cl. *C07D 471/04* (2006.01),
A61K 31/4439 (2006.01), *C07D 417/14* (2006.01),
C07D 471/18 (2006.01), *C07D 487/04* (2006.01),
C07D 498/04 (2006.01)
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(54) Titre : COMPOSES HETEROCYCLIQUES CONDENSES CONTENANT DE L'AZOTE ET LEUR UTILISATION EN
TANT QU'INHIBITEURS DE PRODUCTION DE LA BETA-AMYOIDE
(54) Title: NITROGEN-CONTAINING FUSED HETEROCYCLIC COMPOUNDS AND THEIR USE AS BETA AMYLOID
PRODUCTION INHIBITORS



(57) **Abrégé/Abstract:**

A compound represented by the formula [I]: or a pharmacologically acceptable salt or ester thereof, wherein Ring A represents a five-membered aromatic heterocyclic group or the like fused with a non-aromatic ring group, which may be substituted, Ring B represents a phenyl group or the like which may be substituted, X1 represents a single bond or the like, R1 and R2 each represent a C1-6 alkyl group or the like, m represents an integer of 0 to 3, and n represents an integer of 0 to 2, is effective as a therapeutic agent for a disease caused by A β .

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
2 September 2010 (02.09.2010)(10) International Publication Number
WO 2010/098487 A1

(51) International Patent Classification:

C07D 471/04 (2006.01) *C07D* 487/04 (2006.01)
A61K 31/4439 (2006.01) *C07D* 498/04 (2006.01)
C07D 471/18 (2006.01) *C07D* 417/14 (2006.01)

(21) International Application Number:

PCT/JP2010/053368

(22) International Filing Date:

24 February 2010 (24.02.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2009-043337 26 February 2009 (26.02.2009) JP
 61/155,697 26 February 2009 (26.02.2009) US

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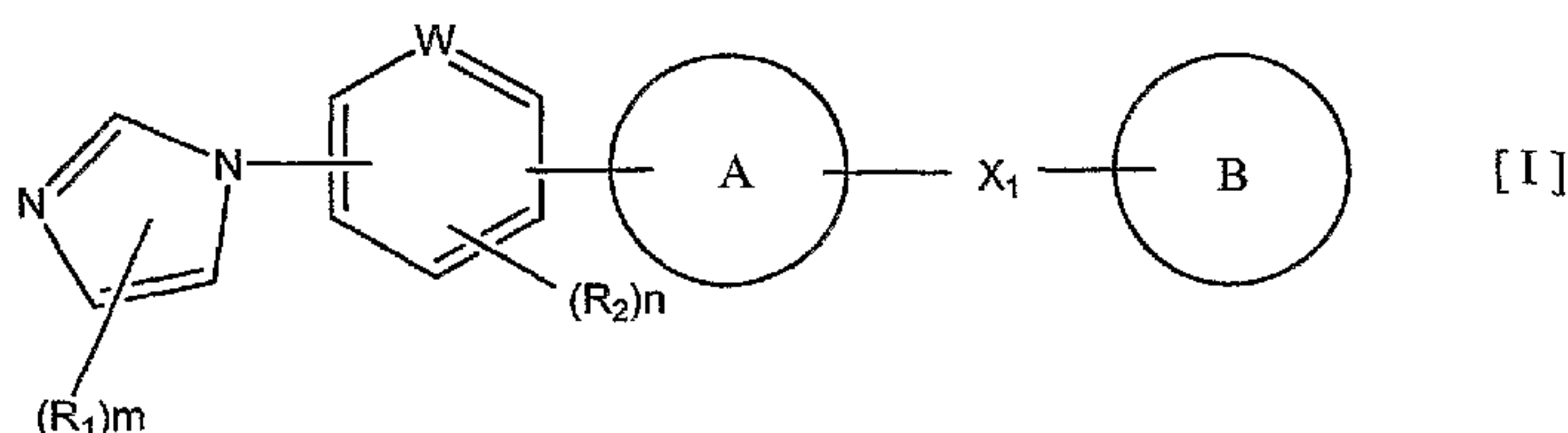
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: NITROGEN-CONTAINING FUSED HETEROCYCLIC COMPOUNDS AND THEIR USE AS BETA AMYLOID PRODUCTION INHIBITORS



(57) Abstract: A compound represented by the formula [I]: or a pharmacologically acceptable salt or ester thereof, wherein Ring A represents a five-membered aromatic heterocyclic group or the like fused with a non-aromatic ring group, which may be substituted, Ring B represents a phenyl group or the like which may be substituted, X1 represents a single bond or the like, R1 and R2 each represent a C1-6 alkyl group or the like, m represents an integer of 0 to 3, and n represents an integer of 0 to 2, is effective as a therapeutic agent for a disease caused by Aβ.

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DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 272

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 272

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NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

DESCRIPTION

Title of the Invention:

**NITROGEN-CONTAINING FUSED HETEROCYCLIC COMPOUNDS
AND THEIR USE AS BETA AMYLOID PRODUCTION INHIBITORS**

TECHNICAL FIELD

[0001]

5 The present invention relates to a pharmaceutical, more particularly, to a nitrogen-containing fused heterocyclic compound effective for the treatment of a neurodegenerative disease caused by amyloid- β (hereinafter referred to as A β) such as Alzheimer's disease or Down's syndrome and a medicine, in particular, a medicine for the treatment of a disease caused by A β comprising the compound as an active ingredient.

10 BACKGROUND ART

[0002]

 Alzheimer's disease is a disease characterized by degeneration and loss of neurons as well as formation of senile plaques and neurofibrillary degeneration. Currently, Alzheimer's disease is treated only with symptomatic treatment using a symptom improving agent typified by
15 an acetylcholinesterase inhibitor, and a fundamental remedy to inhibit progression of the disease has not yet been developed. It is necessary to develop a method for controlling the cause of the onset of pathology in order to create a fundamental remedy for Alzheimer's disease.

 It is assumed that A β -proteins as metabolites of amyloid precursor proteins (hereinafter referred to as APP) are highly involved in degeneration and loss of neurons and
20 onset of symptoms of dementia (see NON-PATENT DOCUMENTS 1 and 2, for example). Main molecular species of A β -protein are A β 40 consisting of 40 amino acids and A β 42 with two amino acids added at the C-terminal. The A β 40 and A β 42 are known to have high aggregability (see NON-PATENT DOCUMENT 3, for example) and to be main components of senile plaques (see NON-PATENT DOCUMENTS 3, 4 and 5, for example). Further, it is known that the A β 40
25 and A β 42 are increased by mutation in APP and presenilin genes which is observed in familial Alzheimer's disease (see NON-PATENT DOCUMENTS 6, 7 and 8, for example). Accordingly, a compound that reduces the production of A β 40 and A β 42 is expected as a progression inhibitor or prophylactic agent for Alzheimer's disease.

A β is produced by cleaving APP by β -secretase and subsequently by γ -secretase. For this reason, attempts have been made to create γ -secretase and β -secretase inhibitors in order to reduce A β production. Many of these secretase inhibitors already known are, for example, peptides and peptide mimetics such as L-685,458 (see NON-PATENT DOCUMENT 9, for example), LY-411,575 (see NON-PATENT DOCUMENTS 10, 11 and 12, for example) and LY-450,139 (see NON-PATENT DOCUMENTS 13, 14 and 15). Nonpeptidic compounds are, for example, MRK-560 (see NON-PATENT DOCUMENTS 16 and 17) and compounds having a plurality of aromatic rings as disclosed in PATENT DOCUMENT 1 and 2. However, the compound represented by the formula (VI) as disclosed in page 17 of the specification of PATENT DOCUMENT 1 differs from the compound of the present invention in that the compound is limited to a compound having a 2-aminothiazolyl group as a main structure. And the compound represented by the formula (I) as disclosed in page 6 of the specification of PATENT DOCUMENT 2 differs from the compound of the present invention in that the compound is limited to a compound having an ethynylene, an ethenylene or methine linker described as X₁.

PRIOR ART DOCUMENTS

PATENT DOCUMENTS

[0003]

PATENT DOCUMENT 1: WO 2004/110350

20 PATENT DOCUMENT 2: WO 2007/102580

NON-PATENT DOCUMENTS

[0004]

NON-PATENT DOCUMENT 1: Klein WL, and seven others, Alzheimer's disease-affected brain: Presence of oligomeric A β ligands (ADDLs) suggests a molecular basis for reversible memory loss, Proceeding of the National Academy of Science USA, 2003, Sep, 2; 100 (18), p. 10417-10422.

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NON-PATENT DOCUMENT 4: Glenner GG, and one other, Alzheimer's disease: initial report of

the purification and characterization of a novel cerebrovascular amyloid protein, Biochemical and Biophysical Research Communications, 1984, May 16, 120 (3), p. 885-890.

NON-PATENT DOCUMENT 5: Masters CL, and five others, Amyloid plaque core protein in Alzheimer disease and Down syndrome, Proceeding of the National Academy of Science USA, 5 1985, Jun, 82 (12), p. 4245-4249.

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NON-PATENT DOCUMENT 9: Shearman MS, and nine others, L-685, 458, an Aspartyl Protease Transition State Mimic, Is a Potent Inhibitor of Amyloid β -Protein Precursor γ -Secretase Activity, Biochemistry, 2000, Aug, 1, 39 (30), p. 8698-8704.

NON-PATENT DOCUMENT 10: Shearman MS, and six others, Catalytic Site-Directed γ - 20 Secretase Complex Inhibitors Do Not Discriminate Pharmacologically between Notch S3 and β -APP Cleavages, Biochemistry, 2003, Jun, 24, 42 (24), p. 7580-7586.

NON-PATENT DOCUMENT 11: Lanz TA, and three others, Studies of A β pharmacodynamics in the brain, cerebrospinal fluid, and plasma in young (plaque-free) Tg2576 mice using the γ -secretase inhibitor N2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyethanoyl]-N1-[(7S)-5-methyl-6- 25 oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-L-alaninamide (LY-411575), The Journal of Pharmacology and Experimental Therapeutics, 2004, Apr, 309 (1), p. 49-55.

NON-PATENT DOCUMENT 12: Wong GT, and twelve others, Chronic treatment with the γ -secretase inhibitor LY-411, 575 inhibits β -amyloid peptide production and alters lymphopoiesis and intestinal cell differentiation, The Journal of Biological Chemistry, 2004, Mar, 26, 279 (13), 30 p. 12876-12882.

NON-PATENT DOCUMENT 13: Gitter BD, and ten others, Stereoselective inhibition of amyloid beta peptide secretion by LY450139, a novel functional gamma secretase inhibitor, Neurology of Aging 2004, 25, sup2, p. 571.

NON-PATENT DOCUMENT 14: Lanz TA, and eighteen others, Concentration-dependent modulation of amyloid- β in vivo and in vitro using the γ -secretase inhibitor, LY-450139, The Journal of Pharmacology and Experimental Therapeutics, 2006, Nov, 319 (2) p. 924-933.

NON-PATENT DOCUMENT 15: Siemers ER, and thirteen others, Effects of a γ -secretase inhibitor in a randomized study of patients with Alzheimer disease, Neurology, 2006, 66, p. 602-604.

NON-PATENT DOCUMENT 16: Best JD, and nine others, In vivo characterization of A β (40) changes in brain and cerebrospinal fluid using the novel γ -secretase inhibitor N-[cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexyl]-1,1,1-trifluoromethanesulphonamide (MK-560) in the rat, The Journal of Pharmacology and Experimental Therapeutics, 2006, May 317 (2) p. 786-790.

NON-PATENT DOCUMENT 17: Best JD, and thirteen others The novel γ -secretase inhibitor N-[cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexyl]-1,1,1-trifluoromethanesulphonamide (MK-560) reduces amyloid plaque deposition without evidence notch-related pathology in the Tg2576 mouse, The Journal of Pharmacology and Experimental Therapeutics, 2007, Feb, 320 (2) p. 552-558.

SUMMARY OF THE INVENTION

PROBLEM TO BE SOLVED BY THE INVENTION

[0005]

As described above, a compound that inhibits the production of A β from APP has been expected as a therapeutic or prophylactic agent for a disease caused by A β which is typified by Alzheimer's disease. However, a nonpeptidic compound having high efficacy which inhibits the production of A β has not yet been known. Accordingly, there is a need for a novel low-molecular-weight compound that inhibits the production of A β .

MEANS FOR SOLVING THE PROBLEM

[0006]

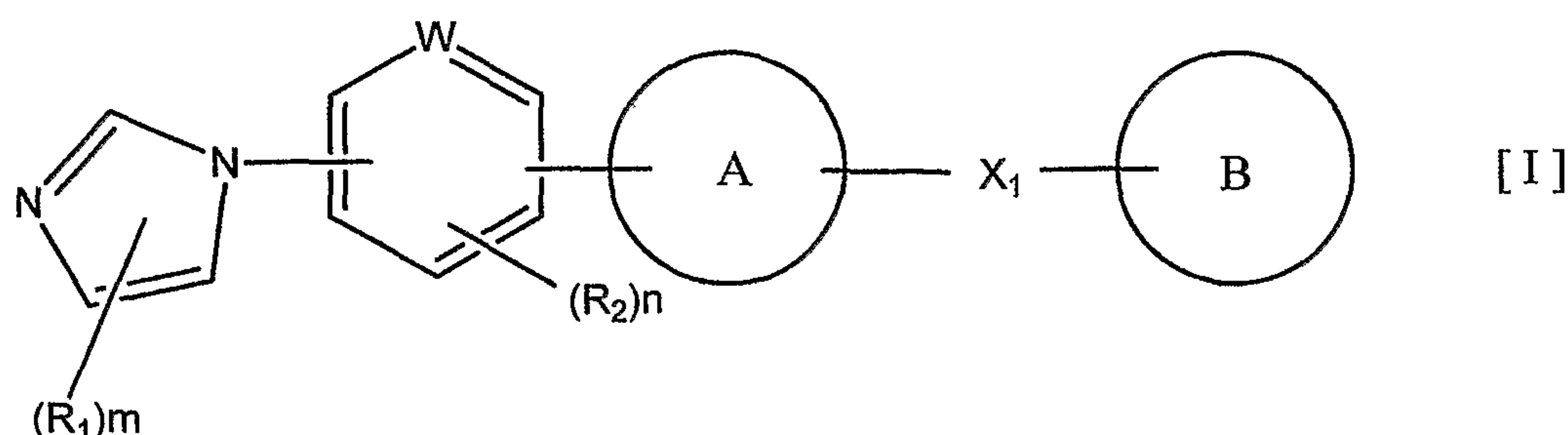
As a result of extensive studies, the present inventors have found a nonpeptidic polycyclic compound that inhibits the production of A β from APP and thus found a therapeutic agent for a disease caused by A β which is typified by Alzheimer's disease. This finding has led to the accomplishment of the present invention.

[0007]

Specifically, the present invention relates to the following 1) to 15):

1) A compound represented by the formula [I]:

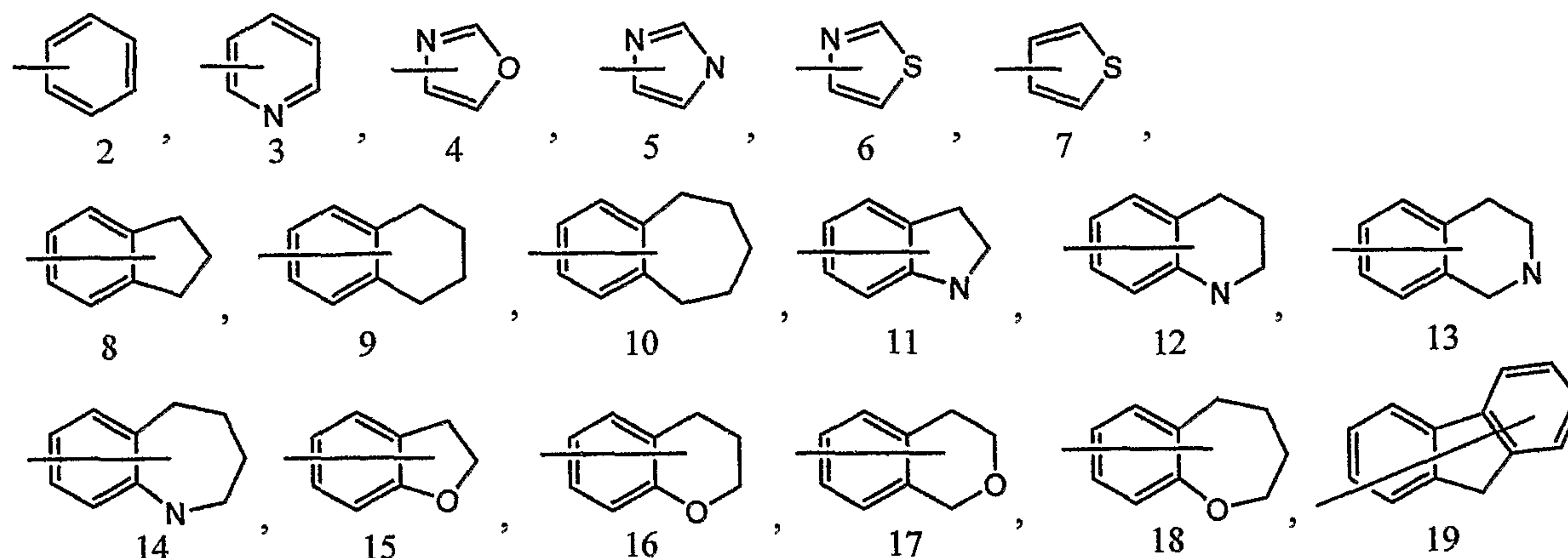
[0008]



[0009]

- 5 or a pharmacologically acceptable salt or ester thereof,
 wherein R_1 and R_2 are the same or different and each represent a substituent selected from the following Substituent Group a1;
 m represents an integer of 0 to 3;
 n represents an integer of 0 to 2;
- 10 W represents a nitrogen atom or a carbon atom;
 Ring A represents a five-membered aromatic heterocyclic group fused with a 5- to 14-membered non-aromatic ring group, which contains two or more nitrogen atoms and may have 1 to 3 substituents selected from the following Substituent Group b1 (wherein the 5- to 14-membered non-aromatic heterocyclic group may have a crosslinked structure);
- 15 X_1 represents i) a single bond, ii) a C1-6 alkylene group, iii) a vinylene group which may have 1 to 2 C1-6 alkyl groups or iv) $-X_2-$ (wherein X_2 represents $-NR_3-$, $-NR_3C(O)-$, $-C(O)NR_3-$, $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$ and R_3 represents a hydrogen atom, a C1-6 alkyl group, a C3-6 cycloalkyl group, a C2-6 alkanoyl group or a C1-6 alkylsulfonyl group); and
 Ring B represents a monocyclic or fused cyclic aromatic ring group selected from the formulas
- 20 [2] to [19]:
- [0010]

6



[0011]

each of which may have 1 to 3 substituents selected from the following Substituent Group c1

[Substituent Group a1: a C1-6 alkyl group, a C3-8 cycloalkyl group, a C2-6 alkenyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, an amino group (wherein the amino group may have one C2-6 alkanoyl group or C1-6 alkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group and a nitro group;

Substituent Group b1: a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C2-6 alkenyl group, a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C4-9 cycloalkylcarbonyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C2-6 alkenylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a C1-6 alkylthio group, a C2-6 alkenylthio group, a C3-8 cycloalkylthio group, an aminosulfonyl group (wherein the aminosulfonyl group may have 1 to 2 C1-6 alkyl groups, C2-6 alkenyl groups or C3-8 cycloalkyl groups), an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group, a nitro group, an oxo group, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 1-homopiperidinyl group, an indolin-1-yl group, a 1,2,3,4-

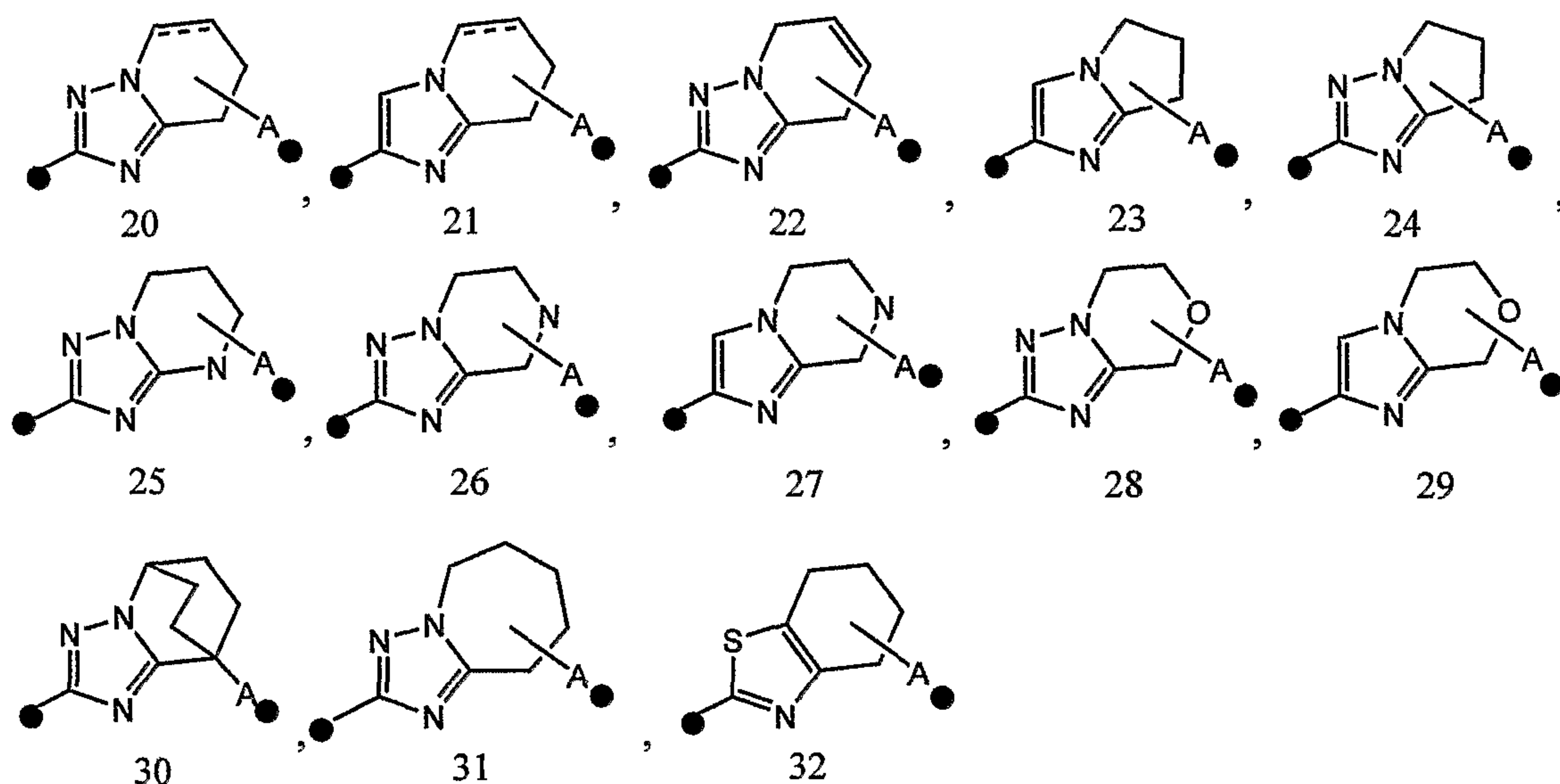
tetrahydroquinolin-1-yl group and a 4-morpholinyl group;

Substituent Group c1: i) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v-i) a C1-6 alkyl group, v-ii) a C2-6 alkenyl group, v-iii) a C2-6 alkynyl group, v-iv) a C1-6 alkoxy group, v-v) a C1-6 alkylaminocarbonyl group, v-vi) a C1-6 alkylaminosulfonyl group, v-vii) a C1-6 alkylsulfonyl group, v-viii) a C1-6 alkylthio group, v-ix) a C2-6 alkanoyl group, v-x) a

phenyl group, v-xi) a pyridyl group, v-xii) a pyridazinyl group, v-xiii) a pyrimidinyl group, v-xiv) a 1-pyrrolidinyl group, v-xv) a 1-piperidinyl group, v-xvi) a 1-homopiperidinyl group and v-xvii) a 4-morpholinyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom];

- 5 2) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein Ring A is any one ring selected from the group consisting of the formulas [20] to [32]:

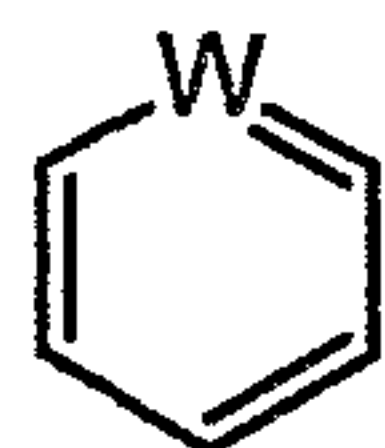
[0012]



[0013]

- 10 each of which may have 1 to 3 substituents selected from Substituent Group b1, wherein • represents a bonding site to the formula [33]:

[0014]



33

[0015]

A• represents a bonding site to X₁, and

- 15 [0016]



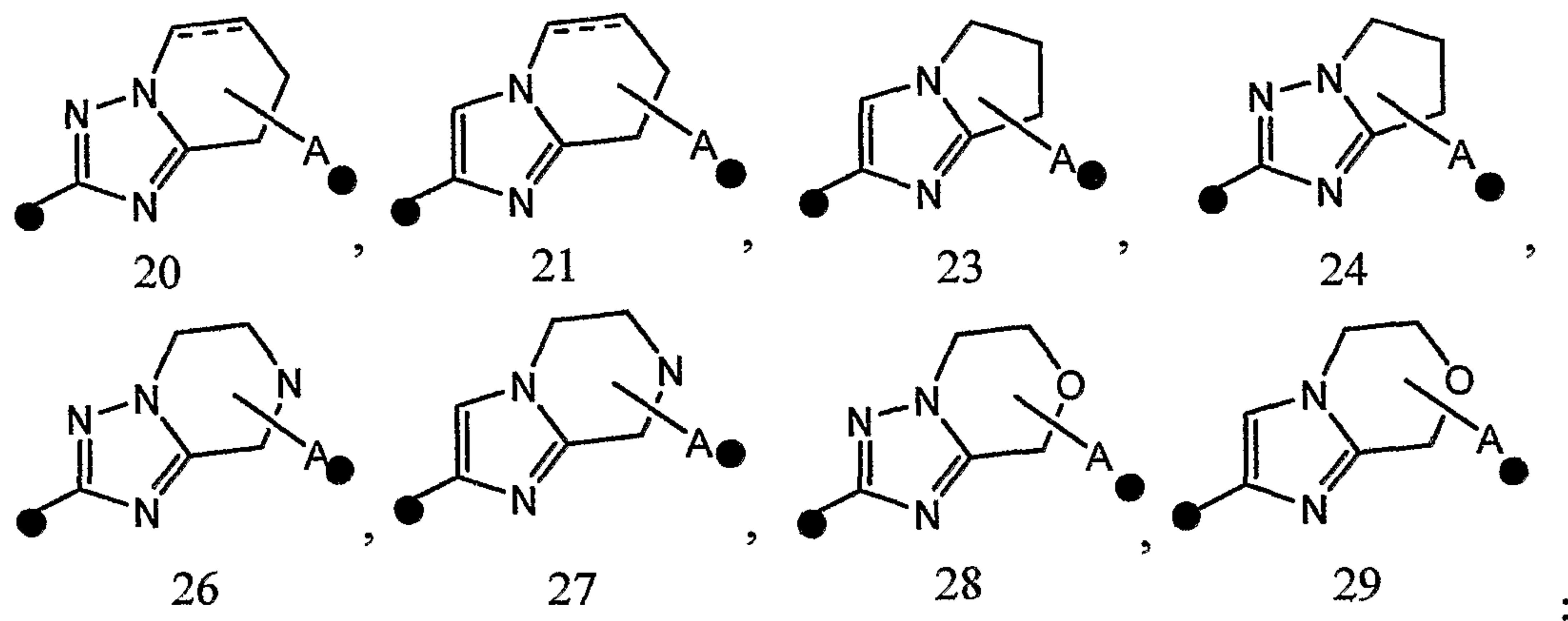
[0017]

represents a single bond or a double bond;

- 3) The compound or pharmacologically acceptable salt or ester thereof according to 2) above, wherein Ring A is any one ring selected from the group consisting of the formulas [20],

[21], [23], [24] and [26] to [29]:

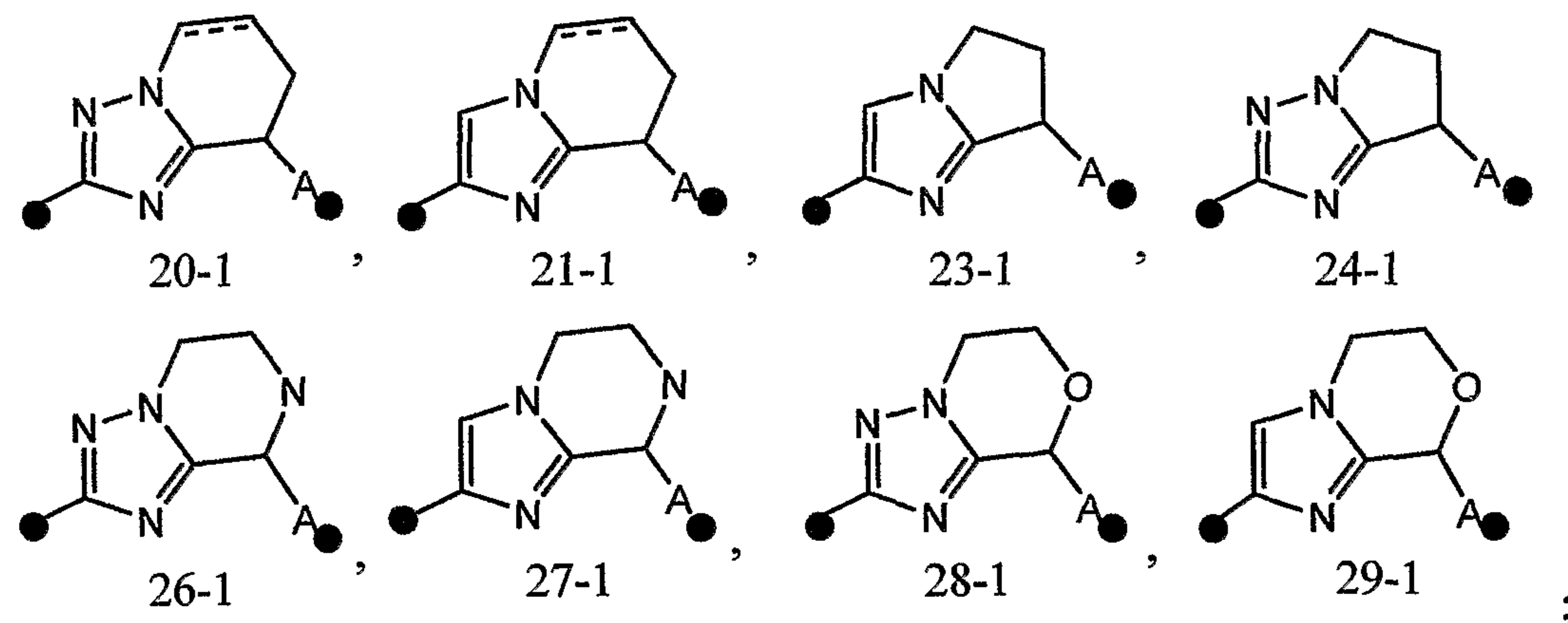
[0018]



[0019]

- 5 4) The compound or pharmacologically acceptable salt or ester thereof according to 2) above, wherein Ring A is any one ring selected from the group consisting of the formulas [20-1], [21-1], [23-1], [24-1] and [26-1] to [29-1]:

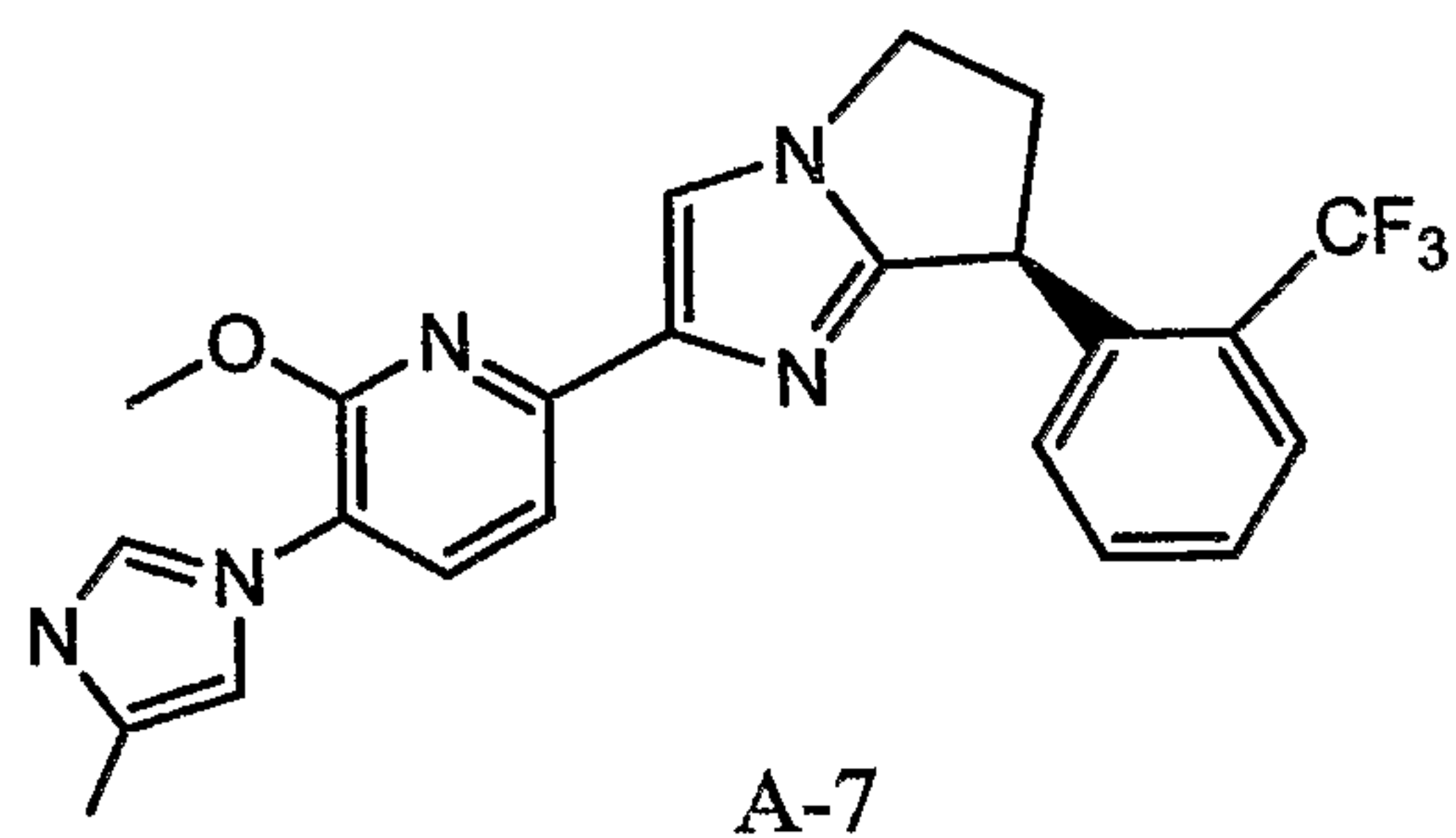
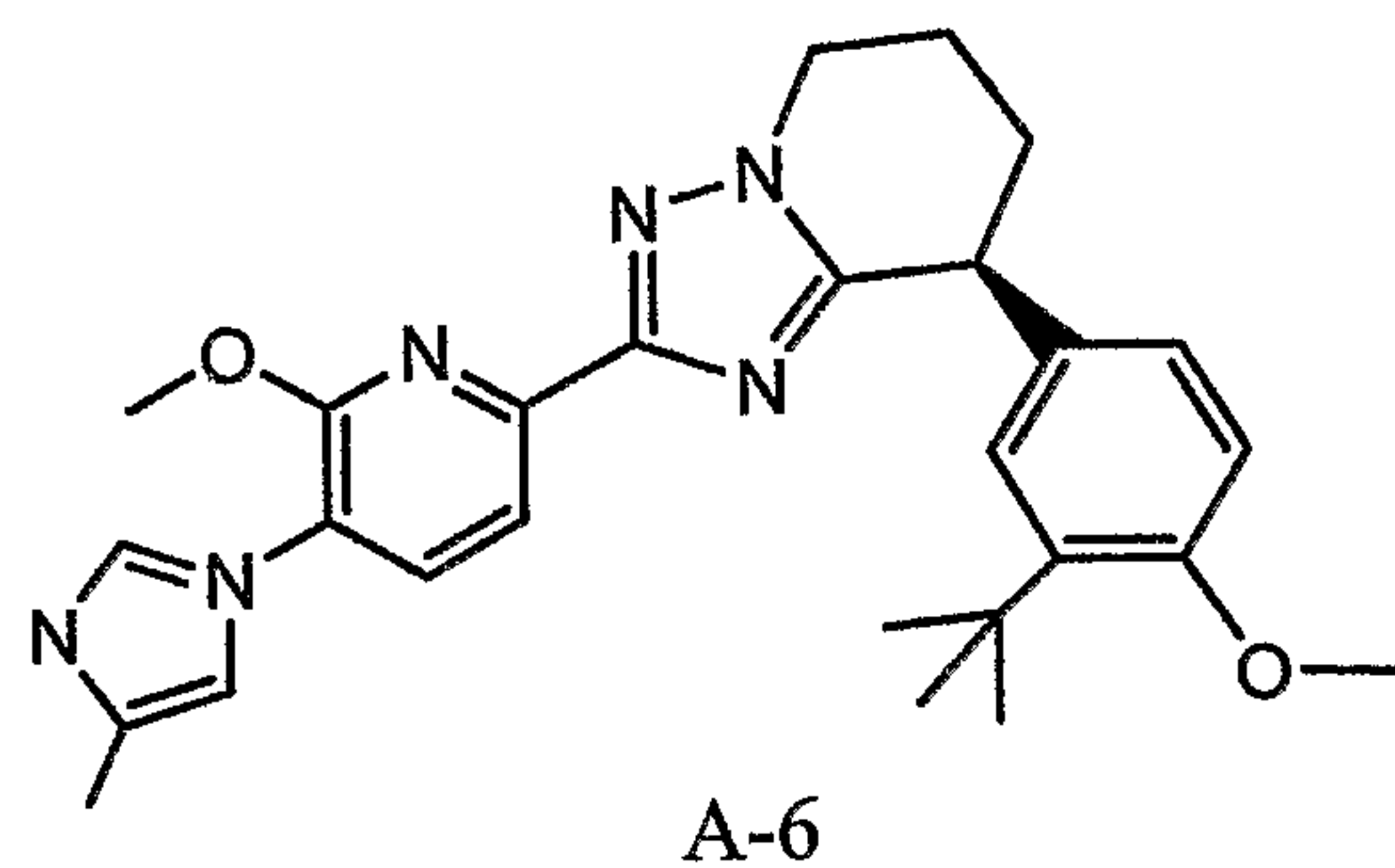
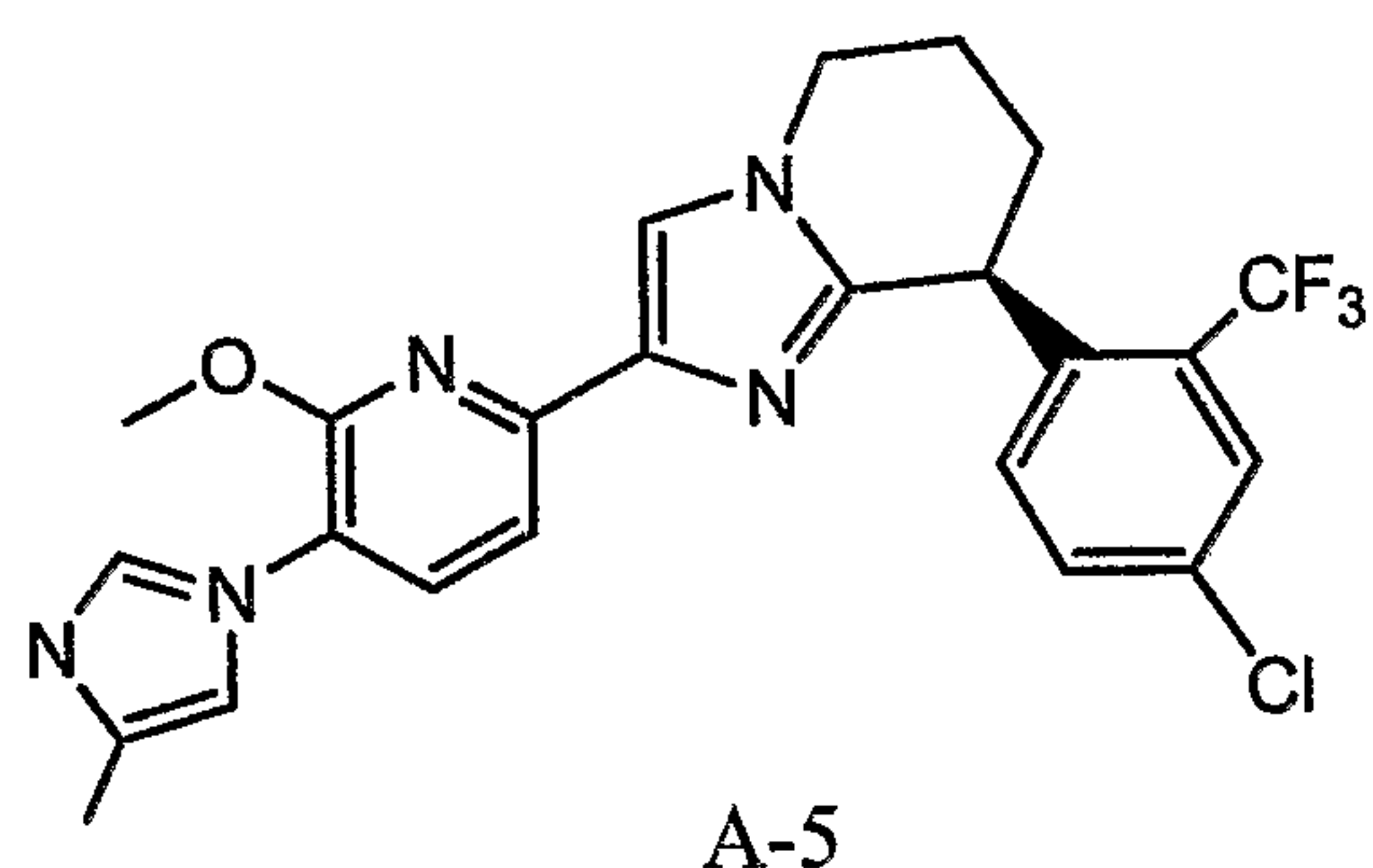
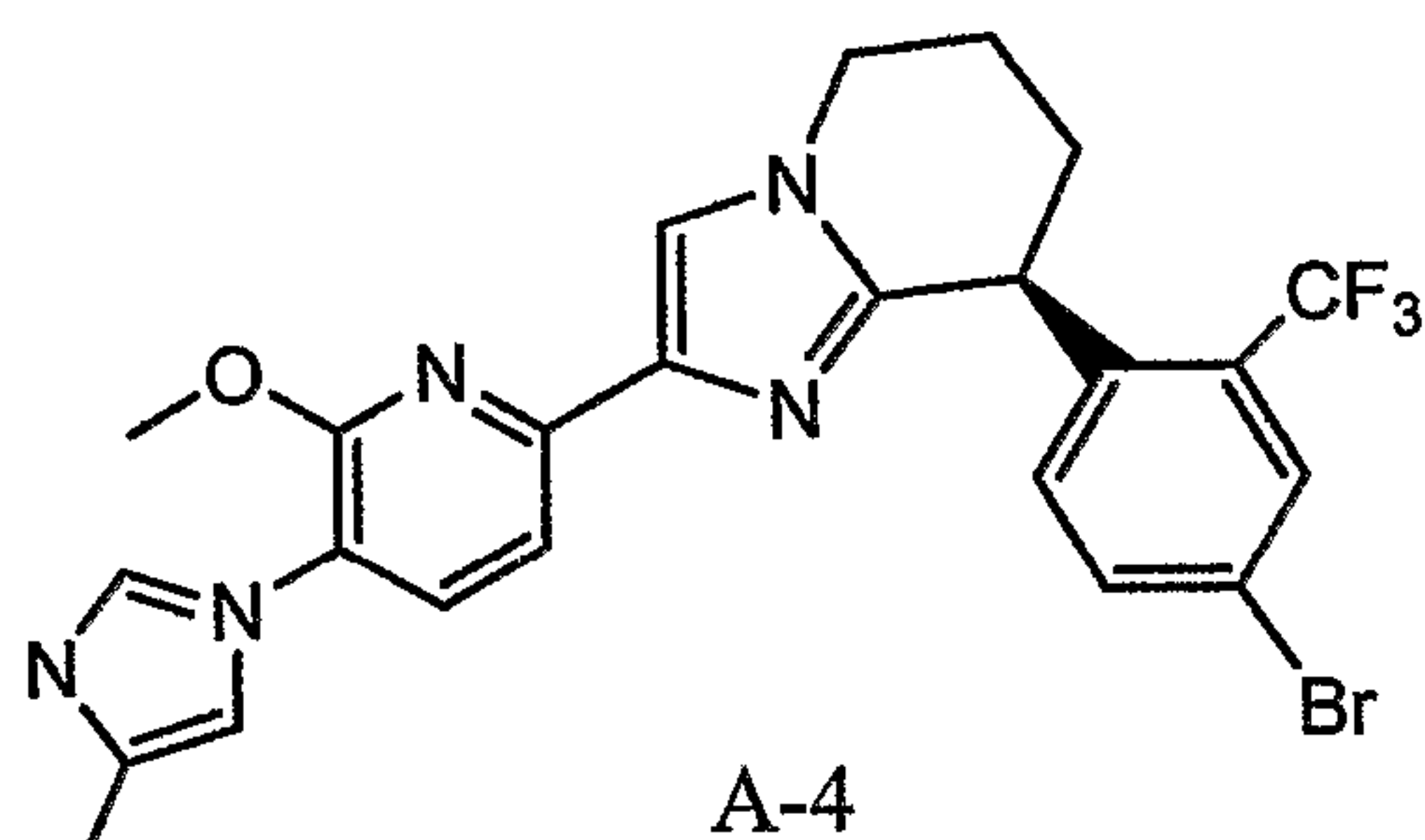
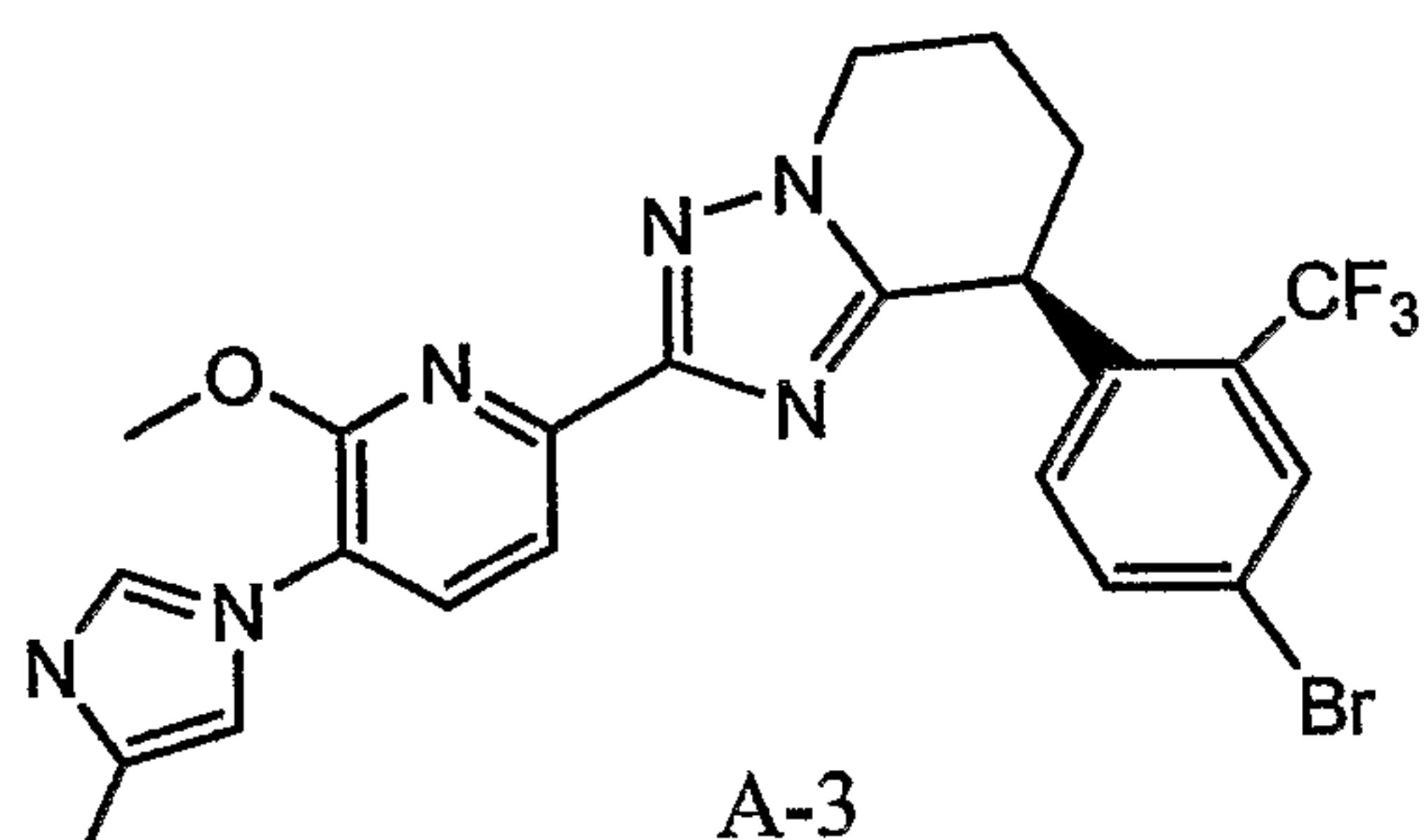
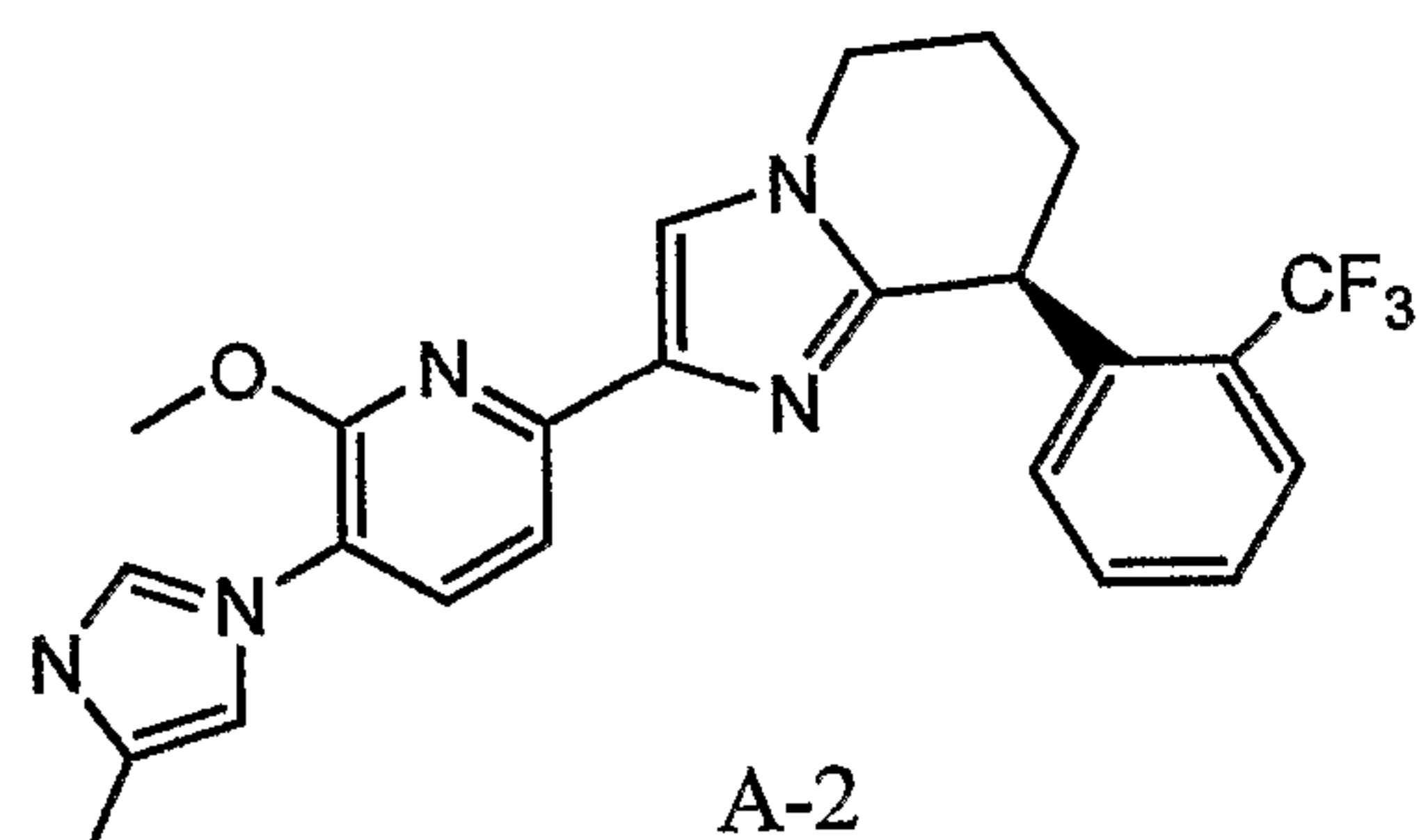
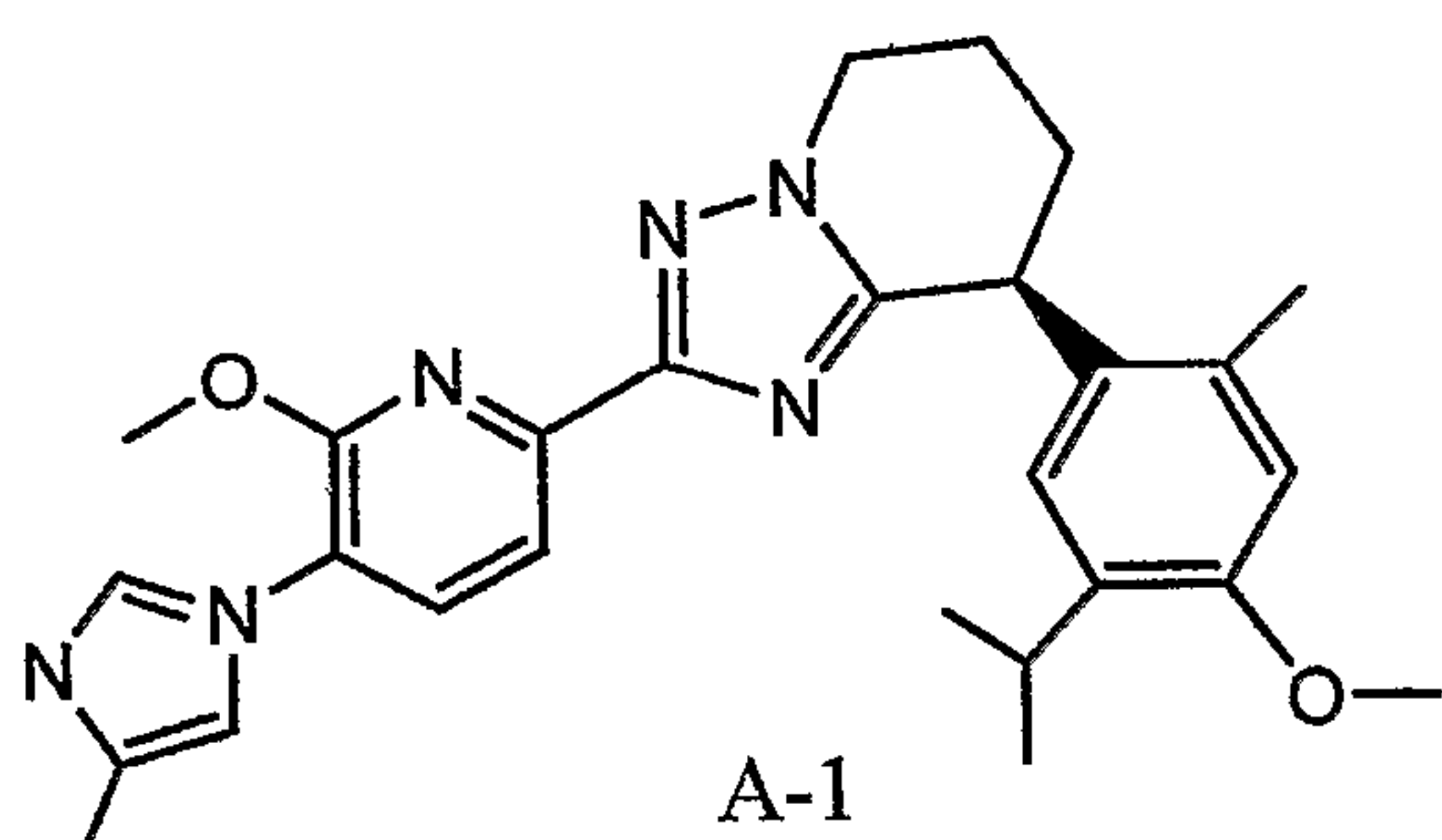
[0020]



10 [0021]

- 5) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein Ring B is a phenyl group, a pyridyl group, an oxazolyl group, an imidazolyl group, an thiazolyl group, a dihydrobenzofuranyl group or a thienyl group;
- 6) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein X_1 is i) a single bond or ii) a C1-6 alkylene group;
- 7) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein W is a carbon atom;
- 8) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein W is a nitrogen atom;
- 20 9) The compound or pharmacologically acceptable salt or ester thereof according to

- 1) above, wherein R₁ is a C1-6 alkyl group or a halogen atom and m is 1 to 2;
- 10) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein R₂ is a C1-6 alkoxy group and n is 1;
- 11) The compound or pharmacologically acceptable salt or ester thereof according to 5 1) above, wherein the substituent for Ring A is selected from the group consisting of: a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a cyano group, a formyl group, a 10 halogen atom, a hydroxyl group and an oxo group;
- 12) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein the substituent for Ring B is selected from the group consisting of: i) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a 15 cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v)-i) a C1-6 alkyl group, v)-ii) a C1-6 alkoxy group, v)-iii) a C1-6 alkylthio group and v)-iv) a phenyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom;
- 13) One compound selected from the group consisting of the following formulas [A- 20 1] to [A-7]:
- [0022]



[0023]

or a pharmacologically acceptable salt or ester thereof;

- 14) A medicine comprising the compound or pharmacologically acceptable salt or ester thereof according to any one of 1) to 13) above as an active ingredient; and
- 15) The medicine according to 14) above for the treatment of a disease selected from Alzheimer's disease, dementia, Down's syndrome and amyloidosis.

MODE FOR CARRYING OUT THE INVENTION

[0024]

The compound of the general formula (I) or pharmacologically acceptable salt thereof according to the present invention and the therapeutic agent for a disease caused by A β according to the present invention are novel inventions that have not yet been described in any documents.

The compound of the present invention can be converted to a chemical probe for capturing a target protein in a bioactive low-molecular compound. Specifically, the compound of the present invention can be converted to an affinity chromatography probe, a photoaffinity probe or the like by introducing a labeling group, a linker or the like into a moiety differing from a structural moiety essential for expression of activity of the compound by a technique described in J. Mass Spectrum. Soc. Jpn. Vol. 51, No. 5, 2003, p. 492-498 or WO 2007/139149, for example.

Examples of the labeling group, the linker or the like used for the chemical probe include groups shown in the following group consisting of (1) to (5):

(1) protein labeling groups such as photoaffinity labeling groups (such as a benzoyl group, a benzophenone group, an azido group, a carbonylazido group, a diaziridine group, an enone group, a diazo group and a nitro group) and chemical affinity groups (such as a ketone group substituted at the α -carbon atom with a halogen atom, a carbamoyl group, an ester group, an alkylthio group, Michael acceptors such as α,β -unsaturated ketones and esters, and an oxirane group),

(2) cleavable linkers such as -S-S-, -O-Si-O-, monosaccharides (such as a glucose group and a galactose group) and disaccharides (such as lactose), and enzymatically cleavable oligopeptide linkers,

(3) fishing tag groups such as biotin and 3-(4,4-difluoro-5,7-dimethyl-4H-3a,4a-diaza-4-bora-s-indacen-3-yl)propionyl,

(4) detectable markers such as radioactive labeling groups such as ^{125}I , ^{32}P , ^3H and ^{14}C ; fluorescence labeling groups such as fluorescein, rhodamine, dansyl, umbelliferone, 7-nitrofurazanyl and 3-(4,4-difluoro-5,7-dimethyl-4H-3a,4a-diaza-4-bora-s-indacen-3-yl)propionyl; chemiluminescent groups such as luciferin and luminol; and heavy metal ions such as lanthanoid metal ions and radium ions, and

(5) groups bound to solid-phase carriers such as glass beads, glass beds, microtiter plates, agarose beads, agarose beds, polystyrene beads, polystyrene beds, nylon beads and nylon beds.

When a probe is prepared by introducing a labeling group or the like selected from the group consisting of (1) to (5) above into the compound of the present invention in accordance with a method described in the above documents or the like, the probe can be used as a chemical probe for identification of labeled proteins useful for searching for novel drug targets, for example.

[0025]

Meanings of symbols, terms and the like used in the present specification will be explained and the present invention will be described in detail below.

[0026]

10 In the present specification, a structural formula of a compound may represent a certain isomer for convenience. However, the present invention includes all isomers and isomer mixtures such as geometric isomers which can be generated from the structure of a compound, optical isomers based on asymmetric carbon, stereoisomers and tautomers. The present invention is not limited to the description of a chemical formula for convenience and may
15 include any one of the isomers or mixtures thereof. Accordingly, the compound of the present invention may have an asymmetric carbon atom in the molecule and exist as an optically active compound or racemate, and the present invention includes each of the optically active compound and the racemate without limitations. Although crystal polymorphs of the compound may be present, the compound is not limited thereto as well and may be present as a single crystal form
20 or a mixture of single crystal forms. The compound may be an anhydride or hydrate.

The present invention also includes isotopically-labelled compounds, which are identical to the compounds of formula (I), except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention
25 include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{14}C , ^{18}F , ^{35}S , ^{123}I and ^{125}I .

Compounds of the present invention and pharmaceutically acceptable derivatives (e.g. salts) of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labelled compounds of
30 the present invention, for example those into which radioactive isotopes such as ^3H and/or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. ^3H and ^{14}C are considered useful due to their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are considered useful in PET (positron emission tomography), and ^{125}I isotopes are considered useful in SPECT (single photon emission computerized tomography), all useful in brain imaging.

Substitution with heavier isotopes such as ^2H can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, are considered useful in some circumstances. Isotopically labelled compounds of formula (I) of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

[0027]

The term "diseases attributable to $\text{A}\beta$ " includes a wide variety of conditions such as Alzheimer's disease (for example, refer to, Klein WL, and 7 others, Alzheimer's disease-affected brain: Presence of oligomeric $\text{A}\beta$ ligands (ADDLs) suggests a molecular basis for reversible memory loss, Proceeding National Academy of Science USA, 2003, Sep 2, 100 (18), p. 10417-10422; Nitsch RM, and 16 others, Antibodies against β -amyloid slow cognitive decline in Alzheimer's disease, Neuron, 2003, May 22, 38 (4), p. 547-554; Jarrett JT, and 2 others, The carboxy terminus of the β amyloid protein is critical for the seeding of amyloid formation: Implications for the pathogenesis of Alzheimer's disease, Biochemistry, 1993, May 11, 32 (18), p. 4693-4697; Glenner GG, and another, Alzheimer's disease; initial report of the purification and characterization of a novel cerebrovascular amyloid protein, Biochemical and biophysical research communications, 1984, May 16, 120 (3), p. 885-890; Masters CL, and 6 others, Amyloid plaque core protein in Alzheimer disease and Down syndrome, Proceeding National Academy of Science USA, 1985, June, 82 (12), p. 4245-4249; Gouras GK, and 11 others, Intraneuronal $\text{A}\beta_{42}$ accumulation in human brain, American journal of pathology, 2000, Jan, 156 (1), p. 15-20; Scheuner D, and 20 others, Secreted amyloid β -protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease, Nature Medicine, 1996, Aug, 2 (8), p. 864-870; Forman MS, and 4 others, Differential effects of the Swedish mutant amyloid precursor protein on β -amyloid accumulation and secretion in neurons and nonneuronal cells, The journal of biological chemistry, 1997, Dec 19, 272 (51), p. 32247-32253), senile dementia (for example, refer to, Blass JP, Brain metabolism and brain disease: Is metabolic deficiency the proximate cause of Alzheimer dementia? Journal of Neuroscience Research, 2001, Dec 1, 66 (5), p. 851-856), frontotemporal dementia (for example, refer to, Evin G, and 11 others, Alternative transcripts of presenilin-1 associated with frontotemporal dementia, Neuroreport, 2002, Apr 16, 13 (5), p. 719-723), Pick disease (for example, refer to, Yasuhara O, and 3 others, Accumulation of amyloid precursor protein in brain lesions of patients with Pick disease, Neuroscience Letters, 1994, Apr

25, 171 (1-2), p. 63-66), Down's syndrome (for example, refer to, Teller JK, and 10 others, Presence of soluble amyloid β -peptide precedes amyloid plaque formation in Down's syndrome, Nature Medicine, 1996, Jan, 2 (1), p. 93-95; Tokuda T, and 6 others, Plasma levels of amyloid β proteins A β 1-40 and A β 1-42 (43) are elevated in Down's syndrome, Annals of Neurology, 1997, 5 Feb, 41 (2), p. 271-273), cerebrovascular angiopathy (for example, refer to, Hayashi Y, and 9 others, Evidence for presenilin-1 involvement in amyloid angiopathy in the Alzheimer's disease-affected brain, Brain Research, 1998, Apr 13, 789 (2), p. 307-314; Barelli H, and 15 others, Characterization of new polyclonal antibodies specific for 40 and 42 amino acid-long amyloid β peptides: their use to examine the cell biology of presenilins and the immunohistochemistry of 10 sporadic Alzheimer's disease and cerebral amyloid angiopathy cases, Molecular Medicine, 1997, Oct, 3 (10), p. 695-707; Calhoun ME, and 10 others, Neuronal overexpression of mutant amyloid precursor protein results in prominent deposition of cerebrovascular amyloid, Proceeding National Academy of Science USA, 1999, Nov 23, 96 (24), p. 14088-14093; Dermaut B, and 10 others, Cerebral amyloid angiopathy is a pathogenic lesion in Alzheimer's Disease due to a novel 15 presenilin-1 mutation, Brain, 2001, Dec, 124 (12), p. 2383-2392), hereditary cerebral hemorrhage with amyloidosis (Dutch type) (for example, refer to, Cras P, and 9 others, Presenile Alzheimer dementia characterized by amyloid angiopathy and large amyloid core type senile plaques in the APP 692Ala --> Gly mutation, Acta Neuropathologica (Berl), 1998, Sep, 96 (3), p. 253-260; Herzig MC, and 14 others, A β is targeted to the vasculature in a mouse model of 20 hereditary cerebral hemorrhage with amyloidosis, Nature Neuroscience, 2004, Sep, 7 (9), p. 954-960; van Duinen SG, and 5 others, Hereditary cerebral hemorrhage with amyloidosis in patients of Dutch origin is related to Alzheimer disease, Proceeding National Academy of Science USA, 1987, Aug, 84 (16), p. 5991-5994; Levy E, and 8 others, Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type, Science, 1990, Jun 1, 248 (4959), 25 p. 1124-1126), cognitive impairment (for example, refer to, Laws SM, and 7 others, Association between the presenilin-1 mutation Glu318Gly and complaints of memory impairment, Neurobiology of Aging, 2002, Jan-Feb, 23 (1), p. 55-58), memory disturbance/learning disturbance (for example, refer to, Vaucher E, and 5 others, Object recognition memory and cholinergic parameters in mice expressing human presenilin 1 transgenes, Experimental 30 Neurology, 2002 Jun, 175 (2), p. 398-406; Morgan D, and 14 others, A β peptide vaccination prevents memory loss in an animal model of Alzheimer's disease, Nature, 2000 Dec 21-28, 408 (6815), p. 982-985; Moran PM, and 3 others, Age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β -amyloid precursor protein, Proceeding

National Academy of Science USA, 1995, June 6, 92 (12), p. 5341-5345), amyloidosis, cerebral ischemia (for example, refer to, Laws SM, and 7 others, Association between the presenilin-1 mutation Glu318Gly and complaints of memory impairment, *Neurobiology of Aging*, 2002, Jan-Feb, 23 (1), p. 55-58; Koistinaho M, and 10 others, β -amyloid precursor protein transgenic mice that harbor diffuse A β deposits but do not form plaques show increased ischemic vulnerability: Role of inflammation, *Proceeding National Academy of Science USA*, 2002, Feb 5, 99 (3), p. 1610-1615; Zhang F, and 4 others, Increased susceptibility to ischemic brain damage in transgenic mice overexpressing the amyloid precursor protein, *The journal of neuroscience*, 1997, Oct 15, 17 (20), p. 7655-7661), cerebrovascular dementia (for example, refer to, Sadowski M, and 6 others, Links between the pathology of Alzheimer's disease and vascular dementia, *Neurochemical Research*, 2004, Jun, 29 (6), p. 1257-1266), ophthalmoplegia (for example, refer to, O'Riordan S, and 7 others, Presenilin-1 mutation (E280G), spastic paraparesis, and cranial MRI white-matter abnormalities, *Neurology*, 2002, Oct 8, 59 (7), p. 1108-1110), multiple sclerosis (for example, refer to, Gehrman J, and 4 others, Amyloid precursor protein (APP) expression in multiple sclerosis lesions, *Glia*, 1995, Oct, 15 (2), p. 141-51; Reynolds WF, and 6 others, Myeloperoxidase polymorphism is associated with gender specific risk for Alzheimer's disease, *Experimental Neurology*, 1999, Jan, 155 (1), p. 31-41), head injury, skull damage (for example, refer to, Smith DH, and 4 others, Protein accumulation in traumatic brain injury, *NeuroMolecular Medicine*, 2003, 4 (1-2), p. 59-72), apraxia (for example, refer to, Matsubara-Tsutsui M, and 7 others, Molecular evidence of presenilin 1 mutation in familial early onset dementia, *American journal of Medical Genetics*, 2002, Apr 8, 114 (3), p. 292-298), prion disease, familial amyloid neuropathy, triplet repeat disease (for example, refer to, Kirkitadze MD, and 2 others, Paradigm shifts in Alzheimer's disease and other neurodegenerative disorders: the emerging role of oligomeric assemblies, *Journal of Neuroscience Research*, 2002, Sep 1, 69 (5), p. 567-577; Evert BO, and 8 others, Inflammatory genes are upregulated in expanded ataxin-3-expressing cell lines and spinocerebellar ataxia type 3 brains, *The Journal of Neuroscience*, 2001, Aug 1, 21 (15), p. 5389-5396; Mann DM, and another, Deposition of amyloid (A4) protein within the brains of persons with dementing disorders other than Alzheimer's disease and Down's syndrome, *Neuroscience Letters*, 1990, Feb 5, 109 (1-2), p. 68-75), Parkinson's disease (for example, refer to, Primavera J, and 4 others, Brain accumulation of amyloid- β in Non-Alzheimer Neurodegeneration, *Journal of Alzheimer's Disease*, 1999, Oct, 1 (3), p. 183-193), Dementia with Lewy bodies (for example, refer to, Giasson BI, and 2 others, Interactions of amyloidogenic proteins. *NeuroMolecular Medicine*, 2003, 4 (1-2), p. 49-58; Masliah E, and 6 others, β -amyloid peptides enhance α -synuclein accumulation and neuronal

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[0028]

The "Substituent Group a1", "Substituent Group b1" and "Substituent Group c1" have the following meanings in the compound represented by the formula (I) effective for the treatment or prevention of a disease caused by A β according to the present invention.

[0029]

The "Substituent Group a1" refers to a group consisting of a C1-6 alkyl group, a C3-8 cycloalkyl group, a C2-6 alkenyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, an amino group (wherein the amino group may have one C2-6 alkanoyl group or C1-6 alkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group and a nitro group.

[0030]

The "Substituent Group b1" refers to a group consisting of a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C2-6 alkenyl group, a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C4-9 cycloalkylcarbonyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C2-6 alkenylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a C1-6 alkylthio group, a C2-6 alkenylthio group, a C3-8 cycloalkylthio group, an aminosulfonyl group (wherein the aminosulfonyl group may have 1 to 2 C1-6 alkyl groups, C2-6 alkenyl groups or C3-8 cycloalkyl groups), an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group, a nitro group, an oxo group, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 1-homopiperidinyl group, an indolin-1-yl group, a 1,2,3,4-tetrahydroquinolin-1-yl group and a 4-morpholinyl group.

[0031]

The "Substituent Group c1" refers to an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v-i) a C1-6 alkyl group, v-ii) a C2-6 alkenyl group, v-iii) a C2-6 alkynyl group, v-iv) a C1-6 alkoxy group, v-v) a C1-6 alkylthio group, v-vi) a C1-6 alkylaminocarbonyl group, v-vii) a C1-6 alkylsulfonyl group, v-viii) a C1-6 alkylaminosulfonyl group, v-ix) a C2-6 alkanoyl group, v-x) a phenyl group, v-xi) a pyridyl group, v-xii) a pyridazinyl group, v-xiii) a

pyrimidinyl group, v-xiv) a 1-pyrrolidinyl group, v-xv) a 1-piperidinyl group, v-xvi) a 1-homopiperidinyl group and v-xvii) a 4-morpholinyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom.

[0032]

5 The "halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom, an iodine atom or the like and is preferably a fluorine atom, a chlorine atom or a bromine atom.

[0033]

 The "C1-6 alkyl group" refers to an alkyl group having 1 to 6 carbon atoms.

Preferable examples of the group include linear or branched alkyl groups such as a methyl group,
10 an ethyl group, an n-propyl group, an i-propyl group, an n-butyl group, an i-butyl group, a tert-butyl group, an n-pentyl group, an i-pentyl group, a neopentyl group, an n-hexyl group, a 1-methylpropyl group, an 1,2-dimethylpropyl group, a 1-ethylpropyl group, a 1-methyl-2-ethylpropyl group, a 1-ethyl-2-methylpropyl group, a 1,1,2-trimethylpropyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl
15 group, a 2-ethylbutyl group, a 1,3-dimethylbutyl group, a 2-methylpentyl group and a 3-methylpentyl group.

[0034]

 The "C1-6 alkylene group" refers to an alkylene group having 1 to 6 carbon atoms. Preferable examples of the group include linear or branched alkyl groups such as a
20 methylene group, an ethylene group, a methylenemethylene group, a propylene group, a methylethylene group, an ethylenemethylene group, a dimethylenemethylene group, a butylene group, a methylpropylene group, an ethylethylene group, a dimethylethylene group, a propylenemethylene group, a pentylene group and a hexylene group. Among these, a methylene group, an ethylene group, a methylenemethylene group, a propylene group, a methylethylene group, an ethylenemethylene
25 group and a dimethylenemethylene group are preferable, for example.

[0035]

 The "C3-8 cycloalkyl group" refers to a cyclic alkyl group having 3 to 8 carbon atoms. Preferable examples of the group include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group and a cyclooctyl group.

30 [0036]

 The "C2-6 alkenyl group" refers to an alkenyl group having 2 to 6 carbon atoms.

Preferable examples of the group include linear or branched alkenyl groups such as a vinyl group, an allyl group, a 1-propenyl group, an isopropenyl group, a 1-buten-1-yl group, a 1-buten-2-yl group, a 1-buten-3-yl group, a 2-buten-1-yl group and a 2-buten-2-yl group.

[0037]

The "C2-6 alkynyl group" refers to an alkynyl group having 2 to 6 carbon atoms. Preferable examples of the group include linear or branched alkynyl groups such as an ethynyl group, a 1-propynyl group, a 2-propynyl group, a butynyl group, a pentynyl group and a hexynyl group.

[0038]

The "C3-8 cycloalkyloxy group" refers to a cyclic alkyl group having 3 to 8 carbon atoms in which one hydrogen atom is replaced by an oxygen atom. Preferable examples of the group include a cyclopropoxy group, a cyclobutoxy group, a cyclopentoxy group, a cyclohexoxy group, a cycloheptyloxy group and a cyclooctyloxy group.

[0039]

The "C3-8 cycloalkylthio group" refers to a cyclic alkyl group having 3 to 8 carbon atoms in which one hydrogen atom is replaced by a sulfur atom. Preferable examples of the group include a cyclopropylthio group, a cyclobutylthio group, a cyclopentylthio group, a cyclohexylthio group, a cycloheptylthio group and a cyclooctylthio group.

[0040]

The "C1-6 alkoxy group" refers to an alkyl group having 1 to 6 carbon atoms in which a hydrogen atom is replaced by an oxygen atom. Preferable examples of the group include a methoxy group, an ethoxy group, an n-propoxy group, an i-propoxy group, an n-butoxy group, an i-butoxy group, a sec-butoxy group, a tert-butoxy group, an n-pentoxy group, an i-pentoxy group, a sec-pentoxy group, a tert-pentoxy group, an n-hexoxy group, an i-hexoxy group, a 1,2-dimethylpropoxy group, a 2-ethylpropoxy group, a 1-methyl-2-ethylpropoxy group, a 1-ethyl-2-methylpropoxy group, a 1,1,2-trimethylpropoxy group, a 1,1,2-trimethylpropoxy group, a 1,1-dimethylbutoxy group, a 2,2-dimethylbutoxy group, a 2-ethylbutoxy group, a 1,3-dimethylbutoxy group, a 2-methylpentoxy group, a 3-methylpentoxy group and a hexyloxy group.

[0041]

The "C1-6 alkylthio group" refers to an alkyl group having 1 to 6 carbon atoms in which one hydrogen atom is replaced by a sulfur atom. Preferable examples of the group include a methylthio group, an ethylthio group, an n-propylthio group, an i-propylthio group, an n-butylthio group, an i-butylthio group, a tert-butylthio group, an n-pentylthio group, an i-pentylthio group, a neopentylthio group, an n-hexylthio group and a 1-methylpropylthio group.

[0042]

The "C2-6 alkanoyl group" refers to an alkyl group having 1 to 6 carbon atoms in

which one hydrogen atom is substituted with a carbonyl group. Preferable examples of the group include an acetyl group, a propionyl group and a butyryl group.

[0043]

The "C1-6 alkylsulfonyl group" refers to an alkyl group having 1 to 6 carbon atoms in which one hydrogen atom is replaced by a sulfonyl group. Preferable examples of the group include a methanesulfonyl group and an ethanesulfonyl group.

[0044]

The "C2-6 alkenyloxy group" refers to an alkenyl group having 2 to 6 carbon atoms in which one hydrogen atom is replaced by an oxygen atom. Preferable examples of the group include linear or branched alkenyloxy groups such as a vinyloxy group, an allyloxy group, a 1-propenyloxy group, an isopropenyloxy group, a 1-buten-1-yloxy group, a 1-buten-2-yloxy group, a 1-buten-3-yloxy group, a 2-buten-1-yloxy group and a 2-buten-2-yloxy group.

[0045]

The "C2-6 alkenylthio group" refers to an alkenyl group having 2 to 6 carbon atoms in which one hydrogen atom is replaced by a sulfur atom. Preferable examples of the group include linear or branched alkenylsulfonyl groups such as a vinylthio group, an allylthio group, a 2-propenylthio group, a 1-buten-1-ylthio group, a 1-buten-2-ylthio group, a 1-buten-3-ylthio group, a 2-buten-1-ylthio group and a 2-buten-2-ylthio group.

[0046]

The "C2-6 alkenylsulfonyl group" refers to an alkenyl group having 2 to 6 carbon atoms in which one hydrogen atom is replaced by a sulfonyl group. Preferable examples of the group include a vinylsulfonyl group, an allylsulfonyl group, a 2-propenylsulfonyl group, a 1-buten-1-ylsulfonyl group, a 1-buten-2-ylsulfonyl group and a 1-buten-3-ylsulfonyl group.

[0047]

The "C3-8 cycloalkylsulfonyl group" refers to a cyclic alkyl group having 3 to 8 carbon atoms in which one hydrogen atom is replaced by a sulfonyl group. Preferable examples of the group include a cyclopropylsulfonyl group, a cyclobutylsulfonyl group, a cyclopentylsulfonyl group, a cyclohexylsulfonyl group, a cycloheptylsulfonyl group and a cyclooctylsulfonyl group.

[0048]

The "C6-14 aryl group" refers to a monocyclic, bicyclic or tricyclic aromatic hydrocarbon ring group having 6 to 14 carbon atoms. Preferable examples of the group include 6- to 14-membered monocyclic, bicyclic or tricyclic aromatic hydrocarbon ring groups such as a phenyl group, an indenyl group, a naphthyl group, an azulenyl group, a heptalenyl group, a

biphenyl group, a fluorenyl group, a phenalenyl group, a phenanthryl group and an anthryl group.

[0049]

The "C7-15 aroyl group" refers to the aforementioned C6-14 aryl group in which one hydrogen atom is replaced by a carbonyl group. Preferable examples of the group include a benzoyl group, an indenecarbonyl group, a naphthoyl group, a biphenylcarbonyl group, a fluorenylcarbonyl group, a phenanthrylcarbonyl group and an anthrylcarbonyl group.

[0050]

The "C6-14 aryl-C1-6 alkyl group" refers to the aforementioned C1-6 alkyl group in which one hydrogen atom is replaced by the aforementioned C6-14 aryl group. Preferable examples of the group include a benzyl group, a phenethyl group, a phenylpropyl group, a naphthylmethyl group and a biphenylmethyl group.

[0051]

The "C6-14 arylsulfonyl group" refers to the aforementioned C6-14 aryl group in which one hydrogen atom is replaced by a sulfonyl group. Preferable examples of the group include a benzenesulfonyl group, a naphthalenesulfonyl group and a biphenylsulfonyl group.

[0052]

The "C1-6 alkylaminocarbonyl group" refers to an alkyl group having 1 to 6 carbon atoms in which one hydrogen atom is replaced by an aminocarbonyl group. Preferable examples of the group include a methylaminocarbonyl group, an ethylaminocarbonyl group, a propylaminocarbonyl group, a butylaminocarbonyl group and a hexylaminocarbonyl group.

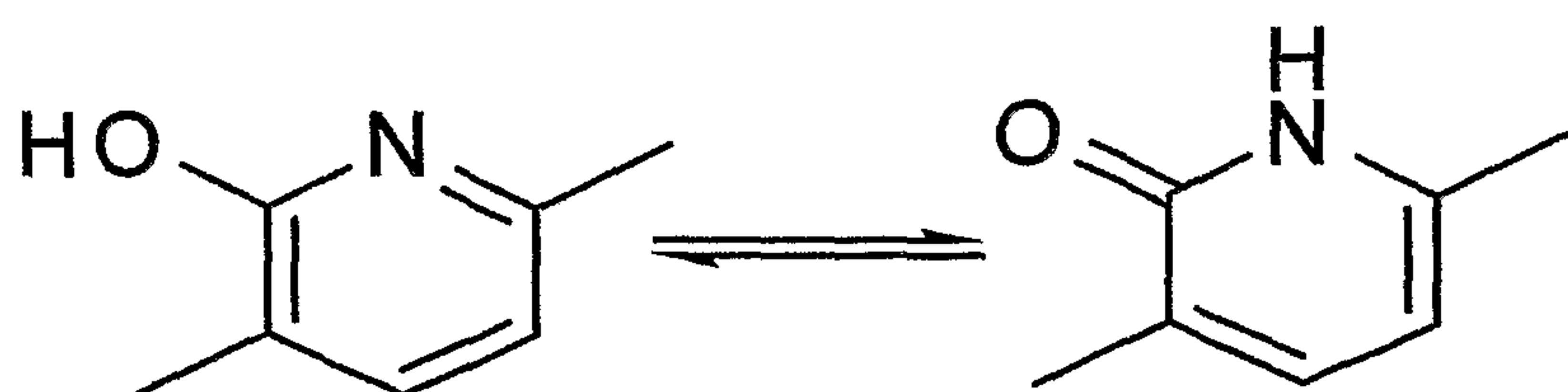
[0053]

The "C1-6 alkylaminosulfonyl group" refers to an alkyl group having 1 to 6 carbon atoms in which one hydrogen atom is replaced by an aminocarbonyl group. Preferable examples of the group include a methylaminosulfonyl group, an ethylaminosulfonyl group, a propylaminosulfonyl group, a butylaminosulfonyl group and a hexylaminosulfonyl group.

[0054]

When W is a nitrogen atom and R² is a hydroxyl group, the compound includes, for example, a tautomer represented by the formula:

30 [0055]



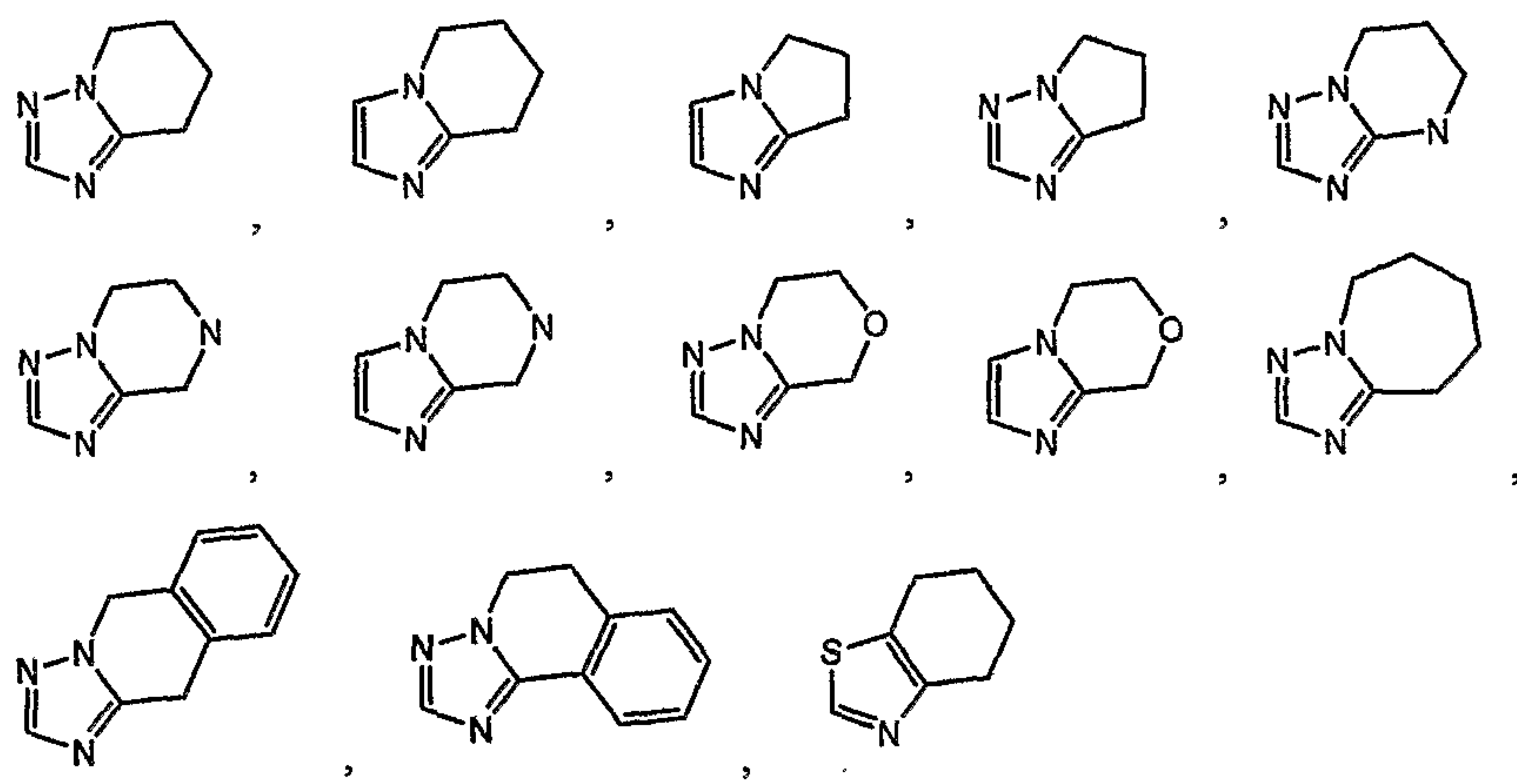
[0056]

The "five-membered aromatic heterocyclic group fused with a 5- to 14-membered non-aromatic ring group, which contains one or more nitrogen atoms and may have 1 to 3 substituents selected from the following Substituent Group b1" in the definition of Ring A refers

5 [0057]

to a five-membered aromatic heterocycle containing one or more nitrogen atoms, such as pyrazole, imidazole, triazole, tetrazole, oxazole, thiazole, oxadiazole or thiadiazole, fused with a 5- to 14-membered non-aromatic ring such as a ring represented by the following formula:

[0058]



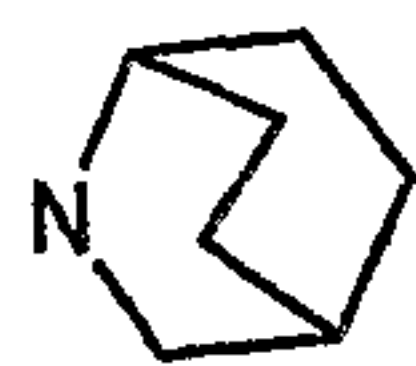
10 [0059]

One to three substituents selected from Substituent Group b1 may exist at any substitutable position on the ring.

[0060]

15 The sentence "the 5- to 14-membered non-aromatic heterocyclic group may have a crosslinked structure" in the definition of Ring A refers to the fact that two carbon atoms on the non-aromatic ring group together can form a crosslinked structure. For example, a ring having a crosslinked structure represented by the formula:

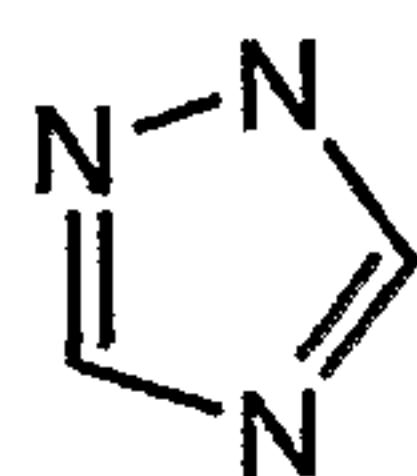
[0061]



[0062]

20 together with the aforementioned five-membered aromatic heterocyclic group such as the following triazolyl ring:

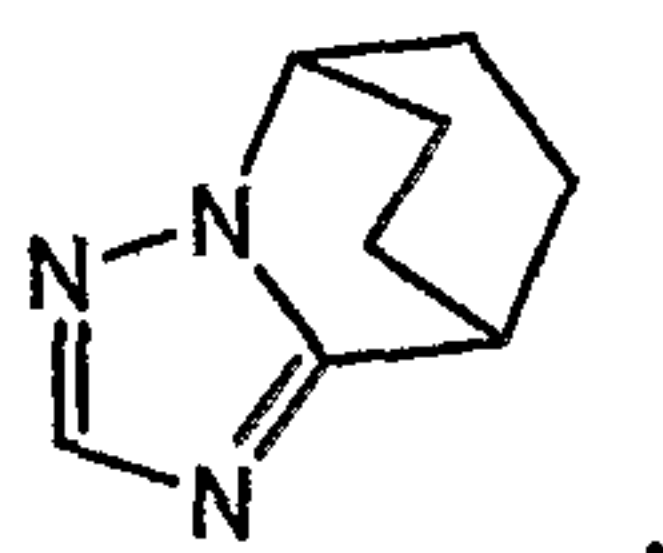
[0063]



[0064]

may form a fused ring represented by the following formula:

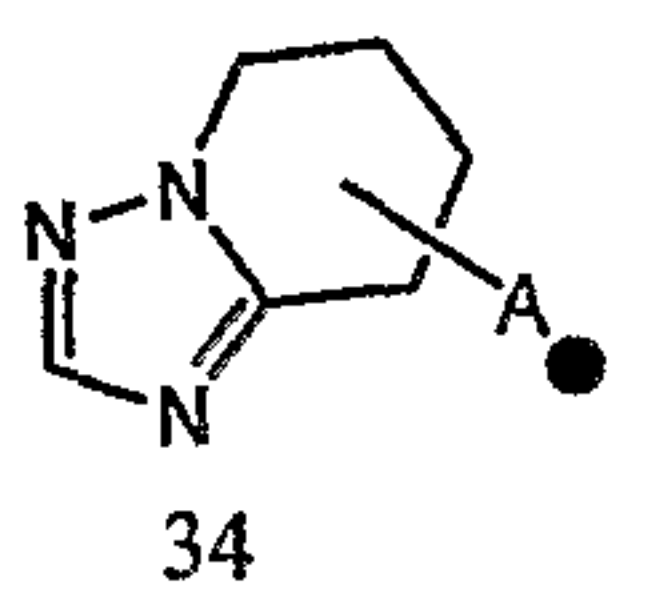
[0065]



[0066]

- 5 Ring A may be connected to X_1 at a substitutable position on the ring other than the five-membered aromatic heterocycle forming the fused ring. For example, when the connection between Ring A and X_1 is represented by the formula [34]:

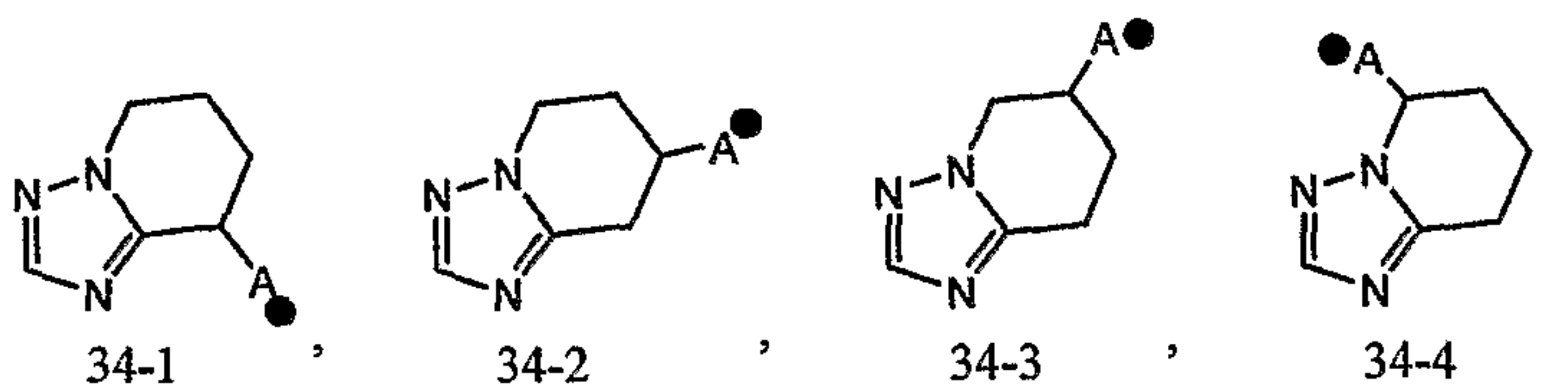
[0067]



- 10 [0068]

Ring A may be connected to X_1 at a substitutable position indicated by any one of the following formulas [34-1] to [34-4]:

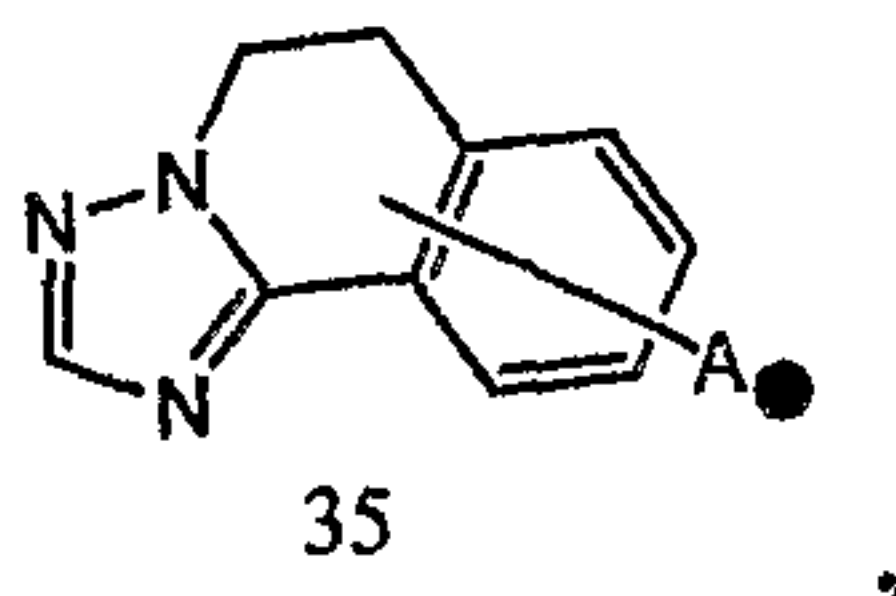
[0069]



- 15 [0070]

When the connection between Ring A and X_1 is represented by the formula [35]:

[0071]

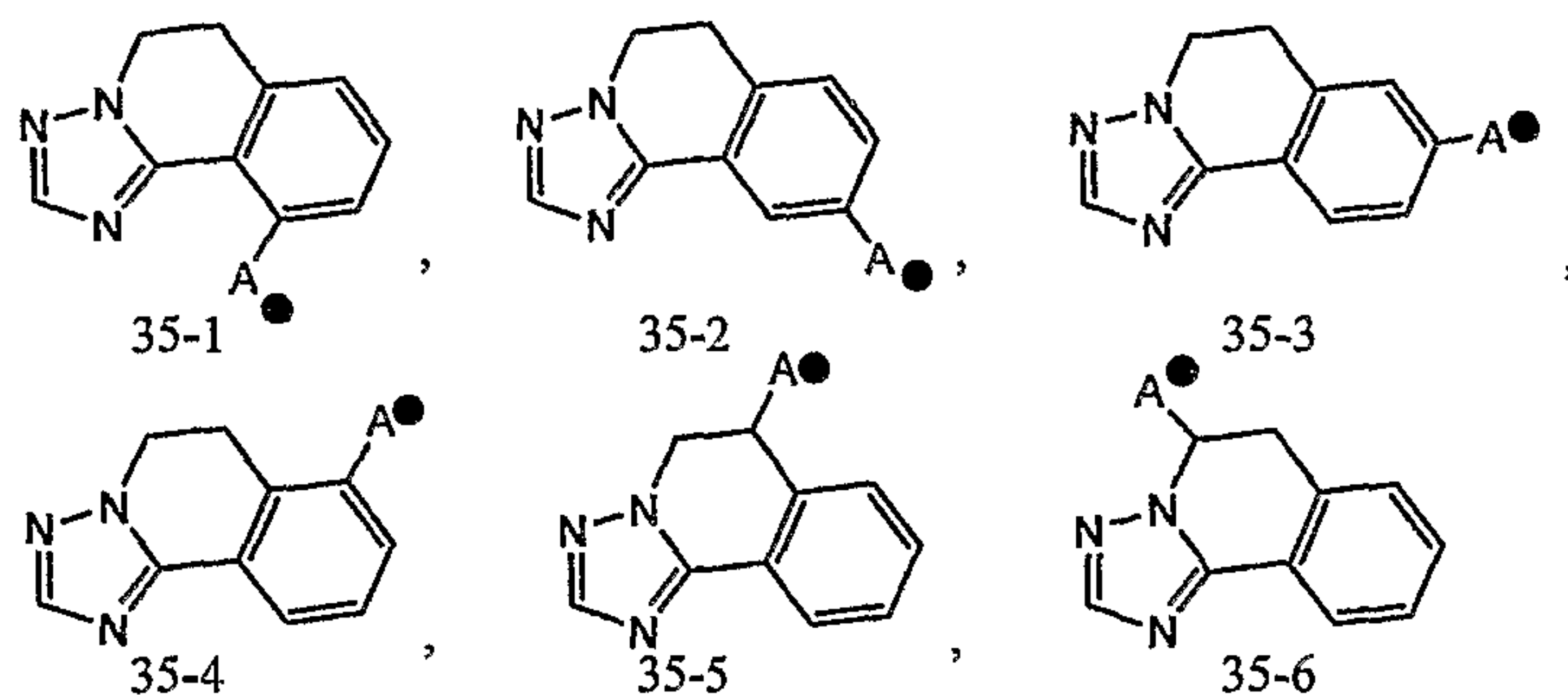


[0072]

- 20 Ring A may be connected to X_1 at a substitutable position indicated by any one of the following formulas [35-1] to [35-6]:

[0073]

25



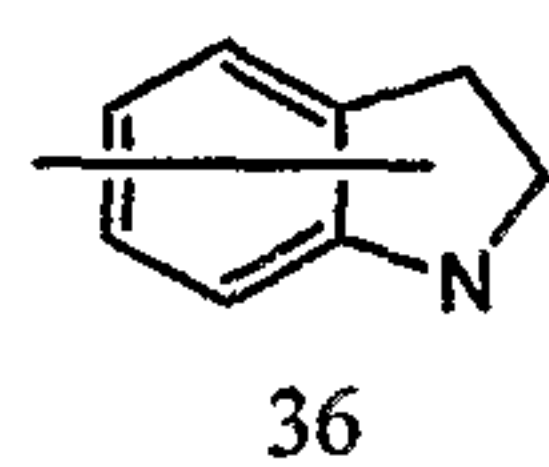
[0074]

One to three substituents selected from Substituent Group c1 in the definition of Ring B may exist at any substitutable position on the ring. Ring B may be connected to X_1 at any substitutable position on the ring.

5 [0075]

For example, when Ring B is represented by the formula [36]:

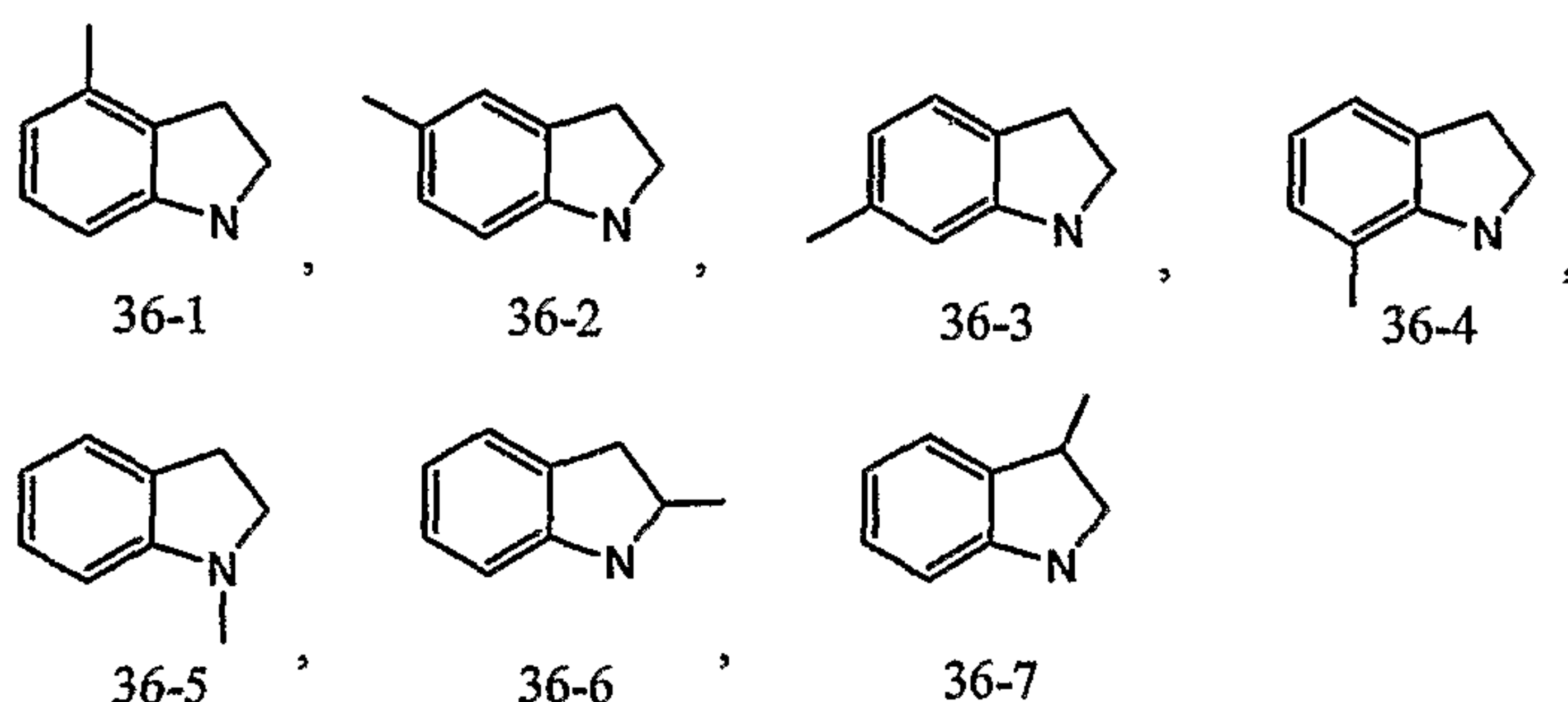
[0076]



[0077]

10 Ring B may be connected to X_1 at a substitutable position indicated by any one of the following formulas [36-1] to [36-7]:

[0078]



[0079]

15 In the present invention, the "pharmacologically acceptable salt" is not particularly limited insofar as it is a pharmacologically acceptable salt formed with the compound of the general formula (I) which is a therapeutic agent for a disease caused by $A\beta$.

[0080]

Preferable specific examples of the salt include hydrohalides (such as hydrofluorides, hydrochlorides, hydrobromides and hydroiodides), inorganic acid salts (such as sulfates, nitrates, perchlorates, phosphates, carbonates and bicarbonates), organic carboxylates (such as acetates,

20

oxalates, maleates, tartrates, fumarates and citrates), organic sulfonates (such as methanesulfonates, trifluoromethanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates and camphorsulfonates), amino acid salts (such as aspartates and glutamates), quaternary amine salts, alkali metal salts (such as sodium salts and potassium salts) and alkali
5 earth metal salts (such as magnesium salts and calcium salts).

[0081]

Next, the compound of the formula [I] according to the present invention will be described.

In the compound of the formula [I] or pharmacologically acceptable salt thereof,
10 preferably, R_1 is a C1-6 alkyl group or a halogen atom and m is an integer of 1 to 2; particularly preferably, R_1 is a C1-6 alkyl group and m is an integer of 1 to 2; and most preferably, R_1 is a methyl group and m is 1.

[0082]

In the compound of the formula [I] or pharmacologically acceptable salt thereof,
15 preferably, R_2 is a halogen atom, a hydroxyl group or a C1-6 alkoxy group and n is an integer of 1 to 2; more preferably, R_2 is a C1-6 alkoxy group and n is an integer of 1 to 2; and particularly preferably, R_2 is a methoxy group and n is 1.

[0083]

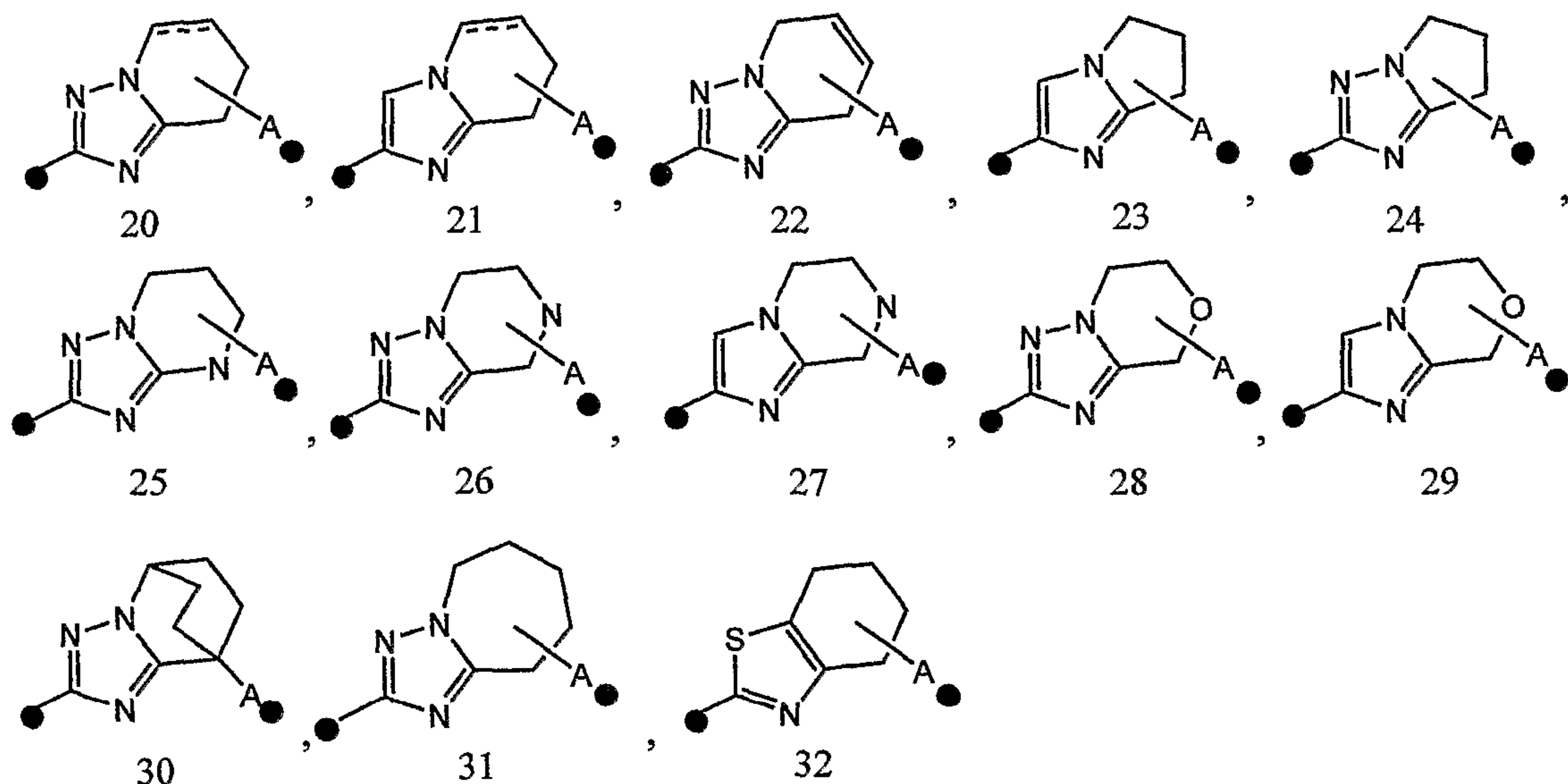
In the compound of the formula [I] or pharmacologically acceptable salt thereof,
20 X_1 is preferably i) a single bond or ii) a C1-6 alkylene group.

[0084]

In the compound of the formula [I] or pharmacologically acceptable salt thereof, Ring A is preferably represented by any one of the following formulas 20 to 32:

[0085]

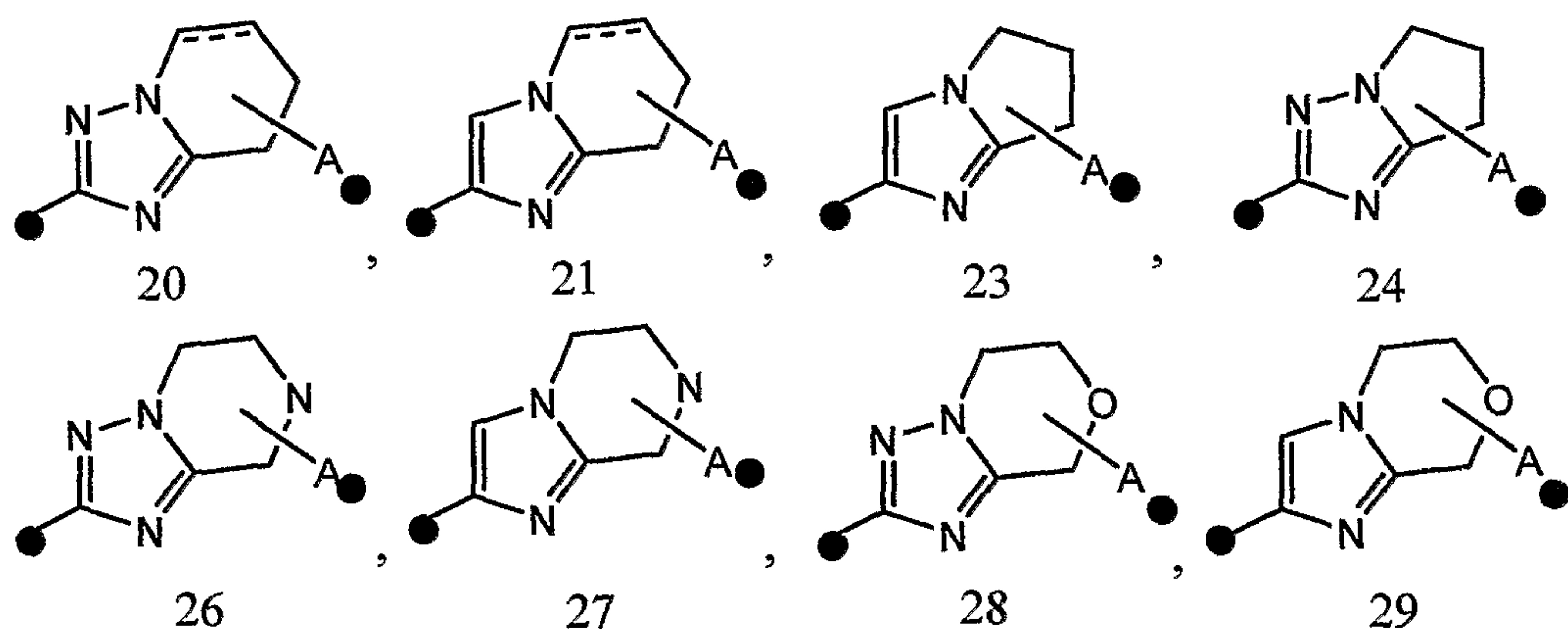
27



[0086]

and is particularly preferably represented by any one of the following formulas:

[0087]



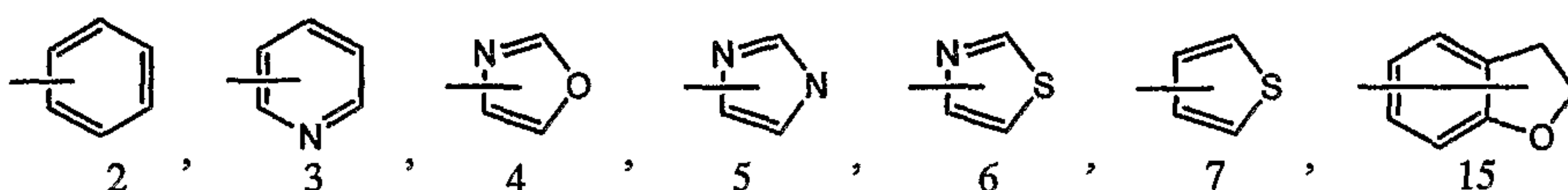
[0088]

5 In the compound of the formula [I] or pharmacologically acceptable salt thereof,

[0089]

Ring B is preferably represented by any one of the formulas:

[0090]



[0091]

10 each of which may be substituted with 1 to 3 substituents selected from Substituent Group c1.

[0092]

Substituent Group b1 is preferably a substituent group consisting of (1) a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), (2) a C3-8

cycloalkyl group, (3) a C6-14 aryl group, (4) a C6-14 aryl-C1-6 alkyl group, (5) a C1-6 alkoxy group, (6) a C3-8 cycloalkyloxy group, (7) a C2-6 alkanoyl group, (8) a C7-15 aroyl group, (9) a C1-6 alkylsulfonyl group, (10) a C3-8 cycloalkylsulfonyl group, (11) a C6-14 arylsulfonyl group, (12) a cyano group, (13) a formyl group, (14) a halogen atom, (15) a hydroxyl group and
5 (16) an oxo group.

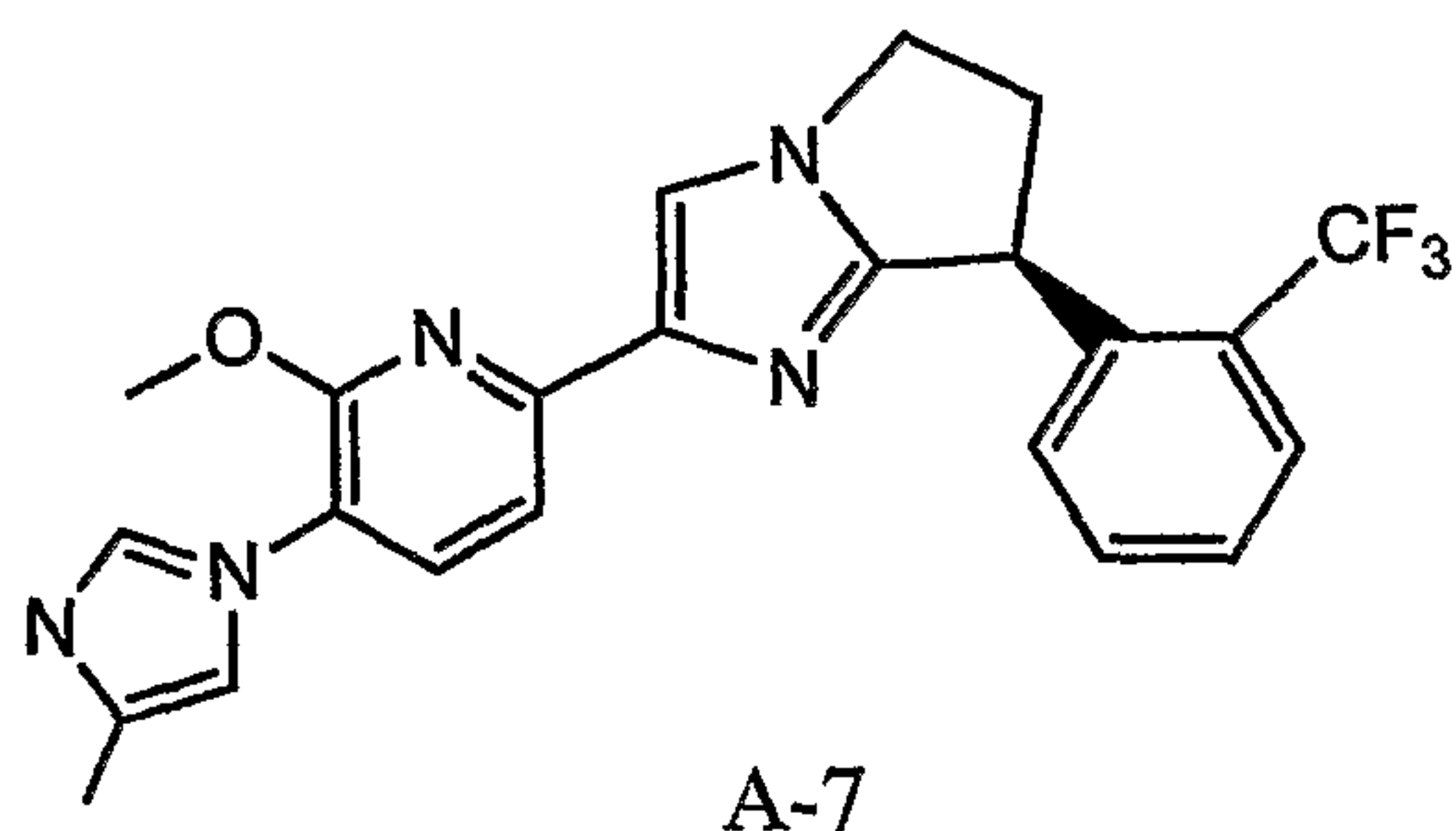
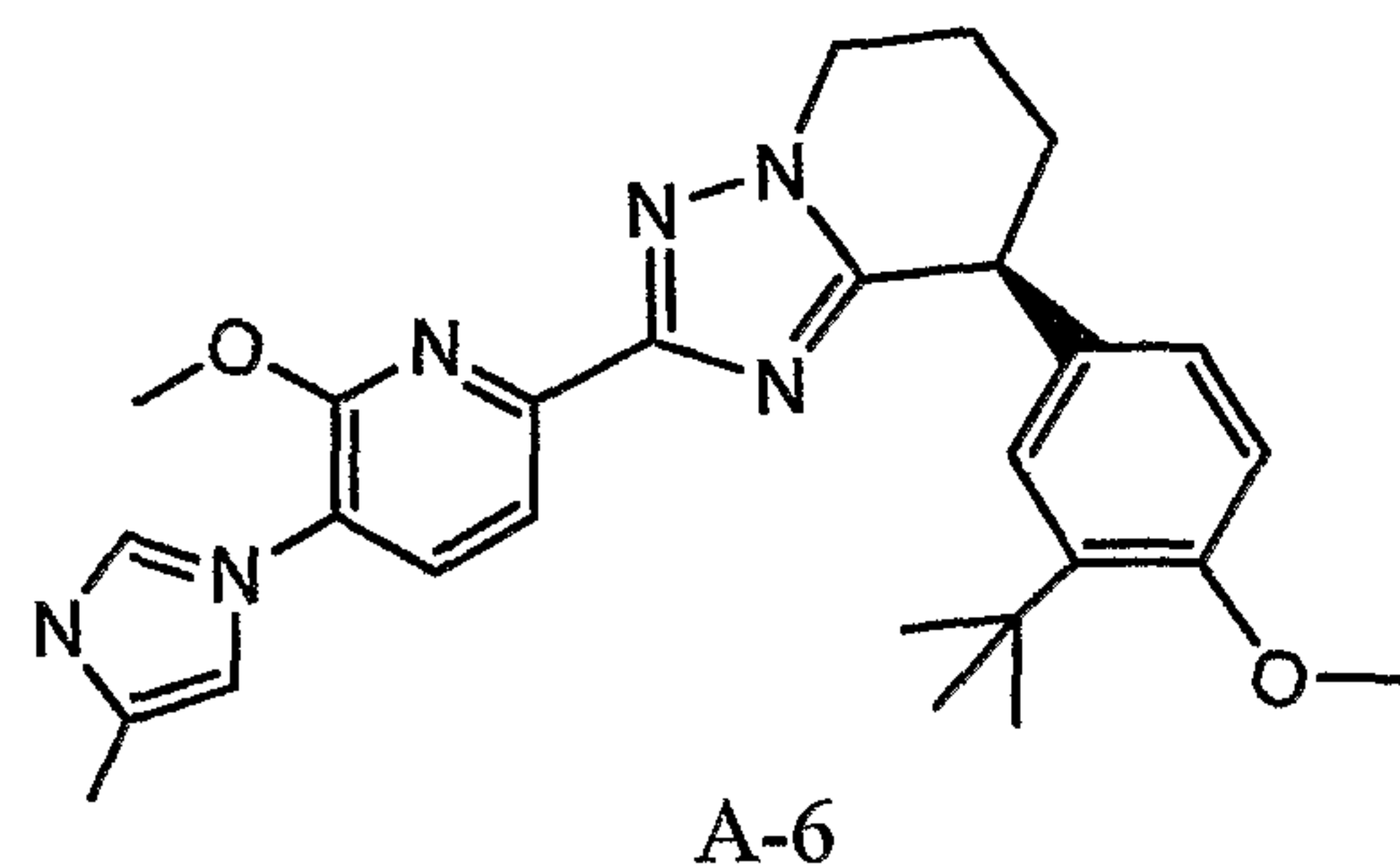
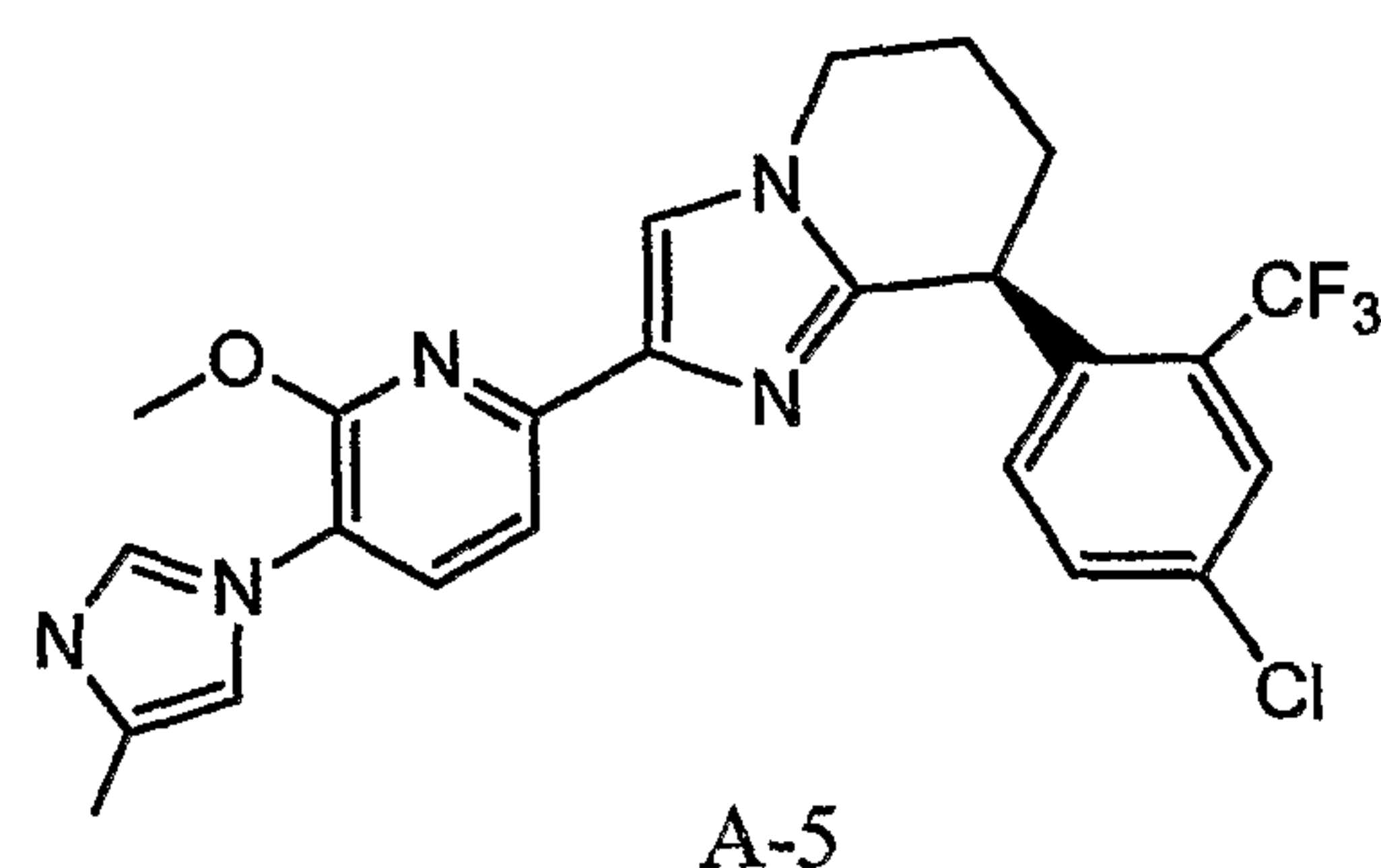
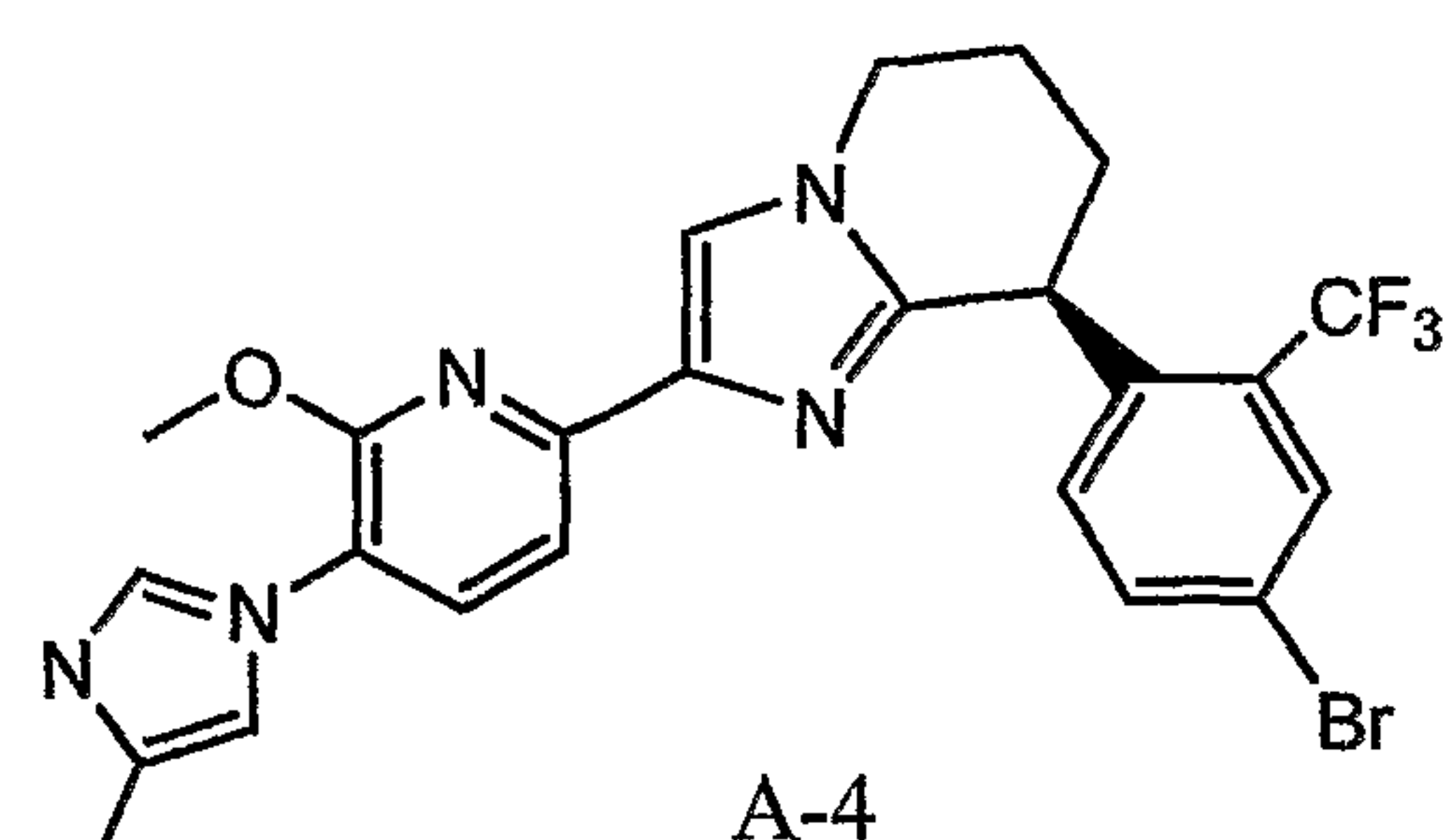
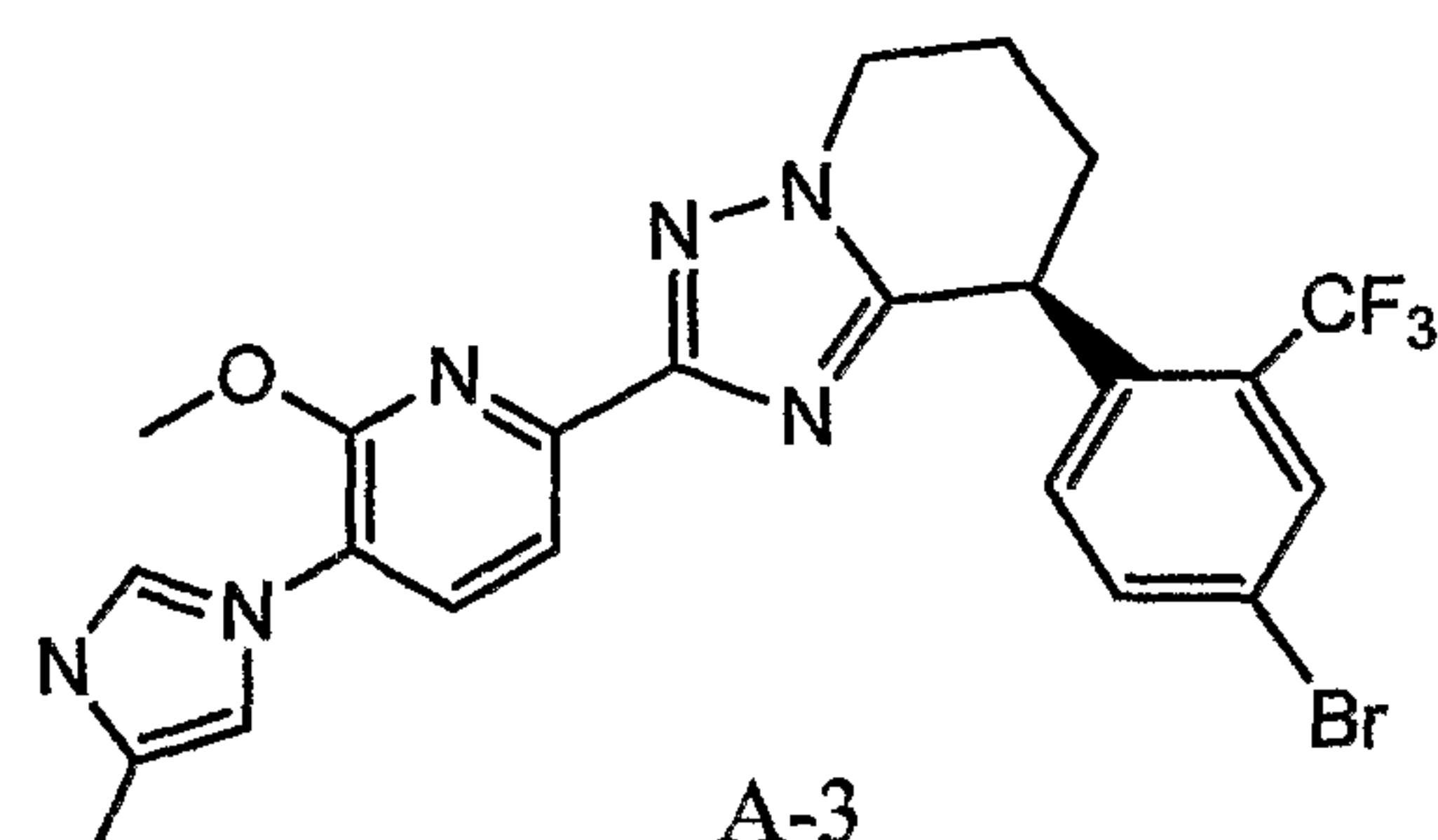
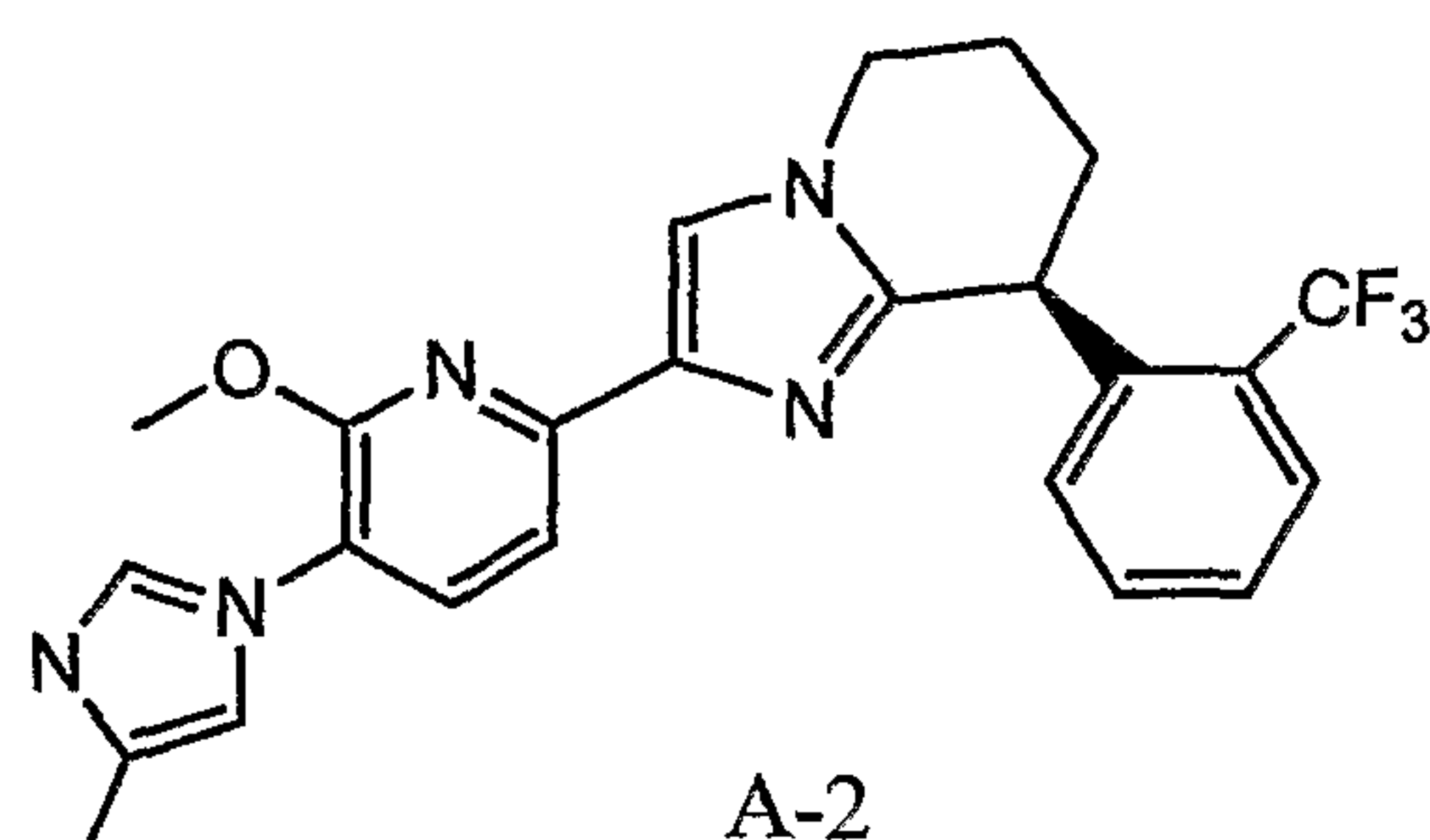
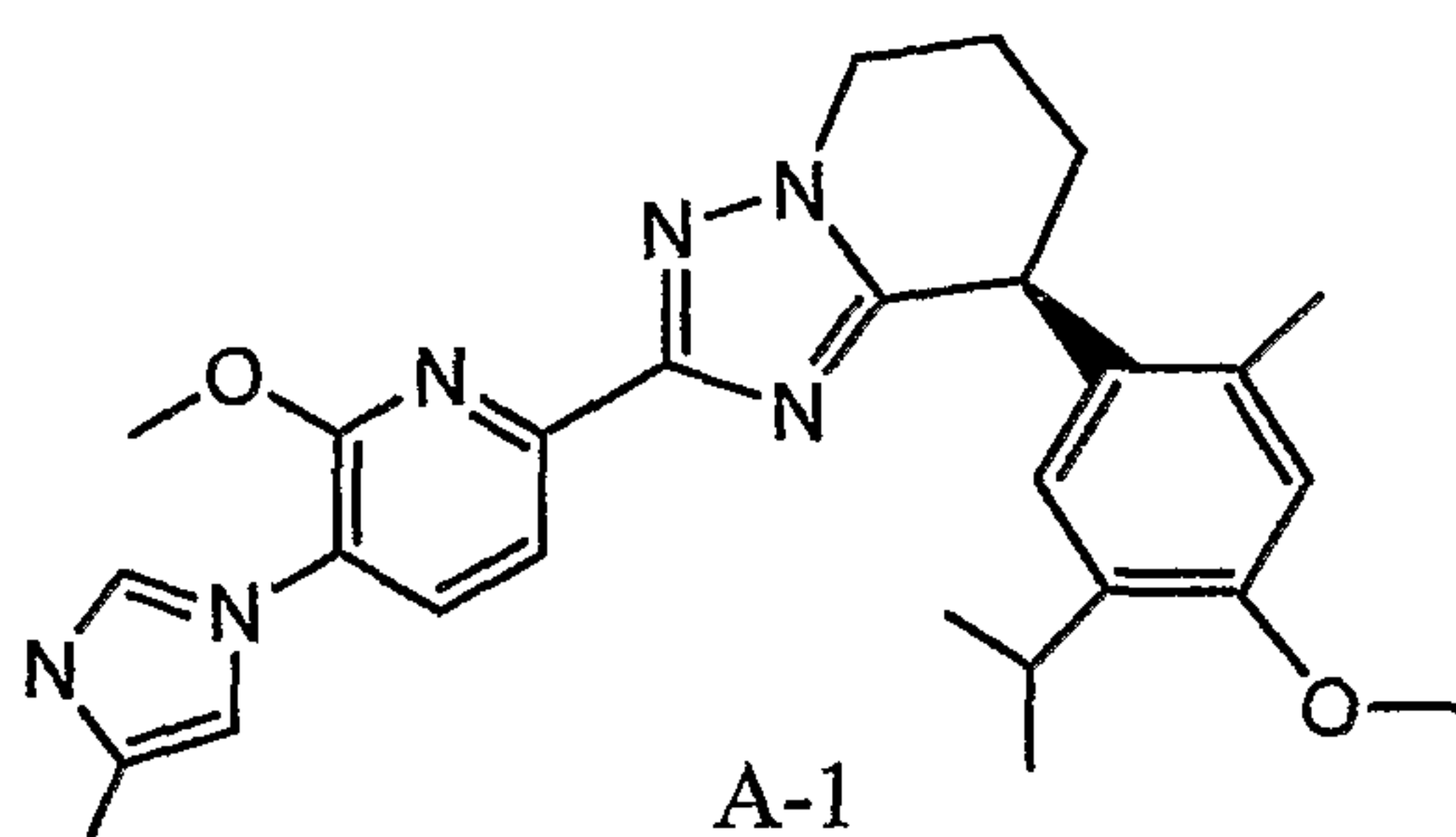
[0093]

Substituent Group c1 is preferably a substituent group consisting of (1) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), (2) a
10 cyano group, (3) a halogen atom, (4) a hydroxyl group and (5) (5)-1) a C1-6 alkyl group, (5)-2) a C1-6 alkoxy group, (5)-3) a C1-6 alkylthio group and (5)-4) a phenyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom.

[0094]

15 At least one compound selected from the group consisting of the following formulas [A-1] to [A-7]:

[0095]



[0096]

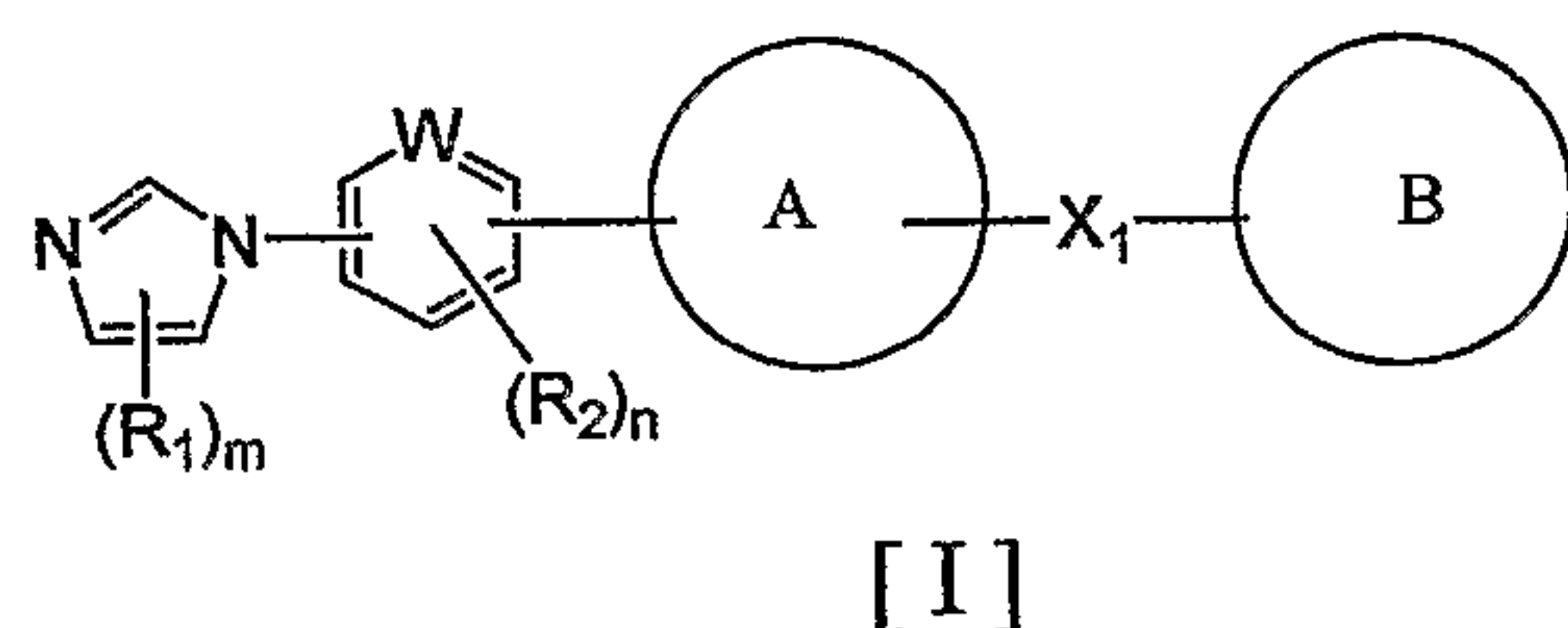
or a pharmacologically acceptable salt thereof is particularly suitable, for example, and is useful as a therapeutic agent for a disease caused by amyloid- β such as Alzheimer's disease, senile
5 dementia, Down's syndrome or amyloidosis.

[0097]

Methods for preparing the compound of the general formula (I) according to the present invention will be described below.

The compound represented by the general formula (I):

10 [0098]



[0099]

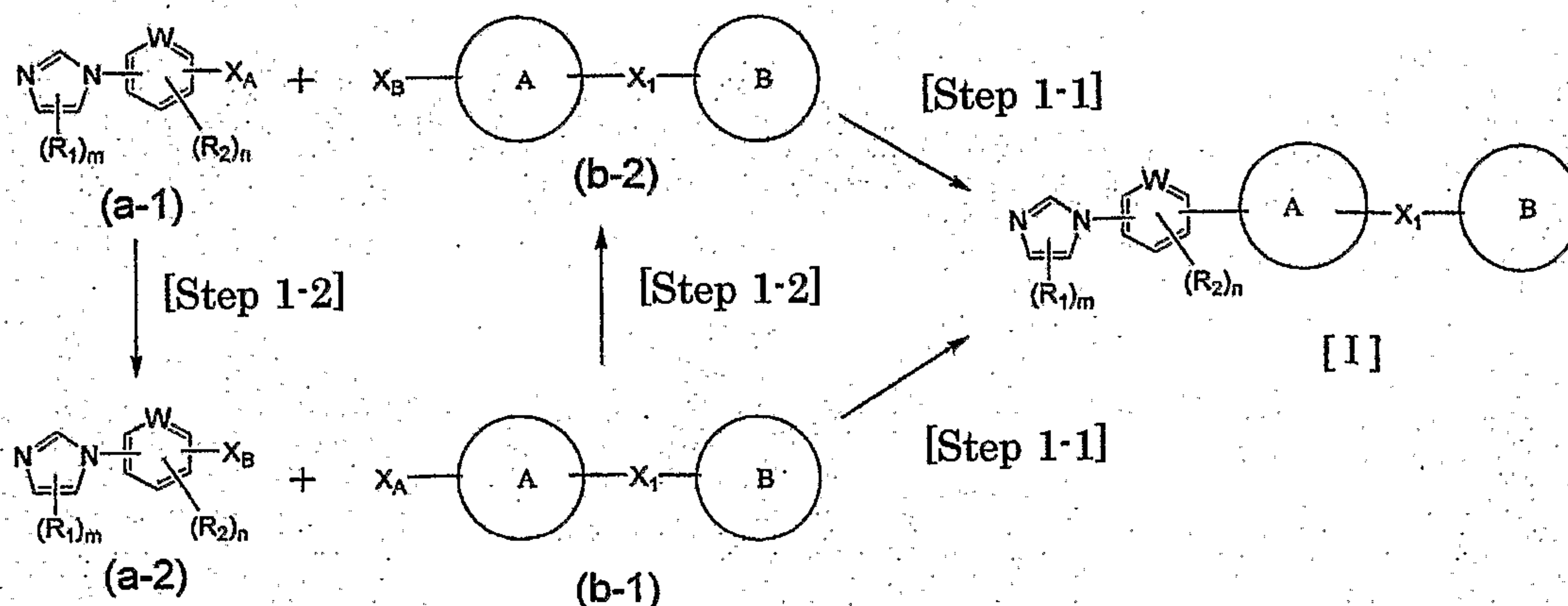
wherein R_1 , R_2 , m , n , W , Ring A, X_1 and Ring B are as defined above, is synthesized according to a method such as the following General Preparation Method 1 to General Preparation Method 8, for example. It is obvious that, in order to prepare the compound of the present invention conveniently, the method comprises a protection reaction step and a deprotection reaction step appropriately, using a protecting group known to a person skilled in the art which is suitably selected for each step (see T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981). It is obvious that, in order to prepare the compound of the present invention conveniently, the method comprises substituent conversion, substituent introduction and the like suitable for each step and known to a person skilled in the art. It is also obvious that, in order to prepare the compound of the present invention conveniently, all isomers and isomer mixtures such as geometric isomers which can be generated from the structure of the compound, optical isomers based on asymmetric carbon, stereoisomers, and tautomers can be prepared as a single compound by a technique known to a person skilled in the art which is suitable for each step such as fractional crystallization or column chromatography.

[0100]

General Preparation Method 1

Typically used General Preparation Method 1 for the compound of the general formula (I) according to the present invention will be described below.

20 [0101]



[0102]

In the formula, R_1 , R_2 , m , n , W , Ring A, X_1 and Ring B are as defined above; X_A represents a halogen atom such as a chlorine atom, a bromine atom or an iodine atom or a sulfonate group such as a methanesulfonate group, a p-toluenesulfonate group or a trifluoromethanesulfonate group; and X_B represents a trialkylstannyl group, a boronic acid group or a boronate group such as a pinacol boronate group.

[0103]

The above General Preparation Method 1 is a method for preparing the compound of the general formula [I] by subjecting to coupling reaction in Step 1-1 a compound of the general formula (a-1) and a compound of the general formula (b-2) or a method for preparing the compound of the general formula [I] by subjecting to coupling reaction in Step 1-1 a compound of the general formula (a-2) and a compound of the general formula (b-1) in which the substituents X_A and X_B are replaced by each other.

[0104]

The coupling reaction in Step 1-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include Suzuki-Miyaura reaction (see A. Suzuki, "Chem. Rev.", 1995, vol. 95, p. 2457, for example) and Stille coupling reaction (see J.K. Stille, "Angew. Chem. Int. Ed. Engl.", 1986, vol. 25, p. 508, for example).

[0105]

In Suzuki-Miyaura reaction, a halogen compound or trifluoromethanesulfonate compound of the general formula (a-1) is preferably coupled with 1.0 to 5.0 equivalents of a compound of the general formula (b-2) (wherein X_B is preferably a boronic acid group, a boronate group such as a pinacol boronate group, an alkylboronalkenyl group or the like) with respect to the compound of the general formula (a-1) in the presence of 0.01 to 0.5 equivalent of a transition metal catalyst with respect to the compound of the general formula (a-1), for example. This reaction is preferably performed in the presence of a solvent from the viewpoint of handleability and stirring efficiency. The solvent used varies according to the starting material and the transition metal catalyst used, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone, N,N-dimethylformamide, water and a mixed solvent thereof. The reaction temperature must be a temperature that can complete the coupling reaction, and is preferably room temperature to 200°C. This reaction is

performed preferably in an inert gas atmosphere, and more preferably in a nitrogen or argon atmosphere. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. The transition metal catalyst is preferably a known palladium complex, and more preferably a known
5 palladium complex such as palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). A phosphorus ligand (preferably triphenylphosphine, tri-*o*-tolylphosphine, tricyclohexylphosphine or tri-*tert*-butylphosphine, for example) may be appropriately added in order to make the reaction efficiently proceed. A quaternary ammonium salt, preferably tetrabutylammonium chloride or
10 tetrabutylammonium bromide, for example, may also be appropriately added in order to make the reaction efficiently proceed. In this reaction, a preferable result may be achieved in the presence of a base. The base used at this time varies according to the starting material, the solvent used and the like, and is not particularly limited. Preferable examples of the base include sodium hydroxide, barium hydroxide, potassium fluoride, cesium fluoride, sodium carbonate,
15 potassium carbonate, cesium carbonate and potassium phosphate. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique.

[0106]

In Stille coupling reaction, a halogen compound or trifluoromethanesulfonate
20 group compound of the general formula (a-1) is preferably coupled with 1.0 to 5.0 equivalents of a compound of the general formula (b-2) (wherein X_B is preferably a trialkylstannyl group) with respect to the compound of the general formula (a-1) in the presence of 0.01 to 0.2 equivalent of a transition metal catalyst with respect to the compound of the general formula (a-1), for example. It is preferable to appropriately use in this reaction 0.1 to 5.0 equivalents of copper (I)
25 halide or/and lithium chloride in order to make the reaction efficiently proceed. Preferable examples of the solvent used in this reaction include toluene, xylene, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, 1-methyl-2-pyrrolidone and dimethyl sulfoxide. The reaction temperature must be a temperature that can complete the coupling reaction, and is preferably room temperature to 150°C. The preferable transition metal catalyst is a palladium complex,
30 preferably a known palladium complex such as palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0), for example, and more preferably palladium (II) acetate, tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0), for example. A phosphorus ligand (preferably triphenylphosphine, tri-*o*-tolylphosphine, 1,3-

bis(diphenylphosphino)propane or tri-tert-butylphosphine, for example) may be appropriately added, for example, in order to make the reaction efficiently proceed. This reaction is performed preferably in an inert gas atmosphere, and more preferably in a nitrogen or argon atmosphere.

Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique.

[0107]

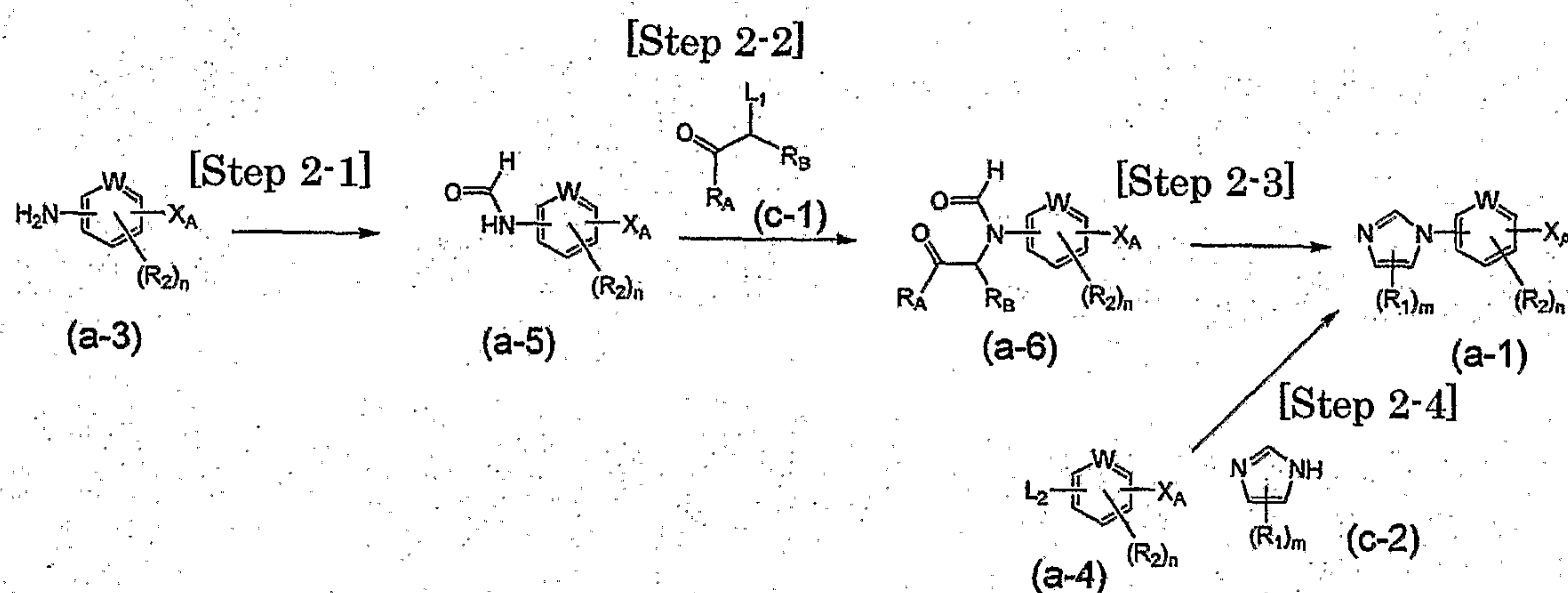
Step 1-2 is an example of a method for preparing a compound of the general formula (a-2) and a compound of the general formula (b-2) in which the substituents X_A and X_B are replaced by each other. This step varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. It is possible to use methods similar to preparation methods such as Suzuki-Miyaura reaction (see A. Suzuki, "Chem. Rev.", 1995, vol. 95, p. 2457, for example) and Stille coupling reaction (see J.K. Stille, "Angew. Chem. Int. Ed. Engl.", 1986, vol. 25, p. 508, for example).

[0108]

Preparation of compound of general formula (a-1)

The following formula shows an example of preparation of the compound of the general formula (a-1).

[0109]



[0110]

In the formula, R_1 , R_2 , m , n , W and X_A are as defined above; R_A and R_B are as defined for R_1 above; L_1 represents a halogen atom such as a chlorine atom, a bromine atom or an iodine atom or a sulfonate group such as a methanesulfonate group, a p-toluenesulfonate group or a trifluoromethanesulfonate group; and L_2 represents a halogen atom such as a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, a sulfonate group such as a

methanesulfonate group, a p-toluenesulfonate group or a trifluoromethanesulfonate group or a boronic acid group.

[0111]

The compound of the general formula (a-1) can be prepared from an amine
5 compound (a-3) as a starting material through formylation in Step 2-1, alkylation reaction in Step 2-2 and formation of an imidazole ring in Step 2-3, or can be prepared from a compound of the general formula (a-4) as a starting material by coupling reaction in Step 2-4.

[0112]

Step 2-1 varies according to the starting material and is not particularly limited
10 insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for example) may be used.

[0113]

15 Step 2-2 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method of stirring a compound of the general formula (a-5) and 1.0 to 10.0 equivalents of a compound of the general formula (c-1) with respect to the compound of the general formula (a-5) in a solvent
20 in the presence of 1.0 to 10.0 equivalents of a base with respect to the compound of the general formula (a-5). The base used varies according to the starting material and is not particularly limited. Preferable examples of the base include alkali metal hydrides (such as sodium hydride and lithium hydride), alkali metal salts (such as potassium carbonate, sodium carbonate and cesium carbonate) and metal alkoxides (such as sodium methoxide and potassium tert-butoxide).
25 The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; halogenated solvents such as methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene and benzene; and mixtures thereof. The
30 reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably 0°C to 200°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product

can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0114]

Step 2-3 varies according to the starting material and is not particularly limited
5 insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemistry of Heterocyclic Compounds. Imidazole and Derivatives, Part I, p. 33, Inters. Publish. 1953) may be used. Preferable examples of the method include a method for preparing the compound of the general formula (a-1) by forming an imidazole ring from a
10 compound of the general formula (a-6) and ammonia, ammonium salt, formamide or the like as a nitrogen source. The solvent used is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include non-polar solvents such as toluene and benzene; alcohol solvents such as methanol and ethanol; organic acids such as acetic acid or trifluoroacetic acid, sulfonic
15 acids such as p-toluenesulfonic acid and trifluoromethanesulfonic acid; water; and mixtures thereof. Formamide may optionally be used as a nitrogen atom source and as a solvent. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably room temperature to 250°C, for example. The yield may be improved when the reaction is performed using a tight container.
20 Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0115]

25 The coupling reaction in Step 2-4 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in D.D. Davey et al., "J. Med. Chem.", 1991, vol. 34, p. 2671-2677) may be used. Examples of the method include a method of stirring a compound of
30 the general formula (a-4) (wherein L₂ is preferably a halogen atom or the like) and 1.0 to 5.0 equivalents of an imidazole compound (c-2) with respect to the compound of the general formula (a-4) in a solvent in the presence or absence of 1.0 to 5.0 equivalents of a base with respect to the compound of the general formula (a-4). Preferable examples of the base used include sodium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate,

cesium carbonate, barium carbonate, pyridine, lutidine and triethylamine. The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include acetonitrile, tetrahydrofuran, dimethyl sulfoxide, N,N-dimethylformamide and N-methylpyrrolidone. The base may optionally be used as a solvent. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably room temperature to 150°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique or/and crystallization.

[0116]

Examples of the coupling reaction in Step 2-4 include a method of stirring a compound of the general formula (a-4) (wherein L₂ is preferably a boronic acid group or the like) in a solvent in the presence of a copper catalyst (such as described in J.P. Collman et al., "Org. Letters.", 2000, vol. 2, p. 1233-1236). Preferable examples of the method include a method of stirring a compound of the general formula (a-4) and 0.1 to 10.0 equivalents of an imidazole compound (c-2) with respect to the compound of the general formula (a-4) in a solvent in the presence of 0.01 to 1.0 equivalent of a copper reagent such as copper, copper bromide or copper iodide with respect to the compound of the general formula (a-4). The copper reagent used varies according to the starting material and is not particularly limited. Preferable examples of the copper reagent include copper (I) halide, copper (II) acetate, copper (II) nitrate and di-μ-hydroxo-bis[(N,N,N',N'-tetramethylethylenediamine)copper (II)] chloride. The solvent used varies according to the starting material, the reagent and the like, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; halogenated solvents such as methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as ethyl acetate, N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene, benzene and dichlorobenzene; and mixtures thereof. A base may be used depending on the starting material, the reagent and the like. Preferable examples of the base include organic bases such as triethylamine, pyridine and tetramethylethylenediamine; alkali metal salts such as potassium carbonate, sodium carbonate, potassium acetate, sodium acetate and cesium carbonate; and metal alkoxides such as sodium methoxide and potassium tert-butoxide. The reaction temperature

must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably room temperature to 200°C, for example. Good results such as reduction in the reaction time and improvement of the yield can be achieved when the reaction is performed in an oxygen atmosphere or air stream. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

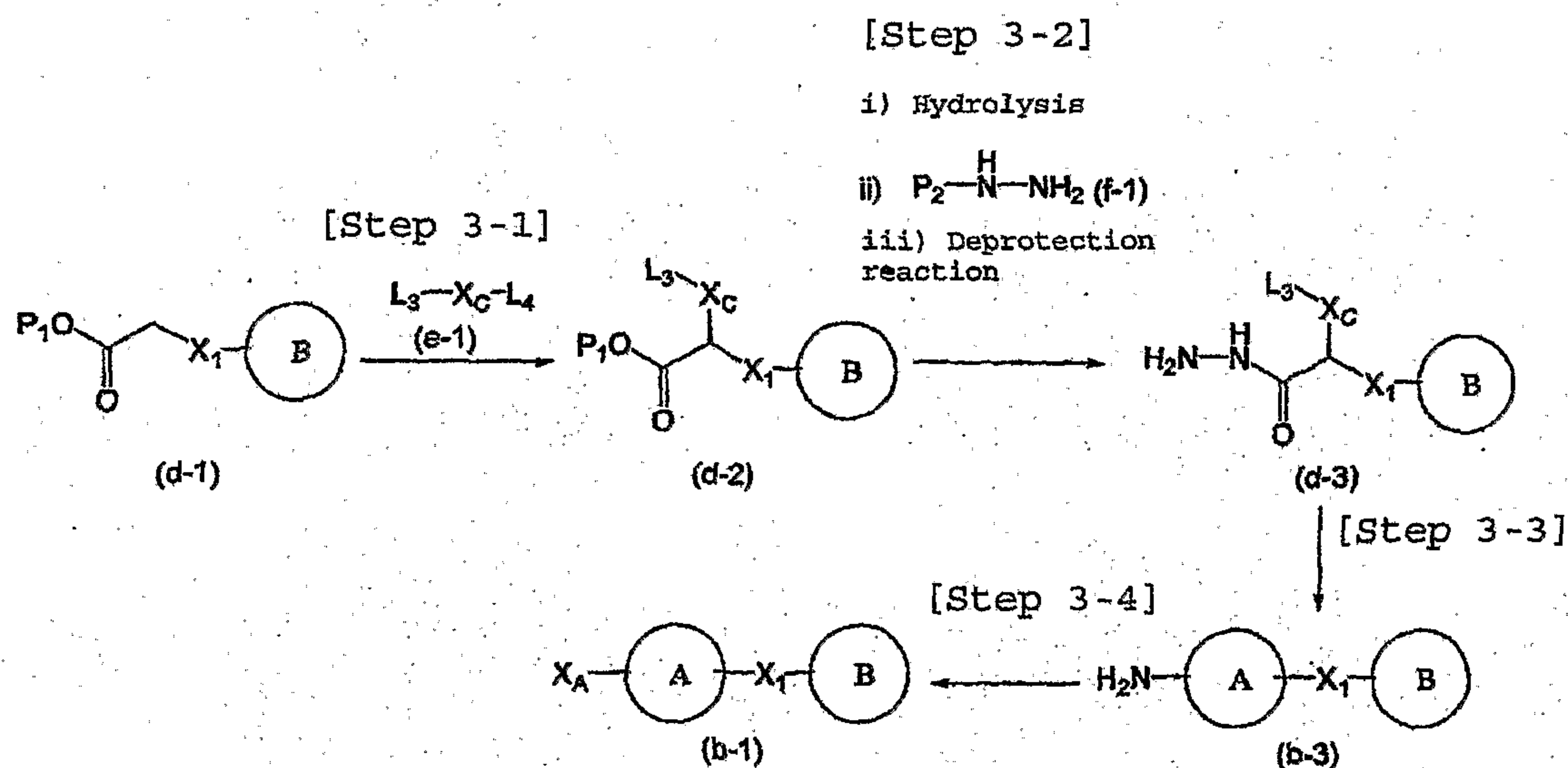
The compound of the formula (a-3), the compound of the formula (a-4), the compound of the formula (c-1) and the compound of the formula (c-2) are known or commercially available compounds or are compounds that can be prepared from these compounds by a conventional method.

[0117]

Preparation of compound of general formula (b-1)

The following formula shows an example of preparation of the compound of the general formula (b-1).

[0118]



[0119]

In the formula, X_1 , X_A , Ring A and Ring B are as defined above; L_3 and L_4 are as defined for L_1 above; X_C represents a C2-4 alkylene group, or a C2-3 alkylene group in which one methylene group is replaced by an oxygen atom or a nitrogen atom (wherein the nitrogen atom may have a substituent such as a C1-6 alkyl group or a benzyl group); P_1 represents a carboxyl-protecting group such as a methyl group, an ethyl group, a benzyl group, an allyl group,

a triphenylmethyl group, a tert-butyl group or a tert-butyldimethylsilyl group, or a hydrogen atom; and P₂ represents a nitrogen-protecting group such as a tert-butoxycarbonyl group or a benzyloxycarbonyl group.

[0120]

5 The compound of the general formula (b-1) can be prepared from a compound of the general formula (d-1) as a starting material through alkylation in Step 3-1, ester hydrolysis, hydrazidation and deprotection reaction in Step 3-2, formation of Ring A in Step 3-3 and Sandmeyer reaction in Step 3-4.

[0121]

10 Step 3-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method of stirring a compound of the general formula (d-1) and 1.0 to 10.0 equivalents of a compound of the general formula (e-1) with respect to the compound of the general formula (d-1) in a solvent
15 in the presence of 1.0 to 10.0 equivalents of a base with respect to the compound of the general formula (d-1). The base used varies according to the starting material and is not particularly limited. Preferable examples of the base include alkali metal hydrides (such as sodium hydride and lithium hydride), alkali metal salts (such as potassium carbonate, sodium carbonate and cesium carbonate), metal alkoxides (such as sodium methoxide and potassium tert-butoxide) and
20 organometallic bases (such as butyllithium, lithium diisopropylamide and lithium bistrimethylsilylamide). The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; halogenated solvents such as methylene
25 chloride, 1,2-dichloroethane and chloroform; polar solvents such as N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene and benzene; and mixtures thereof. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably -100°C to 100°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and
30 the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0122]

The ester hydrolysis reaction as the first stage of Step 3-2 varies according to the

starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A deprotection reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (see T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for example) may be used. The hydrazidation reaction as the second stage varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. An amidation reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 22) Yuki Gosei (Organic Synthesis) [IV], Maruzen Co., Ltd., November 1992, p. 137-144) may be used. The deprotection reaction as the third stage varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A deprotection reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (see T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for example) may be used.

[0123]

The Ring A formation reaction in Step 3-3 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method of heating a compound of the general formula (d-3) and 1.0 to 10.0 equivalents of aminoguanidine, isothioureia, cyanamide or the like with respect to the compound of the general formula (d-3) in a solvent under basic or acidic conditions. The base or acid used varies according to the starting material and is not particularly limited. Examples of the base or acid include bases such as alkali metal hydrides (such as sodium hydride and lithium hydride), alkali metal salts (such as potassium carbonate, sodium carbonate and cesium carbonate), metal alkoxides (such as sodium methoxide and potassium tert-butoxide) and organic bases (such as triethylamine, pyridine and 1,8-diazabicyclo[5.4.0]undec-7-ene); and acids such as hydrochloric acid, sulfuric acid, p-toluenesulfonic acid and camphorsulfonic acid. The solvent used varies according to the starting material, and is not particularly limited insofar as the solvent does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include alcohol solvents such as methanol, ethanol and tert-butanol; ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; halogenated solvents such as methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as acetonitrile, N,N-dimethylformamide and N-

methypyrrolidone; non-polar solvents such as xylene, toluene and benzene; and mixtures thereof. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably -100°C to 100°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 48 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0124]

The Sandmeyer reaction in Step 3-4 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 19) Yuki Gosei (Organic Synthesis) [I], Maruzen Co., Ltd., November 1992, p. 450-453) may be used.

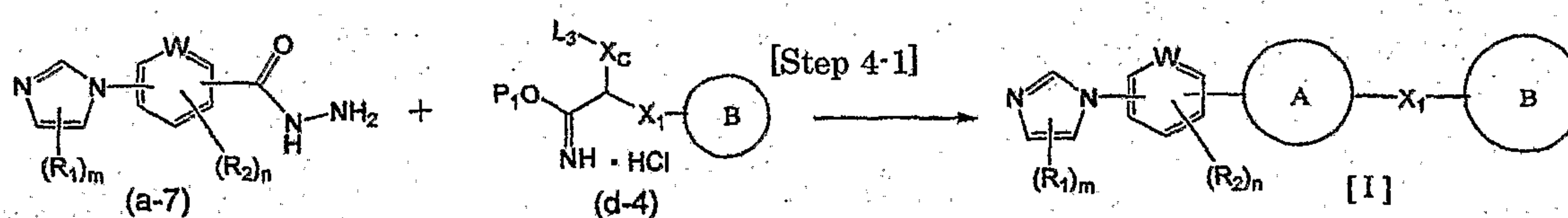
The compound of the formula (d-1), the compound of the formula (e-1) and the compound of the formula (f-1) are known or commercially available compounds or are compounds that can be prepared from these compounds by a conventional method.

[0125]

General Preparation Method 2

Typically used General Preparation Method 2 for the compound of the general formula [I] according to the present invention will be described below.

[0126]



[0127]

In the formula, R_1 , R_2 , X_1 , X_C , P_1 , L_3 , m , n , W , Ring A and Ring B are as defined above.

[0128]

The above General Preparation Method 2 shows an example of a method for preparing the compound of the general formula [I] by subjecting a compound of the general formula (a-7) and a compound of the general formula (d-4) to cyclization reaction in Step 4-1.

[0129]

The Ring A formation reaction in Step 4-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable
5 examples of the method include a method of stirring a compound of the general formula (a-7) and 1.0 to 5.0 equivalents of a compound of the general formula (d-4) with respect to the compound of the general formula (a-7) in a solvent in the presence of 1.0 to 10.0 equivalents of a base with respect to the compound of the general formula (a-7). This reaction is preferably performed in the presence of a solvent from the viewpoint of handleability and stirring
10 efficiency. The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include alcohol solvents such as methanol, ethanol and tert-butanol; ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; halogenated solvents such as methylene chloride, 1,2-dichloroethane and
15 chloroform; polar solvents such as acetonitrile, propionitrile, N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene and benzene; and mixtures thereof. The base used varies according to the starting material and is not particularly limited. Preferable examples of the base include alkali metal hydrides (such as sodium hydride and lithium hydride), alkali metal salts (such as potassium carbonate, sodium carbonate and cesium carbonate), metal
20 alkoxides (such as sodium methoxide and potassium tert-butoxide) and organic bases (such as triethylamine, N,N-diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene and imidazole). The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably room temperature to 200°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 7 days, and
25 the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0130]

Preparation of compound of general formula (a-7)

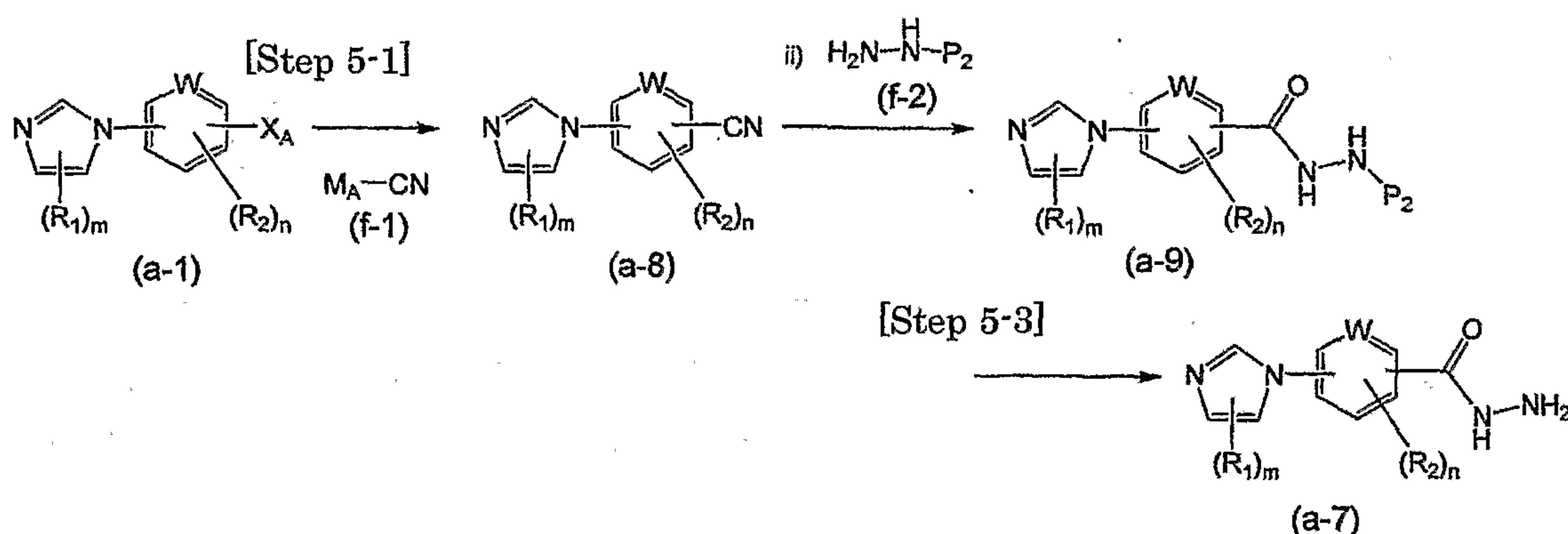
30 The following formula shows an example of preparation of the compound of the general formula (a-7).

[0131]

42

[Step 5-2]

i) Hydrolysis



[0132]

In the formula, R_1 , R_2 , m , n , X_A , W , and P_2 are as defined above; and M_A represents a metal such as zinc or copper.

[0133]

5 The compound of the general formula (a-7) can be prepared from a compound of the general formula (a-1) as a starting material through coupling reaction in Step 5-1, hydrolysis reaction and hydrazidation in Step 5-2 and deprotection reaction in Step 5-3.

[0134]

The coupling reaction in Step 5-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A halogen compound or trifluoromethanesulfonate compound of the general formula (a-1) is preferably coupled with 1.0 to 5.0 equivalents of a metal cyanide such as zinc (II) cyanide represented by the general formula (f-1) with respect to the compound of the general formula (a-1) in the presence of 0.01 to 0.2 equivalent of a transition metal catalyst with respect to the compound of the general formula (a-1), for example. This reaction is preferably performed in the presence of a solvent from the viewpoint of handleability and stirring efficiency. The solvent used varies according to the starting material and the transition metal catalyst used, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone and N,N-dimethylformamide. The reaction temperature must be a temperature that can complete the coupling reaction, and is preferably room temperature to 150°C. This reaction is performed preferably in an inert gas atmosphere, and more preferably in a nitrogen or argon atmosphere.

25 The transition metal catalyst is preferably a palladium complex, for example, and more

preferably a known palladium complex such as palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). It is also preferable to appropriately add a phosphorus ligand (preferably triphenylphosphine, tri-*o*-tolylphosphine, tri-*tert*-butylphosphine or 2-(di-*tert*-butylphosphino)biphenyl, for example) in order to make the reaction efficiently proceed. A preferable result may be achieved in the presence of a base. The base used is not particularly limited insofar as it is used in a coupling reaction similar to this reaction. Preferable examples of the base include triethylamine, *N,N*-diisopropylethylamine, *N,N*-dicyclohexylmethylamine and tetrabutylammonium chloride. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique.

[0135]

The hydrolysis reaction as the first stage of Step 5-2 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 22) Yuki Gosei (Organic Synthesis) [IV], Maruzen Co., Ltd., November 1992, p. 12-13) may be used. The hydrazidation reaction as the second stage varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. An amidation reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 22) Yuki Gosei (Organic Synthesis) [IV], Maruzen Co., Ltd., November 1992, p. 137-144) may be used.

[0136]

The deprotection reaction in Step 5-3 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A deprotection reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (see T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for example) may be used.

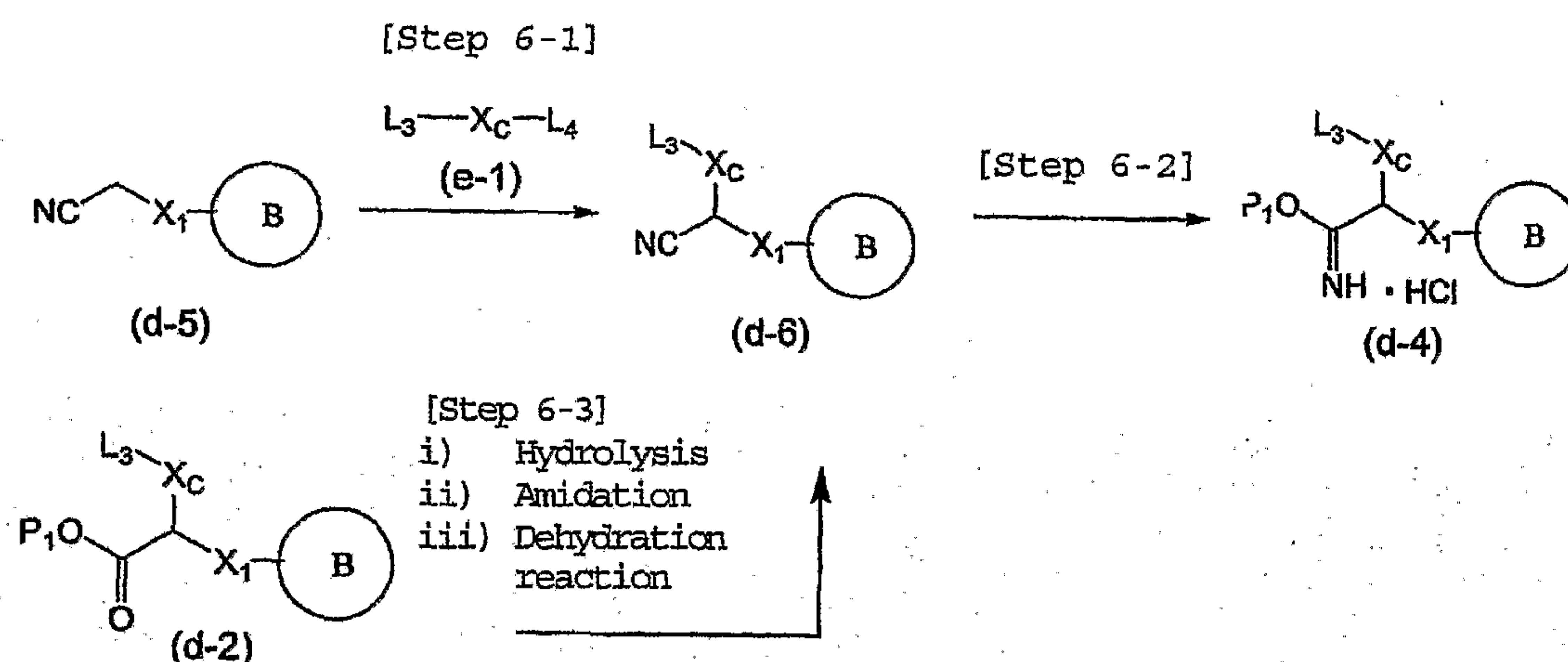
The compound of the formula (f-2) is a known or commercially available compound or is a compound that can be prepared from such a compound by a conventional method.

[0137]

Preparation of compound of general formula (d-4)

The following formula shows an example of preparation of the compound of the general formula (d-4).

[0138]



5 [0139]

In the formula, X_1 , X_C , Ring B, P_1 , L_3 and L_4 are as defined above.

[0140]

The compound of the general formula (d-4) can be prepared from a compound of the general formula (d-5) as a starting material through alkylation reaction in Step 6-1 and imidation in Step 6-2.

A compound of the general formula (d-6) can also be prepared from a compound of the general formula (d-2) as a starting material through hydrolysis reaction, amidation and dehydration reaction in Step 6-3.

[0141]

Step 6-1 is performed by the same method as in the aforementioned Step 3-1 and can prepare a compound of the general formula (d-6) from a compound of the general formula (d-5).

[0142]

Step 6-2 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method of stirring the compound of the general formula (d-6) in an alcohol solvent in the presence of 5.0 to 100.0 equivalents of an acid with respect to the compound of the general formula (d-6). The acid used varies according to the starting material and is not particularly limited. Preferable examples

of the acid include hydrogen chloride gas and acetyl chloride. The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include alcoholic solvents such as methanol, ethanol and tert-butanol. Preferable
5 examples of the solvent also include halogenated solvents such as a methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene and benzene; and mixed solvents thereof. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably 0°C to 100°C, for example.

10 Under preferable reaction conditions, the reaction is completed in 1 to 7 days, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0143]

15 The ester hydrolysis as the first stage of Step 6-3 is performed by the same method as in the aforementioned Step 3-2. The amidation reaction as the second stage is not particularly limited insofar as the conditions are similar to those in this reaction. An amidation reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken
20 Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 22) Yuki Gosei (Organic Synthesis) [IV], Maruzen Co., Ltd., November 1992, p. 137-144) may be used. The dehydration reaction from amide to nitrile as the third stage varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A dehydration reaction known to a person skilled in the art may be used for the reaction. A method
25 reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 20) Yuki Gosei (Organic Synthesis) [IV], Maruzen Co., Ltd., November 1992, p. 449-450) may be used.

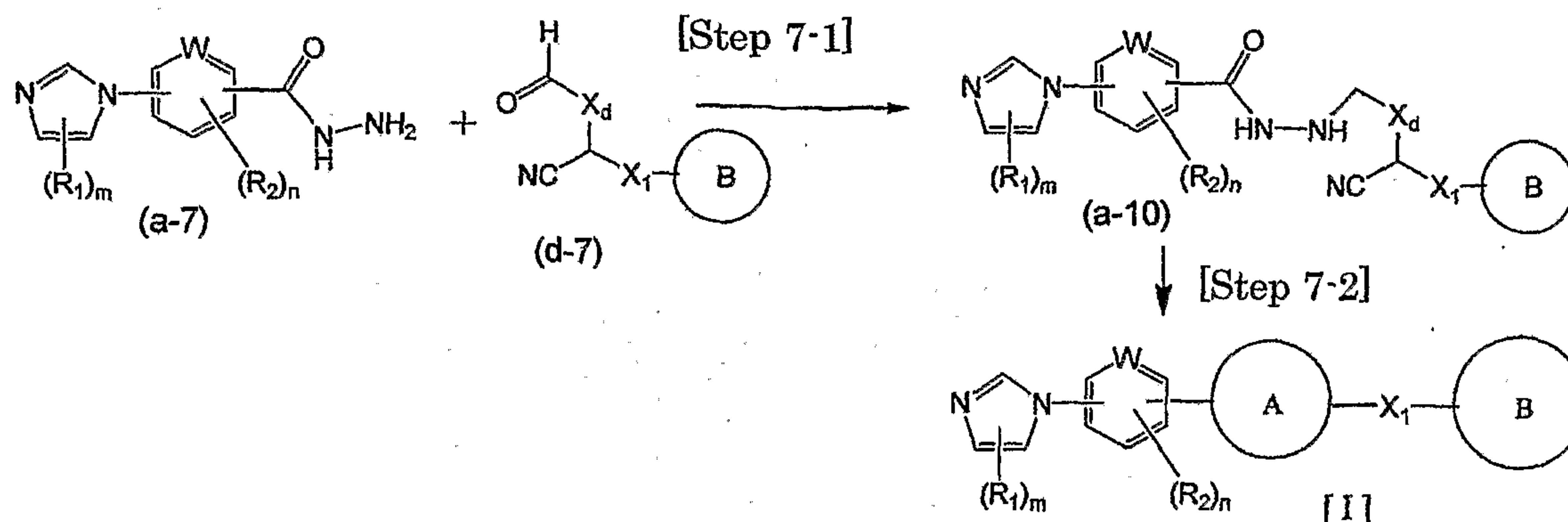
The compound of the formula (d-2) and the compound of the formula (d-5) are known or commercially available compounds or are compounds that can be prepared from these
30 compounds by a conventional method.

[0144]

General Preparation Method 3

Typically used General Preparation Method 3 for the compound of the general formula (I) according to the present invention will be described below.

[0145]



[0146]

In the formula, R_1 , R_2 , m , n , W , Ring A, X_1 and Ring B are as defined above; and X_d represents a C1-3 alkylene group, or a C1-2 alkylene group in which one methylene group is replaced by an oxygen atom or a nitrogen atom (wherein the nitrogen atom may have a substituent such as a C1-6 alkyl group or a benzyl group).

[0147]

The above General Preparation Method 3 shows an example of a method for preparing the compound [I] by condensing a hydrazide compound (a-7) and an aldehyde compound (d-7) in Step 7-1 and then performing intramolecular cyclization in Step 7-2.

[0148]

Although a compound (a-10) may be prepared by alkylation of a hydrazide compound (a-7) and a compound (d-6), it is difficult to control the positions and number of alkylated sites. The compound (a-10) is preferably prepared by condensation of a hydrazide compound (a-7) with an aldehyde compound (d-7).

[0149]

The condensation reaction in Step 7-1 varies according to the material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method using a boron hydride reagent and a method of reductive alkylation using catalytic reduction.

[0150]

In the method using a boron hydride reagent, it is preferable to react a hydrazide compound (a-7) and 1.0 to 1.5 equivalents of an aldehyde compound (d-7) with respect to the compound (a-7) with 1.0 to 4.0 equivalents of sodium triacetoxyhydroborate with respect to the

compound (a-7) in an ether solvent such as tetrahydrofuran or dioxane, a halogenated solvent such as dichloromethane or a mixed solvent thereof in the presence of 2.0 to 6.0 equivalents of acetic acid with respect to the compound (a-7), for example. The reaction temperature is preferably 0°C to room temperature.

5 It is also preferable to react a hydrazide compound (a-7) and 1.0 to 1.5 equivalents of an aldehyde compound (d-7) with respect to the compound (a-7) with 1.0 to 4.0 equivalents of sodium cyanotrihydroborate with respect to the compound (a-7) in an alcohol solvent such as methanol or ethanol, an ether solvent such as tetrahydrofuran or dioxane or a mixed solvent thereof, for example. An acid catalyst such as acetic acid may be added as
10 necessary. The reaction temperature is preferably 0°C to room temperature.

It is also preferable to use a method of subjecting a hydrazide compound (a-7) and an aldehyde compound (d-7) to dehydration reaction in the presence of an acid such as acetic acid or p-toluenesulfonic acid to form an imine and then reducing the imine with a boron hydride reagent.

15 [0151]

In the reductive alkylation using catalytic reduction, it is preferable to catalytically reduce a hydrazide compound (a-7) and 1.0 to 1.5 equivalents of an aldehyde compound (d-7) with respect to the compound (a-7) in an alcohol solvent such as methanol or ethanol, an ether solvent such as tetrahydrofuran or dioxane or a mixed solvent thereof in the
20 presence of a catalyst such as platinum oxide or palladium-carbon in a hydrogen atmosphere at 1 to 4 atm, for example. An acid catalyst such as acetic acid or hydrochloric acid may be added as necessary.

It is also preferable to use a method of subjecting a hydrazide compound (a-7) and an aldehyde compound (d-7) to dehydration reaction in the presence of an acid such as acetic
25 acid or p-toluenesulfonic acid to form an imine and then reductively alkylating the imine using catalytic reduction.

[0152]

Step 7-2 is intramolecular cyclization reaction and is an example of forming at one time a triazole ring fused with a non-aromatic ring group, for example. This reaction varies
30 according to the material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. The reaction solvent is not particularly limited insofar as it does not inhibit the reaction. Examples of the solvent include aromatic hydrocarbon solvents such as an acetic acid solvent, toluene and xylene; ether solvents such as tetrahydrofuran and dioxane; alcohol solvents

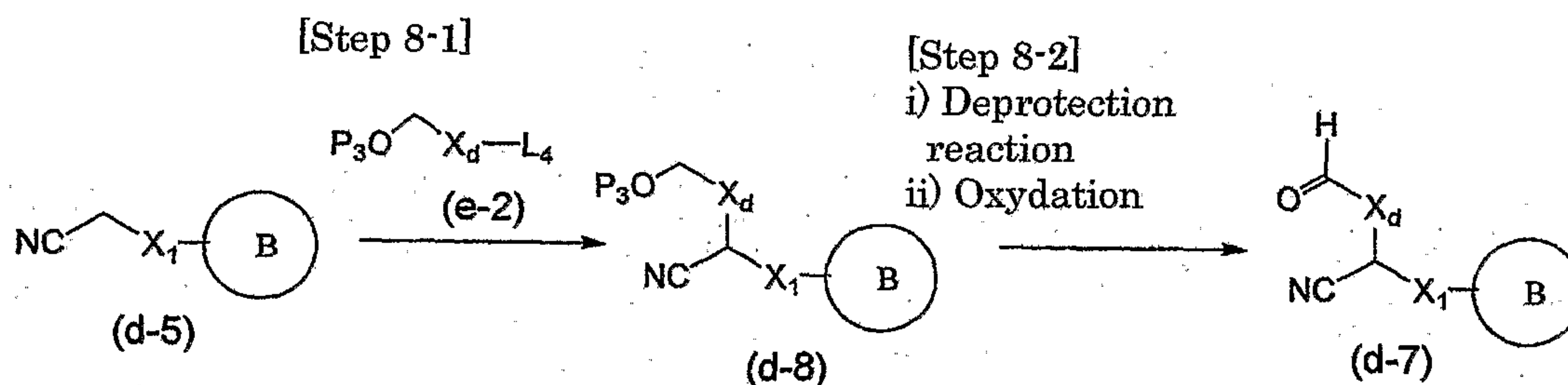
such as methanol and ethanol; and mixed solvents thereof. An acids such as acetic acid, p-toluenesulfonic acid or hydrochloric acid may be added as necessary. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably room temperature to solvent reflux temperature, for example. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0153]

10 Preparation of compound of general formula (d-7)

The following formula shows an example of preparation of the compound of the general formula (d-7).

[0154]



[0155]

15 In the formula, X₁, L₄, X_d and Ring B are as defined above; and P₃ represents an alcohol-protecting group such as a tert-butyldimethylsilyl group or a benzyl group.

[0156]

The aldehyde compound (d-7) can be prepared from a nitrile compound (d-5) as a starting material through alkylation reaction in Step 8-1 and deprotection reaction and alcohol oxidation reaction in Step 8-2.

[0157]

Step 8-1 is performed by the same method as in the aforementioned Step 3-1 and can prepare a compound of the general formula (d-8) from a compound of the general formula (d-5). The alcohol-protecting group P₃ in the compound of the general formula (e-2) is not particularly limited insofar as the protecting group is stable under reaction conditions and can be easily removed. Preferable examples thereof include a tert-butyldimethylsilyl group and a benzyl group. The compound (e-2) is commercially available or may be easily synthesized by protecting an alcohol compound by a method known to a person skilled in the art (see T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for

example).

[0158]

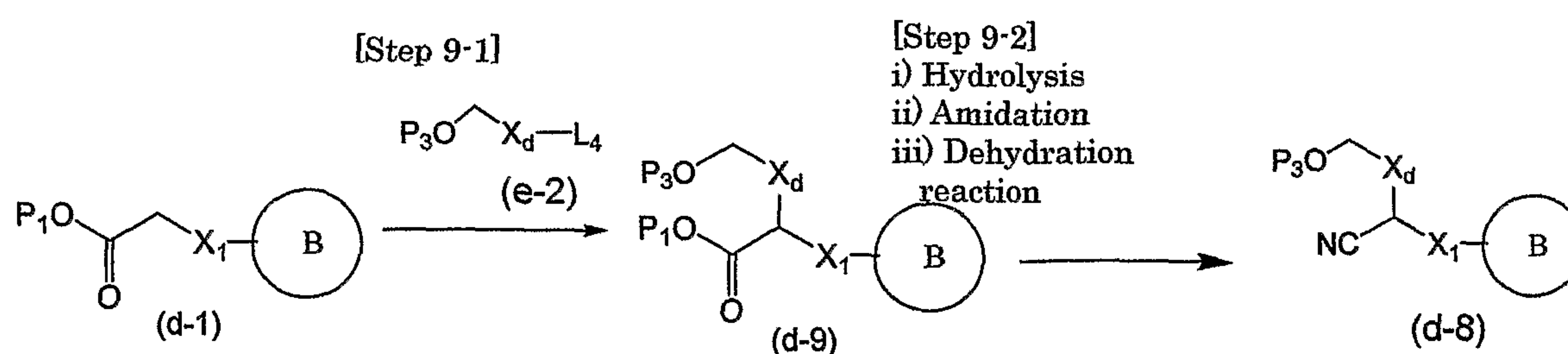
The deprotection reaction as the first stage of Step 8-2 is not particularly limited insofar as the conditions are similar to those in this reaction. A deprotection reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (see T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for example) may be used. For example, when the protecting group is a tert-butyldimethylsilyl group, it is preferable to use an acid such as hydrochloric acid, trifluoroacetic acid, formic acid or acetic acid, or use tetra-n-butylammonium fluoride or the like. When the protecting group is a benzyl group, catalytic hydrogenolysis is preferable. The reaction of oxidation to aldehyde as the second stage varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. An oxidation reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 21) Yuki Gosei (Organic Synthesis) [IV], Maruzen Co., Ltd., November 1992, p. 2-23) may be used. Preferable examples of the method include pyridinium chlorochromate oxidation, Swern oxidation, Pfitzner-Moffatt oxidation and Dess-Martin oxidation.

[0159]

20 Preparation of compound of general formula (d-8)

The following formula shows an example of preparation of the compound of the general formula (d-8).

[0160]



[0161]

25 In the formula, X_1 , X_d , L_4 , P_1 , P_3 and Ring B are as defined above.

[0162]

The nitrile compound (d-8) can be prepared from a compound (d-1) as a starting material through alkylation in Step 9-1 and ester hydrolysis, amidation and dehydration reaction in Step 9-2.

[0163]

Step 9-1 is performed by the same method as in the aforementioned Step 3-1 and can prepare a compound (d-9) from a compound (d-1).

[0164]

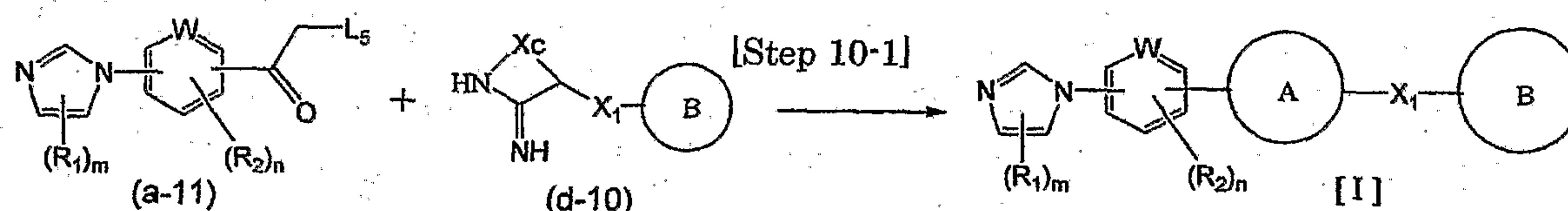
5 Step 9-2 is performed by the same method as in the aforementioned Step 6-3 and can prepare the nitrile compound (d-8) from the compound (d-9).

[0165]

General Preparation Method 4

Typically used General Preparation Method 4 for the compound of the general
10 formula (I) according to the present invention will be described below.

[0166]



[0167]

In the formula, R_1 , R_2 , m , n , W , X_c , Ring A, X_1 and Ring B are as defined above; and L_5 represents a halogen atom such as chlorine, bromine or iodine.

15 [0168]

The above General Preparation Method 4 shows an example of a method for preparing the compound [I] by reacting a compound of the general formula (a-11) with a cyclic amidine compound (d-10).

[0169]

20 Step 10-1 is an example of forming an imidazole ring fused with a non-aromatic ring group, for example, by alkylation and subsequent dehydration reaction of a cyclic amidine compound (d-10). Alkylation proceeds regioselectively, so that a single Ring A is formed (as described in L. Langlois et al., "J. Heterocyclic Chem.", 1982, vol. 19, p. 193-200). Preferable examples of the method include a method of reacting a compound (a-11) with 1.0 to 2.0
25 equivalents of a compound (d-10) with respect to the compound (a-11) in a solvent. The solvent is not particularly limited insofar as it does not inhibit the reaction. Examples of the solvent include ether solvents such as tetrahydrofuran and dioxane; alcohol solvents such as methanol and ethanol; water; and mixed solvents thereof. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is
30 preferably room temperature to solvent reflux temperature, for example. Under preferable

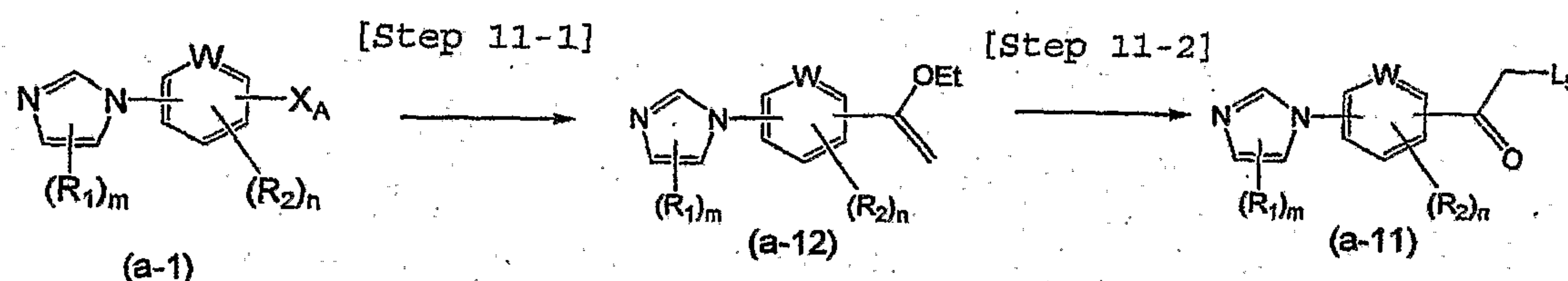
reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

5 [0170]

Preparation of compound of general formula (a-11)

The following formula shows an example of preparation of the compound of the general formula (a-11).

[0171]



10 [0172]

In the formula, R_1 , R_2 , m , n , W , X_A and L_5 are as defined above.

[0173]

The compound of the general formula (a-11) can be prepared from a compound (a-1) as a starting material through coupling reaction in Step 11-1 and halogenation in Step 11-2.

15 [0174]

The coupling reaction in Step 11-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method of reacting a compound (a-1) with 1.0 to 1.2 equivalents of tributyl(1-ethoxyvinyl)tin with respect to the compound (a-1) in a solvent in the presence of a palladium catalyst. The palladium catalyst is preferably 0.02 to 0.1 equivalent of bis(triphenylphosphine)palladium (II) chloride with respect to the compound (a-1), for example. The solvent used varies according to the starting material, the reagent and the like, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include non-polar solvents such as toluene and xylene; ether solvents such as tetrahydrofuran and dioxane; polar solvents such as N,N-dimethylformamide; and mixtures thereof. The reaction temperature is preferably room temperature to solvent reflux temperature.

25

[0175]

Step 11-2 is a step of converting a vinyl ether compound (a-12) to an α -haloketone compound (a-11). This reaction varies according to the starting material and are not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. For example, a method using
5 bromine, iodine, N-bromosuccinimide or the like is preferable.

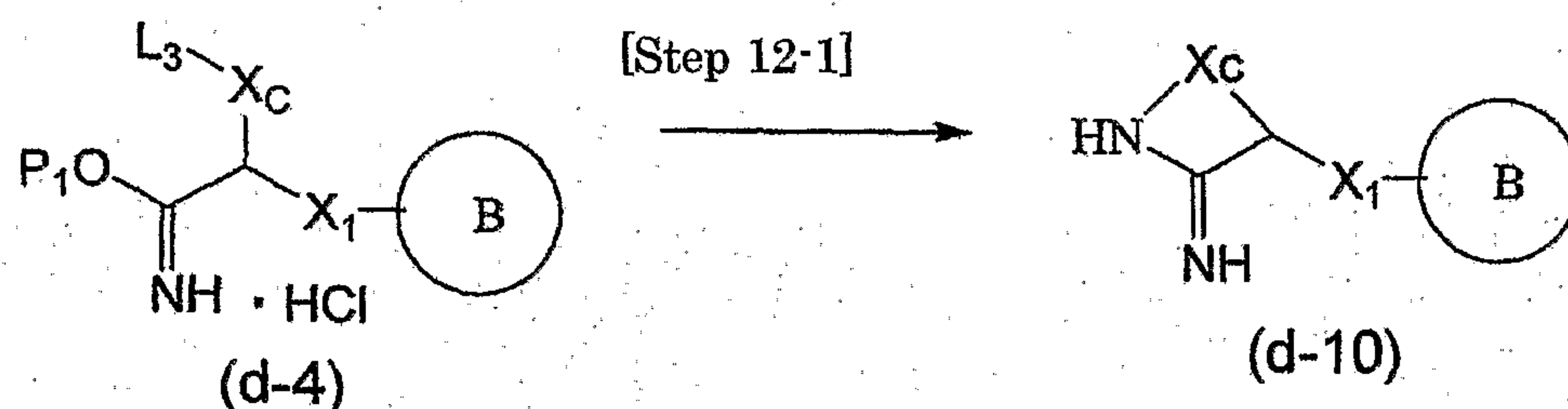
In the method using N-bromosuccinimide, it is preferable to react a vinyl ether compound (a-12) with 1.0 to 1.1 equivalents of N-bromosuccinimide with respect to the compound (a-12) in an ether solvent such as tetrahydrofuran or dioxane, a halogenated solvent such as dichloromethane, an alcohol solvent such as methanol or ethanol, a mixed solvent
10 thereof, or a mixed solvent of these solvents and water, for example. The reaction temperature is preferably 0°C to room temperature. The compound (a-11) may be either taken out as a salt or prepared before use and used as is by a method known to a person skilled in the art.

[0176]

Preparation of compound of general formula (d-10)

15 The following formula shows an example of preparation of the compound of the general formula (d-10).

[0177]



[0178]

In the formula, P₁, L₃, X_c, X₁ and Ring B are as defined above.

20 [0179]

The cyclic amidine compound (d-10) can be prepared from a compound (d-4) as a starting material through amidination and subsequent cyclization reaction in Step 12-1.

[0180]

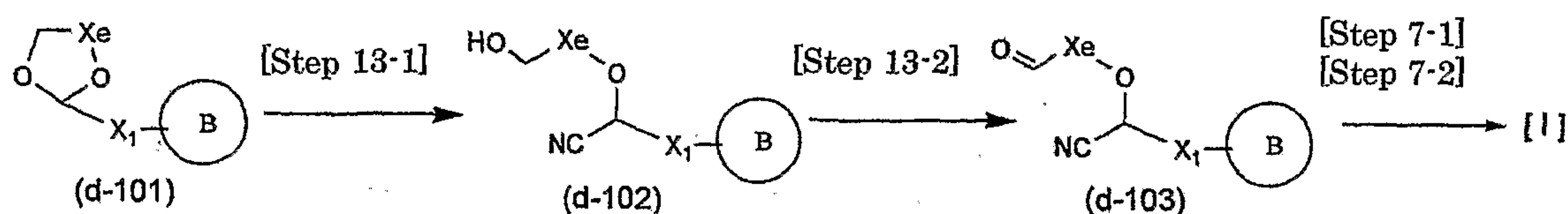
25 The cyclic amidine formation in Step 12-1 is not particularly limited insofar as the conditions are similar to those in this reaction. Examples thereof include a method of stirring an imidate compound (d-4) in a saturated ammonia-alcohol solution. The reaction temperature is preferably room temperature. The progress of the reaction can be monitored by LC-MS.

[0181]

General Preparation Method 5

Typically used General Preparation Method 5 for the compound of the general formula (I) according to the present invention will be described below.

[0182]



In the formula, X_1 and Ring B are as defined above; and X_e represents a C1-2 alkylene group.

5 [0183]

The above General Preparation Method 5 shows a general method for preparing the compound of the general formula (I) having an oxygen atom at the β -position of X_1 .

[0184]

The compound of the general formula (I) can be prepared by making an acetal compound (d-101) as a starting material undergo cyanohydrination following acetal cleavage in Step 13-1 and oxidation reaction in Step 13-2 and subjecting the resulting compound of the general formula (d-103) to the reactions in Steps 7-1 and 7-2 of the aforementioned General Preparation Method 3.

[0185]

15 The cyanohydrination following acetal cleavage in Step 13-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in Synthesis, p. 498, 1983; Tetrahedron Lett., vol. 31, p. 5343, 1990) may be used. Preferably, an acetal compound (d-101) is reacted with 1.0 to 2.0 equivalents of trimethylsilyl cyanide with respect to the compound (d-101) in a solvent or without a solvent in the presence of 0.01 to 0.5 equivalent of a Lewis acid with respect to the compound (d-101) under anhydrous conditions, for example. Examples of the Lewis acid used include zinc (II) iodide, titanium tetrachloride, tin tetrachloride, iron (III) chloride, zinc (II) chloride and zinc (II) bromide. The solvent used varies according to the starting material, and is not particularly limited insofar as the solvent does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include halogenated solvents such as methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as N,N-dimethylformamide, nitromethane

and N-methylpyrrolidone; non-polar solvents such as toluene and benzene; ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; and mixtures thereof. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably 0°C to solvent reflux temperature, for example. The product in the reaction solution is a trimethyl silyl ether of alcohol, and is converted to an alcohol by post-treatment with water.

[0186]

Step 13-2 is performed by the same method as in the oxidation reaction as the second stage of the aforementioned Step 8-2 and can prepare a compound of the general formula (d-103) from an alcohol compound (d-102).

[0187]

The compound of the general formula (I) can be prepared by subjecting the aldehyde compound (d-103) to the reactions in Steps 7-1 and 7-2 of the aforementioned General Preparation Method 3.

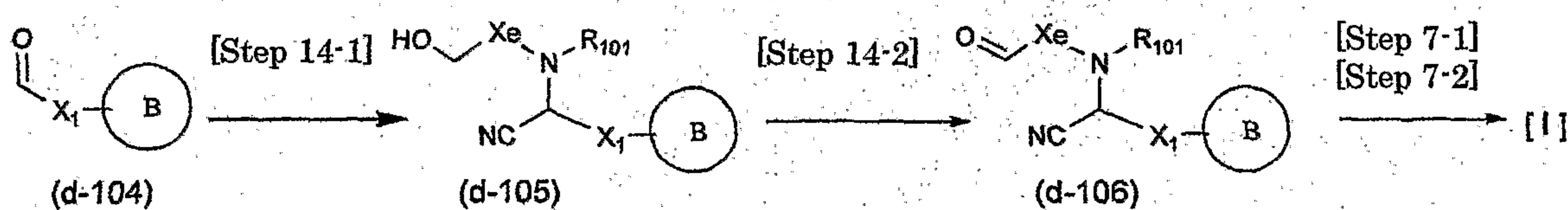
The compound (d-101) is a known or commercially available compound or is a compound that can be prepared from such a compound by a conventional method.

[0188]

General Preparation Method 6

Typically used General Preparation Method 6 for the compound of the general formula (I) according to the present invention will be described below.

[0189]



In the formula, X_1 and Ring B are as defined above; R_{101} represents a substituent for nitrogen (such as a methyl group, an isopropyl group, a phenyl group or a benzyl group); and X_e represents a C1-2 alkylene group.

[0190]

The above General Preparation Method 6 shows a general method for preparing the compound of the general formula (I) having a nitrogen atom at the β -position of X_1 .

[0191]

General Preparation Method 6 is an example of a method for preparing the

compound of the general formula (I) by making an aldehyde compound (d-104) as a starting material undergo aminonitrile formation in Step 14-1 and oxidation reaction in Step 14-2 and subjecting the resulting compound of the general formula (d-106) to the reactions in Steps 7-1 and 7-2 of the aforementioned General Preparation Method 3.

5 [0192]

The aminonitrile formation in Step 14-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in Tetrahedron Lett., vol. 48, p. 8001, 2007; Synthesis, p. 109, 1983) may be used.

[0193]

Step 14-2 is performed by the same method as in the oxidation reaction as the second stage of the aforementioned Step 8-2 and can prepare a compound of the general formula (d-106) from an alcohol compound (d-105).

15 [0194]

The compound [I] can be prepared by subjecting the aldehyde compound (d-106) to the reactions in Steps 7-1 and 7-2 of the aforementioned General Preparation Method 3.

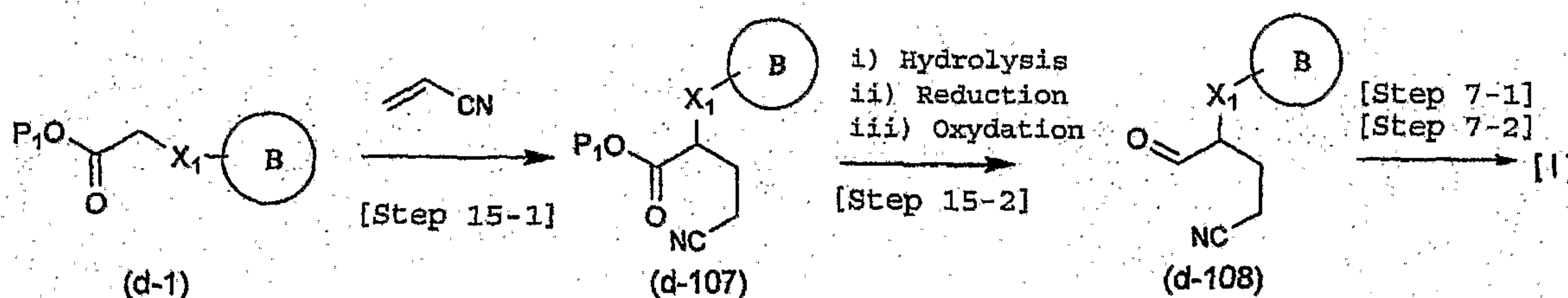
The compound (d-104) is a known or commercially available compound or is a compound that can be prepared from such a compound by a conventional method.

20 [0195]

General Preparation Method 7

Typically used General Preparation Method 7 for the compound of the general formula (I) according to the present invention will be described below.

[0196]



25 [0197]

In the formula, X_1 , P_1 and Ring B are as defined above.

[0198]

The above General Preparation Method 7 shows an example of a general method for preparing the compound of the general formula (I) having a bonding position of X_1 differing

from that of the compound of the general formula (I) derived from the compound of the general formula (d-7).

[0199]

General Preparation Method 7 is an example of a method for preparing the
5 compound of the general formula (I) by making an ester compound (d-1) as a starting material undergo Michael addition reaction in Step 15-1 and conversion from ester to aldehyde in Step 15-2 and subjecting the resulting compound of the general formula (d-108) to the reactions in Steps 7-1 and 7-2 of the aforementioned General Preparation Method 3.

[0200]

10 The Michael addition reaction in Step 15-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in "Modern Synthetic Reactions House 2nd edition" (W.A. Benjamin, Inc., California, 1972) p. 595-623; J. Med. Chem., vol. 36,
15 p. 2416, 1993) may be used.

[0201]

The conversion from ester to aldehyde in Step 15-2 is achieved by hydrolysis of ester, reduction of carboxylic acid to alcohol and oxidation of alcohol to aldehyde. The ester hydrolysis as the first stage is performed by the same method as in the first stage of the
20 aforementioned Step 3-2. The reduction as the second stage is not particularly limited insofar as the conditions are similar to those in this reaction. A reduction reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 20) Yuki Gosei (Organic Synthesis) [IV], Maruzen
25 Co., Ltd., November 1992, p. 10-14) may be used; borane reduction is preferable. The oxidation as the third stage is performed by the same method as in the oxidation as the second stage of the aforementioned Step 8-2 and can prepare a compound of the general formula (d-108) from an ester compound (d-107).

[0202]

30 The compound [I] can be prepared by subjecting the aldehyde compound (d-108) to the reactions in Steps 7-1 and 7-2 of the aforementioned General Preparation Method 3.

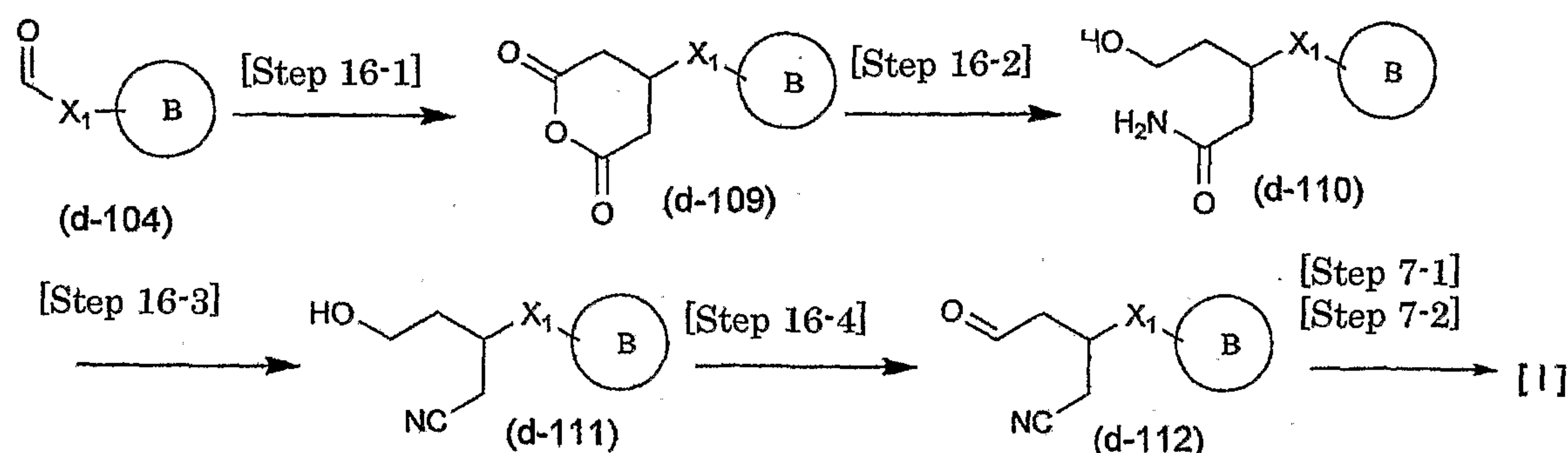
[0203]

General Preparation Method 8

Typically used General Preparation Method 8 for the compound of the general

formula (I) according to the present invention will be described below.

[0204]



[0205]

In the formula, X_1 , P_1 and Ring B are as defined above.

5 [0206]

The above General Preparation Method 8 shows an example of a general method for preparing the compound of the general formula (I) having a bonding position of X_1 differing from that of the compound of the general formula (I) derived from the compound of the general formula (d-7).

10 [0207]

General Preparation Method 8 is an example of a method for preparing the compound of the general formula (I) by making an aldehyde compound (d-104) as a starting material undergo conversion to glutaric anhydride in Step 16-1, conversion to amidoalcohol in Step 16-2, reaction of dehydration of amide in Step 16-3 and reaction of oxidation to aldehyde in Step 16-4 and subjecting the resulting compound of the general formula (d-112) to the reactions in Steps 7-1 and 7-2 of the aforementioned General Preparation Method 3.

[0208]

The conversion to glutaric anhydride in Step 16-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in Tetrahedron Asymmetry, vol. 16, p. 2475, 2005) may be used.

[0209]

Step 16-2 includes cleavage of glutaric anhydride with ammonia and subsequent reaction of reducing carboxylic acid to alcohol. The cleavage of glutaric anhydride with ammonia as the first stage varies according to the starting material and is not particularly limited

insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in J. Med. Chem., vol. 34, p. 1162, 1991) may be used. The reduction as the second stage is performed by the same method as in the reduction reaction as the second stage of the
5 aforementioned Step 15-2.

[0210]

Step 16-3 includes protection of alcohol, reaction of dehydration of amide to nitrile and reaction of deprotection of alcohol. The alcohol protection as the first stage varies according to the starting material and is not particularly limited insofar as the conditions are
10 similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for example) may be used. The protecting group is preferably a tert-butyldiphenylsilyl group in order to ensure stability of the protecting group against the subsequent step. The dehydration reaction as the
15 second stage is performed by the same method as in the dehydration reaction as the third stage of the aforementioned Step 6-3. The deprotection reaction as the third stage varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A deprotection reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (T. Greene et al., "Protective Groups
20 in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for example) may be used.

[0211]

The oxidation in Step 16-4 is performed by the same method as in the oxidation reaction as the second stage of the aforementioned Step 8-2 and can prepare a compound of the general formula (d-112) from an alcohol compound (d-111).

25 [0212]

The compound [I] can be prepared by subjecting the aldehyde compound (d-112) to the reactions in Steps 7-1 and 7-2 of the aforementioned General Preparation Method 3.

[0213]

As described above in detail, the compound of the general formula (I) can be
30 prepared according to General Preparation Methods 1 to 8 for the compound of the present invention, and can also be prepared by another method well known to a person skilled in the art. The examples described later will provide reference to these Preparation Methods, and the compound of the general formula (I) can be easily prepared by a method itself known to a person skilled in the art based on these examples.

[0214]

The compound of the general formula (I) or pharmacologically acceptable salt thereof according to the present invention is effective for the treatment of a disease caused by A β and is excellent in terms of pharmacokinetics, toxicity, stability, absorption and the like.

5 A therapeutic agent for a disease caused by A β comprising the compound of the formula (I) or pharmacologically acceptable salt or ester thereof according to the present invention as an active ingredient can be prepared by a conventional method. Preferable examples of the dosage form include tablets, powders, fine granules, granules, coated tablets, capsules, syrups, troches, inhalants, suppositories, injections, ointments, ophthalmic solutions, 10 ophthalmic ointments, nasal drops, ear drops, cataplasms and lotions. The agent can be prepared by using ingredients typically used such as an excipient, a binder, a lubricant, a colorant and a corrective, and ingredients used where necessary such as a stabilizer, an emulsifier, an absorbefacient, a surfactant, a pH adjuster, a preservative and an antioxidant, and can be prepared by blending ingredients generally used as materials for a pharmaceutical preparation.

15 Examples of such ingredients include animal and vegetable oils such as soybean oil, beef tallow and synthetic glyceride; hydrocarbons such as liquid paraffin, squalane and solid paraffin; ester oils such as octyldodecyl myristate and isopropyl myristate; higher alcohols such as cetostearyl alcohol and behenyl alcohol; a silicone resin; silicone oil; surfactants such as polyoxyethylene fatty acid ester, sorbitan fatty acid ester, glycerin fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene hydrogenated castor oil and a polyoxyethylene-polyoxypropylene 20 block copolymer; water-soluble polymers such as hydroxyethylcellulose, polyacrylic acid, a carboxyvinyl polymer, polyethylene glycol, polyvinylpyrrolidone and methylcellulose; lower alcohols such as ethanol and isopropanol; polyhydric alcohols such as glycerin, propylene glycol, dipropylene glycol and sorbitol; sugars such as glucose and sucrose; inorganic powders 25 such as silicic anhydride, magnesium aluminum silicate and aluminum silicate; and purified water. Examples of the excipient used include lactose, corn starch, saccharose, glucose, mannitol, sorbitol, crystalline cellulose and silicon dioxide. Examples of the binder used include polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, a 30 polypropylene glycol-polyoxyethylene block copolymer and meglumine. Examples of the disintegrant used include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextrin, pectin and carboxymethylcellulose calcium. Examples of the lubricant used include magnesium stearate, talc, polyethylene glycol, silica and hydrogenated vegetable oil. Examples of the colorant used include those permitted to be added

to pharmaceuticals. Examples of the corrective used include cocoa powder, menthol, empassm, mentha oil, borneol and cinnamon powder.

[0215]

For example, an oral preparation is prepared by adding an active ingredient
5 compound or a salt thereof or a hydrate of the compound or salt, an excipient, and, where necessary, a binder, a disintegrant, a lubricant, a colorant and a corrective, for example, and then forming the mixture into powder, fine granules, granules, tablets, coated tablets or capsules, for example, by a conventional method. It is obvious that tablets or granules may be appropriately coated, for example, sugar coated, where necessary. A syrup or an injection preparation is
10 prepared by adding a pH adjuster, a solubilizer and an isotonizing agent, for example, and a solubilizing agent, a stabilizer and the like where necessary by a conventional method. An external preparation may be prepared by any conventional method without specific limitations. As a base material, any of various materials usually used for a pharmaceutical, a quasi drug, a cosmetic or the like can be used. Examples of the base material include materials such as animal
15 and vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals and purified water. A pH adjuster, an antioxidant, a chelator, a preservative and fungicide, a colorant, a flavor or the like may be added where necessary. Further, an ingredient having a differentiation inducing effect such as a blood flow enhancer, a bactericide, an antiphlogistic, a
20 cell activator, vitamin, amino acid, a humectant or a keratolytic agent may be blended where necessary.

[0216]

The dose of the therapeutic agent according to the present invention varies according to the degree of symptoms, age, sex, body weight, mode of administration, type of salt
25 and specific type of disease, for example. Typically, the compound of the formula (I) or pharmacologically acceptable salt thereof is orally administered to an adult at about 30 μ g to 10 g, preferably 100 μ g to 5 g, and more preferably 100 μ g to 100 mg per day, or is administered to an adult by injection at about 30 μ g to 1 g, preferably 100 μ g to 500 mg, and more preferably 100 μ g to 30 mg per day, in a single dose or several divided doses, respectively.

30 [0217]

To treat a disease caused by amyloid- β such as Alzheimer's disease, senile dementia, Down's syndrome or amyloidosis, the compound of the formula (I) or pharmacologically acceptable salt thereof according to the present invention may be used in combination with compounds having the following mechanisms.

For example, such compounds include cholinesterase inhibitors (e.g., donepezil, huperzine A, tacrine, rivastigmine, galantamine); AMPA receptor antagonists (e.g., 1,2-dihydropyridine compounds such as 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one); NMDA receptor antagonists (e.g., memantine); acetylcholine releasing
5 stimulants (e.g., pramiracetam; aniracetam); calcium channel agonists (e.g., nefiracetam); free radical scavengers (e.g., EGb 761); platelet activating factor antagonists (e.g., EGb 761); platelet aggregation antagonists (e.g., EGb 761, triflusal); insulin sensitizers (e.g., rosiglitazone); peroxisome proliferator-activated receptor agonists (e.g., rosiglitazone); peroxisome proliferator-activated receptor gamma agonists (e.g., rosiglitazone); monoamine oxidase B inhibitors (e.g.,
10 rasagiline, selegiline, procaine); carnitine acetyltransferase stimulants (e.g., levacecarnine); NSAIDs (e.g., triflusal, cyclooxygenase-2 inhibitors, such as celecoxib); nerve growth factor agonists (e.g., xaliproden, FPF 1070); beta-amyloid inhibitors (e.g., tarenflurbil, tramiprosate, leuprorelin-D); immunomodulators (e.g., tarenflurbil, immune globulin, icosapentethyl ester); NF-kappa B inhibitors (e.g., tarenflurbil); thyrotropin releasing hormone (e.g., taltirelin);
15 dopamine D2 receptor antagonists (e.g., risperidone); serotonin 2 receptor antagonists (e.g., risperidone); muscarinic M1 receptor agonists (e.g., cevimeline); alpha 1 adrenoceptor agonists (e.g., modafinil); serotonin 3 receptor antagonists (e.g., alosetron); dopamine D2 receptor agonists (e.g., aripiprazole); dopamine D2 receptor antagonists (e.g., aripiprazole); serotonin 1A receptor agonists (e.g., aripiprazole); serotonin 2A receptor antagonists (e.g., aripiprazole);
20 glucocorticoid antagonists (e.g., mifepristone); progesterone antagonists (e.g., mifepristone); HMG-CoA reductase inhibitors (e.g., atorvastatin, simvastatin); adenosine uptake inhibitors (e.g., propentofylline); phosphodiesterase inhibitors (e.g., propentofylline); acetylcholine receptor agonists (e.g., choline alfoscerate); membrane permeability enhancers (e.g., choline alfoscerate); cannabinoid 1 receptor antagonists (e.g., rimonabant); cannabinoid receptor
25 agonists (e.g., dronabinol); angiogenesis inhibitors (e.g., paclitaxel); immunosuppressants (e.g., paclitaxel); tubulin antagonists (e.g., paclitaxel); thromboxane A synthase inhibitors (e.g., triflusal); antioxidants (e.g., idebenone); alpha adrenoreceptor antagonists (e.g., nicergoline); estrogen antagonists (e.g., conjugated estrogens, trilostane); 3-beta hydroxysteroid dehydrogenase inhibitors (e.g., trilostane); signal transduction pathway inhibitors (e.g.,
30 trilostane); melatonin receptor agonists (e.g., ramelteon); immunostimulants (e.g., immune globulin, icosapentethyl ester, procaine); HIV entry inhibitors (e.g., procaine); sodium channel antagonists (e.g., procaine); microtubule inhibitor (e.g., CPH 82); glycine NMDA agonists (e.g., cycloserine); adenosine A1 receptor antagonists (e.g., KW 3902); ATPase stimulants (e.g., triacetyluridine); mitochondrial function enhancers (e.g., triacetyluridine); growth hormone

releasing factor agonists (e.g., tesamorelin);. butylcholine esterase inhibitor (e.g., bisnorcymserine); alpha adrenergic receptor antagonists (e.g., nicergoline); NO synthase type II inhibitors (e.g., arundic acid); chelating agents (e.g., PBT 2); amyloid fibrillogenesis inhibitors (e.g., TTP488, PF 4494700); serotonin 4 receptor agonists (e.g., PRX 03140); serotonin 6
 5 receptor antagonists (e.g., SB 742457); benzodiazepine receptor inverse agonists (e.g., radequinil); Ca channel antagonists (e.g., safinamide); nicotinic receptor agonists (e.g., ispronicline); and BACE inhibitor (e.g., CTS 21166).

[0218]

Further, the above compounds include, for example, donepezil, huperzine A,
 10 tacrine, rivastigmine, galantamine, pramiracetam, aniracetam, nefiracetam, EGb 761, rosiglitazone, rasagiline, levacecarnine, celecoxib, 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one, talampanel, becampanel, memantine, xaliproden, tarenflurbil, tramiprosate, leuprorelin-D, taltirelin, risperidone, cevimeline, modafinil, alosetron, aripiprazole, mifepristone, atorvastatin, propentofylline, choline alfoscerate, FPF 1070 (CAS Number 143637-
 15 01-8), rimonabant, dronabinol, docosahexaenoic acid, paclitaxel, triflusal, idebenone, nicergoline, conjugated estrogens, trilostane, simvastatin, selegiline, ramelteon, immune globulin, icosapentethyl ester, procaine, CPH 82, cycloserine, KW 3902 (CAS Number 136199-02-5), triacetyluridine, estrogen dementia therapeutics (e.g., MIGENIX, Vancouver, Canada), tesamorelin, bisnorcymserine, nicergoline, arundic acid, PBT 2, TTP488, PF 4494700, PRX
 20 03140, SB 742457, radequinil, safinamide, ispronicline, CTS 21166, Bapineuzumab, NP 031112, (2S,3aS,7aS)-1 {[(R,R)-2-Phenylcyclopropyl]carbonyl}-2-[(thiazolidin-3-yl)carbonyl]octahydro-1H-indole, citalopram, venlafaxine, levprorelin, prasterone, peptide T (CAS Number 53-43-0), besipiridine, lexipafant, stacofylline, SGS 742 (CAS Number 123690-78-8), T 588 (CAS Number 142935-03-3), nerispiridine, dexanabinol, sabcomeline, GTS 21 (CAS Number 156223-
 25 05-1), CX 516 (CAS Number 154235-83-3), ABT 089 (CAS Number 161417-03-4), anapsos, tesofensine, SIB 1553A (i.e., 4-[[2-(1-methyl-2-pyrrolidinyl)ethyl]thio]phenol), ladostigil, radequinil, GPI 1485, ispronicline, arundic acid, MEM 1003 (i.e., 3-Isopropyl 5-(2-methoxyl) 4-(2-chloro-3-cyanophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate), V 3381 (i.e., 2-(2,3-Dihydro-1H-inden-3-ylamino)acetamide hydrochloride), farampator, paliroden, prasterone-
 30 paladin, urocortin, DP b99 (i.e., 2,2'-(Ethylenedioxy)bis(2,1-phenylene)bis[N-[2-[2-(octyloxy)ethoxy]-2-oxoethyl]imino]bis(acetic acid))), capserod, DU 125530, bapineuzumab, AL 108 (i.e., L-Asparaginy-L-alanyl-L-prolyl-L-valyl-L-seryl-L-isoleucyl-L-prolyl-L-glutamine), DAS 431, DEBIO 9902, DAR 100, mitoquinone, IPL 455903 (i.e., 5(S)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(S)-(3-methylbenzyl)piperidin-2-one), E2CDS, PYM 50028, PBT 2,

lecozotan, SB 742457, CX 717, AVE 1625 (i.e., 1-(bis(4-chlorophenyl)methyl)-3-((3,5-difluorophenyl)(methylsulfonyl)methylene)azetidine), LY 450139 (i.e., N2-[2(s)-Hydroxy-3-methylbutyryl]-N1-[3-methyl-2-oxo-2,3,4,5-tetrahydro-1H-3-benzazepin-1(S)-yl]-L-alaninamide), EM 1421 (i.e., 4,4'-[(2R,3S)-2,3-Dimethylbutane-1,4-diyl]bis(1,2-dimethoxybenzene), SRN 001, TTP 488, PRX 03140, dimebolin, glycine-proline-glutamate, C105, AL 208, MEM 3454, AC 1202, L 830982, LY 451395 (i.e., (R)-N-[2-[4'-(methylsulfonyl)methyl]biphenyl-4-yl]propyl]propane-2-sulfonamide), MK 0249, LY 2062430, diethylnorspermine, neboglamine, S 18986, SA 4503 (CAS Number 165377-44-6), GRI 1, S 17092 (i.e., (2S,3aS,7aS)-1-[(R,R)-2-Phenylcyclopropyl]carbonyl}-2-[(thiazolidin-3-yl)carbonyl]octahydro-1H-indole), SL 251188, EUK 189, R 1450, 6,6-dimethyl-3-(2-hydroxyethyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one, CERE 110, dexefaroxan, CAD 106, HF 0220, HF 0420, EHT 0202, VP 025, MEM 1414, BGC 201259 (i.e., N,N-Dimethylcarbamic acid, 4-[1(S)-(methylamino)-3-(4-nitrophenoxy)propyl]phenyl ester), EN 100, ABT 834, ABT 239 (i.e., 4-[2-[2-[(2R)-2-Methylpyrrolidinyl]ethyl]-benzofuran-5-yl]benzonitrile), SGS 518, R 1500, C 9138, SSR 180711, alfatradiol, R 1577, T 817MA (i.e., 1-[3-[2-(1-Benzothien-5-yl)ethoxy]propyl]azetidin-3-olmaleate), CNP 1061 (i.e., 4-Methyl-5-(2-nitrooxyethyl)thiazole), KTX 0101 (i.e., sodium beta-hydroxybutyrate), GSK 189254 (i.e., 6-[3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy]-N-methylnicotinamide), AZD 1080, ACC 001, PRX 07034, midazolam, R-phenserine, AZD 103 (CAS Number 488-59-5), SN 522, NGX 267 (CAS Number 503431-81-0), N-PEP-12, RN 1219, FGLL, AVE 8112, EVT 101, NP 031112, MK 0752, MK 0952, LX 6171, PAZ 417, AV 965, PF 3084014, SYN 114, GSI 953, SAM 315, SAM 531, D-serine, letepirim potassium, BR 16A (CAS Number 149175-77-9), RPR 107393 (CAS Number 190841-57-7), NXD 2858, REN 1654, CDD 0102, NC 1900 (CAS Number 132925-74-7), ciclosporin, NCX 2216 (i.e., (E)-4-(Nitrooxy)butyl 3-[4-[2-(2-fluorobiphenyl-4-yl)propanoyloxy]-3-methoxyphenyl]acrylate), NXD 3109, NXD 1191, ZSET 845 (i.e., 3,3-diphenylimidazo[1,2-a]pyridin-2-(3H)-one), ET 002, NT 13, RO 638695 (i.e., [1,6-(1,6-dioxohexyl)]dipyrrolidine-(2R)-carboxylic acid), bisnorcymserine, BA 1016, XD 4241, EUK 207 (i.e., (SP-5-13)-(acetato-κO)[13,16,19,22-tetraoxa-3,6-diazatricyclo[21.3.18,12]octacos-1(27),2,6,8,10,12(28),23,25-octaene-27,28-diolato(2)-κN3,κN6,κO27,κO28]manganese), LG 617 inhibitors, ZSET 1446, PAN 811, F 14413 (i.e., 2-[5-fluoro-2(S)-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]-4,5-dihydro-1H-imidazole), FP 7832 (i.e., N-[2-(5-methoxy-1-nitroso-1H-indol-3-yl)ethyl]acetamide), ARA 014418 (i.e., N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl)urea), AZD 3102, KP 544 (i.e., 2-amino-5-(4-chlorophenylethynyl)-4-(4-trans-hydroxycyclohexylamino)pyrimidine), DP 155, 5-chloro-N-[3-

[2-(dimethylamino)ethyl]-1H-indol-5-yl]naphthalene-2-sulfonamide, TAK 070, huperzine, N-[2-(3,5-dimethyladamant-1-yl)ethyl]acetamidine hydrochloride, 6-[4-[(dimethylamino)methyl]-5-ethyl-2-methoxyphenyl]pyridin-2-amine, 4,6-diphenyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine, N-[(1S,2R)-3-(3,5-difluorophenyl)-1-hydroxy-1-[(5S,6R)-5-methyl-6-(neopentyloxy)morpholin-3-yl]propan-2-yl]acetamide hydrochloride, N-[(1R,2S)-3-(3,5-difluorophenyl)-1-hydroxy-1-[(2R,4R)-4-phenoxyproline-2-yl]propan-2-yl]-3-[(R)-2-(methoxymethyl)pyrrolidine-1-carbonyl]-5-methylbenzamide, R 1589, midafotel, phenserine, coluracetam, physostigmine, ciprofloxacin, nitroflurbiprofen, PPI 1019 (i.e., (3 α , 5 β , 7 α , 12 α)-trihydroxycholestan-24-oyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-alanine), dapsone, MDL 100453 (CAS Number 129938-34-7), NS 377, midaxifylline, propofol phosphate, metrifonate, ceronapril, tenilsetam, sufoxazine, seglitide, ebiratide, nebracetam, milacemide, iododoxorubicin, SM 10888 (CAS Number 129297-21-8), U 80816 (CAS Number 138554-11-7), YM 954 (CAS Number 132041-85-1), SUT 8701 (CAS Number 123577-73-1), apovincamine, FR 121196 (CAS Number 133920-65-7), LY 274614 (CAS Number 136109-04-1), CL 275838 (CAS Number 115931-65-2), igmesine, K 7259 (CAS Number 133667-88-6), vinconate, itasetron, CL 287663 (CAS Number 125109-98-0), WAY 100289 (CAS Number 136013-69-9), SR 46559A (CAS Number 137733-33-6), GYKI 46903 (CAS Number 142999-59-5), L 670548 (CAS Number 121564-89-4), Y 29794 (CAS Number 129184-48-1), AF 125 (CAS Number 7631-86-9), KFM 19 (CAS Number 133058-72-7), ST 796 (i.e., (S)-3-[3-(trifluoromethyl)benzoyl]amino]hexahydroazepin-2-one), RU 33965 (CAS Number 122321-05-5), SDZ 210086 (i.e., (-)-1',2(S)-Dimethylspiro[1,3-dioxane-4,4'-piperidine]), L 689660 (CAS Number 144860-79-7), L 689560 (CAS Number 139051-78-8), ST 618 (i.e., 1-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-naphthyl)-4-hydroxy pyrrolidin-2-one), U 74500A (CAS Number 110101-65-0), GEA 857 (CAS Number 120493-42-7), BIBN 99 (CAS Number 145301-48-0), DX 9366, ONO 1603 (CAS Number 114668-76-7), MDL 102234 (CAS Number 137766-81-5), P 9939 (CAS Number 157971-37-4), PD 140532 (CAS Number 157971-39-6), azetirelin, MR 16728 (CAS Number 147614-21-9), dabelotine, MDL 102503 (i.e., 8-[1(R)-methyl-2-phenylethyl]-1,3-dipropyl-7H-xanthine), PD 141606 (i.e., ($\pm$)-(Z)-3-(3-Phenyl-2-propynyloxyimino)-1-azabicyclo[2.2.1]heptane), SNK 882 (CAS Number 152221-12-0), L 696986 (CAS Number 141553-45-9), tazomeline, LY 235959 (CAS Number 137433-06-8), 2-(2-thiooxopyrrolidin-1-yl)acetamide, AK 30 NGF, ABT 418 (CAS Number 147402-53-7), itameline, HUP 13, sibopirdine, KST 5452 (CAS Number 157998-88-4), TJ 54, U 92798 (i.e., 7-[4-[Bis(4-fluorophenyl)methyl]perhydro-1,4-diazepin-1-ylmethyl]-4-isopropyl-2-methoxy-2,4,6-cycloheptatrien-1-one), U 92032 (CAS Number 142223-92-5), 3-(sulfamoyloxy)estra-1,3,5(10)-

trien-17-one, P 11012 (CAS Number 164723-36-8), A 82695 (CAS Number 147388-86-1), FR 76659 (CAS Number 116904-25-7), apaxifylline, CX 417, 7 MEOTA (CAS Number 5778-80-3), BU 4514N (CAS Number 151013-39-7), pregnenolone, mexidol, ST 857 (CAS Number 154755-63-2), RU 49041 (CAS Number 123828-80-8), RU 35929 (CAS Number 111711-47-8), P 878184, P 128 (CAS Number 157716-52-4), eurystatin A, eurystatin B, LK 12, NBI 108, NBI 107, NBI 117, L 705106, bacoside A+B, clausenamide, SM 21 (CAS Number 155156-22-2), alaptide, RS 17017 (i.e., 1-(4-Amino-5-chloro-2-methoxyphenyl)-5-(1-piperidinyl)-1-pentanone hydrochloride), AF 150(S) (i.e., (S)-[1-Methyl-piperidine-4-spiro-(2'-methylthiazoline)]), RO 153505 (CAS Number 78771-13-8), PV 113 (i.e., 1,2,3,4-Tetrahydropyrrole-[1,2-a]-pyrazine), arisugacin, A 98284 (i.e., 2(R)-(3-Methyloxazol-5-yl) quinuclidine), AP 5 (CAS Number 136941-85-0), BD 1054, SDZ NDD 094 (i.e., bis-(2-(2-methylimidazol-1-yl)methyl)-pyridine-tris(hydrogen-fumarate), AZ 36041 (CAS Number 173324-76-0), quilostigmine, A 84543 (i.e., 3-[1-Methylpyrrolidin-2-(S)-ylmethoxy]pyridine fumarate), BTG 4247 (i.e., (2-[2-Chloroethoxy[4-(dimethylamino)phenyl]phosphoryl]-acetohydrazine), CGP 50068 (CAS Number 158647-49-5), cerebrocrast, desferri-nordanoxamine, isolichenan, MHP 133 (i.e., 3-(N,N-dimethylcarbamoxyloxy)-1-methyl-2-(4-phenyl-semicarbazonomethyl)pyridium chloride), FR 152558 (CAS Number 151098-08-7), GVS 111 (CAS Number 157115-85-0), P 11149 (CAS Number 164724-79-2), PDC 008004, KST 2818 (CAS Number 158623-26-8), KST 5410 (CAS Number 158623-27-9), RU 52583 (CAS Number 123829-33-4), PD 151832 (CAS Number 149929-39-5), UCL 1199 (i.e., 4-[2-[(5-Nitropyridin-2-ylsulfanyl)ethyl]-1H-imidazole), isovanihuperzine A, SIB 1765F (CAS Number 179120-52-6), JWS USC 751X (i.e., 3-[[[2-[(5-dimethylaminoethyl)-2-furanyl]methyl]thio]ethyl]amino]-4-nitropyridazine), GR 175737 (i.e., 3-(4-Chlorobenzyl)-5-[2-(1H-imidazol-4-yl)ethyl]-1,2,4-oxadiazole), KS 505A (CAS Number 131774-53-3), ZTTA 1 (i.e., N-benzyloxycarbonyl-thiopropyl-thiopropynal-dimethylacetal), AGN 190837 (CAS Number 136527-40-7), P 10358 (188240-59-7), WAY 131256 (CAS Number 174001-71-9), DBO 83 (i.e., 3-(6-chloropyrazin-3-yl)-diazabicyclo[3.2.1]octane dihydrochloride monohydrate), FUB 181 (CAS Number 152029-80-6), RJR 2557, WSU 2088, LVV-haemorphin-7, M 40 (i.e., galanin[1-12]-Pro3-(Ala-Leu)₂-Ala-NH₂), SIB 1757, SKF 74652 (i.e., [5-chloro-2-(4-methoxy phenyl)-3-benzofuranyl][4-[3-(dimethylamino)-propoxy]phenyl]methanone), CGP 71982, SCH 57790 (i.e., 4-cyclohexyl-alpha-[4-[[4-methoxyphenyl]sulfinyl]phenyl]-1-piperazineacetonitrile), Putrescine-D-YiAbetal1, DU 14 (i.e., p-O-(sulfamoyl)-N-tetradecanoyl tyramine), CLZ 4, SL 340026, PPRT 424, ciproxifan, UR 1827 (i.e., 2-(1-benzylpiperidin-4-yl)-1-[4-(5-methylpyrimidin-4-ylamino)phenyl]-1-ethanone), caproctamine, TGS 20 (i.e., L-pyroglutamil-D-alanine amide), PG 9 (i.e., alpha-tropanyl 2-[(4-

bromo)phenyl]propionate), TEI 3356 (i.e., (16S)-15-Deoxy-16-hydroxy-16-methyl-9-(O)-methano-DELTA6(9alpha)-prostaglandin I1), LY 392098 (i.e., Thiophene, 3-[(2-methylethyl-2)sulphonylaminopropyl-2]phenyl-4-yl-), PG 1000, DM 232, NEPP 11 (i.e., 12-iso-15-Deoxy-18-(4-methyl)phenyl-13,14-dihydro-delta7-prostaglandinA1 methyl ester), VA 100 (i.e., (2,3-
5 Dihydro-2-[[[(4-fluorobenzoyl)amino]ethyl]-1-methyl-5-phenyl-1H-1,4-benzodiazepine), VA 101 (i.e., (2,3-dihydro-2-[[[(2-thienylcarbonyl)amino]ethyl]-1-methyl-5-phenyl-1H-1,4-benzodiazepine), NC 111585 (i.e., (3S)-1,3-Bis-[3-[(3-azabicyclo[2.2.2]octanyl)-1,2,5-thiadiazol-4-yloxy]-1-propyn-1-yl]benzene, 2L-(+)-tartate), IN 201, imoproxifan, kanokodiol, picroside I, picroside II, DM 235 (i.e., 1-(4-Benzoylpiperazin-1-yl)propan-1-one), monoclonal antibody
10 10D5, JLK2, JLK 6, JLK 7, DAPT (i.e., N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester), huperine X, SGS 111 (i.e., (S)-ethyl 2-[1-(2-phenylacetyl)pyrrolidine-2-carboxamido]acetate), NP 7557, C 9136, C 7617, R 1485, rofecoxib, velnacrine, montirelin, lazabemide, ORG 2766 (CAS Number 50913-82-1), sabeluzole, adafenoxate, CAS Number 9061-61-4, ipidacrine, bemesetron, idazoxan, linopirdine, selfotel,
15 suritozole, milameline, xanomeline, TJ 960, fasoracetam, eptastigmine, ensaculin, zanapezil, posatiorelin, zacopride, RS 86 (CAS Number 3576-73-6), ORG 5667 (CAS Number 37552-33-3), RX 77368 (CAS Number 76820-40-1), BMS 181168 (CAS Number 123259-91-6), BY 1949 (CAS Number 90158-59-1), AWD 5239 (CAS Number 109002-93-9), YM 796 (171252-79-2), aloracetam, CI 933 (CAS Number 91829-95-7), ST 793 (CAS Number 99306-37-3),
20 cebaracetam, zifrosilone, talsaclidine, alvameline, JTP 2942 (148152-77-6), OPC 14117 (CAS Number 103233-65-4), elziverine, AP 521 (i.e., N-(1,3-Benzodioxol-5-ylmethyl)-1,2,3,4-tetrahydro[1]benzothieno[2,3-c]pyridine-3(R)-carboxamide hydrochloride), S 8510 (CAS Number 151466-23-8), JTP 4819 (CAS Number 162203-65-8), icopezil, SC 110, FK 960 (CAS Number 133920-70-4), DMP 543 (CAS Number 160588-45-4), ganstigmine, CI 1017 (i.e., (R)-
25 (-)-(Z)-1-Azabicyclo[2.2.1]heptan-3-one, O-(3-(3'-methoxyphenyl)-2-propionyl)-oxime maleate), T 82 (i.e., 2-[2-(1-Benzylpiperidin-4-yl)ethyl]-2,3-dihydro-9-methoxy-1H-pyrrolo[3,4-b]quinolin-1-one hemifumarate), NGD 971, vaccine of Aspartyl-alanyl-glutamyl-phenylalanyl-arginyl-histidyl-aspartyl-seryl-glycyl-tyrosyl-glutamyl-valyl-histidyl-histidyl-glutaminyl-lysyl-leucyl-valyl-phenylalanyl-phenylalanyl-alanyl-glutamyl-aspartyl-valyl-glycyl-seryl-asparaginyl-
30 lysyl-glycyl-alanyl-isoleucyl-isoleucyl-glycyl-leucyl-methionyl-valyl-glycyl-glycyl-valyl-valyl-isoleucyl-alanine, PBT 1 (CAS Number 130-26-7), TCH 346, FK 962 (i.e., N-(1-acetylpiperidin-4-yl)-4-fluorobenzamide), voxergolide, KW 6055 (CAS Number 63233-46-5), thiopilocarpine, ZK 93426 (CAS Number 89592-45-0), SDZ NVI 085 (CAS Number 104195-17-7), CI 1002 (CAS Number 149028-28-4), Z 321 (CAS Number 130849-58-0), mirisetron, CHF 2060 (i.e., N-

Heptylcarbamic acid 2,4a,9-trimethyl-2,3,4,4a,9,9a-hexahydro-1,2-oxazino[6,5-b]indol-6-yl ester-L-tartrate), gedocarnil, terbequinil, HOE 065 (CAS Number 123060-44-6), SL 650102, GR 253035, ALE 26015, SB 271046 (i.e., 5-Chloro-N-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulfonamide), iAbeta5, SCH 211803 (i.e., Piperidine, 1-[1-(3-methyl-2-aminophenyl)carbonylpiperidin-4-yl]-4-[(3-chlorophenyl)sulphonylphenyl-4]methyl-), EVT 301, alpha-Linolenic acid/linoleic acid, Kamikihi-To, siagoside, FG 7142 (CAS Number 78538-74-6), RU 47067 (CAS Number 111711-92-3), RU 35963 (CAS Number 139886-03-6), FG 7080 (CAS Number 100332-18-1), E 2030 (CAS Number 142007-70-3), transforming growth factor beta-1, A 72055 (i.e., 2',1-Dimethylspiro[piperidine-4,5'oxazolidine]-3'-carboxaldehyde), NS 626, dimiracetam, GT 3001, GT 2501, GT 2342, GT 2016 (CAS Number 152241-24-2), ORG 20091 (CAS Number 141545-50-8), BCE 001 (CAS Number 95678-81-2), CGP 35348 (CAS Number 123690-79-9), WAY 100635 (CAS Number 146714-97-8), E 4804 (CAS Number 162559-34-4), LIGA 20 (CAS Number 126586-85-4), NG 121 (i.e., 2-[4,8-Dimethyl-3(E),7(E)-monoadienyl]-3,5-dihydroxy-2-methyl-3,4,7,9-tetrahydro-2H-fluoro[3,4-h]-1-benzopyran-7-one), MF 247 (i.e., N-[10-(Diethylamino)decyl]carbamic acid (3aS,8aR)-1,3a,8-trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-5-yl ester), JTP 3399 (i.e., N-Benzyl-2(S)-[2(S)-(phenoxyacetyl)pyrrolidin-1-ylcarbonyl]pyrrolidine-1-carboxamide), KF 17329, thioperamide, F 3796 (i.e., 1-[2-(1-Benzylpiperidin-4-yl)ethyl]-3-[3,4-(methylene-dioxy)benzoyl]thiourea), GT 4001, GT 4002, FPL 14995 (CAS Number 123319-03-9), RU 34332 (CAS Number 137157-58-5), SR 96777A (CAS Number 115767-94-7), SIB T1980, NS 649 (CAS Number 146828-02-6), PD 142505 (CAS Number 149929-08-8), GYKI 52466 (CAS Number 102771-26-6), RO 246173 (CAS Number 159723-57-6), SCH 50911 (CAS Number 160415-07-6), Z 4105 (CAS Number 119737-52-9), RS 67333 (CAS Number 168986-60-5), NS 1546, ZM 241385 (CAS Number 139180-30-6), RO 249975 (i.e., [1S,3S(2'S),5R]-3-(1-Benzyl-5-oxopyrrolidin-2-ylmethyl)-5-(1H-imidazol-5-ylmethyl)cyclohexane-1-acetamide), AF 185 (i.e., 8-Methyl-3-(2-propynyl)-1,3,8-triazaspiro[4,5]decane-2,4-dione), CEP 427, CX 423, CX 438, CX 480, CDP-ethanolamine, GT 4003, GT 4011, GT 5011, MS 430 (CAS Number 122113-44-4), MBF 379 (i.e., [3,3-Bis(hydroxymethyl)-8-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-5-yl][3',5'-dihydroxy-4'-(2-oxo-2-phenylethoxy)phenyl]methanone), NGD 187 (CAS Number 163565-48-8), DUP 856, MR 3066, MF 8615 (i.e., 5-Amino-6-chloro-4-hydroxy-3,4-dihydro-1H-thiopyrano-[3,4-b]quinolinone), himbacine, ABS 300, RJR 2403 (CAS Number 538-79-4), MF 268 (CAS Number 174721-00-7), RO 465934 (i.e., N,N-Dimethylcarbamic acid 3-(2-cyclohexyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indol-6-yl ester), NS 393, RGH 2716 (CAS Number 134069-68-4), WIN 678702 (12,12-Bis(3-furyl)-6,11-dihydro-6,11-ethanobenzo[b]quinolizinium

chloride), RS 66252 (i.e., 1-Butyl-2-[(2'-(2H-tetrazol-5-yl)-biphenyl-4-yl)methyl]-1H-indole-3-carboxylic acid), AIT 034 (CAS Number 138117-48-3), NG 012 (CAS Number 131774-53-3), PD 142012 (CAS Number 5778-84-7), GT 4054, GT 4077, GT 4035, P 26 (CAS Number 152191-74-7), RGH 5279 (i.e., (-)-(13aR,13bS)-13a-Ethyl-2,3,5,6,13a,13b-hexahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine-12-carboxylic acid 2-acetoxyethyl ester), AIT 083, CeNeS, estradiol (i.e., 1,3,5(10)-Estratriene-3,17beta-diol), WAY 132983 ((3R,4R)-3-(3-hexasulfanylpirazin-2-yloxy)-1-azabicyclo[2.2.1]heptane hydrochloride), ABS 205, ABS 401, SX 3507 (i.e., 3-(3-Propyl-1,2,4-oxadiazol-5-yl)quinoxaline-2(1H)-one), ARR 17779 (i.e., (-)-Spiro[1-azabicyclo[2.2.2]octaene-3,5-oxazolidine]-2-one), XE 991 (i.e., 10,10-bis(4-Pyridylmethyl)anthracen-10(9H)-one), phenethylnorcymserine, RO 657199, RJR 1781 (i.e., R(+)-2-(3-pyridyl)-1-azabicyclo[2.2.2.]octane), RJR 1782 (i.e., S(-)-2-(3-pyridyl)-1-azabicyclo[2.2.2.]octane), gilatide, tolserine, TC 2559 (i.e., (E)-N-Methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine), ER 127528 (i.e., 1-(3-Fluorobenzyl)-4-[(2-fluoro-5,6-dimethoxy-1-indanone-2-yl)methyl]piperidine hydrochloride), thiatolserine, targacept, axonyx, cymserine, thiacymseline, monoclonal antibody 266, Apan-CH, DP 103, SPI 339 (i.e., 4-[3-(4-Oxo-4,5,6,7-tetrahydroindol-1-yl)propionylamino]benzoic acid ethyl ester), S 37245 (i.e., 4-(1,4-Benzodioxan-5-yl)-1-[3(S)-hydroxy-5-nitro-indan-2-yl]-piperazine), LLG 88, AZD 2858, trometamol, AN 240, NG 002 (i.e., 5-Hydroxy-5-(2-hydroxy-1-methylethyl)-4-methoxyfuran-2(5H)-one), UCB 29427 (i.e., 2-Cyclopropyl-4-(cyclopropylamino)-6-(morpholino)-1,3,5-triazine), TRH-SR, RO 401641 (CAS Number 122199-02-4), MPV 1743AIII (CAS Number 150586-64-4), IDRA 21 (CAS Number 22503-72-6), CEP 431, ACPD (CAS Number 67684-64-4), CT 3577 (i.e., 3,7-Dimethyl-1-[11-(3,4,5-trimethoxybenzylamino)-11-oxoundecyl]xanthine), CT 2583, NXD 9062, Desferri-nordanoxamine, DP b99, PBT 1, T 817MA, Alfatradiol (CAS No. 57-91-0), AL 108, SL 650102, RS 67333 (CAS No. 168986-60-5), RS 17017, SGS 518, SYN 114, SB 271046, RO 657199, PRX 07034, Suritozole (CAS No. 110623-33-19), Terbequinil (CAS No. 113079-82-6), FG 7142 (CAS No. 78538-74-6). RU 34332 (CAS No. 137157-58-5), SX 3507, RO 153505 (CAS No. 78771-13-8), RU 33965 (CAS No. 122321-05-5), S 8510 (CAS No. 151466-23-8), Sabeluzole (CAS No. 104383-17-7), Cerebrocrast (CAS No. 118790-71-9), NS 626, NS 649 (CAS No. 146828-02-6), U 92032 (CAS No. 142223-92-5), MEM 1003, U 92798, RGH 2716 (CAS No. 134069-68-4), Saffinamide (CAS No. 133865-89-1), AZD 0328, MEM 63908, ABT 418 (CAS No. 147402-53-7), ARR 17779, RJR 2403 (CAS No. 538-79-4), TC 2559, A 82695 (CAS No. 147388-86-1), A 84543, A 98284, DBO 83, RJR 2557, SIB 1765F (CAS No. 179120-52-6), GTS 21 (CAS No. 156223-05-1), MEM 3454, SIB 1553A, EVP 6124, SSR 180711, ABT 089 (CAS No. 161417-03-4), ABT 107, ABT 560, TC 5619, TAK 070, N-

[(1S,2R)-3-(3,5-Difluorophenyl)-1-hydroxy-1-[(5S,6R)-5-methyl-6-(neopentyloxy)morpholin-3-yl]propan-2-yl]acetamide hydrochloride, 6-Fluoro-5-(2-fluoro-5-methylphenyl)-3,4-dihydropyridine, 2-Amino-6-[2-(3'-methoxybiphenyl-3-yl)ethyl]-3,6-dimethyl-5,6-hydroxypyrimidin-4(3H)-one, AZD 1080, ARA 014418, XD 4241, Z 321 (CAS No. 130849-58-0), ONO 1603 (CAS No. 114668-76-7), JTP 3399, Eurystatin A (CAS No. 137563-63-4), Eurystatin B (CAS No. 137563-64-5), P 128 (CAS No. 157716-52-4), Y 29794 (CAS No. 129184-48-1), ZTTA 1, JTP 4819 (CAS No. 162203-65-8), Monoclonal antibody 266, duloxetine, escitalopram oxalate, fluoxetine, fluvoxamine maleate, paroxetine, sertraline, dapoxetine, desvenlafaxine, sibutramine, nefazodone, milnacipran, desipramine, duloxetine, and bicifadine.

[0219]

The present invention will now be described in detail with reference to examples; however, the examples are provided only for illustration purposes. The prophylactic or therapeutic agent for a disease caused by A β according to the present invention is not limited to the following specific examples in any cases. A person skilled in the art can fully implement the present invention by making various modifications to not only the following reference examples and examples but also the claims of the present specification, and such modifications are within the scope of the claims of the present specification.

When example compounds have stereoisomers, the names of compounds with optical rotation may not necessarily correspond to the structural formulas sequentially in the following examples, if the absolute configuration is not determined.

[0220]

The following abbreviations are used in the following examples.

DMF: N,N-Dimethylformamide

25 THF: Tetrahydrofuran

EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

HOBT: 1-Hydroxybenzotriazole

IPEA: Diisopropylethylamine

TEA: Triethylamine

30 BOPCl: Bis(2-oxo-3-oxazolidinyl)phosphonic chloride

Chromatography was performed using BW-300 manufactured by Fuji Silysia Chemical Ltd. as a carrier unless otherwise specified.

The preparative columns used for analysis and preparative separation of chiral compounds, CHIRALPAKTM AD-H, CHIRALPAKTM IA, CHIRALPAKTM IB, CHIRALCELTM

OJ-H and CHIRALCEL™ OD-H, were all manufactured by Daicel Chemical Industries, Ltd.

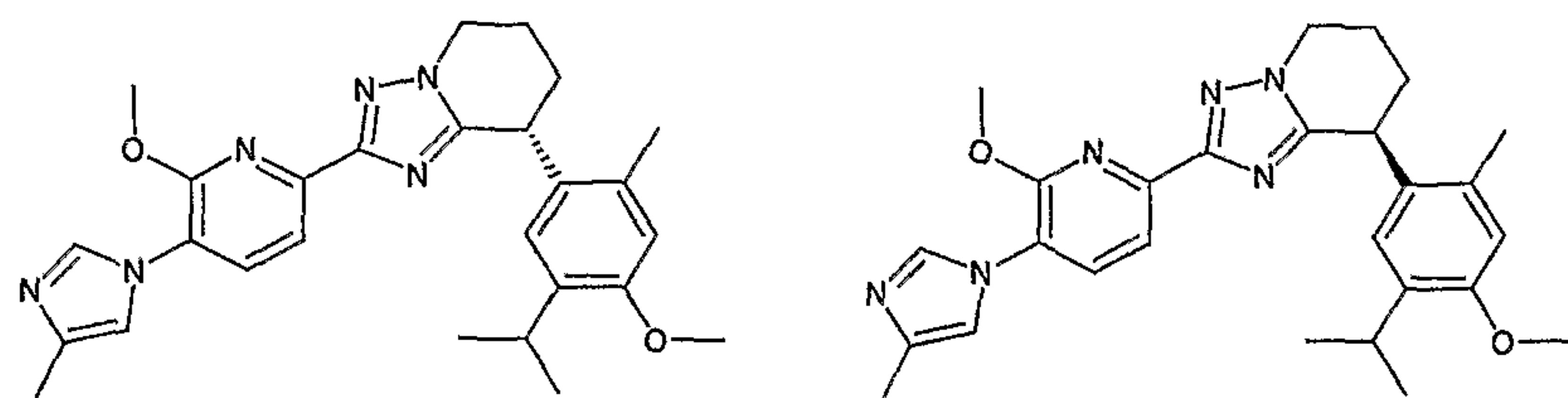
EXAMPLES

[0221]

Examples 1 and 2

- 5 Synthesis of (+)-8-(5-isopropyl-4-methoxy-2-methylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-8-(5-isopropyl-4-methoxy-2-methylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0222]



10 [0223]

- 2-Methoxy-3-(4-methylimidazol-1-yl)-6-tributylstannylpyridine obtained in Preparation Example 1-2 (315 mg), 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-1 (120 mg), 1,3-bis(diphenylphosphino)propane (54 mg) and Copper (I) oxide (94 mg) were suspended in N-methyl-2-pyrrolidinone (5 mL). Palladium (II) acetate (15 mg) was added and the mixture was heated with stirring at 120°C in a nitrogen atmosphere for three hours. After leaving to cool, ethyl acetate and water were added. The reaction solution was filtered through celite and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography to obtain a racemate of the title compound (103 mg). The resulting racemate was separated by CHIRALPAK™ IA (2 cm × 25 cm; mobile phase: hexane:ethanol = 5:5) to obtain the title optically active compound with positive optical rotation (41 mg, >99% ee) and the title optically active compound with negative optical rotation (40 mg, 99% ee).

- 25 The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 237 [$1/2M^+ + H$], 473 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.06 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.90-2.38 (m, 4H), 2.30 (s, 3H), 2.34 (s, 3H), 3.19 (qq, J = 6.8, 6.8 Hz, 1H), 3.81 (s, 3H), 4.17 (s, 3H), 4.39-

4.53 (m, 3H), 6.59 (s, 1H), 6.68 (s, 1H), 7.00 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.80-7.82 (m, 1H).

[0224]

The property values of the title optically active compound with negative optical
5 rotation are as follows.

ESI-MS; m/z 237 [$1/2M^+ + H$], 473 [$M^+ + H$].

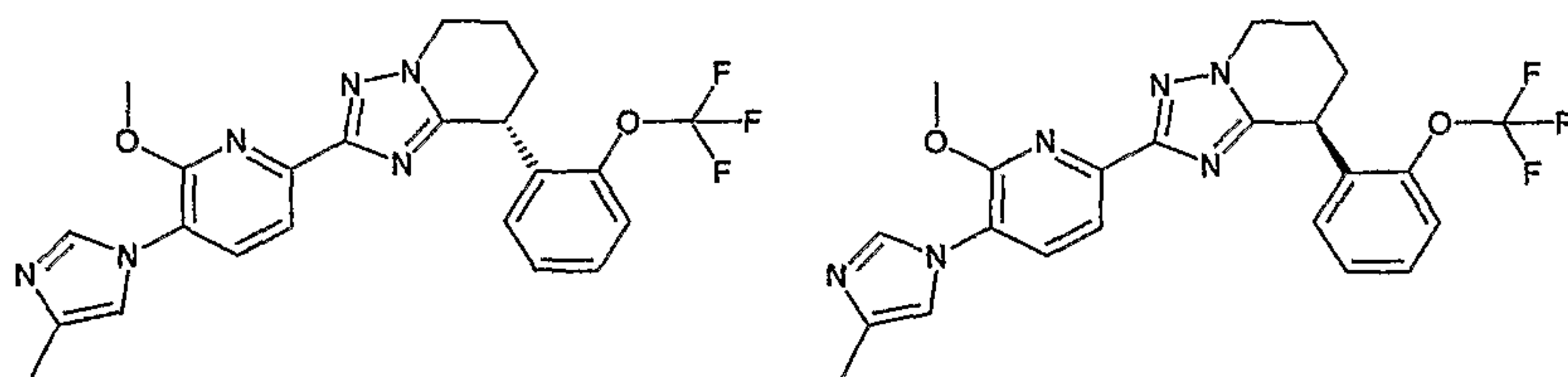
^1H -NMR ($CDCl_3$) δ (ppm): 1.06 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.90-2.38 (m, 4H), 2.30 (s, 3H), 2.34 (s, 3H), 3.19 (qq, J = 6.8, 6.8 Hz, 1H), 3.81 (s, 3H), 4.17 (s, 3H), 4.39-
10 4.53 (m, 3H), 6.59 (s, 1H), 6.68 (s, 1H), 7.00 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0
Hz, 1H), 7.81 (m, 1H).

[0225]

Examples 3 and 4

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-
trifluoromethoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-
15 5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethoxyphenyl)-5,6,7,8-
tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0226]



[0227]

A racemate of the title compound (43 mg) was obtained according to the method
20 of Examples 1 and 2 from 2-bromo-8-(2-trifluoromethoxyphenyl)-5,6,7,8-
tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-2 (120 mg) in place
of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-
a]pyridine. The resulting racemate was separated by CHIRALPAKTM AD-H (2 cm $\times$ 25 cm,
mobile phase: ethanol, flow rate: 10 mL/min) to obtain the title compound with a retention time
25 of 11.6 minutes and positive optical rotation (8 mg) and the title compound with a retention time
of 14.5 minutes and negative optical rotation (6.8 mg).

The property values of the title optically active compound with a retention time of
11.6 minutes are as follows.

^1H -NMR ($CDCl_3$) δ (ppm): 2.00-2.26 (m, 3H), 2.29 (s, 3H), 2.34-2.42 (m, 1H), 4.16 (s, 3H),
30 4.40 (dd, J = 5.5, 5.5 Hz, 2H), 4.70 (dd, J = 7.0, 5.9 Hz, 1H), 6.95 (d, J = 7.4 Hz, 1H), 6.98-7.01

(m, 1H), 7.17-7.23 (m, 1H), 7.29-7.36 (m, 2H), 7.57 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.80-7.84 (m, 1H).

[0228]

The property values of the title optically active compound with a retention time of 14.5 minutes are as follows.

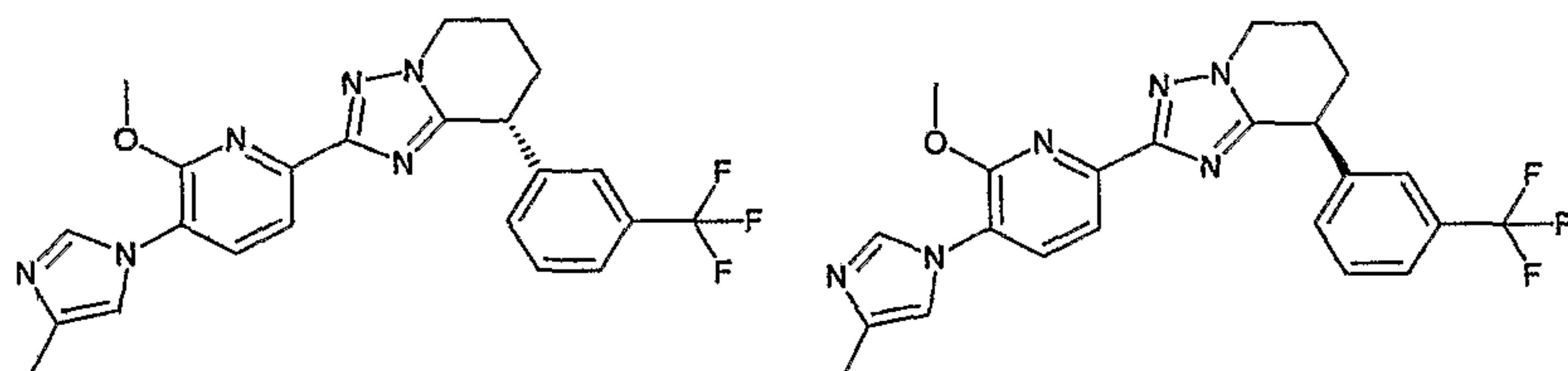
¹H-NMR (CDCl₃) δ (ppm): 2.00-2.26 (m, 3H), 2.29 (s, 3H), 2.34-2.42 (m, 1H), 4.16 (s, 3H), 4.40 (dd, J = 5.5, 5.5 Hz, 2H), 4.70 (dd, J = 7.0, 5.9 Hz, 1H), 6.95 (d, J = 7.4 Hz, 1H), 6.98-7.01 (m, 1H), 7.17-7.23 (m, 1H), 7.29-7.36 (m, 2H), 7.57 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.80-7.84 (m, 1H).

[0229]

Examples 5 and 6

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0230]



[0231]

A racemate of the title compound (125 mg) was obtained according to the method of Examples 1 and 2 from 2-methoxy-3-(4-methylimidazol-1-yl)-6-tributylstannylpyridine obtained in Preparation Example 1-2 (415 mg) and from 2-bromo-8-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-4 (150 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. The resulting racemate was separated by CHIRALPAKTM IB (2 cm × 25 cm; mobile phase: hexane:ethanol = 5:5) to obtain the title optically active compound with positive optical rotation (51 mg, >99% ee) and the title optically active compound with negative optical rotation (51 mg, >99% ee).

The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 228 [1/2M⁺ + H], 455 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 2.05-2.28 (m, 3H), 2.30 (s, 3H), 2.39-2.48 (m, 1H), 4.16 (s, 3H),

4.39-4.51 (m, 3H), 7.00 (m, 1H), 7.32 (d, $J = 6.8$ Hz, 1H), 7.44-7.49 (m, 2H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.59 (d, $J = 7.6$ Hz, 1H), 7.77 (d, $J = 7.6$ Hz, 1H), 7.82-7.83 (m, 1H).

[0232]

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 228 [$1/2M^+ + H$], 455 [$M^+ + H$].

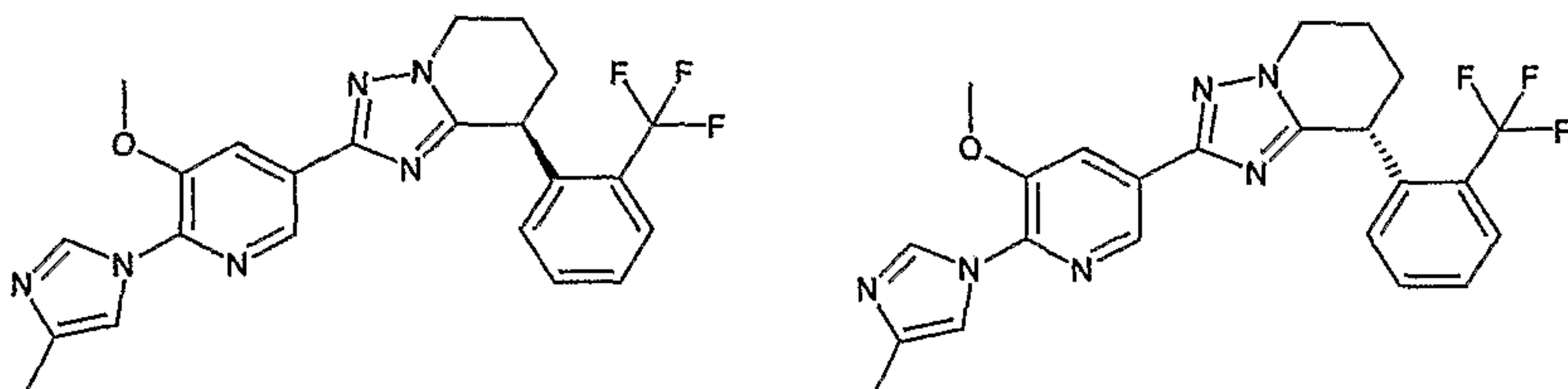
^1H -NMR ($CDCl_3$) δ (ppm): 2.05-2.28 (m, 3H), 2.30 (s, 3H), 2.39-2.48 (m, 1H), 4.16 (s, 3H), 4.39-4.51 (m, 3H), 7.00 (m, 1H), 7.32 (d, $J = 6.8$ Hz, 1H), 7.44-7.49 (m, 2H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.59 (d, $J = 7.6$ Hz, 1H), 7.77 (d, $J = 7.6$ Hz, 1H), 7.82-7.83 (m, 1H).

[0233]

Examples 7 and 8

Synthesis of (-)-2-[5-methoxy-6-(4-methylimidazol-1-yl)pyridin-3-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (+)-2-[5-methoxy-6-(4-methylimidazol-1-yl)pyridin-3-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0234]



[0235]

A racemate of the title compound was obtained according to the method of Examples 1 and 2 from a solution of 3-methoxy-2-(4-methyl-1H-imidazol-1-yl)-5-tributylstannylpyridine obtained in Preparation Example 1-3 (100 mg) in N,N -dimethylformamide (2 mL) and from 2-bromo-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-2 (60 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. The resulting racemate was separated by CHIRALCELTM AD-H (2 cm $\times$ 25 cm; mobile phase: ethanol) to obtain the title optically active compound with a retention time of 11 minutes and negative optical rotation (13.5 mg, >99% ee) and the title optically active compound with a retention time of 17 minutes and positive optical rotation (29.9 mg, >99% ee).

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 455 [$M^+ + H$].

¹H-NMR (CDCl₃) δ (ppm): 1.94-2.04 (m, 1H), 2.10-2.36 (m, 2H), 2.29 (s, 3H), 2.45-2.53 (m, 1H), 3.99 (s, 3H), 4.32-4.45 (m, 2H), 4.73 (dd, J = 8.0, 6.0 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.55 (brs, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 8.37 (brs, 1H), 8.70 (d, J = 2.0 Hz, 1H).

5 [0236]

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 455 [M⁺ + H].

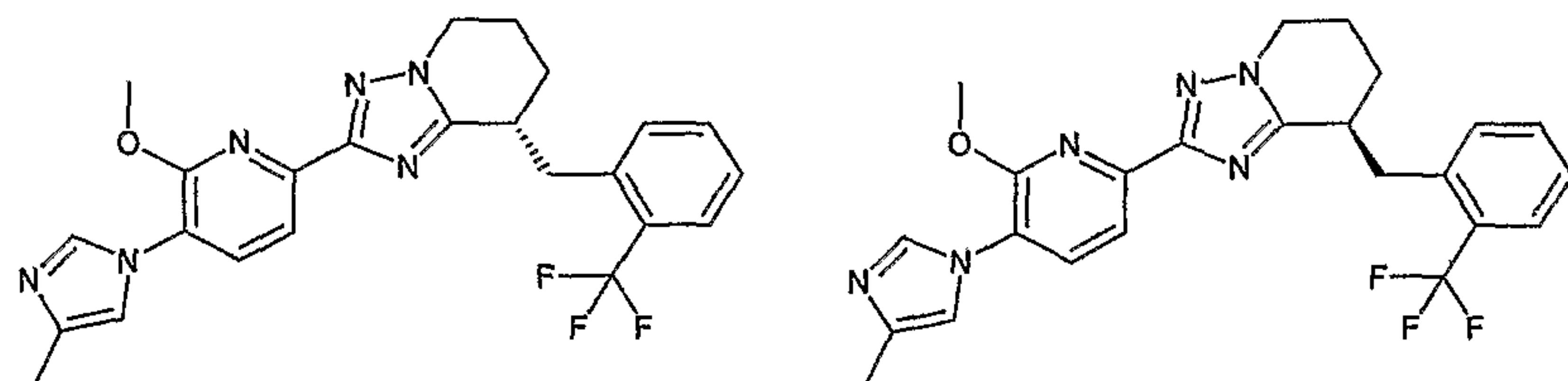
10 ¹H-NMR (CDCl₃) δ (ppm): 1.94-2.04 (m, 1H), 2.10-2.36 (m, 2H), 2.29 (s, 3H), 2.45-2.53 (m, 1H), 3.99 (s, 3H), 4.32-4.45 (m, 2H), 4.73 (dd, J = 8.0, 6.0 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.55 (brs, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 8.37 (brs, 1H), 8.70 (d, J = 2.0 Hz, 1H).

[0237]

Examples 9 and 10

15 Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylbenzyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylbenzyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0238]



20 [0239]

A racemate of the title compound (223 mg) was obtained according to the method of Examples 1 and 2 from 2-methoxy-3-(4-methylimidazol-1-yl)-6-tributylstannylpyridine obtained in Preparation Example 1-2 (377 mg) and from 2-bromo-8-(2-trifluoromethylbenzyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-7 (237 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. The resulting racemate was separated by CHIRALPAKTM AD-H (2 cm × 25 cm; mobile phase: hexane:ethanol = 5:5) to obtain the title optically active compound with positive optical rotation (74 mg, >99% ee) and the title optically active compound with negative optical rotation (74 mg, 99% ee).

30 The property values of the title optically active compound with positive optical

rotation are as follows.

ESI-MS; m/z 235 [$1/2M^+ + H$], 469 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.58-1.70 (m, 1H), 1.89-2.03 (m, 2H), 2.15-2.23 (m, 1H), 2.31 (s, 3H), 3.00-3.10 (m, 1H), 3.36-3.44 (m, 1H), 3.83 (dd, $J = 14.6, 4.6$ Hz, 1H), 4.18 (s, 3H), 4.19-4.27 (m, 1H), 4.30-4.38 (m, 1H), 7.03 (s, 1H), 7.37 (dd, $J = 7.6, 7.2$ Hz, 1H), 7.46-7.55 (m, 2H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.82-7.86 (m, 2H).

[0240]

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 235 [$1/2M^+ + H$], 469 [$M^+ + H$].

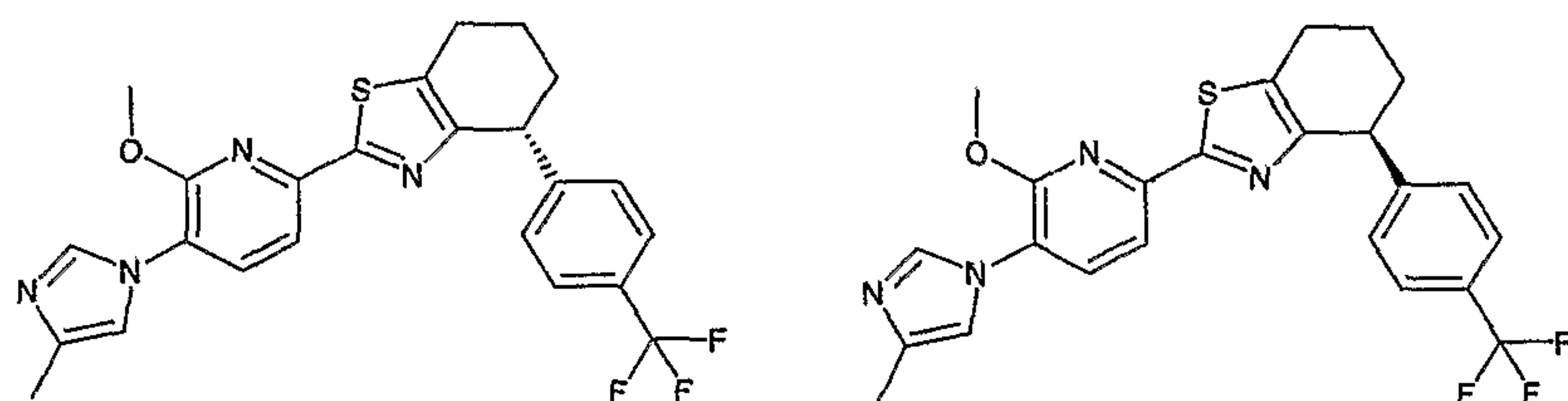
^1H -NMR ($CDCl_3$) δ (ppm): 1.58-1.70 (m, 1H), 1.89-2.03 (m, 2H), 2.15-2.23 (m, 1H), 2.31 (s, 3H), 3.00-3.10 (m, 1H), 3.36-3.44 (m, 1H), 3.83 (dd, $J = 14.6, 4.6$ Hz, 1H), 4.18 (s, 3H), 4.19-4.27 (m, 1H), 4.30-4.38 (m, 1H), 7.03 (s, 1H), 7.37 (dd, $J = 7.6, 7.2$ Hz, 1H), 7.46-7.55 (m, 2H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.82-7.86 (m, 2H).

[0241]

Examples 11 and 12

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydrobenzothiazole and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydrobenzothiazole

[0242]



[0243]

A racemate of the title compound (79 mg) was obtained according to the method of Examples 1 and 2 from 2-methoxy-3-(4-methylimidazol-1-yl)-6-tributylstannylpyridine obtained in Preparation Example 1-2 (198 mg) and from 2-bromo-4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydrobenzothiazole obtained in Preparation Example 2-8 (150 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. The resulting racemate was separated by CHIRALPAKTM IB (2 cm $\times$ 25 cm; mobile phase: hexane:ethanol = 9:1) to obtain the title optically active compound with positive optical rotation (27 mg, >99% ee) and the title optically active compound with negative optical rotation (28 mg, >99% ee).

The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 471 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.85-2.00 (m, 3H), 2.25-2.33 (m, 4H), 2.89-3.04 (m, 2H), 4.10 (s, 3H), 4.36 (t, $J = 5.6$ Hz, 1H), 6.97 (d, $J = 1.2$ Hz, 1H), 7.22 (d, $J = 7.6$ Hz, 2H), 7.51-7.56 (m, 3H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H).

[0244]

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 471 [$M^+ + H$].

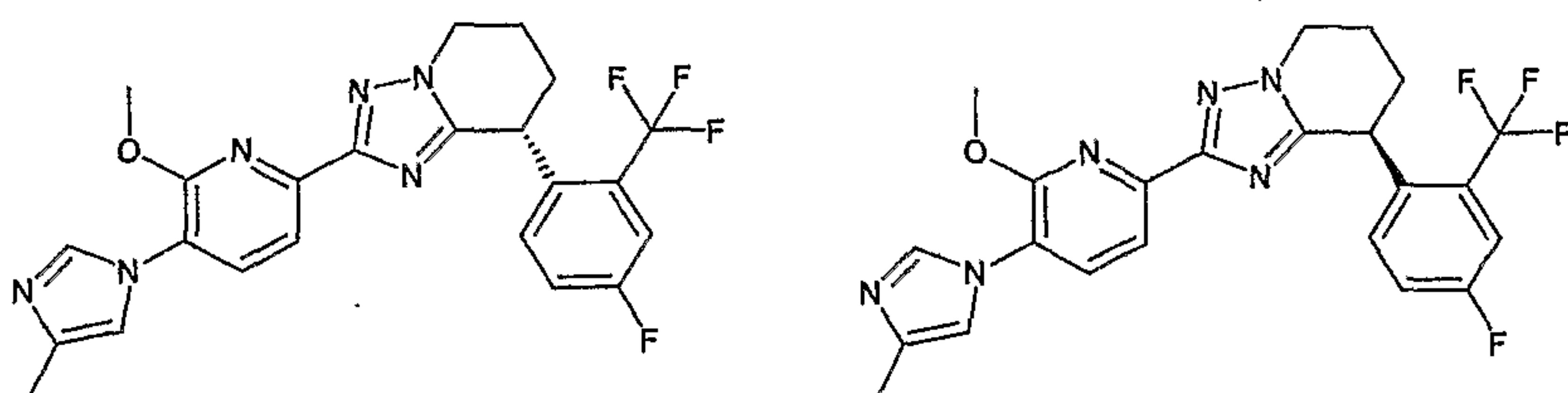
^1H -NMR ($CDCl_3$) δ (ppm): 1.85-2.00 (m, 3H), 2.25-2.33 (m, 4H), 2.89-3.04 (m, 2H), 4.10 (s, 3H), 4.36 (t, $J = 5.6$ Hz, 1H), 6.97 (d, $J = 1.2$ Hz, 1H), 7.22 (d, $J = 7.6$ Hz, 2H), 7.51-7.56 (m, 3H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H).

[0245]

Examples 13 and 14

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-fluoro-2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-fluoro-2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0246]



[0247]

A racemate of the title compound (66 mg) was obtained according to the method of Examples 1 and 2 from 2-bromo-8-(4-fluoro-2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-5 (250 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. The resulting racemate was separated by CHIRALPAKTM IB (2 cm $\times$ 25 cm, mobile phase: ethanol:hexane = 3:7, flow rate: 15 mL/min) to obtain the title compound with a retention time of 16 minutes and positive optical rotation (12.6 mg) and the title compound with a retention time of 18.7 minutes and negative optical rotation (15.1 mg).

The property values of the title optically active compound with a retention time of

16 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.88-2.00 (m, 1H), 2.10-2.23 (m, 1H), 2.23-2.34 (m, 1H), 2.29 (s, 3H), 2.42-2.52 (m, 1H), 4.15 (s, 3H), 4.30-4.50 (m, 2H), 4.70 (dd, J = 8.2, 6.2 Hz, 1H), 6.96-7.01 (m, 2H), 7.14-7.20 (m, 1H), 7.42-7.47 (m, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.80-7.84 (m, 1H).

[0248]

The property values of the title optically active compound with a retention time of 18.7 minutes are as follows.

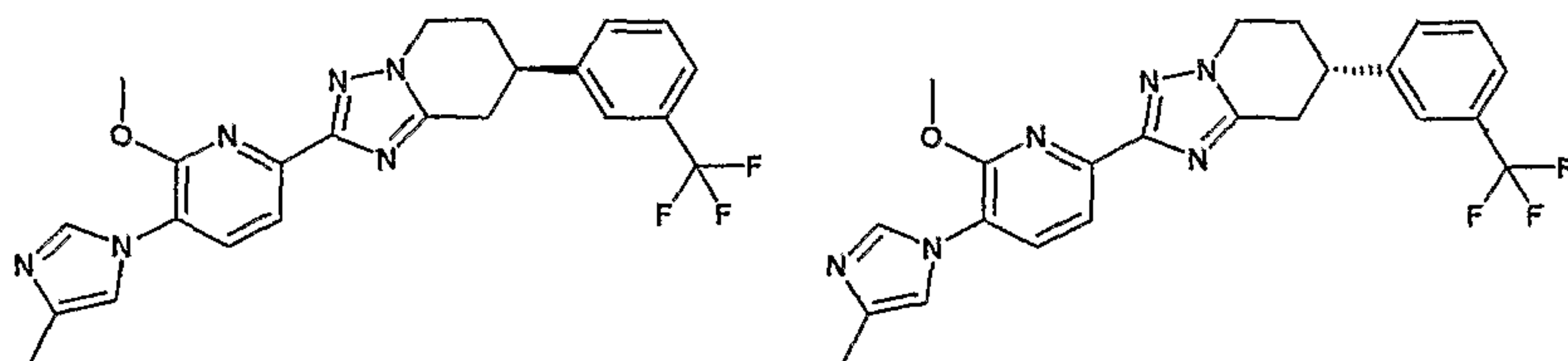
¹H-NMR (CDCl₃) δ (ppm): 1.88-2.00 (m, 1H), 2.10-2.23 (m, 1H), 2.23-2.34 (m, 1H), 2.29 (s, 3H), 2.42-2.52 (m, 1H), 4.15 (s, 3H), 4.30-4.50 (m, 2H), 4.70 (dd, J = 8.2, 6.2 Hz, 1H), 6.96-7.01 (m, 2H), 7.14-7.20 (m, 1H), 7.42-7.47 (m, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.80-7.84 (m, 1H).

[0249]

Examples 15 and 16

15 Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0250]



20 [0251]

A racemate of the title compound (25 mg) was obtained according to the method of Examples 1 and 2 from 2-methoxy-3-(4-methylimidazol-1-yl)-6-tributylstannylpyridine obtained in Preparation Example 1-2 (190 mg) and from 2-bromo-7-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-10 (115 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. The resulting racemate was separated by CHIRALPAKTM IB (2 cm × 25 cm, mobile phase: ethanol:hexane = 3:7, flow rate: 15 mL/min) to obtain the title compound with a retention time of 27 minutes and positive optical rotation (2.0 mg) and the title compound with a retention time of 38.5 minutes and negative optical rotation (1.2 mg).

The property values of the title optically active compound with a retention time of 27 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.31 (s, 3H), 2.33-2.49 (m, 2H), 3.11 (dd, J = 16.0, 9.4 Hz, 1H), 3.33-3.47 (m, 2H), 4.18 (s, 3H), 4.28-4.37 (m, 1H), 4.46 (ddd, J = 8.6, 5.1, 3.1 Hz, 1H), 7.02-7.04 (m, 1H), 7.44-7.61 (m, 4H), 7.64 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 1.2 Hz, 1H).

[0252]

The property values of the title optically active compound with a retention time of 38.5 minutes are as follows.

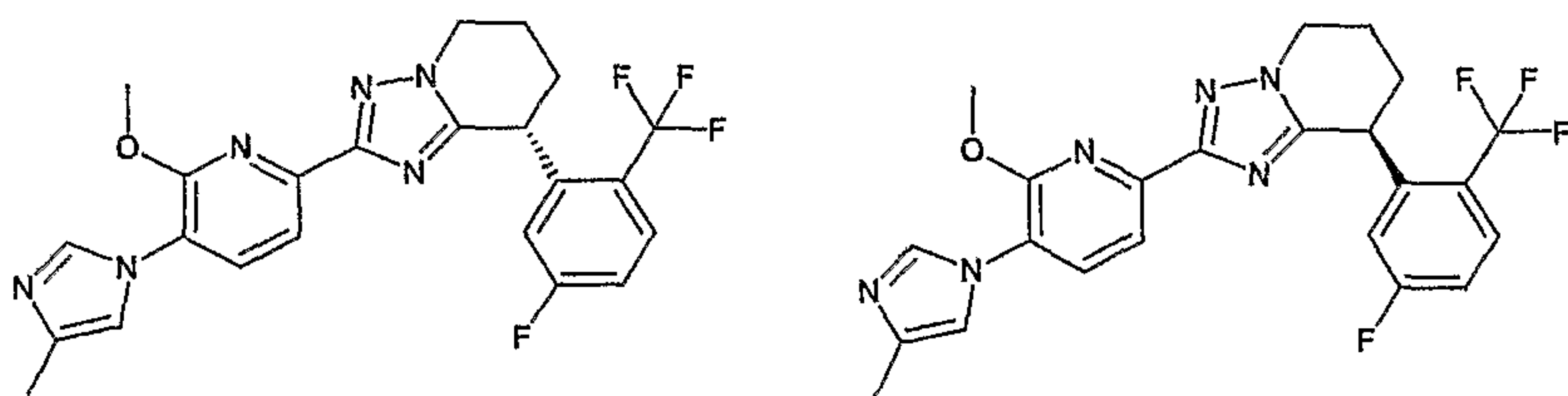
¹H-NMR (CDCl₃) δ (ppm): 2.31 (s, 3H), 2.33-2.49 (m, 2H), 3.11 (dd, J = 16.0, 9.4 Hz, 1H), 3.33-3.47 (m, 2H), 4.18 (s, 3H), 4.28-4.37 (m, 1H), 4.46 (ddd, J = 8.6, 5.1, 3.1 Hz, 1H), 7.02-7.04 (m, 1H), 7.44-7.61 (m, 4H), 7.64 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 1.2 Hz, 1H).

[0253]

Examples 17 and 18

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(5-fluoro-2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(5-fluoro-2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0254]



[0255]

A racemate of the title compound (10.2 mg) was obtained according to the method of Examples 1 and 2 from 2-bromo-8-(5-fluoro-2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-6 (250 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. The resulting racemate was separated by CHIRALPAKTM IA (2 cm × 25 cm, mobile phase: ethanol:hexane = 3:7, flow rate: 15 mL/min) to obtain the title compound with a retention time of 12.5 minutes and positive optical rotation (2.1 mg) and the title compound with a retention time of 22 minutes and negative optical rotation (1.41 mg).

The property values of the title optically active compound with a retention time of

12.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.90-2.01 (m, 1H), 2.10-2.23 (m, 1H), 2.23-2.35 (m, 1H), 2.29 (s, 3H), 2.43-2.53 (m, 1H), 4.16 (s, 3H), 4.38-4.50 (m, 2H), 4.75 (dd, J = 7.4, 6.6 Hz, 1H), 6.67-6.71 (m, 1H), 6.98-7.01 (m, 1H), 7.05-7.11 (m, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.71-7.76 (m, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.79-7.82 (m, 1H).

[0256]

The property values of the title optically active compound with a retention time of 22 minutes are as follows.

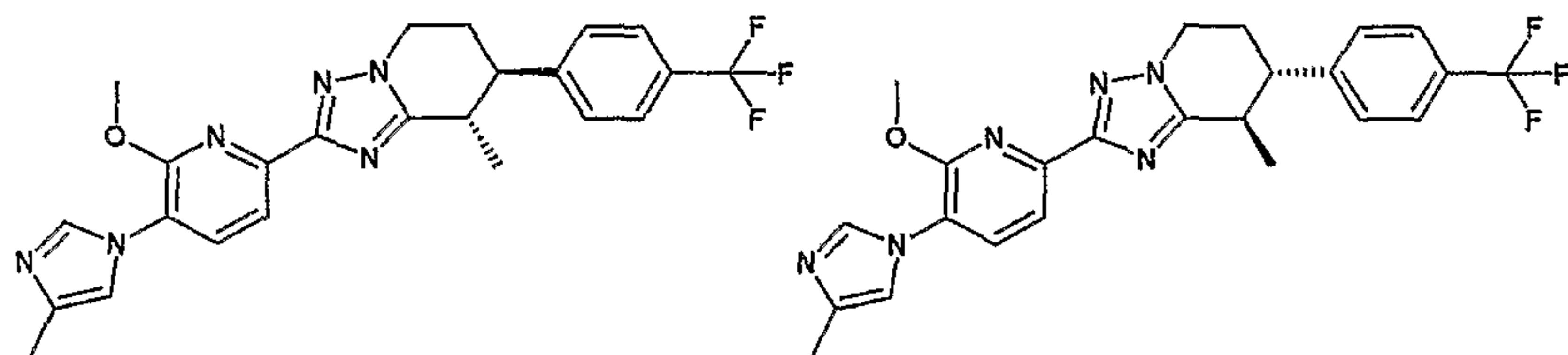
¹H-NMR (CDCl₃) δ (ppm): 1.90-2.01 (m, 1H), 2.10-2.23 (m, 1H), 2.23-2.35 (m, 1H), 2.29 (s, 3H), 2.43-2.53 (m, 1H), 4.16 (s, 3H), 4.38-4.50 (m, 2H), 4.75 (dd, J = 7.4, 6.6 Hz, 1H), 6.67-6.71 (m, 1H), 6.98-7.01 (m, 1H), 7.05-7.11 (m, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.71-7.76 (m, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.79-7.82 (m, 1H).

[0257]

Examples 19 and 20

15 Synthesis of (+)-(7,8-anti)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-methyl-7-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-(7,8-anti)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-methyl-7-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0258]



20 [0259]

A racemate of the title compound (80 mg) was obtained according to the method of Examples 1 and 2 from 2-bromo-8-methyl-7-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-11 in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. The resulting racemate was separated by CHIRALCELTM OD-H (2 cm × 25 cm, mobile phase: ethanol:hexane = 2:8, flow rate: 15 mL/min) to obtain the title compound with a retention time of 28.0 minutes and negative optical rotation (4.8 mg) and the title compound with a retention time of 37.2 minutes and positive optical rotation (6.1 mg).

30 The property values of the title optically active compound with a retention time of 28.0 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.39 (d, J = 7.0 Hz, 3H), 2.31 (s, 3H), 2.31-2.45 (m, 2H), 2.91 (ddd, J = 11.3, 11.3, 3.1 Hz, 1H), 3.18-3.29 (m, 1H), 4.18 (s, 3H), 4.32 (ddd, J = 11.7, 11.7, 3.9 Hz, 1H), 4.45-4.51 (m, 1H), 6.91-6.93 (m, 1H), 7.39 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.63-7.68 (m, 2H), 7.84 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 1.2 Hz, 1H).

5 [0260]

The property values of the title optically active compound with a retention time of 37.2 minutes are as follows.

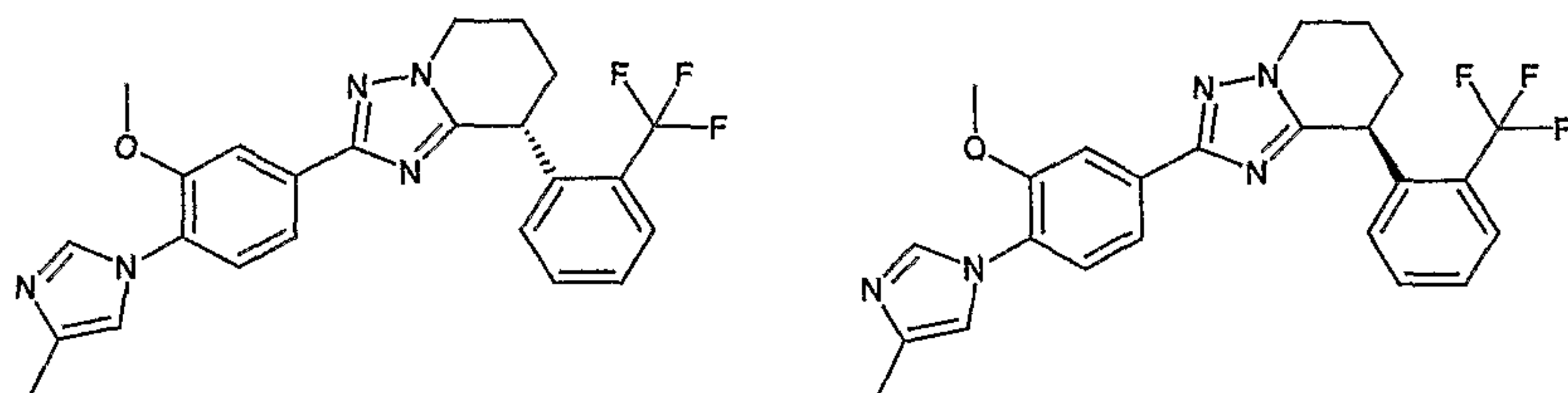
¹H-NMR (CDCl₃) δ (ppm): 1.39 (d, J = 7.0 Hz, 3H), 2.31 (s, 3H), 2.31-2.45 (m, 2H), 2.91 (ddd, J = 11.3, 11.3, 3.1 Hz, 1H), 3.18-3.29 (m, 1H), 4.18 (s, 3H), 4.32 (ddd, J = 11.7, 11.7, 3.9 Hz, 1H), 4.45-4.51 (m, 1H), 6.91-6.93 (m, 1H), 7.39 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.63-7.68 (m, 2H), 7.84 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 1.2 Hz, 1H).

[0261]

Examples 21 and 22

15 Synthesis of (+)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0262]



[0263]

20 A racemate of the title compound was obtained according to the method of Examples 1 and 2 from 1-(2-methoxy-4-tributylstannylphenyl)-4-methyl-1H-imidazole obtained in Preparation Example 1-4 (276 mg) and from 2-bromo-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-3 (100 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. The resulting racemate was separated by CHIRALPAKTM IA (2 cm × 25 cm; mobile phase: hexane:ethanol = 80:20) to obtain the title optically active compound with a retention time of 5.8 minutes and positive optical rotation (35.6 mg, >99% ee) and the title optically active compound with a retention time of 7.2 minutes and negative optical rotation (40.6 mg, >99% ee).

30 The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 454 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.93-2.01 (m, 1H), 2.10-2.20 (m, 1H), 2.24-2.30 (m, 1H), 2.29 (d, $J = 1.2$ Hz, 3H), 2.43-2.51 (m, 1H), 3.90 (s, 3H), 4.36-4.39 (m, 2H), 4.74 (dd, $J = 6.4$ Hz, 8.0 Hz, 1H), 6.94 (t, $J = 1.2$ Hz, 1H), 7.00 (d, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 8.8$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 1H), 7.69 (dd, $J = 1.6$ Hz, 8.8 Hz, 1H), 7.70 (d, $J = 1.6$ Hz, 1H), 7.72 (d, $J = 1.2$ Hz, 1H), 7.73 (d, $J = 7.6$ Hz, 1H).

[0264]

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 454 [$M^+ + H$].

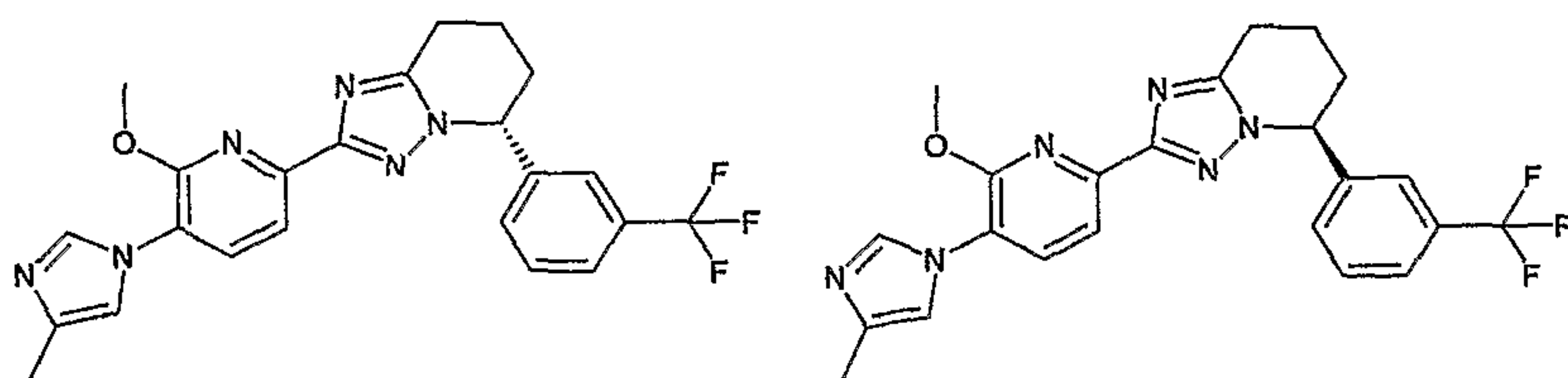
^1H -NMR ($CDCl_3$) δ (ppm): 1.93-2.01 (m, 1H), 2.10-2.20 (m, 1H), 2.24-2.30 (m, 1H), 2.29 (d, $J = 1.2$ Hz, 3H), 2.43-2.51 (m, 1H), 3.90 (s, 3H), 4.36-4.39 (m, 2H), 4.74 (dd, $J = 6.4$ Hz, 8.0 Hz, 1H), 6.94 (t, $J = 1.2$ Hz, 1H), 7.00 (d, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 8.8$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 1H), 7.69 (dd, $J = 1.6$ Hz, 8.8 Hz, 1H), 7.70 (d, $J = 1.6$ Hz, 1H), 7.72 (d, $J = 1.2$ Hz, 1H), 7.73 (d, $J = 7.6$ Hz, 1H).

[0265]

Examples 23 and 24

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]5-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]5-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0266]



[0267]

A racemate of the title compound (38.7 mg) was obtained according to the method of Examples 1 and 2 from 2-methoxy-3-(4-methylimidazol-1-yl)-6-tributylstannylpyridine obtained in Preparation Example 1-2 (62.2 mg) and from 2-bromo-5-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Preparation Example 2-12 (32 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. The resulting racemate was separated by CHIRALPAKTM IA (2 cm $\times$ 25 cm; mobile phase: hexane:ethanol = 60:40) to obtain the title

optically active compound with a retention time of 3.8 minutes and positive optical rotation (13.4 mg, >99% ee) and the title optically active compound with a retention time of 6.3 minutes and negative optical rotation (10.4 mg, >99% ee).

The property values of the title compound with positive optical rotation are as

5 follows.

ESI-MS; m/z 455 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.94-2.00 (m, 2H), 2.16-2.23 (m, 1H), 2.29 (d, $J = 1.2$ Hz, 3H), 2.46-2.55 (m, 1H), 3.07-3.24 (m, 2H), 4.13 (s, 3H), 5.66 (t, $J = 5.2$ Hz, 1H), 7.00 (t, $J = 1.2$ Hz, 1H), 7.14 (d, $J = 7.6$ Hz, 1H), 7.36 (s, 1H), 7.48 (t, $J = 7.6$ Hz, 1H), 7.58 (d, $J = 7.6$ Hz, 2H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H).

[0268]

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 455 [$M^+ + H$].

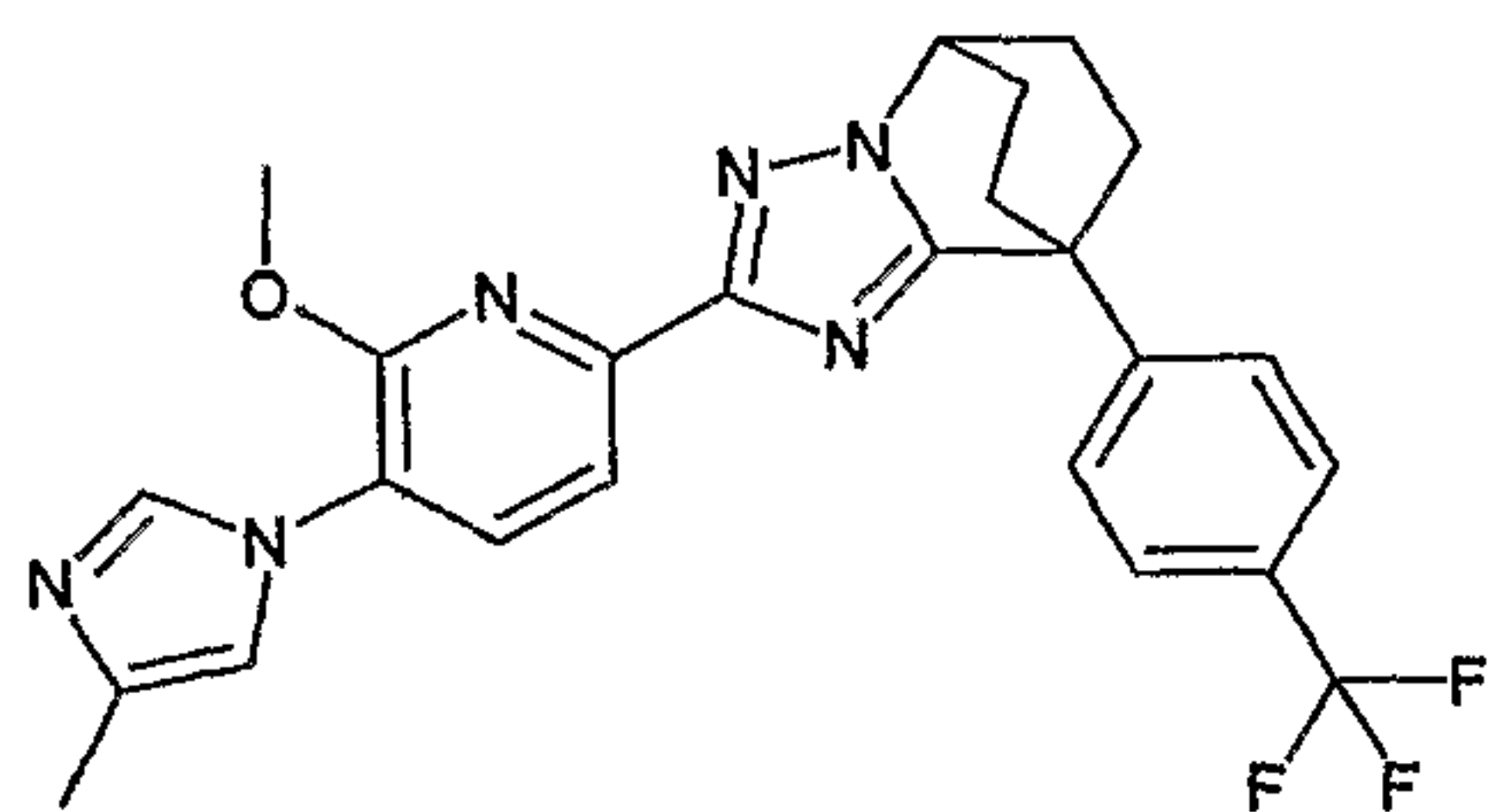
15 ^1H -NMR ($CDCl_3$) δ (ppm): 1.94-2.00 (m, 2H), 2.16-2.23 (m, 1H), 2.29 (d, $J = 1.2$ Hz, 3H), 2.46-2.55 (m, 1H), 3.07-3.24 (m, 2H), 4.13 (s, 3H), 5.66 (t, $J = 5.2$ Hz, 1H), 7.00 (t, $J = 1.2$ Hz, 1H), 7.14 (d, $J = 7.6$ Hz, 1H), 7.36 (s, 1H), 7.48 (t, $J = 7.6$ Hz, 1H), 7.58 (d, $J = 7.6$ Hz, 2H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H).

[0269]

20 Example 25

Synthesis of 4-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-7-(4-trifluoromethylphenyl)2,3,5-triaza-tricyclo[5.2.2.0*2,6*]undeca-3,5-diene

[0270]



[0271]

25 The title compound (0.35 mg) was obtained according to the method of Examples 1 and 2 from 2-methoxy-3-(4-methylimidazol-1-yl)-6-tributylstannylpyridine obtained in Preparation Example 1-2 (10.8 mg) and from 4-bromo-7-(4-trifluoromethylphenyl)-2,3,5-triaza-tricyclo[5.2.2.0*2,6*]undeca-3,5-diene obtained in Preparation Example 2-13 (2.8 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-

a]pyridine. The property values of the compound are as follows.

ESI-MS; m/z 481 [$M^+ + H$].

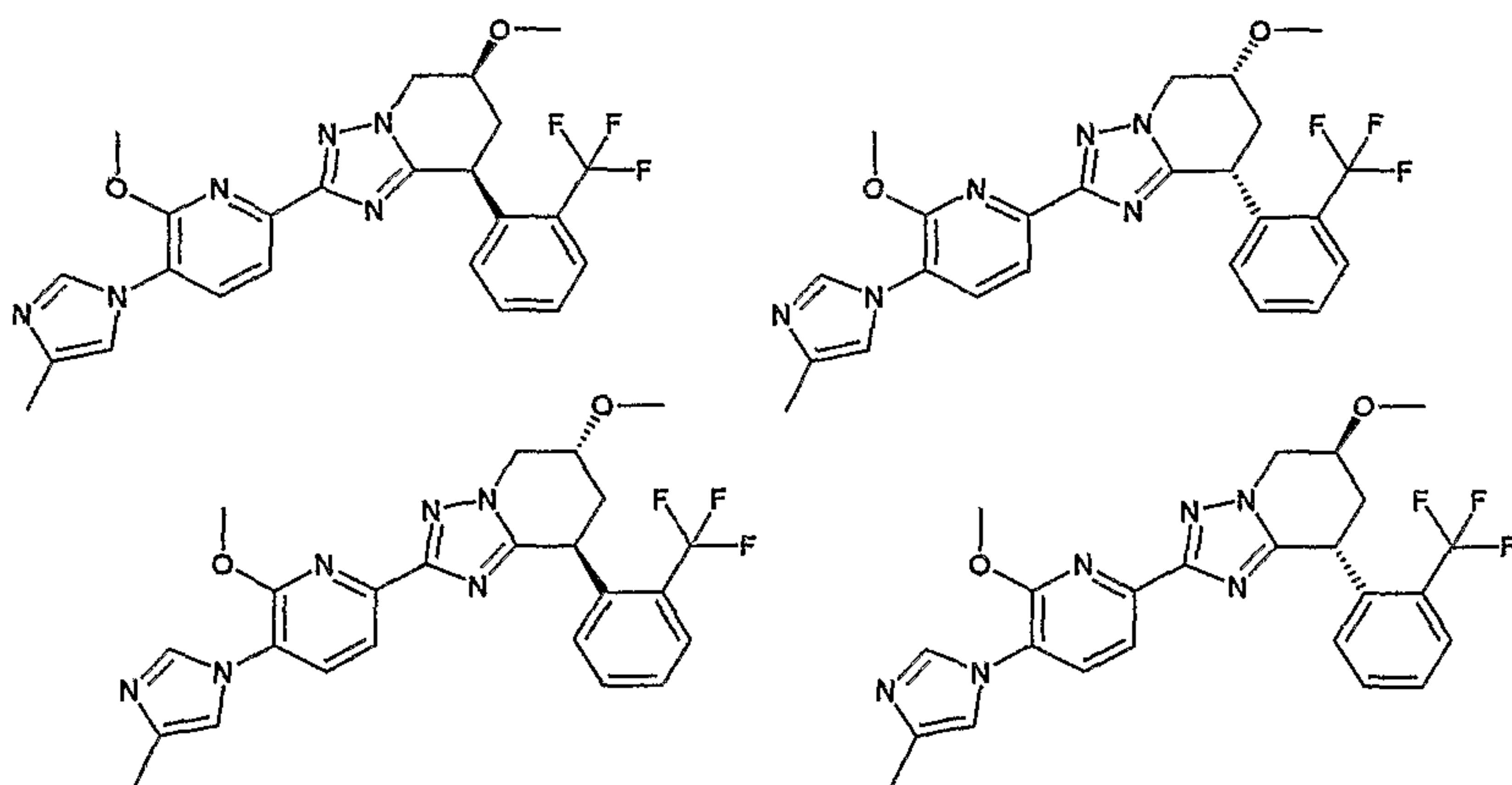
^1H -NMR ($CDCl_3$) δ (ppm): 2.03-2.17 (m, 6H), 2.30 (s, 3H), 2.30-2.35 (m, 2H), 4.17 (s, 3H), 5.13 (s, 1H), 7.01 (s, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 8.4$ Hz, 2H), 7.80-7.87 (m, 4H).

5 [0272]

Examples 26, 27, 28 and 29

10 Synthesis of (+)-(6,8-syn)-6-methoxy-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-(6,8-syn)-6-methoxy-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (+)-(6,8-anti)-6-methoxy-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (+)-(6,8-anti)-6-methoxy-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

15 [0273]



[0274]

Synthesis of 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-6-ol

20 The title compound (910 mg) was obtained as a yellow solid according to the method of Examples 1 and 2 from 2-methoxy-3-(4-methylimidazol-1-yl)-6-tributylstannylpyridine obtained in Preparation Example 1-2 (1.31 g) and from 2-bromo-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-6-ol obtained in Preparation Example 2-9 (900 mg) in place of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine.

25 ESI-MS; m/z 471 [$M^+ + H$].

[0275]

Synthesis of (+)-(6,8-syn)-6-methoxy-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-(6,8-syn)-6-methoxy-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (+)-(6,8-anti)-6-methoxy-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (+)-(6,8-anti)-6-methoxy-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0276]

2-[6-Methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-6-ol (100 mg) was dissolved in tetrahydrofuran (2 mL), and then sodium hydride (21.3 mg) and methyl iodide (19.9 μ L) were added at 0°C. After stirring at room temperature for 24 hours, the reaction solution was partitioned with a saturated sodium bicarbonate solution and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and then concentrated under reduced pressure. The racemic anti-compound purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 100%) (16.9 mg) was separated by CHIRALPAKTM IA (2 cm $\times$ 25 cm, mobile phase: ethanol:hexane = 4:6, flow rate: 13 mL/min) to obtain the title optically active compound with a retention time of 13.5 minutes and positive optical rotation (3.3 mg) and the title optically active compound with a retention time of 19.5 minutes and negative optical rotation (5.4 mg). On the other hand, the racemic syn-compound (25.9 mg) was separated by CHIRALPAKTM IB (2 cm $\times$ 25 cm, mobile phase: ethanol:hexane = 2:8, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 22.6 minutes and positive optical rotation (2.5 mg) and the title optically active compound with a retention time of 38.5 minutes and negative optical rotation (1.4 mg).

The property values of the title optically active compound obtained from the anti-compound with a retention time of 13.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.95 (dd, J = 13.5, 11.3 Hz, 1H), 2.29 (s, 3H), 2.72-2.80 (m, 1H), 3.47 (s, 3H), 4.03-4.09 (m, 1H), 4.15 (s, 3H), 4.43 (dd, J = 14.1, 3.2 Hz, 1H), 4.64 (dd, J = 14.1, 1.5 Hz, 1H), 4.84 (dd, J = 11.3, 4.9 Hz, 1H) 6.96-6.99 (m, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.38-7.45 (m, 1H), 7.46-7.51 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 1.2 Hz, 1H).

[0277]

The property values of the title optically active compound obtained from the anti-

compound with a retention time of 19.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.95 (dd, J = 13.5, 11.3 Hz, 1H), 2.29 (s, 3H), 2.72-2.80 (m, 1H), 3.47 (s, 3H), 4.03-4.09 (m, 1H), 4.15 (s, 3H), 4.43 (dd, J = 14.1, 3.2 Hz, 1H), 4.64 (dd, J = 14.1, 1.5 Hz, 1H), 4.84 (dd, J = 11.3, 4.9 Hz, 1H) 6.96-6.99 (m, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.38-7.45 (m, 1H), 7.46-7.51 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 1.2 Hz, 1H).

[0278]

The property values of the title optically active compound obtained from the syn-compound with a retention time of 22.6 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.02 (ddd, J = 12.9, 9.8, 9.8 Hz, 1H), 2.29 (s, 3H), 2.69-2.78 (m, 1H), 3.41 (s, 3H), 3.96-4.04 (m, 1H), 4.21 (s, 3H), 4.24 (dd, J = 12.9, 8.6 Hz, 1H), 4.68-4.76 (m, 2H), 6.97-6.99 (m, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.37-7.43 (m, 1H), 7.45-7.51 (m, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 1.7 Hz, 1H).

[0279]

The property values of the title optically active compound obtained from the syn-compound with a retention time of 38.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.02 (ddd, J = 12.9, 9.8, 9.8 Hz, 1H), 2.29 (s, 3H), 2.69-2.78 (m, 1H), 3.41 (s, 3H), 3.96-4.04 (m, 1H), 4.21 (s, 3H), 4.24 (dd, J = 12.9, 8.6 Hz, 1H), 4.68-4.76 (m, 2H), 6.97-6.99 (m, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.37-7.43 (m, 1H), 7.45-7.51 (m, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 1.7 Hz, 1H).

[0280]

The compounds of Examples 30 to 41 were obtained by the same method as in Examples 1 and 2 (Table 1).

[0281]

Table 1

Production Ex No.	Structural formula
Example 30	
Example 31	
Example 32	
Example 33	
Example 34	
Example 35	

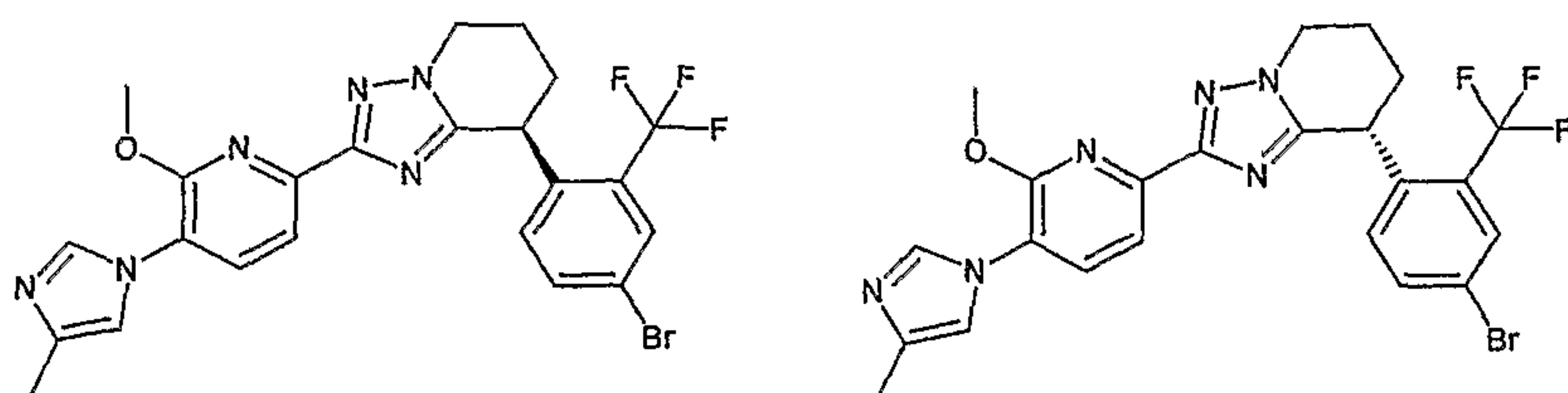
Production Ex No.	Structural formula
Example 36	
Example 37	
Example 38	
Example 39	
Example 40	
Example 41	

[0282]

Examples 42 and 43

- 5 Synthesis of (-)-8-(4-bromo-2-trifluoromethylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (+)-8-(4-bromo-2-trifluoromethylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0283]



[0284]

Ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride obtained in Preparation Example 3-1 (100 mg) was added to a suspension of 6-methoxy-5-(4-methylimidazol-1-yl)pyridine-2-carboxylic acid hydrazide hydrochloride obtained in Preparation Example 1-6 (50 mg) and imidazole (83 mg) in N,N-dimethylformamide (1 mL), and the mixture was stirred at room temperature for three hours. Ethanol (1 mL) was added to the reaction solution, followed by stirring at room temperature for five days. Then, the reaction solution was stirred at 70°C for two hours. The reaction solution was left to cool to room temperature. Then, ethyl acetate, water and 2 N hydrochloric acid (0.3 mL) were added and the organic layer was separated. The resulting organic layer was sequentially washed with water and brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: Chromatorex™ NH; elution solvent: ethyl acetate:heptane = 1:3 → 1:1 → 1:0) to obtain a racemate of the title compound. The resulting racemate was separated by CHIRALPAK™ AD-H (2 cm × 25 cm; mobile phase: ethanol) to obtain the title optically active compound with a retention time of 18 minutes and negative optical rotation (31.3 mg, >99% ee) and the title optically active compound with a retention time of 29 minutes and positive optical rotation (29.9 mg, >98% ee).

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 535 [M^+ + H].

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.87-1.98 (m, 1H), 2.10-2.35 (m, 2H), 2.30 (s, 3H), 2.42-2.53 (m, 1H), 4.15 (s, 3H), 4.35-4.51 (m, 2H), 4.69 (dd, $J = 8.4, 6.0$ Hz, 1H), 6.88 (d, $J = 8.4$ Hz, 1H), 6.99 (brs, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.59 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 1.6$ Hz, 1H), 7.87 (d, $J = 2.0$ Hz, 1H).

[0285]

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 533 [M^+ + H].

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.87-1.98 (m, 1H), 2.10-2.35 (m, 2H), 2.30 (s, 3H), 2.42-2.53 (m,

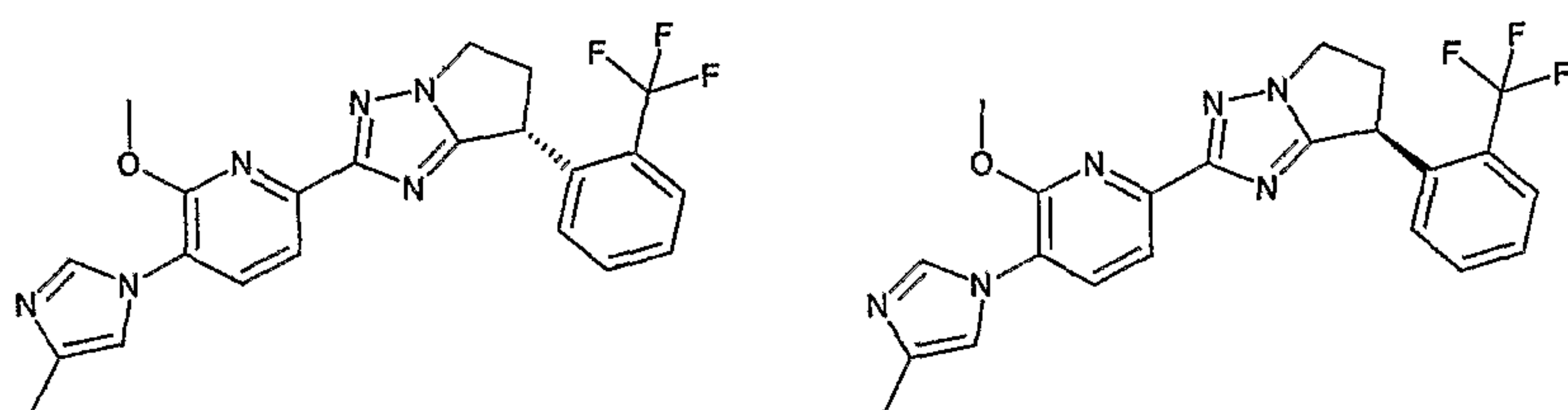
1H), 4.15 (s, 3H), 4.35-4.51 (m, 2H), 4.69 (dd, J = 8.4, 6.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.99 (brs, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.59 (dd, J = 8.4, 2.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H).

[0286]

5 Examples 44 and 45

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(2-trifluoromethylphenyl)-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(2-trifluoromethylphenyl)-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole

10 [0287]



[0288]

A racemate of the title compound (81 mg) was obtained according to the method of Examples 42 and 43 from 6-methoxy-5-(4-methylimidazol-1-yl)pyridine-2-carboxylic acid hydrazide hydrochloride obtained in Preparation Example 1-6 (250 mg) and from ethyl 4-chloro-2-(2-trifluoromethylphenyl)butylimidate hydrochloride obtained in Preparation Example 3-14 (367 mg) in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAK™ IB (2 cm × 25 cm; mobile phase: hexane:ethanol = 7:3) to obtain the title optically active compound with positive optical rotation (10 mg, >99% ee) and the title optically active compound with negative optical rotation (10 mg, >99% ee).

The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 441 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 2.32 (s, 3H), 2.67-2.78 (m, 1H), 3.34-3.43 (m, 1H), 4.10 (s, 3H), 4.46-4.54 (m, 1H), 4.64-4.72 (m, 1H), 4.97 (dd, J = 8.4, 8.0 Hz, 1H), 7.03 (d, J = 1.2 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.41 (dd, J = 8.0, 7.6 Hz, 1H), 7.52 (dd, J = 7.6, 6.8 Hz, 1H), 7.71-7.75 (m, 2H), 7.87 (d, J = 1.2 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H).

[0289]

The property values of the title optically active compound with negative optical

rotation are as follows.

ESI-MS; m/z 441 [$M^+ + H$].

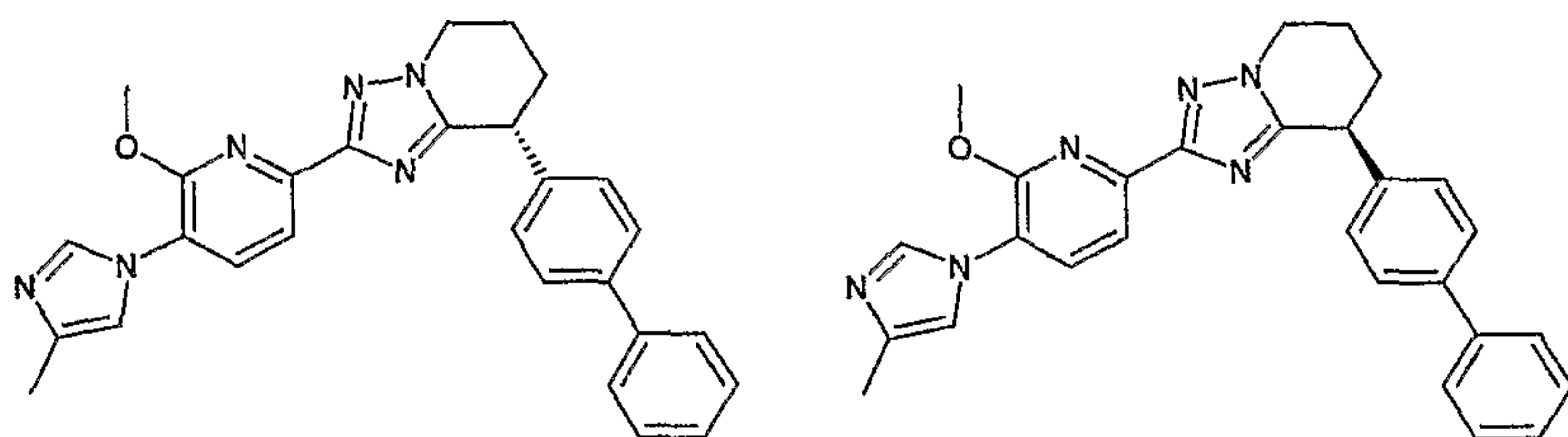
^1H -NMR ($CDCl_3$) δ (ppm): 2.32 (s, 3H), 2.67-2.78 (m, 1H), 3.34-3.43 (m, 1H), 4.10 (s, 3H), 4.46-4.54 (m, 1H), 4.64-4.72 (m, 1H), 4.97 (dd, $J = 8.4, 8.0$ Hz, 1H), 7.03 (d, $J = 1.2$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.41 (dd, $J = 8.0, 7.6$ Hz, 1H), 7.52 (dd, $J = 7.6, 6.8$ Hz, 1H), 7.71-7.75 (m, 2H), 7.87 (d, $J = 1.2$ Hz, 1H), 8.08 (d, $J = 8.0$ Hz, 1H).

[0290]

Examples 46 and 47

10 Synthesis of (+)-8-(biphenyl-4-yl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-8-(biphenyl-4-yl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0291]



[0292]

A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-5 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAKTM IA (2 cm $\times$ 25 cm; mobile phase: 50% ethanol-hexane) to obtain the title optically active compound with a retention time of 13 minutes and positive optical rotation (21.9 mg, >99% ee) and the title optically active compound with a retention time of 20 minutes and negative optical rotation (20.9 mg, >98% ee).

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 463 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 2.05-2.33 (m, 3H), 2.30 (s, 3H), 2.35-2.46 (m, 1H), 4.17 (s, 3H), 4.35-4.51 (m, 3H), 7.00 (brs, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.34 (t, $J = 8.0$ Hz, 1H), 7.43 (t, $J = 8.0$ Hz, 2H), 7.54-7.61 (m, 5H), 7.79-7.85 (m, 2H).

[0293]

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 463 [$M^+ + H$].

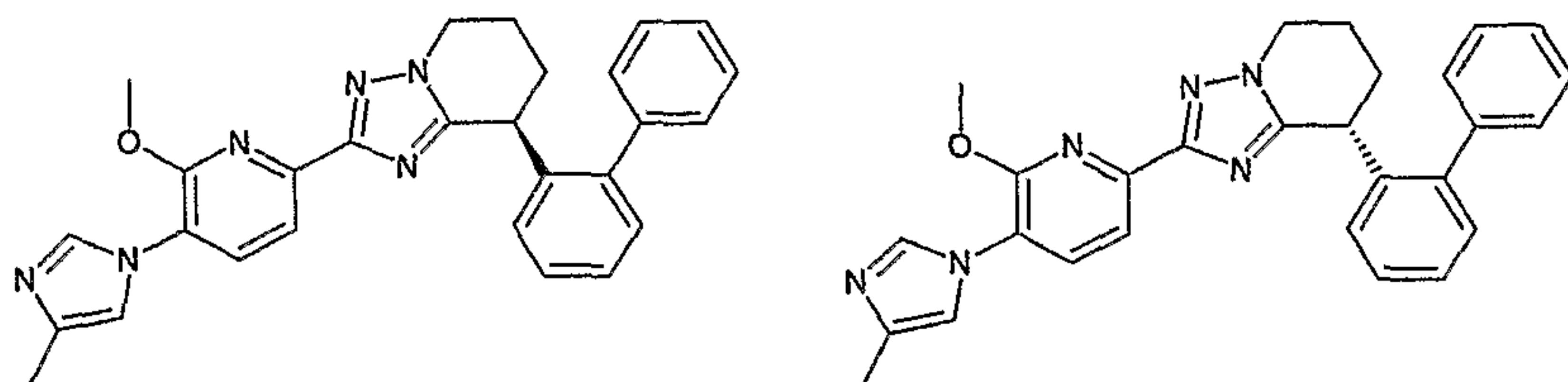
^1H -NMR ($CDCl_3$) δ (ppm): 2.05-2.33 (m, 3H), 2.30 (s, 3H), 2.35-2.46 (m, 1H), 4.17 (s, 3H), 4.35-4.51 (m, 3H), 7.00 (brs, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.34 (t, $J = 8.0$ Hz, 1H), 7.43 (t, $J = 8.0$ Hz, 2H), 7.54-7.61 (m, 5H), 7.79-7.85 (m, 2H).

5 [0294]

Examples 48 and 49

Synthesis of (-)-8-(biphenyl-2-yl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (+)-8-(biphenyl-2-yl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

10 [0295]



[0296]

A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-6 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAKTM IA (2 cm $\times$ 25 cm; mobile phase: 50% ethanol-hexane) to obtain the title optically active compound with a retention time of 9 minutes and negative optical rotation (12.6 mg, >99% ee) and the title optically active compound with a retention time of 12 minutes and positive optical rotation (11.8 mg, >98% ee).

20 The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 463 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.83-1.97 (m, 2H), 2.04-2.21 (m, 2H), 2.30 (s, 3H), 4.16 (s, 3H), 4.25-4.40 (m, 2H), 4.48-4.56 (m, 1H), 6.95 (d, $J = 7.2$ Hz, 1H), 7.00 (brs, 1H), 7.20-7.50 (m, 8H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.82 (brs, 1H).

25 [0297]

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 463 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.83-1.97 (m, 2H), 2.04-2.21 (m, 2H), 2.30 (s, 3H), 4.16 (s, 3H),

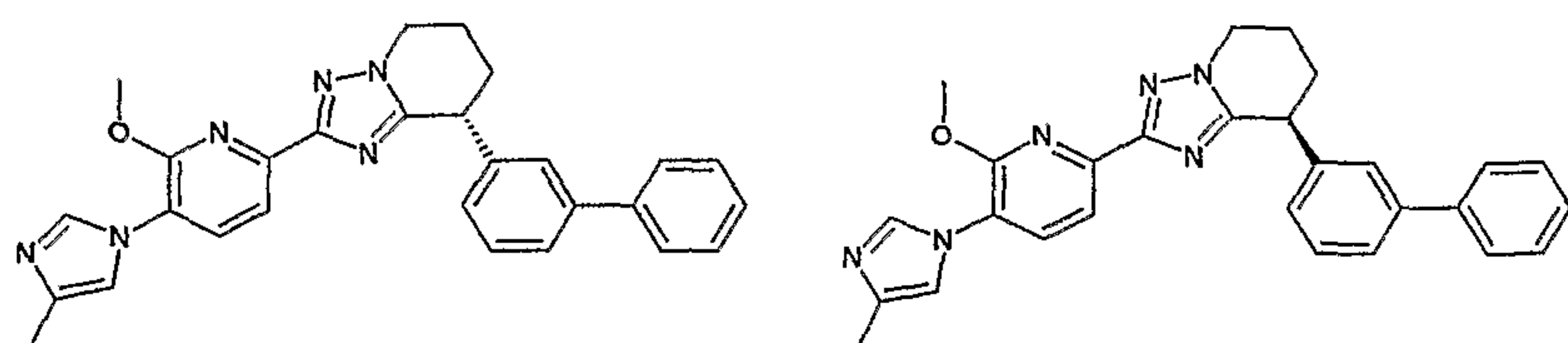
4.25-4.40 (m, 2H), 4.48-4.56 (m, 1H), 6.95 (d, $J = 7.2$ Hz, 1H), 7.00 (brs, 1H), 7.20-7.50 (m, 8H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.82 (brs, 1H).

[0298]

Examples 50 and 51

- 5 Synthesis of (+)-8-(biphenyl-3-yl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-8-(biphenyl-3-yl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0299]



[0300]

- 10 A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-7 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAKTM IA (2 cm × 25 cm; mobile phase: 50% ethanol-hexane) to obtain the title optically active compound with a retention time of 9 minutes and positive optical rotation (40.9 mg, >99% ee) and the title optically active compound with a retention time of 19 minutes and negative optical rotation (39.8 mg, >99% ee).
- 15

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 463 [$M^+ + H$].

- ¹H-NMR (CDCl₃) δ (ppm): 2.05-2.34 (m, 3H), 2.30 (d, $J = 1.2$ Hz, 3H), 2.37-2.47 (m, 1H), 4.17 (s, 3H), 4.35-4.55 (m, 3H), 7.00 (t, $J = 1.2$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 7.31-7.37 (m, 2H), 7.37-7.44 (m, 3H), 7.48-7.56 (m, 3H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.82 (d, $J = 1.2$ Hz, 1H).
- 20

[0301]

- The property values of the title compound with negative optical rotation are as follows.
- 25

ESI-MS; m/z 463 [$M^+ + H$].

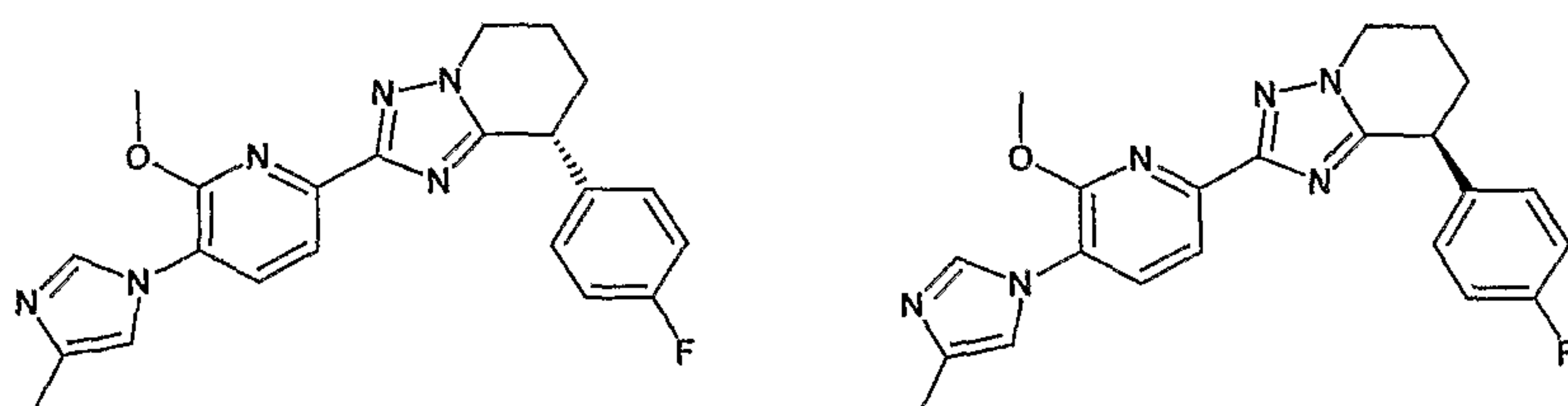
- ¹H-NMR (CDCl₃) δ (ppm): 2.05-2.34 (m, 3H), 2.30 (d, $J = 1.2$ Hz, 3H), 2.37-2.47 (m, 1H), 4.17 (s, 3H), 4.35-4.55 (m, 3H), 7.00 (t, $J = 1.2$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 7.31-7.37 (m, 2H), 7.37-7.44 (m, 3H), 7.48-7.56 (m, 3H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.82 (d, $J = 1.2$ Hz, 1H).
- 30

[0302]

Examples 52 and 53

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-fluorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-5 yl)pyridin-2-yl]-8-(4-fluorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0303]



[0304]

A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-15 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAKTM IB (2 cm × 25 cm; mobile phase: hexane:ethanol = 5:5) to obtain the title optically active compound with positive optical rotation (74 mg, >99% ee) and the title optically active compound with negative optical rotation (75 mg, >99% ee).

15 The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 405 [$M^+ + H$].

¹H-NMR (CDCl₃) δ (ppm): 2.03-2.26 (m, 3H), 2.30 (s, 3H), 2.33-2.40 (m, 1H), 4.16 (s, 3H), 4.34-4.45 (m, 3H), 7.00-7.06 (m, 3H), 7.08-7.13 (m, 2H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J =$

20 8.0 Hz, 1H), 8.82 (d, $J = 1.2$ Hz, 1H).

[0305]

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 405 [$M^+ + H$].

25 ¹H-NMR (CDCl₃) δ (ppm): 2.03-2.26 (m, 3H), 2.30 (s, 3H), 2.33-2.40 (m, 1H), 4.16 (s, 3H), 4.34-4.45 (m, 3H), 7.00-7.06 (m, 3H), 7.08-7.13 (m, 2H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J =$

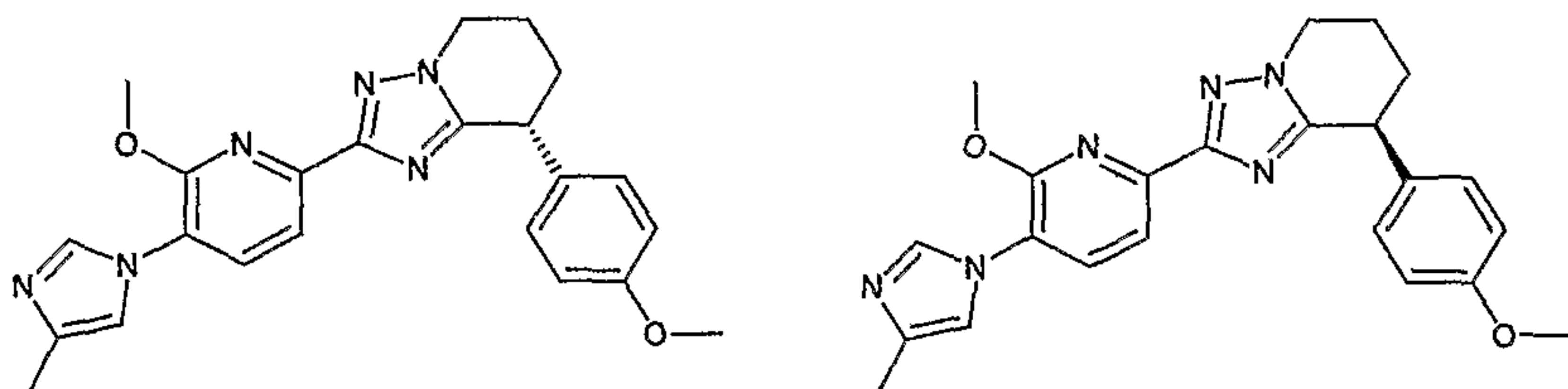
8.0 Hz, 1H), 8.82 (d, $J = 1.2$ Hz, 1H).

[0306]

Examples 54 and 55

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0307]



5 [0308]

A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-16 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAKTM IB (2 cm × 25 cm; mobile phase:

10 hexane:ethanol = 5:5) to obtain the title optically active compound with positive optical rotation (64 mg, >99% ee) and the title optically active compound with negative optical rotation (55 mg, >99% ee).

The property values of the title optically active compound with positive optical rotation are as follows.

15 ESI-MS; m/z 417 [M^+ + H].

¹H-NMR (CDCl₃) δ (ppm): 2.03-2.12 (m, 2H), 2.15-2.26 (m, 1H), 2.30 (s, 3H), 2.30-2.38 (m, 1H), 3.79 (s, 3H), 4.16 (s, 3H), 4.33-4.45 (m, 3H), 6.84-6.89 (m, 2H), 6.99-7.08 (m, 3H), 7.58 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 0.8 Hz, 1H).

[0309]

20 The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 417 [M^+ + H].

¹H-NMR (CDCl₃) δ (ppm): 2.03-2.12 (m, 2H), 2.15-2.26 (m, 1H), 2.30 (s, 3H), 2.30-2.38 (m, 1H), 3.79 (s, 3H), 4.16 (s, 3H), 4.33-4.45 (m, 3H), 6.84-6.89 (m, 2H), 6.99-7.08 (m, 3H), 7.58 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 0.8 Hz, 1H).

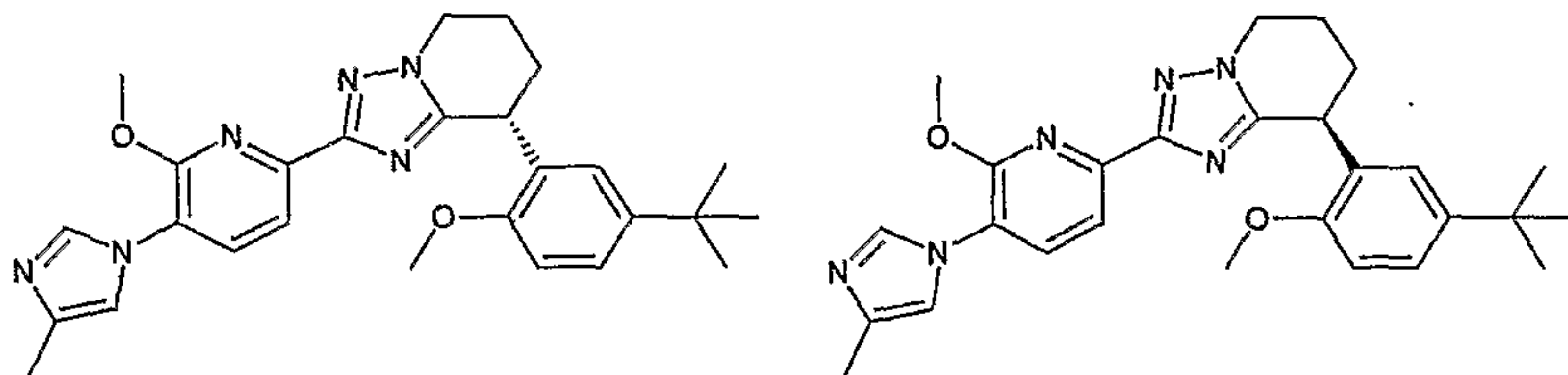
25

[0310]

Examples 56 and 57

Synthesis of (+)-8-(5-tert-butyl-2-methoxyphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-8-(5-tert-butyl-2-

methoxyphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-
tetrahydro[1,2,4]triazolo[1,5-a]pyridine
 [0311]



[0312]

5 A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-3 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAK™ AD-H (2 cm × 25 cm; mobile phase: 25% ethanol-hexane) to obtain the title optically active compound with a retention time of 10 minutes and positive optical rotation (41.8 mg, >99% ee) and the title optically active compound with a retention time of 17 minutes and negative optical rotation (33.5 mg, >99% ee).

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 473 [M^+ + H].

15 $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.23 (s, 9H), 2.00-2.35 (m, 4H), 2.30 (d, $J = 1.2$ Hz, 3H), 3.75 (s, 3H), 4.17 (s, 3H), 4.39 (t, $J = 5.6$ Hz, 2H), 4.62 (t, $J = 6.4$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.91 (d, $J = 2.4$ Hz, 1H), 6.99 (t, $J = 1.2$ Hz, 1H), 7.23-7.29 (m, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H).

[0313]

20 The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 473 [M^+ + H].

25 $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.23 (s, 9H), 2.00-2.35 (m, 4H), 2.30 (d, $J = 1.2$ Hz, 3H), 3.75 (s, 3H), 4.17 (s, 3H), 4.39 (t, $J = 5.6$ Hz, 2H), 4.62 (t, $J = 6.4$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.91 (d, $J = 2.4$ Hz, 1H), 6.99 (t, $J = 1.2$ Hz, 1H), 7.23-7.29 (m, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H).

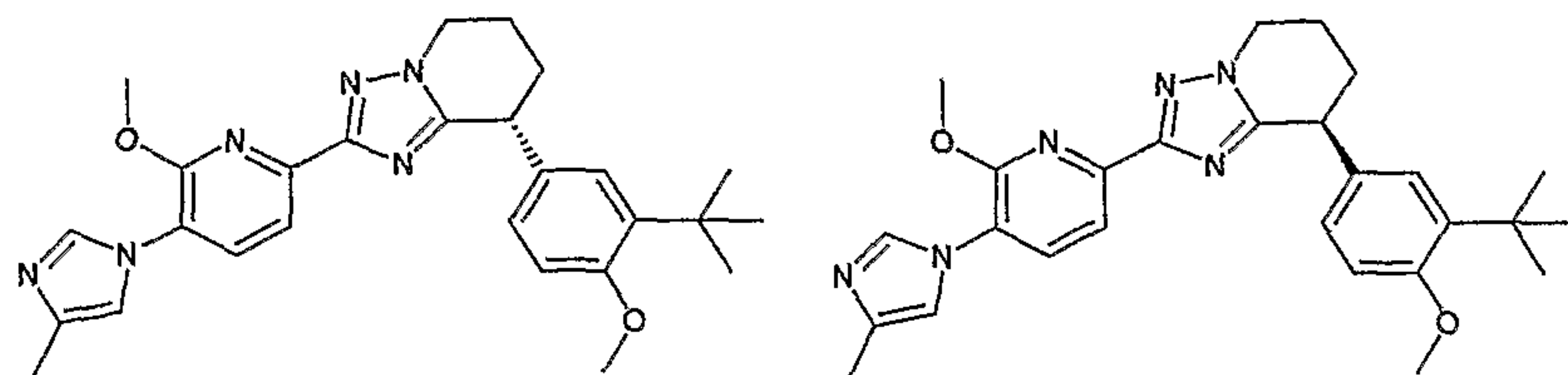
[0314]

Examples 58 and 59

Synthesis of (+)-8-(3-tert-butyl-4-methoxyphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-

yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-8-(3-tert-butyl-4-methoxyphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0315]



5 [0316]

A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-8 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAKTM AD-H (2 cm × 25 cm; mobile phase: 30% ethanol-hexane) to obtain the title optically active compound with a retention time of 11 minutes and positive optical rotation (43.5 mg, >99% ee) and the title optically active compound with a retention time of 18 minutes and negative optical rotation (42.8 mg, >99% ee).

The property values of the title compound with positive optical rotation are as follows.

15 ESI-MS; m/z 473 [$M^+ + H$].

¹H-NMR (CDCl₃) δ (ppm): 1.35 (s, 9H), 2.00-2.40 (m, 4H), 2.30 (s, 3H), 3.81 (s, 3H), 4.17 (s, 3H), 4.30-4.46 (m, 3H), 6.79 (d, $J = 8.4$ Hz, 1H), 6.82 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.00 (brs, 1H), 7.13 ($J = 2.4$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.82 (s, 1H).

[0317]

20 The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 473 [$M^+ + H$].

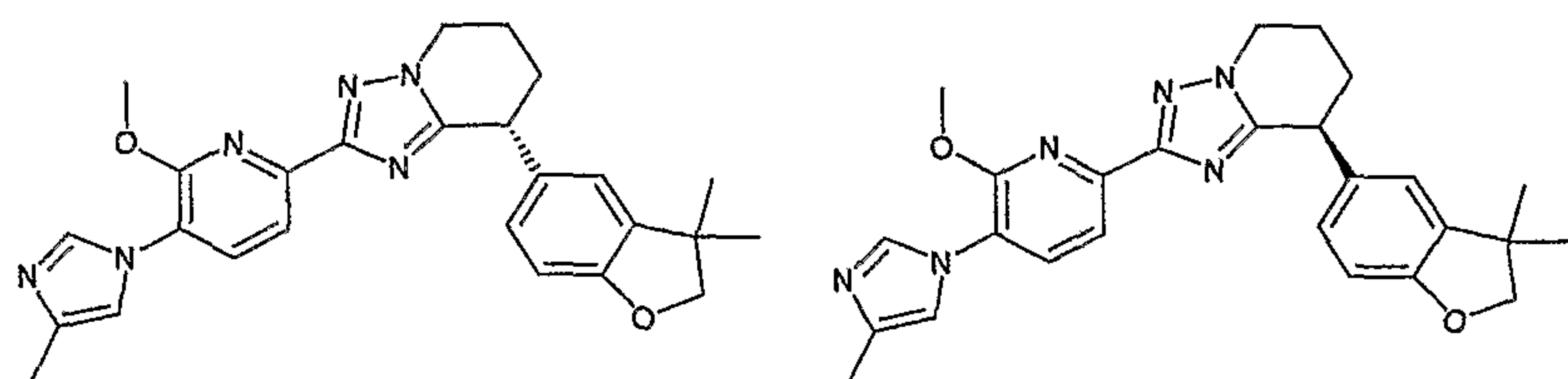
¹H-NMR (CDCl₃) δ (ppm): 1.35 (s, 9H), 2.00-2.40 (m, 4H), 2.30 (s, 3H), 3.81 (s, 3H), 4.17 (s, 3H), 4.30-4.46 (m, 3H), 6.79 (d, $J = 8.4$ Hz, 1H), 6.82 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.00 (brs, 1H), 7.13 ($J = 2.4$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.82 (s, 1H).

[0318]

Examples 60 and 61

Synthesis of (+)-8-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-8-

(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine
[0319]



[0320]

- 5 A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-2 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAK™ AD-H (2 cm × 25 cm; mobile phase: 50% ethanol-hexane) to obtain the title optically active compound with a retention time of 10 minutes and positive optical rotation (54.0 mg, >99% ee) and the title optically active compound with a retention time of 18 minutes and negative optical rotation (47.4 mg, >99% ee).

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 457 [$M^+ + H$].

- 15 $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.30 (s, 3H), 1.32 (s, 3H), 2.00-2.13 (m, 2H), 2.16-2.40 (m, 2H), 2.30 (s, 3H), 4.16 (s, 3H), 4.23 (s, 2H), 4.30-4.47 (m, 3H), 6.72 (d, $J = 8.0$ Hz, 1H), 6.83 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.87 (d, $J = 1.6$ Hz, 1H), 7.00 (brs, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.82 (s, 1H).

[0321]

- 20 The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 457 [$M^+ + H$].

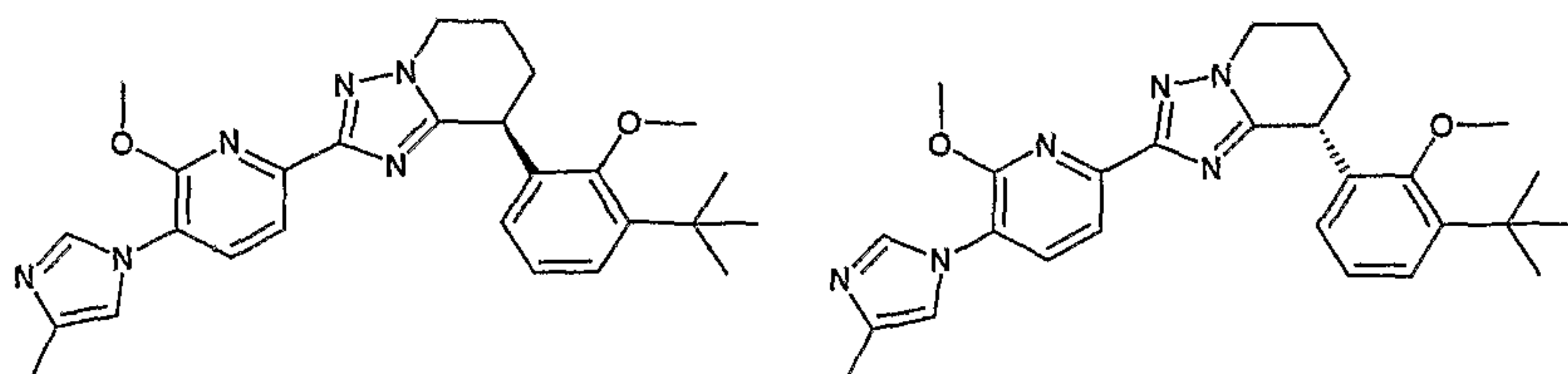
- 25 $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.30 (s, 3H), 1.32 (s, 3H), 2.00-2.13 (m, 2H), 2.16-2.40 (m, 2H), 2.30 (s, 3H), 4.16 (s, 3H), 4.23 (s, 2H), 4.30-4.47 (m, 3H), 6.72 (d, $J = 8.0$ Hz, 1H), 6.83 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.87 (d, $J = 1.6$ Hz, 1H), 7.00 (brs, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.82 (s, 1H).

[0322]

Examples 62 and 63

Synthesis of (-)-8-(3-tert-butyl-2-methoxyphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (+)-8-(3-tert-butyl-2-methoxyphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

5 [0323]



[0324]

A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-9 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAK™ IB (2 cm × 25 cm; mobile phase: 10% ethanol-hexane) to obtain the title optically active compound with a retention time of 23 minutes and negative optical rotation (48.5 mg, >99% ee) and the title optically active compound with a retention time of 38 minutes and positive optical rotation (53.8 mg, >99% ee).

15 The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 473 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.44 (s, 9H), 1.98-2.16 (m, 2H), 2.18-2.40 (m, 2H), 2.30 (d, $J = 1.2$ Hz, 3H), 3.98 (s, 3H), 4.16 (s, 3H), 4.36-4.46 (m, 2H), 4.73 (t, $J = 6.8$ Hz, 1H), 6.71 (dd, $J = 8.0$, 1.6 Hz, 1H), 6.96 (t, $J = 8.0$, 1H), 6.99 (brs, 1H), 7.25-7.29 (m, 1H), 7.56 (d, $J = 7.6$ Hz, 1H), 7.76 (d, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H).

[0325]

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 473 [$M^+ + H$].

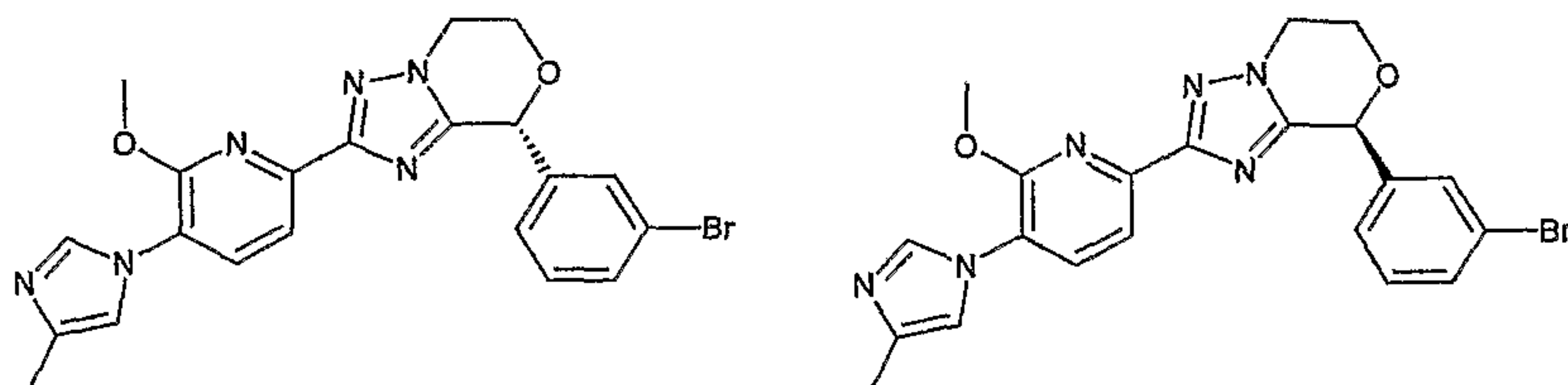
25 ^1H -NMR ($CDCl_3$) δ (ppm): 1.44 (s, 9H), 1.98-2.16 (m, 2H), 2.18-2.40 (m, 2H), 2.30 (d, $J = 1.2$ Hz, 3H), 3.98 (s, 3H), 4.16 (s, 3H), 4.36-4.46 (m, 2H), 4.73 (t, $J = 5.6$ Hz, 1H), 6.71 (dd, $J = 8.0$, 1.6 Hz, 1H), 6.96 (t, $J = 8.0$, 1H), 6.99 (brs, 1H), 7.25-7.29 (m, 1H), 7.56 (d, $J = 7.6$ Hz, 1H), 7.76 (d, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H).

[0326]

Examples 64 and 65

Synthesis of (+)-8-(3-bromophenyl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6-dihydro-8H-[1,2,4]triazolo[1,5-c][1,4]oxazine and (-)-8-(3-bromophenyl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6-dihydro-8H-[1,2,4]triazolo[1,5-c][1,4]oxazine

5 [0327]



[0328]

A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imide hydrochloride obtained in Preparation Example 3-17 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimide hydrochloride. This was separated by CHIRALPAKTM IB (2 cm × 25 cm, mobile phase: hexane:ethanol = 8:2, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 5.27 minutes resulting from analysis by CHIRALPAKTM IB (Lot. IB00CD-LG026, hexane:ethanol = 8:2, 1.0 mL/min) and positive optical rotation and the title optically active compound with a retention time of 7.98 minutes resulting from the same analysis and negative optical rotation, respectively.

The property values of the title optically active compound with positive optical rotation are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.31 (s, 3H), 4.11-4.21 (m, 1H), 4.17 (s, 3H), 4.31 (dt, J = 4.8, 12.4 Hz, 1H), 4.34-4.51 (m, 2H), 5.98 (s, 1H), 7.01 (t, J = 0.8 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.45-7.47 (m, 1H), 7.51-7.54 (m, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 1.6 Hz, 1H).

[0329]

The property values of the title optically active compound with negative optical rotation are as follows.

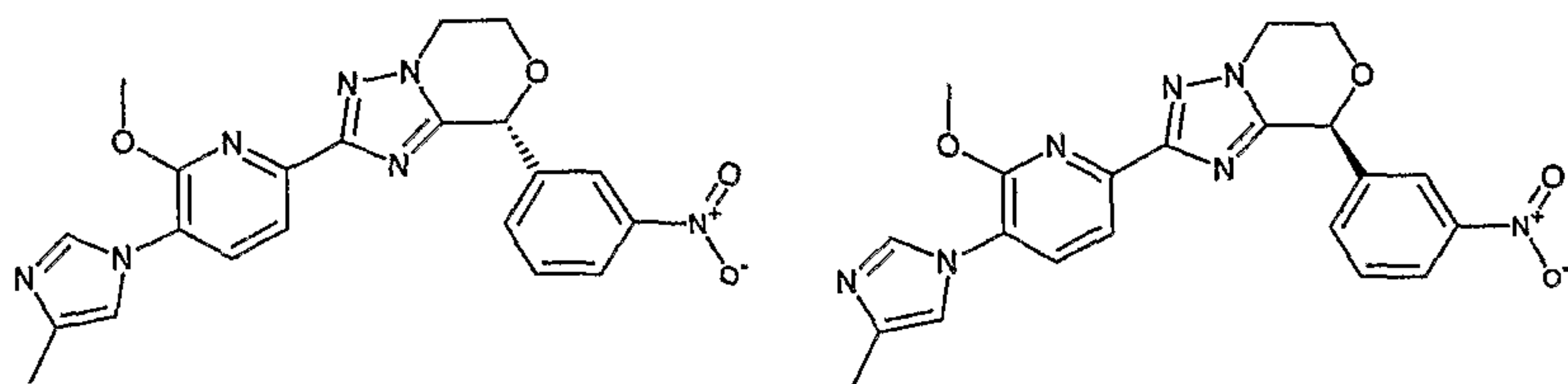
¹H-NMR (CDCl₃) δ (ppm): 2.31 (s, 3H), 4.11-4.21 (m, 1H), 4.17 (s, 3H), 4.31 (dt, J = 4.8, 12.4 Hz, 1H), 4.34-4.51 (m, 2H), 5.98 (s, 1H), 7.01 (t, J = 0.8 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.45-7.47 (m, 1H), 7.51-7.54 (m, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 1.6 Hz, 1H).

[0330]

Examples 66 and 67

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(3-nitrophenyl)-5,6-dihydro-8H-[1,2,4]triazolo[1,5-c][1,4]oxazine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(3-nitrophenyl)-5,6-dihydro-8H-[1,2,4]triazolo[1,5-c][1,4]oxazine

5 [0331]



[0332]

A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-18 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. This was separated by CHIRALPAKTM IB manufactured by Daicel Chemical Industries, Ltd. (2 cm × 25 cm, mobile phase: hexane:ethanol = 8:2, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 10.6 minutes resulting from analysis by CHIRALPAKTM IB (Lot. IB00CD-FD026, hexane:ethanol = 7:3, 1.0 mL/min) and positive optical rotation and the title optically active compound with a retention time of 15.0 minutes resulting from the same analysis and negative optical rotation, respectively.

The property values of the title optically active compound with positive optical rotation are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.31 (s, 3H), 4.16 (s, 3H), 4.25 (ddd, J = 4.4, 8.0, 12.4 Hz, 1H), 4.40 (dt, J = 4.0, 12.4 Hz, 1H), 4.45-4.56 (m, 2H), 6.08 (s, 1H), 7.01 (t, J = 0.8 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H), 7.94-7.96 (m, 1H), 8.25-8.27 (m, 1H), 8.48 (m, 1H).

[0333]

The property values of the title optically active compound with negative optical rotation are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.31 (s, 3H), 4.16 (s, 3H), 4.25 (ddd, J = 4.4, 8.0, 12.4 Hz, 1H), 4.40 (dt, J = 4.0, 12.4 Hz, 1H), 4.45-4.56 (m, 2H), 6.08 (s, 1H), 7.01 (t, J = 0.8 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H), 7.94-7.96 (m, 1H), 8.25-8.27 (m, 1H), 8.48 (m, 1H).

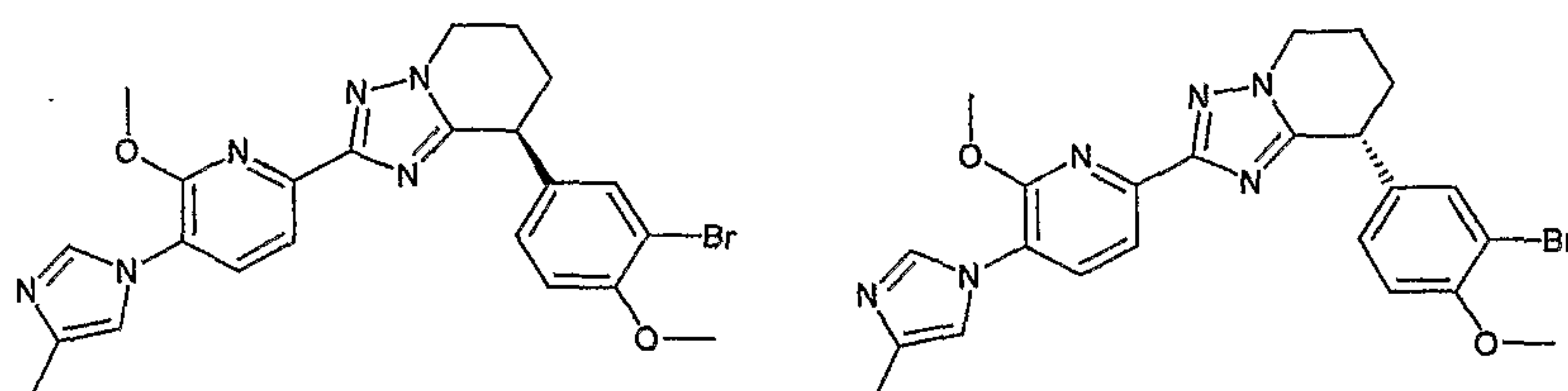
[0334]

Examples 68 and 69

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-bromo-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-bromo-4-methoxyphenyl)-5,6,7,8-

5 tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0335]



[0336]

A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imide hydrochloride obtained in Preparation Example 3-4 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimide hydrochloride. The resulting racemate was separated by CHIRALPAK™ IB (2 cm × 25 cm, mobile phase: ethanol:hexane = 3:7, flow rate: 15 mL/min) to obtain the title compound with a retention time of 37.5 minutes and positive optical rotation (3.52 mg) and the title compound with a retention time of 44 minutes and negative optical rotation (2.53 mg).

15 The property values of the title optically active compound with a retention time of 37.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.12-2.17 (m, 2H), 2.28-2.29 (m, 1H), 2.31-2.41 (m, 1H), 2.41 (s, 3H), 3.89 (s, 3H), 4.19 (s, 3H), 4.32-4.42 (m, 3H), 6.86 (d, J = 8.6 Hz, 1H), 7.03-7.08 (m, 2H), 7.33 (d, J = 1.9 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 1.2 Hz, 1H).

[0337]

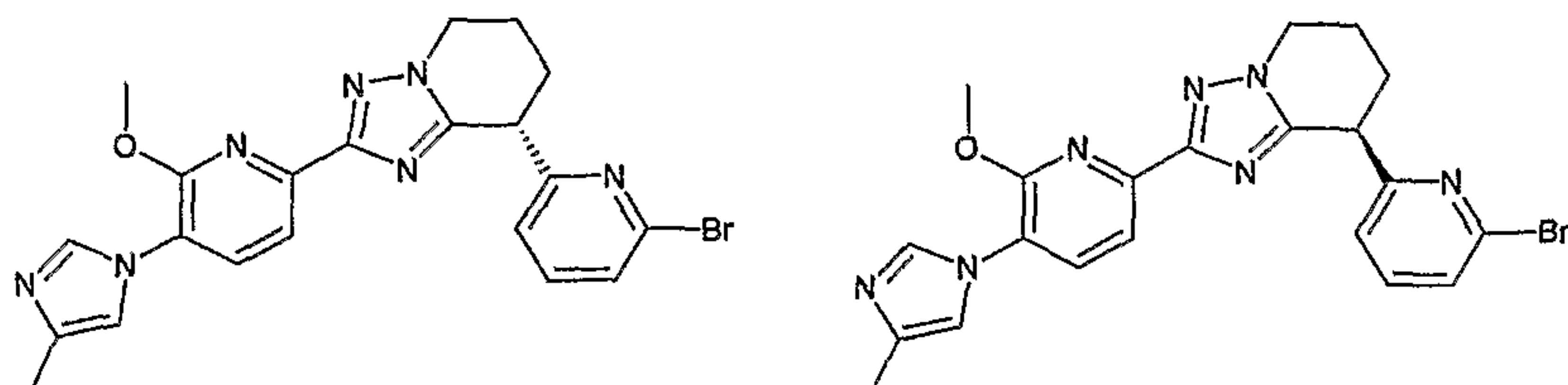
The property values of the title optically active compound with a retention time of 44 minutes are as follows.

25 ¹H-NMR (CDCl₃) δ (ppm): 2.12-2.17 (m, 2H), 2.28-2.29 (m, 1H), 2.31-2.41 (m, 1H), 2.41 (s, 3H), 3.89 (s, 3H), 4.19 (s, 3H), 4.32-4.42 (m, 3H), 6.86 (d, J = 8.6 Hz, 1H), 7.03-7.08 (m, 2H), 7.33 (d, J = 1.9 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 1.2 Hz, 1H).

[0338]

Examples 70 and 71

(+)-8-(6-Bromopyridin-2-yl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-8-(6-bromopyridin-2-yl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine
[0339]



5 [0340]

A racemate of the title compound was obtained according to the method of Examples 42 and 43 from the imide hydrochloride obtained in Preparation Example 3-10 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimide hydrochloride. The resulting racemate (37.2 mg) was separated by CHIRALPAK™ IA manufactured by Daicel Chemical Industries, Ltd. (2 cm × 25 cm; mobile phase: hexane:ethanol = 50:50) to obtain the title optically active compound with a retention time of 5.1 minutes and positive optical rotation (11 mg, >99% ee) and the title optically active compound with a retention time of 8.9 minutes and negative optical rotation (9.1 mg, >99% ee).

15 The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 466 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 2.08-2.27 (m, 2H), 2.30 (d, J = 1.2 Hz, 3H), 2.38-2.43 (m, 2H), 4.16 (s, 3H), 4.31-4.45 (m, 2H), 4.54 (t, J = 6.4 Hz, 1H), 7.00 (t, J = 1.2 Hz, 1H), 7.14 (dd, J = 0.8 Hz, 8.0 Hz, 1H), 7.39 (dd, J = 0.8 Hz, 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H).

[0341]

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 466 [M⁺ + H].

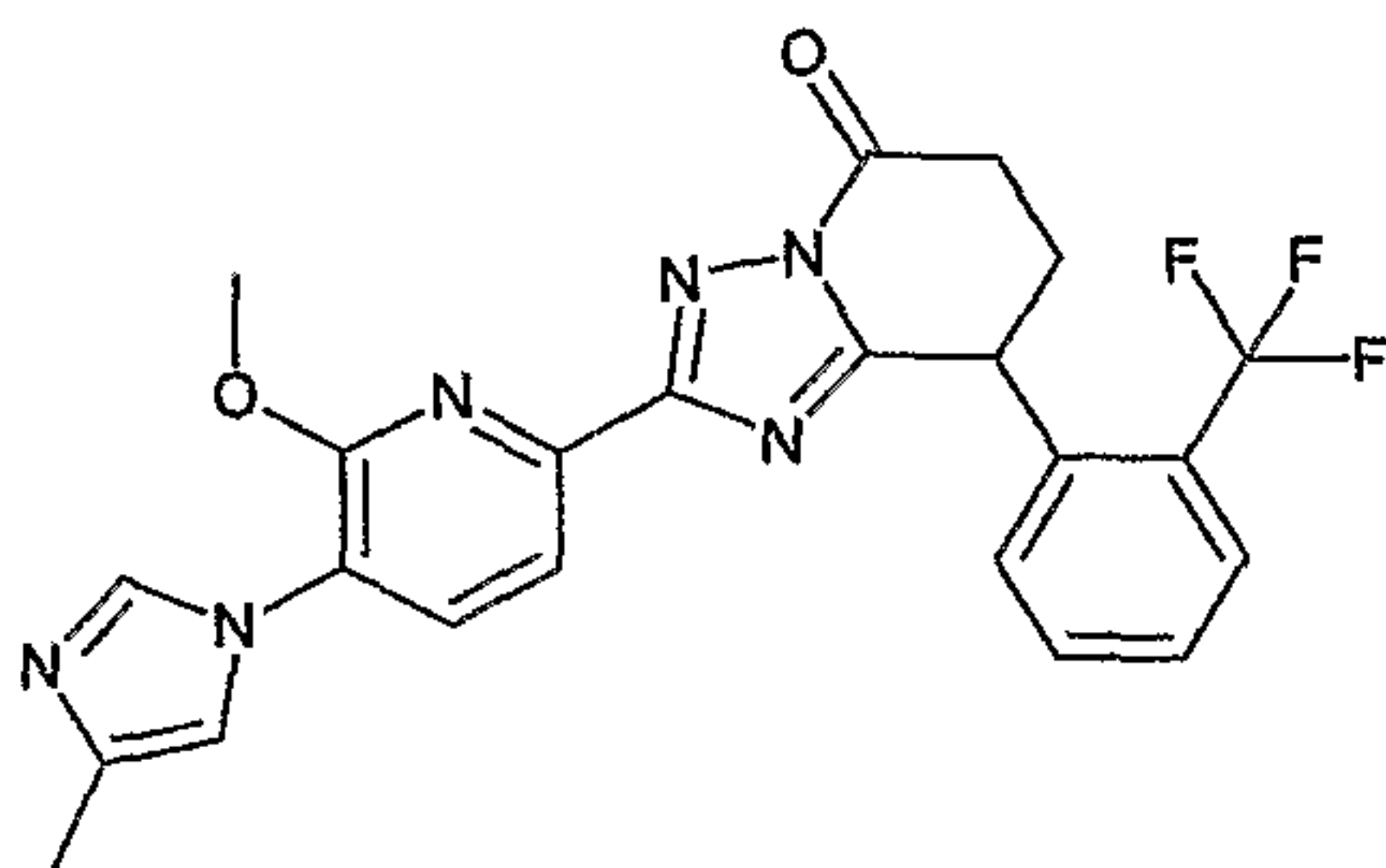
25 ¹H-NMR (CDCl₃) δ (ppm): 2.08-2.27 (m, 2H), 2.30 (d, J = 1.2 Hz, 3H), 2.38-2.43 (m, 2H), 4.16 (s, 3H), 4.31-4.45 (m, 2H), 4.54 (t, J = 6.4 Hz, 1H), 7.00 (t, J = 1.2 Hz, 1H), 7.14 (dd, J = 0.8 Hz, 8.0 Hz, 1H), 7.39 (dd, J = 0.8 Hz, 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H).

[0342]

Example 72

Synthesis of 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-7,8-dihydro-6H-[1,2,4]triazolo[1,5-a]pyridin-5-one

[0343]



5 [0344]

Synthesis of ethyl 4-[5-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-2H-[1,2,4]triazol-3-yl]-4-(2-trifluoromethylphenyl)butyrate

The title compound (370 mg) was obtained according to Examples 42 and 43 from ethyl 4-ethoxycarbonimidoyl-4-(2-trifluoromethylphenyl)butyrate hydrochloride obtained in Preparation Example 3-19 (244 mg). The resulting compound was used directly for the next

[0345]

Synthesis of 4-[5-[6-methoxy-5-(4-methylimidazol-1-yl)-pyridin-2-yl]-2H-[1,2,4]-triazol-3-yl]-4-(2-trifluoromethylphenyl)-butyric acid

Ethyl 4-[5-[6-methoxy-5-(4-methylimidazol-1-yl)-pyridin-2-yl]-2H-[1,2,4]-triazol-3-yl]-4-(2-trifluoromethylphenyl)-butyrate (370 mg) was dissolved in tetrahydrofuran (1 ml). Water (1 ml) and 5 N sodium hydroxide (1 ml) were added and the reaction was initiated. After three hours, the reaction solution was partitioned with diethyl ether and water. The resulting aqueous layer was neutralized with 5 N hydrochloric acid and extracted with methylene chloride twice. Concentration under reduced pressure gave an orange oil (208 mg) which was used for the next step.

ESI-MS; m/z 487 [$M^+ + H$].

[0346]

Synthesis of 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-7,8-dihydro-6H-[1,2,4]triazolo[1,5-a]pyridin-5-one

4-[5-[6-Methoxy-5-(4-methylimidazol-1-yl)-pyridin-2-yl]-2H-[1,2,4]-triazol-3-yl]-4-(2-trifluoromethylphenyl)-butyric acid (208 mg) was dissolved in tetrahydrofuran (4.3 ml). Diisopropylethylamine (220 μ l), 1-hydroxybenzotriazole (86.8 mg) and benzotriazol-1-

yloxytris(pyrrolidino)phosphonium hexafluorophosphate (334 mg) were added at room temperature and the reaction was initiated. After 19 hours, the reaction was terminated with water, followed by dilution with ethyl acetate. The organic layer was washed with saturated ammonium chloride and brine and dried over magnesium sulfate. Concentration under reduced pressure gave an oil. The oil was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 100%) to obtain the title compound (128 mg) as an orange solid.

¹H-NMR (CDCl₃) δ (ppm): 2.17 (s, 3H), 2.18-2.34 (m, 2H), 2.89-2.97 (m, 1H), 3.23-3.34 (m, 1H), 4.09 (s, 3H), 4.87 (dd, J = 11.8, 5.5 Hz, 1H), 7.31-7.35 (m, 1H), 7.40-7.48 (m, 1H), 7.53-7.59 (m, 1H), 7.66-7.75 (m, 2H), 7.82 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.97-8.01 (m, 1H).

[0347]

The compounds of Examples 74 to 83 were obtained by the same method as in Examples 42 and 43 (Table 2).

[0348]

Table 2

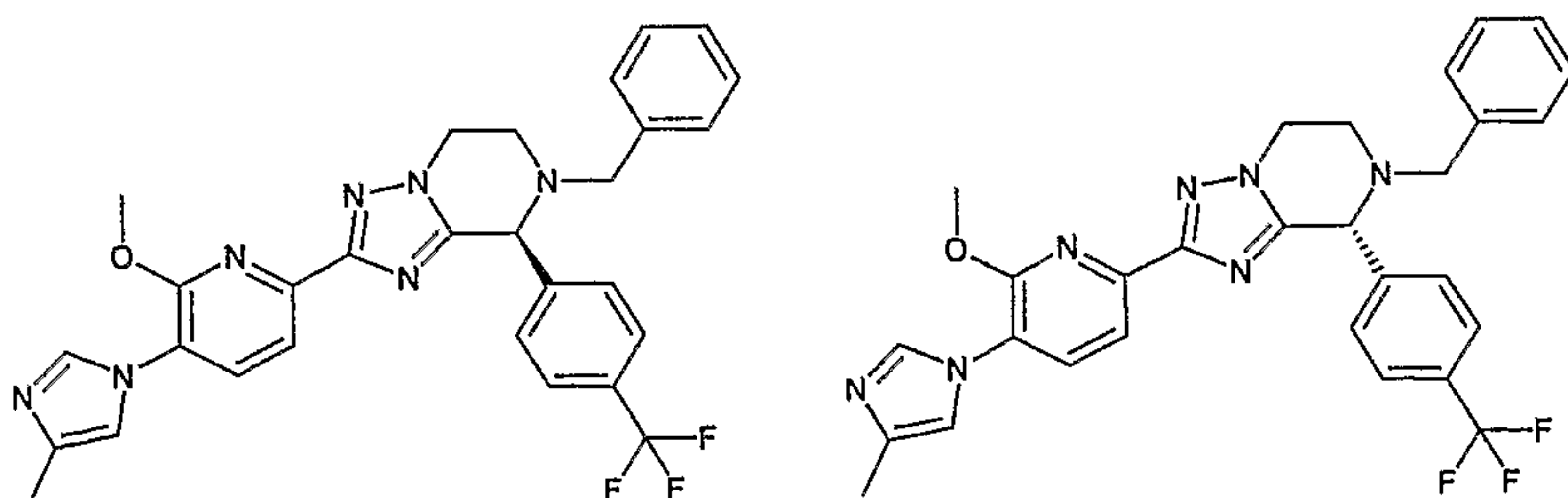
Example No.	Structural formula	Example No.	Structural formula
Example 74		Example 79	
Example 75		Example 80	
Example 76		Example 81	
Example 77		Example 82	
Example 78		Example 83	

[0349]

Examples 84 and 85

5 Synthesis of (+)-7-benzyl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine and (-)-7-benzyl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine

[0350]



[0351]

Synthesis of [benzyl-(2-oxoethyl)amino]-(4-trifluoromethylphenyl)acetonitrile

Dimethyl sulfoxide (689 μ L) was slowly added dropwise to a solution of oxalyl chloride (584 μ L) in dichloromethane (15 mL) at -78°C . After stirring at the same temperature for 10 minutes, a solution of [benzyl-(2-hydroxyethyl)amino]-(4-trifluoromethylphenyl)acetonitrile obtained in Preparation Example 4-1 (1.08 g) in dichloromethane (5 mL) was added to the reaction solution, and the mixture was stirred at the same temperature for 10 minutes. Triethylamine (1.8 mL) was added to the reaction solution, and the mixture was stirred at the same temperature for 10 minutes and then at 0°C for 20 minutes. The reaction solution was partitioned with a saturated sodium bicarbonate solution and ethyl acetate. The resulting organic layer was washed with brine, and dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (elution solvent: heptane:ethyl acetate = 9:1 $\rightarrow$ 8:1) to obtain 959 mg of the title compound. The property values of the compound are as follows.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 3.37-3.47 (m, 2H), 3.62 (d, $J = 13.2$ Hz, 1H), 3.91 (d, $J = 12.8$ Hz, 1H), 5.08 (s, 1H), 7.30-7.43 (m, 5H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 1H) 9.52 (m, 1H).

20 [0352]

Synthesis of 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid N'-(2-{benzyl-[cyano-(4-trifluoromethylphenyl)methyl]amino}ethyl)hydrazide

6-Methoxy-5-(4-methylimidazol-1-yl)pyridine-2-carboxylic acid hydrazide hydrochloride obtained in Preparation Example 1-6 (852 mg), methanol (10 mL) and acetic acid (1 mL) were sequentially added to a solution of [benzyl-(2-oxoethyl)amino]-(4-trifluoromethylphenyl)acetonitrile (950 mg) in dichloromethane (50 mL), and the mixture was stirred at room temperature for five minutes. Sodium cyanoborohydride (359 mg) was added to the reaction solution, followed by stirring at room temperature for 16 hours. The reaction solution was partitioned with a saturated sodium bicarbonate solution and ethyl acetate. The

organic layer was dried over anhydrous magnesium sulfate, allowed to pass through a silica pad and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (elution solvent: ethyl acetate: methanol = 1:0 → 9:1) to obtain 1.31 g of the title compound. The property values of the compound are as follows.

5 ¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H), 2.74-2.96 (m, 3H), 3.03-3.35 (m, 1H), 3.45 (d, J = 13.2 Hz, 1H), 4.02 (s, 3H), 4.07 (d, J = 12.8 Hz, 1H), 5.01 (m, 1H), 5.23 (s, 1H), 7.01 (t, J = 1.2 Hz, 1H), 7.30-7.32 (m, 1H), 7.35-7.39 (m, 2H), 7.44 (m, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.86 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 8.86 (d, J = 7.2 Hz, 1H).

10 [0353]

Synthesis of (+)-7-benzyl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine and (-)-7-benzyl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine

15 Acetic acid (1.37 mL) was added to a solution of 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid N'-(2-{benzyl-[cyano-(4-trifluoromethylphenyl)methyl]amino}ethyl)hydrazide (1.3 g) in toluene (13.7 mL), and the mixture was stirred at 80°C for two days. The reaction solution was concentrated and partitioned with a saturated sodium bicarbonate solution and ethyl acetate. The organic layer was dried over
20 anhydrous magnesium sulfate, allowed to pass through a silica pad and then concentrated under reduced pressure. The resulting residue was recrystallized from heptane-ethyl acetate to obtain 308 mg of a racemate of the title compound. The resulting racemate of the title compound (30 mg) was separated by CHIRALPAK™ IB (2 cm × 25 cm, mobile phase: hexane:ethanol = 7:3, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 13.0
25 minutes resulting from analysis by CHIRALPAK™ IB manufactured by Daicel Chemical Industries, Ltd. (Lot. IB00CD-LG026, hexane:ethanol = 7:3, 1.0 mL/min) (8.6 mg) and the title optically active compound with a retention time of 14.9 minutes resulting from the same analysis (7.4 mg), respectively.

The property values of the title optically active compound with a retention time of
30 13.0 minutes under the analysis conditions are as follows.

ESI-MS; m/z 546 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 2.29 (s, 3H), 2.93 (m, 1H), 3.36 (dt, J = 4.4, 8.4 Hz, 1H), 3.49 (d, J = 13.6 Hz, 1H), 3.87 (d, J = 13.2 Hz, 1H), 4.14 (s, 3H), 4.33-4.44 (m, 2H), 4.97 (s, 1H), 6.99 (s, 1H), 7.29-7.38 (m, 5H), 7.57 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.4 Hz,

2H), 7.73 (d, $J = 7.6$ Hz, 1H), 7.83 (s, 1H).

[0354]

The property values of the title optically active compound with a retention time of 14.9 minutes under the analysis conditions are as follows.

5 ESI-MS; m/z 546 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 2.29 (s, 3H), 2.93 (m, 1H), 3.36 (dt, $J = 4.4, 8.4$ Hz, 1H), 3.49 (d, $J = 13.6$ Hz, 1H), 3.87 (d, $J = 13.2$ Hz, 1H), 4.14 (s, 3H), 4.33-4.44 (m, 2H), 4.97 (s, 1H), 6.99 (s, 1H), 7.29-7.38 (m, 5H), 7.57 (d, $J = 7.6$ Hz, 1H), 7.63 (d, $J = 8.0$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.73 (d, $J = 7.6$ Hz, 1H), 7.83 (d, $J = 1.2$ Hz, 1H).

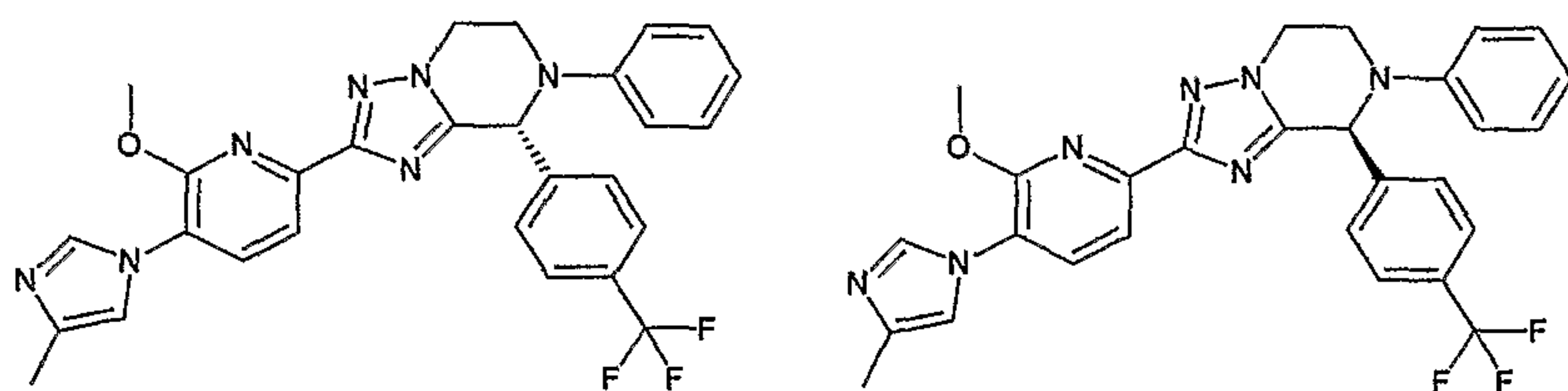
10 [0355]

Examples 86 and 87

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-7-phenyl-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-7-phenyl-8-(4-trifluoromethylphenyl)-5,6,7,8-

15 tetrahydro[1,2,4]triazolo[1,5-a]pyrazine

[0356]



[0357]

A racemate of the title compound (48 mg) was obtained according to the method of Examples 84 and 85 from [(2-hydroxyethyl)phenylamino]-(4-trifluoromethylphenyl)acetonitrile obtained in Preparation Example 4-2 in place of [benzyl-(2-oxoethyl)amino]-(4-trifluoromethylphenyl)acetonitrile. This was separated by CHIRALPAKTM IB manufactured by Daicel Chemical Industries, Ltd. (2 cm $\times$ 25 cm, mobile phase: hexane:ethanol = 8:2, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 8.78 minutes resulting from analysis by CHIRALPAKTM IB (Lot. IB00CD-25 FD026, hexane:ethanol = 8:2, 1.0 mL/min) and negative optical rotation (14 mg, >99% ee) and the title optically active compound with a retention time of 11.27 minutes resulting from the same analysis and positive optical rotation (14 mg, >99% ee).

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 532 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 2.31 (s, 3H), 3.69-3.76 (m, 1H), 4.01-4.05 (m, 1H), 4.17 (s, 3H), 4.33-4.38 (m, 1H), 4.42-4.49 (m, 1H), 6.21 (s, 1H), 6.95-7.03 (m, 4H), 7.28-7.33 (m, 2H), 7.57-7.62 (m, 4H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.86 (d, $J = 1.2$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H).

5 [0358]

The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 532 [$M^+ + H$].

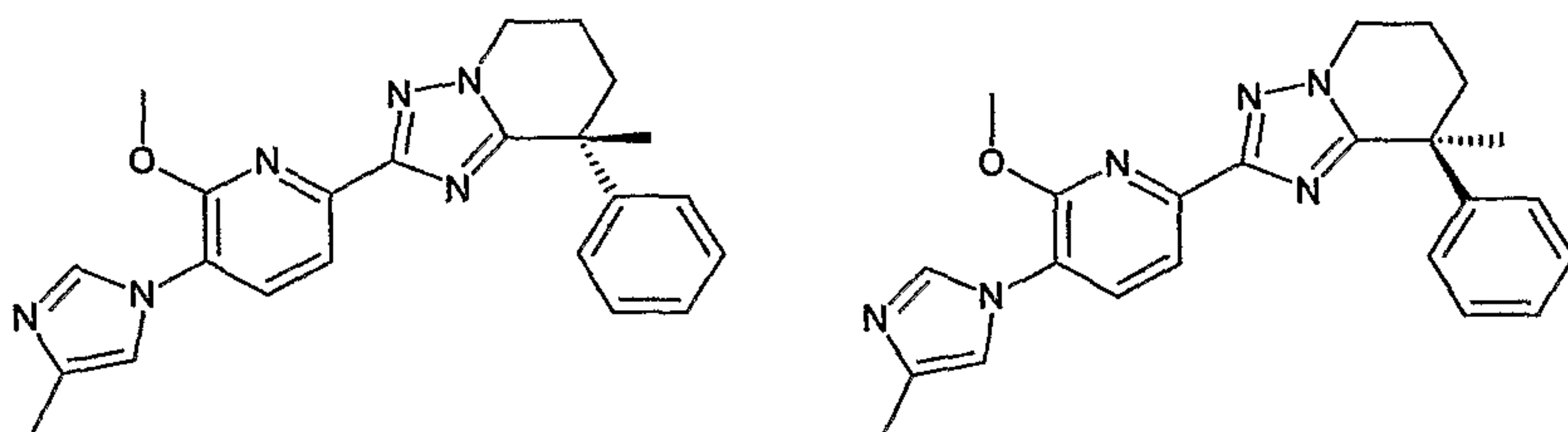
10 ^1H -NMR ($CDCl_3$) δ (ppm): 2.31 (s, 3H), 3.69-3.76 (m, 1H), 4.01-4.05 (m, 1H), 4.17 (s, 3H), 4.33-4.38 (m, 1H), 4.42-4.49 (m, 1H), 6.21 (s, 1H), 6.95-7.03 (m, 4H), 7.28-7.33 (m, 2H), 7.57-7.62 (m, 4H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.86 (d, $J = 1.2$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H).

[0359]

Examples 88 and 89

15 Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-methyl-8-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-methyl-8-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0360]



[0361]

20 A racemate of the title compound was obtained according to Examples 84 and 85 from 5-hydroxy-2-methyl-2-phenylpentanenitrile (CAS #745054-73-3) as a starting material in place of [benzyl-(2-oxoethyl)amino]-(4-trifluoromethylphenyl)acetonitrile. This was separated by CHIRALCELTM IB manufactured by Daicel Chemical Industries, Ltd. (2 cm $\times$ 25 cm, mobile phase: hexane:ethanol = 8:2, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 5.4 minutes resulting from analysis by CHIRALPAKTM IB manufactured by Daicel Chemical Industries, Ltd. (Lot. IB00CD-LG026, hexane:ethanol = 8:2, 1.0 mL/min) and negative optical rotation and the title optically active compound with a retention time of 7.1 minutes resulting from the same analysis and positive optical rotation, respectively.

The property values of the title optically active compound with negative optical

rotation are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.87 (s, 3H), 1.89-2.11 (m, 3H), 2.31 (s, 3H), 2.41 (m, 1H), 4.18 (s, 3H), 4.24 (m, 1H), 4.40 (m, 1H), 7.02 (m, 1H), 7.09-7.12 (m, 2H), 7.20-7.24 (m, 1H), 7.27-7.31 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H).

5 [0362]

The property values of the title optically active compound with positive optical rotation are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.87 (s, 3H), 1.89-2.11 (m, 3H), 2.31 (s, 3H), 2.41 (m, 1H), 4.18 (s, 3H), 4.24 (m, 1H), 4.40 (m, 1H), 7.02 (m, 1H), 7.09-7.12 (m, 2H), 7.20-7.24 (m, 1H), 7.27-7.31 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H).

10 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H).

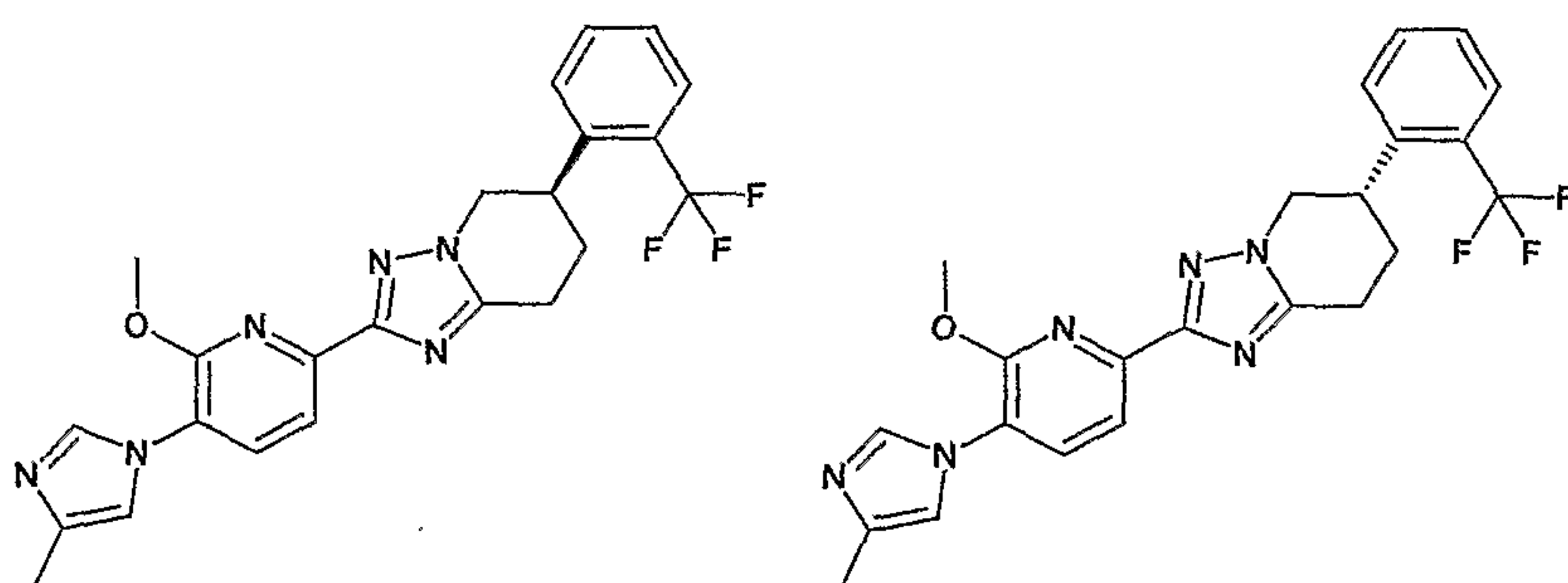
[0363]

Examples 90 and 91

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-6-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-6-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

15 (4-methylimidazol-1-yl)pyridin-2-yl]-6-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0364]



[0365]

A racemate of the title compound (186 mg) was obtained according to Examples 84 and 85 from 5-hydroxy-4-(2-trifluoromethylphenyl)pentanenitrile obtained in Preparation Example 4-3 in place of [benzyl-(2-oxoethyl)amino]-(4-trifluoromethylphenyl)acetonitrile. The resulting racemate was separated by CHIRALPAKTM IB manufactured by Daicel Chemical Industries, Ltd. (2 cm × 25 cm, mobile phase: ethanol:hexane = 3:7, flow rate: 15 mL/min) to obtain the title compound with a retention time of 13.0 minutes and positive optical rotation (42 mg) and the title compound with a retention time of 22.5 minutes and negative optical rotation (49.7 mg).

25 mg) and the title compound with a retention time of 22.5 minutes and negative optical rotation (49.7 mg).

The property values of the title optically active compound with a retention time of

13.0 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.20-2.34 (m, 2H), 2.31 (s, 3H), 3.09 (ddd, J = 15.2, 13.0, 6.2 Hz, 1H), 3.30 (ddd, J = 15.2, 5.1, 2.7 Hz, 1H), 3.72-3.82 (m, 1H), 4.17 (s, 3H), 4.23 (dd, J = 11.7, 11.7 Hz, 1H), 4.60 (dd, J = 15.2, 5.1 Hz, 1H), 7.02-7.04 (m, 1H), 7.43-7.52 (m, 2H), 7.60-7.65 (m, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 1.2 Hz, 1H).

[0366]

The property values of the title optically active compound with a retention time of 22.5 minutes are as follows.

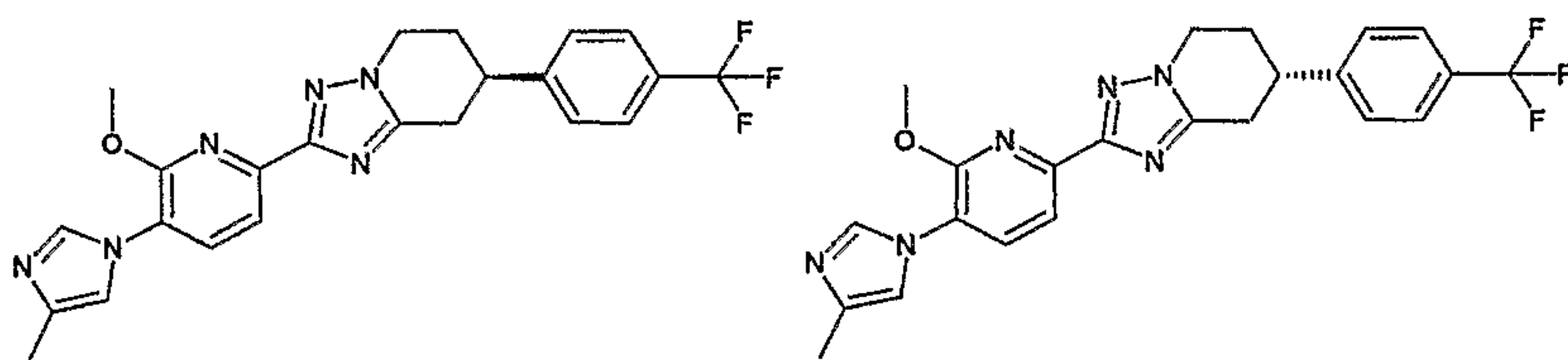
¹H-NMR (CDCl₃) δ (ppm): 2.20-2.34 (m, 2H), 2.31 (s, 3H), 3.09 (ddd, J = 15.2, 13.0, 6.2 Hz, 1H), 3.30 (ddd, J = 15.2, 5.1, 2.7 Hz, 1H), 3.72-3.82 (m, 1H), 4.17 (s, 3H), 4.23 (dd, J = 11.7, 11.7 Hz, 1H), 4.60 (dd, J = 15.2, 5.1 Hz, 1H), 7.02-7.04 (m, 1H), 7.43-7.52 (m, 2H), 7.60-7.65 (m, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 1.2 Hz, 1H).

[0367]

Examples 92 and 93

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0368]



[0369]

A racemate of the title compound (184.1 mg) was obtained according to Examples 84 and 85 from 5-hydroxy-3-(4-trifluoromethylphenyl)pentanenitrile obtained in Preparation Example 4-4 in place of [benzyl-(2-oxoethyl)amino]-(4-trifluoromethylphenyl)acetonitrile. The resulting racemate was separated by CHIRALPAKTM IB manufactured by Daicel Chemical Industries, Ltd. (2 cm × 25 cm, mobile phase: ethanol:hexane = 5:5, flow rate: 13 mL/min) to obtain the title compound with a retention time of 16.5 minutes and positive optical rotation (43.0 mg) and the title compound with a retention time of 23.0 minutes and negative optical

rotation (44.0 mg).

The property values of the title optically active compound with a retention time of 16.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.31 (s, 3H), 2.33-2.49 (m, 2H), 3.11 (dd, J = 16.7, 9.4 Hz, 1H),
 5 3.34-3.47 (m, 2H), 4.18 (s, 3H), 4.28-4.37 (m, 1H), 4.39-4.47 (m, 1H), 7.01-7.05 (m, 1H), 7.40
 (d, J = 8.2 Hz, 2H), 7.62-7.68 (m, 3H), 7.83 (d, J = 7.8 Hz, 1H), 7.84-7.87 (m, 1H).

[0370]

The property values of the title optically active compound with a retention time of 23.0 minutes are as follows.

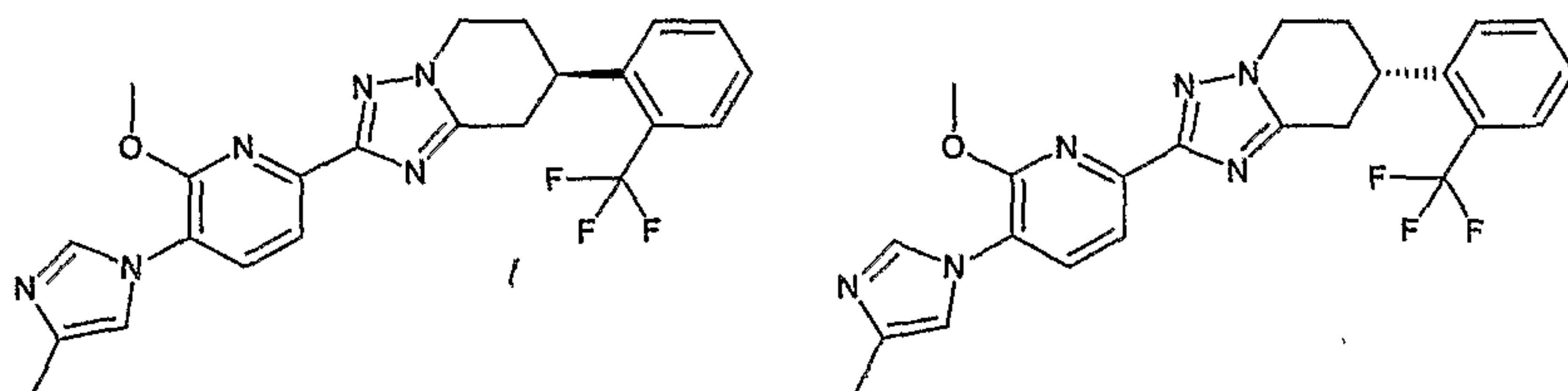
10 ¹H-NMR (CDCl₃) δ (ppm): 2.31 (s, 3H), 2.33-2.49 (m, 2H), 3.11 (dd, J = 16.7, 9.4 Hz, 1H),
 3.34-3.47 (m, 2H), 4.18 (s, 3H), 4.28-4.37 (m, 1H), 4.39-4.47 (m, 1H), 7.01-7.05 (m, 1H), 7.40
 (d, J = 8.2 Hz, 2H), 7.62-7.68 (m, 3H), 7.83 (d, J = 7.8 Hz, 1H), 7.84-7.87 (m, 1H).

[0371]

Examples 94 and 95

15 Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0372]



20 [0373]

A racemate of the title compound (222 mg) was obtained according to the method of Examples 84 and 85 from 5-hydroxy-3-(2-trifluoromethylphenyl)pentanenitrile obtained in Preparation Example 4-5 in place of [benzyl-(2-oxoethyl)amino]-(4-trifluoromethylphenyl)acetonitrile. The resulting racemate was separated by CHIRALCELTM
 25 OD-H (2 cm × 25 cm, mobile phase: ethanol:hexane = 2:8, flow rate: 15 mL/min) to obtain the title compound with a retention time of 22.5 minutes and positive optical rotation (25.1 mg) and the title compound with a retention time of 49.5 minutes and negative optical rotation (35.8 mg).

The property values of the title optically active compound with a retention time of

22.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H), 2.31-2.42 (m, 2H), 3.08 (dd, J = 17.1, 11.7 Hz, 1H), 3.41 (dd, J = 17.1, 5.1 Hz, 1H), 3.62-3.73 (m, 1H), 4.18 (s, 3H), 4.27-4.37 (m, 1H), 4.52 (ddd, J = 13.3, 5.1, 2.3 Hz, 1H), 6.92-6.94 (m, 1H), 7.40-7.45 (m, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 1.0 Hz, 1H).

[0374]

The property values of the title optically active compound with a retention time of 49.5 minutes are as follows.

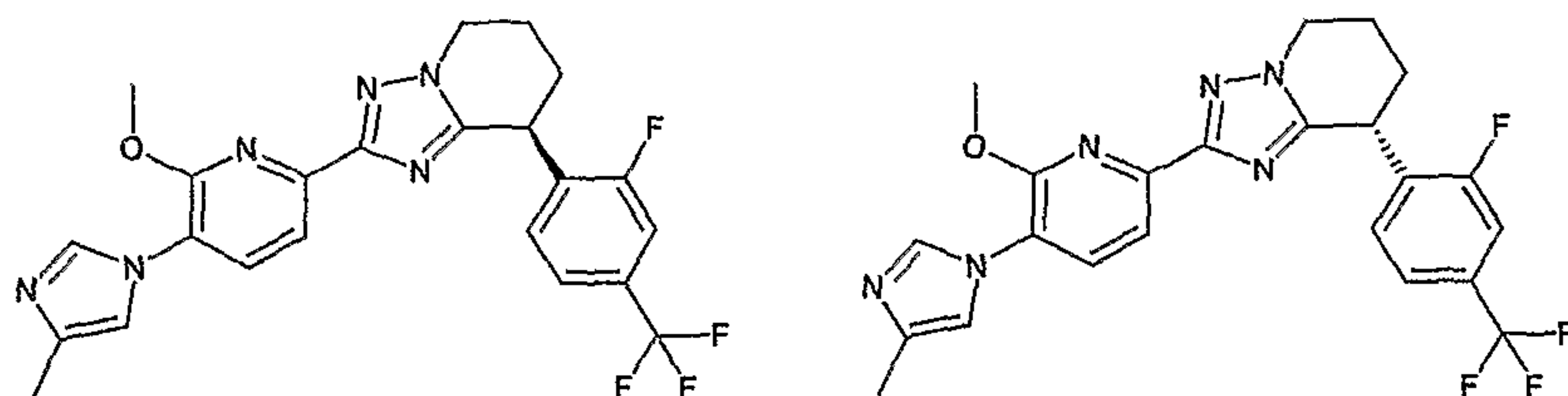
¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H), 2.31-2.42 (m, 2H), 3.08 (dd, J = 17.1, 11.7 Hz, 1H), 3.41 (dd, J = 17.1, 5.1 Hz, 1H), 3.62-3.73 (m, 1H), 4.18 (s, 3H), 4.27-4.37 (m, 1H), 4.52 (ddd, J = 13.3, 5.1, 2.3 Hz, 1H), 6.92-6.94 (m, 1H), 7.40-7.45 (m, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 1.0 Hz, 1H).

[0375]

Examples 96 and 97

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-fluoro-4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-fluoro-4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0376]



[0377]

A racemate of the title compound (52.7 mg) was obtained according to the method of Examples 84 and 85 from 2-(2-fluoro-4-trifluoromethylphenyl)-5-hydroxypentanenitrile obtained in Preparation Example 4-6 in place of [benzyl-(2-oxoethyl)amino]-(4-trifluoromethylphenyl)acetonitrile. The resulting racemate was separated by CHIRALPAKTM IB (2 cm × 25 cm, mobile phase: ethanol:hexane = 2:8, flow rate: 15 mL/min) to obtain the title compound with a retention time of 48 minutes and positive optical rotation

(1.81 mg) and the title compound with a retention time of 56.5 minutes and negative optical rotation (2.15 mg).

The property values of the title optically active compound with a retention time of 48 minutes are as follows.

5 $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.04-2.25 (m, 3H), 2.30 (s, 3H), 2.38-2.48 (m, 1H), 4.16 (s, 3H), 4.42 (dd, $J = 7.4, 5.5$ Hz, 2H), 4.69 (dd, $J = 7.0, 7.0$ Hz, 1H), 6.98-7.01 (m, 1H), 7.08-7.14 (m, 1H), 7.37 (d, $J = 9.0$ Hz, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.76 (d, $J = 7.8$ Hz, 1H), 7.83 (d, $J = 1.2$ Hz, 1H).

[0378]

10 The property values of the title optically active compound with a retention time of 56.5 minutes are as follows.

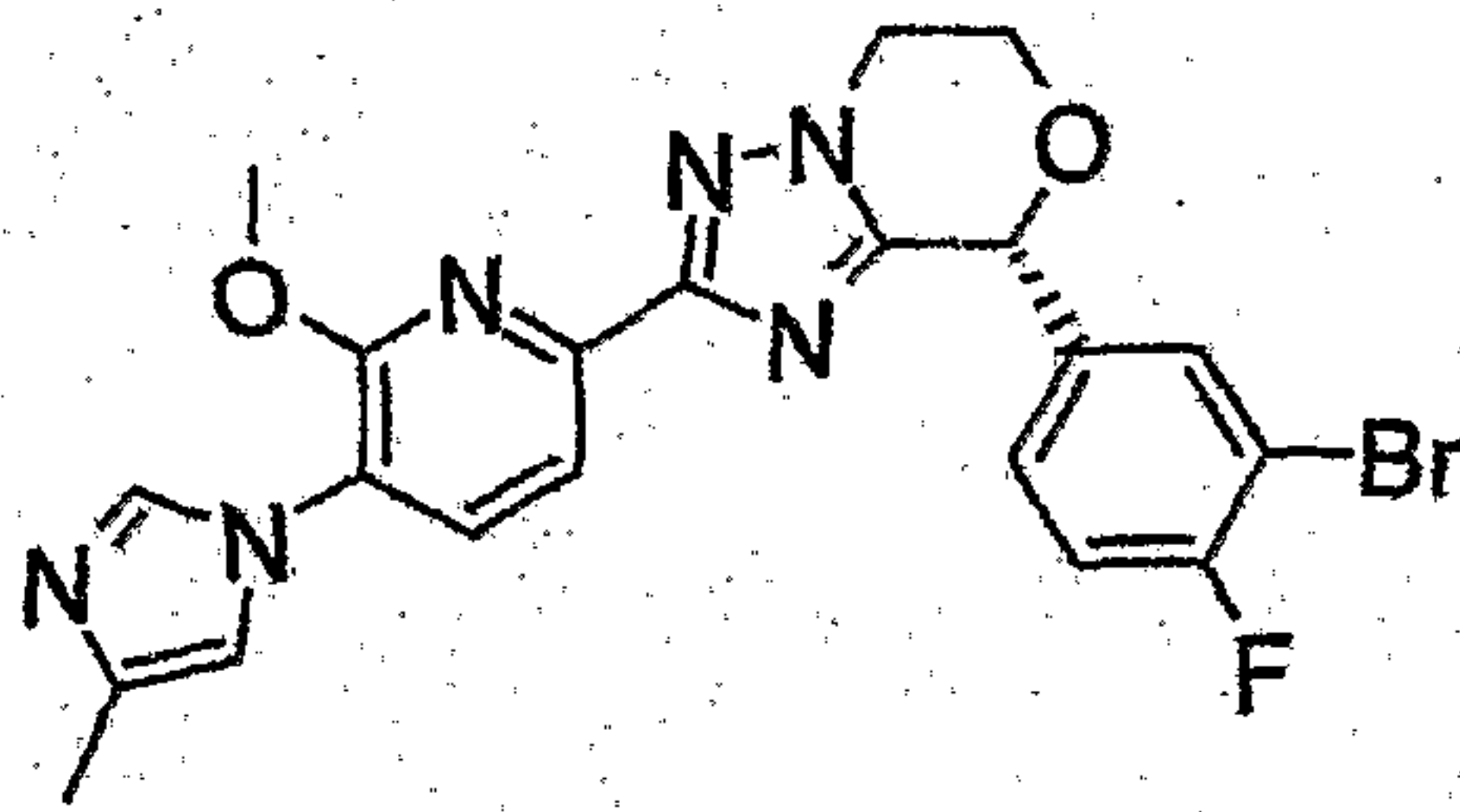
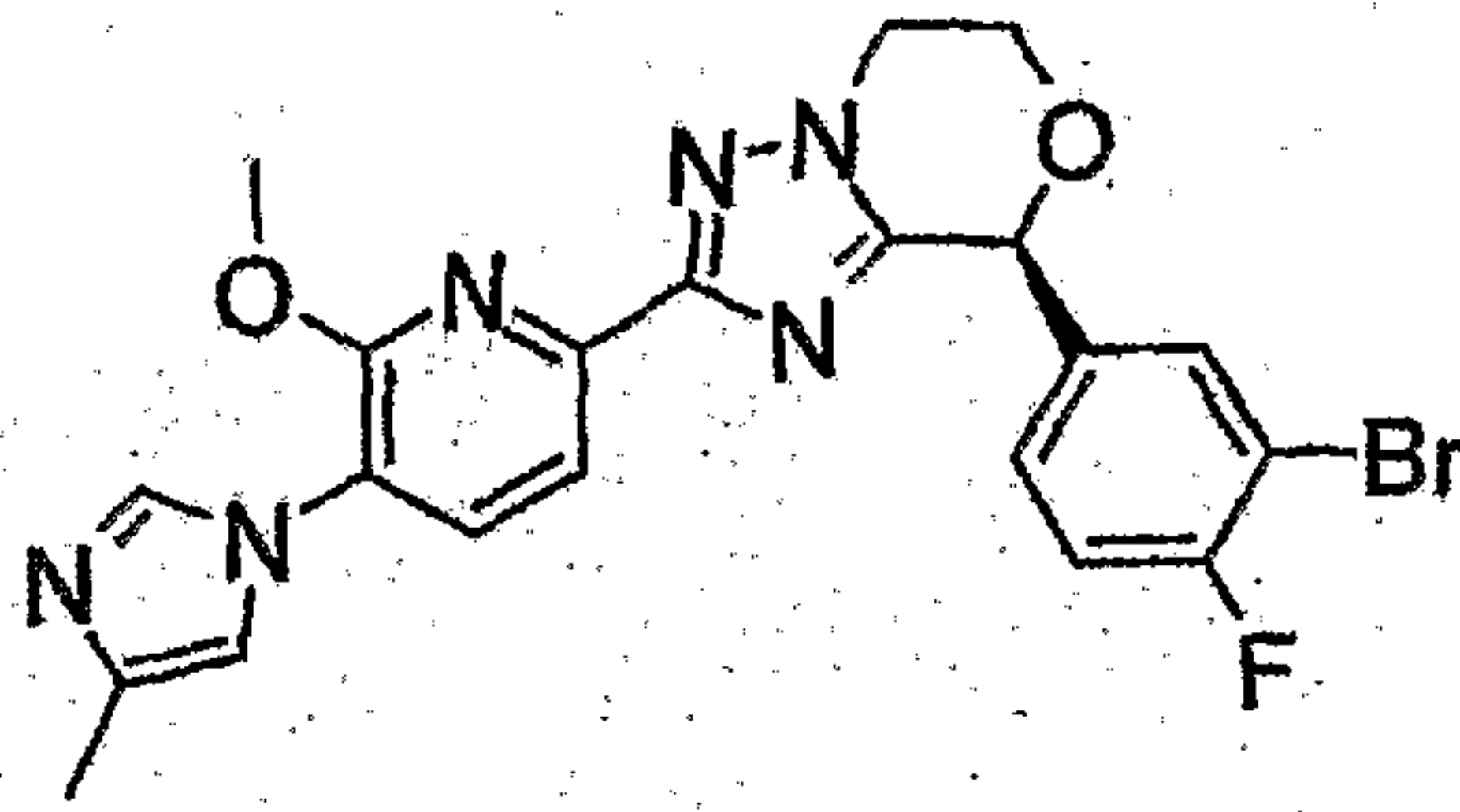
$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.04-2.25 (m, 3H), 2.30 (s, 3H), 2.38-2.48 (m, 1H), 4.16 (s, 3H), 4.42 (dd, $J = 7.4, 5.5$ Hz, 2H), 4.69 (dd, $J = 7.0, 7.0$ Hz, 1H), 6.98-7.01 (m, 1H), 7.08-7.14 (m, 1H), 7.37 (d, $J = 9.0$ Hz, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.76 (d, $J = 7.8$ Hz, 1H), 7.83 (d, $J = 1.2$ Hz, 1H).

15 Hz, 1H).

[0379]

The compounds of Examples 98 to 99 were obtained by the same method as in Examples 84 and 85 (Table 3).

Table 3

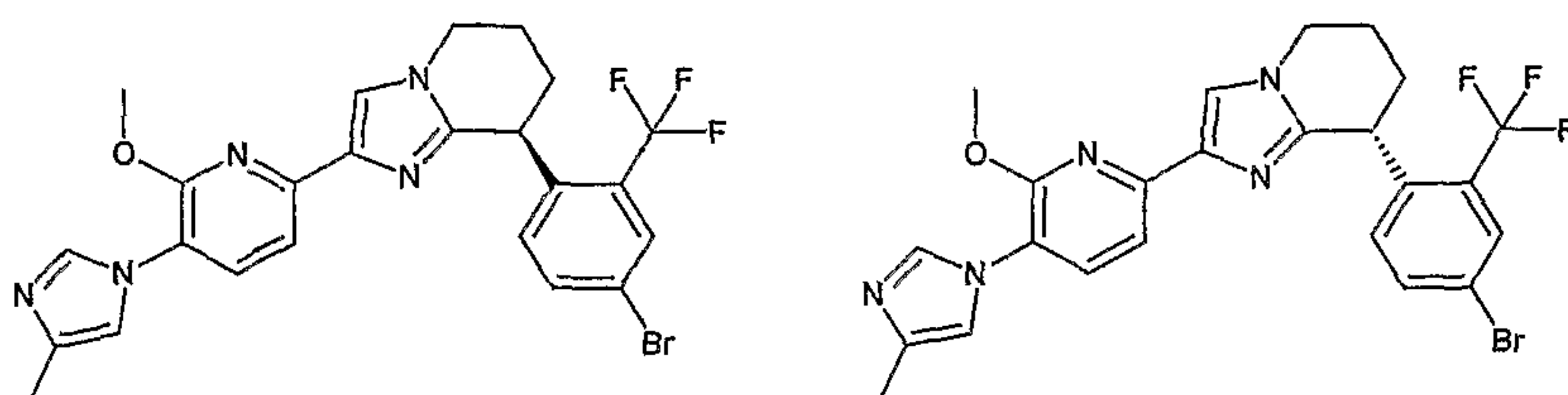
Example No.	Structural formula
Example 98	
Example 99	

[0380]

Examples 100 and 101

Synthesis of (-)-8-(4-bromo-2-trifluoromethylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine and (+)-8-(4-bromo-2-trifluoromethylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

[0381]



[0382]

Synthesis of 3-(4-bromo-2-trifluoromethylphenyl)piperidine-2-ylideneamine

- 10 A saturated ammonia-ethanol solution (2.5 mL) was added to ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride obtained in Preparation Example 3-1 (500 mg), and the mixture was stirred at room temperature for eight days. The insoluble matter was removed by filtration and then the filtrate was concentrated under reduced pressure. Methylene chloride and a 1 N sodium hydroxide solution were added to the resulting residue,
- 15 and the organic layer was separated. The aqueous layer was reextracted with methylene chloride. The combined organic layers were dried over anhydrous potassium carbonate and concentrated under reduced pressure to obtain 320 mg of the title compound. The property values of the compound are as follows.

ESI-MS; m/z 321 [$M^+ + H$].

- 20 ^1H -NMR (DMSO- D_6) δ (ppm): 1.42-1.65 (m, 3H), 1.95-2.05 (m, 1H), 3.35-3.45 (m, 2H), 3.68 (d, $J = 6.8$ Hz, 1H), 5.55 (brs, 2H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.85-7.92 (m, 2H).

[0383]

Synthesis of (-)-8-(4-bromo-2-trifluoromethylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine and (+)-8-(4-bromo-2-trifluoromethylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

N-bromosuccinimide (98 mg) was added to a solution of 6-(1-ethoxyvinyl)-2-methoxy-3-(4-methylimidazol-1-yl)pyridine obtained in Preparation Example 1-7 (130 mg) in Tetrahydrofuran (5 mL)-water (0.2 mL), followed by stirring at room temperature for 15

minutes. A solution of 3-(4-bromo-2-trifluoromethylphenyl)piperidin-2-ylideneamine (318 mg) in ethanol (2 mL) was added to the reaction solution, followed by stirring at room temperature for two hours and 15 minutes. Then, the reaction solution was heated under reflux for one hour and 30 minutes. The reaction solution was left to cool to room temperature. Ethyl acetate, water and a saturated sodium bicarbonate solution were added to the reaction solution, and the organic layer was separated. The resulting organic layer was sequentially washed with half-saturated brine and brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: ChromatorexTM NH; elution solvent: ethyl acetate:heptane = 1:9 → 1:1) to obtain a racemate of the title compound.

The resulting racemate was separated by CHIRALCELTM OD-H (2 cm × 25 cm; mobile phase: 20% isopropanol-hexane) to obtain the title optically active compound with a retention time of 14 minutes and negative optical rotation (36.1 mg, >99% ee) and the title optically active compound with a retention time of 20 minutes and positive optical rotation (36.3 mg, >97% ee).

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 534 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 1.82-1.94 (m, 1H), 2.00-2.22 (m, 2H), 2.29 (s, 3H), 2.35-2.45 (m, 1H), 4.03 (s, 3H), 4.17 (dd, J = 6.8, 5.6 Hz, 2H), 4.65 (dd, J = 8.4, 6.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.93 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.55 (dd, J = 8.4, 2.0 Hz, 1H), 7.74 (d, J = 1.2 Hz, 1H), 7.84 (d, J = 2.0 Hz, 1H).

[0384]

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 534 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 1.82-1.94 (m, 1H), 2.00-2.22 (m, 2H), 2.29 (s, 3H), 2.35-2.45 (m, 1H), 4.03 (s, 3H), 4.17 (dd, J = 6.8, 5.6 Hz, 2H), 4.65 (dd, J = 8.4, 6.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.93 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.55 (dd, J = 8.4, 2.0 Hz, 1H), 7.74 (d, J = 1.2 Hz, 1H), 7.84 (d, J = 2.0 Hz, 1H).

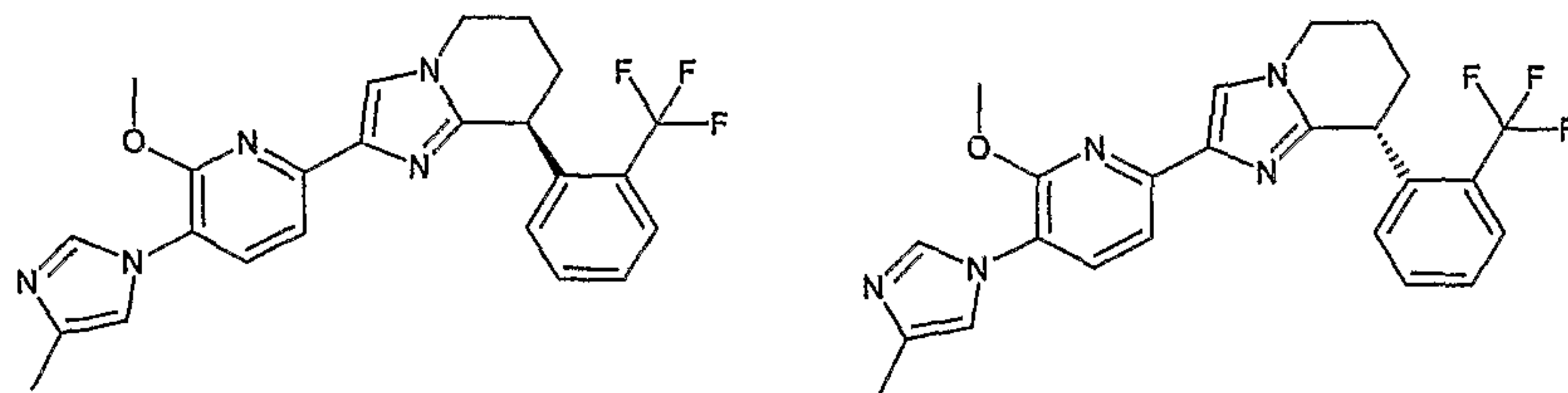
[0385]

Examples 102 and 103

Synthesis of (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine and (+)-2-[6-methoxy-5-(4-

methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

[0386]



[0387]

5 A racemate of the title compound was obtained according to the method of Examples 100 and 101 from ethyl 2-(2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride obtained in Preparation Example 3-12. The resulting racemate was separated by CHIRALCELTM OD-H (2 cm × 25 cm; mobile phase: 30% isopropanol-hexane) to obtain the title optically active compound with a retention time of 10 minutes and negative optical rotation (12.2 mg, >99% ee) and the title optically active compound with a retention time of 22 minutes and positive optical rotation (11.8 mg, >97% ee).

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 454 [M⁺ + H].

15 ¹H-NMR (CDCl₃) δ (ppm): 1.85-2.23 (m, 3H), 2.28 (s, 3H), 2.35-2.45 (m, 1H), 4.04 (s, 3H), 4.10-4.25 (m, 2H), 4.73 (t, J = 6.8 Hz, 1H), 6.92 (brs, 1H), 7.01 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.55 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.74 (brs, 1H).

[0388]

20 The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 454 [M⁺ + H].

25 ¹H-NMR (CDCl₃) δ (ppm): 1.85-2.23 (m, 3H), 2.28 (s, 3H), 2.35-2.45 (m, 1H), 4.04 (s, 3H), 4.10-4.25 (m, 2H), 4.73 (t, J = 6.8 Hz, 1H), 6.92 (brs, 1H), 7.01 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.55 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.74 (brs, 1H).

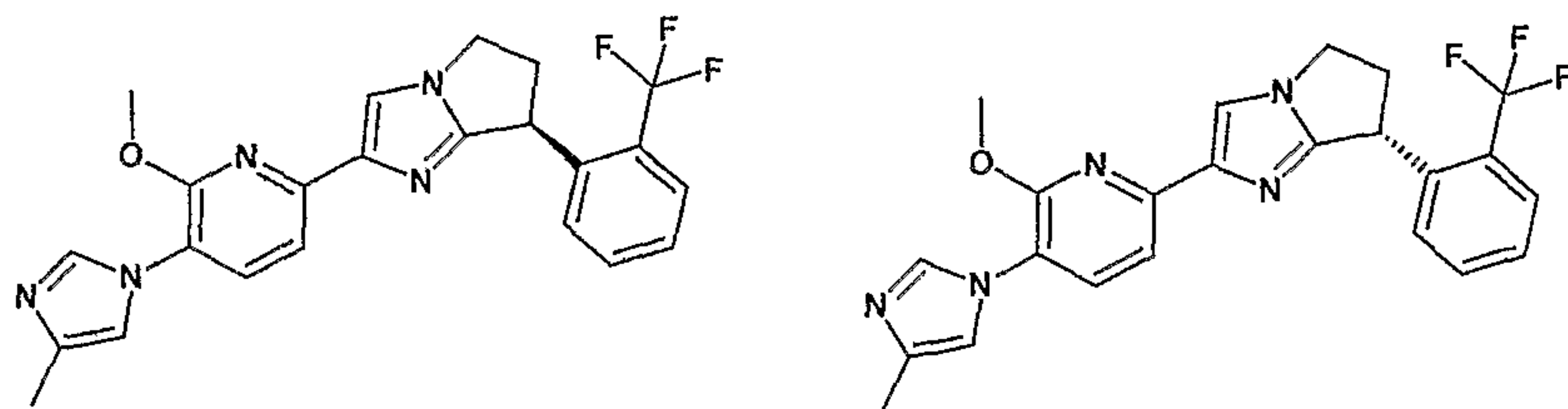
[0389]

Examples 104 and 105

Synthesis of (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(2-

trifluoromethylphenyl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole and (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(2-trifluoromethylphenyl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole

[0390]



5 [0391]

A racemate of the title compound was obtained according to the method of Examples 100 and 101 from ethyl 4-chloro-2-(2-trifluoromethylphenyl)butylimidate hydrochloride obtained in Preparation Example 3-14 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was purified by CHIRALPAK™ IB (2 cm × 25 cm; mobile phase: 30% isopropanol-hexane) and then separated by CHIRALCEL™ OD-H (2 cm × 25 cm; mobile phase: 30% isopropanol-hexane) to obtain the title optically active compound with a retention time of 10 minutes and negative optical rotation (2.43 mg, >99% ee) and the title optically active compound with a retention time of 16 minutes and positive optical rotation (2.00 mg, >99% ee).

15 The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 440 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 2.29 (d, $J = 1.2$ Hz, 3H), 2.40-2.52 (m, 1H), 3.17-3.28 (m, 1H), 4.06 (s, 3H), 4.07-4.21 (m, 2H), 4.82 (dd, $J = 6.0, 8.4$ Hz, 1H), 6.96 (brs, 1H), 7.05 (d, $J = 7.6$ Hz, 1H), 7.37 (t, $J = 7.6$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.68 (s, 1H), 7.71 (d, $J = 7.6$ Hz, 1H), 7.76 (d, $J = 1.6$ Hz, 1H).

[0392]

The property values of the title compound with negative optical rotation are as follows.

25 ESI-MS; m/z 440 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 2.29 (d, $J = 1.2$ Hz, 3H), 2.40-2.52 (m, 1H), 3.17-3.28 (m, 1H), 4.06 (s, 3H), 4.07-4.21 (m, 2H), 4.82 (dd, $J = 6.0, 8.4$ Hz, 1H), 6.96 (brs, 1H), 7.05 (d, $J = 7.6$ Hz, 1H), 7.37 (t, $J = 7.6$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.59 (d, $J = 8.0$

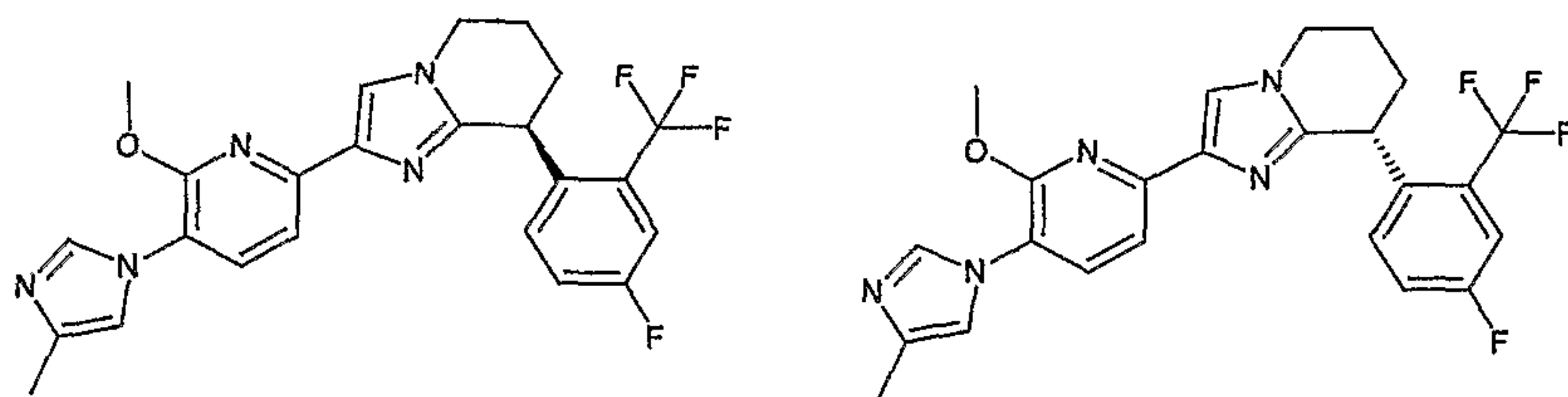
Hz, 1H), 7.68 (s, 1H), 7.71 (d, $J = 7.6$ Hz, 1H), 7.76 (d, $J = 1.6$ Hz, 1H).

[0393]

Examples 106 and 107

Synthesis of (-)-8-(4-fluoro-2-trifluoromethylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine and (+)-8-(4-fluoro-2-trifluoromethylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

[0394]



[0395]

- 10 A racemate of the title compound was obtained according to the method of Examples 100 and 101 from ethyl 2-(4-fluoro-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride obtained in Preparation Example 3-13 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAKTM IA (2 cm × 25 cm; mobile phase: 30% isopropanol-hexane) to
- 15 obtain the title optically active compound with a retention time of 11 minutes and negative optical rotation (14.8 mg, >99% ee) and the title optically active compound with a retention time of 21 minutes and positive optical rotation (22.7 mg, >98% ee).

The property values of the title compound with negative optical rotation are as follows.

20 ESI-MS; m/z 472 [$M^+ + H$].

¹H-NMR (CDCl₃) δ (ppm): 1.84-1.94 (m, 1H), 1.98-2.22 (m, 2H), 2.28 (s, 3H), 2.35-2.46 (m, 1H), 4.03 (s, 3H), 4.17 (dd, $J = 7.2, 4.8$ Hz, 2H), 4.67 (dd, $J = 8.0, 6.0$ Hz, 1H), 6.93 (brs, 1H), 7.02 (dd, $J = 8.4, 5.6$ Hz, 1H), 7.14 (td, $J = 8.4, 2.4$ Hz, 1H), 7.41 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.54 (s, 1H), 7.74 (d, $J = 1.2$ Hz, 1H).

25 [0396]

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 472 [$M^+ + H$].

¹H-NMR (CDCl₃) δ (ppm): 1.84-1.94 (m, 1H), 1.98-2.22 (m, 2H), 2.28 (s, 3H), 2.35-2.46 (m,

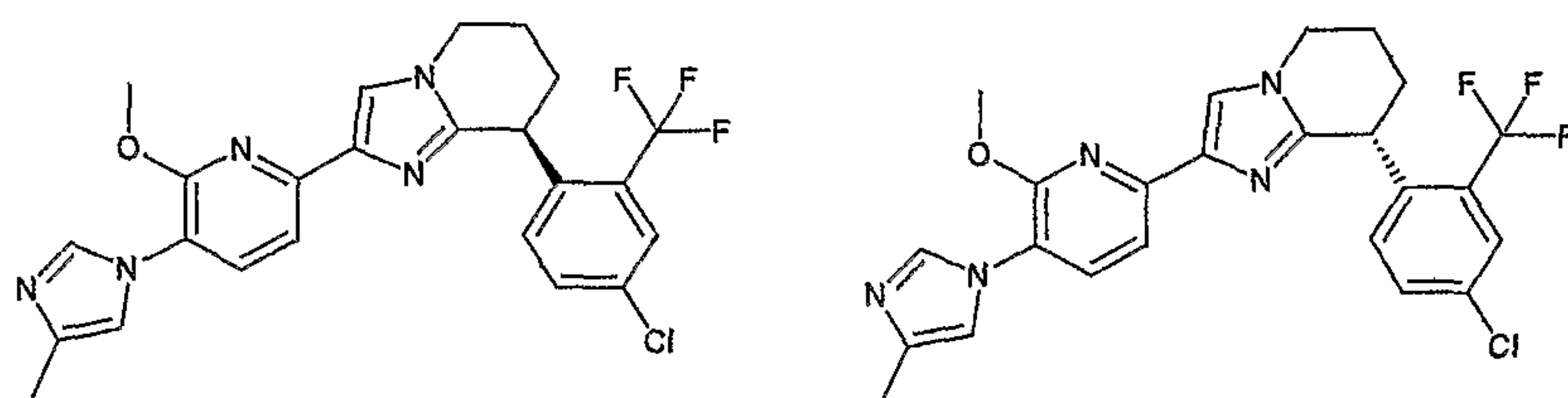
1H), 4.03 (s, 3H), 4.17 (dd, J = 7.2, 4.8 Hz, 2H), 4.67 (dd, J = 8.0, 6.0 Hz, 1H), 6.93 (brs, 1H), 7.02 (dd, J = 8.4, 5.6 Hz, 1H), 7.14 (td, J = 8.4, 2.4 Hz, 1H), 7.41 (dd, J = 8.8, 2.4 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.74 (d, J = 1.2 Hz, 1H).

[0397]

5 Examples 108 and 109

Synthesis of (-)-8-(4-chloro-2-trifluoromethylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine and (+)-8-(4-chloro-2-trifluoromethylphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

10 [0398]



[0399]

A racemate of the title compound was obtained according to the method of Examples 100 and 101 from ethyl 2-(4-chloro-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride obtained in Preparation Example 3-20 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAK™ IA (2 cm × 25 cm; mobile phase: 40% isopropanol-hexane) to obtain the title optically active compound with a retention time of 12 minutes and negative optical rotation (43.0 mg, >99% ee) and the title optically active compound with a retention time of 22 minutes and positive optical rotation (41.2 mg, >98% ee).

20 The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 488 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 1.82-1.95 (m, 1H), 2.00-2.22 (m, 2H), 2.29 (s, 3H), 2.35-2.45 (m, 1H), 4.03 (s, 3H), 4.17 (dd, J = 6.8, 5.2 Hz, 2H), 4.67 (dd, J = 8.0, 6.0 Hz, 1H), 6.93 (brs, 1H), 6.98 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 8.4, 2.4 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.74 (d, J = 1.2 Hz, 1H).

[0400]

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 488 [$M^+ + H$].

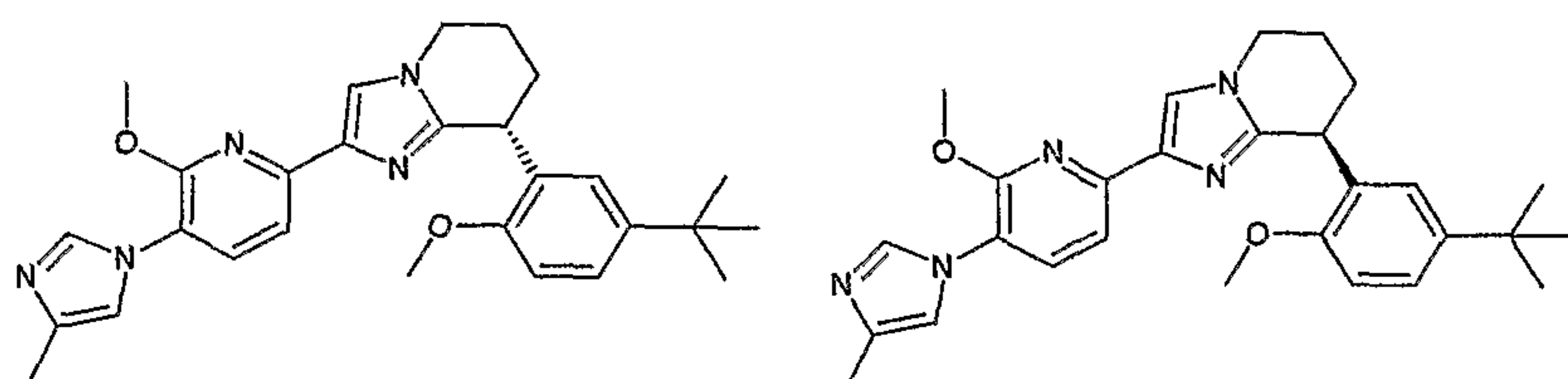
^1H -NMR ($CDCl_3$) δ (ppm): 1.82-1.95 (m, 1H), 2.00-2.22 (m, 2H), 2.29 (s, 3H), 2.35-2.45 (m, 1H), 4.03 (s, 3H), 4.17 (dd, $J = 6.8, 5.2$ Hz, 2H), 4.67 (dd, $J = 8.0, 6.0$ Hz, 1H), 6.93 (brs, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 7.40 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.54 (s, 1H), 7.69 (d, $J = 2.4$ Hz, 1H), 7.74 (d, $J = 1.2$ Hz, 1H).

[0401]

Examples 110 and 111

Synthesis of (+)-8-(5-tert-butyl-2-methoxyphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine and (-)-8-(5-tert-butyl-2-methoxyphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

[0402]



[0403]

A racemate of the title compound was obtained according to the method of Examples 100 and 101 from ethyl 2-(5-tert-butyl-2-methoxyphenyl)-5-chloropentanimidate hydrochloride obtained in Preparation Example 3-3 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALPAKTM IA (2 cm $\times$ 25 cm; mobile phase: 15% isopropanol-hexane) to obtain the title optically active compound with a retention time of 14 minutes and positive optical rotation and the title optically active compound with a retention time of 26 minutes and negative optical rotation.

The respective optically active compounds were purified by CHIRALPAKTM IA (2 cm $\times$ 25 cm; mobile phase: 15% ethanol-hexane) to obtain the title optically active compound with positive optical rotation (14.5 mg, >99% ee) and the title optically active compound with negative optical rotation (14.5 mg, >99% ee).

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 472 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.21 (s, 9H), 1.90-2.35 (m, 4H), 2.29 (s, 3H), 3.78 (s, 3H), 4.00-

4.20 (m, 2H), 4.05 (s, 3H), 4.63 (t, $J = 6.0$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 1H), 6.86 (d, $J = 2.4$ Hz, 1H), 6.94 (s, 1H), 7.22 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.55 (s, 1H), 7.74 (s, 1H).

[0404]

5 The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 472 [$M^+ + H$].

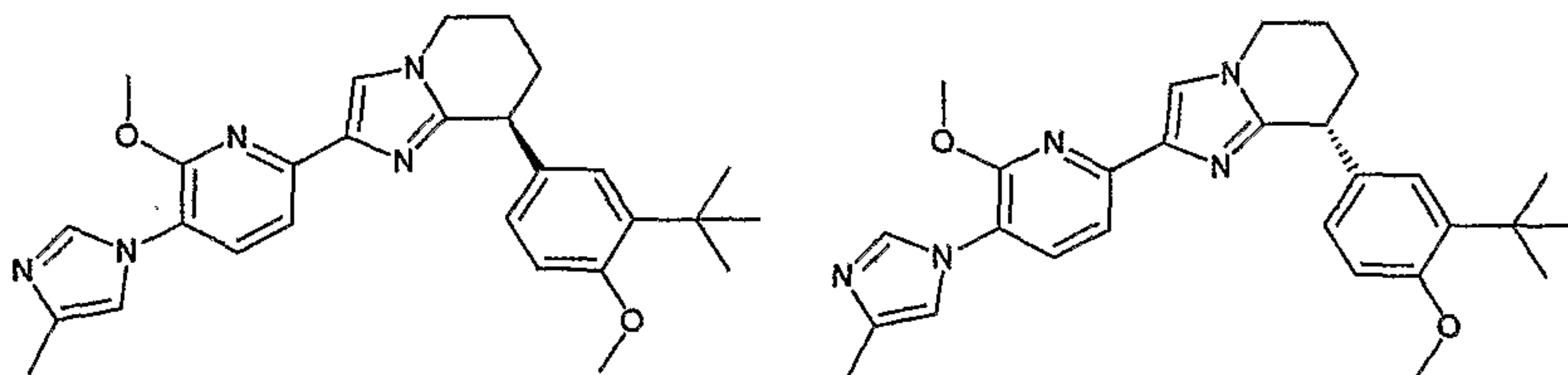
$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.21 (s, 9H), 1.90-2.35 (m, 4H), 2.29 (s, 3H), 3.78 (s, 3H), 4.00-4.20 (m, 2H), 4.05 (s, 3H), 4.63 (t, $J = 6.0$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 1H), 6.86 (d, $J = 2.4$ Hz, 1H), 6.94 (s, 1H), 7.22 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.55 (s, 1H), 7.74 (s, 1H).

[0405]

Examples 112 and 113

15 Synthesis of (-)-8-(3-tert-butyl-4-methoxyphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine and (+)-8-(3-tert-butyl-4-methoxyphenyl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

[0406]



[0407]

20 A racemate of the title compound was obtained according to the method of Examples 100 and 101 from the imidate hydrochloride obtained in Preparation Example 3-8 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was roughly purified by CHIRALPAKTM IB (2 cm $\times$ 25 cm; mobile phase: 20% ethanol-hexane). Then, the racemate was separated by CHIRALPAKTM IB (2 cm $\times$ 25 cm; 25 mobile phase: 10% ethanol-hexane) to obtain the title optically active compound with a retention time of 16 minutes and negative optical rotation and the title optically active compound with a retention time of 18 minutes and positive optical rotation (22.7 mg, >99% ee).

The title optically active compound with negative optical rotation was purified again by CHIRALPAKTM IA (2 cm $\times$ 25 cm; mobile phase: 25% isopropanol-hexane) to obtain

the title optically active compound with negative optical rotation (18.5 mg, >99% ee).

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 472 [$M^+ + H$].

- 5 ^1H -NMR ($CDCl_3$) δ (ppm): 1.35 (s, 9H), 1.90-2.15 (m, 3H), 2.25-2.35 (m, 1H), 2.29 (d, $J = 1.2$ Hz, 3H), 3.80 (s, 3H), 4.03-4.20 (m, 2H), 4.04 (s, 3H), 4.33 (t, $J = 5.6$ Hz, 1H), 6.77 (d, $J = 8.4$ Hz, 1H), 6.80 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.94 (t, $J = 1.2$ Hz, 1H), 7.13 (d, $J = 2.4$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.54 (s, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 1.2$ Hz, 1H).

[0408]

- 10 The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 472 [$M^+ + H$].

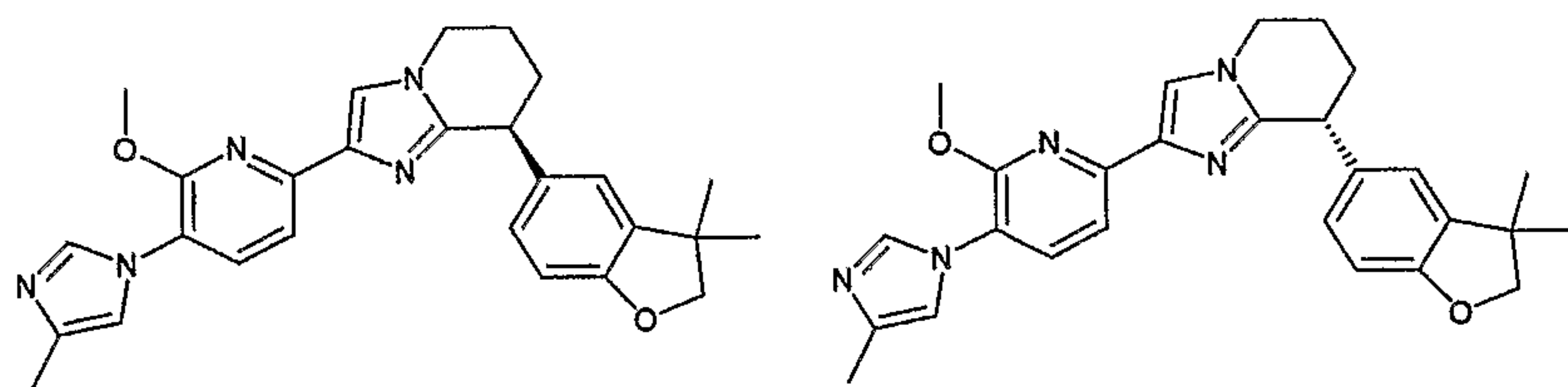
- ^1H -NMR ($CDCl_3$) δ (ppm): 1.35 (s, 9H), 1.90-2.15 (m, 3H), 2.25-2.35 (m, 1H), 2.29 (d, $J = 1.2$ Hz, 3H), 3.80 (s, 3H), 4.03-4.20 (m, 2H), 4.04 (s, 3H), 4.33 (t, $J = 5.6$ Hz, 1H), 6.77 (d, $J = 8.4$ Hz, 1H), 6.80 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.94 (t, $J = 1.2$ Hz, 1H), 7.13 (d, $J = 2.4$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.54 (s, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 1.2$ Hz, 1H).

[0409]

Examples 114 and 115

- 20 Synthesis of (-)-8-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine and (+)-8-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

[0410]



[0411]

- 25 A racemate of the title compound was obtained according to the method of Examples 100 and 101 from the imidate hydrochloride obtained in Preparation Example 3-2 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The resulting racemate was separated by CHIRALCELTM OD-H (2 cm $\times$ 25 cm; mobile phase: 25% isopropyl alcohol-hexane) to obtain the title optically active compound with a retention time of

10 minutes and negative optical rotation and the title optically active compound with a retention time of 16 minutes and positive optical rotation (22.5 mg, >99% ee).

The title optically active compound with negative optical rotation was purified again by CHIRALPAK™ IA (2 cm × 25 cm; mobile phase: 30% ethanol-hexane) to obtain the
5 title optically active compound with negative optical rotation (19.8 mg, >99% ee).

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 456 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 1.31 (s, 6H), 1.90-2.16 (m, 3H), 2.25-2.36 (m, 1H), 2.29 (s, 3H),
10 4.04 (s, 3H), 4.05-4.21 (m, 2H), 4.22 (s, 2H), 4.34 (t, J = 6.0 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H),
6.88 (dd, J = 8.4, 1.6 Hz, 1H), 6.91 (d, J = 1.6 Hz, 1H), 6.94 (brs, 1H), 7.49 (d, J = 8.0 Hz, 1H),
7.55 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.75 (brs, 1H).

[0412]

The property values of the title compound with positive optical rotation are as
15 follows.

ESI-MS; m/z 456 [M⁺ + H].

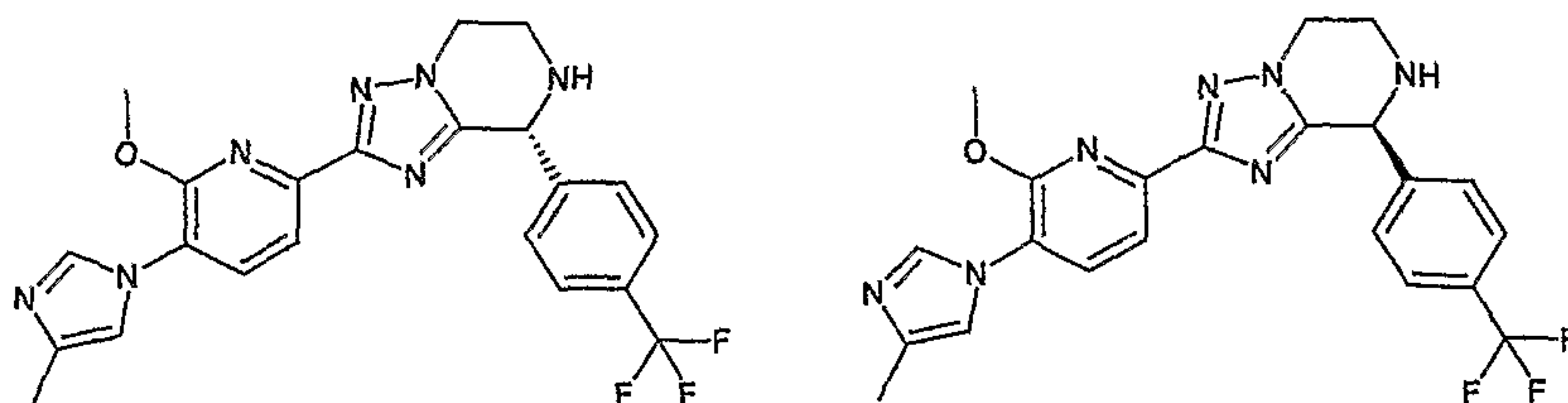
¹H-NMR (CDCl₃) δ (ppm): 1.31 (s, 6H), 1.90-2.16 (m, 3H), 2.25-2.36 (m, 1H), 2.29 (s, 3H),
4.04 (s, 3H), 4.05-4.21 (m, 2H), 4.22 (s, 2H), 4.34 (t, J = 6.0 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H),
6.88 (dd, J = 8.4, 1.6 Hz, 1H), 6.91 (d, J = 1.6 Hz, 1H), 6.94 (brs, 1H), 7.49 (d, J = 8.0 Hz, 1H),
20 7.55 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.75 (brs, 1H).

[0413]

Examples 116 and 117

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-
trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine and (-)-2-[6-methoxy-5-
25 (4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-
tetrahydro[1,2,4]triazolo[1,5-a]pyrazine

[0414]



[0415]

Acetic acid (1 mL) and 20% palladium hydroxide-carbon (400 mg) were added to a solution of 7-benzyl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine obtained in Examples 84 and 85 (411 mg) in methanol (40 mL), and the mixture was stirred at room temperature in a hydrogen atmosphere for two days. After the reaction atmosphere was replaced with nitrogen, ethyl acetate was added to the reaction solution. The mixture was filtered through celite and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: ChromatorexTM NH, elution solvent: ethyl acetate) to obtain 290 mg of a racemate of the title compound. The resulting racemate of the title compound (36 mg) was separated by CHIRALPAKTM IA (2 cm × 25 cm, mobile phase: hexane:ethanol = 1:1, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 8.5 minutes resulting from analysis by CHIRALPAKTM IA (Lot. IA00CE-FA020, hexane:ethanol = 1:1, 1.0 mL/min) and positive optical rotation (10 mg, >99% ee) and the title optically active compound with a retention time of 16.0 minutes resulting from the same analysis and negative optical rotation (11 mg, >99% ee).

The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 456 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H), 3.36-3.49 (m, 2H), 4.16 (s, 3H), 4.34-4.46 (m, 2H), 5.42 (s, 1H), 7.00 (s, 1H), 7.58-7.66 (m, 5H), 7.78 (d, J = 7.6 Hz, 1H), 7.83 (s, 1H).

[0416]

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 456 [M⁺ + H].

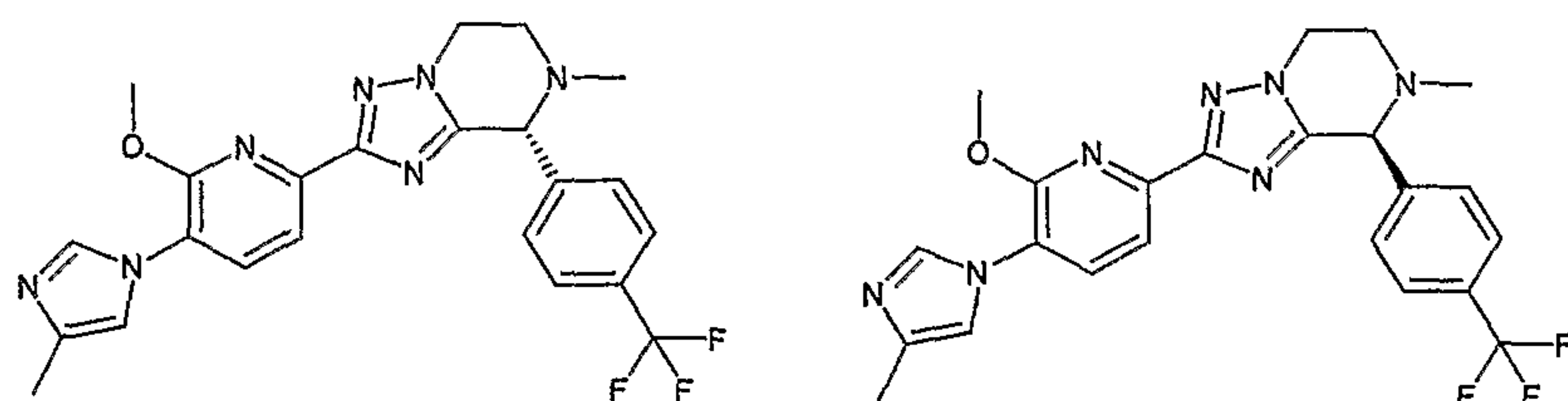
¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H), 3.36-3.49 (m, 2H), 4.16 (s, 3H), 4.34-4.46 (m, 2H), 5.42 (s, 1H), 7.00 (t, J = 1.2 Hz, 1H), 7.58-7.66 (m, 5H), 7.78 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 1.6 Hz, 1H).

[0417]

Examples 118 and 119

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-7-methyl-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-7-methyl-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine

[0418]



[0419]

A 37% formaldehyde solution (2 mL) was added to a solution of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine obtained in Examples 116 and 117 (54 mg) in formic acid (2 mL), and the mixture was stirred with heating under reflux for 3.5 hours. The reaction solution was neutralized with a saturated sodium bicarbonate solution at 0°C and partitioned with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: ChromatorexTM NH, elution solvent: heptane acetate:ethyl acetate = 1:1 -> 0:1) to obtain 24 mg of a racemate of the title compound. The resulting racemate of the title compound was separated by CHIRALPAKTM IA (2 cm × 25 cm, mobile phase: hexane:ethanol = 6:4, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 6.6 minutes resulting from analysis by CHIRALPAKTM IA (Lot. IA00CE-FA020, hexane:ethanol = 1:1, 1.0 mL/min) and positive optical rotation (6.5 mg, >99% ee) and the title optically active compound with a retention time of 15.2 minutes resulting from the same analysis and negative optical rotation (7.5 mg, >99% ee).

The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 470 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 2.29 (s, 3H), 2.38 (s, 3H), 3.03 (ddd, J = 4.4, 9.6, 12.8 Hz, 1H), 3.34 (ddd, J = 2.8, 4.4, 12.4 Hz, 1H), 4.14 (s, 3H), 4.41-4.54 (m, 2H), 4.59 (s, 1H), 6.98 (t, J = 1.2, 1H), 7.53 (d, J = 9.2 Hz, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 1.2 Hz, 1H).

[0420]

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 470 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 2.29 (s, 3H), 2.38 (s, 3H), 3.03 (ddd, J = 4.4, 9.6, 12.8 Hz, 1H), 3.34

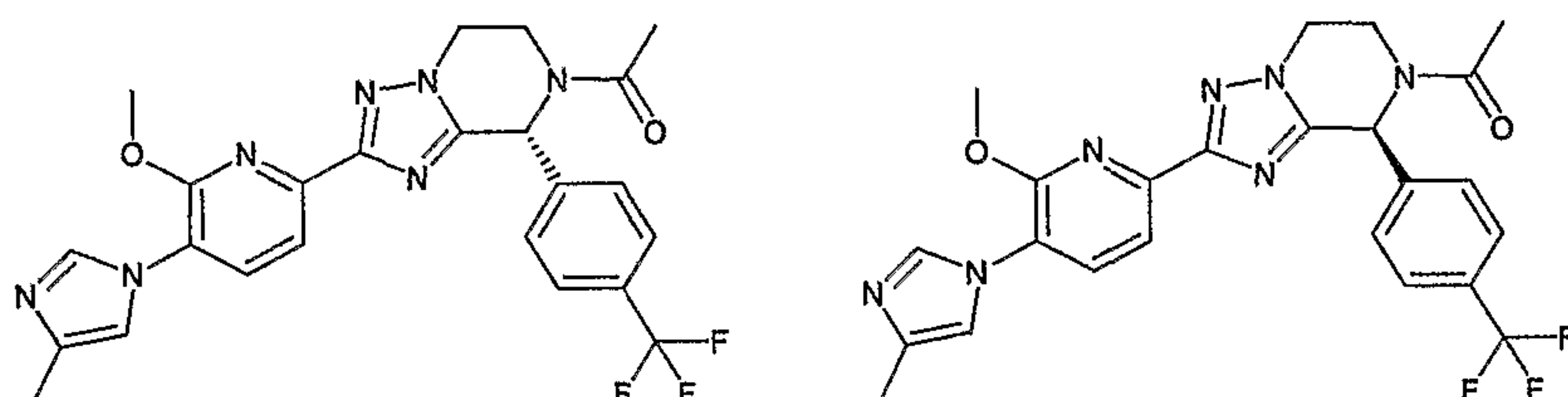
(ddd, $J = 2.8, 4.4, 12.4$ Hz, 1H), 4.14 (s, 3H), 4.41-4.54 (m, 2H), 4.59 (s, 1H), 6.98 (t, $J = 1.2$, 1H), 7.53 (d, $J = 9.2$ Hz, 2H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.65 (d, $J = 8.4$ Hz, 2H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H).

[0421]

5 Examples 120 and 121

Synthesis of (+)-1-[2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6-dihydro-8H-[1,2,4]triazolo[1,5-a]pyrazin-7-yl]ethanone and (-)-1-[2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6-dihydro-8H-[1,2,4]triazolo[1,5-a]pyrazin-7-yl]ethanone

10 [0422]



[0423]

Pyridine (31.3 μ L) and acetic anhydride (14.5 μ L) were added to a solution of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine obtained in Examples 116 and 117 (35 mg) in dichloromethane (1 mL) at 0°C, and the mixture was stirred at room temperature for 1.5 hours. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: ChromatorexTM NH; elution solvent: ethyl acetate:methanol = 1:0 $\rightarrow$ 9:1) to obtain a racemate of the title compound. The resulting racemate of the title compound was separated by CHIRALPAKTM IB (2 cm $\times$ 25 cm, mobile phase: hexane:ethanol = 65:35, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 6.95 minutes resulting from analysis by CHIRALPAKTM IB (Lot. IB00CD-FD025, hexane:ethanol = 8:2, 1.0 mL/min) and positive optical rotation (6.3 mg, >99% ee) and the title optically active compound with a retention time of 8.25 minutes resulting from the same analysis and negative optical rotation (7.4 mg, >99% ee).

The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 498 [$M^+ + H$].

¹H-NMR (CD₃OD) δ (ppm): 2.25 (s, 3H), 2.33 (s, 3H), 3.74-3.81 (m, 1H), 4.13 (s, 3H), 4.37-

4.51 (m, 3H), 7.16 (s, 1H), 7.22 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H).

[0424]

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 498 [M⁺ + H].

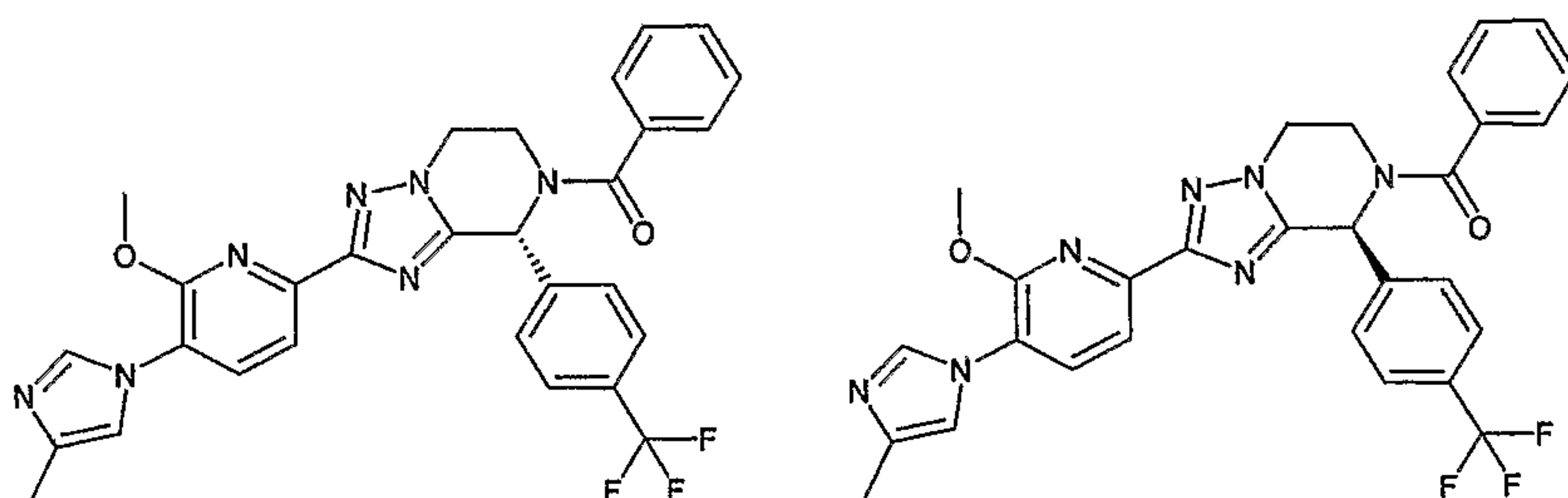
¹H-NMR (CD₃ OD) δ (ppm): 2.25 (s, 3H), 2.33 (s, 3H), 3.74-3.81 (m, 1H), 4.13 (s, 3H), 4.37-4.51 (m, 3H), 7.16 (s, 1H), 7.22 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H).

[0425]

Examples 122 and 123

Synthesis of (+)-[2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6-dihydro-8H-[1,2,4]triazolo[1,5-a]pyrazin-7-yl]phenylmethanone and (-)-[2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6-dihydro-8H-[1,2,4]triazolo[1,5-a]pyrazin-7-yl]phenylmethanone

[0426]



[0427]

A racemate of the title compound was obtained according to the method of Examples 120 and 121 from 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine obtained in Examples 116 and 117. The resulting racemate of the title compound was separated by CHIRALPAKTM IA (2 cm × 25 cm, mobile phase: ethanol, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 7.5 minutes resulting from analysis by CHIRALPAKTM IA (Lot. IA00CE-FA020, ethanol, 1.0 mL/min) and negative optical rotation (6.5 mg, >99% ee) and the title optically active compound with a retention time of 14.4 minutes resulting from the same analysis and positive optical rotation (10.9 mg, >99% ee).

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 560 $[M^+ + H]$.

^1H -NMR ($CDCl_3$) δ (ppm): 2.31 (s, 3H), 3.53-3.65 (m, 2H), 4.17 (s, 3H), 4.40-4.42 (m, 2H), 7.03 (s, 1H), 7.46-7.23 (m, 6H), 7.64-7.68 (m, 5H), 7.85-7.86 (m, 2H).

[0428]

5 The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 560 $[M^+ + H]$.

^1H -NMR ($CDCl_3$) δ (ppm): 2.31 (s, 3H), 3.53-3.65 (m, 2H), 4.17 (s, 3H), 4.40-4.42 (m, 2H), 7.03 (s, 1H), 7.46-7.23 (m, 6H), 7.64-7.68 (m, 5H), 7.85-7.86 (m, 2H).

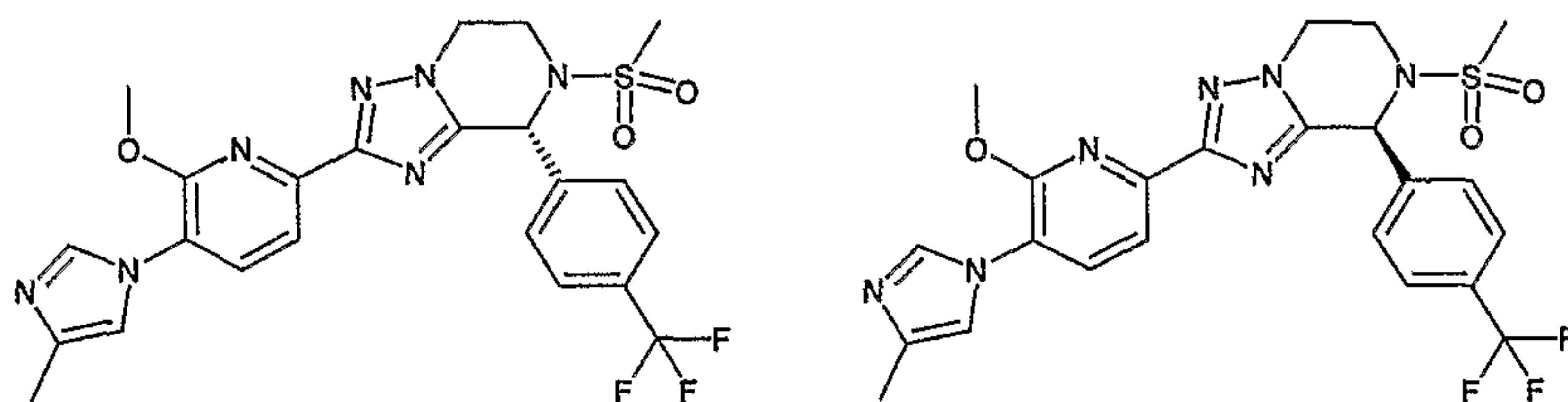
10 [0429]

Examples 124 and 125

Synthesis of (+)-7-methanesulfonyl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine and (-)-7-methanesulfonyl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine

15 trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine

[0430]



[0431]

A racemate of the title compound was obtained according to the method of Examples 120 and 121 from 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine obtained in Examples 116 and 117. The resulting racemate of the title compound was separated by CHIRALPAKTM IB (2 cm $\times$ 25 cm, mobile phase: hexane:ethanol = 65:35, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 7.95 minutes resulting from analysis by CHIRALPAKTM IB (Lot. IB00CD-FD025, hexane:ethanol = 8:2, 1.0 mL/min) and positive optical rotation (16 mg, >99% ee) and the title optically active compound with a retention time of 8.99 minutes resulting from the same analysis and negative optical rotation (14.8 mg, >99% ee).

The property values of the title optically active compound with positive optical

rotation are as follows.

ESI-MS; m/z 534 $[M^+ + H]$.

^1H -NMR ($CDCl_3$) δ (ppm): 2.31 (s, 3H), 2.91 (s, 3H), 3.59 (ddd, $J = 5.2, 11.2, 14.8$ Hz, 1H), 4.17 (s, 3H), 4.25-4.30 (m, 1H), 4.45-4.52 (m, 2H), 6.52 (s, 1H), 7.03 (t, $J = 1.2$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 1.2$ Hz, 1H).

[0432]

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 534 $[M^+ + H]$.

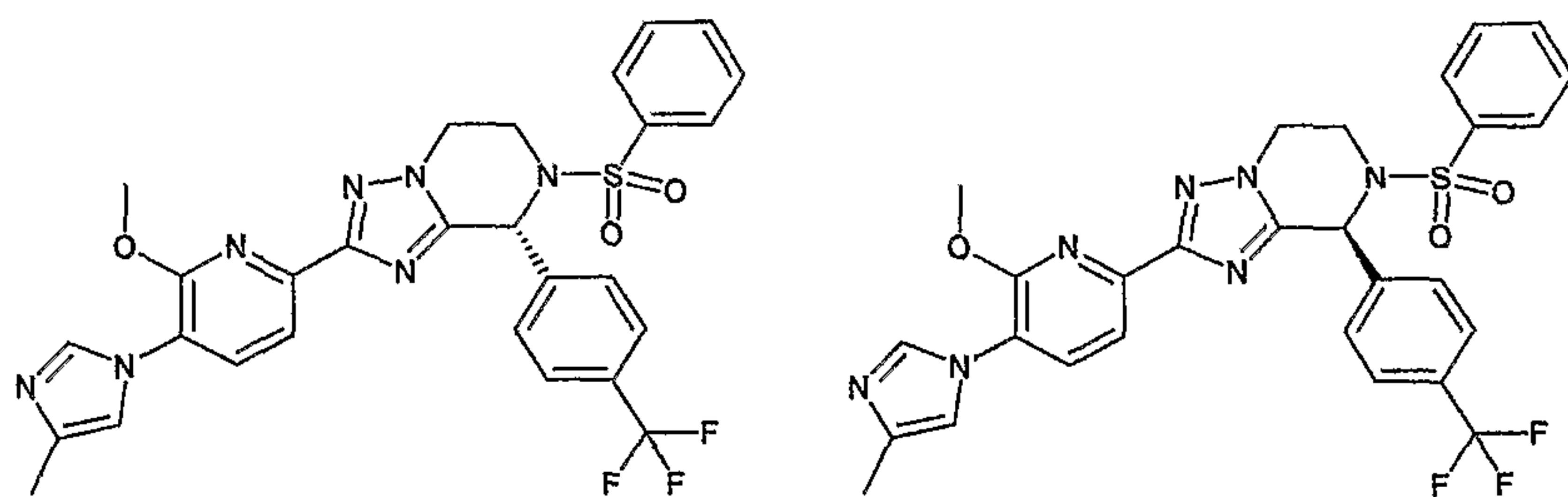
^1H -NMR ($CDCl_3$) δ (ppm): 2.31 (s, 3H), 2.91 (s, 3H), 3.59 (ddd, $J = 5.2, 11.2, 14.8$ Hz, 1H), 4.17 (s, 3H), 4.25-4.30 (m, 1H), 4.45-4.52 (m, 2H), 6.52 (s, 1H), 7.03 (t, $J = 1.2$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 1.2$ Hz, 1H).

[0433]

Examples 126 and 127

Synthesis of (+)-7-benzenesulfonyl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine and (-)-7-benzenesulfonyl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine

[0434]



[0435]

A racemate of the title compound was obtained according to the method of Examples 120 and 121 from 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyrazine obtained in Examples 116 and 117. The resulting racemate of the title compound was separated by CHIRALPAKTM IA (2 cm $\times$ 25 cm, mobile phase: hexane:ethanol = 6:4, flow rate: 15 mL/min) to obtain the title

optically active compound with a retention time of 9.5 minutes resulting from analysis by CHIRALPAK™ IA (Lot. IA00CE-FA020, hexane:ethanol = 1:1, 1.0 mL/min) (11.4 mg, >99% ee) and the title optically active compound with a retention time of 12.9 minutes resulting from the same analysis (16.6 mg, >99% ee).

5 The property values of the title optically active compound with a retention time of 9.5 minutes under the analysis conditions are as follows.

ESI-MS; m/z 596 [M⁺ + H].

¹H-NMR (CDCl₃) δ (ppm): 2.31 (s, 3H), 3.52 (ddd, J = 4.4, 12.0, 15.2 Hz, 1H), 3.98 (dt, J = 5.2, 12.8 Hz, 1H), 4.15 (s, 3H), 4.21 (dd, J = 4.0, 131.2 Hz, 1H), 4.30 (dd, J = 5.2, 15.2 Hz, 1H), 6.62
10 (s, 1H), 7.02 (t, J = 1.2 Hz, 1H), 7.45-7.49 (m, 4H), 7.57-7.62 (m, 3H), 7.64 (d, J = 8.0 Hz, 1H), 7.82-7.86 (m, 4H).

[0436]

The property values of the title optically active compound with a retention time of 12.9 minutes under the analysis conditions are as follows.

15 ESI-MS; m/z 596 [M⁺ + H].

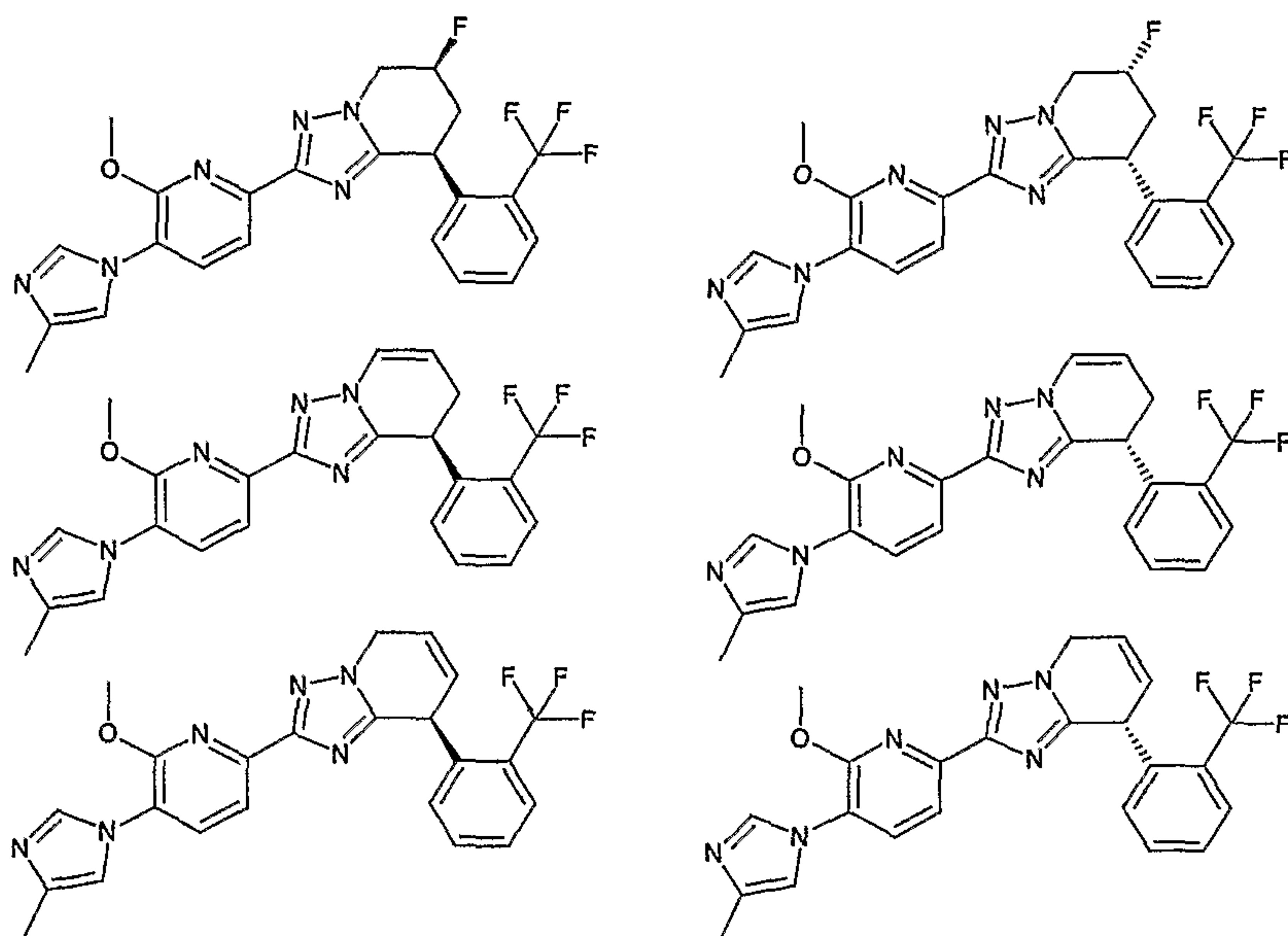
¹H-NMR (CDCl₃) δ (ppm): 2.31 (s, 3H), 3.52 (ddd, J = 4.4, 12.0, 15.2 Hz, 1H), 3.98 (dt, J = 5.2, 12.8 Hz, 1H), 4.15 (s, 3H), 4.21 (dd, J = 4.0, 131.2 Hz, 1H), 4.30 (dd, J = 5.2, 15.2 Hz, 1H), 6.62
(s, 1H), 7.02 (t, J = 1.2 Hz, 1H), 7.45-7.49 (m, 4H), 7.57-7.62 (m, 3H), 7.64 (d, J = 8.0 Hz, 1H), 7.82-7.86 (m, 4H).

20 [0437]

Examples 128, 129, 130, 131, 132 and 133

Synthesis of (+)-(6,8-syn)-6-fluoro-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-(6,8-syn)-6-fluoro-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-7,8-dihydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-7,8-dihydro[1,2,4]triazolo[1,5-a]pyridine and (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,8-dihydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,8-dihydro[1,2,4]triazolo[1,5-a]pyridine
25
30

[0438]



[0439]

2-[6-Methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-6-ol obtained in Example 5 26 (100 mg) was dissolved in methylene chloride (1 mL), and [bis(2-methoxyethyl)amino]sulfur trifluoride (78.5 μ L) was added at room temperature. After stirring for 24 hours, the reaction solution was partitioned with a saturated sodium bicarbonate solution and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and then concentrated under reduced pressure. Purification by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 100%) gave a mixture of a fluorinated compound and two olefin compounds (48.7 mg). The mixture was separated by CHIRALPAKTM AD-H (2 cm $\times$ 25 cm, mobile phase: ethanol:hexane = 3:7, flow rate: 15 mL/min) to obtain a 7,8-dihydro compound with a retention time of 11.8 minutes and positive optical rotation (1.6 mg) and a 7,8-dihydro compound with a retention time of 14.1 minutes and negative optical rotation (1.7 mg), and a 15 fluorinated compound with a retention time of 23.0 minutes and positive optical rotation (2.7 mg) and a fluorinated compound with a retention time of 26.3 minutes and negative optical rotation (3.9 mg). At this time, the 5,8-dihydro compound was recovered as a racemate with a retention time of 15.5 minutes. The racemate was separated by CHIRALPAKTM IA (2 cm $\times$ 25 cm, mobile phase: ethanol:hexane = 4:6, flow rate: 13 mL/min) to obtain a 5,8-dihydro 20 compound with a retention time of 13.4 minutes and positive optical rotation (3.3 mg) and a 5,8-dihydro compound with a retention time of 16.1 minutes and negative optical rotation (2.3 mg).

The property values of the title optically active compound obtained from the

fluorinated compound with a retention time of 23.0 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.29 (s, 3H), 2.52 (ddd, J = 14.8, 14.8, 7.4 Hz, 1H), 2.64-2.80 (m, 1H), 4.15 (s, 3H), 4.59-4.75 (m, 2H), 4.91 (dd, J = 7.0, 7.0 Hz, 1H), 5.25-5.43 (m, 1H), 6.98-7.00 (m, 1H), 7.03 (d, J = 6.6 Hz, 1H), 7.37-7.42 (m, 1H), 7.43-7.48 (m, 1H), 7.57 (d, J = 7.8 Hz, 1H),
5 7.73 (d, J = 6.6 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H).
[0440]

The property values of the title optically active compound obtained from the fluorinated compound with a retention time of 26.3 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.29 (s, 3H), 2.52 (ddd, J = 14.8, 14.8, 7.4 Hz, 1H), 2.64-2.80 (m, 1H), 4.15 (s, 3H), 4.59-4.75 (m, 2H), 4.91 (dd, J = 7.0, 7.0 Hz, 1H), 5.25-5.43 (m, 1H), 6.98-7.00 (m, 1H), 7.03 (d, J = 6.6 Hz, 1H), 7.37-7.42 (m, 1H), 7.43-7.48 (m, 1H), 7.57 (d, J = 7.8 Hz, 1H),
10 7.73 (d, J = 6.6 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H).
[0441]

The property values of the title optically active compound obtained from the 7,8-dihydro compound with a retention time of 11.8 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.29 (s, 3H), 2.59-2.69 (m, 1H), 2.95-3.05 (m, 1H), 4.16 (s, 3H), 4.95 (dd, J = 9.0, 9.0 Hz, 1H), 5.72 (ddd, J = 7.8, 3.9, 3.9 Hz, 1H), 6.90-7.05 (m, 1H), 7.26-7.35 (m, 2H), 7.40-7.45 (m, 1H), 7.49-7.56 (m, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 6.6 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H).
20 [0442]

The property values of the title optically active compound obtained from the 7,8-dihydro compound with a retention time of 14.1 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.29 (s, 3H), 2.59-2.69 (m, 1H), 2.95-3.05 (m, 1H), 4.16 (s, 3H), 4.95 (dd, J = 9.0, 9.0 Hz, 1H), 5.72 (ddd, J = 7.8, 3.9, 3.9 Hz, 1H), 6.90-7.05 (m, 1H), 7.26-7.35 (m, 2H), 7.40-7.45 (m, 1H), 7.49-7.56 (m, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 6.6 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H).
25 [0443]

The property values of the title optically active compound obtained from the 5,8-dihydro compound with a retention time of 13.4 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.29 (s, 3H), 4.16 (s, 3H), 5.00 (dd, J = 17.5, 6.6 Hz, 1H), 5.10 (dd, J = 17.5, 4.7 Hz, 1H), 5.35-5.41 (m, 1H), 6.06 (s, 2H), 6.91 (d, J = 7.4 Hz, 1H), 6.97-7.05 (m, 1H), 7.34-7.46 (m, 2H), 7.57 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.4 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H).
30 [0444]

The property values of the title optically active compound obtained from the 5,8-dihydro compound with a retention time of 16.1 minutes are as follows.

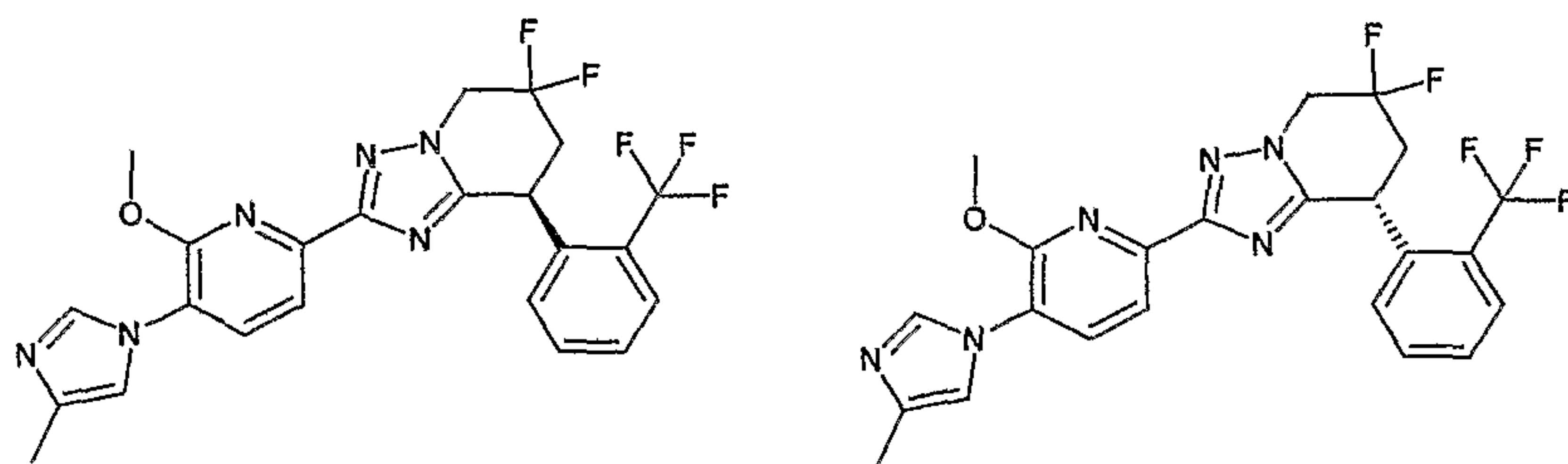
¹H-NMR (CDCl₃) δ (ppm): 2.29 (s, 3H), 4.16 (s, 3H), 5.00 (dd, J = 17.5, 6.6 Hz, 1H), 5.10 (dd, J = 17.5, 4.7 Hz, 1H), 5.35-5.41 (m, 1H), 6.06 (s, 2H), 6.91 (d, J = 7.4 Hz, 1H), 6.97-7.05 (m, 1H), 7.34-7.46 (m, 2H), 7.57 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.4 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H).

[0445]

Examples 134 and 135

Synthesis of (+)-6,6-difluoro-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-6,6-difluoro-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0446]



[0447]

Synthesis of 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-7,8-dihydro-[1,2,4]triazolo[1,5-a]pyridin-6-one

2-[6-Methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-6-ol obtained in Example 26 (125 mg) was dissolved in methylene chloride (3 mL), and Dess-Martin reagent (226 mg) was added at room temperature. After stirring for 30 minutes, the reaction solution was partitioned with a saturated sodium bicarbonate solution and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and then concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 100% → methanol/ethyl acetate = 10%) to obtain the title compound (28 mg).

ESI-MS; m/z 469 [M⁺ + H].

[0448]

Synthesis of (+)-6,6-difluoro-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-

trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-6,6-difluoro-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

A racemate of the title compound was obtained according to the method of

5 Examples 128, 129, 130, 131, 132 and 133 from 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-7,8-dihydro[1,2,4]triazolo[1,5-a]pyridin-6-one (20.6 mg). The resulting racemate (2.5 mg) was separated by CHIRALPAK™ IA (2 cm × 25 cm, mobile phase: ethanol:hexane = 3:7, flow rate: 15 mL/min) to obtain the title compound with a retention time of 22.5 minutes and positive optical rotation (1.4 mg) and the title compound
10 with a retention time of 28.5 minutes and negative optical rotation (0.7 mg). The property values of the title optically active compound with a retention time of 22.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.19-2.38 (m, 1H), 2.30 (s, 3H), 2.54-2.68 (m, 1H), 2.74-2.85 (m, 2H), 4.15 (s, 3H), 4.81 (dd, J = 7.8, 6.6 Hz, 1H), 6.99-7.06 (m, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.43-7.48 (m, 1H), 7.49-7.55 (m, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H).

[0449]

The property values of the title optically active compound with a retention time of 28.5 minutes are as follows.

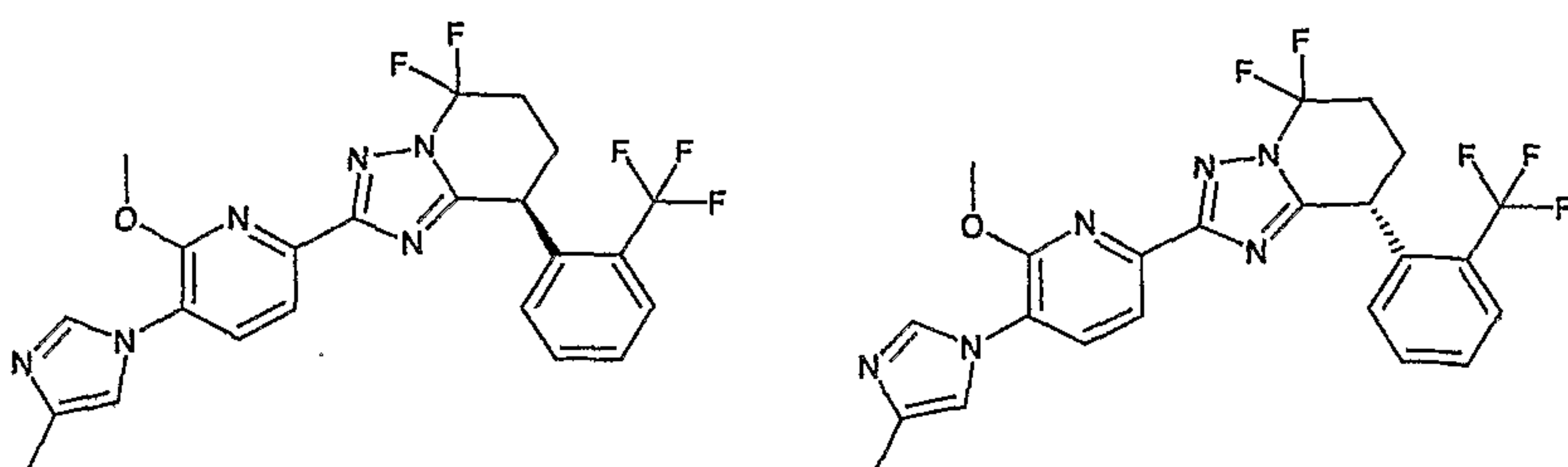
¹H-NMR (CDCl₃) δ (ppm): 2.19-2.38 (m, 1H), 2.30 (s, 3H), 2.54-2.68 (m, 1H), 2.74-2.85 (m, 2H), 4.15 (s, 3H), 4.81 (dd, J = 7.8, 6.6 Hz, 1H), 6.99-7.06 (m, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.43-7.48 (m, 1H), 7.49-7.55 (m, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H).

[0450]

Examples 136 and 137

25 Synthesis of (+)-5,5-difluoro-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-5,5-difluoro-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0451]



[0452]

A racemate of the title compound (15 mg) was obtained according to the method of Examples 134 and 135 from 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(2-trifluoromethylphenyl)-7,8-dihydro-6H-[1,2,4]triazolo[1,5-a]pyridin-5-one obtained in Example 72 (100 mg). The resulting racemate was separated by CHIRALPAK™ IB (2 cm × 25 cm, mobile phase: ethanol:hexane = 2:8, flow rate: 15 mL/min) to obtain the title compound with a retention time of 24.6 minutes and positive optical rotation (1.4 mg) and the title compound with a retention time of 28.5 minutes and negative optical rotation (1.6 mg).

The property values of the title optically active compound with a retention time of 24.6 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.22-2.28 (m, 1H), 2.30 (s, 3H), 2.52-2.67 (m, 2H), 2.74-2.85 (m, 1H), 4.15 (s, 3H), 4.23 (dd, J = 11.7, 11.7 Hz, 1H), 4.82 (dd, J = 7.8, 6.6 Hz, 1H), 6.95-7.01 (m, 1H), 7.05 (d, J = 7.8 Hz, 1H), 7.43-7.48 (m, 1H), 7.49-7.54 (m, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H).

[0453]

The property values of the title optically active compound with a retention time of 28.5 minutes are as follows.

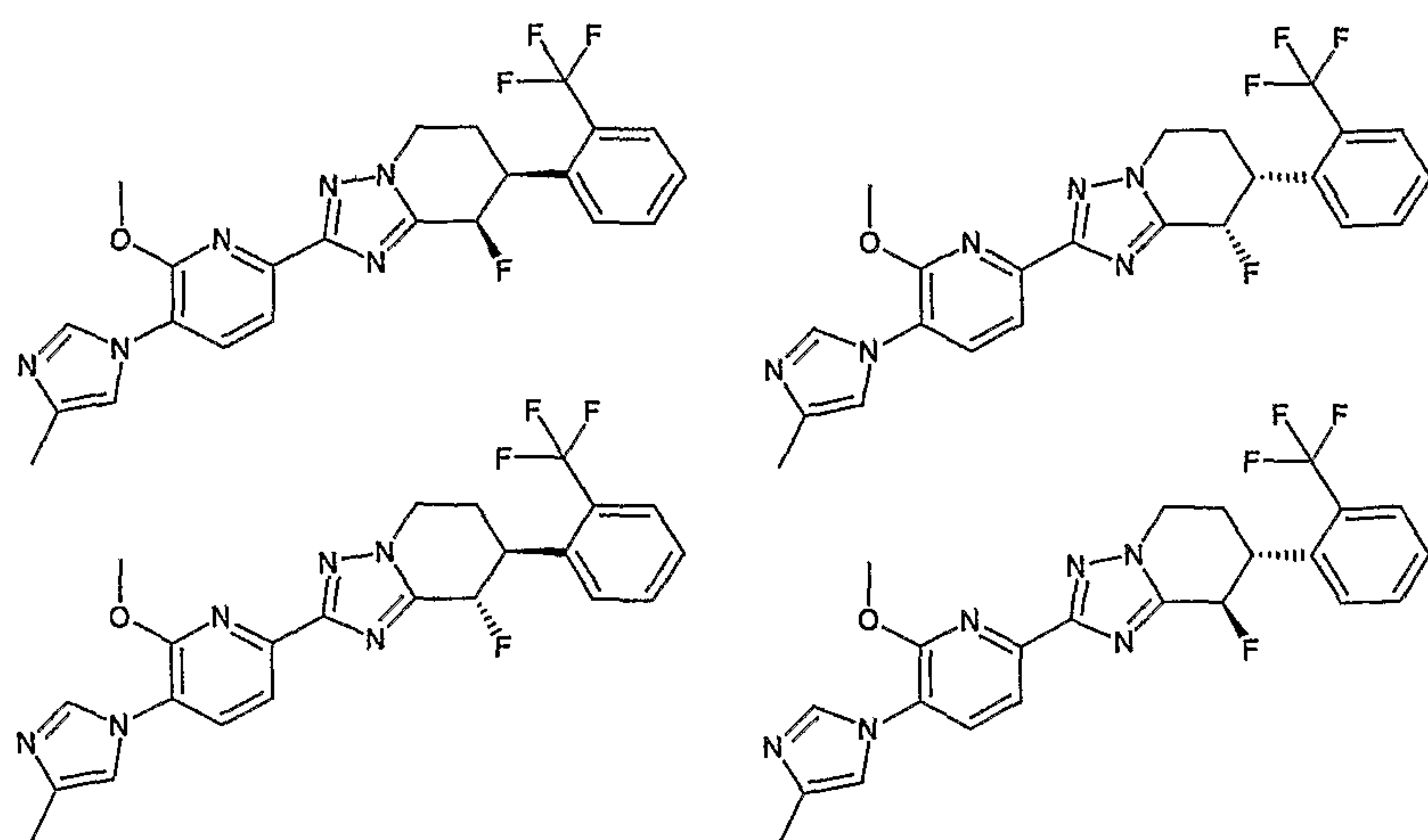
¹H-NMR (CDCl₃) δ (ppm): 2.22-2.28 (m, 1H), 2.30 (s, 3H), 2.52-2.67 (m, 2H), 2.74-2.85 (m, 1H), 4.15 (s, 3H), 4.23 (dd, J = 11.7, 11.7 Hz, 1H), 4.82 (dd, J = 7.8, 6.6 Hz, 1H), 6.95-7.01 (m, 1H), 7.05 (d, J = 7.8 Hz, 1H), 7.43-7.48 (m, 1H), 7.49-7.54 (m, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H).

[0454]

Examples 138, 139, 140 and 141

Synthesis of (+)-(7,8-syn)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-fluoro-7-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-(7,8-syn)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-fluoro-7-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (+)-(7,8-anti)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-fluoro-7-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-(7,8-anti)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-fluoro-7-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0455]



[0456]

A solution of 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-7-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Examples 94 and 95 (50 mg) in tetrahydrofuran (1 mL) was added at 0°C to a lithium diisopropylamine
 5 solution prepared from n-butyllithium (93.1 μ L) and diisopropylamine (35 μ L) in tetrahydrofuran (1 mL). After stirring at the same temperature for 30 minutes, N-fluoro-N'-chloromethyltriethylenediamine bis(tetrafluoroborate) (90.2 mg) was added. After stirring 0°C for 50 minutes, the reaction temperature was raised to room temperature. After further 50 minutes, the reaction solution was partitioned with water and ethyl acetate. The organic layer
 10 was washed with brine and then dried over magnesium sulfate. The oil obtained by removal under reduced pressure was dissolved in methylene chloride (1.1 mL), followed by addition of [bis(2-methoxyethyl)amino]sulfur trifluoride (40.6 μ L). The by-product hydroxide was converted to a fluorinated compound.

The racemic syn-compound purified by silica gel column chromatography
 15 (mobile phase: ethyl acetate/heptane = 0 to 100%) (10.6 mg) was separated by CHIRALPAK™ AD-H (2 cm $\times$ 25 cm, mobile phase: ethanol:hexane = 2:8, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 33.0 minutes and negative optical rotation (1.1 mg) and the title optically active compound with a retention time of 46.0 minutes and positive optical rotation (0.6 mg). On the other hand, the racemic anti-compound (7.1 mg)
 20 was separated by CHIRALPAK™ IA (2 cm $\times$ 25 cm, mobile phase: ethanol:hexane = 2:8, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 42.5 minutes and positive optical rotation (0.68 mg) and the title optically active compound with a retention time of 61.0 minutes and negative optical rotation (0.44 mg). The property values of the title optically active compound obtained from the syn-compound with a retention time of

33.0 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.20-2.30 (m, 1H), 2.31 (s, 3H), 2.95-3.05 (m, 1H), 3.65-3.80 (m, 1H), 4.19 (s, 3H), 4.30-4.40 (m, 1H), 4.65-4.72 (m, 1H), 5.75 (dd, J = 49.2, 5.5 Hz, 1H), 6.92-6.94 (m, 1H), 7.46-7.51 (m, 1H), 6.61-7.71 (m, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.84-7.87 (m, 1H), 7.87 (d, J = 7.8 Hz, 1H).

[0457]

The property values of the title optically active compound obtained from the syn-compound with a retention time of 46.0 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.20-2.30 (m, 1H), 2.31 (s, 3H), 2.95-3.05 (m, 1H), 3.65-3.80 (m, 1H), 4.19 (s, 3H), 4.30-4.40 (m, 1H), 4.65-4.72 (m, 1H), 5.75 (dd, J = 49.2, 5.5 Hz, 1H), 6.92-6.94 (m, 1H), 7.46-7.51 (m, 1H), 6.61-7.71 (m, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.84-7.87 (m, 1H), 7.87 (d, J = 7.8 Hz, 1H).

[0458]

The property values of the title optically active compound obtained from the anti-compound with a retention time of 42.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.25-2.40 (m, 1H), 2.31 (s, 3H), 2.49-2.59 (m, 1H), 3.96-4.08 (m, 1H), 4.19 (s, 3H), 4.30-4.45 (m, 2H), 5.95 (dd, J = 50.0, 7.0 Hz, 1H), 7.03-7.05 (m, 1H), 7.20-7.23 (m, 1H), 7.44-7.49 (m, 1H), 7.56-7.61 (m, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.86-7.88 (m, 1H), 7.92 (d, J = 7.8 Hz, 1H).

[0459]

The property values of the title optically active compound obtained from the anti-compound with a retention time of 61.0 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.25-2.40 (m, 1H), 2.31 (s, 3H), 2.49-2.59 (m, 1H), 3.96-4.08 (m, 1H), 4.19 (s, 3H), 4.30-4.45 (m, 2H), 5.95 (dd, J = 50.0, 7.0 Hz, 1H), 7.03-7.05 (m, 1H), 7.20-7.23 (m, 1H), 7.44-7.49 (m, 1H), 7.56-7.61 (m, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.86-7.88 (m, 1H), 7.92 (d, J = 7.8 Hz, 1H).

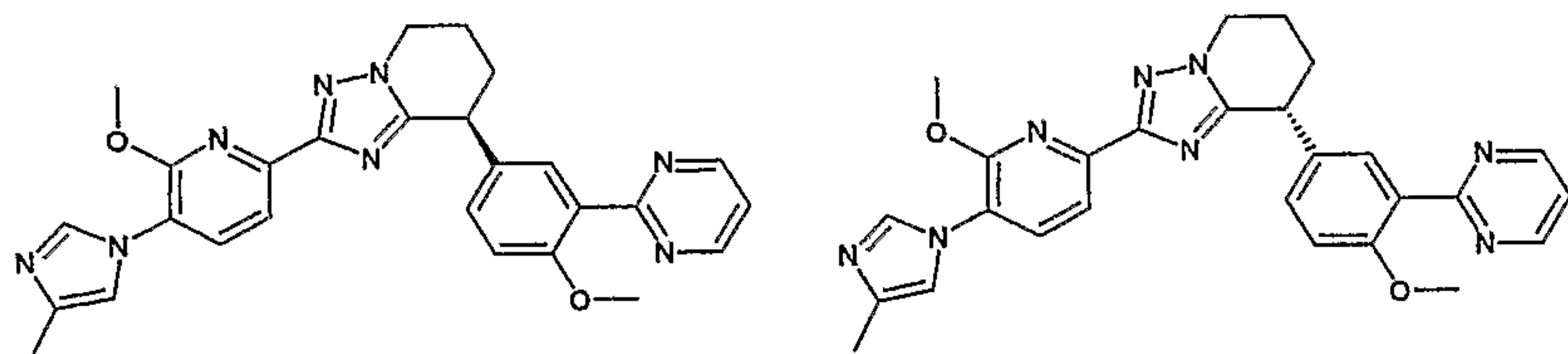
[0460]

Examples 142 and 143

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-methoxy-3-pyrimidin-2-ylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-methoxy-3-pyrimidin-2-ylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0461]

138



[0462]

2-[6-Methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-bromo-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Examples 68 and 69 (61 mg) was dissolved in N-methylpyrrolidone (1.5 mL). Palladium acetate (5.52 mg), 1,3-bis(diphenylphosphino)propane (20.3 mg), 2-tributylstannylpyrimidine (45.4 mg) and cuprous oxide (26.4 mg) were added and the reaction was initiated at 120°C. After 19 hours, the reaction solution was partitioned with ethyl acetate and water. The organic layer was washed with aqueous ammonia (twice) and brine. Concentration under reduced pressure gave an oil. The oil was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 100% -> methanol/ethyl acetate = 10%) to obtain a racemate of the title compound (33 mg). The resulting racemate was separated by CHIRALPAK™ IA (2 cm × 25 cm, mobile phase: ethanol:hexane = 8:2, flow rate: 10 mL/min) to obtain the title compound with a retention time of 38 minutes and positive optical rotation (8.2 mg) and the title compound with a retention time of 57.6 minutes and negative optical rotation (7.8 mg).

The property values of the title optically active compound with a retention time of 38 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.02-2.28 (m, 3H), 2.30 (s, 3H), 2.34-2.43 (m, 1H), 3.87 (s, 3H), 4.16 (s, 3H), 4.34-4.46 (m, 3H), 6.96-7.13 (m, 2H), 7.16-7.25 (m, 2H), 7.55 (d, J = 2.3 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 2.3 Hz, 1H), 8.84 (d, J = 5.0 Hz, 2H).

[0463]

The property values of the title optically active compound with a retention time of 57.6 minutes are as follows.

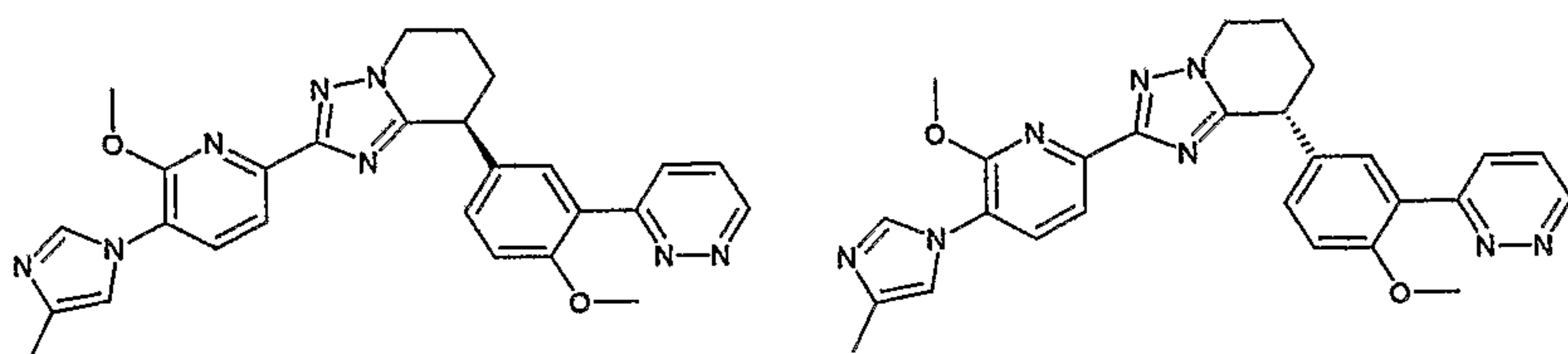
¹H-NMR (CDCl₃) δ (ppm): 2.02-2.28 (m, 3H), 2.30 (s, 3H), 2.34-2.43 (m, 1H), 3.87 (s, 3H), 4.16 (s, 3H), 4.34-4.46 (m, 3H), 6.96-7.13 (m, 2H), 7.16-7.25 (m, 2H), 7.55 (d, J = 2.3 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 2.3 Hz, 1H), 8.84 (d, J = 5.0 Hz, 2H).

[0464]

Examples 144 and 145

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-methoxy-3-pyridazin-3-ylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-methoxy-3-pyridazin-3-ylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

5 [0465]



[0466]

A racemate of the title compound (37.7 mg) was obtained according to the method of Examples 142 and 143 from 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-bromo-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Examples 68 and 69. The resulting racemate was separated by CHIRALPAK™ IA (2 cm × 25 cm, mobile phase: ethanol:hexane = 9:1, flow rate: 10 mL/min) to obtain the title compound with a retention time of 20.5 minutes and positive optical rotation (7.4 mg) and the title compound with a retention time of 65.5 minutes and negative optical rotation (9.9 mg).

The property values of the title optically active compound with a retention time of 20.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.04-2.28 (m, 3H), 2.30 (s, 3H), 2.37-2.45 (m, 1H), 3.85 (s, 3H), 4.16 (s, 3H), 4.37-4.45 (m, 3H), 6.88-6.93 (m, 2H), 7.17-7.24 (m, 2H), 7.59 (d, J = 8.2 Hz, 1H), 7.62 (dd, J = 5.2, 2.2 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 9.17 (dd, J = 5.2, 1.2 Hz, 1H), 9.37 (dd, J = 1.3, 1.2 Hz, 1H).

20 [0467]

The property values of the title optically active compound with a retention time of 65.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.04-2.28 (m, 3H), 2.30 (s, 3H), 2.37-2.45 (m, 1H), 3.85 (s, 3H), 4.16 (s, 3H), 4.37-4.45 (m, 3H), 6.88-6.93 (m, 2H), 7.17-7.24 (m, 2H), 7.59 (d, J = 8.2 Hz, 1H), 7.62 (dd, J = 5.2, 2.2 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 9.17 (dd, J = 5.2, 1.2 Hz, 1H), 9.37 (dd, J = 1.3, 1.2 Hz, 1H).

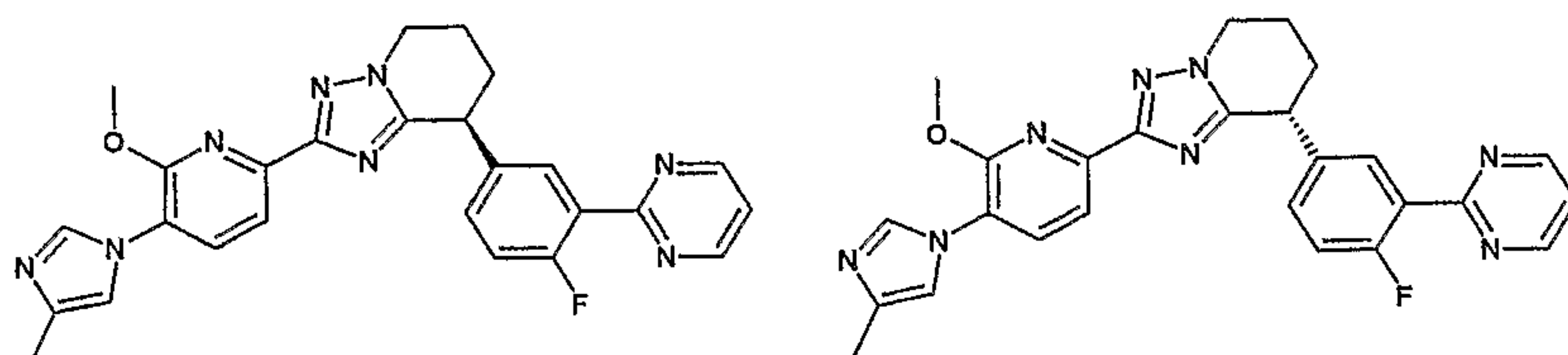
[0468]

Examples 146 and 147

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-fluoro-3-pyrimidin-

2-ylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-fluoro-3-pyrimidin-2-ylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0469]



5 [0470]

A racemate of the title compound (32 mg) was obtained according to the method of Examples 142 and 143 from 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-bromo-4-fluorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Examples 80 and 81 (70 mg). The resulting racemate was separated by CHIRALPAKTM IA (2 cm × 25 cm, mobile phase: ethanol:hexane = 75:25, flow rate: 10 mL/min) to obtain the title compound with a retention time of 25 minutes and positive optical rotation (3.8 mg) and the title compound with a retention time of 34.5 minutes and negative optical rotation (3 mg). The property values of the title optically active compound with a retention time of 25 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.10-2.18 (m, 2H), 2.20-2.25 (m, 1H), 2.30 (s, 3H), 2.37-2.48 (m, 1H), 4.16 (s, 3H), 4.42 (dd, J = 11.7, 6.2 Hz, 2H), 4.48 (dd, J = 6.6, 6.6 Hz, 1H), 6.91-6.98 (m, 1H), 7.15-7.26 (m, 3H), 7.58 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.91 (dd, J = 7.0, 1.2 Hz, 1H), 8.85 (d, J = 5.1 Hz, 2H).

[0471]

The property values of the title optically active compound with a retention time of 34.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.10-2.18 (m, 2H), 2.20-2.25 (m, 1H), 2.30 (s, 3H), 2.37-2.48 (m, 1H), 4.16 (s, 3H), 4.42 (dd, J = 11.7, 6.2 Hz, 2H), 4.48 (dd, J = 6.6, 6.6 Hz, 1H), 6.91-6.98 (m, 1H), 7.15-7.26 (m, 3H), 7.58 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.91 (dd, J = 7.0, 1.2 Hz, 1H), 8.85 (d, J = 5.1 Hz, 2H).

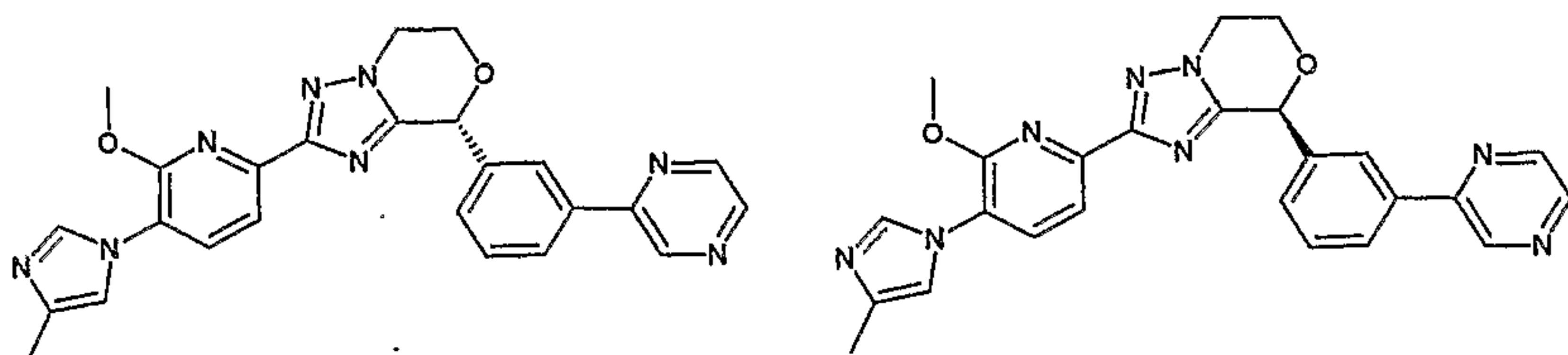
25 [0472]

Examples 148 and 149

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(3-pyrazin-2-ylphenyl)-5,6-dihydro-8H-[1,2,4]triazolo[1,5-c][1,4]oxazine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(3-pyrazin-2-ylphenyl)-5,6-dihydro-8H-[1,2,4]triazolo[1,5-

c][1,4]oxazine

[0473]



[0474]

A racemate of the title compound was obtained according to the method of Examples 142 and 143 from 8-(3-bromophenyl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6-dihydro-8H-[1,2,4]triazolo[1,5-c][1,4]oxazine obtained in Examples 64 and 65 (40 mg). The resulting racemate of the title compound was separated by CHIRALCELTM IB (2 cm × 25 cm, mobile phase: hexane:ethanol = 1:1, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 14.16 minutes resulting from analysis by CHIRALPAKTM IB (Lot. IB00CD-FD026, hexane:ethanol = 7:3, 1.0 mL/min) and positive optical rotation (1.6 mg, >99% ee) and the title optically active compound with a retention time of 18.25 minutes resulting from the same analysis and negative optical rotation (3.5 mg, >99% ee).

The property values of the title optically active compound with positive optical rotation are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H), 4.17 (s, 3H), 4.18-4.25 (m, 1H), 4.38 (dt, J = 4.4, 12.0 Hz, 1H), 4.41-4.56 (m, 2H), 6.11 (s, 1H), 7.00 (d, J = 2.4 Hz, 1H), 7.56-7.63 (m, 3H), 7.81-7.84 (m, 2H), 8.05 (dt, J = 1.6, 7.6 Hz, 1H), 8.19 (t, J = 2.0 Hz, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.64 (dd, J = 1.6, 3.6 Hz, 1H), 9.04 (d, J = 1.2 Hz, 1H).

[0475]

The property values of the title optically active compound with negative optical rotation are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H), 4.17 (s, 3H), 4.18-4.25 (m, 1H), 4.38 (dt, J = 4.4, 12.0 Hz, 1H), 4.41-4.56 (m, 2H), 6.11 (s, 1H), 7.00 (d, J = 2.4 Hz, 1H), 7.56-7.63 (m, 3H), 7.81-7.84 (m, 2H), 8.05 (dt, J = 1.6, 7.6 Hz, 1H), 8.19 (t, J = 2.0 Hz, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.64 (dd, J = 1.6, 3.6 Hz, 1H), 9.04 (d, J = 1.2 Hz, 1H).

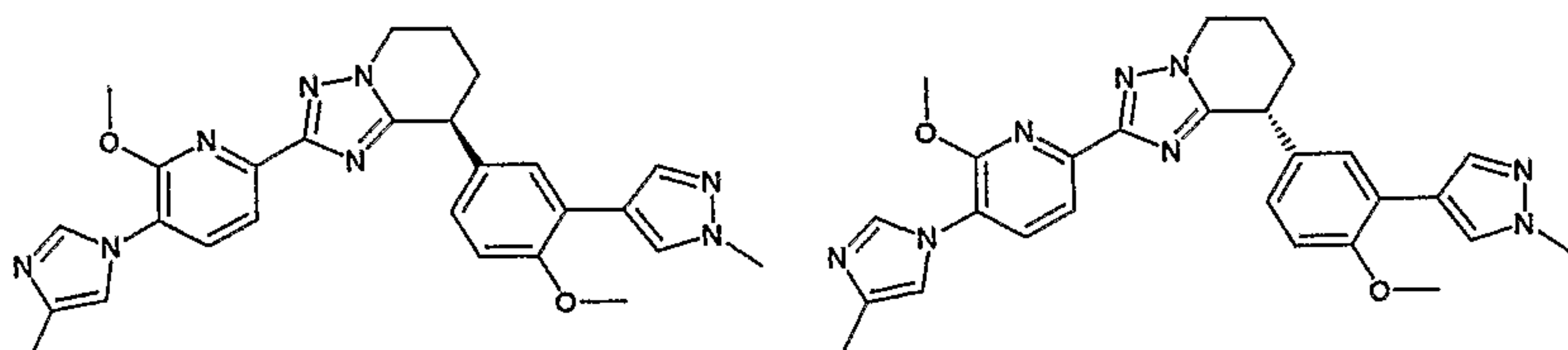
[0476]

Examples 150 and 151

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-methoxy-3-(1-

methyl-1H-pyrazol-4-yl)phenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-methoxy-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0477]



5 [0478]

2-[6-Methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-bromo-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Examples 68 and 69 (100 mg) was dissolved in toluene (3 mL) and methanol (600 μ L). A 2 M sodium carbonate solution (101 μ L), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (63 mg) and tetrakis(triphenylphosphine) palladium (23.4 mg) were added and the mixture was stirred under microwave irradiation at 120°C for three hours. The reaction solution was partitioned with ethyl acetate and water. Then, the organic layer was washed with water and brine and dried over magnesium sulfate. Concentration under reduced pressure gave an oil. The oil was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 100% -> 100% methanol/ethyl acetate = 20%) to obtain a racemate of the title compound (50.6 mg). The resulting racemate was separated by CHIRALPAK™ IB (2 cm $\times$ 25 cm, mobile phase: ethanol:hexane = 5:5, flow rate: 12 mL/min) to obtain the title compound with a retention time of 29.5 minutes and positive optical rotation (13.2 mg) and the title compound with a retention time of 39.0 minutes and negative optical rotation (11.6 mg). The property values of the title optically active compound with a retention time of 29.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.04-2.16 (m, 2H), 2.18-2.27 (m, 1H), 2.30 (s, 3H), 2.34-2.43 (m, 1H), 3.89 (s, 3H), 3.93 (s, 3H), 4.17 (s, 3H), 4.33-4.47 (m, 3H), 6.87-6.94 (m, 2H), 6.99-7.01 (m, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.81-7.83 (m, 3H).

25 [0479]

The property values of the title optically active compound with a retention time of 39.0 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.04-2.16 (m, 2H), 2.18-2.27 (m, 1H), 2.30 (s, 3H), 2.34-2.43 (m, 1H), 3.89 (s, 3H), 3.93 (s, 3H), 4.17 (s, 3H), 4.33-4.47 (m, 3H), 6.87-6.94 (m, 2H), 6.99-7.01 (m,

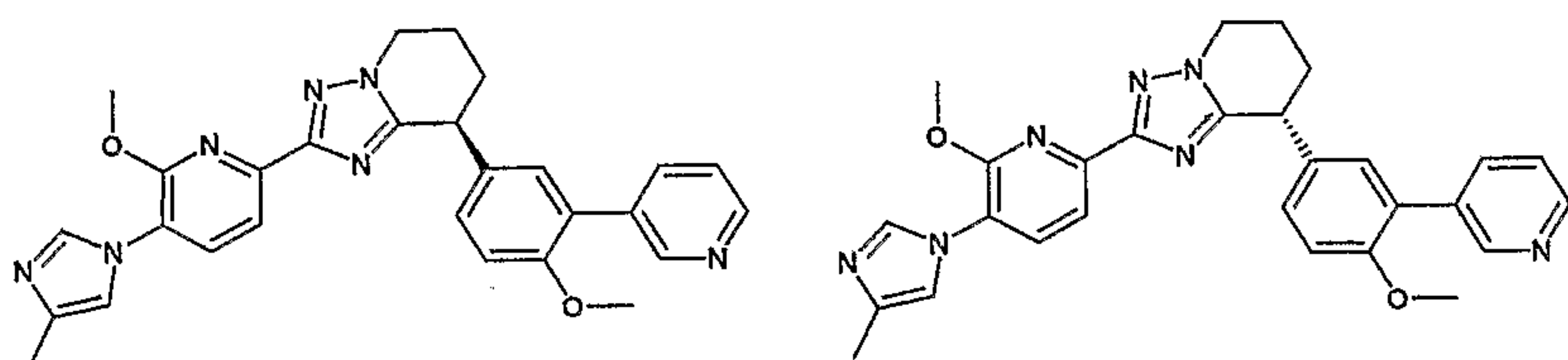
1H), 7.31 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.81-7.83 (m, 3H).

[0480]

Examples 152 and 153

- 5 Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-methoxy-3-pyridin-3-ylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(4-methoxy-3-pyridin-3-ylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0481]



10 [0482]

A racemate of the title compound (56 mg) was obtained according to the method of Examples 150 and 151 from 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-bromo-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Examples 68 and 69 (100 mg). The resulting racemate was separated by CHIRALPAK™ IB (2 cm × 25
15 cm, mobile phase: ethanol:hexane = 3:7, flow rate: 15 mL/min) to obtain the title compound with a retention time of 41.5 minutes and positive optical rotation (17.5 mg) and the title compound with a retention time of 53.5 minutes and negative optical rotation (18 mg).

The property values of the title optically active compound with a retention time of 41.5 minutes are as follows.

- 20 ¹H-NMR (CDCl₃) δ (ppm): 2.06-2.16 (m, 2H), 2.19-2.28 (m, 1H), 2.30 (s, 3H), 2.35-2.44 (m, 1H), 3.81 (s, 3H), 3.99 (s, 3H), 4.16 (s, 3H), 4.34-4.47 (m, 3H), 6.95 (d, J = 9.4 Hz, 1H), 6.95-7.05 (m, 1H), 7.09-7.14 (m, 2H), 7.31 (dd, J = 7.8, 5.7 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.78-7.84 (m, 3H), 7.87 (d, J = 2.0 Hz, 1H), 8.54 (dd, J = 5.7, 2.0 Hz, 1H).

[0483]

- 25 The property values of the title optically active compound with a retention time of 53.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.06-2.16 (m, 2H), 2.19-2.28 (m, 1H), 2.30 (s, 3H), 2.35-2.44 (m, 1H), 3.81 (s, 3H), 3.99 (s, 3H), 4.16 (s, 3H), 4.34-4.47 (m, 3H), 6.95 (d, J = 9.4 Hz, 1H), 6.95-7.05 (m, 1H), 7.09-7.14 (m, 2H), 7.31 (dd, J = 7.8, 5.7 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.78-

7.84 (m, 3H), 7.87 (d, $J = 2.0$ Hz, 1H), 8.54 (dd, $J = 5.7, 2.0$ Hz, 1H).

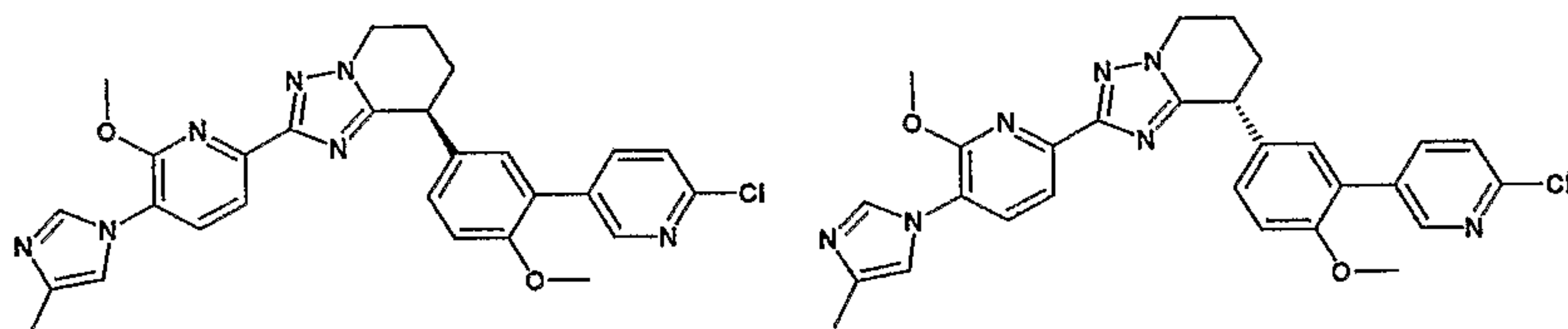
[0484]

Examples 154 and 155

Synthesis of (+)-8-[3-(6-chloropyridin-3-yl)-4-methoxyphenyl]-2-[6-methoxy-5-(4-

5 methylimidazol-1-yl)pyridin-2-yl-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-8-[3-(6-chloropyridin-3-yl)-4-methoxyphenyl]-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0485]



[0486]

10 A racemate of the title compound (90.3 mg) was obtained according to the method of Examples 150 and 151 from 2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-bromo-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Examples 68 and 69 (100 mg). The resulting racemate was separated by CHIRALPAKTM IB (2 cm × 25 cm, mobile phase: ethanol:hexane = 2:8, flow rate: 15 mL/min) to obtain the title
15 compound with a retention time of 42 minutes and positive optical rotation (22 mg) and the title compound with a retention time of 58.5 minutes and negative optical rotation (20 mg).

The property values of the title optically active compound with a retention time of 42 minutes are as follows.

20 ¹H-NMR (CDCl₃) δ (ppm): 2.04-2.17 (m, 2H), 2.18-2.28 (m, 1H), 2.30 (s, 3H), 2.35-2.45 (m, 1H), 3.81 (s, 3H), 3.99 (s, 3H), 4.16 (s, 3H), 4.34-4.47 (m, 3H), 6.95 (d, $J = 8.2$ Hz, 1H), 6.98-7.03 (m, 1H), 7.07-7.16 (m, 2H), 7.34 (d, $J = 8.2$ Hz, 1H), 7.59 (d, $J = 8.2$ Hz, 1H), 7.75-7.85 (m, 3H), 8.49 (d, $J = 2.0$ Hz, 1H).

[0487]

25 The property values of the title optically active compound with a retention time of 58.5 minutes are as follows.

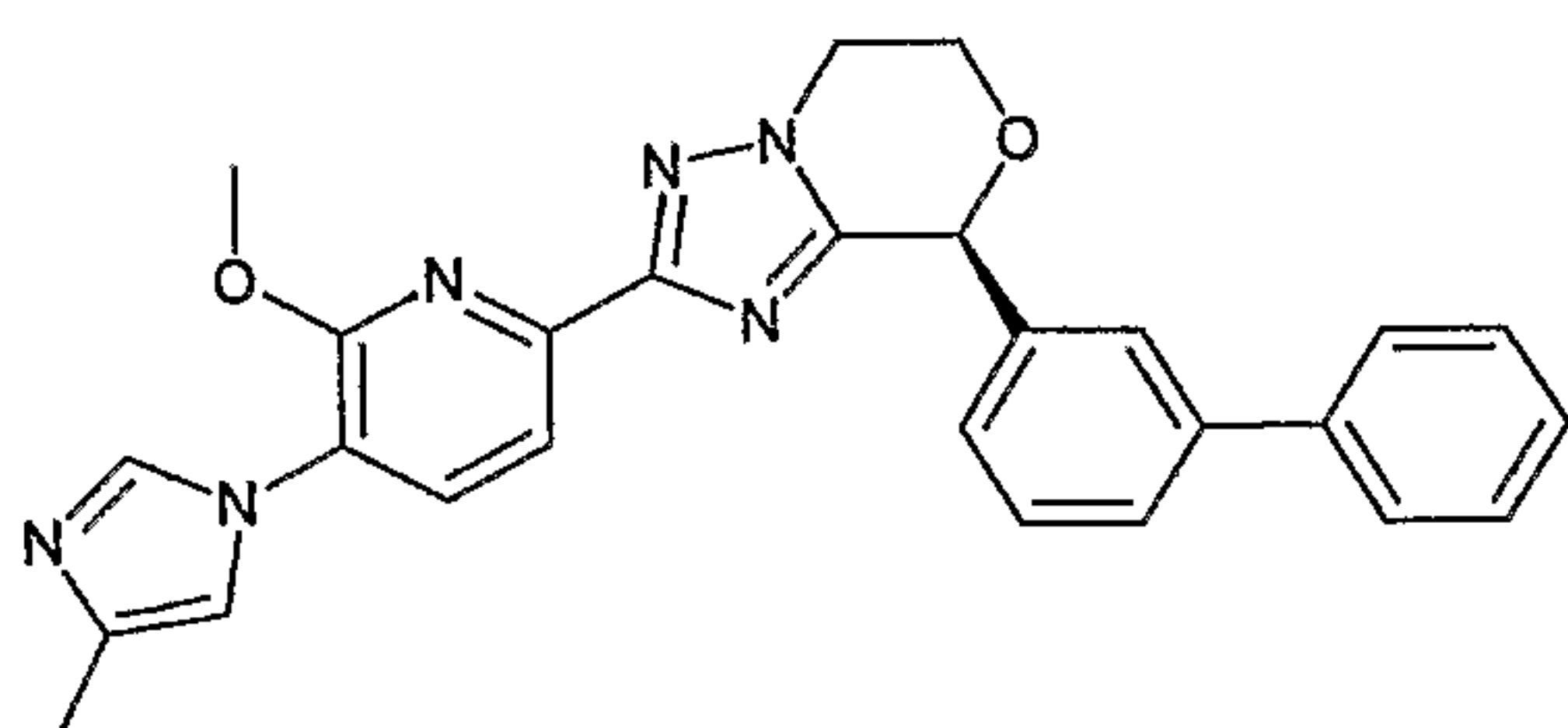
¹H-NMR (CDCl₃) δ (ppm): 2.04-2.17 (m, 2H), 2.18-2.28 (m, 1H), 2.30 (s, 3H), 2.35-2.45 (m, 1H), 3.81 (s, 3H), 3.99 (s, 3H), 4.16 (s, 3H), 4.34-4.47 (m, 3H), 6.95 (d, $J = 8.2$ Hz, 1H), 6.98-7.03 (m, 1H), 7.07-7.16 (m, 2H), 7.34 (d, $J = 8.2$ Hz, 1H), 7.59 (d, $J = 8.2$ Hz, 1H), 7.75-7.85 (m, 3H), 8.49 (d, $J = 2.0$ Hz, 1H).

[0488]

Example 156

Synthesis of (+)-8-biphenyl-3-yl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6-dihydro-8H-[1,2,4]triazolo[1,5-c][1,4]oxazine

5 [0489]



[0490]

The title compound (22 mg) was obtained according to the method of Examples 150 and 151 from (+)-8-(3-bromophenyl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6-dihydro-8H-[1,2,4]triazolo[1,5-c][1,4]oxazine obtained in Example 64 (42.6 mg). The property values of the compound are as follows.

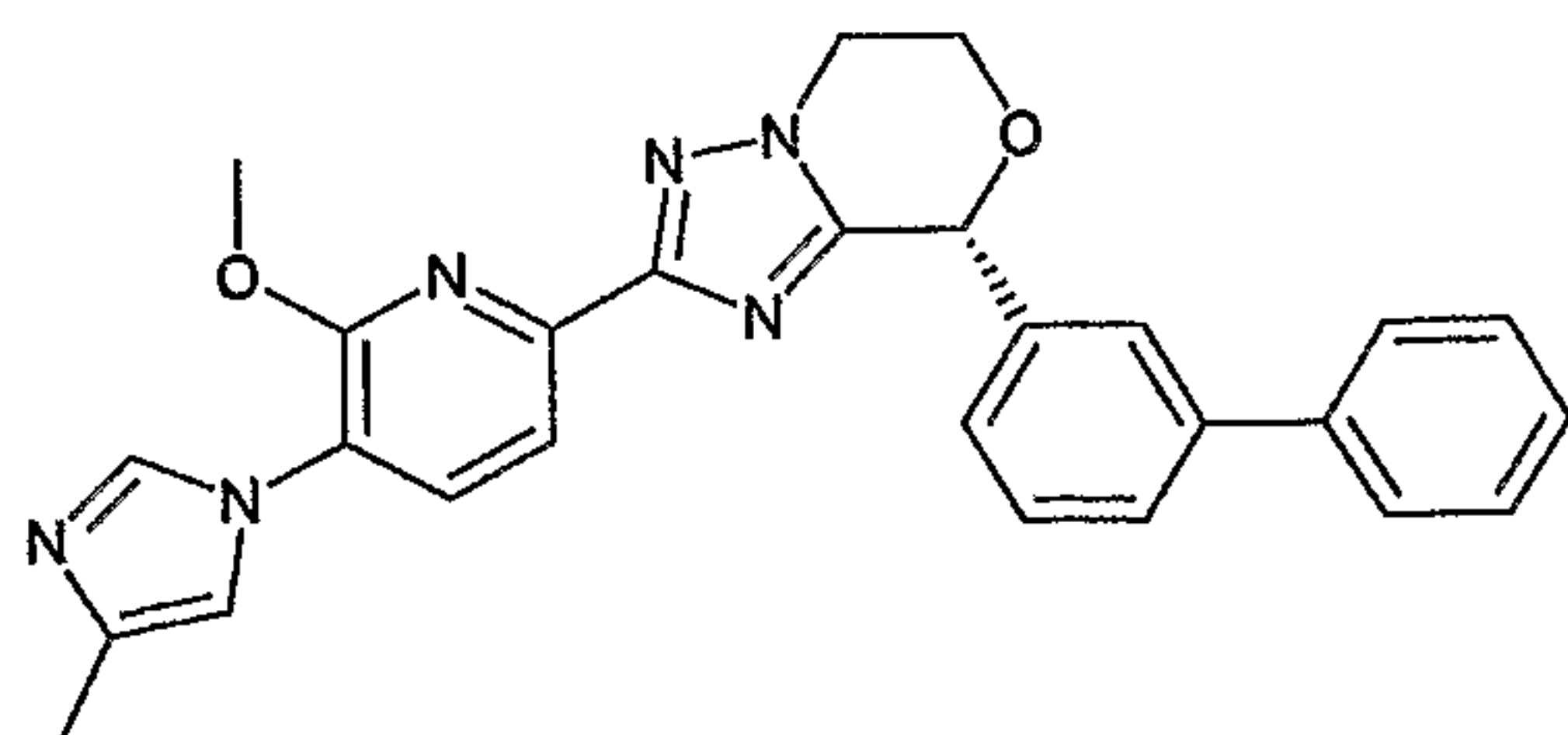
¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H), 4.17 (s, 3H), 4.18-4.22 (m, 1H), 4.36 (dt, J = 4.4, 12.4 Hz, 1H), 4.44-4.52 (m, 2H), 6.08 (s, 1H), 7.01 (t, J = 1.2 Hz, 1H), 7.35 (tt, J = 2.0, 7.2 Hz, 1H), 7.41-7.50 (m, 4H), 7.57-7.63 (m, 4H), 7.70 (t, J = 1.6 Hz, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.83 (s, 1H).

15 [0491]

Example 157

Synthesis of (-)-8-biphenyl-3-yl-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6-dihydro-8H-[1,2,4]triazolo[1,5-c][1,4]oxazine

[0492]



20 [0493]

The title compound (17 mg) was obtained according to the method of Examples 150 and 151 from (-)-8-(3-bromophenyl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-

2-yl]-5,6-dihydro-8H-[1,2,4]triazolo[1,5-c][1,4]oxazine obtained in Example 65 (22.7 mg). The property values of the compound are as follows.

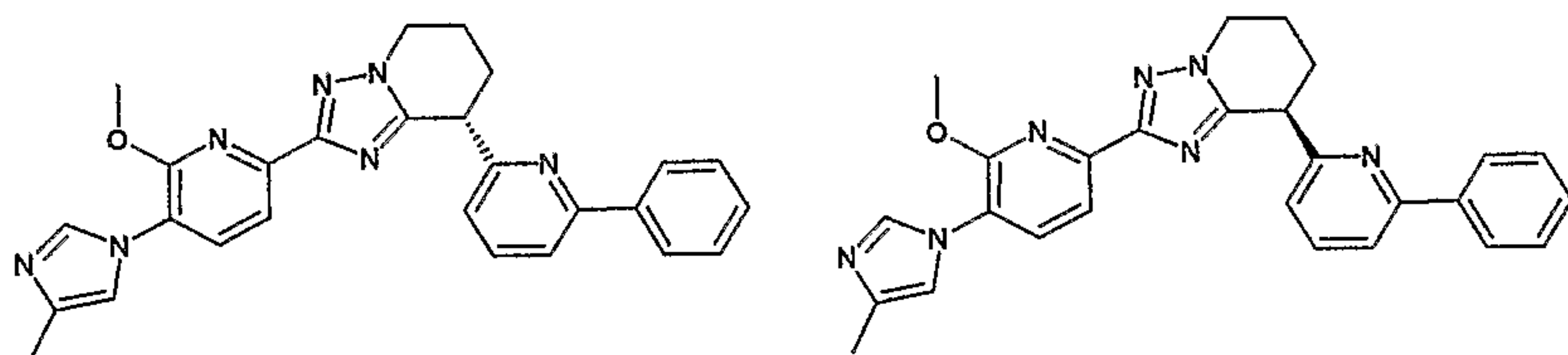
¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H), 4.17 (s, 3H), 4.18-4.22 (m, 1H), 4.36 (dt, J = 4.4, 12.4 Hz, 1H), 4.44-4.52 (m, 2H), 6.08 (s, 1H), 7.01 (t, J = 1.2 Hz, 1H), 7.35 (tt, J = 2.0, 7.2 Hz, 1H),
 5 7.41-7.50 (m, 4H), 7.57-7.63 (m, 4H), 7.70 (t, J = 1.6 Hz, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.83 (s, 1H).

[0494]

Examples 158 and 159

10 (+)-2-[6-Methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(6-phenylpyridin-2-yl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(6-phenylpyridin-2-yl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0495]



[0496]

A racemate of the title compound (19 mg) was obtained according to the method
 15 of Examples 150 and 151 from 8-(6-bromopyridin-2-yl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Examples 70 and 71 (41.7 mg). The resulting racemate was separated by CHIRALPAKTM IA (2 cm × 25 cm; mobile phase: hexane:ethanol = 50:50) to obtain the title optically active compound with a retention time of 4.9 minutes and positive optical rotation (7.1 mg, >99% ee) and the title
 20 optically active compound with a retention time of 7.6 minutes and negative optical rotation (6.3 mg, >99% ee).

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 464 [M⁺+H]. ¹H-NMR (CDCl₃) δ (ppm): 2.09-2.14 (m, 1H), 2.30 (d, J = 1.2 Hz, 3H), 2.31-2.53 (m, 2H), 2.54-2.59 (m, 1H), 4.17 (s, 3H), 4.34-4.39 (m, 1H), 4.44-4.50 (m, 1H),
 25 4.65 (t, J = 6.0 Hz, 1H), 7.00 (t, J = 1.2 Hz, 1H), 7.14 (dd, J = 0.8 Hz, 7.6 Hz, 1H), 7.38-7.47 (m, 3H), 7.58 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 0.8 Hz, 7.6 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.96-7.98 (m, 2H).

[0497]

The property values of the title compound with negative optical rotation are as follows.

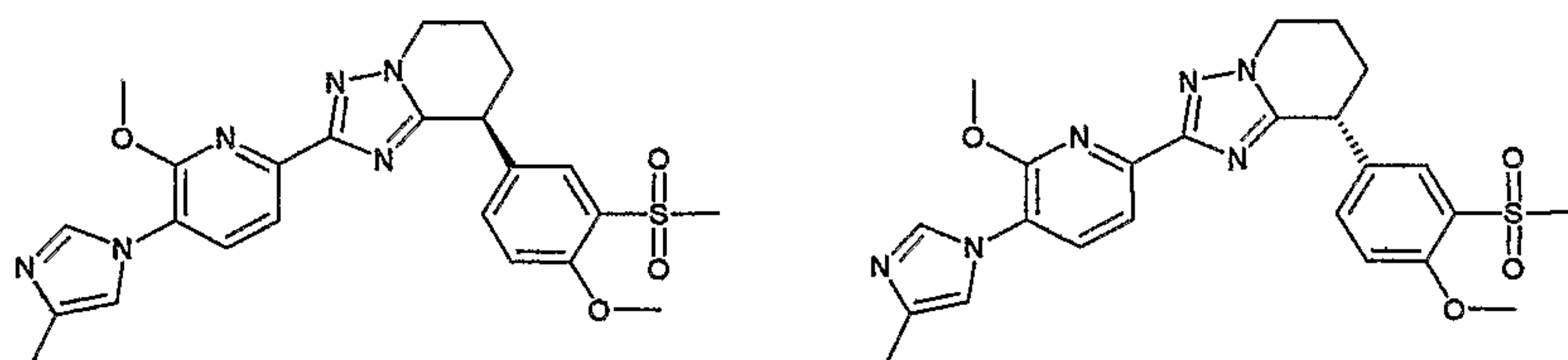
ESI-MS; m/z 464 $[M^+ + H]$. ^1H -NMR ($CDCl_3$) δ (ppm): 2.09-2.14 (m, 1H), 2.30 (d, $J = 1.2$ Hz, 3H), 2.31-2.53 (m, 2H), 2.54-2.59 (m, 1H), 4.17 (s, 3H), 4.34-4.39 (m, 1H), 4.44-4.50 (m, 1H), 4.65 (t, $J = 6.0$ Hz, 1H), 7.00 (t, $J = 1.2$ Hz, 1H), 7.14 (dd, $J = 0.8$ Hz, 7.6 Hz, 1H), 7.38-7.47 (m, 3H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.63 (dd, $J = 0.8$ Hz, 7.6 Hz, 1H), 7.71 (t, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.82 (d, $J = 1.2$ Hz, 1H), 7.96-7.98 (m, 2H).

[0498]

Examples 160 and 161

- 10 Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-methanesulfonyl-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-methanesulfonyl-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0499]



- 15 [0500]

2-[6-Methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-8-(3-bromo-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Examples 68 and 69 (100 mg) was dissolved in dimethyl sulfoxide (2 mL). Sodium methanesulfinate (165 mg), L-proline (18.6 mg), sodium hydroxide (12.8 mg) and copper iodide (30.8 mg) were added. The reaction was initiated under microwave irradiation at 140°C. After three hours, the reaction solution was partitioned with ethyl acetate and water. Then, the organic layer was washed with water and brine and dried over magnesium sulfate. Concentration under reduced pressure gave an oil. The oil was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 100% → methanol/ethyl acetate = 15%) to obtain a racemate of the title compound (58.9 mg). The resulting racemate was separated by CHIRALCEL™ OJ-H (2 cm × 25 cm, mobile phase: ethanol:hexane = 5:5, flow rate: 12 mL/min) to obtain the title compound with a retention time of 16.0 minutes and positive optical rotation (19 mg) and the title compound with a retention time of 22.0 minutes and negative optical rotation (16.5 mg).

The property values of the title optically active compound with a retention time of

16.0 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.03-2.18 (m, 2H), 2.18-2.28 (m, 1H), 2.30 (s, 3H), 2.35-2.44 (m, 1H), 3.24 (s, 3H), 3.99 (s, 3H), 4.16 (s, 3H), 4.36-4.45 (m, 3H), 6.89-6.92 (m, 1H), 6.92 (d, J = 9.0 Hz, 1H), 7.34-7.38 (m, 1H), 7.59 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.81-7.85 (m, 1H), 7.87 (d, J = 2.3 Hz, 1H).

[0501]

The property values of the title optically active compound with a retention time of 22.0 minutes are as follows.

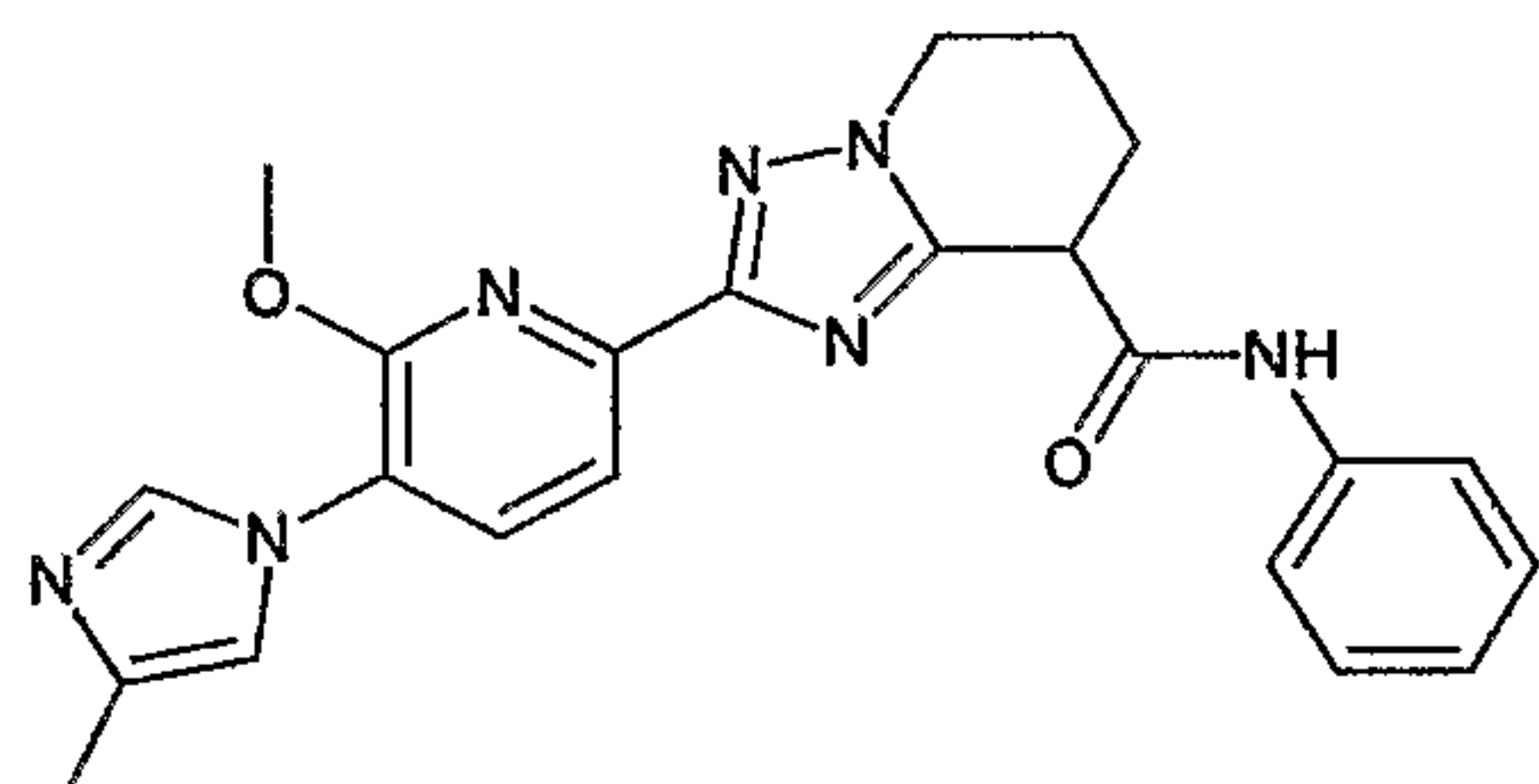
¹H-NMR (CDCl₃) δ (ppm): 2.03-2.18 (m, 2H), 2.18-2.28 (m, 1H), 2.30 (s, 3H), 2.35-2.44 (m, 1H), 3.24 (s, 3H), 3.99 (s, 3H), 4.16 (s, 3H), 4.36-4.45 (m, 3H), 6.89-6.92 (m, 1H), 6.92 (d, J = 9.0 Hz, 1H), 7.34-7.38 (m, 1H), 7.59 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.81-7.85 (m, 1H), 7.87 (d, J = 2.3 Hz, 1H).

[0502]

Example 162

15 2-[6-Methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid phenylamide

[0503]



[0504]

2-[6-Methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid obtained in Preparation Example 5-1 (25 mg) was dissolved in N,N-dimethylformamide (0.5 mL). Aniline (7.2 mg), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (40.6 mg), 1-hydroxybenzotriazole (28.6 mg) and N,N-diisopropylethylamine (75.7 μL) were sequentially added and the mixture was stirred at room temperature for five hours. Ethyl acetate and water were added to the reaction solution, and the organic layer and the aqueous layer were separated. The aqueous layer was further extracted with ethyl acetate. The resulting organic layers were combined, sprayed with nitrogen gas and concentrated. The residue was purified by NH silica gel column chromatography to obtain the title compound (14.1 mg). The compound was further separated by CHIRALPAK™

IA (2 cm × 25 cm; mobile phase: hexane:ethanol = 50:50) to obtain the title compound with a retention time of 7.6 minutes (4.5 mg). The property values of the compound are as follows.

ESI-MS; m/z 430 [$M^+ + H$]. ^1H -NMR ($CDCl_3$) δ (ppm): 2.14-2.34 (m, 2H), 2.32 (d, $J = 1.2$ Hz, 3H), 2.38-2.54 (m, 2H), 4.05 (t, $J = 6.4$ Hz, 1H), 4.19 (s, 3H), 4.27-4.37 (m, 2H), 7.04 (t, $J = 1.2$ Hz, 1H), 7.12 (tt, $J = 0.8$ Hz, 7.6 Hz, 1H), 7.33 (dt, $J = 0.8$ Hz, 7.6 Hz, 2H), 7.58 (dd, $J = 0.8$ Hz, 7.6 Hz, 2H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 1.2$ Hz, 1H), 10.20 (s, 1H).

[0505]

The compounds of Examples 163 to 170 were obtained by the same method as in Example 162 (Table 4).

Table 4

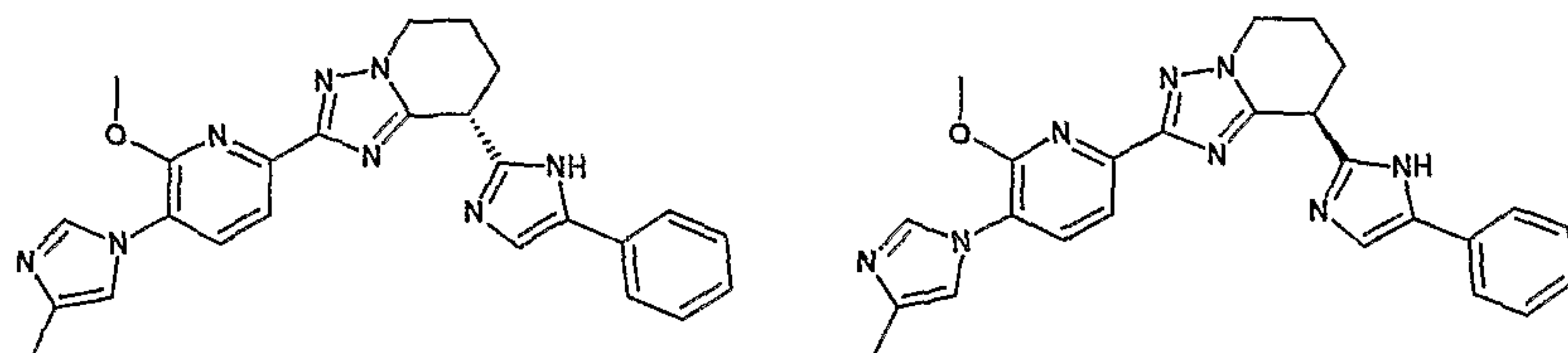
Example No.	Structural formula
Example 163	
Example 164	
Example 165	
Example 166	

Example No.	Structural formula
Example 167	
Example 168	
Example 169	
Example 170	

[0506]

Examples 171 and 172

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(5-phenyl-1H-imidazol-2-yl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(5-phenyl-1H-imidazol-2-yl)-5,6,7,8-

tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0507]

Synthesis of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid (2-oxo-2-phenylethyl)amide

5 The title compound (25.6 mg) was obtained according to the method of Example 162 from 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid obtained in Preparation Example 5-1 (33.2 mg) and α -aminoacetophenone hydrochloride (17.7 mg). The property values of the compound are as follows.

10 $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.12-2.45 (m, 4H), 2.32 (d, $J = 1.2$ Hz, 3H), 3.97 (t, $J = 6.4$ Hz, 1H), 4.22 (s, 3H), 4.25-4.36 (m, 2H), 4.79 (dd, $J = 4.0$ Hz, 19.6 Hz, 1H), 4.87 (dd, $J = 4.0$ Hz, 19.6 Hz, 1H), 7.04 (t, $J = 1.2$ Hz, 1H), 7.51 (dt, $J = 1.2$ Hz, 7.6 Hz, 2H), 7.63 (tt, $J = 1.2$ Hz, 7.6 Hz, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 1.2$ Hz, 1H), 7.99 (dd, $J = 1.2$ Hz, 7.6 Hz, 2H), 8.05 (d, $J = 8.0$ Hz, 1H), 9.07 (t, $J = 4.0$ Hz, 1H).

15 [0508]

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(5-phenyl-1H-imidazol-2-yl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(5-phenyl-1H-imidazol-2-yl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

20 2-[6-Methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid (2-oxo-2-phenylethyl)amide (25 mg) was dissolved in glacial acetic acid (0.5 mL). Ammonium acetate (20.4 mg) was added and the mixture was stirred with heating under reflux for eight hours. The reaction solution was ice-cooled. Then, ethyl acetate, water and concentrated aqueous ammonia (1 mL) were added and
 25 the organic layer was separated. The resulting organic layer was sequentially washed with a saturated sodium bicarbonate solution and brine and dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography to obtain a racemate of the title compound (16.8 mg). The resulting racemate was separated by

CHIRALPAK™ IA (2 cm × 25 cm; mobile phase: hexane:ethanol = 50:50) to obtain the title optically active compound with a retention time of 4.2 minutes and positive optical rotation (6.3 mg, >99% ee) and the title optically active compound with a retention time of 6.1 minutes and negative optical rotation (6.9 mg, >99% ee).

5 The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 453 [M⁺ + H]. ¹H-NMR (CDCl₃) δ (ppm): 2.22-2.76 (m, 4H), 2.31 (s, 3H), 4.11 (s, 3H), 4.25-4.44 (m, 2H), 4.49 (t, J = 6.0 Hz, 1H), 7.01 (s, 1H), 7.01-7.39 (m, 5H), 7.63-7.65 (m, 1H), 7.74 (brs, 1H), 7.84 (brs, 2H), 11.09 (brs, 1H).

10 [0509]

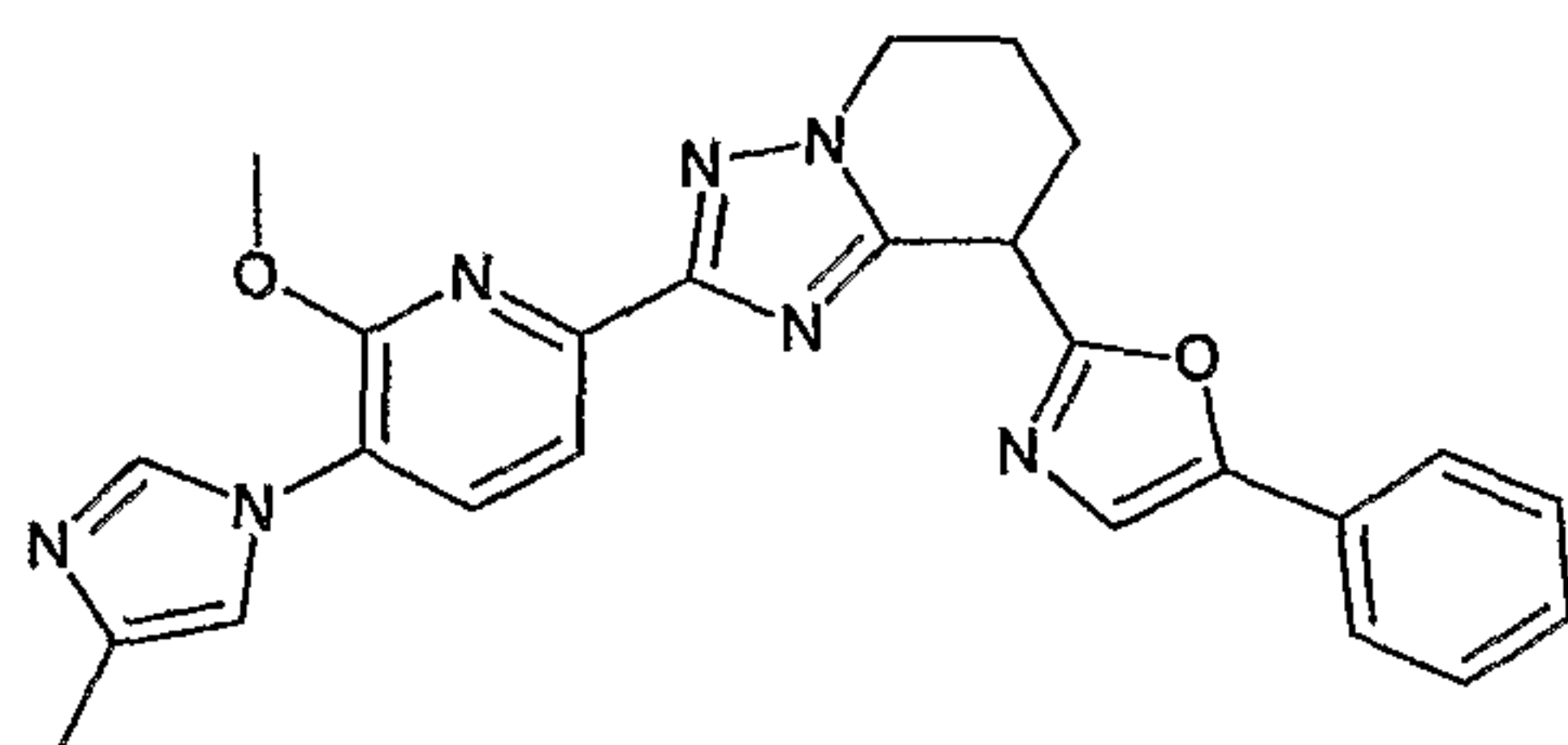
The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 453 [M⁺ + H]. ¹H-NMR (CDCl₃) δ (ppm): 2.22-2.76 (m, 4H), 2.31 (s, 3H), 4.11 (s, 3H), 4.25-4.44 (m, 2H), 4.49 (t, J = 6.0 Hz, 1H), 7.01 (s, 1H), 7.01-7.39 (m, 5H), 7.63-7.65 (m, 1H), 7.74 (brs, 1H), 7.84 (brs, 2H), 11.09 (brs, 1H).

[0510]

Example 173

Synthesis of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(5-phenyloxazol-2-yl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine



20 [0511]

2-[6-Methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid (2-oxo-2-phenylethyl)amide obtained in Example 172 (35.7 mg) was suspended in toluene (0.5 mL). Oxalyl chloride (20.4 mg) was added and the mixture was stirred with heating under reflux for two hours. Toluene (3 mL) and phosphoryl chloride (60 μL) were added, followed by further stirring for two hours and 30 minutes. The reaction solution was ice-cooled. Then, chloroform and a saturated sodium bicarbonate solution were added and the organic layer was separated. The resulting organic layer was concentrated under reduced pressure. The residue was purified by NH silica gel column

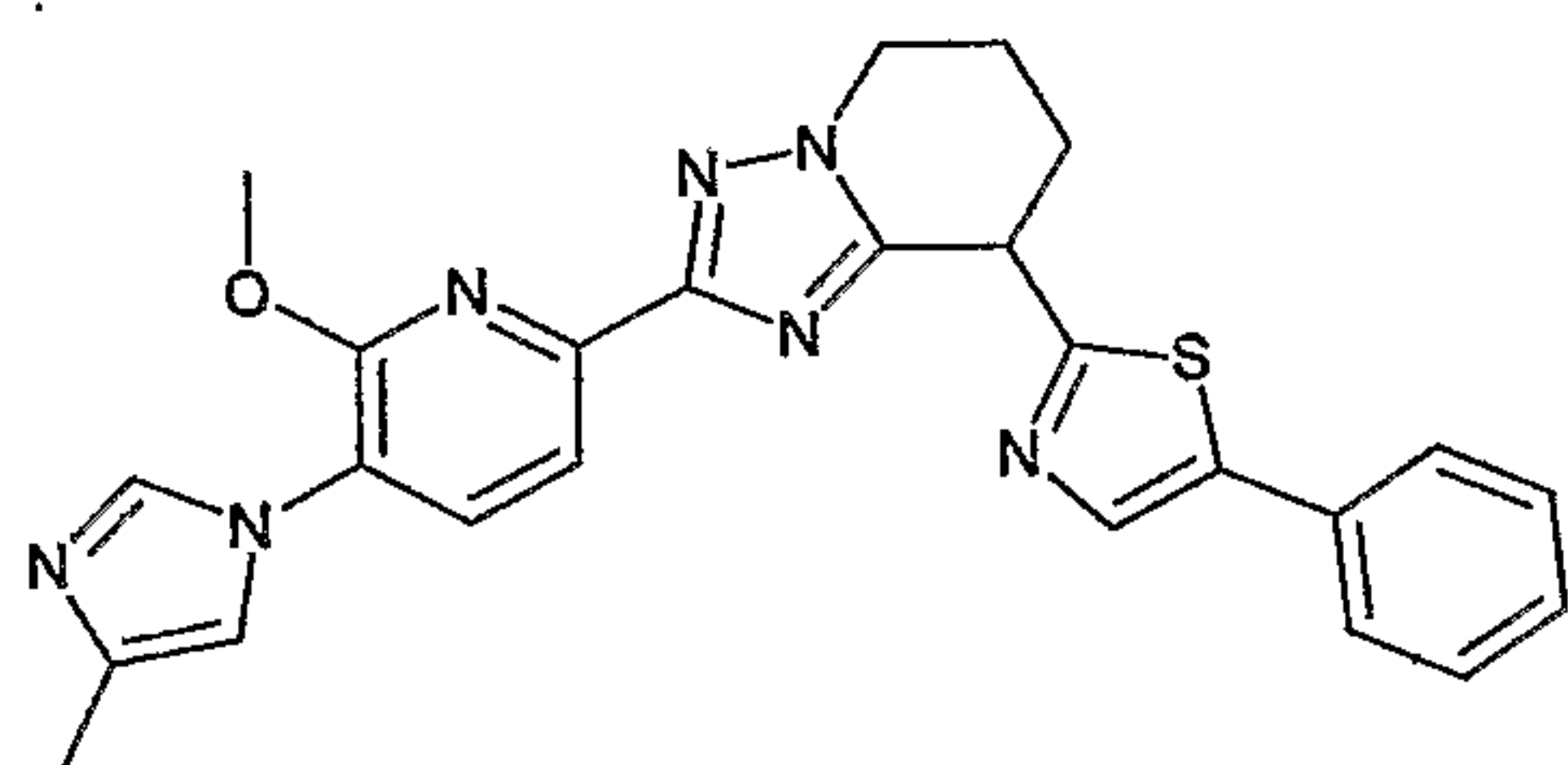
chromatography to obtain the title compound (4.4 mg). The compound was further purified by CHIRALPAK™ IA (2 cm × 25 cm; mobile phase: hexane:ethanol = 50:50) to obtain the title compound (1.2 mg, racemate). The property values of the compound are as follows.

ESI-MS; m/z 454 [$M^+ + H$]. ¹H-NMR (CDCl₃) δ (ppm): 2.18-2.24 (m, 1H), 2.30 (d, $J = 1.2$ Hz, 3H), 2.40-2.55 (m, 3H), 4.16 (s, 3H), 4.32-4.38 (m, 1H), 4.44-4.50 (m, 1H), 4.75 (t, $J = 5.6$ Hz, 1H), 7.00 (t, $J = 1.2$ Hz, 1H), 7.29 (s, 1H), 7.33 (tt, $J = 1.2$ Hz, 7.6 Hz, 1H), 7.41 (dt, $J = 1.2$ Hz, 7.6 Hz, 2H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.62 (dd, $J = 1.2$ Hz, 7.6 Hz, 2H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 1.2$ Hz, 1H).

[0512]

10 Example 174

Synthesis of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(5-phenylthiazol-2-yl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine



[0513]

2-[6-Methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-

15 tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid (2-oxo-2-phenylethyl)amide obtained in Example 172 (26.6 mg) was dissolved in THF (1 mL). Lawesson reagent (45.6 mg) was added and the mixture was stirred with heating under reflux for 11 hours. The reaction solution was ice-cooled. Then, chloroform and a saturated sodium bicarbonate solution were added and the organic layer was separated. The resulting organic layer was dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography to obtain the title compound (2.8 mg). The compound was further purified by CHIRALCEL™ IB (2 cm × 25 cm; mobile phase: hexane:ethanol = 30:70) to obtain the title compound (1.5 mg, racemate). The property values of the compound are as follows.

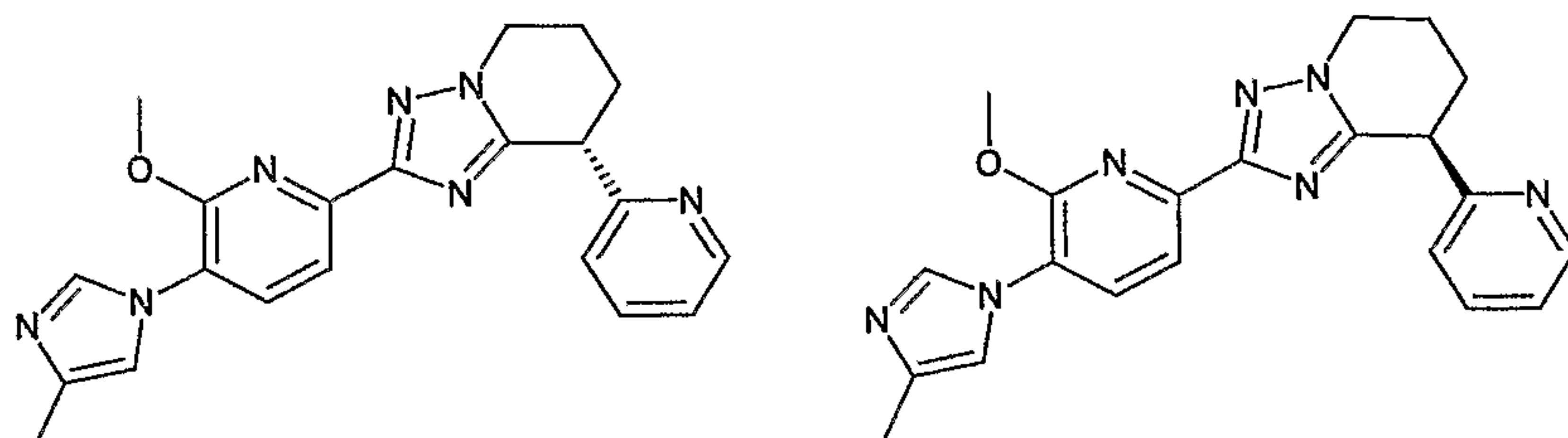
25 ESI-MS; m/z 470 [$M^+ + H$]. ¹H-NMR (CDCl₃) δ (ppm): 2.19-2.22 (m, 1H), 2.31 (s, 3H), 2.34-2.38 (m, 1H), 2.51-2.59 (m, 2H), 4.17 (s, 3H), 4.33-4.45 (m, 2H), 4.81 (t, $J = 6.0$ Hz, 1H), 7.01 (s, 1H), 7.32 (tt, $J = 1.2$ Hz, 7.6 Hz, 1H), 7.39 (dt, $J = 1.2$ Hz, 7.6 Hz, 2H), 7.52 (dd, $J = 1.2$ Hz, 7.6 Hz, 2H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 1.2$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.89 (s,

1H).

[0514]

Examples 175 and 176

(+)-2-[6-Methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-pyridin-2-yl-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-pyridin-2-yl-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine



[0515]

8-(6-bromopyridin-2-yl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Examples 70 and 71 (35 mg) was dissolved in ethanol (2 mL). 10% palladium-carbon (10 mg) was added and the mixture was stirred in a hydrogen atmosphere at 1 atm at room temperature for seven hours. Palladium-carbon was removed by filtration through celite, followed by concentration under reduced pressure. The residue was purified by NH silica gel column chromatography to obtain a racemate of the title compound (16.6 mg). The resulting racemate (16.6 mg) was separated by CHIRALPAK™ AD-H (2 cm × 25 cm; mobile phase: ethanol) to obtain the title optically active compound with a retention time of 4.3 minutes and positive optical rotation (7.3 mg, 70% ee) and the title optically active compound with a retention time of 7.7 minutes and negative optical rotation (5.2 mg, 94% ee).

The property values of the title compound with positive optical rotation are as follows.

ESI-MS; m/z 388 [$M^+ + H$]. ^1H -NMR ($CDCl_3$) δ (ppm): 2.08-2.28 (m, 2H), 2.30 (d, $J = 1.2$ Hz, 3H), 2.34-2.45 (m, 2H), 4.16 (s, 3H), 4.32-4.46 (m, 2H), 4.57 (t, $J = 6.0$ Hz, 1H), 7.00 (t, $J = 1.2$ Hz, 1H), 7.17-7.21 (m, 2H), 7.58 (d, $J = 7.6$ Hz, 1H), 7.65 (dt, $J = 2.0$ Hz, 8.0 Hz, 1H), 7.78 (d, $J = 7.6$ Hz, 1H), 7.82 (d, $J = 1.2$ Hz, 1H), 8.57-8.58 (m, 1H).

[0516]

The property values of the title compound with negative optical rotation are as follows.

ESI-MS; m/z 388 [$M^+ + H$]. ^1H -NMR ($CDCl_3$) δ (ppm): 2.08-2.28 (m, 2H), 2.30 (d, $J = 1.2$ Hz,

3H), 2.34-2.45 (m, 2H), 4.16 (s, 3H), 4.32-4.46 (m, 2H), 4.57 (t, J = 6.0 Hz, 1H), 7.00 (t, J = 1.2 Hz, 1H), 7.17-7.21 (m, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.65 (dt, J = 2.0 Hz, 8.0 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 8.57-8.58 (m, 1H).

[0517]

- 5 The compounds of Examples 177 to 180 were obtained by the same method as in Examples 175 and 176 (Table 5).

Table 5

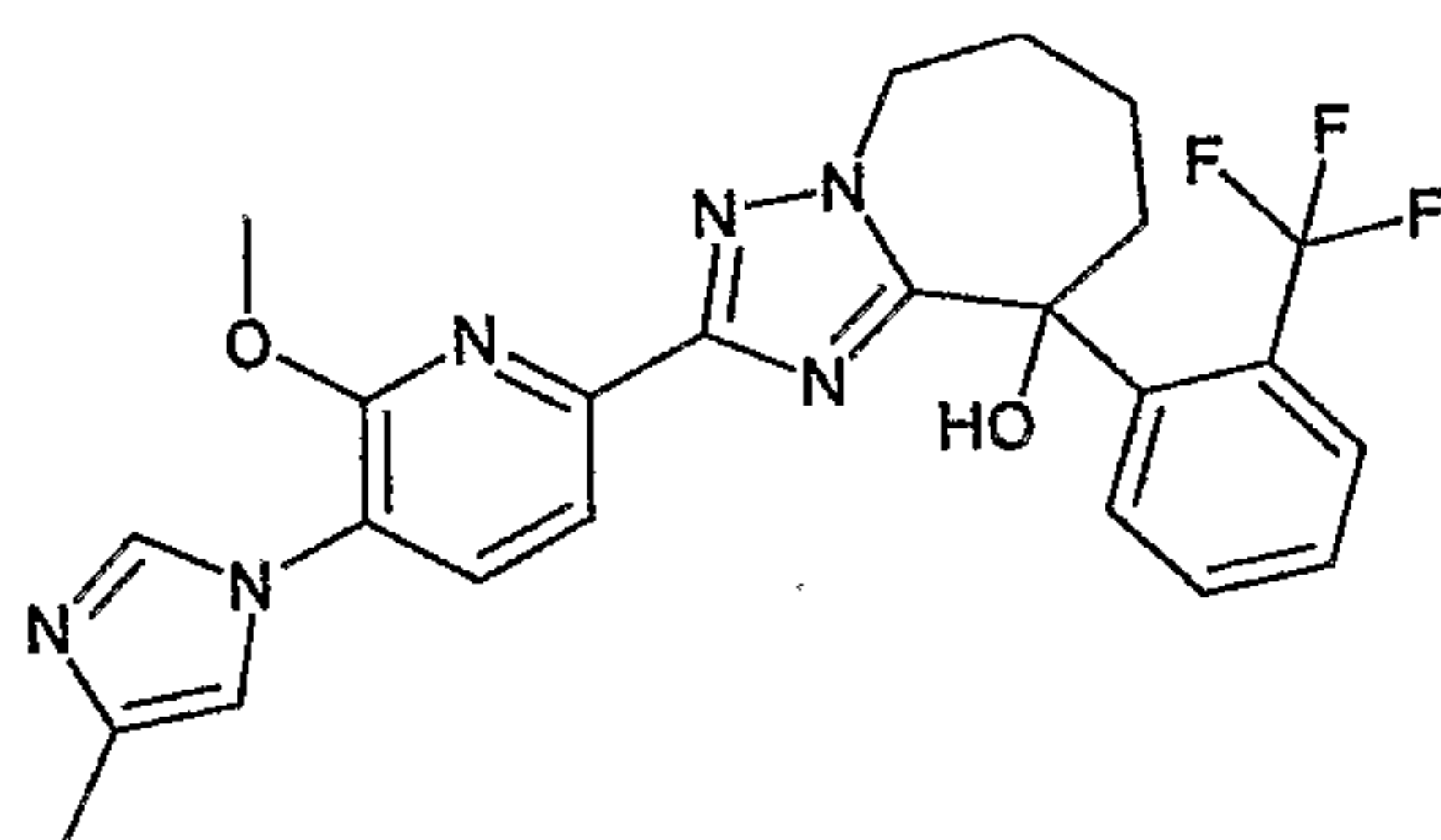
Example No.	Structural formula
Example 177	
Example 178	

Example No.	Structural formula
Example 179	
Example 180	

[0518]

Example 181

- 10 Synthesis of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-9-(2-trifluoromethylphenyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-a]azepin-9-ol



[0519]

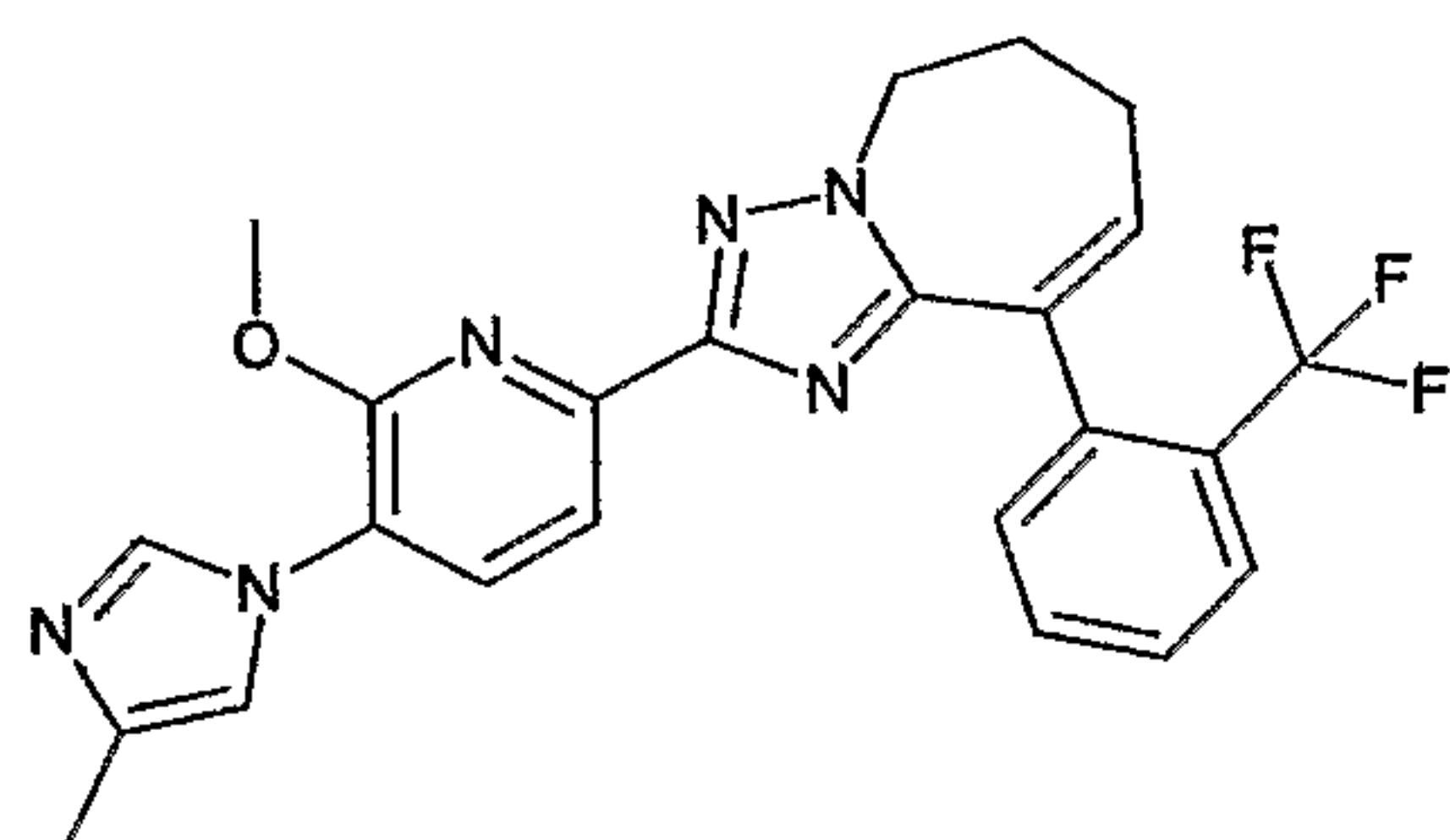
- 15 Sodium hydride (60%) was added to a solution of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-9-(2-trifluoromethylphenyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-a]azepine obtained in Examples 74 and 75 (83 mg) in DMF (5 mL) with stirring under ice-cooling until bubbling was stopped. Thereafter, the mixture was stirred at

room temperature in an oxygen atmosphere. After four days, ice water, chloroform and a saturated sodium thiosulfate solution were added to the reaction solution, and the organic layer was separated. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was diluted with toluene and concentrated under reduced pressure. The residue was diluted again with toluene and concentrated under reduced pressure. The precipitated solid was collected by filtration, washed with chloroform and then air-dried to obtain 36.8 mg of the title compound. The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.78-1.82 (m, 1H), 1.90-2.04 (m, 1H), 2.08-2.30 (m, 3H), 2.28 (s, 3H), 2.55-2.64 (m, 1H), 4.10 (s, 3H), 4.45-4.61 (m, 2H), 4.93 (brs, 1H), 6.93 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.43-7.54 (m, 3H), 7.60 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H).
[0520]

Example 182

Synthesis of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-9-(2-trifluoromethylphenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]azepine



[0521]

A mixture of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-9-(2-trifluoromethylphenyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-a]azepin-9-ol obtained in Example 181 (49 mg), p-toluenesulfonic acid (76 mg) and toluene (7 mL) was heated under reflux for two hours. Ethyl acetate and saturated sodium bicarbonate were added to the reaction solution, and the organic layer was separated. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The solid was removed by filtration. The mother liquor was concentrated under reduced pressure, and then the residue was purified by silica gel column chromatography (chloroform-methanol system) to obtain 3.46 mg of the title compound as an oil. The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.20-2.31 (m, 2H), 2.29 (s, 3H), 2.73-2.77 (m, 2H), 4.12 (s, 3H), 4.58-4.61 (m, 2H), 6.25 (dd, J = 5.2, 5.2 Hz, 1H), 6.96 (s, 1H), 7.44-7.50 (m, 2H), 7.49 (d, J = 7.2 Hz, 1H), 7.59 (t, J = 7.2 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.78 (s,

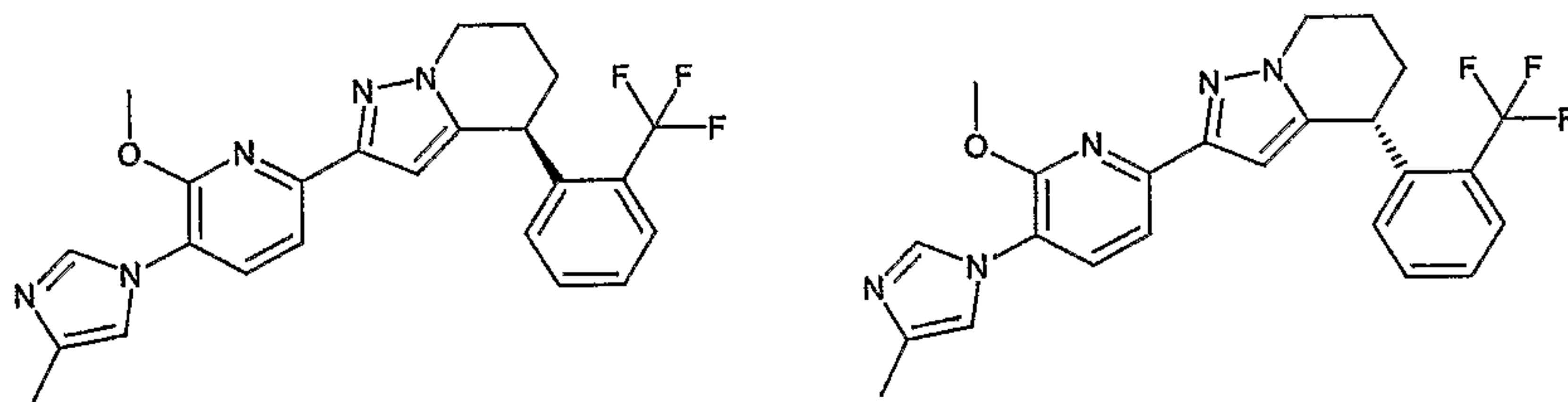
1H).

[0522]

Examples 183 and 184

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-4-(2-

5 trifluoromethylphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-
methylimidazol-1-yl)pyridin-2-yl]-4-(2-trifluoromethylphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-
a]pyridine



[0523]

Synthesis of 5-chloro-2-(2-trifluoromethylphenyl)valeric acid chloride

10 5-Chloro-2-(2-trifluoromethylphenyl)valeric acid obtained in Preparation

Example 2-3 (500 mg) was dissolved in tetrahydrofuran (9 mL). Dimethylformamide (0.1 mL) and oxalyl chloride (184 μ L) were added at 0°C and the reaction was initiated at room temperature. After 1.5 hours, concentration under reduced pressure gave an oil (532 mg), which was used directly for the next reaction as a crude product.

15 [0524]

Synthesis of 7-chloro-1-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-4-(2-
trifluoromethylphenyl)heptane-1,3-dione

A solution of 1-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]ethanone obtained in Preparation Example 1-8 (412 mg) in tetrahydrofuran (10 mL) was added at -30°C to
20 a lithium diisopropylamine solution prepared from n-butyllithium (1.4 mL) and diisopropylamine (528 μ L) in tetrahydrofuran (30 mL). After stirring at the same temperature for 30 minutes, 5-chloro-2-(2-trifluoromethylphenyl)valeric acid chloride (532 mg) was added and the mixture was stirred for 1.5 hours. After further stirring at room temperature for 30
25 minutes, the reaction was terminated with water, followed by dilution with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The oil after concentration under reduced pressure was purified by silica gel chromatography (mobile phase: ethyl acetate/heptane = 0 to 100%) to obtain the title compound (90 mg).
ESI-MS; m/z 494 [M⁺ + H].

[0525]

Synthesis of (+)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-4-(2-trifluoromethylphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-4-(2-trifluoromethylphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine

7-Chloro-1-[6-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl]-4-(2-trifluoromethylphenyl)heptane-1,3-dione (90 mg) was dissolved in ethanol (2 mL), and hydrazine monohydrate (26.5 μ L) was added at room temperature. After 1.5 hours, the mixture was heated under reflux. Further, ethanol (1 mL) and hydrazine monohydrate (13.3 μ L) were added 3.5 hours after the heating. After heating under reflux for 18 hours, the reaction solution was partitioned with ethyl acetate and water. The organic layer was washed with brine and dried over magnesium sulfate. Concentration under reduced pressure gave an oil. The oil was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 100%) to obtain a racemate of the title compound (31.2 mg). The resulting racemate was separated by CHIRALPAKTM AD-H (2 cm $\times$ 25 cm, mobile phase: ethanol:hexane = 3:7, flow rate: 13 mL/min) to obtain the title compound with a retention time of 23.5 minutes and positive optical rotation (9.0 mg) and the title compound with a retention time of 34.2 minutes and negative optical rotation (8.2 mg).

The property values of the title optically active compound with a retention time of 23.5 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.89-1.95 (m, 1H), 2.05-2.40 (m, 3H), 2.29 (s, 3H), 3.99 (s, 3H), 4.25 (ddd, J = 12.9, 10.9, 5.1 Hz, 1H), 4.42 (ddd, J = 12.9, 9.3, 5.4 Hz, 1H), 4.59 (dd, J = 10.2, 5.5 Hz, 1H), 6.28 (s, 1H), 6.95-6.97 (m, 1H), 7.27-7.30 (m, 1H), 7.36-7.41 (m, 1H), 7.48-7.50 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 1.2 Hz, 1H).

[0526]

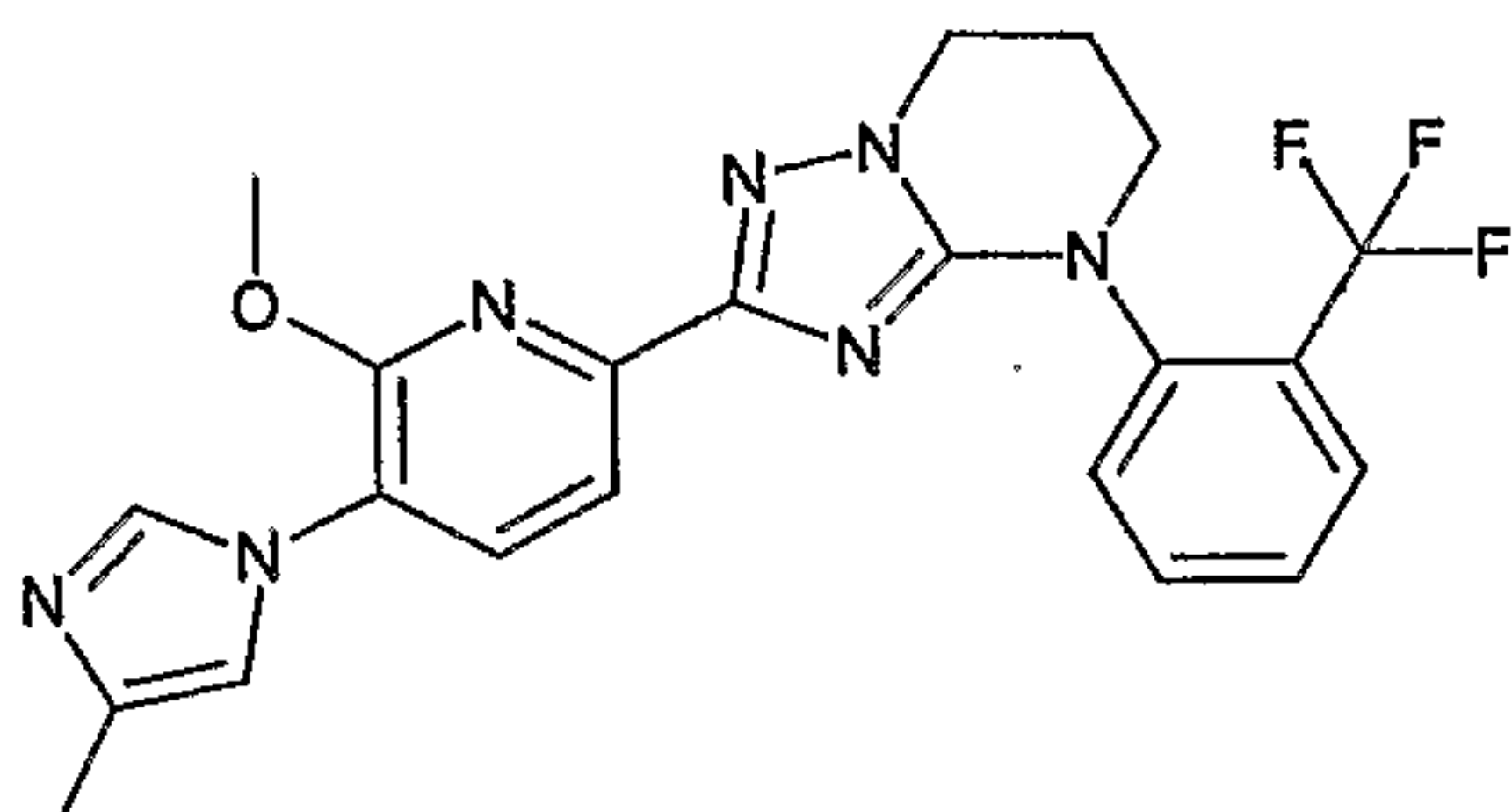
The property values of the title optically active compound with a retention time of 34.2 minutes are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.89-1.95 (m, 1H), 2.05-2.40 (m, 3H), 2.29 (s, 3H), 3.99 (s, 3H), 4.25 (ddd, J = 12.9, 10.9, 5.1 Hz, 1H), 4.42 (ddd, J = 12.9, 9.3, 5.4 Hz, 1H), 4.59 (dd, J = 10.2, 5.5 Hz, 1H), 6.28 (s, 1H), 6.95-6.97 (m, 1H), 7.27-7.30 (m, 1H), 7.36-7.41 (m, 1H), 7.48-7.50 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 1.2 Hz, 1H).

[0527]

Example 185

Synthesis of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-4-(2-trifluoromethylphenyl)-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine
[0528]



5 [0529]

Synthesis of phenyl (2-trifluoromethylphenyl)carbamate

2-Aminobenzotrifluoride (5 mL) and pyridine (6.44 mL) were dissolved in tetrahydrofuran (100 mL), and phenyl chloroformate (5.5 mL) was added dropwise under ice-cooling. After dropwise addition of the reagent, the mixture was brought back to room temperature and stirred for 4.5 hours. Water was added to the reaction solution and the mixture was concentrated under reduced pressure, followed by extraction with ethyl acetate. The resulting organic layer was washed with 2 N hydrochloric acid and brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (12.1 g). The property values of the compound are as follows.

ESI-MS; m/z 282 [$M^+ + H$].

[0530]

Synthesis of (2-trifluoromethylphenyl)carbamic acid hydrazide

20 Phenyl (2-trifluoromethylphenyl)carbamate (12.1 g) was dissolved in ethanol (150 mL). Hydrazine monohydrate (16.7 mL) was added and the mixture was heated under reflux for 2.25 hours. The reaction solution was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (7.5 g). The property values of the compound are as follows.

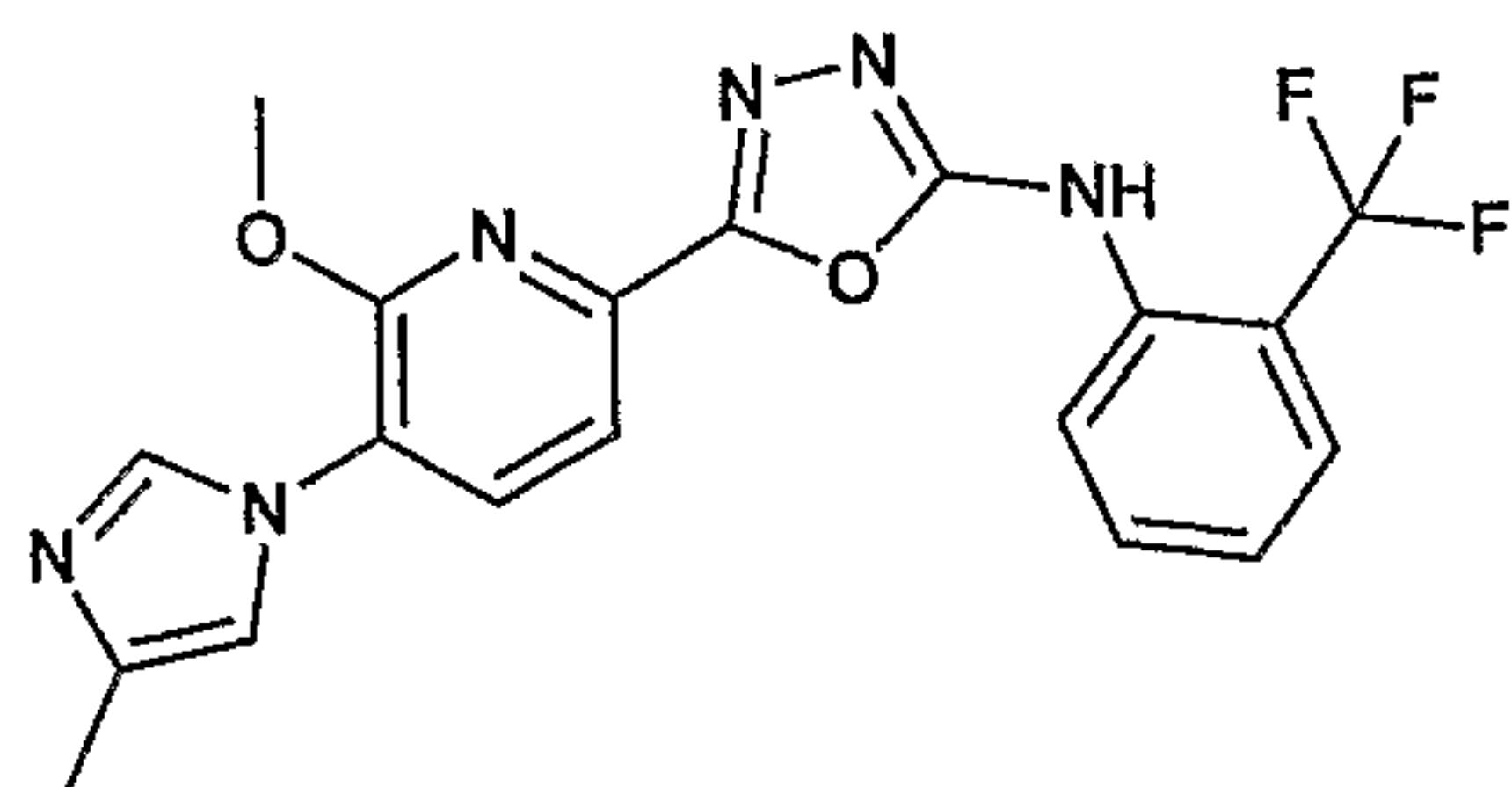
25 $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 3.90 (brs, 2H), 6.29 (brs, 1H), 7.13 (dd, $J = 7.6, 6.4$ Hz, 1H), 7.52 (dd, $J = 8.4, 6.4$ Hz, 1H), 7.58 (d, $J = 7.6$ Hz, 1H), 8.28 (d, $J = 8.4$ Hz, 1H), 8.87 (brs, 1H).

[0531]

Synthesis of {5-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-[1,3,4]oxazol-2-yl}-(2-

trifluoromethylphenyl)amine

[0532]



[0533]

6-Methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid obtained in
 5 Preparation Example 1-5 (581 mg), (2-trifluoromethylphenyl)carbamate (230 mg)
 and N,N-diisopropylethylamine (914 μ L) were dissolved in dichloromethane (10 mL), followed
 by addition of bis(2-oxo-3-oxazolidinyl)phosphinic acid chloride (321 mg). After addition of the
 reagent, the mixture was stirred at room temperature overnight. A sodium bicarbonate solution
 and a 5% methanol/ethyl acetate mixed solvent were added to the reaction solution, and the
 10 organic layer was separated. The resulting organic layer was washed with brine and then dried
 over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the
 organic layer was concentrated under reduced pressure. The residue was purified by silica gel
 column chromatography to obtain a condensate (349 mg).

Phosphorus oxychloride (30 mL) was added to the condensate (2.06 g), and the
 15 mixture was heated with stirring at 120°C for 1.6 hours. After leaving to cool, the reaction
 solution was concentrated under reduced pressure. A sodium hydroxide solution and a 10%
 methanol/chloroform mixed solvent were added and the organic layer was separated. The
 resulting organic layer was washed with 2 N hydrochloric acid and brine and then dried over
 anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic
 20 layer was concentrated under reduced pressure. The resulting residual solid was washed with
 tert-butyl methyl ether to obtain the title compound (754 mg). The property values of the
 compound are as follows.

ESI-MS; m/z 417 [$M^+ + H$].

[0534]

25 Synthesis of (3-chloropropyl)-{5-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-
[1,3,4]oxazol-2-yl}-(2-trifluoromethylphenyl)amine

{5-[6-Methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-[1,3,4]oxazol-2-yl}-
 (2-trifluoromethylphenyl)amine (657 mg) and 1-chloro-3-iodopropane (1.66 mL) were dissolved
 in N,N-dimethylformamide (15 mL), and 60% sodium hydride (172 mg) was added under ice-

cooling. After addition of the reagent, the mixture was brought back to room temperature and stirred for two hours. Water and ethyl acetate were added to the reaction solution, and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography to obtain the title compound (216 mg). The property values of the compound are as follows.

ESI-MS; m/z 493 [$M^+ + H$].

[0535]

10 Synthesis of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-4-(2-trifluoromethylphenyl)-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine

(3-Chloropropyl)-{5-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-[1,3,4]oxazol-2-yl}-(2-trifluoromethylphenyl)amine (239 mg) and ammonium acetate dried under reduced pressure (1.12 g) were suspended in acetic acid (10 mL). The suspension was heated with stirring at 180°C for two hours using a microwave reactor. The reaction solution was concentrated under reduced pressure. A sodium bicarbonate solution and ethyl acetate were added and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography and further purified again by CHIRALPAK™ IB (2 cm × 25 cm; mobile phase: hexane:ethanol = 4:6) to obtain the title compound (30 mg). The property values of the compound are as follows.

ESI-MS; m/z 456 [$M^+ + H$].

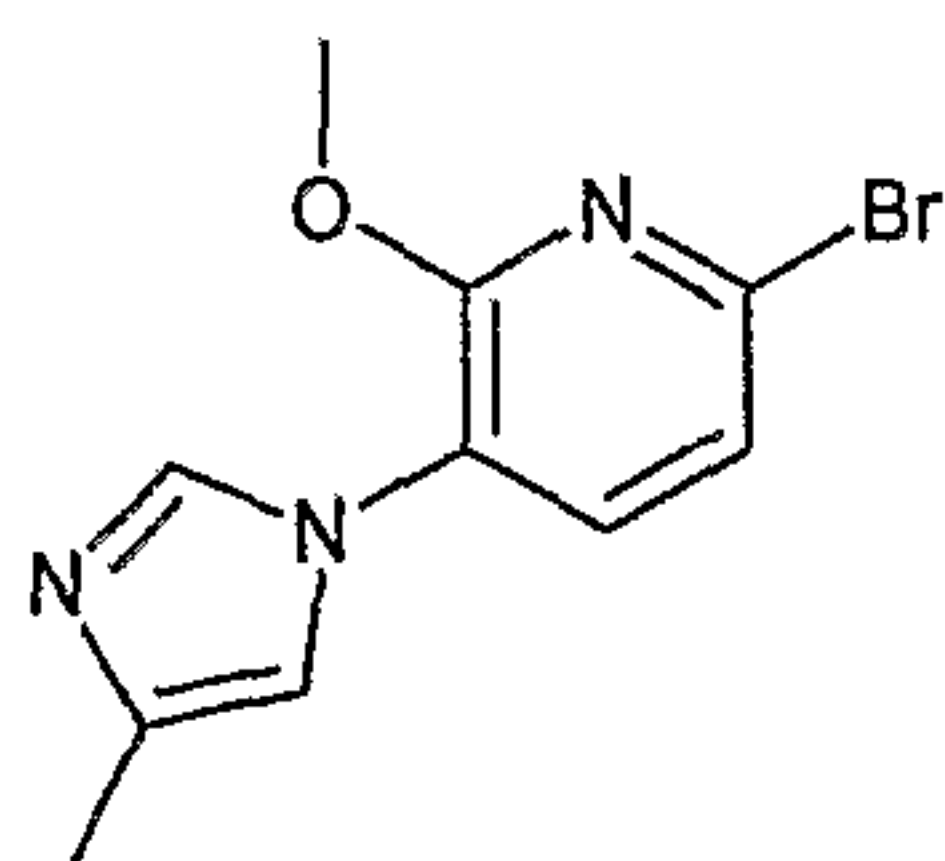
¹H-NMR (CDCl₃) δ (ppm): 2.28 (s, 3H), 2.30-2.50 (m, 2H), 3.64-3.74 (m, 2H), 4.12 (s, 3H), 4.30-7.41 (m, 2H), 6.94-6.98(m, 1H), 7.47-7.54 (m, 3H), 7.59 (d, $J = 7.6$ Hz, 1H), 7.67 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H), 7.76-7.82 (m, 2H).

[0536]

Preparation Example 1-1

Synthesis of 6-bromo-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)pyridine

30 [0537]



[0538]

Synthesis of N-(6-bromo-2-methoxypyridin-3-yl)formamide

Acetic anhydride (203 mL) was added dropwise to formic acid (204 mL) under ice-cooling, and the mixture was stirred at the same temperature for 25 minutes. 6-Bromo-2-methoxypyridine-3-amine powder (CAS #89466-18-2, 146 g) was put into the reaction mixture over 10 minutes, and then the reaction solution was stirred at the same temperature for 30 minutes. The water bath was removed. tert-Butyl methyl ether (300 mL) and n-heptane (500 mL) were sequentially added dropwise to the reaction solution, and then the reaction solution was stirred for 30 minutes. The precipitated powder was collected by filtration. The resulting powder was crushed with a mortar, washed with tert-butyl methyl ether and then dried under reduced pressure to obtain 137.4 g of the title compound.

Then, the combined filtrate and washing solution were concentrated under reduced pressure. The residue was triturated with tert-butyl methyl ether and dried under reduced pressure to obtain 21.9 g of the title compound. The property values of the compound are as follows.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 4.03 (s, 3H), 7.08 (d, $J = 8.0$ Hz, 1H), 7.61 (brs, 1H), 8.47-8.51 (m, 2H).

[0539]

Synthesis of N-(6-bromo-2-methoxypyridin-3-yl)-N-(2-oxopropyl)formamide

Chloroacetone (82 mL) was added dropwise to a suspension of N-(6-bromo-2-methoxypyridin-3-yl)formamide (159.3 g), cesium carbonate (359 g) and potassium iodide (11.4 g) in N,N-dimethylformamide (800 mL) over seven minutes. Then, the reaction solution was stirred at room temperature for one hour and 20 minutes.

The reaction solution was concentrated under reduced pressure. Ethyl acetate and water were added to the resulting residue, and the organic layer was separated. The resulting organic layer was washed with brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 215.2 g of the title compound. The property values of the compound are as follows.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.17 (s, 3H), 4.00 (s, 3H), 4.47 (s, 2H), 7.13 (d, $J = 7.6$ Hz, 1H),

7.48 (d, $J = 7.6$ Hz, 1H), 8.22 (s, 1H).

[0540]

Synthesis of 6-bromo-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)pyridine

A suspension of ammonium acetate (267 g) and N-(6-bromo-2-methoxypyridin-3-yl)-N-(2-oxopropyl)formamide (199 g) in glacial acetic acid (400 mL) was stirred at 130°C for one hour and 10 minutes. The reaction solution was brought back to room temperature. Ethyl acetate and ice water were added to the reaction solution, and the mixture was ice-cooled. Then, concentrated aqueous ammonia (500 mL) was added dropwise and then the organic layer was separated. The resulting organic layer was sequentially washed with water and brine and dried over anhydrous magnesium sulfate. Then, the organic layer was purified by short silica gel column chromatography (carrier: WakogelTM C-200 manufactured by Wako Pure Chemical Industries, Ltd.; elution solvent: ethyl acetate). The eluted fraction was concentrated. The resulting residue was triturated with ethyl acetate and tert-butyl methyl ether and dried under reduced pressure to obtain 107.7 g of the title compound.

Then, the trituration mother liquor was concentrated. The resulting residue was purified by silica gel column chromatography (carrier: WakogelTM C-200; elution solvent: toluene-ethyl acetate system). The target fraction was concentrated. The resulting residue was triturated with tert-butyl methyl ether and dried under reduced pressure to obtain 12.9 g of the title compound.

The property values of the compound are as follows.

ESI-MS; m/z 268 [$M^+ + H$].

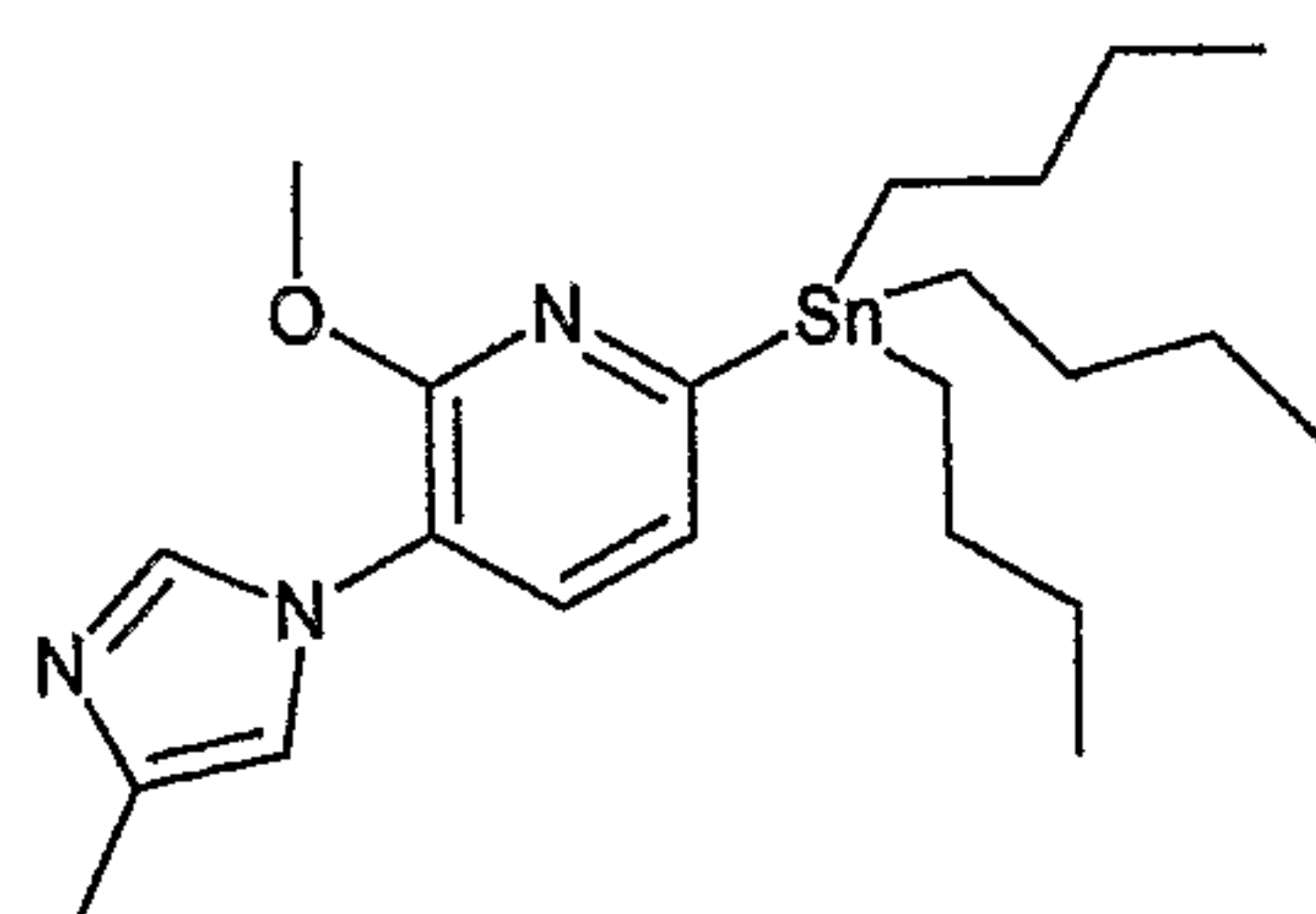
¹H-NMR (CDCl₃) δ (ppm): 2.29 (d, $J = 0.8$ Hz, 3H), 4.03 (s, 3H), 6.92 (dd, $J = 1.2, 0.8$ Hz, 1H), 7.16 (d, $J = 8.0$ Hz, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 1.2$ Hz, 1H).

[0541]

Preparation Example 1-2

Synthesis of 2-methoxy-3-(4-methyl-1H-imidazol-1-yl)-6-tributylstannylpyridine

[0542]



[0543]

6-Bromo-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)pyridine (10 g) and hexa-n-butyltin (31.8 mL) were dissolved in toluene (300 mL).

Tetrakis(triphenylphosphine)palladium (2.2 g) was added and the mixture was heated under reflux in a nitrogen atmosphere for four hours. After leaving to cool, the insoluble matter was removed from the reaction solution by filtration through celite, followed by concentration under reduced pressure. The resulting residue was purified by NH silica gel column chromatography and then by silica gel column chromatography to obtain the title compound (5.4 g). The property values of the compound are as follows.

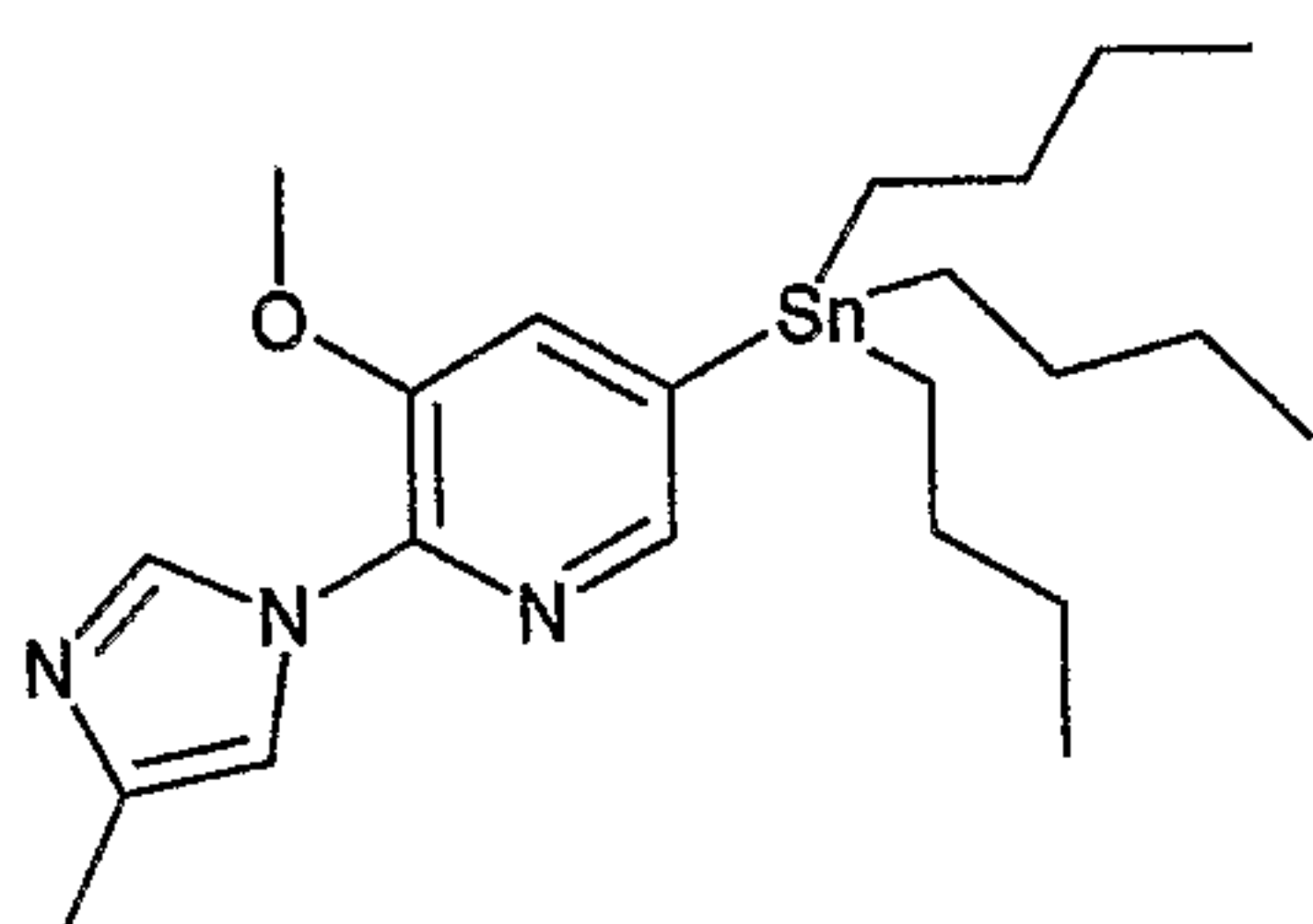
¹H-NMR (CDCl₃) δ (ppm): 0.90 (t, J = 7.2 Hz, 9H), 1.03-1.22 (m, 6H), 1.30-1.40 (m, 6H), 1.49-1.70 (m, 6H), 2.29 (s, 3H), 4.01 (s, 3H), 6.96 (s, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.75-7.77 (m, 1H).

[0544]

Preparation Example 1-3

Synthesis of 3-methoxy-2-(4-methyl-1H-imidazol-1-yl)-5-tributylstannylpyridine

15 [0545]



[0546]

Synthesis of N-(5-bromo-3-methoxypyridin-2-yl)formamide

Iron (67.3 g) and ammonium chloride (129 g) were added to a solution of 5-bromo-3-methoxy-2-nitropyridine (56.0 g, CAS #152684-26-9) in ethanol (500 mL) and water (200 mL). The reaction solution was stirred at 80 to 90°C for one hour and then left to cool to room temperature. The reaction solution was filtered through celite and washed with ethanol. Then, the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate and water, and the organic layer was separated. The resulting organic layer was washed with brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was diluted with THF (84 mL). The THF solution was added dropwise to a mixed solution of formic acid (78.1 mL) and acetic anhydride (78.3 mL) at room temperature. Then, the reaction solution was stirred for one hour. Ice water (500 mL) was added to the reaction solution, and the precipitated crystals were collected by filtration. The crystals were

washed with water and then air-dried. The crystals were recrystallized from toluene to obtain 34.1 g of the title compound. The property values of the compound are as follows.

ESI-MS; m/z 231 [$M^+ + H$].

[0547]

5 Synthesis of N-(5-bromo-3-methoxypyridin-2-yl)-N-(2-oxopropyl)formamide

Cesium carbonate (96 g), potassium iodide (2.45 g) and chloroacetone (23.5 mL) were added to a solution of N-(5-chloro-3-methoxypyridin-2-yl)formamide (34.1 g) in DMF (200 mL), and the mixture was stirred at 80°C for 45 minutes. Ice water and ethyl acetate were added to the reaction solution, and the organic layer was separated. The organic layer was washed with brine and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 52.8 g of the crude title compound. The property values of the compound are as follows.

ESI-MS; m/z 287 [$M^+ + H$].

[0548]

15 Synthesis of 5-bromo-3-methoxy-2-(4-methyl-1H-imidazol-1-yl)pyridine

A mixture of the crude N-(5-bromo-3-methoxypyridin-2-yl)-N-(2-oxopropyl)formamide (26.4 g), acetic acid (52.8 mL) and ammonium acetate (35.5 g) was stirred at 130°C for one hour. The reaction solution was left to cool to room temperature and concentrated under reduced pressure. The residue diluted with ice water, ethyl acetate and aqueous ammonia, and the organic layer was separated. The organic layer was washed with brine and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system) to obtain 5.69 g of the title compound. The property values of the compound are as follows.

25 ESI-MS; m/z 268 [$M^+ + H$].

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.29 (s, 3H), 3.97 (s, 3H), 7.48 (brs, 1H), 7.49 (d, $J = 2.0$ Hz, 1H), 8.12 (d, $J = 2.0$ Hz, 1H), 8.30 (brs, 1H).

[0549]

Synthesis of 3-methoxy-2-(4-methyl-1H-imidazol-1-yl)-5-tributylstannylpyridine

30 Hexa-n-butylditin (2.07 mL) and tetrakis(triphenylphosphine)palladium (0) (319 mg) were added to a suspension of 5-bromo-3-methoxy-2-(4-methyl-1H-imidazol-1-yl)pyridine (740 mg) in xylene (11 mL), and the mixture was stirred at 155°C for two hours and 30 minutes. The reaction solution was purified by silica gel column chromatography (carrier: Wakogel C-200; elution solvent: heptane:ethyl acetate = 3:1) to obtain 325 mg of the title compound. The

property values of the compound are as follows.

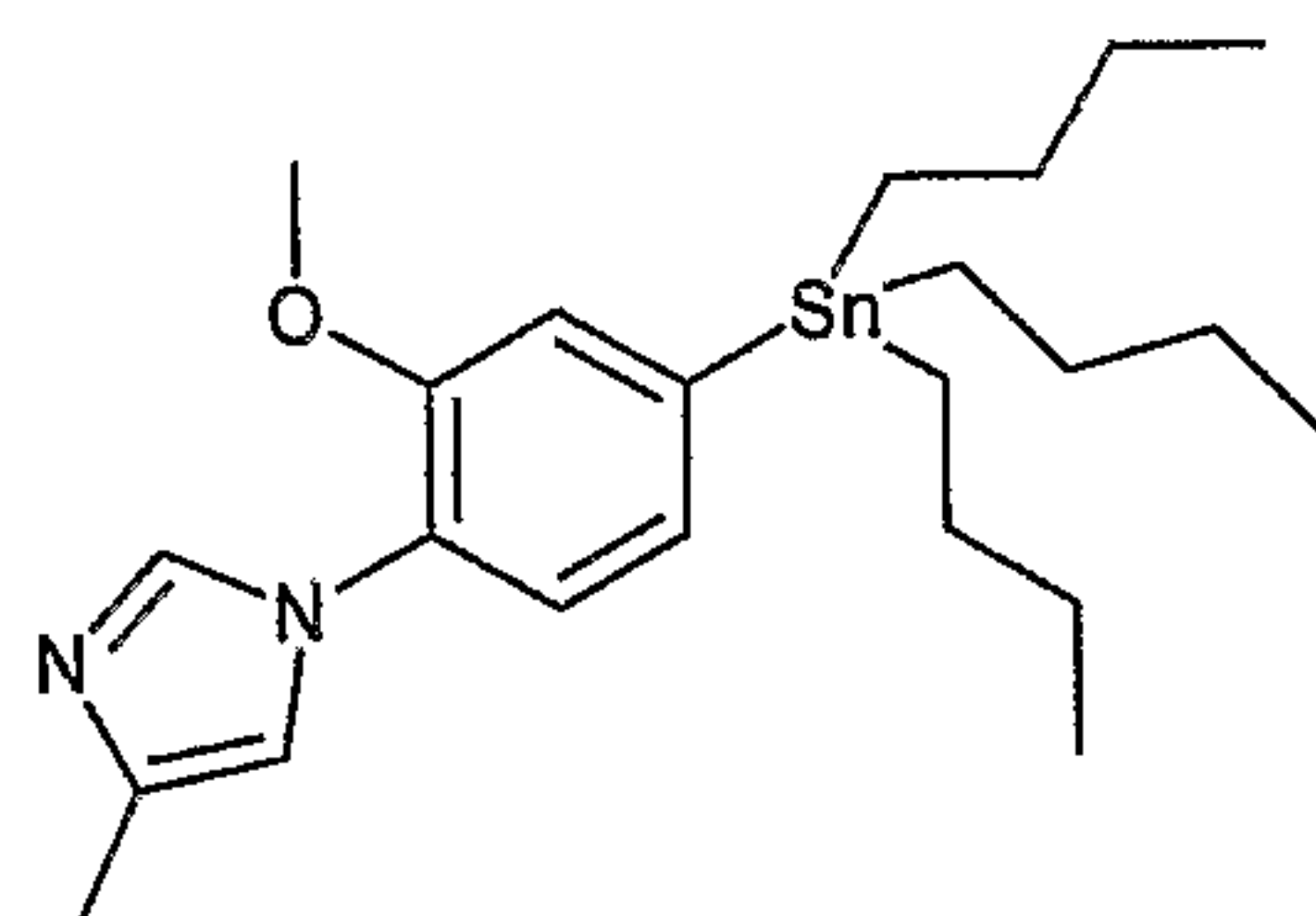
¹H-NMR (CDCl₃) δ (ppm): 0.90 (t, J = 7.2 Hz, 9H), 1.13 (t, J = 7.2 Hz, 6H), 1.30-1.40 (m, 6H), 1.50-1.60 (m, 6H), 2.30 (d, J = 1.2 Hz, 3H), 3.95 (s, 3H), 7.38 (d, J = 1.2 Hz, 1H), 7.52 (t, J = 1.2 Hz, 1H), 8.03 (d, J = 1.2 Hz, 1H), 8.33 (d, J = 1.2 Hz, 1H).

5 [0550]

Preparation Example 1-4

Synthesis of 1-(2-methoxy-4-tributylstannylphenyl)-4-methyl-1H-imidazole

[0551]



[0552]

10 1-(4-bromo-2-methoxy-phenyl)-4-methyl-1H-imidazole (CAS No. 870838-56-5, 900 mg) and hexa-n-butylditin (3.91 g) were dissolved in toluene (20 mL).

Tetrakis(triphenylphosphine) palladium (195 mg) was added and the mixture was stirred with heating under reflux for seven hours and 20 minutes. After leaving to cool, the insoluble matter was removed by filtration through celite, followed by concentration under reduced pressure. The residue was purified by NH silica gel column chromatography to obtain the title compound (893 mg). The property values of the compound are as follows.

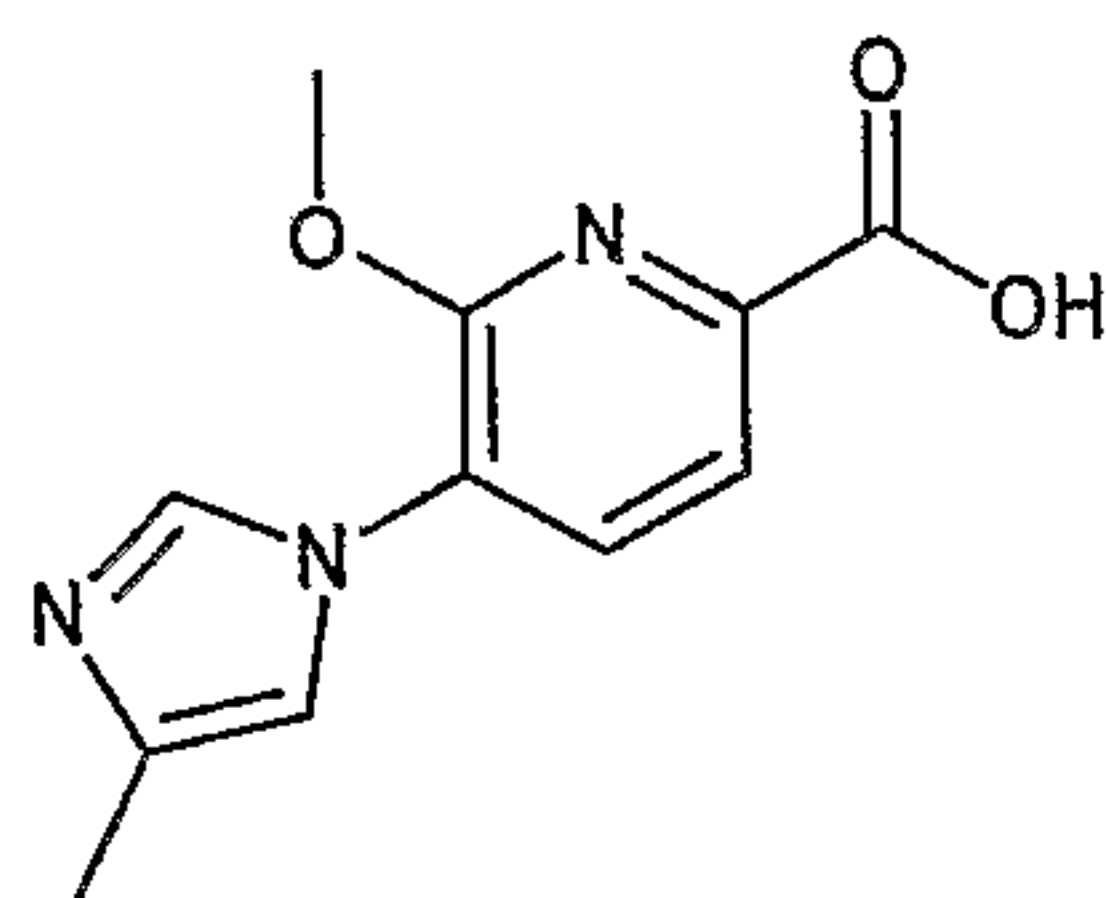
¹H-NMR (CDCl₃) δ (ppm): 0.90 (t, J = 7.2 Hz, 9H), 1.09-1.11 (m, 6H), 1.32-1.40 (m, 6H), 1.53-1.59 (m, 6H), 2.30 (d, J = 1.2 Hz, 3H), 3.85 (s, 3H), 6.92 (t, J = 1.2 Hz, 1H), 7.09 (dd, J = 1.2 Hz, 7.6 Hz, 1H), 7.10 (d, J = 1.2 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 1.2 Hz, 1H).

20 [0553]

Preparation Example 1-5

Synthesis of 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid

[0554]



[0555]

Synthesis of 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carbonitrile

6-Bromo-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)pyridine obtained in

Preparation Example 1-1 (50 g) and zinc (II) cyanide (35 g) were suspended in N-

- 5 methylpyrrolidone (400 mL). Tetrakis(triphenylphosphine)palladium (0) (8.5 g) was added and the mixture was stirred at 100°C for one hour and 10 minutes. The reaction solution was added dropwise to a solution of ice water (1.5L) and concentrated aqueous ammonia (150 mL) mixed by stirring. The precipitated powder was filtered. The resulting powder was washed with water and then air-dried overnight to obtain 56.5 g of the title compound. The property values of the
- 10 compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H), 4.09 (s, 3H), 7.02 (brs, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.90 (brs, 1H).

[0556]

Synthesis of 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid

- 15 Lithium hydroxide powder (13 g) was added to a suspension of 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carbonitrile (52.4 g) in water (464 mL), and the mixture was heated under reflux for three hours. The reaction solution was left to cool to room temperature. The reaction solution was filtered through celite, and the celite was washed with water (100 mL × 4). Concentrated hydrochloric acid was added to the filtrate under ice-cooling
- 20 to adjust the pH to 4 to 5. The precipitated powder was collected by filtration. The resulting powder was washed with water and then air-dried for three days to obtain 51.9 g of the title compound. The property values of the compound are as follows.

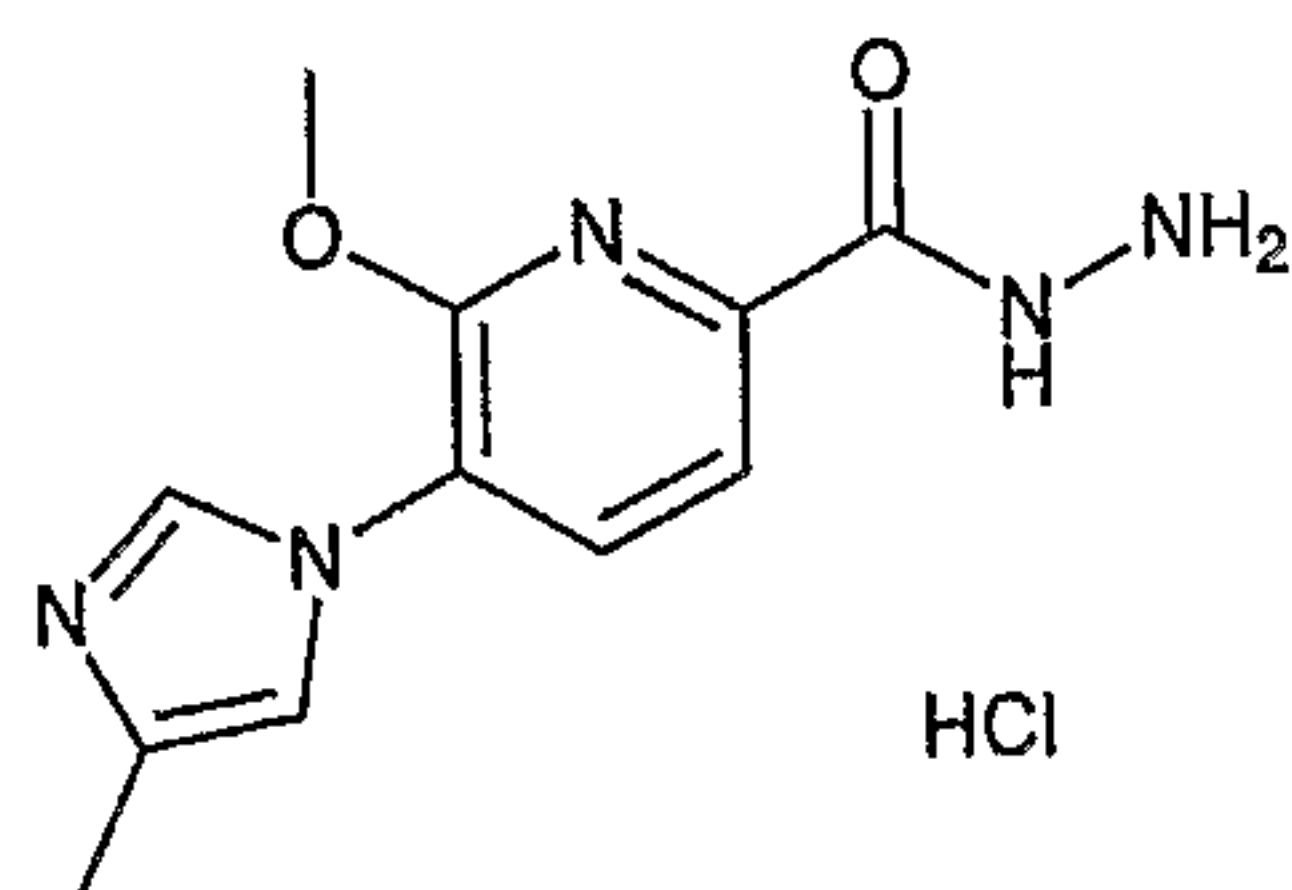
¹H-NMR (DMSO-D₆) δ (ppm): 2.17 (s, 3H), 4.01 (s, 3H), 7.33 (brs, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 8.02 (brs, 1H).

25 [0557]

Preparation Example 1-6

Synthesis of 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid hydrazide and 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid hydrazide hydrochloride

[0558]



[0559]

Synthesis of benzyl N'-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carbonyl]hydrazinecarboxylate

5 Benzyl carbazate (27.8 g), 1-hydroxybenztriazole (24.8 g) and 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (35.4 g) were sequentially added to a solution of 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid obtained in Preparation Example 1-5 (51.9 g) and IPEA (44 mL) in N,N-dimethylformamide (184 mL), and the mixture was stirred at room temperature for six hours and 30 minutes. Ethyl acetate, ice
10 water and a saturated sodium bicarbonate solution were added to the reaction solution, and the organic layer was separated. The resulting organic layer was dried over anhydrous magnesium sulfate and then filtered through an NH silica gel pad. The resulting filtrate was concentrated under reduced pressure. Ethyl acetate was added to the resulting residue, and the powder was collected by filtration. The resulting powder was air-dried to obtain 28.4 g of the title
15 compound.

Further, the aqueous layer already extracted was reextracted with ethyl acetate. The resulting organic layer was washed with brine, dried over anhydrous magnesium sulfate and then filtered through an NH silica gel pad. The resulting filtrate was concentrated under reduced pressure. Ethyl acetate was added to the resulting residue, and the powder was collected by
20 filtration. The resulting powder was air-dried to obtain 9.15 g of the title compound. The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.31 (d, J = 1.2 Hz, 3H), 4.08 (s, 3H), 5.23 (s, 2H), 6.87 (brs, 1H), 7.01 (t, J = 1.2 Hz, 1H), 7.32-7.45 (m, 5H), 7.71 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 9.17 (brs, 1H).

25 [0560]

Synthesis of 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid hydrazide and 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid hydrazide hydrochloride

10% palladium-carbon (50% wet, 2.84g) was added to a solution of benzyl N'-[6-

methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carbonyl]hydrazinecarboxylate (28.4 g) in methanol (300 mL). The mixture was hydrogenated at an intermediate pressure (2 to 3 atm) for five hours. Chloroform (600 mL) was added to the reaction solution, and then the palladium-carbon was removed by filtration through celite. The filtrate was concentrated under reduced pressure to obtain 19.5 mg of a free form of the title compound. The property values of the compound are as follows.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.30 (d, $J = 1.2$ Hz, 3H), 4.06 (s, 3H), 4.10 (s, 1H), 4.11 (s, 1H), 7.01 (t, $J = 1.2$ Hz, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 1.2$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 8.69 (brs, 1H).

A hydrochloride of the title compound was obtained by the same operation, provided that the hydrogenation reaction was performed in a chloroform-methanol mixed solvent. The property values of the compound are as follows.

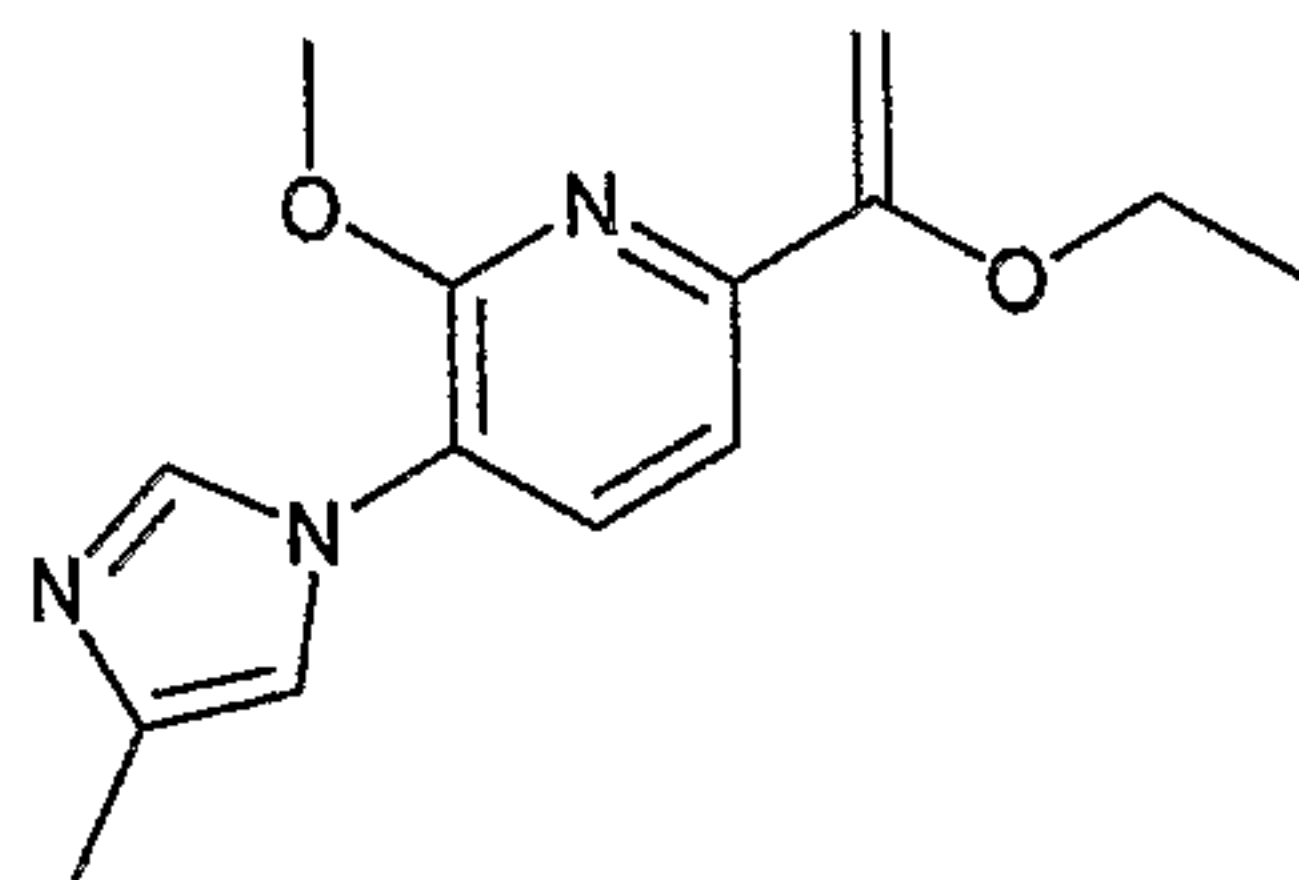
$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.31 (d, $J = 1.2$ Hz, 3H), 4.06 (s, 3H), 7.01 (t, $J = 1.2$ Hz, 1H), 7.71 (d, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 1.2$ Hz, 1H), 7.89 (d, $J = 7.6$ Hz, 1H), 8.69 (brs, 1H).

[0561]

Preparation Example 1-7

Synthesis of 6-(1-ethoxyvinyl)-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)pyridine

[0562]



[0563]

1-Ethoxyvinyltri-n-butyltin (3.7 mL) was added to a suspension of 6-bromo-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)pyridine obtained in Preparation Example 1-1 (2.66 g) and bis(triphenylphosphine)palladium (II) chloride (350 mg) in dioxane (25 mL), and the mixture was stirred at 100°C for five hours and 45 minutes. The reaction solution was left to cool to room temperature and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: WakogelTM C-200; elution solvent: heptane:ethyl acetate = 1:0 -> 9:1 -> 3:1 -> 1:1). The target fraction was concentrated. The resulting powder was triturated with diethyl ether-n-hexane and dried under reduced pressure to obtain 1.57 g of the title compound. Then, the trituration mother liquor was concentrated to obtain 858 mg of the title compound. The property values of the compound are as follows.

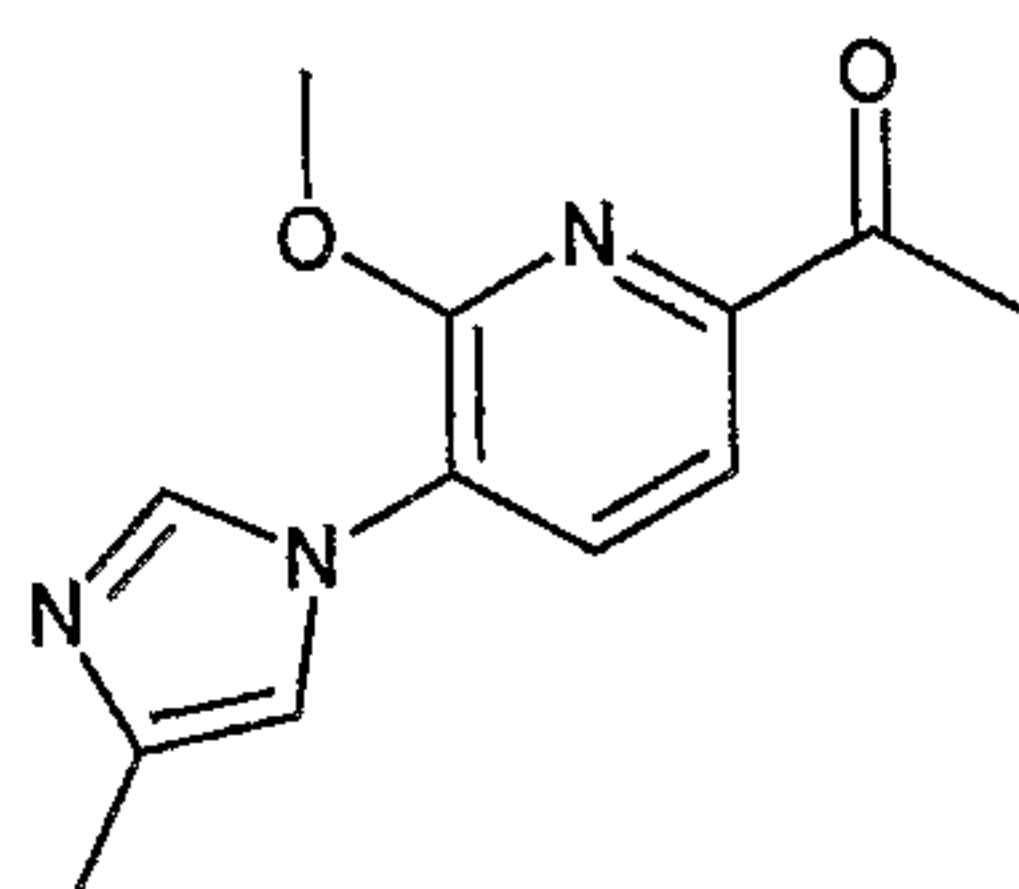
¹H-NMR (CDCl₃) δ (ppm): 1.45 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 3.98 (q, J = 7.2 Hz, 2H), 4.04 (s, 3H), 4.38 (d, J = 1.6 Hz, 1H), 5.48 (d, J = 1.6 Hz, 1H), 6.97 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H).

[0564]

5 Preparation Example 1-8

Synthesis of 1-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]ethanone

[0565]



[0566]

6-Bromo-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)pyridine obtained in

- 10 Preparation Example 1-1 (2.5 g) was dissolved in N-methylpyrrolidone (93 mL). Palladium acetate (418 mg), 1,3-bis(diphenylphosphino)propane (1.54 g), 1-ethoxyvinyltri-N-butyltin (3.15 mL) and cuprous oxide (2 g) were added, followed by stirring at 120°C. After 16 hours, the reaction solution was partitioned with water and ethyl acetate. The organic layer was washed with aqueous ammonia (twice) and brine. After drying over magnesium sulfate, concentration
- 15 under reduced pressure gave an oil. The oil was dissolved in methylene chloride (20 mL), followed by addition of trifluoroacetic acid (20 mL). After stirring for one hour, concentration under reduced pressure gave an oil which was partitioned with water and methylene chloride. The organic layer was washed with 1 N sodium hydroxide, water (four times) and brine and dried over magnesium sulfate. The oil after concentration under reduced pressure was purified
- 20 by silica gel chromatography (mobile phase: ethyl acetate/heptane = 0 to 100%) to obtain the title compound (1 g) as a yellow solid.

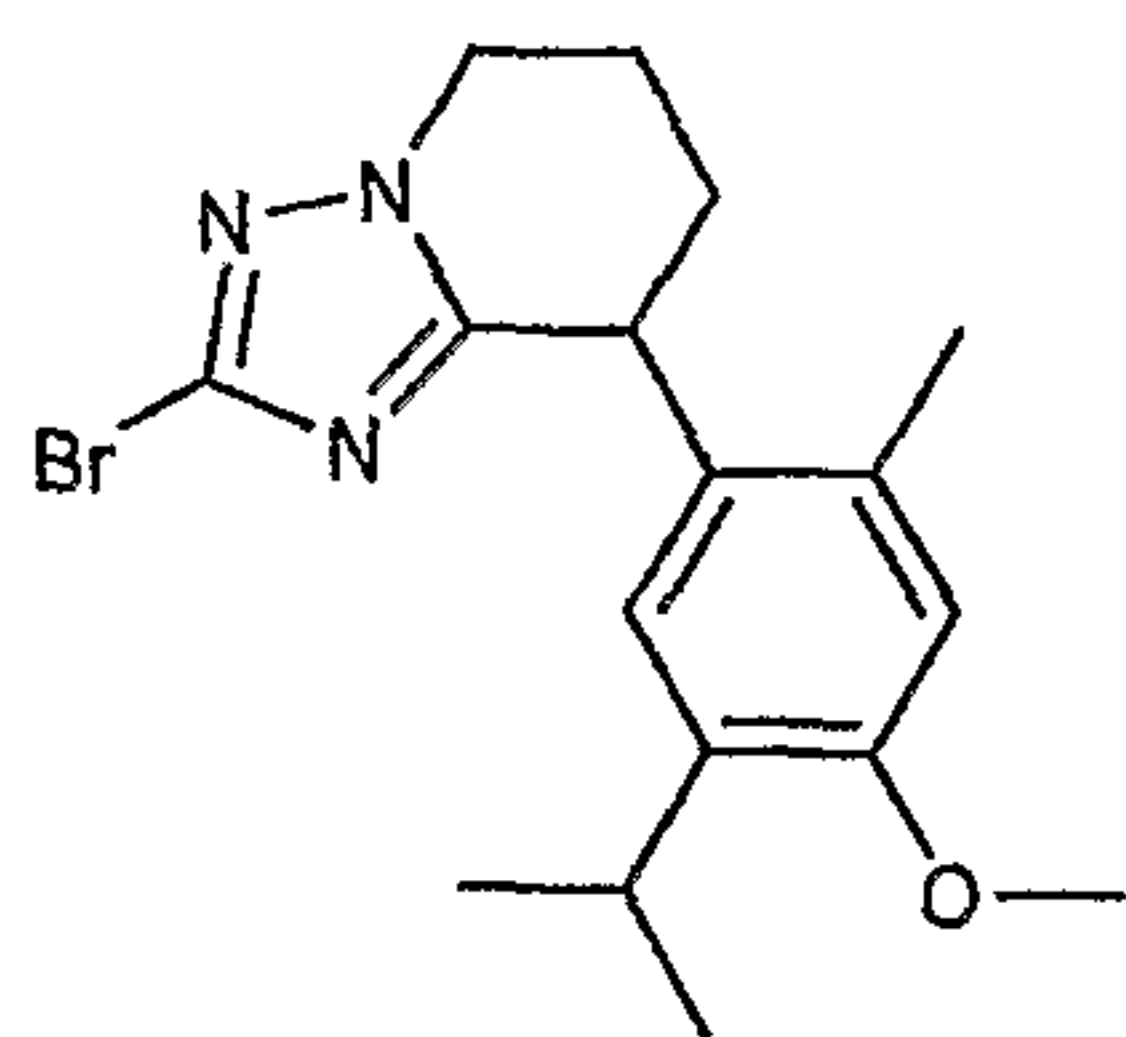
ESI-MS; m/z 232 [M⁺ + H].

[0567]

Preparation Example 2-1

- 25 Synthesis of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0568]



[0569]

Synthesis of methyl (5-isopropyl-4-methoxy-2-methylphenyl)acetate

(5-Isopropyl-4-methoxy-2-methylphenyl)acetic acid (CAS No. 81354-65-6, 5.5 g) was dissolved in methanol (50 mL), and thionyl chloride (3.5 mL) was added dropwise under ice-cooling. After dropwise addition of the reagent, the mixture was brought back to room temperature and stirred for two hours. The reaction solution was concentrated under reduced pressure. A saturated sodium bicarbonate solution and tert-butyl methyl ether were added and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (5.0 g). The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.19 (d, J = 7.2 Hz, 3H), 1.19 (d, J = 7.2 Hz, 3H), 2.28 (s, 3H), 3.25 (qq, J = 7.2, 7.2 Hz, 1H), 3.58 (s, 2H), 3.68 (s, 3H), 3.80 (s, 3H), 6.66 (s, 1H), 7.00 (s, 1H).

[0570]

Synthesis of methyl 5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoate

60% sodium hydride (928 mg) was suspended in anhydrous N,N-dimethylformamide (50 mL). A solution of methyl (5-isopropyl-4-methoxy-2-methylphenyl)acetate (5 g) in anhydrous N,N-dimethylformamide (30 mL) was added in a nitrogen atmosphere, so that the internal temperature was maintained at 4 to 6°C. After stirring at the same temperature for five minutes, 1-chloro-3-iodopropane (4.5 mL) was added so that the internal temperature was maintained at 4 to 6°C. After addition of the reagent, the mixture was brought back to room temperature and stirred for four hours. Ethyl acetate was added to the reaction solution, followed by washing with water. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (7.7 g). The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.17 (d, J = 7.2 Hz, 3H), 1.19 (d, J = 7.2 Hz, 3H), 1.64-1.97 (m, 3H), 2.14-2.25 (m, 1H), 2.35 (s, 3H), 3.24 (qq, J = 7.2, 7.2 Hz, 1H), 3.48-3.56 (m, 2H), 3.64 (s, 3H), 3.77 (t, 7.6 Hz, 1H), 3.08 (s, 3H), 6.64 (s, 1H), 7.08 (s, 1H).

[0571]

5 Synthesis of tert-butyl N'-[5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoyl]hydrazinecarboxylate

Methyl 5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoate (7.7 g) was dissolved in a mixed solvent of methanol (25 mL) and tetrahydrofuran (25 mL). A 5 N sodium hydroxide solution (22 mL) was added and the mixture was stirred at room temperature
10 for four hours. The reaction solution was concentrated under reduced pressure and water was added, followed by washing with heptane. The aqueous layer was made acidic with 5 N hydrochloric acid, followed by extraction with tert-butyl methyl ether. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and the organic layer was concentrated under reduced pressure to
15 obtain 5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoic acid (6.2 g).

5-Chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoic acid (6.2 g), tert-butyl carbazate (4.1 g) and N,N-diisopropylethylamine (10.8 mL) were dissolved in dichloromethane (120 mL). Bis(2-oxo-3-oxazolidinyl)phosphinic acid chloride (7.9 g) was added under ice-cooling. After addition of the reagent, the mixture was brought back to room
20 temperature and stirred overnight. The reaction solution was concentrated under reduced pressure. A sodium bicarbonate solution and tert-butyl methyl ether were added and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column
25 chromatography to obtain the title compound (6.1 g). The property values of the compound are as follows.

ESI-MS; m/z 435 [M⁺+Na].

[0572]

Synthesis of 5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoic acid hydrazide

30 tert-Butyl N'-[5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoyl]hydrazinecarboxylate (6.1 g) was dissolved in ethyl acetate (50 mL). A 4 N hydrochloric acid-ethyl acetate solution (50 mL) was added and the mixture was stirred at room temperature for 3.5 hours. The reaction solution was made alkaline with a 5 N sodium hydroxide solution under ice-cooling, and the organic layer was separated. The resulting organic

layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (4.4 g). The property values of the compound are as follows.

5 ESI-MS; m/z 313 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.186 (d, $J = 6.8$ Hz, 3H), 1.190 (d, $J = 7.2$ Hz, 3H), 1.61-1.85 (m, 2H), 1.93-2.04 (m, 1H), 2.26-2.88 (m, 1H), 2.27 (s, 3H), 3.25 (qq, $J = 7.2, 6.8$ Hz, 1H), 3.48-3.59 (m, 3H), 3.75-3.89 (m, 5H), 6.49 (brs, 1H), 6.65 (s, 1H), 7.08 (s, 1H).

[0573]

10 Synthesis of 8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-2-ylamine

5-Chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoic acid hydrazide (4.4 g) and cyanamide (3.6 g) were dissolved in ethanol (150 mL). *p*-Toluenesulfonic acid monohydrate (4 g) was added and the mixture was heated under reflux at 80°C for two hours.

15 After cooling to room temperature, triethylamine (9.8 mL) was added and the mixture was further heated under reflux at 80°C for three days. The reaction solution was concentrated under reduced pressure. A sodium bicarbonate solution and ethyl acetate were added and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic
20 layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (2.4 g). The property values of the compound are as follows.

ESI-MS; m/z 301 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.12 (d, $J = 6.8$ Hz, 3H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.86-2.26 (m, 4H), 2.27 (s, 3H), 3.19 (qq, $J = 6.8, 6.8$ Hz 1H), 3.79 (s, 3H), 4.02 (brs, 2H), 4.06-4.12 (m, 2H), 4.19-4.24 (m, 1H), 6.64 (s, 1H), 6.69 (s, 1H).

[0574]

Synthesis of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

30 8-(5-Isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-2-ylamine (1.5 g) and copper (II) bromide (1.7 g) were dissolved in acetonitrile (50 mL). Isoamyl nitrite (1 mL) was added and the mixture was heated with stirring at 70°C for 45 minutes. Ethyl acetate was added to the reaction solution, followed by washing with aqueous ammonia. The resulting organic layer was washed with brine and then dried over anhydrous

sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (1.4 g). The property values of the compound are as follows.

5 ESI-MS; m/z 364 [$M^+ + H$].

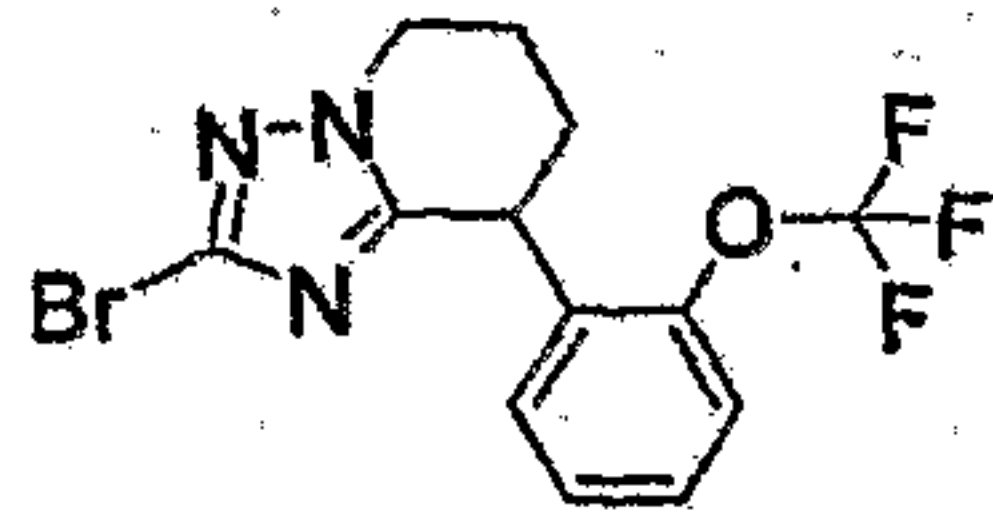
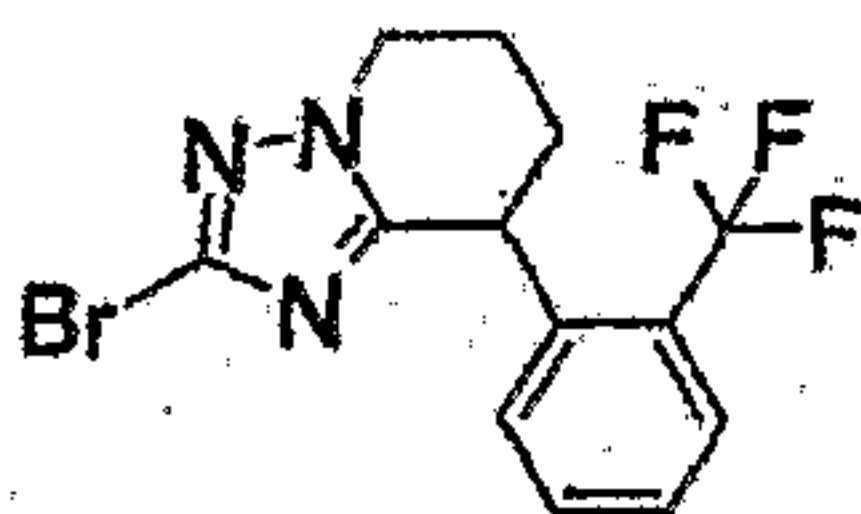
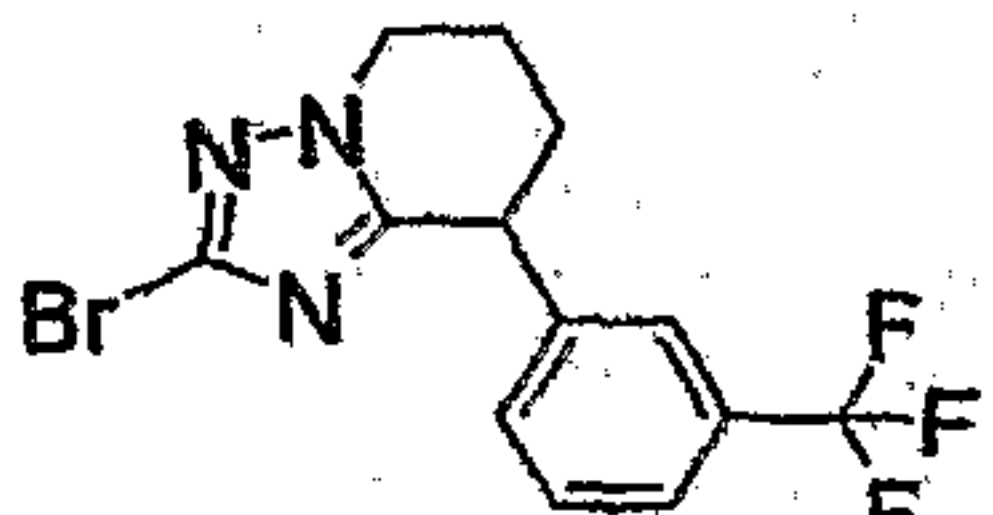
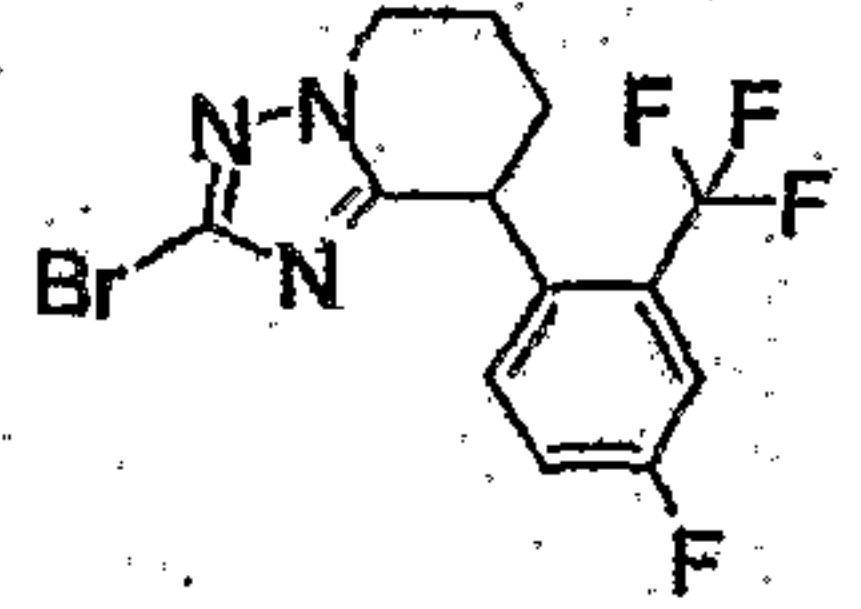
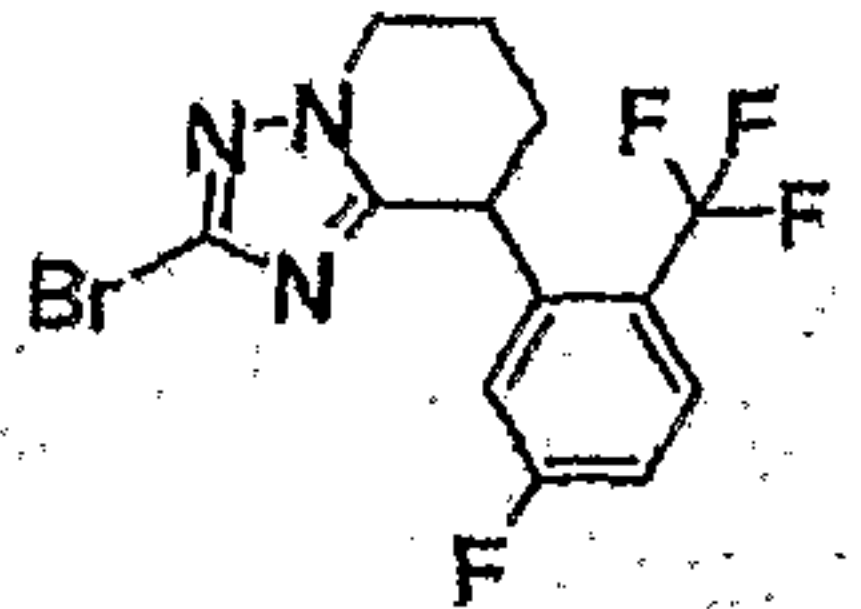
^1H -NMR ($CDCl_3$) δ (ppm): 1.11 (d, $J = 7.2$ Hz, 3H), 1.12 (d, $J = 7.2$ Hz, 3H), 1.90-2.30 (m, 4H), 2.26 (s, 3H), 3.19 (qq, $J = 7.2, 7.2$ Hz, 1H), 3.80 (s, 3H), 4.24-4.29 (m, 2H), 4.30-4.36 (m, 1H), 6.59 (s, 1H), 6.65 (s, 1H).

[0575]

10 The compounds of Preparation Examples 2-2 to 2-6 were obtained by the same method as in Example 2-1 (Table 6).

[0576]

Table 6

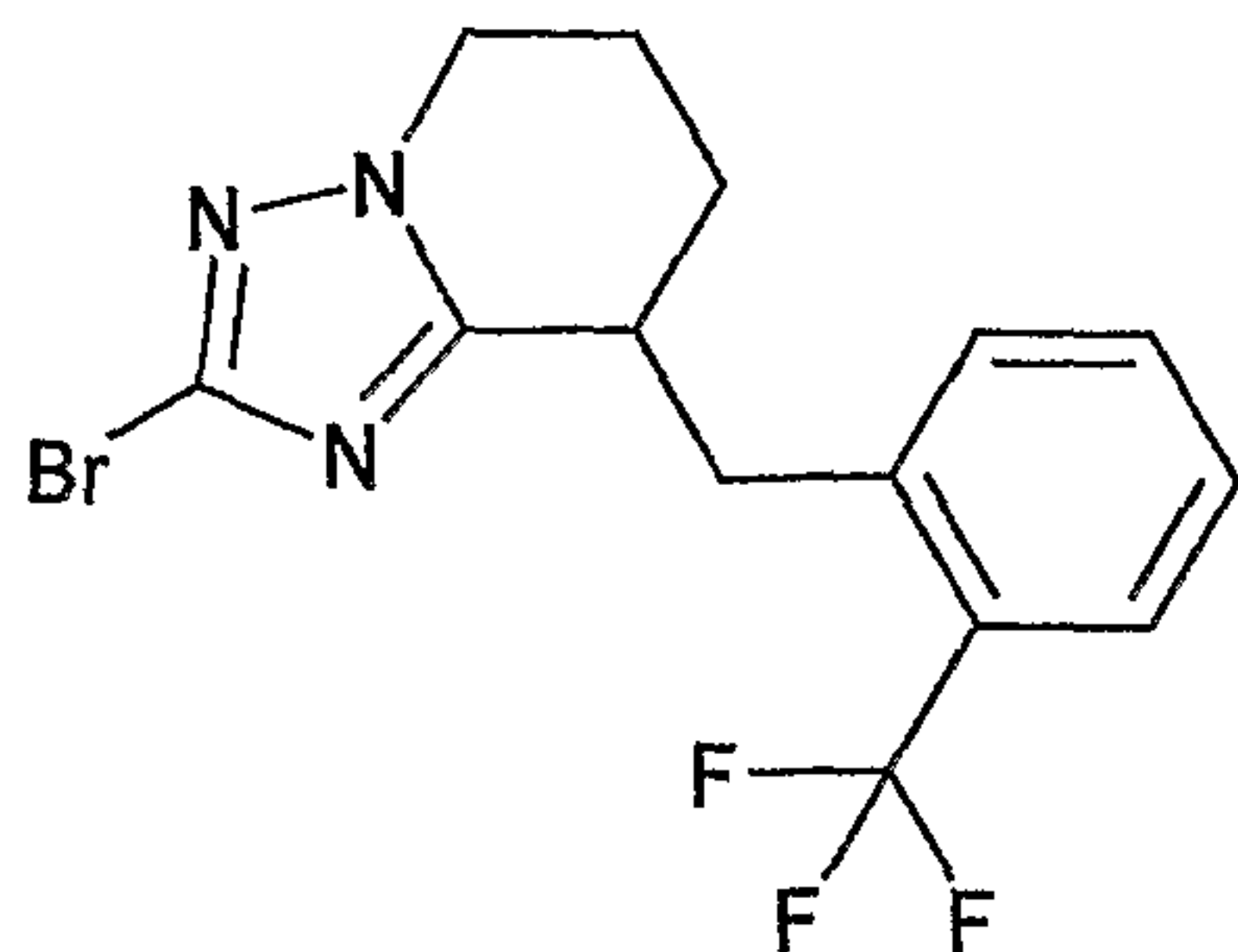
Production Ex No.	Structural formula	^1H -NMR or ESI mass
2-2		ESI-MS; m/z 364 [$M^+ + H$].
2-3		ESI-MS; m/z 346, 348 [$M^+ + H$]. ^1H -NMR ($CDCl_3$) δ (ppm): 1.86-1.96 (m, 1H), 2.06-2.20 (m, 1H), 2.21-2.30 (m, 1H), 2.40-2.49 (m, 1H), 4.22-4.36 (m, 2H), 4.61 (d, $J = 9.2, 6.0$ Hz, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 7.38 (dd, $J = 8.0, 7.2$ Hz, 1H), 7.49 (dd, $J = 8.0, 7.2$ Hz, 1H), 7.69 (d, $J = 8.0$ Hz, 1H).
2-4		ESI-MS; m/z 346, 348 [$M^+ + H$].
2-5		ESI-MS; m/z 364 [$M^+ + H$].
2-6		ESI-MS; m/z 364 [$M^+ + H$].

[0577]

15 Preparation Example 2-7

Synthesis of 2-bromo-8-(2-trifluoromethylbenzyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0578]



[0579]

5 Synthesis of ethyl 5-chloro-2-[1-(2-trifluoromethylphenyl)methylidene]pentanoate

2-(Trifluoromethyl)benzaldehyde (1 g) and ethyl 5-chloro-2-(diethoxyphosphoryl)pentanoate (CAS No. 870843-20-2, 2.1 g) were dissolved in a mixed solvent of tetrahydrofuran (30 mL) and ethanol (10 mL). Lithium hydroxide (412 mg) was added and the mixture was stirred at room temperature overnight. Water was added to the reaction solution, followed by extraction with ethyl acetate. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain a geometric isomer mixture of the title compound (1.4 g).

15 [0580]

Synthesis of 1-amino-3-(2-trifluoromethylbenzyl)piperidin-2-one

The geometric isomer mixture of ethyl 5-chloro-2-[1-(2-trifluoromethylphenyl)methylidene]pentanoate (1.4 g) was dissolved in ethanol (30 mL) and catalytically hydrogenated for two hours using a 10% palladium-carbon cartridge in the H-CubeTM (manufactured by THALES Nanotechnology Inc.) system. The reaction solution was concentrated under reduced pressure to reduce the amount of the catalyst to about half. Hydrazine monohydrate (4.4 mL) was added and the mixture was heated under reflux for 12 hours. The reaction solution was concentrated under reduced pressure and water was added, followed by extraction with ethyl acetate. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography to obtain the title compound (916 mg). The property values of

the compound are as follows.

ESI-MS; m/z 273 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.43-1.53 (m, 1H), 1.65-1.80 (m, 2H), 1.88-1.98 (m, 1H), 2.67-2.76 (m, 1H), 2.80-2.89 (m, 1H), 3.45-3.55 (m, 2H), 3.65 (dd, $J = 14.6, 4.2$ Hz, 1H), 4.53 (brs, 2H),
5 7.31 (dd, $J = 8.0, 7.2$ Hz, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.48 (dd, $J = 7.6, 7.2$ Hz, 1H), 7.64 (d, $J = 7.6$ Hz, 1H).

[0581]

Synthesis of 8-(2-trifluoromethylbenzyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-2-ylamine

10 1-Amino-3-(2-trifluoromethylbenzyl)piperidin-2-one (916 mg) and cyanamide (849 mg) were dissolved in ethanol (15 mL). *p*-Toluenesulfonic acid monohydrate (961 mg) was added and the mixture was heated under reflux at 80°C for 3.5 hours. After cooling to room temperature, triethylamine (2.3 mL) was added and the mixture was further heated under reflux at 80°C for four days. A sodium bicarbonate solution and ethyl acetate were added to the
15 reaction solution, and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The resulting solid was washed with ethyl acetate to obtain the title compound (244 mg). The property values of the compound are as follows.

20 ESI-MS; m/z 297 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 1.48-1.60 (m, 1H), 1.75-1.94 (m, 2H), 2.04-2.13 (m, 1H), 2.92 (ddd, $J = 14.4, 10.8, 1.2$ Hz, 1H), 3.13-3.22 (m, 1H), 3.67 (dd, $J = 14.6, 4.2$ Hz, 1H), 3.88-4.12 (m, 4H), 7.34 (dd, $J = 7.6, 7.2$ Hz, 1H), 7.41 (d, $J = 7.6$ Hz, 1H), 7.51 (dd, $J = 8.0, 7.2$ Hz, 1H), 7.67 (d, $J = 8.0$ Hz, 1H).

25 [0582]

2-Bromo-8-(2-trifluoromethylbenzyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

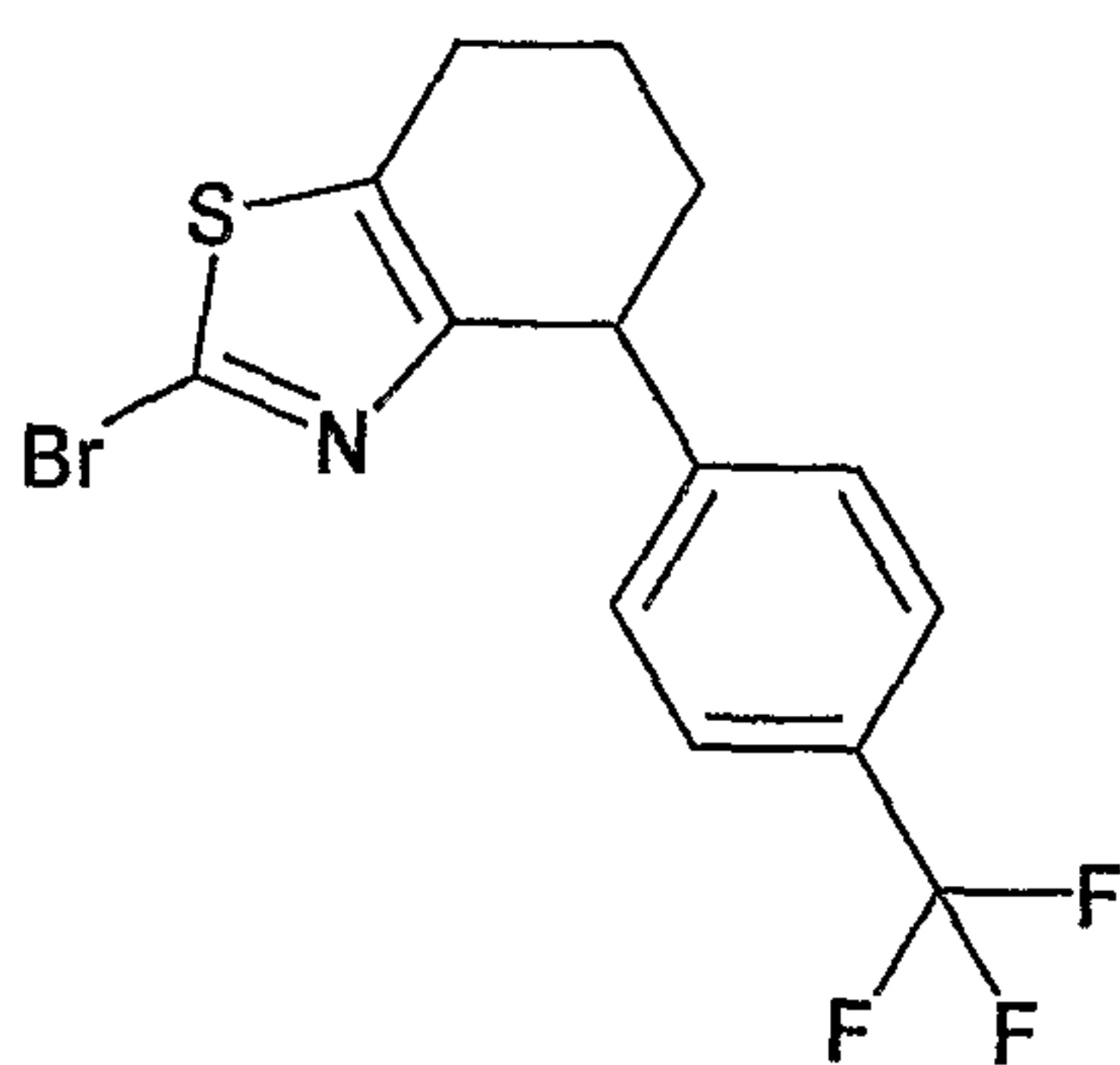
The title compound was obtained by the same method as in Preparation Example 2-1 from 8-(2-trifluoromethylbenzyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-2-ylamine. ESI-MS; m/z 360, 362 [$M^+ + H$].

30 [0583]

Preparation Example 2-8

Synthesis of 2-bromo-4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydrobenzothiazole

[0584]



[0585]

Synthesis of 2-(4-trifluoromethylphenyl)cyclohexanone

1-Bromo-4-trifluoromethylbenzene (5 mL), cyclohexanone (7.4 mL) and potassium tert-butoxide (8 g) were suspended in tetrahydrofuran (100 mL).

- 5 Tris(dibenzylideneacetone)dipalladium (1.3 g) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (843 mg) were added and the mixture was heated with stirring at 70°C in a nitrogen atmosphere for 1.5 hours. After leaving to cool, tert-butyl methyl ether was added, followed by filtration through celite. The resulting organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography three times. The
- 10 resulting solid was washed with heptane to obtain the title compound (2.1 g). The property values of the compound are as follows.

ESI-MS; m/z 243 [$M^+ + H$].

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.80-1.93 (m, 2H), 1.96-2.08 (m, 2H), 2.16-2.24 (m, 1H), 2.26-2.34 (m, 1H), 2.44-2.60 (m, 2H), 3.65-3.77 (m, 1H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.59 (d, $J = 8.0$ Hz, 2H).

15 [0586]

Synthesis of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydrobenzothiazol-2-ylamine

- 2-(4-Trifluoromethylphenyl)cyclohexanone (1.2 g) was dissolved in chloroform (20 mL). A solution of bromine in tetrahydrofuran prepared at 0.3 M (20 mL) was added dropwise while maintaining the internal temperature at 5°C or less. Thereafter, the mixture was
- 20 brought back to room temperature and stirred for three hours. A sodium bicarbonate solution and chloroform were added to the reaction solution, and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain a
- 25 diastereomer mixture of 2-bromo-6-(4-trifluoromethylphenyl)cyclohexanone (1.2 g).

The diastereomer mixture of 2-bromo-6-(4-trifluoromethylphenyl)cyclohexanone

(500 mg) was dissolved in ethanol (10 mL). Thiourea (130 mg) was added and the mixture was stirred at room temperature overnight. A sodium bicarbonate solution and ethyl acetate were added to the reaction solution, and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (394 mg). The property values of the compound are as follows.

ESI-MS; m/z 243 $[M+H]^+$.

^1H -NMR ($CDCl_3$) δ (ppm): 1.74-1.88 (m, 3H), 2.13-2.22 (m, 1H), 2.62-2.77 (m, 2H), 4.00-4.05 (m, 1H), 4.72 (brs, 2H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H).

[0587]

Synthesis of 2-bromo-4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydrobenzothiazole

The title compound was obtained by the same method as in Preparation Example 2-1 from 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydrobenzothiazol-2-ylamine. The property values of the compound are as follows.

ESI-MS; m/z 364 $[M+H]^+$.

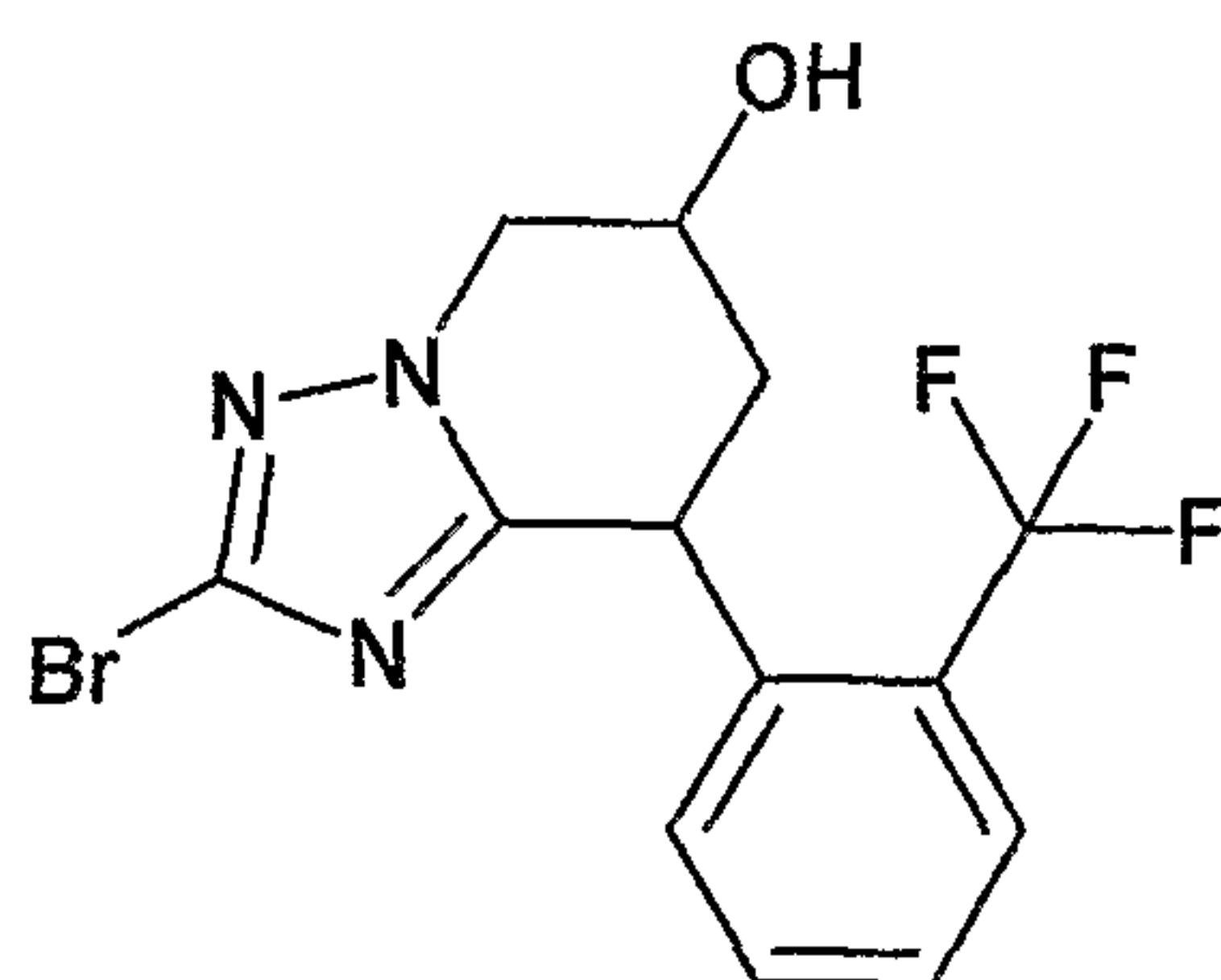
^1H -NMR ($CDCl_3$) δ (ppm): 1.78-1.93 (m, 3H), 2.18-2.28 (m, 1H), 2.75-2.90 (m, 2H), 4.23-4.28 (m, 1H), 7.17 (d, $J = 8.2$ Hz, 2H), 7.54 (d, $J = 8.2$ Hz, 2H).

[0588]

Preparation Example 2-9

Synthesis of 2-bromo-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-6-ol

[0589]



[0590]

25 Synthesis of methyl 3-oxiranyl-2-(2-trifluoromethylphenyl)propionate

Methyl (2-trifluoromethylphenyl)acetate (5.0 g) was dissolved in tetrahydrofuran (10 mL), and the solution was added at $-78^\circ C$ to a solution containing potassium

bis(trimethylsilyl)amide (50 mL) in tetrahydrofuran (190 mL). After stirring for 30 minutes, epibromohydrin (1.96 mL) was added at the same temperature. After further 10 minutes, a boron trifluoride-diethyl ether complex (3.16 mL) was added. After stirring at -78°C for one hour, the reaction was terminated with a saturated sodium bicarbonate aqueous solution. The organic layer diluted with ethyl acetate was washed with a saturated sodium bicarbonate aqueous solution and brine and dried over magnesium sulfate. Concentration under reduced pressure gave a residue which was dissolved in methanol (50 mL) and methylene chloride (50 mL) and treated with potassium carbonate (15.8 g). After one hour, potassium carbonate was precipitated by adding methylene chloride (200 mL) and removed by filtration through celite. The resulting solution was washed with saturated ammonium chloride aqueous solution and brine and dried over magnesium sulfate. Concentration under reduced pressure gave a crude product. The crude product was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 30%) to obtain a diastereomer mixture (2.61 g).

[0591]

15 Synthesis of 1-amino-5-hydroxy-3-(2-trifluoromethylphenyl)piperidin-2-one

Methyl 3-oxiranyl-2-(2-trifluoromethylphenyl)propionate (2.61 g) was dissolved in ethanol (20 mL). Hydrazine monohydrate (2.3 mL) was added at room temperature, and the mixture was reacted for 24 hours. Concentration under reduced pressure gave an oil which was partitioned with methylene chloride and water. The aqueous layer was extracted with methylene chloride four times. After drying over magnesium sulfate, concentration under reduced pressure gave the title compound (1.8 g) as a pale yellow solid.

ESI-MS; m/z 275 [$M^+ + H$].

[0592]

25 Synthesis of 2-bromo-8-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-6-ol

The title compound was obtained as a white solid by the same method as in Preparation Example 2-7 from 1-amino-5-hydroxy-3-(2-trifluoromethylphenyl)piperidin-2-one.

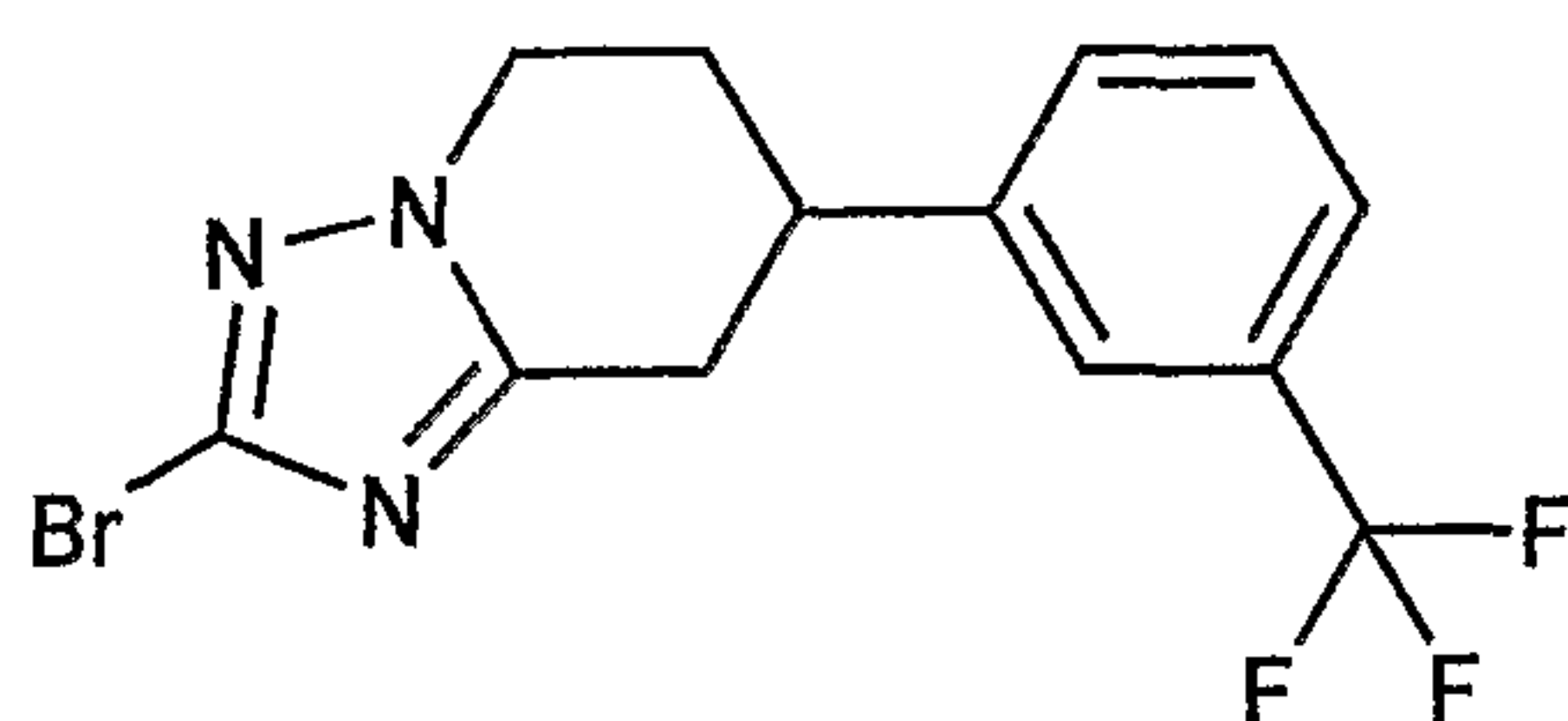
ESI-MS; m/z 362 [$M^+ + H$].

[0593]

30 Preparation Example 2-10

Synthesis of 2-bromo-7-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0594]



[0595]

Synthesis of 4-(3-trifluoromethylphenyl)tetrahydropyran-2-one

(Acetylacetonato)bis(ethylene)rhodium (I) (180 mg) was dissolved in 1,4-dioxane (144 mL). Racemic BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthalene) (867 mg) was added at room temperature, followed by stirring for 30 minutes. Subsequently, water (14.4 mL) and 3-(trifluoromethyl)phenylboronic acid (5.29 g) were added, followed by stirring for 10 minutes. Then, 5,6-dihydro-2H-pyran-2-one (2 mL) was added and the mixture was reacted at 100°C for 12 hours. The reaction solution was partitioned with ethyl acetate and water. Then, the organic layer was washed with a saturated sodium bicarbonate solution and dried over magnesium sulfate. Concentration under reduced pressure gave an oil. The oil was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 60%) to obtain the title compound (2.5 g).

ESI-MS; m/z 245 $[M^+ + H]$.

[0596]

15 Synthesis of 5-hydroxy-3-(3-trifluoromethylphenyl)pentanoic acid hydrazide

4-(3-Trifluoromethylphenyl)tetrahydropyran-2-one (2.5 g) was dissolved in ethanol (10 mL), and hydrazine monohydrate (4.96 mL) was added at room temperature. The mixture was stirred at 80°C for 4.5 hours and then concentrated under reduced pressure. The resulting oil was partitioned with methylene chloride and water. The aqueous layer was extracted with methylene chloride five times. After drying over magnesium sulfate, concentration under reduced pressure and purification by silica gel column chromatography (amino silica gel, mobile phase: ethyl acetate/heptane = 0 to 50% → methanol/ethyl acetate = 10%) gave the title compound (1.55 g).

ESI-MS; m/z 277 $[M^+ + H]$.

25 [0597]

Synthesis of tert-butyl N'-[5-hydroxy-3-(3-trifluoromethylphenyl)pentanoyl]hydrazinecarboxylate

5-Hydroxy-3-(3-trifluoromethylphenyl)pentanoic acid hydrazide (1.55 g) was

dissolved in tetrahydrofuran (26 mL), and di-tert-butyl dicarbonate (1.35 g) was added at room temperature. After stirring for 15 hours, the reaction solution was diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution and brine. After drying over magnesium sulfate, concentration under reduced pressure gave the title compound (2.0 g). The resulting
5 compound was used directly for the next reaction as a crude product.

[0598]

Synthesis of tert-butyl N'-[5-bromo-3-(3-trifluoromethylphenyl)pentanoyl]hydrazinecarboxylate

tert-Butyl N'-[5-hydroxy-3-(3-trifluoromethylphenyl)pentanoyl]hydrazinecarboxylate (2.0 g) was dissolved in methylene
10 chloride (53 mL). Pyridine (1.29 mL), carbon tetrabromide (2.64 g) and triphenylphosphine (2.1 g) were added at room temperature, followed by stirring for 30 minutes. The reaction solution was partitioned with water and ethyl acetate. Then, the organic layer was washed with saturated ammonium chloride aqueous solution and a saturated sodium bicarbonate aqueous solution and dried over magnesium sulfate. Concentration under reduced pressure gave an oil. The oil was
15 purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 50%) to obtain the title compound (1.6 g).

[0599]

Synthesis of 5-bromo-3-(3-trifluoromethylphenyl)pentanoic acid hydrazide

tert-Butyl N'-[5-bromo-3-(3-trifluoromethylphenyl)pentanoyl]hydrazinecarboxylate (1.6 g) was dissolved in methylene
20 chloride (8 mL), and trifluoroacetic acid (10 mL) was added at 0°C. The mixture was stirred at room temperature for two hours and then concentrated under reduced pressure. The resulting oil was diluted with ethyl acetate, and then washed with 1 N sodium hydroxide aqueous solution and brine and dried over magnesium sulfate. The oil after concentration under reduced pressure
25 (990 mg) was used directly for the next reaction as a crude product.

[0600]

Synthesis of 2-bromo-7-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

The title compound was obtained by the same method as in Preparation Example
30 2-1 from 5-bromo-3-(3-trifluoromethylphenyl)pentanoic acid hydrazide.

ESI-MS; m/z 348 [M⁺ + H].

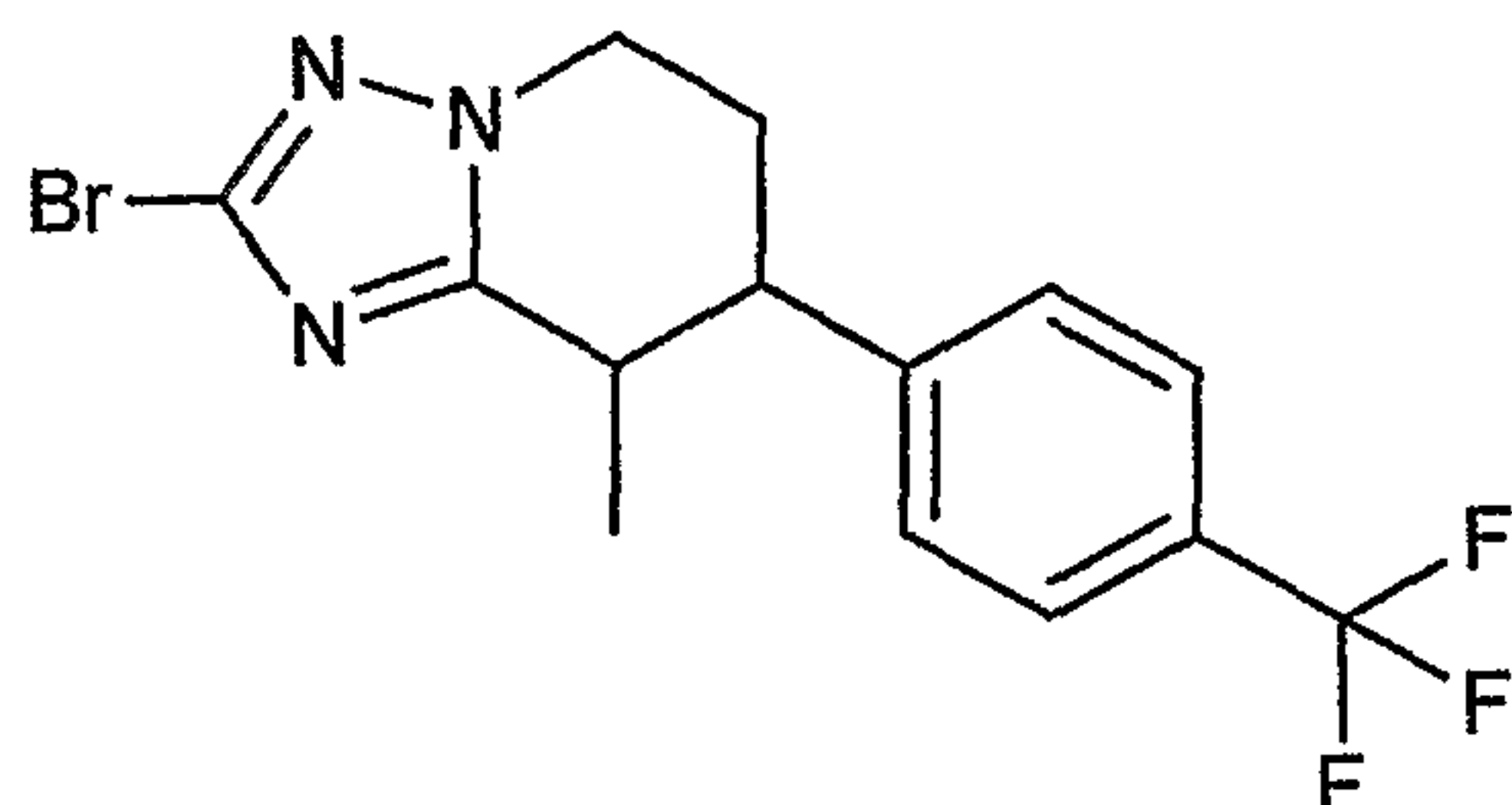
[0601]

Preparation Example 2-11

Synthesis of 2-bromo-8-methyl-7-(4-trifluoromethylphenyl)-5,6,7,8-

tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0602]



[0603]

Synthesis of 3-methyl-4-(4-trifluoromethylphenyl)tetrahydropyran-2-one

5 4-(4-Trifluoromethylphenyl)tetrahydropyran-2-one (995 mg) derived by the same method as in Preparation Example 2-10 from 4-(trifluoromethyl)phenylboronic acid (5.29 g) and 5,6-dihydro-2H-pyran-2-one was dissolved in tetrahydrofuran (10 mL). The solution was added dropwise at -78°C to a lithium diisopropylamide solution previously prepared from n-butyllithium (3.91 mL) and diisopropylamine (1.46 mL) in tetrahydrofuran (30 mL). After
10 stirring at the same temperature for 30 minutes, iodomethane (760 µL) and hexamethylphosphoramide (1.77 mL) were added and stirring was continued. After stirring for 30 minutes, the reaction solution was gradually heated to room temperature over three hours and 20 minutes. The reaction was terminated with saturated ammonium chloride aqueous solution. The organic layer was washed with brine and then dried over magnesium sulfate. Removal
15 under reduced pressure gave an oil. The oil was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 50%) to obtain the title compound (500 mg). ESI-MS; m/z 259 [M⁺ + H].

[0604]

Synthesis of 2-bromo-8-methyl-7-(4-trifluoromethylphenyl)-5,6,7,8-

20 tetrahydro[1,2,4]triazolo[1,5-a]pyridine

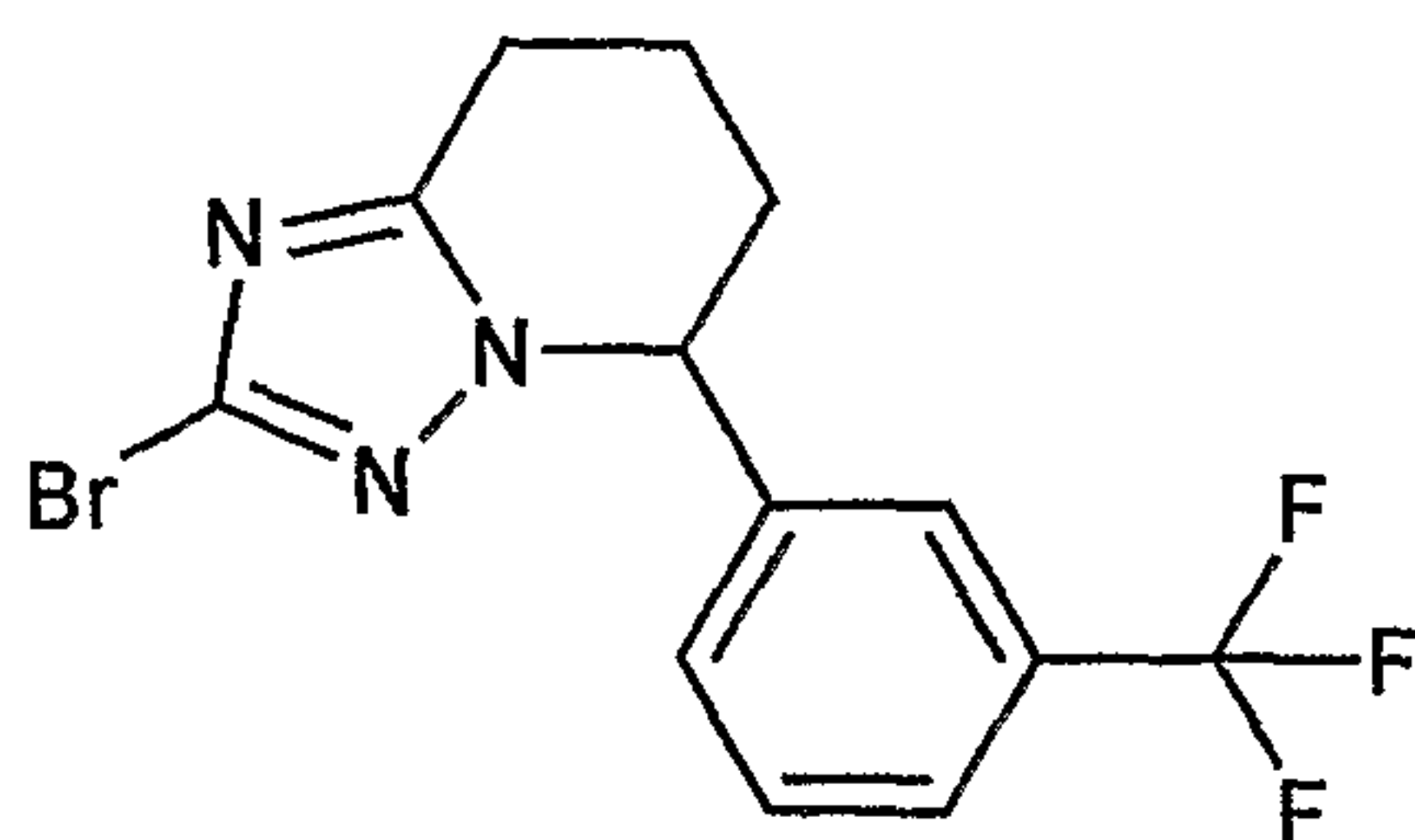
The title compound was obtained by the same method as in Preparation Example 2-10 from 3-methyl-4-(4-trifluoromethylphenyl)tetrahydropyran-2-one.

[0605]

Preparation Example 2-12

25 Synthesis of 2-bromo-5-(3-trifluoromethylphenyl)5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0606]



[0607]

Synthesis of ethyl 5-(N'-tert-butoxycarbonylhydrazino)-5-(3-trifluoromethylphenyl)pentanoate

Ethyl 5-oxo-5-(3-trifluoromethylphenyl)pentanoate (CAS No. 898777-75-8, 330 mg) and tert-butyl carbazate (227 mg) were dissolved in a mixed solvent of THF (6 mL) and acetic acid (3 mL). After stirring at room temperature for 25 minutes, sodium cyanoborohydride (108 mg) was added. After further one hour and 30 minutes, sodium cyanoborohydride (108 mg) was added and the mixture was stirred at room temperature for one hour. A saturated sodium bicarbonate solution and diethyl ether were added to the reaction solution, and the organic layer was separated. The resulting organic layer was washed with a saturated sodium bicarbonate solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (324 mg). The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.22 (t, J = 7.2 Hz, 3H), 1.43 (s, 9H), 1.47-1.84 (m, 4H), 2.27 (t, J = 6.8 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 4.14 (t, J = 7.2 Hz, 1H), 4.25 (brs, 1H), 5.88 (brs, 1H), 7.43-7.62 (m, 4H).

[0608]

Synthesis of tert-butyl [2-oxo-6-(3-trifluoromethylphenyl)piperidin-1-yl]carbamate

Ethyl 5-(N'-tert-butoxycarbonylhydrazino)-5-(3-trifluoromethylphenyl)pentanoate (323 mg) was dissolved in methanol (7 mL). A 1 N sodium hydroxide solution (5 mL) was added and the mixture was stirred at room temperature for two hours and 30 minutes. 1 N hydrochloric acid (5 mL) and ethyl acetate were added to the reaction solution, and the organic layer was separated and dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residue was dissolved in dimethylformamide (8 mL). 1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (317 mg) and 1-hydroxybenzotriazole (223 mg) were added and the mixture was stirred at room temperature for 13 hours. 1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (317 mg) was added to the reaction solution, and the mixture was further stirred

for one hour. Diethyl ether and water were added to the reaction solution, and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column

5 chromatography to obtain the title compound (214 mg). The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.43 (s, 9H), 1.86-1.94 (m, 3H), 2.26-2.39 (m, 1H), 2.59-2.69 (m, 2H), 4.99 (brs, 1H), 6.39 (brs, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.44 (s, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H).

10 [0609]

Synthesis of 1-amino-6-(3-trifluoromethylphenyl)piperidin-2-one

tert-Butyl [2-oxo-6-(3-trifluoromethylphenyl)piperidin-1-yl]carbamate (210 mg) was dissolved in chloroform (4 mL), followed by addition of trifluoroacetic acid (2 mL). After stirring at room temperature for four hours, concentration under reduced pressure gave the title
15 compound (119 mg). The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.72-1.92 (m, 3H), 2.23-2.59 (m, 1H), 2.59 (dt, J = 2.4 Hz, 6.4 Hz, 2H), 4.36 (s, 2H), 4.79 (t, J = 6.4 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.44 (s, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H).

[0610]

20 Synthesis of 2-bromo-5-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

The title compound was obtained according to the method of Preparation Example 2-7 from 1-amino-6-(3-trifluoromethylphenyl)piperidin-2-one. The property values of the compound are as follows.

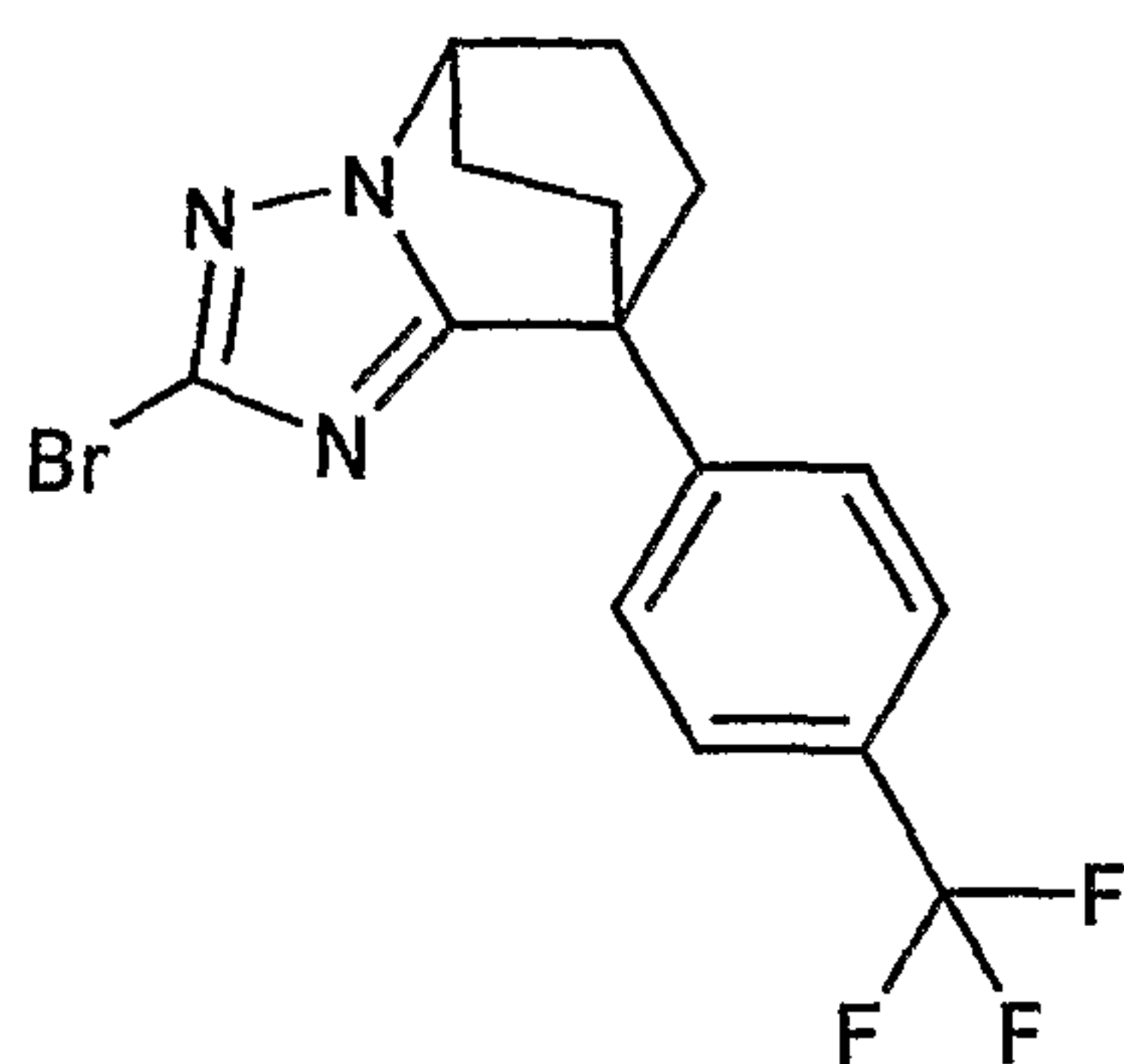
25 ¹H-NMR (CDCl₃) δ (ppm): 1.89-2.04 (m, 2H), 2.07-2.15 (m, 1H), 2.41-2.49 (m, 1H), 3.03 (dt, J = 3.2 Hz, 6.8 Hz, 2H), 5.46 (t, J = 6.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.33 (s, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H).

[0611]

Preparation Example 2-13

30 Synthesis of 4-bromo-7-(4-trifluoromethylphenyl)-2,3,5-triaza-tricyclo[5.2.2.0*2,6*]undeca-3,5-diene

[0612]



[0613]

Synthesis of dimethyl 4-hydroxy-1-(4-trifluoromethylphenyl)-3-cyclohexene-1,3-dicarboxylate

Methyl (4-trifluorophenyl)acetate (CAS No. 135325-18-7, 1 g) and methyl acrylate (789 mg) were dissolved in THF (13 mL). Potassium tert-Butoxide (617 mg) was added and the mixture was stirred at room temperature for 14 hours and 30 minutes. Water was added to the reaction solution, followed by stirring at 85°C for five hours and 30 minutes. After leaving to cool, ethyl acetate was added to the reaction solution, followed by neutralization with 1 N hydrochloric acid. The organic layer was separated, washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (1.13 g). The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.13-2.60 (m, 4H), 2.75 (d, J = 16.4 Hz, 1H), 3.08 (d, J = 16.4 Hz, 1H), 3.66 (s, 3H), 3.82 (s, 3H), 7.47 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 12.11 (s, 1H).

[0614]

Synthesis of methyl 4-oxo-1-(4-trifluoromethylphenyl)cyclohexanecarboxylate

Dimethyl 4-hydroxy-1-(4-trifluoromethylphenyl)-3-cyclohexene-1,3-dicarboxylate (1.13 g) was dissolved in a mixed solvent of THF (3 mL) and methanol (3 mL). A 1 N potassium hydroxide solution (1.89 mL) was added and the mixture was stirred at 100°C for eight hours. After leaving to cool, ethyl acetate and water were added to the reaction solution, followed by neutralization with 1 N hydrochloric acid. The organic layer was separated, washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (272 mg). The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.21-2.28 (m, 2H), 2.41-2.47 (m, 2H), 2.52-2.60 (m, 2H), 2.77-2.83

(m, 2H), 3.74 (s, 3H), 7.54 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H).

[0615]

Synthesis of methyl 4-(N'-tert-butoxycarbonylhydrazino)-1-(4-trifluoromethylphenyl)cyclohexanecarboxylate

5 Methyl 4-oxo-1-(4-trifluoromethylphenyl)cyclohexanecarboxylate (100 mg) and tert-butyl carbazate (66 mg) were dissolved in a mixed solvent of THF (6 mL) and acetic acid (3 mL). After stirring at room temperature for 50 minutes, sodium cyanoborohydride (31.4 mg) was added. After further two hours, sodium cyanoborohydride (31.4 mg) was added and the mixture was stirred at room temperature for one hour. Diethyl ether and a saturated sodium
10 bicarbonate solution were added to the reaction solution, and the organic layer was separated. The resulting organic layer was washed with a saturated sodium bicarbonate solution and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (74.5 mg). The property values of the
15 compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.28-1.36 (m, 2H), 1.47 (s, 9H), 1.60-1.66 (m, 2H), 1.94-1.96 (m, 2H), 2.66-2.69 (m, 2H), 2.87 (brs, 1H), 3.66 (s, 3H), 4.05 (brs, 1H), 6.08 (brs, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H).

[0616]

20 Synthesis of tert-butyl [3-oxo-4-(4-trifluoromethylphenyl)-2-aza-bicyclo[2.2.2]oct-2-yl]carbamate

Methyl 4-(N'-tert-butoxycarbonylhydrazino)-1-(4-trifluoromethylphenyl)cyclohexanecarboxylate (74.5 mg) was dissolved in methanol (1.5 mL), followed by addition of a 1 N sodium hydroxide solution (1 mL). The mixture was stirred at
25 room temperature for 15 hours and then stirred with heating under reflux for 11 hours and 30 minutes. After leaving to cool, diethyl ether was added to the reaction solution, followed by neutralization with 1 N hydrochloric acid. The organic layer was separated and then washed with brine. The resulting organic layer was dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced
30 pressure. The residue was purified by silica gel column chromatography to obtain the title compound (35.7 mg). The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.48 (s, 9H), 1.80-1.85 (m, 2H), 2.02-2.11 (m, 2H), 2.22-2.32 (m, 4H), 3.90 (s, 1H), 6.77 (brs, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H).

[0617]

Synthesis of 4-bromo-7-(4-trifluoromethylphenyl)-2,3,5-triaza-tricyclo[5.2.2.0*2,6*]undeca-3,5-diene

The title compound was obtained according to the method of Preparation

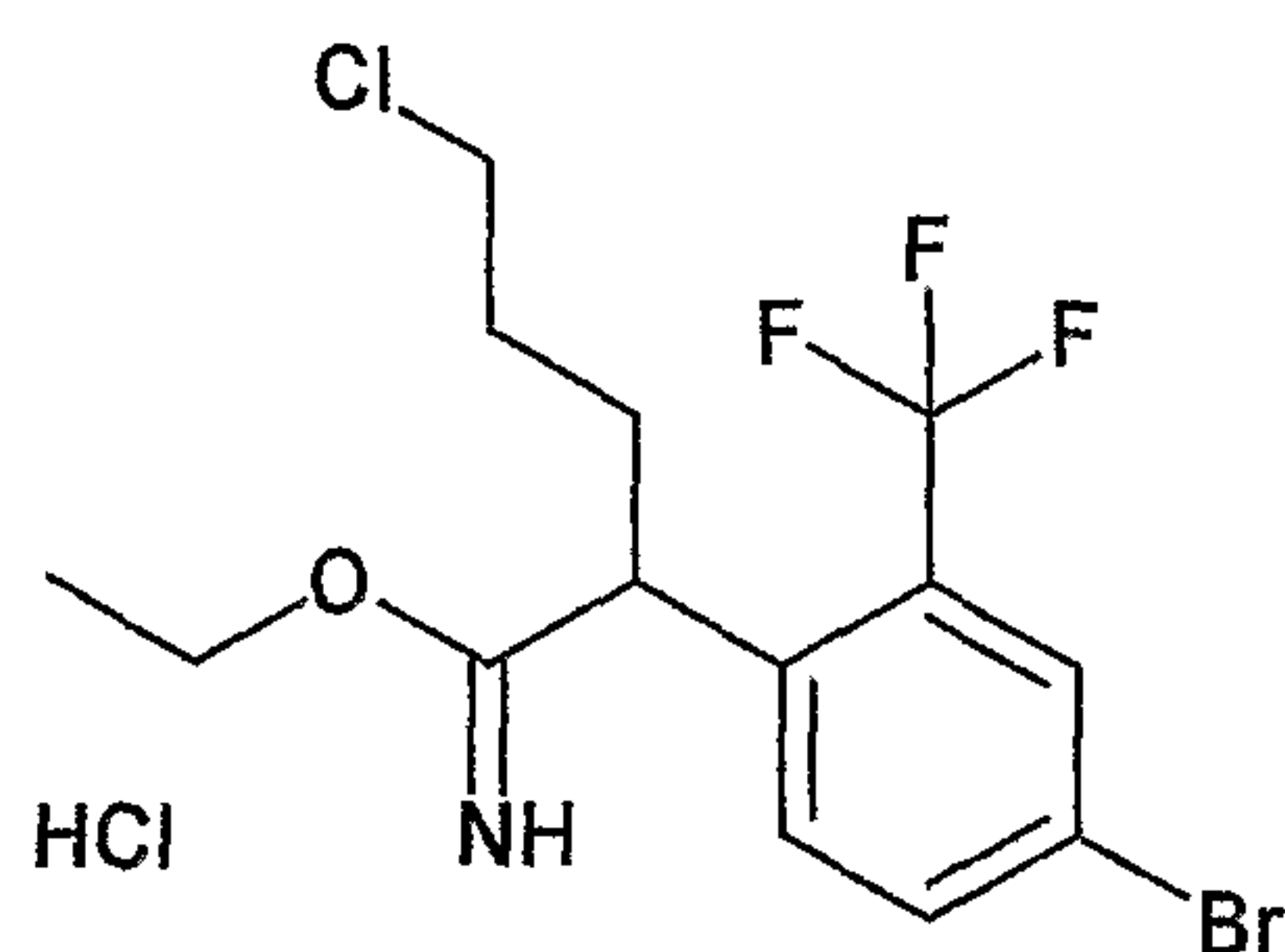
Example 2-12 from tert-butyl [3-oxo-4-(4-trifluoromethylphenyl)-2-aza-bicyclo[2,2,2]oct-2-yl]carbamate. The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.93-2.12 (m, 6H), 2.24-2.30 (m, 2H), 4.97 (tt, J = 1.6 Hz, 3.2 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H).

[0618]

Preparation Example 3-1

Synthesis of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride
[0619]



[0620]

Synthesis of 4-bromo-1-bromomethyl-2-trifluoromethylbenzene

N-Bromosuccinimide (2.6 g) and 2,2'-azobis(isobutyronitrile) (35 mg) were added to a solution of 5-bromo-2-methylbenzotrifluoride (CAS #86845-27-4, 3.5 g) in carbon tetrachloride (35 mL), and the mixture was heated under reflux for five hours. The reaction solution was ice-cooled and then the insoluble matter was removed by filtration. The filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: Wakogel C-200; elution solvent: heptane) to obtain 3.86 g of the title compound. The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 4.58 (s, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 8.4, 2.0 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H).

[0621]

Synthesis of (4-bromo-2-trifluoromethylphenyl)acetonitrile

Potassium cyanide (630 mg) was added to an emulsion of 4-bromo-1-bromomethyl-2-trifluoromethylbenzene (3.86 g) in ethanol (15 mL)-water (5 mL), and the mixture was stirred at 70°C for three hours and 15 minutes. Water and ethyl acetate were added

to the reaction solution, and the organic layer was separated. The resulting organic layer was washed with brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: Wakogel C-200; elution solvent: heptane:ethyl acetate = 9:1) to obtain 2.28 g of the title compound. The property values of the compound are as follows.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 3.91 (s, 2H), 7.57 (d, $J = 8.4$ Hz, 1H), 7.76 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.85 (d, $J = 2.0$ Hz, 1H).

[0622]

Synthesis of 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanenitrile

10 A solution of (4-bromo-2-trifluoromethylphenyl)acetonitrile (2.28 g) in tetrahydrofuran (6 mL) was added to a suspension of sodium hydride (containing 60% in mineral oil, 362 mg) in tetrahydrofuran (12 mL) under ice-cooling. The mixture was stirred at the same temperature for 20 minutes. 1-Chloro-3-iodopropane (0.94 mL) was added dropwise to the reaction solution, and then the reaction solution was stirred at room temperature for 40 minutes. 15 Ice water and heptane were added to the reaction solution, and the organic layer was separated. The resulting organic layer was washed with brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: WakogelTM C-200; elution solvent: heptane:ethyl acetate = 49:1 $\rightarrow$ 19:1) to obtain 2.67 g of the title compound. The property values of the compound are as 20 follows.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.88-2.17 (m, 4H), 3.58 (t, $J = 6.0$ Hz, 2H), 4.13 (t, $J = 7.2$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 7.78 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.84 (d, $J = 2.0$ Hz, 1H).

[0623]

Synthesis of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride

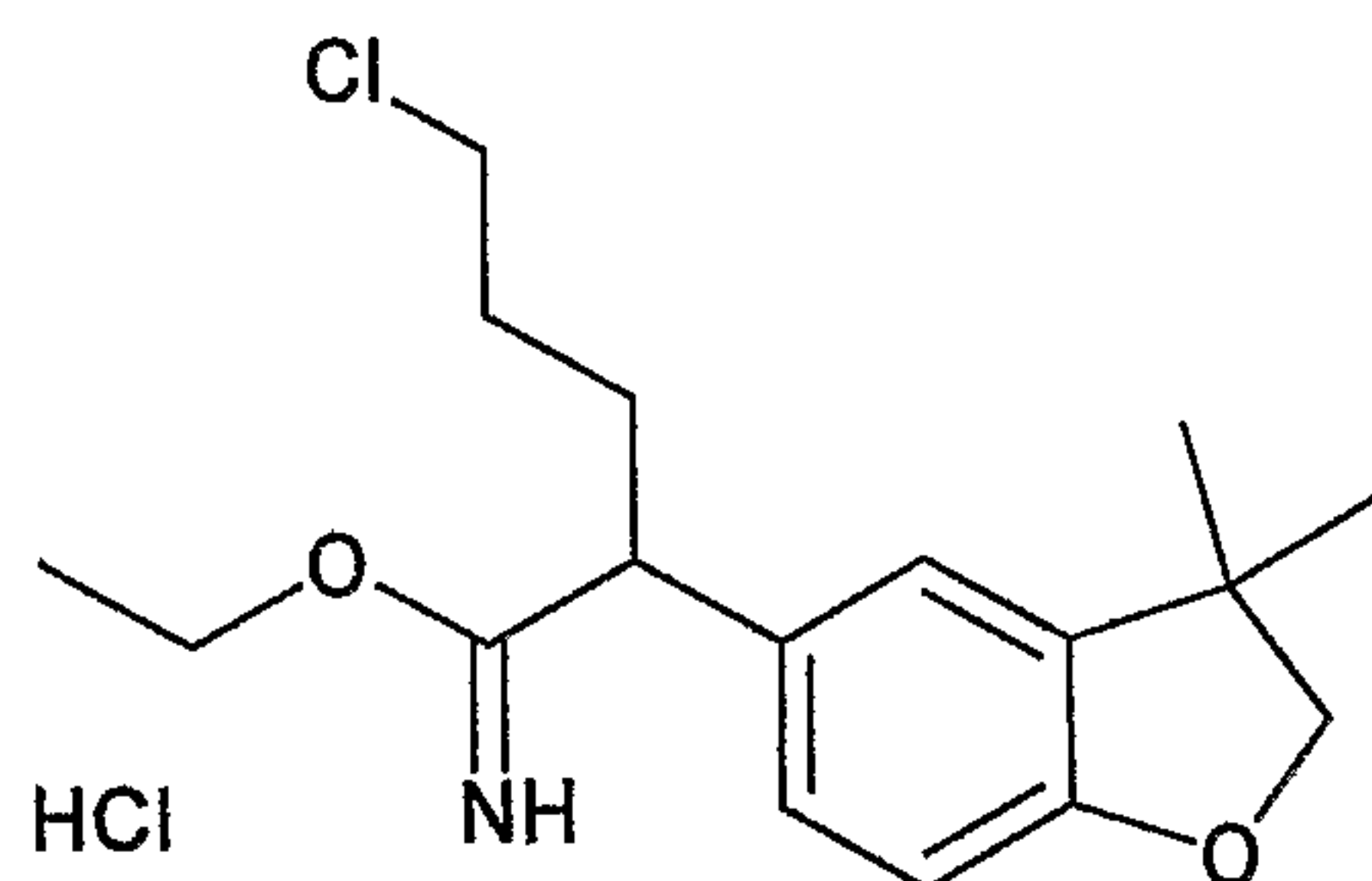
25 A solution of 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanenitrile (2.67 g) in ethanol (7.5 mL) was bubbled with hydrogen chloride gas under ice-cooling for 15 minutes. The reaction solution was stirred at room temperature for one day. The reaction solution was concentrated under reduced pressure. Diethyl ether was added to the residue, and the resulting powder was collected by filtration. The product collected by filtration was dried under reduced 30 pressure to obtain 2.96 g of the title compound. The property values of the compound are as follows.

ESI-MS; m/z 388 [$\text{M}^+ + \text{H-HCl}$].

$^1\text{H-NMR}$ (DMSO-D_6) δ (ppm): 1.27 (t, $J = 7.2$ Hz, 3H), 1.49-1.75 (m, 2H), 2.10-2.35 (m, 2H), 3.64 (t, $J = 6.4$ Hz, 2H), 4.26 (t, $J = 7.6$ Hz, 1H), 4.34-4.50 (m, 2H), 7.73 (d, $J = 8.4$ Hz, 1H),

Synthesis of ethyl 5-chloro-2-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)pentanimidate

[0625]



Synthesis of 3,3,5-trimethyl-2,3-dihydrobenzofuran

3-Chloro-2-methylpropene (9.7 mL) was added dropwise to a mixed solution of p-cresol (CAS #106-44-5, 10.8g) and concentrated sulfuric acid (2.5 g), and the mixture was stirred at room temperature for one hour and 20 minutes. The reaction solution was ice-cooled and a 5 N sodium hydroxide aqueous solution (20 mL) was added, followed by stirring at 90°C for 45 minutes. A 5 N sodium hydroxide aqueous solution (10 mL) was added to the reaction solution, and the mixture was stirred at 90°C for two hours and 45 minutes. The reaction solution was left to cool to room temperature. tert-Butyl methyl ether was added to the reaction solution, and the organic layer was separated. The resulting organic layer was sequentially washed with water (three times) and brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: Merck silica gel 60 (230-400 mesh); elution solvent: heptane:ethyl acetate = 1:0 -> 49:1). The target fraction was concentrated and the resulting residue was purified again by silica gel column chromatography (carrier: ChromatorexTM NH; elution solvent: heptane). The target fraction was concentrated and the resulting residue was distilled under reduced pressure to obtain 1.87 g of the target compound (bp. 102°C/20 mmHg). The property values of the compound are as follows.

25 ¹H-NMR (CDCl₃) δ (ppm): 1.33 (s, 6H), 2.30 (s, 3H), 4.20 (s, 2H), 6.68 (d, J = 7.6 Hz, 1H), 6.88-6.95 (m, 2H).

[0627]

Synthesis of ethyl 5-chloro-2-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)pentanimidate hydrochloride

The title compound was obtained according to the method of Preparation

Example 3-1 from 3,3,5-trimethyl-2,3-dihydrobenzofuran. The property values of the compound
5 are as follows.

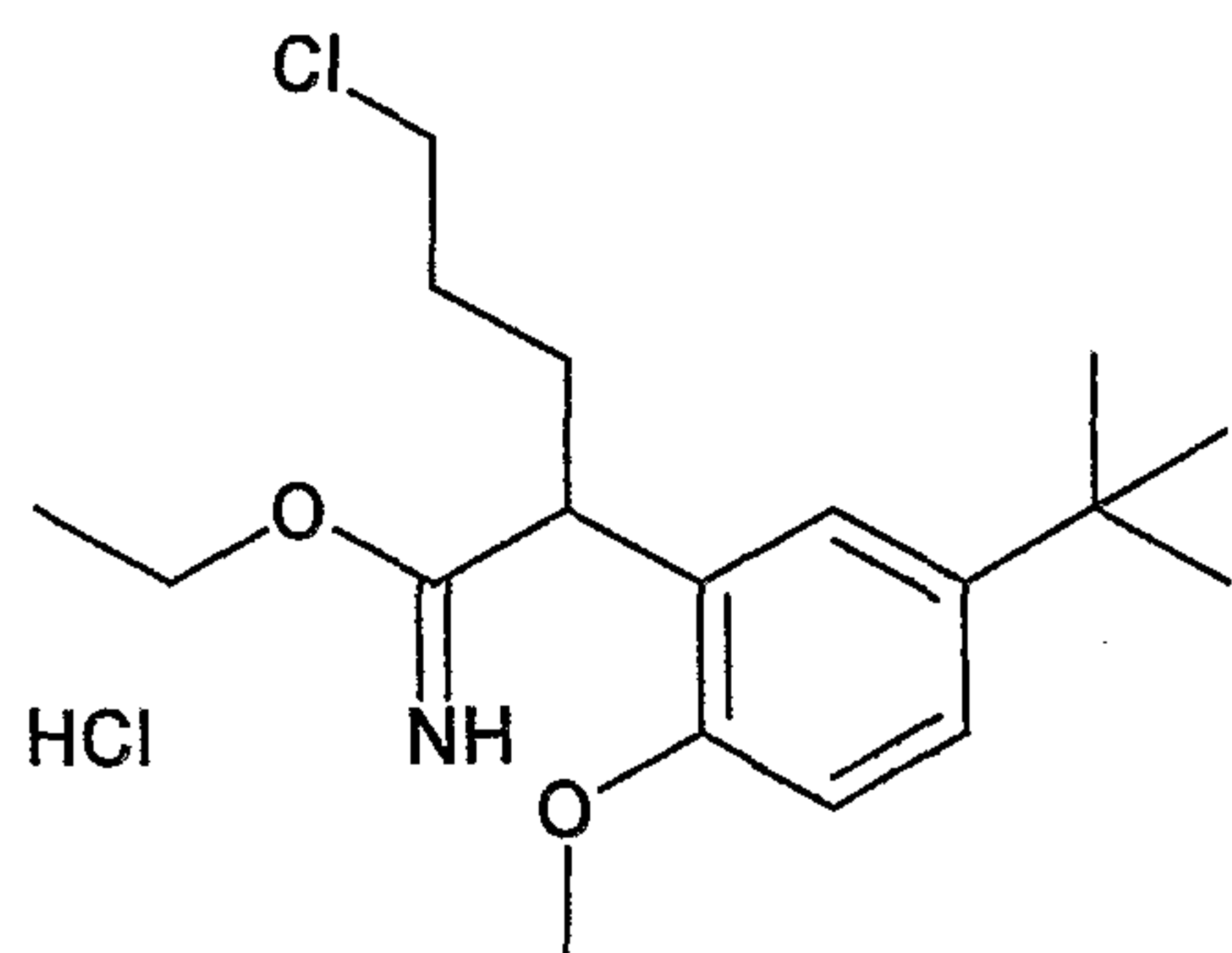
ESI-MS; m/z 310 [$M^+ + H - HCl$].

[0628]

Preparation Example 3-3

Synthesis of ethyl 2-(5-tert-butyl-2-methoxyphenyl)-5-chloropentanimidate hydrochloride

10 [0629]



[0630]

Synthesis of 4-tert-butyl-1-methoxy-2-methylbenzene

Potassium carbonate (8.4 g) and methyl iodide (2.9 mL) were added to a solution of 4-tert-butyl-2-methylphenol (CAS #98-27-1, 5.0 g) in N,N-dimethylformamide (25 mL), and
15 the mixture was stirred at room temperature for three days. Ice water and hexane were added to the reaction solution, and the organic layer was separated. The resulting organic layer was sequentially washed with water and brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 5.16 g of the title compound. The property values of the compound are as follows.

20 ^1H -NMR ($CDCl_3$) δ (ppm): 1.30 (s, 9H), 2.22 (s, 3H), 3.81 (s, 3H), 6.76 (d, $J = 9.2$ Hz, 1H), 7.15-7.19 (m, 2H).

[0631]

Synthesis of 2-bromomethyl-4-tert-butyl-1-methoxybenzene

N-Bromosuccinimide (5.66 g) and 2,2'-azobis(isobutyronitrile) (71 mg) were
25 added to a solution of 4-tert-butyl-1-methoxy-2-methylbenzene (5.16 g) in carbon tetrachloride (25 mL), and the mixture was heated under reflux for 1.5 hours. The reaction solution was ice-

cooled and then the insoluble matter was removed by filtration. The filtrate was concentrated under reduced pressure to obtain 7.78 g of the title compound. The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.30 (s, 9H), 3.88 (s, 3H), 4.58 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H),
5 7.31 (dd, J = 8.4, 2.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H).

[0632]

Synthesis of (5-tert-butyl-2-methoxyphenyl)acetonitrile

Potassium cyanide (2.96 g) was added to a solution of 2-bromomethyl-4-tert-butyl-1-methoxybenzene (7.78 g) in dimethyl sulfoxide (50 mL), and the mixture was stirred at
10 room temperature for 16 hours. Ice and tert-butyl methyl ether were added to the reaction solution, and the organic layer was separated. The aqueous layer was reextracted with tert-butyl methyl ether. The combined organic layers were sequentially washed with water (twice) and brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: ChromatorexTM
15 NH; elution solvent: heptane → ethyl acetate:heptane = 1:49). The target fraction was concentrated. The resulting residue was triturated with hexane to obtain 1.90 g of the title compound. The trituration mother liquor was concentrated. Then, the resulting residue was triturated with hexane to obtain 0.47 g of the title compound. The property values of the compound are as follows.

20 ¹H-NMR (CDCl₃) δ (ppm): 1.31 (s, 9H), 3.68 (s, 2H), 3.85 (s, 3H), 6.82 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 8.4, 2.4 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H).

[0633]

Synthesis of 2-(5-tert-butyl-2-methoxyphenyl)-5-chloropentanenitrile

A solution of n-butyllithium in hexane (2.69 M, 3.0 mL) was added to a solution
25 of N,N-diisopropylamine (1.2 mL) in THF (15 mL) under ice-cooling, and the mixture was stirred at the same temperature for 10 minutes. The solution was cooled to -78°C and a solution of (5-tert-butyl-2-methoxyphenyl)acetonitrile (1.5 g) in THF (6.5 mL) was added dropwise. The solution was stirred at -30°C for 25 minutes and then cooled again to -78°C. 1-Chloro-3-iodopropane (1.2 mL) was added dropwise to the solution, and then the reaction solution was
30 gradually heated to room temperature. After ice-cooling the reaction solution, a solution of lithium hexamethyldisilazide in tetrahydrofuran (1.0 M, 4.4 mL) was added to the reaction solution. Then, a lithium diisopropylamide solution prepared from N,N-diisopropylamine (0.6 mL) and a solution of n-butyllithium in hexane (2.69 M, 1.5 mL) was added to the reaction solution. A saturated ammonium chloride aqueous solution was added to the reaction solution.

Then, ethyl acetate and water were added and the organic layer was separated. The resulting organic layer was sequentially washed with 1 N hydrochloric acid, water, a saturated sodium bicarbonate aqueous solution and brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: Merck silica gel 60 (230-400 mesh); elution solvent: heptane:ethyl acetate = 1:49) to obtain 864 mg of a 1:7 mixture of (5-tert-butyl-2-methoxyphenyl)acetonitrile and the title compound. The property values of the title compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.31 (s, 9H), 1.86-2.12 (m, 4H), 3.54-3.60 (m, 2H), 3.84 (s, 3H), 4.18-4.24 (m, 1H), 6.83 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 8.4, 2.4 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H).

[0634]

Synthesis of ethyl 2-(5-tert-butyl-2-methoxyphenyl)-5-chloropentanimidate hydrochloride and ethyl 2-(5-tert-butyl-2-methoxyphenyl)acetimidate hydrochloride

A solution of the 1:7 mixture of (5-tert-butyl-2-methoxyphenyl)acetonitrile and 2-(5-tert-butyl-2-methoxyphenyl)-5-chloropentanenitrile (864 mg) in ethanol (8 mL) was bubbled with hydrogen chloride gas under ice-cooling for 15 minutes. The reaction solution was stirred at room temperature for one day. The reaction solution was concentrated under reduced pressure to obtain a mixture of the title compound.

The property values of ethyl 2-(5-tert-butyl-2-methoxyphenyl)-5-chloropentanimidate hydrochloride are as follows.

ESI-MS; m/z 326 [M⁺ + H - HCl].

[0635]

The property values of ethyl 2-(5-tert-butyl-2-methoxyphenyl)acetimidate hydrochloride are as follows.

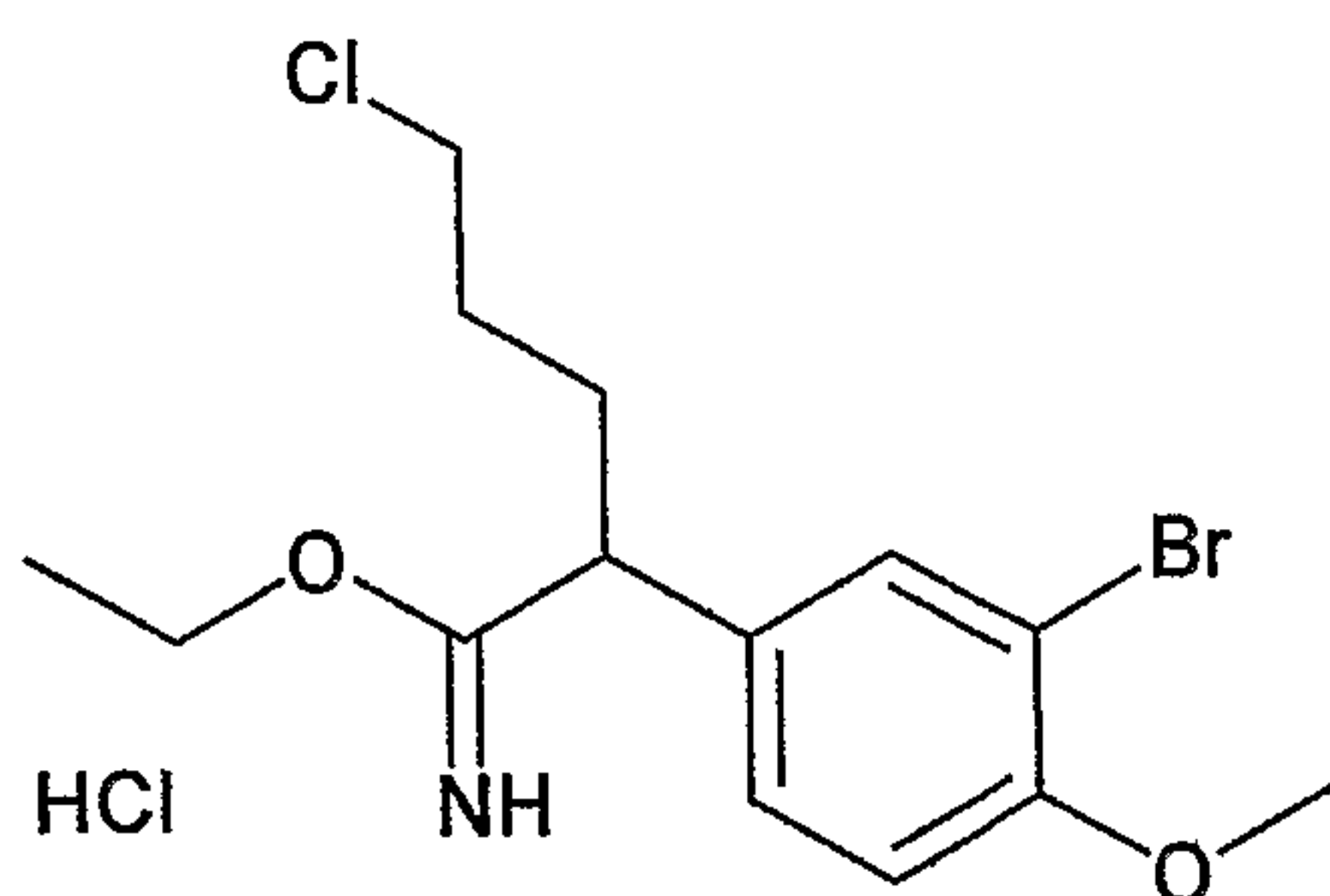
ESI-MS; m/z 250 [M⁺ + H - HCl].

[0636]

Preparation Example 3-4

Synthesis of ethyl 2-(3-bromo-4-methoxyphenyl)-5-chloropentanimidate hydrochloride

[0637]



The title compound (3.62 g) was obtained as a white solid from 3-bromo-4-methoxyphenylacetonitrile (3.0 g) according to the method of Example 3-1.

ESI-MS; m/z 350 [$M^+ + H - HCl$].

5 The compounds of Preparation Examples 3-5 to 3-13 were obtained below by the same method as in Example 3-1 (Table 7).

[0638]

Table 7

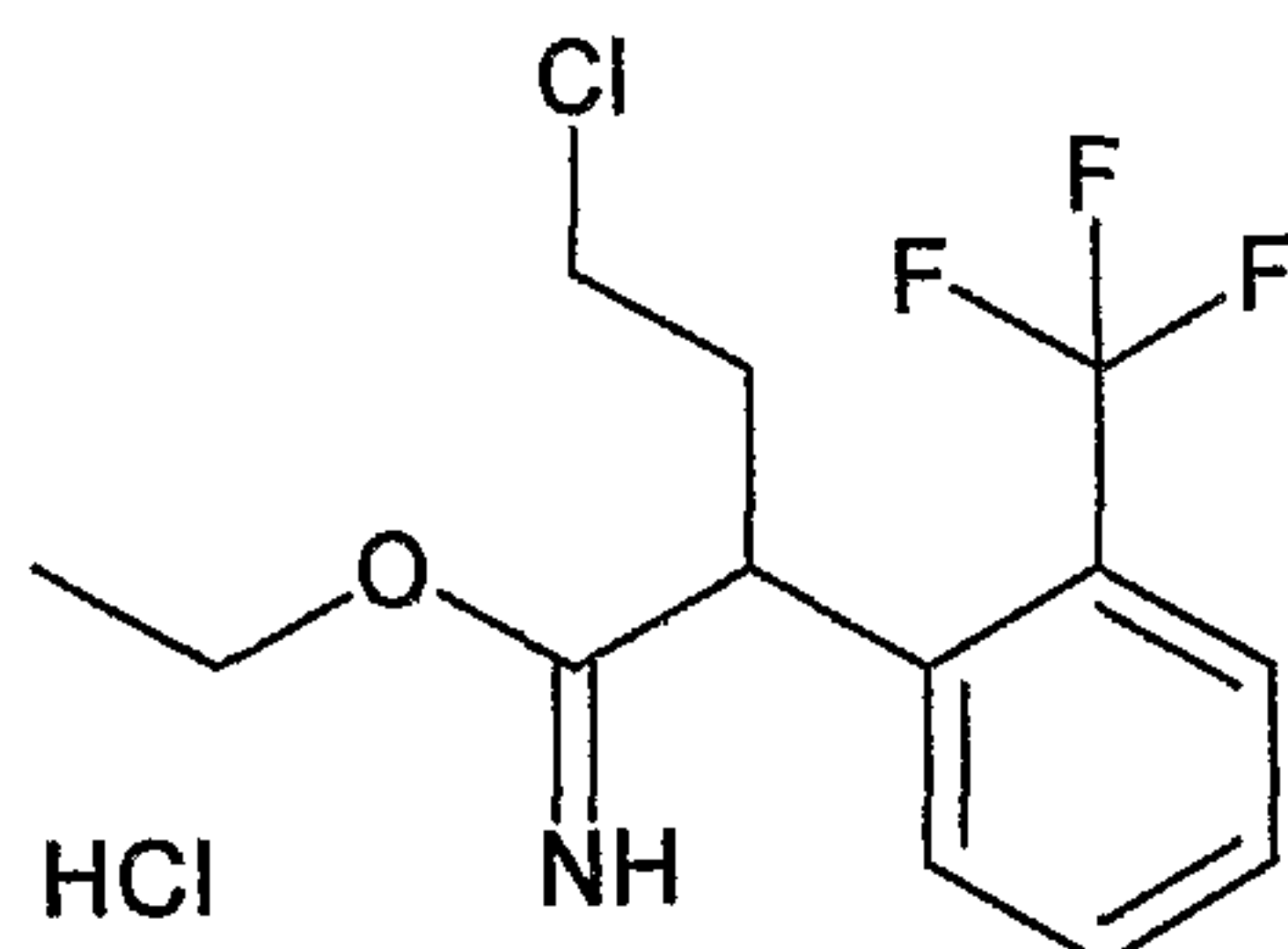
Production Ex No.	Structural formula	Production Ex No.	Structural formula
3-5		3-10	
3-6		3-11	
3-7		3-12	
3-8		3-13	
3-9			

[0639]

Preparation Example 3-14

Synthesis of ethyl 4-chloro-2-(2-trifluoromethylphenyl)butanimidate hydrochloride

[0640]



5 [0641]

Synthesis of 4-(tert-butyldimethylsilyloxy)-2-(2-trifluoromethylphenyl)butyronitrile

(2-Trifluoromethylphenyl)acetonitrile (3 g) and tetrabutylammonium bisulfate (550 mg) were suspended in toluene (30 mL), and a 50% sodium hydroxide aqueous solution (15 mL) was added dropwise under ice-cooling. After stirring for 10 minutes, (2-bromoethoxy)-tert-butyl-
 10 butyldimethylsilane (5.2 mL) was added at the same temperature. The mixture was brought back to room temperature and stirred overnight. Water was added to the reaction solution, followed by extraction with tert-butyl methyl ether. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by
 15 silica gel column chromatography to obtain the title compound (5 g). The property values of the compound are as follows.

ESI-MS; m/z 344 [$M^+ + H$].

^1H -NMR ($CDCl_3$) δ (ppm): 0.08 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.98-2.14 (m, 2H), 3.80-3.95 (m, 2H), 4.52 (dd, $J = 10.2, 6.2$ Hz, 1H), 7.42-7.48 (m, 1H), 7.59-7.65 (m, 1H), 7.68-7.74 (m,
 20 2H).

[0642]

Synthesis of 4-hydroxy-2-(2-trifluoromethylphenyl)butyronitrile

4-(tert-Butyldimethylsilyloxy)-2-(2-trifluoromethylphenyl)butyronitrile (5 g) was dissolved in tetrahydrofuran (70 mL). Tetrabutylammonium fluoride (1 M solution in
 25 tetrahydrofuran) (18 mL) was added and the mixture was stirred at room temperature for 4.5 hours. The reaction solution was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (3.1 g). The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.11-2.19 (m, 2H), 3.86-3.97 (m, 2H), 4.49 (dd, J = 8.6, 7.0 Hz, 1H), 7.45-7.51 (m, 1H), 7.62-7.68 (m, 1H), 7.69-7.76 (m, 2H).

[0643]

Synthesis of 4-chloro-2-(2-trifluoromethylphenyl)butyronitrile

5 4-Hydroxy-2-(2-trifluoromethylphenyl) butyronitrile (2.6 g) was dissolved in pyridine (10 mL). Thionyl chloride (2.1 mL) was carefully added and the mixture was heated with stirring at 60°C for four hours. Water was added to the reaction solution, followed by extraction with ethyl acetate. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the
10 organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (1.3 g). The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 2.27-2.44 (m, 2H), 3.72-3.79 (m, 2H), 4.53 (dd, J = 9.8, 5.0 Hz, 1H), 7.46-7.53 (m, 1H), 7.62-7.66 (m, 1H), 7.70-7.76 (m, 2H).

15 [0644]

Synthesis of ethyl 4-chloro-2-(2-trifluoromethylphenyl)butanimidate hydrochloride

The title compound (1.3 g) was obtained by the same method as in Preparation Example 3-1 from 4-chloro-2-(2-trifluoromethylphenyl) butyronitrile (1.5 g). The property values of the compound are as follows.

20 ESI-MS; m/z 294 [M⁺ + H-HCl].

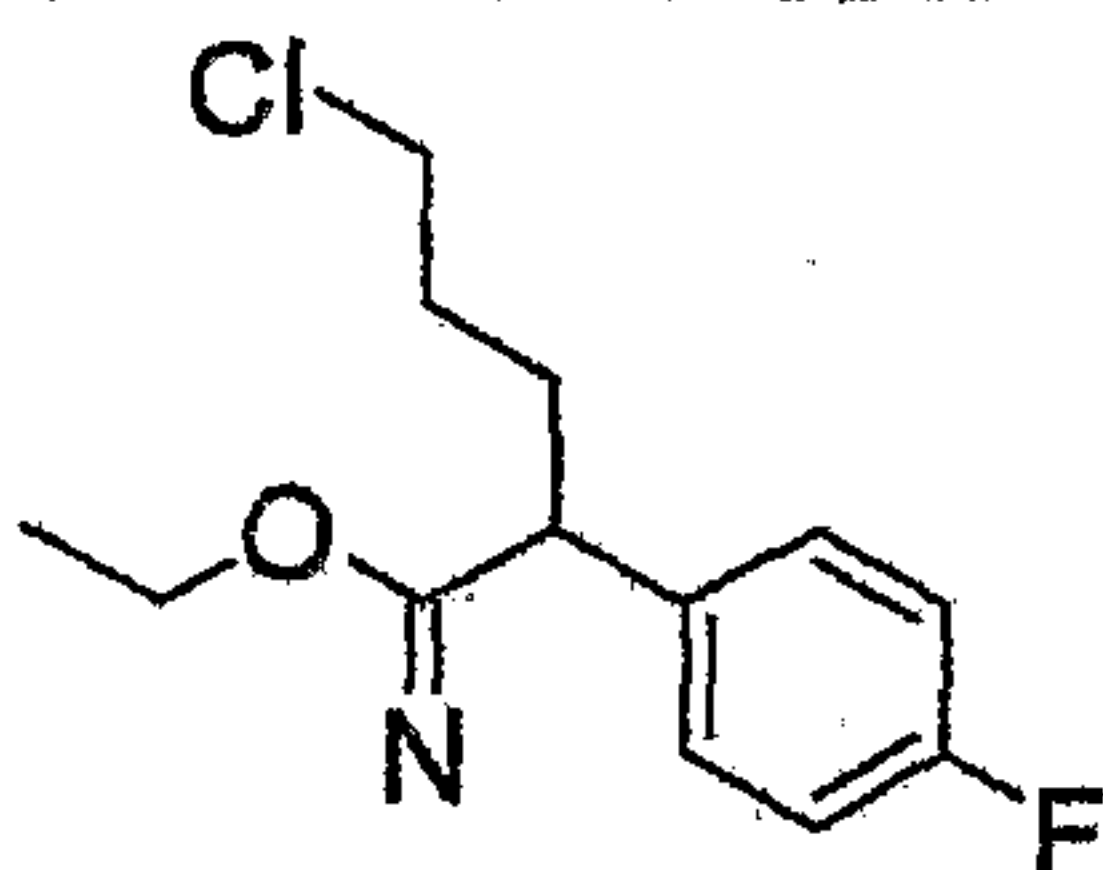
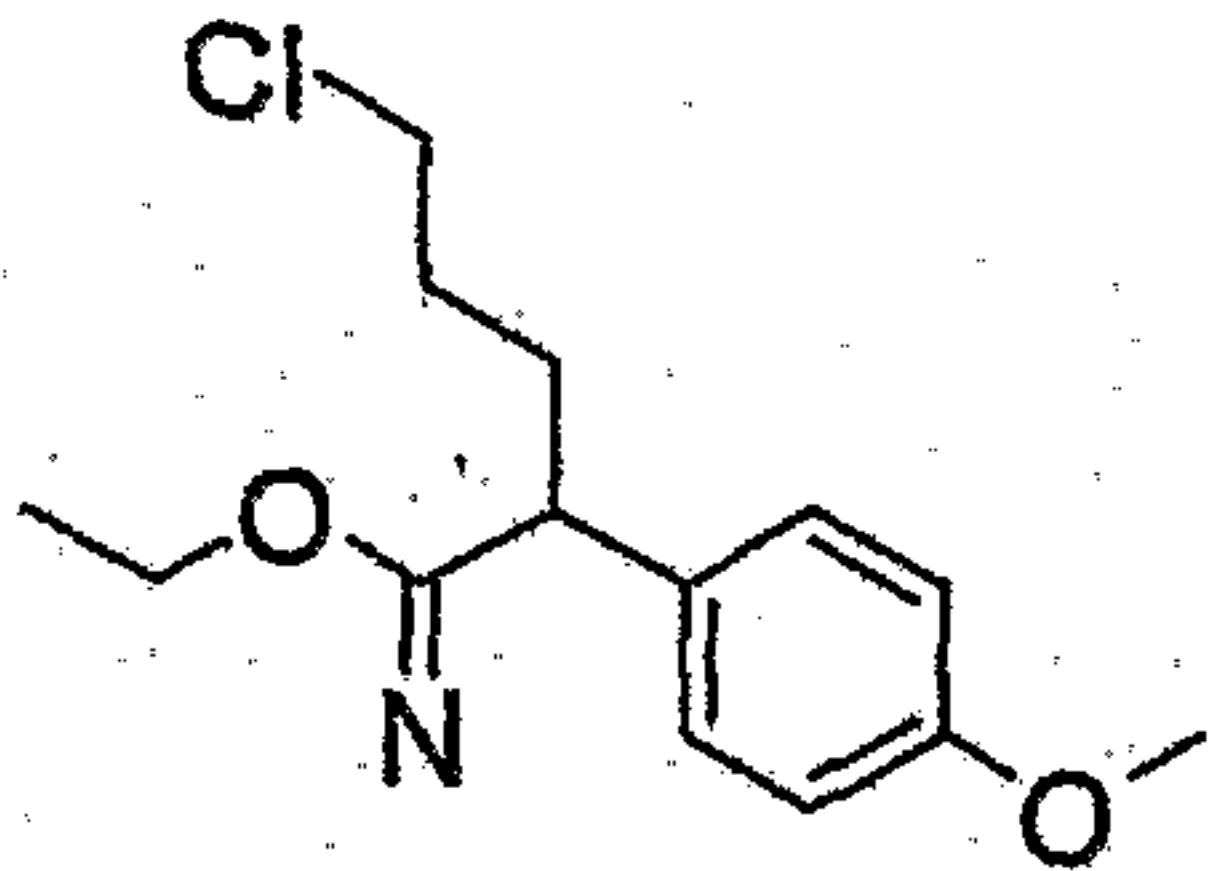
¹H-NMR (CDCl₃) δ (ppm): 1.41 (t, J = 7.0 Hz, 3H), 2.56-2.66 (m, 1H), 3.03-3.14 (m, 1H), 3.56-3.68 (m, 2H), 4.59-4.75 (m, 3H), 7.50 (dd, J = 7.6, 7.6 Hz, 1H), 7.68 (dd, J = 7.6, 7.6 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H).

[0645]

25 The compounds of Preparation Examples 3-15 to 3-16 were obtained by the same method as in Example 3-14 (Table 8).

[0646]

Table 8

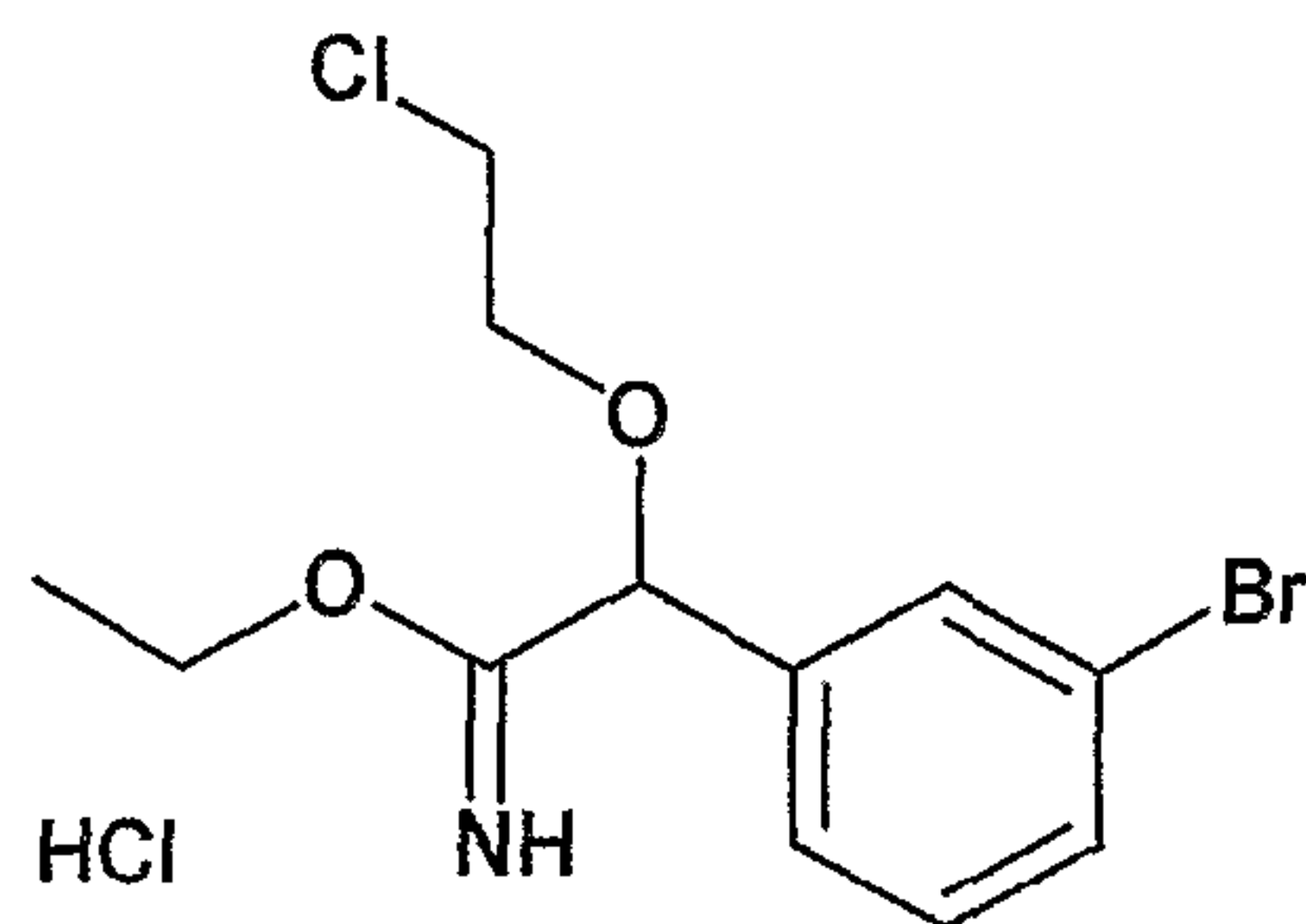
Production Ex No.	Structural formula
3-15	
3-16	

[0647]

Preparation Example 3-17

Synthesis of ethyl 2-(3-bromophenyl)-2-(2-chloroethoxy)acetimidate hydrochloride

5 [0648]



[0649]

Synthesis of (3-bromophenyl)-(2-hydroxyethoxy)acetonitrile

10 Zinc iodide (50.6 mg) was added to a mixture of 2-(3-bromophenyl)-1,3-dioxolane (3 mL) and trimethylsilyl cyanide (2.49 mL), followed by stirring at room temperature for 1.5 hours. A saturated sodium bicarbonate aqueous solution was added to the reaction solution, followed by extraction with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Then, the resulting residue was purified by silica gel column chromatography (elution solvent: heptane:ethyl acetate = 7:3 ->

1:1) to obtain 3.93 g of the title compound. The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.83 (br, 1H), 3.73-3.78 (m, 1H), 3.84-3.90 (m, 3H), 5.33 (s, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.44-7.47 (m, 1H), 7.56-7.59 (m, 1H), 7.67 (dt, J = 0.4, 1.2 Hz, 1H).

[0650]

5 Synthesis of (3-bromophenyl)-(2-chloroethoxy)acetonitrile

Thionyl chloride (1.23 mL) was added dropwise to a solution of (3-bromophenyl)-(2-hydroxyethoxy)acetonitrile (3.62 g) in pyridine (12.1 mL) at 50°C, and the mixture was stirred at 60°C for two hours. Water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Then, the resulting residue was purified by silica gel column chromatography (elution solvent: heptane:ethyl acetate = 9:1 → 8:2) to obtain 3.21 g of the title compound. The property values of the compound are as follows.

15 ¹H-NMR (CDCl₃) δ (ppm): 3.70-3.73 (m, 2H), 3.87 (ddd, J = 5.2, 6.4, 10.4 Hz, 1H), 4.01 (ddd, J = 5.6, 5.6, 10.0 Hz, 1H), 5.36 (s, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.45-7.48 (m, 1H), 7.57-7.59 (m, 1H), 7.67 (dt, J = 0.4, 1.6 Hz, 1H).

[0651]

Synthesis of ethyl 2-(3-bromophenyl)-2-(2-chloroethoxy)acetimidate hydrochloride

20 The title compound (2.71 g) was obtained by the same method as in Preparation Example 3-1 from (3-bromophenyl)-(2-chloroethoxy)acetonitrile (3.21 g). The property values of the compound are as follows.

¹H-NMR (DMSO-D₆) δ (ppm): 1.24 (t, J = 7.2 Hz, 3H), 3.76-3.90 (m, 4H), 4.41-4.43 (m, 2H), 5.50 (s, 1H), 7.40-7.47 (m, 2H), 7.63-7.68 (m, 2H).

[0652]

25 The compound of Preparation Example 3-18 were obtained by the same method as in Example 3-17 (Table 9).

[0653]

Table 9

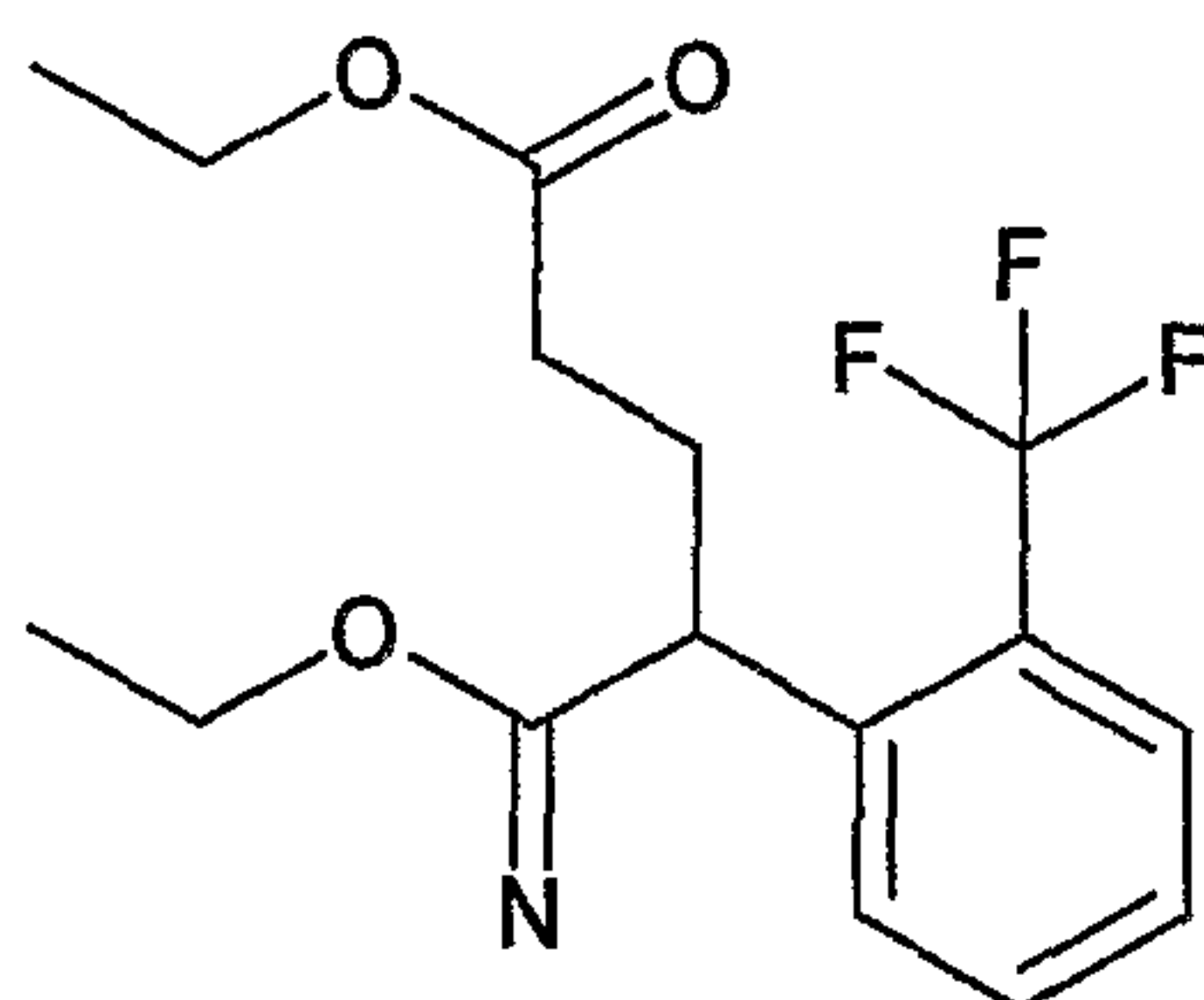
Production Ex No.	Structural formula
3-18	

[0654]

Preparation Example 3-19

Synthesis of ethyl 4-ethoxycarbonimidoyl-4-(2-trifluoromethylphenyl)butanoate

5 [0655]



[0656]

Synthesis of methyl 4-cyano-4-(2-trifluoromethylphenyl)butanoate

2-(Trifluoromethyl)phenylacetonitrile (2.0 g) was dissolved in tetrahydrofuran (50 mL). Potassium tert-butoxide (60.6 mg), 18-crown-6 (2.85 g) and methyl acrylate (973 μ L) were added at 0°C and the mixture was stirred at the same temperature for 40 minutes. The reaction was terminated with saturated ammonium chloride, followed by dilution with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. Concentration under reduced pressure gave an oil. The oil was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 30%) to obtain the title compound (2.2 g).

15 $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.25 (dd, $J = 14.9, 7.4$ Hz, 2H), 2.51-2.65 (m, 2H), 3.70 (s, 3H), 4.31 (t, $J = 7.8$ Hz, 1H), 7.46-7.51 (m, 1H), 7.65-7.67 (m, 1H), 7.69-7.73 (m, 2H).

[0657]

Synthesis of ethyl 4-ethoxycarbonimidoyl-4-(2-trifluoromethylphenyl)butanoate hydrochloride

20 Methyl 4-cyano-4-(2-trifluoromethylphenyl)butanoate (200 mg) was dissolved in ethanol (1.03 mL), and acetyl chloride (838 μ L) was added at 0°C. The mixture was heated to

room temperature and the reaction was initiated. After stirring for 24 hours, concentration under reduced pressure gave a crude product of the title compound as an oil (300 mg).

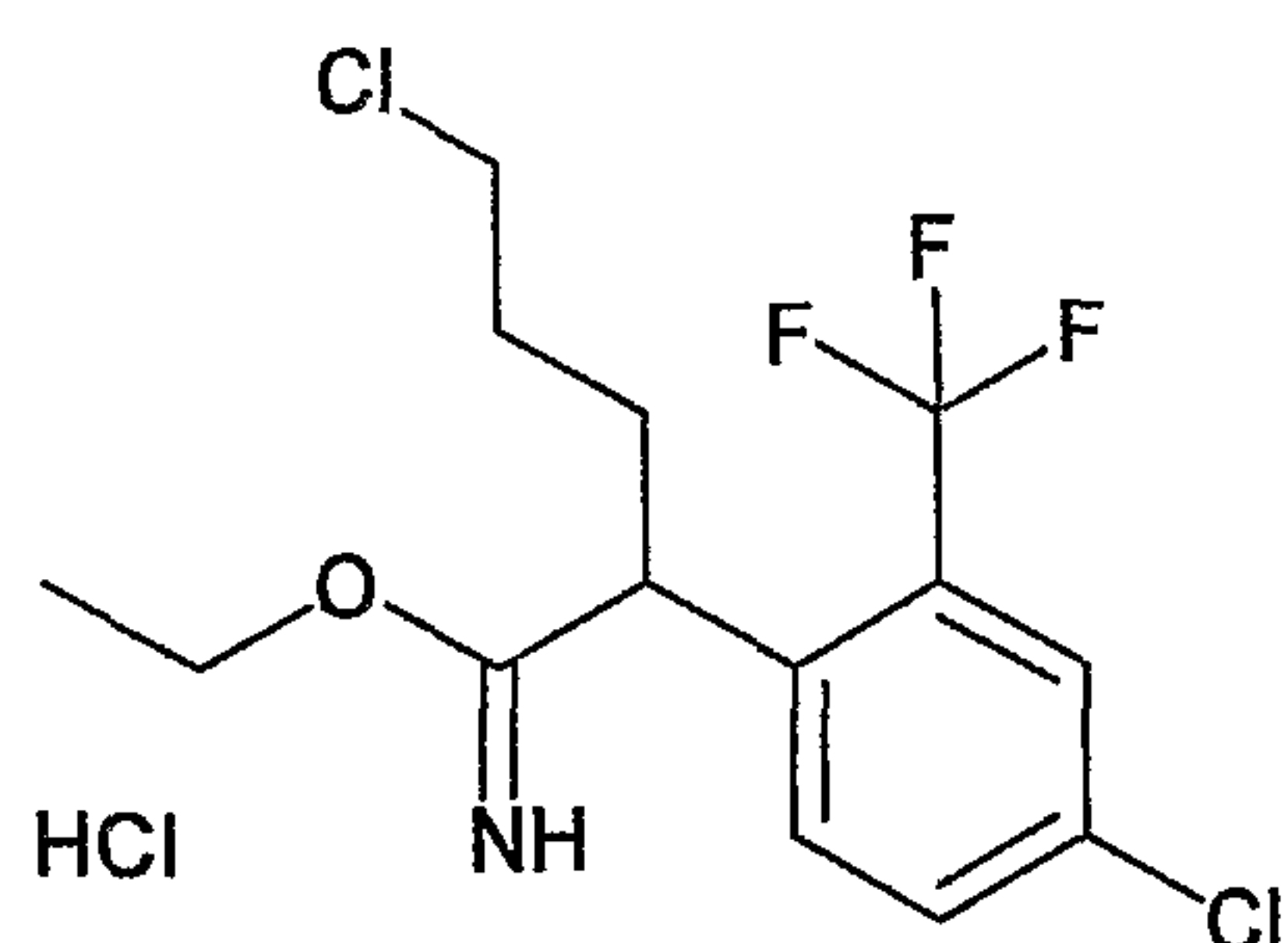
ESI-MS; m/z 332 [$M^+ + H - HCl$].

[0658]

5 Preparation Example 3-20

Synthesis of ethyl 2-(4-chloro-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride

[0659]



[0660]

Synthesis of methyl (4-chloro-2-trifluoromethylphenyl)acetate

- 10 Thionyl chloride (9.5 mL) was added dropwise to a solution of 4-chloro-2-(trifluoromethyl)phenylacetic acid (CAS #601513-31-9, 10.5 g) in methanol (50 mL) under ice-cooling. Then, the reaction solution was heated under reflux for three hours. The reaction solution was concentrated under reduced pressure. A saturated sodium bicarbonate solution and ethyl acetate were added to the resulting residue, and the organic layer was separated. The
- 15 resulting organic layer was sequentially washed with a saturated sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 10.96 g of the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 3.71 (s, 3H), 3.80 (s, 2H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.50 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.65 (d, $J = 2.0$ Hz, 1H).

20 [0661]

Synthesis of methyl 5-chloro-2-(4-chloro-2-trifluoromethylphenyl)pentanoate

- A solution of methyl (4-chloro-2-trifluoromethylphenyl)acetate (5.5 g) and 3-chloro-1-iodopropane (4.6 mL) in tetrahydrofuran (15 mL) was added dropwise to a suspension of sodium hydride (containing 60% in mineral oil, 955 mg) in tetrahydrofuran (50 mL) under
- 25 ice-cooling. The reaction solution was stirred at the same temperature for 10 minutes and then at room temperature for three hours and 20 minutes. Ice water and ethyl acetate were added to the reaction solution, and the organic layer was separated. The aqueous layer was reextracted with

ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate, followed by concentration under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: WakogelTM C-200; elution solvent: heptane:ethyl acetate = 19:1) to obtain 5.30 g of the title compound. The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.59-1.71 (m, 1H), 1.76-1.96 (m, 2H), 2.17-2.28 (m, 1H), 3.51 (t, J = 6.4 Hz, 2H), 3.68 (s, 3H), 3.99 (t, J = 7.2 Hz, 1H), 7.52 (dd, J = 8.4, 2.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H).

[0662]

10 Synthesis of 5-chloro-2-(4-chloro-2-trifluoromethylphenyl)pentanoic acid

A 5 N sodium hydroxide aqueous solution (13 mL) was added to a mixed solution of methyl 5-chloro-2-(4-chloro-2-trifluoromethylphenyl)pentanoate (5.3 g) in tetrahydrofuran (15 mL)-methanol (15 mL), and the mixture was stirred at room temperature for two hours and 10 minutes. After adding ice water to the reaction solution, the organic solvent was evaporated from the reaction solution under reduced pressure. The resulting aqueous layer was washed with heptane. The aqueous layer was made acidic with 5 N hydrochloric acid under ice-cooling, followed by extraction with ethyl acetate twice. The combined ethyl acetate layers were washed with brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 4.75 g of the title compound.

20 ¹H-NMR (CDCl₃) δ (ppm): 1.59-1.71 (m, 1H), 1.79-2.01 (m, 2H), 2.19-2.30 (m, 1H), 3.51 (t, J = 6.4 Hz, 2H), 4.03 (t, J = 7.6 Hz, 1H), 7.54 (brs, 2H), 7.67 (brs, 1H).

[0663]

Synthesis of 5-chloro-2-(4-chloro-2-trifluoromethylphenyl)pentanoic acid amide

Ammonium chloride (3.23 g), 1-hydroxybenzotriazole (2.45 g), IPEA (13.7 mL) and benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (9.43 g) were sequentially added to a solution of 5-chloro-2-(4-chloro-2-trifluoromethylphenyl)pentanoic acid (4.75 g) in N,N-dimethylformamide (45 mL). The mixture was stirred at room temperature overnight. Ice water and tert-butyl methyl ether were added to the reaction solution, and the organic layer was separated. The aqueous layer was reextracted with tert-butyl methyl ether. The combined organic layers were sequentially washed with 1 N hydrochloric acid, water, a saturated sodium bicarbonate aqueous solution and brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: WakogelTM C-200; elution solvent: heptane:ethyl acetate = 4:1 -> 3:1) to obtain 3.89 g of the title compound. The property values of the

compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.60-1.67 (m, 1H), 1.80-1.97 (m, 2H), 2.20-2.31 (m, 1H), 3.45-3.56 (m, 2H), 3.77 (t, J = 7.2 Hz, 1H), 5.30 (brs, 1H), 5.41 (brs, 1H), 7.54 (dd, J = 8.4, 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H).

5 [0664]

Synthesis of 5-chloro-2-(4-chloro-2-trifluoromethylphenyl)pentanenitrile

Methyl dichlorophosphate (1.9 mL) was added dropwise at 20°C or less to an ice-cooled solution of 5-chloro-2-(4-chloro-2-trifluoromethylphenyl)pentanoic acid amide (3.0 g) and 1,8-diazabicyclo[5,4,0]undec-7-ene (6.4 mL) in methylene chloride (30 mL). After
10 completion of the dropwise addition, the reaction solution was stirred at room temperature for one hour and 25 minutes. A saturated sodium bicarbonate aqueous solution was added to the reaction solution. After stirring for five minutes, the organic layer was separated. The aqueous layer was reextracted with methylene chloride. The combined organic layers were sequentially washed with 1 N hydrochloric acid, water, a saturated sodium bicarbonate aqueous solution and
15 brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: Wakogel C-200; elution solvent: heptane:ethyl acetate = 49:1 → 19:1) to obtain 2.25 g of the title compound. The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.89-2.18 (m, 4H), 3.58 (t, J = 6.0 Hz, 2H), 4.15 (dd, J = 8.0, 6.4
20 Hz, 1H), 7.63 (dd, J = 8.4, 2.0 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H).

[0665]

Synthesis of ethyl 2-(4-chloro-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride

The title compound was obtained by the same method as in Preparation Example 3-1 from 5-chloro-2-(4-chloro-2-trifluoromethylphenyl)pentanenitrile.

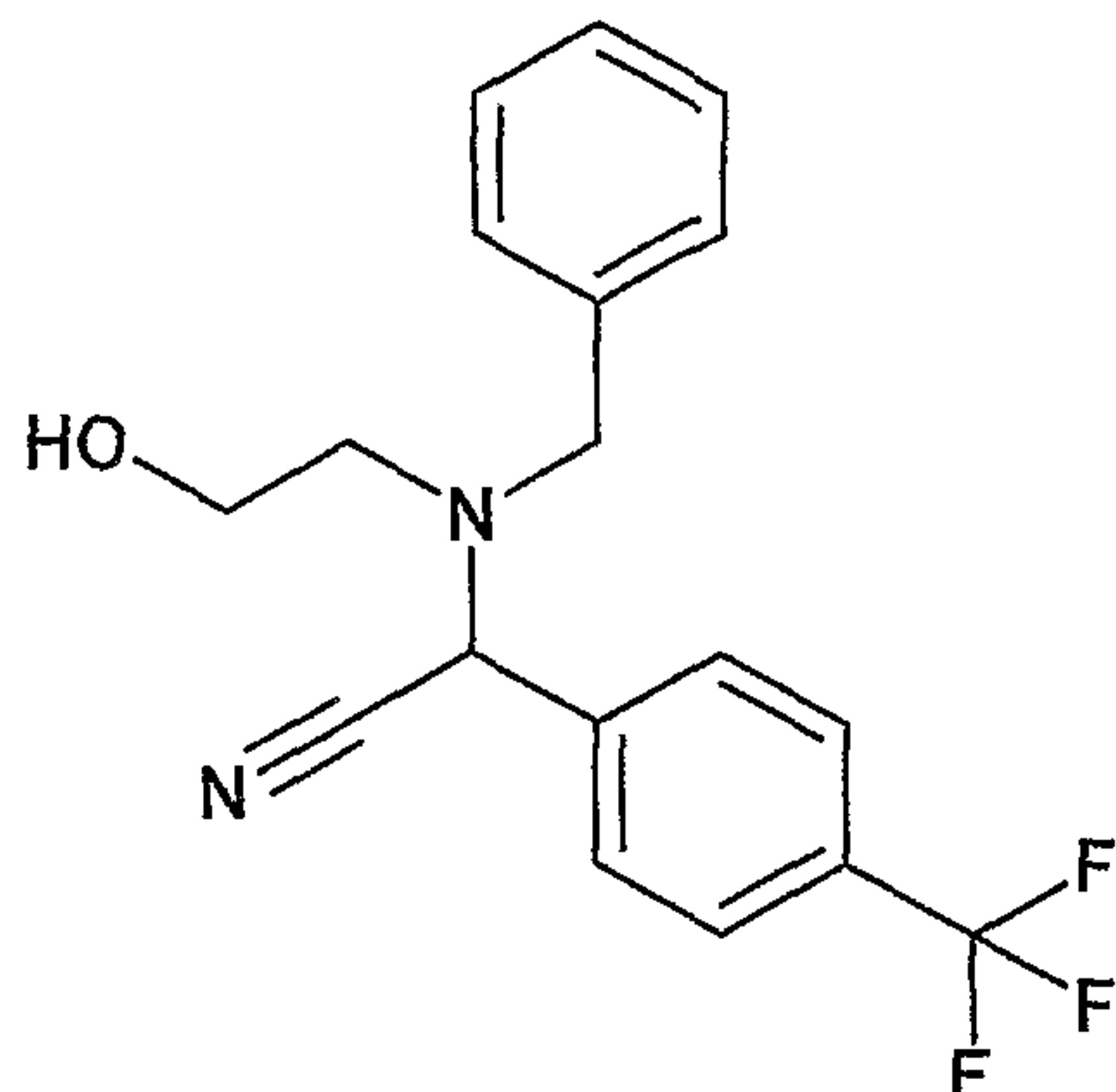
25 ESI-MS; m/z 342 [M⁺ + H - HCl].

[0666]

Preparation Example 4-1

Synthesis of [benzyl(2-hydroxyethyl)amino]-(4-trifluoromethylphenyl)acetonitrile

[0667]



[0668]

4-(Trifluoromethyl)benzaldehyde (CAS #455-19-6, 2 g) and methanol (1 mL) were added to a solution of sodium bisulfite (1.33 g) in water (40 mL) at room temperature, and the mixture was stirred at room temperature for 10 minutes. Sodium cyanide (1.33 g) was added to the reaction solution, and the mixture was stirred at the same temperature for 40 minutes. N-Benzylethanolamine (1.83 g) and methanol (3 mL) were added to the reaction solution, and the mixture was stirred at the same temperature for 16 hours. The reaction solution was partitioned with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (elution solvent: heptane:ethyl acetate = 9:1 → 1:1) to obtain 1.79 g of the title compound. The property values of the compound are as follows.

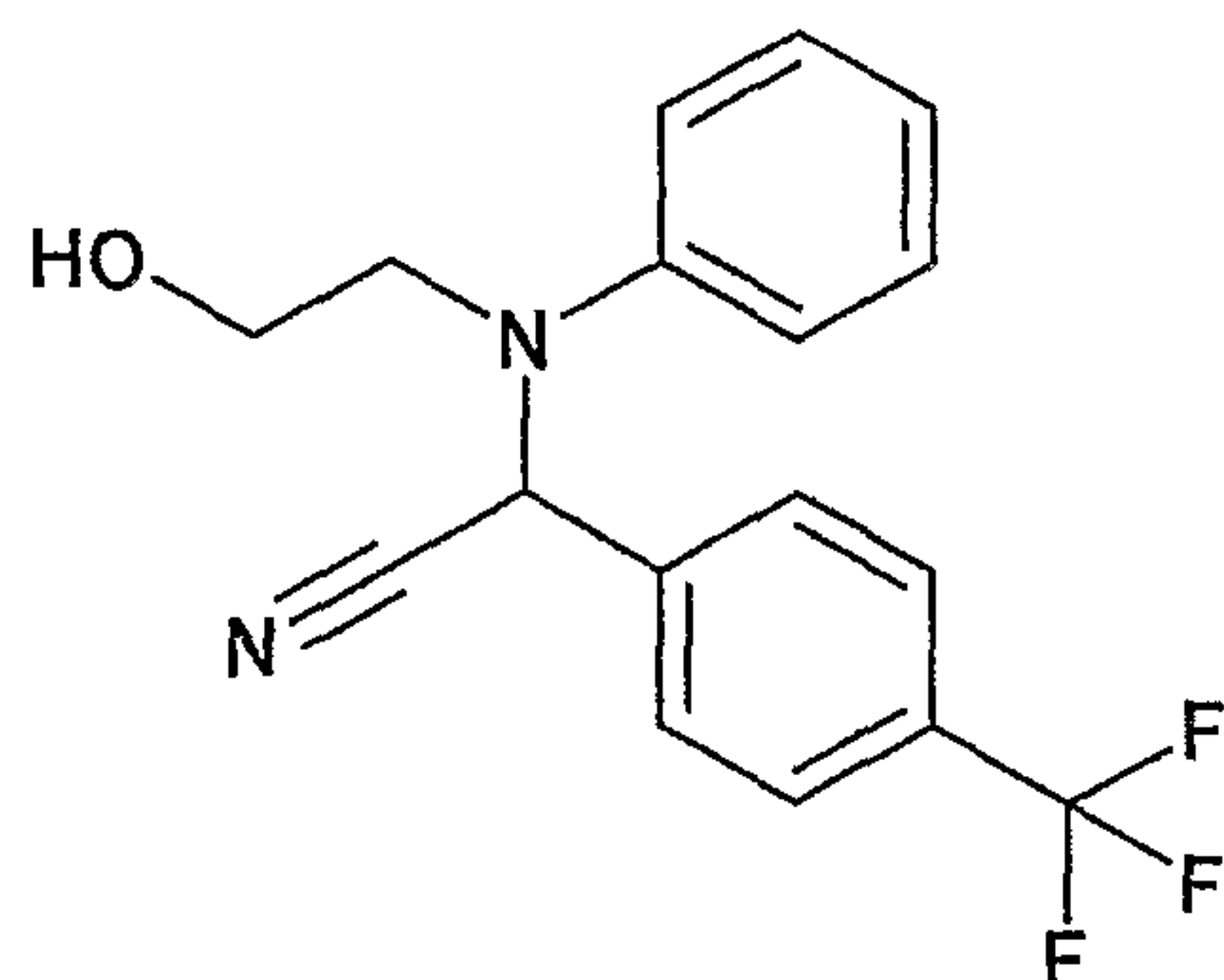
¹H-NMR (CDCl₃) δ (ppm): 1.66 (brs, 1H), 2.70-2.81 (m, 2H), 3.55 (d, J = 13.6 Hz, 1H), 3.58-3.61 (m, 1H), 3.75-3.82 (m, 1H), 4.02 (d, J = 13.2 Hz, 1H), 5.06 (s, 1H), 7.30-7.40 (m, 5H), 7.64-7.71 (m, 4H).

[0669]

Preparation Example 4-2

Synthesis of [(2-hydroxyethyl)phenylamino]-(4-trifluoromethylphenyl)acetonitrile

20 [0670]



[0671]

Trimethylsilyl cyanide (723 μ L) was added to a mixture of 4-(trifluoromethyl)benzaldehyde (CAS #455-19-6, 1 g), N-phenylethanolamine (870 mg) and
 5 sulfamic acid (28 mg), and the mixture was stirred at room temperature for 20 hours. The reaction solution was partitioned with water and chloroform. The organic layer was dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (elution solvent: heptane:ethyl acetate = 9:1 $\rightarrow$ 1:1) to obtain 775 mg of the title compound. The property values
 10 of the compound are as follows.

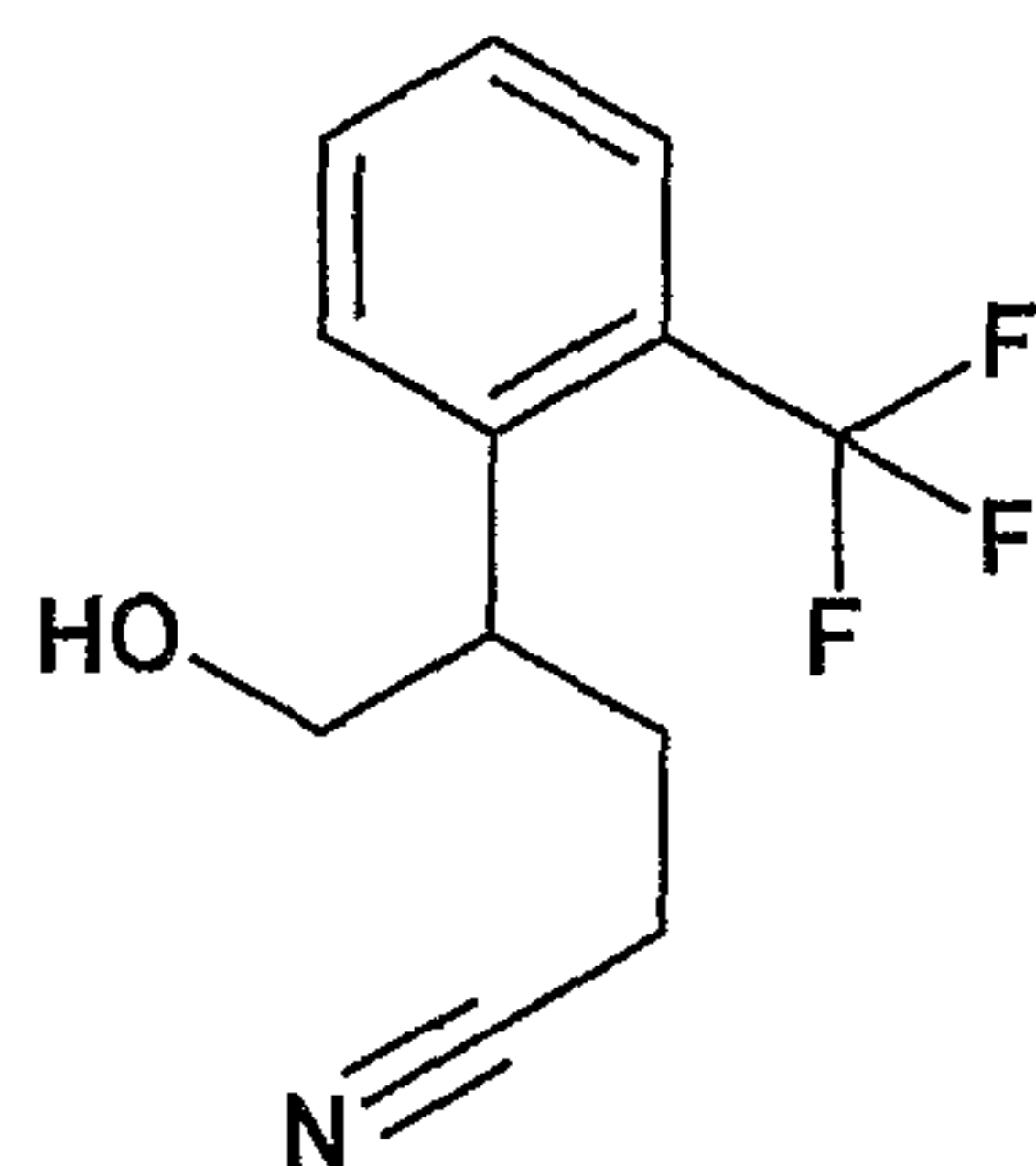
$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.59 (brs, 1H), 3.30 (ddd, $J = 5.6, 7.2, 12.4$ Hz, 1H), 3.53 (ddd, $J = 4.8, 7.2, 7.2$ Hz, 1H), 3.64-3.69 (m, 2H), 5.70 (s, 1H), 7.01-7.06 (m, 3H), 7.31-7.35 (m, 2H), 7.69-7.72 (m, 4H).

[0672]

15 Preparation Example 4-3

Synthesis of 5-hydroxy-4-(2-trifluoromethylphenyl)pentanenitrile

[0673]



[0674]

Synthesis of tert-butyl (2-trifluoromethylphenyl)acetate

20 (2-Trifluoromethyl)phenylacetic acid (10.5 g) was dissolved in tetrahydrofuran

(150 mL), and tert-butyl 2,2,2-trichloroacetimidate (18.4 mL) and a boron trifluoride-diethyl ether complex (323 μ L) were added at 0°C. After stirring at room temperature for 22 hours, the reaction was terminated with a saturated sodium bicarbonate aqueous solution, followed by dilution with ethyl acetate. The organic layer was washed with a saturated sodium bicarbonate aqueous solution and brine and dried over magnesium sulfate. Concentration under reduced pressure gave a white solid. The solid was simply purified by an amino silica gel pad (mobile phase: ethyl acetate:heptane = 1:15) to obtain the title compound (13.0 g).

Synthesis of tert-butyl 4-cyano-2-(2-trifluoromethylphenyl)butanoate

tert-Butyl (2-trifluoromethylphenyl)acetate (12.9 g) was dissolved in toluene (129 mL). Benzyltrimethylammonium hydroxide (782 μ L) was added at room temperature, followed by stirring for 10 minutes. Thereafter, acrylonitrile (6.49 mL) was added at 0°C and the reaction was initiated. After stirring at room temperature for 12 hours, the reaction was terminated with 2 N hydrochloric acid, followed by dilution with diethyl ether. The organic layer was washed with water (twice) and brine and dried over magnesium sulfate. Concentration under reduced pressure gave a yellow oil (17 g), which was used directly for the next reaction as a crude product.

Synthesis of 4-cyano-2-(2-trifluoromethylphenyl)butanoic acid

tert-Butyl 4-cyano-2-(2-trifluoromethylphenyl)butanoate (7.2 g) was dissolved in methylene chloride (40 mL). Trifluoroacetic acid (50 mL) was added at 0°C and the reaction was initiated. After stirring at room temperature for one hour, concentration under reduced pressure gave an oil. The resulting oil was dissolved in diethyl ether, washed with water (three times) and brine and dried over magnesium sulfate. Concentration under reduced pressure gave a yellow oil. The oil was dissolved again in diethyl ether and partitioned between diethyl ether and 5 N sodium hydroxide (15 mL). The resulting aqueous layer was made acidic with 5 N hydrochloric acid (16 mL) and extracted with methylene chloride twice to obtain the title compound (6.76 g) as a colorless transparent oil.

Synthesis of 5-hydroxy-4-(2-trifluoromethylphenyl)pentanenitrile

Thionyl chloride (8.25 mL) was added to 4-cyano-2-(2-trifluoromethylphenyl)butanoic acid (2.9 g), and the mixture was heated under reflux. After one hour, concentration under reduced pressure gave an oil. The oil was dissolved in tetrahydrofuran (50 mL) and ethanol (20 mL), and sodium borohydride (855 mg) was added at 0°C. After stirring at room temperature for one hour, the reaction was terminated with water, followed by dilution with ethyl acetate. The organic layer was washed with 1 N hydrochloric acid, a saturated sodium bicarbonate aqueous solution and brine and dried over magnesium sulfate.

Concentration under reduced pressure gave a pale yellow oil. The oil was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 50%) to obtain the title compound (2.14 g).

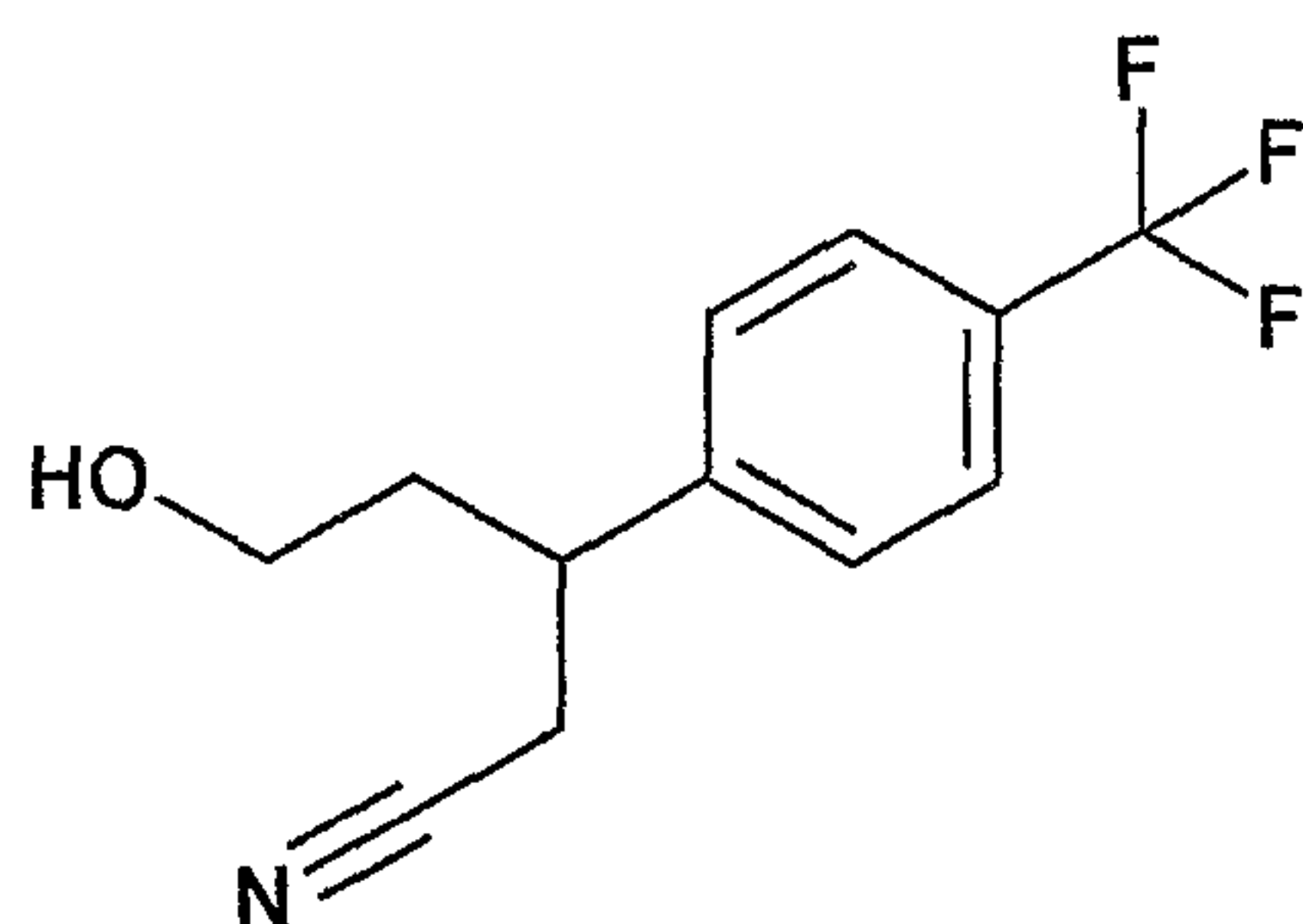
ESI-MS; m/z 244 $[M^+ + H]$.

5 [0675]

Preparation Example 4-4

Synthesis of 5-hydroxy-3-(4-trifluoromethylphenyl)pentanenitrile

[0676]



[0677]

10 Synthesis of 5-hydroxy-3-(4-trifluoromethylphenyl)pentanoic acid amide

Saturated ammonia/methanol (10 mL) was added to 4-(3-trifluoromethylphenyl)tetrahydropyran-2-one obtained according to the method of Preparation Example 2-10 (1.0 g), and the mixture was stirred at 60°C for 23 hours. To complete the reaction, saturated ammonia/methanol (5 mL) was further added and stirring was continued at the same temperature. After 24 hours, concentration under reduced pressure and purification by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 100%) gave the title compound (850 mg).

ESI-MS; m/z 262 $[M^+ + H]$.

[0678]

20 Synthesis of 5-(tert-butyldiphenylsilyloxy)-3-(4-trifluoromethylphenyl)pentanoic acid amide

5-Hydroxy-3-(4-trifluoromethylphenyl)pentanoic acid amide (350 mg) was dissolved in dimethylformamide (13 mL), and imidazole (365 mg) and tert-butyldiphenylsilyl chloride (697 μ L) were added at room temperature. After stirring for one hour, the reaction solution was partitioned with ethyl acetate and water. The organic layer was washed with water (twice), 1 N hydrochloric acid and brine. After drying over magnesium sulfate, concentration under reduced pressure and purification by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 0 to 90%) gave the title compound (680 mg).

ESI-MS; m/z 500 $[M^+ + H]$.

[0679]

Synthesis of 5-(tert-butyldiphenylsilanyloxy)-3-(4-trifluoromethylphenyl)-pentanenitrile

5-(tert-Butyldiphenylsilanyloxy)-3-(4-trifluoromethylphenyl)pentanoic acid

5 amide (640 mg) was dissolved in methylene chloride (13 mL), and 1,8-diazabicyclo[5,4,0]undec-7-ene (862 μ L) and methyl dichlorophosphate (301 μ L) were added at 0°C. After stirring at room temperature for 1.5 hours, the reaction was terminated with a saturated sodium bicarbonate aqueous solution. The organic layer was washed with brine and then dried over magnesium sulfate. Concentration under reduced pressure gave an oil. The oil was allowed to pass through
10 a silica gel pad (mobile phase: ethyl acetate:heptane = 1:2) to obtain the title compound (600 mg).

[0680]

Synthesis of 5-hydroxy-3-(4-trifluoromethylphenyl)pentanenitrile

5-(tert-Butyldiphenylsilanylsilanyloxy)-3-(4-trifluoromethylphenyl)pentanenitrile

15 (600 mg) was dissolved in tetrahydrofuran (6 mL), and tetrabutylammonium fluoride (1.5 mL) was added at room temperature. After two hours, the mixture was partitioned with water and ethyl acetate. The organic layer was washed with brine and then dried over magnesium sulfate. Concentration under reduced pressure gave an oil. The oil was purified by silica gel column chromatography (mobile phase: ethyl acetate/heptane = 70%) to obtain the title compound (306
20 mg).

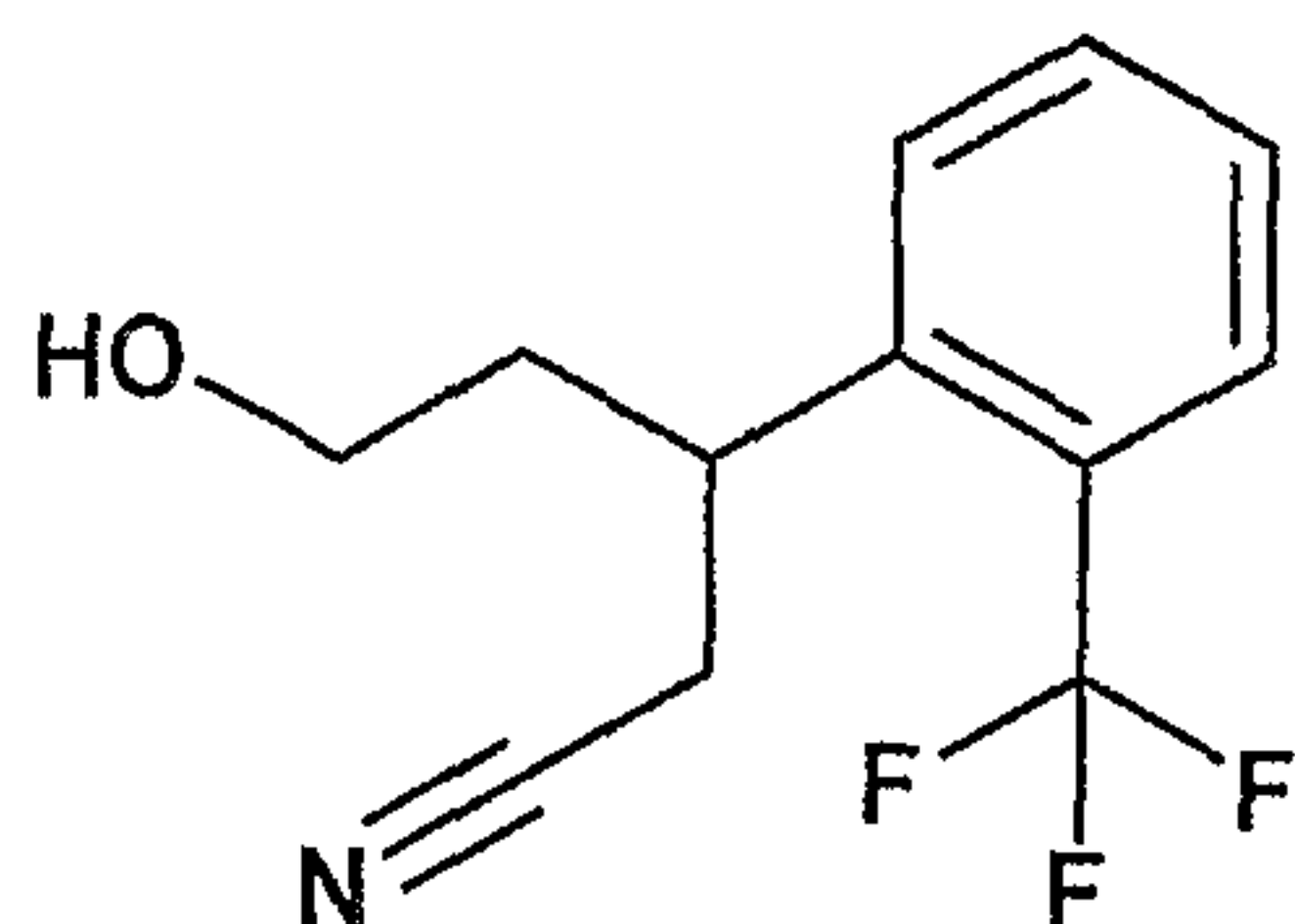
ESI-MS; m/z 244 $[M^+ + H]$.

[0681]

Preparation Example 4-5

Synthesis of 5-hydroxy-3-(2-trifluoromethylphenyl)pentanenitrile

25 [0682]



[0683]

Synthesis of 3-(2-trifluoromethylphenyl)pentanedioic acid

Piperidine (1.0 mL) was added to 2-trifluoromethylbenzaldehyde (5.0 g) and ethyl

acetoacetate (7.27 mL) at 0°C. Then, the mixture was brought to room temperature and stirred for four days. Ethanol (50 mL) was added to the resulting reaction mixture, which was stirred with refluxing for five hours. Concentration under reduced pressure gave an oil. The resulting oil was simply purified by silica gel column chromatography (mobile phase: ethyl

- 5 acetate/heptane = 0 to 40%). Although the oil (7.81 g) contained a large amount of impurities, the oil was dissolved in ethanol (18.5 mL) and water (24.9 mL) to use the oil directly for the next reaction. Potassium hydroxide (32.7 g) was added and the reaction was initiated by heating under reflux. After 1.5 hours, the reaction mixture was partitioned with water and diethyl ether. The resulting aqueous layer was neutralized with concentrated hydrochloric acid (20 mL).
10 Following extraction with methylene chloride twice, drying over magnesium sulfate and concentration under reduced pressure gave a yellow solid. The resulting crude product was recrystallized from ethyl acetate (30 mL) and heptane (65 mL) to obtain the title compound (1.2 g) as a white powder.

ESI-MS; m/z 277 [$M^+ + H$].

15 [0684]

Synthesis of 4-(2-trifluoromethylphenyl)dihydropyrane-2,6-dione

- 3-(2-Trifluoromethylphenyl)pentanedioic acid (1.2 g) was dissolved in acetic anhydride (12 mL), and the mixture was stirred at 110°C for two hours. The oil after concentration under reduced pressure was dissolved in ethyl acetate and washed with a saturated
20 sodium bicarbonate solution and brine. After drying over magnesium sulfate, concentration under reduced pressure gave an orange solid. The solid was recrystallized from ethyl acetate (10 mL) and heptane (70 mL) to obtain the title compound (636 mg) as a white powder.

- $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.19-2.35 (m, 2H), 2.91 (ddd, $J = 18.3, 12.5, 6.2$ Hz, 1H), 3.10 (ddd, $J = 18.3, 4.3, 2.7$ Hz, 1H), 4.2 (dd, $J = 12.0, 5.9$ Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.45 (m, 1H),
25 7.60-7.65 (m, 1H), 7.75 (d, $J = 7.8$ Hz, 1H).

[0685]

Synthesis of 4-carbamoyl-3-(2-trifluoromethylphenyl)butanoic acid

- Saturated ammonia/methanol (10 mL) was added to 4-(2-trifluoromethylphenyl)dihydropyrane-2,6-dione (636 mg), and the mixture was stirred at room
30 temperature for 15 hours. Concentration under reduced pressure gave a crude product (716 mg) which was used for the next reaction without purification.

[0686]

Synthesis of 5-hydroxy-3-(2-trifluoromethylphenyl)pentanoic acid amide

4-Carbamoyl-3-(2-trifluoromethylphenyl)butanoic acid (646 mg) was dissolved in

methylene chloride (32 mL), and a diborane-tetrahydrofuran solution (7.12 mL) was added at 0°C. After stirring at room temperature for two hours, the reaction solution was cooled to 0°C. The reaction was terminated with 1 N hydrochloric acid, followed by dilution with ethyl acetate. The organic layer was washed with 1 N sodium hydroxide and brine and dried over magnesium sulfate. Concentration under reduced pressure gave a crude product (388 mg) which was used for the next reaction without purification.

[0687]

Synthesis of 5-hydroxy-3-(2-trifluoromethylphenyl)pentanenitrile

The title compound was obtained according to the method of Preparation

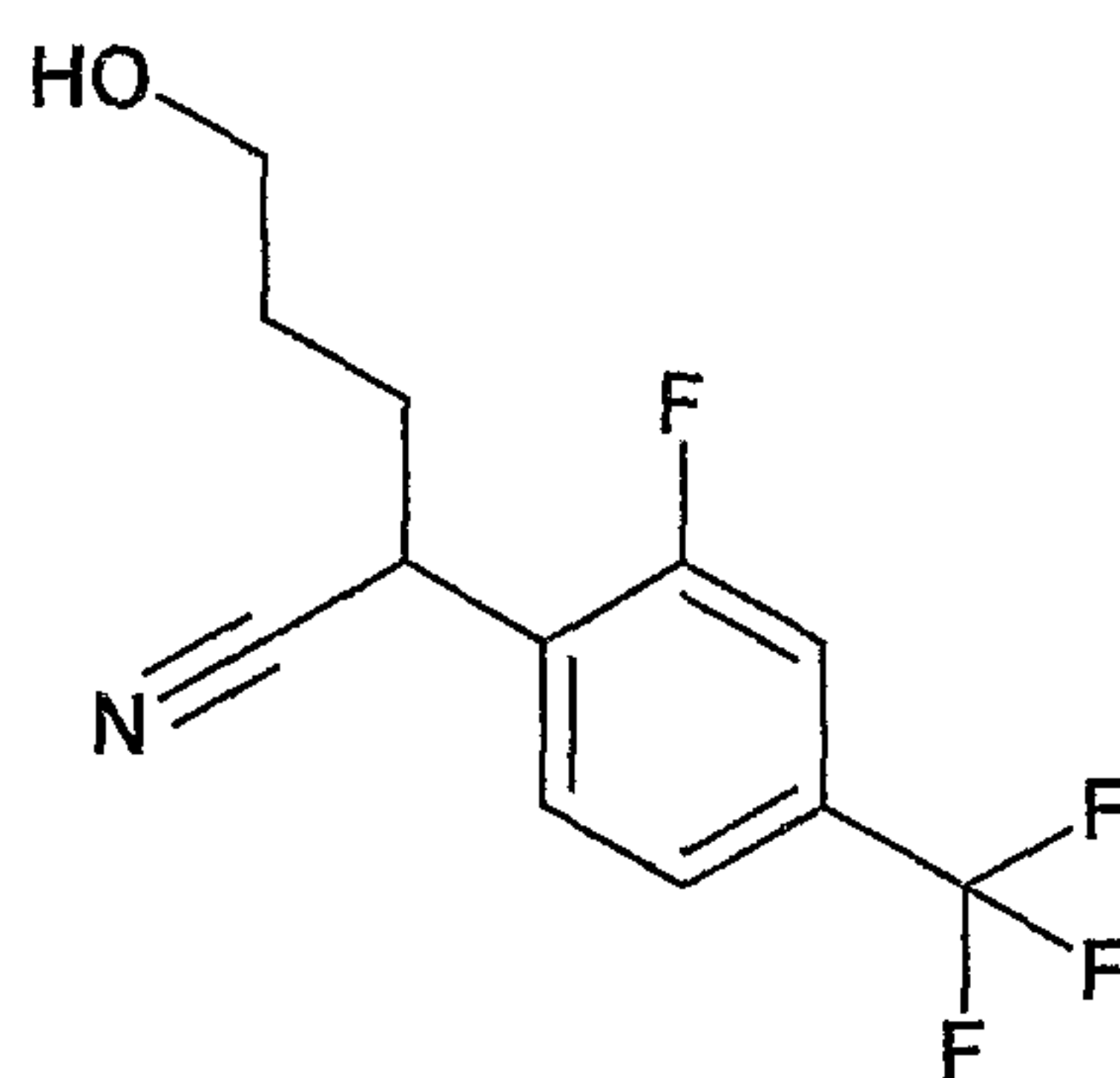
10 Example 4-4 from 5-hydroxy-3-(2-trifluoromethylphenyl)pentanoic acid amide.

[0688]

Preparation Example 4-6

Synthesis of 2-(2-fluoro-4-trifluoromethylphenyl)-5-hydroxypentanenitrile

[0689]



15 [0690]

The title compound (1.3 g) was obtained according to the method of Example 4-1 from 2-fluoro-4-(trifluoromethyl)phenylacetonitrile (2 g).

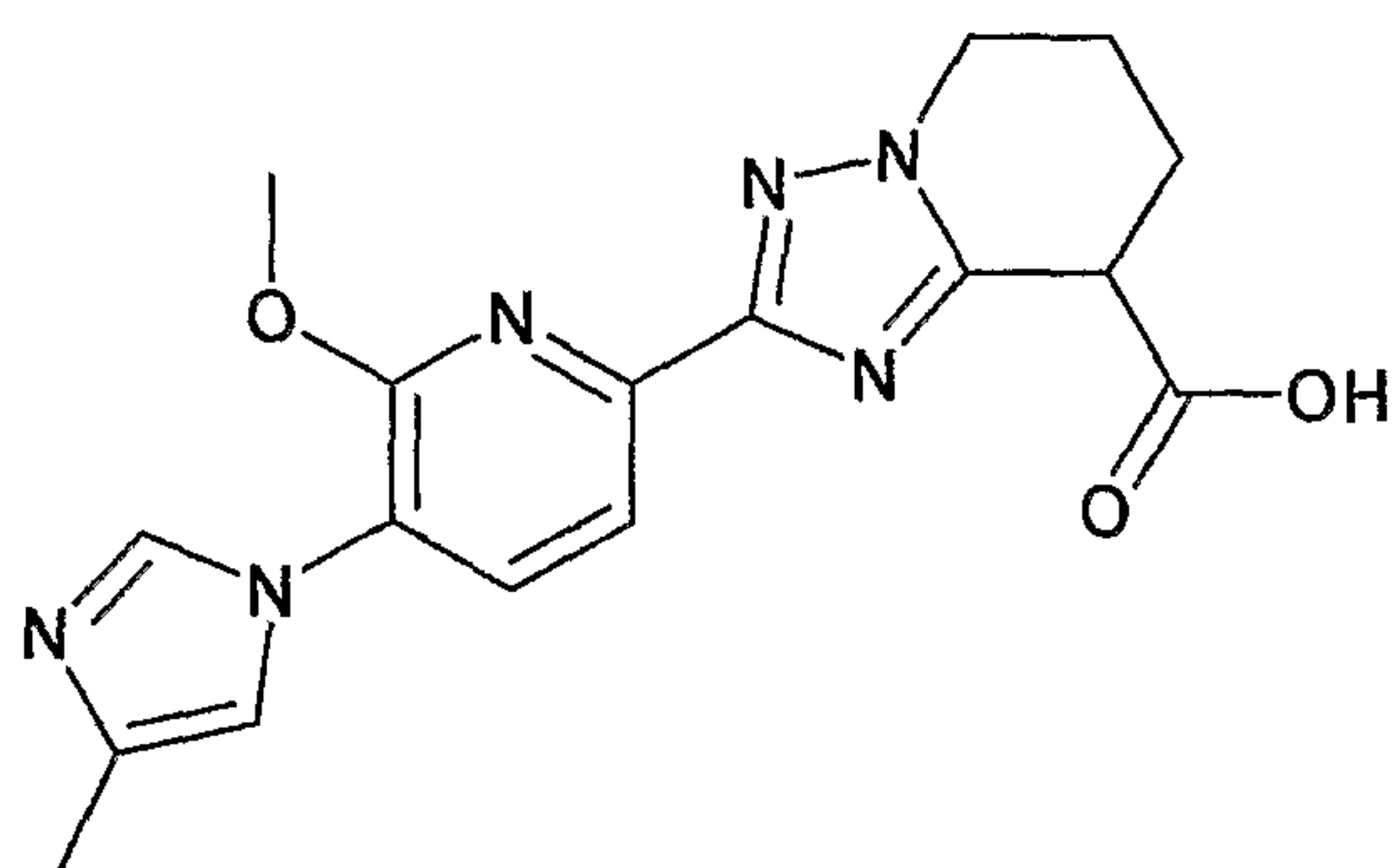
¹H-NMR (CDCl₃) δ (ppm): 1.70-1.84 (m, 2H), 1.98-2.14 (m, 2H), 3.66-3.78 (m, 2H), 4.25 (t, J = 6.8 Hz, 1H), 7.35 (d, J = 9.8 Hz, 1H), 7.49 (d, J = 9.8 Hz, 1H), 7.61-7.66 (m, 1H).

20 [0691]

Preparation Example 5-1

Synthesis of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid

[0692]



[0693]

Synthesis of ethyl 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate

The title compound (695 mg) was obtained according to the method of Examples 42 and 43 from the imidate hydrochloride obtained in Preparation Example 3-11 in place of ethyl 2-(4-bromo-2-trifluoromethylphenyl)-5-chloropentanimidate hydrochloride. The property values of the compound are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.30 (t, J = 7.2 Hz, 3H), 2.10-2.40 (m, 4H), 2.30 (s, 3H), 4.11 (t, J = 6.0 Hz, 1H), 4.16 (s, 3H), 4.20-4.39 (m, 4H), 7.01 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H).

[0694]

Synthesis of 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid

Ethyl 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate (331 mg) was dissolved in a mixed solvent of THF (5 mL) and methanol (5 mL). A 5 N sodium hydroxide aqueous solution (693 μL) was added and the mixture was stirred at room temperature for two days. The reaction solution was neutralized with 5 N hydrochloric acid (693 μL), and then concentrated under reduced pressure to remove the organic solvent. Methanol (2 mL) was added to the residue, and the precipitated salt was separated by filtration. Thereafter, the filtrate was concentrated under reduced pressure to obtain the title compound.

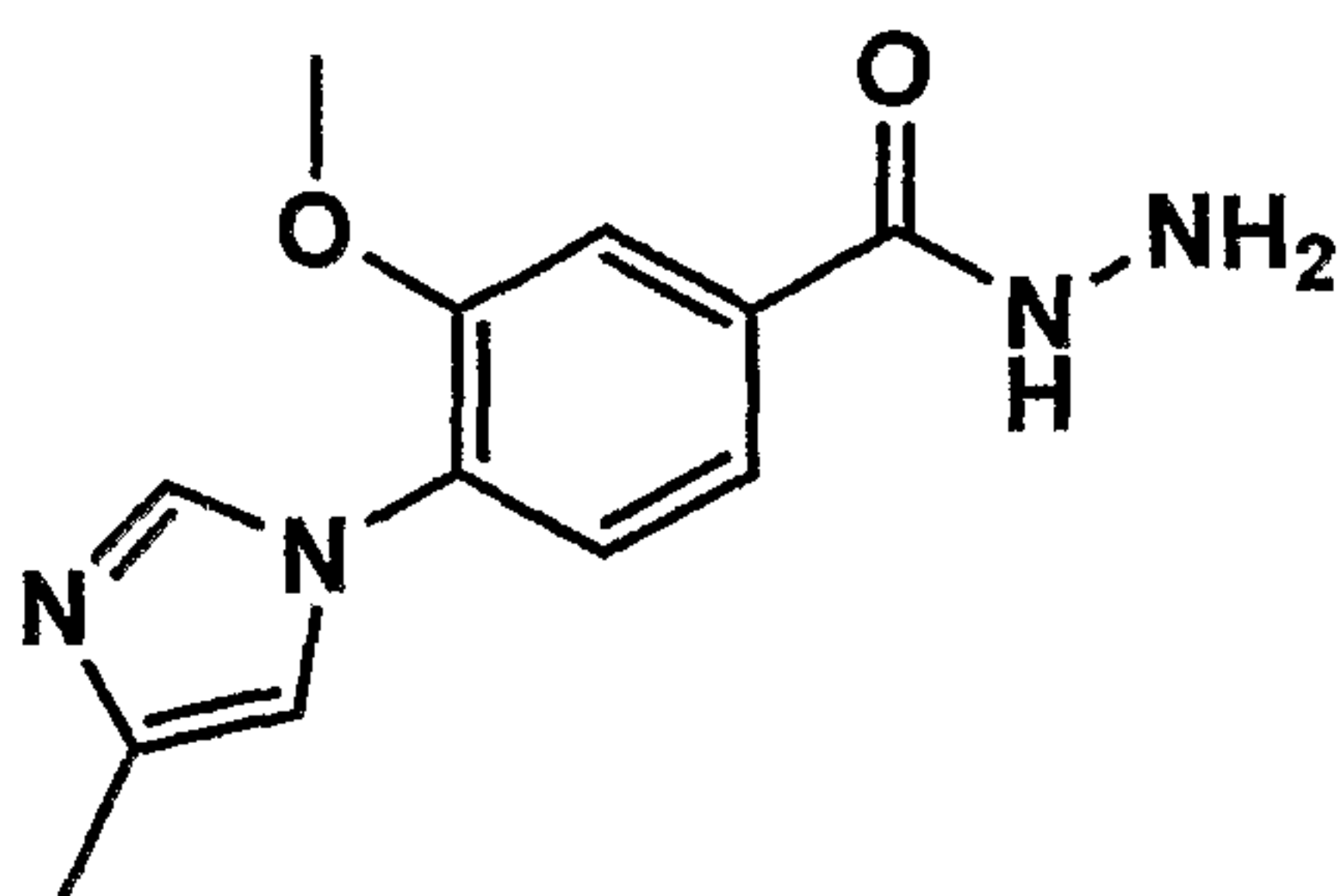
ESI-MS; m/z 355 [M⁺ + H].

[0695]

Preparation Example 1-9

Synthesis of 3-methoxy-4-(4-methylimidazol-1-yl)benzoic acid hydrazide

[0696]



[0697]

Synthesis of benzyl N'-[3-methoxy-4-(4-methylimidazol-1-yl)benzoyl] hydrazinecarboxylate

IPEA (1.05 mL) and 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (1.16 g) were sequentially added to a solution of 3-methoxy-4-(4-methylimidazol-1-yl)benzoic acid (CAS#937026-26-1, 933mg), benzyl carbazate (737 mg) and HOBt (817mg) in DMF (15 mL), and the mixture was stirred at room temperature overnight. Ethyl acetate, ice water and a saturated sodium bicarbonate solution were added to the reaction solution, and the organic layer was separated. The resulting organic layer was sequentially washed with water and brine. The combined aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. Ethyl acetate and NH silica gel were added to the resulting residue and then the mixture was concentrated under reduced pressure.

The resulting residue was purified by silica gel column chromatography (carrier: ChromatorexTM NH; elution solvent: ethyl acetate:heptane = 1:1 -> 10:1 -> 10% methanol in ethyl acetate). The target fraction was concentrated. The resulting powder was triturated with ethyl acetate and tert-butyl methyl ether to obtain 1.30 g of the title compound. The property values of the compound are as follows.

¹H-NMR (DMSO-D₆) δ (ppm): 2.16 (s, 3H), 3.90 (s, 3H), 5.14 (s, 2H), 7.22 (s, 1H), 7.25-7.45 (m, 5H), 7.52 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.88 (s, 1H), 9.43 (brs, 1H), 10.46 (brs, 1H).

[0698]

Synthesis of 3-methoxy-4-(4-methylimidazol-1-yl)benzoic acid hydrazide

To a solution of benzyl N'-[3-methoxy-4-(4-methylimidazol-1-yl)benzoyl] hydrazinecarboxylate (1.25 g) in methanol (60 mL) was added 20% palladium hydroxide-carbon (50% wet, 250mg) and the mixture was hydrogenated at an intermediate pressure (3.8 atm) for two hours and 30 minutes. The palladium-carbon was removed by filtration through celite. The filtrate was concentrated under reduced pressure to obtain 826 mg of the title compound. The

property values of the compound are as follows.

ESI-MS; m/z 247 [$M^+ + H$].

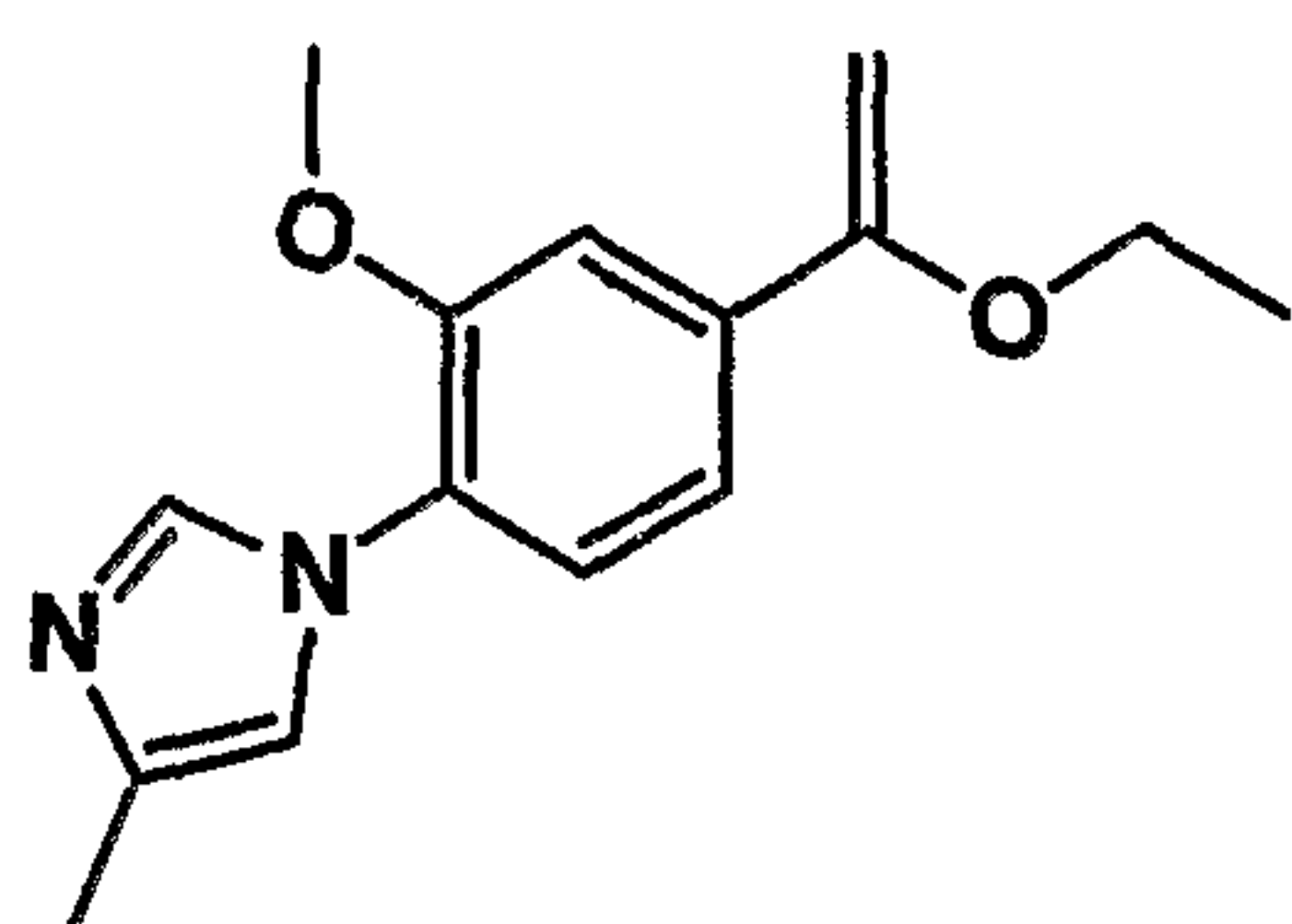
^1H -NMR (DMSO- D_6) δ (ppm): 2.16 (d, $J = 1.2$ Hz, 3H), 3.89 (s, 3H), 4.55 (brs, 2H), 7.20 (s, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.52 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.64 (d, $J = 1.6$ Hz, 1H), 7.84 (d, $J = 1.2$ Hz, 1H), 9.90 (brs, 1H).

[0699]

Preparation Example 1-10

Synthesis of 1-[4-(1-ethoxyvinyl)-2-methoxyphenyl]-4-methyl-1H-imidazol

[0700]



10 [0701]

According to the method of Preparation Example 1-7, 575 mg of the title compound was obtained from 1-(4-bromo-2-methoxyphenyl)-4-methyl-1H-imidazol (CAS #87038-56-5, 1.5g). The property values of the compound are as follows.

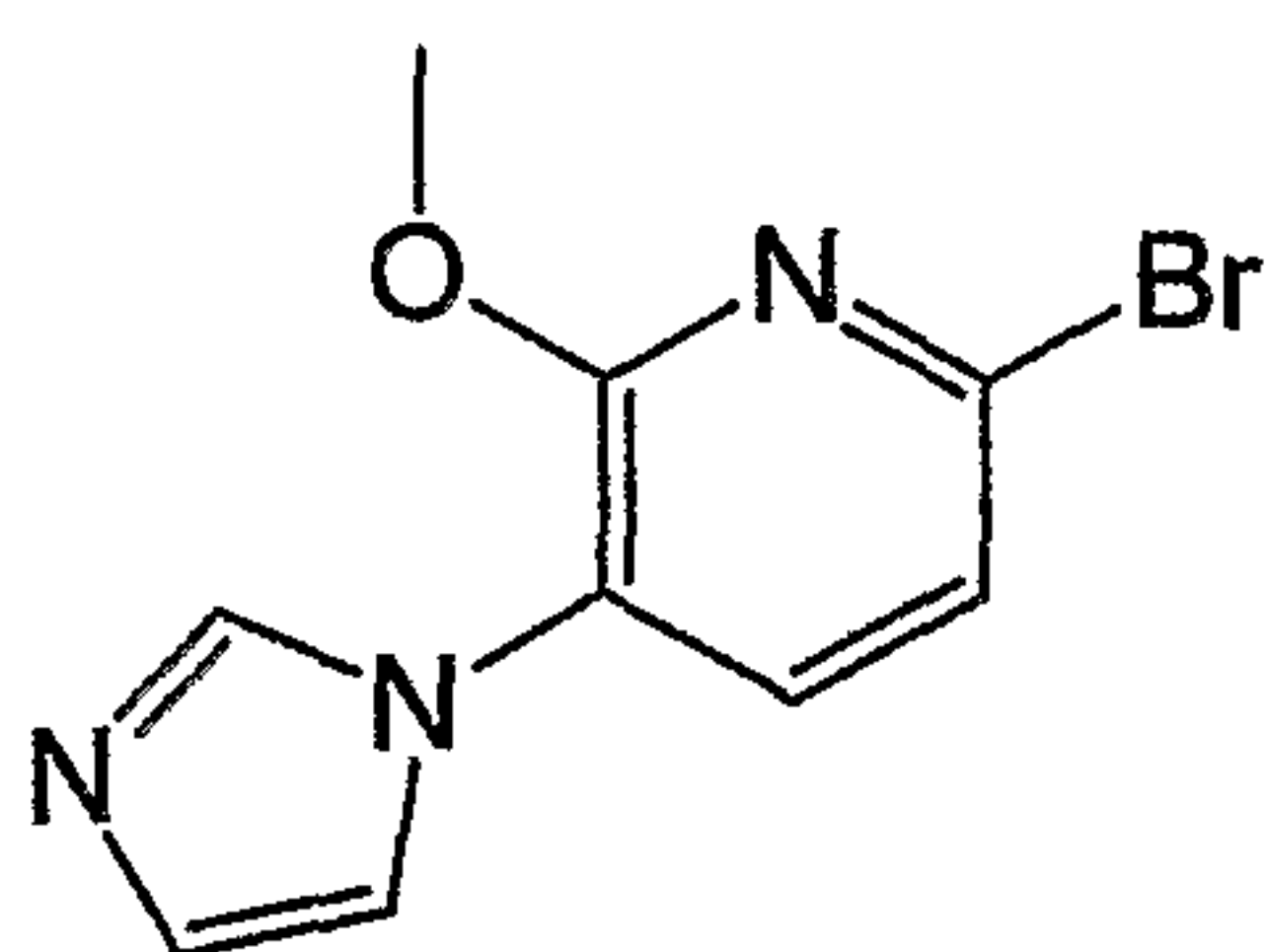
^1H -NMR ($CDCl_3$) δ (ppm): 1.45 (t, $J = 7.2$ Hz, 3H), 2.49 (s, 3H), 3.95 (q, $J = 7.2$ Hz, 2H), 3.96 (s, 3H), 4.27 (d, $J = 2.8$ Hz, 1H), 4.70 (d, $J = 2.8$ Hz, 1H), 7.33 (d, $J = 1.6$ Hz, 1H), 7.34 (dd, $J = 8.8, 1.6$ Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 1H), 8.65 (s, 1H).

[0702]

Preparation Example 1-11

Synthesis of 6-bromo-3-imidazol-1-yl-2-methoxypyridine

20 [0703]



According to the method of Preparation Example 1-1, 257mg of the title compound was obtained from N-(6-bromo-2-methoxypyridine-3-yl)formamide

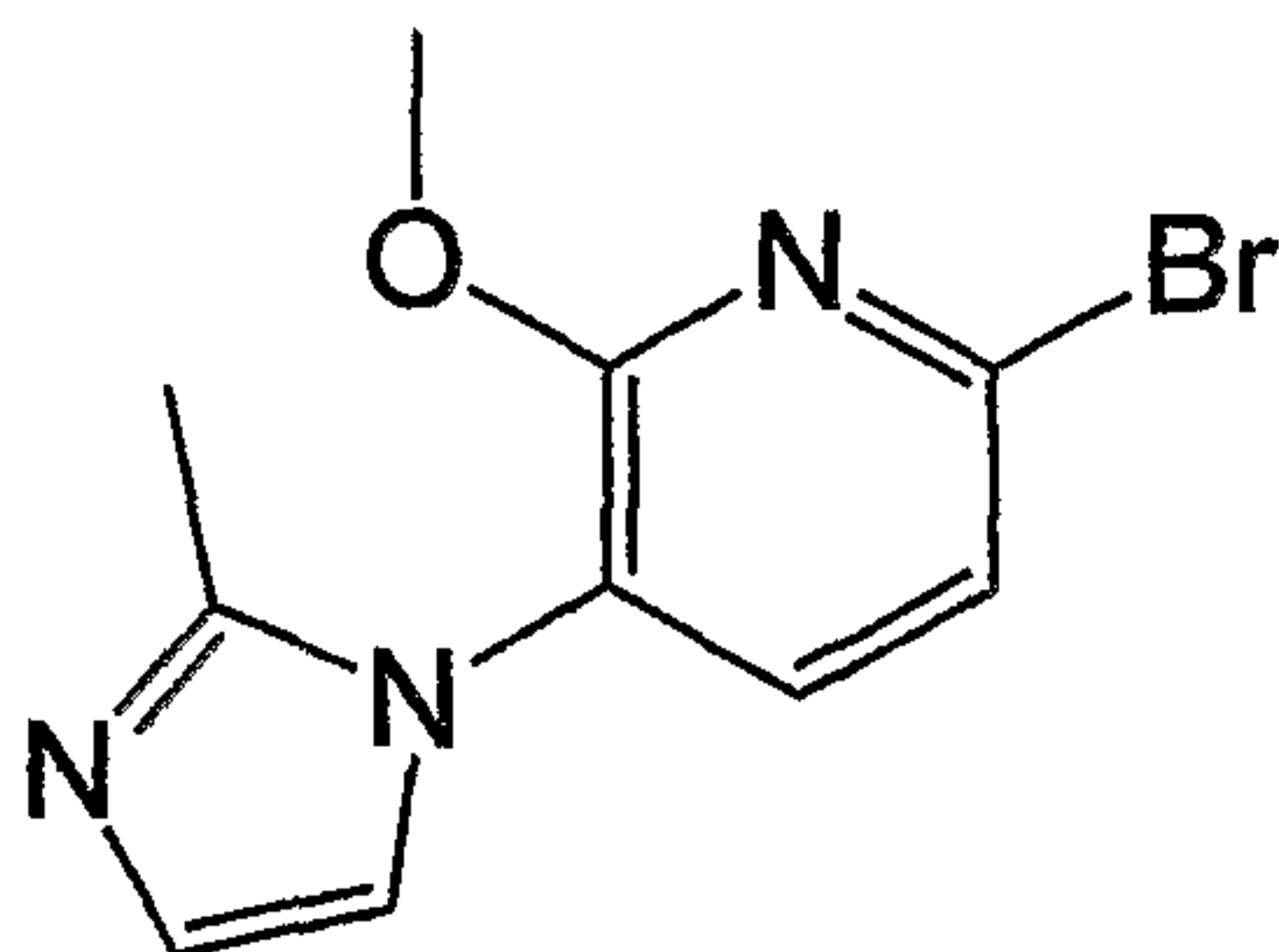
ESI-MS; m/z 254 $[M^+ + H]$.

[0704]

Preparation Example 1-12

Synthesis of 6-bromo-2-methoxy-3-(2-methyl-1H-imidazol-1-yl)pyridine

5 [0705]



[0706]

Synthesis of 6-bromo-2-methoxypyridyl-3-boronic acid

To an ice-cold solution of diisopropylamine (777 μ L) in THF (20 mL) was added n-butyllithium (2.6M hexane solution) and the mixture was stirred at same temperature for 10 minutes. The solution was cooled to -78°C then 2-Bromo-6-methoxypyridine (CAS#40473-07-2, 799 mg) and triisopropyl borate (1.27 mL) were added dropwise. The reaction temperature was raised to room temperature and stirred for an hour. To the reaction mixture was added an ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residual crystal was collected by filtration and washed with diethyl ether to obtain the title compound (545 mg).

[0707]

Synthesis of 6-bromo-2-methoxy-3-(2-methyl-1H-imidazol-1-yl)pyridine

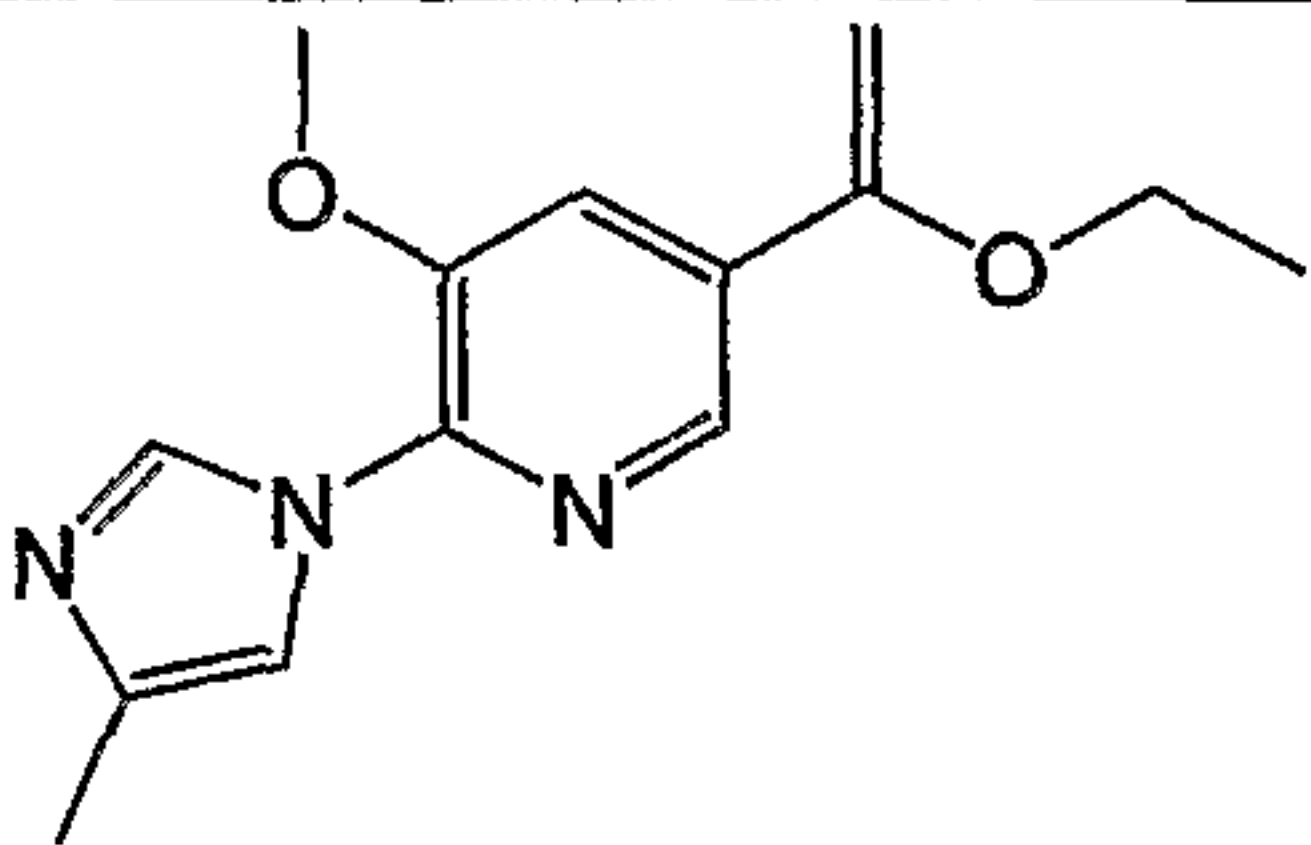
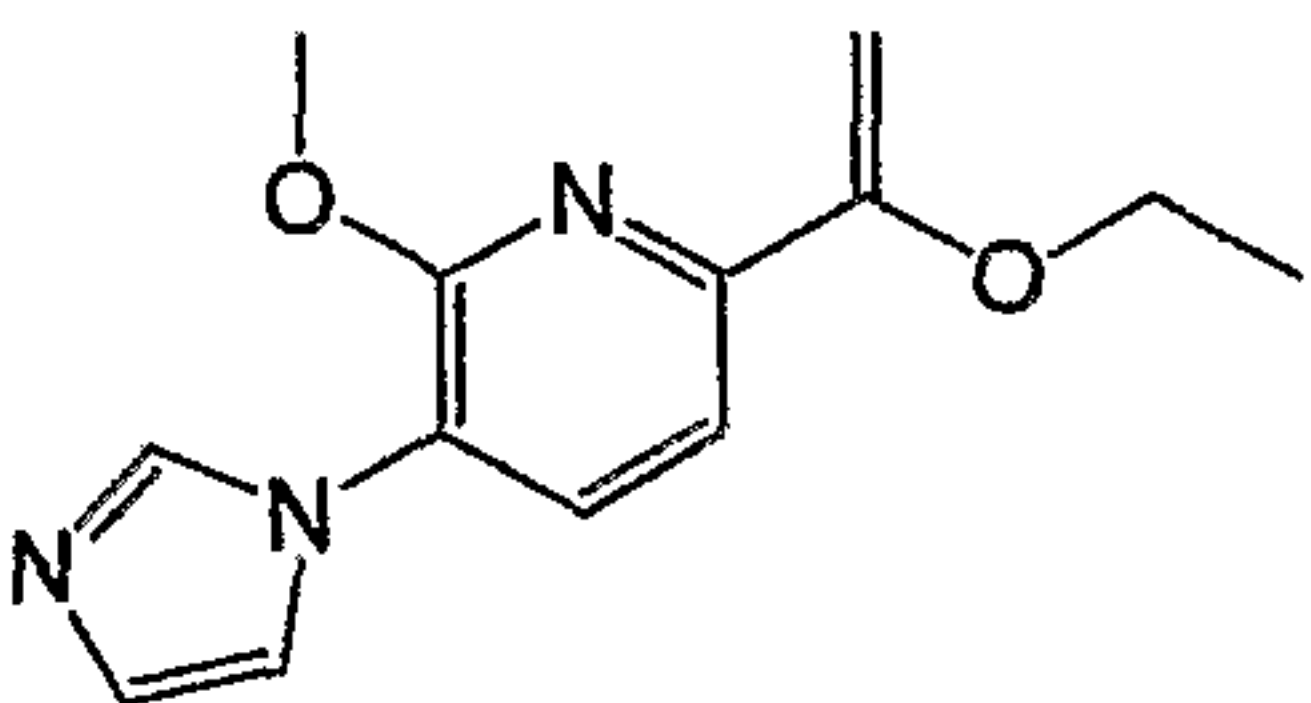
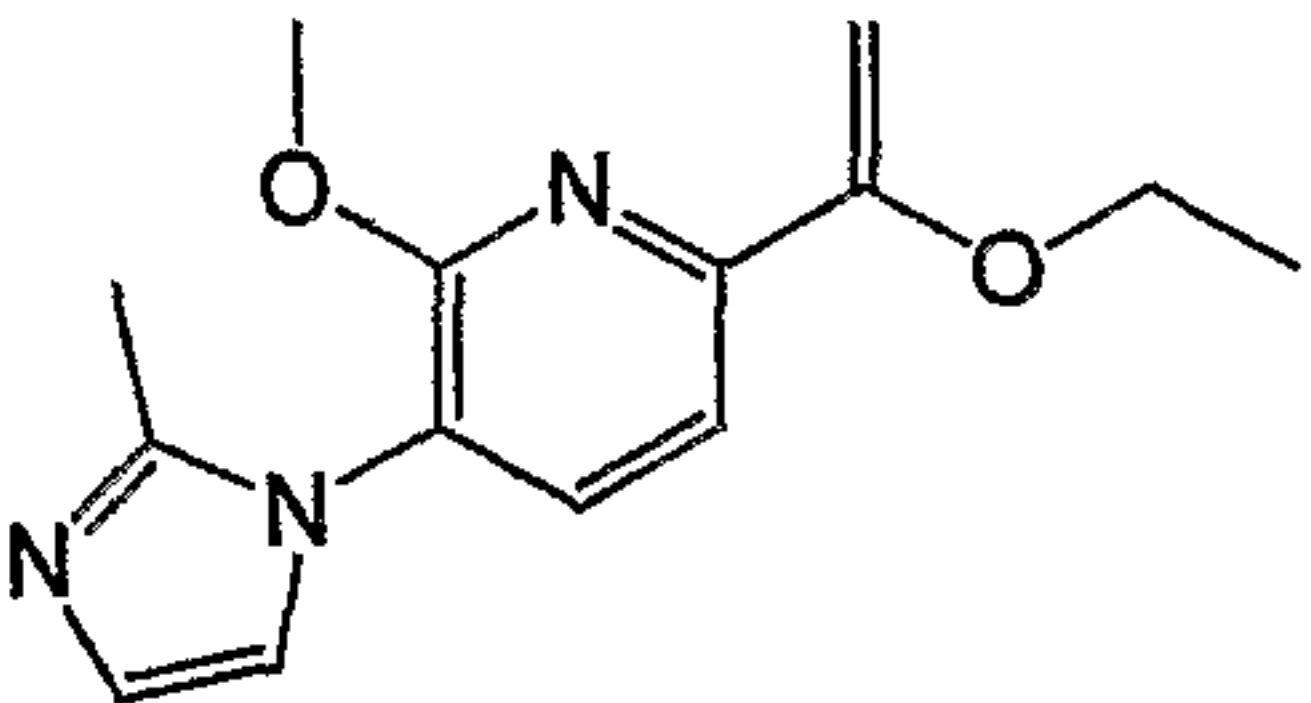
20 To a solution of 6-bromo-2-methoxypyridyl-3-boronic acid (1 g) and 2-methyl-1H-imidazol (354 mg) in dichloromethane (20 mL) was added di- μ -hydroxo-bis[(N,N,N',N'-tetramethylethylenediamine)copper (II)] chloride (300 mg). The reaction mixture was stirred in an oxygen atmosphere at room temperature for 3 days. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (311 mg).

[0708]

The compounds of Preparation Example 1-13 to Preparation Example 1-15 were

obtained according to the methods of Preparation Example 1-7. (Table11)

Table11

Preparation Example No.	Structural formula
1-13	
1-14	
1-15	

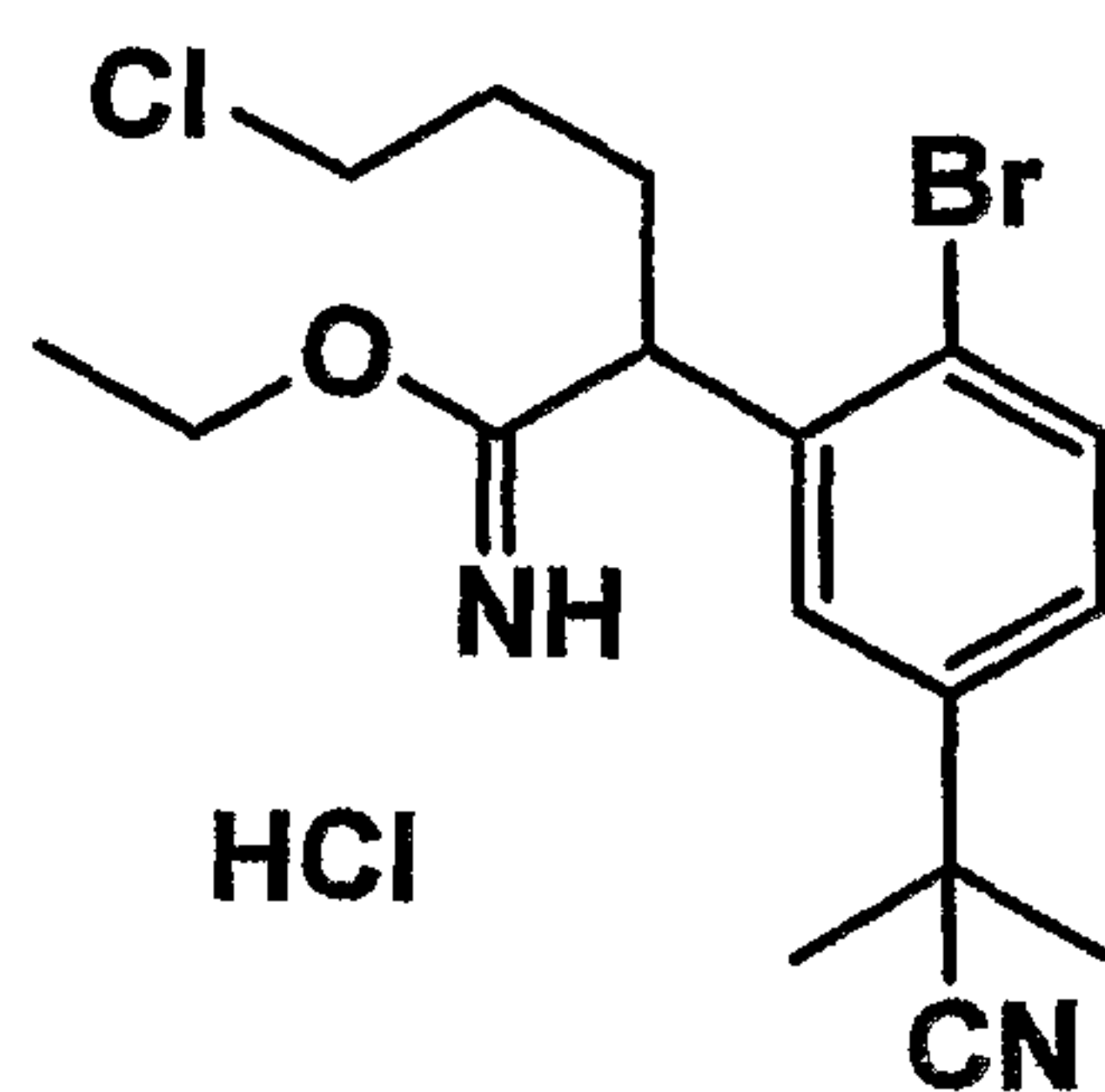
5

[0709]

Preparation Example 3-21

Synthesis of 2-[2-bromo-5-(cyano-dimethyl-methyl)phenyl]-5-chloropentanimidic acid ethyl ester hydrochloride

10 [0710]



[0711]

Synthesis of 2-(4-bromo-3-methylphenyl)-2-methylpropionitrile

To an ice-cold suspension of sodium hydride (60% in oil, 524 mg) in THF (5 ml) and N-methylpyrrolidone (5 ml) was added the solution of (4-bromo-3-methylphenyl)acetonitrile

(CAS #215800-25-2, 1.1g) and iodomethane (1 ml) in THF (3 ml) and N-methylpyrrolidone (3 ml). After stirring for 40 minutes at room temperature, water and tert-butyl methyl ether was added. The organic layer was separated and the aqueous layer was extracted with tert-butyl methyl ether. The combined organic layer was washed with water (twice) and brine. After
5 drying over anhydrous magnesium sulfate, the drying agent was separated by filtration and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (carrier: Wakogel™ C-200; elution solvent: heptane:ethyl acetate = 19:1) to obtain the title compound (1.06 g). The property values of the compound are as follows.
10 ¹H-NMR (CDCl₃) δ (ppm): 1.71 (s, 6H), 2.43 (s, 3H), 7.14 (dd, J = 8.4, 2.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H).

[0712]

Synthesis of 2-(4-bromo-3-cyanomethyl-phenyl)-2-methylpropionitrile

N-bromosuccinimide (1.04 g) and 2,2'-azobis (isobutylnitrile) (30 mg) were added to the carbon tetrachloride solution (7 ml) of 2-(4-bromo-3-methylphenyl)-2-methylpropionitrile (1.26 g) and then the solution was refluxed with heating for an hour. The
15 solution was cooled on ice, then after removing the insoluble substances by filtration, the filtrate was concentrated under reduced pressure. The obtained residue was dissolved in ethanol (10 ml) and water (1 ml) and a solution of potassium cyanide (0.41 g) was added to the solution. The reaction mixture was stirring overnight at room temperature. To the reaction mixture was added
20 the ice-cold water and ethyl acetate, and the organic layer was separated. The obtained organic layer was sequentially washed with water (twice) and brine. After drying over anhydrous magnesium sulfate, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (carrier; Wakogel™ C-200; elution solvent; heptane:ethyl acetate, 19:1 → 5:1) to obtain the title compound. (917 mg) The property values of
25 the obtained compound are as follows; ¹H-NMR (CDCl₃) δ (ppm): 1.74 (s, 6H), 3.87 (s, 2H), 7.38 (dd, J = 8.4, 2.4 Hz, 1H), 7.57 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H).

[0713]

Synthesis of 2-[2-bromo-5-(cyano-dimethyl-methyl)phenyl]-5-chloropentanitrile

30 Under ice-cold condition, to the mixture solution of 2-(4-bromo-3-cyanomethyl-phenyl)-2-methylpropionitrile in THF (5 ml) and DMF (5 ml) was added sodium hydride (60% in oil, 144 mg), and the reaction mixture was stirred for 10 minutes under the same temperature. To the reaction mixture was added 1-bromo-3-chloropropane (0.44 ml) and the mixture was stirred for 25 minutes under the same temperature. The ice-cold water and tert-butyl methyl ether

was added to the reaction mixture and then the organic layer was separated. The water layer was re-extracted by the tert-butyl methyl ether. The combined organic layer was washed with brine and dried over anhydrous magnesium sulfate.

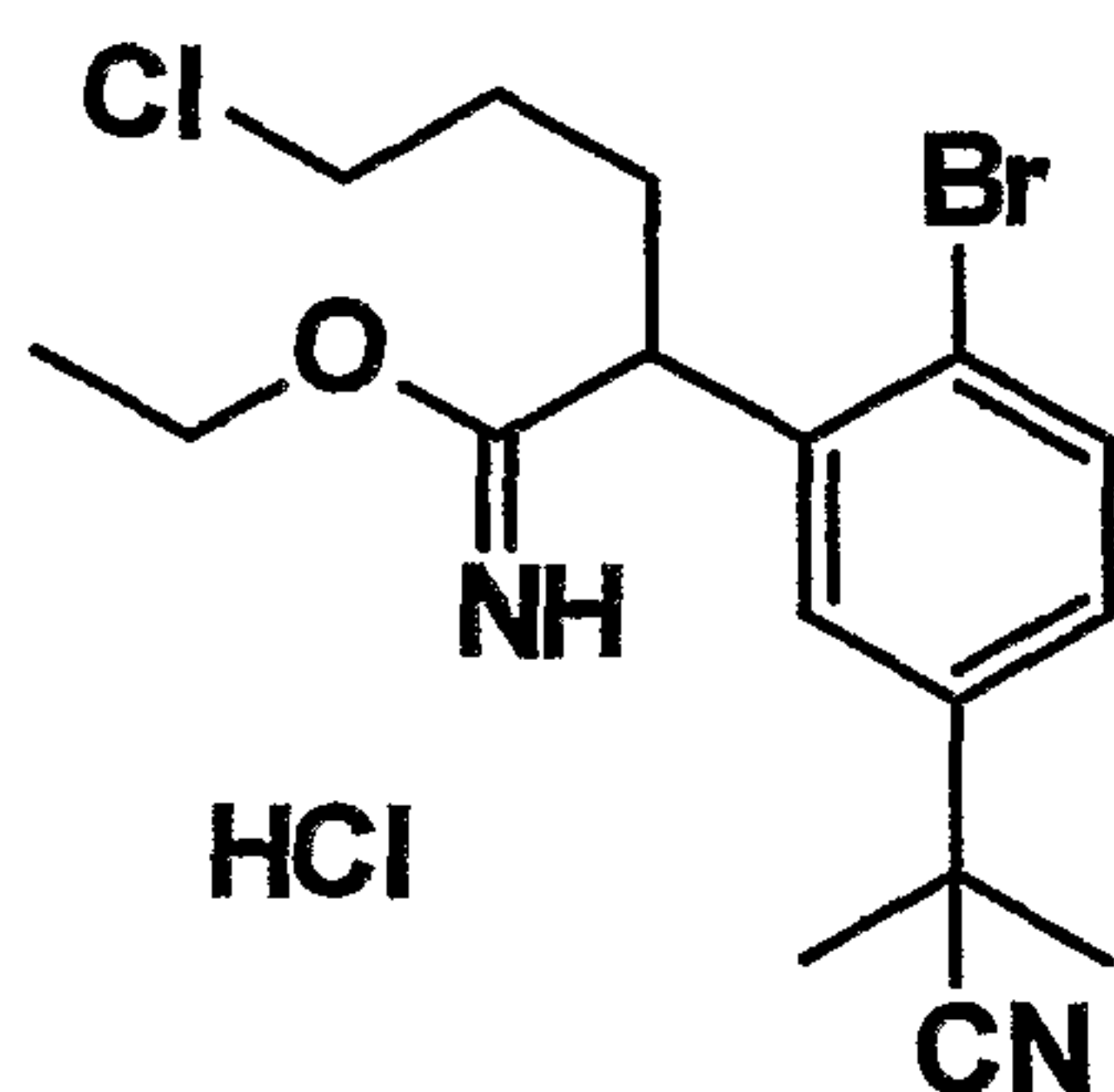
After concentration, the obtained residue was purified by silica gel column chromatography

5 (carrier: Wakogel™ C-200, elution solvent: heptane:ethyl acetate, 19:1 → 5:1) to obtain the title compound (941 mg). The property values of the obtained compound are as follows; ¹H-NMR (CDCl₃) δ (ppm): 1.75 (s, 6H), 1.87-2.18 (m, 4H), 3.61 (t, J=6.0 Hz, 2H), 4.31-4.36 (M, 1H), 7.38 (dd, J = 8.4, 2.4 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H).

[0714]

10 Synthesis of ethyl 2-[2-bromo-5-(cyano-dimethyl-methyl) phenyl]-5-chloropentanimidate
hydrochloride

[0715]



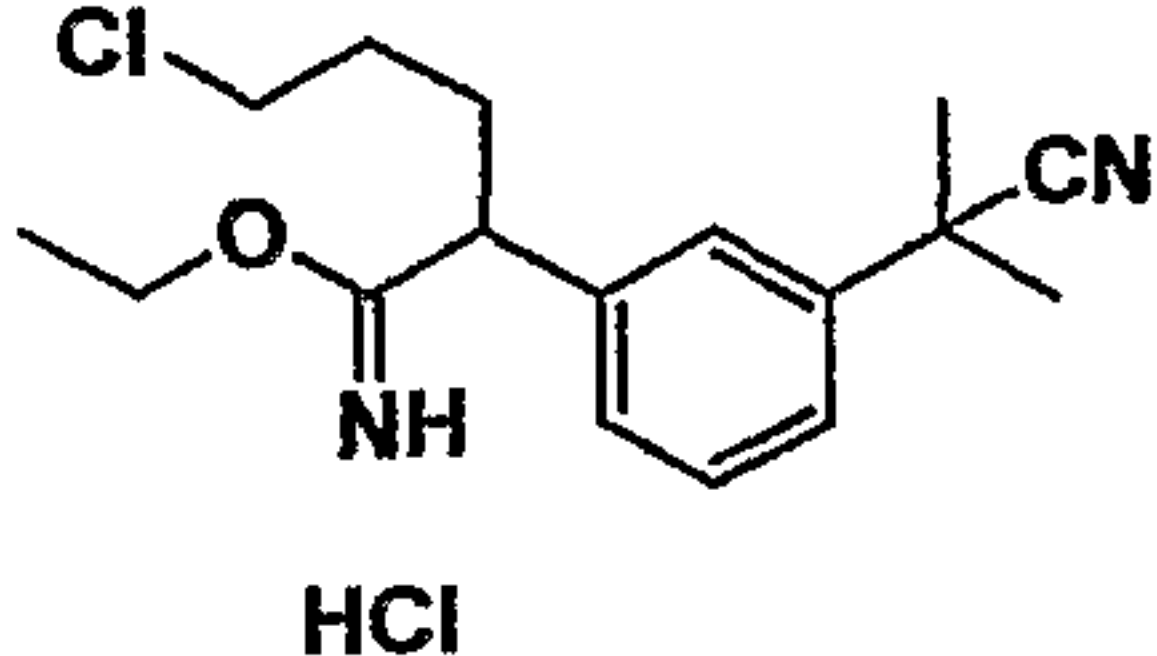
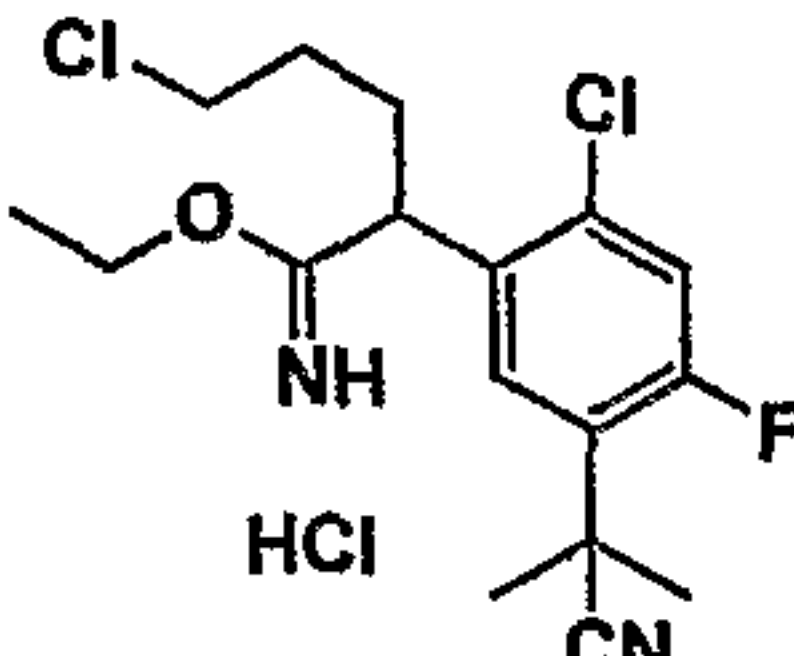
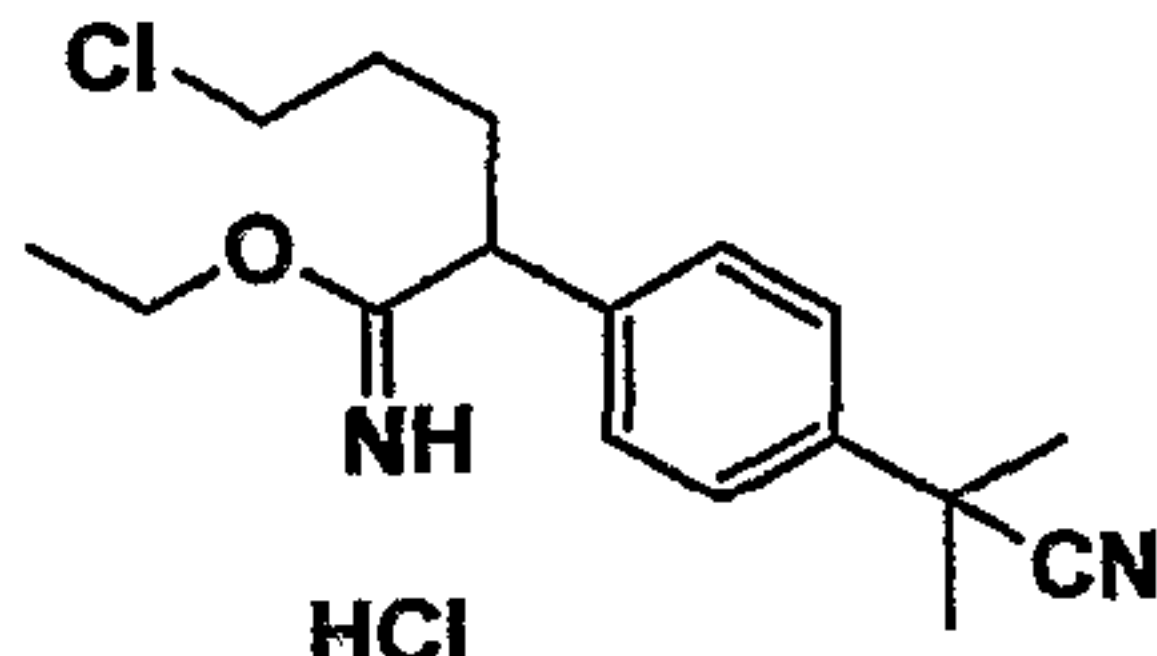
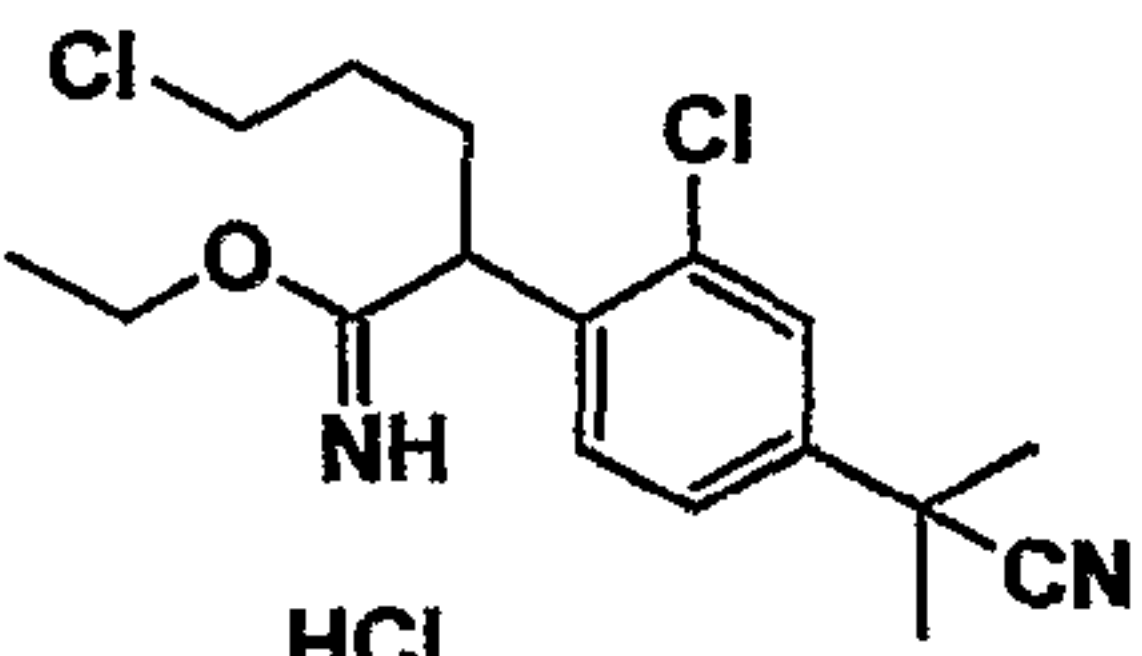
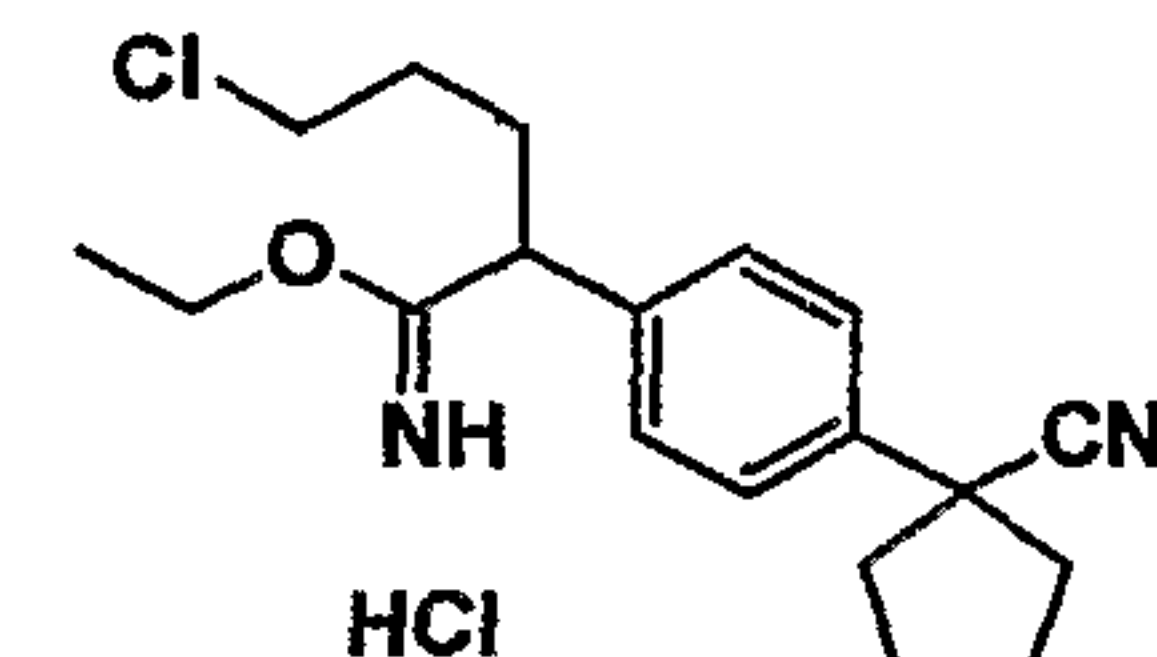
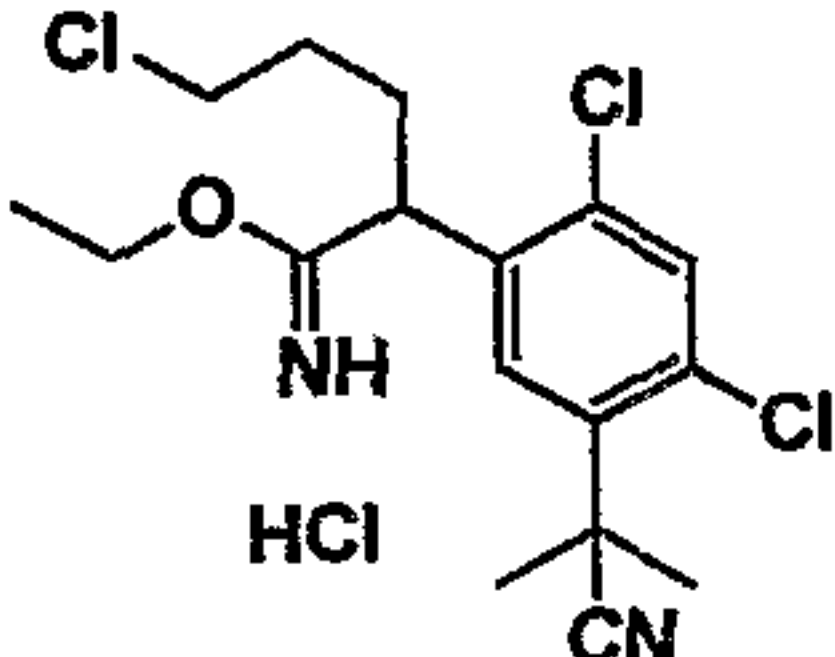
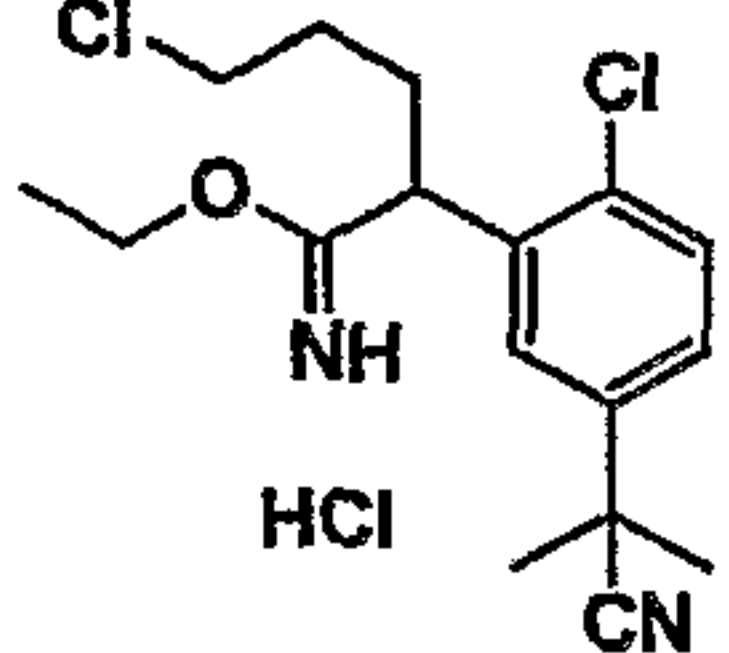
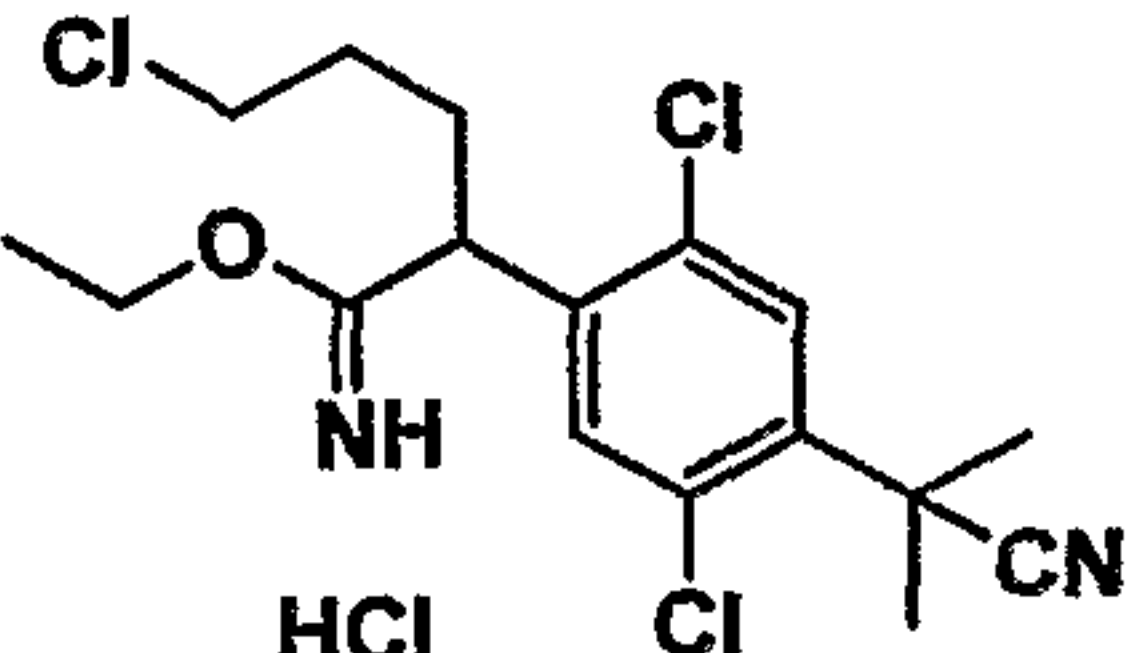
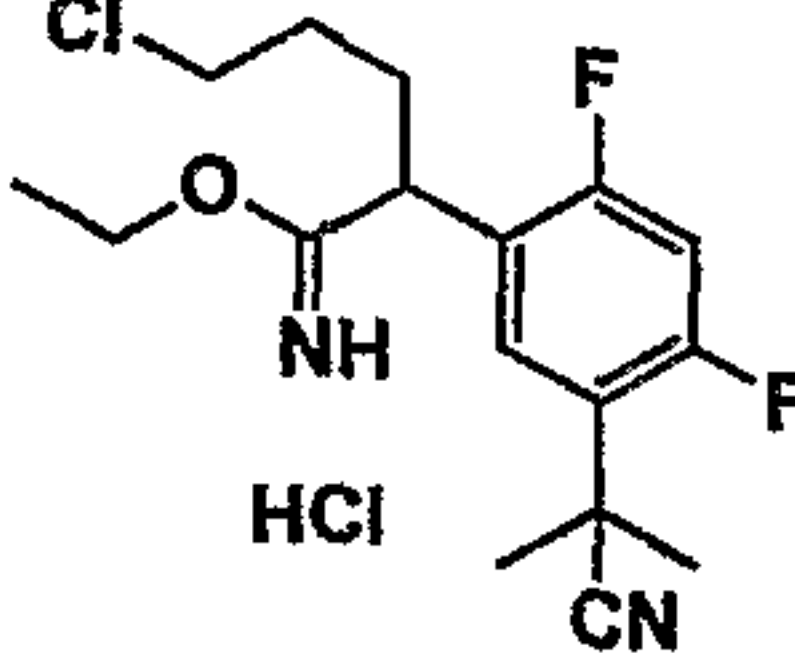
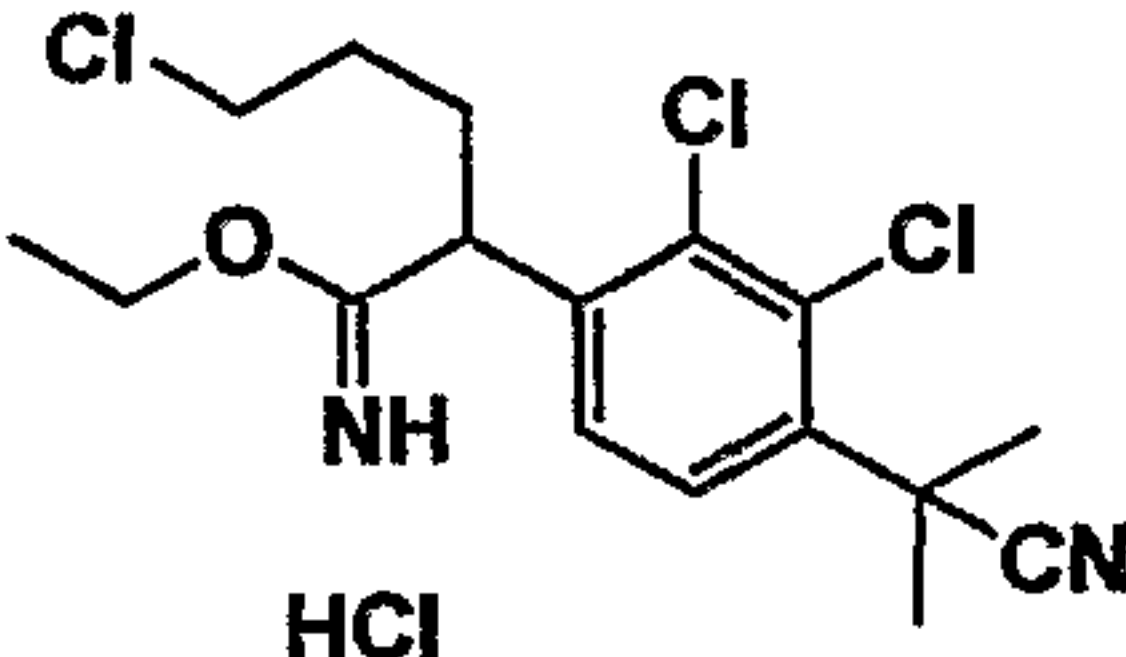
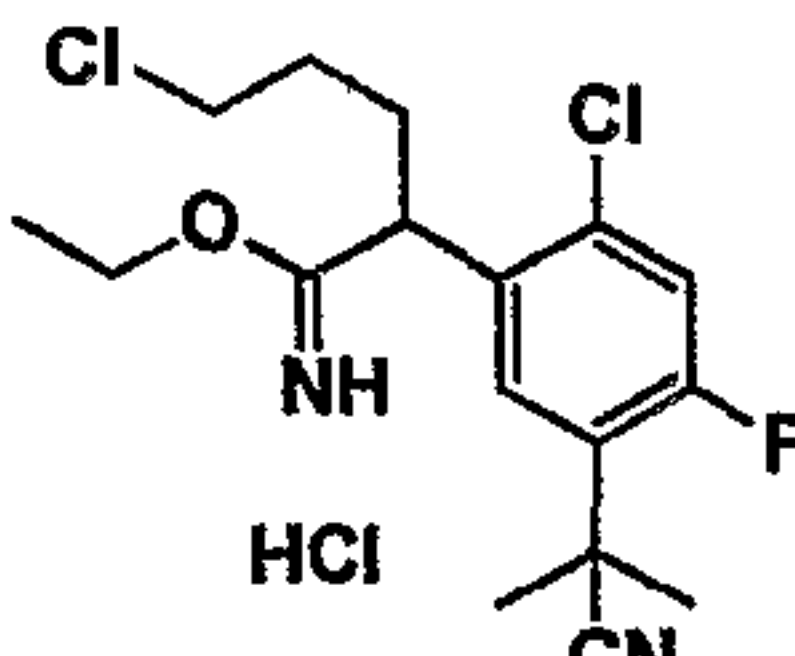
[0716]

Under the ice-cold condition, a solution of 2-[2-bromo-5-(cyano-dimethyl-phenyl)]-5-chloropentanenitrile (100 mg) in ethanol (4 ml) was bubbled with hydrogen chloride gas for 10 minutes. After the reaction solution was stirred at room temperature for 2 hours, the solution was concentrated under reduced pressure. Tert-butyl methyl ether was added to the residue and the solution was concentrated under reduced pressure to obtain the title compound (124 mg). The property value of the obtained compound is as follows; ESI-MS; m/z 387 $[M^+ + H - HCl]$.

[0717]

The compounds of Preparation Example 3-22 to Preparation Example 3-32 were obtained according to the methods described in Preparation Example 3-21.

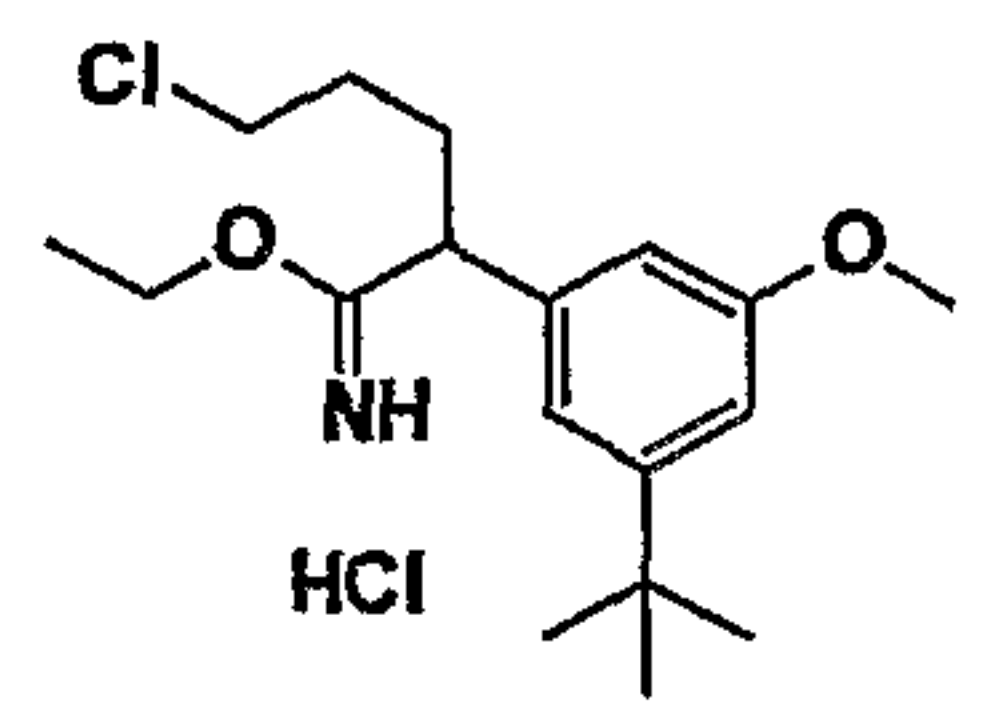
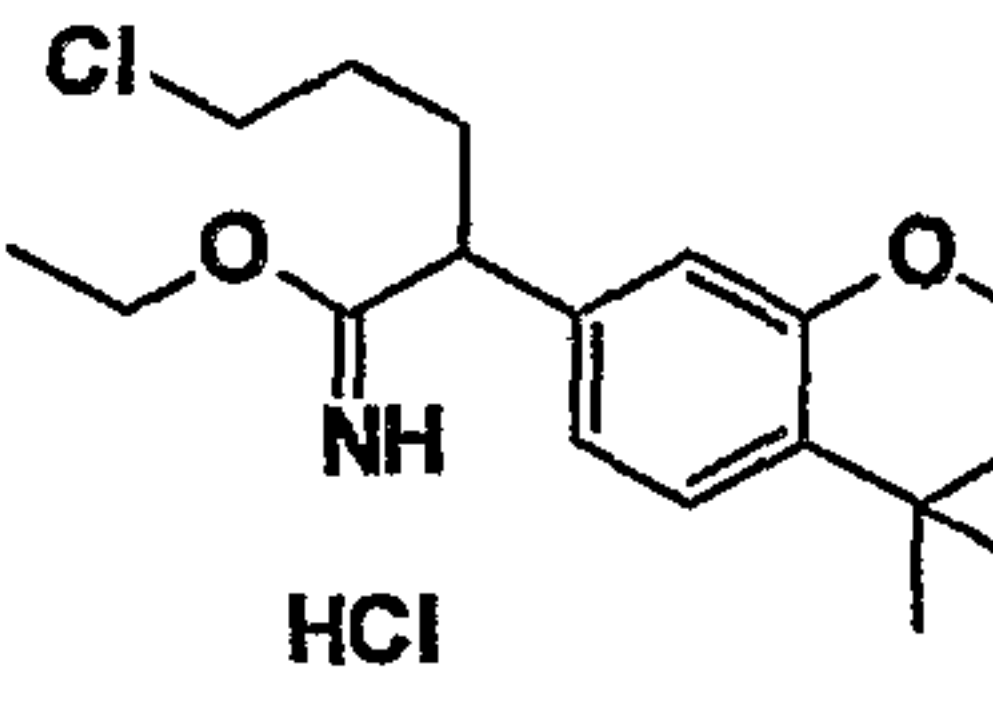
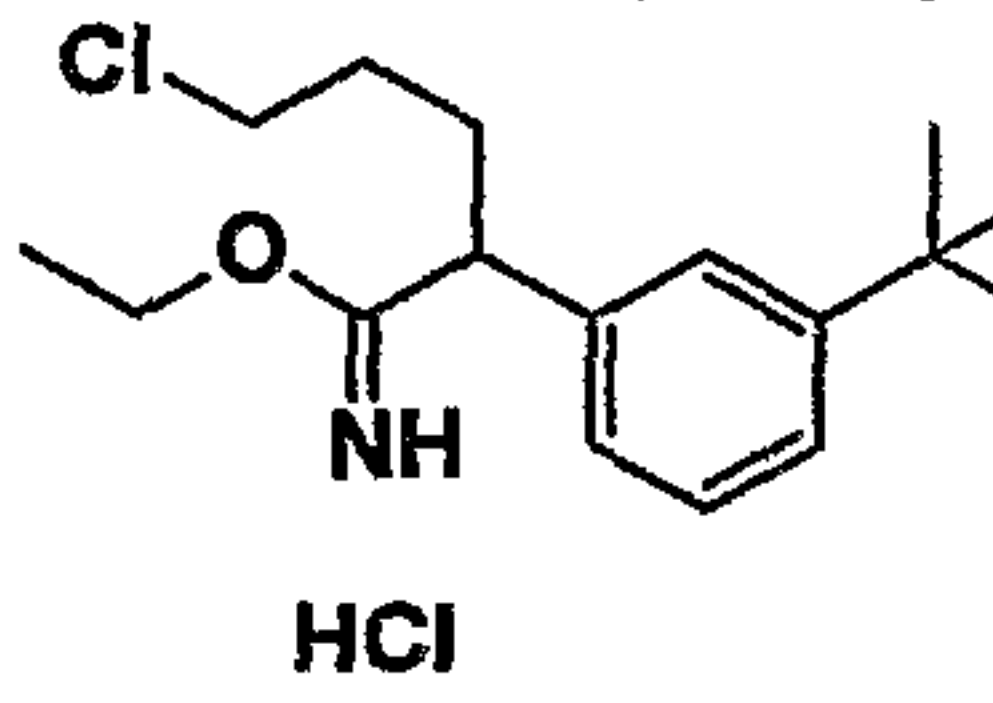
Table 12

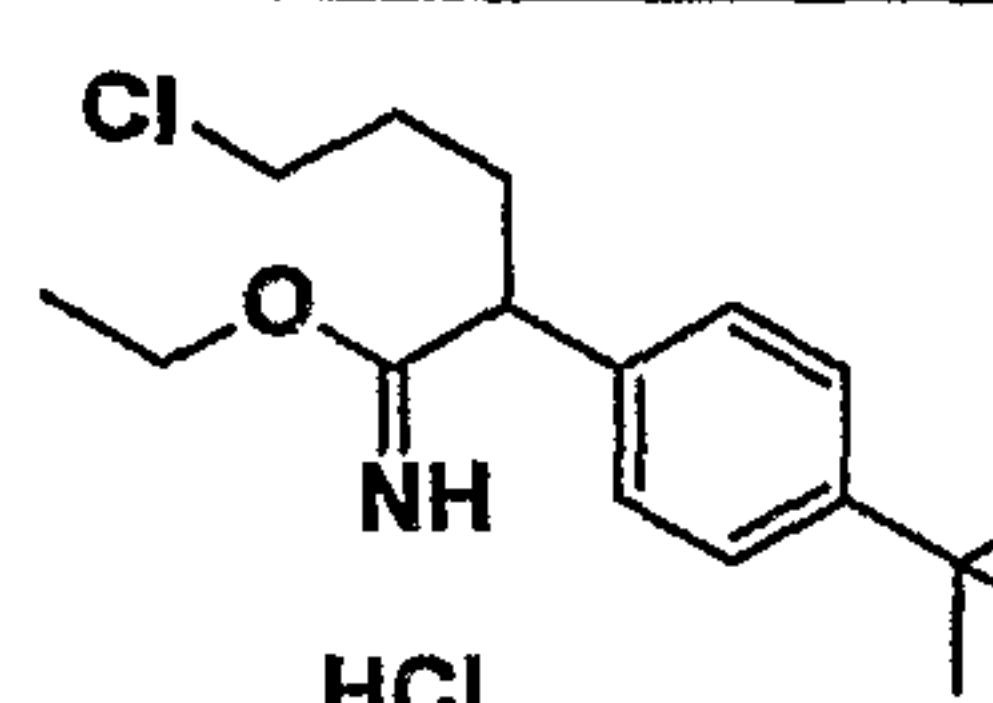
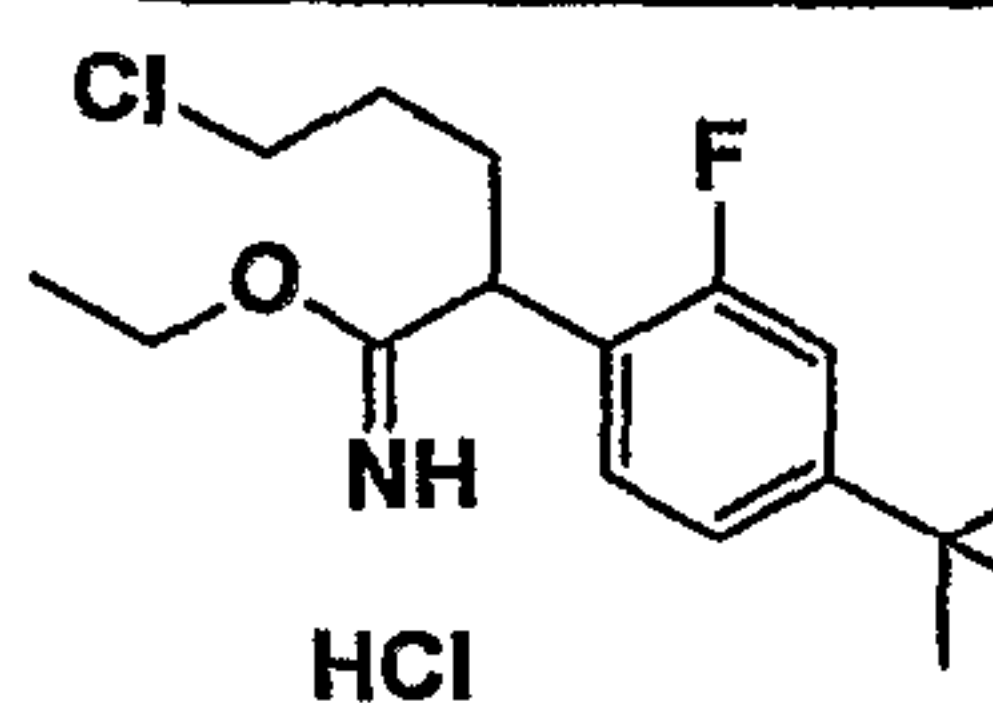
Preparation Example	Structural formula	Preparation Example	Structural formula
3-22		3-28	
3-23		3-29	
3-24		3-30	
3-25		3-31	
3-26		3-32	
3-27			

[0718]

The compounds of Preparation Example 3-33 to Preparation Example 3-37 were obtained according to the methods described in Preparation Example 3-3.

Table 13

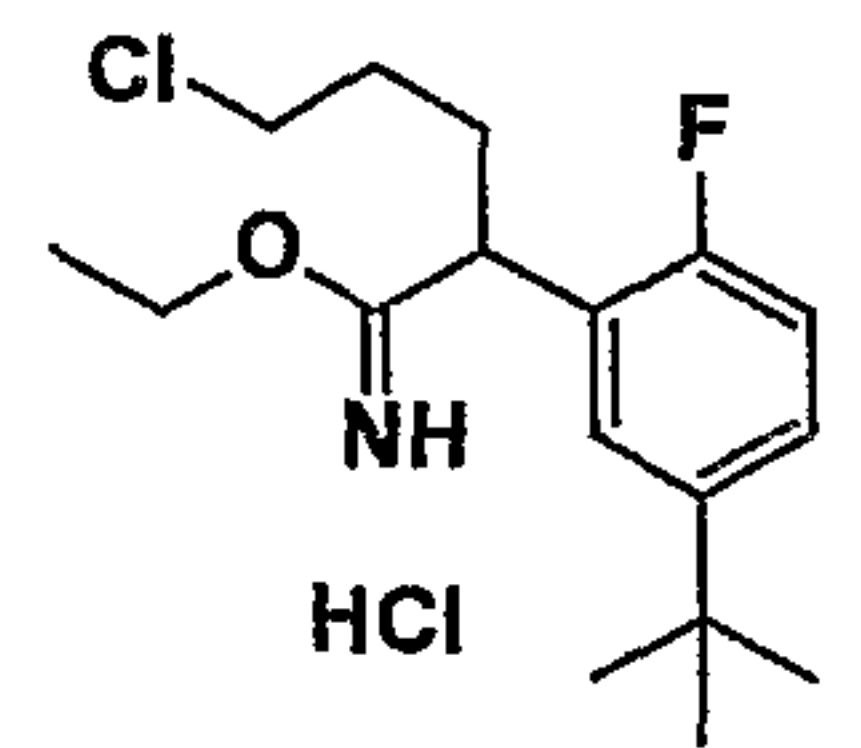
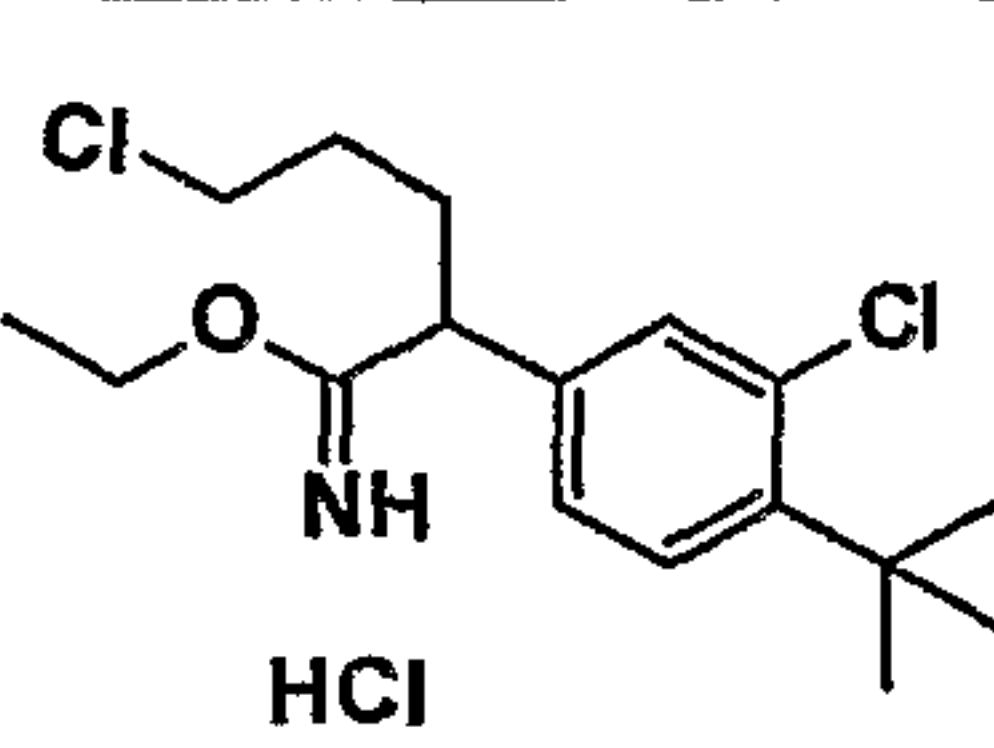
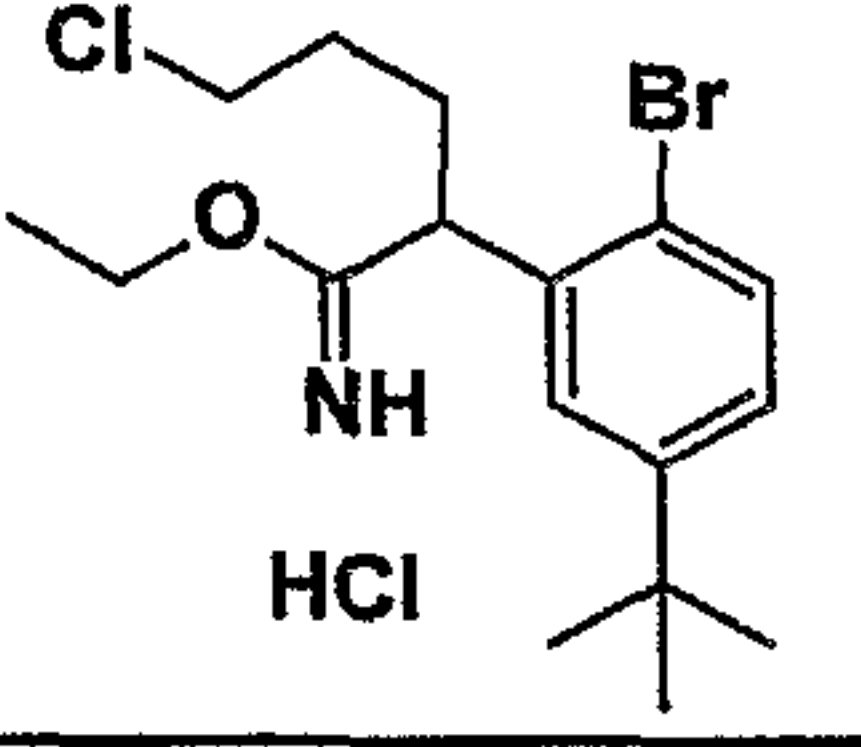
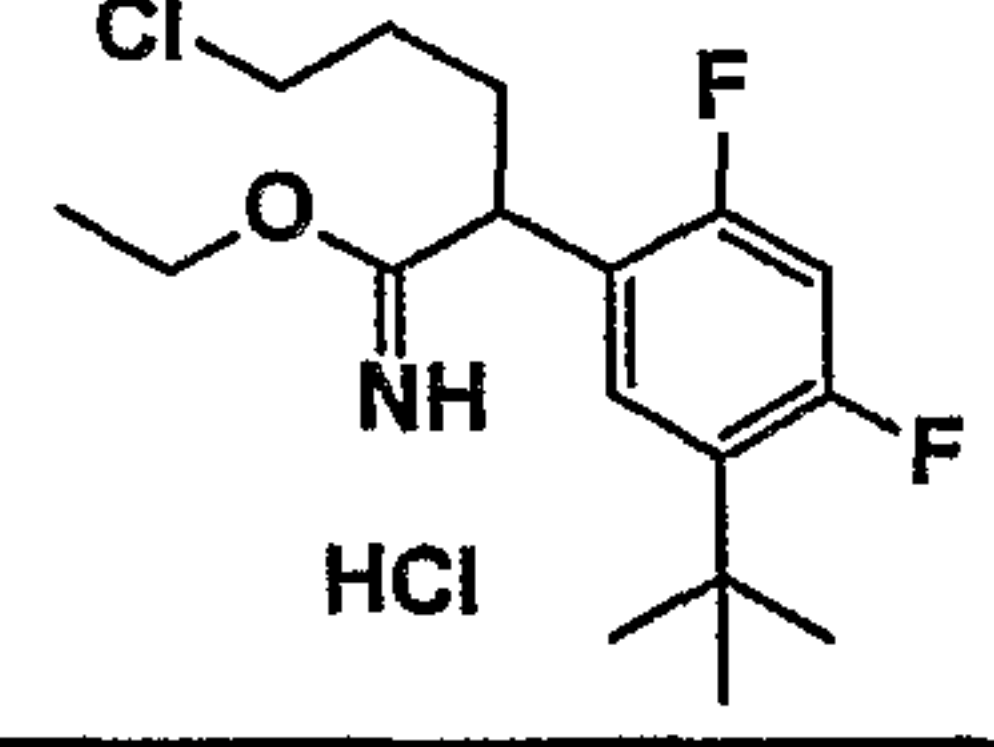
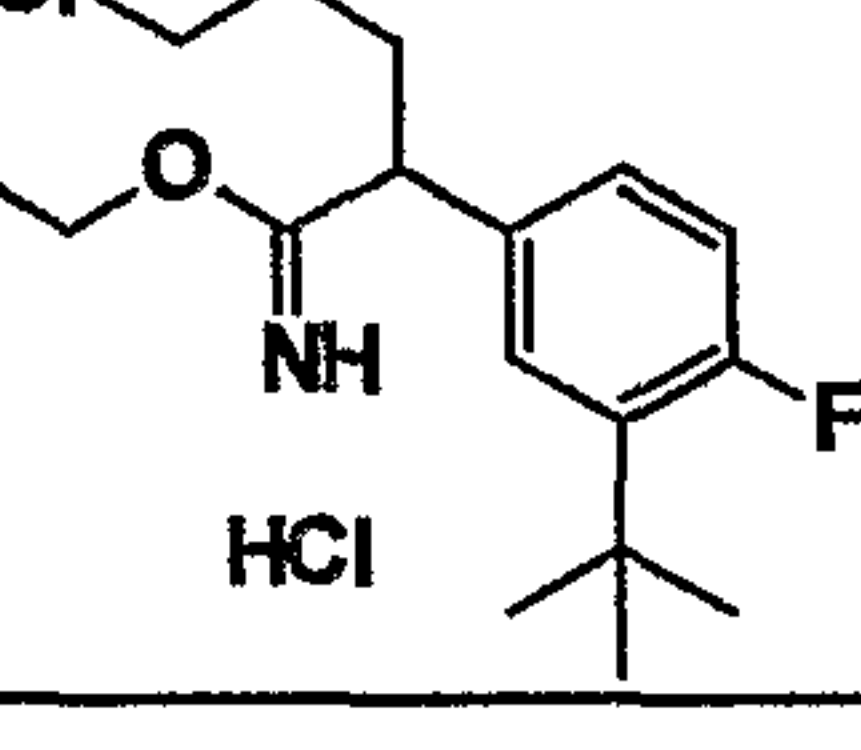
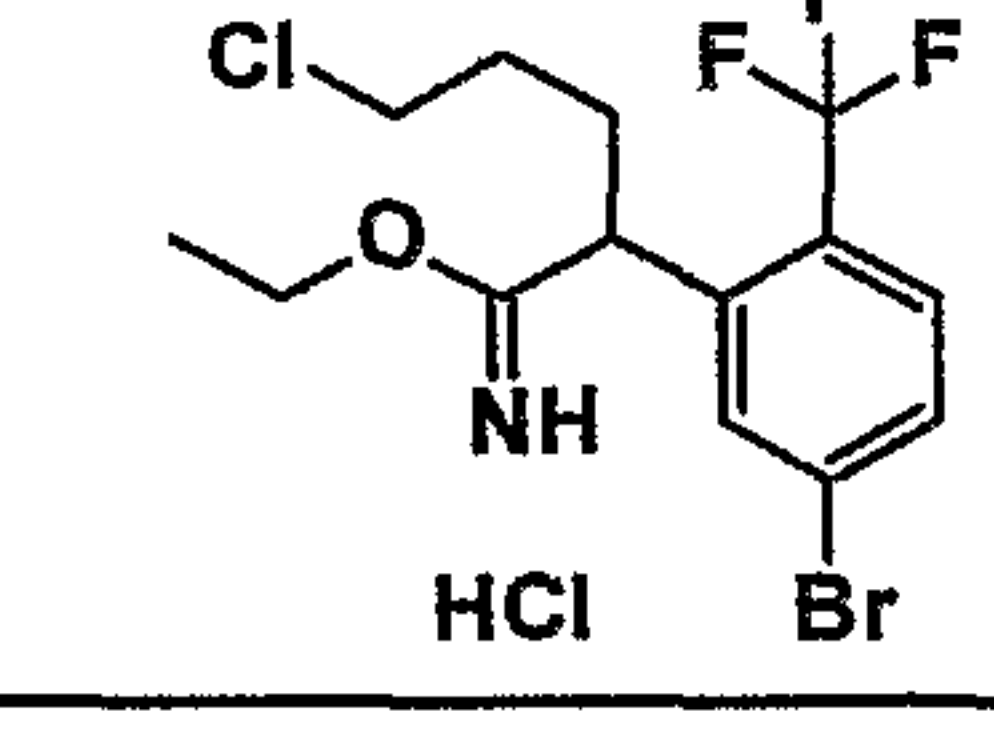
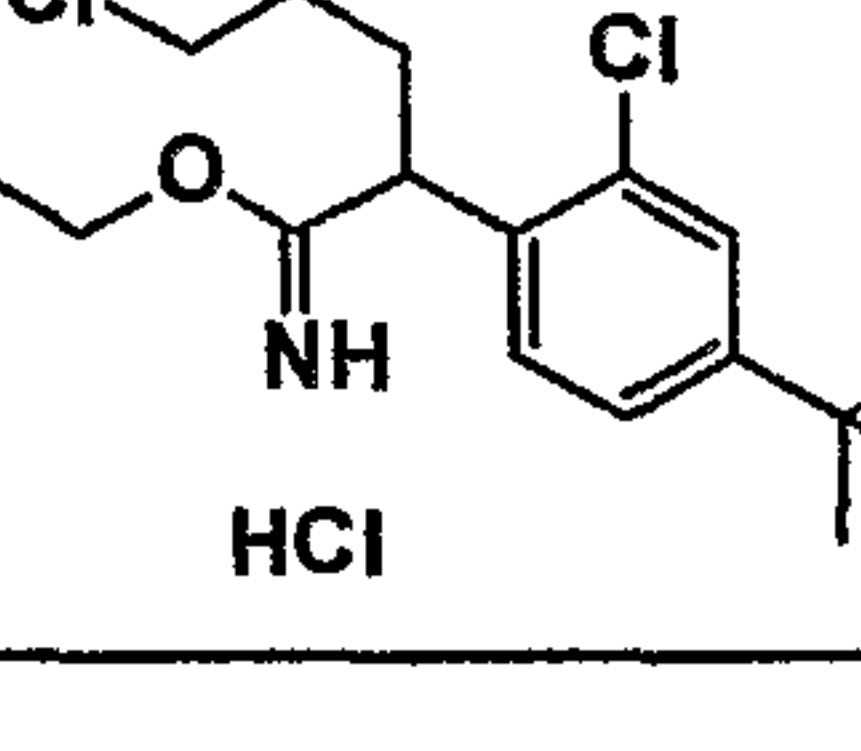
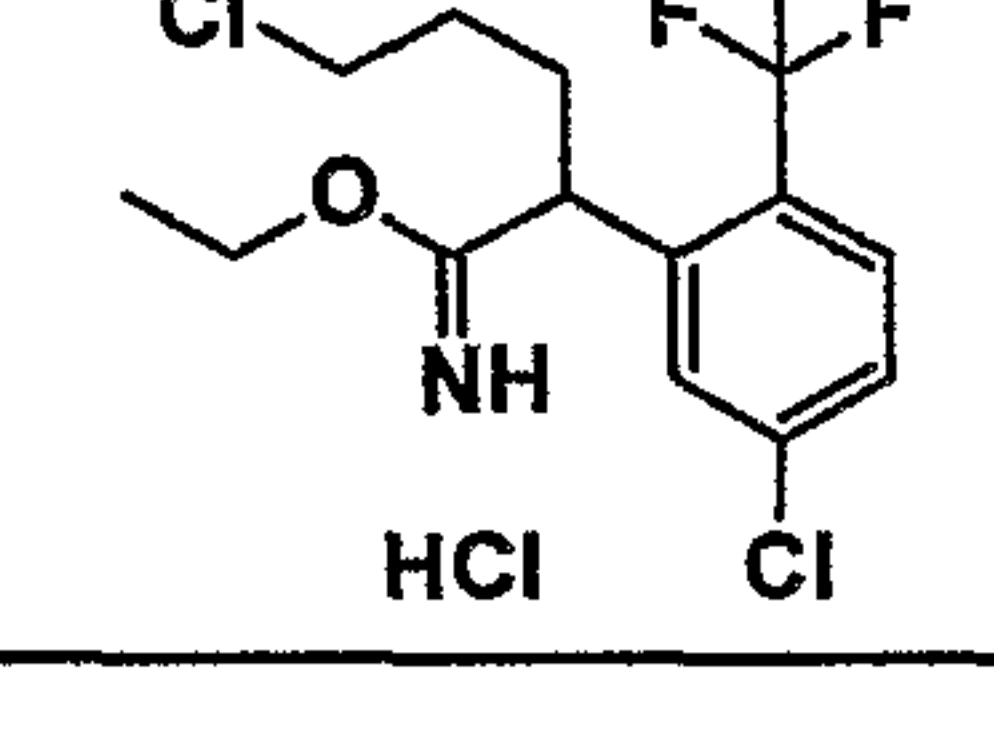
Preparation Example	Structural formula
3-33	
3-34	
3-35	

Preparation Example	Structural formula
3-36	
3-37	

[0719]

The compounds of Preparation Example 3-38 to Preparation Example 3-45 were obtained according to the methods described in Preparation Example 3-1.

Table 14

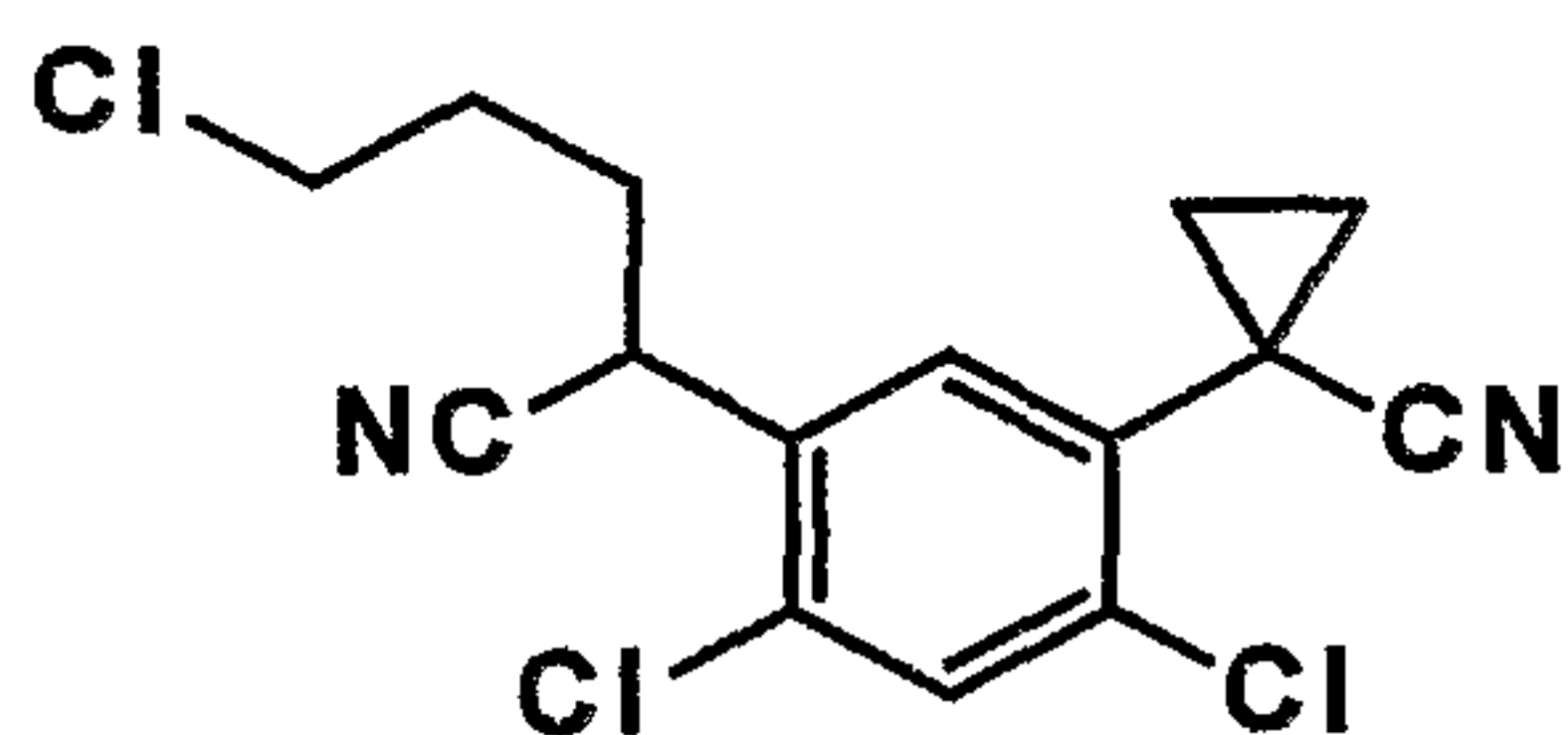
Preparation Example	Structural formula	Preparation Example	Structural formula
3-38		3-42	
3-39		3-43	
3-40		3-44	
3-41		3-45	

[0720]

Preparation example of the compound 3-46

Synthesis of 1-[2,4-dichloro-5-(4-chloro-1-cyanobutyl)phenyl]cyclopropanecarbonitrile.

5 [0721]



[0722]

Synthesis of (2,4-dichloro-5-methylphenyl)acetonitrile.

To a solution of 1,5-dichloro-2-chloromethyl-4-methylbenzene (CAS #101349-87-5, 5.22 g) in dimethyl sulfoxide (20 ml) was added potassium cyanide (1.36 g) and the reaction solution was stirred at room temperature for 6 hours.

Potassium cyanide (0.68 g) was added to the reaction solution and the solution was further stirred at room temperature overnight. To the reaction solution were added ice-cold water and tert-butyl methyl ether and the organic layer was separated. The water layer was re-extracted by the tert-butyl methyl ether. The combined organic layer was sequentially washed with water (twice) and brine. After drying over anhydrous magnesium sulfate, the organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (carrier: WakogelTM C-200; elution solvent: heptane:ethyl acetate 49:1 → 19:1) to obtain the title compound (1.88 g). The property values of the obtained compound are as follows; ¹H-NMR (CDCl₃) δ (ppm): 2.38 (s, 3H), 3.78 (s, 2H), 7.38 (s, 1H), 7.43 (s, 1H).

10 [0723]

Synthesis of 1-(2,4-dichloro-5-methylphenyl)cyclopropanecarbonitrile.

To a mixture of (2,4-dichloro-5-methylphenyl) acetonitrile (385 mg) and 1,2-dibromoethane (1.0 g) were added benzyltriethylammonium-chloride (44 mg) and a 50 % solution of sodium hydroxide (0.8 ml) and the mixture was stirred overnight at room temperature. Ice-cold water and tert-butyl methyl ether were added to the reaction mixture and the organic layer was separated. The obtained organic layer was sequentially washed with water (twice) and brine. After drying over anhydrous magnesium sulfate, the organic layer was concentrated under reduced pressure. The obtained residue was purified by silica column chromatography (carrier: WakogelTM C-200; elution solvent: heptane:ethyl acetate 49:1 → 19:1) to obtain the title compound (317 mg). The property values of the obtained compound are as follows; ¹H-NMR (CDCl₃) δ (ppm): 1.32 (dd, J=7.6, 5.2 Hz, 2H), 1.72 (dd, J=7.6, 5.2 Hz, 2H), 2.34 (s, 3H), 7.20 (s, 1H), 7.43 (s, 1H).

[0724]

25 Synthesis of 1-[2,4-dichloro-5-(4-chloro-1-cyanobutyl)phenyl] cyclopropane-carbonitrile.

Similar to the methods of Preparation Example 3-21, the title compound (113 mg) was obtained from 1-(2,4-dichloro-5-methylphenyl)cyclopropanecarbonitrile (317 mg). The property values of the obtained compound are as follows; ¹H-NMR (CDCl₃) δ (ppm): 1.30-1.34 (m, 1H), 1.40-1.45 (m, 1H), 1.77-1.85 (m, 2H), 1.93-2.15 (m, 4H), 3.61 (t, J=5.6 Hz, 2H), 4.23-4.29 (m, 1H), 7.54 (s, 1H).

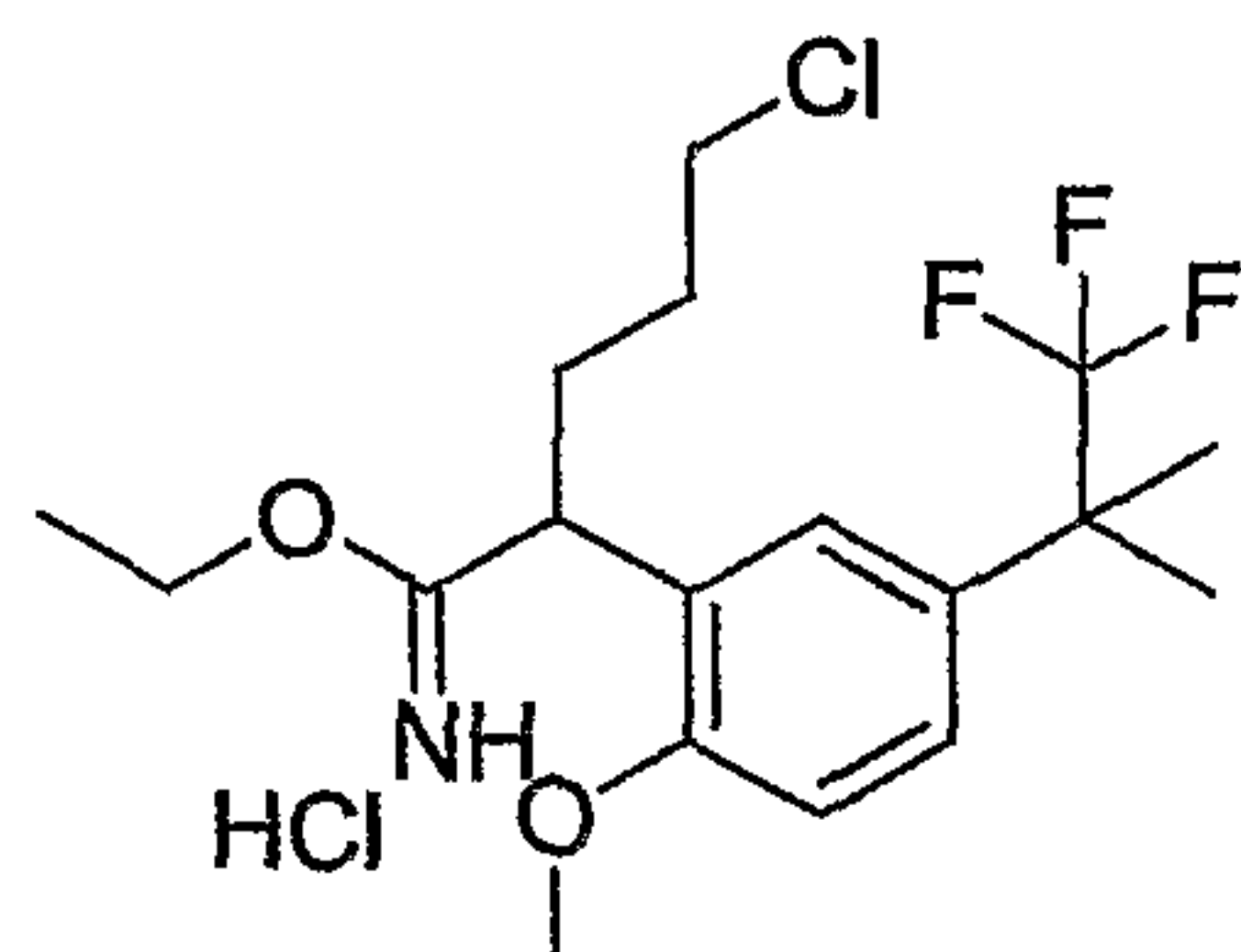
[0725]

Preparation Example 3-47

Synthesis of ethyl 5-chloro-2-[2-methoxy-5-

(2,2,2-trifluoro-1,1-dimethylethyl)phenyl]pentanimidate.

[0726]



[0727]

Synthesis of 1-(4-methoxy-3-methylphenyl)ethanone.

5 To a solution of 4-hydroxy-3-methylacetophenone (CAS #876-02-8, 5 g) in DMF (30 ml) were added potassium carbonate (9.21 g) and iodomethane (6.14 g). The reaction solution was stirred at room temperature for 3 days. Water and heptane were added to the reaction mixture and the organic layer was separated. The obtained organic layer was washed with brine and was dried over anhydrous magnesium sulfate. After filtration for removing the

10 drying agent, the organic layer was concentrated under reduced pressure. The residue was dissolved in a solution of heptane and ethyl acetate mixture (heptane:ethyl acetate, 3:1), and the solution was passed through silica gel column chromatography. The solution was concentrated under the reduced pressure to obtain the title compound (5.7 g). The property values of the compound are as follows; ¹H-NMR (CDCl₃) δ (ppm): 2.25 (s, 3H), 2.55 (s, 3H), 3.90 (s, 3H),

15 6.85 (d, J=8.4 Hz, 1H), 7.78 (d, J=2.0 Hz, 1H), 7.83 (dd, J=8.4, 2.0 Hz, 1H).

[0728]

Synthesis of trimethyl-[2,2,2-trifluoro-1-(4-methoxy-3-methylphenyl)-1-methylethoxy]silane.

To an ice-cold solution of 1-(4-methoxy-3-methylphenyl)ethanone (1 g) in DMF (6 ml) were added lithium acetate (20.1 mg) and (trifluoromethyl)trimethylsilane (1.04 g).

20 Under the same temperature, the solution was stirred for 1.5 hours and then stirred for 3.5 hours at room temperature. Water and heptane were added to the reaction solution and the organic layer was separated. The obtained organic layer was washed with brine and dried over anhydrous magnesium sulfate. After removing the drying agent, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column

25 chromatography (elution solvent: heptane → heptane:ethyl acetate 7:3) to obtain the title compound (711 mg). The property values of the obtained compound are as follows; ¹H-NMR (CDCl₃) δ (ppm): 0.13 (s, 3H), 1.79 (s, 3H), 2.23 (s, 3H), 3.84 (s, 3H), 6.80 (d, J=8.8 Hz, 1H),

7.27 (d, J=2.4 Hz, 1H), 7.32 (dd, J=8.8, 2.4 Hz, 1H)

[0729]

Synthesis of 1,1,1-trifluoro-2-(4-methoxy-3-methylphenyl)-propane-2-ol.

5 Trimethyl-[2,2,2-trifluoro-1-(4-methoxy-3-methylphenyl)-1-methylethoxy]silane (711 mg) was dissolved in THF (20 ml) and 1N HCl solution (20 ml) was added. After stirring at room temperature for 6 days, water and ethyl acetate were added to the reaction mixture and the organic layer was separated. The obtained organic layer was washed with brine and dried over anhydrous magnesium sulfate. After
10 removing the drying agent, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane → heptane:ethyl acetate 7:3) to obtain the title compound (442 mg). The property values of the obtained compound are as follows; ¹H-NMR (CDCl₃) δ (ppm): 1.76 (s, 3H), 2.24 (s, 3H), 3.84 (s, 3H), 6.83 (d, J=8.4 Hz, 1H), 7.34-7.37 (m, 2H).

15 [0730]

Synthesis of 1-methoxy-2-methyl-4-(2,2,2-trifluoro-1,1-dimethylethyl)benzene.

To an ice-cold solution of 1,1,1-trifluoro-2-(4-methoxy-3-methylphenyl)-propane-2-ol (440 mg) in dichloromethane (20 ml) were added
20 titanium tetrachloride (357 mg). Under the same temperature, it was stirred for 2 hours. Ice-cold water and dichloromethane were added to the organic layer and the organic layer was separated. The obtained organic layer was washed with saturated sodium bicarbonate solution and dried over anhydrous potassium carbonate. After removing the drying agent, the organic layer was concentrated under reduced pressure. After the residue was dissolved in dichloro methane (15
25 ml), it was cooled at -70°C and titanium tetrachloride (302 mg) and dimethylzinc (1M, n-hexane solution, 3.18 ml) was added. The mixture was brought back to room temperature and stirred for 3 hours. Ice-cold water and dichloromethane were added to the solution and the organic layer was separated. The obtained organic layer was washed with saturated sodium bicarbonate solution and then dried over anhydrous magnesium sulfate. After removing the drying agent,
30 the organic layer was concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (elution solvent: heptane → heptane:ethyl acetate 9:1) to obtain the title compound (203 mg). The property values of the obtained compound are as follows; ¹H-NMR (CDCl₃) δ (ppm): 1.54 (s, 6H), 2.23 (s, 3H), 3.83

(s, 3H), 6.80 (d, J=8.4 Hz, 1H), 7.25-7.29 (m, 2H).

[0731]

Synthesis of ethyl 5-chloro-2-[2-methoxy-5-(2,2,2-trifluoro-1-methoxy-1-methylethyl)phenyl]pentanimidate hydrochloride

5 According to the method of Preparation Example 3-1, the titled compound was obtained from 1-methoxy-2-methyl-4-(2,2,2-trifluoro-1,1-dimethylethyl)benzene.

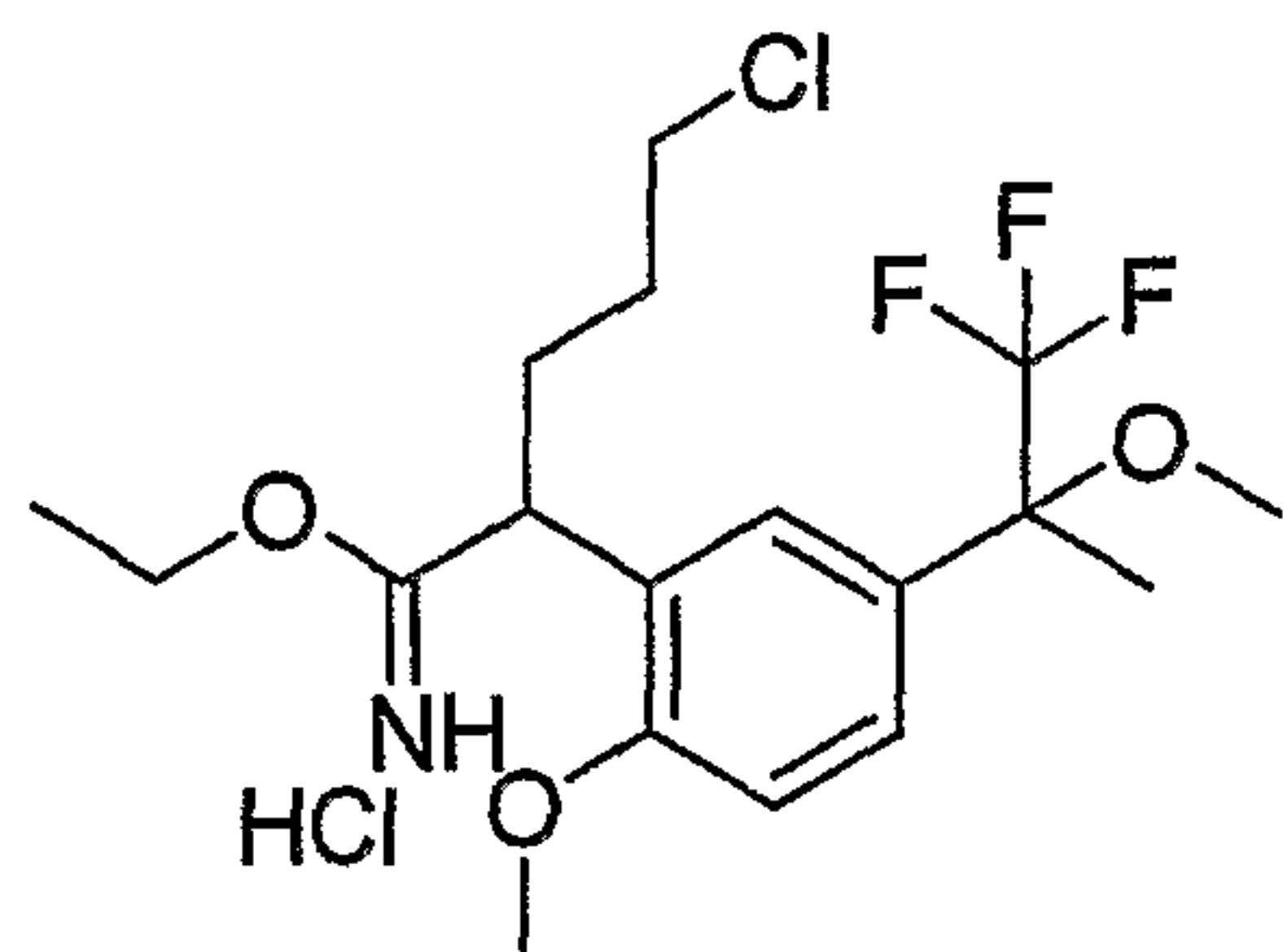
[0732]

Preparation Example 3-48

Synthesis of ethyl 5-chloro-2-[2-methoxy-5-(2,2,2-trifluoro-1-methoxy-1-methylethyl)phenyl]pentanimidate hydrochloride

10

[0733]



[0734]

Synthesis of 1-methoxy-2-methyl-4-(2,2,2-trifluoro-1-methoxy-1-methylethyl)benzene.

15 To a solution of 1,1,1-trifluoro-2-(4-methoxy-3-methylphenyl)-propane-2-ol (1 g) in DMF (20 ml) were added sodium hydride (60% in mineral oil, 205 mg) and iodomethane (727 mg). After stirring for 5 hours at room temperature, the reaction mixture was ice cooled, then water and ethyl acetate were added to the reaction mixture. The organic layer was separated and washed with brine, and dried over anhydrous magnesium sulfate. After removing the drying agent, the organic layer was concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (elution solvent: heptane → heptane:ethyl acetate 9:1) to obtain the title compound (747 mg). The property values of the obtained compound are as follows; ¹H-NMR (CDCl₃) δ (ppm): 1.74 (s, 3H), 2.24 (s, 3H), 3.21 (s, 3H), 3.85 (s, 3H), 6.83 (d, J=8.4 Hz, 1H), 7.25-7.30 (m, 2H).

25

[0735]

Synthesis of ethyl 5-chloro-2-[2-methoxy-5-(2,2,2-trifluoro-

1-methoxy-1-methylethyl)phenyl]pentanimidate hydrochloride

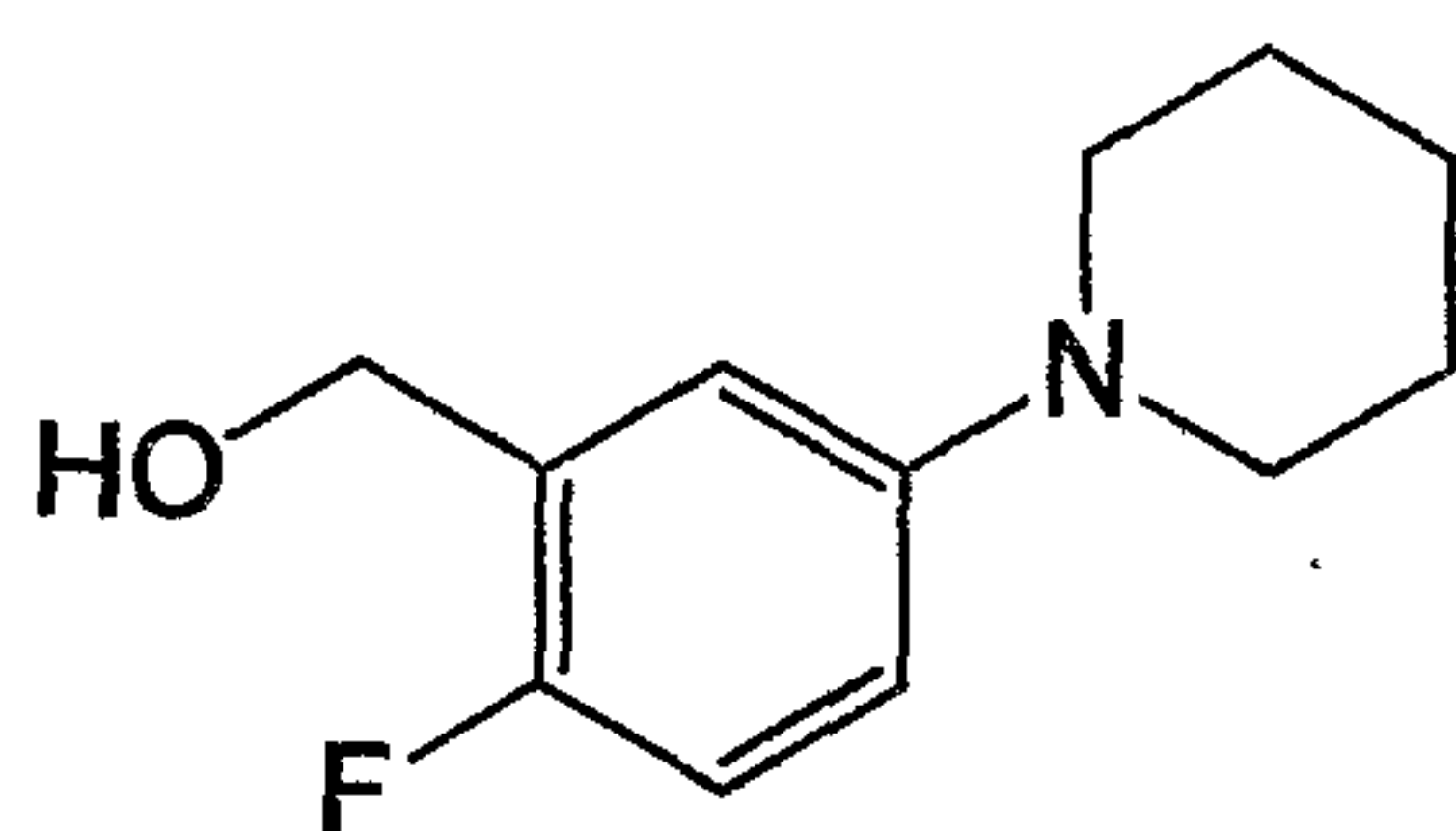
According to the method of Preparation Example 3-1, the title compound was obtained from 1-methoxy-2-methyl-4-(2,2,2-trifluoro-1-methoxy-1-methylethyl)benzene.

5 [0736]

Preparation Example 6-1

Synthesis of (2-fluoro-5-piperidin-1-ylphenyl)methanol

[0737]



[0738]

10 Synthesis of methyl 2-fluoro-5-nitro benzoate

To an ice-cold solution of 2-fluoro-5-nitro benzoic acid (3 g) in methanol (30 ml) was added thionyl chloride (2.32 ml) dropwise. After stirring overnight at room temperature, the reaction mixture was concentrated under reduced pressure. Ethyl acetate and sodium bicarbonate aqueous solution were added to the residue and the organic layer was separated. The obtained organic layer was washed with brine and then dried over anhydrous sodium sulfate. After removing the drying agent, the organic layer was concentrated under reduced pressure to obtain the title compound (3.28 g).

[0739]

Synthesis of methyl 5-amino-2-fluoro benzoate

20 To a solution of methyl 2-fluoro-5-nitro benzoate (2 g) in methanol (80 ml) was added nickel dichloride (II) 6 hydrate (475 mg), and the reaction mixture was cooled to -30°C. Under the same temperature, sodium borohydride (1.13 g) was added portionwise. The solution was warmed up to -20°C and stirred for 20 minutes, then potassium carbonate aqueous solution was added. After removing the insoluble substance by celite filtration, the filtrate was
25 concentrated under the reduced pressure to remove methanol. The obtained residue was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate. After removing the drying agent by filtration, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (1.5 g).

[0740]

Synthesis of methyl 2-fluoro-5-(piperidin-1-yl)benzoate

Methyl 5-amino-2-fluoro benzoate (1.5 g), 1,5-dibromopentane (5.93 ml) and IPEA (7.66 ml) were dissolved in toluene (30 ml) and the mixture was stirred at 100°C for 15 hours. After cooling, ethyl acetate was added to the solution and the organic layer was separated. The organic layer was washed with water, brine and dried with anhydrous sodium sulfate. After removing the drying agent by filtration, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (2.12 g). The property value of the obtained compound is as follows; ESI-MS; m/z 238 [M⁺ +H].

[0741]

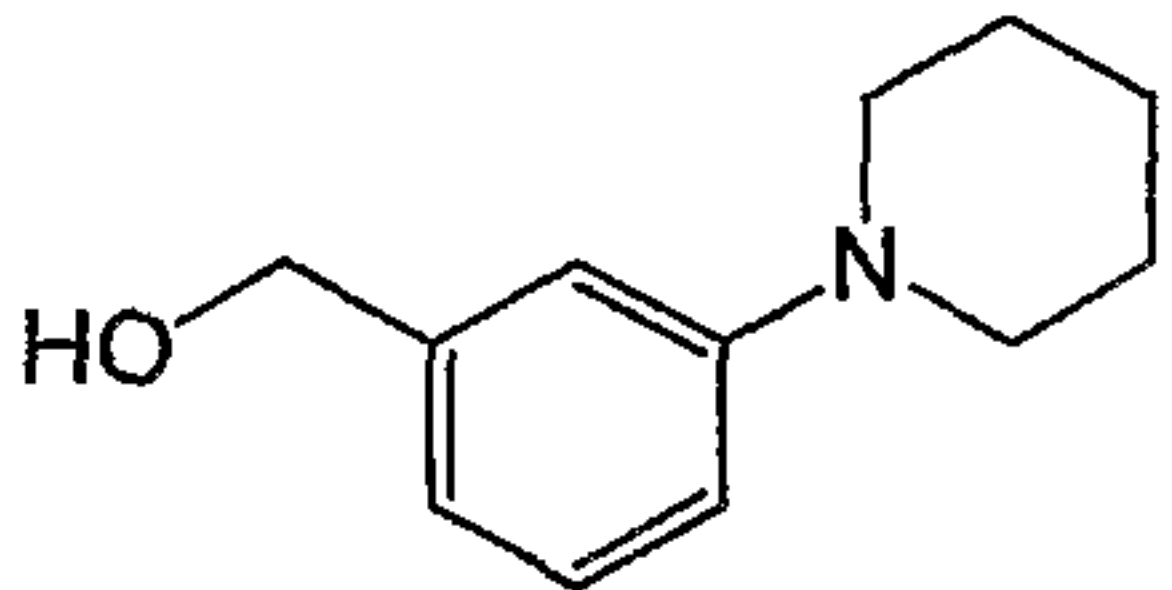
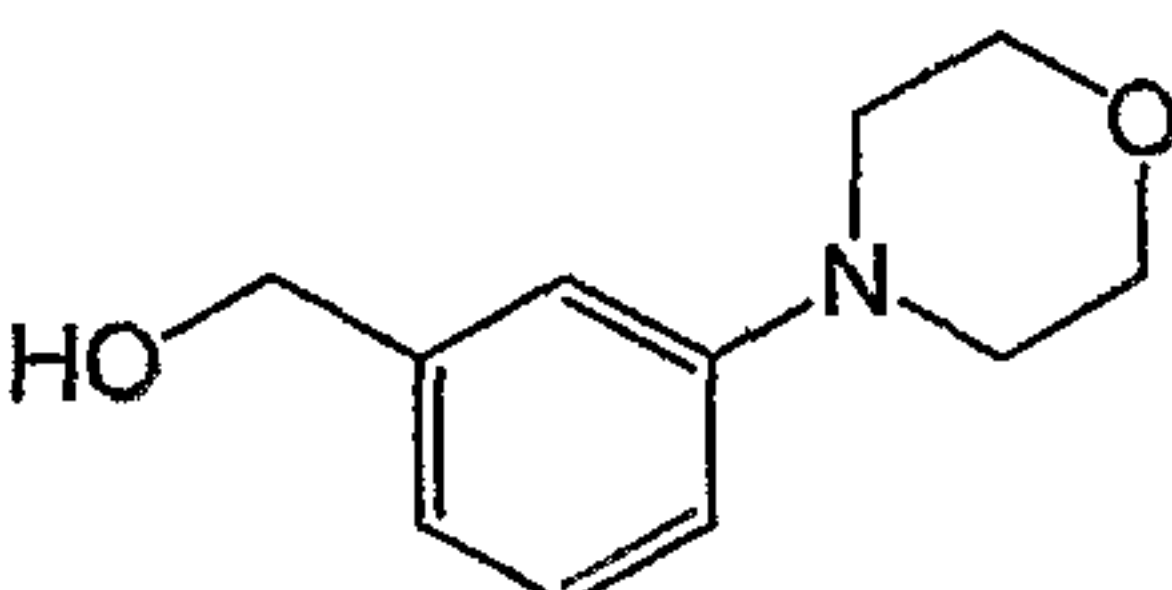
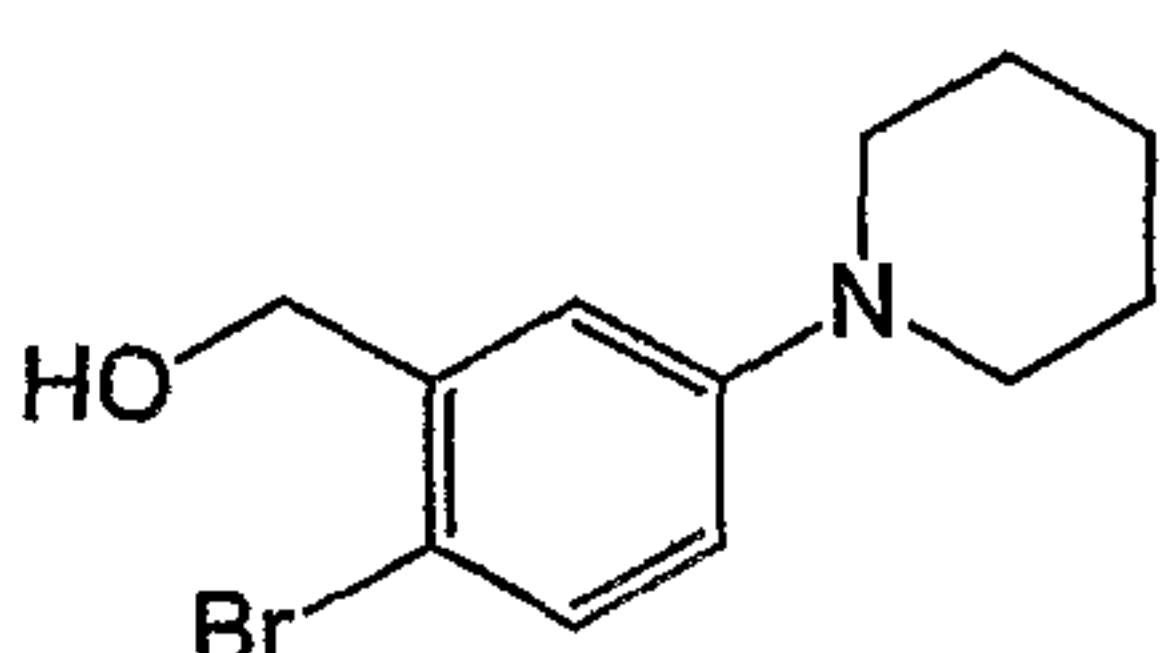
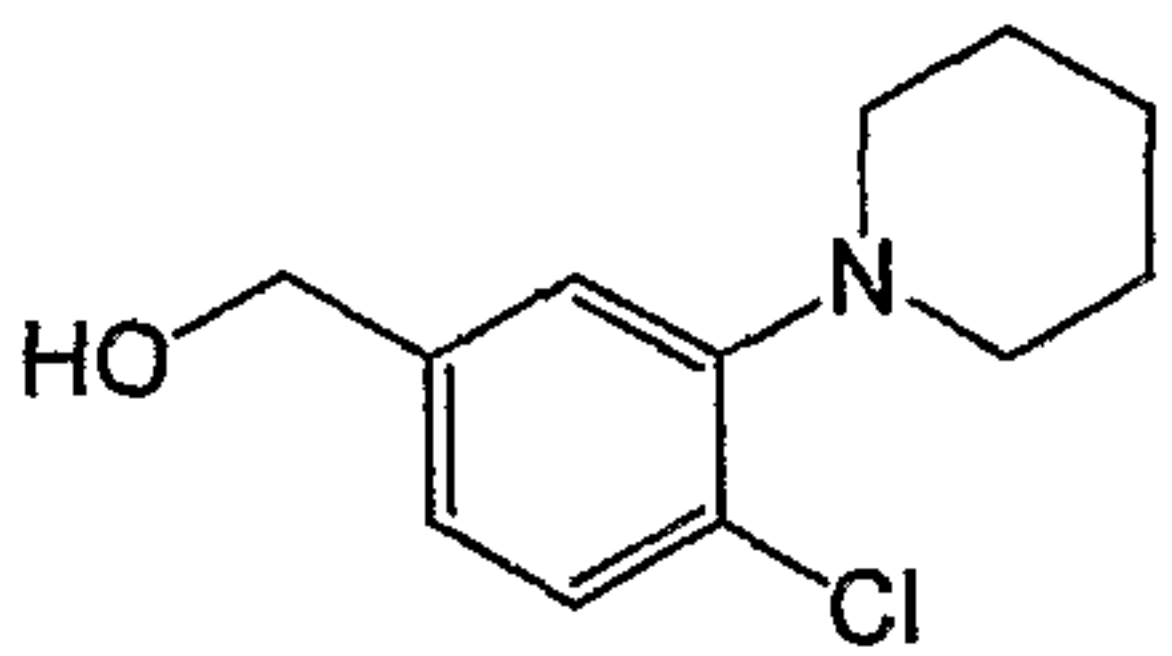
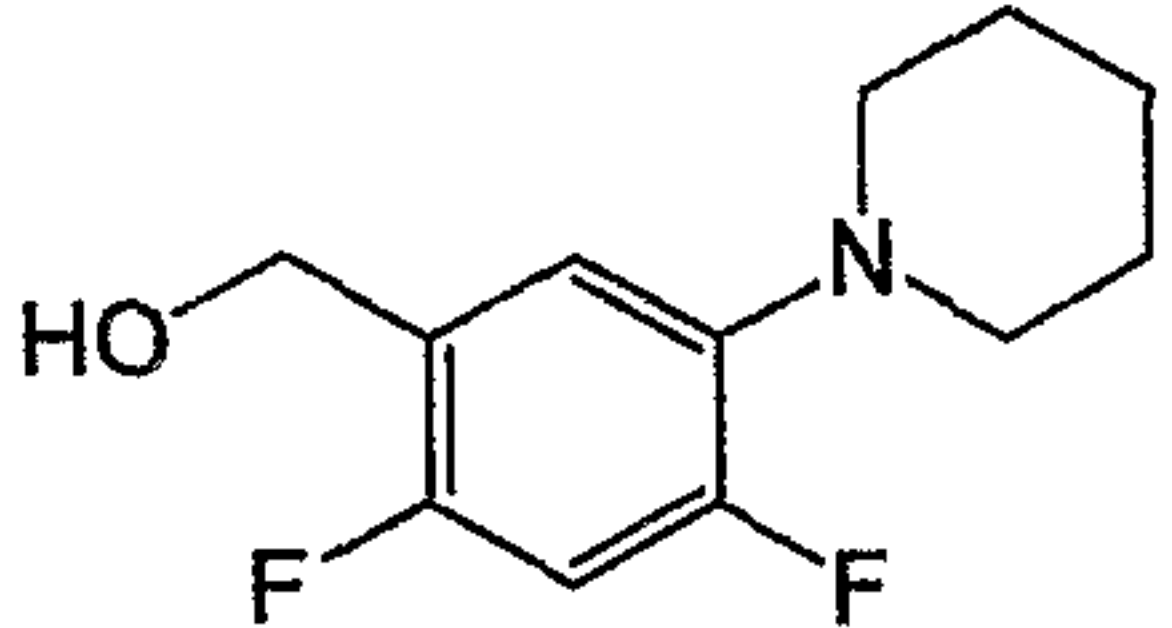
Synthesis of (2-fluoro-5-piperidin-1-yl)phenyl methanol

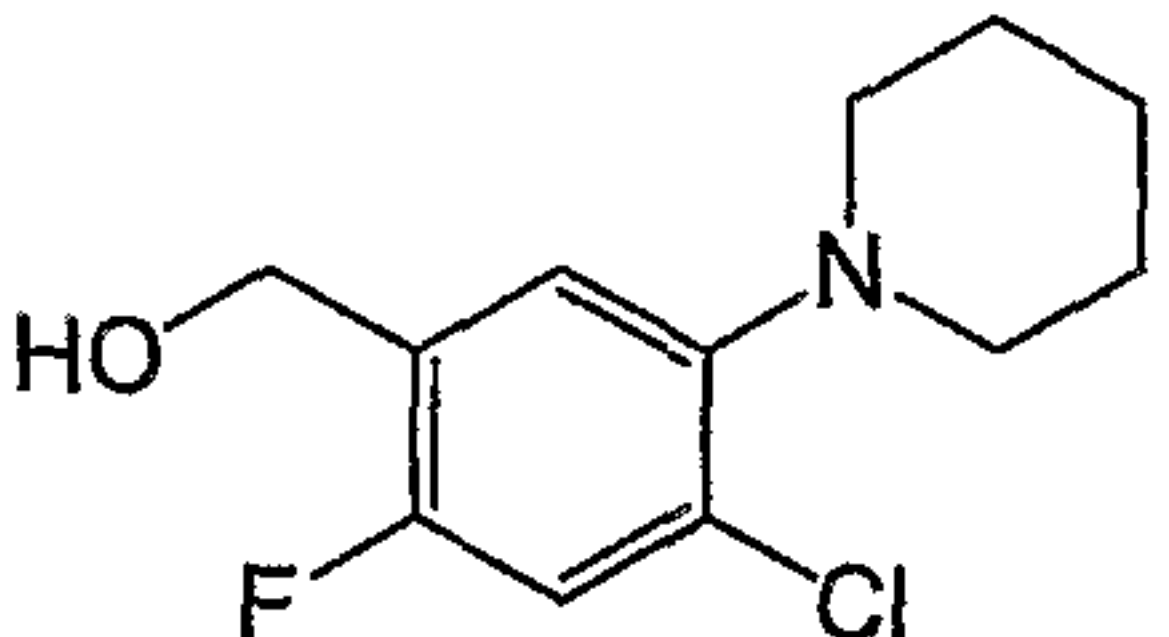
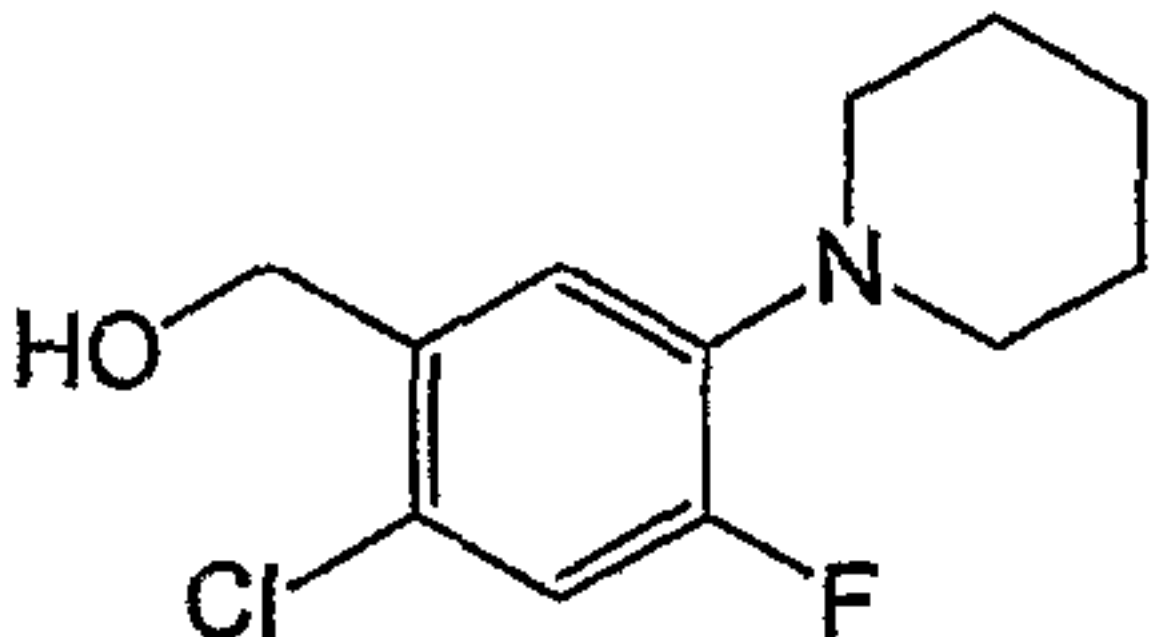
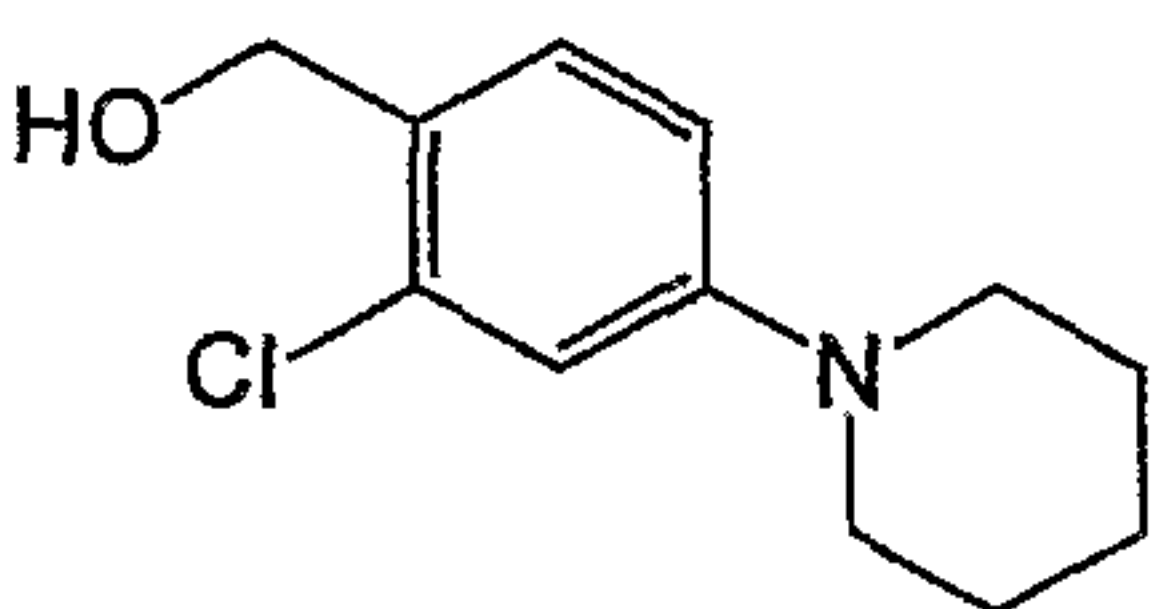
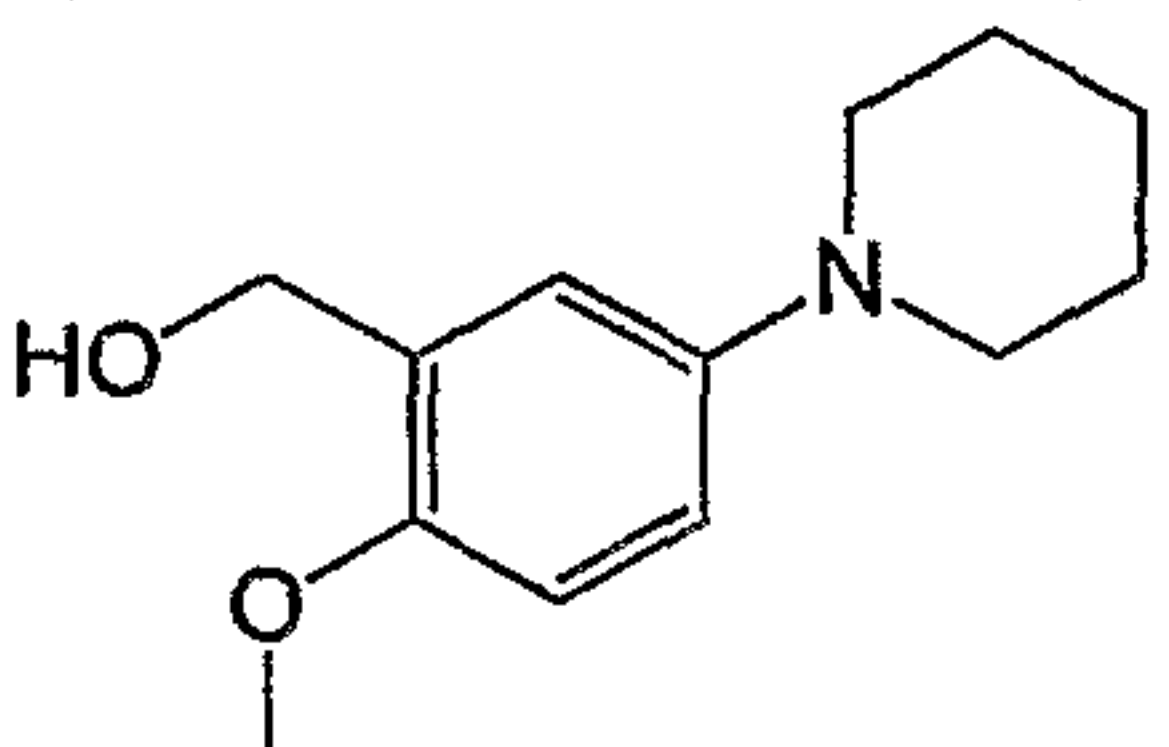
Methyl 2-fluoro-5-(piperidine-1-yl)benzoate (2.12 g) was added dropwise to a suspension of lithium aluminum hydride (372 mg) in THF (30 ml) under ice-cooling. After the completion of addition, the mixture was warmed to room temperature and stirred for 1 hour. Water (372ml), 5N aqueous sodium hydroxide solution (372ml) and water (1.12 ml) was sequentially added to the mixture under ice-cooling. The precipitate was removed by filtration through Celite and the filtrate was concentrated under reduced pressure to obtain the title compound (1.88 g). ESI-MS;m/z 210[M⁺+H].

[0742]

The compounds of Preparation Example 6-2 to Preparation Example 6-10 were obtained according to the method of Preparation Example 6-1 (Table 15).

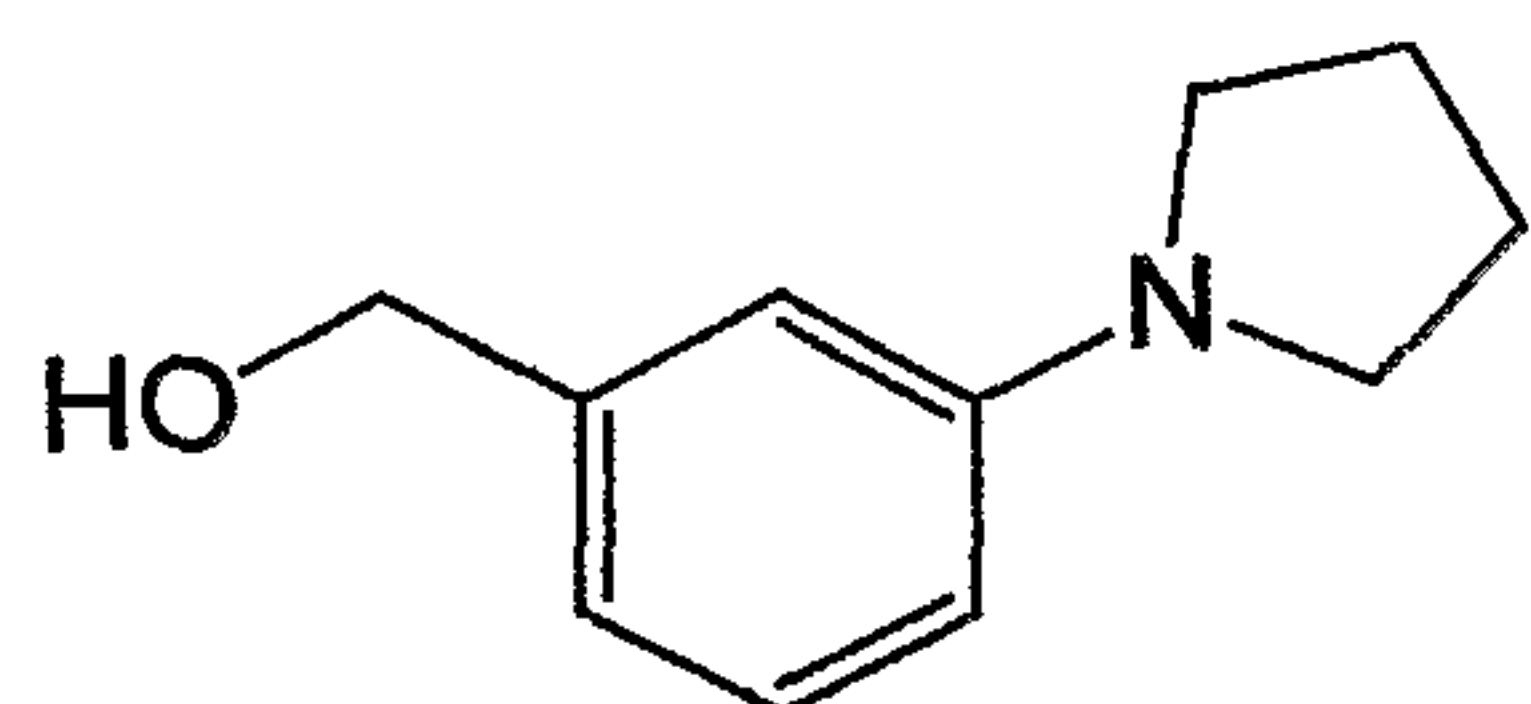
Table 15

Preparation Example No.	Structural formula
6-2	
6-3	
6-4	
6-5	
6-6	

Preparation Example No.	Structural formula
6-7	
6-8	
6-9	
6-10	

[0743]

Preparation Example 6-11

Synthesis of (3-pyrrolidin-1-yl)phenyl methanol

[0744]

5 Synthesis of 1-[3-(tert-butyl dimethylsilyloxymethyl)phenyl]pyrrolidine

Tris(dibenzylideneacetone)dipalladium (152 mg) was added to a suspension of (3-

Bromobenzyloxy)-tert-butyldimethylsilane (1.00 g) obtained in Preparation Example 7-2, pyrrolidine (416 μ l), BINAP (310 mg) and sodium tert-butoxide (348 mg) in toluene (20 ml) under a nitrogen atmosphere. The mixture was heated at 80 °C with stirring for 3 hours and then cooled to room temperature. The mixture was diluted with ethyl acetate, filtered through Celite
5 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (913 mg).

ESI-MS; m/z 292 [$M^+ + H$].

[0745]

Synthesis of (3-pyrrolodin-1-yl)phenyl methanol

10 Thetrabutylammonium fluoride (1.0 M solution in THF, 3.8 ml) was added to a solution of 1-[3-(tert-butyldimethylsilyloxymethyl)phenyl]pyrrolidine in THF (20 ml) and the mixture was stirred at room temperature for 3.5 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (557 mg).

15 ESI-MS; m/z 178 [$M^+ + H$].

[0746]

The compounds of Preparation Examples 6-12 to 6-16 were obtained according to the method of Preparation Example 6-11 (Table 16).

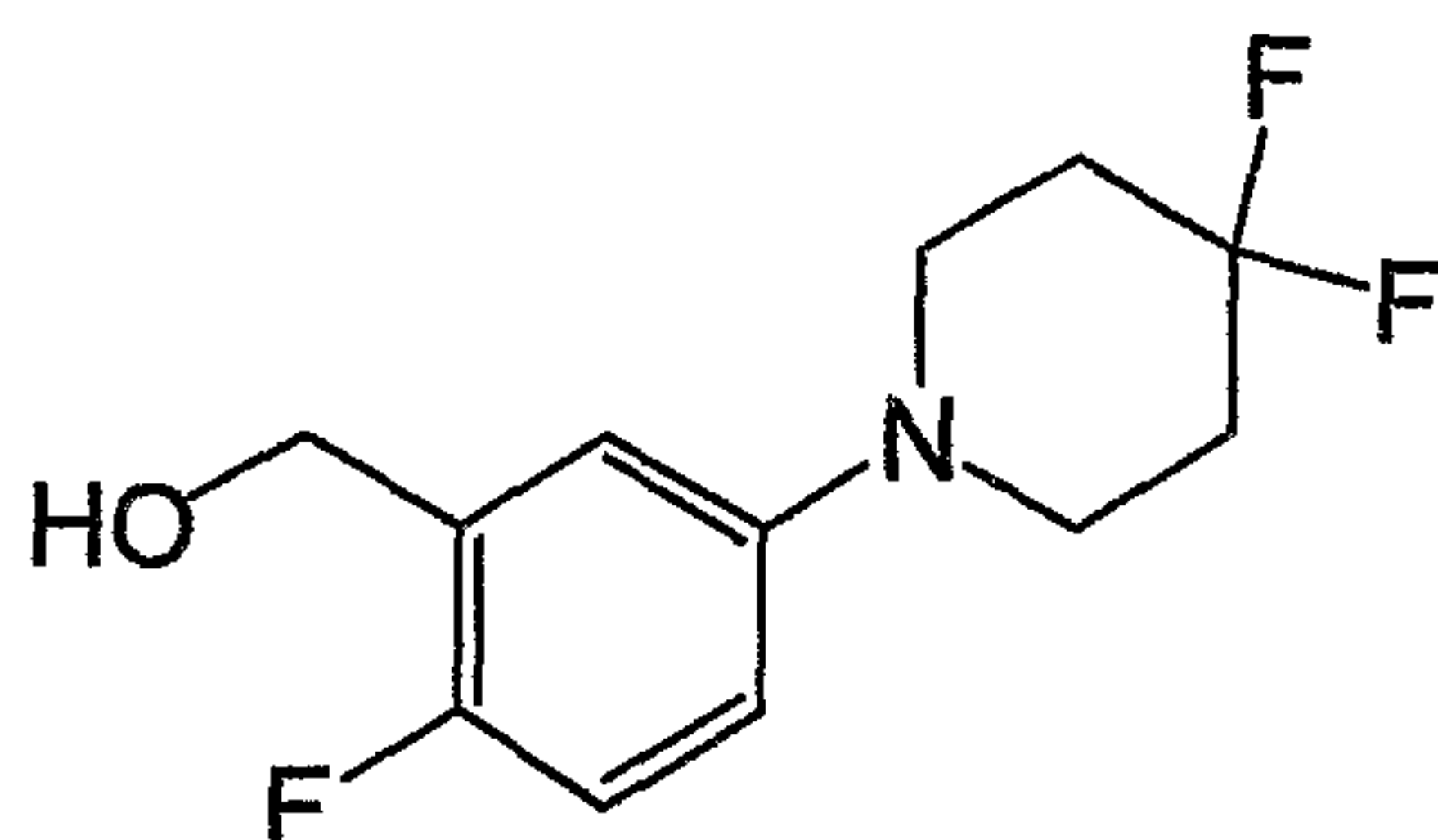
Table 16

Preparation Example No.	Structural formula
6-12	
6-13	
6-14	

Preparation Example No.	Structural formula
6-15	
6-16	

[0747]

Preparation Example 6-17

Synthesis of [5-(4,4-difluoropiperidin-1-yl)-2-fluorophenyl]methanol

[0748]

5 Synthesis of 1-benzyl-1-methyl-4-oxopiperidinium iodide

Iodomethane (20.2 ml) was added to a solution of 1-benzyl-4-piperidone (50 ml) in acetone (300 ml) and the mixture was stirred at room temperature overnight. The deposited crystals were collected and washed with acetone to obtain a title compound (77.1 g).

[0749]

10 Synthesis of methyl 2-fluoro-5-(4-oxopiperidin-1-yl)benzoate

Potassium carbonate (149 mg) and 1-benzyl-1-methyl-4-oxopiperidinium iodide (2.87 g) were sequentially added to a solution of methyl 5-amino-2-fluorobenzoate (1.22 g)

obtained in Preparation Example 6-1 in a mixed solvent of ethanol (10 ml) and water (5 ml). The reaction mixture was refluxed for 2.5 hours. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (1.22 g).

ESI-MS; m/z 252 $[M^+ + H]$.

[0750]

Synthesis of methyl 5-(4,4-difluoropiperidin-1-yl)-2-fluorobenzoate

Diethylaminosulfur trifluoride (1.72 ml) was added to a solution of methyl 2-fluoro-5-(4-oxopiperidin-1-yl)benzoate (1.22 g) in dichloromethane (20 ml). The reaction mixture was stirred at room temperature for 1.5 hours. An aqueous saturated solution of sodium bicarbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (878 mg).

ESI-MS; m/z 274 $[M^+ + H]$.

[0751]

Synthesis of [5-(4,4-difluoropiperidin-1-yl)-2-fluorophenyl]methanol

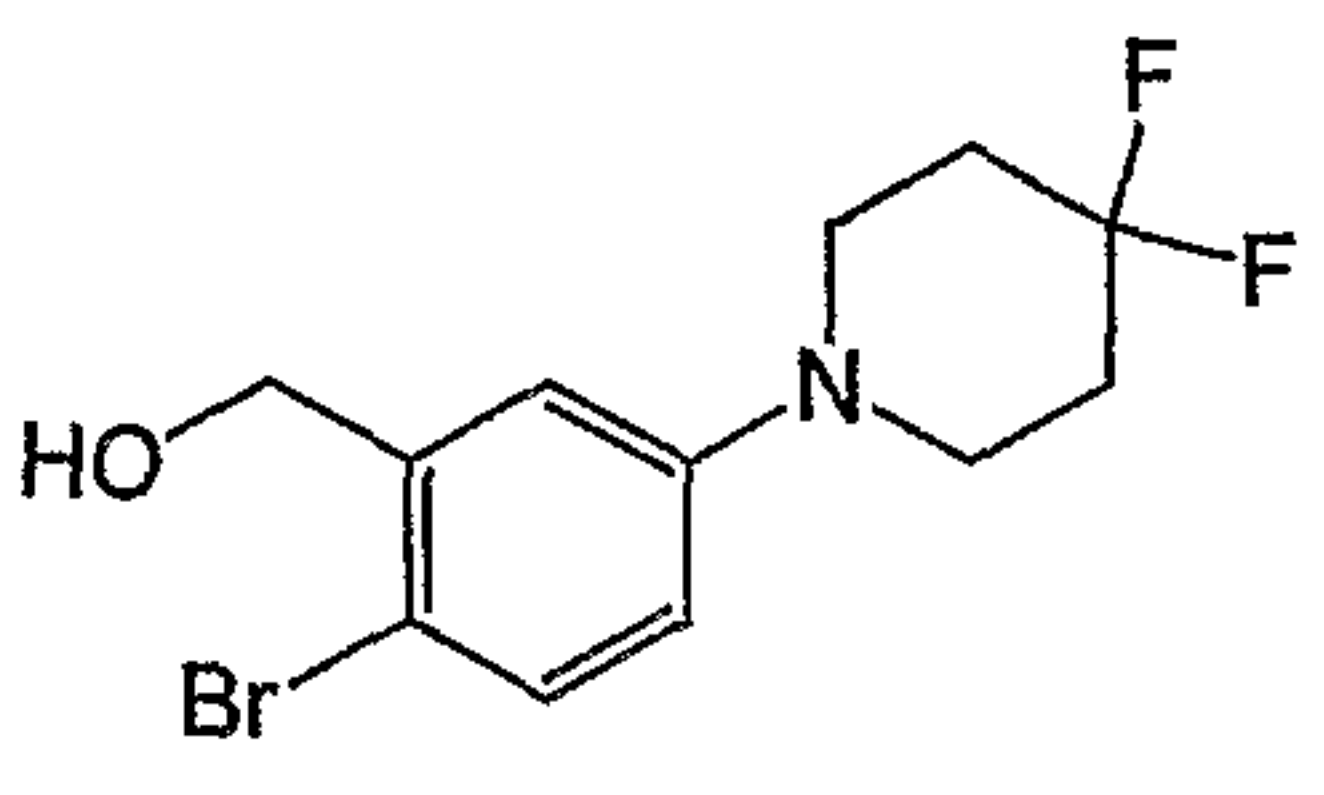
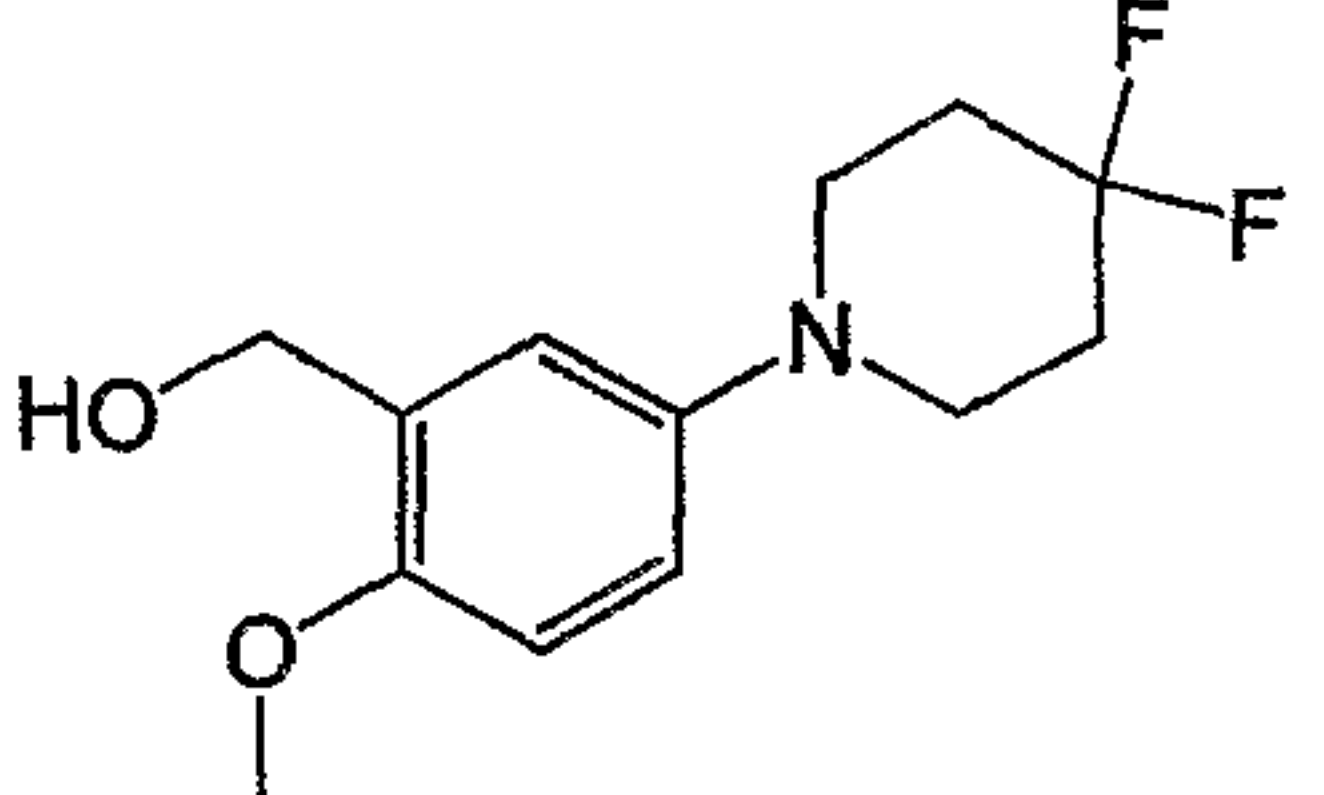
According to the method of Preparation Example 6-1, a title compound (761 mg) was obtained from methyl 5-(4,4-difluoropiperidin-1-yl)-2-fluorobenzoate (878 mg).

ESI-MS; m/z 246 $[M^+ + H]$.

[0752]

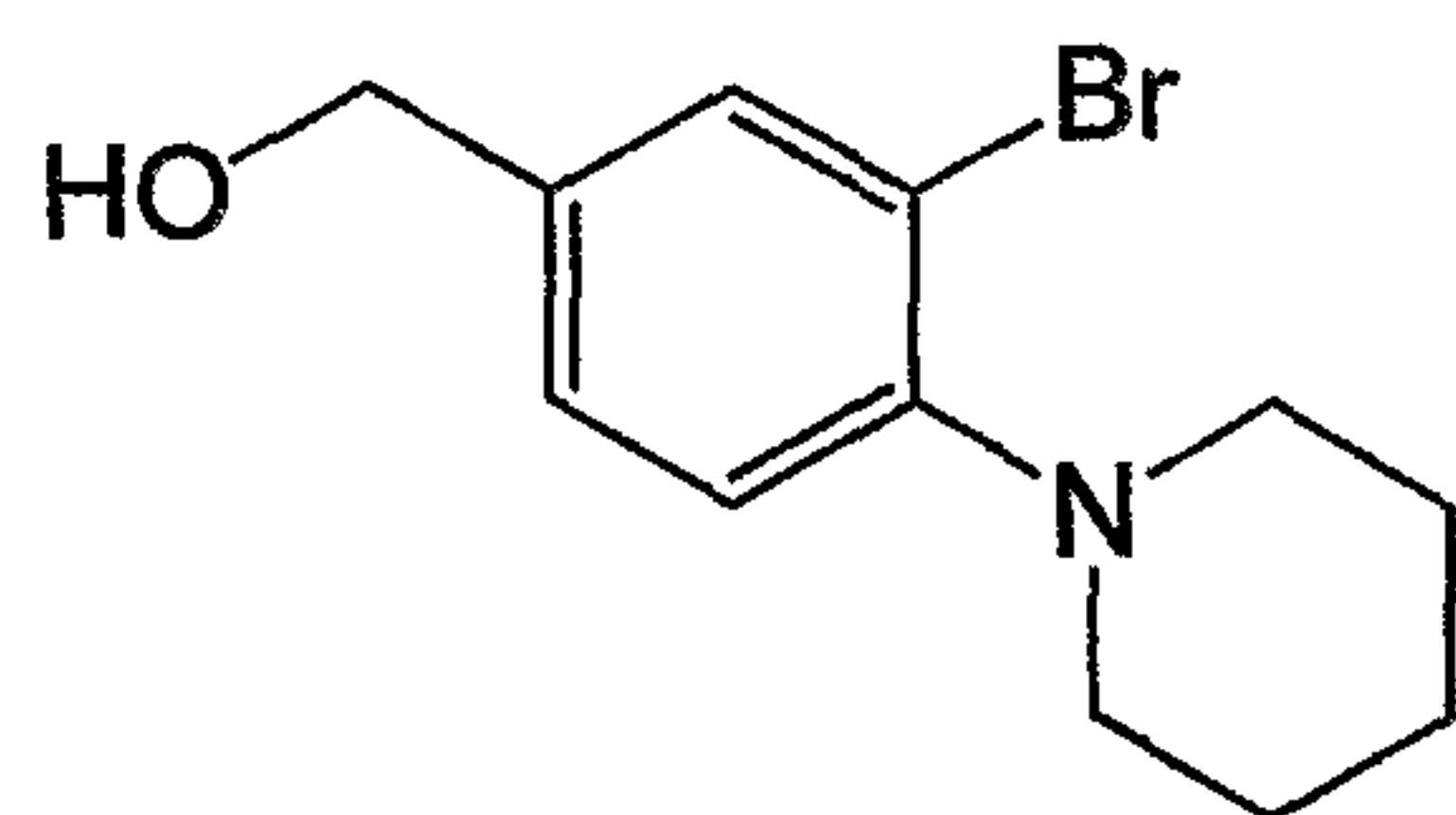
The compounds of Preparation Examples 6-18 and 6-19 were obtained according to the method of Preparation Example 6-17 (Table 17).

Table 17

Preparation Example No.	Structural formula
6-018	
6-019	

[0753]

Preparation Example 6-20

Synthesis of [(3-bromo-4-piperidin-1-yl)phenyl]methanol

[0754]

5 Synthesis of methyl 4-fluoro-3-nitrobenzoate

According to the method of Preparation Example 6-1, a title compound (2.19 g) was obtained from 4-fluoro-3-nitrobenzoic acid (2.00 g).

[0755]

Synthesis of methyl 3-nitro-4-(piperidine-1-yl)benzoate

10 Piperidine (1.24 ml) was added to a solution of methyl 4-fluoro-3-nitrobenzoate (1.00 g) in DMF (20 ml) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, sequentially washed with water and brine, and dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (1.50 g).

15

ESI-MS; m/z 265 $[M^+ + H]$.

[0756]

Synthesis of methyl 3-amino-4-(piperidin-1-yl)benzoate

Using 10 % palladium carbon cartridge, a solution of methyl 3-nitro-4-(piperidin-1-yl)benzoate (3.07 g) in methanol (50 ml) was pumped through the H-CubeTM reactor (ThalesNano Inc.). After all the reaction mixture had passed through the H-CubeTM reactor, the reaction mixture was concentrated under reduced pressure. The residue was purified by NH-silica gel column chromatography to obtain a title compound (2.32 g).
ESI-MS;m/z 235 [M⁺+H].

[0757]

10 Synthesis of methyl 3-bromo-4-(piperidin-1-yl)benzoate

Isoamyl nitrite (439 μ l) was added to the mixture of methyl 3-amino-4-(piperidin-1-yl)benzoate (500 mg) and copper (II) bromide (714 mg) in acetonitrile (25 ml). The reaction mixture was stirred at 70°C for 30 minutes. The mixture was diluted with ethyl acetate, sequentially washed with ammonium solution and brine, and then dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (158 mg).

[0758]

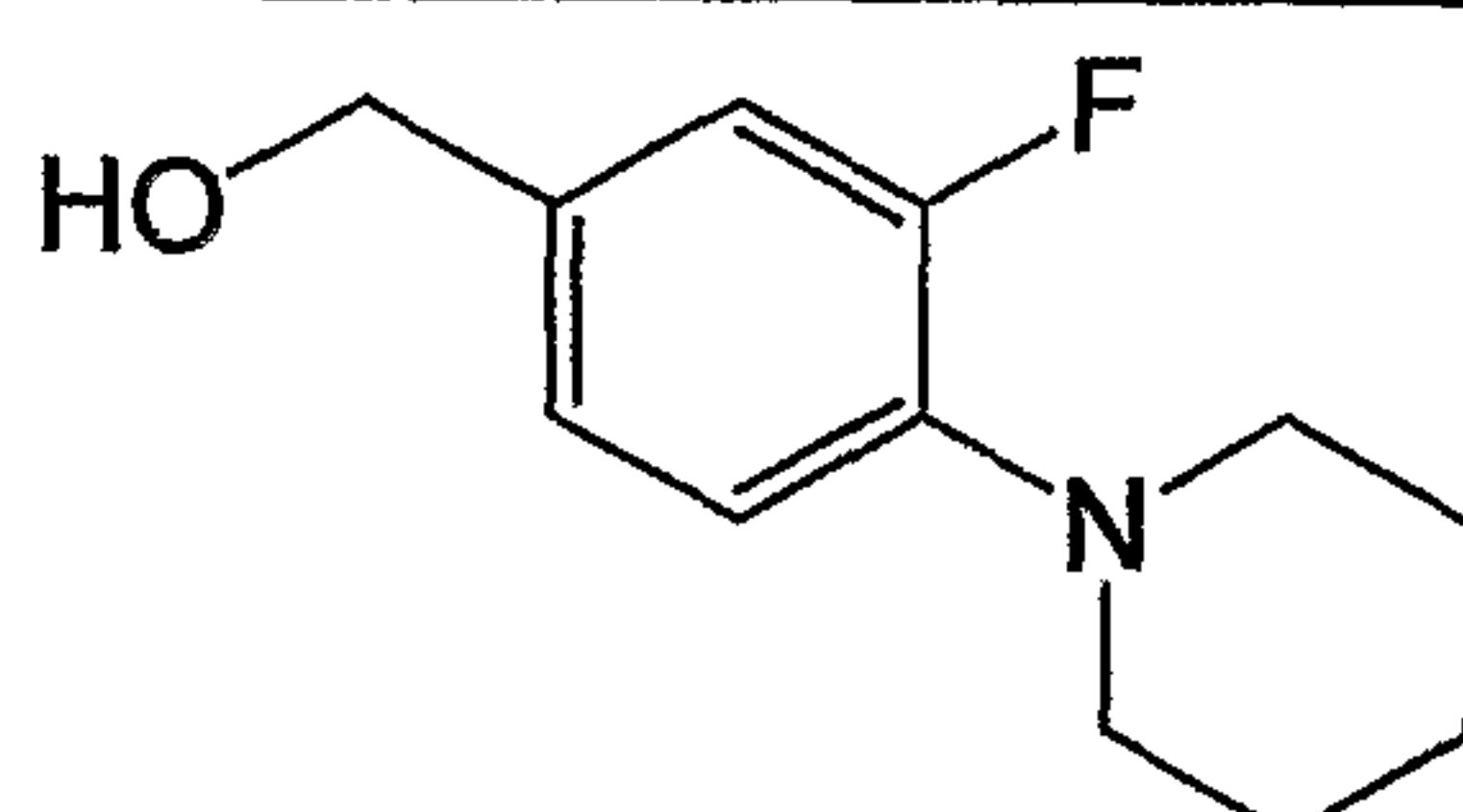
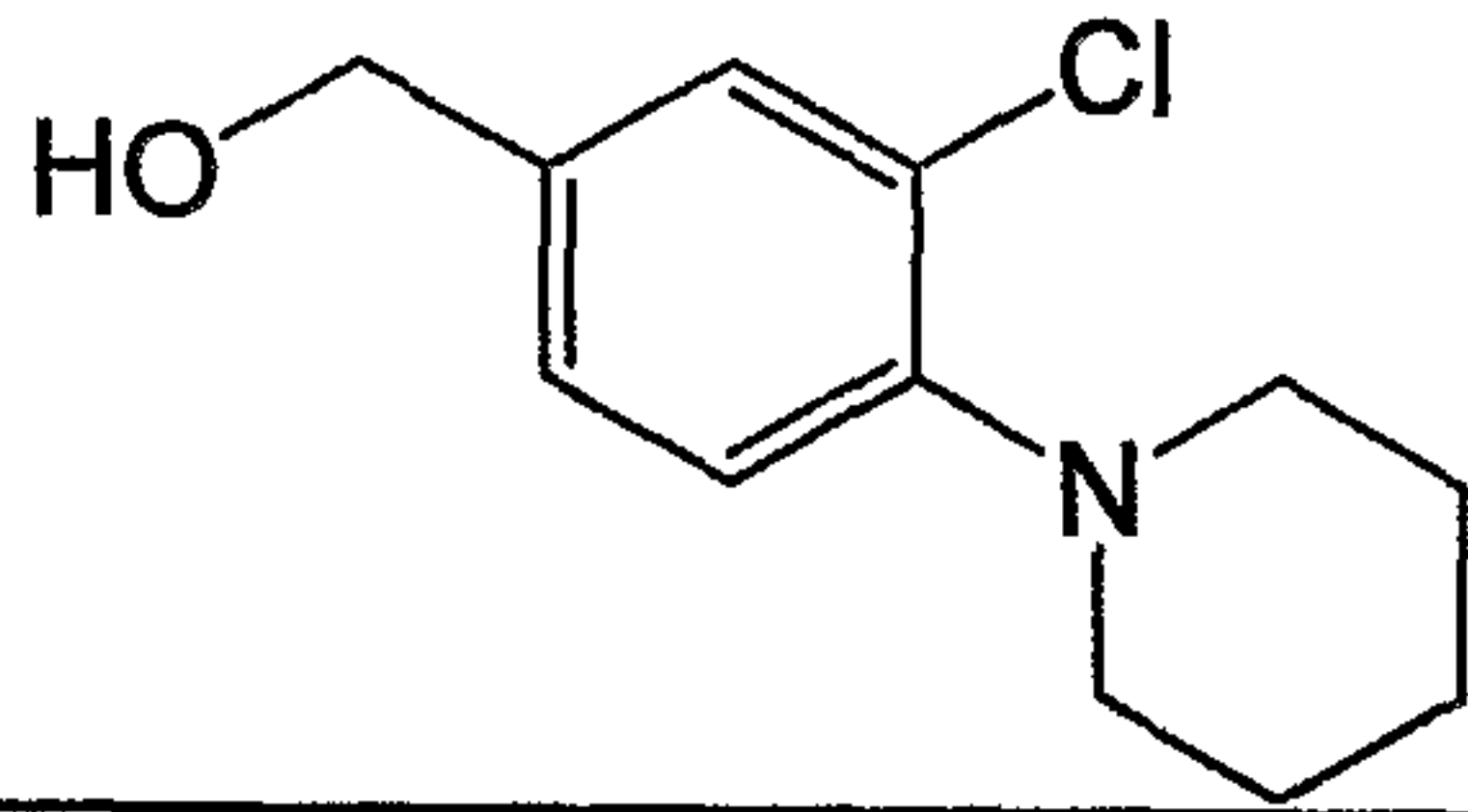
Synthesis of (3-bromo-4-piperidin-1-yl)phenyl methanol

According to the method of Preparation Example 6-1, a title compound (488 mg) was obtained from methyl 3-bromo-4-(piperidin-1-yl)benzoate (546 mg).

[0759]

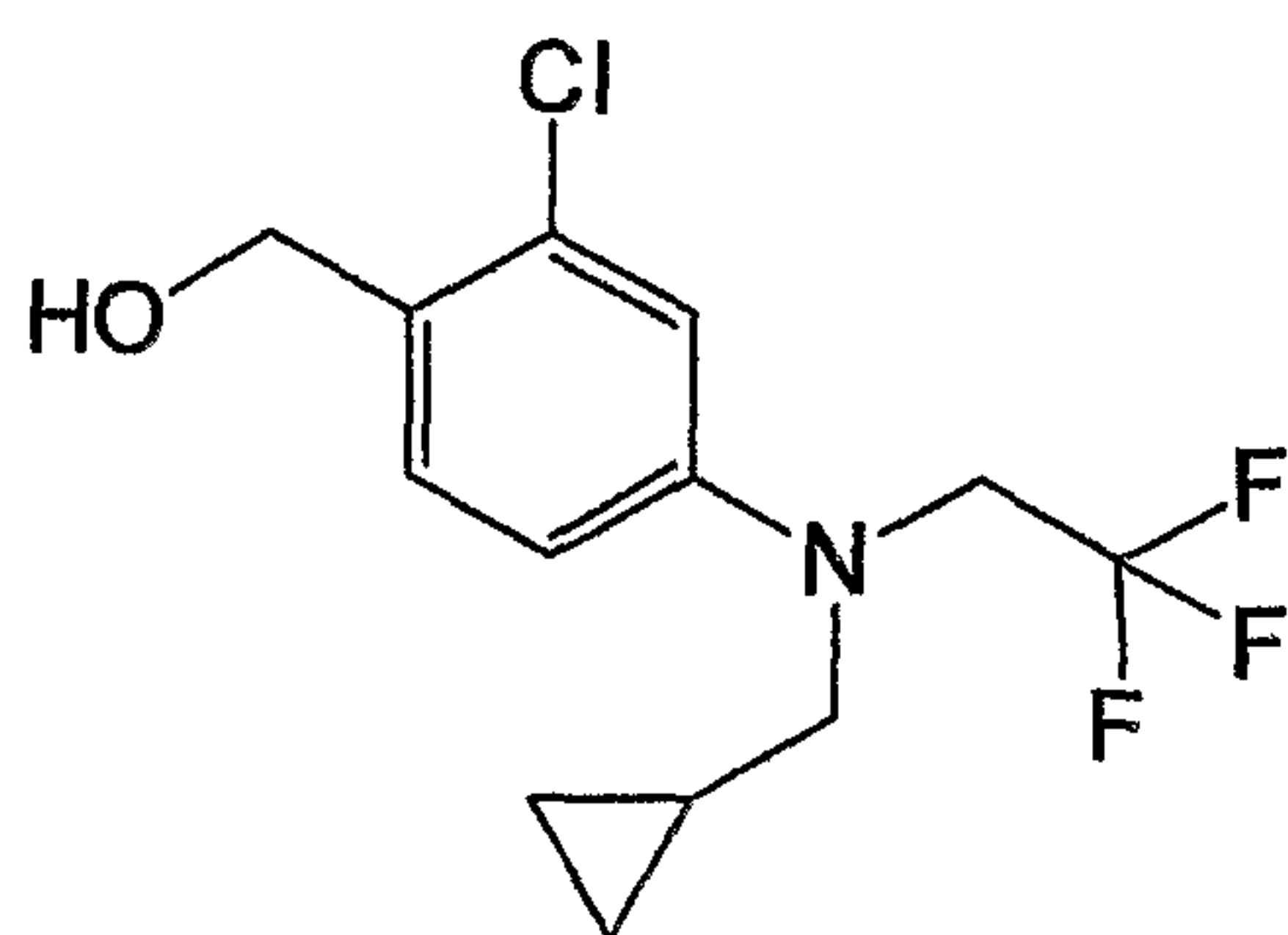
The compounds of Preparation Example 6-21 and Preparation Example 6-22 were obtained according to the method of Preparation Example 6-20 (Table 18).

Table 18

Preparation Example No.	Structural formula
6-21	
6-22	

[0760]

Preparation Example 6-23

Synthesis of {2-chloro-4-[cyclopropyl(2,2,2-trifluoromethyl)amino]phenyl}methanol

[0761]

5 Synthesis of methyl 2-chloro-4-fluorobenzoate

According to the method of Preparation Example 6-1, a title compound (4.37 g) was obtained from 2-chloro-4-fluorobenzoic acid (4.00 g).

[0762]

Synthesis of methyl 2-chloro-4-(cyclopropylmethylamino)benzoate

10 Cyclopropylmethylamine (1.51 g) and potassium carbonate (1.46 g) were added to a solution of methyl 2-chloro-4-fluorobenzoate (1.00 g). The reaction mixture was stirred at room temperature for 6 hours and then heated with stirring at 100°C for 6 hours under a microwave reactor. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The

filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (1.23 g).

ESI-MS; m/z 240 $[M^+ + H]$.

[0763]

5 Synthesis of methyl 2-chloro-4-[cyclopropylmethyl(2,2,2-trifluoroacetyl)amino]benzoate

Trifluoroacetic anhydride (1.18 ml) was added to a solution of methyl 2-chloro-4-(cyclopropylmethylamino)benzoate (1.00 g) and pyridine (686 μ l) in dichloromethane (40 ml).

The reaction mixture was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to

10 obtain the title compound (1.42 g).

[0764]

Synthesis of {2-chloro-4-[cyclopropylmethyl(2,2,2-trifluoroethyl)amino]phenyl}methanol

Borane-THF complex (1.0M solution in THF, 13.7 ml) was added under ice-cooling to a solution of methyl 2-chloro-4-[cyclopropylmethyl(2,2,2-

15 trifluoroacetyl)amino]benzoate (500 mg) in dichloromethane (10 ml). The reaction mixture was then refluxed overnight. After cooling to room temperature, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate.

The filtrate was concentrated under reduced pressure and the residue was purified by silica gel
20 column chromatography to obtain the title compound (257 mg).

ESI-MS; m/z 294 $[M^+ + H]$.

[0765]

The compound of Preparation Example 6-24 was obtained according to the method of Preparation Example 6-23 (Table 19).

Table 19

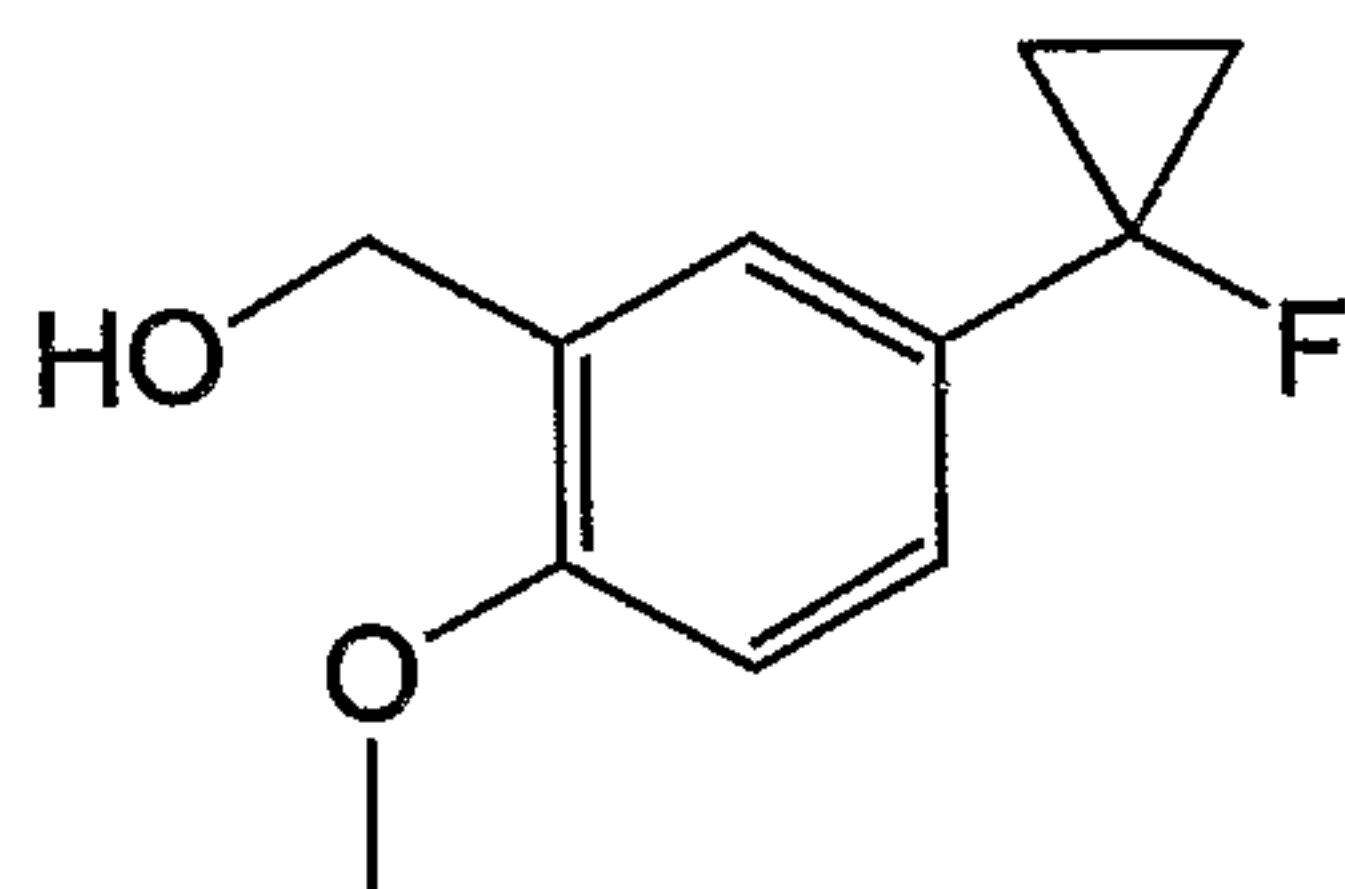
Preparation Example No.	Structural formula
6-24	

[0766]

Preparation Example 6-25

Synthesis of [5-(1-fluorocyclopropyl)-2-methoxyphenyl]methanol

[0767]



5 [0768]

Synthesis of 1-(3-bromo-4-methoxyphenyl)cyclopropanol

Ethylmagnesium bromide (3M solution in diethyl ether, 54.4 ml) was added at room temperature to a solution of methyl 3-bromo-4-methoxybenzoate (CAS No. 35450-37-4, 10 g) and titanium (IV) isopropoxide (23.9 ml) in THF (100 ml). The reaction mixture was stirred at room temperature overnight. Ethyl acetate and water were added to the reaction mixture and the precipitate was removed through Celite. The organic layer was separated, washed with brine and dried over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (7.77 g).

15 [0769]

Synthesis of [1-(3-bromo-4-methoxyphenyl)cyclopropyloxy]trimethylsilane

Trimethylsilyl chloride (6.54 ml) was added to a solution of 1-(3-bromo-4-methoxyphenyl)cyclopropanol (5.0 g) and triethylamine (8.61 ml) in THF (100 ml). The reaction mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (3.84 g).

[0770]

25 Synthesis of 2-bromo-4-(1-fluorocyclopropyl)-1-methoxybenzene

Diethylaminosulfur trifluoride (2.4 ml) was added to a solution of [1-(3-bromo-4-methoxyphenyl)cyclopropyloxy]trimethylsilane (3.84 g) in dichloromethane (68 ml). The reaction mixture was stirred at room temperature for 2.5 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried

over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (1.88 g).

[0771]

5 Synthesis of 5-(1-fluorocyclopropyl)-2-methoxybenzaldehyde

n-Butyllithium (2.7M solution in hexane, 3.42 ml) was added at -78°C to a solution of 2-bromo-4-(1-fluorocyclopropyl)-1-methoxybenzene (1.88 g) in THF (62 ml), followed by addition of a solution of DMF (650 μl) in THF. After the reaction mixture was stirred at -78°C for 30 minutes, a saturated aqueous solution of sodium bicarbonate was added to the reaction mixture and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (1.00 g).

[0772]

15 Synthesis of [5-(1-fluorocyclopropyl)-2-methoxyphenyl]methanol

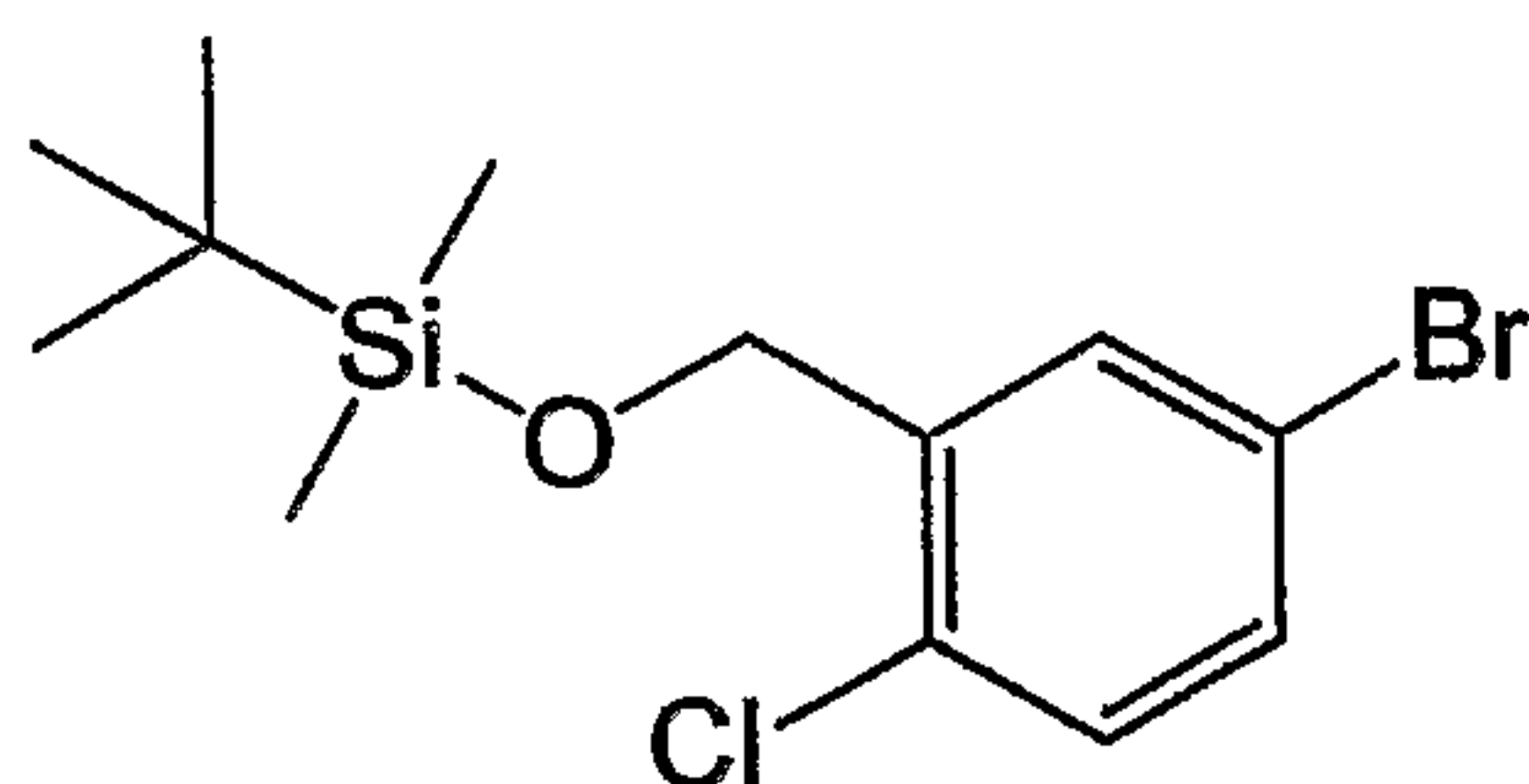
Sodium borohydride (194 mg) was added under ice-cooling to a solution of 5-(1-fluorocyclopropyl)-2-methoxybenzaldehyde (500 mg) in methanol (10 ml). After the reaction mixture was stirred at room temperature for 2 hours, a saturated aqueous solution of sodium bicarbonate was added to the reaction mixture and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (400 mg).

[0773]

Preparation Example 7-1

25 Synthesis of (5-bromo-2-chlorobenzyloxy)-tert-butyldimethylsilane

[0774]



[0775]

Synthesis of methyl 5-bromo-2-chlorobenzoate

According to the method of Preparation Example 6-1, a title compound (9.23 g)

was obtained from 5-bromo-2-chlorobenzoic acid (10.0 g).

[0776]

Synthesis of (5-bromo-2-chlorophenyl)methanol

A solution of methyl 5-bromo-2-chlorobenzoate (9.23 g) in THF (50 ml) was
5 added dropwise under ice-cooling to a suspension of lithium aluminum hydride (1.42 g) in THF
(100 ml). After the completion of addition, the reaction mixture was stirred at room temperature
for 45 minutes. Water (1.4 ml), 5N sodium hydroxide solution (1.4 ml) and water (4.2 ml) were
sequentially added under ice-cooling to the reaction mixture. The precipitate was removed
through Celite and the filtrate was concentrated under reduced pressure to obtain a title
10 compound (7.56 g).

[0777]

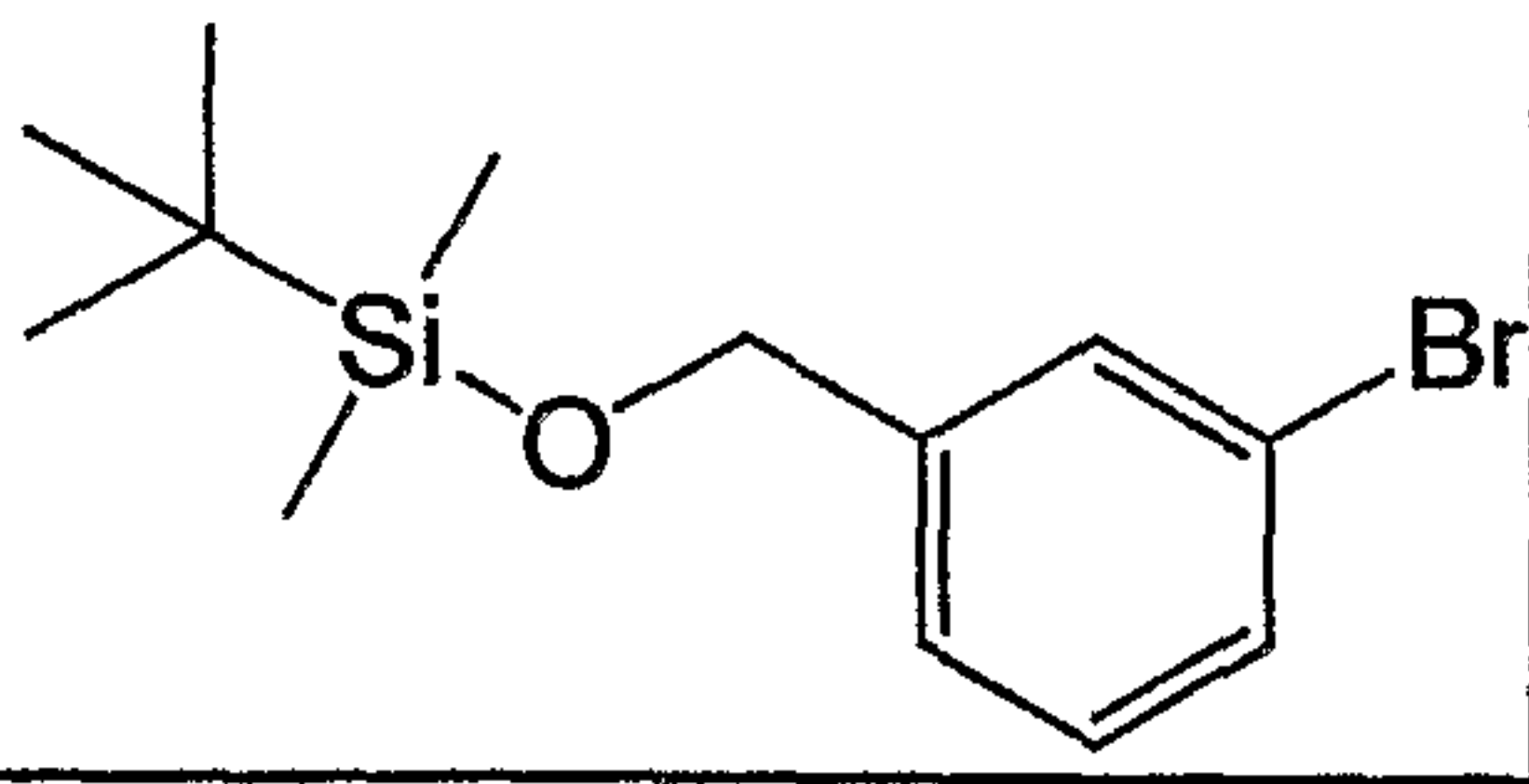
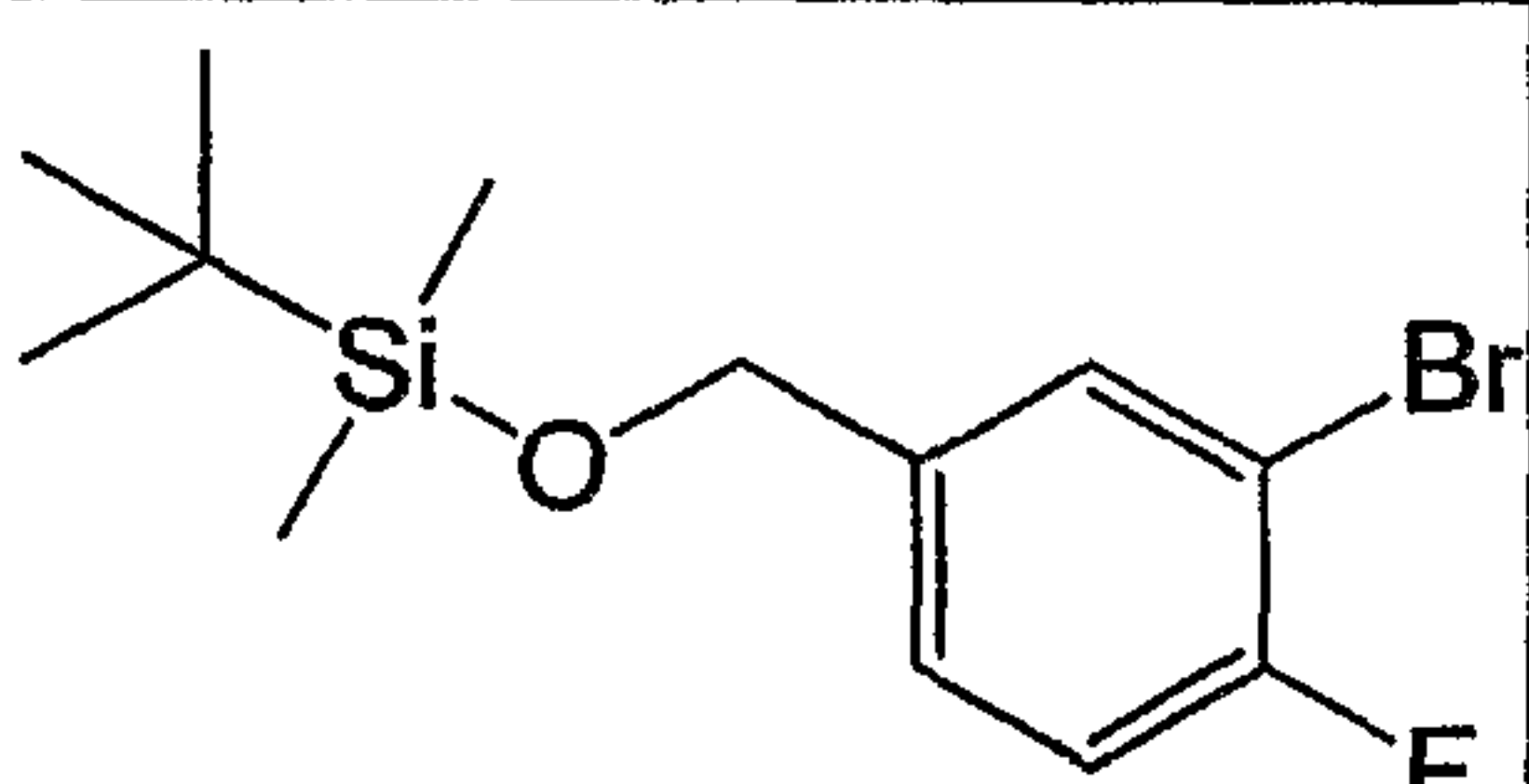
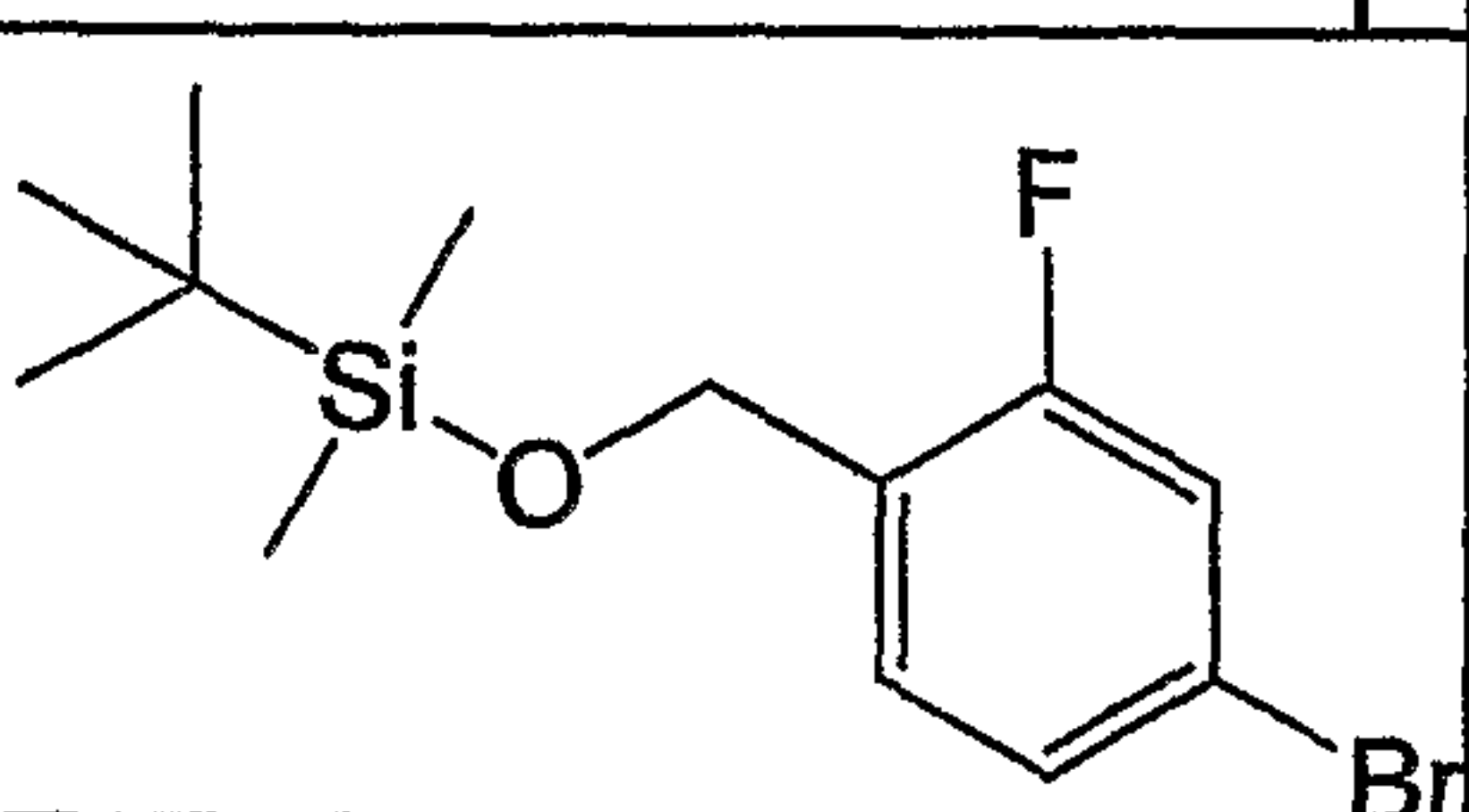
Synthesis of (5-bromo-2-chlorobenzyloxy)-tert-butyldimethylsilane

Imidazole (5.22 g) and tert-butyldimethylsilyl chloride (8.64 g) were added to a
solution of (5-bromo-2-chlorophenyl)methanol (8.47 g) in DMF (80 ml). The reaction mixture
15 was stirred at room temperature overnight. The mixture was diluted with ethyl acetate and
washed twice with water. The aqueous layer was again extracted with ethyl acetate. The
combined organic layer was washed with brine and dried over anhydrous magnesium sulfate.
The filtrate was concentrated under reduced pressure and the residue was purified by silica gel
column chromatography to obtain the title compound (12.6 g).

20 [0778]

The compounds of Preparation Examples 7-2 to 7-4 were obtained according to the method of
Preparation Example 7-1 (Table 20).

Table 20

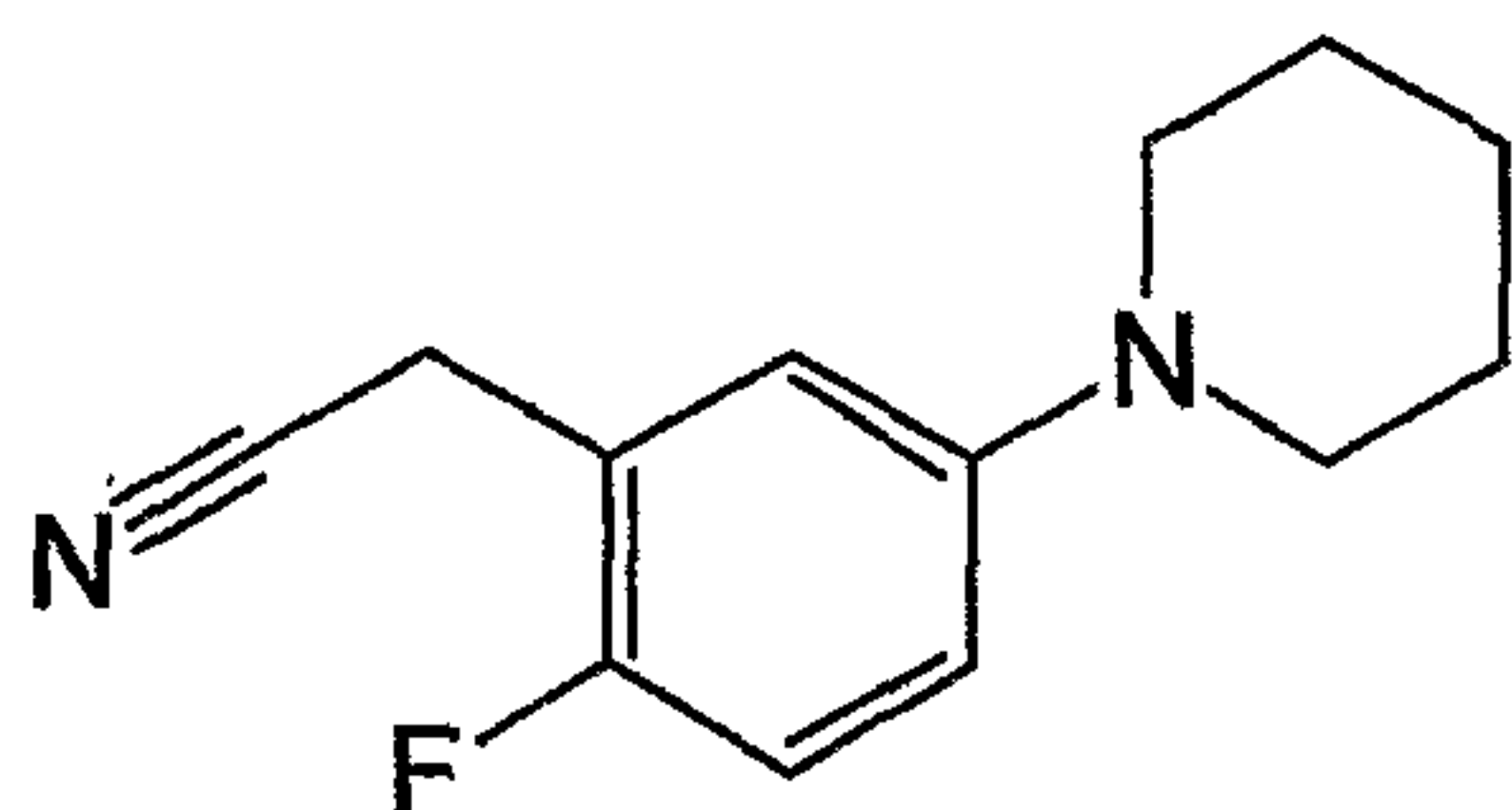
Preparation Example No.	Structural formula
7-2	
7-3	
7-4	

[0779]

Preparation Example 8-1

Synthesis of [(2-fluoro-5-piperidin-1-yl)phenyl]acetonitrile

[0780]



5 [0781]

Thionyl chloride (1.05 ml) was added dropwise to a solution of (2-fluoro-5-piperidin-1-yl)phenylmethanol (1.0 g) obtained in Preparation Example 6-1 in toluene (10 ml). The reaction mixture was stirred at room temperature for 8.5 hours. The reaction mixture was diluted with tert-butyl methyl ether and washed with 1N sodium hydroxide solution and saturated aqueous solution of sodium bicarbonate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and then the filtrate was concentrated under reduced pressure. Potassium cyanide (623 mg) was added to a solution of the obtained residue in DMF

(10 ml). After stirring at room temperature for 12 hours, tert-butyl methyl ether and water were added to the reaction mixture. The organic layer was separated, washed with water and brine, and dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound

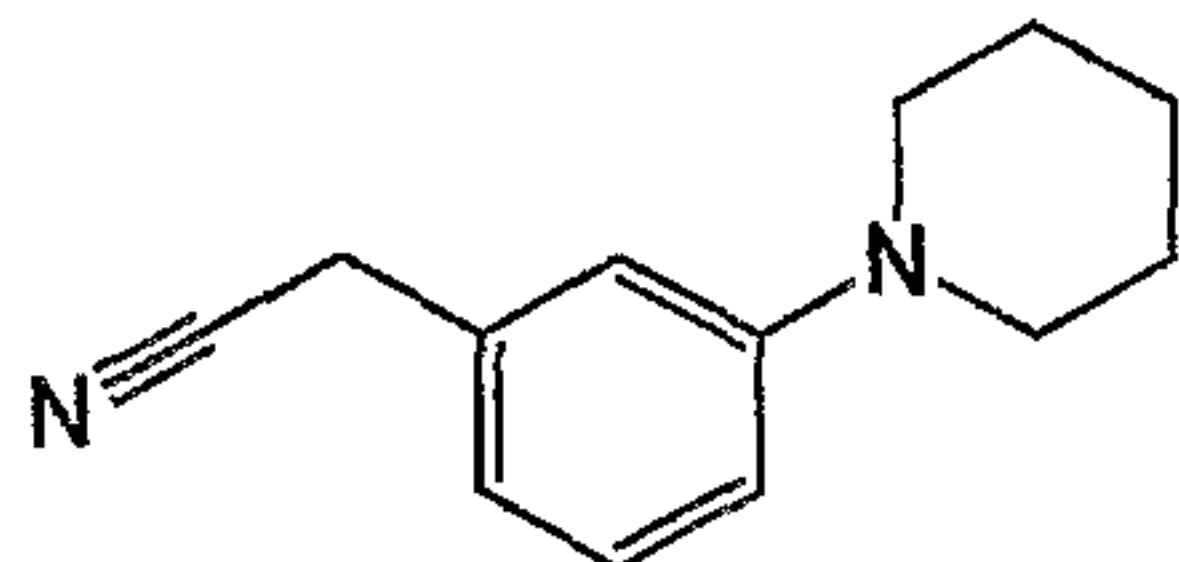
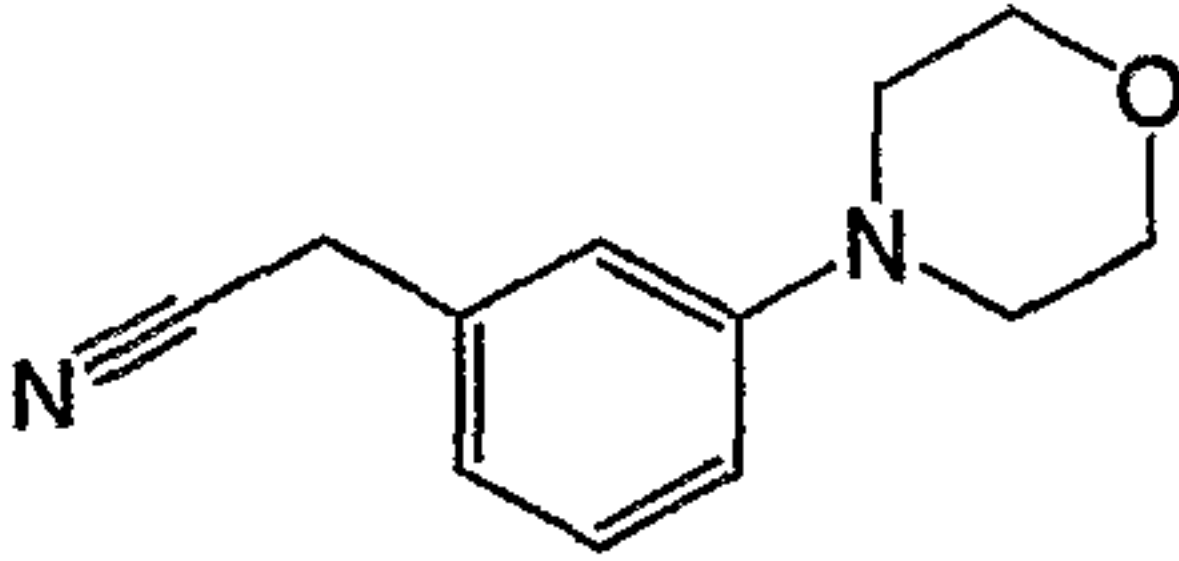
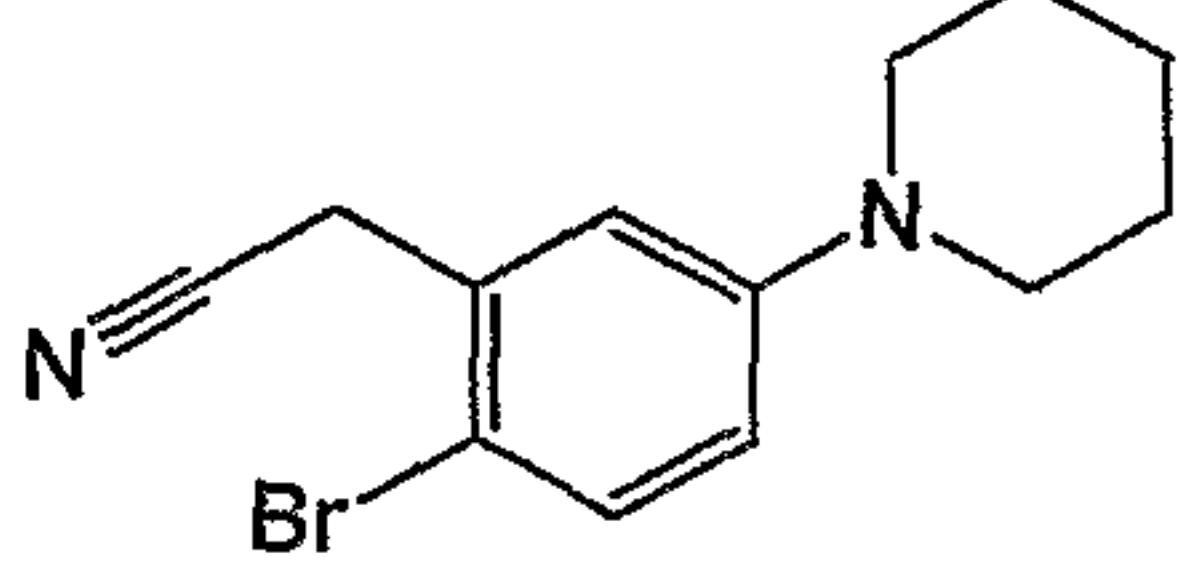
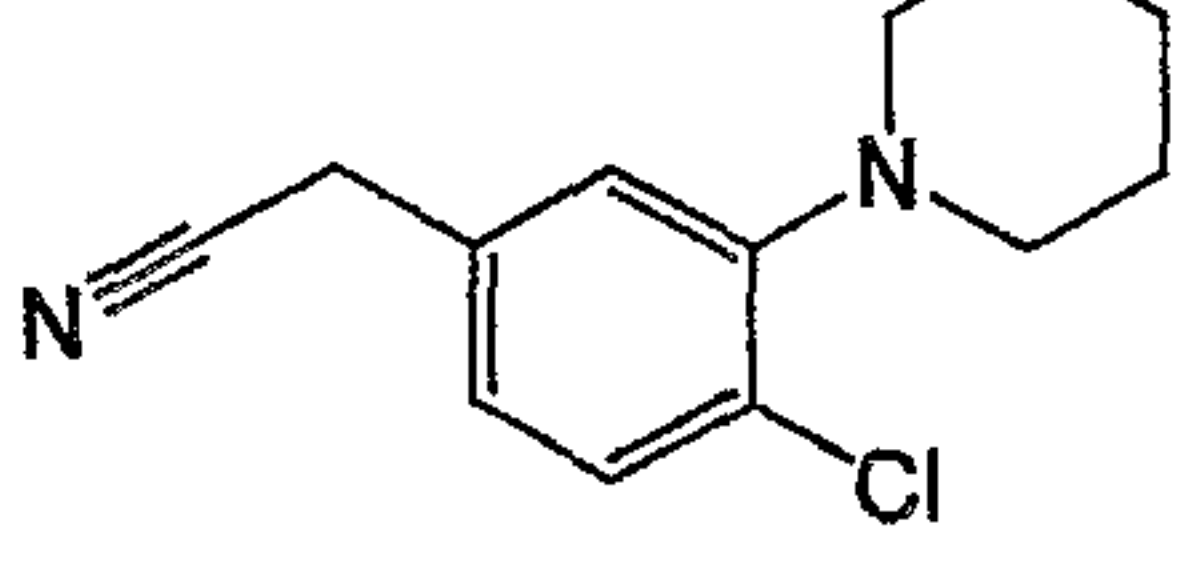
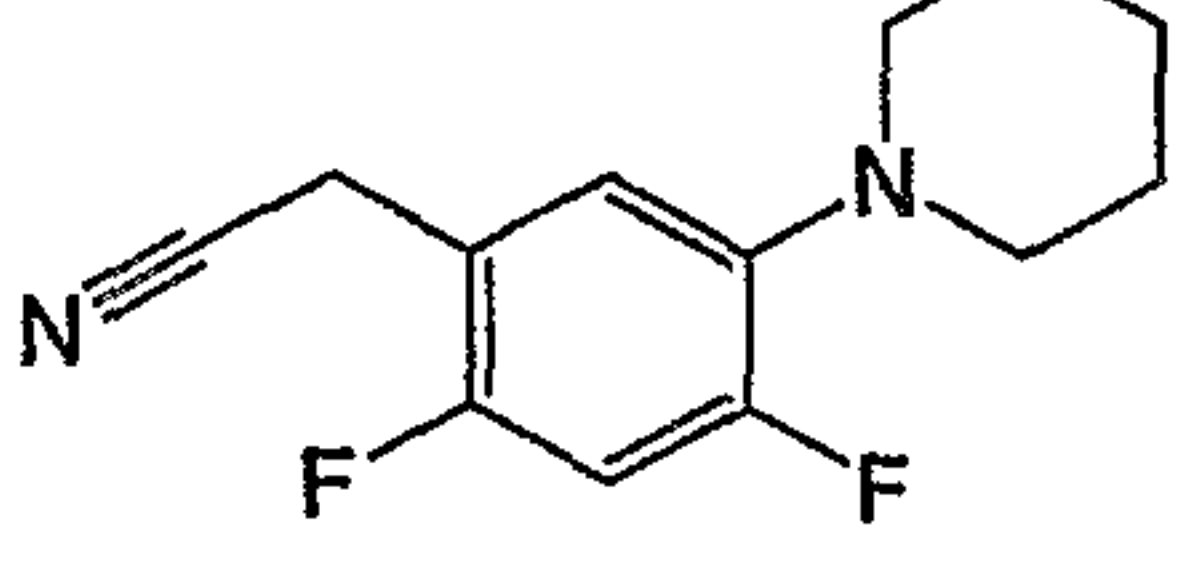
5 (908 mg).

ESI-MS;m/z 219 [M⁺+H].

[0782]

The compounds of Preparation Examples 8-2 to 8-19 were obtained according to the method of Preparation Example 8-1 (Table 21).

Table 21

Preparation Example No.	Structural formula
8-2	
8-3	
8-4	
8-5	
8-6	

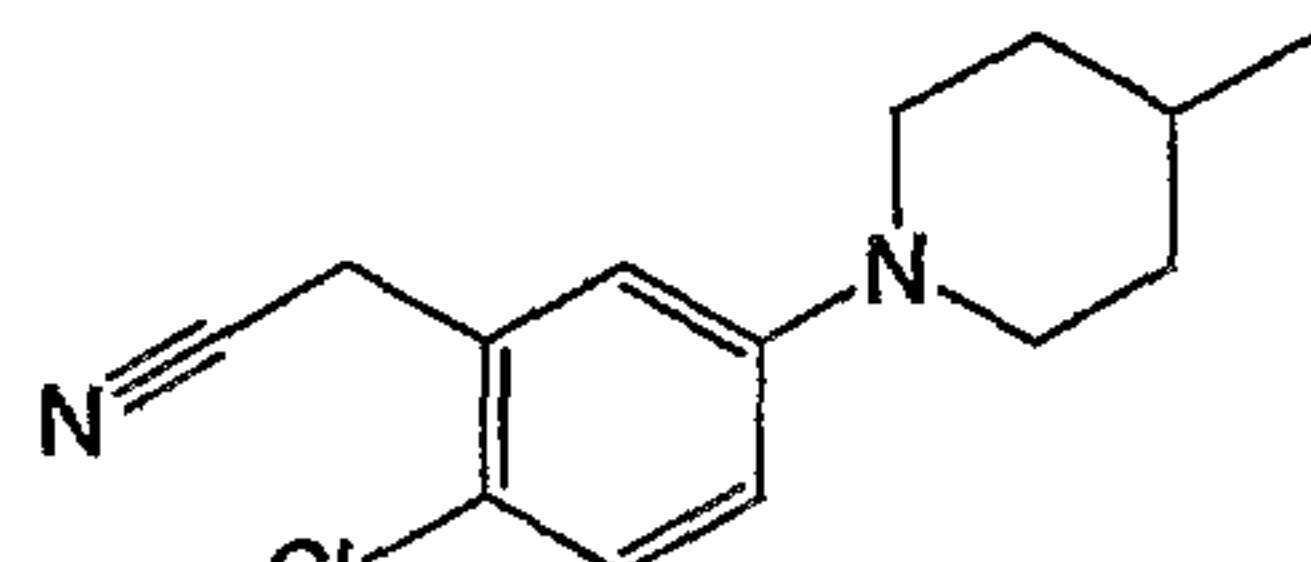
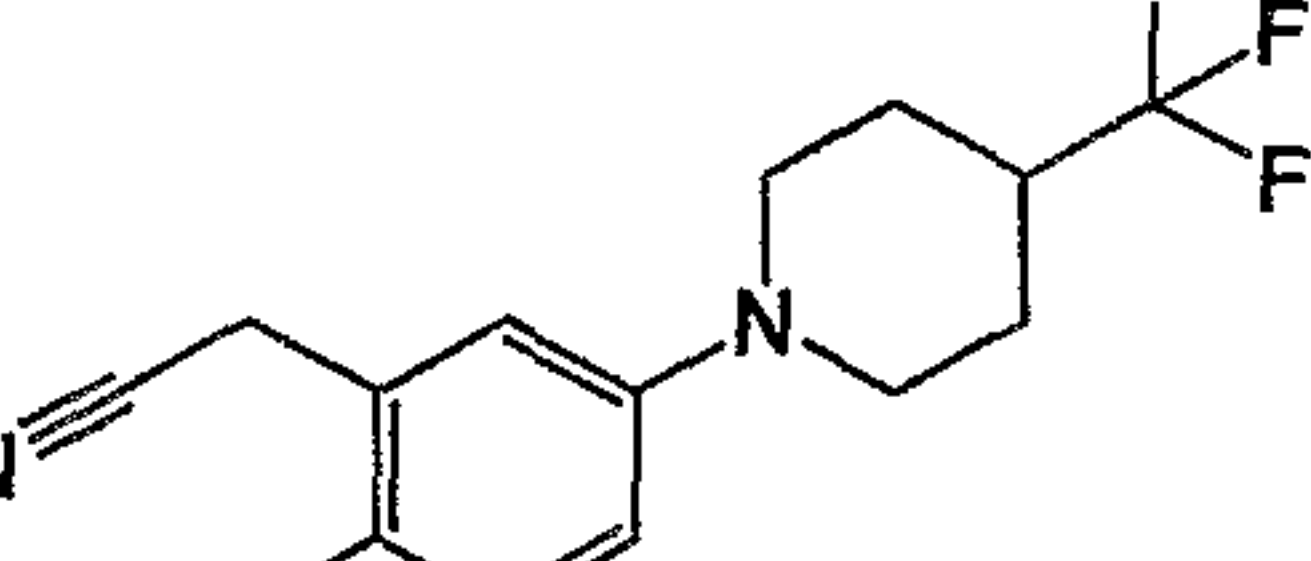
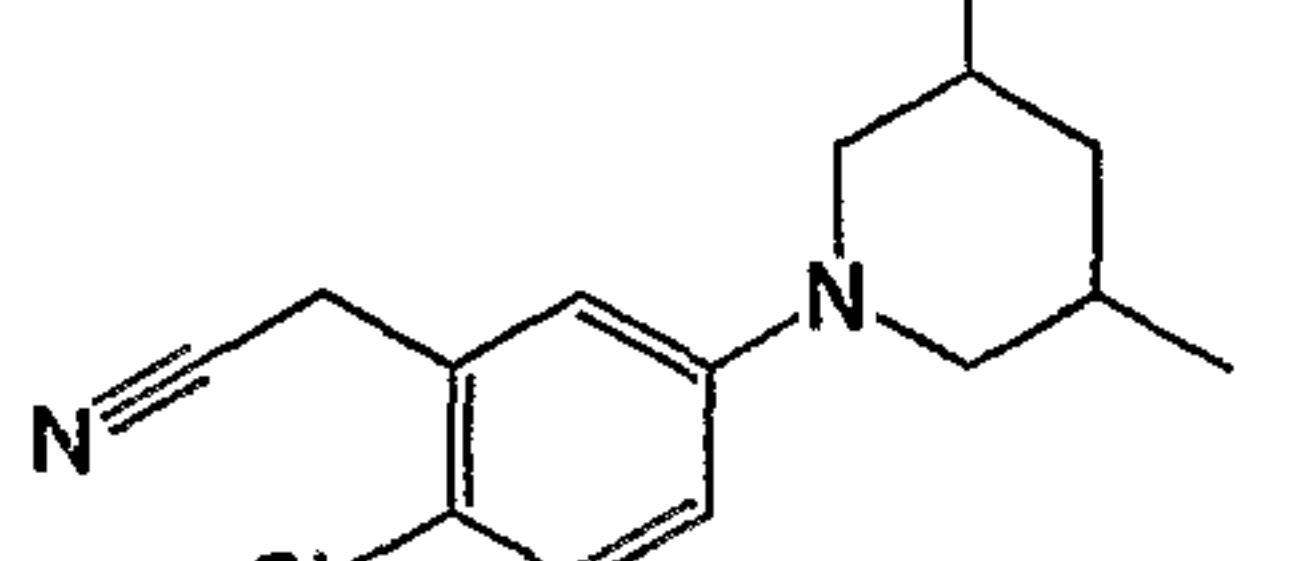
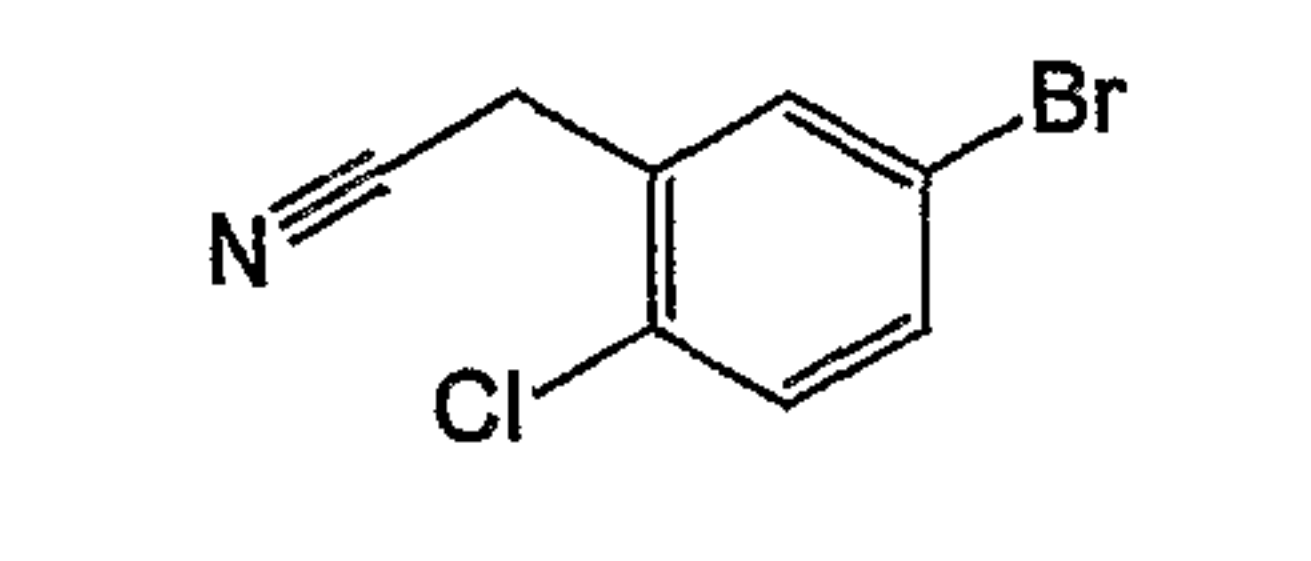
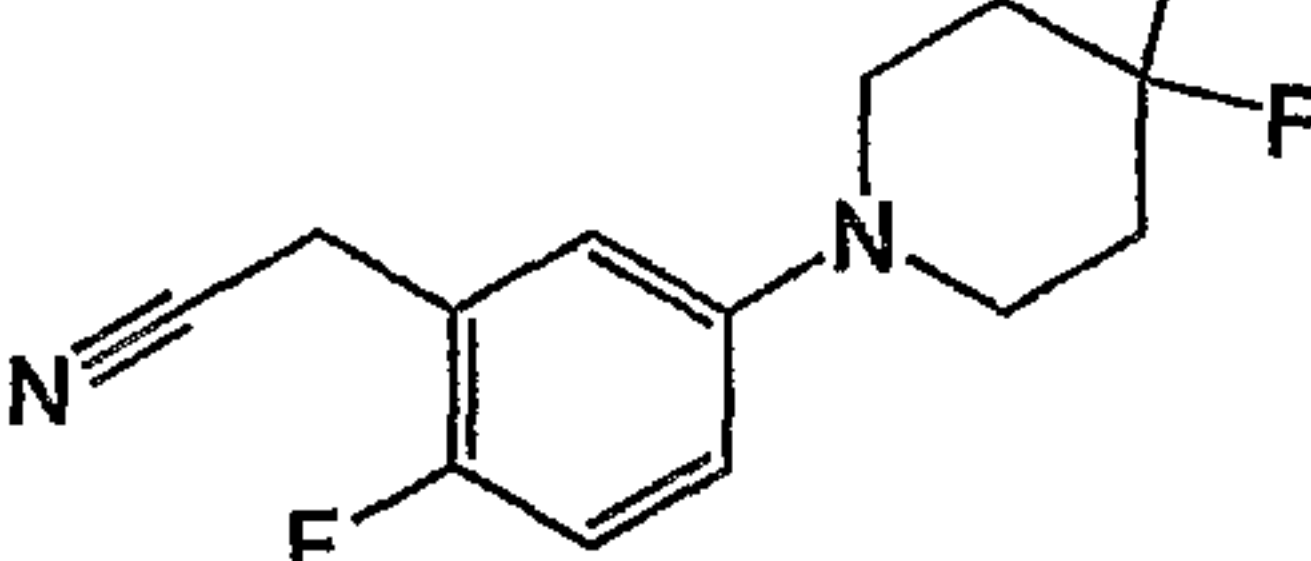
Preparation Example No.	Structural formula
8-11	
8-12	
8-13	
8-14	
8-15	

Table 21 (Continued)

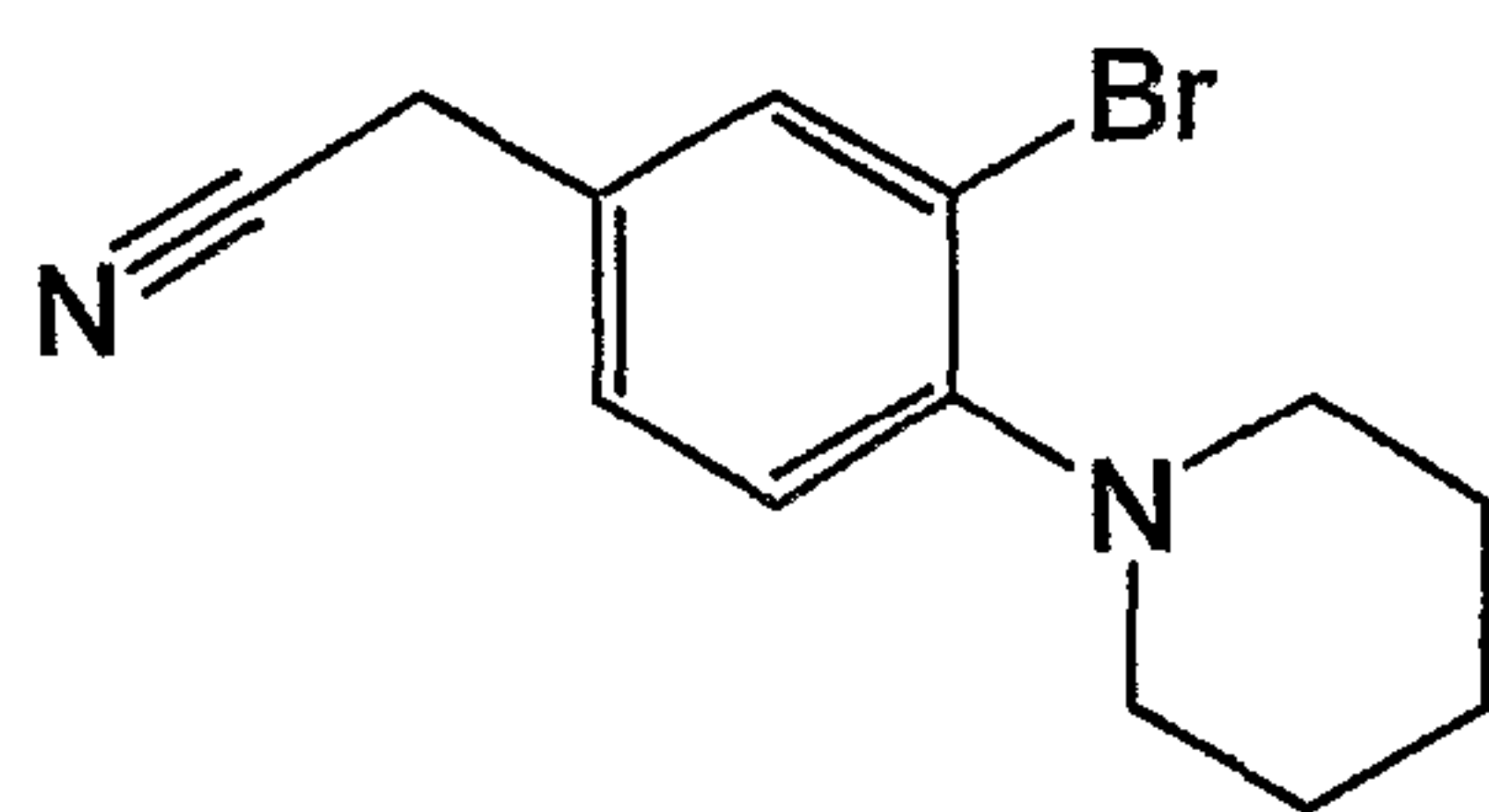
8-7	
8-8	
8-9	
8-10	
8-16	
8-17	
8-18	
8-19	

[0783]

Preparation Example 8-20

Synthesis of (3-bromo-4-piperidin-1-yl)phenylacetonitrile

[0784]



5 [0785]

Synthesis of (3-bromo-4-piperidin-1-yl)benzaldehyde

Manganese dioxide (1.26 g) was added to a solution of (3-bromo-4-piperidin-1-yl)phenylmethanol (488 mg) obtained in Preparation Example 6-20 in chloroform (20 ml). The reaction mixture was heated with stirring at 90 °C for 2 hours. The reaction mixture was filtered by filter paper, then through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (386 mg).

[0786]

Synthesis of [(3-bromo-4-piperidin-1-yl)phenyl]acetonitrile

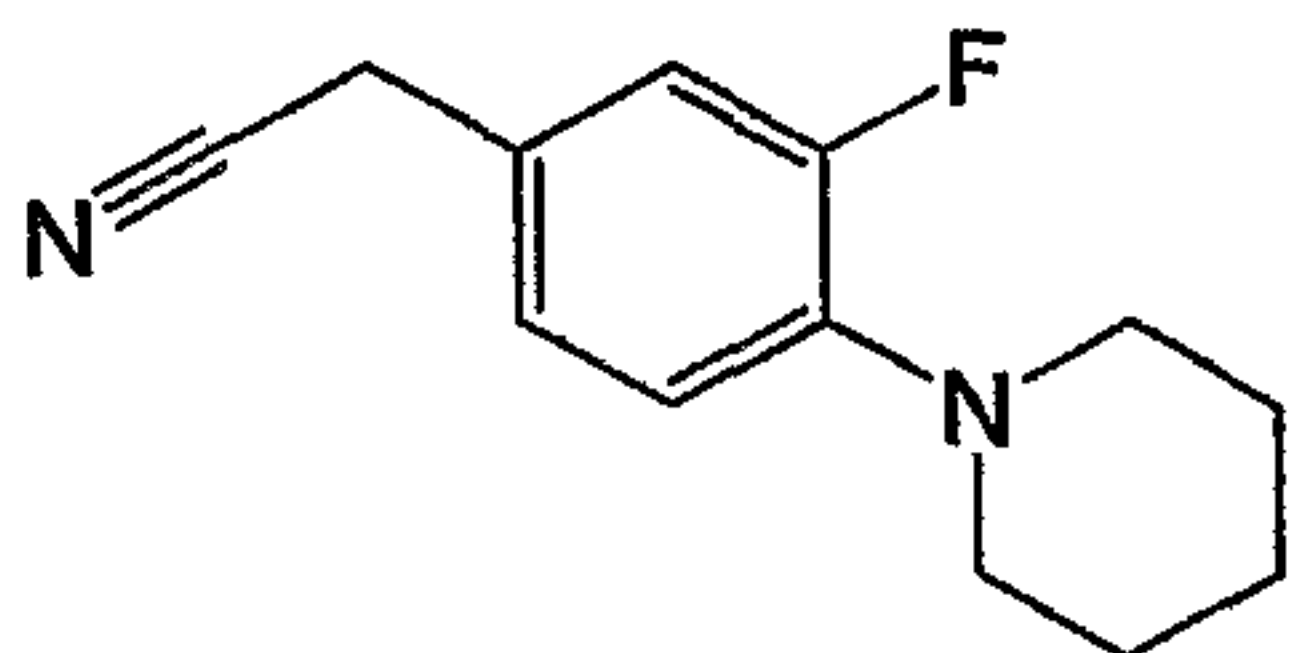
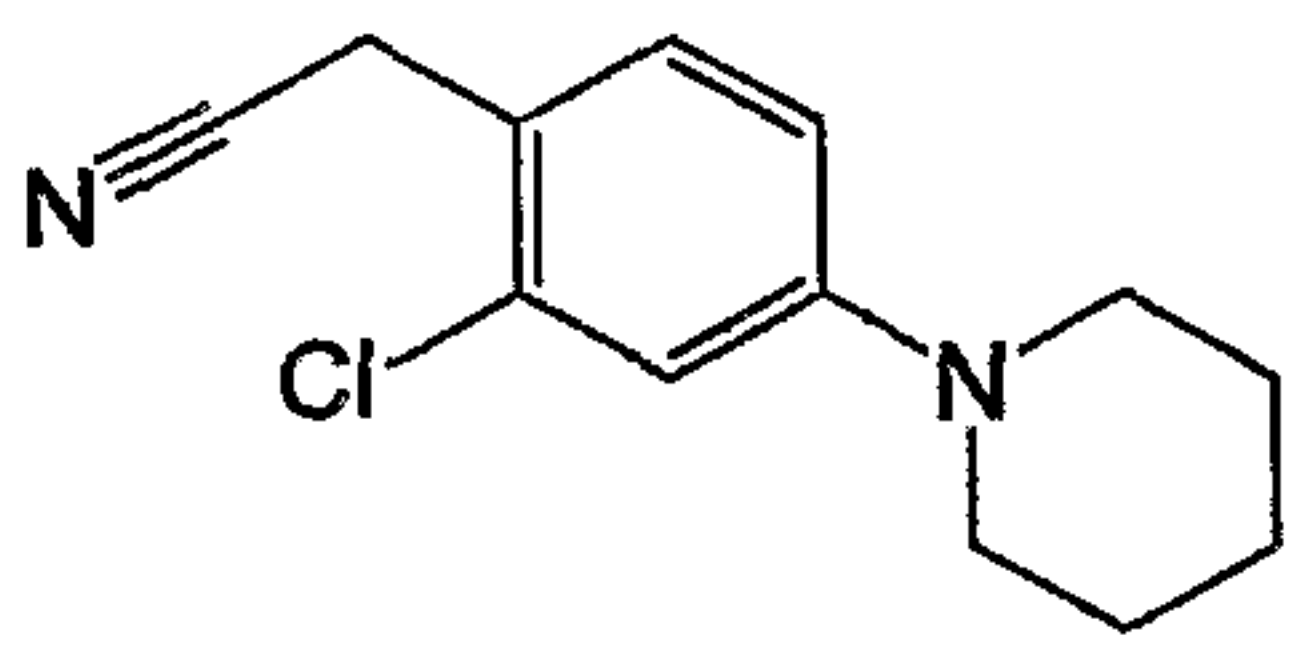
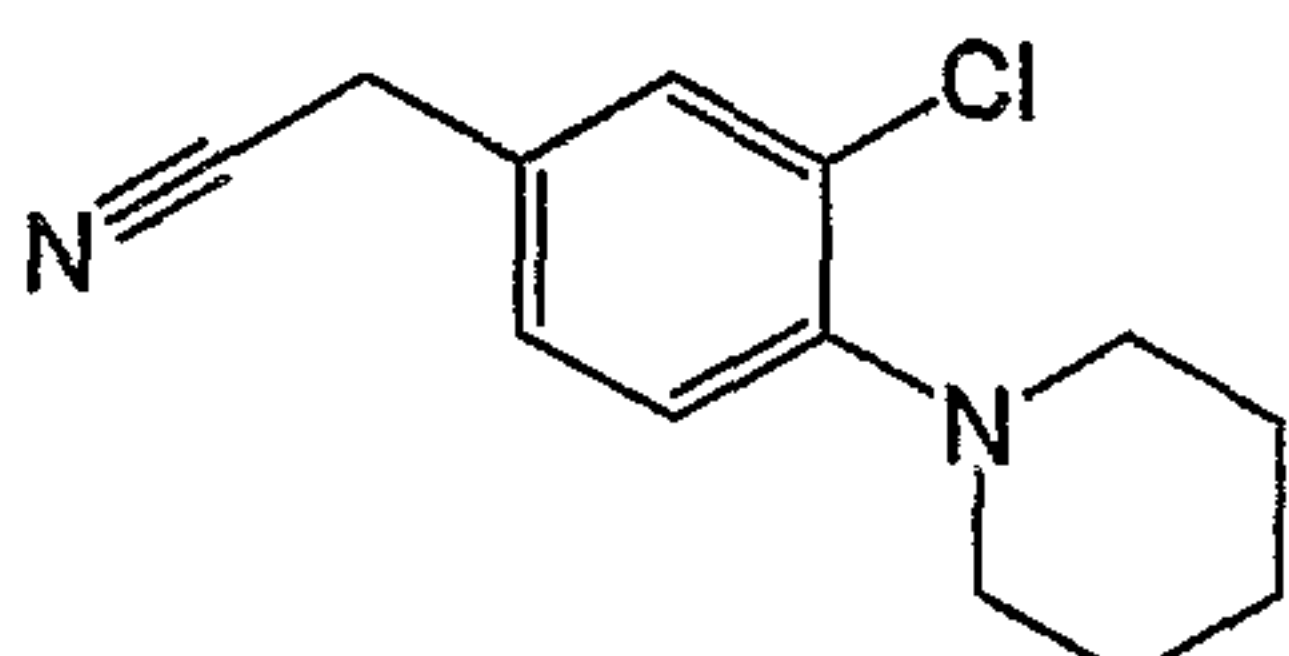
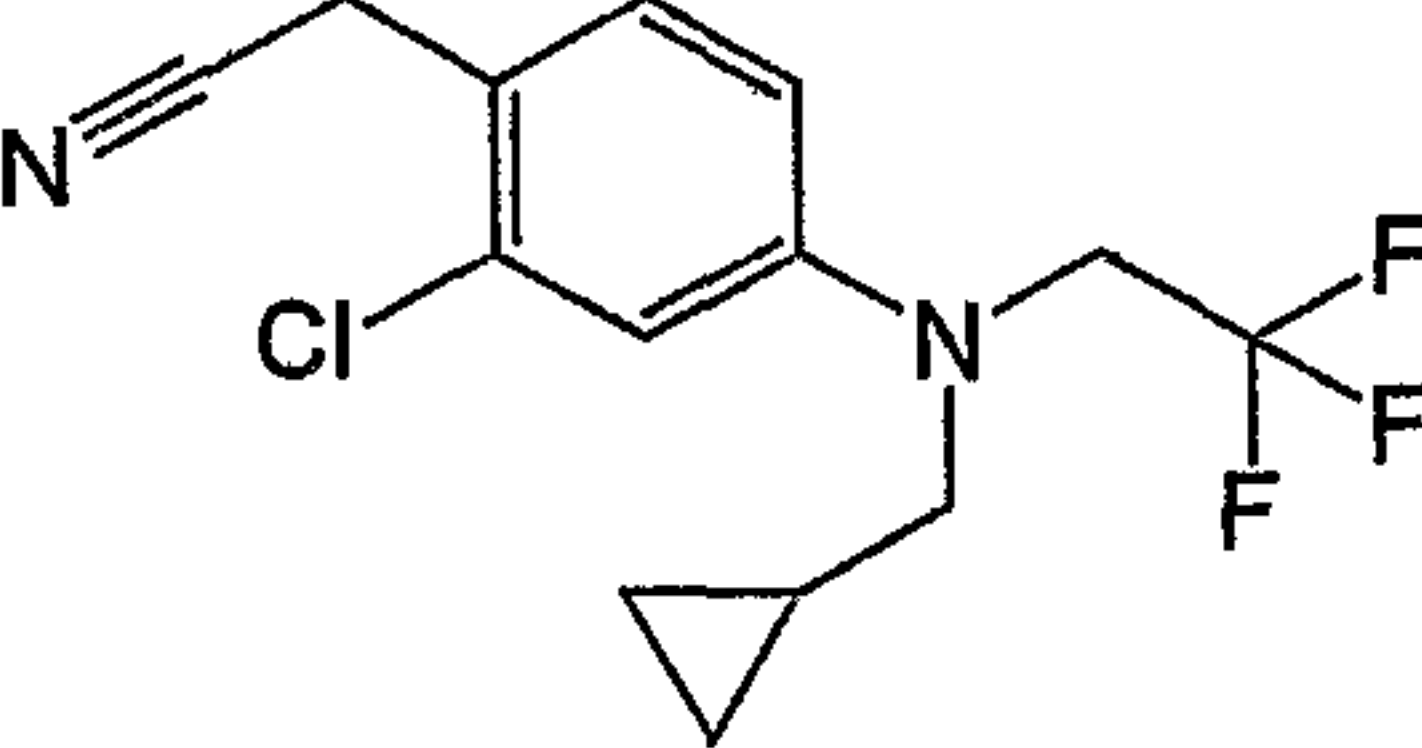
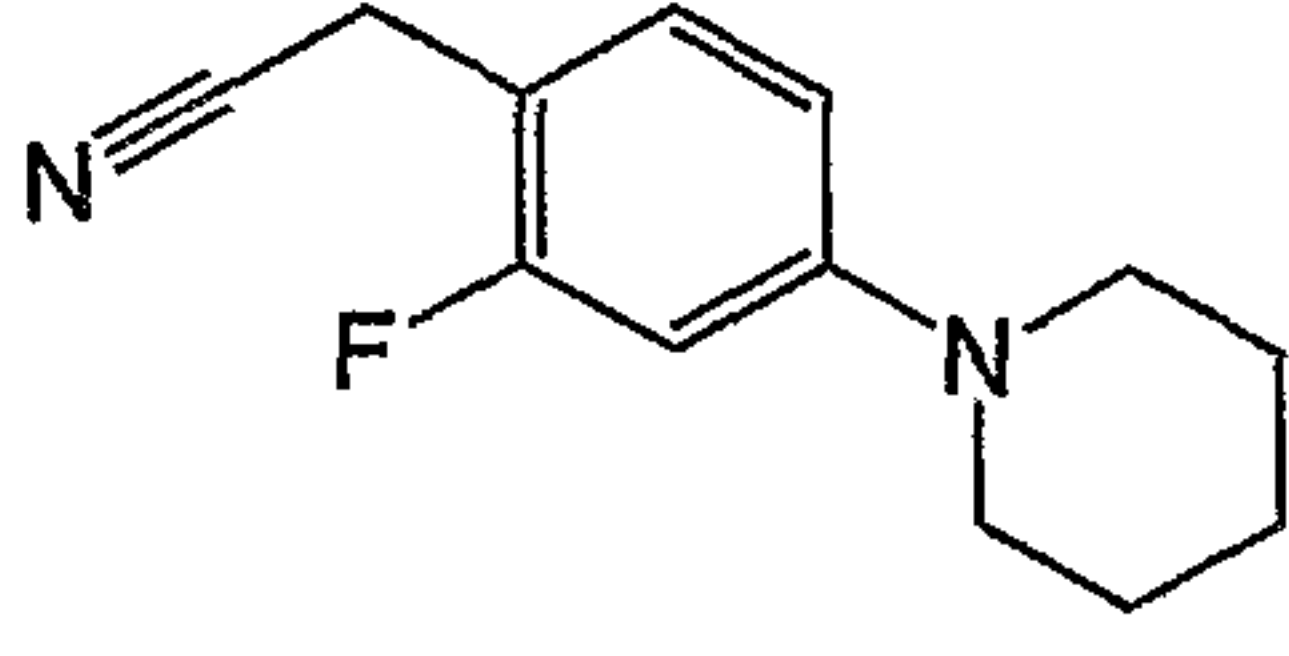
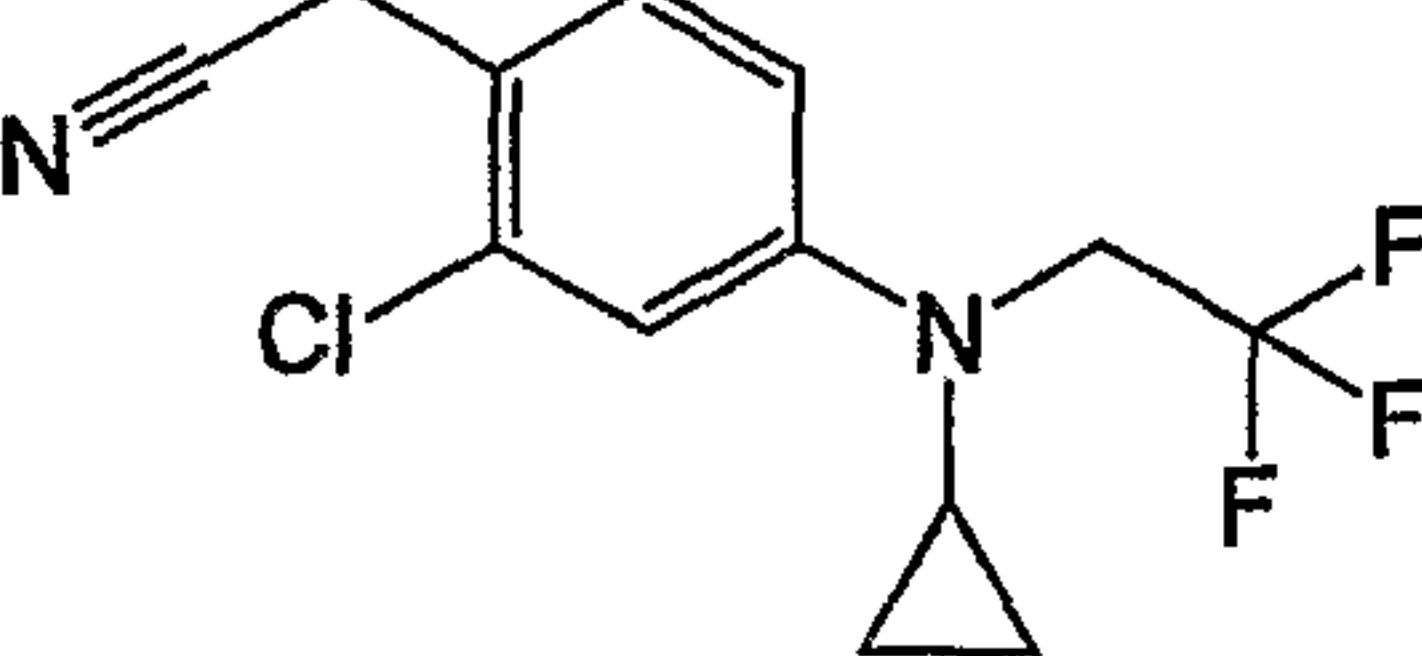
A solution of p-toluenesulfonyl isocyanide (309 ml) in 1,2-dimethoxyethane (8 ml) was added to a suspension of potassium tert-butoxide (355 mg) in 1,2-dimethoxyethane (8 ml) at -30 °C. After stirring for 10 minutes, a solution of (3-bromo-4-piperidin-1-yl)benzaldehyde (386 mg) in 1,2-dimethoxyethane (8 ml) was added to the mixture. The mixture was stirred at -30 °C for 1.5 hours. Ethanol (5 ml) was added to the reaction mixture and the mixture was refluxed for 20 minutes. The mixture was cooled to room temperature, followed by addition of water and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to obtain the title compound (255 mg).

ESI-MS; m/z 279, 281 [M⁺+H].

[0787]

The compounds of Preparation Examples 8-21 to 8-26 were obtained according to the method of Preparation Example 8-20 (Table 22).

Table 22

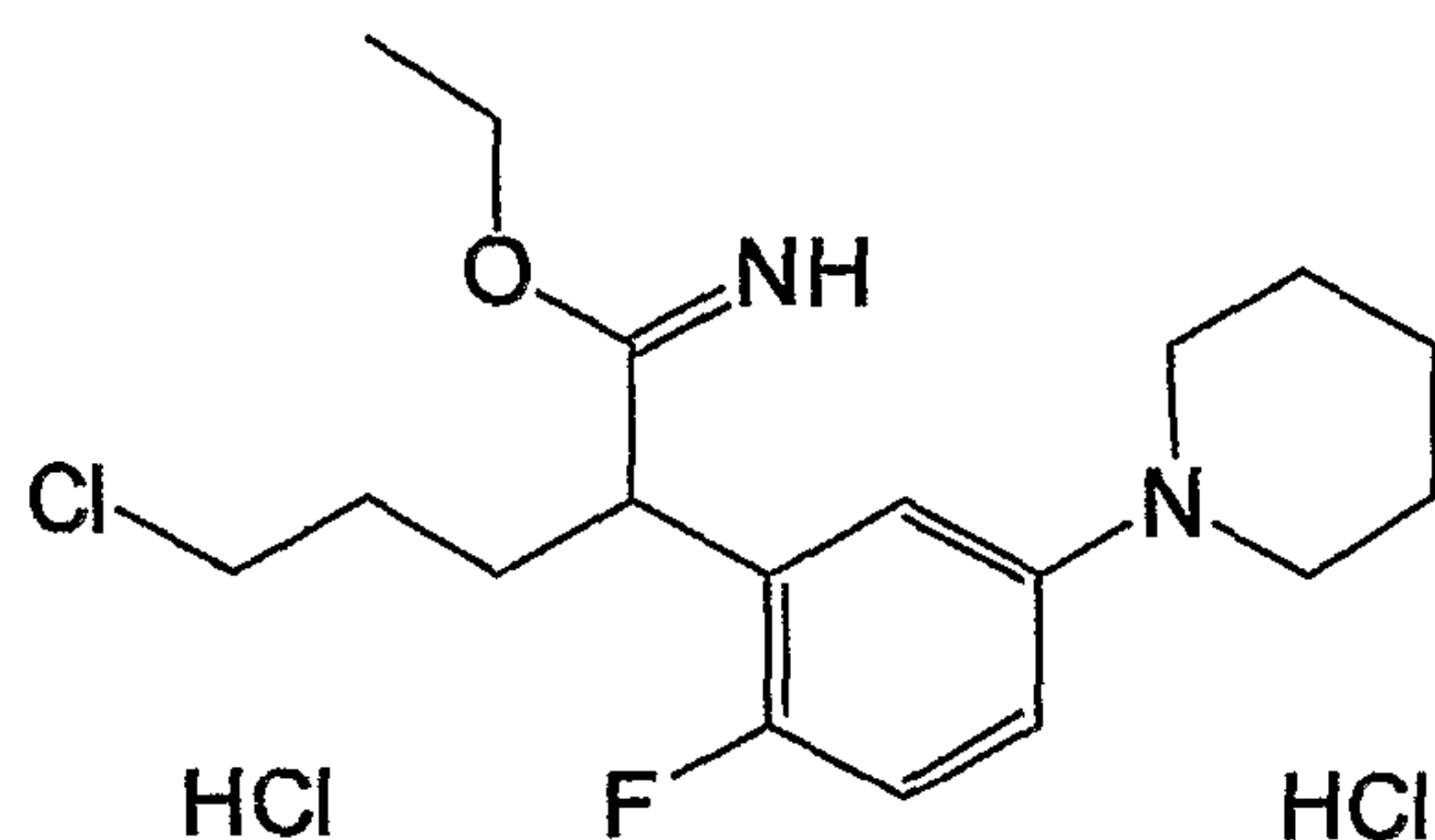
Preparation Example No.	Structural formula	Preparation Example No.	Structural formula
8-21		8-24	
8-22		8-25	
8-23		8-26	

[0788]

Preparation Example 3-51

Synthesis of ethyl [5-chloro-2-(2-fluoro-5-piperidin-1-yl)phenyl]pentaneimideate hydrochloride

[0789]



5 [0790]

Synthesis of ethyl [5-chloro-2-(2-fluoro-5-piperidin-1-yl)phenyl]pentaneimideate hydrochloride

According to the method of Preparation Example 3-1, a title compound (1.54 g) was obtained from [(2-fluoro-5-piperidin-1-yl)phenyl]acetonitrile (908 mg) obtained in Preparation Example 8-1.

10 [0791]

The compounds of Preparation Examples 3-52 to 3-84 were obtained according to the method of Preparation Example 3-51 (Table 23).

Table 23

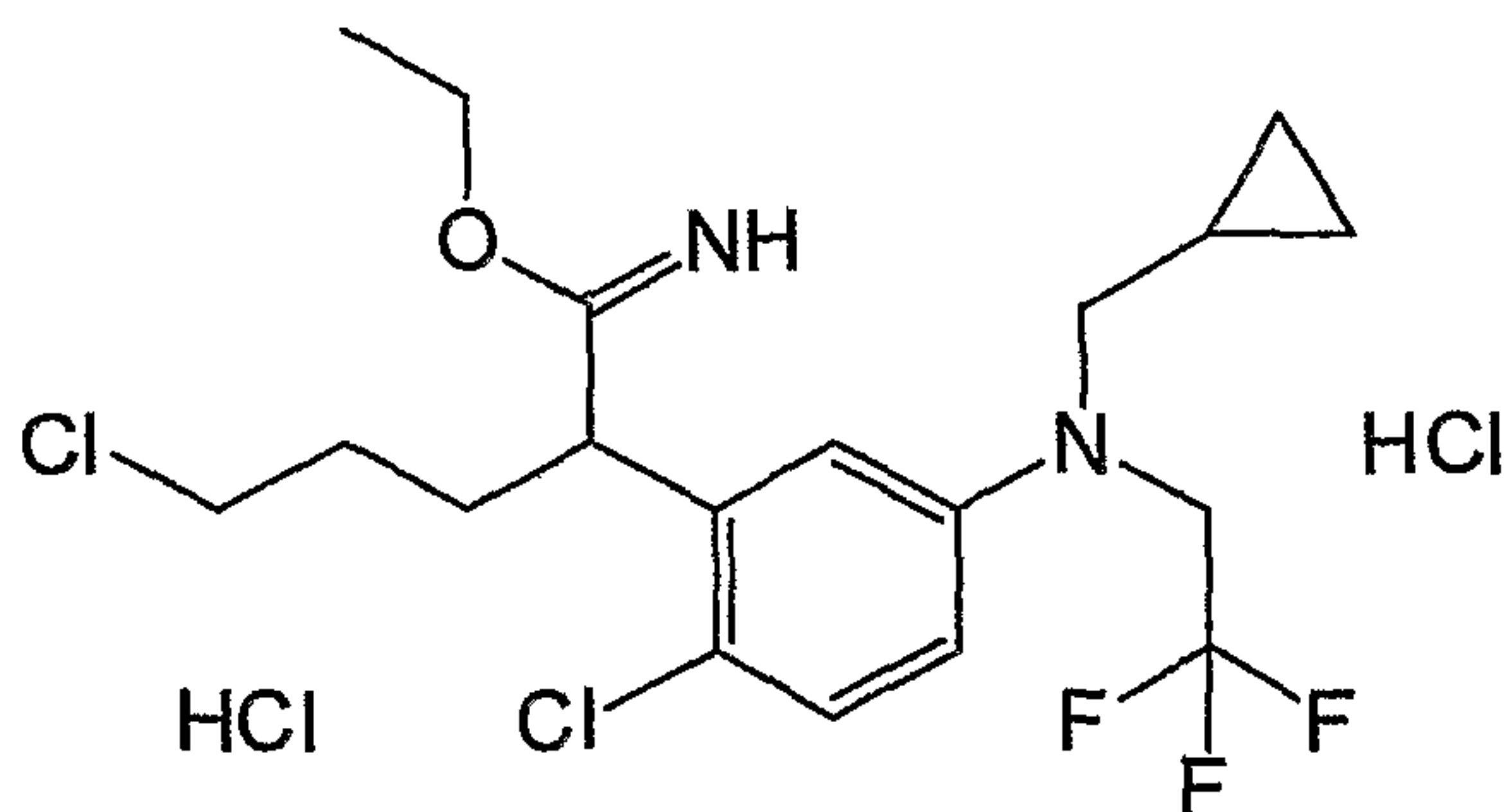
Preparation Example No.	Structural formula	Preparation Example No.	Structural formula	Preparation Example No.	Structural formula
3-52		3-63		3-74	
3-53		3-64		3-75	
3-54		3-65		3-76	
3-55		3-66		3-77	
3-56		3-67		3-78	
3-57		3-68		3-79	
3-58		3-69		3-80	
3-59		3-70		3-81	
3-60		3-71		3-82	
3-61		3-72		3-83	
3-62		3-73		3-84	

[0792]

Preparation Example 3-85

Synthesis of ethyl 5-chloro-2-{2-chloro-5-[cyclopropylmethyl(2,2,2-trifluoroethyl)amino]phenyl}pentanimidate hydrochloride

[0793]



[0794]

5 Synthesis of ethyl 5-amino-2-chlorobenzoate

According to the method of Preparation Example 6-1, title compound (85.9g) was obtained from 5-amino-2-chlorobenzoic acid (5g).

ESI-MS; m/z 200 [M⁺+H]

[0795]

10 Syntheses of ethyl 2-chloro-5-(cyclopropylmethylamino)benzoate and ethyl 5-[bis(cyclopropylmethyl)amino]-2-chlorobenzoate

To the mixture of ethyl 5-amino-2-chlorobenzoate, cyclopropanecarboxaldehyde (458 μl) and acetic acid (1.43 ml) dissolved in methanol (20 ml), α-picoline borane (804 mg) was added at ice cool temperature, and was stirred under nitrogen atmosphere overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, sodium hydrogencarbonate aqueous solution was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography, and ethyl 2-chloro-5-(cyclopropylmethylamino)benzoate (881mg) and ethyl 5-[bis(cyclopropylmethyl)amino]-2-chlorobenzoate (423mg) were obtained.

The property value of ethyl 2-chloro-5-(cyclopropylmethylamino)benzoate is as follows.

ESI-MS; m/z 254 [M⁺+H]

[0796]

25 The property value of ethyl 5-[bis(cyclopropylmethyl)amino]-2-chlorobenzoate is as follows.

ESI-MS; m/z 308 [M⁺+H]

[0797]

242

Synthesis of ethyl 5-chloro-2-{2-chloro-5-[cyclopropylmethyl-(2,2,2-trifluoroethyl)amino]phenyl}pentanimidate hydrochloride

According to the method of Preparation Example 6-23 and Preparation Example 3-51, the title compound (501mg) was obtained from ethyl 2-chloro-5-

5 (cyclopropylmethylamino)benzoate (881mg)

ESI-MS; m/z 425 [$M^+ + H - HCl$]

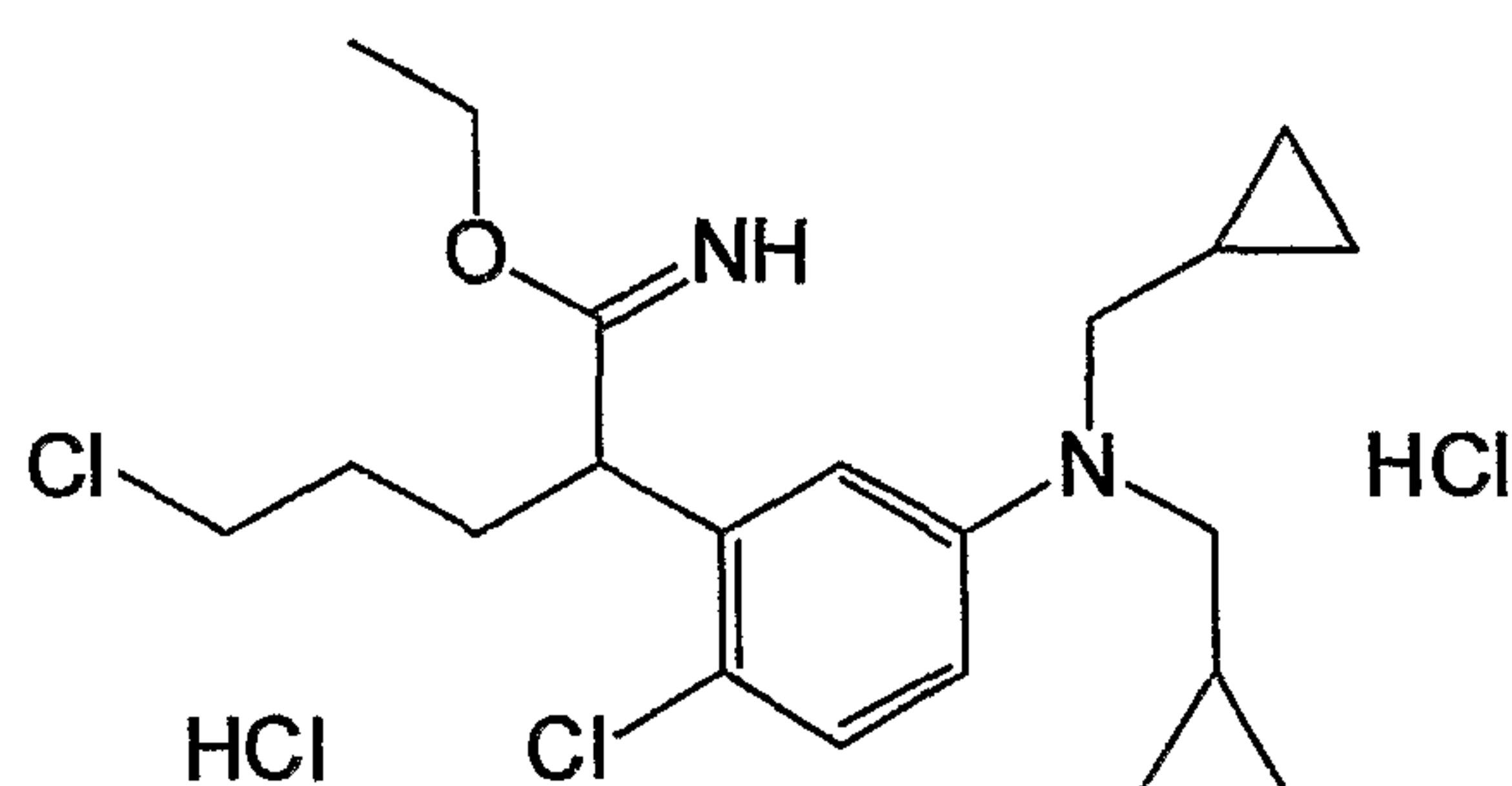
[0798]

Preparation Example 3-86

Synthesis of ethyl 2-{5-[bis(cyclopropylmethyl)amino]-2-chlorophenyl}-5-chloropentanimidate

10 hydrochloride

[0799]



[0800]

According to the method of Preparation Example 3-51, the title compound (578 mg) was obtained from ethyl 5-[bis(cyclopropylmethyl)amino]-2-chlorobenzoate (423 mg).

15 ESI-MS; m/z 397 [$M^+ + H - HCl$]

[0801]

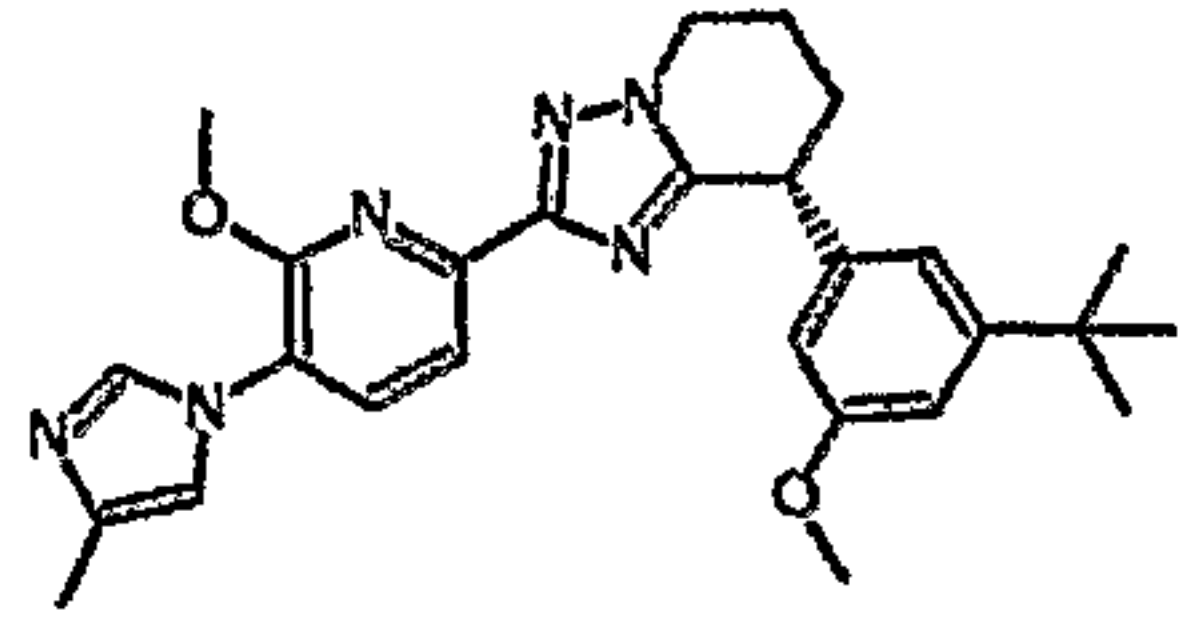
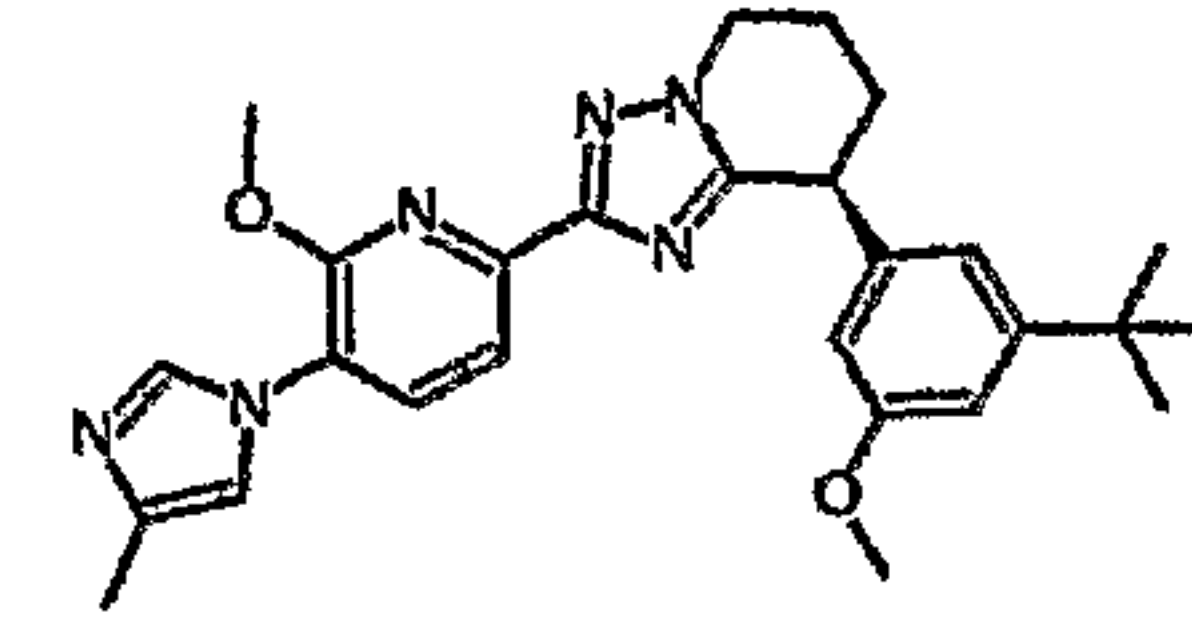
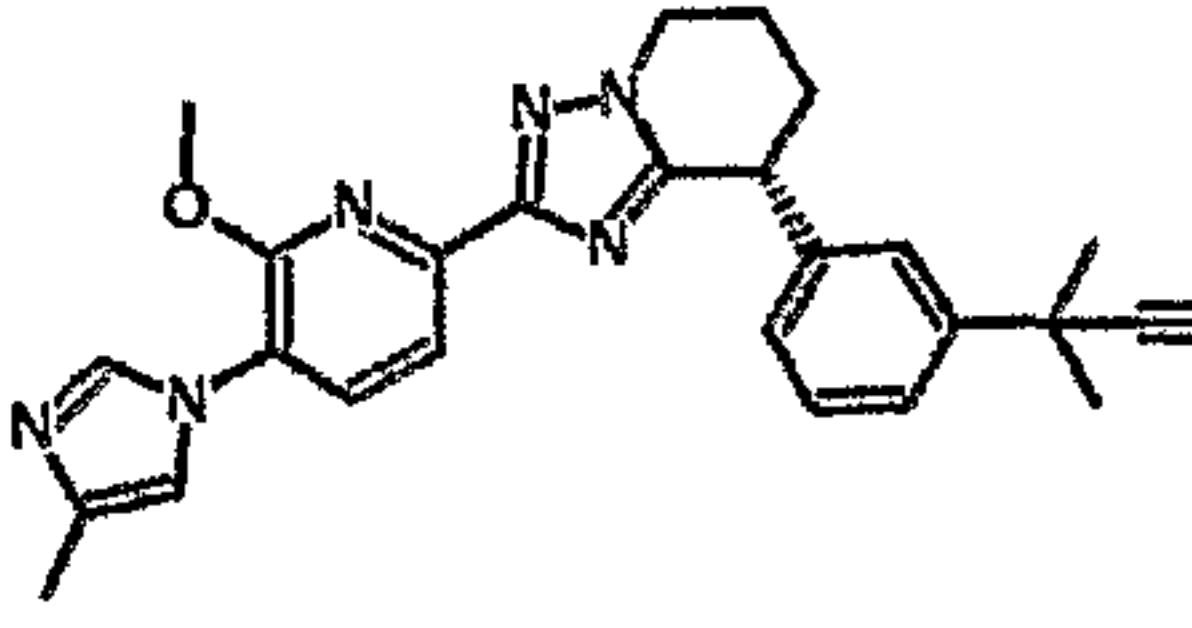
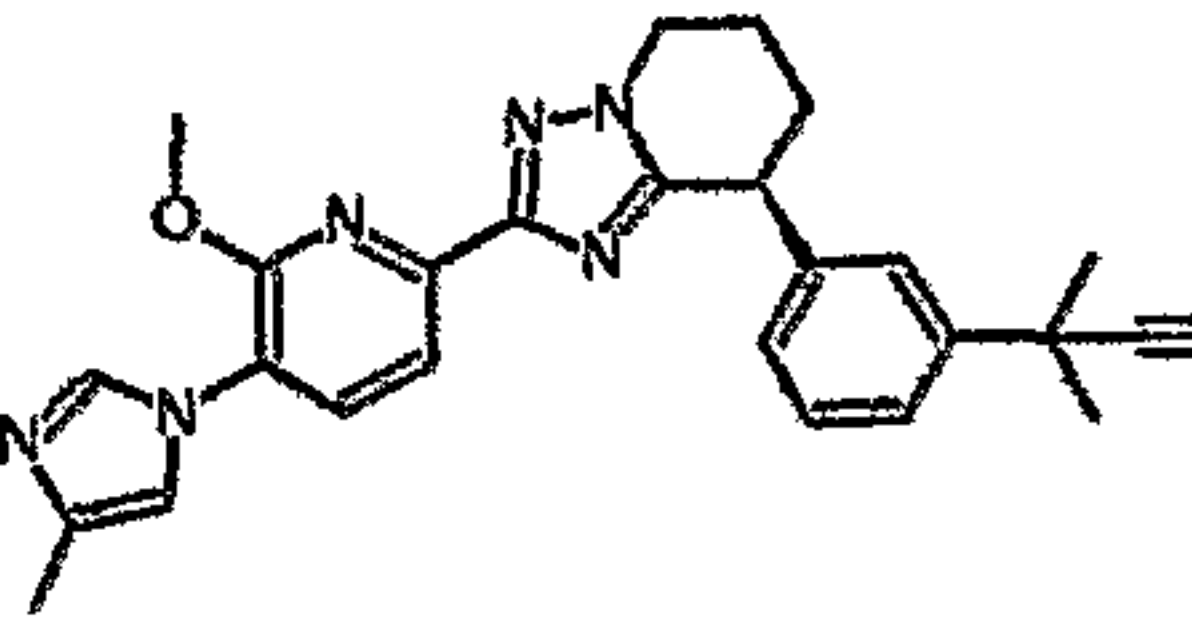
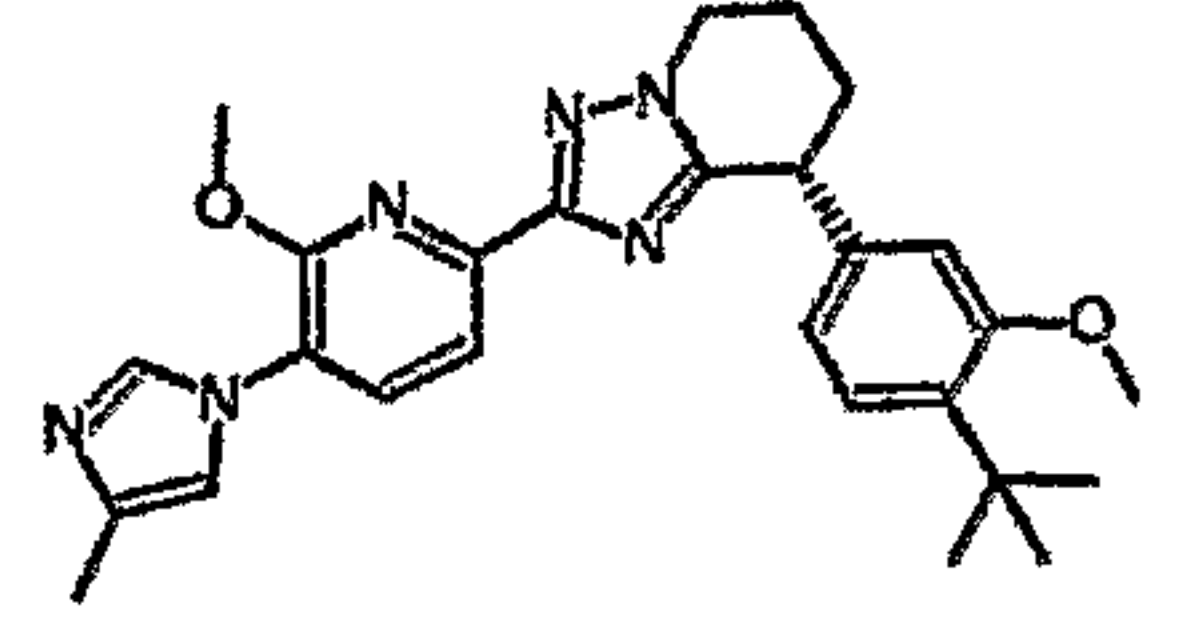
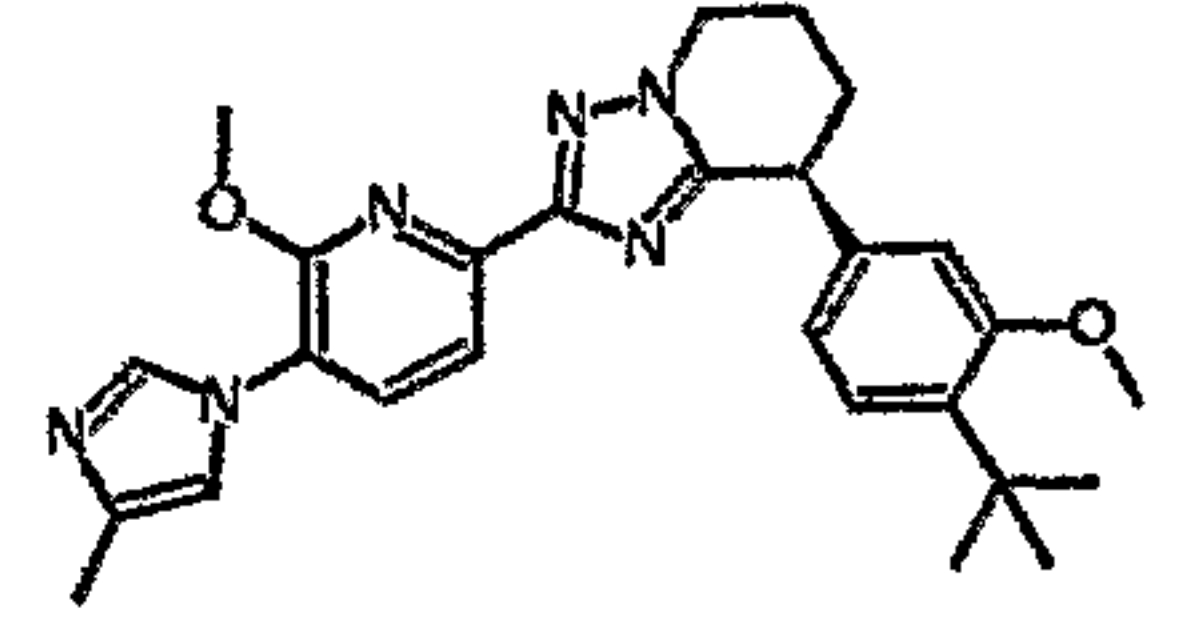
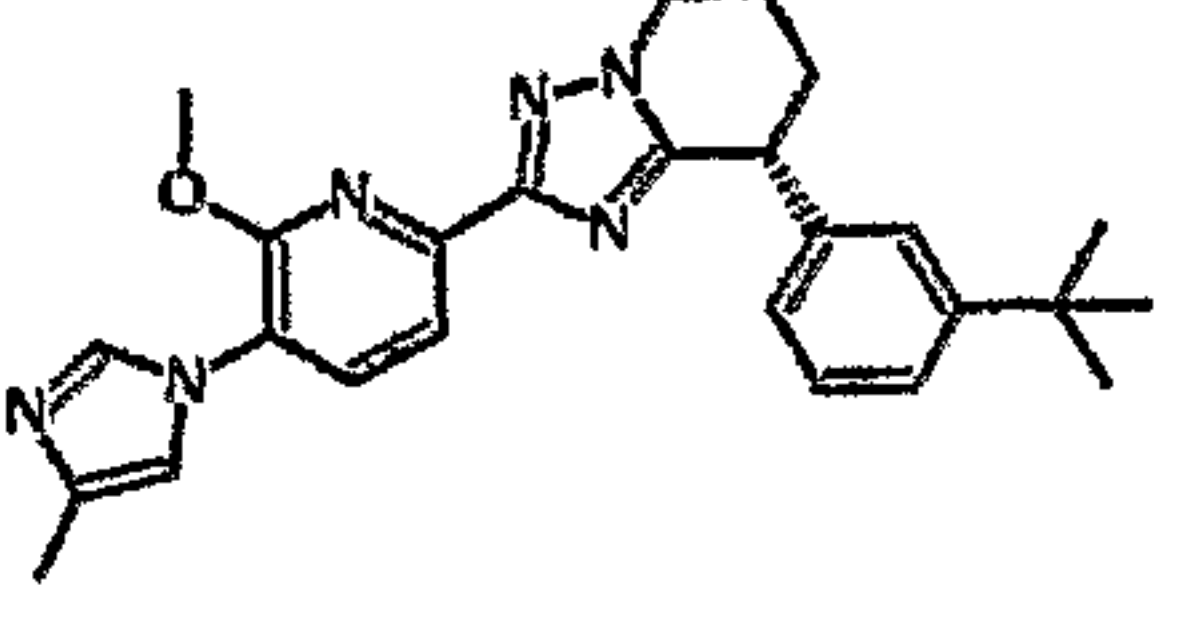
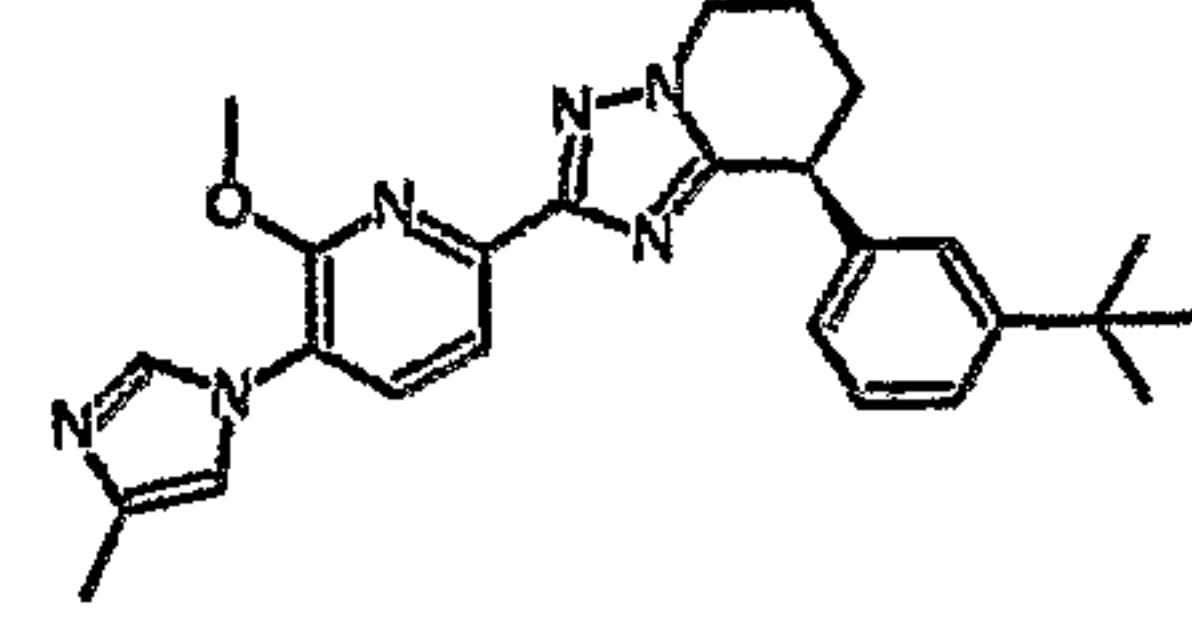
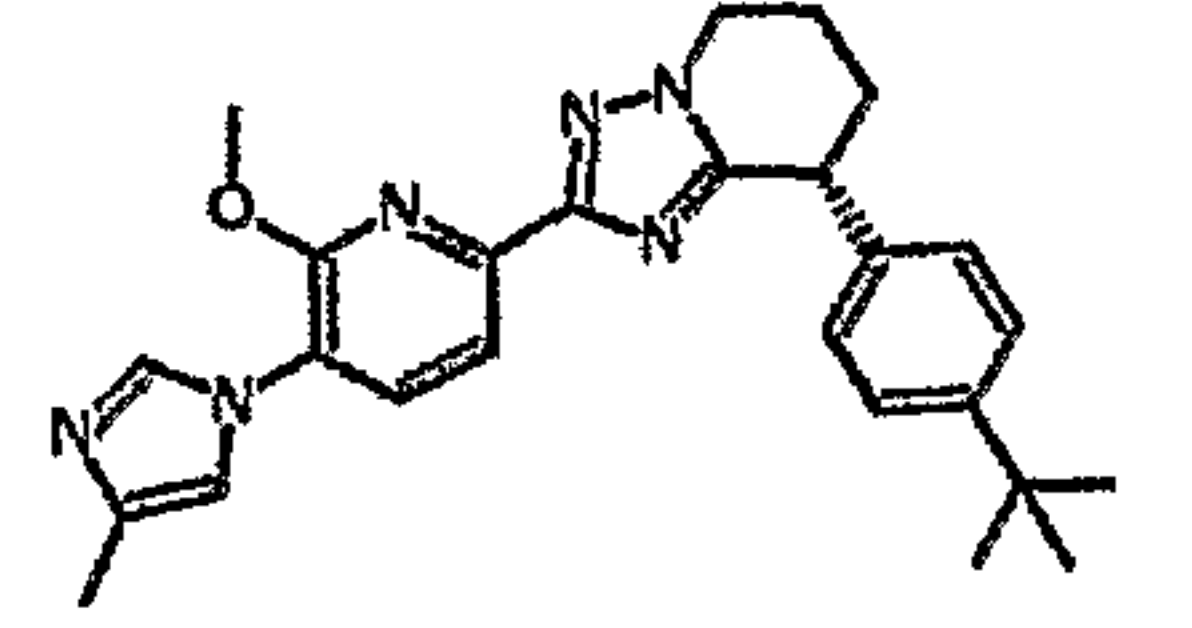
Example 186 - 233

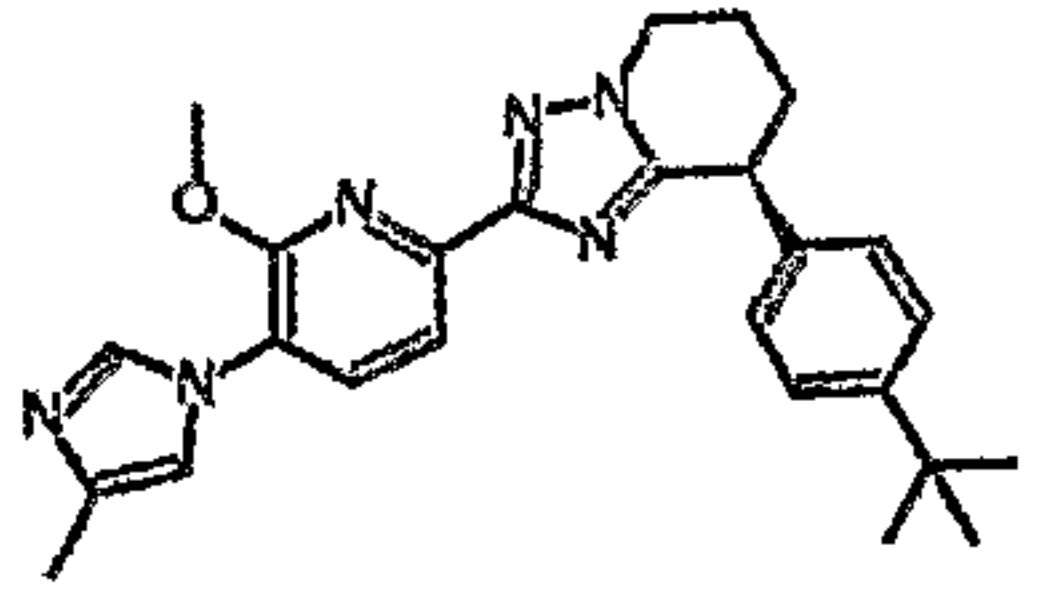
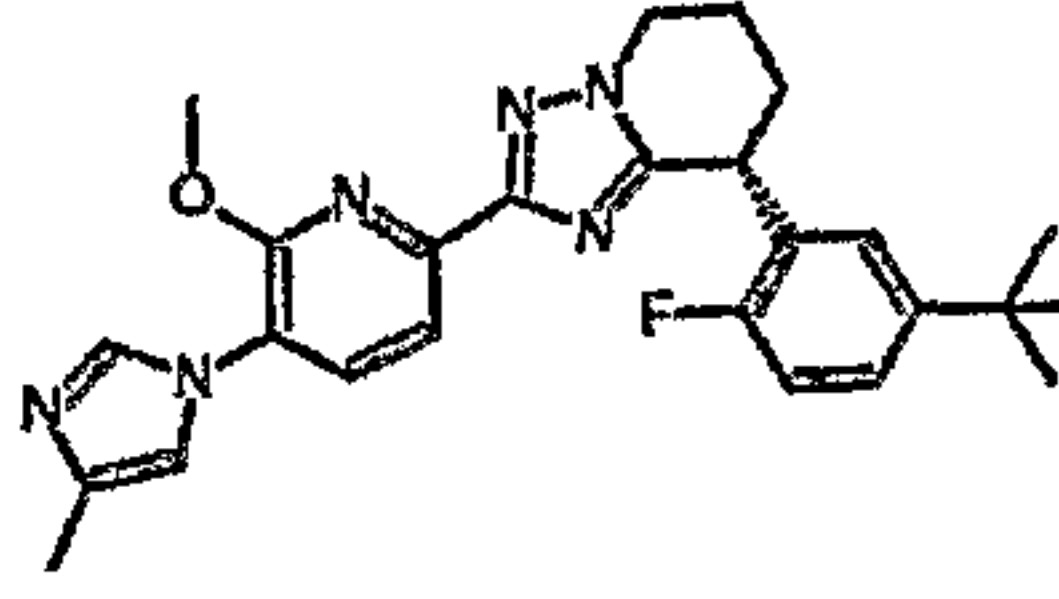
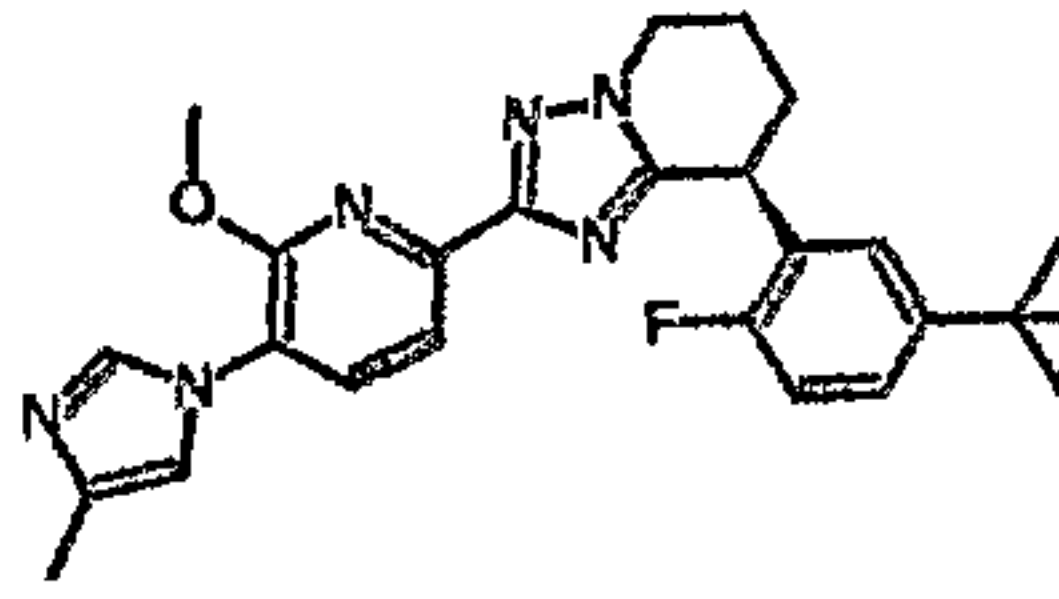
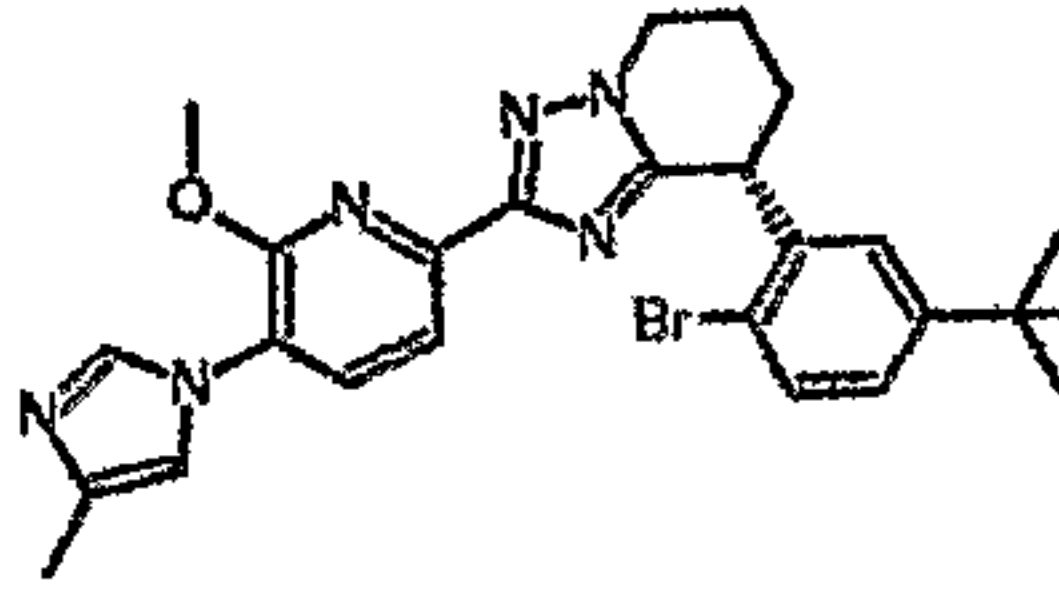
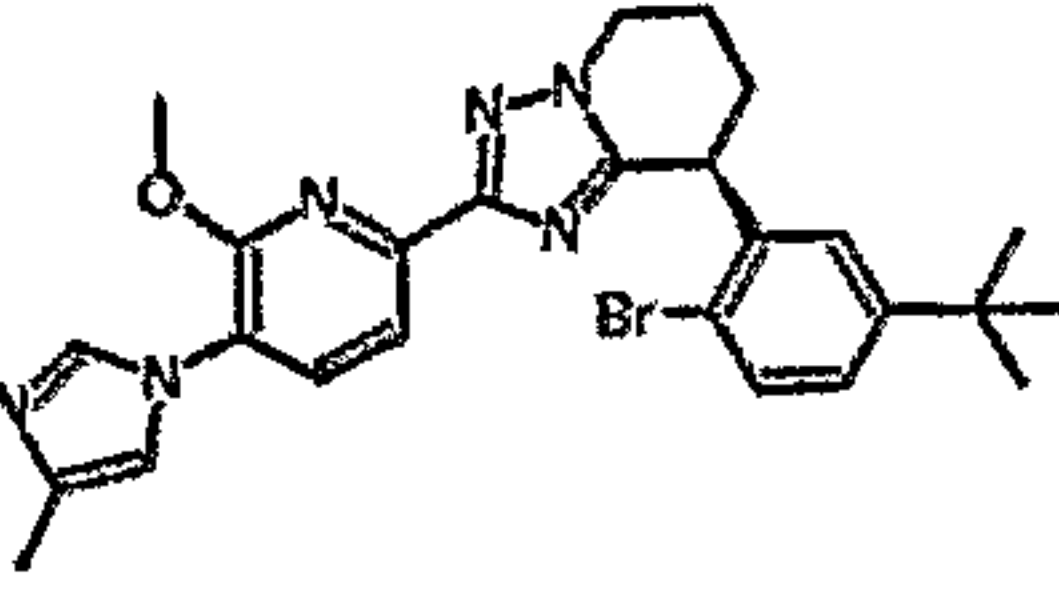
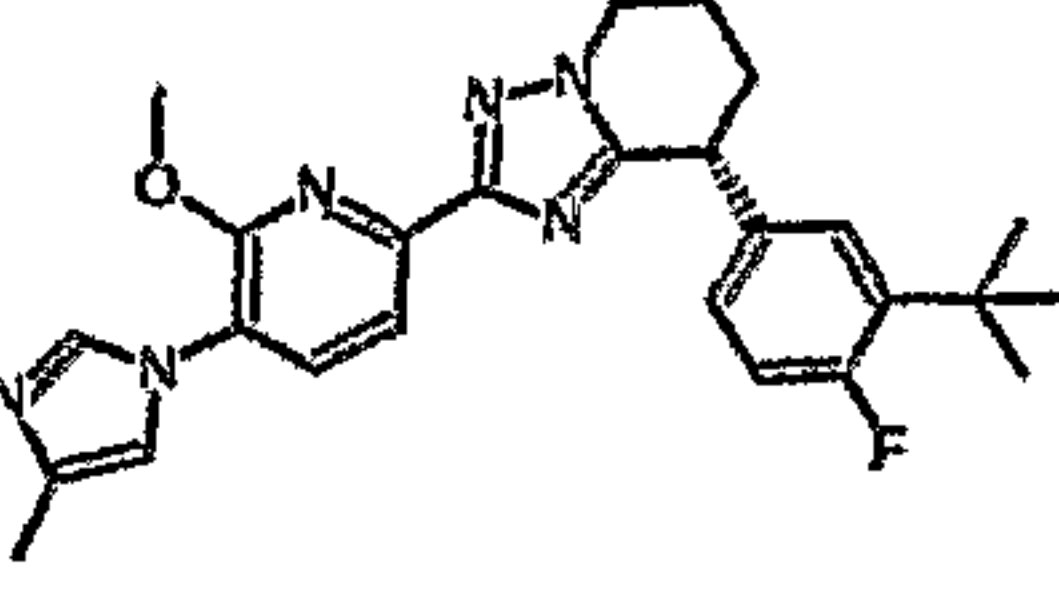
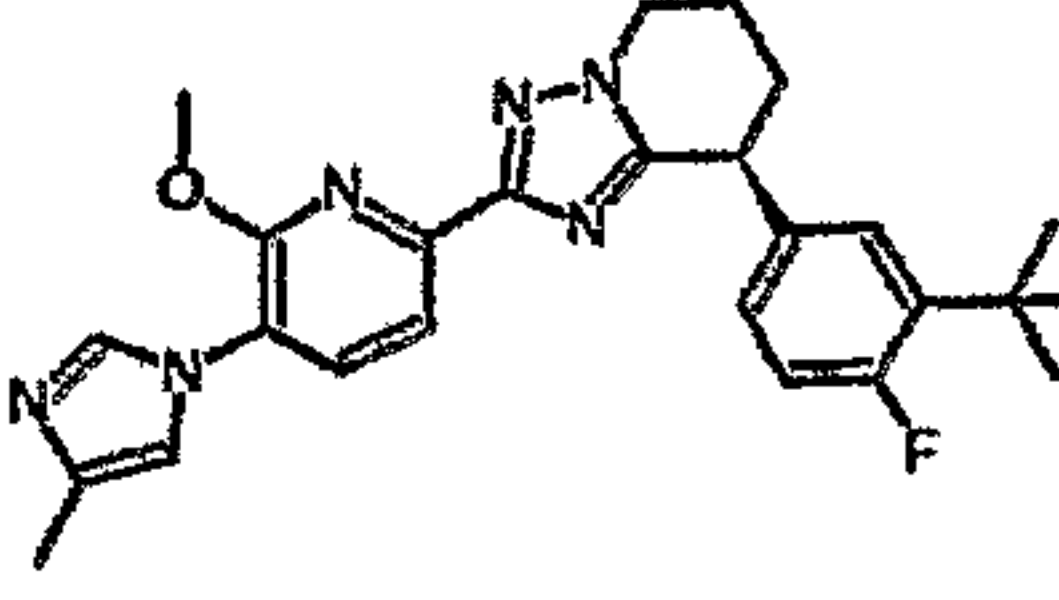
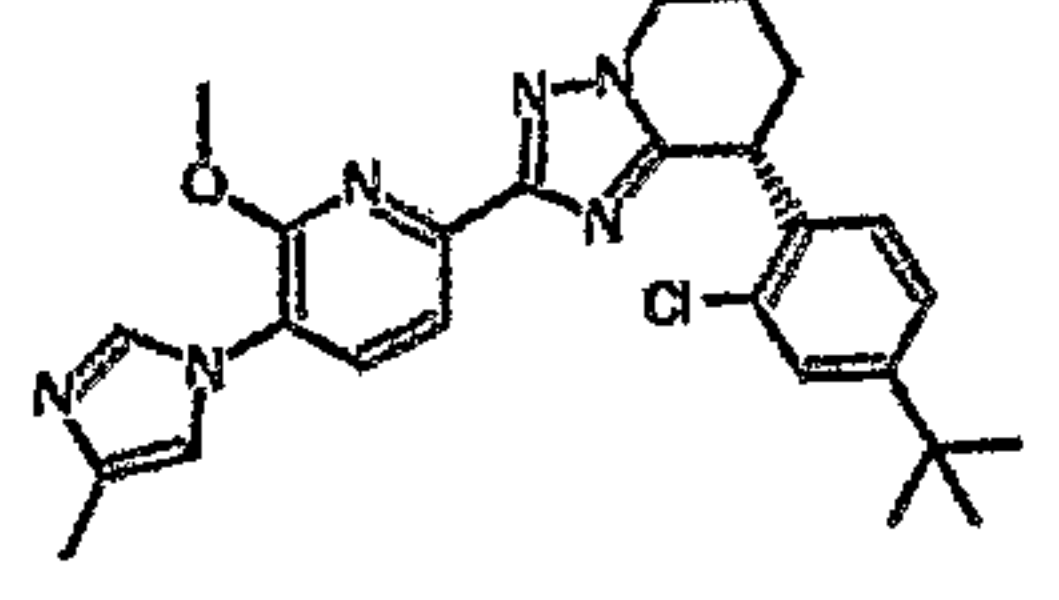
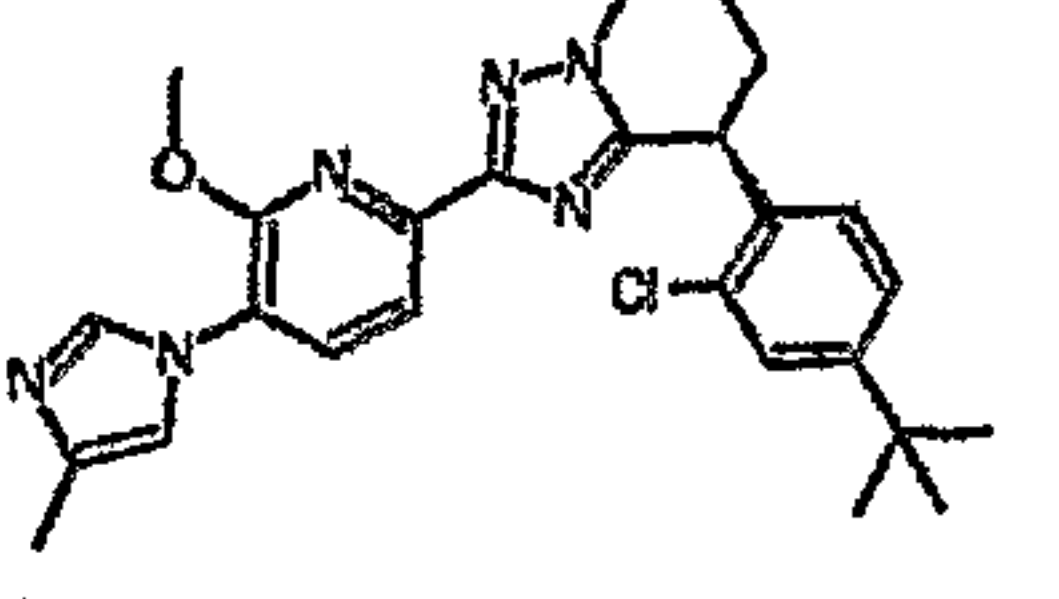
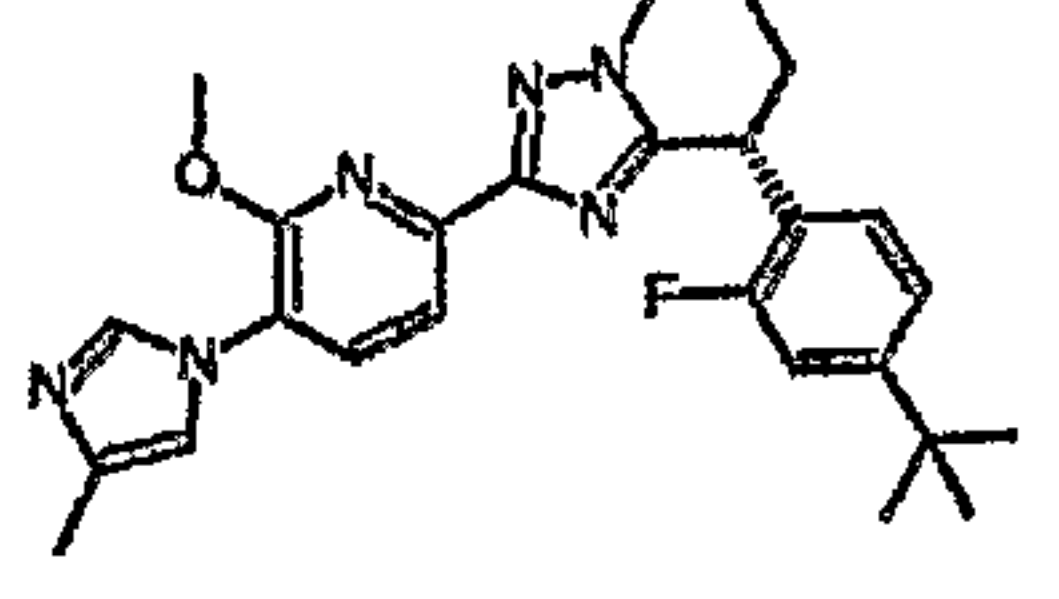
According to the methods of Example 42 and 43, the compounds of Example 186 to Example 233 were obtained from imidate hydrochlorides obtained in Preparation Example 3-21 to Preparation Example 3-44, and 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid hydrazide obtained in Preparation Example 1-6. (Table 24)

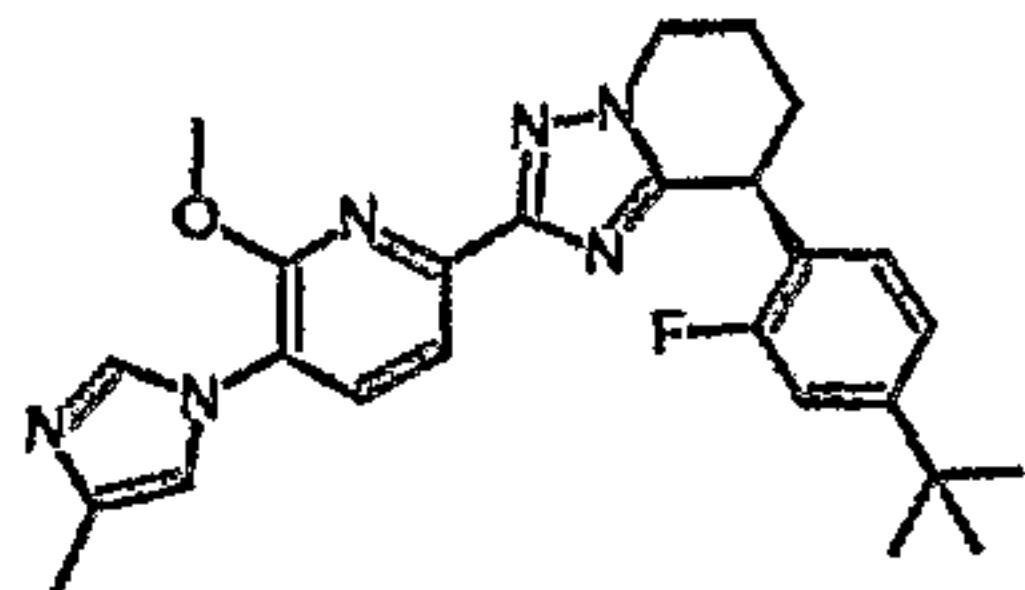
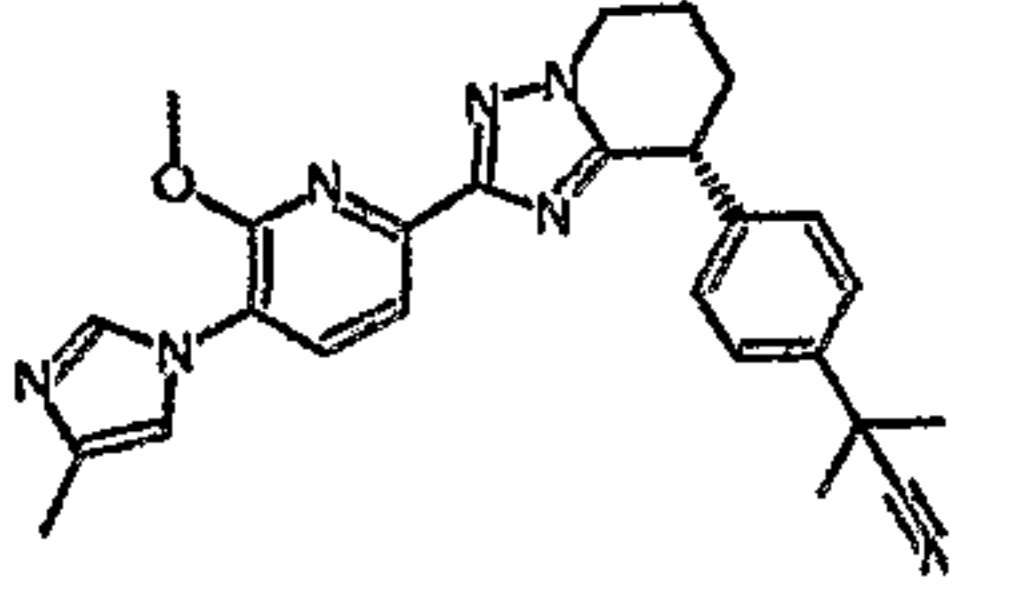
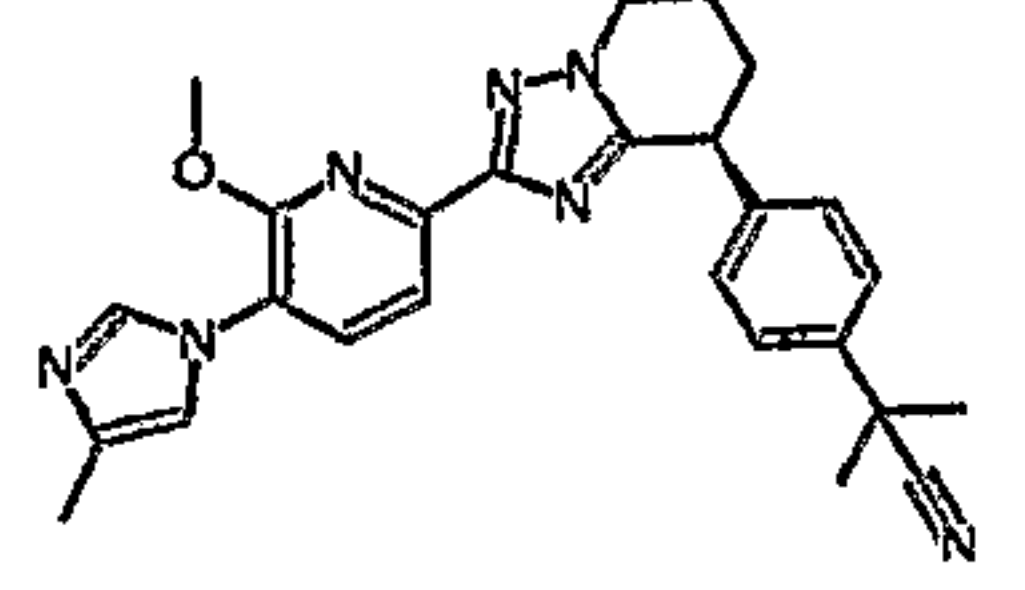
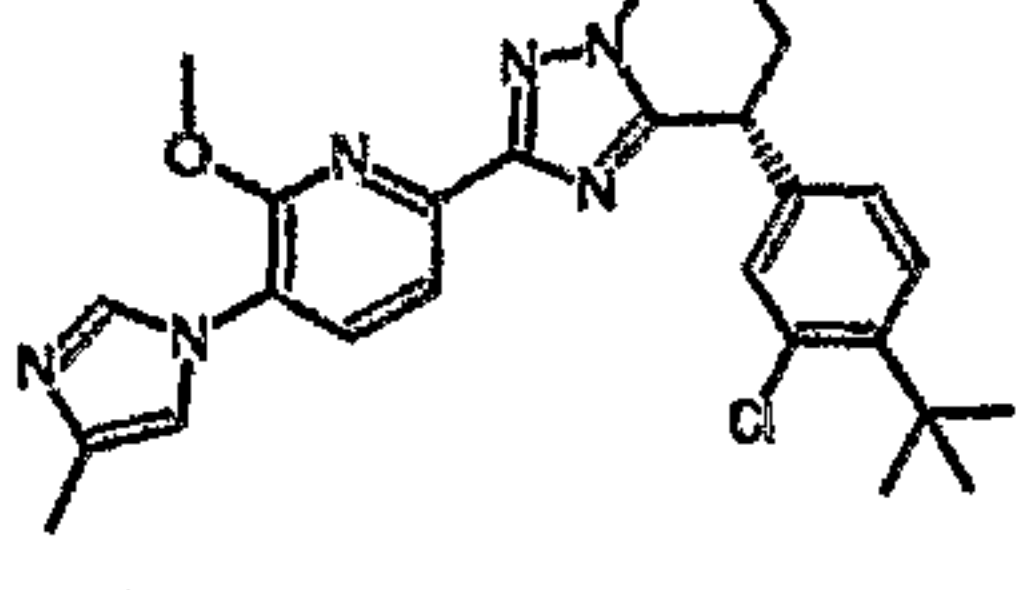
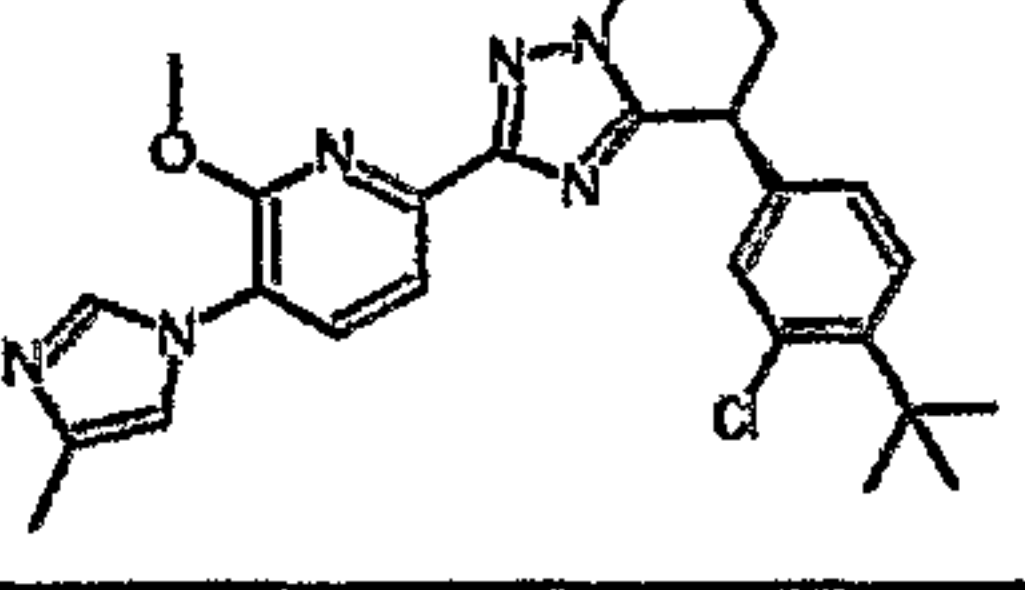
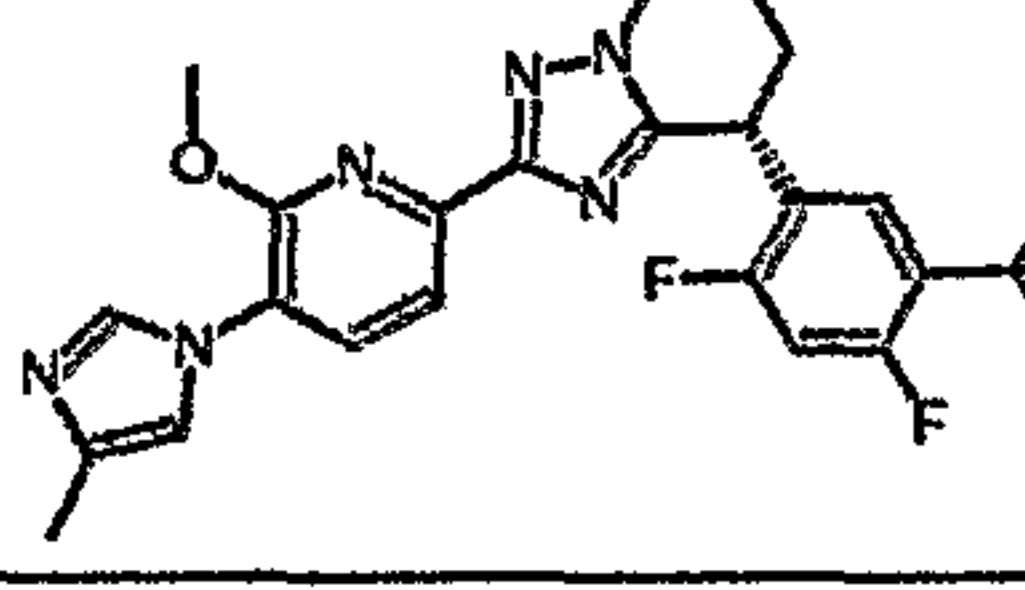
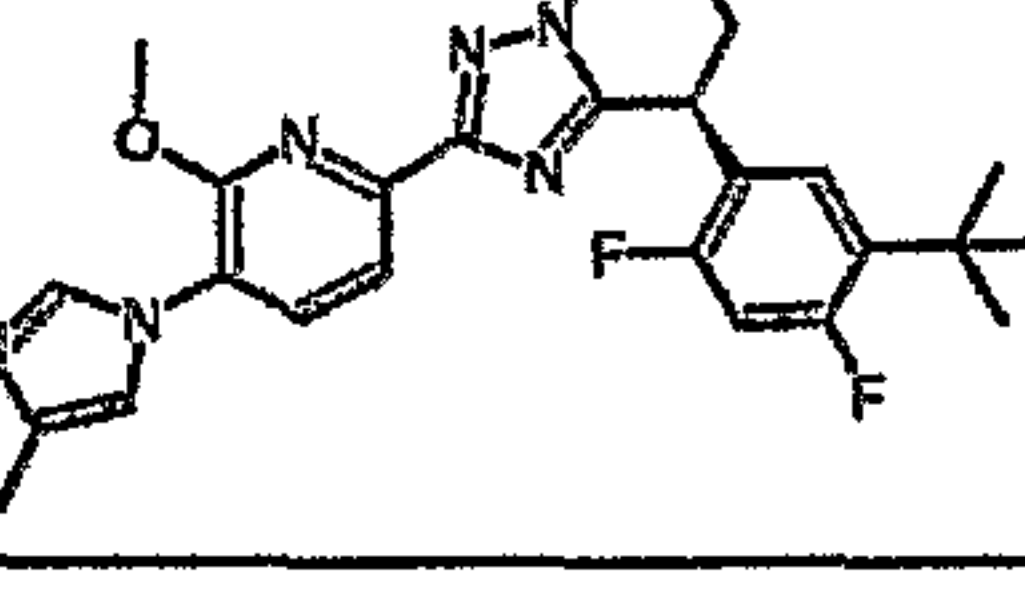
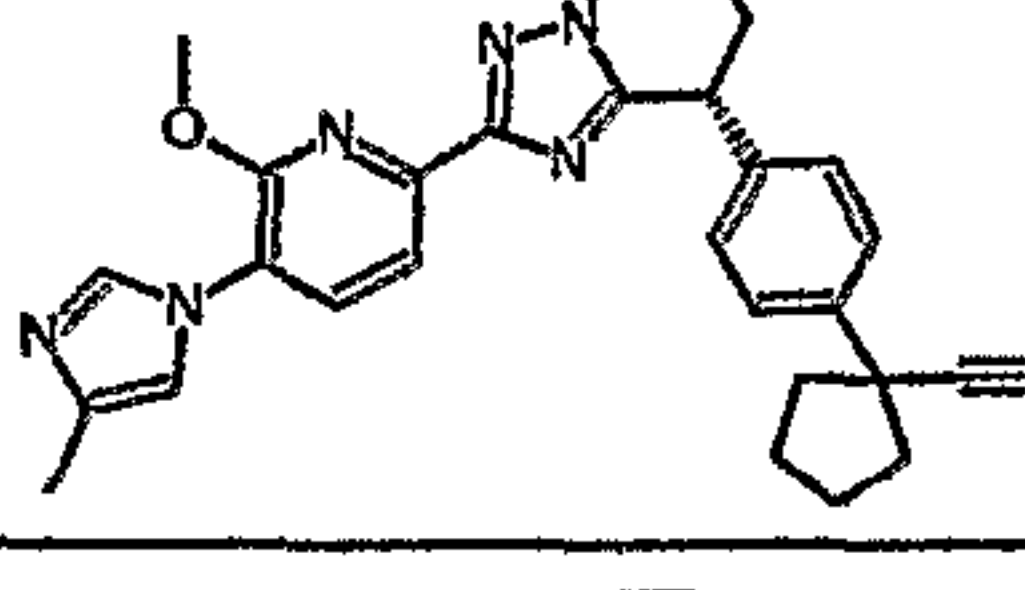
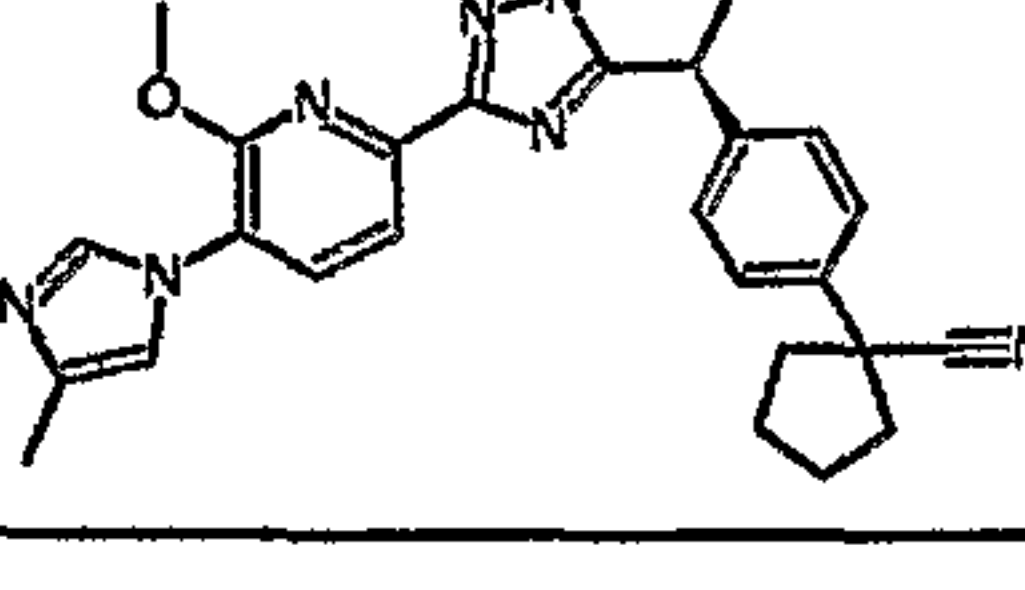
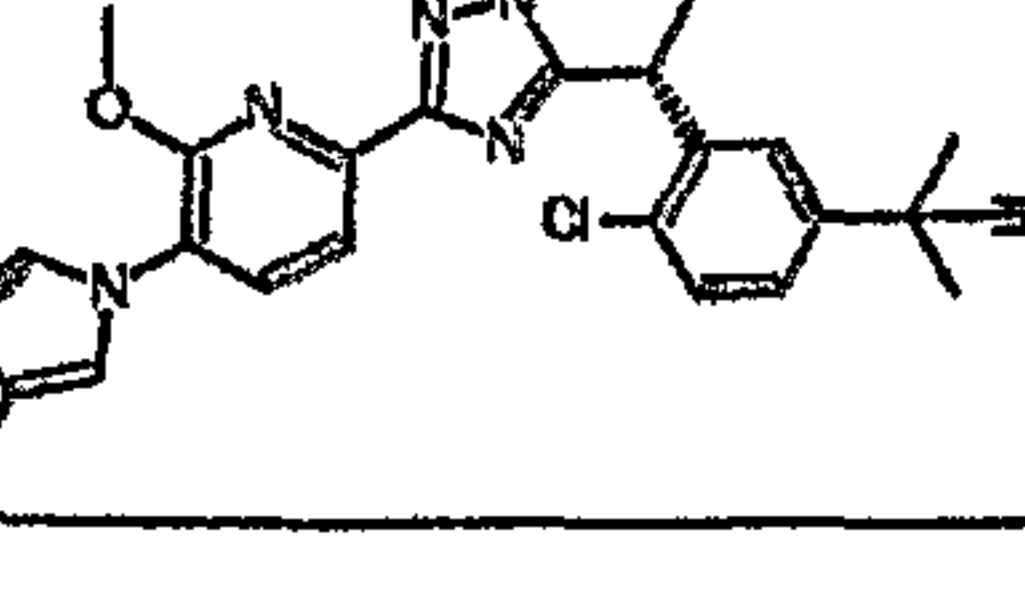
20 21 to Preparation Example 3-44, and 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-

carboxylic acid hydrazide obtained in Preparation Example 1-6. (Table 24)

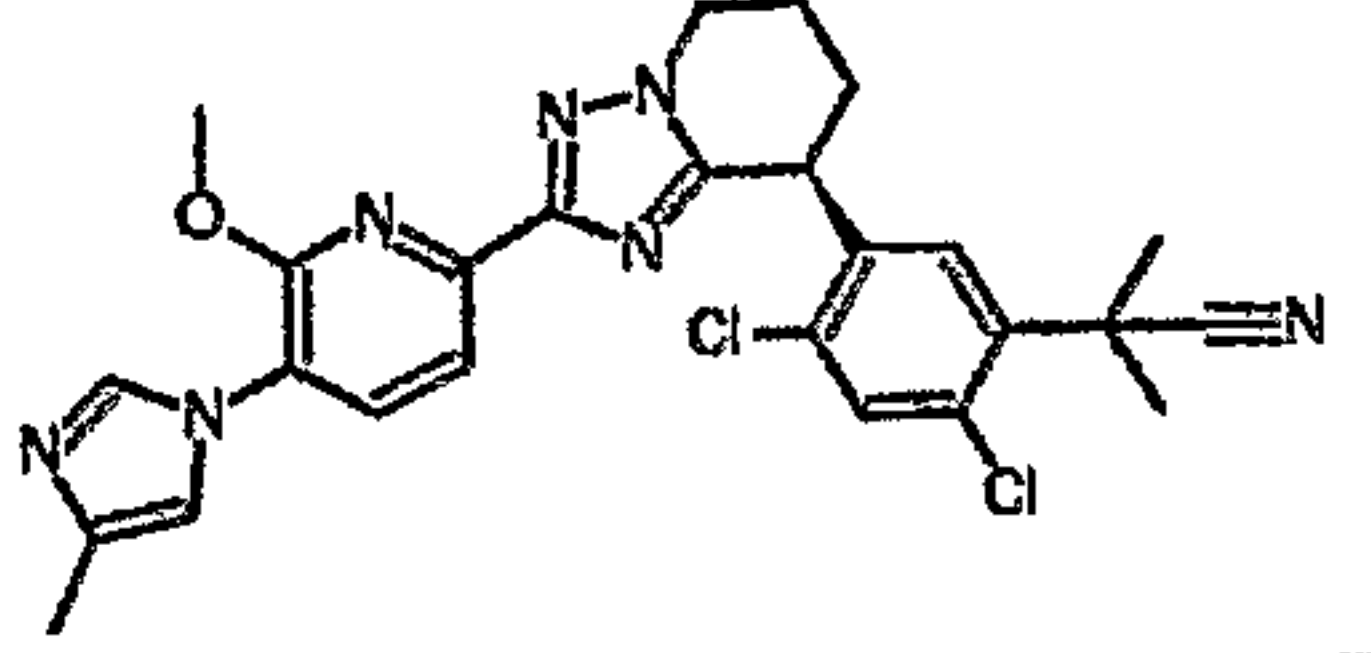
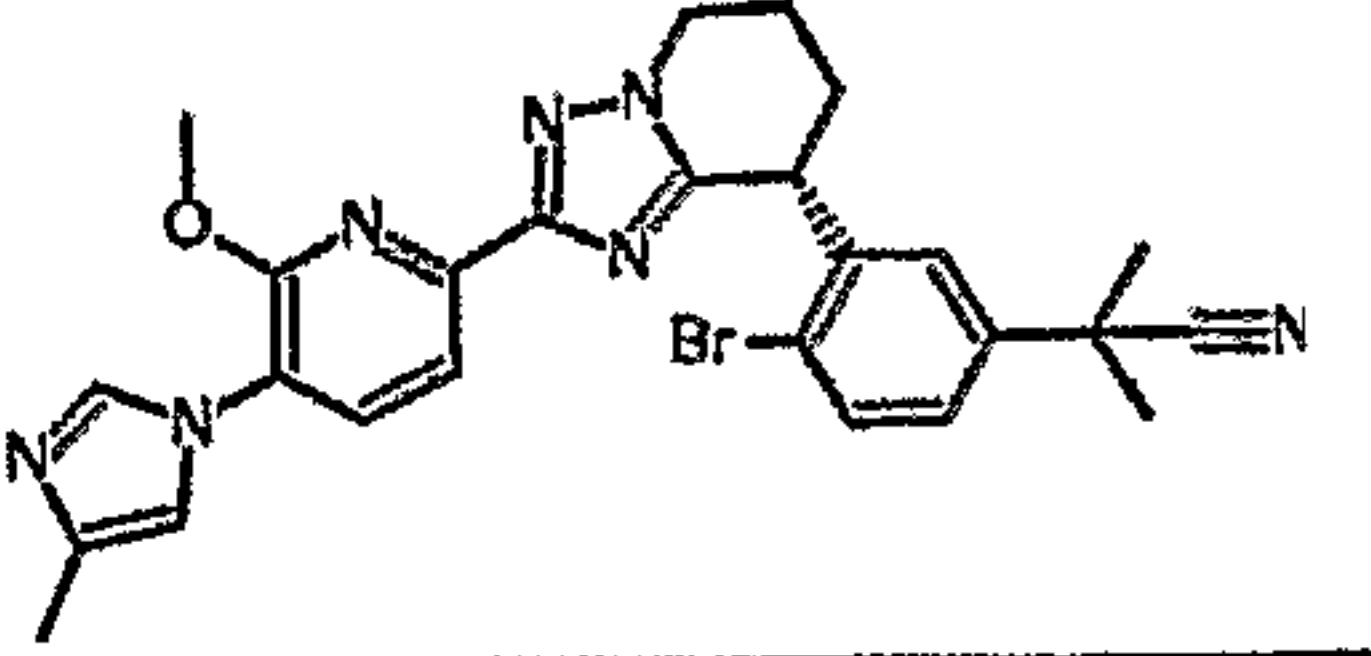
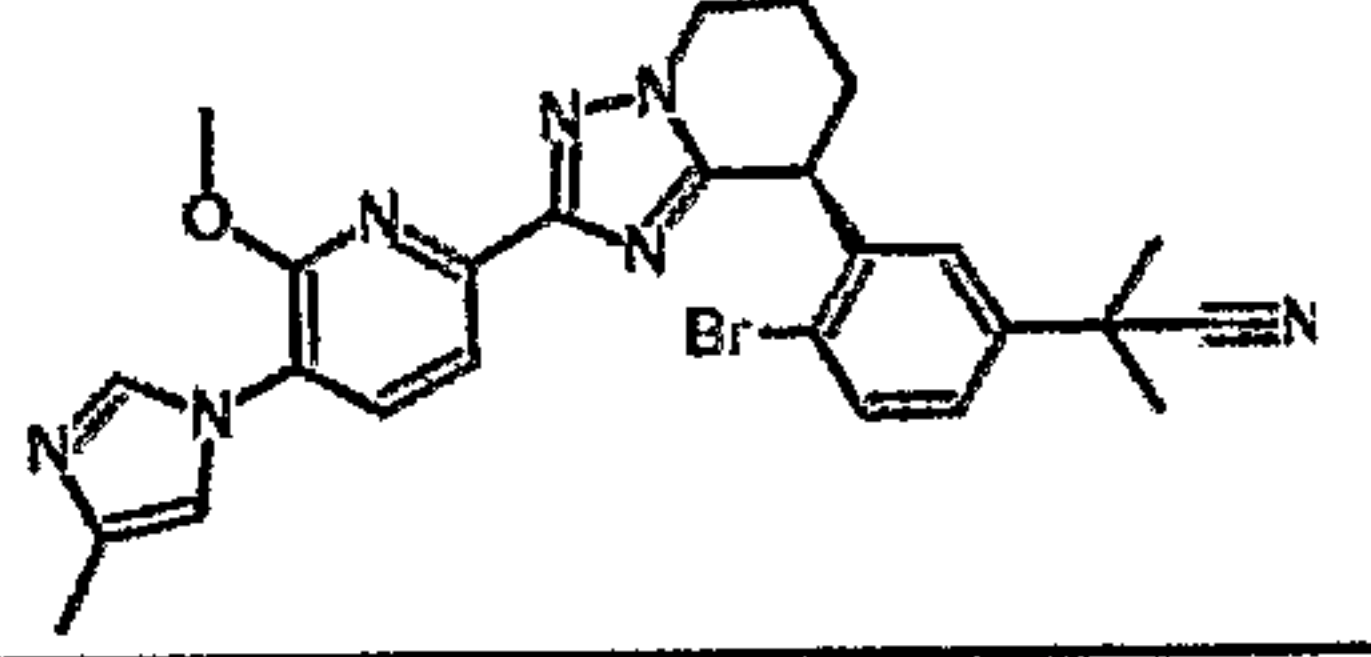
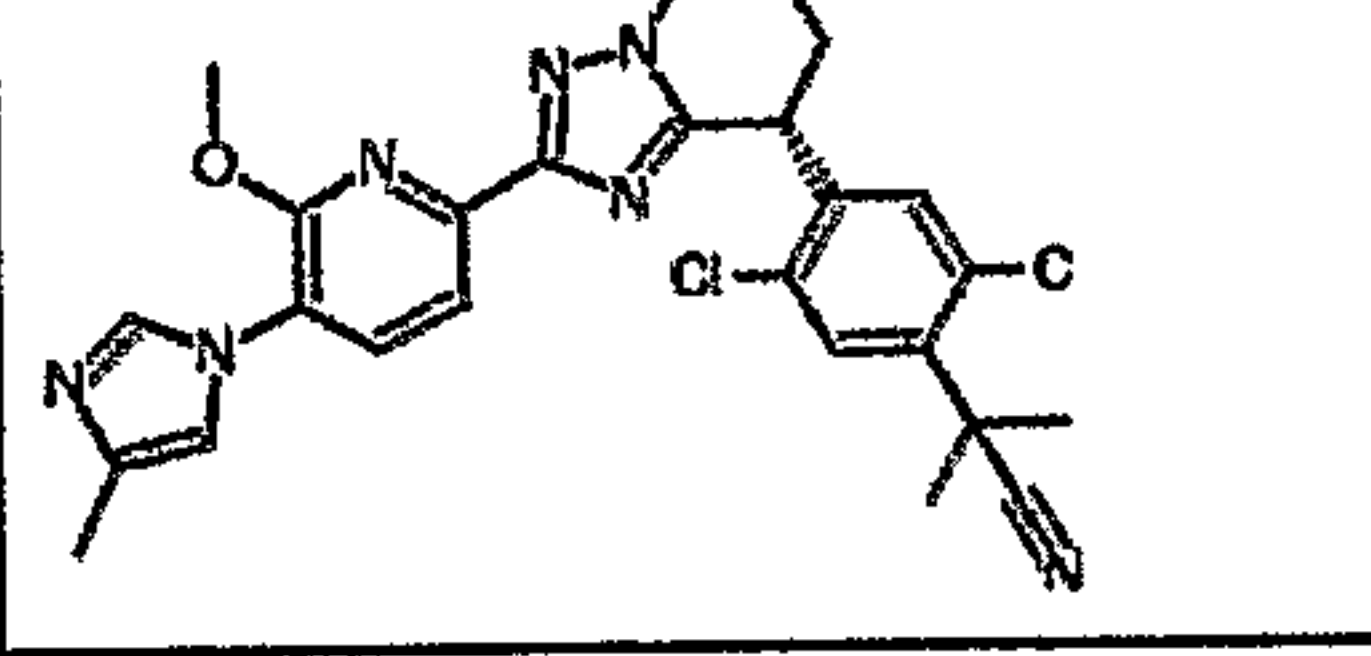
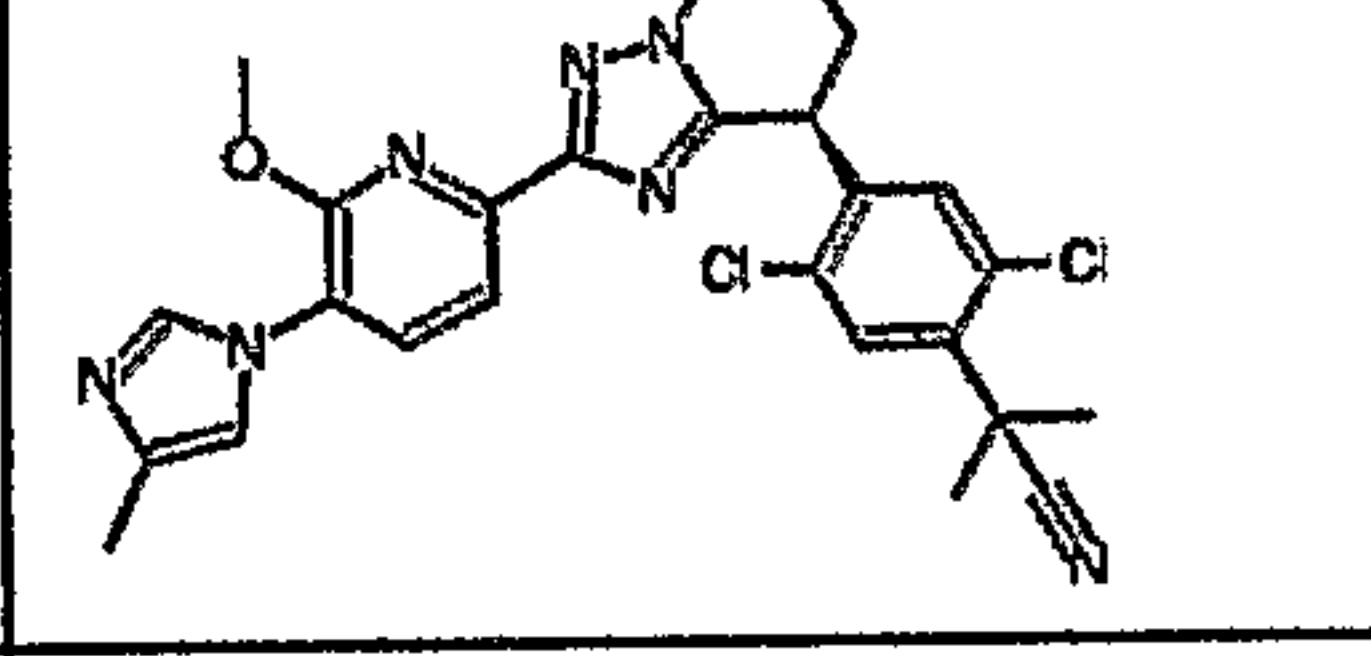
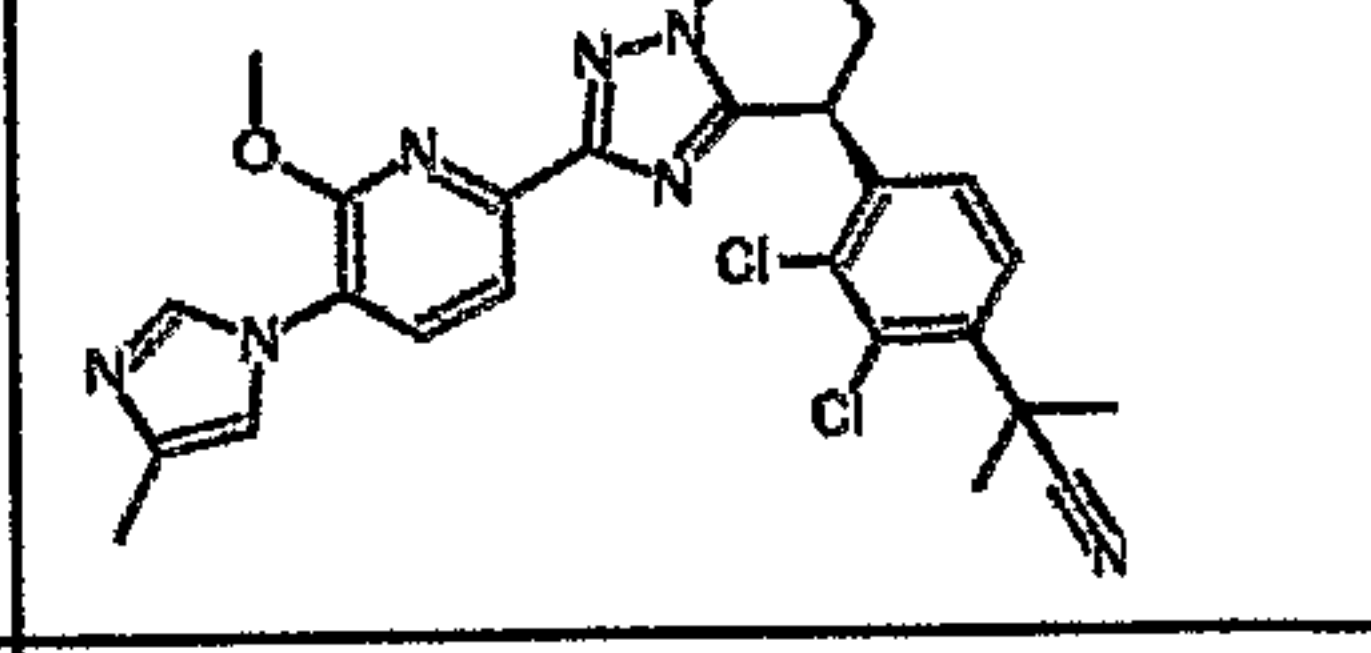
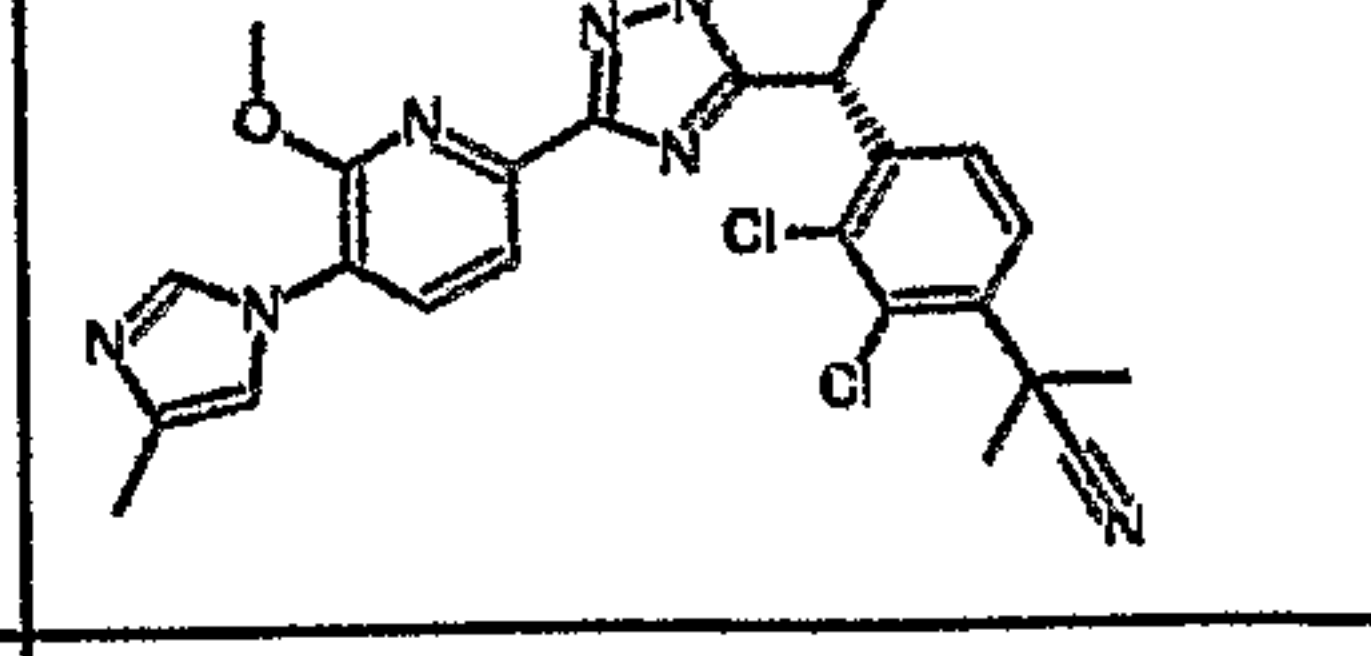
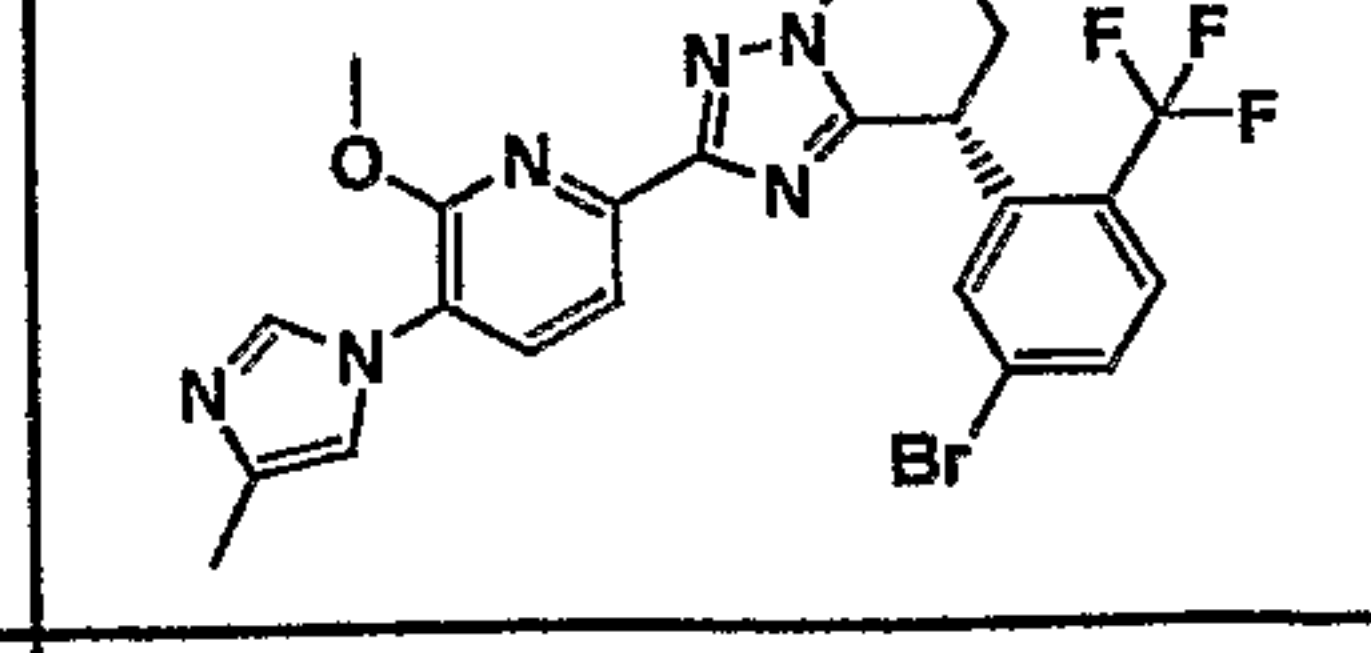
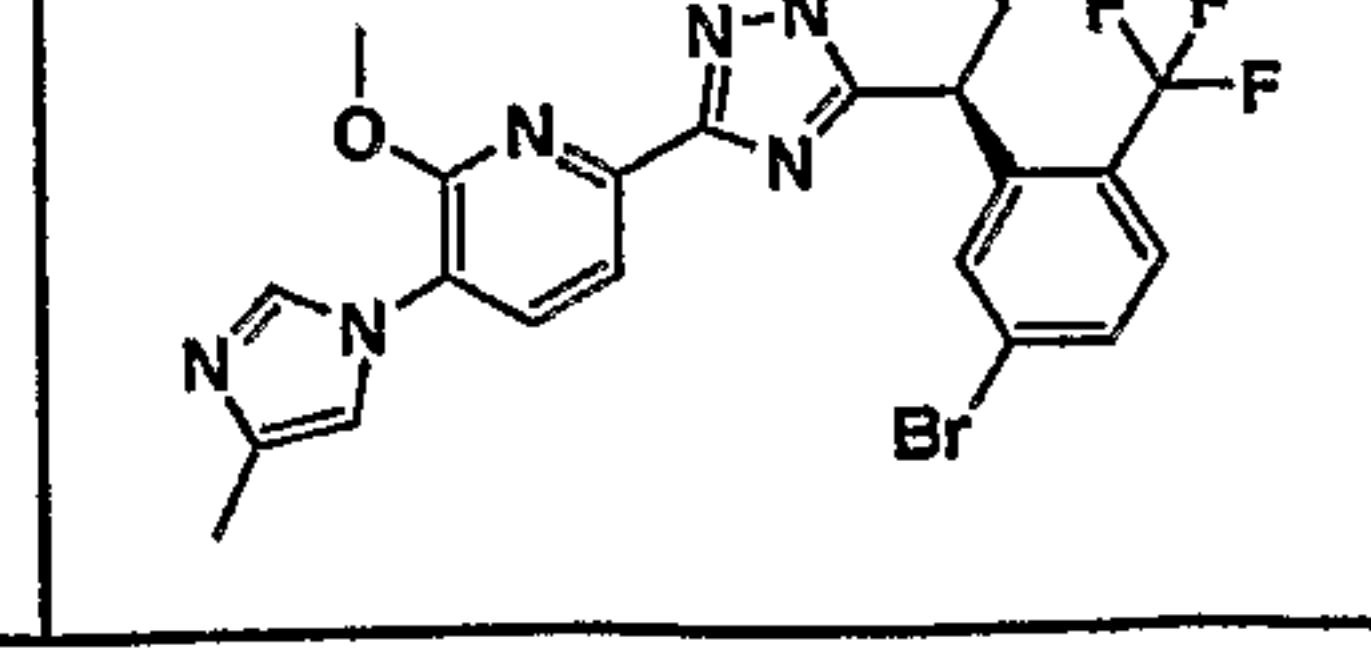
Table 24

Example No.	Structural formula	ESI mass
Example186		ESI-MS; m/z 473[M ⁺ +H].
Example187		ESI-MS; m/z 473[M ⁺ +H].
Example188		ESI-MS; m/z 454[M ⁺ +H].
Example189		ESI-MS; m/z 454[M ⁺ +H].
Example190		ESI-MS; m/z 473[M ⁺ +H].
Example191		ESI-MS; m/z 473[M ⁺ +H].
Example192		ESI-MS; m/z 443[M ⁺ +H].
Example193		ESI-MS; m/z 443[M ⁺ +H].
Example194		ESI-MS; m/z 443[M ⁺ +H].

Example195		ESI-MS;m/z 443[M ⁺ +H].
Example196		ESI-MS;m/z 461[M ⁺ +H].
Example197		ESI-MS;m/z 461[M ⁺ +H].
Example198		ESI-MS;m/z 521[M ⁺ +H].
Example199		ESI-MS;m/z 523[M ⁺ +H].
Example200		ESI-MS;m/z 461[M ⁺ +H].
Example201		ESI-MS;m/z 461[M ⁺ +H].
Example202		ESI-MS;m/z 477[M ⁺ +H].
Example203		ESI-MS;m/z 477[M ⁺ +H].
Example204		ESI-MS;m/z 461[M ⁺ +H].

Example205		ESI-MS;m/z 461[M ⁺ +H].
Example206		ESI-MS;m/z 454[M ⁺ +H].
Example207		ESI-MS;m/z 454[M ⁺ +H].
Example208		ESI-MS;m/z 477[M ⁺ +H].
Example209		ESI-MS;m/z 477[M ⁺ +H].
Example210		ESI-MS;m/z 479[M ⁺ +H].
Example211		ESI-MS;m/z 479[M ⁺ +H].
Example212		ESI-MS;m/z 480[M ⁺ +H].
Example213		ESI-MS;m/z 480[M ⁺ +H].
Example214		ESI-MS;m/z 488[M ⁺ +H].

Example215		ESI-MS;m/z 488[M ⁺ +H].
Example216		ESI-MS;m/z 490[M ⁺ +H].
Example217		ESI-MS;m/z 490[M ⁺ +H].
Example218		ESI-MS;m/z 506[M ⁺ +H].
Example219		ESI-MS;m/z 506[M ⁺ +H].
Example220		ESI-MS;m/z 506[M ⁺ +H].
Example221		ESI-MS;m/z 506[M ⁺ +H].
Example222		ESI-MS;m/z 488[M ⁺ +H].
Example223		ESI-MS;m/z 488[M ⁺ +H].
Example224		ESI-MS;m/z 522[M ⁺ +H].

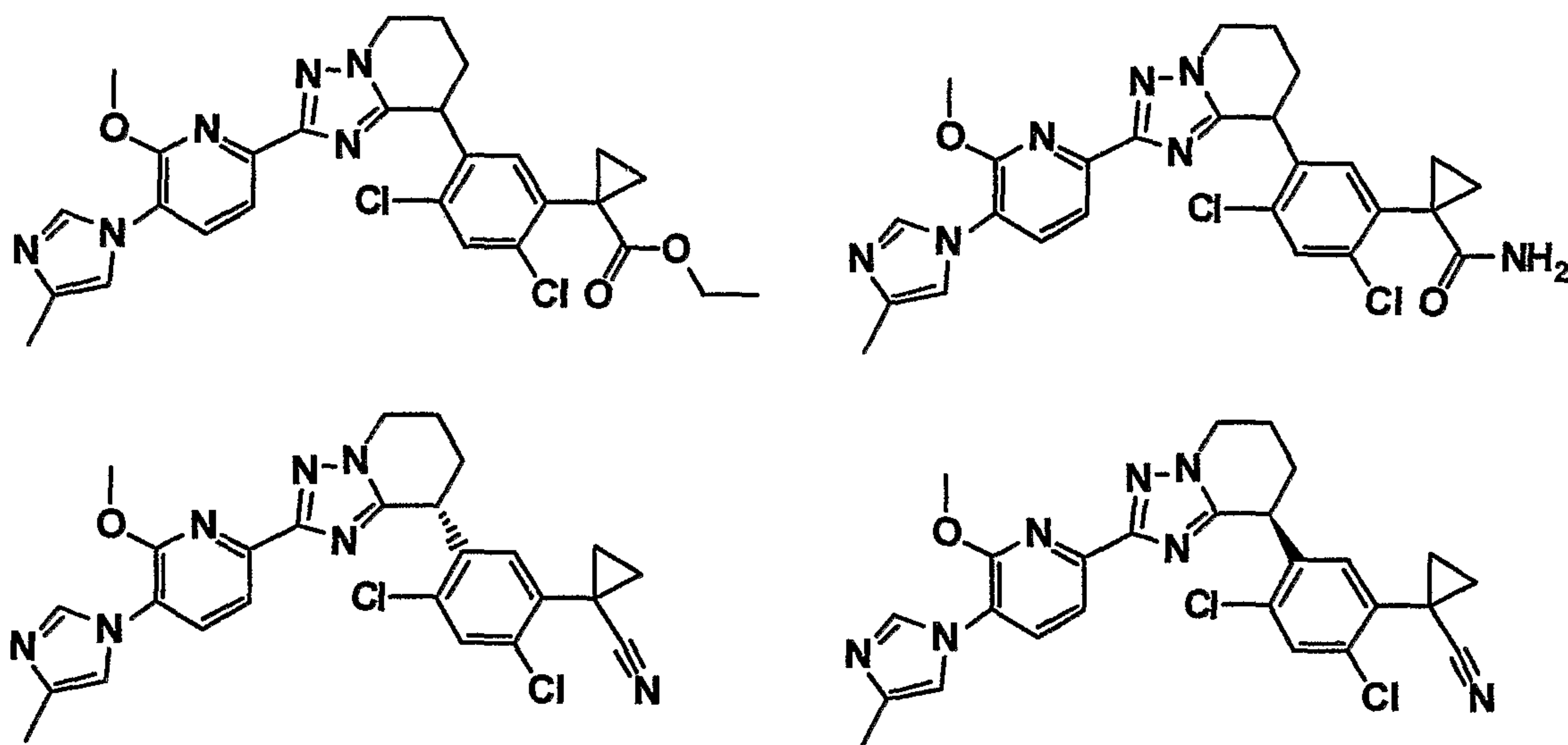
Example225		ESI-MS;m/z 522[M ⁺ +H].
Example226		ESI-MS;m/z 532[M ⁺ +H].
Example227		ESI-MS;m/z 534[M ⁺ +H].
Example228		ESI-MS;m/z 522[M ⁺ +H].
Example229		ESI-MS;m/z 522[M ⁺ +H].
Example230		ESI-MS;m/z 522[M ⁺ +H].
Example231		ESI-MS;m/z 522[M ⁺ +H].
Example232		ESI-MS;m/z 535[M++H].
Example233		ESI-MS;m/z 535[M++H].

[0802]

Example 234, Example 235, Example 236 and Example 237

Syntheses of ethyl 1-(2,4-dichloro-5-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-8-yl}phenyl)cyclopropanecarboxylate, 1-(2,4-dichloro-5-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-8-yl}phenyl)cyclopropanecarboxylic acid amide, (+)-1-(2,4-dichloro-5-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-8-yl}phenyl)cyclopropanecarbonitrile and (-)-1-(2,4-dichloro-5-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-8-yl}phenyl)cyclopropanecarbonitrile.

[0803]



[0804]

Into a ethanol (4 ml) solution of 1-[2,4-dichloro-5-(4-chloro-1-cyanobutyl)phenyl]cyclopropanecarbonitrile (113 mg) obtained in Preparation Example 3-46, hydrogen chloride gas was bubbled for 10 minutes. The reaction mixture was stirred for 2 hours at room temperature, and then was concentrated under reduced pressure. The residue was dissolved in tert-butyl methyl ether and the solution was concentrated again under reduced pressure. The resulted residue was dissolved in DMF (2 ml), and to the solution, imidazole (125 mg) and 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid hydrazide obtained in Preparation Example 1-6 was added sequentially, the reaction mixture was stirred over night at room temperature, and then for 3.5 hours at 110°C. To the reaction mixture, after cooling, ethyl acetate, water and 1N-hydrochloric acid (0.5 ml) were added, and the organic layer was

separated. The organic layer was washed with water and brine sequentially, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative thin layer silica gel chromatography (carrier: ChromatorexTM NH; elution solvent: ethyl acetate) to obtain racemic 1-(2,4-dichloro-5-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-8-yl}phenyl)cyclopropanecarboxylic acid ethyl ester (11.7mg). The property values of the compound are as follows.

ESI-MS; m/z 589 [M⁺+Na]. ¹H-NMR (CDCl₃) δ (ppm): 1.00-1.30 (m, 2H), 1.15 (t, J=7.2Hz, 3H), 1.50-1.75 (m, 2H), 2.00-2.26 (m, 3H), 2.31 (s, 3H), 2.36-2.50 (m, 1H), 4.03-4.15 (m, 2H), 4.16 (s, 3H), 4.41 (t, J=6.0Hz, 2H), 4.75 (t, J=6.0Hz, 1H), 6.86 (s, 1H), 7.01 (brs, 1H), 7.46 (s, 1H), 7.60 (d, J=8.0Hz, 1H), 7.75 (d, J=8.0Hz, 1H), 7.85 (brs, 1H).

[0805]

And also, racemic 1-(2,4-dichloro-5-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-8-yl}phenyl)cyclopropanecarboxylic acid amide (11.9mg) was obtained. The property values of the compound are as follows.

ESI-MS; m/z 560 [M⁺+Na]. ¹H-NMR (CDCl₃) δ (ppm): 1.01 (brs, 2H), 1.97-2.35 (m, 3H), 2.30 (s, 3H), 2.40-2.50 (m, 1H), 4.13 (s, 3H), 4.35-4.51 (m, 2H), 4.65-4.75 (m, 1H), 5.27 (brs, 1H), 5.69 (brs, 1H), 7.00 (s, 1H), 7.09 (s, 1H), 7.52 (s, 1H), 7.60 (d, J=8.0Hz, 1H), 7.71 (d, J=8.0Hz, 1H), 7.84 (brs, 1H).

[0806]

And also, racemic 1-(2,4-dichloro-5-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-8-yl}phenyl)cyclopropanecarbonitrile (15.7mg) was obtained. This racemic compound was purified with CHIRALCELTM IA (Daicel Chemical Industries, Ltd.; 2cm x 25cm; eluting solvent: 70% ethanol/hexane) to isolate the rotation (+)- optical isomer which retention time was 13 minutes (2.0mg, >99% ee.) and the rotation (-)-optical isomer which retention time was 43 minutes (1.4mg, >99% ee.).

The property values of the rotation (+)- optical isomer are as follows.

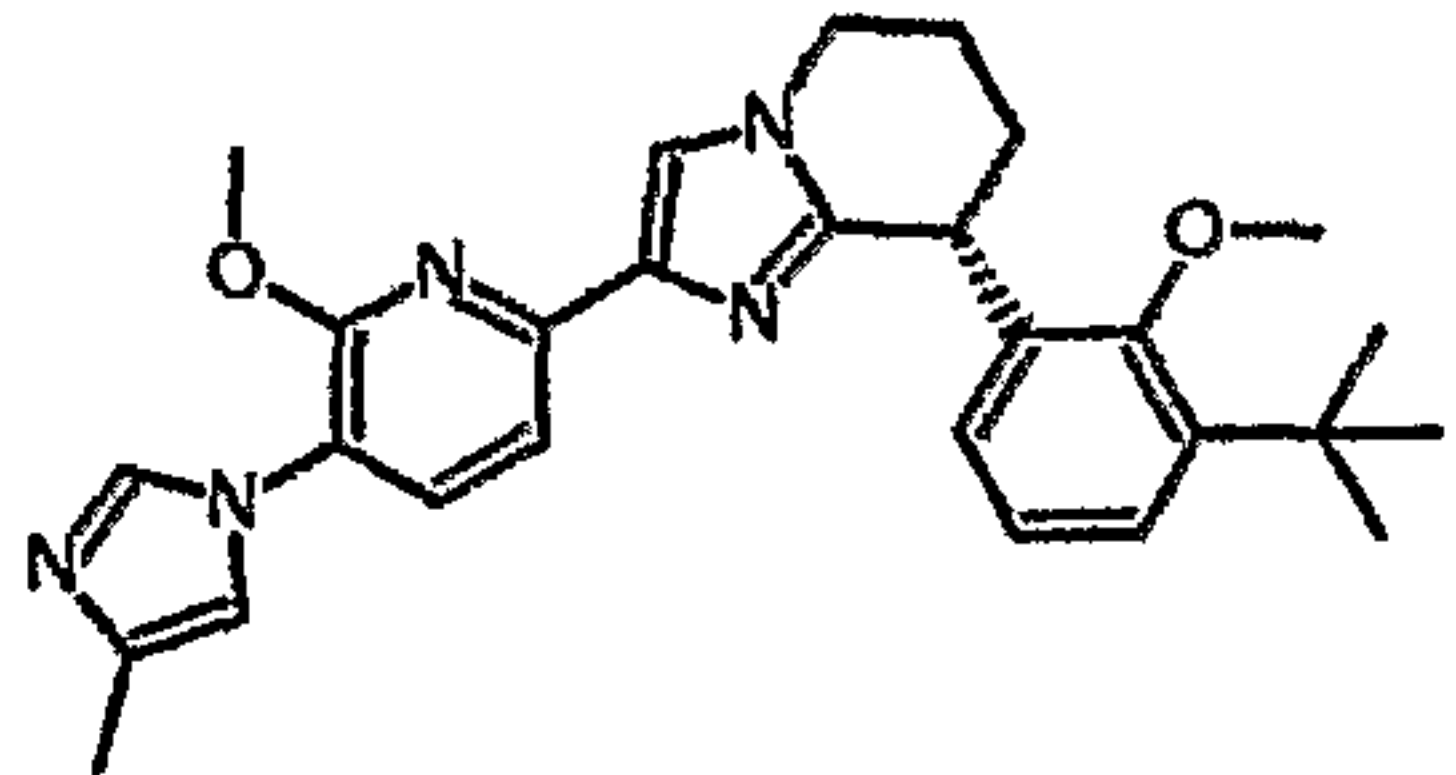
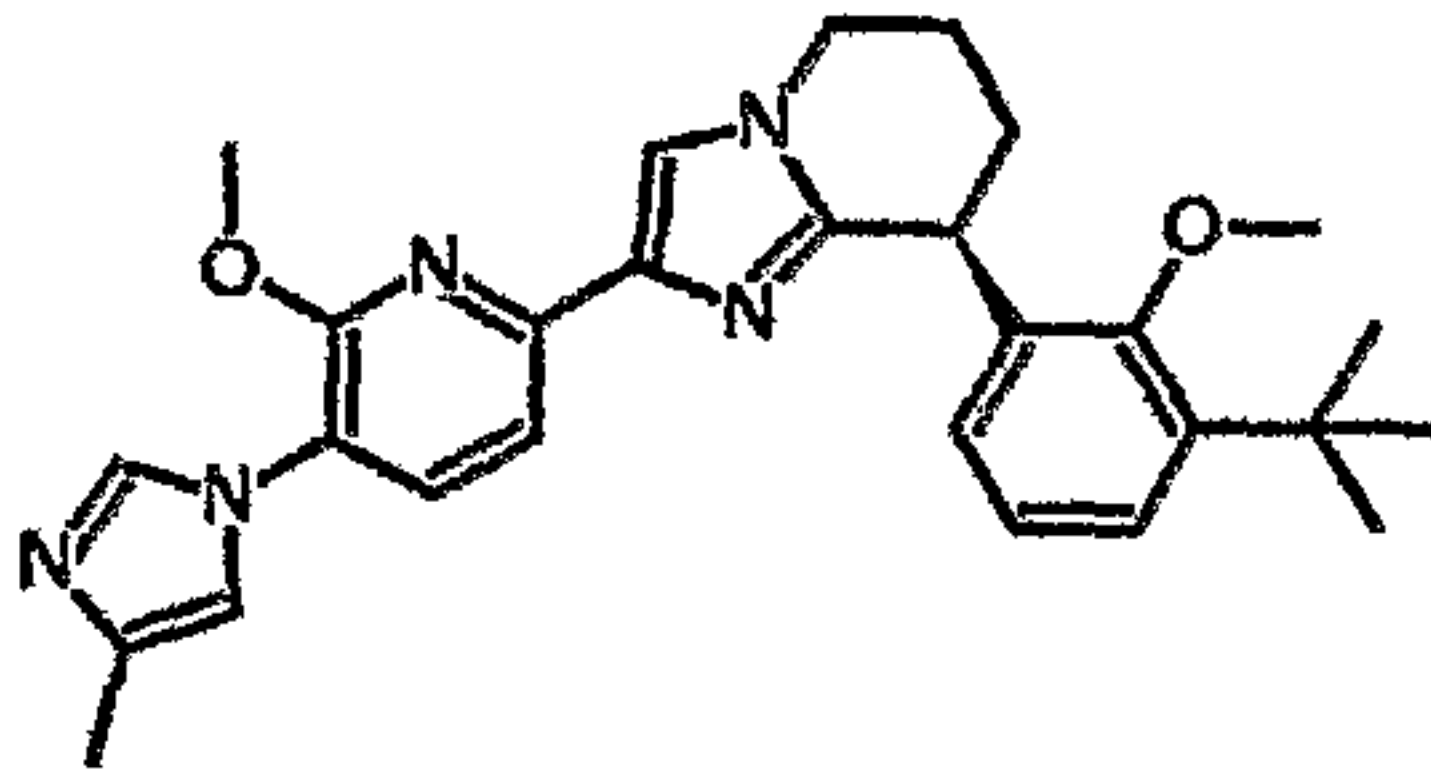
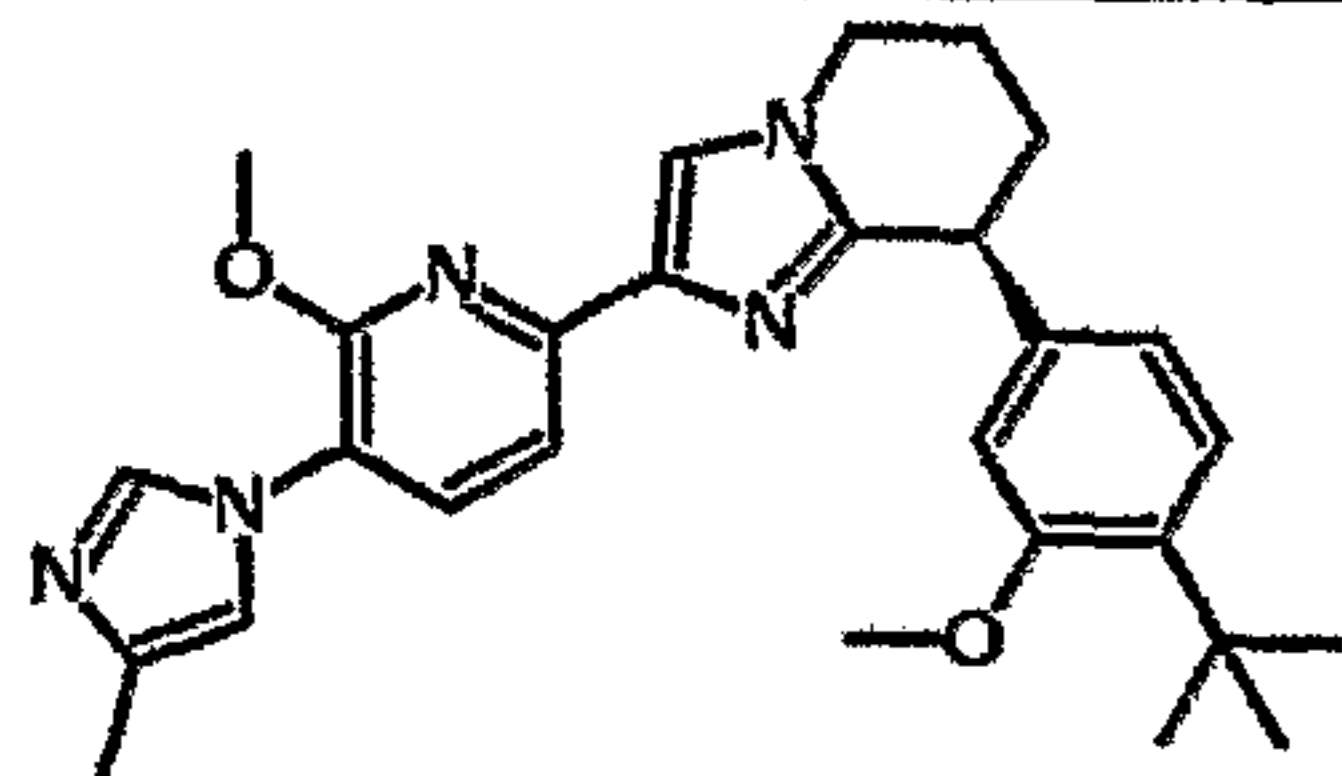
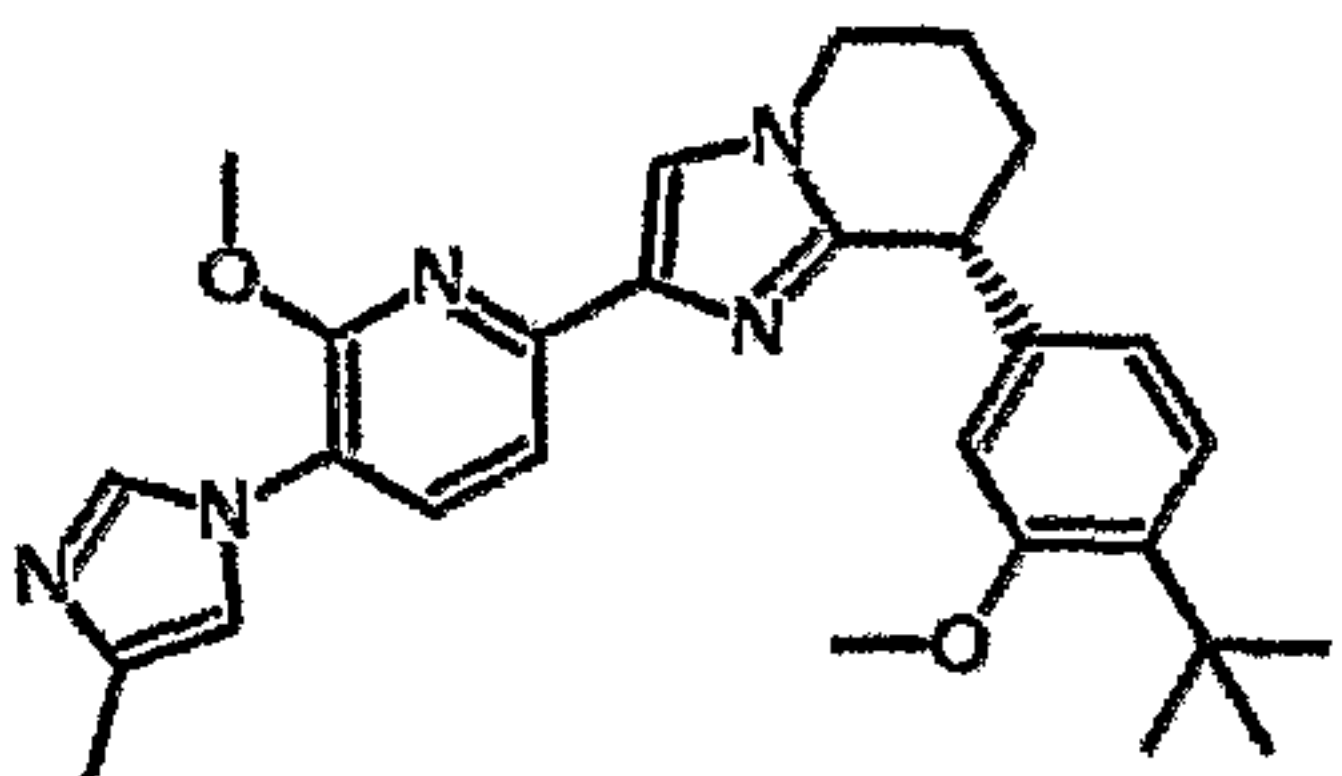
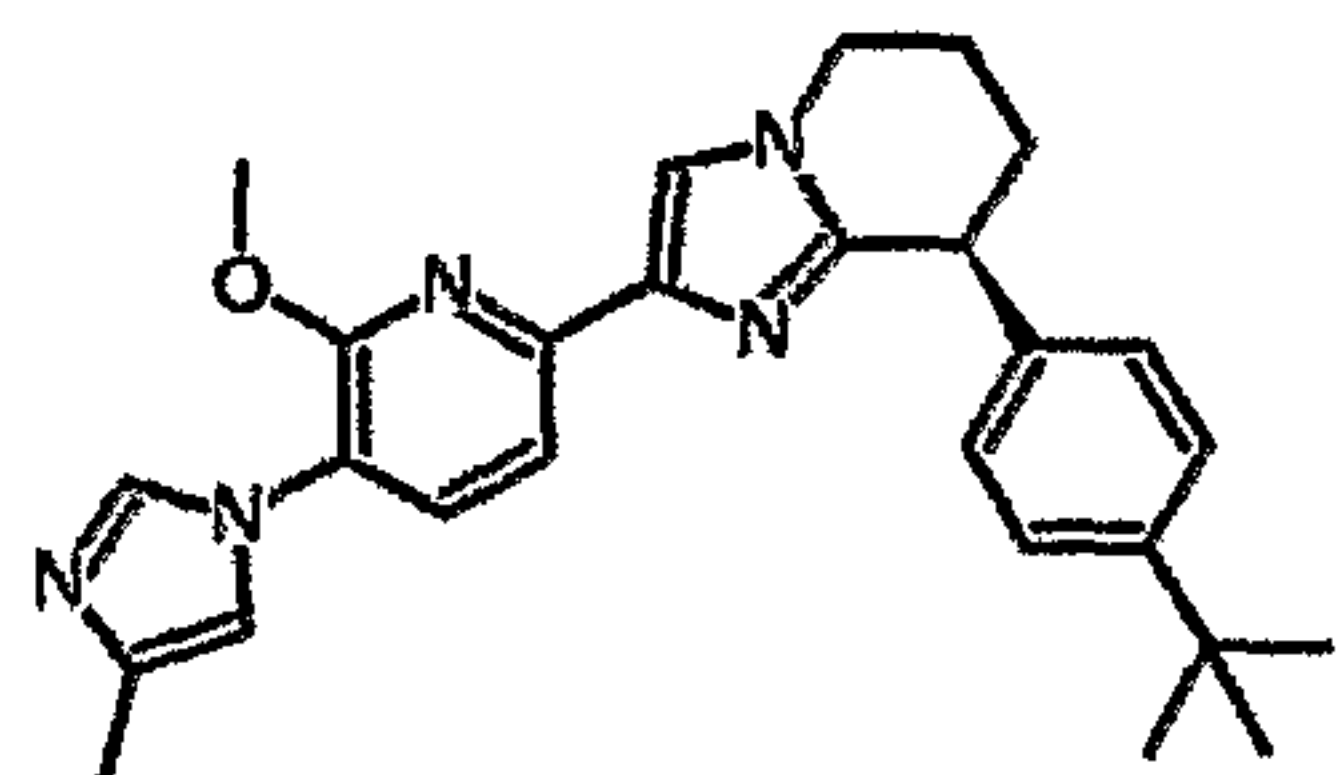
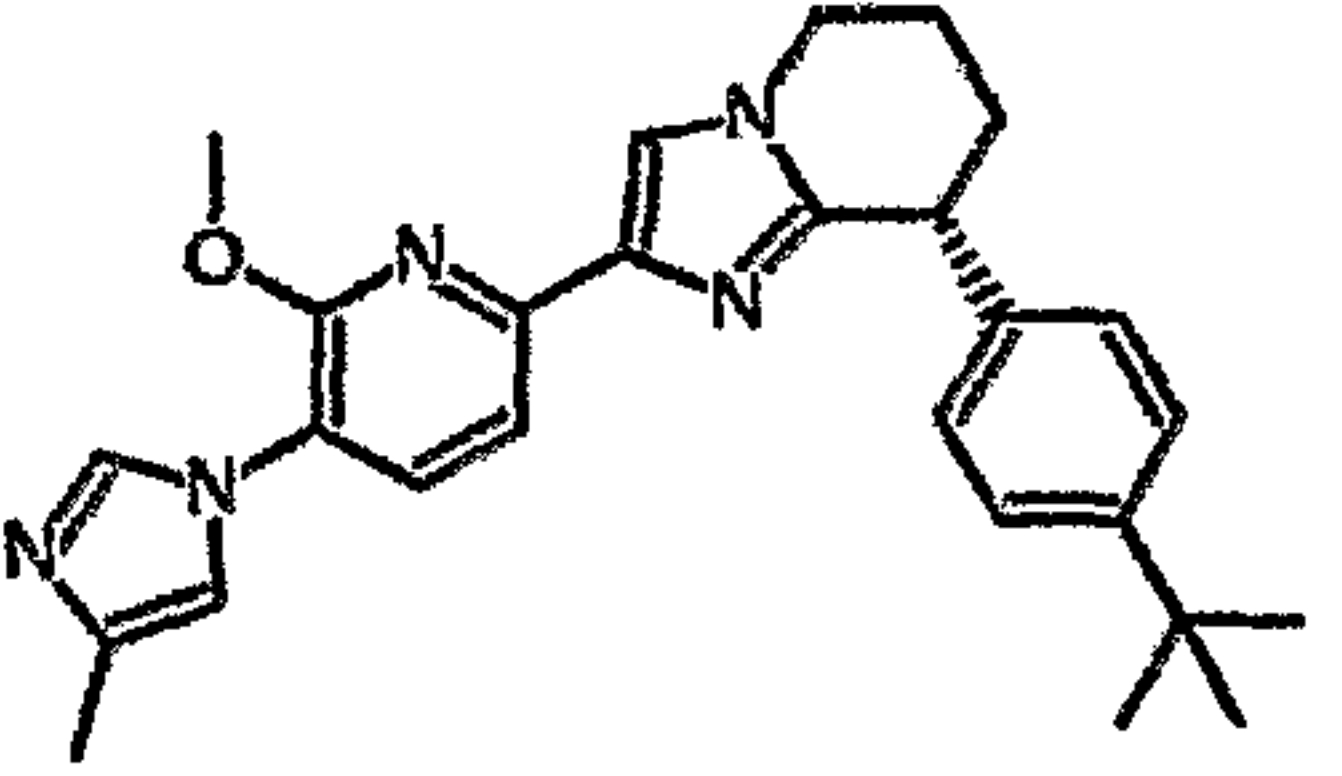
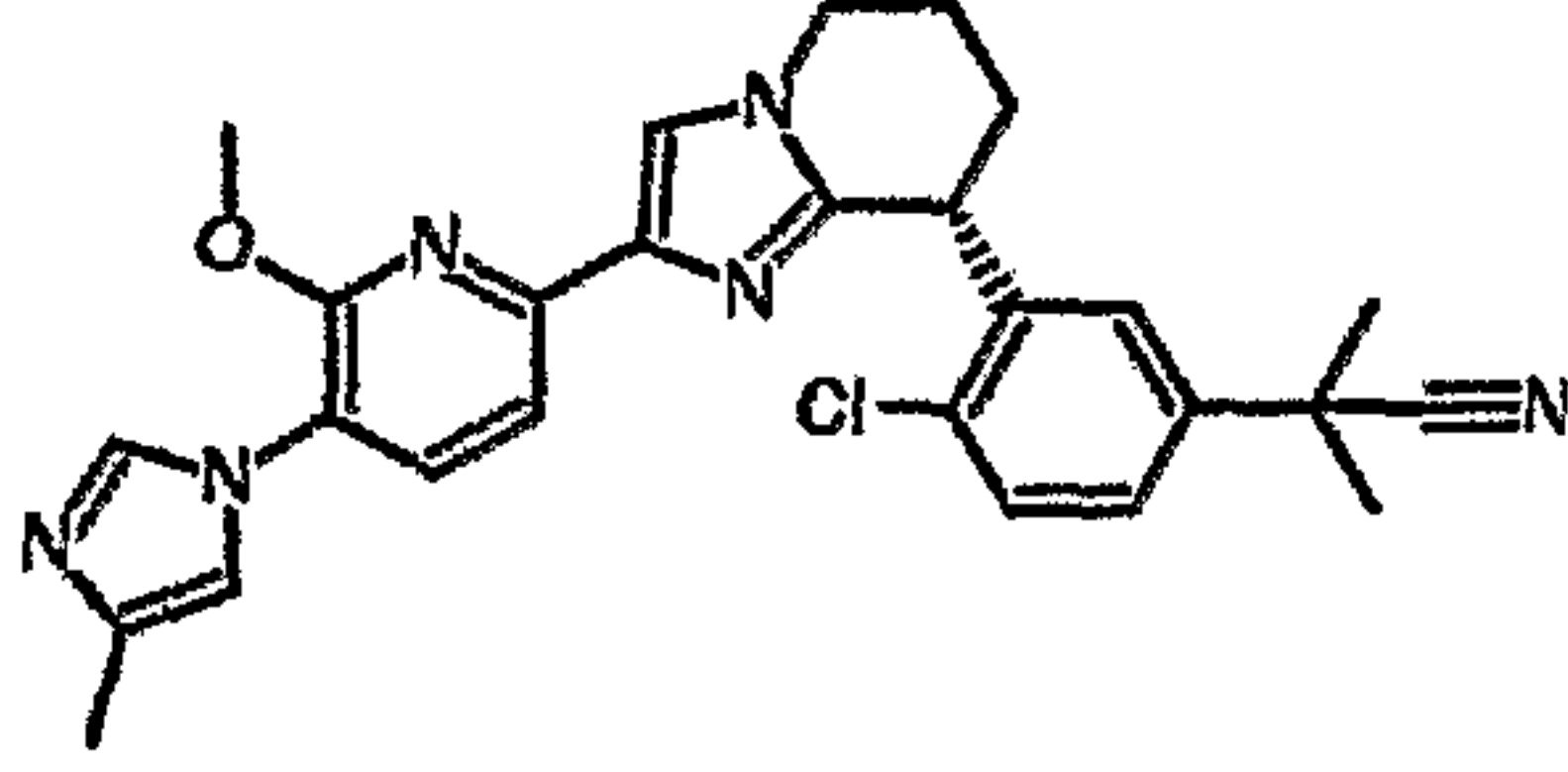
ESI-MS; m/z 520 [M⁺+H]. ¹H-NMR (CDCl₃) δ (ppm): 1.15-1.30 (m, 2H), 1.60-1.75 (m, 2H), 1.95-2.35 (m, 3H), 2.31 (s, 3H), 2.40-2.50 (m, 1H), 4.16 (s, 3H), 4.35-4.50 (m, 2H), 4.65-4.75 (m, 1H), 6.94 (s, 1H), 7.01 (brs, 1H), 7.53 (s, 1H), 7.60 (d, J=7.6Hz, 1H), 7.74 (d, J=7.6Hz, 1H), 7.86(brs,1 H).

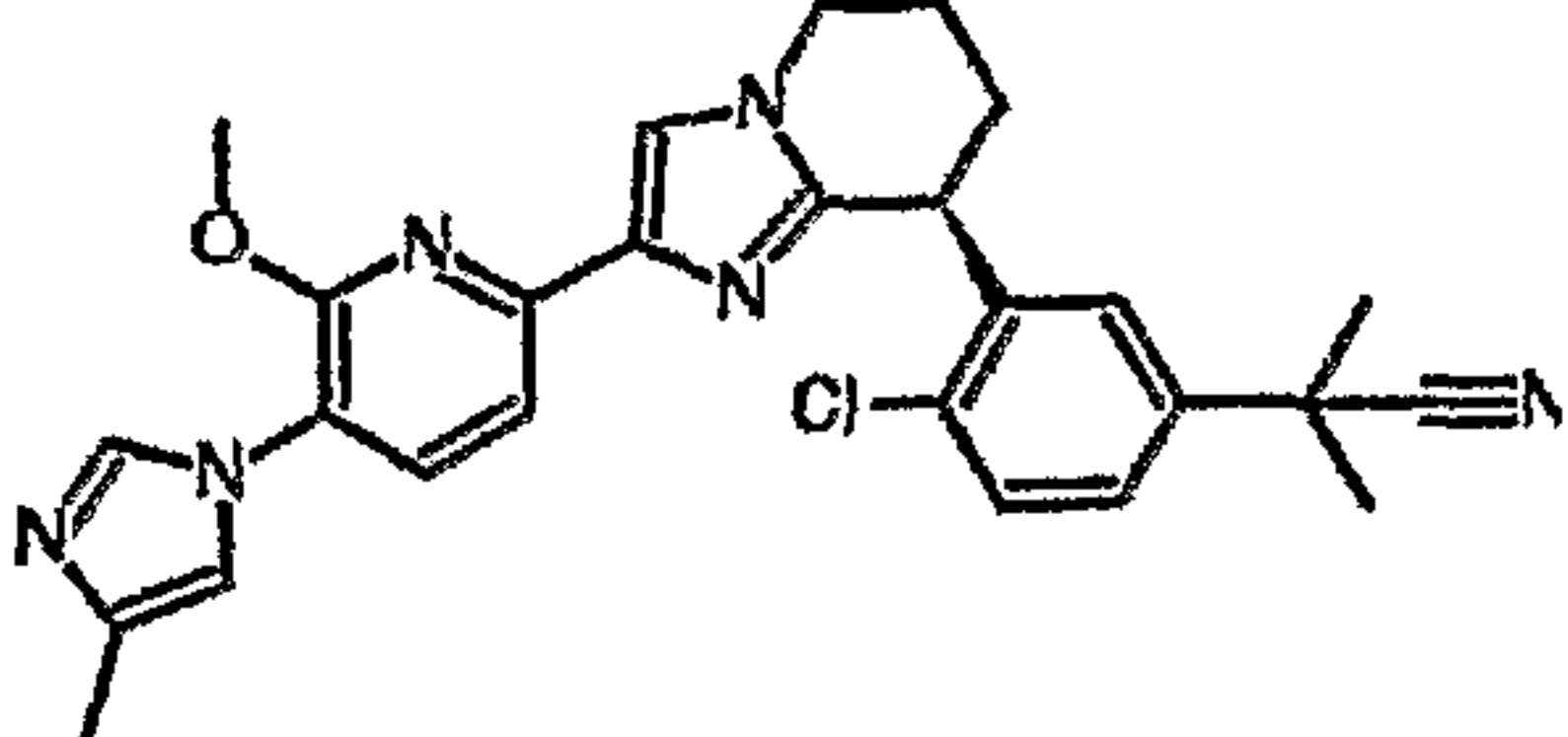
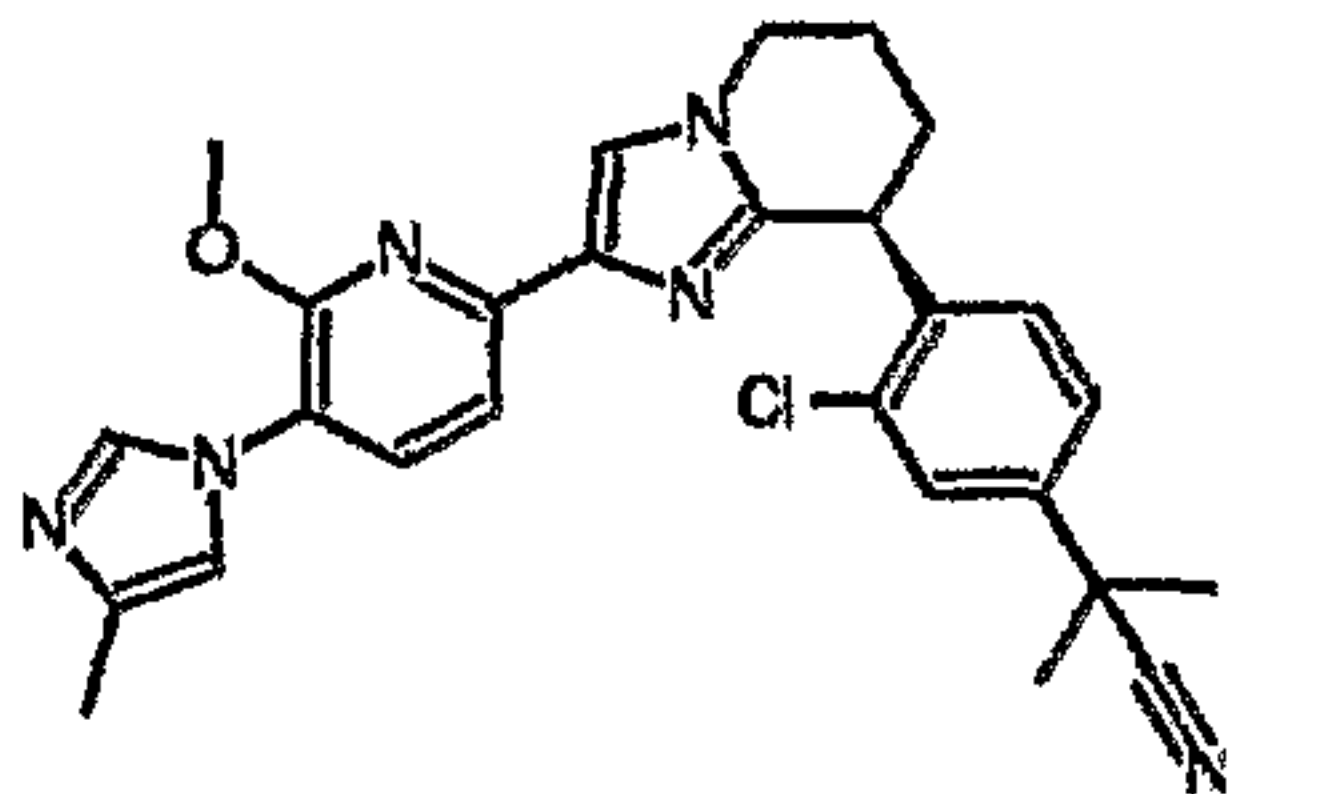
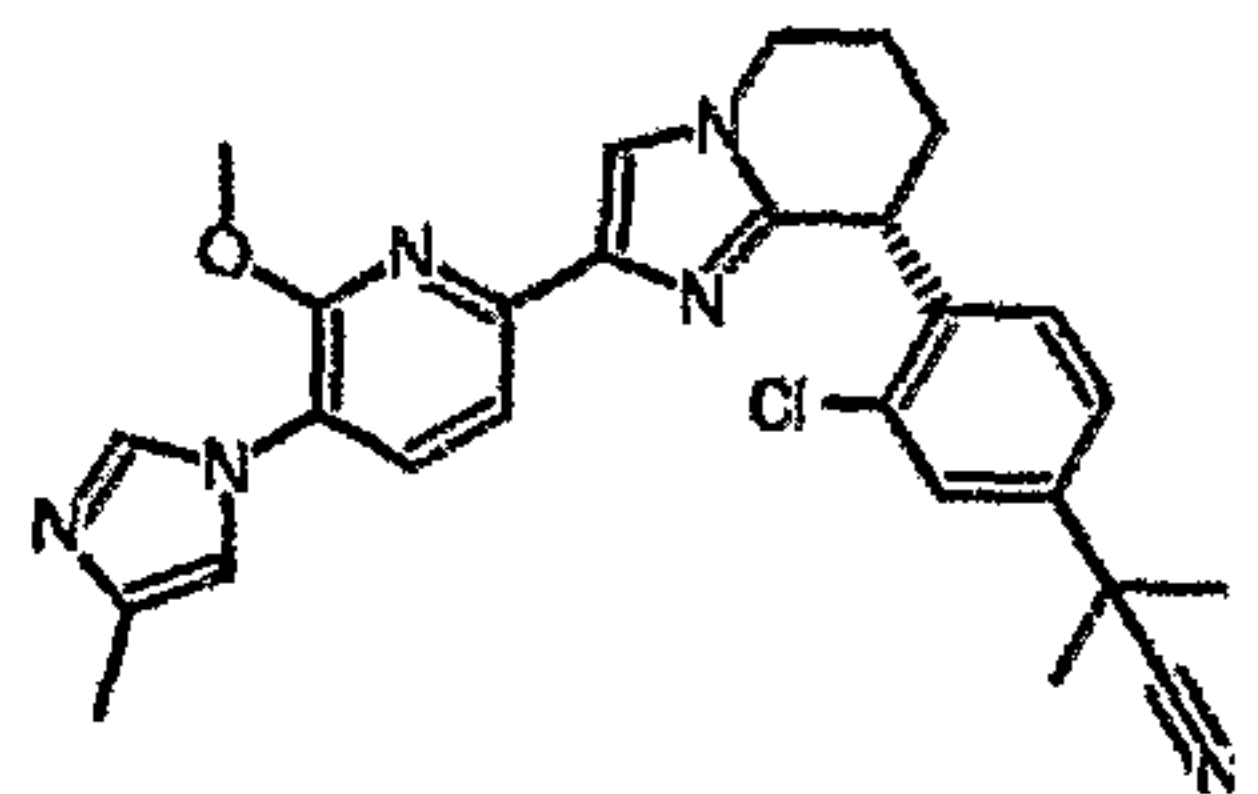
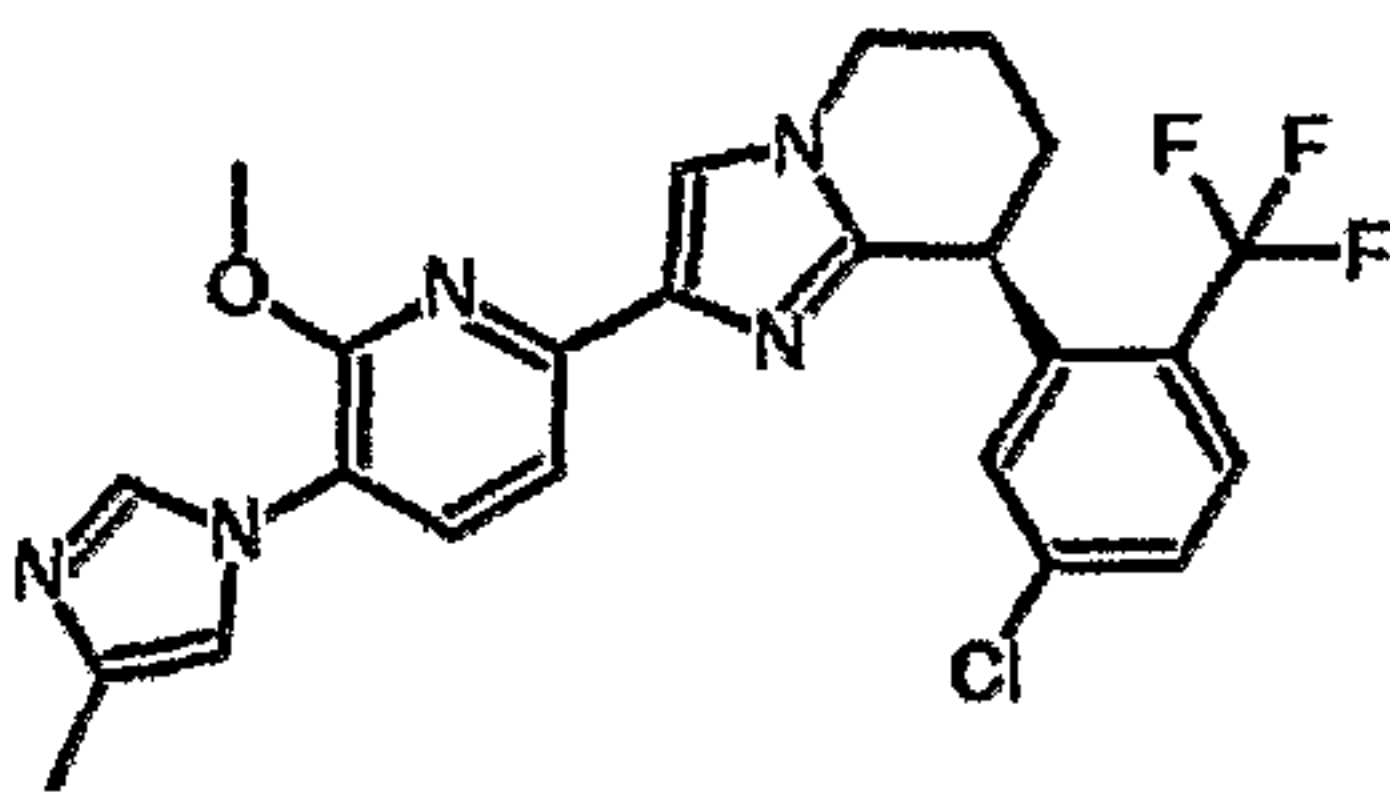
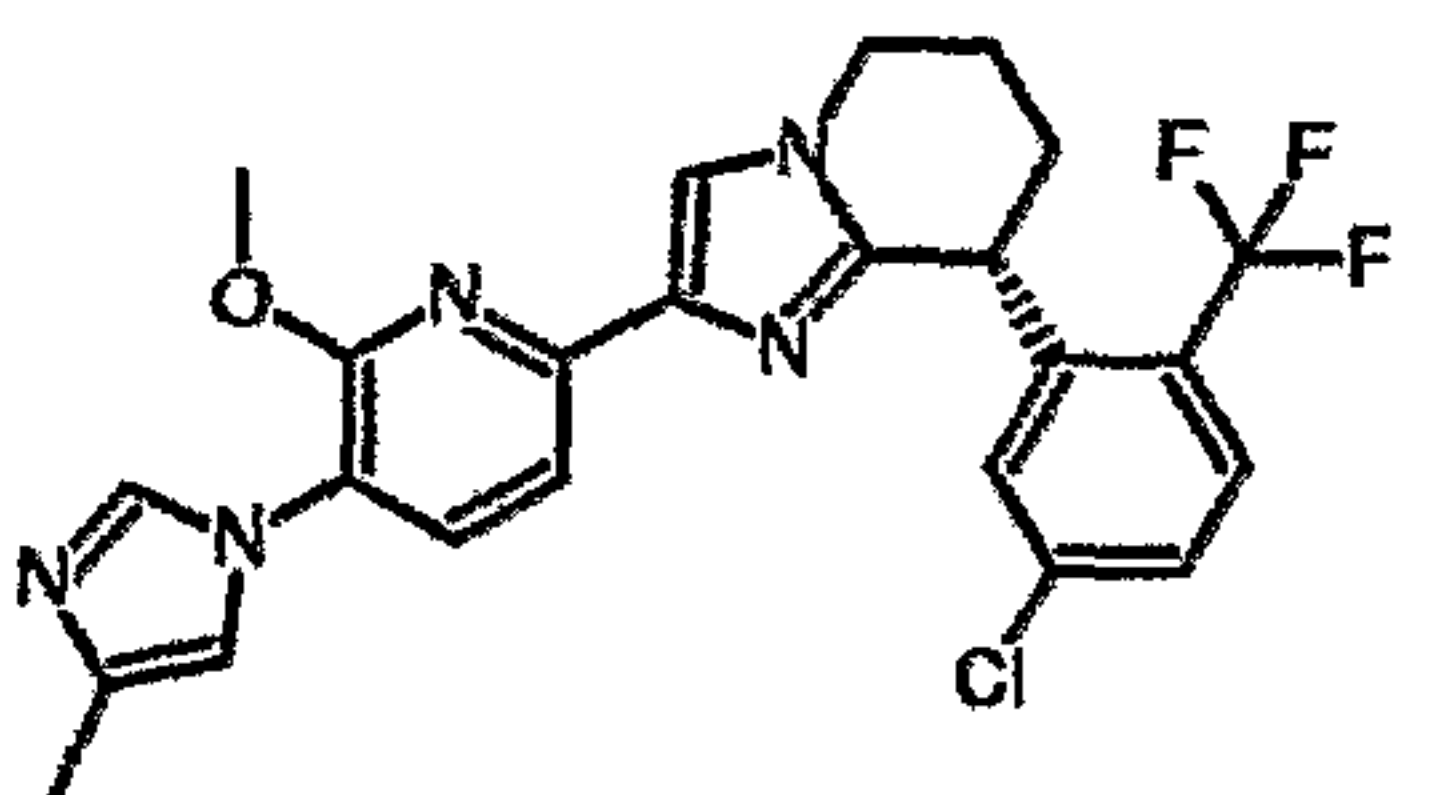
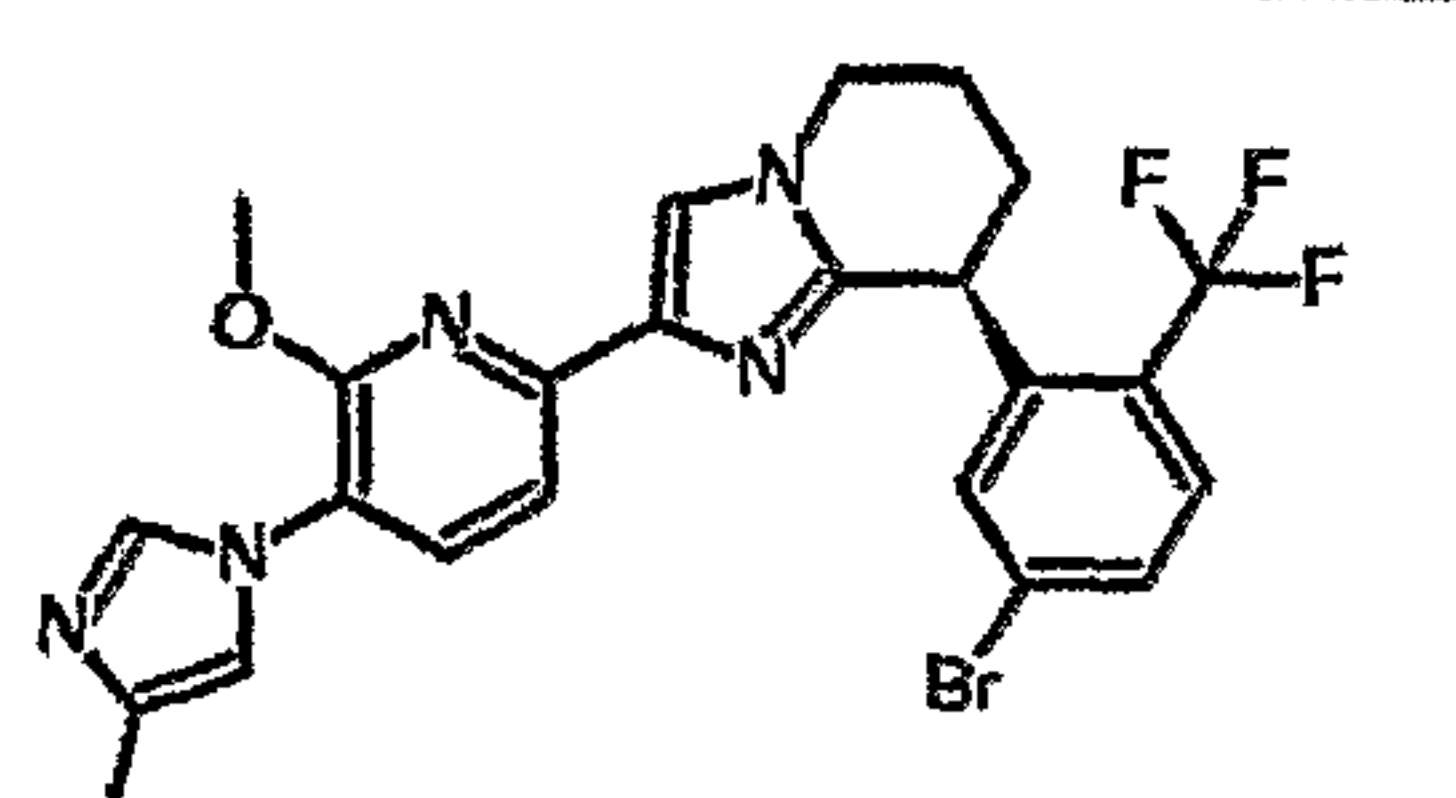
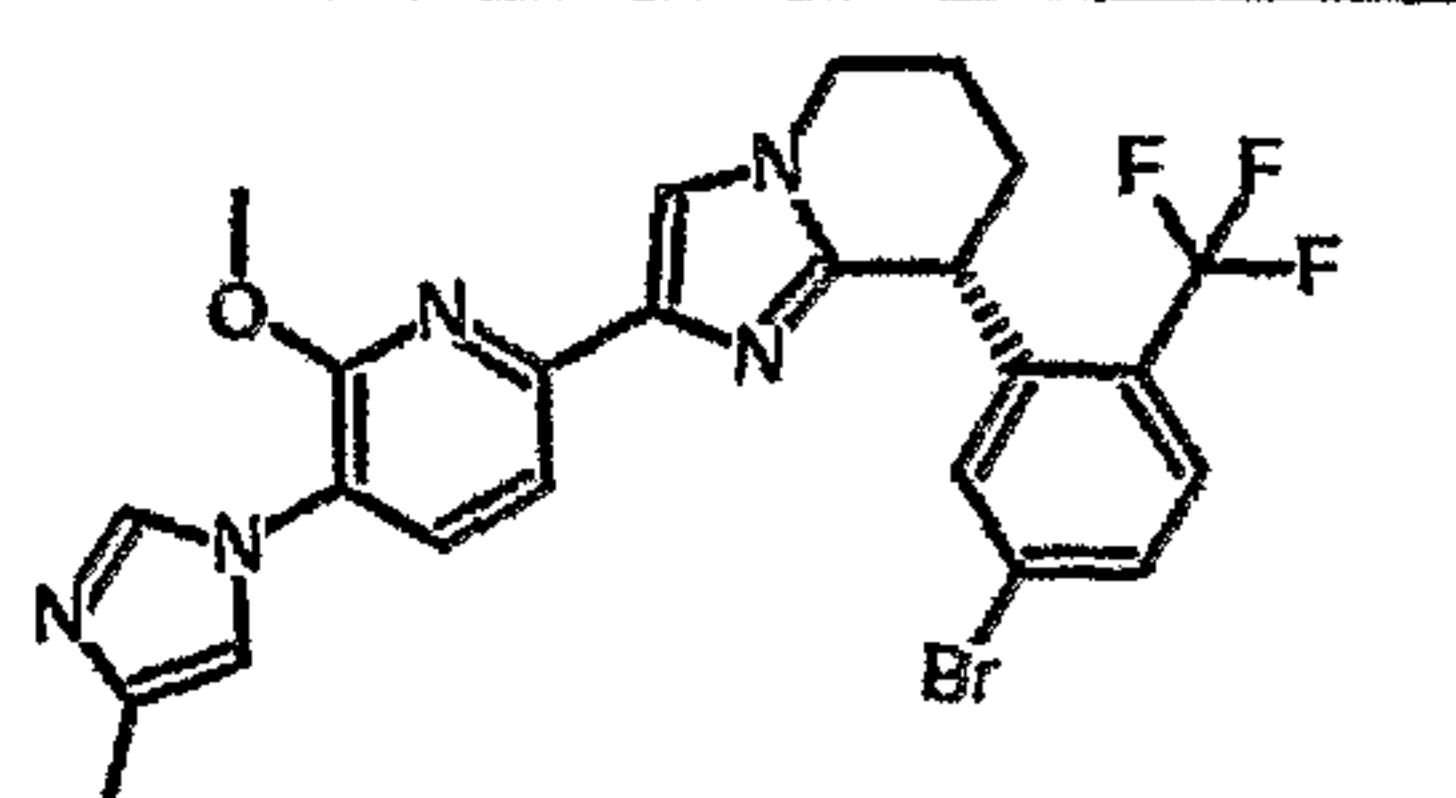
The property values of the rotation (-)- optical isomer are identical with (+)-isomer.

[0807]

According to Example 100 and Example 101, the compounds of Example 238 to Example 251 (Table 25) from the imidate hydrochlorides obtained in Preparation Example 3-9, Preparation Example 3-25, Preparation Example 3-29, Preparation Example 3-34, Preparation
5 Example 3-36, Preparation Example 3-44 and Preparation Example 3-45 and 6-(1-ethoxyvinyl)-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)pyridine obtained in Preparation Example 1-7.

Table 25

Example No.	Structural formula	ESI mass
Example238		ESI-MS; m/z 472 [$M^+ + H$].
Example239		ESI-MS; m/z 472 [$M^+ + H$].
Example240		ESI-MS; m/z 472 [$M^+ + H$].
Example241		ESI-MS; m/z 472 [$M^+ + H$].
Example242		ESI-MS; m/z 442 [$M^+ + H$].
Example243		ESI-MS; m/z 442 [$M^+ + H$].
Example244		ESI-MS; m/z 487 [$M^+ + H$].

Example245		ESI-MS; m/z 487[M ⁺ +H].
Example246		ESI-MS; m/z 487[M ⁺ +H].
Example247		ESI-MS; m/z 487[M ⁺ +H].
Example248		ESI-MS; m/z 488[M ⁺ +H].
Example249		ESI-MS; m/z 488[M ⁺ +H].
Example250		ESI-MS; m/z 534[M ⁺ +H].
Example251		ESI-MS; m/z 534[M ⁺ +H].

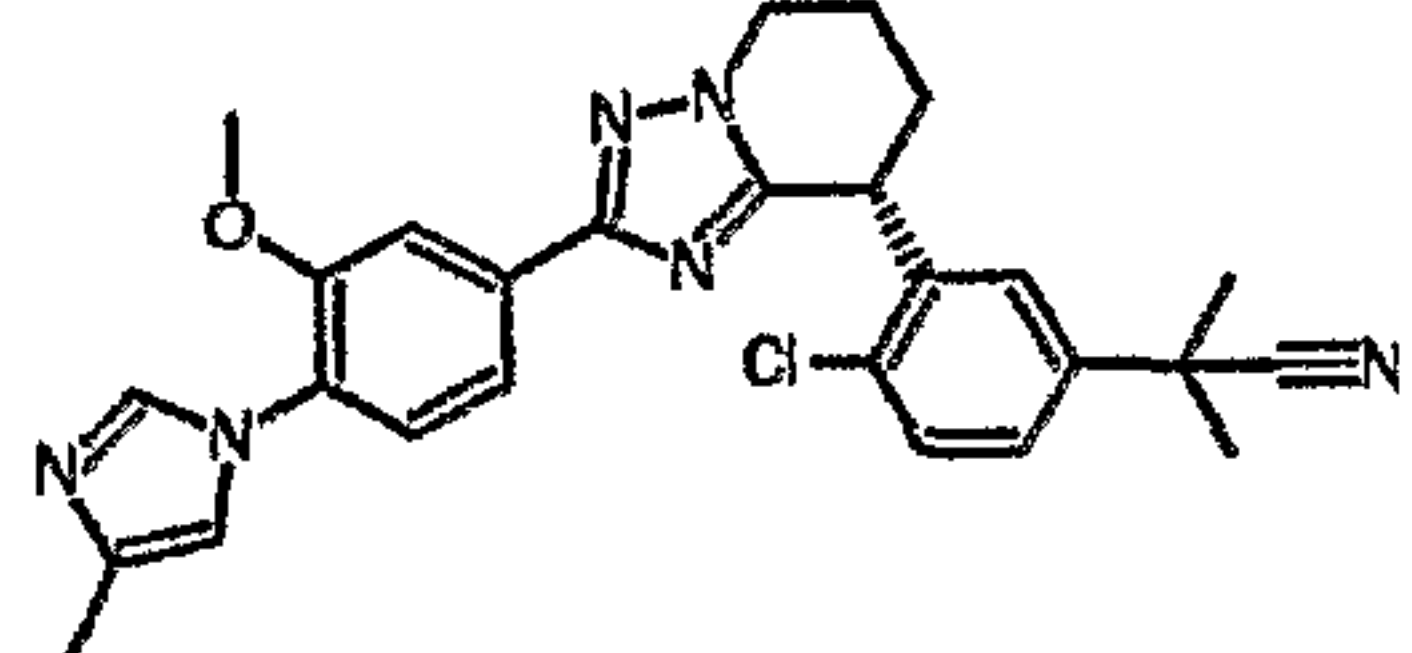
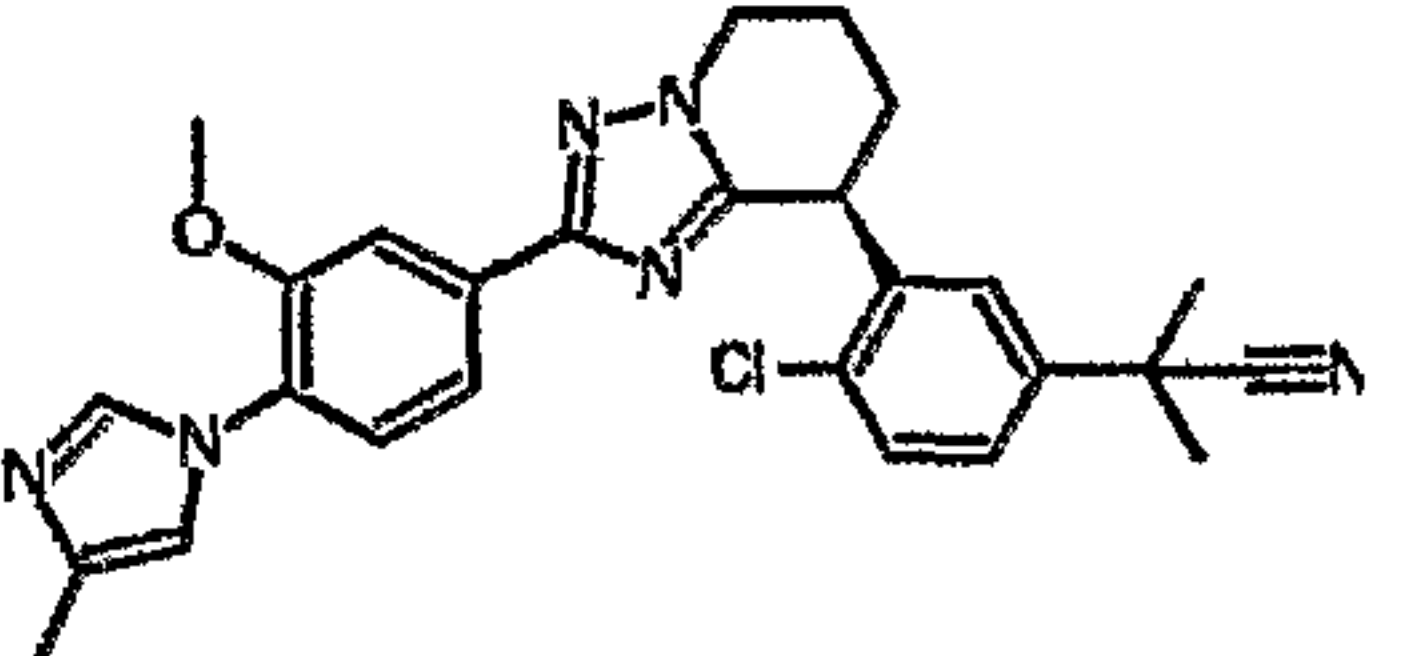
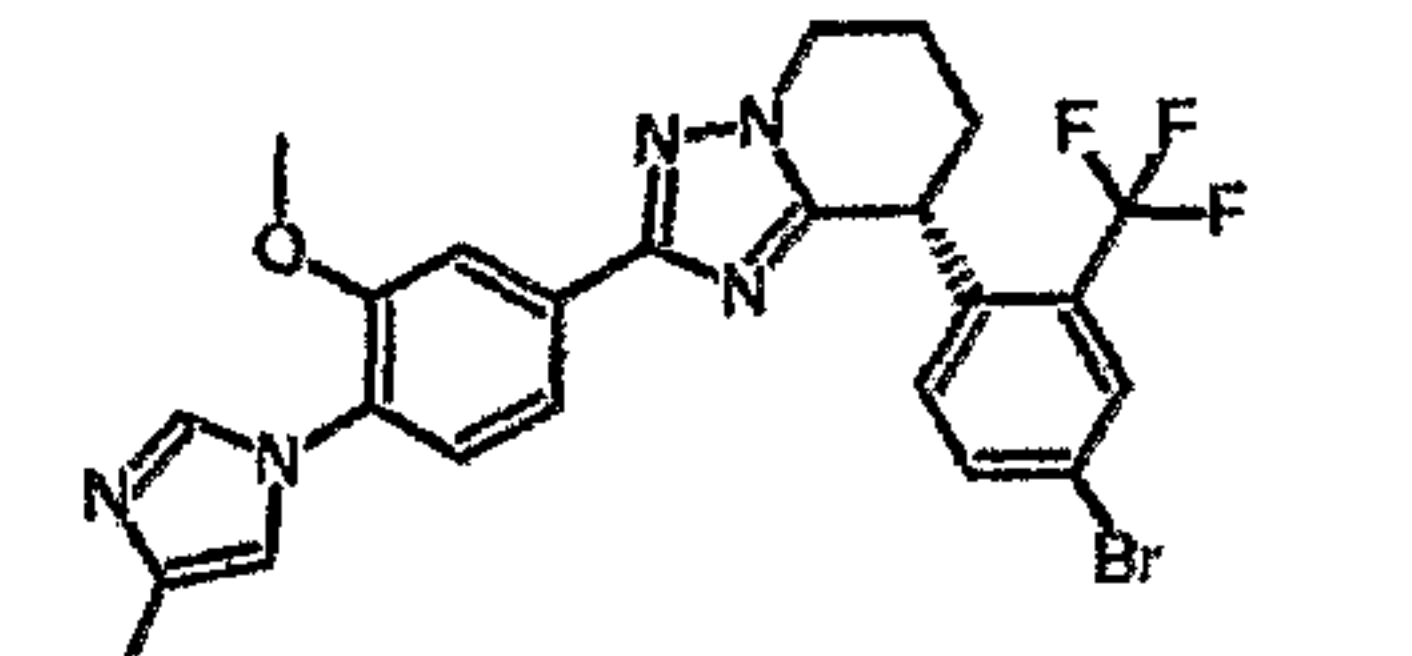
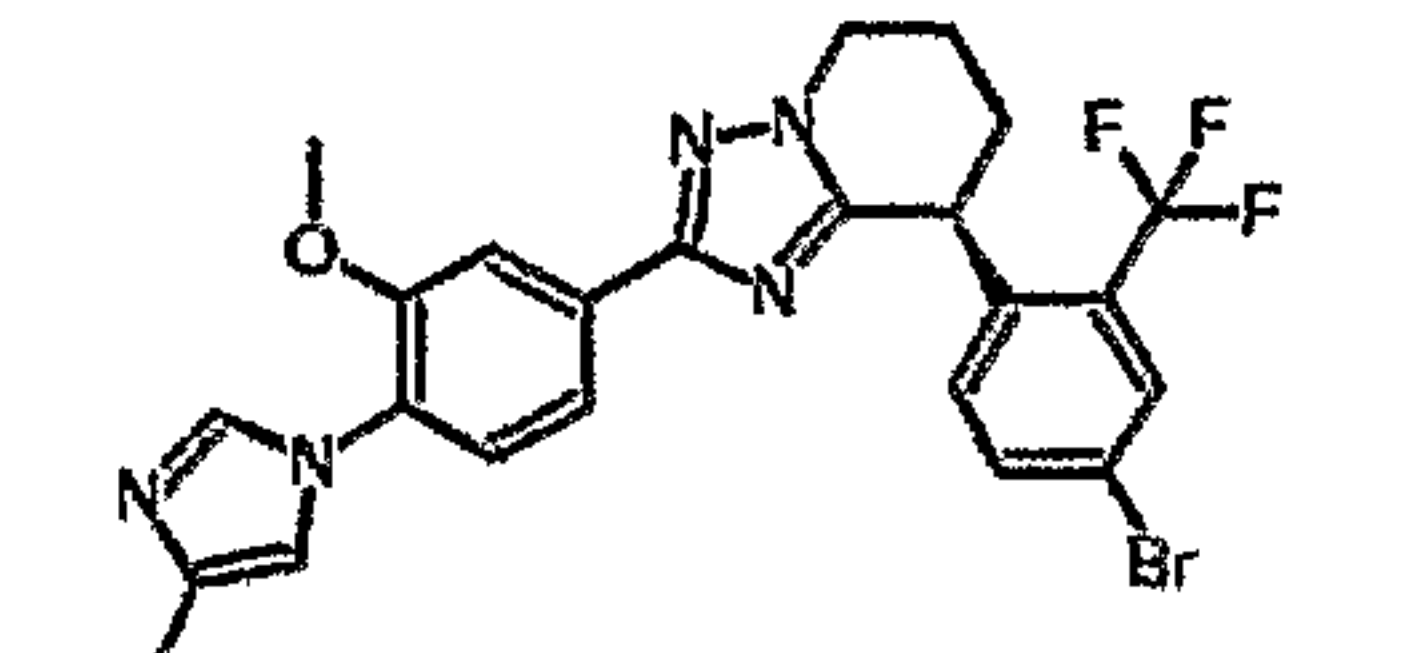
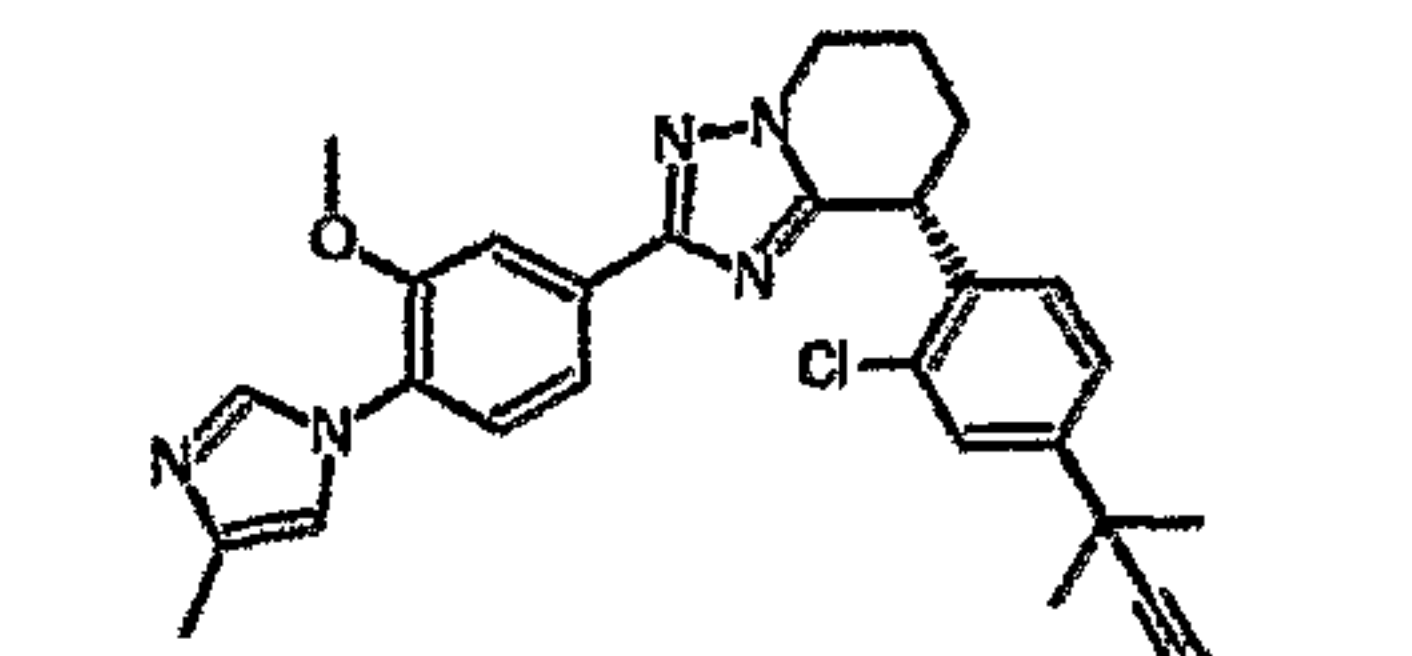
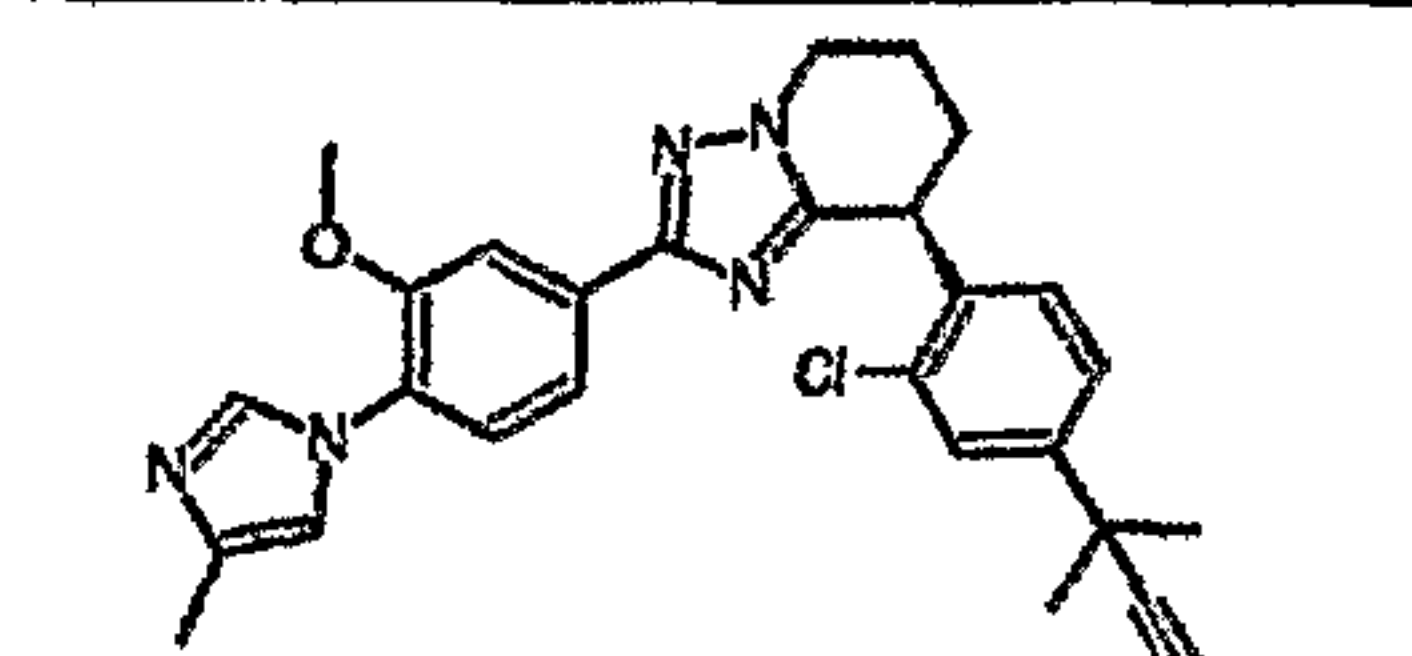
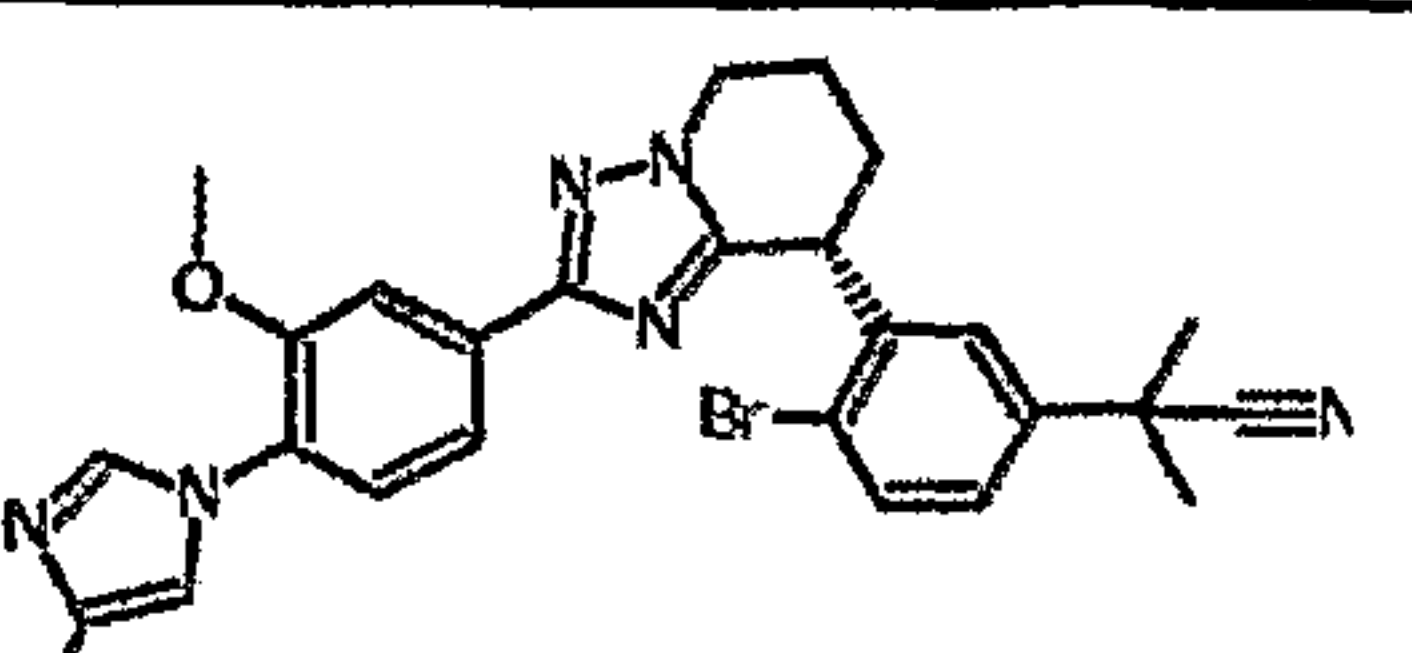
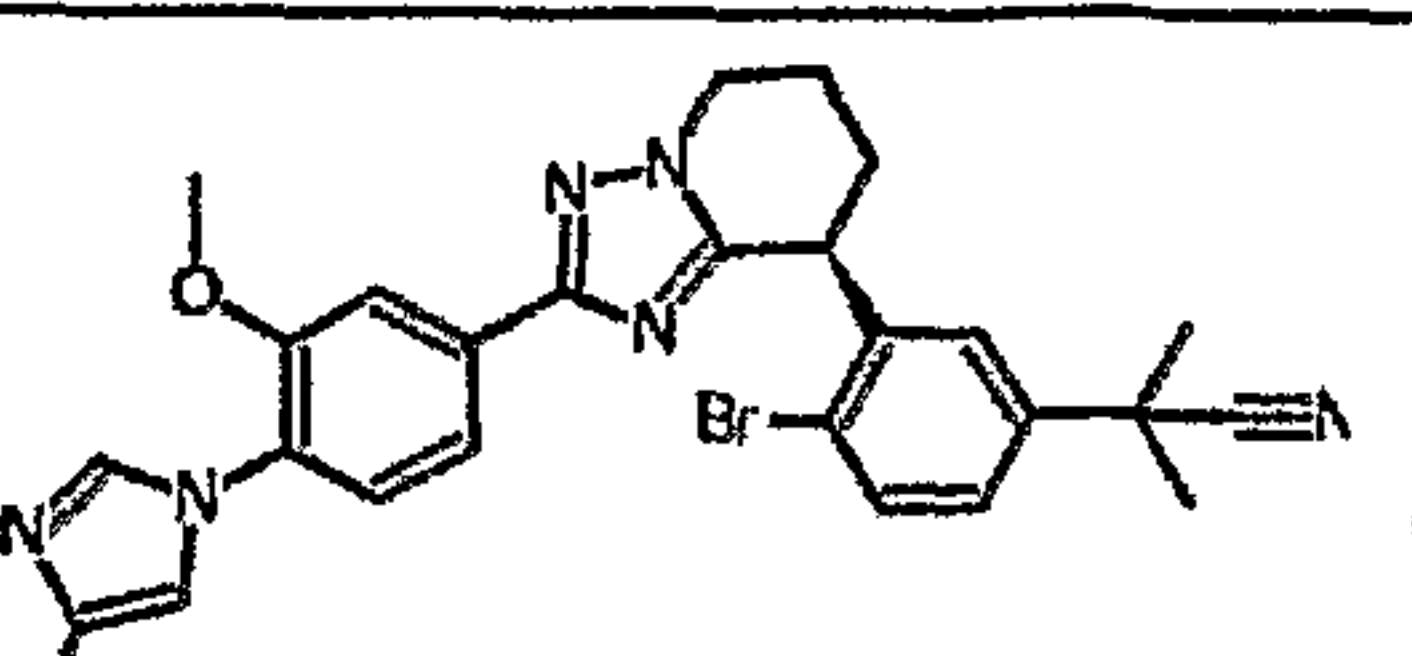
[0808]

According to the method of Examples 42 and 43, the compounds of Example 252 to Example 259 (Table 26) were obtained from the imidate hydrochlorides obtained in Preparation Example 3-1, Preparation Example 3-21, Preparation Example 3-25 and Preparation Example 3-29 and 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzoic acid hydrazide obtained in

Preparation Example 1-9.

[0809]

Table 26

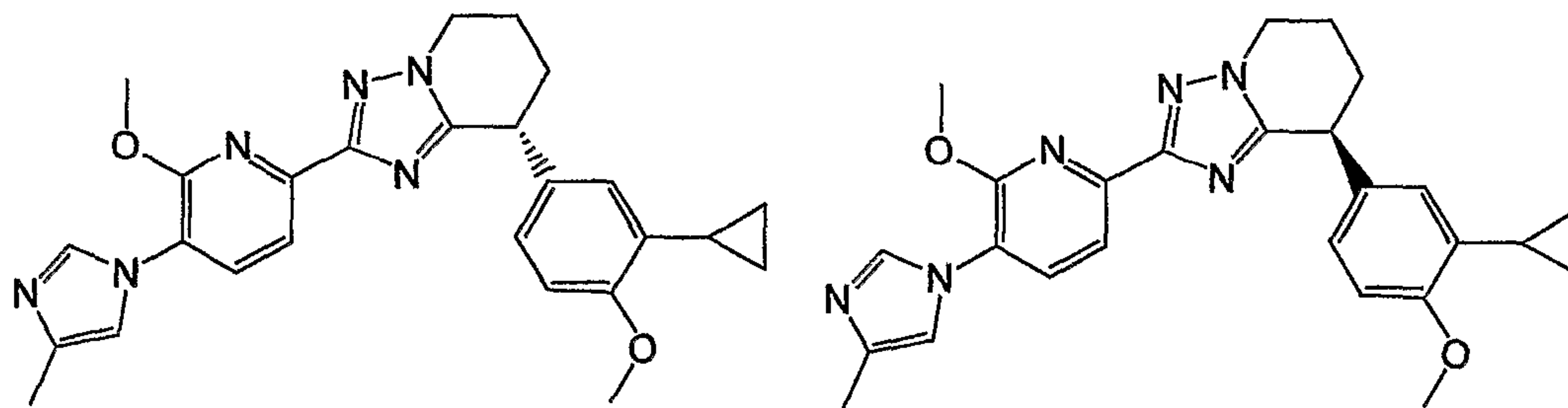
Example No.	Structural formula	ESI mass
Example252		ESI-MS; m/z 487[M ⁺ +H].
Example253		ESI-MS; m/z 487[M ⁺ +H].
Example254		ESI-MS; m/z 534[M ⁺ +H].
Example255		ESI-MS; m/z 532[M ⁺ +H].
Example256		ESI-MS; m/z 487[M ⁺ +H].
Example257		ESI-MS; m/z 487[M ⁺ +H].
Example258		ESI-MS; m/z 531[M ⁺ +H].
Example259		ESI-MS; m/z 531[M ⁺ +H].

[0810]

Example 260 and Example 261

Syntheses of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(3-cyclopropyl-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(3-cyclopropyl-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0811]



[0812]

According to Example 150 and Example 151, racemic title compound (65.1mg) was obtained starting from 2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-8-(3-bromo-4-methoxyphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine. This racemic compound was purified with CHIRALCEL™ IA (Daicel Chemical Industries, Ltd.; 2cm x 25cm; eluting solvent: 30% ethanol/hexane) to isolate the rotation (+)- optical isomer which retention time was 16 minutes (4.2mg) and the rotation (-)-optical isomer which retention time was 28.5 minutes (3.7mg). The property value of the title compounds is as follows.

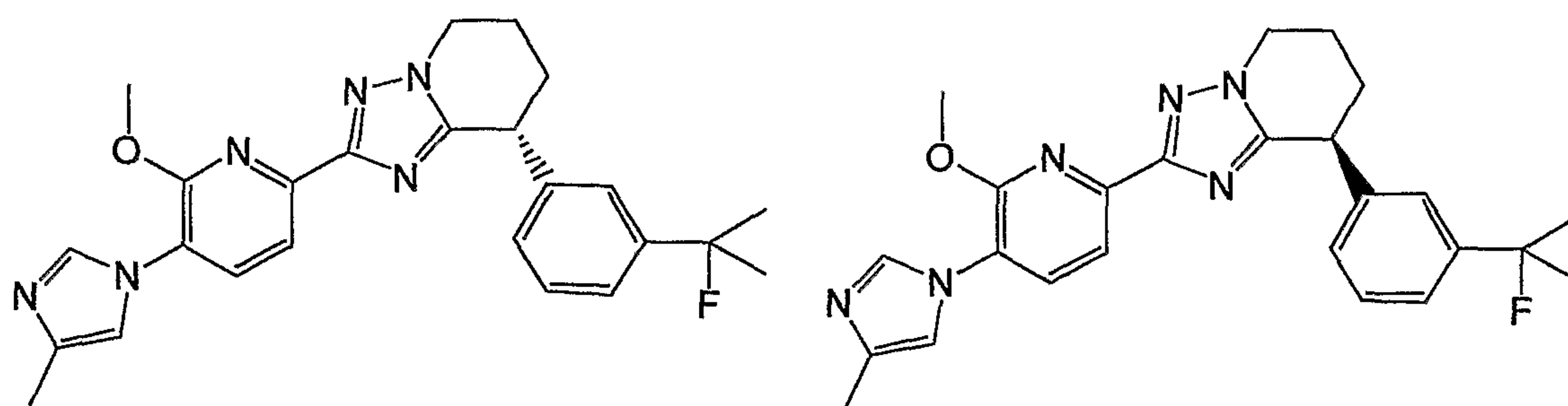
ESI-MS; m/z 457 [M⁺+H]

[0813]

Example 262 and Example 263

Syntheses of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-[3-(1-fluoro-1-methylethyl)phenyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-[3-(1-fluoro-1-methylethyl)phenyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0814]



[0815]

Synthesis of methyl 3-(4-chloro-1-ethoxycarbonimidoylbutyl)-benzoate

According to the method of Preparation Example 3-1, the title compound (1.47 g) was obtained from methyl 3-cyanomethyl-benzoate (999 mg). The property value of the title compounds is as follows.

ESI-MS; m/z 298 [M⁺+H]

[0816]

Synthesis of methyl 3-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-yl}benzoate

According to the method of Examples 42 and 43, title compound (1.64 g) was obtained from methyl 3-(4-chloro-1-ethoxycarbonimidoylbutyl)-benzoate hydrochloride (1.47 g) and 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-carboxylic acid hydrazide (1.09 g) obtained in Preparation Example 1-6. The property value of the title compounds is as follows.

ESI-MS; m/z 445 [M⁺+H]

[0817]

Synthesis of 2-(3-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-yl})-phenyl-propan-2-ol

To the THF (19.5ml) solution of methyl 3-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridine-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-8-yl}benzoate (866 mg), methymagnesium bromide (10.1 ml) was added at 10°C and the reaction mixture was stirred at the same temperature. The reaction mixture was quenched by adding saturated ammonium chloride aqueous solution and extracted with ethyl acetate. This organic phase was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual oily material was purified by silica gel column chromatography (carrier: Yamazen silica gel, elution solvent: ethyl acetate/heptane = 0~100 % and then methanol/ethyl acetate=15 %) to obtain the title compound (785 mg). The property values of the title compounds are as follows.

¹H-NMR (CDCl₃) δ (ppm): 1.59 (s, 6H), 2.06-2.16 (m, 2H), 2.16-2.27 (m, 1H), 2.30 (s, 3H), 2.34-2.44 (m, 1H), 4.16 (s, 3H), 4.32-4.47 (m, 3H), 6.94-6.98 (m, 1H), 6.99-7.01 (m, 1H), 7.30 (d, J=7.8Hz, 1H), 7.35-7.38 (m, 2H), 7.58 (d, J=7.8Hz, 1H), 7.78 (d, J=7.8Hz, 1H), 7.82 (d, J=1.5Hz, 1H).

5 [0818]

Syntheses of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-[3-(1-fluoro-1-methylethyl)phenyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-[3-(1-fluoro-1-methylethyl)phenyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

10 2-(3-{6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl}-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-8-yl)-phenyl-propan-2-ol (159 mg) was dissolved in methylene chloride (3.6 ml), and to the mixture, [bis(2-methoxyethyl)amino]sulfur trifluoride (79.6 μl) was added at room temperature. After 18 hour stirring, the reaction mixture was quenched by adding saturated sodium hydrogen carbonate aqueous solution, and extracted by
15 ethyl acetate. The organic phase was washed with saturated sodium hydrogen carbonate aqueous solution and brine sequentially, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residual oily material was purified by silica gel column chromatography (carrier: Yamazen silica gel, elution solvent: chloroform/methanol=25/1) to obtain the title compound (115.5 mg) as a mixture with exo-olefin compound. Subsequently, resulted material
20 was dissolved in THF (2.7 ml), and to the mixture, 9-borabicyclo[3,3,1]nonane (644 μl) was added at room temperature, and the reaction mixture was stirred at 80°C for 17 hours. To the reaction mixture, after cooling to 0°C, ethanol (0.9 ml), 2N-sodium hydroxide aqueous solution (0.9 ml) and hydrogen peroxide aqueous solution (0.75 ml) were added, and then the reaction mixture was stirred for 2 hours at 80°C. The reaction mixture was quenched by adding saturated
25 sodium thiosulfate aqueous solution, and extracted with ethyl acetate. The organic layer was washed with water and brine sequentially, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual oily material was purified by silica gel column chromatography (carrier: Yamazen silica gel, elution solvent: ethyl acetate/heptane=0~100% and then methanol/ethyl acetate=10%) to obtain the title compound (52
30 mg).

[0819]

The resulting racemate was separated by CHIRALPAKTM IB (2 cm × 25 cm, mobile phase: 20% ethanol-hexane) to obtain the title compound with a retention time of 28 minutes and positive optical rotation (14.4 mg) and the title compound with a retention time of

54 minutes and negative optical rotation (12.4 mg).

The property values of the title optically active compound with positive optical rotation are as follows.

¹H-NMR(CDCl₃)δ(ppm): 1.64(s, 3H), 1.69(s, 3H), 2.04-2.16(m, 2H), 2.20(ddd, J=8.1, 8.1, 6.3Hz, 1H), 2.30(s, 3H), 2.34-2.44(m, 1H), 4.16(s, 3H), 4.32-4.48(m, 3H), 6.96-7.01(m, 2H), 7.23-7.33(m, 3H), 7.58(d, J=7.8Hz, 1H), 7.78(d, J=7.8Hz, 1H), 7.81-7.83(m, 1H).

The property values of the title optically active compound with negative optical rotation are as follows.

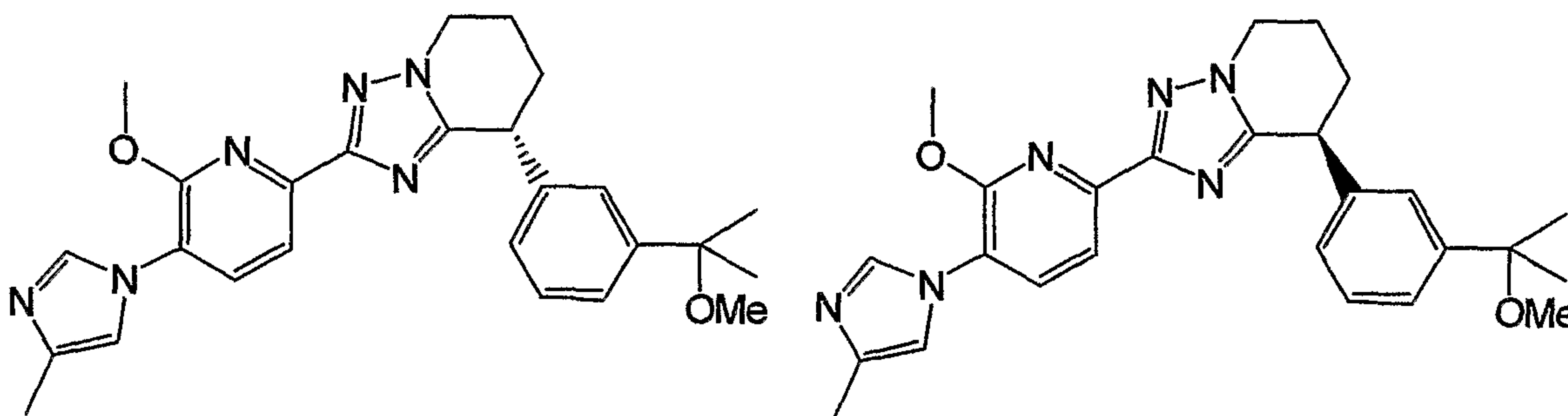
¹H-NMR(CDCl₃)δ(ppm): 1.64(s, 3H), 1.69(s, 3H), 2.04-2.16(m, 2H), 2.20(ddd, J=8.1, 8.1, 6.3Hz, 1H), 2.30(s, 3H), 2.34-2.44(m, 1H), 4.16(s, 3H), 4.32-4.48(m, 3H), 6.96-7.01(m, 2H), 7.23-7.33(m, 3H), 7.58(d, J=7.8Hz, 1H), 7.78(d, J=7.8Hz, 1H), 7.81-7.83(m, 1H).

[0820]

Examples 264 and 265

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(3-(1-methoxy-1-methylethyl)phenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-((3-(1-methoxy-1-methylethyl)phenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a] pyridine

[0821]



[0822]

20 2-(3-{2-[6-Methoxy-5-(4-methy-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-8-yl}-phenyl-2-ol (60 mg) was dissolved in methanol (1.3 ml) and then DOWEXTM 50X8 (6 mg) was added at room temperature. After stirring at room temperature for 24 hours, DOWEXTM 50X8 (20 mg) was further added and the mixture was stirred for 6 hours at the same temperature. Trimethyl orthoformate (44.3 μL) was added to the reaction solution, followed by stirring for 19 hours.

p-Toluenesulfonic acid mono hydrate (5.1 mg) was added thereto followed by stirring for 24 hour. Further p-toluenesulfonic acid mono hydrate (5.1 mg) was added thereto followed by

stirring for 4 days, and the reaction was quenched with a saturated potassium carbonate solution, followed by extraction with ethyl acetate. The organic layer was washed with a saturated potassium carbonate solution and dried over sodium sulfate. The solvent was removed and the resulting crude product was purified by silica gel column chromatography (carrier: Yamazen
5 Silica gel; elution solvent: ethyl acetate: heptane = 0:100 → 100:0, then 15% methanol-ethyl acetate) to obtain the title compound.

The resulting racemate was separated by CHIRALPAK™ IB (2cmx25cm:mobile phase;20% ethanol-hexane) to obtain the title compound with a retention time of 23.5 minutes and positive optical rotation (21.9 mg) and the title compound with a retention time of 47 minutes and
10 negative optical rotation (15.1 mg).

The property values of the title optically active compound with positive optical rotation are as follows.

¹H-NMR(CDCl₃)δ(ppm): 1.50(s, 6H), 2.04-2.16(m, 2H), 2.16-2.27(m, 1H), 2.30(s, 3H), 2.34-2.44(m, 1H), 3.07(s, 3H), 4.16(s, 3H), 4.32-4.48(m, 3H), 6.94-6.98(m, 1H), 6.99-7.01(m, 1H),
15 7.24-7.27(m, 1H), 7.29(d, J=5.1Hz, 1H), 7.58(d, J=7.8Hz, 1H), 7.77(d, J=7.8Hz, 1H), 7.82(d, J=1.2Hz, 1H).

The property values of the title optically active compound with negative optical rotation are as follows.

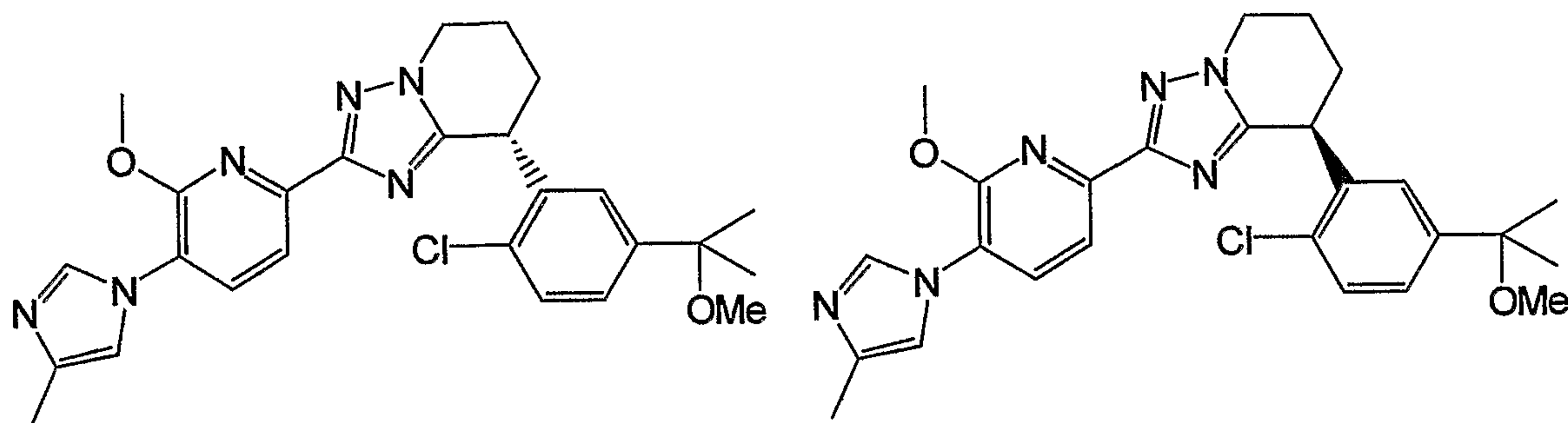
¹H-NMR(CDCl₃)δ(ppm): 1.50(s, 6H), 2.04-2.16(m, 2H), 2.16-2.27(m, 1H), 2.30(s, 3H), 2.34-2.44(m, 1H), 3.07(s, 3H), 4.16(s, 3H), 4.32-4.48(m, 3H), 6.94-6.98(m, 1H), 6.99-7.01(m, 1H),
20 7.24-7.27(m, 1H), 7.29(d, J=5.1Hz, 1H), 7.58(d, J=7.8Hz, 1H), 7.77(d, J=7.8Hz, 1H), 7.82(d, J=1.2Hz, 1H).

[0823]

Examples 266 and 267

25 Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(2-chloro-5-(1-methoxy-1-methylethyl)phenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(2-chloro-5-(1-methoxy-1-methylethyl)phenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

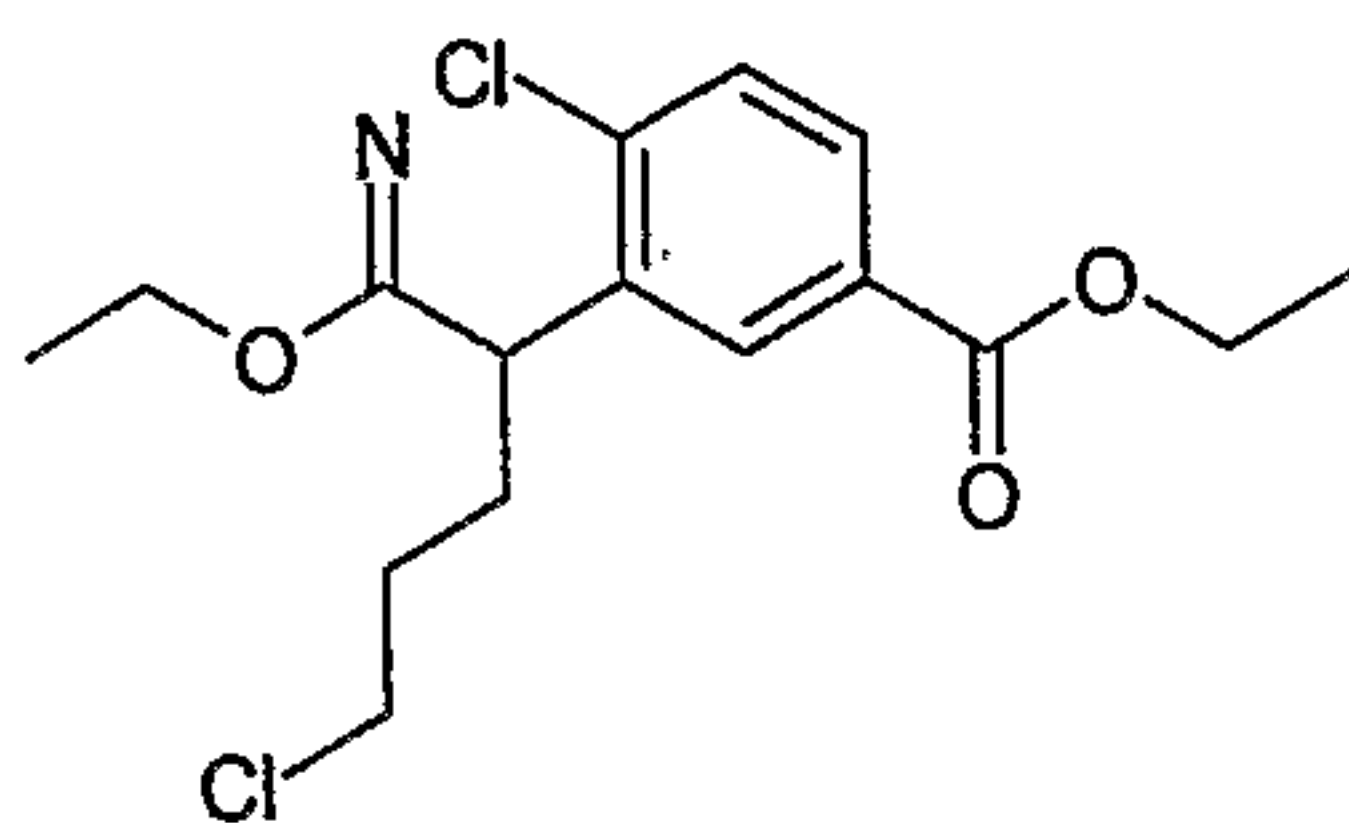
[0824]



[0825]

Synthesis of ethyl 4-chloro-3-(4-chloro-1-ethoxycarbonimidolybutyl)benzoate hydrochloride

[0826]



5 [0827]

The title compound (1.46 g) was obtained according to the method of Preparation Example 3-1 from ethyl 4-chloro-3-cyanomethylbenzoate (1.32 g). The property value of the compound is as follows.

ESI-MS; m/z 346 $[M^+ + H]$

10 [0828]

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(2-chloro-5-(1-methoxy-1-methylethyl)phenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(2-chloro-5-(1-methoxy-1-methylethyl)phenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

15

The racemate of the title compound (65 mg) was obtained according to the method of Examples 262 and 263 from 2-(4-chloro-3-{2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-8-yl}-phenyl)propan-2-ol (76 mg) and ethyl 4-chloro-3-(4-chloro-1-ethoxycarbonimidolybutyl)benzoate hydrochloric acid.

The resulting racemate was separated by CHIRALPAK™ IB (2 cm × 25 cm, mobile phase: 20% ethanol-hexane) to obtain the title compound with a retention time of 19.5 minutes and positive optical rotation (24 mg) and the title compound with a retention time of 30 minutes and negative optical rotation (22 mg).

20

The property values of the title optically active compound with positive optical rotation are as

follows.

$^1\text{H-NMR}(\text{CDCl}_3)\delta(\text{ppm})$: 1.41(s, 6H), 1.41(s, 6H), 2.00-2.25(m, 3H), 2.30(s, 3H), 2.38-2.48(m, 1H), 3.00(s, 3H), 4.15(s, 3H), 4.36-4.45(m, 2H), 4.78(dd, $J=7.4, 5.9\text{Hz}$, 1H), 6.97-7.11(m, 2H), 7.21-7.25(m, 1H), 7.37(d, $J=8.2\text{Hz}$, 1H), 7.57(d, $J=7.8\text{Hz}$, 1H), 7.74(d, $J=7.8\text{Hz}$, 1H), 7.82(d, $J=1.2\text{Hz}$, 1H).

The property values of the title optically active compound with negative optical rotation are as follows.

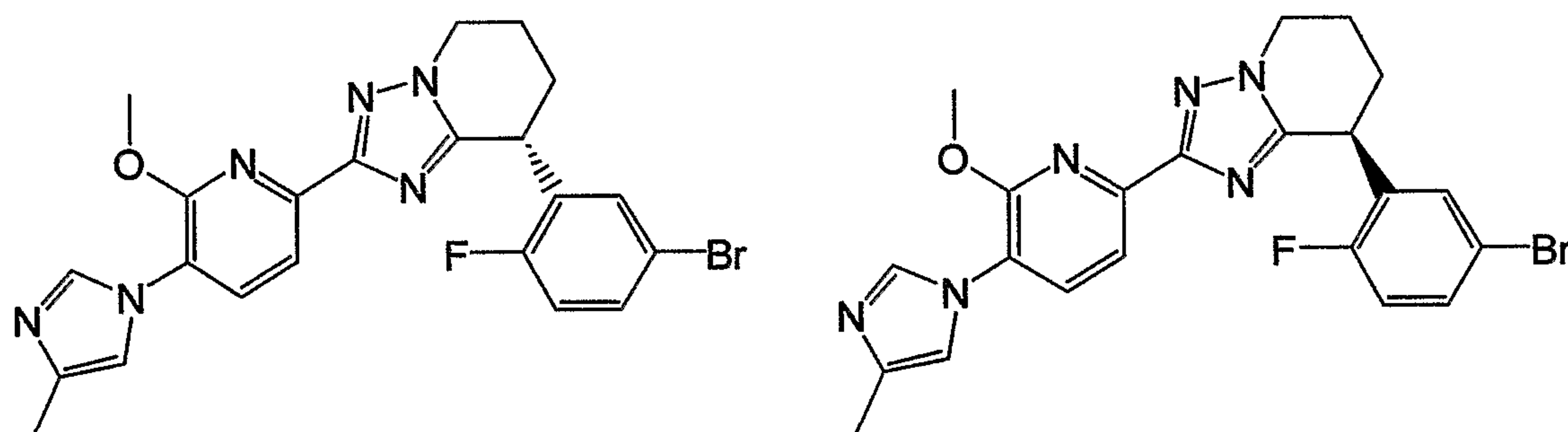
$^1\text{H-NMR}(\text{CDCl}_3)\delta(\text{ppm})$: 1.41(s, 6H), 1.41(s, 6H), 2.00-2.25(m, 3H), 2.30(s, 3H), 2.38-2.48(m, 1H), 3.00(s, 3H), 4.15(s, 3H), 4.36-4.45(m, 2H), 4.78(dd, $J=7.4, 5.9\text{Hz}$, 1H), 6.97-7.11(m, 2H), 7.21-7.25(m, 1H), 7.37(d, $J=8.2\text{Hz}$, 1H), 7.57(d, $J=7.8\text{Hz}$, 1H), 7.74(d, $J=7.8\text{Hz}$, 1H), 7.82(d, $J=1.2\text{Hz}$, 1H).

[0829]

Examples 268 and 269

Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(5-bromo-2-fluorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(5-bromo-2-fluorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0830]



[0831]

20 Synthesis of ethyl 2-(5-bromo-2-fluorophenyl)-5-chloropentaneimide

The title compound (3.1g) was obtained according to the method of Preparation Example 3-1 from (5-bromo-2-fluorophenyl)acetonitrile. The property value of the compound is as follows.

ESI-MS; m/z 336 $[M^+ + H]$

[0832]

25 Synthesis of (+)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(5-bromo-2-fluorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-8-(5-bromo-2-fluorophenyl)-5,6,7,8-

tetrahydro[1,2,4]triazolo[1,5-a]pyridine

The racemate of the title compound (1.80 g) was obtained according to the method of Examples 42 and 43 from hydrazide 6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-carboxylate (2.05g) obtained in Preparation Example 1-6 and ethyl 2-(5-bromo-2-fluorophenyl)-5-chloropentaneimide (3.1 g).

The resulting racemate was separated by CHIRALPAK™ IB (2 cm × 25 cm, mobile phase: 15% ethanol-hexane) to obtain the title compound with a retention time of 24.5 minutes and positive optical rotation (21 mg) and the title compound with a retention time of 43 minutes and negative optical rotation (22.5 mg).

10 The property values of the title optically active compound with positive optical rotation are as follows.

¹H-NMR(CDCl₃)δ(ppm): 2.01-2.26(m, 3H), 2.30(s, 3H), 2.34-2.42(m, 1H), 4.17(s, 3H), 4.36-4.43(m, 2H), 4.60(dd, J=6.6, 6.2Hz, 1H), 6.96-7.02(m, 2H), 7.07(dd, J=16.6, 2.3Hz, 1H), 7.36-7.41(m, 1H), 7.60(d, J=7.8Hz, 1H), 7.77(d, J=7.8Hz, 1H), 7.83(d, J=1.2Hz, 1H).

15 The property values of the title optically active compound with negative optical rotation are as follows.

¹H-NMR(CDCl₃)δ(ppm): 2.01-2.26(m, 3H), 2.30(s, 3H), 2.34-2.42(m, 1H), 4.17(s, 3H), 4.36-4.43(m, 2H), 4.60(dd, J=6.6, 6.2Hz, 1H), 6.96-7.02(m, 2H), 7.07(dd, J=16.6, 2.3Hz, 1H), 7.36-7.41(m, 1H), 7.60(d, J=7.8Hz, 1H), 7.77(d, J=7.8Hz, 1H), 7.83(d, J=1.2Hz, 1H).

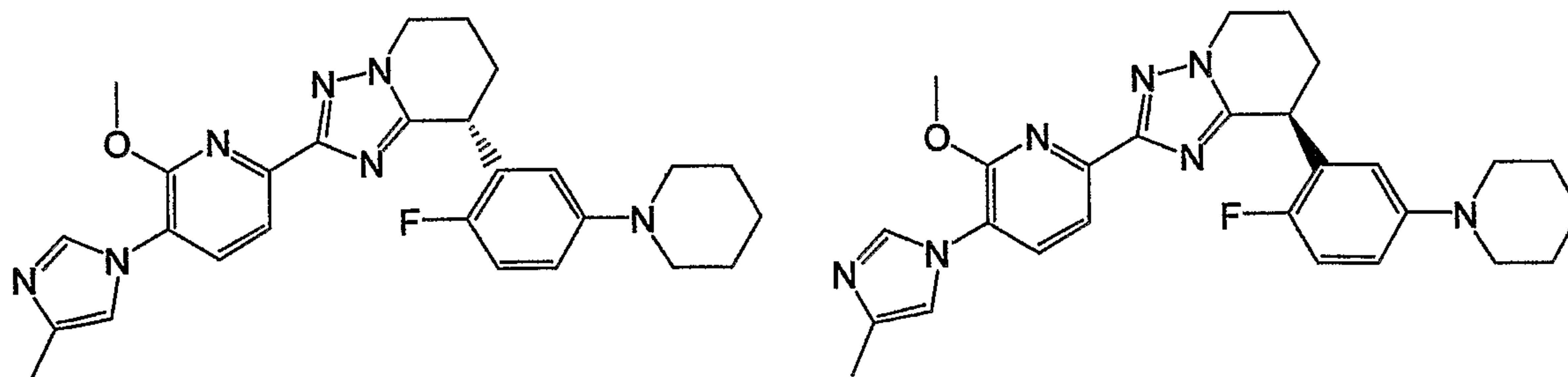
20 [0833]

Examples 270 and 271

Synthesis of (+)-8-(2-fluoro-5-piperidin-1-ylphenyl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine and (-)-8-(2-fluoro-5-piperidin-1-ylphenyl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]-5,6,7,8-

25 tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0834]



[0835]

The racemate of the title compound (164 mg) was obtained according to the

method of Examples 42 and 43 from 6-methoxy-5-(4-methy-1H-imidazol-1-yl)pyridin-2-carboxylic acid hydrazide hydrochloride (200 mg) obtained in Preparation Example 1-6 and ethyl 5-chloro-2-(2-fluoro-5-piperidin-1-ylphenyl)pentaneimide hydrochloride (350 mg) obtained in Preparation Example 3-51.

- 5 The resulting racemate was separated by CHIRALPAKTM IA (2 cm × 25 cm, mobile phase: 50% ethanol-hexane) to obtain the title compound with positive optical rotation (59 mg, >99 %ee) and the title compound with negative optical rotation (56 mg, >99 %ee).

The property values of the title optically active compound with positive optical rotation are as follows.

- 10 ESI-MS; m/z 245[1/2M⁺+H], 488[M⁺+H].

The property values of the title optically active compound with negative optical rotation are as follows.

ESI-MS; m/z 245[1/2M⁺+H], 488[M⁺+H].

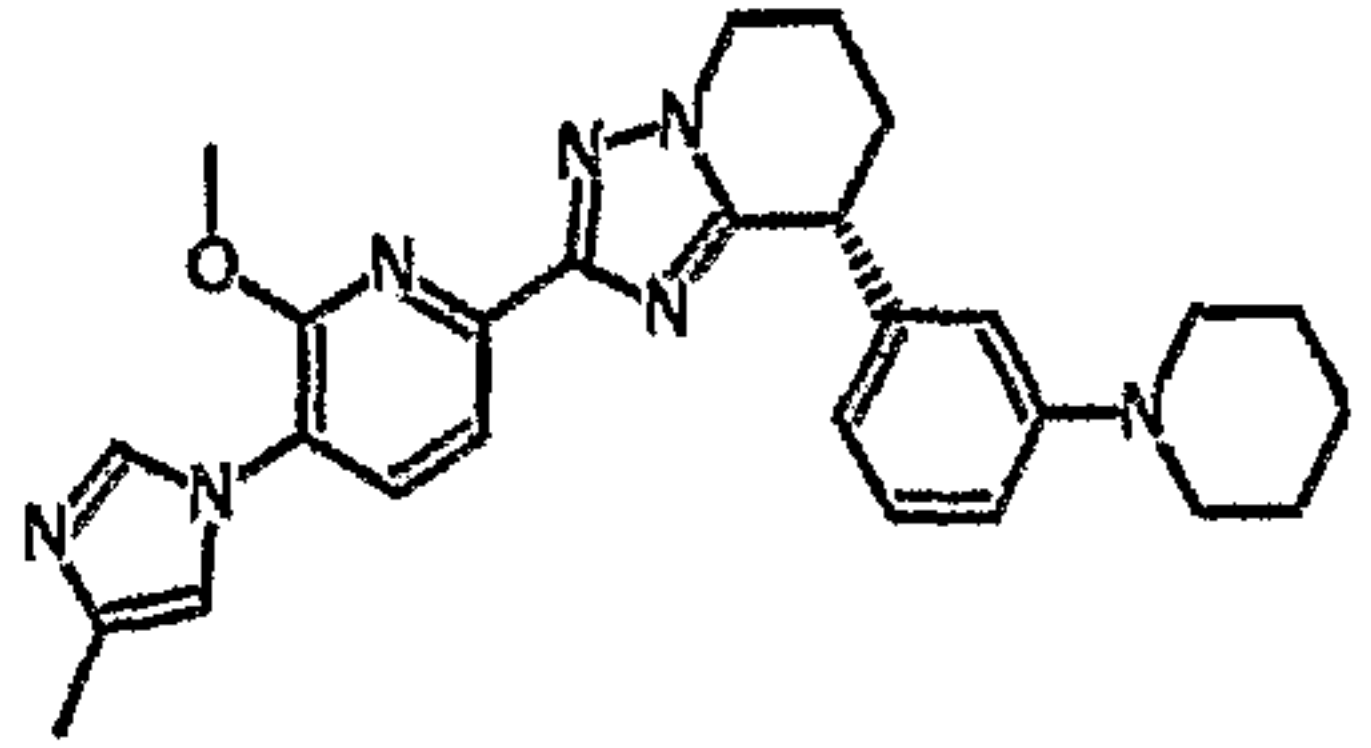
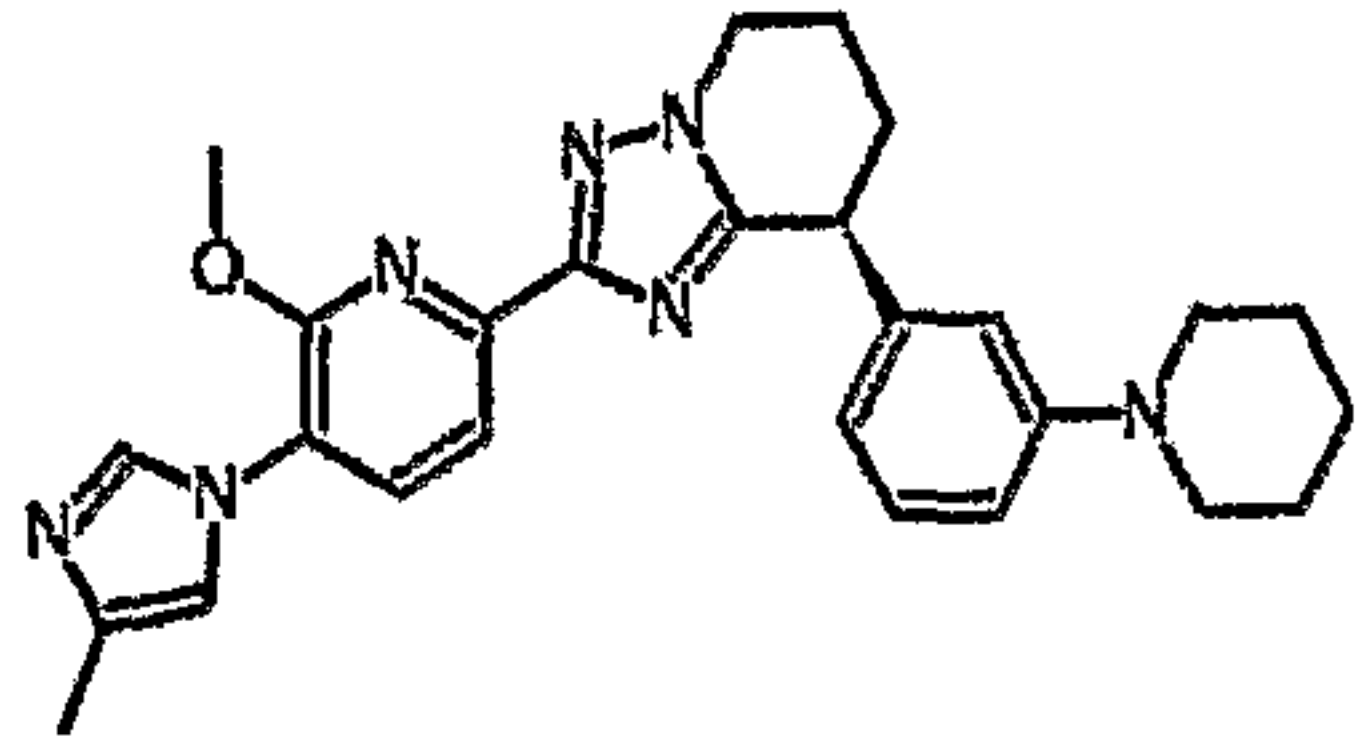
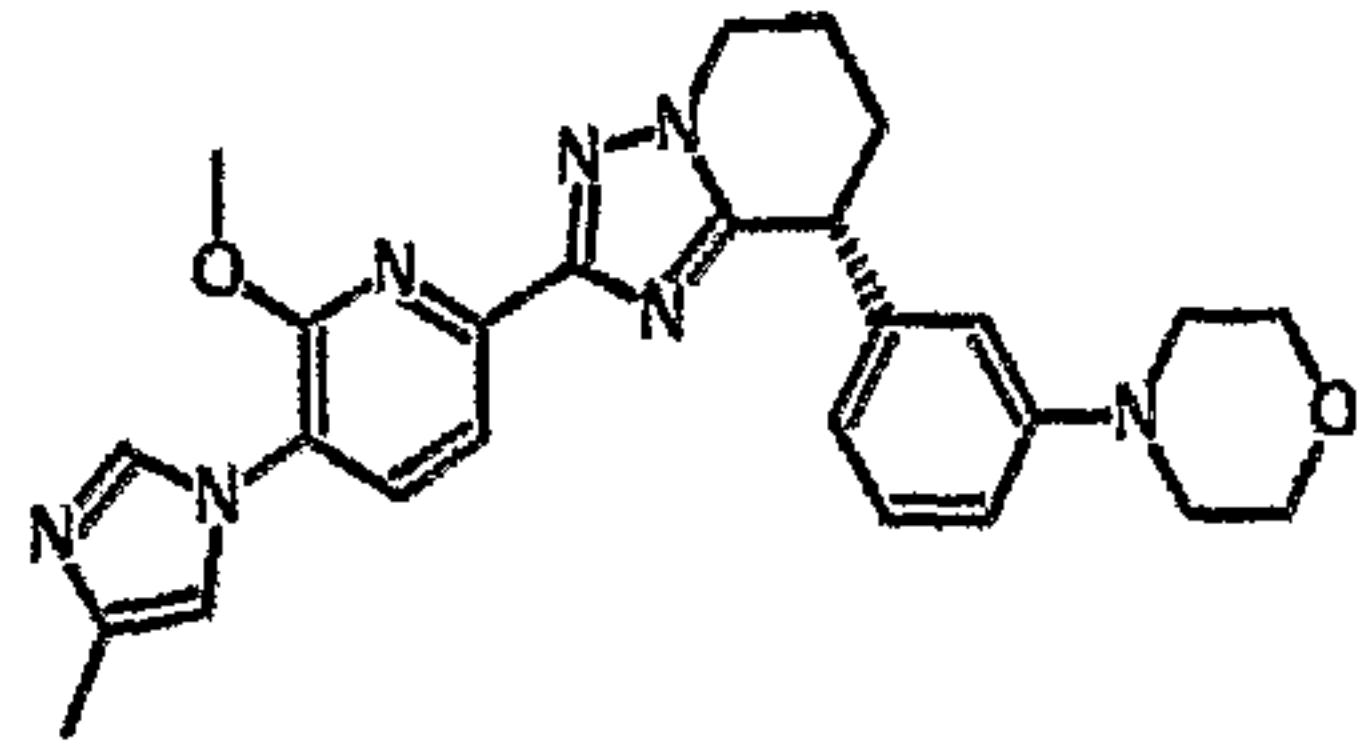
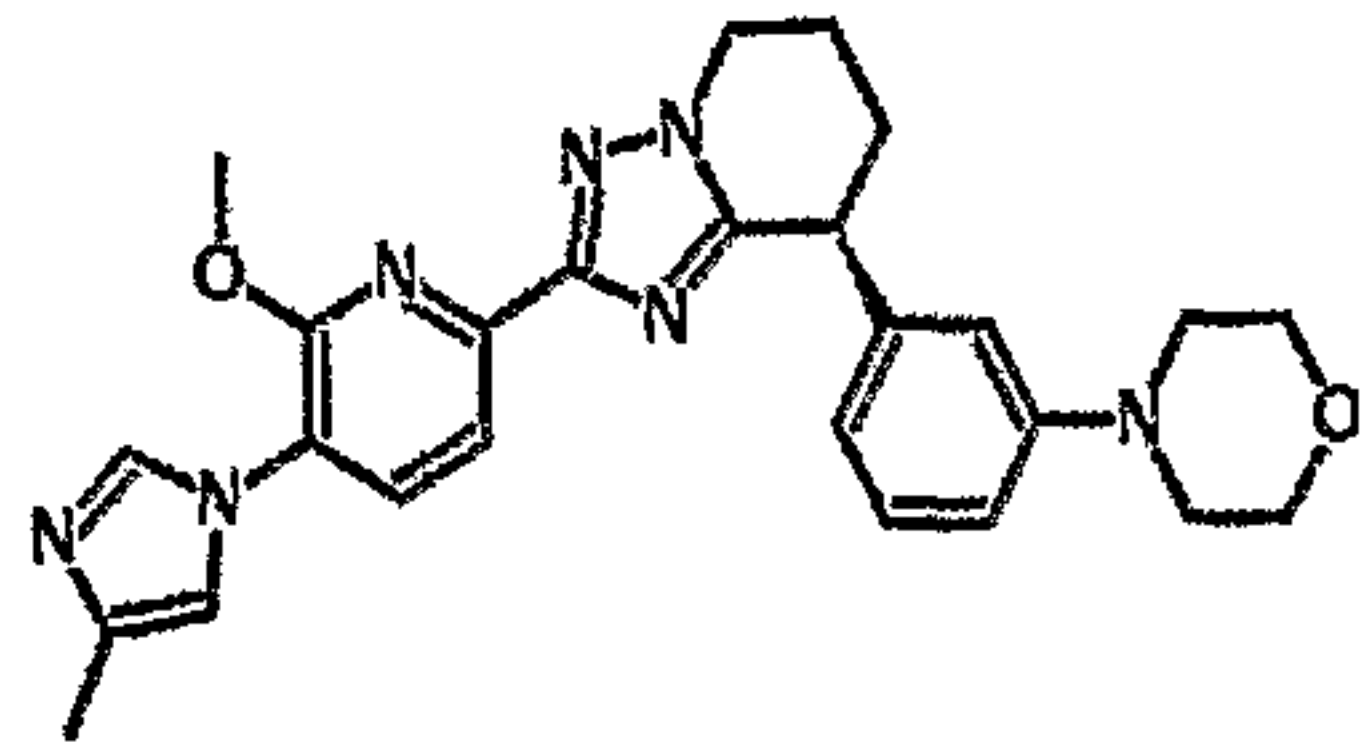
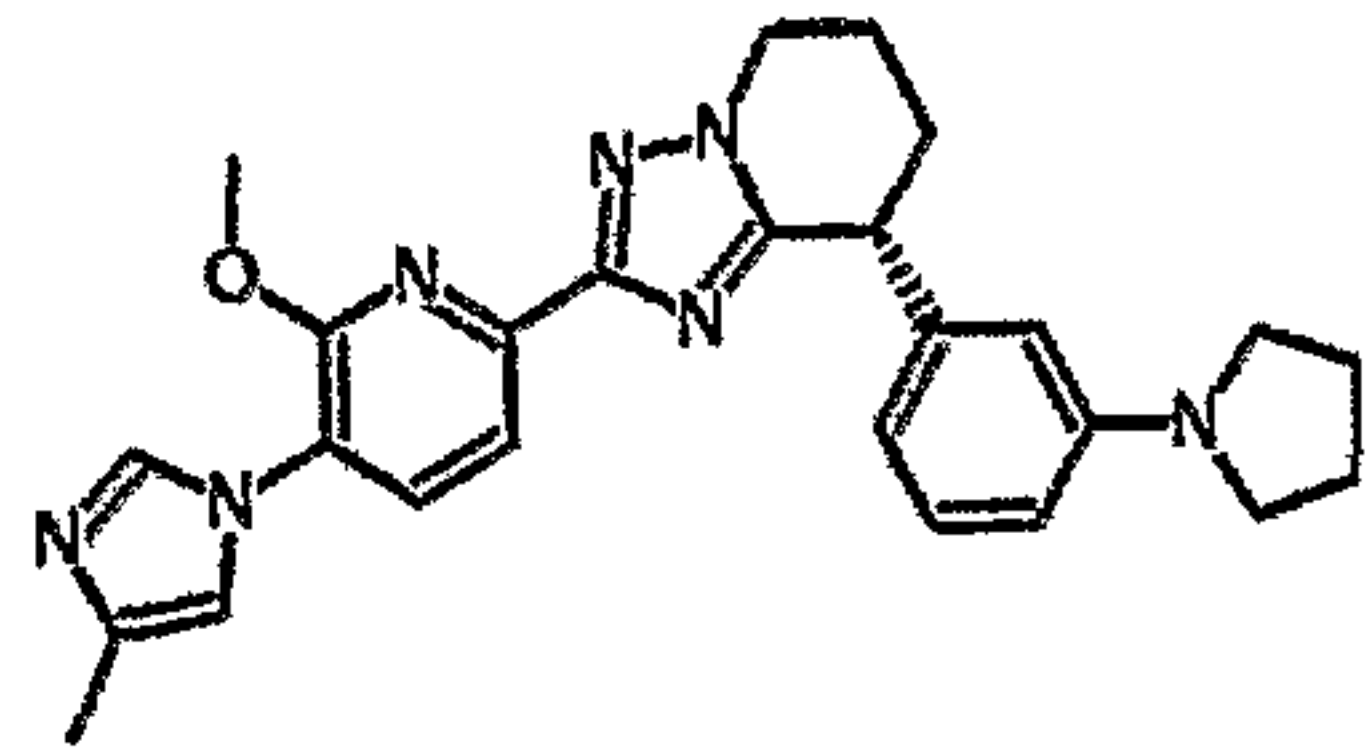
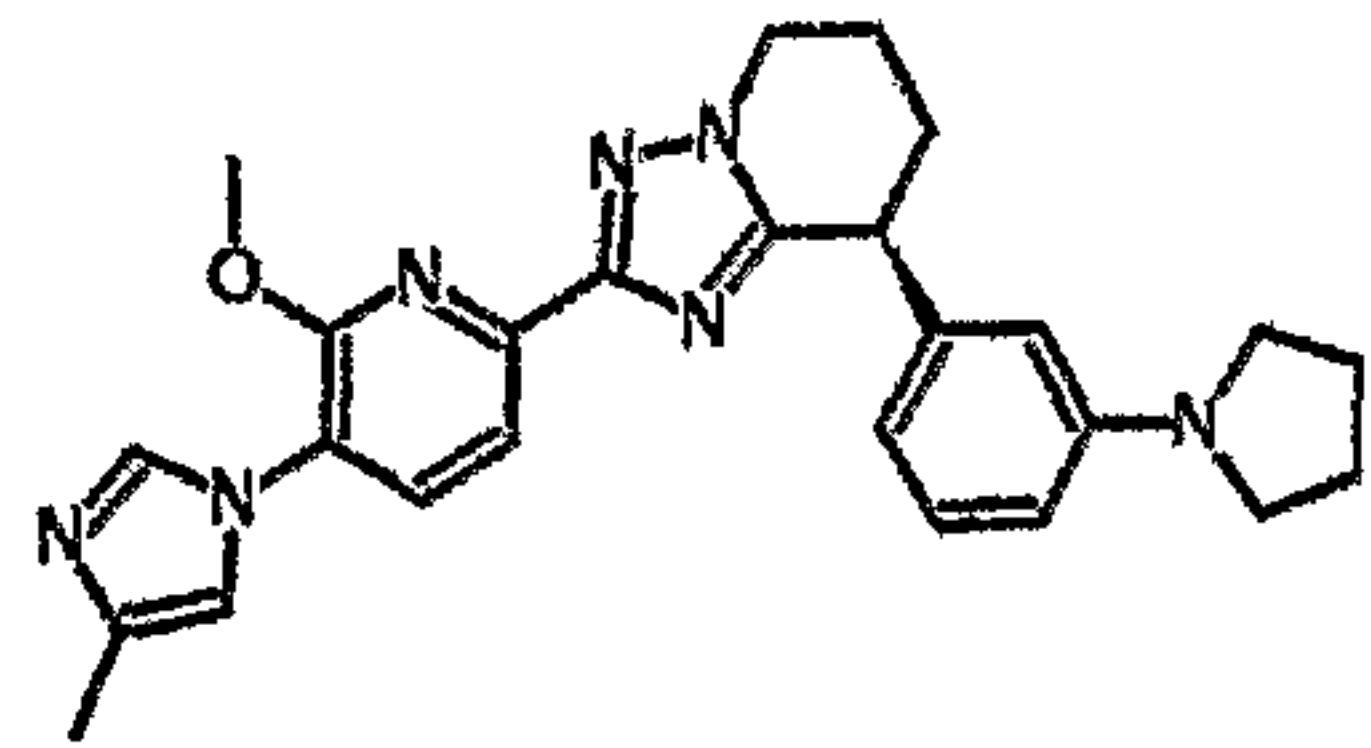
[0836]

- 15 Examples 272-349

Compounds of Examples 272-349 were obtained according to the method of Examples 270 and 271 shown in Tables 27-39.

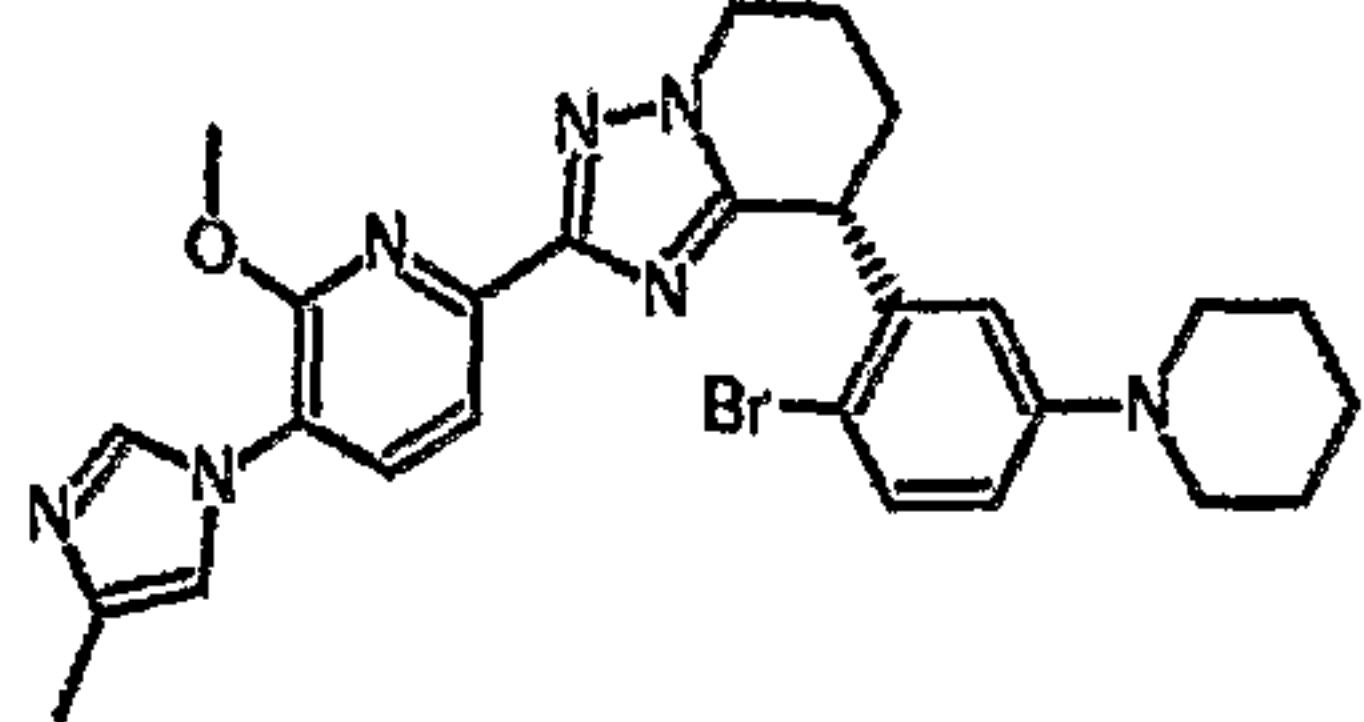
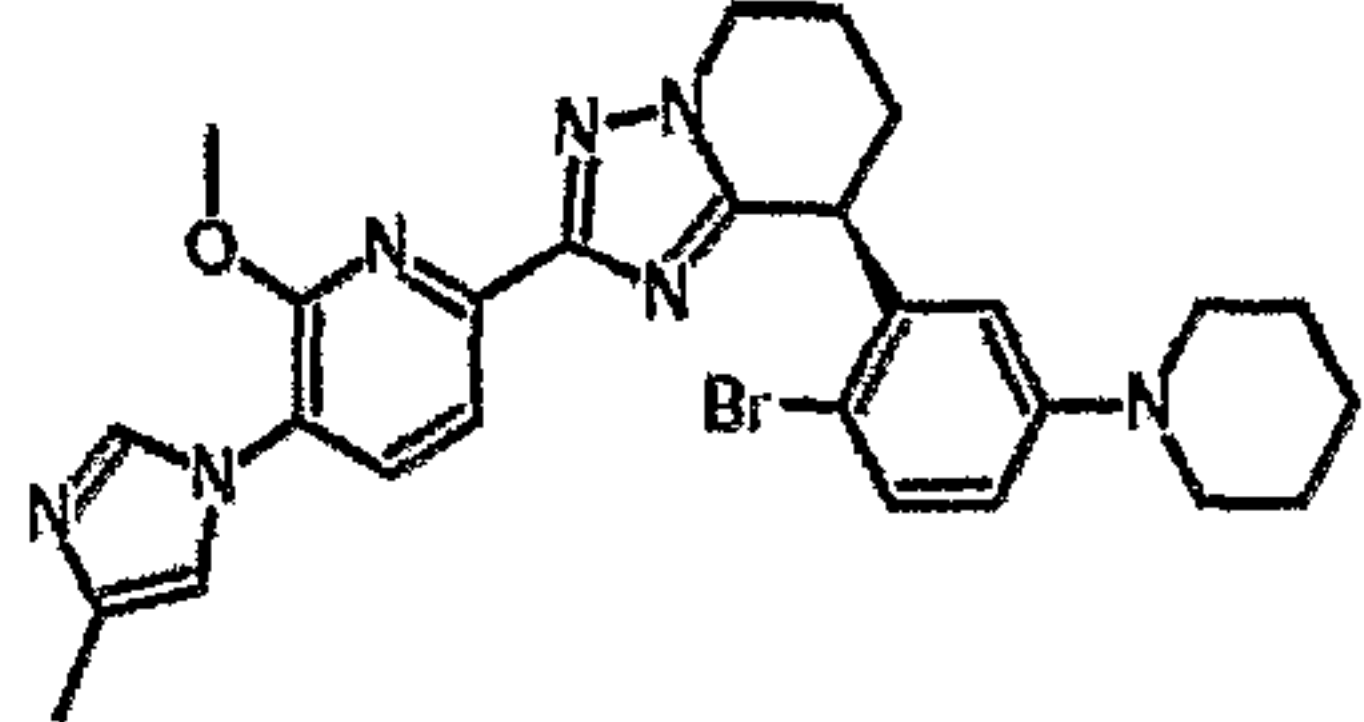
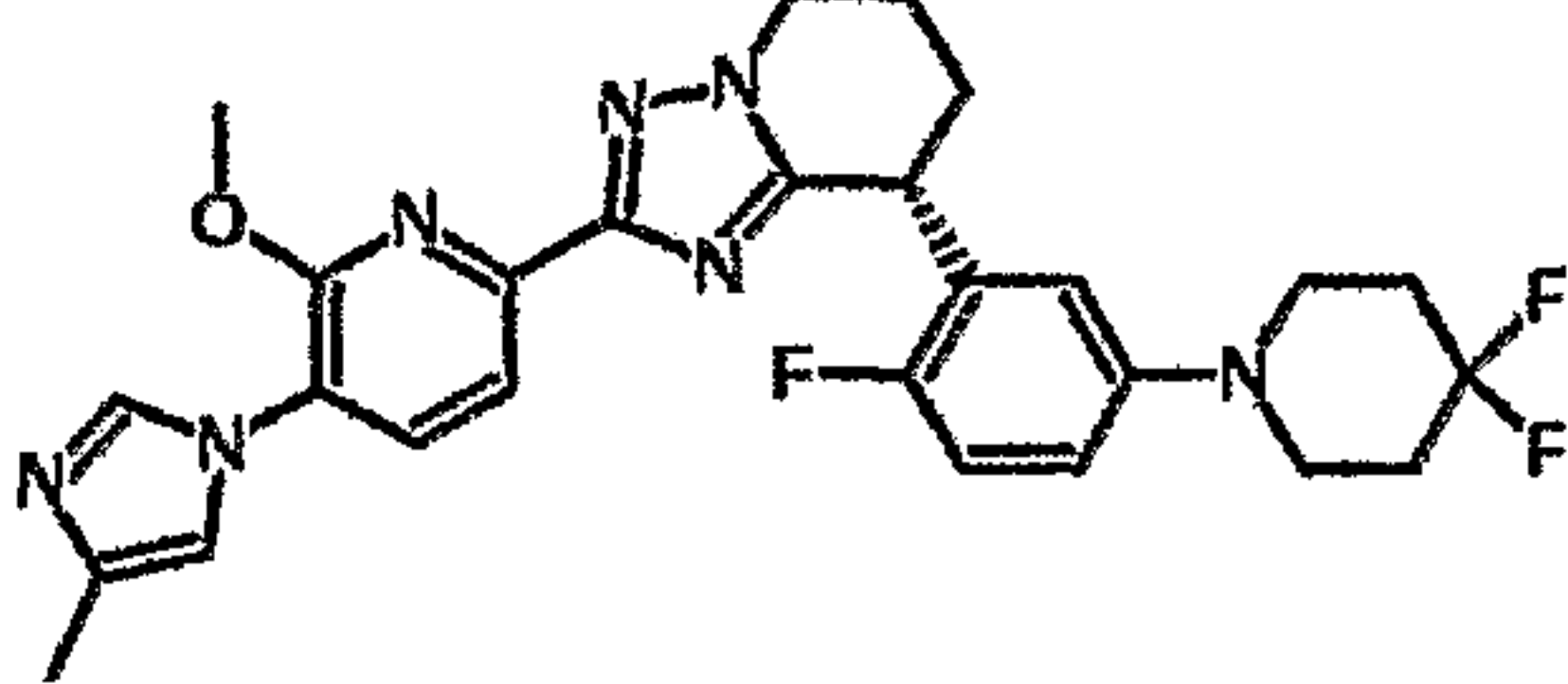
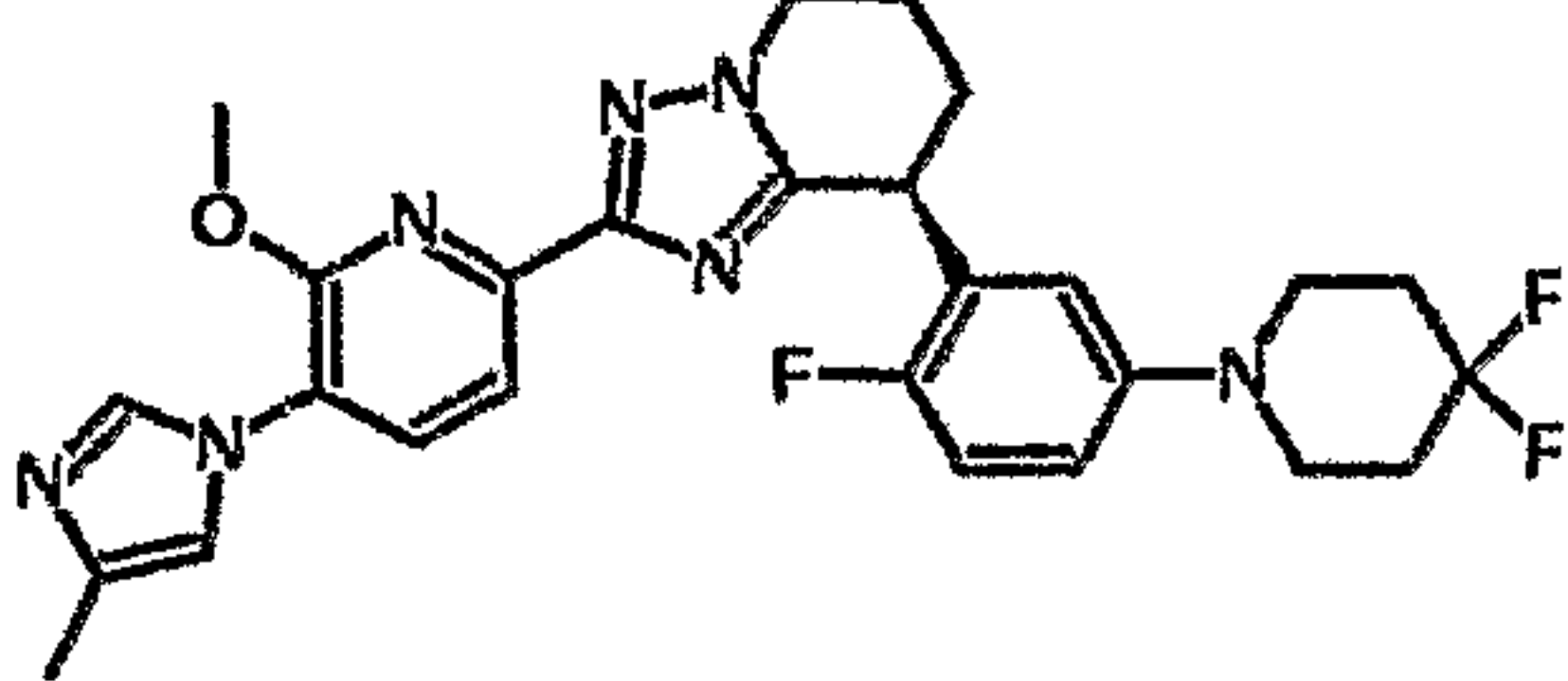
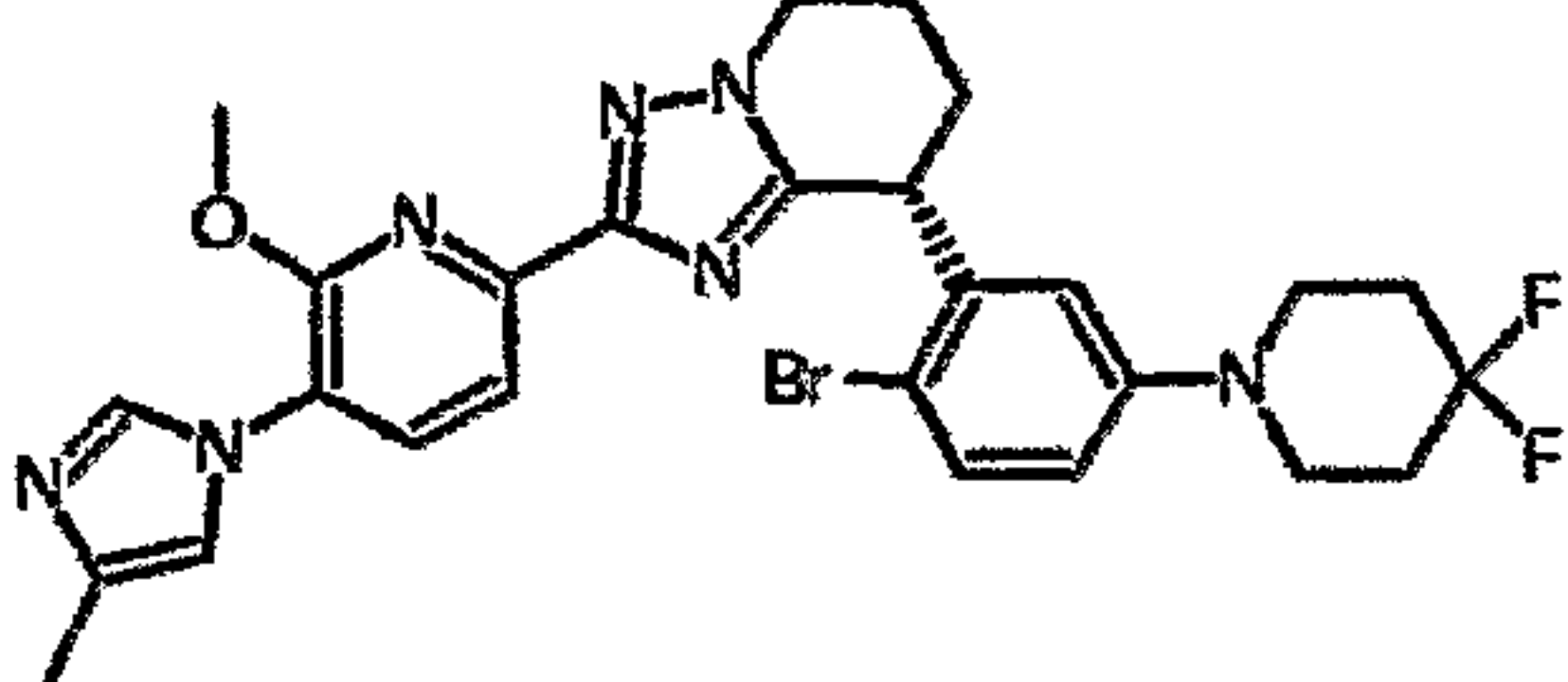
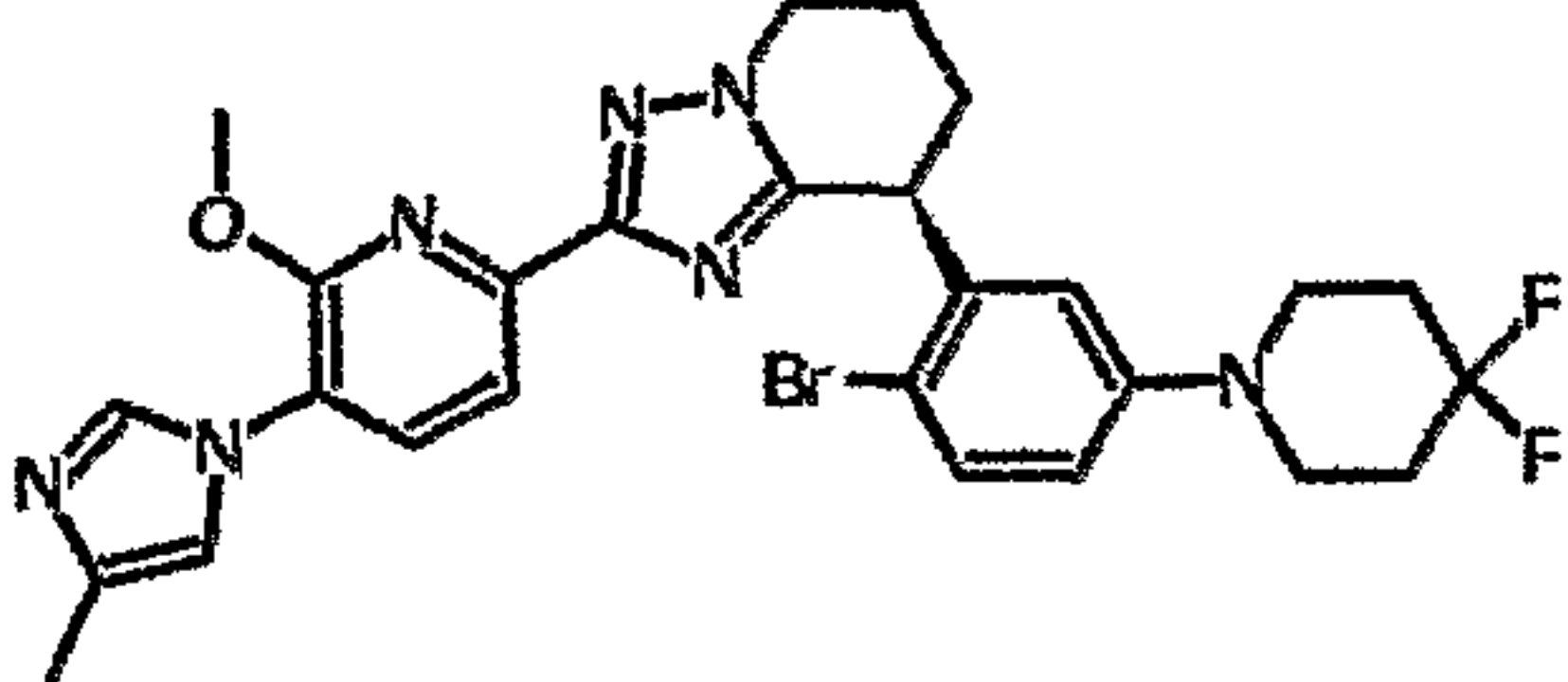
[0837]

Table 27

Example No.	Structural formula	$^1\text{H-NMR}$ or ESI mass
Example272		ESI-MS; m/z 236[1/2 M^+ +H], 470[M^+ +H].
Example273		ESI-MS; m/z 236[1/2 M^+ +H], 470[M^+ +H].
Example274		ESI-MS; m/z 237[1/2 M^+ +H], 472[M^+ +H].
Example275		ESI-MS; m/z 237[1/2 M^+ +H], 472[M^+ +H].
Example276		ESI-MS; m/z 228[1/2 M^+ +H], 456[M^+ +H].
Example277		ESI-MS; m/z 228[1/2 M^+ +H], 456[M^+ +H].

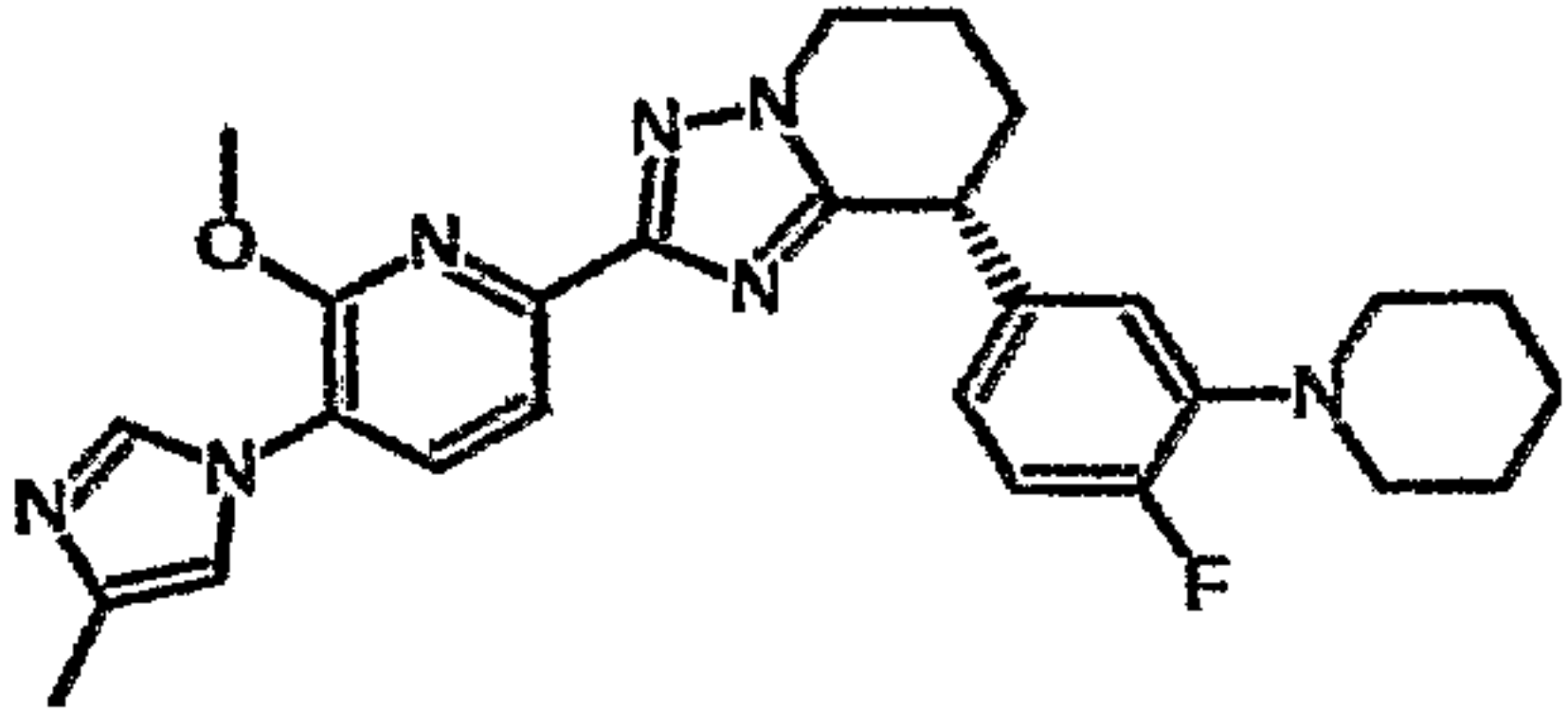
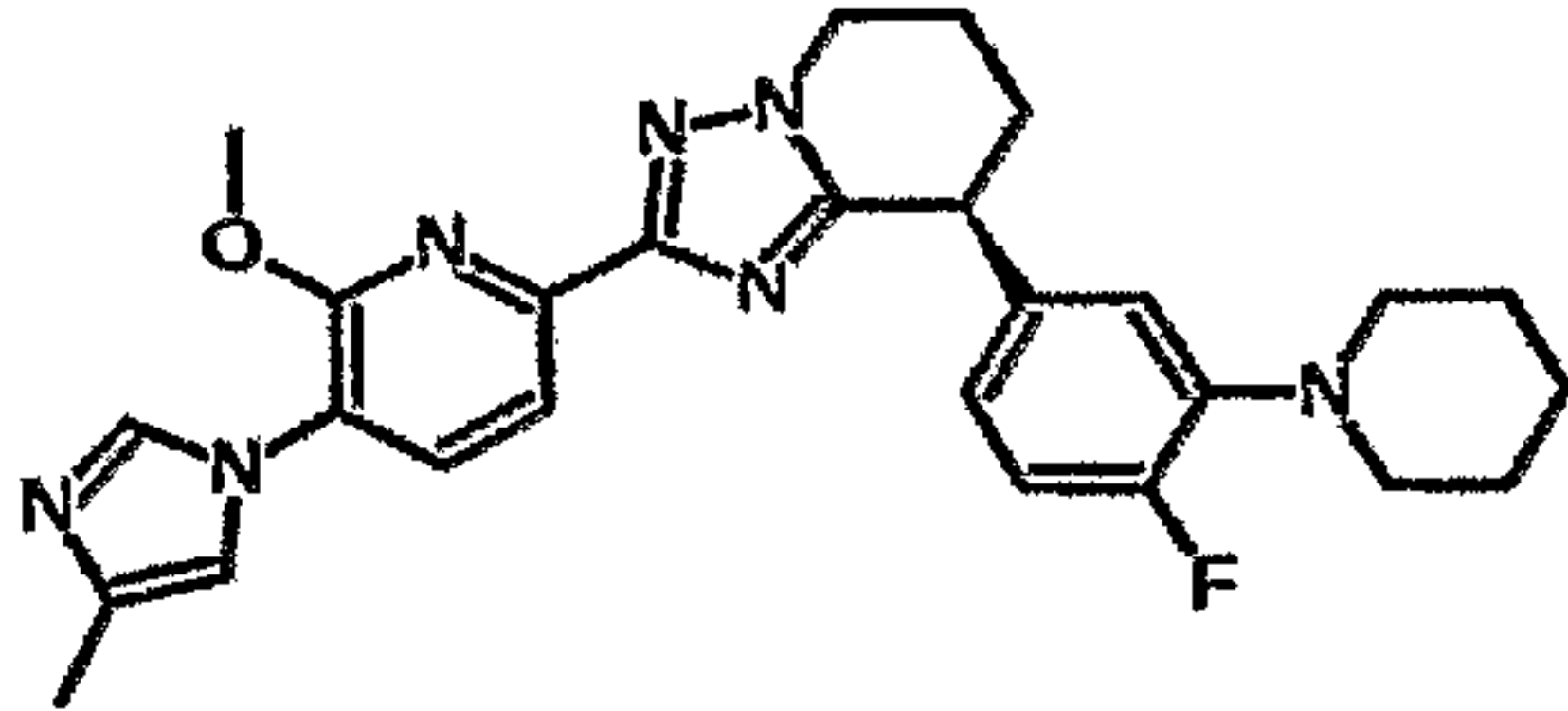
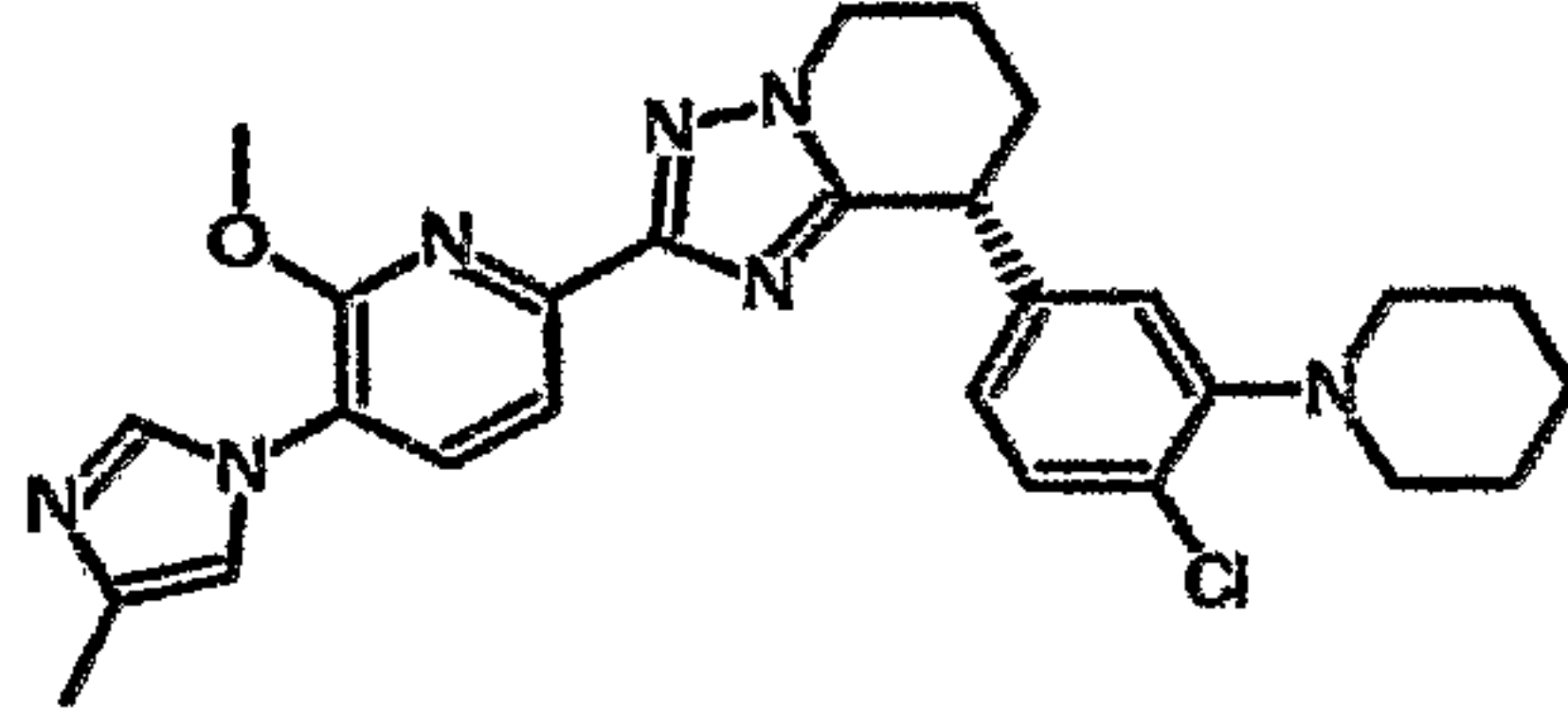
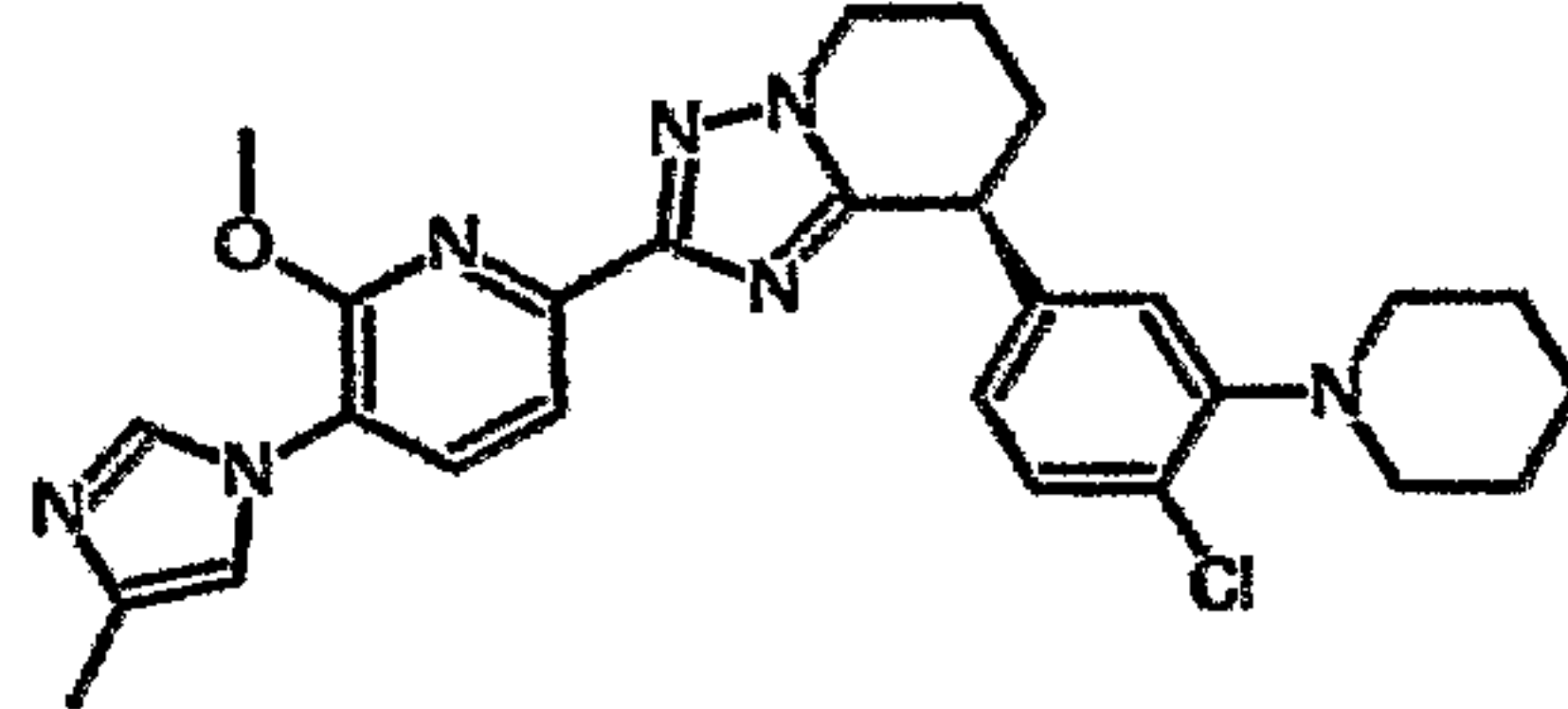
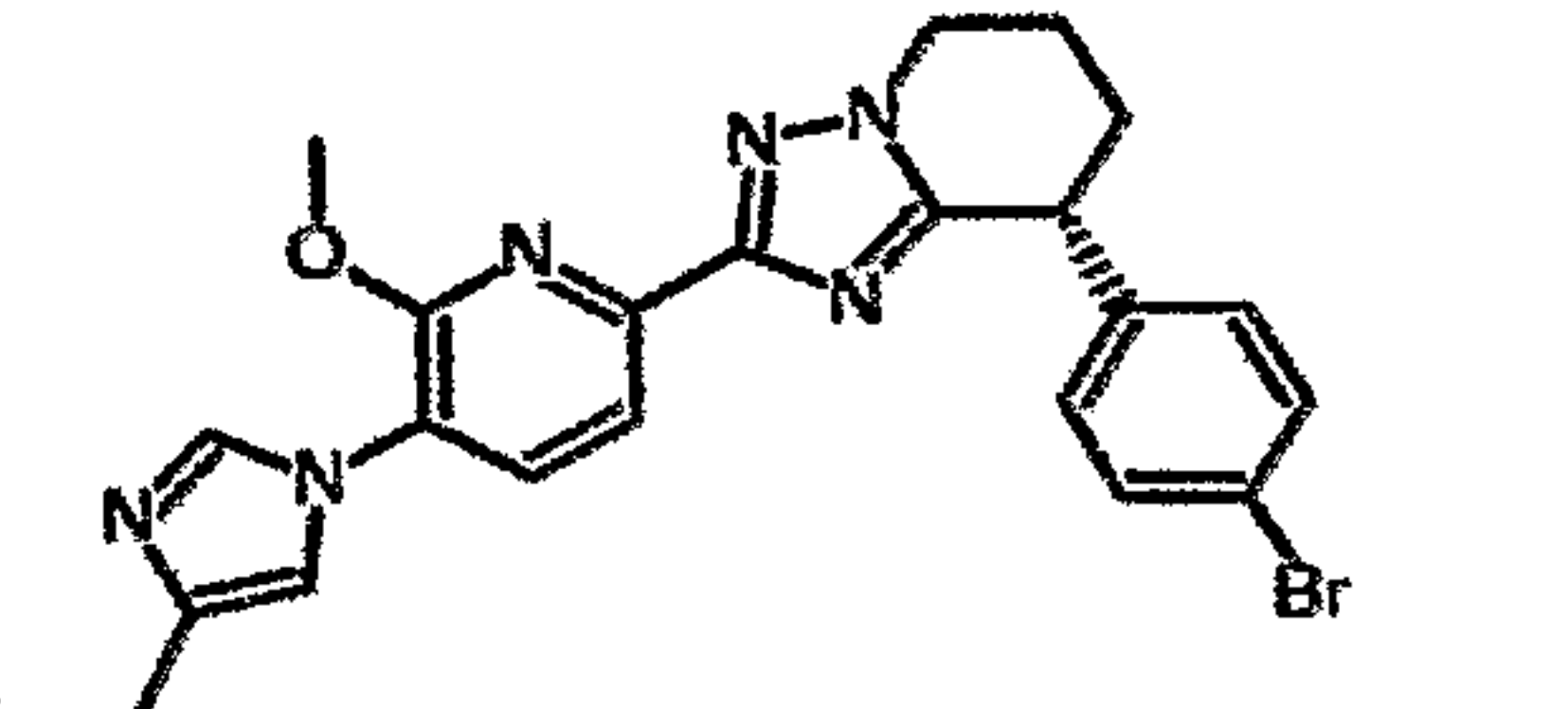
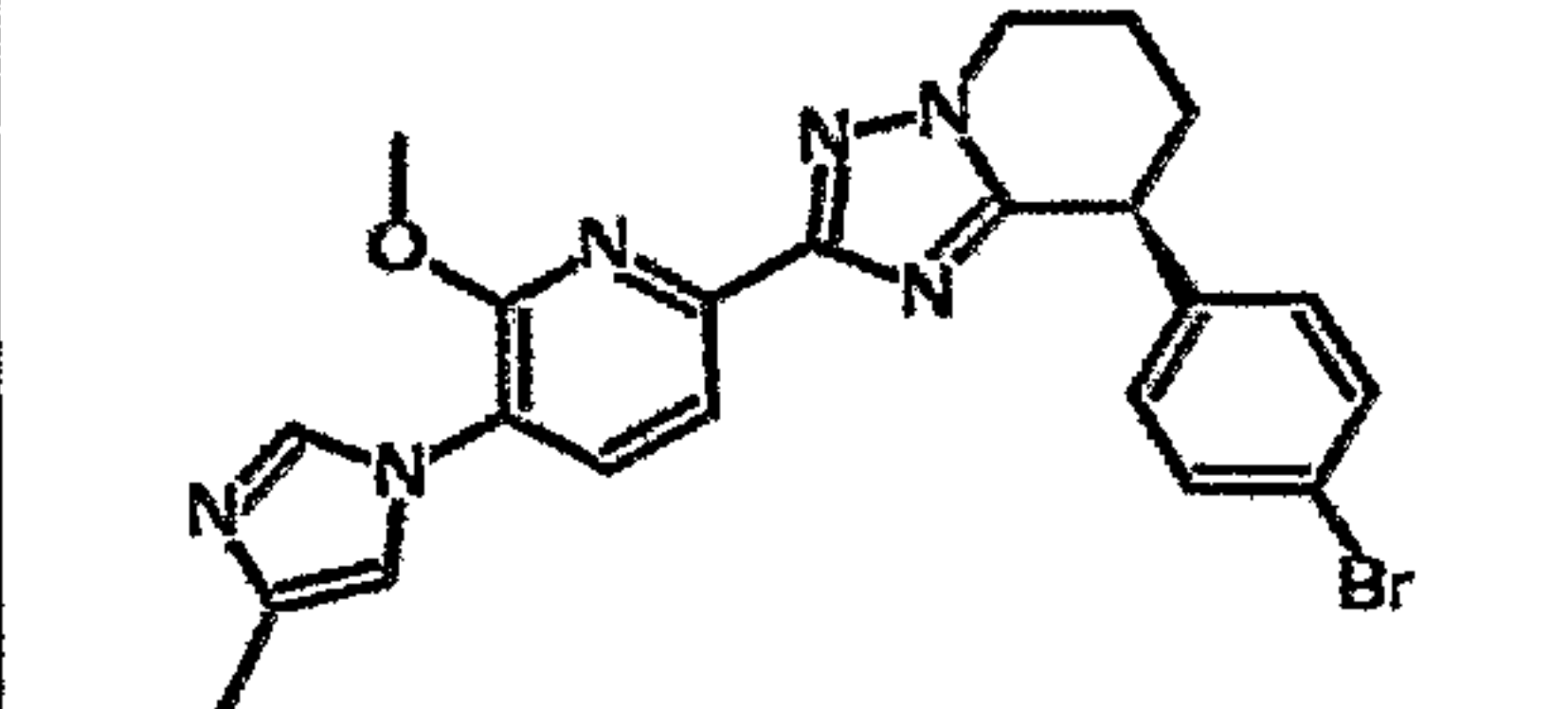
[0838]

Table 28

Example No.	Structural formula	$^1\text{H-NMR}$ or ESI mass
Example278		ESI-MS; m/z 548, 550 [$\text{M}^+ + \text{H}$].
Example279		ESI-MS; m/z 548, 550 [$\text{M}^+ + \text{H}$].
Example280		ESI-MS; m/z 263 [$1/2\text{M}^+ + \text{H}$], 524 [$\text{M}^+ + \text{H}$].
Example281		ESI-MS; m/z 263 [$1/2\text{M}^+ + \text{H}$], 524 [$\text{M}^+ + \text{H}$].
Example282		ESI-MS; m/z 584, 586 [$\text{M}^+ + \text{H}$].
Example283		ESI-MS; m/z 584, 586 [$\text{M}^+ + \text{H}$].

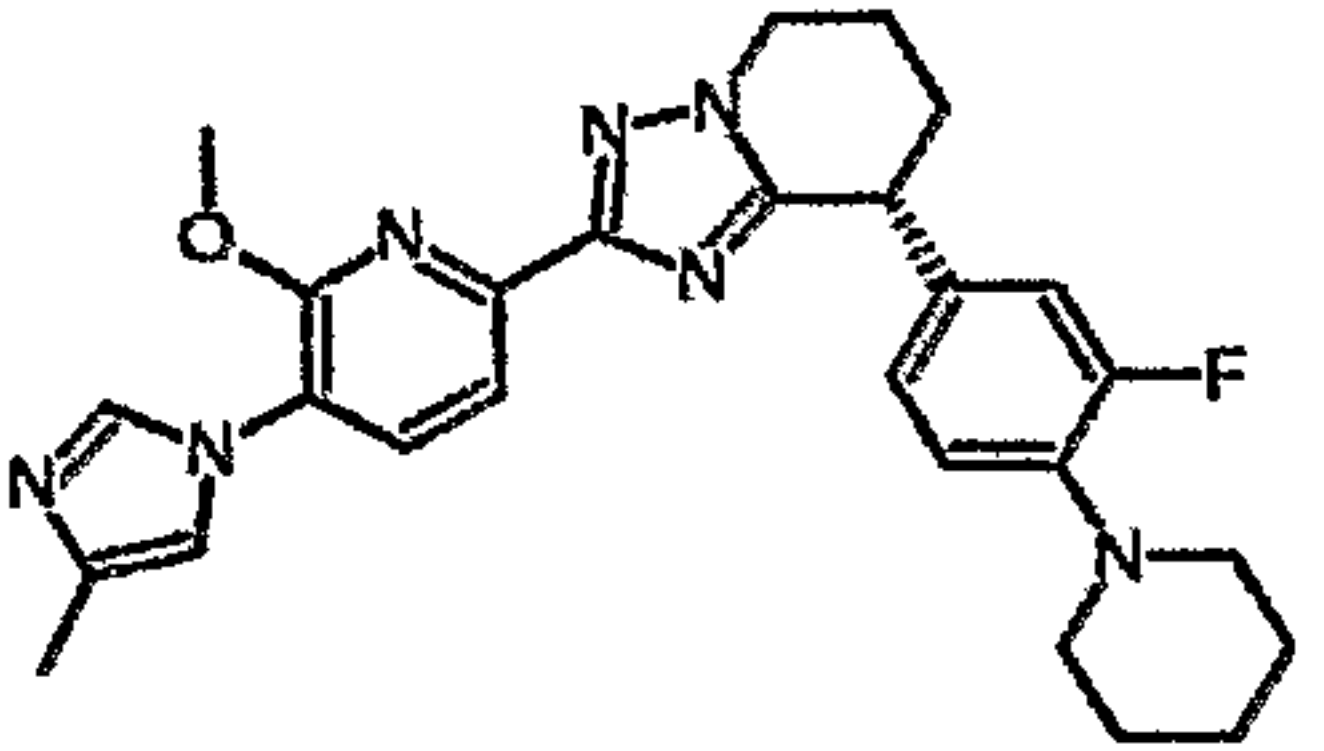
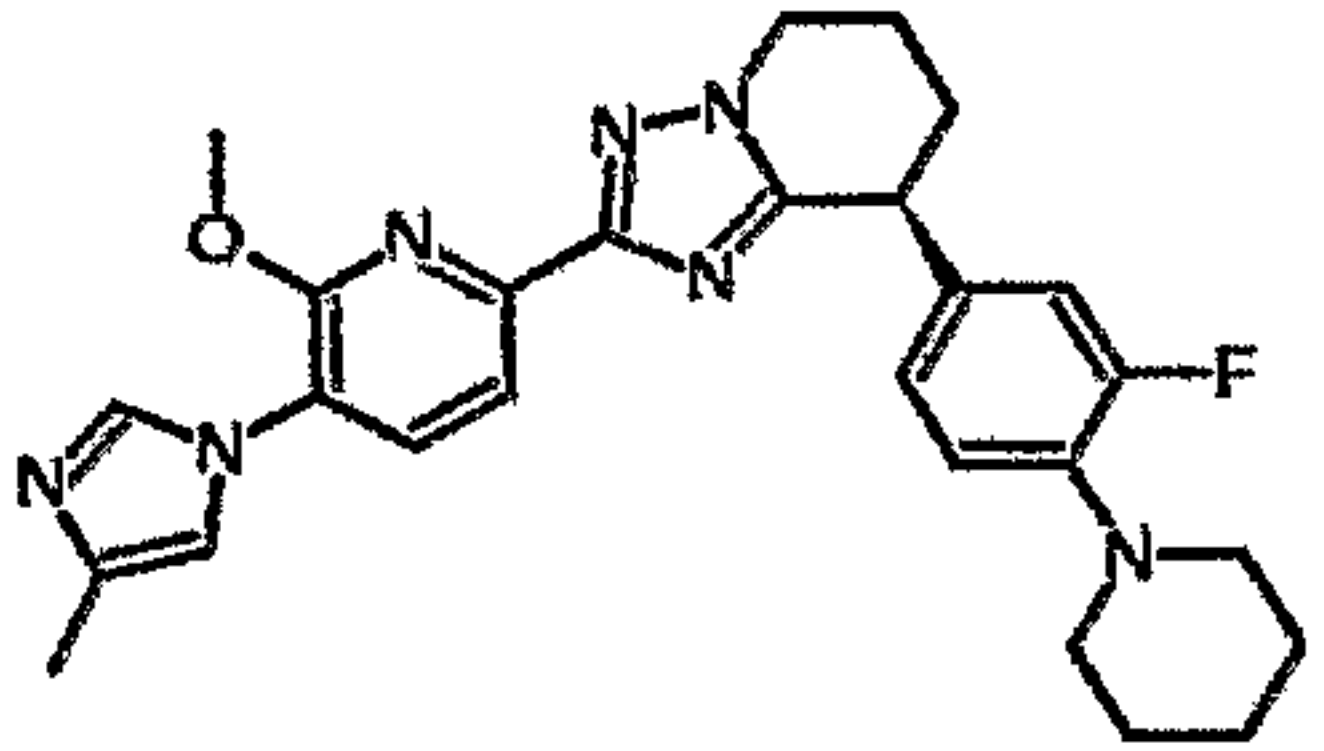
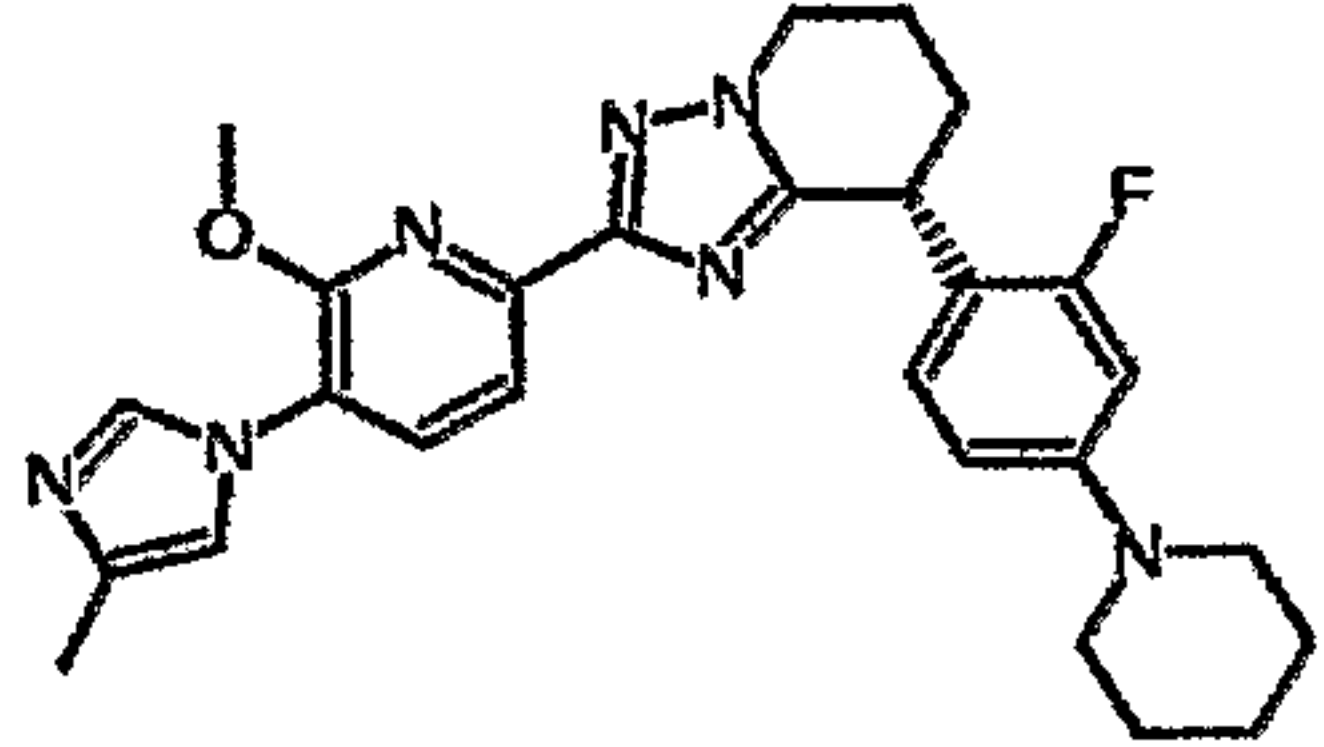
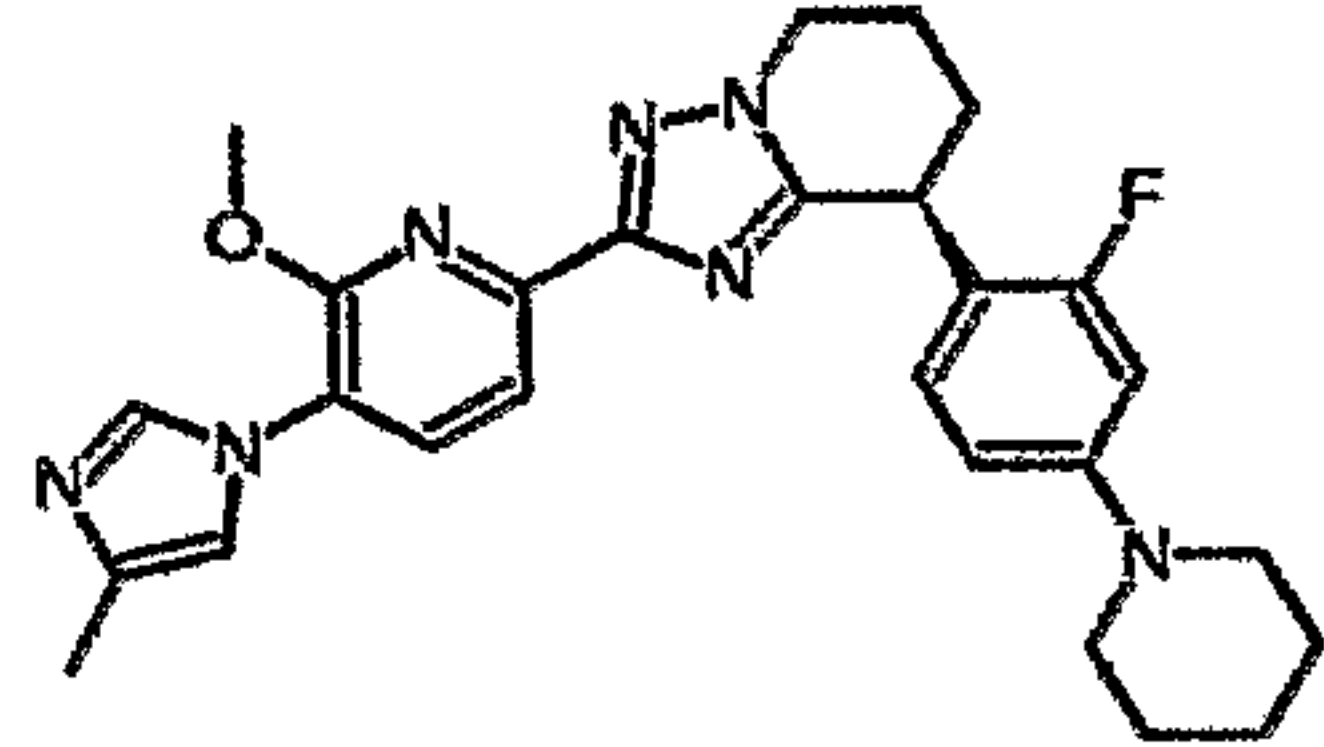
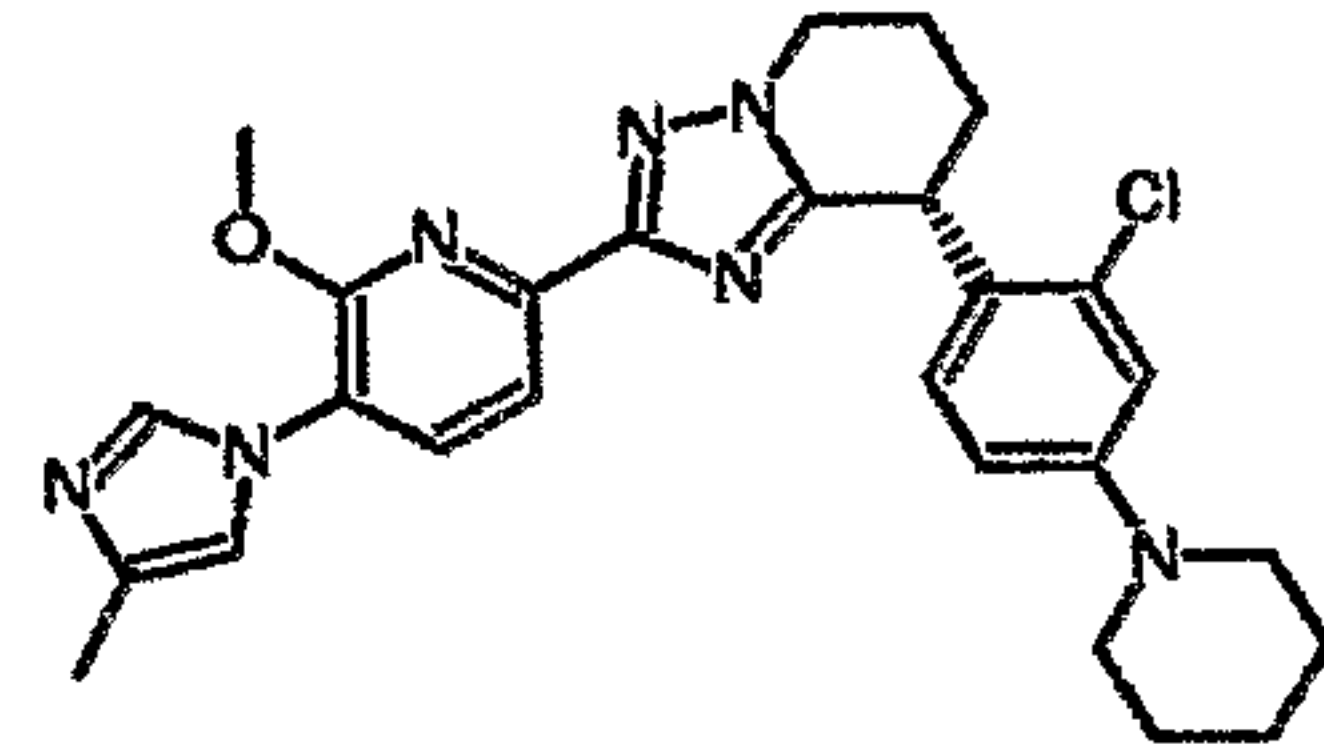
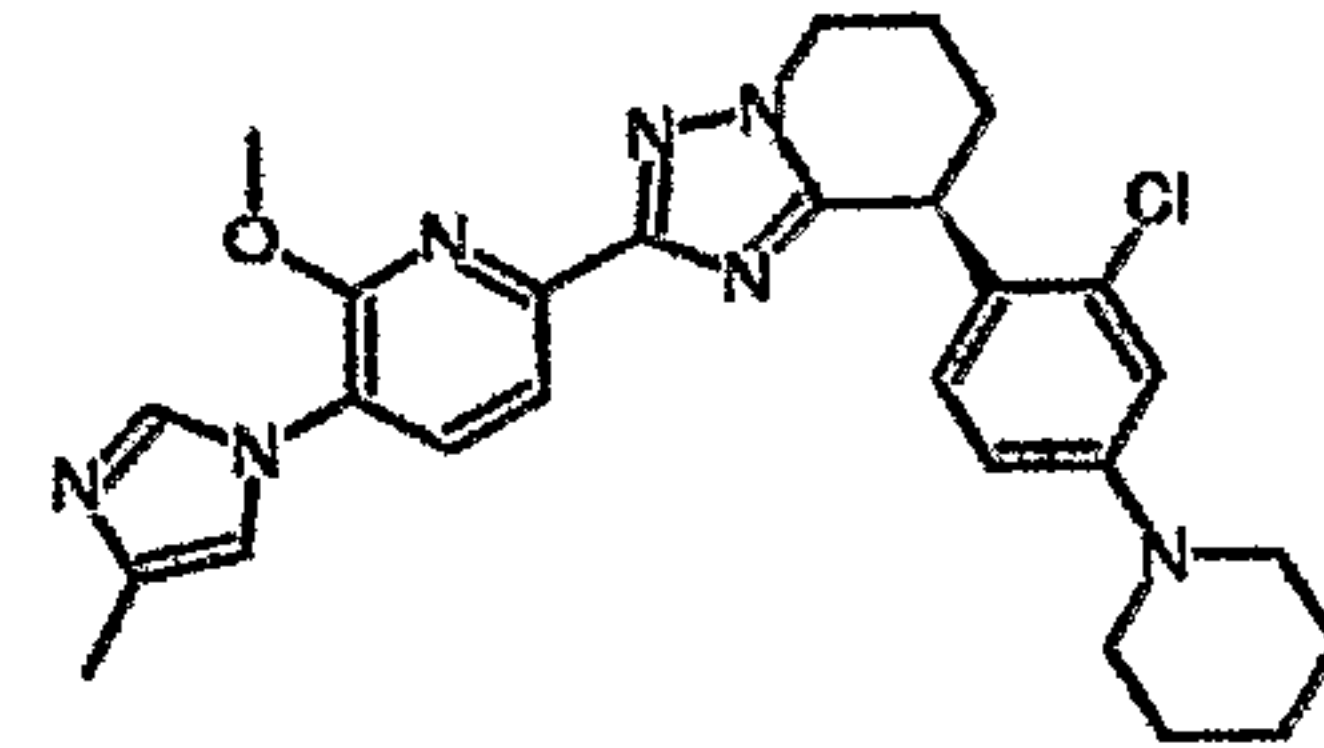
[0839]

Table 29

Example No.	Structural formula	$^1\text{H-NMR}$ or ESI mass
Example284		ESI-MS; m/z 245 [$1/2M^+ + H$], 488 [$M^+ + H$].
Example285		ESI-MS; m/z 245 [$1/2M^+ + H$], 488 [$M^+ + H$].
Example286		ESI-MS; m/z 253 [$1/2M^+ + H$], 504 [$M^+ + H$].
Example287		ESI-MS; m/z 253 [$1/2M^+ + H$], 504 [$M^+ + H$].
Example288		ESI-MS; m/z 465, 467 [$M^+ + H$].
Example289		ESI-MS; m/z 465, 467 [$M^+ + H$].

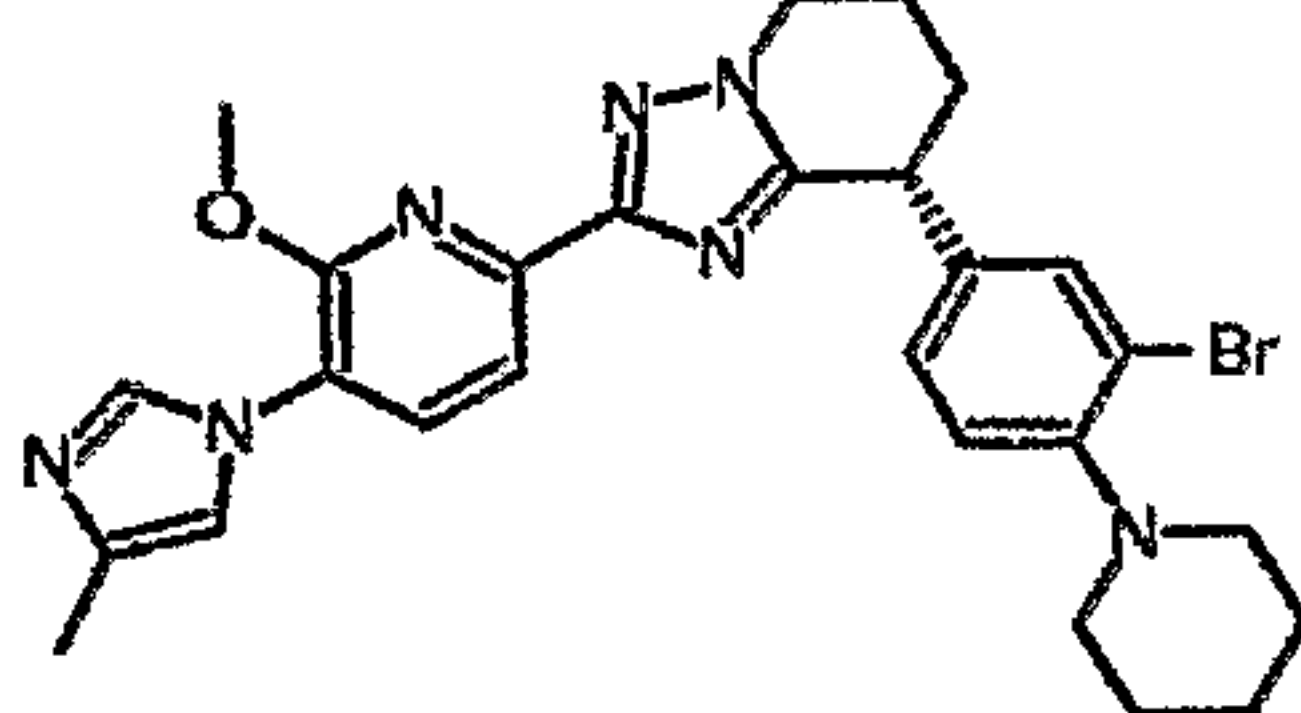
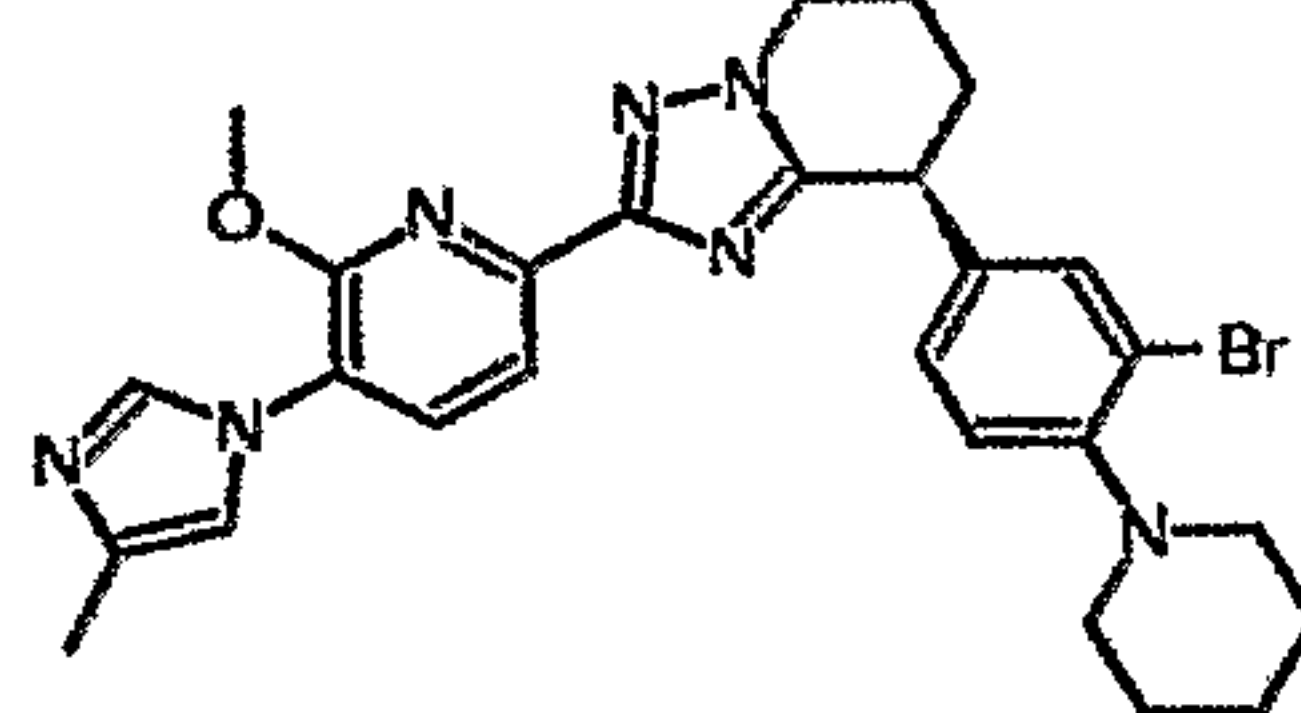
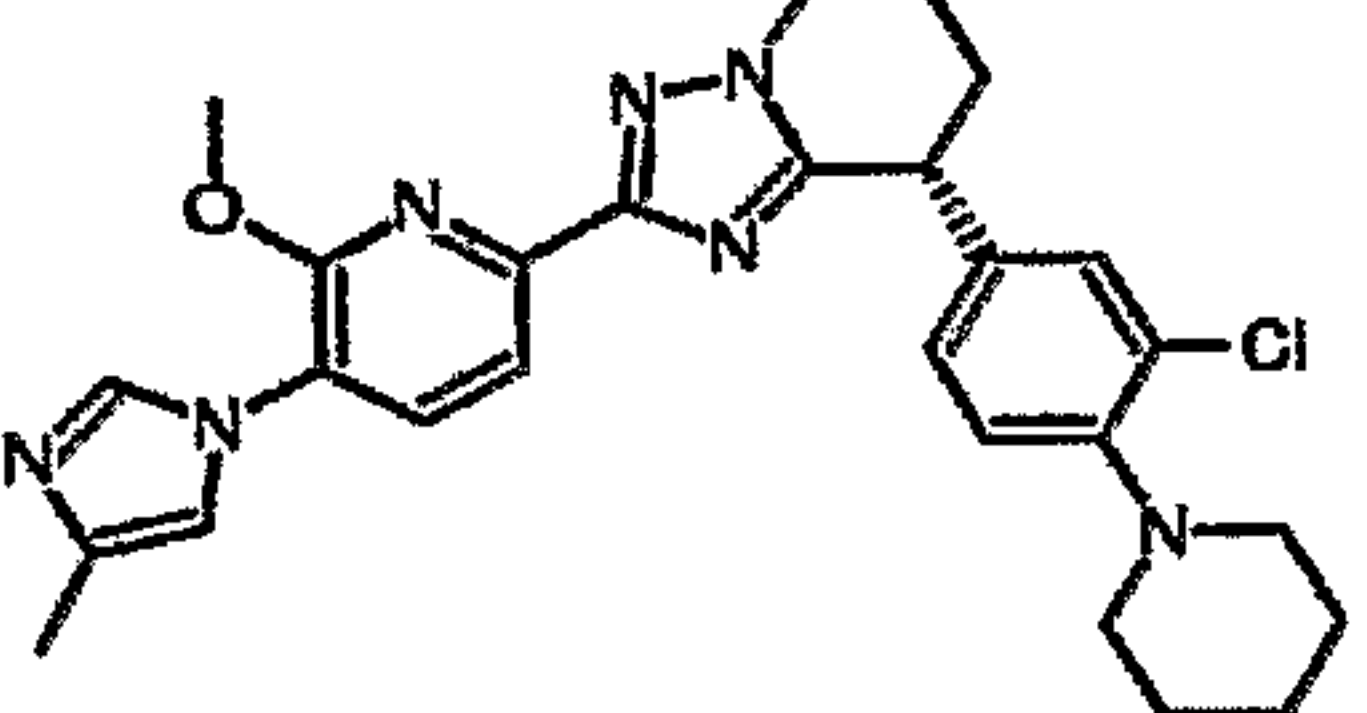
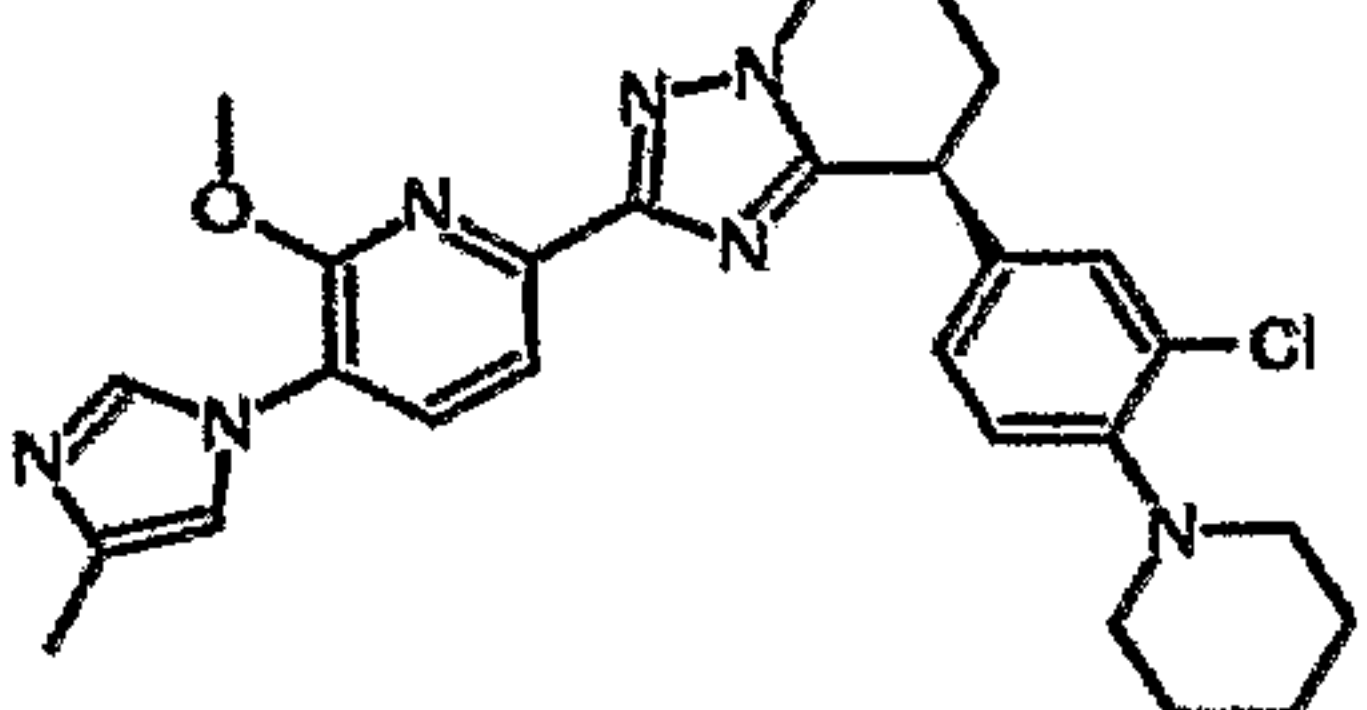
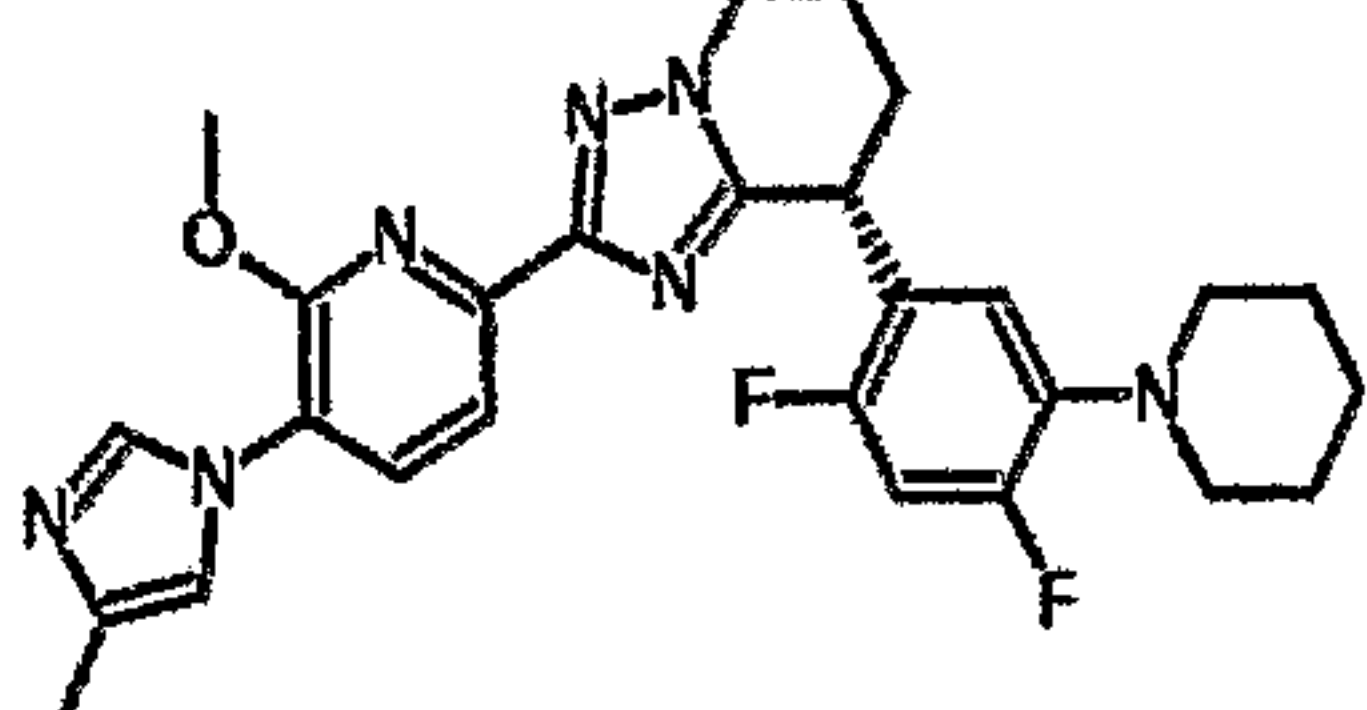
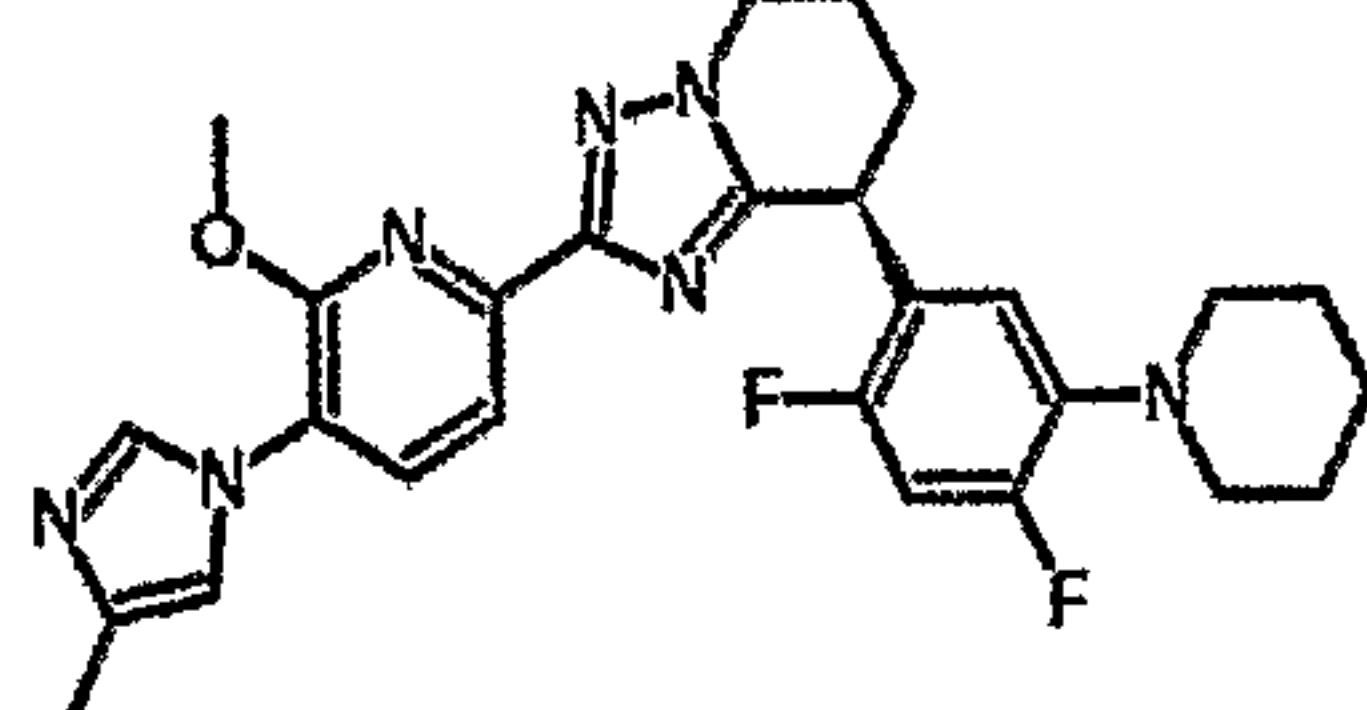
[0840]

Table 30

Example No.	Structural formula	¹ H-NMR or ESI mass
Example290		ESI-MS;m/z 488[M ⁺ +H].
Example291		ESI-MS;m/z 488[M ⁺ +H].
Example292		ESI-MS;m/z 488[M ⁺ +H].
Example293		ESI-MS;m/z 488[M ⁺ +H].
Example294		ESI-MS;m/z 505[M ⁺ +H].
Example295		ESI-MS;m/z 505[M ⁺ +H].

[0841]

Table 31

Example No.	Structural formula	¹ H-NMR or ESI mass
Example296		ESI-MS; m/z 548, 550[M ⁺ +H].
Example297		ESI-MS; m/z 548, 550[M ⁺ +H].
Example298		ESI-MS; m/z 504[M ⁺ +H].
Example299		ESI-MS; m/z 504[M ⁺ +H].
Example300		ESI-MS; m/z 254[1/2M ⁺ +H], 506[M ⁺ +H].
Example301		ESI-MS; m/z 254[1/2M ⁺ +H], 506[M ⁺ +H].

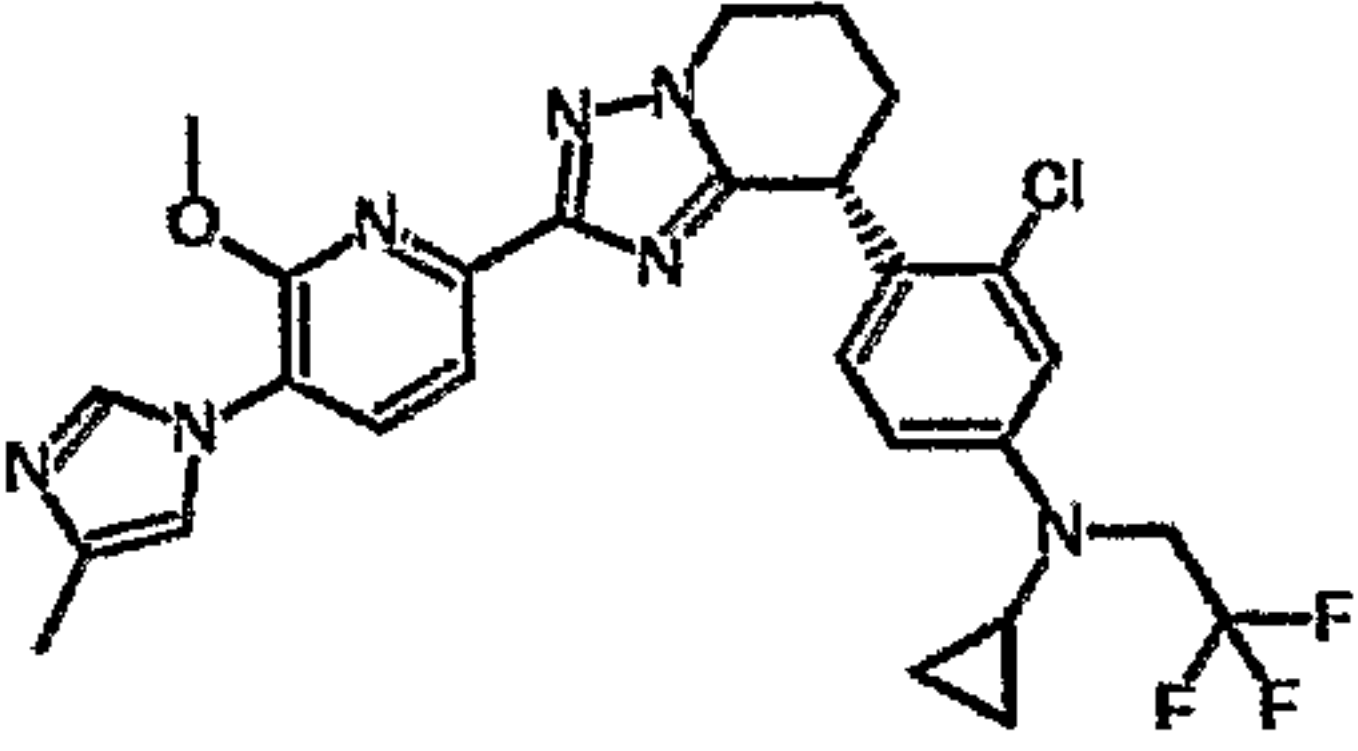
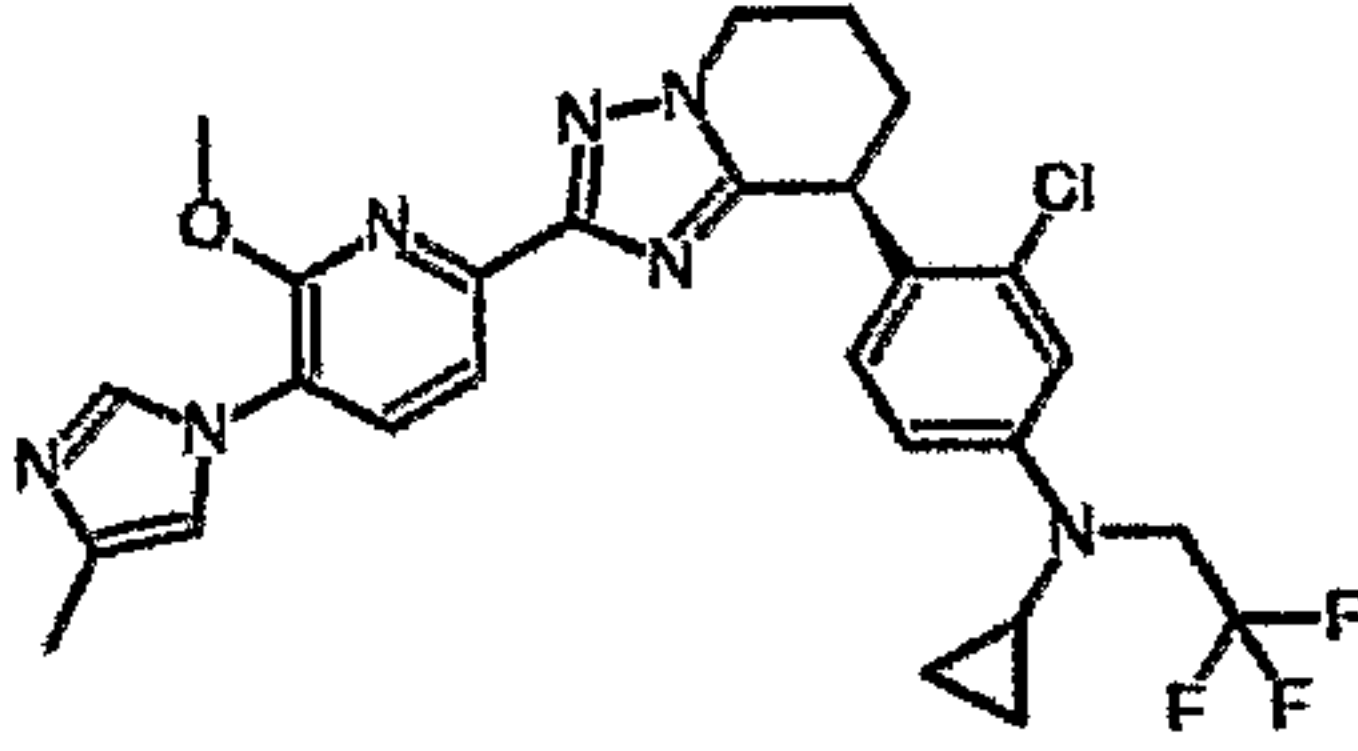
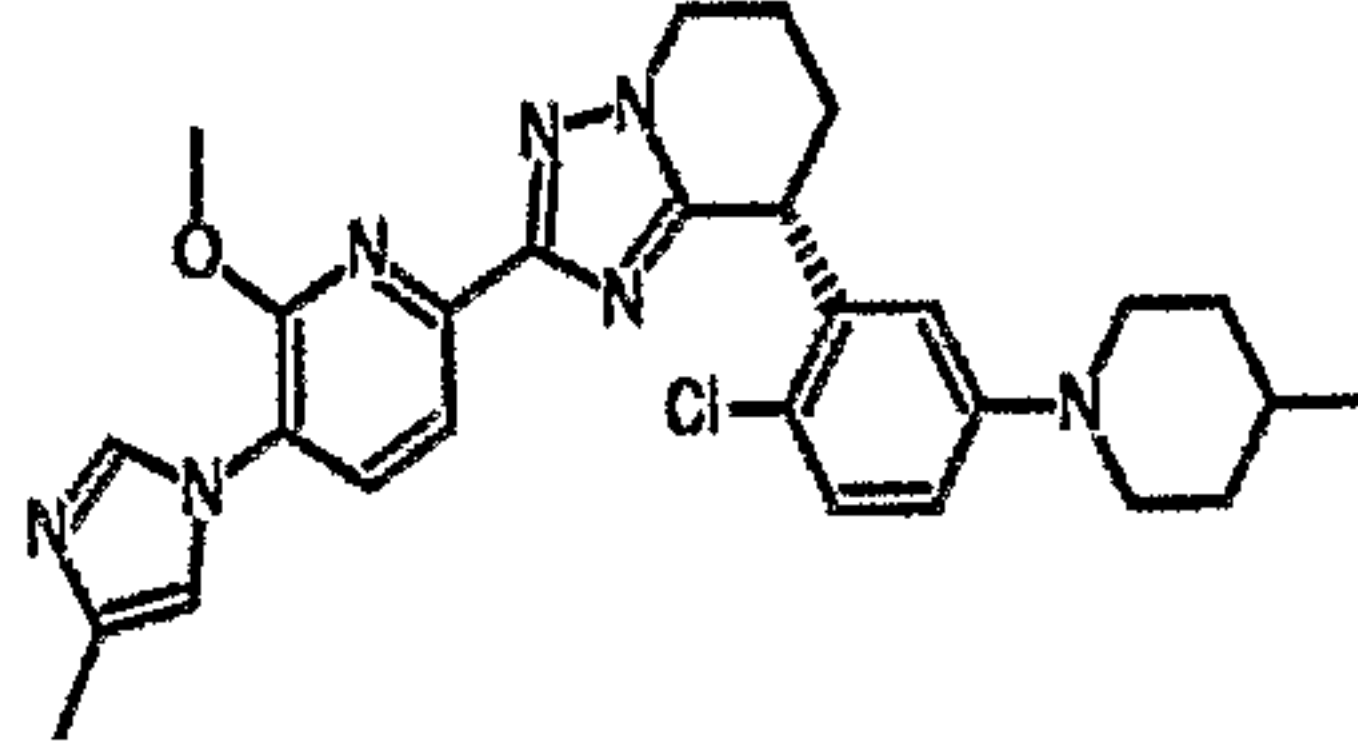
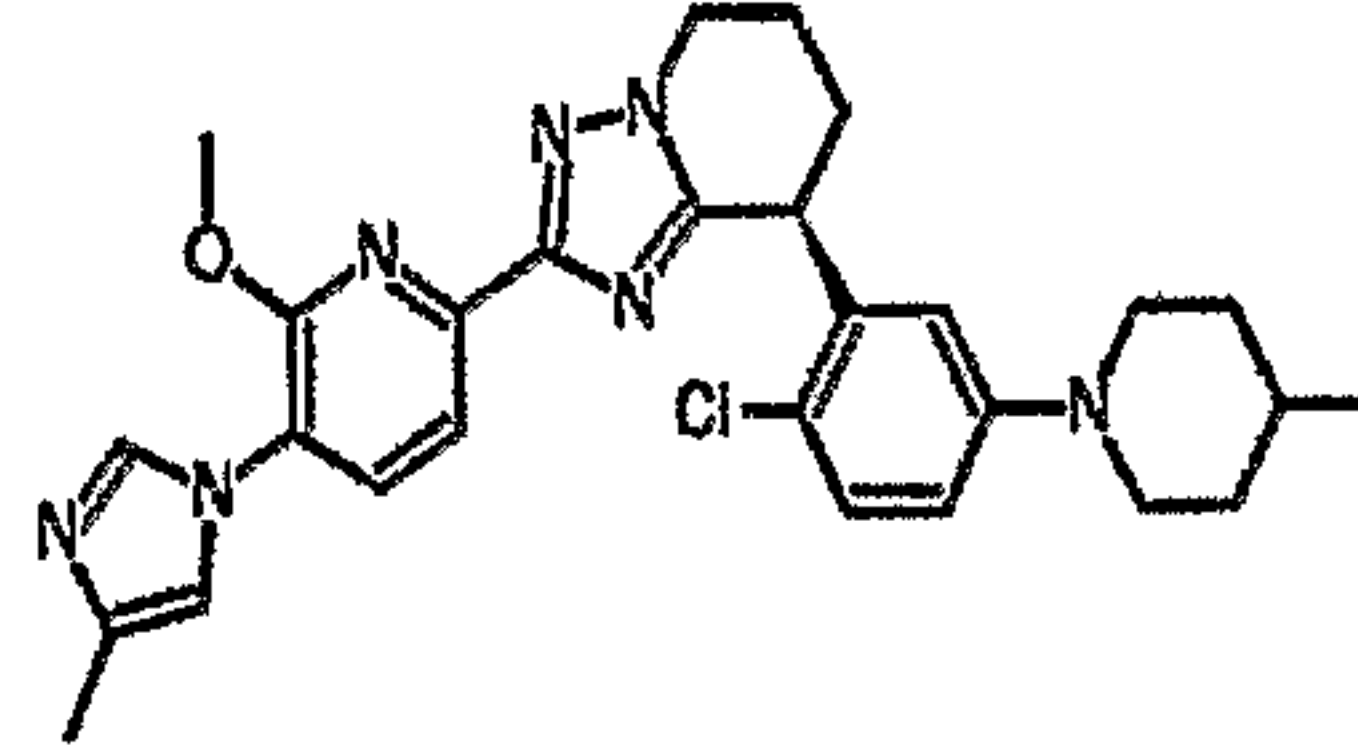
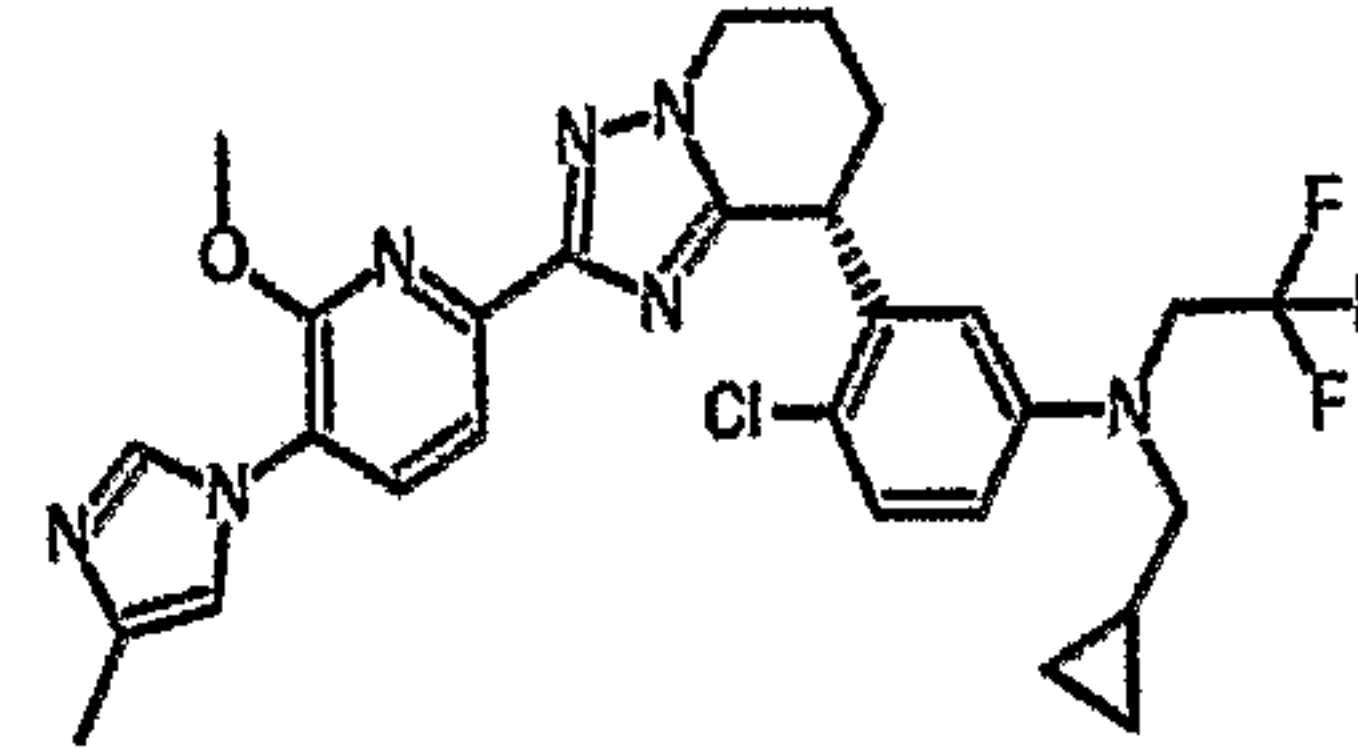
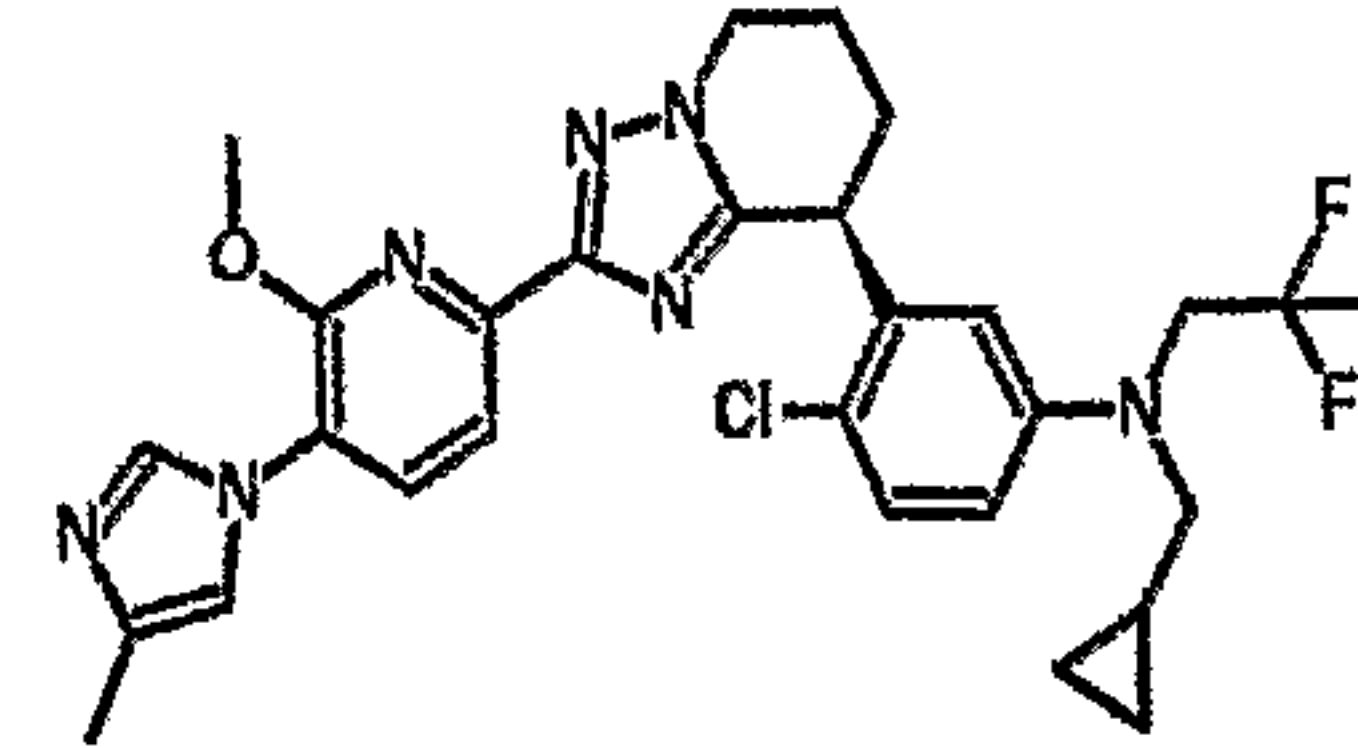
[0842]

Table 32

Example No.	Structural formula	$^1\text{H-NMR}$ or ESI mass
Example302		ESI-MS; m/z 262[1/2M ⁺ +H], 522[M ⁺ +H].
Example303		ESI-MS; m/z 262[1/2M ⁺ +H], 522[M ⁺ +H].
Example304		ESI-MS; m/z 262[1/2M ⁺ +H], 522[M ⁺ +H].
Example305		ESI-MS; m/z 262[1/2M ⁺ +H], 522[M ⁺ +H].
Example306		ESI-MS; m/z 286[1/2M ⁺ +H], 572[M ⁺ +H].
Example307		ESI-MS; m/z 286[1/2M ⁺ +H], 572[M ⁺ +H].

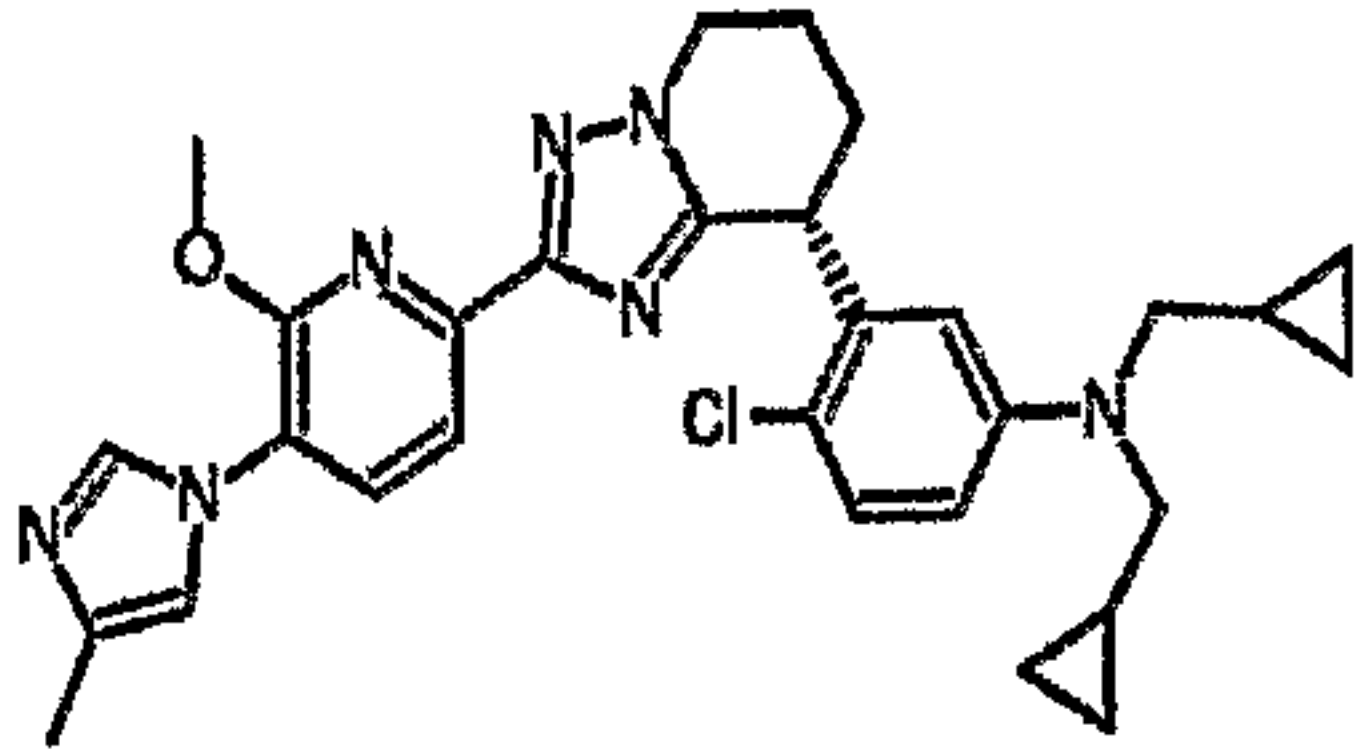
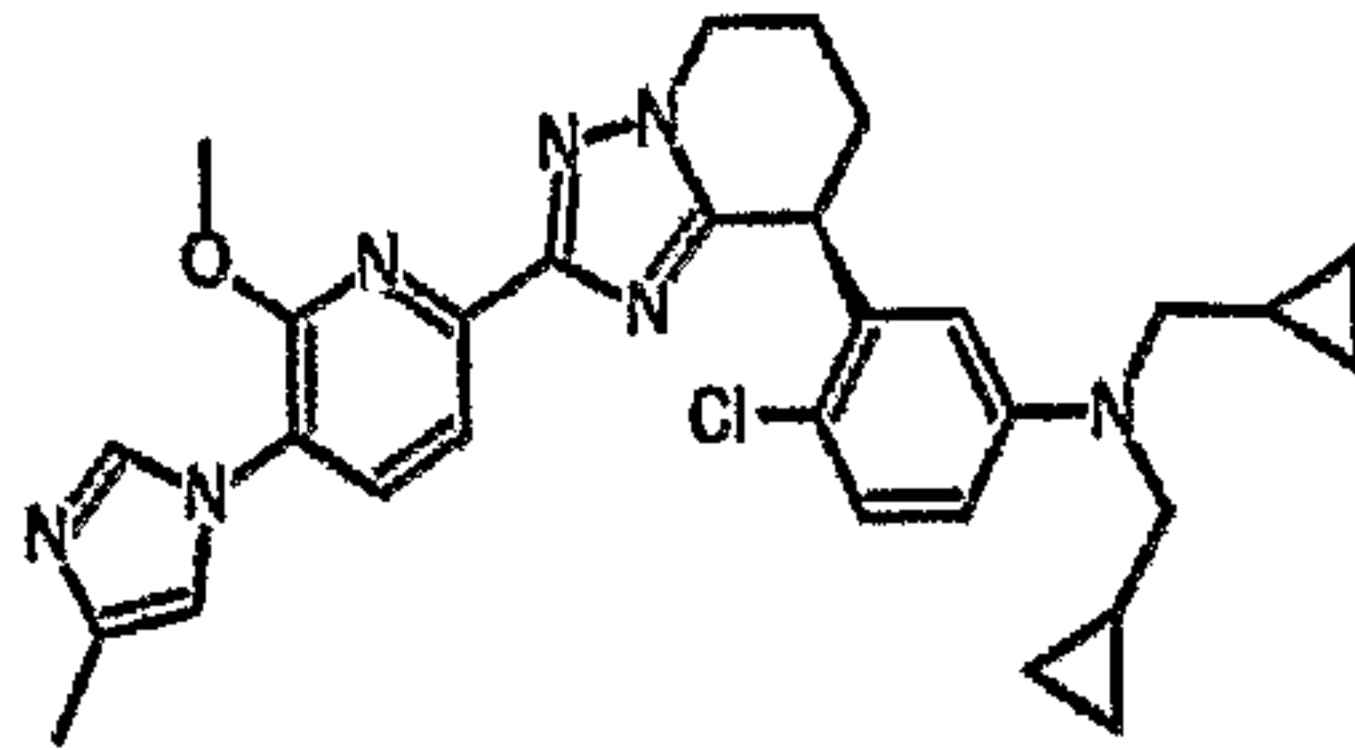
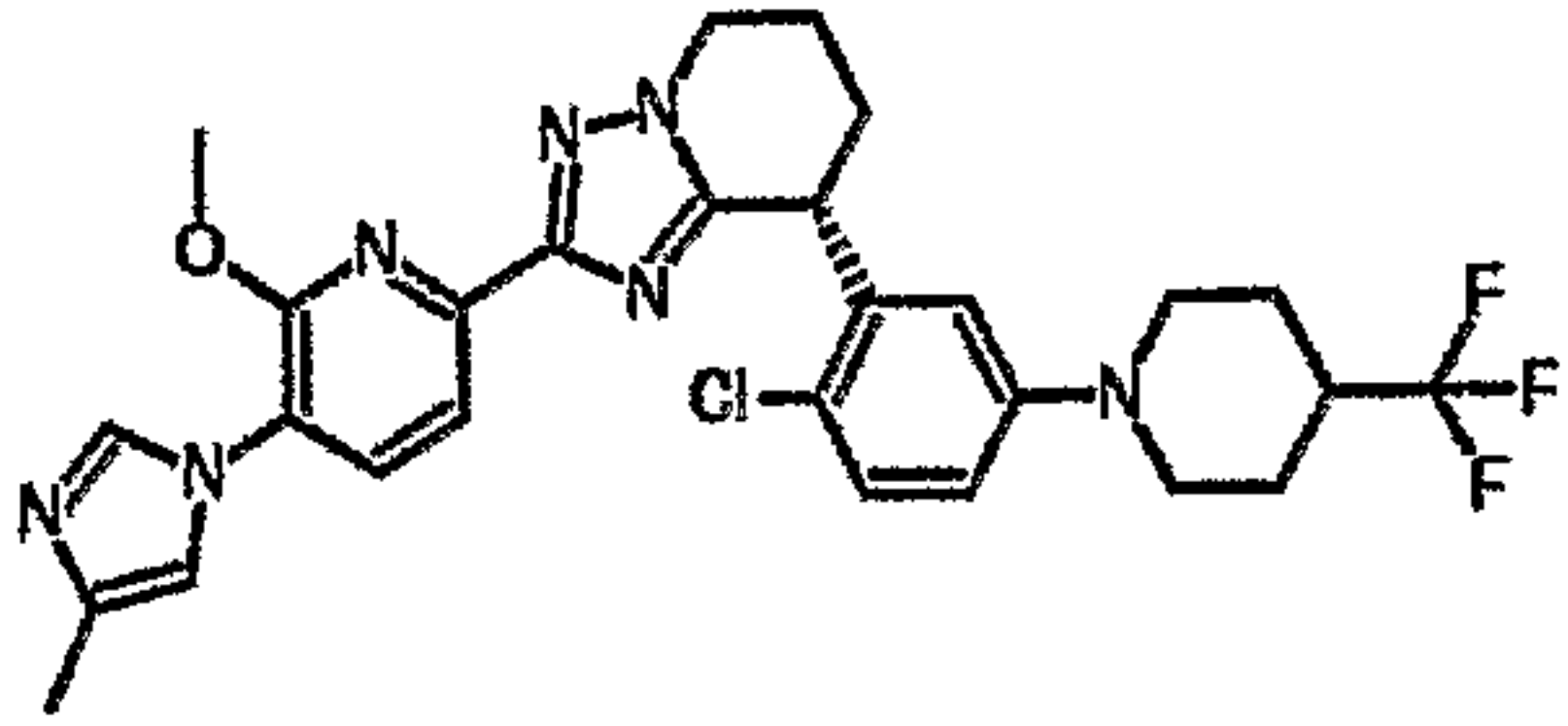
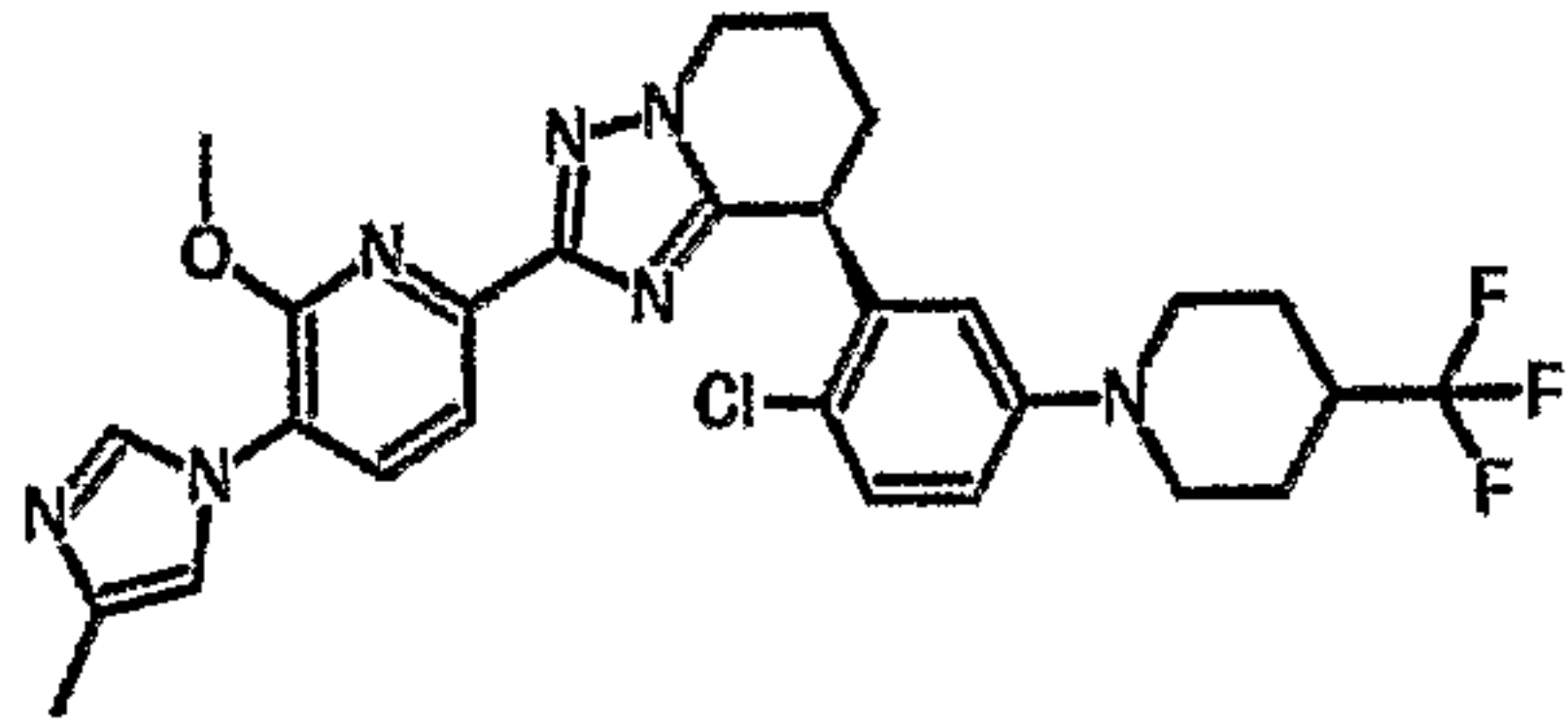
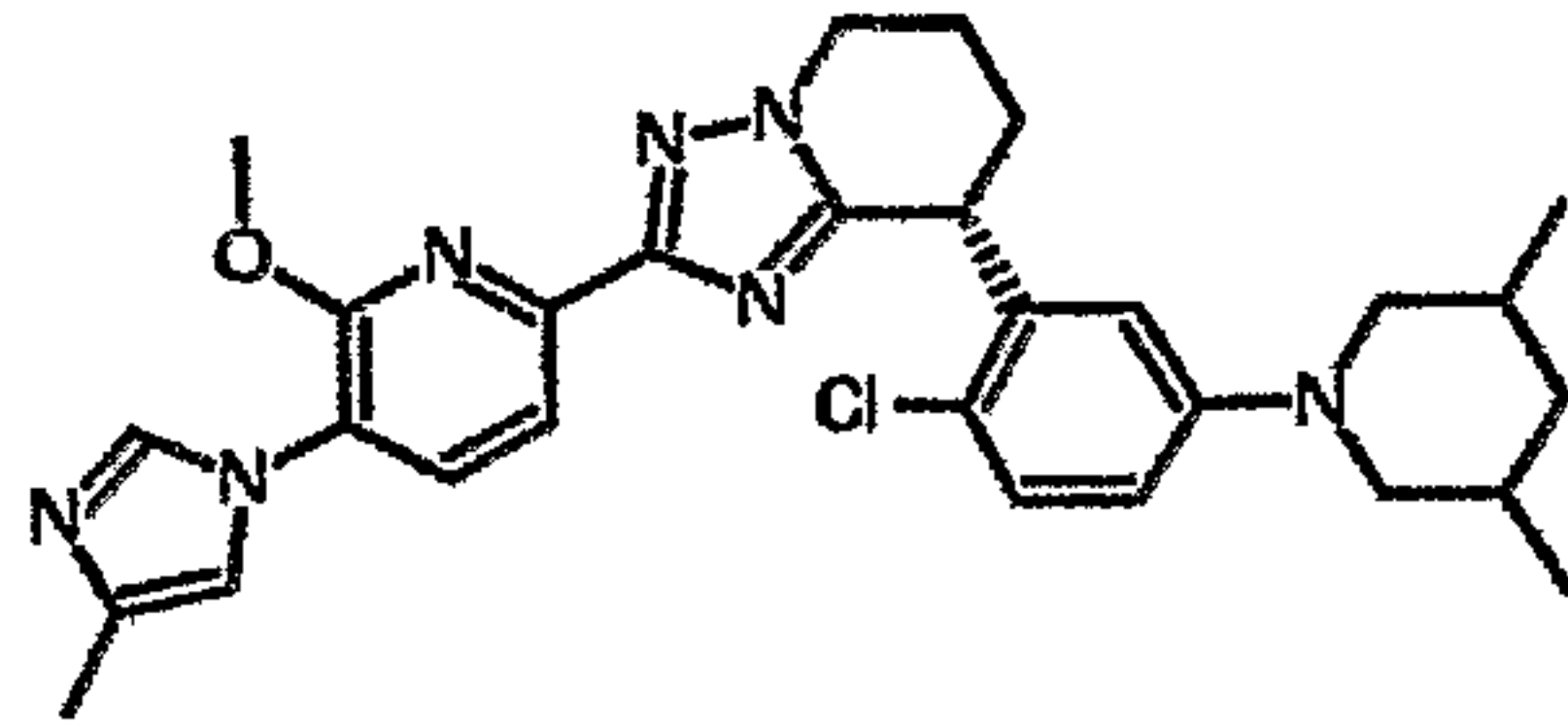
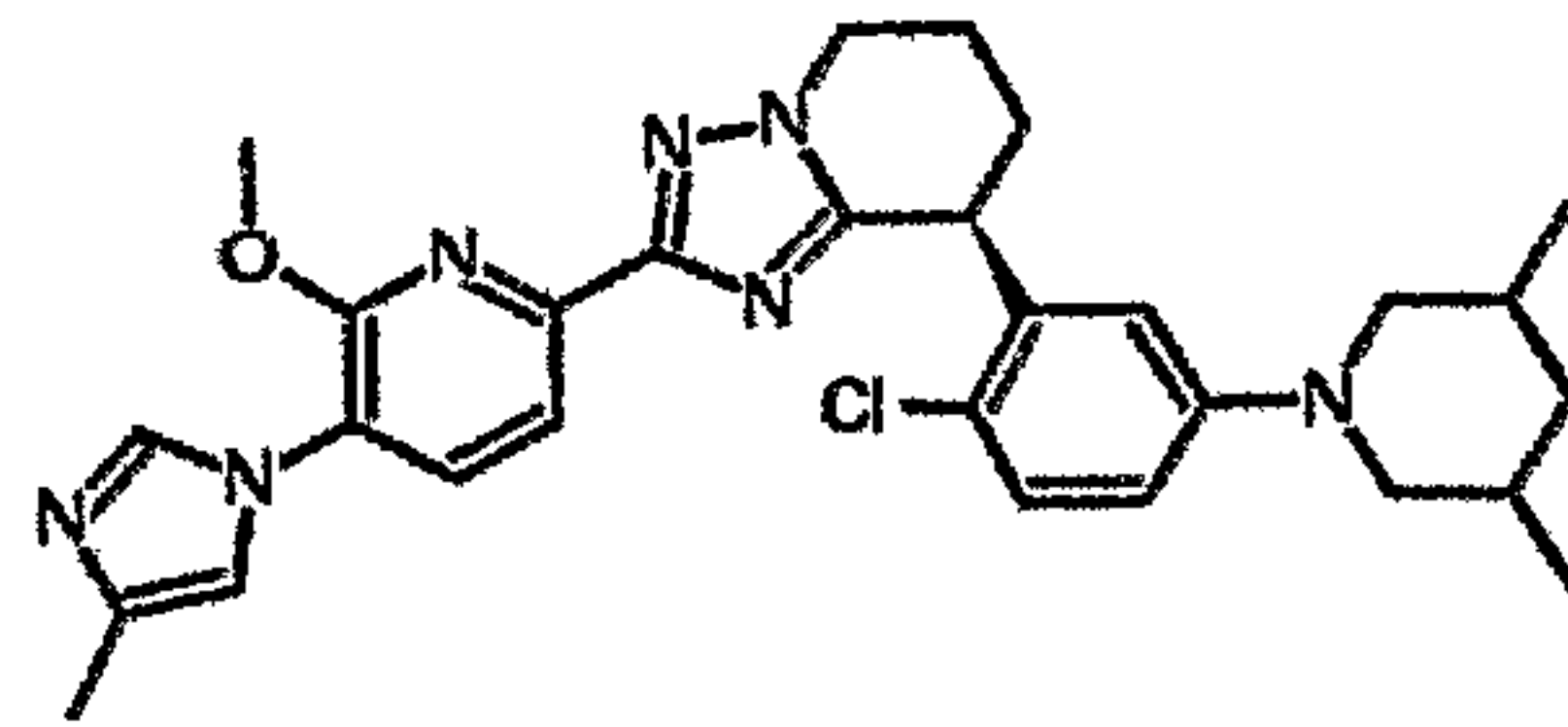
[0843]

Table 33

Example No.	Structural formula	$^1\text{H-NMR}$ or ESI mass
Example308		ESI-MS; m/z 279[1/2 M^+ +H], 558[M^+ +H].
Example309		ESI-MS; m/z 279[1/2 M^+ +H], 558[M^+ +H].
Example310		ESI-MS; m/z 260[1/2 M^+ +H], 518[M^+ +H].
Example311		ESI-MS; m/z 260[1/2 M^+ +H], 518[M^+ +H].
Example312		ESI-MS; m/z 572[M^+ +H].
Example313		ESI-MS; m/z 572[M^+ +H].

[0844]

Table 34

Example No.	Structural formula	¹ H-NMR or ESI mass
Example314		ESI-MS;m/z 544[M ⁺ +H].
Example315		ESI-MS;m/z 544[M ⁺ +H].
Example316		ESI-MS;m/z 572[M ⁺ +H].
Example317		ESI-MS;m/z 572[M ⁺ +H].
Example318		ESI-MS;m/z 532[M ⁺ +H].
Example319		ESI-MS;m/z 532[M ⁺ +H].

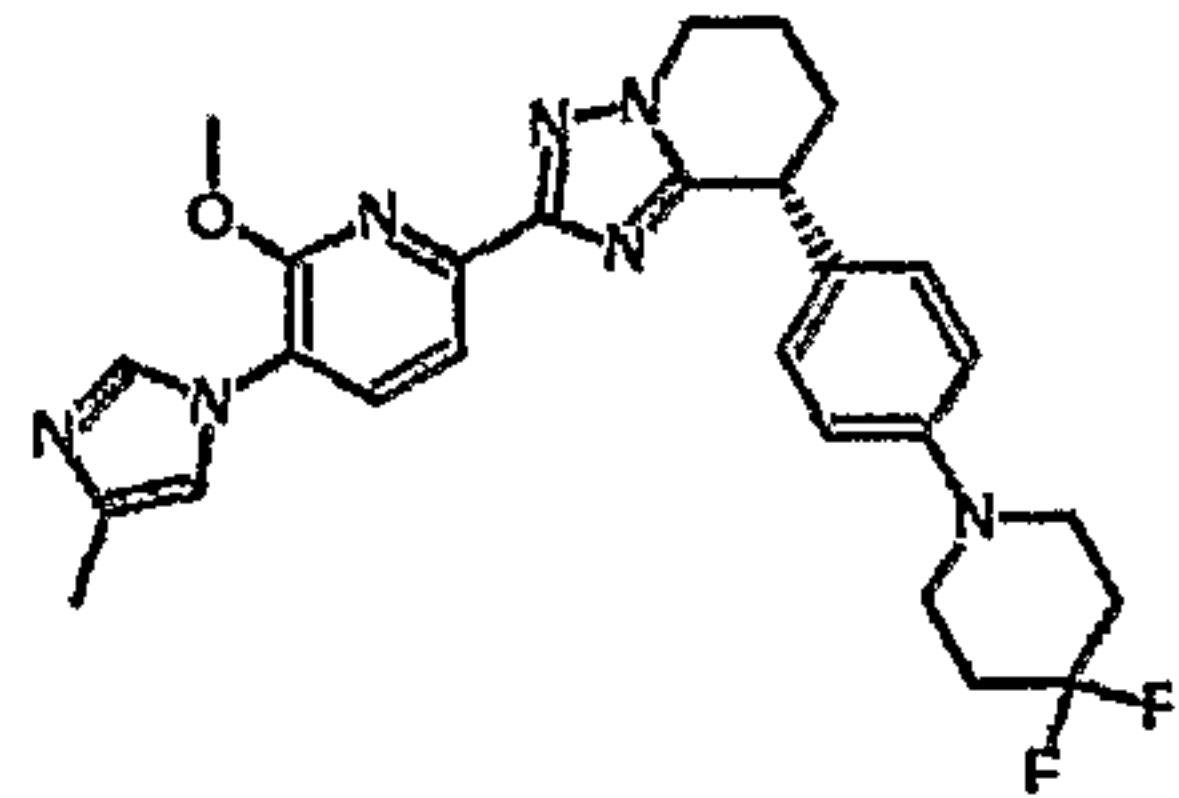
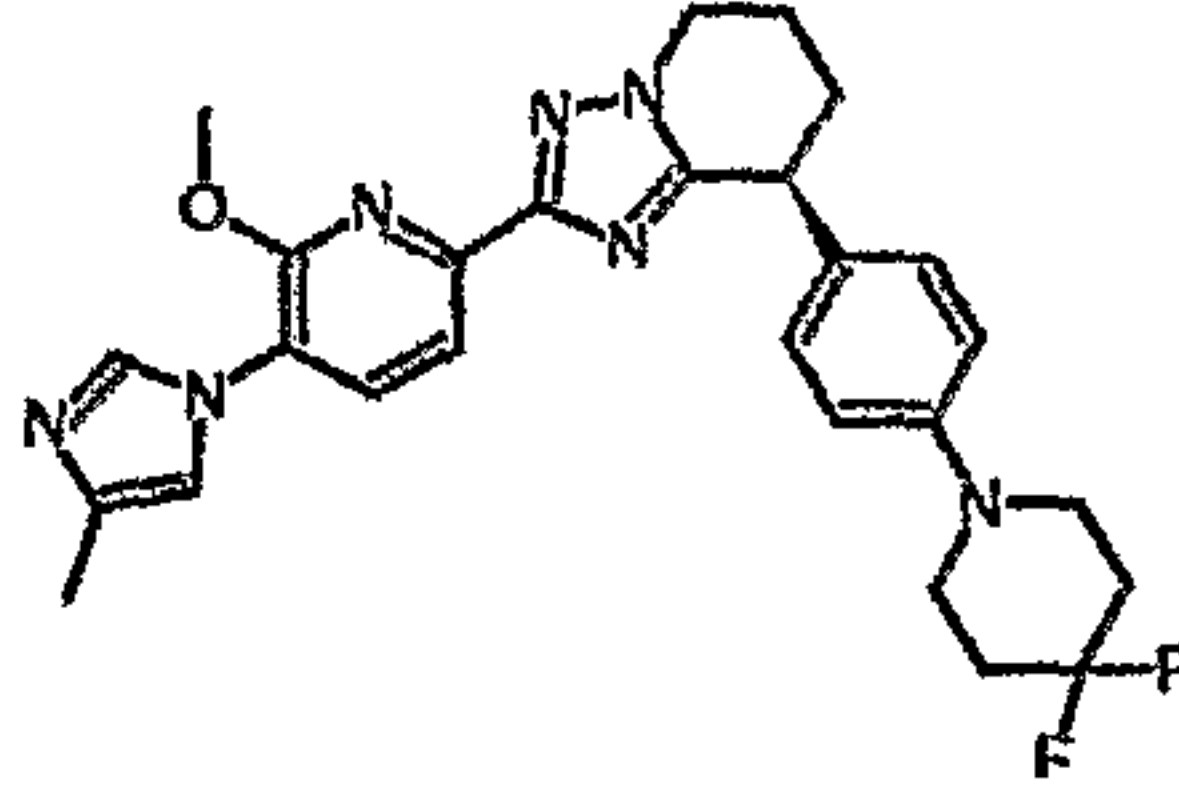
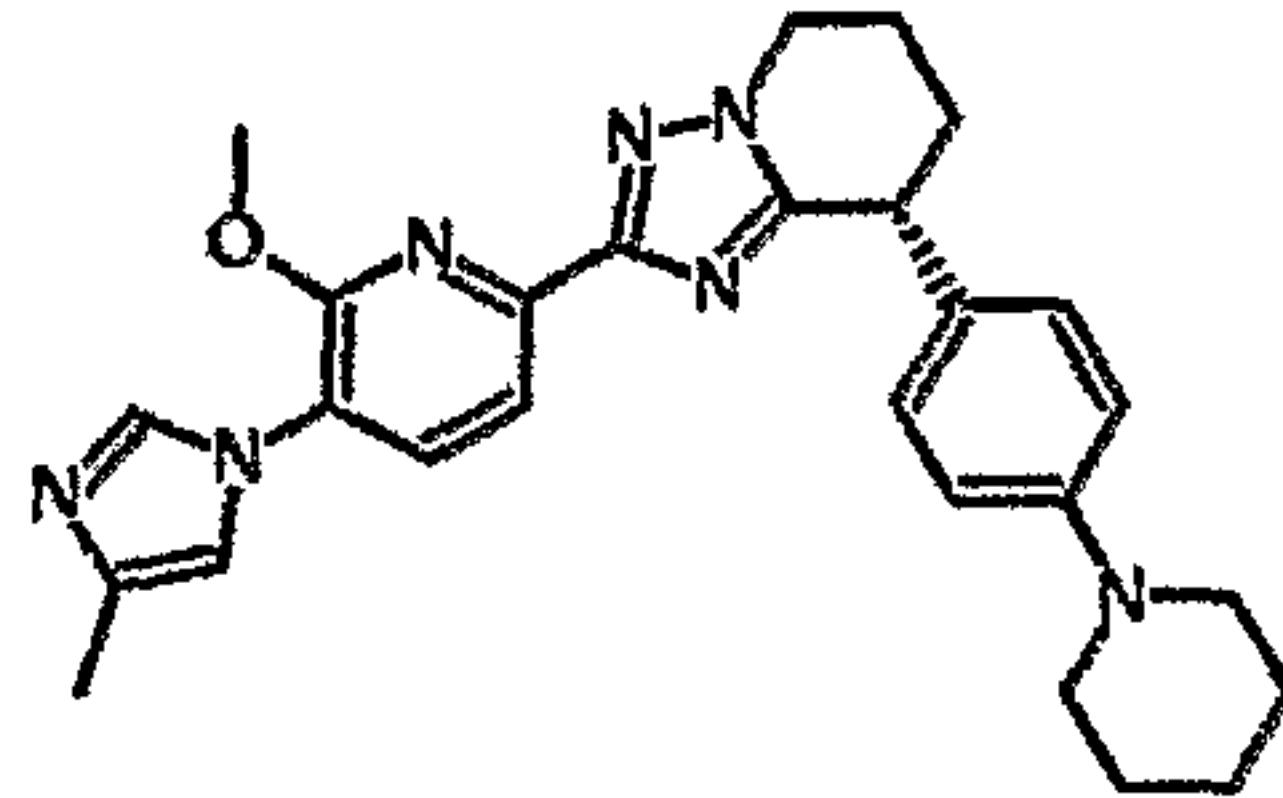
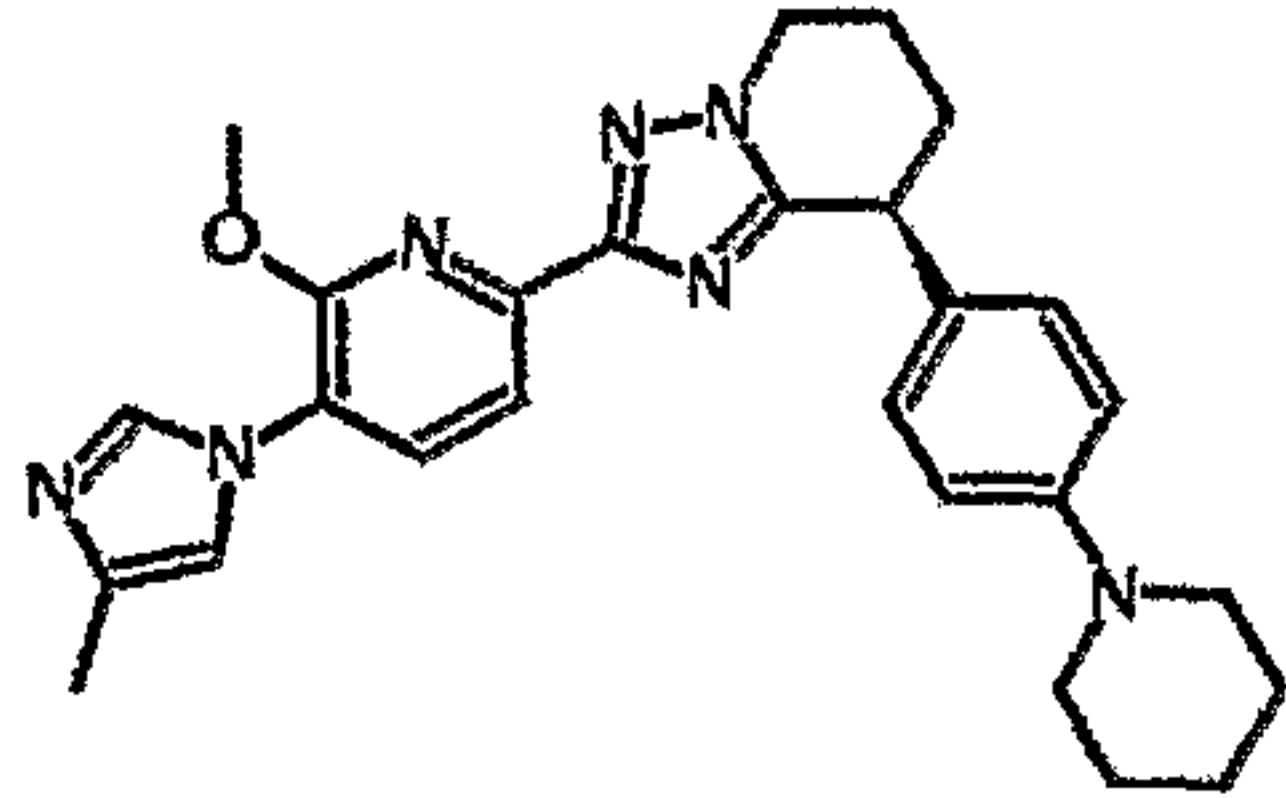
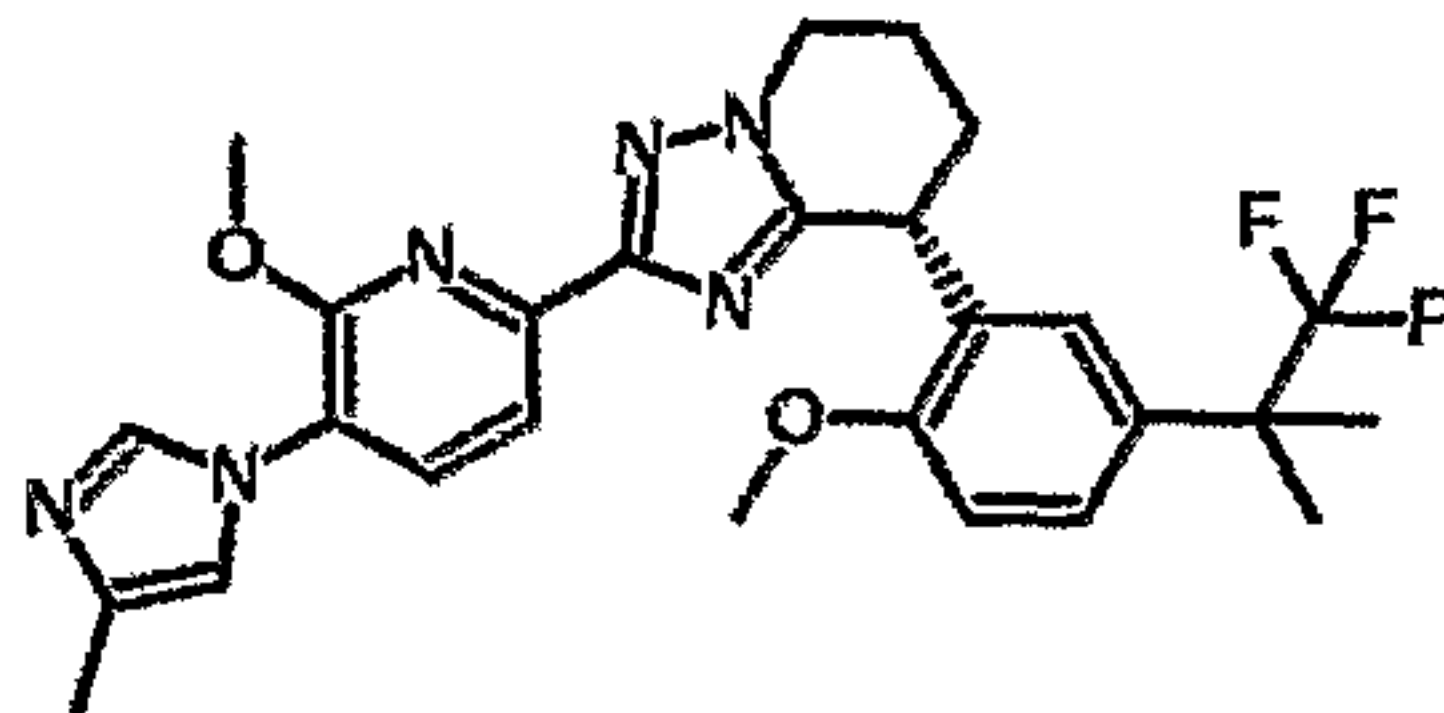
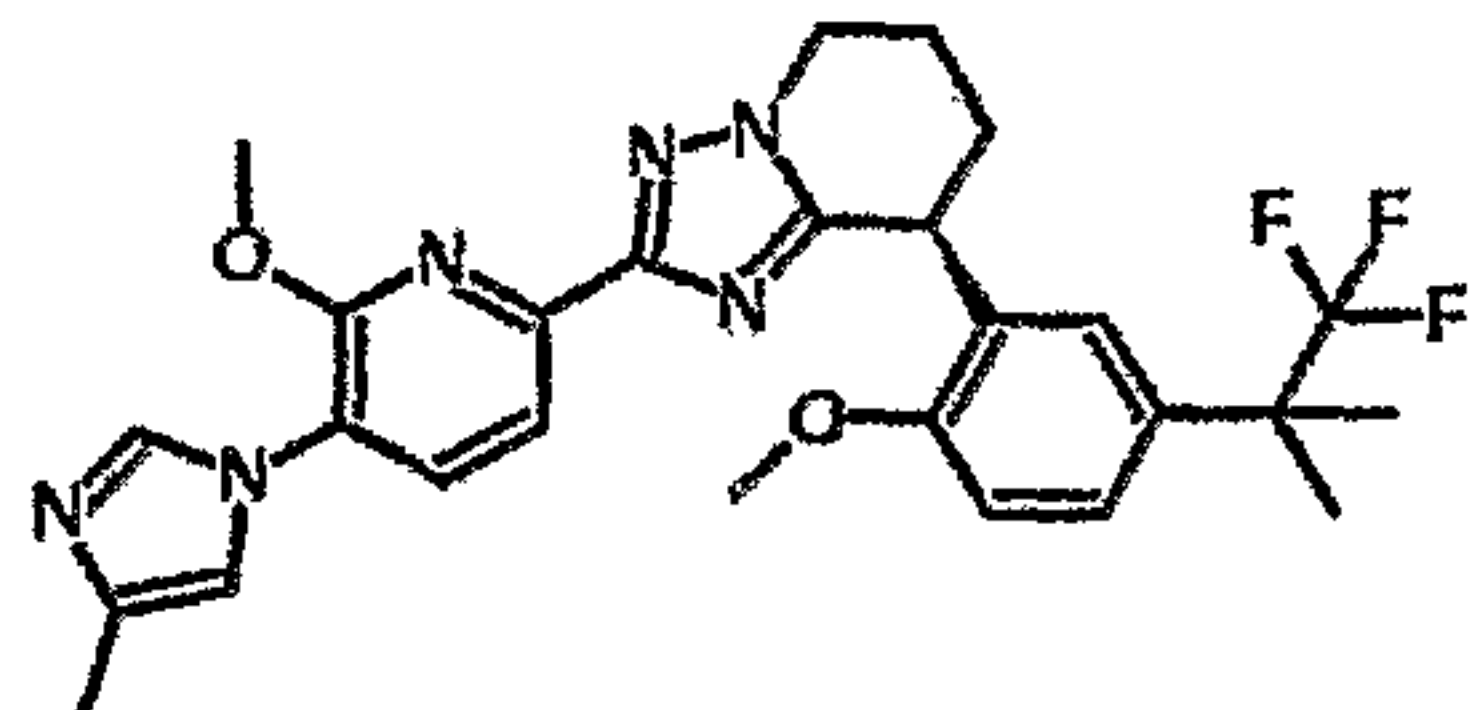
[0845]

Table 35

Example No.	Structural formula	$^1\text{H-NMR}$ or ESI mass
Example320		ESI-MS; m/z 475 [$\text{M}^+ + \text{H}$].
Example321		ESI-MS; m/z 475 [$\text{M}^+ + \text{H}$].
Example322		ESI-MS; m/z 500 [$\text{M}^+ + \text{H}$].
Example323		ESI-MS; m/z 500 [$\text{M}^+ + \text{H}$].
Example324		ESI-MS; m/z 536 [$\text{M}^+ + \text{H}$].
Example325		ESI-MS; m/z 536 [$\text{M}^+ + \text{H}$].

[0846]

Table 36

Example No.	Structural formula	¹ H-NMR or ESI mass
Example326		ESI-MS;m/z 506[M ⁺ +H].
Example327		ESI-MS;m/z 506[M ⁺ +H].
Example328		ESI-MS;m/z 470[M ⁺ +H].
Example329		ESI-MS;m/z 470[M ⁺ +H].
Example330		ESI-MS;m/z 527[M ⁺ +H].
Example331		ESI-MS;m/z 527[M ⁺ +H].

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 272

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 272

NOTE: For additional volumes, please contact the Canadian Patent Office

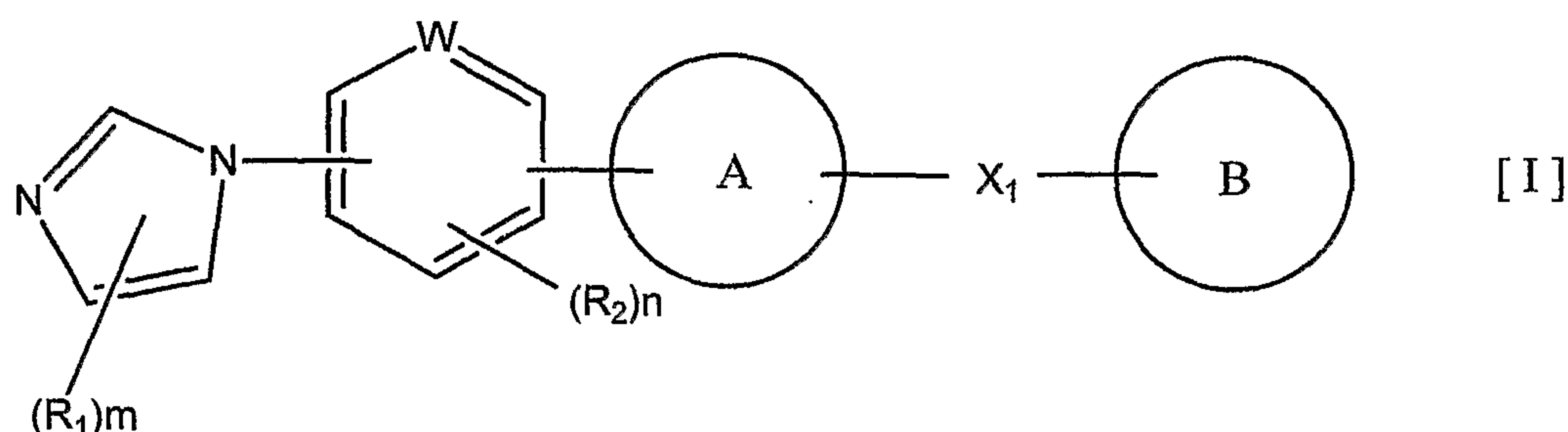
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CLAIMS

1. A compound represented by the formula [I]:



or a pharmacologically acceptable salt or ester thereof,

wherein R_1 and R_2 are the same or different and each represent a substituent selected from the following Substituent Group a1;

m represents an integer of 0 to 3;

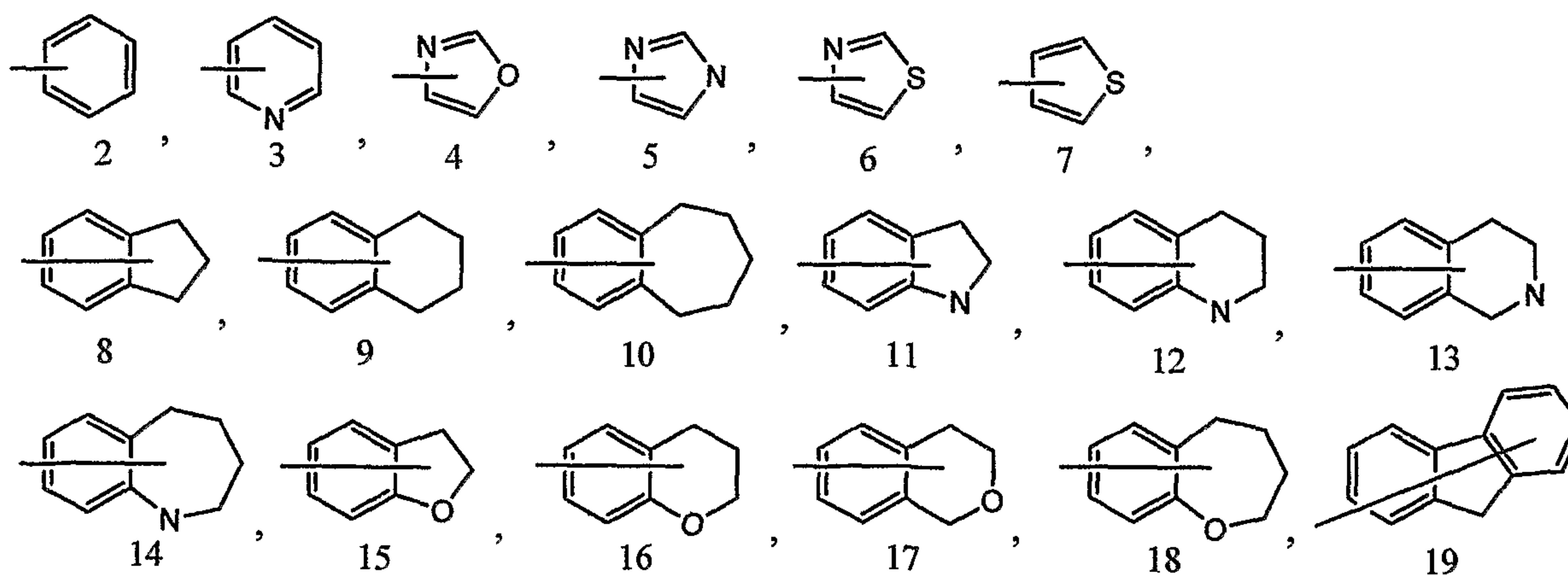
n represents an integer of 0 to 2;

W represents a nitrogen atom or a carbon atom;

Ring A represents a five-membered aromatic heterocyclic group fused with a 5- to 14-membered non-aromatic ring group, which contains two or more nitrogen atoms and may have 1 to 3 substituents selected from the following Substituent Group b1 (wherein the 5- to 14-membered non-aromatic heterocyclic group may have a crosslinked structure);

X_1 represents i) a single bond, ii) a C1-6 alkylene group, iii) a vinylene group which may have 1 to 2 C1-6 alkyl groups or iv) $-X_2-$ (wherein X_2 represents $-NR_3-$, $-NR_3C(O)-$, $-C(O)NR_3-$, $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$ and R_3 represents a hydrogen atom, a C1-6 alkyl group, a C3-6 cycloalkyl group, a C2-6 alkanoyl group or a C1-6 alkylsulfonyl group); and

Ring B represents a monocyclic or fused cyclic aromatic ring group selected from the formulas [2] to [19]:



each of which may have 1 to 3 substituents selected from the following

Substituent Group c1

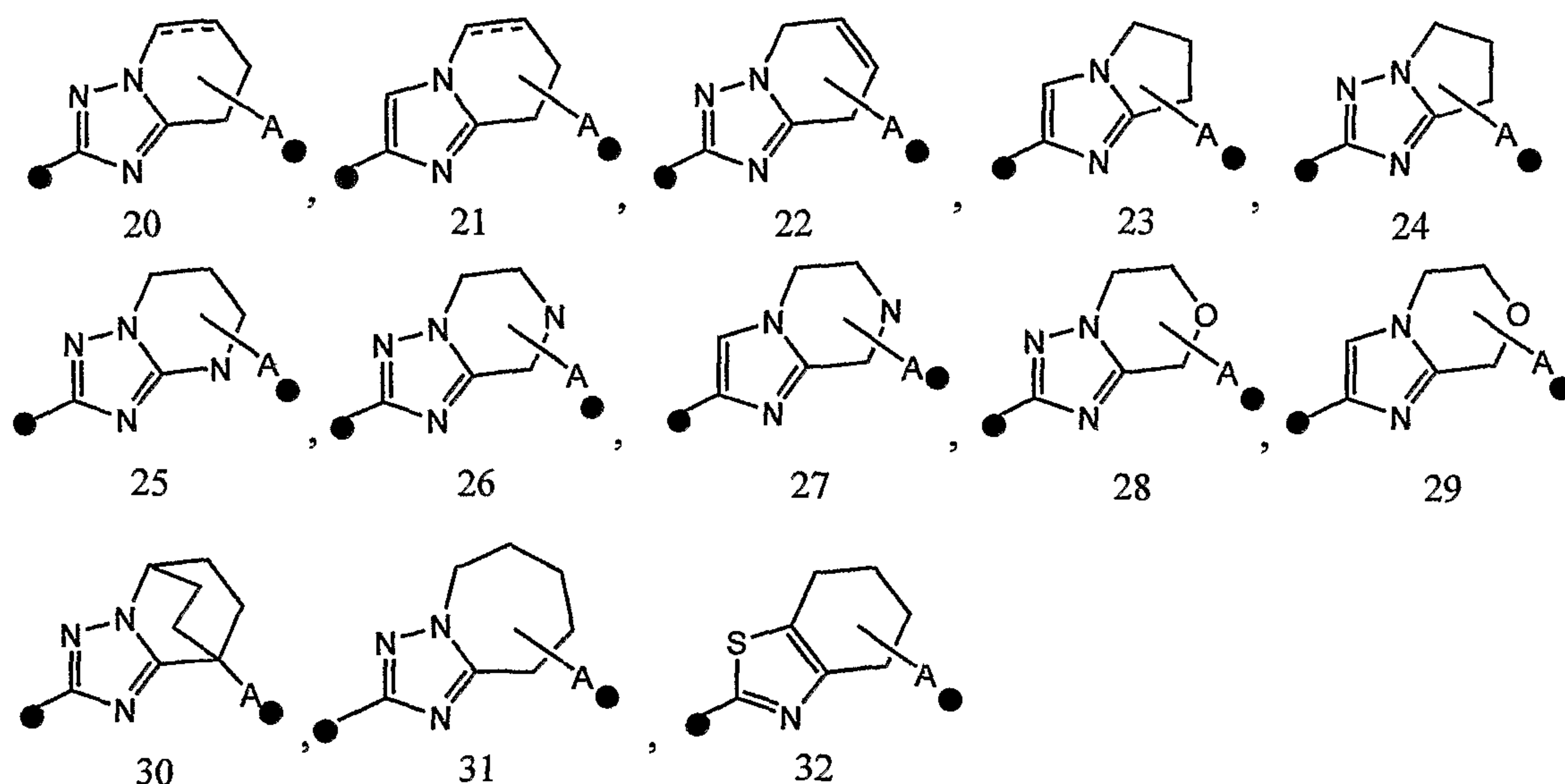
[Substituent Group a1: a C1-6 alkyl group, a C3-8 cycloalkyl group, a C2-6 alkenyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, an amino group (wherein the amino group may have one C2-6 alkanoyl group or C1-6 alkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group and a nitro group;

Substituent Group b1: a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C2-6 alkenyl group, a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C4-9 cycloalkylcarbonyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C2-6 alkenylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a C1-6 alkylthio group, a C2-6 alkenylthio group, a C3-8 cycloalkylthio group, an aminosulfonyl group (wherein the aminosulfonyl group may have 1 to 2 C1-6 alkyl groups, C2-6 alkenyl groups or C3-8 cycloalkyl groups), an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group, a nitro group, an oxo group, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 1-homopiperidinyl group, an indolin-1-yl group, a 1,2,3,4-tetrahydroquinolin-1-yl group and a 4-morpholinyl group;

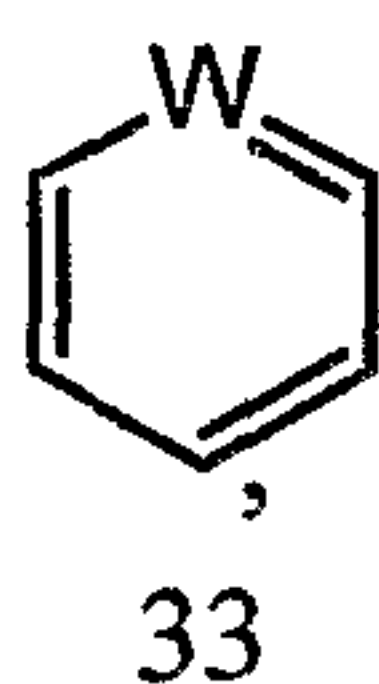
Substituent Group c1: i) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v-i) a C1-6 alkyl group, v-ii) a C2-6 alkenyl group, v-iii) a C2-6 alkynyl group, v-iv) a C1-6 alkoxy group, v-v) a C1-6 alkylaminocarbonyl group, v-vi) a C1-6 alkylaminosulfonyl group, v-vii) a C1-6 alkylsulfonyl group, v-viii) a C1-6 alkylthio group, v-ix) a C2-6 alkanoyl group, v-x) a phenyl group, v-xi) a pyridyl group, v-xii) a pyridazinyl group, v-xiii) a pyrimidinyl group, v-xiv) a 1-pyrrolidinyl group, v-xv) a 1-piperidinyl group, v-xvi) a 1-homopiperidinyl group and v-xvii) a 4-morpholinyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom].

2. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein Ring A is any one ring selected from the group consisting of the formulas [20] to [32]:

300



each of which may have 1 to 3 substituents selected from Substituent Group b1, wherein • represents a bonding site to the formula [33]:

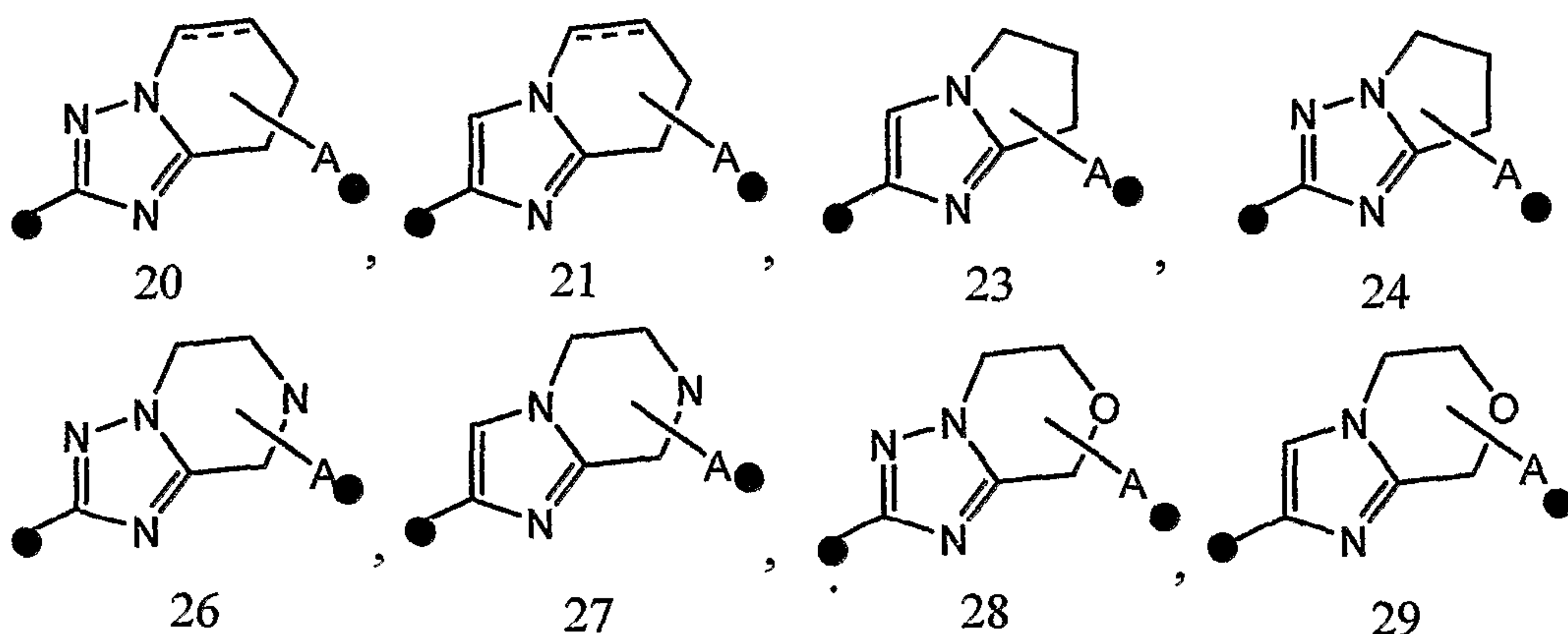


A• represents a bonding site to X₁, and



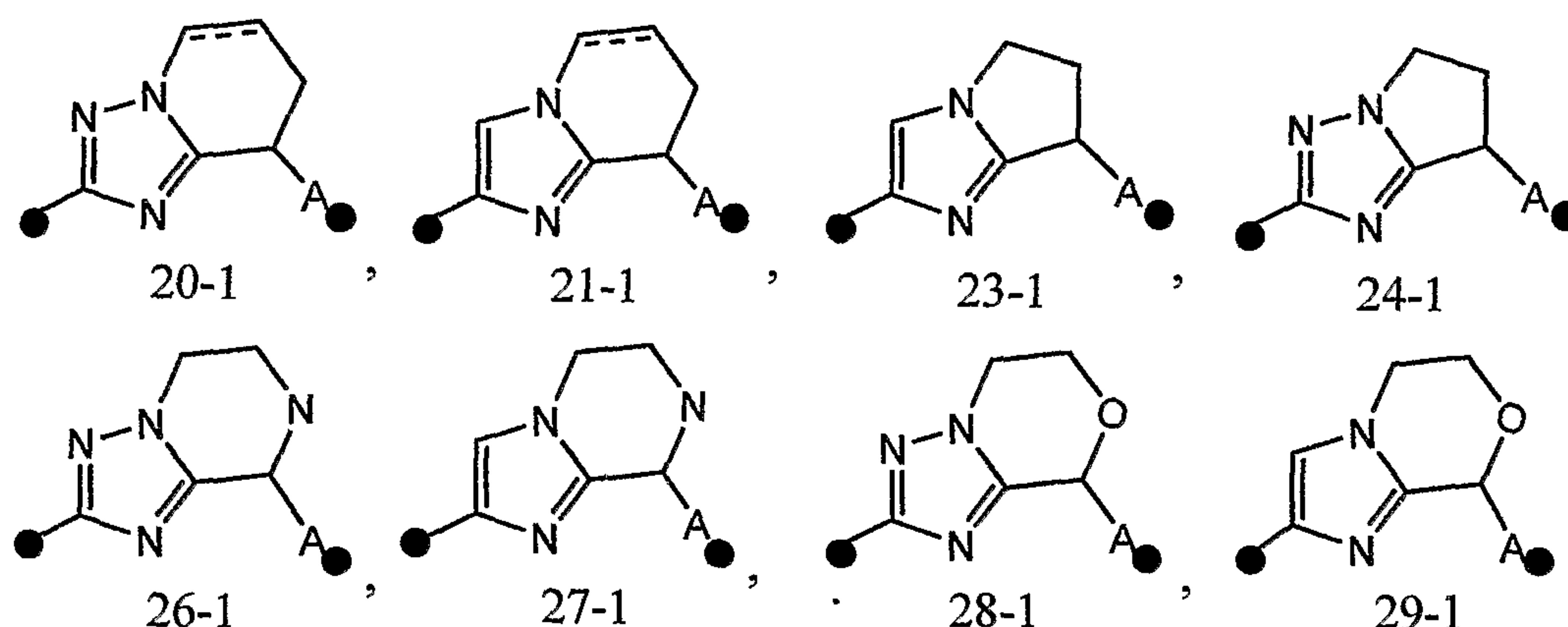
represents a single bond or a double bond.

3. The compound or pharmacologically acceptable salt or ester thereof according to claim 2, wherein Ring A is any one ring selected from the group consisting of the formulas [20], [21], [23], [24] and [26] to [29]:



4. The compound or pharmacologically acceptable salt or ester thereof according to

claim 2, wherein Ring A is any one ring selected from the group consisting of the formulas [20-1], [21-1], [23-1], [24-1] and [26-1] to [29-1]:



5. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein Ring B is a phenyl group, a pyridyl group, an oxazolyl group, an imidazolyl group, an thiazolyl group, a dihydrobenzofuranyl group or a thienyl group.

6. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein X_1 is i) a single bond or ii) a C1-6 alkylene group.

7. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein W is a carbon atom.

8. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein W is a nitrogen atom.

9. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein R_1 is a C1-6 alkyl group or a halogen atom and m is 1 to 2.

10. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein R_2 is a C1-6 alkoxy group and n is 1.

11. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein the substituent for Ring A is selected from the group consisting of:

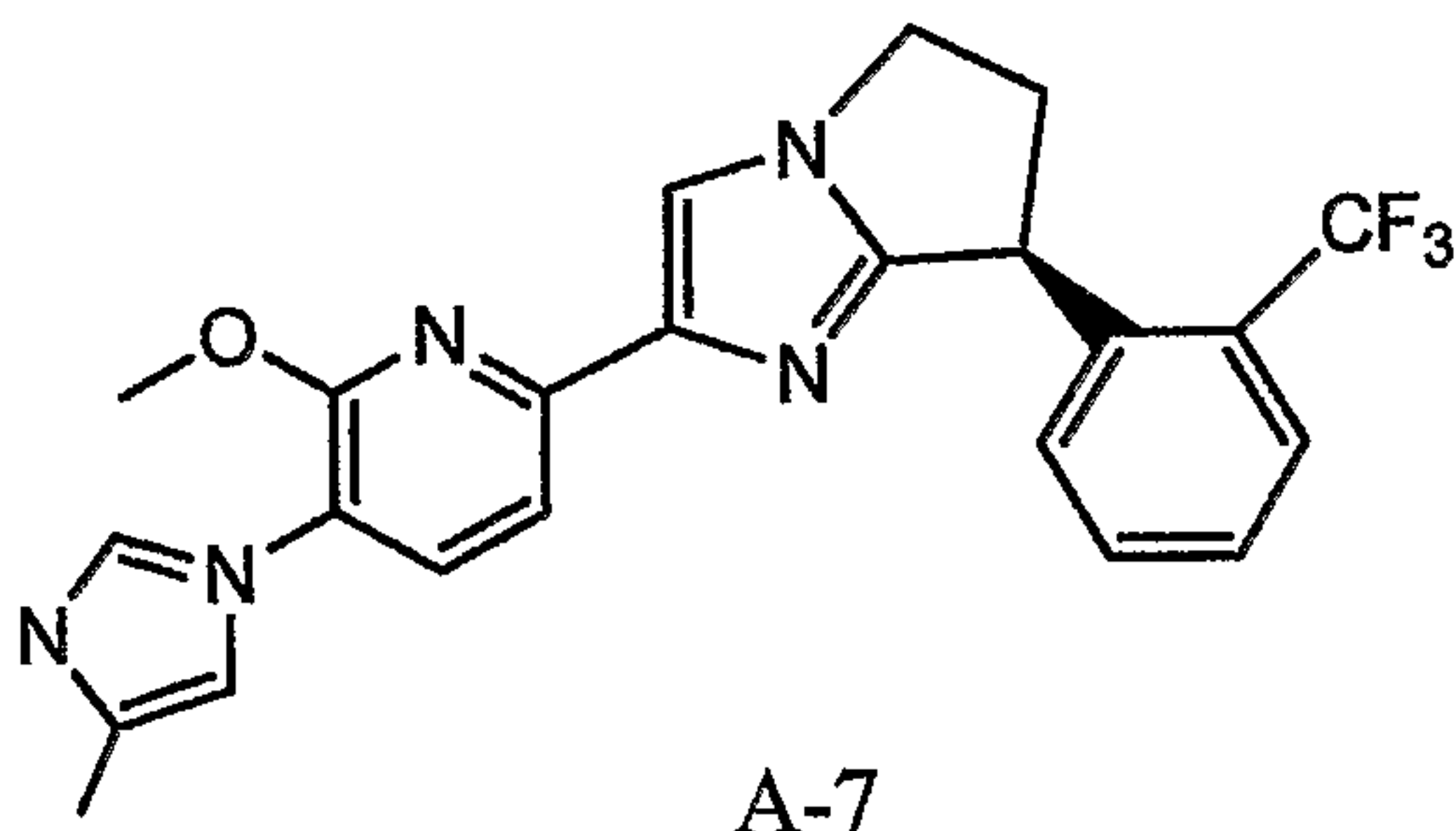
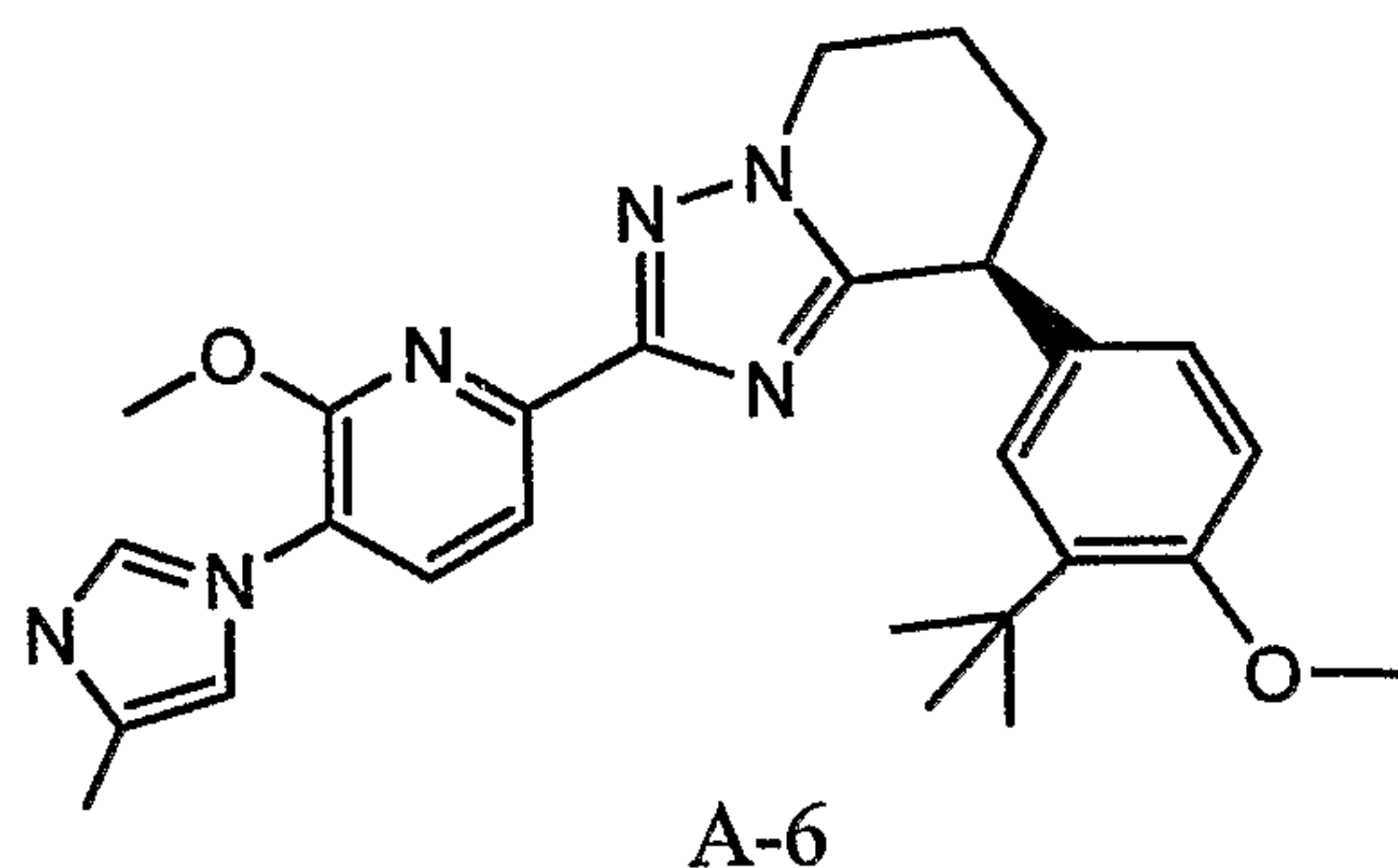
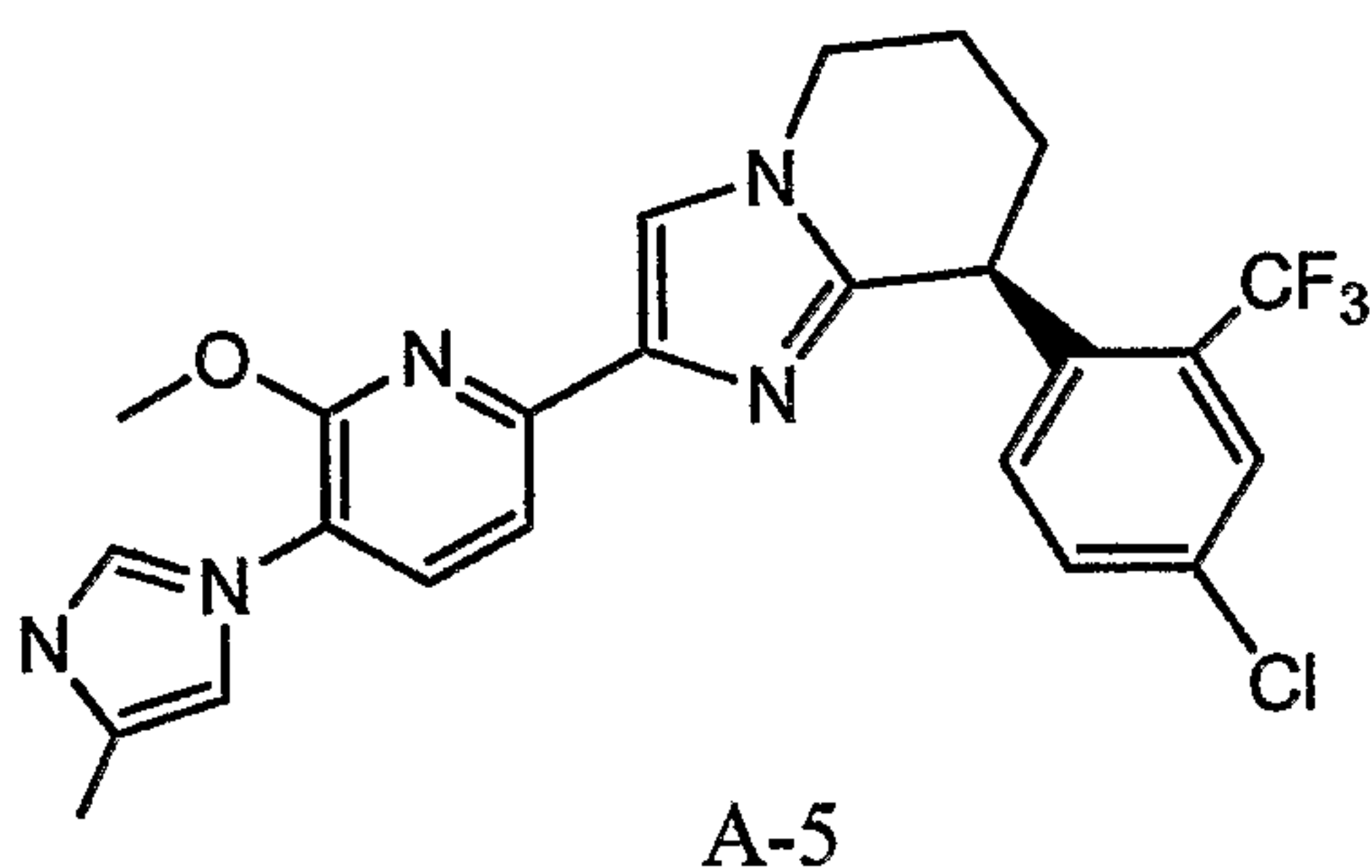
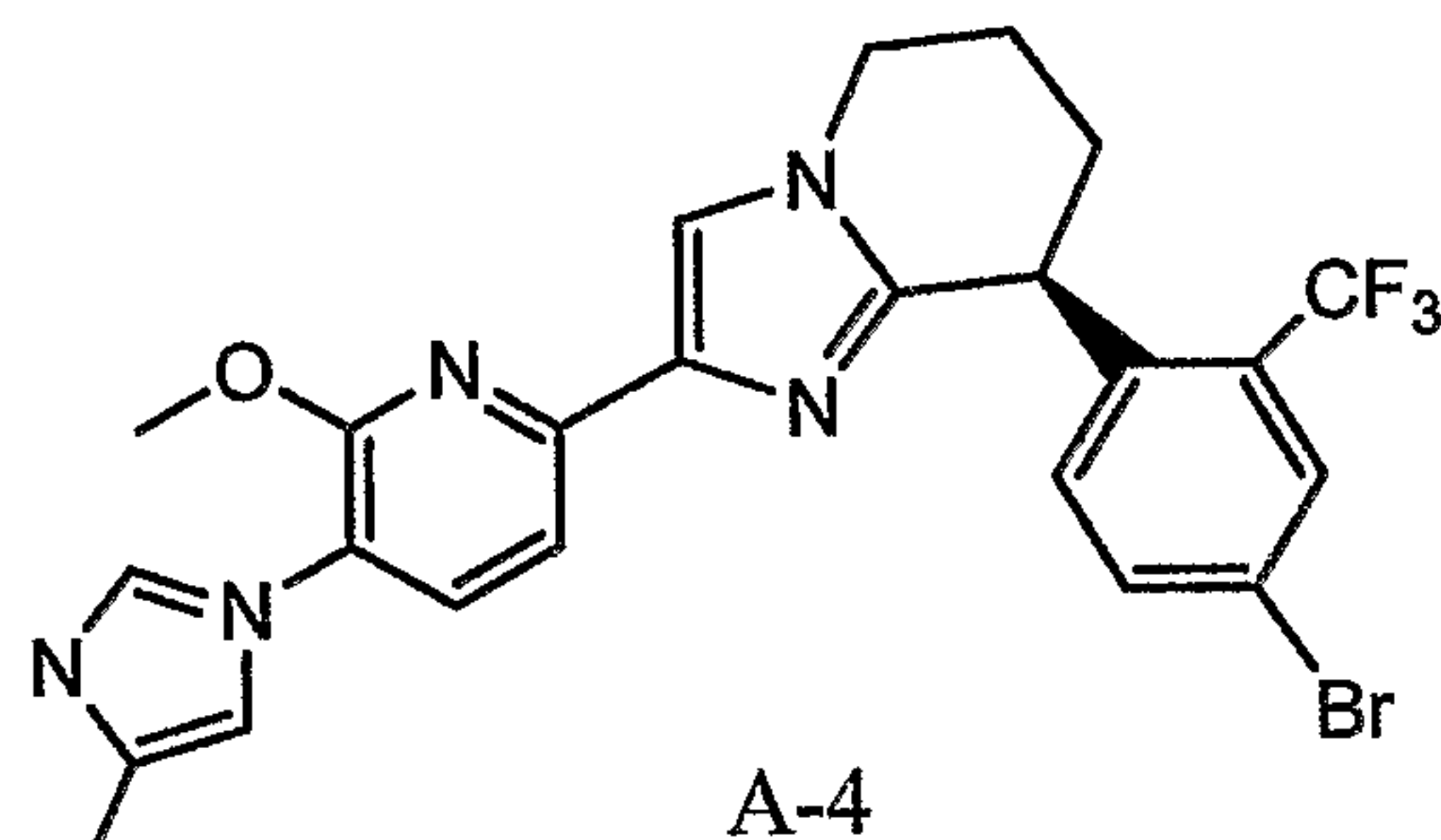
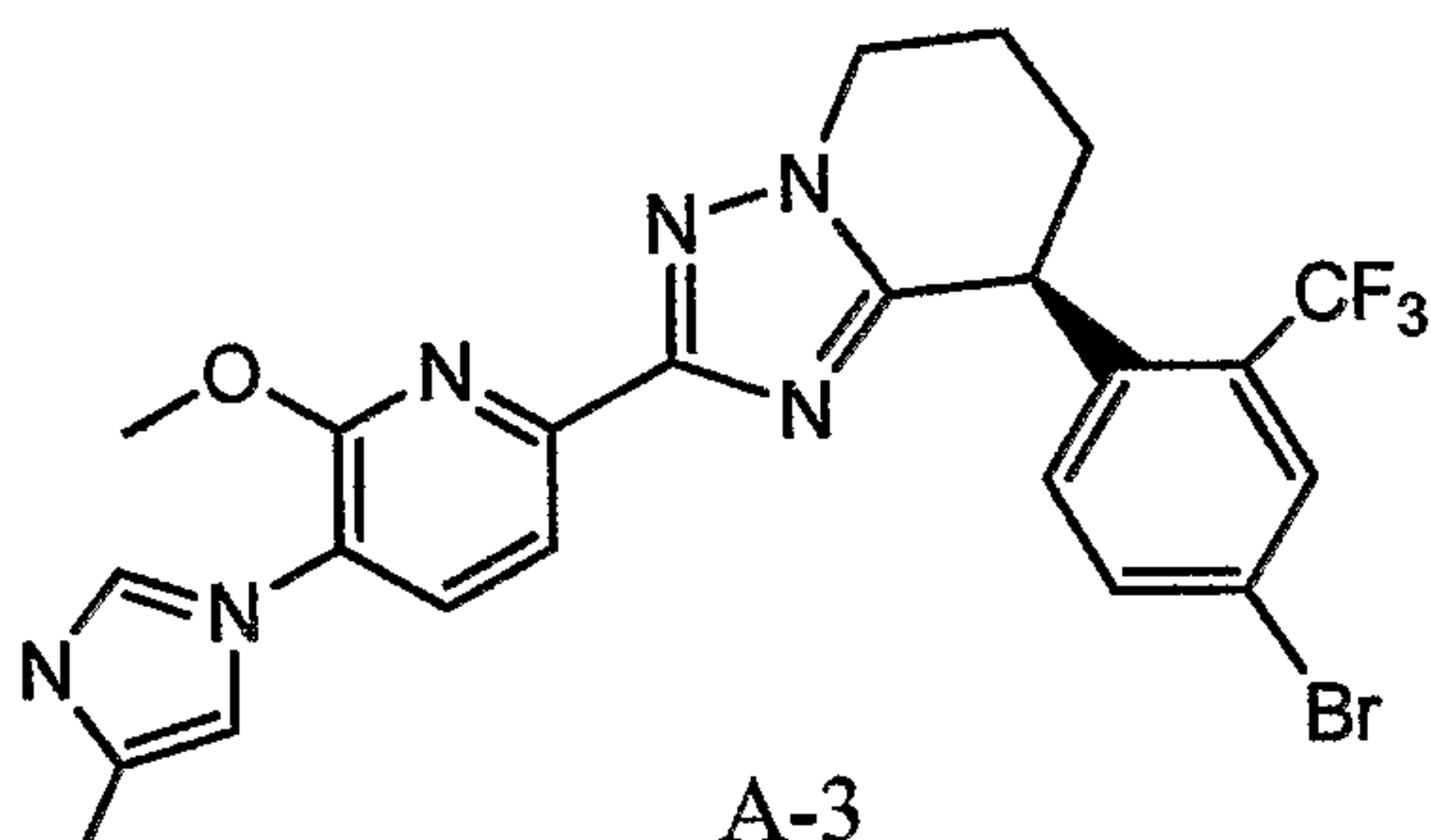
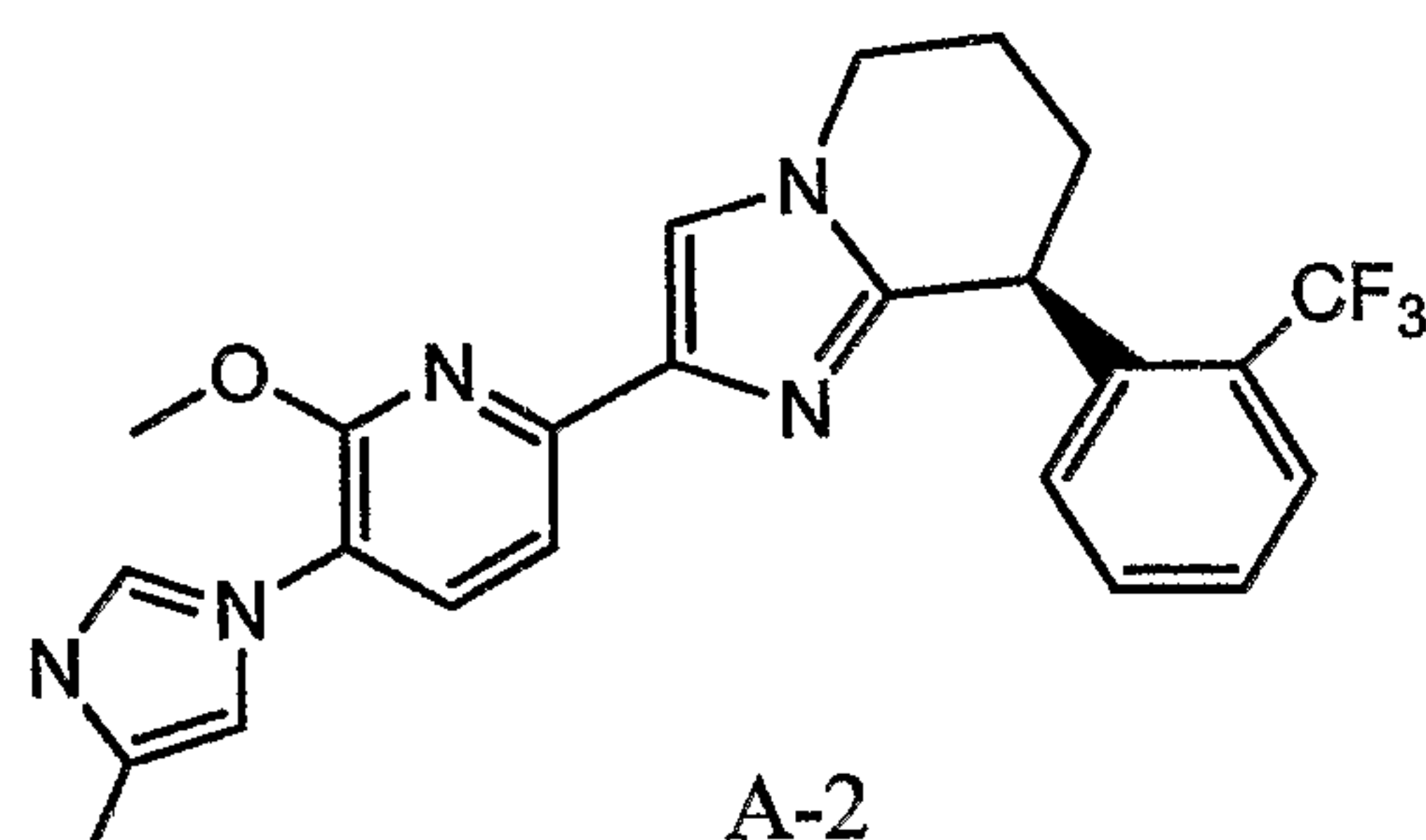
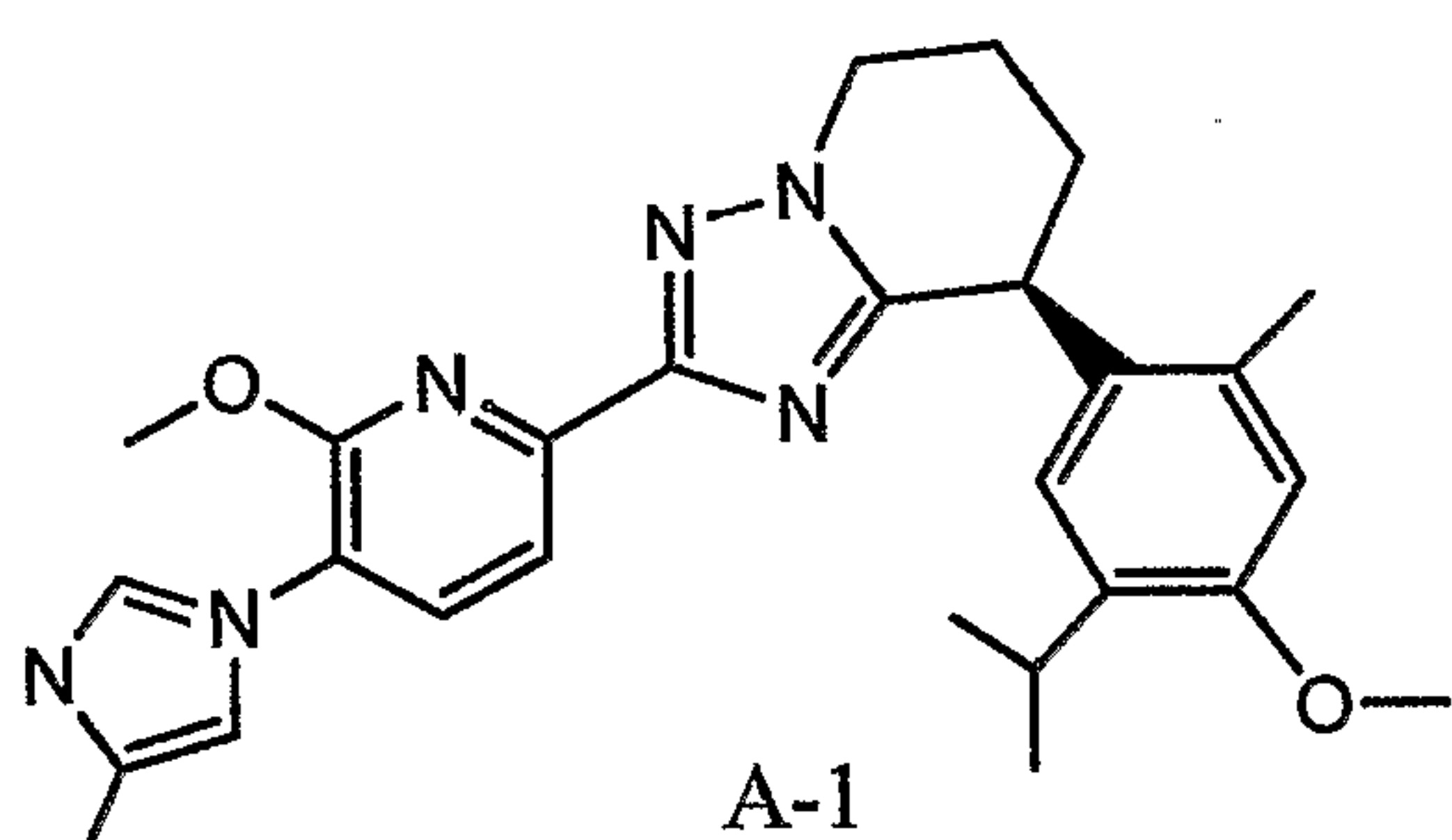
a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a cyano group, a formyl group, a halogen atom, a hydroxyl group and an oxo group.

12. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein the substituent for Ring B is selected from the group consisting of:

i) an amino group (wherein the amino group may have one C2-6 alkanoyl group,

C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v)-i) a C1-6 alkyl group, v)-ii) a C1-6 alkoxy group, v)-iii) a C1-6 alkylthio group and v)-iv) a phenyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom.

13. One compound selected from the group consisting of the following formulas [A-1] to [A-7]:



or a pharmacologically acceptable salt or ester thereof.

14. A medicine comprising the compound or pharmacologically acceptable salt or ester thereof according to any one of claims 1 to 13 as an active ingredient.
15. The medicine according to claim 14 for the treatment of a disease selected from Alzheimer's disease, dementia, Down's syndrome and amyloidosis.

