DESCRIPTION

Title of Invention: NITROGEN-CONTAINING COMPOUND AND PHARMACEUTICAL COMPOSITION

TECHNICAL FIELD

The present invention relates to a nitrogen-containing compound and a pharmaceutical composition containing the same.

BACKGROUND ART

Atrial fibrillation (hereinafter referred to as "AF") is the most frequently observed type of arrhythmia in clinical examinations. Although not a lethal arrhythmia, AF causes cardiogenic cerebral embolism, and is therefore recognized as an arrhythmia that greatly affects vital prognoses and QOL. It is known that the onset of AF increases with age, and that repeated AF strokes lead to chronic (serious) AF (The Journal of American Medical Association, 285, 2370-2375 (2001) and Circulation, 114, 119-123 (2006)).

To prevent chronic AF, which causes difficulty in restoring sinus rhythm and increases the risk of cardiogenic cerebral embolism, early defibrillation and subsequent prevention of recurrence (maintenance of the sinus rhythm) are required. Antiarrhythmic drugs (classes I and III) are most commonly used as pharmacotherapy, but these drugs achieve insufficient therapeutic effects, while causing serious side effects such as a proarrhythmic effect (Am. J. Cardiol., 72, B44-B49 (1993)).

The onset of AF is triggered by atrial premature contraction with underlining causes such as intra-atrial conduction delay, shortening and heterogeneity of the atrial refractory period (Nature Reviews DRUG DISCOVERY 4, 899-910 (2005)). It is known that the prolongation of refractory period of atrial muscle can terminate AF (defibrillation) or prevent the occurence of AF. The action potential duration of the mammalian cardiac muscle is predominantly determined by voltage-dependent $K^+$ channels. Inhibition of the $K^+$ channel prolongs myocardial action potential duration, which results in prolongation of the refractory period (Nature Reviews DRUG DISCOVERY

5, 1034-49 (2006)). The action mechanism of class III antiarrhythmic drugs (e.g., Dofetilide) is to inhibit rapid delayed rectifier $K^+$ current ($I_{Kr}$), $K^+$ current encoded by HERG. However, since $I_{Kr}$ is present in both the atria and ventricles, such drugs might cause ventricular arrhythmias, such as torsades de pointes (Trends Pharmacol. soc., 22, 240-246 (2001)).

Ultra-rapid delayed rectifier $K^+$ current ($I_{Kur}$), $K^+$ current encoded by Kv1.5, has been identified as $K^+$ channel that is specifically expressed only in human atria (Cric. Res., 73, 1061-1076 (1993), J. Physiol., 491, 31-50 (1996) and Cric. Res., 80, 572-579 (1997)). Muscarine potassium current ($I_{KACh}$) encoded by two genes called GIRK1 and GIRK4 is known as a $K^+$ channel specifically expressed in human atria (Nature 374, 135-141 (1995)). Accordingly, a pharmacologically acceptable substance that selectively blocks the $I_{Kur}$ current (the Kv1.5 channel) or the $I_{KACh}$ current (GIRK1/4 channel) can act selectively on the atrial muscle and is considered effective to exclude the proarrhythmic effect caused by prolonged action potential duration of the ventricular muscle.

## SUMMARY OF INVENTION

The present specification discloses three inventions (three nitrogen-containing compounds each having a different structure). The inventions are respectively expressed as a "First Invention", "Second Invention", and "Third Invention", which are described in detail below.

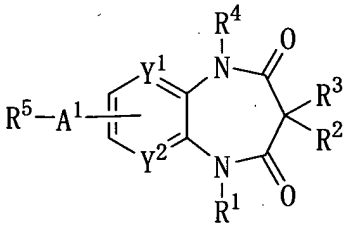
### 1. First Invention (diazepine compound)

The present inventors conducted extensive research to develop a compound that blocks the $I_{Kur}$ current (Kv1.5 channel) and/or the $I_{KACh}$ current (GIRK1/4 channel) potently and more selectively than other $K^+$ channels. As a result, the inventors found that a novel diazepine compound represented by General Formula (1) below could be the desired compound. The present invention has been accomplished based on the above findings.

The present invention provides diazepine compounds, and pharmaceutical compositions comprising the diazepine compounds as

summarized in items 1 to 16 below.

Item 1. A diazepine compound represented by General Formula (1)



(1)

or a salt thereof,

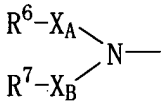
wherein $R^1$, $R^2$, $R^3$, and $R^4$ are each independently hydrogen, lower alkyl, cyclo lower alkyl or lower alkoxy lower alkyl;

$R^2$ and $R^3$ may be linked to form lower alkylene;

$A^1$ is lower alkylene optionally substituted with one or more substituents selected from the group consisting of hydroxyl and oxo;

$Y^1$ and $Y^2$ are each independently -N= or -CH=;

$R^5$ is group represented by



wherein $R^6$ and $R^7$ are each independently hydrogen or an organic group;

$R^6$ and $R^7$ may be linked to form a ring together with the neighboring group $-X_A-N-X_B-$;

$X_A$ and $X_B$ are each independently a bond, alkylene, alkenylene, -CO-, $-SO_2-$, or -CONH-, wherein each of the alkylene and alkenylene chains can optionally contain one or more substituents selected from the group consisting of -S-, -C(=S)-, $-SO_2-$, -CO-, -O-, -NH-, -CONH- and $-SO_2NH-$, and the hydrogen atom (H) bonded to the nitrogen atom (N) in $X_A$ and $X_B$ is optionally substituted with a substituent selected from the group consisting of lower alkyl, phenyl lower alkyl and phenyl.

Item 2. A diazepine compound or a salt thereof according to Item 1, wherein $R^6$ and $R^7$ are each independently hydrogen, lower alkyl, cyclo lower alkyl, aryl or heterocyclic group, each of which is optionally substituted, and $X_A$ and $X_B$ are each independently a bond, lower alkylene, lower alkenylene, -CO-, $-SO_2-$, -lower alkylene-$SO_2-$, -lower alkylene-CO-, -lower alkenylene-CO-, -lower alkylene-CO-N(lower alkyl)-lower alkylene-, -N(lower alkyl)-lower

alkylene-, -CO-N(lower alkyl)-lower alkylene-, -O-lower alkylene-, -N(phenyl lower alkyl)-lower alkylene-, -CO-lower alkylene-CO-, -CO-NH-lower alkylene-, -lower alkylene-N(lower alkyl)-lower alkylene-, -lower alkylene-N(lower alkyl)-lower alkylene-O-, -lower alkylene-NH-lower alkylene-, -lower alkylene-$SO_2$-NH-lower alkylene-, -N(lower alkyl)-CO-lower alkylene-, -N(lower alkyl)-lower alkylene-CO-, -N(lower alkyl)-lower alkylene-N(lower alkyl)-lower alkylene-, -N(phenyl)-lower alkylene-CO-, -N(phenyl)-lower alkylene-CO-, -NH-CO-, -NH-CO-lower alkylene-, -NH-lower alkylene-, -O-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -O-lower alkylene-CO-, -NH-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -S-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -$SO_2$-N(lower alkyl)-lower alkylene-, -$SO_2$-NH-lower alkylene-, -lower alkenylene-CO-N(lower alkyl)-lower alkylene-, lower alkylene-N(phenyl lower alkyl)-lower alkylene-, -N(phenyl lower alkyl)-lower alkylene-, -N(phenyl)-lower alkylene-CO-N(lower alkyl)-lower alkylene-, or -CO-lower alkylene-O-CO-lower alkylene-O-.

Item 3. A diazepine compound or a salt thereof according to Item 2, wherein $R^6$ and $R^7$ are each independently hydrogen, lower alkyl, cyclo lower alkyl, aryl or saturated or unsaturated monocyclic or polycyclic heterocyclic groups containing at least one hetero atom selected from the group consisting of oxygen, sulfur and nitrogen, each of which is optionally substituted.

Item 4. A diazepine compound or a salt thereof according to Item 3, wherein $R^6$ and $R^7$ are each independently hydrogen, lower alkyl, cyclo lower alkyl, phenyl, naphthyl, piperidyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, triazolyl, imidazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazo[2,1-b]thiazolyl, thieno[2,3-b]pyrazinyl, 2,3-dihydroimidazo[2,1-b]thiazolyl, benzothiazolyl, indolyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, benzothienyl, benzimidazolyl, 2,3-dihydrobenzimidazolyl,

2,3-dihydrobenzo[b]furyl, benzofuryl, indazolyl, furo[2,3-c]pyridyl, 6,7-dihydrofuro[2,3-c]pyridyl, furo[3,2-c]pyridyl, 4,5-dihydrofuro[3,2-c]pyridyl, furo[2,3-b]pyridyl, 6,7-dihydrofuro[2,3-b]pyridyl, thieno[2,3-c]pyridyl, 6,7-dihydrothieno[2,3-c]pyridyl, thieno[3,2-c]pyridyl, 4,5-dihydrothieno[3,2-c]pyridyl, thieno[2,3-b]pyridyl, 6,7-dihydrothieno[2,3-b]pyridyl, benzo[1,3]dioxolyl, benzisoxazolyl, pyrazolo[2,3-a]pyridyl, indolizinyl, 2,3-dihydroindolyl, isoquinolyl, 1,2-dihydroisoquinolyl, 1,2,3,4-tetrahydro-1H-isoquinolyl, carbostyril, 3,4-dihydrocarbostyril, quinolyl, 1,4-dihydroquinolyl, 1,2-dihydroquinolyl, 3,4-dihydroquinolyl, 1,2,3,4-tetrahydroquinolyl, pyrido[3,4-d]imidazolyl, pyrido[2,3-d]imidazolyl, chromanyl, 5,6,7,8-tetrahydroisoquinolyl, 3,4-dihydro-1H-isoquinolyl, 3,4-dihydroisoquinolyl, naphthyridinyl, 1,4-benzodioxanyl, cinnolinyl, quinoxalinyl, 2,3-dihydrobenz-1,4-oxazinyl, azetidinyl, 1,2,4-oxadiazolyl and azepanyl, each of which is optionally substituted.

Item 5. A diazepine compound or a salt thereof according to Item 4, wherein $R^6$ and $R^7$ are each independently selected from the group consisting of the following substituents (1) to (54):

(1) hydrogen;

(2) lower alkyl;

(3) cyclo lower alkyl optionally substituted with one or more phenyl lower alkoxys;

(4) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4-1) to (4-27):

(4-1) cyano;

(4-2) hydroxyl;

(4-3) halogen;

(4-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, lower alkoxy, imidazolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl and morpholinyl;

(4-5) lower alkoxy optionally substituted with one or more

substituents selected from the group consisting of amino and lower alkyl amino;

(4-6) pyridyl;

(4-7) thienyl;

(4-8) piperazinyl optionally substituted with one or more lower alkyls;

(4-9) phenyl;

(4-10) pyrazolyl optionally substituted with one or more lower alkyls;

(4-11) pyrimidinyl optionally substituted with one or more lower alkyls;

(4-12) piperidyl optionally substituted with one or more lower alkyls;

(4-13) furyl;

(4-14) carboxy;

(4-15) lower alkoxycarbonyl;

(4-16) amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl and lower alkylsulfonyl;

(4-17) lower alkylthio;

(4-18) triazolyl;

(4-19) imidazolyl;

(4-20) pyrrolidinyl optionally substituted with one or more oxos;

(4-21) lower alkylsulfonyl;

(4-22) lower alkylenedioxy optionally substituted with one or more halogens;

(4-23) nitro;

(4-24) oxazolyl;

(4-25) thiazolyl optionally substituted with one or more lower alkyls;

(4-26) lower alkanoyl; and

(4-27) morpholinyl;

(5) naphthyl;

(6) furyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, carboxy, sulfo, pyridyloxy, lower

alkoxycarbonyl and phenyl;

(7) thienyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylenedioxy, carboxy, halogen, pyridyl, lower alkoxy, lower alkoxycarbonyl, oxazolyl and furyl;

(8) imidazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl and halogen;

(9) pyrazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen or lower alkoxy; cyclo lower alkyl; halogen; phenyl optionally substituted with lower alkoxy; furyl and thienyl;

(10) oxazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl;

(11) isoxazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl, thienyl and furyl;

(12) thiazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen or lower alkoxy; phenyl; phenoxy and lower alkanoylamino;

(13) pyrrolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and lower alkoxycarbonyl;

(14) triazolyl optionally substituted with one or more lower alkyls;

(15) pyridyl optionally substituted with one or more substituents selected from the group consisting of the following (15-1) to (15-14):

(15-1) halogen;

(15-2) cyano;

(15-3) amino optionally substituted with one or more substituents selected from the group consisting of lower alkanoyl and lower alkylsulfonyl;

(15-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkoxy, lower alkanoyloxy, cyclo lower alkyl amino, lower alkyl amino, lower alkanoyl amino, hydroxyl and pyrrolidinyl optionally substituted with one or more hydroxyls;

(15-5) oxo;

(15-6) hydroxyl;

(15-7) lower alkoxy optionally substituted with one or more phenyls;

(15-8) pyrrolidinyl;

(15-9) lower alkanoyl;

(15-10) morpholinyl;

(15-11) phenoxy;

(15-12) pyrazolyl;

(15-13) thienyl; and

(15-14) N-oxide

(16) pyrimidinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl;

(17) pyridazinyl;

(18) pyrazinyl optionally substituted with one or more phenyl lower alkoxys;

(19) imidazo[2,1-b]thiazolyl optionally substituted with one or more halogens;

(20) thieno[2,3-b]pyrazinyl;

(21) 2,3-dihydroimidazo[2,1-b]thiazolyl optionally substituted with one or more phenyls;

(22) benzothiazolyl optionally substituted with one or more lower alkyls;

(23) indolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl and halogen;

(24) imidazo[1,2-a]pyridyl or imidazo[1,5-a]pyridyl, each of which is optionally substituted with one or more lower alkyls;

(25) benzothienyl optionally substituted with one or more lower alkyls;

(26) benzimidazolyl optionally substituted with one or more lower alkyls;

(27) 2,3-dihydrobenzo[b]furyl;

(28) benzofuryl optionally substituted with one or more halogens;

(29) indazolyl optionally substituted with one or more lower alkyls;

(30) furo[2,3-c]pyridyl or 6,7-dihydrofuro[2,3-c]pyridyl, each of which is optionally substituted with one or more substituents selected

from the group consisting of oxo and lower alkyl optionally substituted with lower alkoxy;

(31) furo[3,2-c]pyridyl or 4,5-dihydrofuro[3,2-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl optionally substituted with halogen or lower alkoxy, halogen, furyl, pyridyl and phenyl optionally substituted with one or more substituents selected from the group consisting of amino and lower alkoxy;

(32) thieno[2,3-c]pyridyl or 6,7-dihydrothieno[2,3-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo group and lower alkyl;

(33) thieno[3,2-c]pyridyl or 4,5-dihydrothieno[3,2-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(34) thieno[2,3-b]pyridyl;

(35) benzo[1,3]dioxolyl optionally substituted with one or more halogens;

(36) benzisoxazolyl;

(37) pyrazolo[2,3-a]pyridyl;

(38) indolizinyl;

(39) 2,3-dihydroindolyl optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl and lower alkanoyl;

(40) isoquinolyl or 1,2-dihydroisoquinolyl, each of which is optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halogen and oxo;

(41) 1,2,3,4-tetrahydroisoquinolyl optionally substituted with one or more oxos;

(42) quinolyl optionally substituted with one or more substituents selected from the group consisting of amino optionally substituted with one or two lower alkyls, lower alkoxy, lower alkyl and oxo

(43) 1,2,3,4-tetrahydroquinolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, pyridyl lower alkyl, aralkyl, lower alkoxy and oxo;

(44) 1,2-dihydroquinolyl optionally substituted with one or more substituents selected from the group consisting of amino optionally

substituted with one or two lower alkyls, lower alkoxy, lower alkyl and oxo;

(45) chromanyl optionally substituted with one or more lower alkyls;

(46) 5,6,7,8-tetrahydroisoquinolyl optionally substituted with one or more oxos;

(47) 3,4-dihydroisoquinolyl optionally substituted with one or more oxos;

(48) naphthyridinyl;

(49) 1,4-benzodioxanyl;

(50) cinnolinyl;

(51) quinoxalinyl;

(52) 2,3-dihydrobenz-1,4-oxazinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo;

(53) 2,3-dihydro-1H-benzo[d]imidazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo; and

(54) piperidyl optionally substituted with one or more aryl carbonyls.

Item 6. A diazepine compound or a salt thereof according to Item 5, wherein $R^6$ and $R^7$ are each independently (1), (4a), (6a), (7a), (8a), (9a), (10a), (11a), (12a), (15a), (16a), (17), (18), (23a), (24a), (24b), (26), (29), (30a), (30b), (31a), (31b), (32a), (32b), (33a), (33b), (35), (40a), (40b), (42a), (43a), (44a), and (53):

(1) hydrogen;

(4a) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4-1), (4-2), (4-4), (4a-5), (4-10), (4a-16), (4-18), (4-19), (4-23), (4-26), and (4-27):

(4-1) cyano;

(4-2) hydroxyl;

(4-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogens, hydroxyl, 2-oxo-1,2,3,4-tetrahydroquinolyl, lower alkoxy, imidazolyl, and morpholinyl;

(4a-5) lower alkoxy;

(4-10) pyrazolyl optionally substituted with one or more lower

alkyls;

(4a-16) amino optionally substituted with one or more lower alkylsulfonyls;

(4-18) triazolyl;

(4-19) imidazolyl;

(4-23) nitro;

(4-26) lower alkanoyl; and

(4-27) morpholinyl;

(6a) furyl optionally substituted with one or more lower alkyls optionally substituted with halogen;

(7a) thienyl optionally substituted with one or more lower alkyls;

(8a) imidazolyl optionally substituted with one or more lower alkyls;

(9a) pyrazolyl optionally substituted with one or more lower alkyls optionally substituted with lower alkoxy;

(10a) oxazolyl optionally substituted with one or more lower alkyls;

(11a) isoxazolyl optionally substituted with one or more lower alkyls;

(12a) thiazolyl optionally substituted with one or more lower alkyls optionally substituted with halogen;

(15a) pyridyl optionally substituted with one or more substituents selected from the group consisting of the following (15-1) to (15-5), (15a-7), (15-9), (15-11), (15-12) and (15-14):

(15-1) halogen;

(15-2) cyano;

(15-3) amino optionally substituted with one or more substituents selected from the group consisting of lower alkanoyl and lower alkylsulfonyl;

(15-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkoxy, lower alkanoyloxy, cyclo lower alkyl amino, lower alkyl amino, lower alkanoyl amino, hydroxyl and pyrrolidinyl optionally substituted with one or more hydroxyls;

(15-5) oxo;

(15a-7) lower alkoxy;

(15-9) lower alkanoyl;

(15-11) phenoxy;

(15-12) pyrazolyl; and

(15-14) N-oxide

(16a) pyrimidinyl optionally substituted with one or more lower alkyls;

(17) pyridazinyl

(18) pyrazinyl optionally substituted with one or more phenyl lower alkoxys;

(23a) indolyl optionally substituted with one or more lower alkyls;

(24a) imidazo[1,2-a]pyridyl;

(24b) imidazo[1,5-a]pyridyl optionally substituted with one or more lower alkyls;

(26) benzimidazolyl optionally substituted with one or more lower alkyls;

(29) indazolyl optionally substituted with one or more lower alkyls;

(30a) furo[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(30b) 6,7-dihydrofuro[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(31a) furo[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(31b) 4,5-dihydrofuro[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl optionally substituted with halogen or lower alkoxy;

(32a) thieno[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(32b) 6,7-dihydrothieno[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo group and lower alkyl;

(33a) thieno[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(33b) 4,5-dihydrothieno[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(35a) benzo[1,3]dioxolyl;

(40a) isoquinolyl optionally substituted with one or more oxos;

(40b) 1,2-dihydroisoquinolyl optionally substituted with one or more

substituents selected from the group consisting of oxo and lower alkyl;
(42a) quinolyl optionally substituted with one or more oxos;
(43a) 1,2,3,4-tetrahydroquinolyl optionally substituted with one or more substituents selected from the group consisting of aralkyl (e.g., phenyl lower alkyl, etc.), pyridyl lower alkyl and oxo;
(44) 1,2-dihydroquinolyl optionally substituted with one or more oxos; and
(53) 2,3-dihydrobenzo[d]imidazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo.

Item 7. A diazepine compound or a salt thereof according to Item 6, wherein $R^6$ and $R^7$ are each independently phenyl, pyridyl, pyrazolyl, indolyl, 4,5-dihydrofuro[3,2-c]pyridyl, and 1,2-dihydroisoquinolyl, each of which is optionally substituted with one or two substituents selected from the group consisting of oxo, lower alkyl, lower alkoxy lower alkyl, and lower alkylsulfonylamino.

Item 8. A diazepine compound or a salt thereof according to Item 7, which is selected from the group consisting of the following compounds:
1-ethyl-3,3,5-trimethyl-7-(3-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}propyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(2-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}ethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(2-{N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}ethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-{2-[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,

N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-4-methyl-N-(2-pyridin-3-ylethyl)benzamide,
N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-pyridin-3-ylethyl)benzenesulfonamide,
7-{[N-benzyl-N-(2-pyridin-3-ylethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
N-(2-{[(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)(2-pyridin-3-ylethyl)amino]methyl}phenyl)methanesulfonamide,
7-{[N-[2-(2,7-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(1-methyl-1H-indol-3-yl)-N-(2-pyridin-3-ylethyl)acetamide.

Item 9. A diazepine compound according to Item 8, which is selected from the group consisting of the following compounds:
1-ethyl-3,3,5-trimethyl-7-(3-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}propyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-(2-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}ethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-(2-{N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}ethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-{2-[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]

pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-4-methyl-N-(2-pyridin-3-ylethyl)benzamide hydrochloride,
N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-pyridin-3-ylethyl)benzenesulfonamide,
7-{[N-benzyl-N-(2-pyridin-3-ylethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride,
N-(2-{[(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)(2-pyridin-3-ylethyl)amino]methyl}phenyl)methanesulfonamide dihydrochloride,
7-{[N-[2-(2,7-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione, and
N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(1-methyl-1H-indol-3-yl)-N-(2-pyridin-3-ylethyl)acetamide hydrochloride.

Item 10. A diazepine compound or a salt thereof according to Item 1, wherein $Y^1$ and $Y^2$ are each -CH=.

Item 11. A pharmaceutical composition comprising a diazepine compound or a salt thereof according to Item 1, and a pharmacologically acceptable carrier.

Item 12. A pharmaceutical composition according to Item 11 for preventing and/or treating arrhythmia.

Item 13. A diazepine compound or a salt thereof according to Item 1 for use in the pharmaceutical composition.

Item 14. Use of a diazepine compound or a salt thereof according to Item 1 as a pharmaceutical composition.

Item 15. Use of a diazepine compound or a salt thereof according to Item 1 for the production of a pharmaceutical composition.

Item 16. A method of preventing and/or treating arrhythmia, comprising administering to a patient a diazepine compound or a salt thereof according to Item 1.

The groups represented by, or substituents of, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $A^1$, $X_A$, $X_B$, $Y^1$ and $Y^2$ in the specification are described below.

The term "one or more" may be preferably 1 to 6, more preferably 1 to 3.

Examples of "lower alkyl" include linear or branched alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, neopentyl, n-hexyl, isohexyl, and 3-methylpentyl.

Examples of "alkylene" include linear or branched alkylene groups having 1 to 12 carbon atoms, such as the following "lower alkylene", heptamethylene, octamethylene, decamethylene, and dodecamethylene.

Examples of "lower alkylene" include linear or branched alkylene groups having 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, dimethylmethylene, tetramethylene, pentamethylene, and hexamethylene.

Examples of "alkenylene" include linear or branched alkylene groups having 2 to 12 carbon atoms, such as the following "lower alkenylene", heptenylene, octenylene, decenylene, and dodecenylene.

Examples of "lower alkenylene" include linear or branched alkylene groups having 2 to 6 carbon atoms, such as, ethenylene, propenylene, butenylene, pentenylene, and hexenylene.

Examples of "cyclo lower alkyl" include linear or branched cyclo alkyl having 3 to 8 carbon atoms, preferably 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl and cyclohexylmethyl.

Examples of "lower alkoxy" include linear or branched alkoxy groups having 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, sec-butoxy, n-pentyloxy, neopentyloxy, n-hexyloxy, isohexyloxy, and 3-methylpentyloxy.

Examples of "halogen" are fluorine, chlorine, bromine, and iodine.

Examples of "lower alkylenedioxy" include linear or branched alkylene groups having 1 to 4 carbon atoms, such as methylenedioxy, ethylenedioxy, trimethylenedioxy, and tetramethylenedioxy.

Examples of "lower alkanoyl" include linear or branched alkanoyl groups having 1 to 6 carbon atoms, such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, and hexanoyl.

Examples of "lower alkoxycarbonyl" include (linear or branched alkoxy having 1 to 6 carbon atoms)carbonyls, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, and tert-butoxycarbonyl.

Examples of "aralkyl group" include lower alkyl group substituted with one or more aryl groups, such as benzyl and phenethyl.

Examples of "organic group" include lower alkyl, cyclo lower alkyl, aryl, and heterocyclic group, each of which is optionally substituted.

Examples of "aryl group" include monocyclic or polycyclic

aryl groups, such as phenyl, tolyl, xylyl, and naphthyl.

Examples of "aroyl group" include benzoyl and naphthoyl.

Examples of "heterocyclic group" include saturated or unsaturated monocyclic or polycyclic heterocyclic groups containing at least one hetero atom selected from the group consisting of oxygen, sulfur and nitrogen. Examples of preferable heterocyclic groups include the following (a) to (n):

(a) unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic groups containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, tetrahydropyridyl (e.g., 1,2,3,6-tetrahydropyridyl), pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H- 1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc. ) , tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.;

(b) saturated 3 to 8-membered, preferably 5 or 7- membered heteromonocyclic groups containing 1 to 4 nitrogen atom(s), for example, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidyl, pyrazolidinyl, piperazinyl, azepanyl, 1,4-diazepanyl, etc.;

(c) saturated or unsaturated condensed 7 to 12-membered heterocyclic groups containing 1 to 5 nitrogen atom(s), for example, decahydroquinolyl, indolyl, dihydroindolyl (e.g., 2,3-dihydroindolyl, etc.), isoindolyl, indolizinyl, benzimidazolyl, dihydrobenzimidazolyl (e.g., 2,3-dihydro-1H-benzo[d]imidazolyl, etc.), quinolyl, dihydroquinolyl (e.g. 1,4-dihydroquinolyl, 1,2-dihydroquinolyl, etc.), tetrahydroquinolyl (1,2,3,4-tetrahydroquinolyl, etc.), isoquinolyl, dihydroisoquinolyl (e.g., 3,4-dihydro-1H-isoquinolyl, 1,2-dihydroisoquinolyl, etc.), tetrahydroisoquinolyl (e.g., 1,2,3,4-tetrahydro-1H-isoquinolyl, 5,6,7,8-tetrahydroisoquinolyl, etc.), carbostyril, dihydrocarbostyril (e.g., 3,4- dihydrocarbostyril, etc.), indazolyl, benzotriazolyl (e.g. benzo[d][1,2,3]triazolyl, etc.), tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, imidazopyridyl (e.g., imidazo[1,2-a]pyridyl, imidazo[4,5-c]pyridyl,

imidazo[1,5-a]pyridyl, etc.), naphthyridinyl, cinnolinyl, quinoxalinyl, quinazolinyl, pyrazolopyridyl (e.g., pyrazolo[2,3-a]pyridyl, etc.), tetrahydropyridoindolyl (e.g., 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indolyl, etc.), azasbicyclooctanyl (e.g., (1R,5S)-8-azabicyclo[3.2.1]octanyl), etc.;

(d) saturated or unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic groups containing 1 to 2 oxygen atom(s), for example, furyl, tetrahydropyranyl (e.g., tetrahydro-2H-pyranyl, etc.), tetrahydrofuryl, etc.;

(e) unsaturated condensed 7 to 12-membered heterocyclic groups containing 1 to 3 oxygen atom(s), for example, benzofuryl, dihydrobenzofuryl (e.g. 2,3-dihydrobenzo[b]furyl, etc.), chromanyl, benzodioxanyl (e.g., 1,4-benzodioxanyl, etc.), benzodioxolyl (benzo[1,3]dioxolyl, etc.), etc.;

(f) unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4- oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

(g) saturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, etc.;

(h) unsaturated condensed 7 to 12-membered heterocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, benzisoxazolyl, dihydrobenzoxazinyl (e.g., 2,3-dihydrobenz-1,4-oxazinyl, etc.), furopyridyl (e.g., furo[2,3-c]pyridyl, 6,7-dihydrofuro[2,3-c]pyridyl, furo[3,2-c]pyridyl, 4,5-dihydrofuro[3,2-c]pyridyl, furo[2,3-b]pyridyl, 6,7-dihydrofuro[2,3-b]pyridyl, etc.), furopyrrolyl (e.g., furo[3,2-b]pyrrolyl etc.), etc.;

(i) unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5- thiadiazolyl,

1,2,3-thiadiazolyl, etc. ), isothiazolyl , etc.;

(j) saturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

(k) unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic groups containing a sulfur atom, for example, thienyl, etc.;

(l) unsaturated condensed 7 to 12-membered heterocyclic groups containing 1 to 3 sulfur atom(s), for example, benzothienyl (e.g. benzo[b]thienyl, etc.);

(m) unsaturated condensed 7 to 12-membered heterocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, thienopyridyl (e.g., thieno[2,3-c]pyridyl, 6,7-dihydrothieno[2,3-c]pyridyl, thieno[3,2-c]pyridyl, 4,5-dihydrothieno[3,2-c]pyridyl, thieno[2,3-b]pyridyl, 6,7-dihydrothieno[2,3-b]pyridyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridyl, etc.), imidazothiazolyl (e.g., imidazo[2,1-b]thiazolyl, etc.), dihydroimidazothiazolyl (e.g., 2,3-dihydroimidazo[2,1-b]thiazolyl, etc.), thienopyrazinyl (e.g., thieno[2,3-b]pyrazinyl, etc.), etc.; and

(n) saturated or unsaturated 7-to 12-membered heterocyclic spiro groups containing 1 to 2 nitrogen atom(s), for example, azaspiroundecanyl (e.g., 3-azaspiro[5.5]undecanyl), etc.; and the like;

wherein said heterocyclic groups may be substituted with one or more suitable substituents.

Examples of more preferable heterocyclic groups include piperidyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, triazolyl, imidazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazo[2,1-b]thiazolyl, thieno[2,3-b]pyrazinyl, 2,3-dihydroimidazo[2,1-b]thiazolyl, benzothiazolyl, indolyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, benzothienyl, benzimidazolyl, 2,3-dihydrobenzimidazolyl, 2,3-dihydrobenzo[b]furyl, benzofuryl, indazolyl, furo[2,3-c]pyridyl,

6,7-dihydrofuro[2,3-c]pyridyl, furo[3,2-c]pyridyl, 4,5-dihydrofuro[3,2-c]pyridyl, furo[2,3-b]pyridyl, 6,7-dihydrofuro[2,3-b]pyridyl, thieno[2,3-c]pyridyl, 6,7-dihydrothieno[2,3-c]pyridyl, thieno[3,2-c]pyridyl, 4,5-dihydrothieno[3,2-c]pyridyl, thieno[2,3-b]pyridyl, 6,7-dihydrothieno[2,3-b]pyridyl, benzo[1,3]dioxolyl, benzisoxazolyl, pyrazolo[2,3-a]pyridyl, indolizinyl, 2,3-dihydroindolyl, isoquinolyl, 1,2-dihydroisoquinolyl, 1,2,3,4-tetrahydro-1H-isoquinolyl, carbostyril, 3,4-dihydrocarbostyril, quinolyl, 1,4-dihydroquinolyl, 1,2-dihydroquinolyl, 3,4-dihydroquinolyl, 1,2,3,4-tetrahydroquinolyl, pyrido[3,4-d]imidazolyl, pyrido[2,3-d]imidazolyl, chromanyl, 5,6,7,8-tetrahydroisoquinolyl, 3,4-dihydro-1H-isoquinolyl, 3,4-dihydroisoquinolyl, naphthyridinyl, 1,4-benzodioxanyl, cinnolinyl, quinoxalinyl, 2,3-dihydrobenz-1,4-oxazinyl, azetidinyl, 1,2,4-oxadiazolyl, and azepanyl, each of which is optionally substituted.

Substituents of "aryl group which is optionally substituted" represented by $R^6$ and $R^7$ are independently one or more substituents selected from the group consisting of:

(a1) cyano;

(a2) hydroxyl;

(a3) halogen;

(a4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, lower alkoxy, imidazolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl and morpholinyl;

(a5) lower alkoxy optionally substituted with one or more substituents selected from the group consisting of amino and lower alkyl amino;

(a6) pyridyl;

(a7) thienyl;

(a8) piperazinyl optionally substituted with one or more lower alkyls;

(a9) phenyl;

(a10) pyrazolyl optionally substituted with one or more lower alkyls;

(a11) pyrimidinyl optionally substituted with one or more lower alkyls;

(a12) piperidyl optionally substituted with one or more lower alkyls;
(a13) furyl;
(a14) carboxy;
(a15) lower alkoxycarbonyl;
(a16) amino optionally substituted with one or more substituents selected from the group consisting of lower alkanoyl and lower alkylsulfonyl;
(a17) lower alkylthio;
(a18) triazolyl;
(a19) imidazolyl;
(a20) pyrrolidinyl optionally substituted with one or more oxos;
(a21) lower alkylsulfonyl;
(a22) lower alkylenedioxy optionally substituted with one or more halogens;
(a23) nitro;
(a24) oxazolyl;
(a25) thiazolyl optionally substituted with one or more lower alkyls;
(a26) lower alkanoyl;
(a27) sulfo; and
(a28) morpholinyl.

Substituents of "heterocyclic group which is optionally substituted" represented by $R^6$ and $R^7$ are independently one or more substituents selected from the group consisting of:
(h1) oxo;
(h2) lower alkyl optionally substituted with one or more substitutents selected from the group consisting of the following (h2-1) to (h2-10):
(h2-1) halogen;
(h2-2) hydroxyl;
(h2-3) amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, cyclo lower alkyl and lower alkanoyl;
(h2-4) pyridyl;
(h2-5) lower alkanoyloxy;
(h2-6) lower alkoxy;
(h2-7) aryloxy;

(h2-8) pyrimidinyl;

(h2-9) pyrrolidinyl optionally substituted with one or more hydroxyls; and

(h2-10) imidazolyl optionally substituted with one or more lower alkyls;

(h3) cyclo lower alkyl;

(h4) lower alkoxy optionally substituted with one or more substitutents selected from the group consisting of pyridyl and aryl;

(h5) aryl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with one or more halogens; lower alkoxy; lower alkanoyl; hydroxyl; halogen; carboxy; lower alkoxycarbonyl; amino; lower alkyl amino, aryl and cyano;

(h6) aralkyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, hydroxyl, halogen, carboxy, lower alkoxycarbonyl, amino, lower alkyl amino, cyano and oxo;

(h7) heterocyclic group optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, hydroxyl, halogen, carboxy, lower alkoxycarbonyl, amino, lower alkyl amino, cyano and oxo;

(h8) hydroxyl;

(h9) halogen;

(h10) carboxy;

(h11) lower alkanoyl;

(h12) lower alkoxycarbonyl;

(h13) lower alkylenedioxy;

(h14) cyano;

(h15) nitro;

(h16) sulfo;

(h17) amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, aryl, aroyl, lower alkylsulfonyl and lower alkanoyl;

(h18) lower alkylthio;

(h19) lower alkylsulfonyl; and

(h20) aryloxy.

Preferable substituents represented by $R^6$ and $R^7$ are each independently selected from the group consisting of the following substituents (1) to (54):

(1) hydrogen;

(2) lower alkyl;

(3) cyclo lower alkyl optionally substituted with one or more phenyl lower alkoxys;

(4) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4-1) to (4-27):

(4-1) cyano;

(4-2) hydroxyl;

(4-3) halogen;

(4-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, lower alkoxy, imidazolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl and morpholinyl;

(4-5) lower alkoxy optionally substituted with one or more substituents selected from the group consisting of amino and lower alkyl amino;

(4-6) pyridyl;

(4-7) thienyl;

(4-8) piperazinyl optionally substituted with one or more lower alkyls;

(4-9) phenyl;

(4-10) pyrazolyl optionally substituted with one or more lower alkyls;

(4-11) pyrimidinyl optionally substituted with one or more lower alkyls;

(4-12) piperidyl optionally substituted with one or more lower alkyls;

(4-13) furyl;

(4-14) carboxy;

(4-15) lower alkoxycarbonyl;

(4-16) amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl

and lower alkylsulfonyl;

(4-17) lower alkylthio;

(4-18) triazolyl;

(4-19) imidazolyl;

(4-20) pyrrolidinyl optionally substituted with one or more oxos;

(4-21) lower alkylsulfonyl;

(4-22) lower alkylenedioxy optionally substituted with one or more halogens;

(4-23) nitro;

(4-24) oxazolyl;

(4-25) thiazolyl optionally substituted with one or more lower alkyls;

(4-26) lower alkanoyl; and

(4-27) morpholinyl;

(5) naphthyl;

(6) furyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, carboxy, sulfo, pyridyloxy, lower alkoxycarbonyl and phenyl;

(7) thienyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylenedioxy, carboxy, halogen, pyridyl, lower alkoxy, lower alkoxycarbonyl, oxazolyl and furyl;

(8) imidazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl and halogen;

(9) pyrazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen or lower alkoxy; cyclo lower alkyl; halogen; phenyl optionally substituted with lower alkoxy; furyl and thienyl;

(10) oxazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl;

(11) isoxazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl, thienyl and furyl;

(12) thiazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally

substituted with halogen or lower alkoxy; phenyl; phenoxy and lower alkanoylamino;

(13) pyrrolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and lower alkoxycarbonyl;

(14) triazolyl optionally substituted with one or more lower alkyls;

(15) pyridyl optionally substituted with one or more substituents selected from the group consisting of the following (15-1) to (15-14):

(15-1) halogen;

(15-2) cyano;

(15-3) amino optionally substituted with one or more substituents selected from the group consisting of lower alkanoyl and lower alkylsulfonyl;

(15-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkoxy, lower alkanoyloxy, cyclo lower alkyl amino, lower alkyl amino, lower alkanoyl amino, hydroxyl and pyrrolidinyl optionally substituted with one or more hydroxyls;

(15-5) oxo;

(15-6) hydroxyl;

(15-7) lower alkoxy optionally substituted with one or more phenyls;

(15-8) pyrrolidinyl;

(15-9) lower alkanoyl;

(15-10) morpholinyl;

(15-11) phenoxy;

(15-12) pyrazolyl;

(15-13) thienyl; and

(15-14) N-oxide;

(16) pyrimidinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl;

(17) pyridazinyl;

(18) pyrazinyl optionally substituted with one or more phenyl lower alkoxys;

(19) imidazo[2,1-b]thiazolyl optionally substituted with one or more halogens;

(20) thieno[2,3-b]pyrazinyl;

(21) 2,3-dihydroimidazo[2,1-b]thiazolyl optionally substituted with one or more phenyls;

(22) benzothiazolyl optionally substituted with one or more lower alkyls;

(23) indolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl and halogen;

(24) imidazo[1,2-a]pyridyl or imidazo[1,5-a]pyridyl, each of which is optionally substituted with one or more lower alkyls;

(25) benzothienyl optionally substituted with one or more lower alkyls;

(26) benzimidazolyl optionally substituted with one or more lower alkyls;

(27) 2,3-dihydrobenzo[b]furyl;

(28) benzofuryl optionally substituted with one or more halogens;

(29) indazolyl optionally substituted with one or more lower alkyls;

(30) furo[2,3-c]pyridyl or 6,7-dihydrofuro[2,3-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl optionally substituted with lower alkoxy;

(31) furo[3,2-c]pyridyl or 4,5-dihydrofuro[3,2-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl optionally substituted with halogen or lower alkoxy, halogen, furyl, pyridyl and phenyl optionally substituted with one or more substituents selected from the group consisting of amino and lower alkoxy;

(32) thieno[2,3-c]pyridyl or 6,7-dihydrothieno[2,3-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo group and lower alkyl;

(33) thieno[3,2-c]pyridyl or 4,5-dihydrothieno[3,2-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(34) thieno[2,3-b]pyridyl;

(35) benzo[1,3]dioxolyl optionally substituted with one or more halogens;

(36) benzisoxazolyl;

(37) pyrazolo[2,3-a]pyridyl;

(38) indolizinyl;

(39) 2,3-dihydroindolyl optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl and lower alkanoyl;

(40) isoquinolyl or 1,2-dihydroisoquinolyl, each of which is optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halogen and oxo;

(41) 1,2,3,4-tetrahydroisoquinolyl optionally substituted with one or more oxos;

(42) quinolyl optionally substituted with one or more substituents selected from the group consisting of amino optionally substituted with one or two lower alkyls, lower alkoxy, lower alkyl and oxo

(43) 1,2,3,4-tetrahydroquinolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, pyridyl lower alkyl, aralkyl (e.g., phenyl lower alkyl), lower alkoxy and oxo;

(44) 1,2-dihydroquinolyl optionally substituted with one or more substituents selected from the group consisting of amino optionally substituted with one or two lower alkyls, lower alkoxy, lower alkyl and oxo;

(45) chromanyl optionally substituted with one or more lower alkyls;

(46) 5,6,7,8-tetrahydroisoquinolyl optionally substituted with one or more oxos;

(47) 3,4-dihydroisoquinolyl optionally substituted with one or more oxos;

(48) naphthyridinyl;

(49) 1,4-benzodioxanyl;

(50) cinnolinyl;

(51) quinoxalinyl;

(52) 2,3-dihydrobenz-1,4-oxazinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo;

(53) 2,3-dihydro-1H-benzo[d]imidazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo; and

(54) piperidyl optionally substituted with one or more aryl carbonyls (e.g., phenyl carbonyl).

Examples of more preferable substituents represented by $R^6$ and $R^7$ include the following substituents (1), (4a), (6a), (7a), (8a), (9a), (10a), (11a), (12a), (15a), (16a), (17), (18), (23a), (24a), (24b), (26), (29), (30a), (30b), (31a), (31b), (32a), (32b), (33a), (33b), (35a), (40a), (40b), (42a), (43a), (44a), and (53):

(1) hydrogen;

(4a) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4-1), (4-2), (4a-4), (4a-5), (4-10), (4a-16), (4-18), (4-19), (4-23), (4-26) and (4-27):

(4-1) cyano;

(4-2) hydroxyl;

(4a-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, 2-oxo-1,2,3,4-tetrahydroquinolyl, lower alkoxy, imidazolyl and morpholinyl;

(4a-5) lower alkoxy;

(4-10) pyrazolyl optionally substituted with one or more lower alkyls;

(4a-16) amino optionally substituted with one or more lower alkylsulfonyls;

(4-18) triazolyl

(4-19) imidazolyl;

(4-23) nitro;

(4-26) lower alkanoyl; and

(4-27) morpholinyl;

(6a) furyl optionally substituted with one or more lower alkyls optionally substituted with halogen;

(7a) thienyl optionally substituted with one or more lower alkyls;

(8a) imidazolyl optionally substituted with one or more lower alkyls;

(9a) pyrazolyl optionally substituted with one or more lower alkyls optionally substituted with lower alkoxy;

(10a) oxazolyl optionally substituted with one or more lower alkyls;

(11a) isoxazolyl optionally substituted with one or more lower alkyls;

(12a) thiazolyl optionally substituted with one or more lower alkyls optionally substituted with halogen;

(15a) pyridyl optionally substituted with one or more substituents selected from the group consisting of the following (15-1) to (15-5), (15a-7), (15-9), (15-11), (15-12) and (15-14):

(15-1) halogen;

(15-2) cyano;

(15-3) amino optionally substituted with one or more substituents selected from the group consisting of lower alkanoyl and lower alkylsulfonyl;

(15-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkoxy, lower alkanoyloxy, cyclo lower alkyl amino, lower alkyl amino, lower alkanoyl amino, hydroxyl and pyrrolidinyl optionally substituted with one or more hydroxyls;

(15-5) oxo;

(15a-7) lower alkoxy;

(15-9) lower alkanoyl;

(15-11) phenoxy;

(15-12) pyrazolyl; and

(15-14) N-oxide;

(16a) pyrimidinyl optionally substituted with one or more lower alkyls;

(17) pyridazinyl;

(18) pyrazinyl optionally substituted with one or more phenyl lower alkoxys;

(23a) indolyl optionally substituted with one or more lower alkyls;

(24a) imidazo[1,2-a]pyridyl;

(24b) imidazo[1,5-a]pyridyl optionally substituted with one or more lower alkyls;

(26) benzimidazolyl optionally substituted with one or more lower alkyls;

(29) indazolyl optionally substituted with one or more lower alkyls;

(30a) furo[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(30b) 6,7-dihydrofuro[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(31a) furo[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(31b) 4,5-dihydrofuro[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl optionally substituted with halogen or lower alkoxy;

(32a) thieno[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(32b) 6,7-dihydrothieno[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo group and lower alkyl;

(33a) thieno[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(33b) 4,5-dihydrothieno[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(35a) benzo[1,3]dioxolyl;

(40a) isoquinolyl optionally substituted with one or more oxos;

(40b) 1,2-dihydroisoquinolyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(42a) quinolyl optionally substituted with one or more oxos;

(43a) 1,2,3,4-tetrahydroquinolyl optionally substituted with one or more substituents selected from the group consisting of aralkyl (e.g., phenyl lower alkyl), pyridyl lower alkyl and oxo;

(44a) 1,2-dihydroquinolyl optionally substituted with one or more oxos; and

(53) 2,3-dihydrobenzo[d]imidazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo.

Preferred embodiments of the diazepine compound of Formula (1) are described below.

$R^1$, $R^2$, $R^3$ and $R^4$ are each independently hydrogen, lower alkyl, cyclo lower alkyl or lower alkoxy lower alkyl, and preferably hydrogen, $C_{1-6}$

alkyl (e.g., methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl and sec-butyl), $C_{1-6}$ cyclo alkyl (e.g., cyclopropyl, cyclopropylmethyl, cyclopentyl and cyclohexyl), or $C_{1-6}$ alkoxy $C_{1-6}$ alkyl (e.g., 2-methoxyethyl and 2-ethoxyethyl).

Both $Y^1$ and $Y^2$ are -C=.

$A^1$ is lower alkylene, and preferably $C_{1-6}$ alkylene such as methylene, ethylene, trimethylene, or tetramethylene. $X_A$ and $X_B$ are each independently lower alkylene, which is preferably $C_{1-6}$ alkylene such as methylene, ethylene, trimethylene, or tetramethylene; a bond; -CO-; or $-SO_2-$.

$R^6$ and $R^7$ are each independently a group selected from (1), (4a), (6a), (7a), (8a), (9a), (10a), (11a), (12a), (15a), (16a), (17), (18), (23a), (24a), (24b), (26), (29), (30b), (31b), (32b), (33b), (35a), (40b), (42a), (43a), (44a), and (53):

Examples of $X_A$ and $X_B$ include a bond, lower alkylene, lower alkenylene, -CO-, $-SO_2-$, -lower alkylene-$SO_2$-, -lower alkylene-CO-, -lower alkenylene-CO-, -lower alkylene-CO-N(lower alkyl)-lower alkylene-, -N(lower alkyl)-lower alkylene-, -CO-N(lower alkyl)-lower alkylene-, -O-lower alkylene-, -N(phenyl lower alkyl)-lower alkylene-, -CO-lower alkylene-CO-, -CO-NH-lower alkylene-, -lower alkylene-N(lower alkyl)-lower alkylene-, -lower alkylene-N(lower alkyl)-lower alkylene-O-, -lower alkylene-NH-lower alkylene-, -lower alkylene-$SO_2$-NH-lower alkylene-, -N(lower alkyl)-CO-lower alkylene-, -N(lower alkyl)-lower alkylene-CO-, -N(lower alkyl)-lower alkylene-N(lower alkyl)-lower alkylene-, -N(phenyl)-lower alkylene-CO-, -N(phenyl)-lower alkylene-CO-, -NH-CO-, -NH-CO-lower alkylene-, -NH-lower alkylene-, -O-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -O-lower alkylene-CO-, -NH-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -S-lower alkylene-CO-N(lower alkyl)-lower alkylene-, $-SO_2$-N(lower alkyl)-lower alkylene-, $-SO_2$-NH-lower alkylene-, -lower alkenylene-CO-N(lower alkyl)-lower alkylene-, lower alkylene-N(phenyl lower alkyl)-lower alkylene-, -N(phenyl lower alkyl)-lower alkylene-, -N(phenyl)-lower alkylene-CO-N(lower alkyl)-lower alkylene-, and -CO-lower alkylene-O-CO-lower

alkylene-O-.

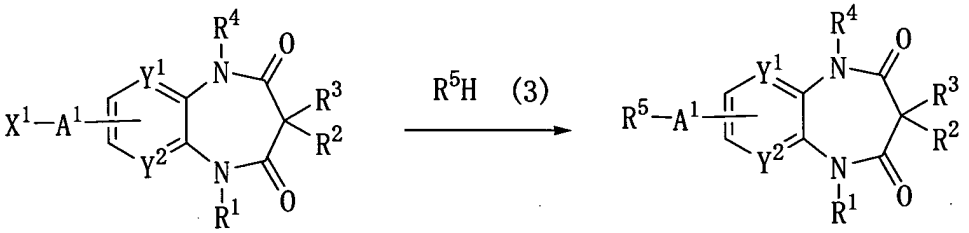
Preferred examples of $X_A$ and $X_B$ include a bond, lower alkylene, lower alkenylene, -CO-, -$SO_2$-, -lower alkylene-$SO_2$-, -lower alkylene-CO-, -lower alkenylene-CO-, -lower alkylene-CO-N(lower alkyl)-lower alkylene-, -N(lower alkyl)-lower alkylene-, -CO-N(lower alkyl)-lower alkylene-, and -O-lower alkylene-.

Either of the two bonds in $X_A$ may be bonded to $R^1$ or N, and either of the two bonds in $X_B$ may be bonded to $R^2$ or N.

The ring formed when $R^6$ and $R^7$ are linked together with the neighboring group -$X_A$-N-$X_B$- is a nitrogen-containing heterocyclic group optionally having one or more substituents. Examples of the nitrogen-containing heterocyclic group include the above-mentioned heterocyclic groups (a) to (c), (f) to (j), and (m) to (n). Examples of substituents of the nitrogen-containing heterocyclic group optionally having one or more substituents include the above-mentioned substituents (h1) to (h20).

The diazepine compound of the present invention represented by Formula (1) or its salt can be readily produced by persons skilled in the art using technical knowledge, based on the Examples and Reference Examples of the present specification. For example, the diazepine compound or its salt can be produced according to the processes shown in the following reaction formulae.

Reaction Formula 1




(2) (1)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $A^1$, $Y^1$ and $Y^2$ are the same as above, and $X^1$ is a leaving group.

The reaction of the compound of Formula (2) with the compound of Formula (3) can be performed in a general inert solvent or without

using any solvent, in the presence or absence of a basic compound and/or catalyst.

Examples of the leaving groups represented by $X^1$ include halogen atoms (e.g., chlorine, bromine, iodine, and like atoms), lower alkane sulfonyloxy (e.g., methanesulfonyloxy), halo substituted lower alkane sulfonyloxy (e.g., trifluoromethanesulfonyloxy), arylene sulfonyloxy (e.g., p-toluenesulfonyloxy, benzenesulfonyloxy), etc.

Examples of inert solvents include water; ethers such as dioxane, tetrahydrofuran, diethyl ether, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; lower ($C_{1-6}$) alcohols such as methanol, ethanol, and isopropanol; ketones such as acetone and methyl ethyl ketone; polar solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile; and mixtures thereof.

A wide variety of known basic compounds can be used as the basic compound. Examples of such basic compounds include inorganic bases, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, cesium hydroxide, and lithium hydroxide; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate, lithium hydrogencarbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; alkali metals such as sodium and potassium; sodium amide; sodium hydride; and potassium hydride; and organic bases, for example, alkali metal alcoholates such as sodium methoxide, sodium ethoxide, potassium methoxide, and potassium ethoxide; triethylamine; tripropylamine; pyridine; quinoline; 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); and 1,4-diazabicyclo[2.2.2]octane (DABCO). These basic compounds can be used singly or in a combination of two or more.

Examples of the catalyst include palladium compounds such as palladium acetate, bis(tributyltin)/bis(dibenzylideneacetone) palladium, copper iodide/2,2'-bipyridyl, bis (dibenzylideneacetone) palladium, copper iodide/bis (triphenylphosphine) palladium

dichloride, tris(dibenzylideneacetone) dipalladium, R-tris (dibenzylideneacetone)-dipalladium, S-tris (dibenzylideneacetone) dipalladium, palladium(II) acetate, [1,1'-bis(diphenylphosphino) -ferrocene] dichloropalladium(II), and tetrakis (triphenylphosphine) palladium.

Additives (ligands etc.) can be used together with the catalyst. Examples of the additive include compounds such as R-2,2'-bis diphenylphosphino)-1,1' -binaphthyl (R-BINAP), S-2,2'-bis(diphenylphosphino)-1,1' -binaphthyl (S-BINAP), RAC-2,2'-bis(diphenylphosphino)-1,1' -binaphthyl (RAC-BINAP), and 2,2-bis(diphenylimidazolidinyliden), xanthene compounds such as 4,5-bis (diphenylphosphino)-9,9- dimethylxanthene, and borates such as tri-tert-butylphosphine tetrafluoroborate, and a mixture thereof.

The above reaction may be performed by adding to the reaction system, as required, an alkali metal iodide serving as a reaction accelerator, such as potassium iodide or sodium iodide.

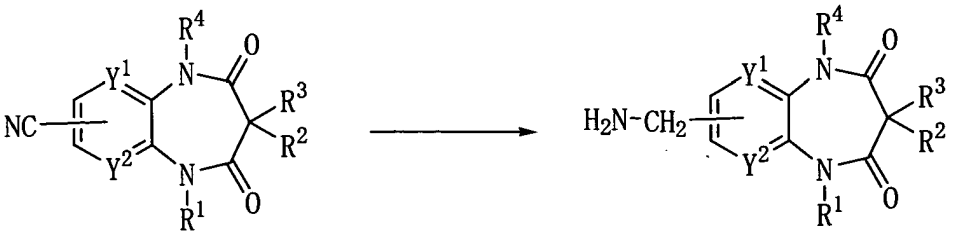
The compound of Formula (3) is typically used in an amount of at least 0.5 moles, and preferably about 0.5 to about 10 moles, per mole of the compound of Formula (2).

The amount of basic compound is typically 0.5 to 10 moles, and preferably 0.5 to 6 moles, per mole of the compound of Formula (2).

The catalyst is appropriately used in a typical catalytic amount, preferably 0.0001 to 1 moles, and more preferably 0.001 to 0.5 moles, per mole of the compound (2).

The reaction is typically performed at a temperature of 0 to 250°C, and preferably 0 to 200°C, and is typically completed in about 1 to about 80 hours.

Reaction Formula 2



(4) (1a)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $Y^1$ and $Y^2$ are the same as above.

The reaction converting the compound of Formula (4) to the compound of Formula (1a) can be performed by catalytic reduction of the compound of Formula (4) in a suitable solvent, in the presence of a catalytic hydrogenation reducing agent.

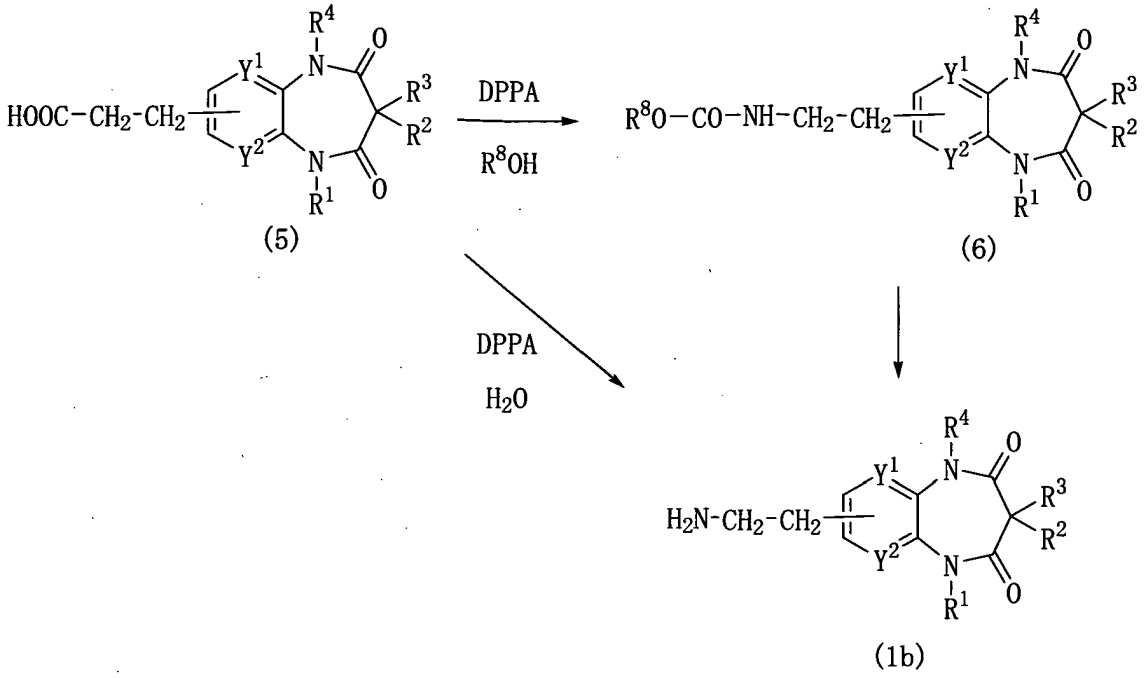
The solvent is not limited as long as it does not adversely affect the reduction reaction. Examples of such solvents include carboxylic acids such as formic acid and acetic acid; ethers such as dioxane, tetrahydrofuran, diethyl ether, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; and lower (e.g., $C_{1-6}$) alcohols such as methanol, ethanol, and isopropanol.

Examples of catalytic hydrogenation reducing agents include palladium black, palladium carbon, platinum oxide, platinum black, and Raney nickel.

The amount of catalytic hydrogenation reducing agent is typically 0.1 to 40 wt%, and preferably 1 to 20 wt%, based on the compound of Formula (4).

The reaction can be typically performed in a hydrogen atmosphere at atmospheric pressure to about 20 atm, and preferably atmospheric pressure to 10 atm; or in the presence of a hydrogen donor such as formic acid, ammonium formate, cyclohexene, or hydrazine hydrate. The reaction temperature may typically be about -30 to about 100°C, and preferably about 0 to about 60°C.

Reaction formula 3




(5) (6) (1b)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $Y^1$ and $Y^2$ are the same as above; and $R^8$ is lower alkyl.

The reaction converting the compound of Formula (5) to the compound of Formula (6) can be performed in a general inert solvent or without using any solvent, in the presence of an azide compound, a basic compound, and a lower ($C_{1-6}$) alcohol ($R^8OH$).

Examples of "lower alkyl" represented by $R^8$ include linear or branched alkyl groups with 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, and tert-butyl, with tert-butyl being preferred.

Examples of inert solvents include ethers such as dioxane, tetrahydrofuran, diethylether, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; and mixtures thereof.

Examples of azide compounds include sodium azide, lithium azide, and diphenylphosphoryl azide (DPPA).

Examples of usable basic compounds include organic bases such as triethylamine; tripropylamine; diisopropylethylamine; pyridine; quinoline; 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); and 1,4-diazabicyclo[2.2.2]octane (DABCO).

The reaction temperature is not limited, and the reaction is usually carried out under conventional conditions.

In the reaction, a carboxylic azide is produced from the carboxylic compound of Formula (5) and an azide compound, and the carboxylic azide undergoes subsequent Curtius rearrangement to produce an isocyanate. The isocyanate reacts with a lower ($C_{1-6}$) alcohol ($R^8OH$) to produce a urethane compound of Formula (6).

Next, the reaction converting the compound of Formula (6) to the compound of Formula (1b) can be performed by solvolysis in a suitable solvent, in the presence of an acid or basic compound.

Examples of usable solvents include water; lower ($C_{1-6}$) alcohols such as methanol, ethanol, isopropanol, and tert-butanol; ketones such as acetone and methyl ethyl ketone; ethers such as diethylether, dioxane, tetrahydrofuran, monoglyme, and diglyme; aliphatic acids such as acetic acid and formic acid; esters such as methyl acetate and ethyl acetate; halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; dimethyl sulfoxide, N,N-dimethylformamide, hexamethylphosphoric triamide, and mixtures thereof.

Examples of acids include mineral acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid; and organic acids such as formic acid, acetic acid, thioglycolic acid, trifluoroacetic acid, and sulfonic acids such as p-toluenesulfonic acid. These acids may be used singly or in a combination of two or more.

Examples of basic compounds include carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; and metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide, and lithium hydroxide. These basic compounds can be used singly or in a combination of two or more.

The amount of acid or basic compound is typically at least 1 mole, and preferably about 1 to about 10 moles, per mole of the compound of Formula (6).

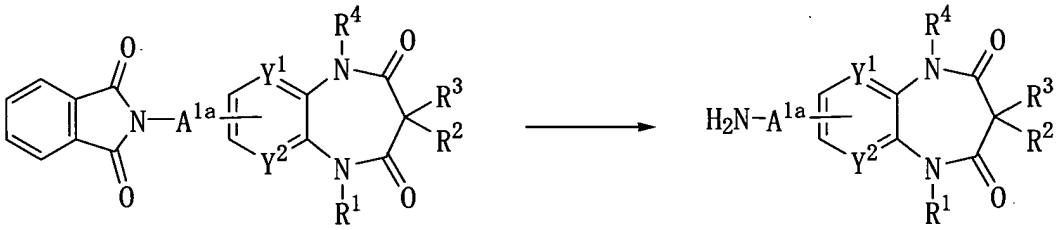
The solvolysis reaction (particularly the hydrolysis) advantageously proceeds typically at about 0 to about 200°C, and

preferably at about 0 to about 150°C, and is typically completed in about 10 minutes to about 80 hours.

Particularly when $R^8$ is tert-butyl, the solvolysis can be easily accomplished using the above-mentioned acids (particularly hydrochloric acid and the like) to produce the compound of Formula (1b).

Alternatively, the compound of Formula (5) can be directly converted to the compound of Formula (1b). This reaction can be performed by reacting the compound (5) with an azide compound in a general inert solvent or without using any solvent, in the presence of a basic compound, followed by treating the product with water. In this reaction, an isocyanate is produced from the above-mentioned carboxylic compound of Formula (5) and azide compound, and the isocyanate is hydrolyzed to produce the amine compound of Formula (1b).

Reaction Formula 4



(7) (1c)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $Y^1$ and $Y^2$ are the same as above; and $A^{1a}$ is lower alkylene with 3 or more carbon atoms.

Examples of "lower alkylene with 3 or more carbon atoms" represented by $A^{1a}$ include alkylene groups with 3 to 6 carbon atoms, such as trimethylene, tetramethylene, pentamethylene, and hexamethylene.

The reaction converting the compound of Formula (7) to the compound of Formula (1c) can be performed by reacting the compound (7) with hydrazine in a suitable solvent, or by hydrolysis. Here, hydrazine hydrate may be used as the hydrazine.

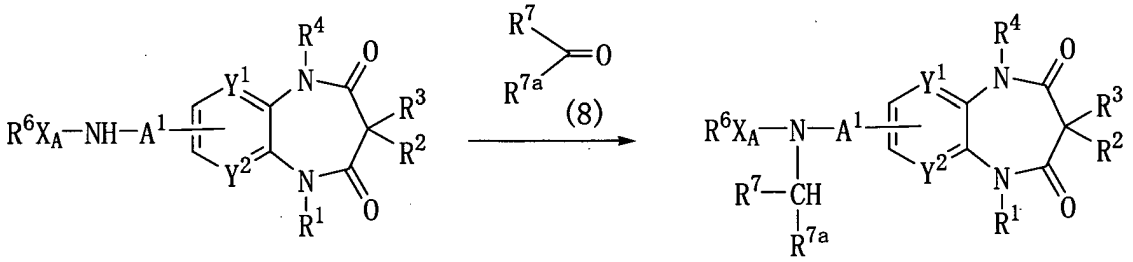
Examples of solvents used in reacting the hydrazine include

water; halogenated hydrocarbons such as chloroform, dichloromethane, and dichloroethane; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, and dimethoxyethane; esters such as methyl acetate and ethyl acetate; aprotic polar solvents such as N,N-dimethylformamide, dimethyl sulfoxide, and hexamethylphosphoric triamide; alcohols such as methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve, and methyl cellosolve; acetonitrile; pyridine; and mixtures thereof.

The amount of hydrazine is typically at least about 1 mole, and preferably about 1 to about 5 moles, per mole of the compound of Formula (7).

The reaction is performed typically at about 0 to about 120°C, and preferably at about 0 to about 100°C, and is typically completed in about 0.5 to about 5 hours.

Reaction Formula 5



(1d) (8) (1e)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $R^7$, $X_A$, $A^1$, $Y^1$ and $Y^2$ are the same as above; and $R^{7a}$ is hydrogen or lower alkyl.

Examples of "lower alkyl" represented by $R^{7a}$ include linear or branched alkyl groups with 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, neopentyl, n-hexyl, isohexyl, and 3-methylpentyl.

The reaction between the compound of Formula (1d) and the compound of Formula (8) is performed, for example, in a suitable solvent or without using any solvent, in the presence of a reducing agent.

Examples of usable solvents include water; lower ($C_{1-6}$) alcohols such as methanol, ethanol, isopropanol, butanol, tert-butanol, and

ethylene glycol; aliphatic acids such as formic acid, and acetic acid; ethers such as diethylether, tetrahydrofuran, dioxane, monoglyme, and diglyme; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; acetonitrile; and mixtures thereof.

Examples of reducing agents include aliphatic acids such as formic acid; aliphatic acid alkali metal salts such as sodium formate; hydride reducing agents such as sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, sodium trimethoxyborohydride, lithium aluminium hydride, and mixtures thereof, or mixtures of aliphatic acids or aliphatic acid alkali metal salts with hydride reducing agents; and catalytic hydrogenation reducing agents such as palladium black, palladium carbon, platinum oxide, platinum black, and Raney nickel.

When an aliphatic acid such as formic acid, or an aliphatic acid alkali metal salt such as sodium formate is used as a reducing agent, a suitable reaction temperature is typically about room temperature to about 200°C, and preferably about 50 to about 150°C. The reaction is typically completed in about 10 minutes to about 10 hours. Preferably, the aliphatic acid or aliphatic acid alkali metal salt is used in large excess relative to the compound of Formula (1d).

When a hydride reducing agent is used, a suitable reaction temperature is typically about -80 to about 100°C, and preferably about -80 to about 70°C. The reaction is typically completed in about 30 minutes to about 60 hours. The hydride reducing agent is typically used in an amount of about 1 to about 20 moles, and preferably about 1 to about 10 moles, per mole of the compound of Formula (1d). Particularly when lithium aluminium hydride is used as a hydride reducing agent, it is preferable to use as a solvent an ether such as diethyl ether, tetrahydrofuran, dioxane, monoglyme, or diglyme; or an aromatic hydrocarbon such as benzene, toluene, or xylene. To the reaction system may be added an amine such as trimethylamine, triethylamine, or N-ethyldiisopropylamine; or a molecular sieve such as molecular sieve 3A (MS-3A) or molecular sieve 4A (MS-4A).

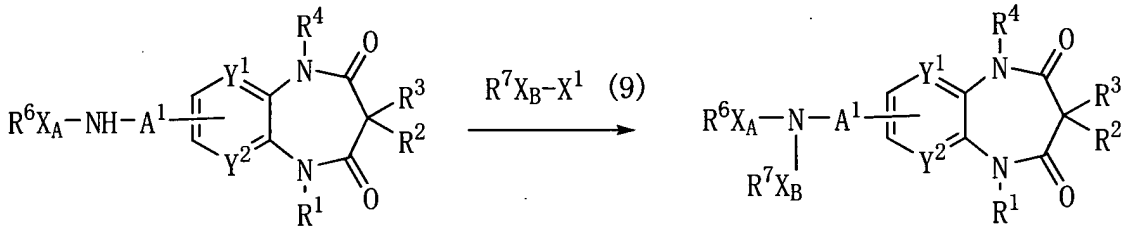
When a catalytic hydrogenation reducing agent is used, the

reaction is typically performed at about -30 to about 100°C, and preferably at about 0 to about 60°C, in a hydrogen atmosphere at typically about atmospheric pressure to about 20 atm, and preferably at about atmospheric pressure to about 10 atm, or in the presence of a hydrogen donor such as formic acid, ammonium formate, cyclohexene, or hydrazine hydrate. The reaction is typically completed in about 1 to about 12 hours. The catalytic hydrogenation reducing agent is typically used in an amount of about 0.1 to about 40 wt%, and preferably about 1 to about 20 wt%, based on the compound of Formula (1d).

In the reaction of the compound of Formula (1d) and the compound of Formula (8), the compound of Formula (8) is typically used in an amount of at least 1 mole, and preferably 1 to 5 moles, per mole of the compound of Formula (1d).

The compound of Formula (8) may also be a hydrated compound wherein a water molecule is attached to a carbonyl group.

Reaction Formula 6




(1d) (1e-1)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^6$, $R^7$, $X_A$, $X_B$, $A^1$, $X^1$, $Y^1$ and $Y^2$ are the same as above.

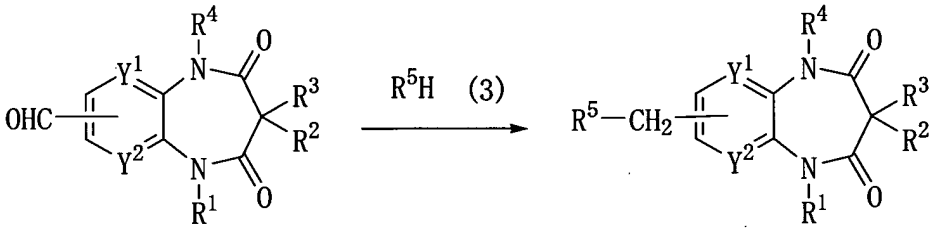
The reaction of the compound of Formula (1d) with the compound of Formula (9) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (2) with the compound of Formula (3) shown in Reaction Formula 1 above.

Alternatively, the reaction of the compound of Formula (1d) with the compound of Formula (9) can be performed by the known "Ullmann condensation" etc. The reaction can be preferably adopted especially when $X_B$ is a bond and $R^7$ is aryl or heterocyclic (especially unsaturated heterocyclic) group optionally substituted. For example, the reaction can be carried out in a solvent (e.g., toluene,

tetrahydrofuran (THF), N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP) and dimethyl sulfoxide (DMSO)), in the presence of copper compound (e.g., copper oxides, copper halides such as copper iodide), a basic compound (e.g., sodium tert-butoxide, K3PO4 and Cs2CO3), and if necessary a phosphine (e.g., triphenylphosphine, xantphos, tri-tert-butylphosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl(BINAP), tetrafluoroborate, N,N'-dimethylethylenediamine, and L-proline).

The reaction temperature is not limited, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Reaction Formula 7

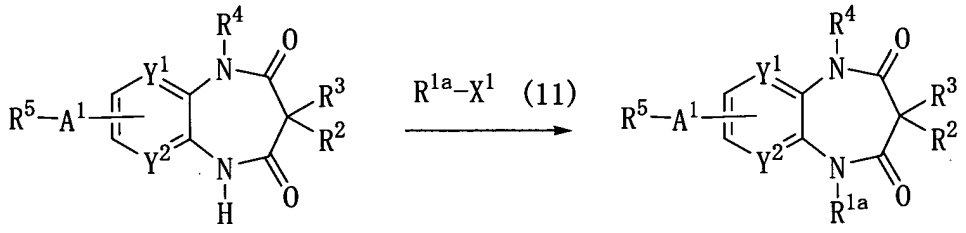


(10) (1f)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $Y^1$ and $Y^2$ are the same as above.

The reaction of the compound of Formula (10) with the compound of Formula (3) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (1d) with the compound of Formula (8) shown in Reaction Formula 5 above.

Reaction Formula 8



(1g) (1h)

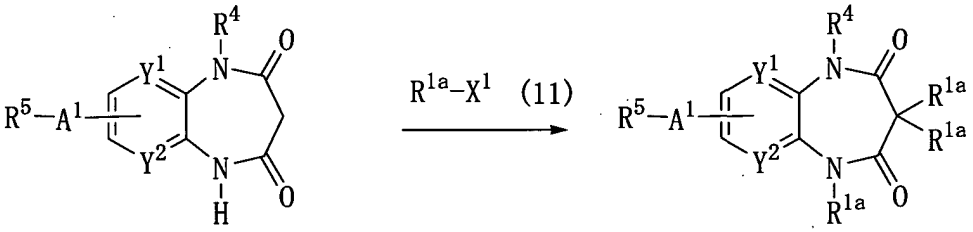
wherein $R^2$, $R^3$, $R^4$, $R^5$, $A^1$, $X^1$, $Y^1$ and $Y^2$ are the same as above; and $R^{1a}$ is lower alkyl.

Examples of "lower alkyl" represented by $R^{1a}$ include linear or branched alkyl groups with 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and sec-butyl.

The reaction of the compound of Formula (1g) with the compound of Formula (11) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (2) with the compound of Formula (3) shown in Reaction Formula 1 above.

In this reaction, when $R^4$ is hydrogen in the compound of Formula (1g), a compound may be obtained wherein the 1- and 5-positions of the benzodiazepine skeleton are simultaneously replaced by the group $R^{1a}$.

Reaction Formula 9



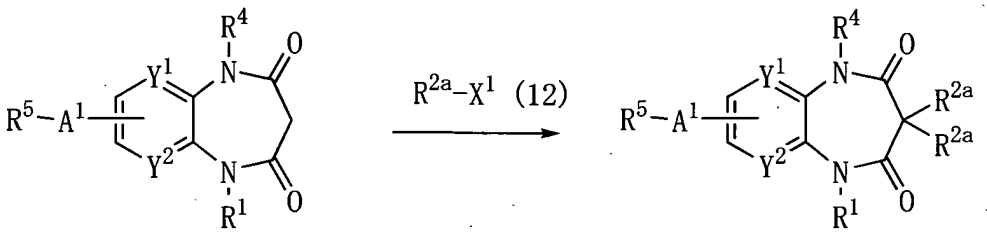

(1i) (1j)

wherein $R^{1a}$, $R^4$, $R^5$, $A^1$, $X^1$, $Y^1$ and $Y^2$ are the same as above.

The reaction of the compound of Formula (1i) with the compound of Formula (11) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (2) with the compound of Formula (3) shown in Reaction Formula 1 above.

In this reaction, when $R^4$ is hydrogen in the compound of Formula (1i), a compound may be obtained wherein the 1-, 3-, and 5-positions of the benzodiazepine skeleton are simultaneously replaced by the group $R^{1a}$.

Reaction Formula 10




(1k) (1ℓ)

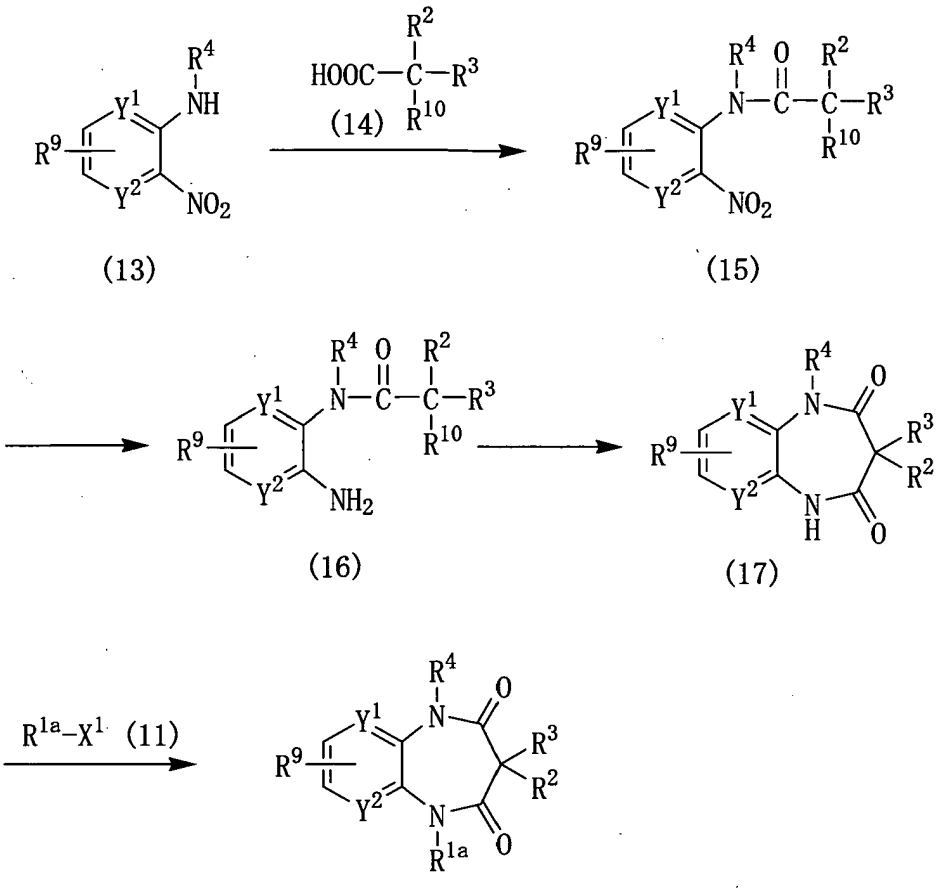
wherein $R^1$, $R^4$, $R^5$, $A^1$, $X^1$, $Y^1$ and $Y^2$ are the same as above; and $R^{2a}$ is lower alkyl.

Examples of "lower alkyl" represented by $R^{2a}$ include linear or branched alkyl groups with 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and sec-butyl.

The reaction of the compound of Formula (1k) with the compound of Formula (11) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (2) with the compound of Formula (3) shown in Reaction Formula 1 above.

In this reaction, when $R^1$ and/or $R^4$ is hydrogen in the compound of Formula (1k), a compound may be obtained wherein the 1-, 3-, and 5-positions of the benzodiazepine skeleton are simultaneously replaced by the group $R^{2a}$.

Reaction Formula 11



(13) (15) (16) (17) (18a)

wherein $R^2$, $R^3$, $R^4$, $R^{1a}$, $X^1$, $Y^1$ and $Y^2$ are the same as above; $R^9$ is lower alkoxy; and $R^{10}$ is lower alkoxycarbonyl.

Examples of "lower alkoxy" represented by $R^9$ include linear or branched alkoxy groups with 1 to 6 carbon atoms, such as methoxy, and ethoxy. Examples of "lower alkoxycarbonyl" represented by $R^{10}$ include ($C_{1-6}$ alkoxy)carbonyl groups, such as methoxycarbonyl, ethoxycarbonyl.

In the reaction of the compound of Formula (13) with the compound of Formula (14), the compound of Formula (13) is reacted with the carboxylic acid compound of Formula (14) through a general amide bond formation reaction. Conditions for known amide bond formation reactions can be easily employed in this amide formation reaction. For example, the following reaction methods can be employed: (i) a mixed acid anhydride method, in which Carboxylic Acid (14) is reacted with an alkyl halocarboxylate to form a mixed acid anhydride, which is then reacted with Amine (13); (ii) an active ester method, in which Carboxylic Acid (14) is converted to an activated ester such as a phenyl

ester, p-nitrophenyl ester, N-hydroxysuccinimide ester, or 1-hydroxybenzotriazole ester, or to an activated amide with benzoxazoline-2-thione, and the activated ester or amide is reacted with Amine (13); (iii) a carbodiimide method, in which Carboxylic Acid (14) is subjected to a condensation reaction with Amine (13) in the presence of an activating agent such as dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC), or carbonyldiimidazole; and (iv) other methods, for example, a method in which Carboxylic Acid (14) is converted to a carboxylic anhydride using a dehydrating agent such as acetic anhydride, and the carboxylic anhydride is reacted with Amine (13), a method in which an ester of Carboxylic Acid (14) with a lower ($C_{1-6}$) alcohol is reacted with Amine (13) at a high pressure and a high temperature, and a method in which an acid halide of Carboxylic Acid (14), i.e., a carboxylic acid halide, is reacted with Amine (13).

Generally, the mixed acid anhydride method(i) is performed in a solvent, in the presence or absence of a basic compound. Any solvents used for conventional mixed acid anhydride methods are usable. Specific examples of usable solvents include halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, and dimethoxyethane; esters such as methyl acetate, ethyl acetate, and isopropyl acetate; aprotic polar solvents such as N,N-dimethylformamide, dimethylsulfoxide, and hexamethylphosphoric triamide; and mixtures thereof.

Examples of usable basic compounds include organic bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyldiisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO); inorganic bases, for example, carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; metal hydroxides such as sodium hydroxide, potassium hydroxide, and calcium hydroxide; potassium hydride; sodium hydride; potassium; sodium; sodium amide;

and metal alcoholates such as sodium methylate and sodium ethylate.

Examples of alkyl halocarboxylates usable in the mixed acid anhydride method include methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, and isobutyl chloroformate. In this method, Carboxylic Acid (14), an alkyl halocarboxylate, and Amine (13) are preferably used in equimolar amounts, but each of the alkyl halocarboxylate and Carboxylic Acid (14) can also be used in an amount of about 1 to about 1.5 moles per mole of Amine (13).

The reaction is typically performed at about -20 to about 150°C, and preferably at about 10 to about 50°C, typically for about 5 minutes to about 30 hours, and preferably for about 5 minutes to about 25 hours.

Method (iii), in which a condensation reaction is performed in the presence of an activating agent, can be performed in a suitable solvent in the presence or absence of a basic compound. Solvents and basic compounds usable in this method include those mentioned hereinafter as solvents and basic compounds usable in the method in which a carboxylic acid halide is reacted with Amine (13) mentioned above as one of the other methods (iv). A suitable amount of activating agent is typically at least 1 mole, and preferably 1 to 5 moles per mole of Compound (13). When WSC is used as an activating agent, the addition of 1-hydroxybenzotriazol to the reaction system allows the reaction to proceed advantageously. The reaction is typically performed at about -20 to about 180°C, and preferably at about 0 to about 150°C, and is typically completed in about 5 minutes to about 90 hours.

When the method in which a carboxylic acid halide is reacted with Amine (13), mentioned above as one of the other methods (iv), is employed, the reaction is performed in the presence of a basic compound in a suitable solvent. Examples of usable basic compounds include a wide variety of known basic compounds, such as those for use in the Schotten-Baumann reaction described above. In addition to those usable in the mixed acid anhydride method, usable solvents include alcohols such as methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve, and methyl cellosolve; acetonitrile; pyridine; acetone; and water. The ratio of

the carboxylic acid halide to Amine (13) is not limited, and can be suitably selected from a wide range. It is typically suitable to use, for example, at least about 1 mole, and preferably about 1 to about 5 moles of the carboxylic acid halide per mole of Amine (13). The reaction is typically performed at about -20 to about 180°C, and preferably at about 0 to about 150°C, and is typically completed in about 5 minutes to about 30 hours.

The amide bond formation reaction shown in Reaction Formula 11 can also be performed by reacting Carboxylic Acid (14) with Amine (13) in the presence of a phosphorus compound serving as a condensing agent, such as triphenylphosphine, diphenylphosphinyl chloride, phenyl-N-phenylphosphoramide chloridate, diethyl chlorophosphate, diethyl cyanophosphate, diphenylphosphoric azide, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, or the like.

The reaction is performed in the presence of a solvent and a basic compound usable for the method in which a carboxylic acid halide is reacted with Amine (13), typically at about -20 to about 150°C, and preferably at about 0 to about 100°C, and is typically completed in about 5 minutes to about 30 hours. It is suitable to use each of the condensing agent and Carboxylic Acid (14) in amounts of at least about 1 mole, and preferably about 1 to about 2 moles, per mole of Amine (13).

The reaction converting the compound of Formula (15) to the compound of Formula (16) can be performed by, for example, [1] reducing the compound of Formula (15) in a suitable solvent using a catalytic hydrogenation reducing agent, or [2] reducing the compound of Formula (15) in a suitable inert solvent using a reducing agent such as a mixture of an acid with a metal or metal salt, a mixture of a metal or metal salt with an alkali metal hydroxide, sulfide, or ammonium salt.

When Method [1] in which a catalytic hydrogenation reducing agent is used, examples of usable solvents are water; acetic acid; alcohols such as methanol, ethanol and isopropanol; hydrocarbons such as n-hexane and cyclohexane; ethers such as dioxane, tetrahydrofuran, diethyl ether and diethylene glycol dimethyl ether; esters such as ethyl acetate and methyl acetate; aprotic polar solvents such as

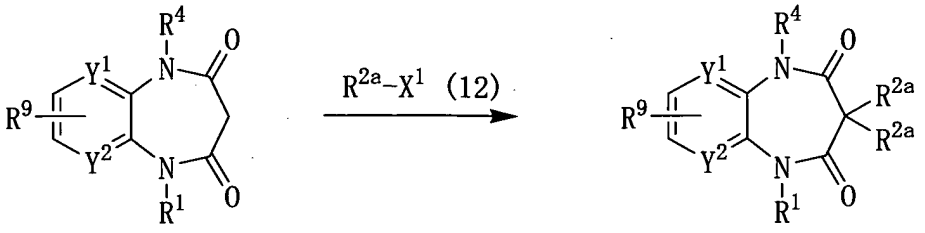
N,N-dimethylformamide; and mixtures thereof. Examples of usable catalytic hydrogenation reducing agents include palladium, palladium black, palladium carbon, platinum carbon, platinum, platinum black, platinum oxide, copper chromite, and Raney nickel. The reducing agent is typically used in an amount of about 0.02 times to about equal to the weight of the compound of Formula (15). The reaction temperature is typically about -20 to about 150°C, and preferably about 0 to about 100°C. The hydrogen pressure is typically about 1 to 10 atm. The reaction is typically completed in about 0.5 to about 100 hours. An acid such as hydrochloric acid may be added to the reaction.

When Method [2] above is used, a mixture of iron, zinc, tin, or tin (II) chloride, with a mineral acid such as hydrochloric acid or sulfuric acid; or a mixture of iron, iron (II) sulfate, zinc, or tin, with an alkali metal hydroxide such as sodium hydroxide, a sulfide such as ammonium sulfide, aqueous ammonia solution, or an ammonium salt such as ammonium chloride, can be used as a reducing agent. Examples of inert solvents are water; acetic acid; alcohols such as methanol and ethanol; ethers such as dioxane; and mixtures thereof. Conditions for the reduction reaction can be suitably selected according to the reducing agent to be used. For example, when a mixture of tin (II) chloride and hydrochloric acid is used as a reducing agent, the reaction is advantageously performed at about 0 to about 150°C for about 0.5 to about 10 hours. A reducing agent is used in an amount of at least 1 mole, and preferably about 1 to 5 moles, per mole of the compound of Formula (15).

The reaction converting the compound of Formula (16) to the compound of Formula (17) is performed under the same reaction conditions as those for the reaction of the compound of Formula (13) with the compound of Formula (14).

The reaction of the compound of Formula (17) with the compound of Formula (11) is performed under the same reaction conditions as those for the reaction of the compound of Formula (1g) with the compound of Formula (11) in Reaction Formula 8.

Reaction Formula 12




(19) (18b)

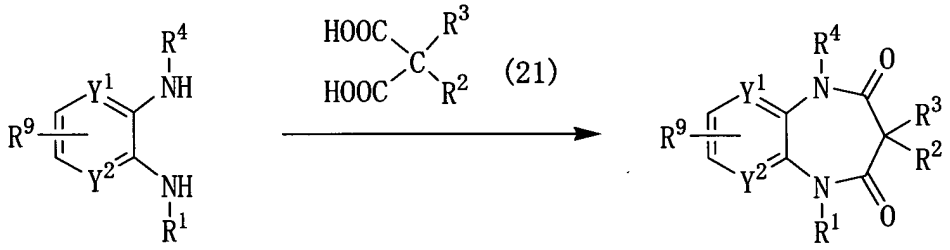
wherein $R^1$, $R^{2a}$, $R^4$, $R^9$, $X^1$, $Y^1$ and $Y^2$ are the same as above.

The reaction of the compound of Formula (19) with the compound of Formula (12) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (2) with the compound of Formula (3) shown in Reaction Formula 1 above.

When $R^1$ and/or $R^4$ is hydrogen in the reaction of the compound of Formula (19) with the compound of Formula (12), the hydrogen atom may be replaced with $R^{2a}$.

The compound of Formula (18) can also be produced according to the process shown in the following Reaction Formula 13.

Reaction Formula 13

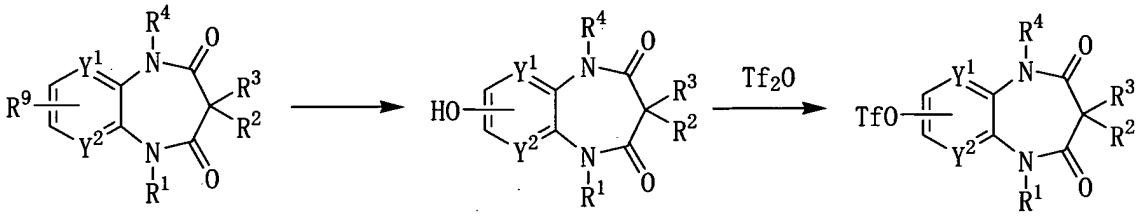



(20) (18)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^9$, $Y^1$ and $Y^2$ are the same as above.

The reaction of the compound of Formula (20) with the compound of Formula (21) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (13) with the compound of Formula (14) shown in Reaction Formula 11 above.

Reaction Formula 14



(18) (22) (23)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^9$, $Y^1$ and $Y^2$ are the same as above; and Tf is trifluoromethanesulfonyl ($CF_3SO_2$-).

The reaction converting the compound of Formula (18) to the compound of Formula (22) can be performed in a suitable solvent in the presence of an acid.

Examples of solvents include water; lower ($C_{1-6}$) alcohols such as methanol, ethanol, and isopropanol; ethers such as dioxane, tetrahydrofuran, and diethylether; halogenated hydrocarbons such as dichloromethane, chloroform, and carbon tetrachloride; polar solvents such as acetonitrile; and mixtures thereof. Examples of acids include mineral acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid; aliphatic acids such as formic acid and acetic acid; sulfonic acids such as p-toluenesulfonic acid; Lewis acids such as boron fluoride, aluminium chloride, and boron tribromide; iodides such as sodium iodide and potassium iodide; and mixtures of these iodides and Lewis acids.

The reaction is performed typically at about 0 to about 200°C, and preferably at about 0 to about 150°C, and is typically completed in about 0.5 to about 25 hours. The amount of acid is typically about 1 to about 10 moles, and preferably about 1 to about 2 moles, per mole of the compound of Formula (18).

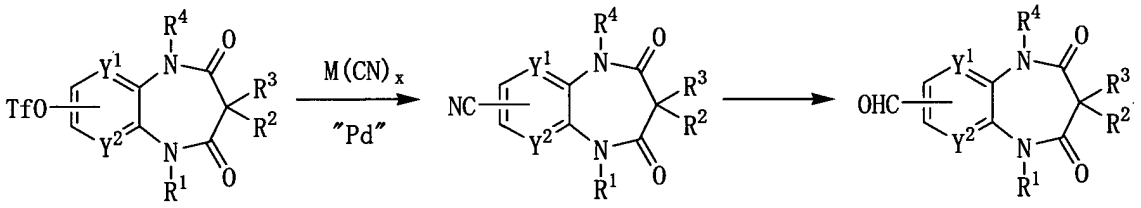
The reaction converting the compound of Formula (22) to the compound of Formula (23) is performed by reacting the compound of Formula (22) with trifluoromethanesulfonic anhydride in a suitable solvent, in the presence or absence of a basic compound.

Examples of solvents include ethers such as dioxane, tetrahydrofuran, and diethylether; halogenated hydrocarbons such as dichloromethane, chloroform, and carbon tetrachloride; polar solvents

such as acetonitrile; and mixtures thereof. Examples of basic compounds include organic bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyldiisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,4-diazabicyclo[2.2.2]octane (DABCO).

The reaction temperature is not limited, and the reaction is usually carried out under conventional conditions.

Reaction Formula 15




(23) (4) (10)

wherein $R^1$, $R^2$, $R^3$, $R^4$, Tf, $Y^1$ and $Y^2$ are the same as above; M is a metal, for example, Na, K, Ag, Zu, Cu, and the like; and X is a positive number.

The reaction converting the compound of Formula (23) to the compound of Formula (4) can be performed by reacting the compound of Formula (23) with a cyano metal in a suitable solvent, in the presence of a catalyst.

Examples of metal cyanides ($M(CN)_x$) include sodium cyanide, potassium cyanide, silver cyanide, zinc cyanide, and cuprous cyanide.

Examples of solvents usable in this reaction include water; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethylether, tetrahydrofuran, dioxane, 2-methoxyethanol, monoglyme, and diglyme; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; lower ($C_{1-6}$) alcohols such as methanol, ethanol, isopropanol, butanol, tert-butanol, and ethylene glycol; aliphatic acids such as acetic acid; esters such as ethyl acetate and methyl acetate; ketones such as acetone and methyl ethyl ketone; acetonitrile; pyridine; dimethyl sulfoxide; N,N-dimethylformamide;

hexamethylphosphoric triamide; and mixtures thereof.

Examples of catalysts include palladium compounds such as tetrakis(triphenylphosphine)palladium (0); dichlorobis(triphenylphosphine)palladium (II); and tris(dibenzylideneacetone)dipalladium (0).

A ligand such as 1,1'-bis(diphenylphosphino)ferrocene or zinc dust may be added, as required, in order to promote the reaction.

The catalyst can be typically used in an amount of 0.01 to 1 mole, and preferably 0.01 to 0.5 moles, per mole of the compound of Formula (23).

The metal cyanide can be typically used in an amount of at least 1 mole, and preferably 1 to 3 moles, per mole of the compound of Formula (23).

The reaction is typically performed at room temperature to 200°C, and preferably at about room temperature to about 150°C. The reaction is typically completed in about 1 hour to about 1 week.

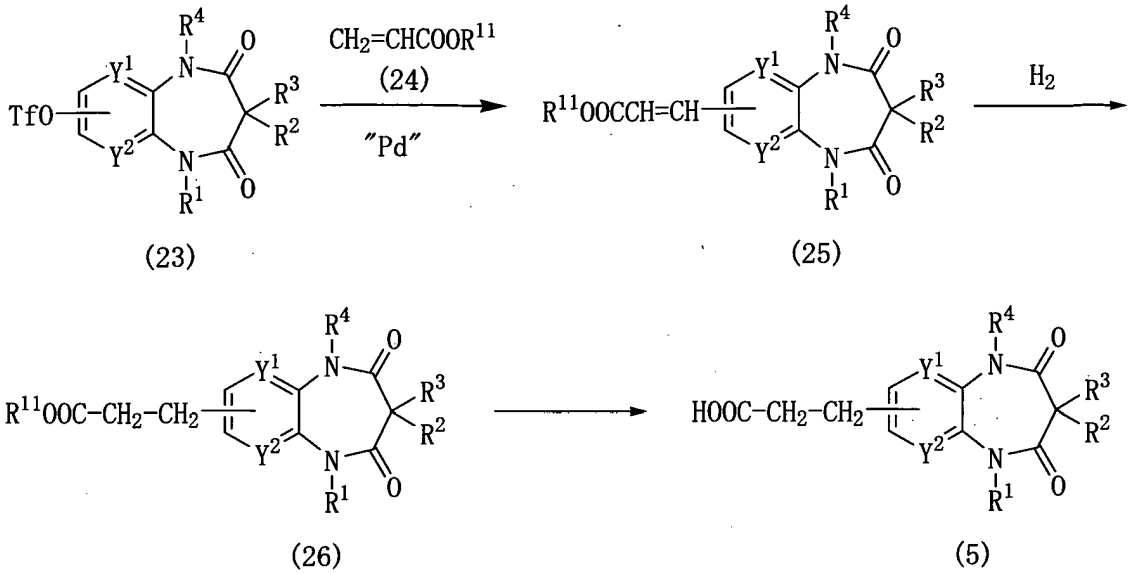
The reaction converting the compound of Formula (4) to the compound of Formula (10) is performed in a suitable solvent, in the presence of a reducing agent.

Examples of solvents include aliphatic acids such as formic acid; ethers such as dioxane, tetrahydrofuran, diethylether, and diethylene glycol dimethyl ether; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; and mixtures thereof.

Examples of reducing agents include alkylaluminum hydrides such as diisobutylaluminum hydride; and Raney nickel. The reducing agent is typically used in an amount at least equal to, and preferably from an equal weight to 5 times the weight of the compound of Formula (4).

The reaction is typically performed at room temperature to 200°C, and preferably at about room temperature to about 150°C. The reaction is typically completed in about 0.5 to about 20 hours.

Reaction Formula 16




(23) (25) (26) (5)

wherein $R^1$, $R^2$, $R^3$, $R^4$, Tf, $Y^1$ and $Y^2$ are the same as above; and $R^{11}$ is lower alkyl.

Examples of "lower alkyl" represented by $R^{11}$ include linear or branched alkyl groups with 1 to 6 carbon atoms, such as methyl, and ethyl.

The reaction converting the compound of Formula (23) and the compound of Formula (24) to the compound of Formula (25) can be performed in a suitable solvent, in the presence of a catalyst.

Examples of usable solvents include water; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethylether, tetrahydrofuran, dioxane, 2-methoxyethanol, monoglyme, and diglyme; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; lower ($C_{1-6}$) alcohols such as methanol, ethanol, isopropanol, butanol, tert-butanol, and ethylene glycol; aliphatic acids such as acetic acid; esters such as ethyl acetate and methyl acetate; ketones such as acetone and methyl ethyl ketone; acetonitrile; pyridine; dimethyl sulfoxide; N,N-dimethylformamide; hexamethylphosphoric triamide; and mixtures thereof.

Preferable as the catalyst are palladium compounds, for example, tetrakis(triphenylphosphine)palladium (0); dichlorobis(triphenylphosphine)palladium (II); and the like. The catalyst is typically used in an amount of about 0.01 to about 1 mole,

and preferably about 0.01 to about 0.5 moles, per mole of the compound of Formula (23).

Further, a basic compound such as triethylamine, pyridine, may be added, as required.

The reaction temperature is not limited, and the reaction is usually carried out under conventional conditions.

The reaction converting the compound of Formula (25) to the compound of Formula (26) can be performed by catalytic reduction of the compound of Formula (25) in a suitable solvent in a hydrogen atmosphere.

Known hydrogenolysis methods can be widely employed in hydrogenolysis. Examples of such hydrogenolysis methods include chemical reduction and catalytic reduction.

Catalysts suitable for use in catalytic reduction include platinum catalysts, such as platinum plates, spongy platinum, platinum black, colloid platinum, platinum oxide, and platinum wires; palladium catalysts, such as spongy palladium, palladium black, palladium oxide, palladium carbon, palladium/barium sulfate, and palladium/barium carbonate; nickel catalysts, such as reduced nickel, nickel oxide, and Raney nickel; cobalt catalysts, such as reduced cobalt and Raney cobalt; and iron catalysts, such as reduced iron.

The amount of the catalyst used for catalytic reduction is not limited, and may be an amount generally used.

The reaction temperature is typically 0 to 120°C, preferably room temperature to about 100°C, and more preferably room temperature to 80°C. The reaction time is typically 30 minutes to 24 hours, preferably 30 minutes to 10 hours, and more preferably 30 minutes to 4 hours.

The reaction converting the compound of Formula (26) to the compound of Formula (5) can be performed by hydrolysis of the compound (26).

This hydrolytic reaction is performed in a suitable solvent or without any solvent, in the presence of an acid or basic compound.

Examples of solvents include water; lower ($C_{1-6}$) alcohols such

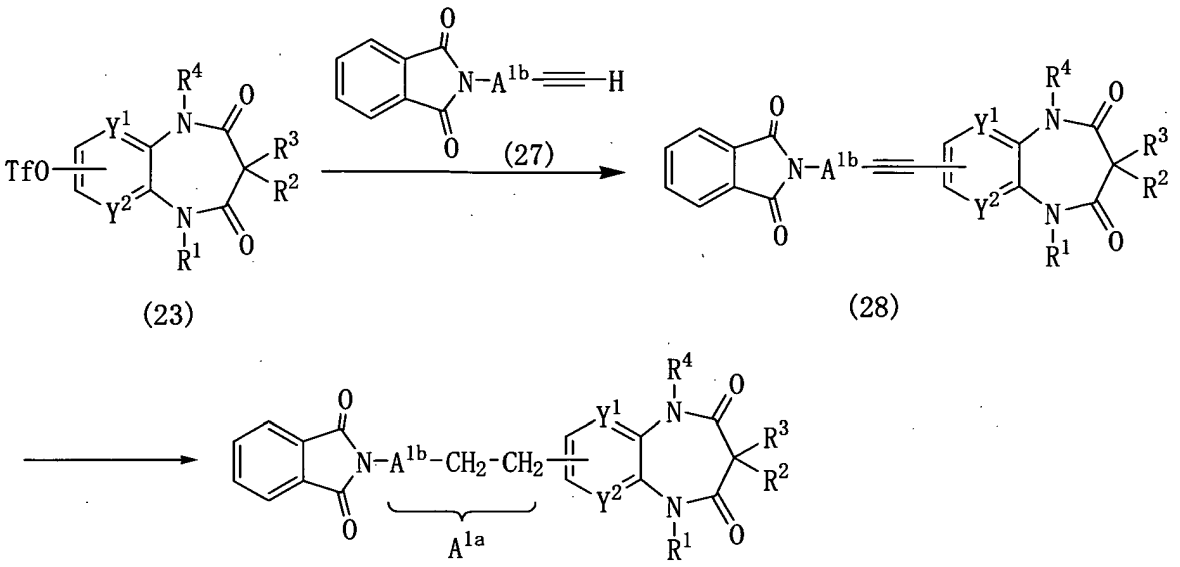
as methanol, ethanol, isopropanol, and tert-butanol; ketones such as acetone and methyl ethyl ketone; ethers such as diethylether, dioxane, tetrahydrofuran, monoglyme, and diglyme; aliphatic acids such as acetic acid and formic acid; esters such as methyl acetate and ethyl acetate; halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; dimethyl sulfoxide; N,N-dimethylformamide; hexamethylphosphoric triamide; and mixtures thereof.

Examples of acids include mineral acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid; and organic acids such as formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, and like sulfonic acids. These acids may be used singly or in a combination of two or more.

Examples of basic compounds include carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; and metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide, and lithium hydroxide. These basic compounds can be used singly or in a combination of two or more.

The hydrolytic reaction advantageously proceeds typically at about 0 to about 200°C, and preferably at about 0 to about 150°C. The reaction is typically completed in about 10 minutes to about 30 hours.

Reaction Formula 17



(23) (27) (28)

(7)

wherein $R^1$, $R^2$, $R^3$, $R^4$, Tf, $Y^1$ and $Y^2$ are the same as above; and $A^{1b}$ is lower alkylene.

Examples of "lower alkylene" represented by $A^{1b}$ include alkylene groups with 1 to 4 carbon atoms, such as methylene, ethylene, trimethylene, and tetramethylene.

The reaction converting the compound of Formula (23) and the compound of Formula (27) to the compound of Formula (28) can be performed in a suitable solvent, in the presence of a copper halide and a palladium catalyst.

Examples of solvents include ketones such as acetone and methyl ethyl ketone; ethers such as diethylether, dioxane, tetrahydrofuran, monoglyme, and diglyme; aliphatic acids such as acetic acid and formic acid; esters such as methyl acetate and ethyl acetate; halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; dimethyl sulfoxide; N,N-dimethylformamide; hexamethylphosphoric triamide; and mixtures thereof.

Examples of copper halides include copper (I) chloride, copper (I) bromide, and copper (I) iodide.

Examples of palladium catalysts include palladium compounds such as tetrakis(triphenylphosphine)palladium (0); and dichlorobis(triphenylphosphine)palladium (II).

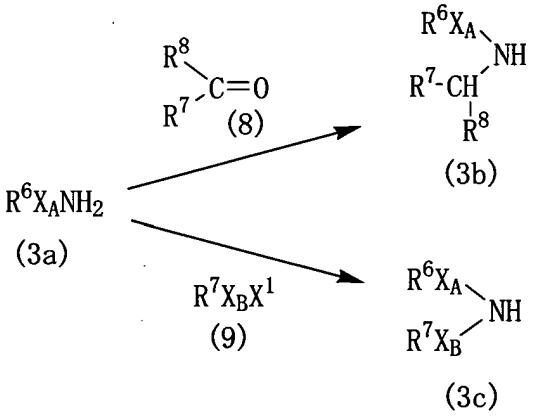
A basic compound may be added, as required. Examples of basic compounds include triethylamine, diisopropylethylamine, pyridine,

and diethylamine. The basic compound can be typically used in an amount of 0.01 to 10 mole, and preferably 0.01 to 1 moles, per mole of the compound of Formula (23).

The reaction advantageously proceeds typically at about 0 to about 200°C, and preferably at about 0 to about 180°C. The reaction is typically completed in about 10 minutes to about 30 hours.

The reaction converting the compound of Formula (28) to the compound of Formula (7) can be performed under the same reaction conditions as those for the reaction converting the compound of Formula (25) to the compound of Formula (26) shown in Reaction Formula 16 above.

Reaction Formula 18



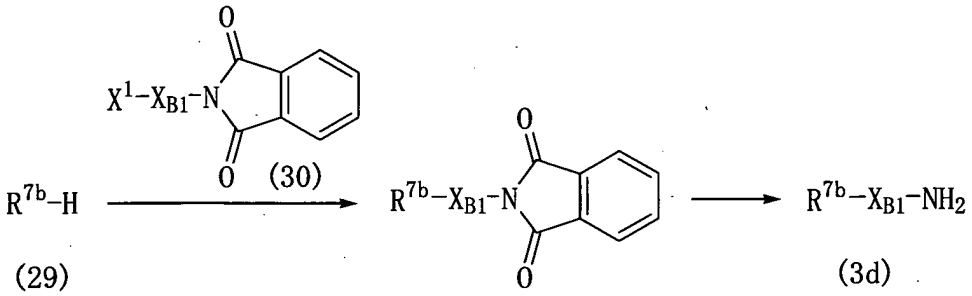

wherein $R^6$, $R^7$, $R^8$, $X_A$, $X_B$, and $X^1$ are the same as above.

The reaction of the compound of Formula (3a) with the compound of Formula (8) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (1d) with the compound of Formula (8) shown in Reaction Formula 5 above.

The reaction of the compound of Formula (3a) with the compound of Formula (9) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (2) with the compound of Formula (3) shown in Reaction Formula 1 above.

The compound of Formula (3), which is used as a starting material, can be easily prepared by the process shown in the following reaction formula.

Reaction Formula 19




wherein $R^{7b}$ is a nitrogen-containing heterocyclic group optionally having one or more substituents; and

$X_{B1}$ is lower alkylene.

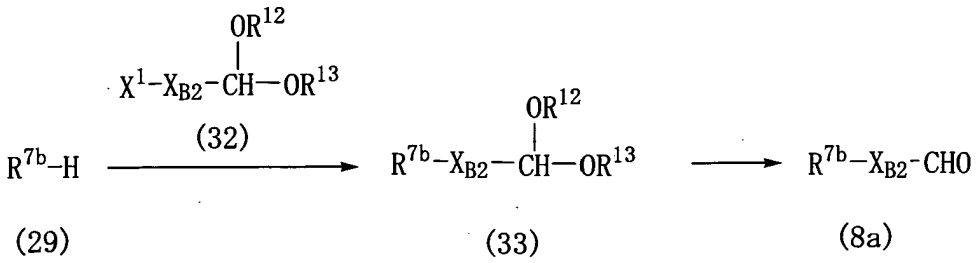
Examples of $R^{7b}$ include, among groups represented by the group $R^7$ mentioned above, groups obtained by removing hydrogen from saturated or unsaturated, monocyclic or polycyclic, heterocyclic compounds having an N-H bond, and groups optionally having one or more substituents.

Examples of "lower alkylene" represented by $X_{B1}$ include alkylene groups with 2 to 4 carbon atoms, such as ethylene and trimethylene.

The reaction of the compound of Formula (29) with the compound of Formula (30) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (2) and the compound of Formula (3) shown in Reaction Formula 1 above.

The reaction converting the compound of Formula (31) to the compound of Formula (3d) can be performed under the same reaction conditions as those for the reaction converting the compound of Formula (7) to the compound of Formula (1c) shown in Reaction Formula 4 above.

Reaction Formula 20




(29) (33) (8a)

wherein $R^{7b}$ is the same as above; $X_{B2}$ is lower alkylene; and $R^{12}$ and $R^{13}$ are each independently lower alkyl, or $R^{12}$ and $R^{13}$ are linked to form lower alkylene.

Examples of "lower alkyl" represented by $R^{12}$ and $R^{13}$ include linear or branched alkylene groups with 1 to 6 carbon atoms, such as methyl, ethyl, and n-propyl. Examples of "lower alkylene" formed by $R^{12}$ and $R^{13}$ when they are linked include alkylene groups with 1 to 4 carbon atoms, such as methylene, ethylene, trimethylene, and tetramethylene.

Examples of "lower alkylene" represented by $X_{B2}$ include alkylene groups with 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, and tetramethylene.

The reaction of the compound of Formula (29) with the compound of Formula (32) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (2) and the compound of Formula (3) shown in Reaction Formula 1 above.

The reaction converting the compound of Formula (33) to the compound of Formula (8a) can be performed by hydrolysis of the compound (33).

This hydrolytic reaction is performed in a suitable solvent or without any solvent, in the presence of an acidic compound.

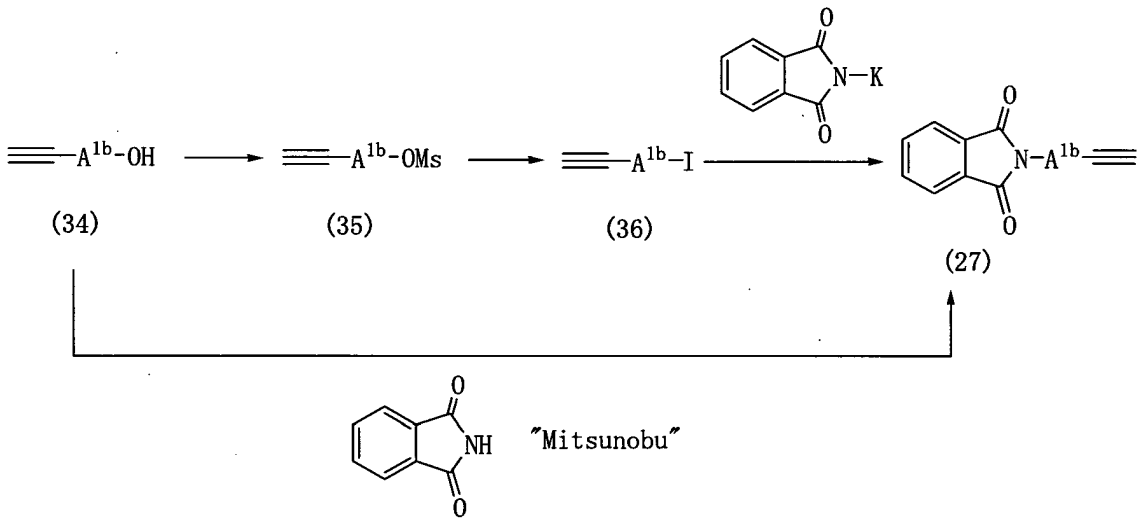
Examples of solvents include water; lower ($C_{1-6}$) alcohols such as methanol, ethanol, isopropanol, and tert-butanol; ketones such as acetone and methyl ethyl ketone; ethers such as diethylether, dioxane, tetrahydrofuran, monoglyme, and diglyme; aliphatic acids such as acetic acid and formic acid; esters such as methyl acetate and ethyl acetate; halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; dimethyl sulfoxide; N,N-dimethylformamide; hexamethylphosphoric triamide; and mixtures

thereof.

Examples of acids include mineral acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid; and organic acids such as formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, pyridinium p-toluenesulfonic acid (PPTS), and like sulfonic acids. These acids may be used singly or in a combination of two or more.

The hydrolytic reaction advantageously proceeds typically at about 0 to about 100°C, and preferably at about 0 to about 80°C. The reaction is typically completed in about 10 minutes to about 30 hours.

Reaction Formula 21




wherein $A^{1b}$ is the same as above; and Ms is methanesulfonyl ($CH_3SO_2$-).

The reaction converting the compound of Formula (34) to the compound of Formula (35) is performed by methanesulfonylation (mesylation) of the compound of Formula (34) using a conventional method. Typically, the compound of Formula (35) can be produced by reacting the compound of Formula (34) with trifluoromethanesulfonic anhydride in a suitable solvent (e.g., dichloromethane), in the presence of a basic compound (e.g., triethylamine).

The reaction converting the compound of Formula (35) to the compound of Formula (36) is performed by iodination of the compound of Formula (35) with an iodinating agent such as sodium iodide, in a suitable solvent (e.g., acetone).

The reaction converting the compound of Formula (36) to the

compound of Formula (27) can be performed by reacting the compound of Formula (36) with potassium phthalimide in a suitable solvent (e.g., N,N-dimethylformamide).

Alternatively, the compound of Formula (27) can be directly produced by reacting the compound of Formula (34) with phthalimide under the Mitsunobu reaction conditions (e.g., using diethyl azodicarboxylate (DEAD) and triphenylphosphine).

The compound of Formula (1) according to the present invention and the starting materials thereof can be produced using a known or conventional synthetic method other than the production method described above.

In addition, compounds in the form in which a solvate (for example, a hydrate, ethanolate, etc.) was added to the starting material compounds and object compounds shown in each of the reaction formulae are included in each of the formulae.

The compound of Formula (1) according to the present invention includes stereoisomers and optical isomers.

The starting material compounds and object compounds represented by each of the reaction formulae can be used in an appropriate salt form.

Each of the object compounds obtained according to the above reaction formulae can be isolated and purified from the reaction mixture by, for example, after cooling the reaction mixture, performing an isolation procedure such as filtration, concentration, extraction, etc., to separate a crude reaction product, and then subjecting the crude reaction product to a general purification procedure such as column chromatography, recrystallization, etc.

Among the compounds of the present invention, those having a basic group or groups can easily form salts with common pharmaceutically acceptable acids. Examples of such acids include hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and other inorganic acids, methansulfonic acid, p-toluenesulfonic acid, acetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, lactic acid and other organic acids, etc.

Among the compounds of the present invention, those having an acidic group or groups can easily form salts by reacting with pharmaceutically acceptable basic compounds. Examples of such basic compounds include sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, etc.

In the compound of the present invention, one or more atoms can be substituted with one or more isotopic atoms. Examples of the isotopic atoms include deuterium ($^{2}H$), tritium ($^{3}H$), $^{13}C$, $^{14}N$, $^{18}O$, etc.

The following is an explanation of pharmaceutical preparations comprising the compound of the present invention as an active ingredient.

Such pharmaceutical preparations are obtained by formulating the compound of the present invention into general pharmaceutical preparations, using typically employed diluents or excipients such as fillers, extenders, binders, wetting agents, disintegrants, surfactants, lubricants, etc.

The form of such pharmaceutical preparations can be selected from various forms according to the purpose of therapy. Typical examples include tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.) and the like.

To form tablets, any of various known carriers can be used, including, for example, lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose and other excipients; water, ethanol, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate, polyvinylpyrrolidone and other binders; dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, aliphatic acid esters of polyoxyethylenesorbitan, sodium laurylsulfate, stearic acid monoglyceride, starch, lactose and other disintegrants; white sugar, stearin, cacao butter, hydrogenated oils and other disintegration inhibitors; quaternary ammonium base, sodium lauryl sulfate and other absorption promoters; glycerin, starch and other wetting agents; starch, lactose, kaolin, bentonite,

colloidal silicic acid and other adsorbents; purified talc, stearates, boric acid powder, polyethylene glycol and other lubricants; etc.

Such tablets may be coated with general coating materials as required, to prepare, for example, sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double- or multi-layered tablets, etc.

To form pills, any of various known carriers can be used, including, for example, glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc and other excipients; gum arabic powder, tragacanth powder, gelatin, ethanol and other binders; laminaran, agar and other disintegrants; etc.

To form suppositories, any of various known carriers can be used, including, for example, polyethylene glycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semisynthetic glycerides, etc.

To form an injection, a solution, emulsion or suspension is sterilized and preferably made isotonic with blood. Any of various known widely used diluents can be employed to prepare the solution, emulsion or suspension. Examples of such diluents include water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, aliphatic acid esters of polyoxyethylene sorbitan, etc. In this case, the pharmaceutical preparation may contain sodium chloride, glucose or glycerin in an amount sufficient to prepare an isotonic solution, and may contain general solubilizers, buffers, analgesic agents, etc., and further, if necessary, coloring agents, preservatives, flavors, sweetening agents, etc., and/or other medicines.

The proportion of the compound of the present invention in the pharmaceutical preparation is not limited and can be suitably selected from a wide range. It is typically preferable that the pharmaceutical preparation contain the compound of the present invention in a proportion of 1 to 70 wt.%.

The route of administration of the pharmaceutical preparation according to the present invention is not limited, and the preparation can be administered by a route suitable for the form of the preparation, the patient's age and sex, the conditions of the

disease, and other conditions.

For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. Injections are intravenously administered singly or as mixed with general injection transfusions such as glucose solutions, amino acid solutions or the like, or singly administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally, as required. Suppositories are administered intrarectally.

The dosage of the pharmaceutical preparation is suitably selected according to the method of use, the patient's age and sex, the severity of the disease, and other conditions, and is typically about 0.001 to about 100 mg/kg body weight/day, and preferably 0.001 to 50 mg/kg body weight/day, in single or divided doses.

Since the dosage varies depending on various conditions, a dosage smaller than the above range may be sufficient, or a dosage larger than the above range may be required.

When administered to the human body as a pharmaceutical, the compound of the present invention may be used concurrently with, or before or after, antithrombotics such as blood clotting inhibitors and antiplatelet agents (e.g., warfarin, aspirin, etc.). Further, the present compound may be used concurrently with, or before or after, drugs for treating chronic diseases, such as antihypertensive drugs (ACE inhibitors, beta blockers, angiotensin II receptor antagonists), heart failure drugs (cardiotonic agents, diuretics), and diabetes treatment agents.

The compound of the present invention has potent blocking effects on human Kv1.5 and/or GIRK1/4 channels, and weak blocking effects on HERG channels. Thus, the compound of the invention has characteristics as an atrial-selective $K^+$ channel-blocking agent.

Therefore, the compound of the invention can be used as a pharmacologically active substance that is safer and provides a more potent effect on the prolongation of the atrial refractory period than conventional antiarrhythmic agents. The compound of the invention is preferably used as a therapeutic agent for arrhythmia such as atrial fibrillation, atrial flutter, and atrial tachycardia (elimination of arrhythmia and/or prevention of the occurrence of arrhythmia). The

compound of the invention is particularly preferably used as a therapeutic agent for atrial fibrillation (defibrillation and maintenance of sinus rhythm). The compound of the invention can also be used as a prophylactic agent for thromboembolism such as cerebral infarction and as a therapeutic agent for heart failure.

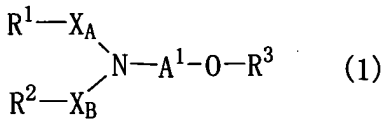
The compound having potent blocking effects on both human Kv1.5 and human GIRK1/4 channels has more potent atrial refractory period prolongation effects and is highly safe, compared to compounds inhibiting either one of the channels. Furthermore, this compound has greater therapeutic effects on atrial fibrillation (defibrillation and maintenance of sinus rhythm) than compounds inhibiting either one of the channels. Therefore, the compound having potent blocking effects on both the human Kv1.5 and human GIRK1/4 channels is particularly useful as a therapeutic agent for arrhythmia such as atrial fibrillation, atrial flutter, and atrial tachycardia (termination of arrhythmia and/or prevention of the occurrence of arrhythmia). This compound is particularly useful as a therapeutic agent for atrial fibrillation (defibrillation and maintenance of sinus rhythm).

2. Second Invention (amino compound)

The present inventors conducted extensive research to develop a compound that blocks the $I_{Kur}$ current (Kv1.5 channel) and/or the $I_{KA}C_h$ current (GIRK1/4 channel) potently and more selectively than other $K^+$ channels. As a result, the inventors found that a novel amino compound represented by General Formula (1) below could be the desired compound. The present invention has been accomplished based on the above findings.

The present invention provides amino compounds, and pharmaceutical compositions comprising the amino compounds as summarized in items 1 to 7 below.

Item 1. An amino compound represented by General Formula (1):



$$\begin{array}{l} R^1-X_A \\ \qquad\quad \diagdown \\ \qquad\quad N-A^1-O-R^3 \\ \qquad\quad \diagup \\ R^2-X_B \end{array} \qquad (1)$$

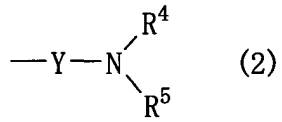
or a salt thereof,

wherein $R^1$ and $R^2$ are each independently hydrogen or organic group; $X_A$ and $X_B$ are each independently a bond, alkylene, alkenylene, -CO-, $-SO_2-$, or -CONH-, wherein each of the alkylene and alkenylene chains can optionally contain one or more substituents selected from the group consisting of -S-, -C(=S)-, $-SO_2-$, -CO-, -O-, -NH-, -CONH- and $-SO_2NH-$, and the hydrogen atom (H) bonded to the nitrogen atom (N) in $X_A$ and $X_B$ is optionally substituted with a substituent selected from the group consisting of lower alkyl, phenyl lower alkyl and phenyl;

$A^1$ is lower alkylene optionally substituted with one or more substituents selected from the group consisting of hydroxyl and oxo;

$R^3$ is (i) a heterocyclic group which is optionally substituted with one or more substituents, or

(ii) an aryl group substituted with one or more substituents selected from the group consisting of oxo, lower alkyl, carboxyl, halo-lower alkyl, lower alkanoyl lower alkyl, phenyl lower alkyl, cyclo lower alkyl, lower alkoxy, halo lower alkoxy, phenyl lower alkoxy, phenoxy, cyano, hydroxyl, halogen, nitro, lower alkyl thio, lower alkanoyl, lower alkoxy carbonyl, lower alkenyl, phenyl, triazolyl, isoxazolyl, imidazolyl, pyrrolyl, benzo[d]oxazolyl, benzo[d]thiazolyl and the group represented by General Formula (2):



(2)

wherein Y is a bond, lower alkylene, or -CO-; $R^4$ and $R^5$ are each independently hydrogen, lower alkyl, cyclo lower alkyl, phenyl, or lower alkanoyl; or $R^4$ and $R^5$ may be linked to form a ring together with the neighboring nitrogen, and the ring may optionally have one or more substituents.

Item 2. A pharmaceutical composition comprising an amino compound represented by Formula (1) or a salt thereof according to Item 1, and a pharmacologically acceptable carrier.

Item 3. A pharmaceutical composition according to Item 1 for preventing and/or treating arrhythmia.

Item 4. An amino compound represented by Formula (1) or a salt thereof according to Item 1 for use in the pharmaceutical

composition.

Item 5. Use of an amino compound represented by Formula (1) or a salt thereof according to Item 1 as a pharmaceutical composition.

Item 6. Use of an amino compound represented by Formula (1) or a salt thereof according to Item 1 for the production of a pharmaceutical composition.

Item 7. A method of preventing and/or treating arrhythmia, comprising administering to a patient an amino compound represented by Formula (1) or a salt thereof according to Item 1.

The groups represented by, or substituents of, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $A^1$, $X_A$, $X_B$ and Y in the specification are described below.

The term "one or more" may be preferably 1 to 6, more preferably 1 to 3.

Examples of "lower alkyl" include linear or branched alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, neopentyl, n-hexyl, isohexyl, and 3-methylpentyl.

Examples of "alkylene" include linear or branched alkylene groups having 1 to 12 carbon atoms, such as the following "lower alkylene", heptamethylene, octamethylene, decamethylene, and dodecamethylene.

Examples of "lower alkylene" include linear or branched alkylene groups having 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, dimethylmethylene, tetramethylene, pentamethylene, and hexamethylene.

Examples of "alkenylene" include linear or branched alkylene groups having 2 to 12 carbon atoms, such as the following "lower alkenylene", heptenylene, octenylene, decenylene, and dodecenylene.

Examples of "lower alkenylene" include linear or branched alkylene groups having 2 to 6 carbon atoms, such as ethenylene, propenylene, butenylene, pentenylene, and hexenylene.

Examples of "lower alkylidene" include linear or branched

alkylidene groups having 1 to 6 carbon atoms, such as methylidene, ethylidene, propylidene, and butylidene.

Examples of "cyclo lower alkyl" include linear or branched cyclo alkyl having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

Examples of "lower alkoxy" include linear or branched alkoxy groups having 1 to 8 carbon atoms , preferably 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, sec-butoxy, n-pentyloxy, neopentyloxy, n-hexyloxy, isohexyloxy, and 3-methylpentyloxy.

Examples of "halogen" include fluorine, chlorine, bromine, and iodine.

Examples of "lower alkylenedioxy" include linear or branched alkylene groups having 1 to 4 carbon atoms, such as methylenedioxy, ethylenedioxy, trimethylenedioxy, and tetramethylenedioxy.

Examples of "lower alkanoyl" include linear or branched alkanoyl groups having 1 to 6 carbon atoms, such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, and hexanoyl.

Examples of "lower alkoxycarbonyl" include (linear or branched alkoxy having 1 to 6 carbon atoms)carbonyls, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, and tert-butoxycarbonyl.

Examples of "aralkyl group" include lower alkyl group substituted with one or more aryl groups, such as benzyl and phenethyl.

Examples of "organic group" include lower alkyl, lower alkoxy, cyclo lower alkyl, amino, lower alkyl thio, aryl, and heterocyclic group, each of which is optionally substituted.

Examples of "aryl group" include monocyclic or polycyclic aryl groups, such as phenyl, tolyl, xylyl, naphthyl and tetrahydronaphthyl, indenyl, and dihydroindenyl.

Examples of "heterocyclic group" include saturated or unsaturated monocyclic or polycyclic heterocyclic groups containing at least one hetero atom selected from the group consisting of oxygen, sulfur and nitrogen. More preferable examples of heterocyclic groups

include the following (a) to (o):

(a) unsaturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.;

(b) saturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atom(s), for example, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidyl, pyrazolidinyl, piperazinyl, 1,4-diazepanyl, etc.;

(c) saturated or unsaturated condensed 7- to 14-membered heterocyclic groups containing 1 to 5 nitrogen atom(s), for example, decahydroquinolyl, indolyl, dihydroindolyl (e.g., 2,3-dihydroindolyl, etc.), isoindolyl, indolizinyl, benzimidazolyl, dihydrobenzimidazolyl (e.g., 2,3-dihydro-1H-benzo[d]imidazolyl, etc.), quinolyl, dihydroquinolyl (e.g. 1,4-dihydroquinolyl, 1,2-dihydroquinolyl, etc.), tetrahydroquinolyl (1,2,3,4-tetrahydroquinolyl, etc.), isoquinolyl, dihydroisoquinolyl (e.g., 3,4-dihydro-1H-isoquinolyl, 1,2-dihydroisoquinolyl, etc.), tetrahydroisoquinolyl (e.g., 1,2,3,4-tetrahydro-1H-isoquinolyl, 5,6,7,8-tetrahydroisoquinolyl, etc.), carbostyril, dihydrocarbostyril (e.g., 3,4-dihydrocarbostyril, etc.), indazolyl, benzotriazolyl (e.g. benzo[d][1,2,3]triazolyl, etc.), tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, imidazopyridyl (e.g., imidazo[1,2-a]pyridyl, imidazo[4,5-c]pyridyl, etc.,), naphthyridinyl, cinnolinyl, quinoxalinyl, quinazolinyl, pyrazolopyridyl (e.g., pyrazolo[2,3-a]pyridyl, etc.) tetrahydropyridoindolyl (e.g., 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indolyl, etc.), etc.;

(d) saturated or unsaturated 3- to 8-membered, preferably 5- or 6- membered heteromonocyclic groups containing 1 to 2 oxygen atom(s), for example, furyl, tetrahydropyranyl (e.g.,

tetrahydro-2H-pyranyl, etc.), tetrahydrofuryl, etc.;

(e) unsaturated condensed 7- to 12-membered heterocyclic groups containing 1 to 3 oxygen atom(s), for example, benzofuryl, dihydrobenzofuryl (e.g. 2,3-dihydrobenzo[b]furyl, etc.), chromanyl, benzodioxanyl (e.g., 1,4-benzodioxanyl, etc.), benzodioxolyl (benzo[1,3]dioxolyl, etc.), etc.;

(f) unsaturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

(g) saturated 3- to 8-membered, preferably 5- or 6- membered heteromonocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, etc.;

(h) unsaturated condensed 7- to 12-membered heterocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, benzisoxazolyl, dihydrobenzoxazinyl (e.g., 2,3-dihydrobenz-1,4-oxazinyl, etc.), furopyridyl (e.g., furo[2,3-c]pyridyl, 6,7-dihydrofuro[2,3-c]pyridyl, furo[3,2-c]pyridyl, 4,5-dihydrofuro[3,2-c]pyridyl, furo[2,3-b]pyridyl, 6,7-dihydrofuro[2,3-b]pyridyl, etc.), furopyrrolyl (e.g., furo[3,2-b]pyrrolyl etc.) etc.;

(i) unsaturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5- thiadiazolyl, 1,2,3-thiadiazolyl, etc.), isothiazolyl, etc.;

(j) saturated 3- to 8-membered, preferably 5- or 6- membered heteromonocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

(k) unsaturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing a sulfur atom, for example, thienyl, etc.;

(l) unsaturated condensed 7- to 12-membered heterocyclic

groups containing 1 to 3 sulfur atom(s), for example, benzothienyl (e.g. benzo[b]thienyl), etc.;

(m) unsaturated condensed 7-to 12-membered heterocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzo[d]isothiazolyl, 2,3-dihydro benzo[d]isothiazolyl, benzothiadiazolyl, thienopyridyl (e.g., thieno[2,3-c]pyridyl, 6,7-dihydrothieno[2,3-c]pyridyl, thieno[3,2-c]pyridyl, 4,5-dihydrothieno[3,2-c]pyridyl, thieno[2,3-b]pyridyl, 6,7-dihydrothieno[2,3-b]pyridyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridyl, etc.), imidazothiazolyl (e.g., imidazo[2,1-b]thiazolyl, etc.), dihydroimidazothiazolyl (e.g., 2,3-dihydroimidazo[2,1-b]thiazolyl, etc.), thienopyrazinyl (e.g., thieno[2,3-b]pyrazinyl, etc.), etc.;

(n) saturated or unsaturated 7- to 12-membered heterocyclic spiro groups containing 1 to 2 nitrogen atom(s), for example, azaspiroundecanyl (e.g., 3-azaspiro[5.5]undecanyl), etc.; and

(o) saturated 7- to 12-membered hetero bicyclic groups containing 1 to 3 nitrogen atom(s), for example, azabicyclooctanyl (e.g., (1R,5S)-8-azabicyclo[3.2.1]octanyl), etc;

wherein said heterocyclic group may be substituted by one or more suitable substituents.

Substituents of "aryl group which is optionally substituted" represented by $R^1$ and $R^2$ are each independently one or more substituents selected from the group consisting of:

(a1) cyano;

(a2) hydroxyl;

(a3) halogen;

(a4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, halogen, hydroxyl, imidazolyl, morpholinyl, triazolyl and phenyl;

(a5) lower alkoxy optionally substituted with one or more substituents selected from the group consisting of halogen, amino, lower alkyl amino and phenyl;

(a6) pyridyl;

(a7) thienyl;

(a8) piperazinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and halo phenyl lower alkyl;

(a9) phenyl;

(a10) pyrazolyl optionally substituted with one or more lower alkyl;

(a11) pyrimidinyl optionally substituted with one or more lower alkyls;

(a12) piperidyl optionally substituted with one or more lower alkyls;

(a13) furyl;

(a14) carboxy;

(a15) lower alkoxycarbonyl;

(a16) amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, phenyl, lower alkanoyl and lower alkylsulfonyl;

(a17) lower alkylthio;

(a18) triazolyl;

(a19) imidazolyl;

(a20) pyrrolidinyl optionally substituted with one or more oxos;

(a21) lower alkylsulfonyl;

(a22) lower alkylenedioxy optionally substituted with one or more halogens;

(a23) nitro;

(a24) oxazolyl;

(a25) thiazolyl optionally substituted with one or more lower alkyls;

(a26) lower alkanoyl;

(a27) sulfo;

(a28) carbamoyl optionally substituted with one or two lower alkyls;

(a29) phenoxy;

(a30) isoxazolyl;

(a31) pyrrolyl;

(a32) lower alkenyl;

(a33) cyclo lower alkyl;

(a34) benzo[d]oxazolyl; and

(a35) oxo.

Substituents of "heterocyclic group which is optionally substituted" represented by $R^1$ and $R^2$ are each independently one or

more substituents selected from the group consisting of:

(h1) oxo;

(h2) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, phenyl amino, cyclo lower alkyl, lower alkoxy, pyridyl, mono- or di-lower alkyl amino, hydroxyl, lower alkyl substituted isoxazolyl, 1,3-dioxolanyl, lower alkyl substituted piperidinyl, mono or di lower alkyl amino, fulyl, imidazolyl, morpholinyl, lower alkyl substituted 1,4-diazepanyl, phenyl thiazolyl, phenyl lower alkyl tetrazolyl, lower alkyl tetrazolyl, quinolyl, pyrrolyl, imidazolyl, 2,3-dihydrobenzofuryl and benzodioxolyl;

(h3) cyclo lower alkyl;

(h4) lower alkoxy optionally substituted with one or more substituents selected from the group consisting of pyridyl, halo-lower alkoxy pheny, halo phenyl, phenyl, and halo-lower alkyl phenyl;

(h5) aryl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halo-lower alkyl, lower alkoxy, halo lower alkoxy, lower alkanoyl, hydroxyl, halogen, carboxy, lower alkoxycarbonyl, amino, lower alkyl amino, and cyano;

(h6) aralkyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halo-lower alkyl, lower alkoxy, halo-lower alkoxy, lower alkanoyl, hydroxyl, halogen, carboxy, lower alkoxycarbonyl, amino, lower alkyl amino, cyano, phenyl, and oxo, on the aryl and/or lower alkyl group of aralkyl;

(h7) heterocyclic group optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, hydroxyl, halogen, carboxy, lower alkoxycarbonyl, amino, lower alkyl amino, cyano, phenyl, and oxo;

(h8) hydroxyl;

(h9) halogen;

(h10) carboxy;

(h11) lower alkanoyl;

(h12) lower alkoxycarbonyl;

(h13) lower alkylenedioxy;

(h14) cyano;

(h15) nitro;

(h16) sulfo;

(h17) amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, mono- or di-lower alkyl amino lower alkyl, (lower alkyl)(phenyl) amino lower alkyl, lower alkyl substituted phenoxy lower alkyl, phenyl lower alkyl, cyclo lower alkyl lower alkyl, lower alkyoxy phenyl lower alkyl, lower alkyl phenyl lower alkyl, triazolyl lower alkyl, halo substituted phenyl, halo-lower alkyl substituted phenyl, halo-lower alkoxy substituted phenyl, piperazinyl lower alkyl carbonyl, phenyl lower alkyl carbonyl and lower alkoxy dihydroindenyl;

(h18) lower alkylthio;

(h19) lower alkylsulfonyl;

(h20) lower alkenyl optionally substituted with one or more phenyls;

(h21) benzo[d][1,3]dioxolyl carbonyl;

(h22) 2,3-dihydroindenyl;

(h23) phenoxy substituted with one or more substituents selected from the group consisting of halo-lower alkoxy and halogen;

(h24) lower alkylidene substituted with one or more lower alkoxy phenyls;

Substituents of "lower alkyl group which is optionally substituted" represented by $R^1$ and $R^2$ are each independently one or more substituents selected from the group consisting of oxo and phenyl.

Substituents of "cyclo lower alkyl group which is optionally substituted" represented by $R^1$ and $R^2$ are each independently one or more substituents selected from the group consisting of lower alkyl phenyl and phenyl.

Substituents of "amino group which is optionally substituted" represented by $R^1$ and $R^2$ are each independently one or more substituents selected from the group consisting of of lower alkyl, lower alkanoyl, and phenyl lower alkyl.

Substituents of "dihydroindenyl group which is optionally substituted" represented by $R^1$ and $R^2$ are each independently one or more oxos.

Preferable substituents represented by $R^1$ and $R^2$ are each independently selected from the group consisiting of the following

substituents (1) to (69):

(1) hydrogen;

(2) lower alkyl optionally substituted with one or more substituents selected from the group consisting of oxo and phenyl;

(3) cyclo lower alkyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl phenyl and phenyl;

(4) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4-1) to (4-25):

(4-1) cyano;

(4-2) hydroxyl;

(4-3) halogen;

(4-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, imidazolyl, hydroxyl, triazolyl (e.g, 1,2,4-triazolyl) and morpholinyl;

(4-5) lower alkoxy optionally substituted with one or more substituents selected from the group consisting of amino and lower alkyl amino;

(4-6) pyridyl;

(4-7) thienyl;

(4-8) piperazinyl optionally substituted with one or more lower alkyls;

(4-9) phenyl;

(4-10) pyrazolyl optionally substituted with one or more lower alkyls;

(4-11) pyrimidinyl optionally substituted with one or more lower alkyls;

(4-12) piperidyl optionally substituted with one or more lower alkyls;

(4-13) furyl;

(4-14) carboxy;

(4-15) lower alkoxycarbonyl;

(4-16) amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl and lower alkylsulfonyl;

(4-17) lower alkylthio;

(4-18) triazolyl;

(4-19) imidazolyl;

(4-20) pyrrolidinyl optionally substituted with one or more oxos;

(4-21) lower alkylsulfonyl;

(4-22) lower alkylenedioxy optionally substituted with one or more halogens;

(4-23) nitro;

(4-24) oxazolyl;

(4-25) thiazolyl optionally substituted with one or more lower alkyls;

(4-26) phenoxy; and

(4-27) carbamoyl optionally substituted with one or two lower alkyls;

(5) naphthyl;

(6) furyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, carboxy, sulfo, pyridyloxy, lower alkoxycarbonyl, and phenyl;

(7) thienyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylenedioxy, carboxy, halogen, pyridyl, lower alkoxy, lower alkoxycarbonyl, oxazolyl, and furyl;

(8) imidazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl, and halogen;

(9) pyrazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, halogen, phenyl optionally substituted with lower alkoxy, furyl, and thienyl;

(10) oxazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl;

(11) isoxazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl, thienyl, and furyl;

(12) thiazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with lower alkoxy, phenyl, and lower alkanoylamino;

(13) pyrrolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and lower alkoxycarbonyl;

(14) triazolyl optionally substituted with one or more lower alkyls;

(15) pyridyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, oxo, hydroxyl, lower alkoxy, halogen, pyrrolidinyl, morpholinyl, thienyl, piperazinyl lower alkyl carbonyl amino;

(16) pyrimidinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl;

(17) pyridazinyl;

(18) pyrazinyl;

(19) imidazo[2,1-b]thiazolyl optionally substituted with one or more halogens;

(20) thieno[2,3-b]pyrazinyl;

(21) 2,3-dihydroimidazo[2,1-b]thiazolyl optionally substituted with one or more phenyls;

(22) benzothiazolyl optionally substituted with one or more lower alkyls;

(23) indolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl, and halogen;

(24) imidazo[1,2-a]pyridyl optionally substituted with one or more lower alkyls;

(25) benzothienyl optionally substituted with one or more lower alkyls;

(26) benzimidazolyl optionally substituted with one or more lower alkyls;

(27) 2,3-dihydrobenzo[b]furyl;

(28) benzofuryl optionally substituted with one or more halogens;

(29) indazolyl optionally substituted with one or more lower alkyls;

(30) furo[2,3-c]pyridyl or 6,7-dihydrofuro[2,3-c]pyridyl, each of wich is optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(31) furo[3,2-c]pyridyl or 4,5-dihydrofuro[3,2-c]pyridyl, each of

wich is optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl optionally substituted with halogen, halogen, furyl, pyridyl, and phenyl optionally substituted with one or more substituents selected from the group consisting of amino and lower alkoxy;

(32) thieno[2,3-c]pyridyl or 6,7-dihydrothieno[2,3-c]pyridyl, each of wich is optionally substituted with one or more substituents selected from the group consisting of oxo group and lower alkyl;

(33) thieno[3,2-c]pyridyl or 4,5-dihydrothieno[3,2-c]pyridyl, each of wich is optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(34) thieno[2,3-b]pyridyl;

(35) benzo[1,3]dioxolyl optionally substituted with one or more halogens;

(36) benzisoxazolyl;

(37) pyrazolo[2,3-a]pyridyl;

(38) indolizinyl;

(39) 2,3-dihydroindolyl optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl, and lower alkanoyl;

(40) isoquinolyl or 1,2-dihydroisoquinolyl, each of wich is optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halogen, lower alkoxy and oxo;

(41) 1,2,3,4-tetrahydroisoquinolyl optionally substituted with one or more oxos;

(42) 1,2-dihydroquinolyl optionally substituted with one or more substituents selected from the group consisting of lower alkoxy and oxo;

(43) 1,2,3,4-tetrahydroquinolyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkoxy;

(44) quinolyl optionally substituted with one or more substituents selected from the group consisting of amino optionally substituted with one or two lower alkyl, lower alkoxy, lower alkyl, and oxo;

(45) chromanyl optionally substituted with one or more lower alkyls;

(46) 5,6,7,8-tetrahydroisoquinolyl optionally substituted with one

or more oxos;

(47) 3,4-dihydroisoquinolyl optionally substituted with one or more oxos;

(48) naphthyridinyl;

(49) 1,4-benzodioxanyl;

(50) cinnolinyl;

(51) quinoxalinyl;

(52) 2,3-dihydrobenz-1,4-oxazinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo;

(53) 2,3-dihydroindenyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkoxy;

(54) amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl and phenyl lower alkyl;

(55) lower alkoxy;

(56) lower alkylthio;

(57) decahydroquinolyl;

(58) piperazinyl optionally substituted with one or more substituents selected from the group consisting of

(58-1) lower alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkoxy, 1,3-dioxolanyl, lower alkyl-substituted piperidyl, furyl, imidazolyl, phenyl amino, phenyl-substituted thiazolyl, phenyl lower alkyl-substituted tetrazolyl, lower alkyl-substituted tetrazolyl, quinolyl, pyrrolyl, mono- or di-lower alkyl amino, pyridyl and benzo[d][1,3]dioxolyl;

(58-2) oxo;

(58-3) halo-lower alkyl substituted phenyl amino;

(58-4) cyclo lower alkyl;

(58-5) 2,3-dihydroindenyl;

(58-6) phenyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halo-lower alkyl and halo-lower alkoxy; and

(58-7) phenyl lower alkyl optionally substituted with one or more

substituents selected from the group consisting of halogen, halo-lower alkyl, halo-lower alkoxy and pyridyl, on the benzene ring and/or lower alkyl of phenyl lower alkyl;

(59) 1,4-diazepanyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, pyridyl and morpholinyl lower alkyl;

(60) piperidyl optionally substituted with one or more substituents selected from the group consisting of:

(60-1) lower alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, mono- or di-lower alkylamino, 2,3-dihydrobenzofuryl and imidazolyl;

(60-2) amino optionally substituted with one or two substituents selected from the group consisting of lower alkyl, halo-phenyl, halo-lower alkoxy-substituted phenyl, mono- or di-lower alkyl amino lower alkyl, lower alkyl-substituted phenoxy lower alkyl, phenyl lower alkyl, phenyl lower alkyl carbonyl, cyclo lower alkyl lower alkyl, lower alkoxy phenyl lower alkyl, 1,2,4-triazolyl lower alkyl, pyridyl phenyl, (phenyl)(lower alkyl)amino lower alkyl, lower alkoxy-substituted 2,3-dihydro-1H-indenyl and lower alkyl phenyl lower alkyl;

(60-3) lower alkoxy optionally substituted with one or more substituents selected from the group consisting of phenyl, halo-phenyl, halo-lower alkoxy-substituted phenyl, halo-lower alkyl substituted phenyl and pyridyl;

(60-4) phenoxy optionally substituted with one or more substituents selected from the group consisting of halogen, and halo-lower alkoxy;

(60-5) phenyl lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, oxo, lower alkoxy and amino, on the benzene ring and/or lower alkyl of phenyl lower alkyl;

(60-6) lower alkoxy phenyl lower alkylidene;

(60-7) phenyl imidazolyl;

(60-8) phenyl morpholinyl; and

(60-9) phenyl;

(61) morpholinyl optionally substituted with one or more mono- or di-lower alkyl amino-substituted piperidyl lower alkyls;

(62) benzo[d][1,2,3]triazolyl optionally substituted with one or more lower alkyls;

(63) 4,5,6,7-tetrahydrothieno [2,3-c]pyridyl;

(64) 2,3,4,9-tetrahydropyrido[3,4-b]indolyl);

(65) 3-azaspiro[5,5]undecanyl;

(66) 8-azabicyclo[3,2,1]octanyl;

(67) tetrahydro-2H-pyranyl;

(68) furo[3,2-b]pyrrolyl optionally substituted with one or more lower alkyls; and

(69) tetrahydrofuryl.

Preferable examples of "aryl group which is optionally substituted" for $R^1$ and $R^2$ include the substituents (4), (5) and (53).

Preferable examples of "heterocyclic group which is optionally substituted" for $R^1$ and $R^2$ include the substituents (6) to (52) and (57) to (69).

Examples of $X_A$ and $X_B$ include a bond, lower alkylene, lower alkenylene, -CO-, -$SO_2$-, -lower alkylene-$SO_2$-, -lower alkylene-CO-, -lower alkenylene-CO-, -lower alkylene-CO-N(lower alkyl)-lower alkylene-, -N(lower alkyl)-lower alkylene-, -CO-N(lower alkyl)-lower alkylene-, -O-lower alkylene-, -N(phenyl lower alkyl)-lower alkylene-, -CO-lower alkylene-CO-, -CO-NH-lower alkylene-, -lower alkylene-N(lower alkyl)-lower alkylene-, -lower alkylene-N(lower alkyl)-lower alkylene-O-, -lower alkylene-NH-lower alkylene-, -lower alkylene-$SO_2$-NH-lower alkylene-, -N(lower alkyl)-CO-lower alkylene-, -N(lower alkyl)-lower alkylene-CO-, -N(lower alkyl)-lower alkylene-N(lower alkyl)-lower alkylene-, -N(phenyl)-lower alkylene-CO-, -NH-CO-, -NH-CO-lower alkylene-, -NH-lower alkylene-, -O-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -O-lower alkylene-CO-, -NH-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -S-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -$SO_2$-N(lower alkyl)-lower alkylene-, -$SO_2$-NH-lower alkylene-, -lower alkenylene-CO-N(lower alkyl)-lower alkylene-, -N(phenyl)-lower alkylene-CO-N(lower alkyl)-lower alkylene-, and -CO-lower

alkylene-O-CO-.

Either of the two bonds in $X_A$ may be bonded to $R^1$ or N, and either of the two bonds in $X_B$ may be bonded to $R^2$ or N.

Examples of "lower alkylene optionally substituted with one or more substituents selected from the group consisting of hydroxyl and oxo" represented by $A^1$ are $C_{1-6}$ alkylene and -CO-$C_{1-6}$ alkylene-.

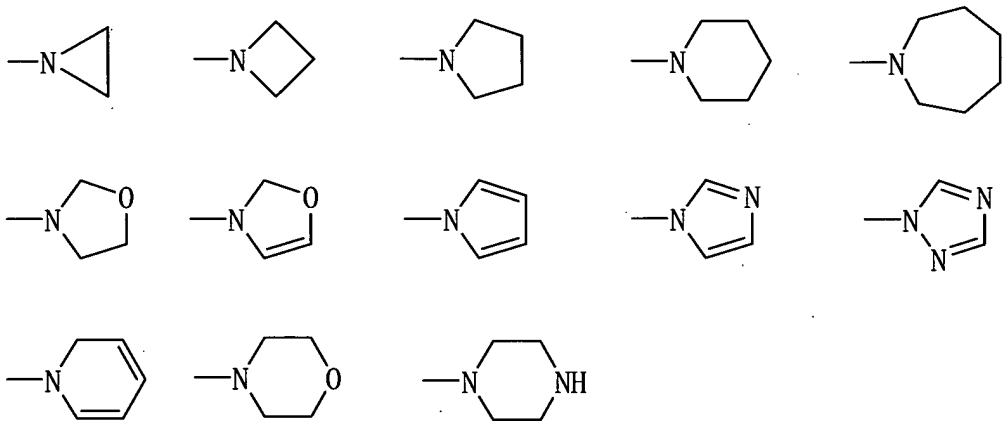
Examples of heterocyclic groups of "heterocyclic group which is optionally substituted" represented by $R^3$ include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydroquinolyl, isoquinolyl, 1,2-dihydroisoquinolyl, 1,2,3,4-tetrahydroisoquinolyl, quinazolinyl, 1,2,3,4-tetrahydroquinazolinyl, quinoxalinyl, 1,2,3,4-tetrahydroquinoxalinyl, indolyl, 2,3-dihydroindolyl, isoindolyl, 1,3-dihydroisoindolyl, benzimidazolyl, 2,3-dihydrobenzimidazolyl, benzo[d]isothiazolyl, 2,3-dihydrobenzo[d]isothiazolyl, 2,3,4,5-tetrahydrobenz[f]1,4-thiazepinyl, 1,7-naphthyridinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, benzo[d][1,3]dioxolyl, benzo[d]thiazolyl, benzo[d][1,3]oxathiolyl, 2H-chromenyl, 2H-pyranyl, benzofuryl, 3,4-dihydro-2H-benzo[b][1,4]thiazinyl, 2,3,4,5-tetrahydrobenzo[e][1,4]diazepinyl, 2,3,4,5-tetrahydrobenzo[b]azepinyl, 2,3-dihydrobenzo[d]thiazolyl, 2,3-dihydrobenzo[d]oxazolyl, 2,3,4,5-tetrahydrobenzo[c]azepinyl, 2,3,4,5-tetrahydrobenzo[b][1,4]thiazepinyl, benzo[d]oxazolyl, benzo[d]isoxazolyl, benzo[c][1,2,5]oxadiazolyl, 2H-pyranyl, 3,4-dihydroisoquinolyl, 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepinyl, 1,2,3,5-tetrahydrobenzo[e][1,4]oxazepinyl, 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepinyl, dibenzo[b,d]furyl, 9H-carbazolyl, benzo[c][1,2,5]oxadiazolyl, 1,2,3,4,5,6-hexahydrobenzo[b]azocinyl, 2,3-dihydrobenzofuryl, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 2,4-dihydro-1H-benzo[d][1,3]oxazinyl, and benzo[b]thiophenyl.

Examples of substituents of "substituted heterocyclic

group" represented by $R^3$ include the substituents (h1) to (h17) and (h20) to (h24), which are mentioned as substituents of heterocyclic groups represented by $R^1$ and $R^2$. Among these, preferable substituents are (h1), (h2), (h5), (h6), (h8), (h10), (h11), (h12) and (h20), and more preferable substituents are (h1) and/or (h2).

Examples of aryl groups of "ary group which is substituted" represented by $R^3$ include those as defined above.

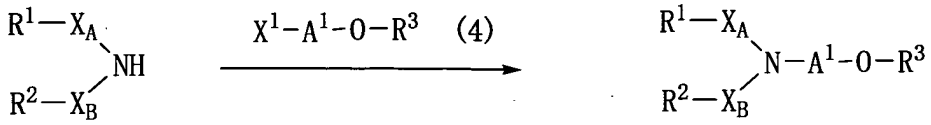
When $R^4$ and $R^5$ in General Formula (2) are linked to form a ring together with the neighboring nitrogen, examples of the group $-N\ R^4R^5$ include the following:



Each of the ring may optionally have one or more substituents selected from the group consisting of oxo; lower alkyl; phenyl lower alkyl; halo-phenyl lower alkyl; and amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, phenyl and halo-phenyl.

The amino compound of the present invention represented by General Formula (1) or its salt can be readily produced by persons skilled in the art using technical knowledge, based on the Examples and Reference Examples of the present specification. For example, the amino compound or its salt can be produced according to the processes shown in the following reaction formulae.

Reaction Formula 1:



(3) (1)

wherein $R^1$, $R^2$, $R^3$, $X_A$, $X_B$ and $A^1$ are the same as above; and $X^1$ is a leaving group.

The reaction of the compound of Formula (3) with the compound of Formula (4) can be performed in a general inert solvent or without using any solvent, in the presence or absence of a basic compound.

Examples of the leaving groups represented by $X^1$ include halogen atoms (e.g., chlorine, bromine, iodine, and like atoms), lower alkane sulfonyloxy (e.g., methanesulfonyloxy), halo substituted lower alkane sulfonyloxy (e.g., trifluoromethanesulfonyloxy), arylene sulfonyloxy (e.g., p-toluenesulfonyloxy, benzenesulfonyloxy), etc.

Examples of inert solvents include water; ethers such as dioxane, tetrahydrofuran, diethylether, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; lower ($C_{1-6}$) alcohols such as methanol, ethanol, and isopropanol; ketones such as acetone and methyl ethyl ketone; polar solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile; and mixtures thereof.

A wide variety of known basic compounds can be used as the basic compound. Examples of usable basic compounds include inorganic bases, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, cesium hydroxide, and lithium hydroxide; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate, lithium hydrogencarbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; alkali metals such as sodium and potassium; sodium amide; sodium hydride; and potassium hydride; and organic bases, for example, alkali metal alcoholates such as sodium methoxide, sodium ethoxide, potassium

methoxide, and potassium ethoxide; triethylamine, tripropylamine, pyridine, quinoline, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU), and 1,4-diazabicyclo[2.2.2]octane (DABCO). These basic compounds can be used singly or in a combination of two or more.

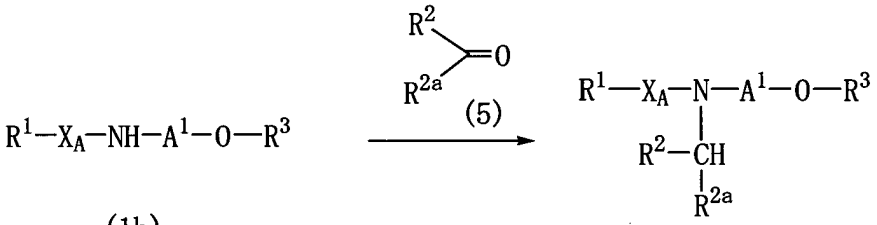
The above reaction may be performed by adding as a reaction accelerator an alkali metal iodide such as potassium iodide or sodium iodide to the reaction system, as required.

The compound of Formula (4) is typically used in an amount of at least 0.5 moles, and preferably about 0.5 to about 10 moles, per mole of the compound of Formula (3).

The amount of basic compound is typically 0.5 to 10 moles, and preferably 0.5 to 6 moles, per mole of the compound of Formula (3).

The reaction is typically performed at a temperature of 0 to 250°C, and preferably 0 to 200°C, and is typically completed in about 1 to about 80 hours.

Reaction Formula 2



(1b) (1a)

wherein $R^1$, $R^2$, $R^3$, $X_A$ and $A^1$ are the same as above; and $R^{2a}$ is hydrogen or lower alkyl.

Examples of lower alkyl groups represented by $R^{2a}$ include linear or branched alkyl groups with 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, and isopropyl.

The reaction between the compound of Formula (1b) and the compound of Formula (5) is performed, for example, in an inert solvent or suitable solvent, in the presence of a reducing agent.

Examples of usable solvents include water; lower ($C_{1-6}$) alcohols such as methanol, ethanol, isopropanol, butanol,

tert-butanol, and ethylene glycol; aliphatic acids such as acetonitrile, formic acid, and acetic acid; ethers such as diethylether, tetrahydrofuran, dioxane, monoglyme, and diglyme; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; and mixtures thereof.

Examples of reducing agents include aliphatic acids such as formic acid; aliphatic acid alkali metal salts such as sodium formate; hydride reducing agents such as sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, sodium trimethoxyborohydride, and lithium aluminium hydride; and mixtures thereof, or mixtures of aliphatic acids or aliphatic acid alkali metal salts and hydride reducing agents; and catalytic hydrogenation reducing agents such as palladium black, palladium carbon, platinum oxide, platinum black, and Raney nickel.

When an aliphatic acid such as formic acid, or an aliphatic acid alkali metal salt such as sodium formate is used as a reducing agent, a suitable reaction temperature is typically about room temperature to about 200°C, and preferably about 50 to about 150°C. The reaction is typically completed in about 10 minutes to about 10 hours. Preferably, the aliphatic acid or aliphatic acid alkali metal salt is used in large excess relative to the compound of Formula (1b).

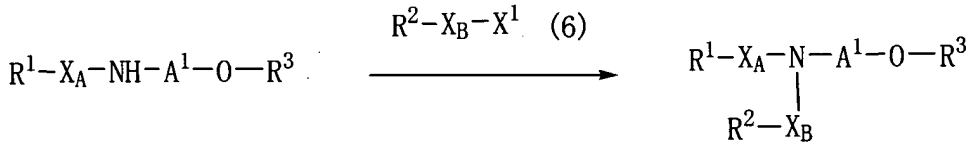
When a hydride reducing agent is used, a suitable reaction temperature is typically about -80 to about 100°C, and preferably about -80 to about 70°C. The reaction is typically completed in about 30 minutes to about 60 hours. The hydride reducing agent is typically used in an amount of about 1 to about 20 moles, and preferably about 1 to about 10 moles, per mole of the compound of Formula (1b). Particularly when lithium aluminium hydride is used as a hydride reducing agent, it is preferable to use as a solvent an ether such as diethyl ether, tetrahydrofuran, dioxane, monoglyme, and diglyme; or an aromatic hydrocarbon such as benzene, toluene, or xylene. To the reaction system of the reaction may be added an amine such as trimethylamine, triethylamine, or N-ethyldiisopropylamine; or a molecular sieve such as molecular sieve 3A (MS-3A) or molecular sieve 4A (MS-4A).

When a catalytic hydrogenation reducing agent is used, the reaction is typically performed at about -30 to about 100°C, and preferably about 0 to about 60°C, in a hydrogen atmosphere at typically about atmospheric pressure to about 20 atm, and preferably at about atmospheric pressure to about 10 atm, or in the presence of a hydrogen doner such as formic acid, ammonium formate, cyclohexene, or hydrazine hydrate. The reaction is typically completed in about 1 to about 12 hours. The catalytic hydrogenation reducing agent is typically used in an amount of about 0.1 to about 40 wt%, and preferably about 1 to about 20 wt%, based on the compound of Formula (1b).

In the reaction of the compound of Formula (1b) and the compound of Formula (5), the compound of Formula (5) is typically used in an amount of at least 1 mole, and preferably 1 to 5 moles, per mole of the compound of Formula (1b).

The compound of Formula (5) may also be a hydrated compound wherein a water molecule is attached to a carbonyl group.

Reaction Formula 3



(1b) (1c)

wherein $R^1$, $R^2$, $R^3$, $X_A$, $X_B$, $A^1$ and $X^1$ are the same as above.

The reaction of the compound of Formula (1b) with the compound of Formula (6) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (3) with the compound of Formula (4) shown in Reaction Formula 1 above.

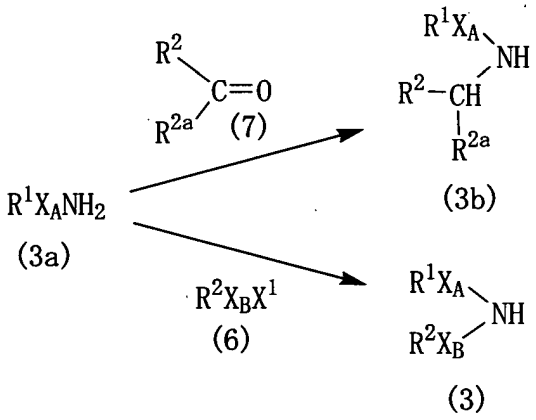
Alternatively, the reaction of the compound of Formula (1b) with the compound of Formula (6) can be performed by the known "Ullmann condensation", "Palladium coupling reaction", etc. The reaction can be preferably adopted especially when $X_B$ is a bond and $R^2$ is aryl or heterocyclic (especially unsaturated heterocyclic) group optionally substituted. For example, the reaction can be carried out in a solvent (e.g., toluene, tetrahydrofuran(THF), N,N-dimethylformamide(DMF),

N-methylpyrrolidone(NMP) and dimethyl sulfoxide(DMSO)), in the presence of transition metal compound (e.g., $Pd(OAc)_2$, $Pd_2(dba)_3$ and copper iodide), a basic compound (e.g., sodium tert-butoxide, $K_3PO_4$ and $Cs_2CO_3$), and if necessary a phosphine (e.g., xantphos, tri-tert-butylphosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl(BINAP), tetrafluoroborate, N,N'-dimethylethylenediamine, and L-proline).

The reaction temperature is not limited, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The compound of Formula (3), which is used as a starting material, can be easily prepared by the process shown in the following reaction formula.

Reaction Formula 4

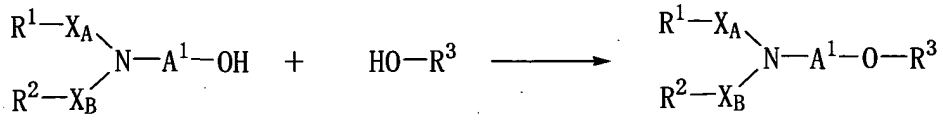



wherein $R^1$, $R^2$, $R^{2a}$, $X_A$, $X_B$ and $X^1$ are the same as above.

The reaction of the compound of Formula (3a) with the compound of Formula (7) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (1b) with the compound of Formula (5) shown in Reaction Formula 2 above.

The reaction of the compound of Formula (3a) with the compound of Formula (6) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (3) with the compound of Formula (4) shown in Reaction Formula 1 above.

Reaction Formula 5

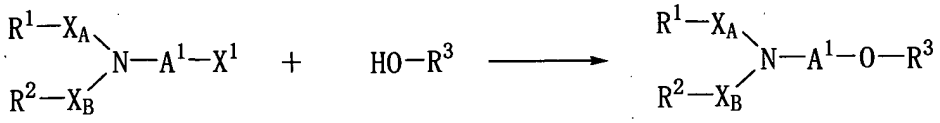


(8) (9) (1)

wherein $R^1$, $R^2$, $R^3$, $X_A$, $X_B$ and $A^1$ are the same as above.

The reaction of the compound of Formula (8) with the compound of Formula (9) can be performed by the known "Mitsunobu reaction" conditions (e.g., using diethyl azodicarboxylate (DEAD) and triphenylphosphine).

Reaction Formula 6



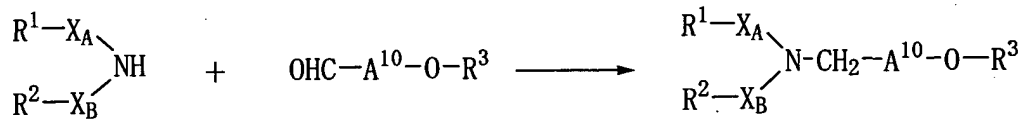
(10) (9) (1)

wherein $R^1$, $R^2$, $R^3$, $X_A$, $X_B$, $X^1$ and $A^1$ are the same as above.

The reaction of the compound of Formula (10) with the compound of Formula (9) can be performed by the known O-alkylation reaction. For example, The reaction can be performed in the presence of an inert solvent (e.g., DMF, THF, dioxane and acetonitrile) and in the presence of a basic compound (e.g., $K_2CO_3$ and $Cs_2CO_3$).

The reaction temperature is not limited, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Reaction Formula 7

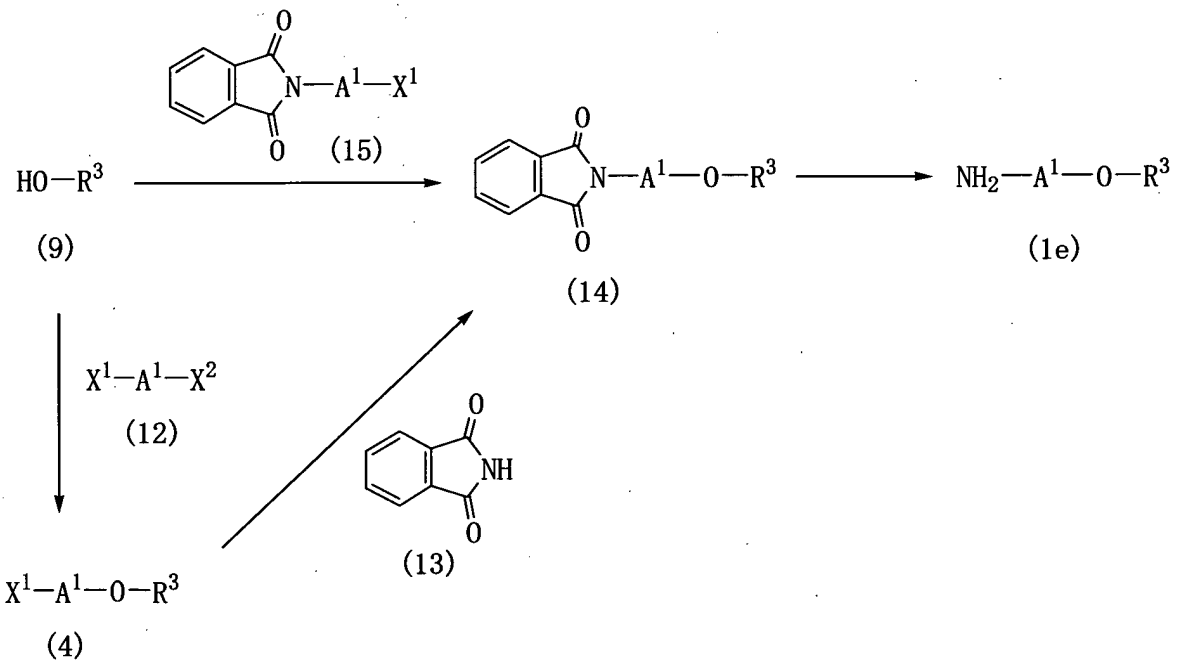


(3) (11) (1d)

wherein $R^1$, $R^2$, $R^3$, $X_A$ and $X_B$ are the same as above; and $A^{10}$ is a divalent residue which is obtained by removing $-CH_2-$ from group $A^1$.

The reaction of the compound of Formula (3) with the compound of Formula (11) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (1b) with the compound of Formula (5) shown in Reaction Formula 2 above,

Reaction Formula 8




wherein $R^3$, $X^1$, $X^2$ and $A^1$ are the same as above.

The reaction of the compound of Formula (9) with the compound of Formula (15) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (9) with the compound of Formula (10) shown in Reaction Formula 6 above.

The reaction of the compound of Formula (9) with the compound of Formula (12) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (9) with the compound of Formula (10) shown in Reaction Formula 6 above.

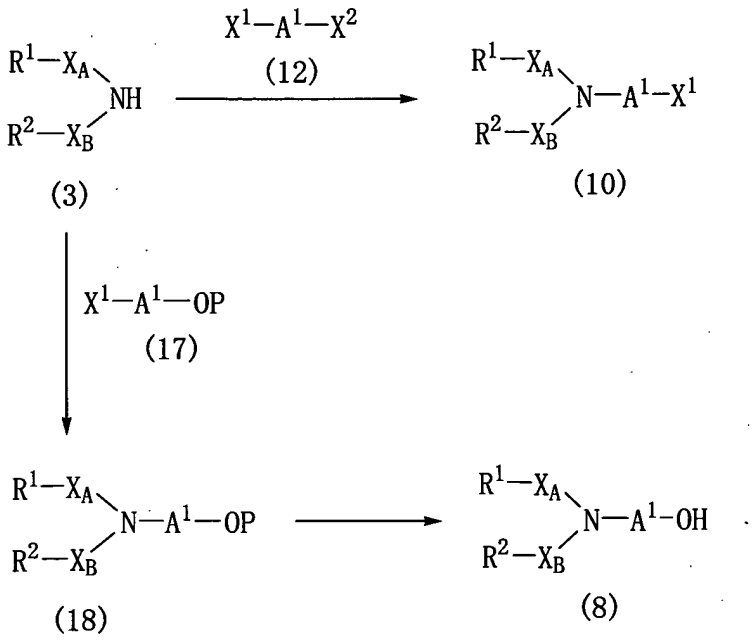
The reaction of the compound of Formula (4) with the compound of Formula (13) can be performed by the known N-alkylation reaction. For example, The reaction can be performed in the presence of an inert solvent (e.g., DMF, THF, dioxane and acetonitrile) and in the presence of a basic compound (e.g., $K_2CO_3$ and $Cs_2CO_3$).

The N-alkylation reaction temperature is not limited, and

the reaction is usually carried out at ambient temperature, under warming or under heating.

The reaction converting the compound of Formula (14) to the compound of Formula (1e) can be performed by the known method. For example, The reaction can be performed in the presence of hydrazine.

Reaction Formula 9




wherein $R^1$, $R^2$, $X_A$, $X_B$, $X^1$ and $A^1$ are the same as above; and P is a hydroxyl-protecting group and $X^2$ is a leaving group.

Examples of hydroxyl-protecting groups represented by P include tetrahydropyran-2-yl, methoxymethyl, benzyl.

Examples of the leaving groups represented by $X^2$ include halogen atoms (e.g., chlorine, bromine, iodine, and like atoms), lower alkane sulfonyloxy (e.g., methanesulfonyloxy), halo substituted lower alkane sulfonyloxy (e.g., trifluoromethanesulfonyloxy), arylene sulfonyloxy (e.g., p-toluenesulfonyloxy, benzenesulfonyloxy), etc.

When $X^1$ and $X^2$ are both halogen atoms, the halogen atom represented by $X^2$ is preferably one having an atomic number equal to or higher than that of the halogen atom represented by $X^1$.

The reaction of the compound of Formula (3) with the

compound of Formula (12) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (3) with the compound of Formula (4) shown in Reaction Formula 1 above.

The reaction of the compound of Formula (3) with the compound of Formula (17) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (3) with the compound of Formula (4) shown in Reaction Formula 1 above.

The reaction converting the compound of Formula (18) to the compound of Formula (8) can be performed under the known deprotection method depending on the type of the protecting group (P).

The compound of Formula (1) according to the present invention and the starting materials thereof can be produced using a known or conventional synthetic method other than the production method described above.

In addition, compounds in the form in which a solvate (for example, a hydrate, ethanolate, etc.) was added to the starting material compounds and object compounds shown in each of the reaction formulae are included in each of the formulae.

The compound of Formula (1) according to the present invention includes stereoisomers and optical isomers.

The starting material compounds and object compounds represented by each of the reaction formulae can be used in an appropriate salt form.

Each of the object compounds obtained according to the above reaction formulae can be isolated and purified from the reaction mixture by, for example, after cooling the reaction mixture, performing an isolation procedure such as filtration, concentration, extraction, etc., to separate a crude reaction product, and then subjecting the crude reaction product to a usual purification procedure such as column chromatography, recrystallization, etc.

Among the compounds of the present invention, those having a basic group or groups can easily form salts with common pharmaceutically acceptable acids. Examples of such acids include hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and other inorganic acids, methansulfonic acid,

p-toluenesulfonic acid, acetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, lactic acid and other organic acids, etc.

Among the compounds of the present invention, those having an acidic group or groups can easily form salts by reacting with pharmaceutically acceptable basic compounds. Examples of such basic compounds include sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, etc.

In the compound of the present invention, one or more atoms can be substituted with one or more isotopic atoms. Examples of the isotopic atoms include deuterium ($^{2}H$), tritium ($^{3}H$), $^{13}C$, $^{14}N$, $^{18}O$, etc.

The following is an explanation of pharmaceutical preparations comprising the compound of the present invention as an active ingredient.

Such pharmaceutical preparations are obtained by formulating the compound of the present invention into usual pharmaceutical preparations, using usually employed diluents or excipients such as fillers, extenders, binders, wetting agents, disintegrants, surfactants, lubricants, etc.

The form of such pharmaceutical preparations can be selected from various forms according to the purpose of therapy. Typical examples include tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.) and the like.

To form tablets, any of various known carriers can be used, including, for example, lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose and other excipients; water, ethanol, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate, polyvinylpyrrolidone and other binders; dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, aliphatic acid esters of polyoxyethylenesorbitan, sodium laurylsulfate, stearic acid monoglyceride, starch, lactose and other disintegrants; white sugar, stearin, cacao butter, hydrogenated

oils and other disintegration inhibitors; quaternary ammonium base, sodium lauryl sulfate and other absorption promoters; glycerin, starch and other wetting agents; starch, lactose, kaolin, bentonite, colloidal silicic acid and other adsorbents; purified talc, stearates, boric acid powder, polyethylene glycol and other lubricants; etc.

Such tablets may be coated with usual coating materials as required, to prepare, for example, sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double- or multi-layered tablets, etc.

To form pills, any of various known carriers can be used, including, for example, glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc and other excipients; gum arabic powder, tragacanth powder, gelatin, ethanol and other binders; laminaran, agar and other disintegrants; etc.

To form suppositories, any of various known carriers can be used, including, for example, polyethylene glycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semisynthetic glycerides, etc.

To form an injection, a solution, emulsion or suspension is sterilized and preferably made isotonic with blood. Any of various known widely used diluents can be employed to prepare the solution, emulsion or suspension. Examples of such diluents include water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, aliphatic acid esters of polyoxyethylene sorbitan, etc. In this case, the pharmaceutical preparation may contain sodium chloride, glucose or glycerin in an amount sufficient to prepare an isotonic solution, and may contain usual solubilizers, buffers, analgesic agents, etc., and further, if necessary, coloring agents, preservatives, flavors, sweetening agents, etc., and/or other medicines.

The proportion of the compound of the present invention in the pharmaceutical preparation is not limited and can be suitably selected from a wide range. It is usually preferable that the pharmaceutical preparation contain the compound of the present invention in a proportion of 1 to 70 wt.%.

The route of administration of the pharmaceutical

preparation according to the present invention is not limited, and the preparation can be administered by a route suitable for the form of the preparation, the patient's age and sex, the conditions of the disease, and other conditions.

For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. Injections are intravenously administered singly or as mixed with usual injection transfusions such as glucose solutions, amino acid solutions or the like, or singly administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally, as required. Suppositories are administered intrarectally.

The dosage of the pharmaceutical preparation is suitably selected according to the method of use, the patient's age and sex, the severity of the disease, and other conditions, and is usually about 0.001 to about 100 mg/kg body weight/day, and preferably 0.001 to 50 mg/kg body weight/day, in single or divided doses.

Since the dosage varies depending on various conditions, a dosage smaller than the above range may be sufficient, or a dosage larger than the above range may be required.

When administered to the human body as a pharmaceutical, the compound of the present invention may be used concurrently with, or before or after, antithrombotics such as blood clotting inhibitors and antiplatelet agents (e.g., warfarin, aspirin, etc.). Further, the present compound may be used concurrently with, or before or after, drugs for treating chronic diseases, such as antihypertensive drugs (ACE inhibitors, beta blockers, angiotensin II receptor antagonists), heart failure drugs (cardiotonic agents, diuretics), and diabetes treatment agents.

The compound of the present invention has potent blocking effects on human Kv1.5 and/or GIRK1/4 channels, and weak blocking effects on HERG channels. Thus, the compound of the invention has characteristics as an atrial-selective $K^+$ channel-blocking agent.

Therefore, the compound of the invention can be used as a pharmacologically active substance that is safer and provides a more potent effect on the prolongation of the atrial refractory period than conventional antiarrhythmic agents. The compound of the invention is

preferably used as a therapeutic agent for arrhythmia such as atrial fibrillation, atrial flutter, and atrial tachycardia (elimination of arrhythmia and/or prevention of the occurrence of arrhythmia). The compound of the invention is particularly preferably used as a therapeutic agent for atrial fibrillation (defibrillation and maintenance of sinus rhythm). The compound of the invention can also be used as a prophylactic agent for thromboembolism such as cerebral infarction and as a therapeutic agent for heart failure.

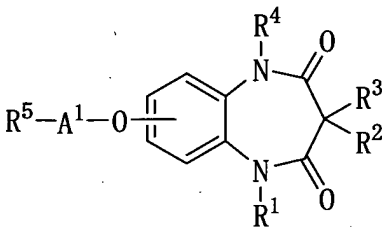
The compound having potent blocking effects on both human Kv1.5 and human GIRK1/4 channels has more potent atrial refractory period prolongation effects and is highly safe, compared to compounds inhibiting either one of the channels. Furthermore, this compound has greater therapeutic effects on atrial fibrillation (defibrillation and maintenance of sinus rhythm) than compounds inhibiting either one of the channels. Therefore, the compound having potent blocking effects on both the human Kv1.5 and human GIRK1/4 channels is particularly useful as a therapeutic agent for arrhythmia such as atrial fibrillation, atrial flutter, and atrial tachycardia (termination of arrhythmia and/or prevention of the occurrence of arrhythmia). This compound is particularly useful as a therapeutic agent for atrial fibrillation (defibrillation and maintenance of sinus rhythm).

3. Third Invention (benzodiazepine compound)

The present inventors conducted extensive research to develop a compound that blocks the $I_{Kur}$ current (Kv1.5 channel) and/or the $I_{KA}C_h$ current (GIRK1/4 channel) potently and more selectively than other $K^+$ channels. As a result, the inventors found that a novel benzodiazepine compound represented by General Formula (1) below could be the desired compound. The present invention has been accomplished based on the above findings.

The present invention provides benzodiazepine compounds, and pharmaceutical compositions comprising the benzodiazepine compounds as summarized in items 1 to 7 below.

Item 1. A benzodiazepine compound represented by General Formula (1):



(1)

or a salt thereof,

wherein $R^1$, $R^2$, $R^3$, and $R^4$ are each independently hydrogen or lower alkyl; $R^2$ and $R^3$ may be linked to form lower alkylene; $A^1$ is lower alkylene optionally substituted with one or more hydroxyls; and $R^5$ is an aryl or heterocyclic group, each of which is optionally substituted.

Item 2. A pharmaceutical composition comprising a benzodiazepine compound represented by Formula (1) or a salt thereof according to Item 1, and a pharmacologically acceptable carrier.

Item 3. A pharmaceutical composition according to Item 1 for preventing and/or treating arrhythmia.

Item 4. A benzodiazepine compound represented by Formula (1) or a salt thereof according to Item 1 for use in the pharmaceutical composition.

Item 5. Use of a benzodiazepine compound represented by Formula (1) or a salt thereof according to Item 1 as a pharmaceutical composition.

Item 6. Use of a benzodiazepine compound represented by Formula (1) or a salt thereof according to Item 1 for the production of a pharmaceutical composition.

Item 7. A method of preventing and/or treating arrhythmia, comprising administering to a patient a benzodiazepine compound represented by Formula (1) or a salt thereof according to Item 1.

The groups represented by, or substituents of, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $A^1$ in the specification are described below.

The term "one or more" may be preferably 1 to 6, and more preferably 1 to 3.

Examples of "lower alkyl" include linear or branched alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl,

isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, neopentyl, n-hexyl, isohexyl, and 3-methylpentyl.

Examples of "lower alkylene" include linear or branched alkylene groups having 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, tetramethylene, pentamethylene, and hexamethylene.

Examples of "lower alkenylene" include linear or branched alkylene groups having 2 to 6 carbon atoms, such as, ethenylene, propenylene, butenylene, pentenylene, and hexenylene.

Examples of "cyclo lower alkyl" include linear or branched cyclo alkyl having 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

Examples of "lower alkoxy" include linear or branched alkoxy groups having 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, sec-butoxy, n-pentyloxy, neopentyloxy, n-hexyloxy, isohexyloxy, and 3-methylpentyloxy.

Examples of "halogen" are fluorine, chlorine, bromine, and iodine.

Examples of "lower alkylenedioxy" include linear or branched alkylene groups having 1 to 4 carbon atoms, such as methylenedioxy, ethylenedioxy, trimethylenedioxy, and tetramethylenedioxy.

Examples of "lower alkanoyl" include linear or branched alkanoyl groups having 1 to 6 carbon atoms, such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, and hexanoyl.

Examples of "lower alkoxycarbonyl" include (linear or branched alkoxy having 1 to 6 carbon atoms)carbonyls, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, and tert-butoxycarbonyl.

Examples of "aralkyl group" include groups wherein aryl groups are substituted on the alkyl groups, such as benzyl and phenethyl.

Examples of "aryl group" include monocyclic or polycyclic

aryl groups, such as phenyl, tolyl, xylyl, and naphthyl.

Examples of "heterocyclic group" include saturated or unsaturated monocyclic or polycyclic heterocyclic groups containing at least one hetero atom selected from the group consisting of oxygen, sulfur and nitrogen. Examples of preferable heterocyclic groups include the followings (a) to (m) groups:

(a) unsaturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.;

(b) saturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atom(s), for example, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrazolidinyl, piperazinyl, etc.;

(c) unsaturated condensed 7- to 12-membered heterocyclic groups containing 1 to 5 nitrogen atom(s), for example, indolyl, dihydroindolyl (e.g., 2,3-dihydroindolyl, etc.), isoindolyl, indolizinyl, benzimidazolyl, quinolyl, dihydroquinolyl (e.g. 1,4-dihydroquinolyl, etc.), tetrahydroquinolyl (1,2,3,4-tetrahydroquinolyl, etc.), isoquinolyl, dihydroisoquinolyl (e.g., 3,4-dihydro-1H-isoquinolyl, 1,2-dihydroisoquinolyl, etc.), tetrahydroisoquinolyl (e.g., 1,2,3,4-tetrahydro-1H-isoquinolyl, 5,6,7,8-tetrahydroisoquinolyl, etc.), carbostyril, dihydrocarbostyril (e.g., 3,4-dihydrocarbostyril, etc.), indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, imidazopyridyl (e.g., imidazo[1,2-a]pyridyl, imidazo[4,5-c]pyridyl, etc.,), naphthyridinyl, cinnolinyl, quinoxalinyl, quinazolinyl, pyrazolopyridyl (e.g., pyrazolo[2,3-a]pyridyl, etc.), etc.;

(d) unsaturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing 1 to 2 oxygen atom(s), for example, furyl, etc.;

(e) unsaturated condensed 7- to 12-membered heterocyclic groups containing 1 to 3 oxygen atom(s), for example, benzofuryl, dihydrobenzofuryl (e.g. 2,3-dihydrobenzo[b]furyl, etc.), chromanyl, benzodioxanyl (e.g., 1,4-benzodioxanyl, etc.), dihydrobenzoxazinyl (e.g., 2,3-dihydrobenz-1,4-oxazinyl, etc.), benzodioxolyl (benzo[1,3]dioxolyl, etc.), etc.;

(f) unsaturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

(g) saturated 3- to 8-membered, preferably 5- or 6- membered heteromonocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, etc.;

(h) unsaturated condensed 7 to 12-membered heterocyclic groups containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, benzisoxazolyl, furopyridyl (e.g., furo[2,3-c]pyridyl, 6,7-dihydrofuro[2,3-c]pyridyl, furo[3,2-c]pyridyl, 4,5-dihydrofuro[3,2-c]pyridyl, furo[2,3-b]pyridyl, 6,7-dihydrofuro[2,3-b]pyridyl, etc.), etc.;

(i) unsaturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5- thiadiazolyl, 1,2,3-thiadiazolyl, etc.), etc.;

(j) saturated 3- to 8-membered, preferably 5- or 6- membered heteromonocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

(k) unsaturated 3- to 8-membered, preferably 5- or 6-membered heteromonocyclic groups containing a sulfur atom, for example, thienyl, etc.;

(l) unsaturated condensed 7- to 12-membered heterocyclic groups containing 1 to 3 sulfur atom(s), for example, benzothienyl (e.g. benzo[b]thienyl, etc.); and

(m) unsaturated condensed 7- to 12-membered heterocyclic groups containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, thienopyridyl (e.g., thieno[2,3-c]pyridyl, 6,7-dihydrothieno[2,3-c]pyridyl, thieno[3,2-c]pyridyl, 4,5-dihydrothieno[3,2-c]pyridyl, thieno[2,3-b]pyridyl, 6,7-dihydrothieno[2,3-b]pyridyl, , etc.), imidazothiazolyl (e.g., imidazo[2,1-b]thiazolyl, etc.), dihydroimidazothiazolyl (e.g., 2,3-dihydroimidazo[2,1-b]thiazolyl, etc.), thienopyrazinyl (e.g., thieno[2,3-b]pyrazinyl, etc.), etc.; wherein said heterocyclic groups may be substituted by one or more suitable substituents.

Substituents of "aryl and heterocyclic group, each of which is optionally substituted" represented by $R^5$ are each independently one or more substituents selected from the group consisting of:

(1) oxo;

(2) lower alkyl optionally substituted with one or more halogens or heterocyclic groups optionally substituted with one or more substituents selected from the group consisting of lower alkyl; lower alkoxy; lower alkanoyl; lower alkylsulfonyl; hydroxyl; halogen; carboxy; lower alkoxycarbonyl; amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl, and lower alkylsulfonyl; lower alkyl thio; cyano; and oxo;

(3) cyclo lower alkyl;

(4) lower alkoxy;

(5) aryl optionally substituted with one or more substituents selected from the group consisting of lower alkyl; lower alkoxy; lower alkanoyl; lower alkylsulfonyl; hydroxyl; halogen; carboxy; lower alkoxycarbonyl; amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl, and lower alkylsulfonyl; lower alkyl thio; and cyano;

(6) aralkyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl; lower alkoxy; lower alkanoyl; lower alkylsulfonyl; hydroxyl; halogen; carboxy; lower alkoxycarbonyl; amino optionally substituted with one or more

substituents selected from the group consisting of lower alkyl, lower alkanoyl, and lower alkylsulfonyl; lower alkyl thio; cyano; and oxo;
(7) a heterocyclic group optionally substituted with one or more substituents selected from the group consisting of lower alkyl; lower alkoxy; lower alkanoyl; lower alkylsulfonyl; hydroxyl; halogen; carboxy; lower alkoxycarbonyl; amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl, and lower alkylsulfonyl; lower alkyl thio; cyano; and oxo;
(8) hydroxyl;
(9) halogen;
(10) carboxy;
(11) lower alkanoyl;
(12) lower alkoxycarbonyl;
(13) lower alkylenedioxy;
(14) cyano;
(15) nitro;
(16) sulfo;
(17) amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl, and lower alkylsulfonyl;
(18) lower alkylsulfonyl; and
(19) lower alkyl thio.

The "heterocyclic group" in Item (7) above can be selected from the above-mentioned groups (a) to (m).

Examples of preferable benzodiazepine compounds represented by General Formula (1) include those wherein:
$R^1$, $R^2$, $R^3$, and $R^4$ are each independently lower alkyl;
$A^1$ is lower alkylene; and $R^5$ is piperidyl, piperazinyl, indolyl, benzimidazolyl, 2,3-dihydrobenzimidazolyl, 2,3-dihydroindolyl, furo[2,3-c]pyridyl, 6,7-dihydrofuro[2,3-c]pyridyl, furo[3,2-c]pyridyl, 4,5-dihydrofuro[3,2-c]pyridyl, furo[2,3-b]pyridyl, 6,7-dihydrofuro[2,3-b]pyridyl, thieno[2,3-c]pyridyl, 6,7-dihydrothieno[2,3-c]pyridyl, 1,2,3,4-tetrahydro-1H-isoquinolyl, carbostyril, 3,4-dihydrocarbostyril, quinolyl, 1,4-dihydroquinolyl,

1,2,3,4-tetrahydroquinolyl, pyrido[3,4-d]imidazolyl, or pyrido[2,3-d]imidazolyl; each of which is optionally substituted with one or more substituents selected from the group consisting of:

(1) oxo;

(2a) lower ($C_{1-3}$) alkyl optionally substituted with 6,7-dihydrofuro[2,3-c]pyridyl or 4,5-dihydrofuro[3,2-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(4a) $C_{1-3}$ alkoxy;

(5a) phenyl;

(6a) benzyl;

(7a) pyridyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and lower alkoxy;

(9) halogen;

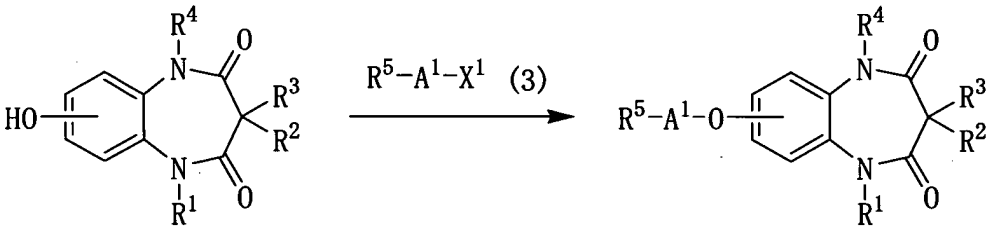
(10) carboxy;

(12a) $C_{1-3}$ alkoxycarbonyl; and

(13a) $C_{1-4}$ alkylenedioxy.

The benzodiazepine compound of the present invention represented by Formula (1) or its salt can be readily produced by persons skilled in the art using technical knowledge, based on the Examples and Reference Examples of the present specification. For example, the benzodiazepine compound or its salt can be produced according to the processes shown in the following reaction formulae.

Reaction Formula 1




(2) (1)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, and $A^1$ are the same as above, and $X^1$ is halogen or hydroxyl.

The reaction of the compound of Formula (2) with the compound of Formula (3) wherein $X^1$ is halogen can be performed in a general inert solvent or without using any solvent in the presence or absence of a basic compound.

Examples of inert solvents include water; ethers such as dioxane, tetrahydrofuran, diethyl ether, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; lower ($C_{1-6}$) alcohols such as methanol, ethanol, and isopropanol; ketones such as acetone and methyl ethyl ketone; polar solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile; and mixed solvents of such solvents.

The basic compound may be selected from various known compounds. Examples of such compounds include inorganic bases, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, cesium hydroxide, and lithium hydroxide; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate, lithium hydrogencarbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; alkali metals such as sodium and potassium; sodium amide; sodium hydride; and potassium hydride; and organic bases, for example, alkali metal alcoholates such as sodium methoxide, sodium ethoxide, potassium methoxide, and potassium ethoxide; triethylamine; tripropylamine; pyridine; quinoline; 1,5-diazabicyclo[4.3.0]nonene-5 (DBN); 1,8-diazabicyclo[5.4.0]undecene-7 (DBU); and 1,4-diazabicyclo[2.2.2]octane (DABCO). These basic compounds can be used singly or in a combination of two or more.

The above reaction may be performed by adding an alkali metal iodide such as potassium iodide or sodium iodide to the reaction system, as required.

The compound of Formula (3) is typically used in an amount of at least 0.5 moles, and preferably 0.5 to 10 moles, per mole of the compound of Formula (2).

The basic compound is typically used in an amount of 0.5

to 10 moles, and preferably 0.5 to 6 moles, per mole of the compound of Formula (2).

The reaction is typically performed at a temperature of 0°C to 250°C, and preferably 0°C to 200°C, and is typically completed in about 1 to about 80 hours.

The reaction of the compound of Formula (2) with the compound of Formula (3) wherein $X^1$ is hydroxyl is performed in a suitable solvent in the presence of a condensing agent.

Examples of solvents usable herein include water; halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, and dimethoxyethane; esters such as methyl acetate, ethyl acetate, and isopropyl acetate; alcohols such as methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve, and methyl cellosolve; aprotic polar solvents such as acetonitrile, pyridine, acetone, N,N-dimethyl formamide, dimethyl sulfoxide, and hexamethylphosphoric triamide; and mixtures of such solvents.

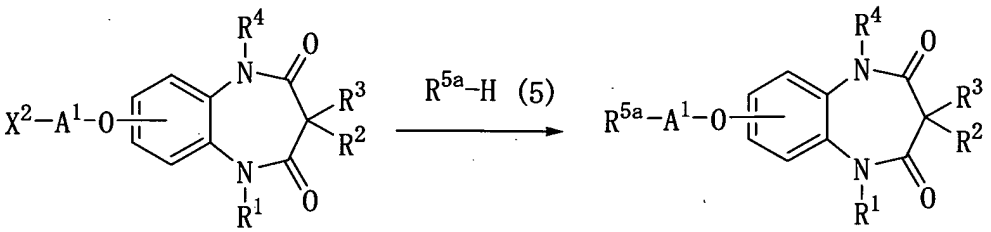
Examples of condensing agents include azocarboxylates such as di-tert-butyl azodicarboxylate, N,N,N',N'-tetramethyl azodicarboxamide, 1,1'-(azodicarbonyl)dipiperidine, diethyl azodicarboxylate; and phosphorus compounds such as triphenylphosphine and tri-n-butylphosphine.

In this reaction, the compound (3) is typically used in an amount of at least 1 mole, and preferably 1 to 2 moles, per mole of the compound (2).

The condensing agent is typically used in an amount of at least 1 mole, and preferably 1 to 2 moles, per mole of the compound (2).

The reaction proceeds typically at 0 to 200°C, and preferably at about 0 to about 150°C, and is completed in about 1 to about 10 hours.

Reaction Formula 2




(4) (1a)

wherein $R^1$, $R^2$, $R^3$, $R^4$, and $A^1$ are the same as above; $R^{5a}$ is a nitrogen-containing heterocyclic group optionally having substituent(s); and $X^2$ is a halogen atom.

Examples of $R^{5a}$ include, among groups represented by the group $R^5$ mentioned above, groups obtained by removing hydrogen from saturated or unsaturated, monocyclic or polycyclic, heterocyclic compounds with an N-H bond, the groups optionally having substituent(s).

The reaction of the compound of Formula (4) with the compound of Formula (5) can be performed in a general inert solvent or without using any solvent, in the presence or absence of a basic compound.

Examples of halogen atoms represented by $X^2$ include chlorine, bromine, iodine, and like atoms.

Examples of inert solvents include water; ethers such as dioxane, tetrahydrofuran, diethylether, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; lower alcohols such as methanol, ethanol, and isopropanol; ketones such as acetone and methyl ethyl ketone; polar solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile; and mixtures thereof.

A wide variety of known basic compounds can be used as the basic compound. Examples of such basic compounds include inorganic bases, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, cesium hydroxide, and lithium hydroxide; alkali

metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate, lithium hydrogencarbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; alkali metals such as sodium and potassium; sodium amide; sodium hydride; and potassium hydride; and organic bases, for example, alkali metal alcoholates such as sodium methoxide, sodium ethoxide, potassium methoxide, and potassium ethoxide; triethylamine; tripropylamine; pyridine; quinoline; 1,5-diazabicyclo[4.3.0]nonene-5 (DBN); 1,8-diazabicyclo[5.4.0]undecene-7 (DBU); and 1,4-diazabicyclo[2.2.2]octane (DABCO). These basic compounds can be used singly or in a combination of two or more.

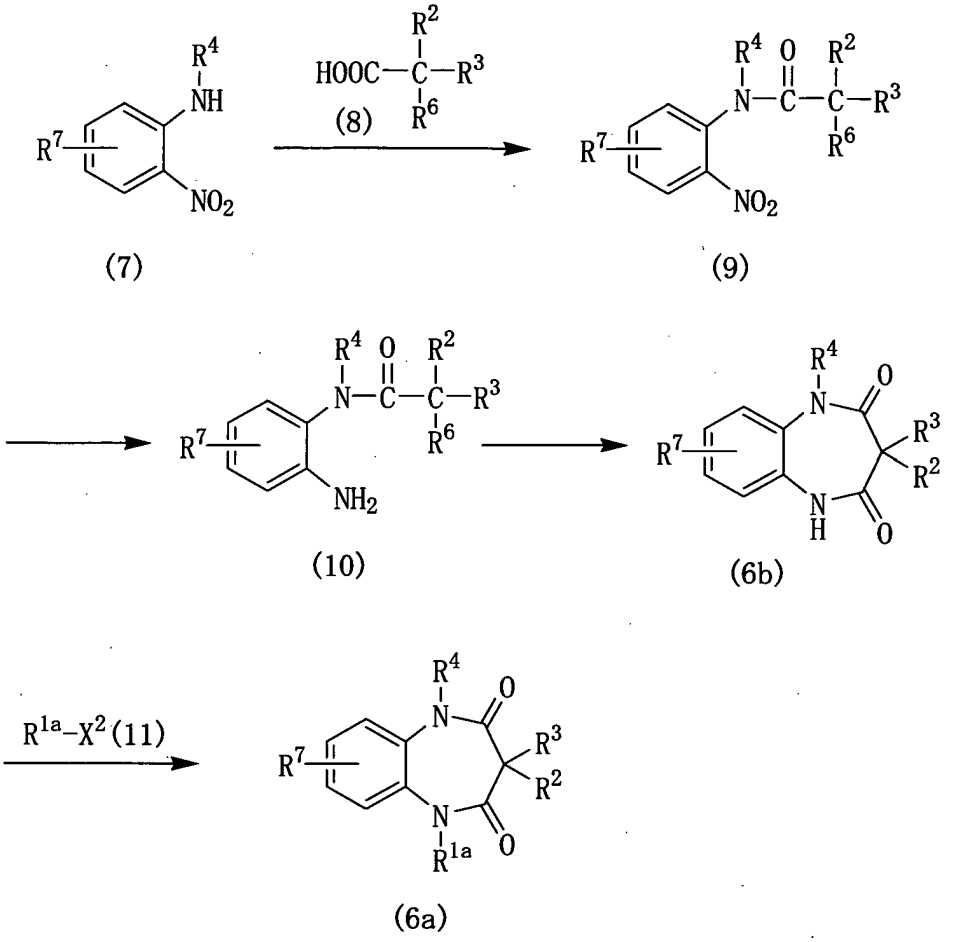
The above reaction may be performed by adding as a reaction accelerator an alkali metal iodide such as potassium iodide or sodium iodide to the reaction system, as required.

The compound of Formula (5) is typically used in an amount of at least 0.5 moles, and preferably about 0.5 to about 10 moles, per mole of the compound of Formula (4).

The amount of basic compound is typically 0.5 to 10 moles, and preferably 0.5 to 6 moles, per mole of the compound of Formula (4).

The reaction is typically performed at a temperature of 0 to 250°C, and preferably 0 to 200°C, and is typically completed in about 1 to about 80 hours.

Reaction Formula 3



wherein $R^2$, $R^3$, $R^4$, and $X^2$ are as defined above; $R^{1a}$ is lower alkyl; $R^7$ is lower alkoxy; and $R^6$ is lower alkoxycarbonyl.

Examples of lower alkyl groups represented by $R^{1a}$ include alkyl groups with 1 to 6 carbon atoms, such as methyl, ethyl, and propyl groups.

Examples of lower alkoxycarbonyl groups represented by $R^6$ include ($C_{1-6}$ alkoxy)carbonyl groups, such as methoxycarbonyl, and ethoxycarbonyl.

Examples of lower alkoxy groups represented by $R^7$ include linear or branched alkoxy groups with 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, and butoxy.

In the reaction of the compound of Formula (7) with the compound of Formula (8), the compound of Formula (7) is reacted with the carboxylic acid compound of Formula (8) through a general amide bond formation reaction. Conditions for known amide bond formation reactions can be easily employed in the amide formation reaction.

For example, the following reaction methods can be employed: (i) a mixed acid anhydride method, in which Carboxylic Acid (8) is reacted with an alkyl halocarboxylate to form a mixed acid anhydride, which is then reacted with Amine (7); (ii) an active ester method, in which Carboxylic Acid (8) is converted to an activated ester such as a phenyl ester, p-nitrophenyl ester, N-hydroxysuccinimide ester, 1-hydroxybenzotriazole ester or the like, or an activated amide with benzoxazoline-2-thione, and the activated ester or amide is reacted with Amine (7); (iii) a carbodiimide method, in which Carboxylic Acid (8) is subjected to a condensation reaction with Amine (7) in the presence of an activating agent such as dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC), carbonyldiimidazole or the like; and (iv) other methods, for example, a method in which Carboxylic Acid (8) is converted to a carboxylic anhydride using a dehydrating agent such as acetic anhydride, and the carboxylic anhydride is reacted with Amine (7), a method in which an ester of Carboxylic Acid (8) with a lower alcohol is reacted with Amine (7) at a high pressure and a high temperature, and a method in which an acid halide of Carboxylic Acid (8), i.e., a carboxylic acid halide, is reacted with Amine (7).

Generally, the mixed acid anhydride method(i) is performed in a solvent, in the presence or absence of a basic compound. Any solvents used for conventional mixed acid anhydride methods are usable. Specific examples of usable solvents include halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, and dimethoxyethane; esters such as methyl acetate, ethyl acetate, and isopropyl acetate; aprotic polar solvents such as N,N-dimethylformamide, dimethylsulfoxide, and hexamethylphosphoric triamide; and mixtures thereof.

Examples of usable basic compounds include organic bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyldiisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and

1,4-diazabicyclo[2.2.2]octane (DABCO); inorganic bases, for example, carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; metal hydroxides such as sodium hydroxide, potassium hydroxide, and calcium hydroxide; potassium hydride; sodium hydride; potassium; sodium; sodium amide; and metal alcoholates such as sodium methylate and sodium ethylate.

Examples of alkyl halocarboxylates usable in the mixed acid anhydride method include methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, and isobutyl chloroformate. In this method, Carboxylic Acid (8), an alkyl halocarboxylate, and Amine (7) are preferably used in equimolar amounts, but each of the alkyl halocarboxylate and Carboxylic Acid (8) can also be used in an amount of about 1 to about 1.5 moles per mole of Amine (7).

The reaction is typically performed at about -20 to about 150°C, and preferably at about 10 to about 50°C, typically for about 5 minutes to about 30 hours, and preferably for about 5 minutes to about 25 hours.

Method (iii), in which a condensation reaction is performed in the presence of an activating agent, can be performed in a suitable solvent in the presence or absence of a basic compound. Solvents and basic compounds usable in this method include those mentioned hereinafter as solvents and basic compounds usable in the method in which a carboxylic acid halide is reacted with Amine (7) mentioned above as one of the other methods (iv). A suitable amount of activating agent is typically at least 1 mole, and preferably 1 to 5 moles per mole of Compound (7). When WSC is used as an activating agent, addition of 1-hydroxybenzotriazol to the reaction system allows the reaction to proceed advantageously. The reaction is typically performed at about -20 to about 180°C, and preferably at about 0 to about 150°C, and is typically completed in about 5 minutes to about 90 hours.

When the method in which a carboxylic acid halide is reacted with Amine (7), mentioned above as one of the other methods (iv), is employed, the reaction is performed in the presence of a basic compound in a suitable solvent. Examples of usable basic compounds include a

wide variety of known basic compounds, such as those for use in the method(i) above. In addition to those usable in the mixed acid anhydride method, usable solvents include alcohols such as methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethylcellosolve, and methylcellosolve; acetonitrile; pyridine; acetone; and water. The ratio of the carboxylic acid halide to Amine (7) is not limited and can be suitably selected from a wide range. It is typically suitable to use, for example, at least about 1 mole, and preferably about 1 to about 5 moles of the carboxylic acid halide per mole of Amine (7). The reaction is typically performed at about -20 to about 180°C, and preferably at about 0 to about 150°C, and typically completed in about 5 minutes to about 30 hours.

The amide bond formation reaction shown in Reaction Formula 3 above can also be performed by reacting Carboxylic Acid (8) with Amine (7) in the presence of a phosphorus compound serving as a condensing agent, such as triphenylphosphine, diphenylphosphinyl chloride, phenyl-N-phenylphosphoramide chloridate, diethyl chlorophosphate, diethyl cyanophosphate, diphenylphosphoric azide, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, or the like.

The reaction is performed in the presence of a solvent and a basic compound usable for the method in which a carboxylic acid halide is reacted with Amine (7), typically at about -20 to about 150°C, and preferably at about 0 to about 100°C, and is typically completed in about 5 minutes to about 30 hours. It is suitable to use each of the condensing agent and Carboxylic Acid (8) in amounts of at least about 1 mole, and preferably about 1 to about 2 moles, per mole of Amine (7).

The reaction converting the compound of Formula (9) to the compound of Formula (10) can be performed by, for example, [1] reducing the compound of Formula (9) in a suitable solvent using a catalytic hydrogenation reducing agent, or [2] reducing the compound of Formula (9) in a suitable inert solvent using as a reducing agent such as a mixture of an acid with a metal or metal salt, a mixture of a metal or metal salt with an alkali metal hydroxide, sulfide, or ammonium salt.

When Method [1] in which a catalytic hydrogenation reducing

agent is used, examples of usable solvents are water; acetic acid; alcohols such as methanol, ethanol and isopropanol; hydrocarbons such as n-hexane and cyclohexane; ethers such as dioxane, tetrahydrofuran, diethyl ether and diethylene glycol dimethyl ether; esters such as ethyl acetate and methyl acetate; aprotic polar solvents such as N,N-dimethylformamide; and mixtures thereof. Examples of usable catalytic hydrogenation reducing agents include palladium, palladium black, palladium carbon, platinum carbon, platinum, platinum black, platinum oxide, copper chromite, and Raney nickel. The reducing agent is typically used in an amount of about 0.02 times to about equal to the weight of the compound of Formula (9). The reaction temperature is typically about -20 to about 150°C, and preferably about 0 to about 100°C. The hydrogen pressure is typically about 1 to 10 atm. The reaction is typically completed in about 0.5 to about 100 hours. An acid such as hydrochloric acid may be added to the reaction.

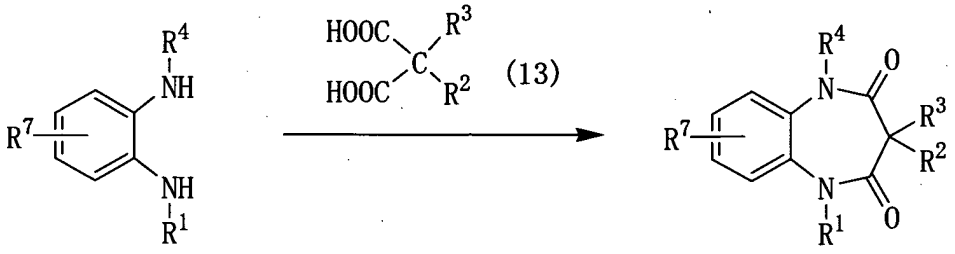
When Method [2] above is used, a mixture of iron, zinc, tin, or tin (II) chloride with a mineral acid such as hydrochloric acid or sulfuric acid; or a mixture of iron, iron (II) sulfate, zinc, or tin with an alkali metal hydroxide such as sodium hydroxide, a sulfide such as ammonium sulfide, aqueous ammonia solution, or an ammonium salt such as ammonium chloride or the like, can be used as a reducing agent. Examples of inert solvents are water; acetic acid; alcohols such as methanol and ethanol; ethers such as dioxane; and mixtures thereof. Conditions for the reduction reaction can be suitably selected according to the reducing agent to be used. For example, when a mixture of tin (II) chloride and hydrochloric acid is used as a reducing agent, the reaction is advantageously performed at about 0 to about 150°C for about 0.5 to about 10 hours. A reducing agent is used in an amount of at least 1 mole, and preferably about 1 to 5 moles, per mole of the compound of Formula (9).

The reaction converting the compound of Formula (10) to the compound of Formula (6b) is performed under the same reaction conditions as those for the reaction of the compound of Formula (7) with the compound of Formula (8).

The reaction of the compound of Formula (6b) with the compound of Formula (11) can be performed under the same reaction

conditions as those for the reaction of the compound of Formula (2) and the compound of Formula (3) shown in Reaction Formula 1 above.

Reaction Formula 4

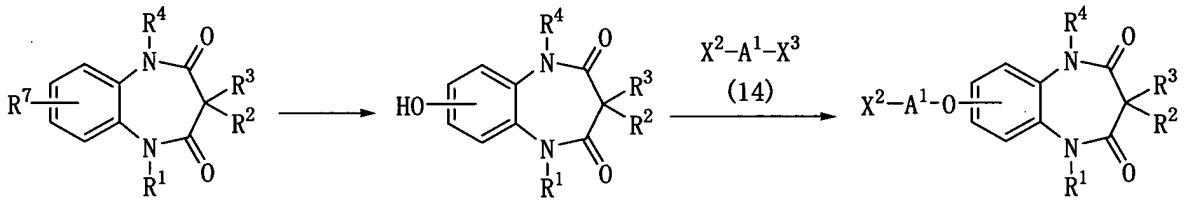


(12) (6)

wherein $R^1$, $R^2$, $R^3$, $R^4$, and $R^7$ are the same as above.

The reaction of the compound of Formula (12) with the compound of Formula (13) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (7) with the compound of Formula (8) shown in Reaction Formula 3 above.

Reaction Formula 5



(6) (2) (4)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^7$, $A^1$, and $X^2$ are the same as above; and $X^3$ is a halogen atom.

The reaction converting the compound of Formula (6) to the compound of Formula (2) can be performed in a suitable solvent in the presence of an acid.

Examples of solvents include water; lower ($C_{1-6}$) alcohols such as methanol, ethanol, and isopropanol; ethers such as dioxane, tetrahydrofuran, and diethylether; halogenated hydrocarbons such as dichloromethane, chloroform, and carbon tetrachloride; polar solvents such as acetonitrile; and and mixtures thereof. Examples of acids

include mineral acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid; aliphatic acids such as formic acid and acetic acid; sulfonic acids such as p-toluenesulfonic acid; Lewis acids such as boron fluoride, aluminium chloride, and boron tribromide; iodides such as sodium iodide and potassium iodide; and mixtures of these iodides and Lewis acids.

The reaction is performed typically at about 0 to about 200°C, and preferably at about 0 to about 150°C, and is typically completed in about 0.5 to about 25 hours. The amount of acid is typically about 1 to about 10 moles, and preferably about 1 to about 2 moles, per mole of the compound of Formula (6).

Examples of halogen atoms represented by $X^3$ include chlorine, bromine, iodine, and like atoms. The halogen atom represented by $X^3$ is preferably one having an atomic number equal to or higher than that of the halogen atom represented by $X^2$.

The reaction of the compound of Formula (2) with the compound of Formula (14) can be performed under the same reaction conditions as those for the reaction of the compound of Formula (2) with the compound of Formula (3) shown in Reaction Formula 1 above, wherein $X^1$ is a halogen atom.

The compound of Formula (1) according to the present invention and the starting materials thereof can be produced using a known or conventional synthetic method other than the production method described above.

In addition, compounds in the form in which a solvate (for example, a hydrate, ethanolate, etc.) was added to the starting material compounds and object compounds shown in each of the reaction formulae are included in each of the formulae.

The compound of Formula (1) according to the present invention includes stereoisomers and optical isomers.

The starting material compounds and object compounds represented by each of the reaction formulae can be used in a suitable salt form.

Each of the object compounds obtained according to the above reaction formulae can be isolated and purified from the reaction

mixture by, for example, after cooling the reaction mixture, performing an isolation procedure such as filtration, concentration, extraction, etc., to separate a crude reaction product, and then subjecting the crude reaction product to a general purification procedure such as column chromatography, recrystallization, etc.

Among the compounds of the present invention, those having a basic group or groups can easily form salts with common pharmaceutically acceptable acids. Examples of such acids include hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and other inorganic acids, methansulfonic acid, p-toluenesulfonic acid, acetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, lactic acid and other organic acids, etc.

Among the compounds of the present invention, those having an acidic group or groups can easily form salts by reacting with pharmaceutically acceptable basic compounds. Examples of such basic compounds include sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, etc.

In the compound of the present invention, one or more atoms can be substituted with one or more isotopic atoms. Examples of the isotopic atoms include deuterium ($^{2}H$), tritium ($^{3}H$), $^{13}C$, $^{14}N$, $^{18}O$, etc.

The following is an explanation of pharmaceutical preparations comprising the compound of the present invention as an active ingredient.

Such pharmaceutical preparations are obtained by formulating the compound of the present invention into general pharmaceutical preparations, using typically employed diluents or excipients such as fillers, extenders, binders, wetting agents, disintegrants, surfactants, lubricants, etc.

The form of such pharmaceutical preparations can be selected from various forms according to the purpose of therapy. Typical examples include tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.) and the like.

To form tablets, any of various known carriers can be used,

including, for example, lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose and other excipients; water, ethanol, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate, polyvinylpyrrolidone and other binders; dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, aliphatic acid esters of polyoxyethylenesorbitan, sodium laurylsulfate, stearic acid monoglyceride, starch, lactose and other disintegrants; white sugar, stearin, cacao butter, hydrogenated oils and other disintegration inhibitors; quaternary ammonium base, sodium lauryl sulfate and other absorption promoters; glycerin, starch and other wetting agents; starch, lactose, kaolin, bentonite, colloidal silicic acid and other adsorbents; purified talc, stearates, boric acid powder, polyethylene glycol and other lubricants; etc.

Such tablets may be coated with general coating materials as required, to prepare, for example, sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double- or multi-layered tablets, etc.

To form pills, any of various known carriers can be used, including, for example, glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc and other excipients; gum arabic powder, tragacanth powder, gelatin, ethanol and other binders; laminaran, agar and other disintegrants; etc.

To form suppositories, any of various known carriers can be used, including, for example, polyethylene glycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semisynthetic glycerides, etc.

To form an injection, a solution, emulsion or suspension is sterilized and preferably made isotonic with blood. Any of various known widely used diluents can be employed to prepare the solution, emulsion or suspension. Examples of such diluents include water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, aliphatic acid esters of polyoxyethylene sorbitan, etc. In this case, the pharmaceutical preparation may contain sodium chloride, glucose or glycerin in an

amount sufficient to prepare an isotonic solution, and may contain general solubilizers, buffers, analgesic agents, etc., and further, if necessary, coloring agents, preservatives, flavors, sweetening agents, etc., and/or other medicines.

The proportion of the compound of the present invention in the pharmaceutical preparation is not limited and can be suitably selected from a wide range. It is typically preferable that the pharmaceutical preparation contain the compound of the present invention in a proportion of 1 to 70 wt.%.

The route of administration of the pharmaceutical preparation according to the present invention is not limited, and the preparation can be administered by a route suitable for the form of the preparation, the patient's age and sex, the conditions of the disease, and other conditions.

For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. Injections are intravenously administered singly or as mixed with general injection transfusions such as glucose solutions, amino acid solutions or the like, or singly administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally, as required. Suppositories are administered intrarectally.

The dosage of the pharmaceutical preparation is suitably selected according to the method of use, the patient's age and sex, the severity of the disease, and other conditions, and is typically about 0.001 to about 100 mg/kg body weight/day, and preferably 0.001 to 50 mg/kg body weight/day, in single or divided doses.

Since the dosage varies depending on various conditions, a dosage smaller than the above range may be sufficient, or a dosage larger than the above range may be required.

When administered to the human body as a pharmaceutical, the compound of the present invention may be used concurrently with, or before or after, antithrombotics such as blood clotting inhibitors and antiplatelet agents (e.g., warfarin, aspirin, etc.). Further, the present compound may be used concurrently with, or before or after, drugs for treating chronic diseases, such as antihypertensive drugs (ACE inhibitors, beta blockers, angiotensin II receptor antagonists),

heart failure drugs (cardiotonic agents, diuretics), and diabetes treatment agents.

The compound of the present invention has potent blocking effects on human Kv1.5 and/or GIRK1/4 channels, and weak blocking effects on HERG channels. Thus, the compound of the invention has characteristics as an atrial-selective $K^+$ channel-blocking agent.

Therefore, the compound of the invention can be used as a pharmacologically active substance that is safer and provides a more potent effect on the prolongation of the atrial refractory period than conventional antiarrhythmic agents. The compound of the invention is preferably used as a therapeutic agent for arrhythmia such as atrial fibrillation, atrial flutter, and atrial tachycardia (elimination of arrhythmia and/or prevention of the occurrence of arrhythmia). The compound of the invention is particularly preferably used as a therapeutic agent for atrial fibrillation (defibrillation and maintenance of sinus rhythm). The compound of the invention can also be used as a prophylactic agent for thromboembolism such as cerebral infarction and as a therapeutic agent for heart failure.

The compound having potent blocking effects on both human Kv1.5 and human GIRK1/4 channels has more potent atrial refractory period prolongation effects and is highly safe, compared to compounds inhibiting either one of the channels. Furthermore, this compound has greater therapeutic effects on atrial fibrillation (defibrillation and maintenance of sinus rhythm) than compounds inhibiting either one of the channels. Therefore, the compound having potent blocking effects on both the human Kv1.5 and human GIRK1/4 channels is particularly useful as a therapeutic agent for arrhythmia such as atrial fibrillation, atrial flutter, and atrial tachycardia (termination of arrhythmia and/or prevention of the occurrence of arrhythmia). This compound is particularly useful as a therapeutic agent for atrial fibrillation (defibrillation and maintenance of sinus rhythm).

## DESCRIPTION OF EMBODIMENTS

The following Examples are intended to illustrate the present invention in further detail.

1. First Invention

▪ Reference Example 1

· Synthesis of
8-methoxy-1-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium ethoxide (204mg) was added to an ethanol solution (15ml) of N-(2-amino-5-methoxyphenyl)-N-methylmalonamic acid ethyl ester (266mg). The mixture was stirred at 65°C for 2.5 hours. The reaction liquid was cooled to room temperature, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane: methanol =1:0→10:1). The purified product was condensed to dryness under reduced pressure to give the title compound (176.3mg) as a white powder.

$^1$H-NMR ($CDCl_3$) δppm : 3.36 (2H, s), 3.43 (3H, s), 3.84 (3H, s), 6.79-6.83 (1H, m), 7.06-7.09 (1H, m), and 8.72 (1H, br-s).

▪ Reference Example 2

· Synthesis of
1-ethyl-7-methoxy-5-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium hydride (60% in oil, 44mg) was suspended in of DMF(8ml), and was cooled to 0°C in an ice water bath.
8-Methoxy-1-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (220mg) was added thereto at the same temperature, and the mixture was stirred at 0°C for an hour. Ethyl iodide (187mg) was added thereto, and the mixture was stirred at room temperature overnight. Water was added to the reaction liquid, followed by extraction by ethyl acetate. The organic layer was dried over sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=4:1→1:1). The purified product was condensed to dryness to give the title compound (190.2mg) as a yellow solid.

$^1$H-NMR ($CDCl_3$) δppm: 1.11 (3H, t, J = 7.1 Hz), 3.32 (2H, m), 3.59 - 3.68 (1H, m), 3.85 (3H, s), 4.18 - 4.30 (1H, m), 6.78 (1H, d, J= 2.8 Hz), 6.84 (1H, dd, J = 9.0 and 2.8 Hz), 7.26 (1H, d, J = 9.0 Hz).

▪ Reference Example 3

· Synthesis of 1-ethyl-7-methoxy-3,3,5-trimethyl-1, 5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium hydride (60% in oil, 76mg) was suspended in of DMF(8ml). 1-ethyl-7-methoxy-5-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (190mg) was added thereto at 0°C. The mixture was stirred at the same temperature for an hour. Methyl iodide (0.19ml) was added thereto, and the mixture was stirred at room temperature for three days. Water was added to the reaction mixture, followed by extraction by ethyl acetate. The organic layer was dried over sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate). The purified product was condensed to dryness to give the title compound(169mg) as yellow powder.

$^1$H-NMR ($CDCl_3$) δppm: 0.86 (3H, s), 1.15 (3H, t, J=7.1 Hz), 1.53 (3H, s), 3.40 (3H, s), 3.65-3.76 (1H, m), 3.85 (3H, s), 4.12 - 4.24 (1H, m), 6.73 (1H, d, J= 2.8 Hz), 6.83 (1H, dd, J = 9.0 and 2.8 Hz), and 7.22 (1H, d, J = 9.0 Hz).

▪ Reference Example 4

· Synthesis of 7-methoxy-1,3,3,5-tetramethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium hydride (60% in oil, 128mg) was suspended in of DMF(10ml). 8-methoxy-1-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (176mg) was added thereto at 0°C. The mixture was stirred at the same temperature for an hour. Methyl iodide(0.25mg) was added thereto, and the mixture was stirred at room temperature overnight. Water was added to the reaction liquid, followed by extraction by ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and condensed under reduced pressure. The residue was recrystallized from hexane to give the title compound(161.6mg) as a white powder.

$^1$H-NMR ($CDCl_3$) δppm: 0.87 (3H, s), 1.54 (3H, s), 3.40 (3H, s), 3.42 (3H, s), 3.84 (3H, s), 6.73 (1H, s), 6.84 (1H, d, J= 8.9 Hz), 7.14

(1H, d, J = 8.9 Hz).

▪ Reference Example 5

·Synthesis of
1-ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

1.0M-boron tribromide/dichloromethane solution (1.22ml) was added to a dichloromethane solution (3ml) of 1-ethyl-7-methoxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (169mg) at 0°C. The mixture was stirred at room temperature overnight. Water and methanol were added to the reaction mixture, and extraction was performed using a dichloromethane/methanol mixture (dichloromethane:methanol = 10:1). The organic layer was dried over anhydrous sodium sulfate, and condensed to dryness under reduced pressure to give the title compound(156.4 mg) as a white powder.
$^1$H-NMR ($CDCl_3$) δppm: 0.90 (3H, s), 1.16 (3H, t, J =7.0Hz), 1.55 (3H, s), 3.41 (3H, s), 3.66-3.78 (1H, m), 4.12-4.23 (1H, m), 6.79 (1H, d,J =2.7 Hz), 6.84 (1H, dd, J= 8.8 and 2.7 Hz), 6.88 (1H, s), 7.18 (1H, d, J = 8.8 Hz).

▪ Reference Example 6

·Synthesis of
7-hydroxy-1,3,3,5-tetramethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Reference Example 5 using appropriate starting materials.
$^1$H-NMR ($CDCl_3$) δppm: 0.90 (3H, s), 1.49 (3H, s), 3.39 (3H, s), 3.40 (3H, s), 6.73 (1H, d, J = 2.7 Hz), 6.80 (1H, dd, J = 8.9 and 2.7 Hz), 7.13 (1H, d, J = 8.9 Hz).

▪ Reference Example 7

· Synthesis of trifluoromethanesulfonic acid
1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl ester

A dichloromethane solution (50ml) of

1-ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo [b][1,4]diazepine-2,4-dione(2.6g) was cooled with ice. After adding of triethylamine(1.5ml) to the solution, trifluoromethane sulfonic anhydride(1.9ml) was added, and the mixture was stirred at room temperature for 4 hours. Triethylamine(0.75ml) and trifluoromethane sulfonic anhydride(0.75ml) were further added thereto, and the mixture was stirred at room temperature overnight. Water was added to the reaction liquid, followed by extraction by ethyl acetate. The organic layer was condensed under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane: ethyl acetate=10:1→5:5). The purified product was condensed to dryness under reduced pressure to give the title compound(3.4g) as a white solid (yield = 86%).

$^1$H-NMR ($CDCl_3$) δppm: 0.87 (3H, s), 1.23 (3H, t, J =7.2Hz), 1.52 (3H, s), 3.42 (3H, s), 3.81-3.91 (1H, m), 4.04-4.14 (1H, m), 7.15-7.22 (2H, m), 7.40 (1H, d, J = 8.9 Hz).

▪ Reference Example 8

· Synthesis of trifluoromethanesulfonic acid 1,5-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl ester

The synthesis of the title compound was performed in the same manner as in Reference Example 7 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δppm: 3.29 (1H, d, J =12.7Hz), 3.43 (6H, s), 3.48 (1H, d, J =12.7Hz), 7.21-7.26 (2H, m), 7.38-7.41 (1H, m).

▪ Reference Example 9

· Synthesis of trifluoromethanesulfonic acid 1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl ester

The synthesis of the title compound was performed in the same manner as in Reference Example 7 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δppm: 0.88 (3H, s), 1.56 (3H, s), 3.44 (3H, s), 3.45 (3H, s), 7.16-7.21 (2H, m), 7.33 (1H, d, J = 8.9 Hz).

▪ Reference Example 10

· Synthesis of
1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

Trifluoromethanesulfonic acid 1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-yl ester(0.12g), zinc cyanide(70mg), tris(dibenzylideneacetone) dipalladium(7mg), 1,1'-bis(diphenylphosphino) ferrocene(8mg), and zinc powder(2mg) were added to DMF(1ml), and the mixture was heated for 20 minutes at 170°C (microwave reactor). The reaction liquid was cooled to room temperature, and subjected to celite filtration. The filtrate was condensed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane: ethyl acetate=50:50→0:100). The purified product was condensed under reduced pressure to give the title compound(77mg) as a white solid.

$^1$H-NMR ($CDCl_3$) δppm: 0.88 (3H, s), 1.25 (3H, t, J =7.1 Hz), 1.55 (3H, s), 3.44 (3H, s), 3.89-3.95 (1H, m), 4.05-4.11 (1H, m), 7.43 (1H, d, J = 9.1 Hz), 7.53-7.56 (2H, m).

▪ Reference Example 11

· Synthesis of
1,5-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δppm: 3.25 (1H, d, J = 12.7 Hz), 3.438 (3H, s), 3.444 (3H, s), 3.50 (1H, d, J = 12.7 Hz), 7.42 (1H, J = 8.4 Hz), 7.57-7.62 (2H, m).

▪ Reference Example 12

· Synthesis of
1,3,3,5-tetramethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting

materials.

$^1$H-NMR ($CDCl_3$) δppm: 0.88 (3H, s), 1.56 (3H, s), 3.45 (3H, s), 3.46 (3H, s), 7.34-7.37 (1H, m), 7.53-7.57 (2H, m).

▪ Reference Example 13

· Synthesis of 1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4] diazepine-7-carbonitrile(1.0g) and Raney nickel(3.0g) were suspended in formic acid(10ml), and the mixture was stirred at 100°C for 2 hours. The reaction mixture was filtered to remove insoluble matter, and the filtrate was condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=50:50→20:80). The purified product was condensed under reduced pressure to give the title compound(0.92g) as a yellowish-white solid (yield = 92%).

$^1$H-NMR ($CDCl_3$) δppm: 0.88 (3H, s), 1.26 (3H, t, J =7.1 Hz), 1.56 (3H, s), 3.48 (3H, s), 3.92-3.99 (1H, m), 4.07-4.15 (1H, m), 7.50 (1H, d, J = 8.9 Hz), 7.77-7.80 (2H, m), 10.01 (1H, s).

▪ Reference Example 14

· Synthesis of 7-[4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)but-1-ynyl]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Trifluoromethane sulfonic acid 1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-yl ester(0.59g), 2-(but-3-ynyl)isoindol-1,3-dione(0.3g), dichlorobis(triphenyl phosphine)palladium (II)(53mg), copper(I) iodide(29mg), and triethylamine(0.39ml) were added to DMF(4ml). The mixture was heated at 150°C (microwave reactor) for 10 minutes. The reaction liquid was cooled to room temperature, and subjected to celite filtration. The filtrate was condensed under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate=60:40→30:70). The purified product was condensed under

reduced pressure to give the title compound(0.51g) as a yellowish-white solid.

$^1$H-NMR ($CDCl_3$) δppm: 0.84 (3H, s), 1.17 (3H, t, J =7.1 Hz), 1.52 (3H, s), 2.84 (2H, t, J = 6.3Hz), 3.38 (3H, s), 3.68-3.80 (1H, m), 3.99 (2H, t, J = 6.3 Hz), 4.00-4.15 (1H, m), 7.19-7.20 (3H, m), 7.73-7.76 (2H, m), 7.87-7.89 (2H, m).

▪ Reference Example 15

· Synthesis of 7-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-prop-1-ynyl]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Reference Example 14 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δppm: 0.83 (3H, s), 1.17 (3H, t, J =7.1 Hz), 1.52 (3H, s), 3.38 (3H, s), 3.71-3.89 (1H, m), 4.03-4.18 (1H, m) 4.70 (2H, s), 7.20-7.31 (3H, m), 7.75-7.78 (2H, m), 7.90-7.93 (2H, m).

▪ Reference Example 16

· Synthesis of (E)-3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)acrylic acid ethyl ester

Trifluoromethane sulfonic acid 1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl ester(0.40g), ethyl acrylate(0.13g), dichlorobis(triphenylphosphine) palladium (II)(35mg),lithium chloride(64mg), and triethylamine(0.19ml) were added to DMF(4ml). The mixture was heated at 180°C (microwave reactor) for 20 minutes. The reaction liquid was cooled to room temperature, and subjected to celite filtration. The filtrate was condensed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane: ethyl acetate=70:30→30:70). The purified product was condensed under reduced pressure to give the title compound(0.36g) as a pale yellow solid.

$^1$H-NMR ($CDCl_3$) δppm: 0.88 (3H, s), 1.22 (3H, t, J = 7.2 Hz), 1.35 (3H, t, J = 7.1 Hz), 1.55 (3H, s), 3.44 (3H, s), 3.81-3.90 (1H, m),

4.08-4.25(1H, m), 4.13 (2H, q, J = 7.1 Hz), 6.45 (1H, d, J = 16.0 Hz), 7.25-7.27 (1H, m),7.32-7.37 (2H, m), 7.65 (1H, d, J = 16.0 Hz).

▪ Reference Example 17

· Synthesis of 3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl) propionic acid ethyl ester

10% Palladium on carbon(0.1g) was added to a methanol solution(10ml) of (E)-3-(1-ethyl 3,3,5-trimethyl 2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl) acrylic acid ethyl ether(0.36g). The mixture was subjected to catalytic reduction at room temperature and under normal pressure. The catalyst was removed by celite filtration, followed by concentration under reduced pressure to give the title compound(0.29g) as a brown solid.

$^1$H-NMR ($CDCl_3$) δppm: 0.83 (3H, s), 1.18 (3H, t, J = 7.2 Hz), 1.23 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.65 (2H, t, J = 7.5 Hz), 2.98 (2H, t, J =7.5 Hz), 3.40 (3H, s), 3.77-3.90 (1H, m), 4.01-4.21 (3H, m), 7.07-7.11 (2H, m), 7.21-7.26 (1H, m).

▪ Reference Example 18

· Synthesis of 3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)propionic acid

50% Sodium hydroxide aqueous solution(1ml) was added to a methanol (20ml) solution of 3-(1-ethyl 3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl) propionic acid ethyl ester(1.1g). The mixture was stirred at room temperature overnight. Water was added to the reaction liquid, followed by washing with ether. A hydrochloric acid was added to the aqueous layer, followed by extraction using ethyl acetate and drying using magnesium sulfate. The dried product was condensed under reduced pressure to give the title compound(0.97g) as a colorless oily matter.

$^1$H-NMR ($CDCl_3$) δppm: 0.82 (3H, s), 1.18 (3H, t, J = 7.2 Hz), 1.52 (3H, s), 2.72 (2H, t, J = 7.5 Hz), 3.00 (2H, t, J = 7.5 Hz), 3.40 (3H, s),

3.72-3.88 (1H, m), 4.03-4.21 (1H, m), 7.09-7.13 (2H, m), 7.23-7.26 (1H, m).

▪ Reference Example 19

· Synthesis of 2-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl) ethyl carbamic acid tert-butyl ester

Diphenylphosphoryl azide(1.0ml) and tert-butanol(10ml) were added to a THF solution (10ml) of 3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl) propionic acid(0.97g) and triethylamine(0.67ml). The mixture was stirred at 100°C overnight. The reaction liquid was cooled to room temperature, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=80:20→50:50). The purified product was condensed under reduced pressure to give the title compound(0.38g) as a colorless oily matter.

$^1$H-NMR ($CDCl_3$) δppm: 0.83 (3H, s), 1.18 (3H, t, J = 7.2 Hz), 1.43 (9H, s), 1.53 (3H, s), 2.83 (2H, t, J = 7.1 Hz), 3.38 (2H, t, J = 7.1 Hz), 3.41 (3H, s), 3.71-3.85 (1H, m), 4.03-4.19 (1H, m), 4.57 (1H, br), 7.06-7.11 (2H, m), 7.22-7.27 (1H, m).

▪ Reference Example 20

· Synthesis of 5-(2,2-dihydroxyethyl)-5H-furo[3,2-c]pyridin-4-one

Sodium hydride (60% in oil, 0.36g) was suspended in DMF(10ml), and was cooled to 0°C in an ice water bath. 5H-Furo[3,2-c]pyridin-4-one(1.0g) was added thereto at the same temperature, and the mixture was stirred at 0°C for an hour. Bromoacetaldehyde diethylacetal(2.6ml) was added thereto, and the mixture was stirred at 80°C for 5 hours. Water was added to the reaction liquid, followed by extraction by ethyl acetate. The organic layer was dried over sodium sulfate, and condensed under reduced pressure. A 3N-hydrochrolic acid(5.8ml) was added to an acetone solution (20ml) of the residue, and the liquid was stirred at 60°C for 5 hours. Water was added to the reaction liquid and stirred at room temperature. The precipitated insoluble matter was separated, washed with water, and

dried to give the title compound(0.90g) as a white solid.

$^1$H-NMR (DMSO-$d_6$) δppm:

3.88 (d, J=5.4 Hz, 2H), 4.95-5.03 (m, 1H), 6.08 (d, J=6.4 Hz, 2H), 6.69 (dd, J=7.4, 0.8 Hz, 1H), 6.94 (dd, J=2.1 and 0.8 Hz, 1H), 7.50 (d, J=7.4 Hz, 1H), 7.86 (d, J=2.1 Hz, 1H).

▪ Reference Example 21

· Synthesis of

5-(2,2-dihydroxy-ethyl)-7-methyl-5H-furo[3,2-c]pyridin-4-one

The synthesis of the title compound was performed in the same manner as in Reference Example 20 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δppm: 2.28 (3H, d, J = 1.0 Hz), 3.85 (2H, d, J = 5.4 Hz), 4.95-5.02 (1H, m), 6.06 (2H, d, J = 6.3 Hz), 6.95 (1H, d, J = 2.1 Hz), 7.33 (1H, d, J = 1.0 Hz), 7.90 (1H, d, J = 2.1 Hz).

▪ Reference Example 22

· Synthesis of

5-(2,2-dihydroxyethyl)-2-methyl-5H-furo[3,2-c]pyridin-4-one

The synthesis of the title compound was performed in the same manner as in Reference Example 20 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$), δppm : 2.36 (s, 3H), 3.86 (d, J = 5.4 Hz, 2H), 4.94-4.98 (m, 1H), 6.04 (d, J = 6.4 Hz, 2H), 6.52 (s, 1H), 6.59 (d, J = 7.4 Hz, 1H), 7.41 (d, J = 7.4 H, 1H).

▪ Reference Example 23

· Synthesis of

5-(2,2-dihydroxyethyl)-2,3-dimethyl-5H-furo[3,2-c]pyridin-4-one

The synthesis of the title compound was performed in the same manner as in Reference Example 20 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$), δppm: 2.18 (3H, s), 2.28 (3H, s), 3.84 (2H, d, J = 5.4 Hz), 4.95-5.02 (1H, m), 6.04 (2H, d, J = 6.2 Hz), 6.53 (1H, d, J = 7.4 Hz), 7.38 (1H, d, J = 7.4 Hz).

▪ Reference Example 24

· Synthesis of

5-(2,2-dihydroxyethyl)-2,7-dimethyl-5H-furo[3,2-c]pyridin-4-one

The synthesis of the title compound was performed in the same manner as in Reference Example 20 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$), δppm: 2.14 (3H, s), 2.39 (3H, s), 3.82 (2H, d, J = 5.4 Hz), 4.95-5.01 (1H, m), 6.10 (2H, d, J = 6.2 Hz), 6.55 (1H, s), 7.24 (1H, s).

▪ Reference Example 25

· Synthesis of

6-(2,2-dihydroxyethyl)-4-methyl-6H-furo[2,3-c]pyridin-7-one

The synthesis of the title compound was performed in the same manner as in Reference Example 20 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$), δppm: 2.17(3H, s), 3.86 (2H, d, J = 5.4 Hz), 4.95-5.01 (1H, m), 6.06 (2H, d, J = 6.2 Hz), 6.92 (1H, d, J = 1.8 Hz), 7.17 (1H, s), 8.10 (1H, d, J = 1.8 Hz).

▪ Reference Example 26

· Synthesis of 5-(2,2-dihydroxyethyl)-5H-thieno[3,2-c]pyridin-4-one

The synthesis of the title compound was performed in the same manner as in Reference Example 20 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$), δppm : 3.90 (d, J = 6.3 Hz, 2H), 4.99-5.04 (m, 1H), 6.07 (d, J = 6.3 Hz, 2H), 6.86 (d, J = 7.2 Hz, 1H), 7.41-7.49 (m, 2H), 7.57-7.64 (m, 1H).

▪ Reference Example 27

· Synthesis of 6-(2,2-dihydroxyethyl)-6H-thieno[2,3-c]pyridin-7-one

The synthesis of the title compound was performed in the same manner as in Reference Example 20 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$), δppm : 3.98 (d, J = 5.3 Hz, 2H), 5.11-5.16 (m, 1H), 6.04 (d, J = 6.4 Hz, 1H), 6.66 (d, J = 7.1 Hz, 2H), 7.27 (d, J = 5.2

Hz, 1H), 7.41 (d, J = 7.1 Hz, 1H), 7.84 (d, J = 5.2 H, 1H).

▪ Reference Example 28

(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-acetonitrile

To a solution of 7-chloromethyl-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (1.11g) in DMF(15ml) was added sodium cyanide(0.59g) at room temperature, the mixture was stirred overnight. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried with magnesium sulfate, and was condensed under reduced pressure to give the title compound(0.84g) as a pale yellow oil.

$^1$H NMR ($CDCl_3$), δppm: : 0.85 (3H, s), 1.19 (3H, t, *J* = 7.1 Hz), 1.54 (3H, s), 3.43 (3H, s), 3.77-3.86 (3H, m), 4.09-4.19 (1H, m), 7.21-7.24 (2H, m), 7.34 (1H, d, *J* = 8.3 Hz).

▪ Reference Example 29

2-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-2-methyl-propionitrile

(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-acetonitrile (0.84g) was disolved in DMF(20ml), and was cooled to 0°C in ice water bath. Sodium hydride (60% in oil, 0.259g) was added thereto at the same temperature, and the mixture was stirred at 0°C for 0.5 hours. Methyl iodide (0.405ml) was added thereto, and the mixture was stirred at room temperature overnight. Methanol was added to the reaction mixture, and the mixture was condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=4:1→1:1). The purified product was condensed to dryness under reduced pressure to give the title compound(0.9g) as a white powder.

$^1$H NMR ($CDCl_3$), δppm: 0.84 (3H, s), 1.20 (3H, t, *J* = 7.06 Hz), 1.54 (3H, s), 1.77 (6H, s), 3.45 (3H, s), 3.78-3.87 (1H, m), 4.09-4.18 (1H, m), 7.34 (3H, s).

▪ Reference Example 30

1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carboxylic acid

To a t-butanol(20ml) H2O(5ml) solution of 1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde (2.25g) and 2-methyl-2-butene(3.25ml) were added sodium dihydrogenphosphate (0.92g) and sodium chlorite (2.081g), and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried with sodium sulfate, and was condensed under reduced pressure to give the title compound (0.98g) as a white powder.

mp:296-299°C

▪ Reference Example 31

7-Bromomethyl-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

Lithium bromide (0.678g) was added to an THF solution (2.3ml) of 7-chloromethyl-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione (0.23g), and the mixture was stirred at room temperature overnightr. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried with magnesium sulfate, and was condensed under reduced pressure to give the title compound(0.24g) as a white solid.

$^1$H NMR ($CDCl_3$), δppm: 0.85 (3H, s), 1.20 (3H, t, $J$ = 7.1 Hz), 1.53 (3H, s), 3.43 (3H, s), 3.77-3.87 (1H, m), 4.08-4.17 (1H, m), 4.49 (2H, s), 7.28-7.29 (3H, m).

▪ Reference Example 32

1-Ethyl-7-(3-hydroxy-propyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

3-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)propionic acid (1.0g) was dissolved in THF(20ml) and was cooled to 0°C in ice water bath. Triethylamine(0.525ml) and ethyl chloroformate(0.325ml) were added to this solution and stirred for 30 minutes at same temperature. Sodium

borohydride(0.36g) was added to the mixture under cooling in ice methanol bath. Methanol(0.64ml) was added dropwise to the mixture and stirred for 1 hour at same temperature. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried with magnesium sulfate, and was was condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=1:1→0:1). The purified product was condensed to dryness under reduced pressure to give the title compound(0.71g) as a colorless oil.

$^1$H NMR ($CDCl_3$), δppm : 0.83 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 1.88-1.95(2H, m), 2.76 (2H, t, J = 7.8 Hz), 3.41 (3H, s), 3.71 (2H, t, J = 6.3 Hz), 3.74-3.83 (1H, m), 4.10-4.19 (1H, m), 7.07 (1H, d, J = 1.8 Hz), 7.11 (1H, dd, J = 8.3 and 1.8 Hz), 7.23 (1H, d, J = 8.3 Hz)

• Reference Example 33

1-(2-Methoxy-ethyl)-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

mp:184-185°C

• Reference Example 34

1-Isobutyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

mp:204-205°C

• Reference Example 35

1-(2-Methoxy-ethyl)-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting

materials.

mp:163-166°C

▪ Reference Example 36

1-Isobutyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

mp:154-155°C

▪ Reference Example 37

1-Cyclopropyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.43 (2H, br), 1.07 (2H, br), 1.66 (3H, br), 3.17-3.23 (1H, m), 7.35 (1H, br), 7.50-7.56 (2H, m), 8.67 (1H, br).

▪ Reference Example 38

1-Cyclopropylmethyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.22-0.23 (2H, m), 0.46-0.48 (2H, m), 0.98-1.07 (1H, m), 3.90 (1H, br-d), 7.38-7.54 (3H, m), 9.42 (1H, br).

▪ Reference Example 39

1-Cyclopropyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.44 (2H, br), 1.08 (2H, br), 1.30 (6H, br),

3.20-3.25 (1H, m), 7.49 (1H, d, $J$ = 1.8 Hz), 7.58 (1H, d, $J$ = 8.4 Hz), 7.78 (1H, dd, $J$ = 8.4, 1.8 Hz), 9.98 (1H, s).

▪ Reference Example 40

1-Cyclopropylmethyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

mp:124-125°C

▪ Reference Example 41

1-Cyclopropyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

1-(2-Methoxy-ethyl)-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile(1.0g) was disolved in DMF(10ml), and was cooled to 0°C in ice water bath. Sodium hydride (60% in oil, 0.167g) was added thereto at the same temperature, and the mixture was stirred at 0°C for 0.5 hours. Methyl iodide (0.261ml) was added thereto, and the mixture was stirred at room temperature overnight. Water(100ml) was added to the reaction mixture, and was cooled to 0°C in ice water bath. The precipitated insoluble matter was separated and dried to give the title compound(0.61g) as a white powder.

$^1$H NMR ($CDCl_3$), δppm: 0.10-0.17 (1H, m), 0.66-0.73 (1H, m), 0.82-0.92 (1H, m), 0.89 (3H, s), 1.21-1.29 (1H, m), 1.55 (3H, s), 3.16-3.22 (1H, m), 3.41 (3H, s), 7.50-7.57 (3H, m).

▪ Reference Example 42

1-Isobutyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 41 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.72 (3H, d, $J$ = 6.7 Hz), 0.75 (3H, d, $J$ = 6.7 Hz), 0.86 (3H, s), 1.55 (3H, s), 1.77-1.88 (1H, m), 3.35 (1H, dd, $J$

= 13.7, 6.6 Hz), 3.45 (3H, s), 4.40 (1H, dd, $J$ = 13.7, 8.4 Hz), 7.41 (1H, d, $J$ = 8.4 Hz), 7.53-7.57 (2H, m).

▪ Reference Example 43

1-(2-Methoxy-ethyl)-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 41 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.89 (3H, s), 1.55 (3H, s), 3.32 (3H, s), 3.43 (3H, s), 3.59 (1H, ddd, $J$ = 10.4, 5.0, 3.7 Hz), 3.75 (1H, ddd, $J$ = 10.4, 7.8, 3.4 Hz), 3.94 (1H, ddd, $J$ = 14.4, 7.8, 3.7 Hz), 4.12 (1H, ddd, $J$ = 14.4, 5.0, 3.4 Hz), 7.52-7.55 (2H, m), 7.81-7.84 (1H, m).

Reference Example 44

5-Cyclopropyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

mp:252-253°C

▪ Reference Example 45

5-Isobutyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

mp:219-220°C

▪ Reference Example 46

5-Cyclopropylmethyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

mp:234-236°C

▪ Reference Example 47

5-(2-Methoxy-ethyl)-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

mp:247-248°C

▪ Reference Example 48

Methanesulfonic acid 3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-propyl ester

The synthesis of the title compound was obtained from 1-ethyl-7-(3-hydroxypropyl)-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine and methanesulfonyl chloride in a conventional matter.

$^1$H NMR ($CDCl_3$), δppm : 0.86 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.05-2.16(2H, m), 2.79 (2H, t, J = 7.6 Hz), 3.03 (3H, s), 3.42 (3H, s), 3.74-3.83 (1H, m), 4.10-4.18 (1H, m), 4.26 (2H, t, J = 6.2 Hz), 7.07 (1H, dd, J = 8.3 and 2.0 Hz), 7.10 (1H, d, J = 2.0 Hz), 7.25 (1H, d, J = 8.3 Hz).

▪ Reference Example 49

1-Cyclopropyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.10-0.20 (1H, m), 0.66-0.73 (1H, m), 0.73-0.94 (1H, m), 0.89 (3H, s), 1.21-1.28 (1H, m), 1.55 (3H, s), 3.91-3.45 (1H, m), 3.45 (3H, s), 7.57 (1H, d, 8.4 Hz), 7.74 (1H, d, $J$ = 1.8 Hz), 7.79 (1H, dd, $J$ = 8.4, 1.8 Hz), 10.01 (1H, s).

▪ Reference Example 50

1-Isobutyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.71 (3H, d, $J$ = 6.7 Hz), 0.75 (3H, d, $J$ = 6.7 Hz), 0.86 (3H, s), 1.53 (3H, s), 1.76-1.90 (1H, m), 3.39 (1H, dd, $J$ = 13.6, 6.6 Hz), 3.49 (3H, s), 4.42 (1H, dd, $J$ = 13.6, 8.4 Hz), 7.47 (1H, d, $J$ = 9.0 Hz), 7.76-7.79 (2H, m), 10.01 (1H, s).

▪ Reference Example 51

1-(2-Methoxy-ethyl)-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.88 (3H, s), 1.55 (3H, s), 3.31 (3H, s), 3.48 (3H, s), 3.60 (1H, ddd, $J$ = 10.4, 5.2, 4.1 Hz), 3.74 (1H, ddd, $J$ = 10.4, 7.1, 4.1 Hz), 4.01-4.15 (2H, m), 7.75-7.78 (2H, m), 7.80-7.83 (1H, m), 10.01 (1H, s).

▪ Reference Example 52

5-Isobutyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

mp:208-211°C

▪ Reference Example 53

5-Cyclopropylmethyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

mp:183-188°C

▪ Reference Example 54

1,3,3-Trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

mp:289-294°C

▪ Reference Example 55

1-Ethyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

mp:215-218°C

▪ Reference Example 56

3,3,5-Trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

mp:250-251°C

▪ Reference Example 57

5-Ethyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 10 using appropriate starting materials.

mp:241-247°C

▪ Reference Example 58

1,3,3-Trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

mp:208-210°C

▪ Reference Example 59

1-Ethyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 1.07 (3H, br), 1.29 (3H, t, $J$ = 7.1 Hz), 1.57 (3H, br), 4.57 (2H, q, $J$ = 7.1 Hz), 7.50 (1H, d, $J$ = 8.5 Hz), 7.57 (1H, br), 7.77 (1H, dd, $J$ = 8.5, 1.8 Hz), 8.42 (1H, br). 9.99 (1H, s).

▪ Reference Example 60

3,3,5-Trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

mp:197-202°C

▪ Reference Example 61

5-Ethyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

mp:188-191°C

▪ Reference Example 62

5-Cyclopropylmethyl-1-(2-methoxy-ethyl)-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same

manner as in Reference Example 41 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.15-0.24 (2H, m), 0.38-0.51 (2H, m), 0.87 (3H, s), 0.93-1.01 (1H, m), 1.55 (3H, s), 3.32 (3H, s), 3.53-3.62 (1H, m), 3.73-3.79 (1H, m), 3.97-4.04 (1H, m), 4.06-4.13 (1H, m), 7.55 (1H, dd, $J$ = 8.5, 1.9 Hz), 7.66 (1H, d, $J$ = 1.9 Hz), 7.82 (1H, d, $J$ = 8.5 Hz).

▪ Reference Example 63

1-Cyclopropylmethyl-5-(2-methoxy-ethyl)-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 41 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.14-0.22 (2H, m), 0.38-0.49 (2H, m), 0.87 (3H, s), 0.93-1.02 (1H, m), 1.55 (3H, s), 3.34 (3H, s), 3.53-3.65 (1H, m), 3.77-3.83 (1H, m), 3.91-3.98 (1H, m), 4.05-4.13 (1H, m), 7.45 (1H, d, $J$ = 8.5 Hz), 7.53 (1H, dd, $J$ = 8.5, 1.9 Hz), 8.10 (1H, d, $J$ = 1.9 Hz).

▪ Reference Example 64

5-Cyclopropyl-1-cyclopropylmethyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

The synthesis of the title compound was performed in the same manner as in Reference Example 41 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.03-0.19 (3H, m), 0.27-0.41 (2H, m), 0.61-0.68 (1H, m), 0.81-0.93 (1H, m), 0.88 (3H, s), 1.21-1.29 (2H, m), 1.54 (3H, s), 3.06-3.26 (1H, m), 3.42 (1H, dd, $J$ = 14.3, 6.8 Hz), 4.31 (1H, dd, $J$ = 14.3, 7.5 Hz), 7.38 (1H, d, $J$ = 8.5. Hz), 7.53 (1H, dd, $J$ = 8.5, 1.8 Hz), 7.72 (1H, d, $J$ = 1.8 Hz).

▪ Reference Example 65

5-Cyclopropylmethyl-1-(2-methoxy-ethyl)-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same

manner as in Reference Example 13 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.13-0.25 (2H, m), 0.37-0.48 (2H, m), 0.87 (3H, s), 0.96-1.03 (1H, m), 1.55 (3H, s), 3.32 (3H, s), 3.54-3.59 (1H, m), 3.66 (1H, dd, $J$ = 14.2, 6.4 Hz), 3.75 (1H, ddd, $J$ = 10.3, 7.2, 4.7 Hz), 4.04-4.19 (3H, m), 7.78 (1H, dd, $J$ = 8.4, 1.7 Hz), 7.82 (1H, d, $J$ = 8.4 Hz), 7.88 (1H, d, $J$ = 1.7 Hz), 10.0 (1H, s).

▪ Reference Example 66

1-Cyclopropylmethyl-5-(2-methoxy-ethyl)-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.14-0.24 (2H, m), 0.38-0.50 (2H, m), 0.87 (3H, s), 0.97-1.07 (1H, m), 1.55 (3H, s), 3.33 (3H, s), 3.53-3.59 (1H, m), 3.65 (1H, dd, $J$ = 14.2, 6.4 Hz), 3.73-3.79 (1H, m), 4.03-4.16 (3H, m), 7.51 (1H, d, $J$ = 8.4 Hz), 7.79 (1H, dd, $J$ = 8.4, 1.9 Hz), 8.19 (1H, d, $J$ = 1.9 Hz), 10.0 (1H, s).

▪ Reference Example 67

5-Cyclopropyl-1-cyclopropylmethyl-3,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde

The synthesis of the title compound was performed in the same manner as in Reference Example 13 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.09-0.07 (1H, m), 0.09-0.20 (2H, m), 0.27-0.40 (2H, m), 0.62-0.68 (1H, m), 0.83-0.92 (1H, m), 0.88 (3H, s), 1.20-1.28 (2H, m), 1.54 (3H, s), 3.27-3.33 (1H, m), 3.45 (1H, dd, $J$ = 14.3, 6.8 Hz), 4.34 (1H, dd, $J$ = 14.3, 7.5 Hz), 7.43 (1H, d, $J$ = 8.4 Hz), 7.77 (1H, dd, $J$ = 8.4, 1.9 Hz), 7.92 (1H, d, $J$ = 1.9 Hz), 10.0 (1H, s).

▪ Example 1

· Synthesis of 7-[4-(1,3-dioxo-1,3-dihydroisoindol-2-yl) butyl]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

10% Palladium on carbon(0.52g) was added to a methanol solution (50ml) of 7-[4-(1,3-dioxo-1,3-dihydroisoindol-2-yl) but-1-ynyl]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diaze pine-2,4-dione(2.2g). The mixture was subjected to catalytic reduction at room temperature under normal pressure. The catalyst was removed by celite filtration, followed by concentration under reduced pressure to give the title compound(1.93g) as a brown solid.
$^1$H-NMR ($CDCl_3$) δppm: 0.81 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.61-1.79 (4H, m), 2.68 (2H, t, J = 7.0 Hz), 3.40 (3H, s), 3.71-3.81 (3H, m), 4.01-4.18 (1H, m), 7.02-7.08 (2H, m), 7.20 (1H, d, J = 8.3 Hz), 7.70-7.74 (2H, m), 7.83-7.86 (2H, m).

▪ Example 2

· Synthesis of
7-(4-aminobutyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

Hydrazine hydrate(0.5ml) was added to a methanol solution (60ml) of
7-[4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyl]-1-ethyl-3,3,5-tri methyl-1,5-dihydrobenzo[b][1,4]diazepine 2,4-dione(1.93g). The mixture was stirred for 5.5 hours while heated under reflux. After cooled to room temperature, a 1N-sodium hydroxide aqueous solution was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and condensed under reduced pressure to give the title compound(1.2g) as a yellow solid.
$^1$H-NMR ($CDCl_3$) δppm: 0.83 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.47-1.58 (2H, m), 1.52 (3H, s), 1.62-1.73 (4H, m), 2.66 (2H, t, J = 7.6 Hz), 2.76 (2H, t, J = 7.0 Hz), 3.41 (3H, s), 3.71-3.84 (1H, m), 4.03-4.18 (1H, m), 7.02-7.09 (2H, m), 7.21 (1H, d, J = 8.3 Hz).

▪ Example 3

Synthesis of
1-ethyl-3,3,5-trimethyl-7-{4-[(pyridin-4-ylmethyl)amino]butyl}-1, 5-dihydrobenzo[b][1,4]diazepine-2,4-dione

4-Pyridine carbaldehyde(0.15ml) was added to a methanol

solution (10ml) of 7-(4-aminobutyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.51g). The mixture was stirred for an hour at room temperature under nitrogen atmosphere. Sodium borohydride (0.2g) was added to the mixture, and the mixture was stirred at room temperature overnight. The liquid was then condensed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate: methanol=9:1→3:2). The purified product was condensed under reduced pressure to give the title compound(0.38g) as a colorless oily matter.

$^1$H-NMR ($CDCl_3$) δppm: 0.82 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.47-1.58 (2H, m), 1.53 (3H, s), 1.53-1.60 (2H, m), 1.62-1.71 (2H, m), 2.62-2.68 (4H, m), 3.40 (3H, s), 3.69-3.81 (3H, m), 4.03-4.19 (1H, m), 7.01 (1H, d, J = 1.9Hz), 7.06 (1H, dd, J = 8.3, 1.9 Hz), 7.21 (1H, d, J = 8.3 Hz), 7.25-7.28 (2H, m), 8.53-3.56 (2H, m).

▪ Example 4

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-(4-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}butyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

(2-Methyl-4-oxo-4H-furo[3,2-c]pyridin 5-yl)acetaldehyde(0.18g) and acetic acid(0.1ml) were added to a 1,2-dichloroethane solution (5ml) of 1-ethyl-3,3,5-trimethyl-7-{4-[(pyridin-4-ylmethyl)amino]butyl}-1,5-dihydrobenzo[b][1,4]diazepine 2,4-dione(0.38g). The mixture was stirred for 30 minutes at room temperature. sodium triacetoxyborohydride(0.32g) was added to the mixture, and the mixture was stirred at room temperature overnight. The reaction mixture was condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol =1:0→9:1). The purified product was condensed under reduced pressure. A 6N-hydrogen chloride ethyl acetate solution(1.0ml) was added to an ethyl acetate solution (20ml) of the residue, and the liquid was stirred at room temperature. The precipitated insoluble matter was separated, washed with ethyl acetate, and dried to give the title compound(0.43g) as

a white solid.

$^1$H-NMR (DMSO$d_6$) δppm: 0.69 (3H, s), 1.03 (3H, t, J = 7.1 Hz), 1.30 (3H, s), 1.56 (2H, br), 1.76 (2H, br), 2.38 (3H, s), 2.59 (2H, t, J = 7.6 Hz), 3.13 (2H, br), 3.31 (3H, s), 3.22-3.38 (2H, m), 3.40-3.55 (1H, m), 3.99-4.08(1H, m), 4.42 (2H, br), 4.64 (2H, br), 6.56 (1H, s), 6.75 (1H, d, J = 7.4 Hz), 7.13 (1H, d, J = 8.4 Hz), 7.25 (1H, s), 7.38 (1H, d, J = 8.4 Hz), 7.63 (1H, br), 8.22 (2H, br), 8.92 (2H, br).

▪ Example 5

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{4-[(2-methylpyridin-3-ylmethyl)amino]butyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δppm: 0.82 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 1.52-1.61 (2H, m), 1.63-1.70 (2H, m), 2.56 (3H, s), 2.62-2.73 (4H, m), 3.40 (3H, s), 3.68-3.81 (3H, m), 4.02-4.19 (1H, m), 7.01-7.11 (3H, m), 7.20 (1H, d, J = 8.3 Hz), 7.58-7.61 (1H, m), 8.38-8.40 (1H, m).

▪ Example 6

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-(4-{N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}butyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δppm: 0.70 (3H, s), 1.04 (3H, t, J = 7.1 Hz), 1.31 (3H, s), 1.59 (2H, br), 1.74 (2H, br), 2.50 (3H, s), 2.61 (2H, t, J = 7.6 Hz), 2.80 (2H, br), 3.10 (2H, br), 3.31 (3H, s), 3.55-3.70 (1H,m), 3.95-4.08 (1H, m), 4.37 (4H, br), 6.56 (1H, s), 6.82 (1H, br), 6.95 (1H, s), 7.13 (1H, d, J = 8.4 Hz), 7.25 (1H, s), 7.39 (1H, d, J = 8.4 Hz), 7.68 (1H, br), 7.81 (1H, br), 7.91 (1H, br), 8.71 (2H, br).

▪ Example 7

· Synthesis of 7-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propyl]-1-ethyl-3,3,5-tr

imethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 1 using appropriate starting materials.

$^1$H NMR ($CDCl_3$) δppm : 0.80 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.00-2.13 (2H, m), 2.72 (2H, t, J = 7.7 Hz), 3.42 (3H, s), 3.68-3.73 (3H, m), 3.98-4.11 (1H, m), 7.07-7.10 (2H, m), 7.17-7.20 (1H, m), 7.70-7.75 (2H, m), 7.82-7.85 (2H, m).

▪ Example 8

· Synthesis of 7-(3-aminopropyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 2 using appropriate starting materials.

$^1$H NMR ($CDCl_3$) δppm : 0.84 (3H, s), 1.19 (3H, t, J = 7.1 Hz), 1.54 (3H, s), 1.76 (2H, br), 1.74-1.91 (2H, m), 2.71 (2H, t, J = 8.2 Hz), 2.84 (2H, t, J = 7.0 Hz), 3.42 (3H, s), 3.81-3.95 (1H, m), 4.08-4.19 (1H, m), 7.09-7.14 (2H, m), 7.22-7.26 (1H, m).

▪ Example 9

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[(pyridin-4-ylmethyl)amino]propyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H NMR ($CDCl_3$) δppm : 0.81 (3H, s), 1.20 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 1.78-1.91 (2H, m), 2.66-2.74 (4H, m), 3.39 (3H, s), 3.71-3.89 (3H, m), 4.05-4.16 (1H, m), 7.02-7.10 (3H, m), 7.19-7.26 (2H, m), 8.52-8.56 (2H, m).

▪ Example 10

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-(3-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}propyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 4 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.69 (3H, s), 1.03 (3H, t, J = 7.1 Hz), 1.32 (3H, s), 2.05 (2H, br), 2.38 (3H, s), 2.60 (2H, br), 3.04 (2H, br), 3.31 (3H, s), 3.25-3.50 (2H, m), 3.40-3.65 (1H, m), 3.91-4.08 (1H, m), 4.38 (2H, br), 4.58 (2H, br), 6.55 (1H, s), 6.75 (1H, d, J = 7.4 Hz), 7.13 (1H, d, J = 8.4 Hz), 7.25 (1H, s), 7.38 (1H, d, J = 8.4 Hz), 7.63 (1H, d, J = 7.4 Hz), 8.17 (2H, br), 8.88 (2H, br).

▪ Example 11

· Synthesis of
7-(2-aminoethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

A 4N-hydrogen chloride ethyl acetate solution(6ml) was added to an ethyl acetate solution (20ml) of [2-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-yl) ethyl] carbamic acid tert-butyl ester(0.38g), and the mixture was stirred at room temperature overnight. The reaction mixture was condensed under reduced pressure to give the title compound(0.26g) as a pale orange amorphous solid.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.79 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.39 (3H, s), 2.91-3.00 (2H, m), 3.02-3.13 (2H, m), 3.38 (3H, s), 3.68-3.83 (1H,m), 3.95-4.11 (1H, m), 7.11-7.16 (1H, m), 7.23 (1H, br), 7.31-7.35 (1H, m), 8.06 (3H, br).

▪ Example 12

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{2-[(pyridin-4-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Triethylamine(0.1ml) and 4-pyridine carbaldehyde(0.094ml) were added to a methanol solution (10ml) of 7-(2-aminoethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine 2,4-dione hydrochloride(0.26g). The mixture was stirred at room temperature for 1 hour. Sodium borohydride(0.11g) was added, and the mixture was further stirred at room temperature overnight. The reaction liquid was condensed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl

acetate: methanol=9:1→3:2). The purified product was condensed under reduced pressure to give the title compound (0.21g) as a colorless oily matter.

$^1$H-NMR ($CDCl_3$) δppm: 0.83 (3H, s), 1.86 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.82-2.94 (4H, m), 3.40 (3H, s), 3.73-3.85 (1H, m), 3.84 (2H, s), 4.02-4.18 (1H, m), 7.05-7.11 (2H, m), 7.20-7.26 (3H, m), 8.52-8.55 (2H, m).

▪ Example 13

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{2-[(2-methylpyridin-3-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δppm: 0.82 (3H, s), 1 18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.52 (3H, s), 2.82-2.88 (2H, m), 2.93-2.99 (2H, m), 3.40 (3H, s), 3.75-3.82 (1H, m), 3.81 (3H, s), 4.11-4.18 (1H, m), 7.06-7.12 (2H, m), 7.22-7.26 (2H, m), 7.53-7.57 (1H, m), 8.37-8.40 (1H, m).

▪ Example 14

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{2-[(4-methylpyridin-3-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δppm: 0.82 (3H, s), 1 18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.33 (3H, s), 2.82-2.87 (2H, m), 2.93-2.99 (2H, m), 3.39 (3H, s), 3.75-3.84 (1H, m), 3.82 (3H, s), 4.10-4.20 (1H, m), 7.06-7.12 (3H, m), 7.21-7.26 (1H, m), 8.38 (1H, d, J = 4.9 Hz), 8.41 (1H, s).

▪ Example 15

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-(2-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}ethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride.

The synthesis of the title compound was performed in the same

manner as in Example 4 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.69 (3H, s), 1.02 (3H, t, J = 7.1 Hz), 1.31 (3H, s), 2.39 (3H, s), 3.08 (2H, br), 3.29 (3H, s), 3.11-3.42 (2H, m), 3.42-3.70 (3H, m), 3.91-4.10 (1H, m), 4.36 (2H, br), 4.57 (2H, br), 6.54 (1H, s), 6.71 (1H, d, J = 7.2 Hz), 7.15-7.20 (1H, m), 7.30 (1H, s), 7.37-7.40 (1H, m), 7.60-7.63 (1H, m), 8.16 (2H, br), 8.86 (2H, br).

▪ Example 16

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-(2-{N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}ethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.70 (3H, s), 1.03 (3H, t, J = 7.1 Hz), 1.32 (3H, s), 2.50 (3H, s), 2.84 (2H, br), 3.14 (2H, br), 3.34 (3H, s), 3.25-3.45(2H, m), 3.50-3.70 (1H, m), 3.90-4.08 (1H, m), 4.38 (2H, br), 4.47 (2H, br), 6.76 (1H, d, J = 7.1 Hz), 6.93 (1H, s), 7.23 (1H, d, J = 8.2 Hz), 7.36 (1H, s), 7.40 (1H, d, J = 8.2 Hz), 7.69 (1H, br), 7.82 (1H, br), 7.90 (1H, d, J = 2.1 Hz),8.71 (2H, br).

▪ Example 17

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{2-[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.72 (3H, s), 1.04 (3H, t, J = 7.1 Hz), 1.33 (3H, s), 2.40 (3H, s), 2.51 (3H, s), 2.89 (4H, br), 3.31 (3H, s), 3.50 (2H, br), 3.72-3.77 (1H, m), 4.02-4.07 (1H, m), 4.42 (2H, br), 4.61 (2H, br), 6.54 (1H, s), 6.70 (1H, br), 7.23 (1H, br), 7.34 (1H, s), 7.40 (1H, br), 7.64 (1H, br),7.86 (1H, br), 8.73 (2H, br).

▪ Example 18

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{2-[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.71 (3H, s), 1.04 (3H, t, J = 7.1 Hz), 1.33 (3H, s), 2.39 (3H, s), 2.51 (3H, s), 2.74 (2H, br), 3.15 (2H, br), 3.33 (3H,s), 3.51 (2H, br), 3.72-3.77 (1H, m), 4.02-4.07 (1H, m), 4.42 (2H, br), 4.75 (2H, br), 6.53 (1H, s), 6.70 (1H, br), 7.23-7.26 (1H, m), 7.36 (1H, s), 7.42-7.44(1H, m), 7.64 (1H, br), 7.86 (1H, br), 8.76 (1H, br), 9.20 (1H, br).

▪ Example 19

· Synthesis of
7-aminomethyl-1,5-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

10% Palladium on carbon(0.1g) was added to an acetic acid solution (20ml) of
1,5-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile(0.3g), and catalytic reduction was carried out at room temperature under 4 atm. The catalyst was removed by celite filtration, followed by concentration under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=9:1→5:5). The purified product was condensed under reduced pressure to give the title compound(0.17g) as a yellowish white solid.
$^1$H NMR ($CDCl_3$) δppm : 3.28 (1H, d, J = 12.4 Hz), 3.42 (3H, s), 3.44 (3H, s), 3.38-3.42 (1H, m), 3.94 (2H, s), 7.26-7.29 (3H, m).

▪ Example 20

· Synthesis of
7-aminomethyl-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 19 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δppm: 0.84 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 3.43 (3H, s), 3.75-3.82 (1H, m), 3.93 (2H, s), 4.13-4.19 (1H, m), 7.20-7.23 (1H, m), 7.25-7.27 (2H, m).

▪ Example 21

· Synthesis of 7-aminomethyl-1,3,3,5-tetramethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 19 using appropriate starting materials.
$^1$H NMR ($CDCl_3$) δppm : 0.85 (3H, s), 1.54 (3H, s), 3.42 (3H, s), 3.44 (3H, s), 3.93 (2H, s), 7.18-7.26 (3H, m).

▪ Example 22

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[(pyridin-4-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
$^1$H-NMR ($CDCl_3$) δppm: 0.83 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 3.42 (3H, s), 3.69-3.82 (1H, m), 3.84 (2H, s), 3.87 (2H, s), 4.04-4.20 (1H, m), 7.23-7.26 (3H, m), 7.29-7.32 (2H, m), 8.56-8.58 (2H, m).

▪ Example 23

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
$^1$H-NMR ($CDCl_3$) δppm: 0.84 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.56 (3H, s), 3.42 (3H, s), 3.77-3.88 (1H, m), 3.84 (2H, s), 3.88 (2H, s), 4.09-4.18 (1H, m), 7.11-7.15 (1H, m), 7.24-7.29 (3H, m), 7.63-7.65 (1H, m), 8.41-8.43 (1H, m).

▪ Example 24

· Synthesis of
1,5-dimethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
$^1$H NMR ($CDCl_3$) δppm : 2.59 (3H, s), 3.27 (1H, d, J = 12.4 Hz), 3.37-3.43 (7H, m), 3.82 (2H, s), 3.86 (2H, s), 7.10-7.14 (1H, m), 7.23-7.26 (3H, m), 7.61-7.65 (1H, m), 8.39-8.42 (1H, m).

▪ Example 25

· Synthesis of
1,3,3,5-tetramethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
$^1$H NMR ($CDCl_3$) δppm : 0.85 (3H, s), 1.54 (3H, s), 2.56 (3H, s), 3.43 (3H, s), 3.44 (3H, s), 3.82 (2H, s), 3.88 (2H, s), 7.11-7.15 (1H, m), 7.20-7.26 (3H, m), 7.62-7.64 (1H, m), 8.41-8.43 (1H, m).

▪ Example 26

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-[[[2-(pyridin-3-yl)ethyl]amino]methyl]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Trimethyl orthoformate(9ml) was added to a methanol solution (50ml) of
1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde(2.2g) and
3-(2-aminoethyl)pyridine(1.0g). The mixture was stirred at room temperature for 2 hours.
The reaction liquid was condensed under reduced pressure, and a methanol solution (50ml) of the residue was cooled with ice. Sodium borohydride(0.34g) was added thereto, and the mixture was stirred at room temperature for 30 minutes. Water was added to the reaction liquid, followed by concentration under reduced pressure. The residue was extracted by ethyl acetate. The organic layer was dried by anhydrous sodium sulfate, and condensed under reduced pressure. The

residue was purified by NH silica gel column chromatography (ethyl acetate: methanol=9:1). The purified product was condensed under reduced pressure to give the title compound(2.5g) as a colorless oily matter.

$^1$H NMR ($CDCl_3$) δppm : 0.82 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.80-2.90 (2H, m), 2.90-2.99 (2H, m), 3.39 (3H, s), 3.72-3.90 (1H, m), 3.83 (2H, s), 4.06-4.22 (1H, m), 7.14-7.20 (2H, m), 7.20-7.28 (2H, m), 7.54 (1H, td, J = 2.0, 7.8 Hz ), 8.45-8.53 (2H, m).

▪ Example 27

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethylamino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium borohydride(0.15g) was added to a methanol solution (150ml) of 1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde(1.1g) and 5-(2-aminoethyl)-2-methyl-5H-furo[3,2-c]pyridin-4-one(1.0g), and the mixture was stirred at room temperature overnight. The reaction liquid was filtered to remove insoluble matter, and the filtrate was condensed under reduced pressure.

The residue was purified by silica gel column chromatography (ethyl acetate: methanol =9:1→5:5). The purified product was condensed under reduced pressure to give the title compound(1.1g) as a colorless amorphous solid.

$^1$H NMR ($CDCl_3$) δppm : 0.79 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.15 (1H, br), 2.42 (3H, s), 3.02-3.10 (2H, m), 3.36 (3H, s), 3.75-3.81 (1H, m), 3.86 (2H, s), 4.09-4.20 (3H, m), 6.49 (1H, d, J = 6.7 Hz), 6.53 (1H, d, J = 1.9 Hz), 7.15-7.21 (4H, m).

▪ Example 28

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethylamino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same

manner as in Example 27 using appropriate starting materials.
$^1$H-NMR ($CDCl_3$) δppm: 0.80 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.95 (2H, br), 3.36 (3H, s), 3.74-3.82 (1H, m), 3.86 (2H, br), 4.02-4.14 (1H, m), 4.20 (2H, br), 6.57 (1H, d, J = 7.3 Hz), 6.96 (1H, d, J = 2.0 Hz), 7.14-7.26 (4H, m), 7.50 (1H, d, J = 2.0 Hz).

▪ Example 29

· Synthesis of
7,7'-azanediylbis(methylene)bis(1-ethyl-3,3,5-trimethyl-1H-benzo[b][1,4]diazepine-2,4-dione)

10% Palladium on carbon(0.3g) was added to an acetic acid solution (20ml) of
1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbonitrile(1.4g), and catalytic reduction was carried out at room temperature under 4 atm. The catalyst was removed by celite filtration, followed by concentration under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=9:1→5:5). The purified product was condensed under reduced pressure to give the title compound(0.19g) as a colorless oily matter.
$^1$H-NMR ($CDCl_3$) δppm: 0.84 (6H, s), 1.19 (6H, t, J = 7.1 Hz), 1.54 (6H, s), 3.43 (6H, s), 3.71-3.92 (2H, m), 3.87 (4H, s), 4.01-4.18 (2H, m), 7.24-7.27 (6H, m).

▪ Example 30

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

5-(2,2-Dihydroxyethyl)-2-methyl-5H-furo[3,2-c]pyridine-4-one(0.21g) and acetic acid(0.1ml) were added to a 1,2-dichloroethane solution(15ml) of 1-ethyl-3,3,5-trimethyl-7-{[(pyridin-4-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.38g), and the mixture was stirred for 30 minutes at room temperature. Sodium triacetoxy borohydride(0.42g) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was condensed

under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol =1:0→4:1). The purified product was condensed under reduced pressure, and the residue was recrystallized from ether to give the title compound(0.47g) as a white powder.

mp: 143 to 145°C

▪ Example 31

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (ether)

mp: 153 to 154°C

▪ Example 32

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (ether)

mp: 172 to 173°C

▪ Example 33

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[N-[3-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)propyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δppm: 0.66 (3H, s), 1.04 (3H, br), 1.33 (3H, s), 2.29 (2H, br), 2.41 (3H, s), 2.80 (3H, br).3.08 (2H, br), 3.33 (3H, s),

3.73-3.79 (1H, m), 3.93-4.01 (3H, m), 4.46 (2H, br), 4.57 (2H, br), 6.56 (1H, s), 6.67(1H, d, J = 6.2 Hz), 7.42-7.44 (1H, m), 7.48-7.59 (2H, m), 7.88 (2H, br), 8.76 (1H, br), 8.93 (1H, br).

▪ Example 34

· Synthesis of 7,7'-(pyridin-4-ylmethylazanediyl)bis(methylene)bis(1-ethyl-3,3,5-trimethyl-1H-benzo[b][1,4]diazepine-2,4-dione) dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δppm: 0.69 (6H, s), 1.07 (6H, t, J = 7.1 Hz), 1.32 (6H, s), 3.35 (6H, s), 3.74-3.81 (2H, m), 3.94-4.04 (2H, m), 4.52 (2H, br), 4.82 (4H, s), 7.45-7.47 (4H, m), 8.08 (2H, d, J = 6.7 Hz), 8.05-8.40 (2H, m), 8.88 (2H, d, J = 6.7 Hz).

▪ Example 35

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δppm: 0.67 (3H, s), 1.01 (3H, t, J = 7.1 Hz), 1.32 (3H, s), 2.41-2.59 (5H, m), 2.83 (2H, br), 3.25 (3H, s), 3.61-3.83 (3H, m),3.92-3.97 (1H, m), 4.16 (2H, br), 6.58 (1H, br), 7.22 (2H, br), 7.40 (2H, br), 7.48-7.63 (2H, m), 7.67-7.68 (1H, m), 7.71-7.75 (1H, m), 8.10-8.12 (1H, m), 8.24(1H, br), 8.44 (1H, br).

▪ Example 36

· Synthesis of 1,5-dimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δppm: 2.38 (3H, s), 2.51 (3H, s), 2.54 (2H, br), 2.75

(2H, br), 3.05 (1H, d, J = 12.4 Hz), 3.26 (6H, s), 3.32 (1H, d, J = 12.4Hz), 3.75 (2H, br), 4.14 (2H, br), 6.45 (1H, br), 6.63 (1H, br), 7.24 (1H, br),7.33 (1H, br), 7.50 (2H, br), 7.68 (1H, br), 8.25 (1H, br), 8.56 (1H, br).

▪ Example 37

· Synthesis of 1,3,3,5-tetramethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.70 (3H, s), 1.34 (3H, s), 2.51 (3H, s),2.55 (2H, br), 2.82 (2H, br), 3.30 (6H, s), 3.78 (2H, br), 4.19 (2H, br), 6.73(1H, br), 6.88 (1H, br), 7.31 (3H, br), 7.60 (2H, br), 7.91 (1H, d, J = 2.0 Hz),8.26 (1H, br), 8.56 (1H, br).

▪ Example 38

· Synthesis of 1,3,3,5-tetramethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.70 (3H, s), 1.34 (3H, s), 2.41 (3H, s), 2.51 (3H, s), 2.56 (2H, br), 2.79 (2H, br), 3.30 (6H, s), 3.77 (2H, br), 4.15 (2H, br), 6.46 (1H, br), 6.63 (1H, br), 7.31 (3H, br), 7.50 (1H, br), 7.68 (1H, br), 8.24 (1H, br), 8.56 (1H, br).

▪ Example 39

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde(0.92g) and acetic acid(0.1ml)

were added to a 1,2-dichloroethane solution (15ml) of (2-pyridine 3-ylethyl)pyridin-4-ylmethylamine(0.81g), and the mixture was stirred for 30 minutes at room temperature. Sodium triacetoxyborohydride(0.90g) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol =100:0→90:10). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution(1.0ml) was added to an ethyl acetate solution (20ml) of the residue, and the liquid was stirred at room temperature. The precipitated insoluble matter was separated, washed with ethyl acetate, and dried to give the title compound(0.83g) as a white solid $^1$H-NMR (DMSO-$d_6$) δppm: 0.68 (3H, s), 1.06 (3H, t, J = 7.1 Hz), 1.33 (3H, s), 3.00 (2H, br), 3.32 (3H, s), 3.10-3.45 (4H, m), 3.74-3.79 (1H, m),3.94-4.00 (3H, m), 7.43 (2H, br), 7.98-8.02 (2H, m), 8.45 (1H, d, J = 8.0 Hz), 8.82-8.88 (6H, m).

▪ Example 40

· Synthesis of N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-pyridin-3-ylethyl)benzamide hydrochloride

Benzoyl chloride(0.13ml) was added to an acetonitrile solution (6ml) of 1-ethyl-3,3,5-trimethyl-7-[(2-pyridin-3-ylethylamino)methyl]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.38g) and triethylamine(0.17ml) under ice cooling. The mixture was stirred at room temperature overnight. An aqueous sodium hydrogencarbonate solution was added to the reaction mixture, followed by extraction by ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol =91:9). The purified product was condensed under reduced pressure. A 1N-hydrogen chloride ethanol solution(0.87ml) was added to an isopropyl alcohol solution (10ml) of the residue, and the liquid was condensed under reduced pressure. The residue was recrystallized from

the ethanol-ether mixture to give the title compound(0.26g) as a pale brown white powder.

$^1$H NMR (DMSO-$d_6$) δppm : 0.73 (3H, bs), 0.98-1.14 (3H, m), 1.34 (3H, s), 2.74-3.94 (8H, m), 3.94-4.11 (1H, m), 4.52 and 4.82 (2H, bs), 6.90-7.60(8H, m), 7.60-9.10(4H, m).

▪ Example 41

· Synthesis of N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-4-methyl-N-(2-pyridin-3-ylethyl)benzamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 40 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$) δppm : 0.73 (3H, s), 1.09 (3H, t, J = 7.0 Hz), 1.34 (3H, s), 2.31 (3H, s), 2.88-3.94 (8H, m), 3.94-4.11 (1H, m), 4.35-5.05 (2H, m), 6.88-7.63(7H, m), 7.63-9.10(4H, m).

▪ Example 42

· Synthesis of N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-pyridin-3-ylethyl)benzenesulfonamide

Triethylamine(0.15ml) was added to a acetonitrile solution (6ml) of 1-ethyl-3,3,5-trimethyl-7-[(2-pyridin-3-yl-ethylamino)methyl]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.35g). The mixture was cooled with ice. Benzenesulphonyl chloride(0.13ml) was added, and the mixture was stirred at room temperature overnight. The reaction liquid was condensed under reduced pressure. Water was added to the residue, followed by extraction by ethyl acetate.

The organic layer was dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by NH silica gel column chromatography (hexane: ethyl acetate=30:70). The purified product was condensed under reduced pressure, and the residue was recrystallized from the ethyl acetate-ether mixture to give the title compound(0.1g) as a white powder.

mp: 143.2 to 146.4°C

▪ Example 43

· Synthesis of

7-{[N-benzyl-N-(2-pyridin-3-ylethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$) δppm : 0.72 (3H, s), 1.05 (3H, t, J = 7.0 Hz), 1.34 (3H, s), 2.59-3.72 (8H, m), 3.72-3.94 (1H, m), 3.94-4.11 (1H, m), 4.33-4.65 (3H, m), 6.85-8.18(10H, m), 8.30-8.77(2H, m), 11.17 (1H, bs).

▪ Example 44

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-({N-(4-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (ether)

mp: 160 to 161°C

▪ Example 45

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (ether)

mp: 171 to 174°C

▪ Example 46

· Synthesis of

7-({N-(2,6-dimethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-fu

ro[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (ether)

mp: 148 to 149°C

▪ Example 47

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(6-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (ether)

mp: 123 to 125°C

▪ Example 48

· Synthesis of

N-[2-({[(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-7-yl)methyl][2-(pyridin-3-yl)ethyl]amino}methyl)phenyl]methanesulfonamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$) δppm : 0.71 and 0.73 (3H, s), 0.90-1.20 (3H, m), 1.33 (3H, s), 2.69-2.80 (1H, bs), 2.85 (2H, bs), 2.92-3.10 (4H, m), 3.20-3.70 (3H, m), 3.70-3.96 (3H, m), 3.96-4.10 (1H, m), 4.46-4.73 (2H, m), 7.00-7.70(7H, m), 7.70-8.30(2H, m), 8.52-8.80(2H, m), 9.30-9.59(1H, m),10.90 (1H, bs).

▪ Example 49

· Synthesis of

7-{[N-(2,4-dimethylthiazol-5-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 4 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$) δppm : 0.73 (3H, s), 1.09 (3H, t, J = 7.0 Hz), 1.34 (3H, s), 2.30 (3H, bs), 2.59 (3H, s), 2.65-5.20 (13H, m), 6.32-8.07(4H, m), 8.16-8.40(1H, m), 8.66-8.90(2H, m),11.91 (1H, bs).

▪ Example 50

· Synthesis of
N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-methyl-N-(2-pyridin-3-ylethyl)benzamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 40 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$) δppm : 0.71 and 0.75 (3H, s), 1.00-1.12 (3H, m), 1.32 and 1.34(3H, s), 2.03 and 2.04(3H, s), 2.85-5.50 (8H, m), 3.26 and 3.34(3H, s), 6.86(0.4H, d, J = 7.8 Hz), 7.05-7.98(8.3H, m), 8.39(0.9H, bs), 8.63(0.4H, bs), 8.74(0.5H, bs), 8.87(0.5H, bs).

▪ Example 51

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{[N-(2-methylpyridin-3-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.72 (3H, s), 1.06 (3H, t, J = 7.1 Hz), 1.34 (3H, s), 2.68 (3H, br), 3.10 (2H, br), 3.34 (3H, s), 3.18-3.60 (4H, m), 3.74-3.90 (3H, m), 3.99-4.05 (1H, m), 7.49 (2H, br), 7.73 (1H, br), 7.87 (1H, br), 7.98-8.01 (1H, br), 8.45 (1H, br), 8.68-8.70 (2H, m), 8.81 (1H, d, J = 5.5 Hz), 8.89 (1H, br).

▪ Example 52

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-({N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(thiazol-2-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same

manner as in Example 30 using appropriate starting materials.
White powder (ether)
mp: 171 to 172°C

▪ Example 53

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(thiazol-2-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (ether)
mp: 146 to 147°C

▪ Example 54

· Synthesis of
7-{[N-(2,6-dimethylpyridin-3-ylmethyl)-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.68 (3H, s), 1.02 (3H, t, J = 7.1 Hz), 1.32 (3H, s), 3.32 (9H, s), 3.32 (3H, s), 3.67 (2H, br), 3.60-3.82 (1H, m), 3.78 (2H, br), 3.82 (2H, br), 3.97-4.04 (1H, m), 7.28 (1H, br), 7.34 (1H, br), 7.39-7.41 (1H, m), 7.67 (1H, d, J = 7.8 Hz), 7.82-7.85 (1H, m), 8.43 (1H, br), 8.56 (1H, br), 8.61 (1H, br).

▪ Example 55

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{[N-(2-methylpyridin-3-ylmethyl)-N-(4-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.67 (3H, s), 1.01 (3H, t, J = 7.1 Hz), 1.32 (3H, s), 2.48 (3H, s), 2.70 (3H, s), 3.31 (3H, s), 3.63-3.75 (3H, m),

3.87 (4H, br), 3.95-4.08 (1H, m), 7.25 (1H, m), 7.34 (1H, m), 7.38-7.40 (1H, m), 7.81-7.86 (2H, m), 8.55 (1H, br), 8.62 (1H, d, J = 5.2 Hz), 8.69 (1H, d, J = 5.9 Hz), 8.86 (1H, br).

▪ Example 56

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[N-(4-methylpyridin-3-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 39 using appropriate starting materials.
White powder
$^1$H NMR (DMSO-$d_6$) δppm : 0.70 (3H, s), 1.03 (3H, br), 1.33 (3H, s), 2.33 (3H, br), 2.86 (2H, br), 3.10 (2H, br), 3.32 (3H, s), 3.31-3.41 (1H, m), 3.77 (4H, br), 4.00-4.06 (1H, m), 7.20 (1H, br), 7.43 (2H, br), 7.80 (1H, br), 7.97 (1H, br), 8.41 (1H, br), 8.70 (2H, br), 8.79-8.81 (2H, m).

▪ Example 57

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-({N-(4-methylthiazol-5-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (ether)
mp: 161 to 162°C

▪ Example 58

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylthiazol-5-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (ether)

mp: 188 to 189°C

▪ Example 59

· Synthesis of 2-methyl-2H-pyrazole-3-sulfonic acid N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-pyridin-3-ylethyl) amide

The synthesis of the title compound was performed in the same manner as in Example 42 using appropriate starting materials.

White powder (ethyl acetate)

mp: 123 to 124°C

▪ Example 60

· Synthesis of 7-{[N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

White powder (diethyl ether)

mp: 136 to 145°C

▪ Example 61

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[N-(2-methylpyridin-3-ylmethyl)-N-(2-pyridin-4-ylethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 39 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$) δppm : 0.71 (3H, s), 1.07 (3H, t, J = 7.1 Hz), 1.34 (3H, s), 2.71 (5H, br), 3.20-3.39 (3H, m), 3.37 (3H, s), 3.55 (2H, br), 3.77 (2H, br), 3.99-4.04 (1H, m), 7.31 (1H, br), 7.47 (2H, br), 7,85 (2H, br), 7.95 (2H, br), 8.68 (1H, br), 8.85 (2H, br).

▪ Example 62

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]py

ridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 164 to 165°C

▪ Example 63

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 181 to 183°C

▪ Example 64

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylthiazol-5-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 134 to 136°C

▪ Example 65

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[(thiazol-2-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H NMR ($CDCl_3$) δppm : 0.83 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 3.43 (3H, s), 3.74-3.84 (1H, m), 3.92 (2H, s), 4.09-4.18 (3H, m), 7.25-7.27 (3H, m), 7.30 (1H, d, J = 3.3 Hz), 7.75 (1H, d, J = 3.3 Hz).

▪ Example 66

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[(4-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H NMR ($CDCl_3$) δppm : 0.83 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.38 (3H, s), 3.42 (3H, s), 3.74-3.84 (1H, m), 3.83 (2H, s), 3.87 (2H, s), 4.09-4.18 (1H, m), 7.09 (1H, d, J = 4.9 Hz), 7.24-7.27 (3H, m), 8.39 (1H, d, J = 4.9 Hz), 8.46 (1H, s).

▪ Example 67

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[(4-methylthiazol-5-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H NMR ($CDCl_3$) δppm : 0.83 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.40 (3H, s), 3.43 (3H, s), 3.75-3.84 (1H, m), 3.86 (2H, s), 3.97 (2H, s), 4.09-4.18 (1H, m), 7.22-7.28 (3H, m), 8.65 (1H, s).

▪ Example 68

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[N-[2-(4-methyl-7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (diethyl ether)

mp: 164-165°C

▪ Example 69

· Synthesis of

7-{[N-[2-(2,7-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl

-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (diethyl ether)

mp: 193-195°C

▪ Example 70

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[N-[2-(4-methyl-7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (diethyl ether)

mp: 203-204°C

▪ Example 71

· Synthesis of

7-{[N-[2-(2,7-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (diethyl ether)

mp: 181-182°C

▪ Example 72

· Synthesis of

7-({N-[2-(2,7-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(thiazol-2-ylmethyl)amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (diethyl ether)

mp: 157-159°C

▪ Example 73

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[N-(2-methylpyridin-3-ylmethyl)-N-(4-methylthiazol-5-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δppm : 0.68 (3H, s), 1.03 (3H, t, J = 7.1 Hz), 1.32 (3H, s), 2.30 (3H, s), 2.70 (3H, s), 3.32 (3H, s), 3.68 (2H, s), 3.67-3.76 (1H, m), 3.84 (4H, br), 3.97-4.06 (1H, m), 7.25-7.27 (1H, m), 7.34 (1H, s), 7.43 (1H, d, J = 8.4 Hz), 7.84 (1H, dd, J = 6.0, 7.7 Hz), 8.48-8.50 (1H, m), 8.62 (1H, d, J = 5.5 Hz), 8.95-8.97 (1H, m).

▪ Example 74

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{(N-[(1-methyl-1H-indazol-3-yl)methyl]-N-[2-(pyridin-3-yl)ethyl]amino)methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR ($D_2O$), δppm : 0.73 (3H, s), 1.11 (3H, t, J = 7.0 Hz), 1.41 (3H, s), 3.15-3.29 (2H, m), 3.30 (3H, s), 3.38-3.58 (2H, m), 3.68-3.88 (1H, m), 4.00-4.20 (1H, m), 4.04 (3H, s), 4.37 (2H, bs), 4.44 (2H, bs), 7.08-7.21(1H, m), 7.35(1H, d, J = 7.8 Hz), 7.39-7.60(5H, m), 7.65(1H, dd, J = 6.0, 7.5 Hz), 8.10(1H, d, J = 7.8 Hz), 8.35- 8.49 (2H, m).

▪ Example 75

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-{[N-(2-methyloxazol-4-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR ($D_2O$), δppm : 0.79 (3H, s), 1.14 (3H, t, J = 7.0 Hz), 1.43 (3H, s), 2.48 (3H, s), 3.21-3.33 (2H, m), 3.37-3.52 (2H, m), 3.40 (3H, s),

3.77-3.93 (1H, m), 4.07-4.21 (1H, m), 4.36 (2H, s), 4.47 (2H, dd, J = 13.6, 22.0 Hz), 7.50(1H, dd, J = 1.4, 8.4 Hz), 7.54-7.60(1H, m), 7.63(1H, d, J = 8.4 Hz), 7.73(1H, dd, J = 5.6, 7.9 Hz), 7.95 (1H, bs), 8.09(1H, d, J = 7.9 Hz), 8.54 (1H, bs), 8.58 (1H, d, J = 5.6 Hz).

▪ Example 76

· Synthesis of
7-{[N-[2-(2,3-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : 0.70 (3H, s), 1.04 (3H, t, $J$ = 7.1 Hz), 1.33 (3H, s), 2.12 (3H, s), 2.31 (3H, s), 2.45 (3H, br), 2.77 (2H, br), 3.28 (3H, s), 3.71-3.83 (3H, m), 3.94-4.07 (3H, m), 4.08 (2H, br), 6.54 (1H, br), 7.24 (1H, br), 7.35 (2H, br), 7.42 (1H, br), 7.67 (1H, br), 8.26 (1H, br), 8.52 (1H, br).

▪ Example 77

· Synthesis of
7-{[N-[2-(2,3-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : 0.70 (3H, s), 1.03 (3H, t, $J$ = 7.1 Hz), 1.33 (3H, s), 2.11 (3H, s), 2.24 (3H, br), 2.31 (3H, s), 2.80 (2H, br), 3.28 (3H, s), 3.71-3.84 (3H, m), 3.94-4.11 (5H, m), 6.50 (1H, br), 7.24 (1H, br), 7.36 (2H, br), 7.40 (1H, br), 7.59 (1H, br), 8.59 (1H, br), 8.64 (1H, br).

▪ Example 78

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methylpyridin-3-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 39 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : 0.72 (3H, s), 1.05 (3H, t, $J$ = 7.1 Hz), 1.34 (3H, s), 2.70 (8H, br), 3.34 (3H, br), 3.78 (3H, br), 4.01-4.20 (5H, m), 7.47 (1H, br), 7.52 (1H, br), 7.85 (2H, br), 8.35 (2H, br), 8.65 (2H, br), 9.00 (1H, br).

▪ Example 79

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{[N-[2-(4-methylpyridin-3-yl)ethyl]-N-(4-methylthiazol-5-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : 0.73 (3H, s), 1.06 (3H, t, $J$ = 7.1 Hz), 1.34 (3H, s), 2.43 (3H, s), 2.46 (3H, s), 3.36 (5H, br), 3.45 (2H, br), 3.77-3.88 (1H, m), 4.00-4.12 (1H, m), 4.45 (2H, br), 4.65 (2H, br), 7.52-7.54 (1H, m), 7.60 (1H, br), 7.88 (1H, d, $J$ = 6.0 Hz), 7.90 (1H, br), 7.71 (1H, d, $J$ = 6.0 Hz), 8.77 (1H, s), 9.15 (1H, s).

▪ Example 80

· Synthesis of
7-({N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(4-methylpyridin-3-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : 0.73 (3H, s), 1.07 (3H, t, $J$ = 7.1 Hz), 1.34 (3H, s), 2.11 (3H, s), 2.45 (3H, s), 3.36 (5H, br), 3.50 (2H, br), 3.50-3.82 (4H, m), 3.95-4.08 (1H, m), 4.45 (2H, br), 4.53 (2H, br), 6.51 (1H, br), 7.56 (1H, br), 7.61 (1H, br), 7.87-7.89 (1H, m), 8.02 (1H, m), 8.71 (1H, d, $J$ = 5.8 Hz), 8.78 (1H, s).

▪ Example 81

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methylpyridin-3-yl)ethyl]-N-(

4-methylthiazol-5-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δppm : 0.74 (3H, s), 1.06 (3H, t, $J$ = 7.1 Hz), 1.34 (3H, s), 2.41 (3H, s), 2.65 (3H, s), 3.36 (7H, br), 3.70-3.79 (1H, m), 3.95-4.08 (1H, m), 4.47 (2H, br), 4.73 (2H, br), 7.54 (1H, br), 7.60 (1H, br), 7.87 (1H, dd, $J$ =7.8, 5.7 Hz ), 7.92 (1H, br), 8.33 (1H, d, $J$ = 7.8 Hz), 8.66 (1H, d, $J$ = 5.7 Hz), 9.12 (1H, s).

▪ Example 82

· Synthesis of 7-({N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(2-methylpyridin-3-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δppm : 0.75 (3H, s), 1.07 (3H, t, $J$ = 7.1 Hz), 1.35 (3H, s), 2.12 (3H, s), 2.67 (3H, s), 3.36 (5H, br), 3.43 (2H, br), 3.70-3.90 (4H, m), 4.00-4.08 (1H, m), 4.45 (2H, br), 4.50 (2H, br), 6.50 (1H, br), 7.55-7.57 (1H, m), 7.61 (1H, br), 7.85-7.88 (1H, m), 7.94 (1H, br), 8.36 (1H, br), 8.67 (1H, d, $J$ = 5.6 Hz).

▪ Example 83

· Synthesis of 7-({N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (diethyl ether)

mp: 152-153°C

▪ Example 84

· Synthesis of 1-ethyl-7-({N-(4-methoxypyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-

4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.14 (3H, t, $J$ = 7.1 Hz), 1.50 (3H, s), 2.43 (3H, s), 2.77-2.87 (2H, m), 3.29 (3H, s), 3.61 (1H, d, $J$ = 14.3 Hz), 3.68-3.74 (2H, m), 3.78 (1H, d, $J$ = 14.3 Hz), 3.86 (3H, s), 3.97-4.08 (1H, m), 4.09-4.19 (3H, m), 6.43-6.46 (2H, m), 6.78 (1H, d, $J$ = 5.8 Hz), 7.00 (2H, br), 7.05 (1H, s), 7.10 (1H, d, $J$ = 7.3 Hz), 8.39-8.40 (2H, m).

▪ Example 85

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-trifluoromethylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (diethyl ether)

mp: 162-164°C

▪ Example 86

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[N-(4-methylthiazol-5-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde(0.423g) and acetic acid(0.14g) were added to a 1,2-dichloroethane solution (10ml) of N-(4-methylthiazol-5-ylmethyl)-N-(2-pyridin-3-ylethyl)amine(0.36g). The mixture was stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride(0.48g) was added, and the mixture was stirred at room temperature overnight. The reaction liquid was condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=100:0→50:50). The purified product was condensed under reduced pressure. The residue was washed

with diethyl ether, and dried to give the title compound(0.37g) as a white powder.
mp: 118-120°C

▪ Example 87

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(5-trifluoromethylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (diethyl ether)
mp: 138-140°C

▪ Example 88

· Synthesis of
1-ethyl-7-({N-(5-fluoropyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (diethyl ether)
mp: 144-146°C

▪ Example 89

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(3-methylpyridin-4-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (diethyl ether)
mp: 153-154°C

▪ Example 90

· Synthesis of

1-Ethyl-7-({N-(3-fluoropyridin-4-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (diethyl ether)
mp: 149-151°C

▪ Example 91

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{[N-(2-methyl-2H-pyrazol-3-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H NMR ($D_2O$), δppm : 0.79 (3H, s), 1.11 (3H, t, J = 7.0 Hz), 1.43 (3H, s), 3.09-3.70 (5H, m), 3.39 (3H, s), 3.45 (2H, s), 3.70-3.94 (1H, m), 3.94-4.59 (5H, m), 6.3-6.57(1H, m), 7.30-7.65(4H, m), 7.82-8.06(1H,m), 8.15-8.47 (1H, m), 8.51 (1H, bs), 8.54-8.74 (1H, m).

▪ Example 92

· Synthesis of
1-ethyl-7-{[N-(1H-indol-7-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
White powder (ethanol)
mp: 155-167.8°C

▪ Example 93

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{[2-(4-methylpyridin-3-yl)ethylamino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 27 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.18 (3H, t, $J$ = 7.1 Hz), 1.53 (3H, s), 2.32 (3H, s), 2.94-2.96 (2H, m), 3.00 (2H, br), 3.42 (3H, s), 3.74-3.74 (1H, m), 3.96 (2H, br), 4.04-4.11 (1H, m), 7.07 (1H, d, $J$ = 4.9 Hz), 7.26-7.28 (2H, m), 7.34 (1H, br), 8.33 (1H, d, $J$ = 4.9 Hz), 8.38 (1H, s).

▪ Example 94

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{[2-(2-methylpyridin-3-yl)ethylamino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 27 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.18 (3H, t, $J$ = 7.1 Hz), 1.53 (3H, s), 2.55 (3H, s), 2.85-2.93 (4H, m), 3.41 (3H, s), 3.75-3.83 (1H, m), 3.86 (2H, s), 4.11-4.17 (1H, m), 7.08 (1H, dd, $J$ = 7.6, 4.8 Hz), 7.19-7.21 (2H, m), 7.24-7.26 (1H, m), 7.44 (1H, dd, $J$ = 7.6, 1.6 Hz), 8.37 (1H, dd, 4.8, 1.6 Hz).

▪ Example 95

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-({N-(2-methyloxazol-4-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$) , δppm: 0.69 (3H, s), 1.06 (3H, t, J = 7.1 Hz), 1.33 (3H, s), 2.395 (3H, s), 2.404 (3H, s), 3.32 (3H, s), 3.47 (2H, br), 3.74-3.81 (1H, m), 3.95-4.06 (1H, m), 4.23 (2H, br), 4.37 (4H, br), 6.55 (1H, s), 6.76 (1H, d, J = 7.4 Hz), 7.48 (2H, br), 7.57 (1H, d, J = 7.4 Hz), 7.67 (1H, br), 8.14 (1H, br).

▪ Example 96

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(oxazol-5-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$) , δppm: 0.66 (3H, s), 1.03 (3H, t, J = 7.1 Hz), 1.32 (3H, s), 2.39 (3H, s), 3.21 (3H, s), 3.28-3.49 (2H, m), 3.74 (1H, br), 3.91-3.97 (1H, m), 4.20 (6H, br), 6.69 (1H, s), 6.69-6.71 (1H, m), 7.11-7.31 (4H, m), 7.54 (1H, d, J = 7.5 Hz), 8.33 (1H, br).

▪ Example 97

· Synthesis of
7-({N-(2,4-dimethylthiazol-5-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
Pale yellow powder
mp: 187-188°C

▪ Example 98

· Synthesis of
7-{[N-(2-chloropyridin-3-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
white powder
mp: 183-187°C

▪ Example 99

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{[N-(2-pyridin-3-ylethyl)-N-(quinolin-5-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
white powder
mp: 136-141°C

▪ Example 100

· Synthesis of

7-{[N-[2-(2,6-dimethylpyridin-3-yl)ethyl]-N-(4-methylthiazol-5-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 136-137°C

▪ Example 101

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 139-140°C

▪ Example 102

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-({N-(4-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 145-147°C

▪ Example 103

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-({N-(4-methylpyridin-3-ylmethyl)-N-[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 138-142°C

▪ Example 104

· Synthesis of
7-{[N-[2-(2,7-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 144-145°C

▪ Example 105

· Synthesis of
7-{[N-[2-(2,3-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 148-150°C

▪ Example 106

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 125-127°C

▪ Example 107

· Synthesis of
7-({N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 193-195°C

▪ Example 108

· Synthesis of
7-({N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-[2-(2,6-dimethylpyridin-3-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
white powder
$^1$H NMR (DMSO-$d_6$) , δppm: 0.75 (3H, s), 1.07 (3H, t, J = 7.1 Hz), 1.35 (3H, s), 2.11 (3H, s), 2.65 (3H, br), 2.71 (3H, br), 3.36 (5H, br), 3.50 (3H, s), 3.60-3.82 (3H, m), 4.00-4.10 (1H, m), 4.44 (2H, br), 4.53 (2H, br), 6.50 (1H, br), 7.57-7.67 (2H, m), 7.69 (1H, d, J = 7.9 Hz), 8.00 (1H, br), 8.23 (1H, br).

The following compounds shown in Examples 109 to 308 can be prepared by the same manner as mentioned above or a conventional manner using appropriate starting materials.

▪ Example 109

1-Ethyl-3,3,5-trimethyl-7-{[oxazol-5-ylmethyl-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 110

1-Ethyl-3,3,5-trimethyl-7-{[(2-pyridin-3-yl-ethyl)-thiazol-2-ylmethyl-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 111

1-Ethyl-3,3,5-trimethyl-7-{[(2-pyridin-3-yl-ethyl)-thiazol-5-ylmethyl-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 112

1-Ethyl-3,3,5-trimethyl-7-{[(2-pyridin-3-yl-ethyl)-thiazol-4-ylmethyl-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 113

1-Ethyl-3,3,5-trimethyl-7-{[(4-methyl-thiazol-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 114

7-{[(4,5-Dimethyl-thiazol-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 115

1-Ethyl-3,3,5-trimethyl-7-{[(2-methyl-pyridin-4-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 116

1-Ethyl-7-{[(3-fluoro-pyridin-4-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 117

1-Ethyl-3,3,5-trimethyl-7-{[(3-methyl-pyridin-4-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 118

1-Ethyl-3,3,5-trimethyl-7-{[(2-methyl-pyridin-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 119

7-{[[2-(2,6-Dimethyl-pyridin-3-yl)-ethyl]-(2-methyl-pyridin-3-ylmethyl)-amino]-methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 120

1-Ethyl-3,3,5-trimethyl-7-{[(3-methyl-pyridin-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 121

1-Ethyl-3,3,5-trimethyl-7-{[(2-pyridin-3-yl-ethyl)-(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 122

1-Ethyl-7-{[(2-methoxy-pyridin-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 123

7-{[(2,6-Dimethyl-pyridin-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 124

1-Ethyl-7-{[(3-hydroxy-benzyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 125

1-Ethyl-7-{[furan-2-ylmethyl-(2-pyridin-3-yl-ethyl)-amino]-methyl}-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 126

1-Ethyl-7-{[furan-3-ylmethyl-(2-pyridin-3-yl-ethyl)-amino]-methyl

}-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 127

1-Ethyl-3,3,5-trimethyl-7-{[(5-methyl-furan-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 128

1-Ethyl-3,3,5-trimethyl-7-{[(2-methyl-furan-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 129

7-{[(4,5-Dimethyl-furan-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 130

1-Ethyl-3,3,5-trimethyl-7-{[(2-pyridin-3-yl-ethyl)-(5-trifluoromethyl-furan-2-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 131

1-Ethyl-3,3,5-trimethyl-7-{[(3-methyl-thiophen-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 132

1-Ethyl-3,3,5-trimethyl-7-{[(2-pyridin-3-yl-ethyl)-thiophen-2-ylmethyl-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 133

7-{[(4,5-Dimethyl-thiophen-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 134

1-Ethyl-3,3,5-trimethyl-7-{2-[(4-methyl-thiazol-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 135

1-Ethyl-3,3,5-trimethyl-7-{2-[(4-methyl-thiazol-5-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 136

1-Ethyl-3,3,5-trimethyl-7-{2-[(2-methyl-pyridin-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 137

1-Ethyl-3,3,5-trimethyl-7-{2-[(4-methyl-pyridin-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 138

1-Ethyl-3,3,5-trimethyl-7-{2-[(3-methyl-pyridin-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 139

7-{2-[(2,6-Dimethyl-pyridin-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 140

N-(2-{[[2-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-ethyl]-(2-pyridin-3-yl-ethyl)-amino]-methyl}-phenyl)-methanesulfonamide

▪ Example 141

7-{2-[(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 142

1-Ethyl-3,3,5-trimethyl-7-{3-[(4-methyl-thiazol-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 143

1-Ethyl-3,3,5-trimethyl-7-{3-[(4-methyl-thiazol-5-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 144

1-Ethyl-3,3,5-trimethyl-7-{3-[(2-methyl-pyridin-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 145

1-Ethyl-3,3,5-trimethyl-7-{3-[(4-methyl-pyridin-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 146

1-Ethyl-3,3,5-trimethyl-7-{3-[(3-methyl-pyridin-2-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 147

N-(2-{[[3-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-propyl]-(2-pyridin-3-yl-ethyl)-amino]-methyl}-phenyl)-methanesulfonamide

- Example 148

7-{3-[(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-(2-pyridin-3-yl-ethyl)

-amino]-propyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 149

1-Ethyl-3,3,5-trimethyl-7-({(2-methyl-pyridin-3-ylmethyl)-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 150

1-Ethyl-3,3,5-trimethyl-7-({oxazol-5-ylmethyl-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 151

1-Ethyl-3,3,5-trimethyl-7-({[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-thiazol-2-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 152

1-Ethyl-3,3,5-trimethyl-7-({[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-thiazol-4-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 153

1-Ethyl-3,3,5-trimethyl-7-({(4-methyl-thiazol-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 154

7-({(4,5-Dimethyl-thiazol-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 155

7-({(2,4-Dimethyl-thiazol-5-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihy

dro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 156

1-Ethyl-3,3,5-trimethyl-7-({[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-pyridin-4-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 157

1-Ethyl-3,3,5-trimethyl-7-({(2-methyl-pyridin-4-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 158

1-Ethyl-7-({(3-fluoro-pyridin-4-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 159

1-Ethyl-3,3,5-trimethyl-7-({(3-methyl-pyridin-4-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 160

1-Ethyl-3,3,5-trimethyl-7-({[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-pyridin-3-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 161

1-Ethyl-3,3,5-trimethyl-7-({(3-methyl-pyridin-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 162

1-Ethyl-3,3,5-trimethyl-7-{[[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 163

1-Ethyl-7-({(2-methoxy-pyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 164

7-({(2,6-Dimethyl-pyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 165

N-[2-({(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 166

1-Ethyl-7-({(3-hydroxy-benzyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 167

1-Ethyl-7-({furan-2-ylmethyl-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 168

1-Ethyl-7-({furan-3-ylmethyl-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 169

1-Ethyl-3,3,5-trimethyl-7-({(5-methyl-furan-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 170

1-Ethyl-3,3,5-trimethyl-7-({(2-methyl-furan-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 171

7-({(4,5-Dimethyl-furan-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 172

1-Ethyl-3,3,5-trimethyl-7-{[[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(5-trifluoromethyl-furan-2-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 173

7-({(4,5-Dimethyl-thiophen-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 174

1-Ethyl-3,3,5-trimethyl-7-({[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-thiophen-2-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 175

1-Ethyl-3,3,5-trimethyl-7-({(3-methyl-thiophen-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 176

7-({(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 177

1-Ethyl-3,3,5-trimethyl-7-({[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-oxazol-4-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 178

1-Ethyl-3,3,5-trimethyl-7-({[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-thiazol-5-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 179

1-Ethyl-3,3,5-trimethyl-7-({[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-thiazol-4-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 180

1-Ethyl-3,3,5-trimethyl-7-{[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-2-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 181

7-({(4,5-Dimethyl-thiazol-2-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 182

1-Ethyl-3,3,5-trimethyl-7-{[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(2-methyl-pyridin-4-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 183

1-Ethyl-3,3,5-trimethyl-7-({[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-pyridin-3-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 184

1-Ethyl-3,3,5-trimethyl-7-{[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyri

din-5-yl)-ethyl]-(3-methyl-pyridin-2-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 185

1-Ethyl-7-({(2-methoxy-pyridin-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 186

N-[2-({(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 187

1-Ethyl-7-({(3-hydroxy-benzyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 188

1-Ethyl-7-({furan-2-ylmethyl-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 189

1-Ethyl-7-({furan-3-ylmethyl-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 190

1-Ethyl-3,3,5-trimethyl-7-({(5-methyl-furan-2-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 191

1-Ethyl-3,3,5-trimethyl-7-({(2-methyl-furan-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1,5-d

ihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 192

7-({(4,5-Dimethyl-furan-2-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 193

1-Ethyl-3,3,5-trimethyl-7-{[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(5-trifluoromethyl-furan-2-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 194

1-Ethyl-3,3,5-trimethyl-7-({[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-thiophen-2-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 195

1-Ethyl-3,3,5-trimethyl-7-{[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(3-methyl-thiophen-2-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 196

7-({(4,5-Dimethyl-thiophen-2-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 197

1-Ethyl-3,3,5-trimethyl-7-{[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-2-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 198

1-Ethyl-3,3,5-trimethyl-7-{[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(3-methyl-pyridin-2-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 199

N-[2-({(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 200

1-Ethyl-3,3,5-trimethyl-7-{[[2-(3-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(2-methyl-pyridin-3-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 201

7-{[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-2-ylmethyl)-amino]-methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 202

7-{[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-5-ylmethyl)-amino]-methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 203

7-{[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(3-methyl-pyridin-2-ylmethyl)-amino]-methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 204

N-(2-{[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-amino]-methyl}-phenyl)-methanesulfonamide

▪ Example 205

1-Ethyl-3,3,5-trimethyl-7-(2-{(4-methyl-thiazol-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-ethyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 206

1-Ethyl-3,3,5-trimethyl-7-(2-{(4-methyl-thiazol-5-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-ethyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 207

1-Ethyl-3,3,5-trimethyl-7-(2-{(4-methyl-pyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-ethyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 208

1-Ethyl-3,3,5-trimethyl-7-(2-{(3-methyl-pyridin-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-ethyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 209

N-[2-({[2-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-ethyl]-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 210

7-(2-{(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-ethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 211

1-Ethyl-3,3,5-trimethyl-7-{2-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-2-ylmethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 212

1-Ethyl-3,3,5-trimethyl-7-{2-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-5-ylmethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 213

1-Ethyl-3,3,5-trimethyl-7-{2-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(3-methyl-pyridin-2-ylmethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 214

7-(2-{(2,6-Dimethyl-pyridin-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-ethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 215

N-[2-({[2-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-ethyl]-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 216

7-(2-{(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-ethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 217

1-Ethyl-3,3,5-trimethyl-7-{2-[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-2-ylmethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 218

1-Ethyl-3,3,5-trimethyl-7-{2-[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-5-ylmethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 219

1-Ethyl-3,3,5-trimethyl-7-{2-[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(2-methyl-pyridin-3-ylmethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 220

1-Ethyl-3,3,5-trimethyl-7-{2-[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-pyridin-3-ylmethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 221

1-Ethyl-3,3,5-trimethyl-7-{2-[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(3-methyl-pyridin-2-ylmethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 222

N-[2-({[2-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-ethyl]-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 223

7-(2-{(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-ethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 224

7-{2-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-2-ylmethyl)-amino]-ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 225

7-{2-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-5-ylmethyl)-amino]-ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 226

7-{2-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(2-methyl-pyridin-3-ylmethyl)-amino]-ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 227

7-{2-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-pyridin-3-ylmethyl)-amino]-ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 228

7-{2-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(3-methyl-pyridin-2-ylmethyl)-amino]-ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 229

N-[2-({[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-[2-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 230

7-{2-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-amino]-ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 231

1-Ethyl-3,3,5-trimethyl-7-(3-{(4-methyl-thiazol-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 232

1-Ethyl-3,3,5-trimethyl-7-(3-{(4-methyl-thiazol-5-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 233

1-Ethyl-3,3,5-trimethyl-7-(3-{(2-methyl-pyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

• Example 234

1-Ethyl-3,3,5-trimethyl-7-(3-{(4-methyl-pyridin-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

• Example 235

1-Ethyl-3,3,5-trimethyl-7-(3-{(3-methyl-pyridin-2-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

• Example 236

N-[2-({[3-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-propyl]-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

• Example 237

7-(3-{(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-propyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

• Example 238

1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-2-ylmethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

• Example 239

1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-5-ylmethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

• Example 240

1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(2-methyl-pyridin-3-ylmethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 241

1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-pyridin-3-ylmethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 242

1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(3-methyl-pyridin-2-ylmethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 243

7-{3-[(2,6-Dimethyl-pyridin-3-ylmethyl)-(2-pyridin-3-yl-ethyl)-amino]-propyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 244

7-(3-{(2,6-Dimethyl-pyridin-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-propyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 245

N-[2-({[3-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-propyl]-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 246

7-(3-{(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-propyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 247

1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-2-ylmethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 248

1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-5-ylmethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 249

1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(2-methyl-pyridin-3-ylmethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 250

1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-pyridin-3-ylmethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 251

1-Ethyl-3,3,5-trimethyl-7-{3-[[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(3-methyl-pyridin-2-ylmethyl)-amino]-propyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 252

N-[2-({[3-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-propyl]-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 253

7-(3-{(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-amino}-propyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 254

7-{3-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-2-ylmethyl)-amino]-propyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 255

7-{3-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-thiazol-5-ylmethyl)-amino]-propyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 256

7-{3-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(2-methyl-pyridin-3-ylmethyl)-amino]-propyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 257

7-{3-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-pyridin-3-ylmethyl)-amino]-propyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 258

7-{3-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(3-methyl-pyridin-2-ylmethyl)-amino]-propyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 259

N-[2-({[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)-propyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 260

7-{3-[[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-amino]-propyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 261

1-Ethyl-3,3,5-trimethyl-7-(3-{(2-methyl-pyridin-3-ylmethyl)-[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)-ethyl]-amino}-propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 262

1-Ethyl-3,3,5-trimethyl-7-{[[2-(4-methyl-7-oxo-7H-thieno[2,3-c]pyridin-6-yl)-ethyl]-(2-methyl-pyridin-3-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 263

1-Ethyl-3,3,5-trimethyl-7-{[[2-(4-methyl-7-oxo-7H-thieno[2,3-c]pyridin-6-yl)-ethyl]-(4-methyl-pyridin-3-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 264

1-Ethyl-3,3,5-trimethyl-7-(3-{(2-methyl-pyridin-3-ylmethyl)-[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)-ethyl]-amino}-propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 265

1-Ethyl-3,3,5-trimethyl-7-{[[2-(7-methyl-4-oxo-4H-thieno[3,2-c]pyridin-5-yl)-ethyl]-(2-methyl-pyridin-3-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 266

1-Ethyl-3,3,5-trimethyl-7-{[[2-(7-methyl-4-oxo-4H-thieno[3,2-c]pyridin-5-yl)-ethyl]-(4-methyl-pyridin-3-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 267

1-Ethyl-3,3,5-trimethyl-7-({oxazol-5-ylmethyl-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 268

1-Ethyl-3,3,5-trimethyl-7-({[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-thiazol-2-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 269

1-Ethyl-3,3,5-trimethyl-7-({[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-thiazol-5-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 270

1-Ethyl-3,3,5-trimethyl-7-({[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-thiazol-4-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 271

1-Ethyl-3,3,5-trimethyl-7-({(4-methyl-thiazol-2-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 272

1-Ethyl-3,3,5-trimethyl-7-({(4-methyl-thiazol-5-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 273

7-({(4,5-Dimethyl-thiazol-2-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 274

7-({(2,4-Dimethyl-thiazol-5-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 275

1-Ethyl-3,3,5-trimethyl-7-({[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-pyridin-4-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 276

1-Ethyl-3,3,5-trimethyl-7-({(2-methyl-pyridin-4-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 277

1-Ethyl-7-({(3-fluoro-pyridin-4-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 278

1-Ethyl-3,3,5-trimethyl-7-({(3-methyl-pyridin-4-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 279

1-Ethyl-3,3,5-trimethyl-7-({[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-pyridin-3-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 280

1-Ethyl-3,3,5-trimethyl-7-({(4-methyl-pyridin-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 281

1-Ethyl-3,3,5-trimethyl-7-{[[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 282

1-Ethyl-7-({(2-methoxy-pyridin-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

- Example 283

7-({(2,6-Dimethyl-pyridin-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-

yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 284

N-[2-({(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-phenyl]-methanesulfonamide

▪ Example 285

1-Ethyl-7-({(3-hydroxybenzyl)-[2-(1-oxo-2H-isoquinolin-2-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

▪ Example 286

1-Ethyl-7-({furan-2-ylmethyl-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 287

1-Ethyl-7-({furan-3-ylmethyl-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 288

1-Ethyl-3,3,5-trimethyl-7-({(5-methyl-furan-2-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 289

1-Ethyl-3,3,5-trimethyl-7-({(2-methyl-furan-3-ylmethyl)-[2-(2-oxo-3,4-divinyl-2H-pyridin-1-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 290

7-({(4,5-Dimethyl-furan-2-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo

[b][1,4]diazepine-2,4-dione

▪ Example 291

1-Ethyl-3,3,5-trimethyl-7-{[[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-(5-trifluoromethyl-furan-2-ylmethyl)-amino]-methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 292

1-Ethyl-3,3,5-trimethyl-7-({[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-thiophen-2-ylmethyl-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 293

1-Ethyl-3,3,5-trimethyl-7-({(3-methyl-thiophen-2-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 294

7-({(4,5-Dimethyl-thiophen-2-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 295

7-({(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 296

1-Ethyl-3,3,5-trimethyl-7-(2-{(4-methyl-thiazol-5-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-ethyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 297

1-Ethyl-3,3,5-trimethyl-7-(2-{(4-methyl-pyridin-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-ethyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 298

1-Ethyl-3,3,5-trimethyl-7-(2-{(2-methyl-pyridin-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-ethyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 299

7-(2-{(2,6-Dimethyl-pyridin-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-ethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 300

7-(2-{(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-ethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 301

1-Ethyl-3,3,5-trimethyl-7-(3-{(4-methyl-thiazol-5-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 302

1-Ethyl-3,3,5-trimethyl-7-(3-{(4-methyl-pyridin-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 303

1-Ethyl-3,3,5-trimethyl-7-(3-{(2-methyl-pyridin-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 304

7-(3-{(2,6-Dimethyl-pyridin-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-propyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 305

7-(3-{(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-[2-(1-oxo-2H-isoquinolin-2-yl)-ethyl]-amino}-propyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 306

1-Ethyl-3,3,5-trimethyl-7-({(2-methyl-pyridin-3-ylmethyl)-[2-(2-oxo-2H-quinolin-1-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 307

1-Ethyl-3,3,5-trimethyl-7-({(4-methyl-pyridin-3-ylmethyl)-[2-(2-oxo-2H-quinolin-1-yl)-ethyl]-amino}-methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 308

7-({(2,6-Dimethyl-pyridin-3-ylmethyl)-[2-(2-oxo-2H-quinolin-1-yl)-ethyl]-amino}-methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

▪ Example 309

7-{[N-(4-Chloropyridin-3-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
white powder
mp: 200-205°C (dec.)

▪ Example 310

7-({N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder

mp: 161-165°C

▪ Example 311

7-({N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 144-146°C

▪ Example 312

7-({N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 127-128°C

▪ Example 313

7-({N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 197-199°C

▪ Example 314

7-({N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(4-methyl-7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 190-193°C

▪ Example 315

1-Ethyl-3,3,5-trimethyl-7-{[N-(4-methylthiazol-2-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
white amorphous
$^1$H NMR ($D_2O$), δppm : 0.75 (3H, s), 1.10 (3H, t, J = 7.2 Hz), 1.42 (3H, s), 2.39 (3H, s), 3.25-3.36 (4H, m), 3.37 (3H, s), 3.73-3.87 (1H, m), 4.07-4.22 (3H, m), 4.41 (2H, s), 7.18 (1H, d, J = 1.0 Hz), 7.32-7.38 (1H, m), 7.38-7.43 (1H, m), 7.49 (1H, d, J = 8.3 Hz), 7.99 (1H, dd, J = 6.0, 8.0 Hz), 8.44 (1H, d, J = 8.3 Hz), 8.66-8.73 (2H, m)

▪ Example 316

1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 123-125°C

▪ Example 317

1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 127-129°C

▪ Example 318

1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimet

hyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 104-111°C

▪ Example 319

1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione dihydrochloride

4 M HCl/AcOEt (90 μl) was added to an ethyl acetate solution (1 ml) of 1-ethyl-7-({(2-methoxymethylpyridin-3-ylmethyl)-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (26 mg) and stirred for 5 minutes at room temperature. The resulting precipitate was collected and washed with ether to give the title compound as a white powder (14 mg).

$^1$H NMR (DMSO-$d_6$), δ ppm : 0.75 (3H, s), 1.05 (3H, t, $J$ = 7.1 Hz), 1.35 (3H, s), 2.16 (3H, s), 3.27-3.33 (8H, m), 3.70-4.40 (6H, m), 4.52 (2H, br), 4.65 (2H, br), 6.93 (1H, s), 7.28-7.48 (4H, m), 7.72-7.84 (1H, m), 7.97 (1H, s), 8.35 (1H, br), 8.53-8.65 (1H, m).

▪ Example 320

1-Ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-2-trifluoromethyl-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 132-134°C

▪ Example 321

1-Ethyl-3,3,5-trimethyl-7-({N-(3-methyl-3H-imidazol-4-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 106-108°C

▪ Example 322

1-Ethyl-3,3,5-trimethyl-7-({N-(3-methyl-3H-imidazol-4-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 100-105°C

▪ Example 323

1-Ethyl-7-({N-[2-(2-methoxymethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
ivory powder
mp: 123-126°C

▪ Example 324

1-Ethyl-7-({N-[2-(2-methoxymethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
pale yellow powder
$^1$H NMR (DMSO-$d_6$), δppm : 0.69 (3H, s), 1.01 (3H, t, $J$ = 7.1 HZ), 1.33 (3H, s), 2.22 (3H, s), 2.80 (2H, s), 3.27 (3H, s), 3.30 (3H, s), 3.61-4.05 (6H, m), 4.12 (2H, br), 4.48 (2H, s), 6.63 (1H, d, $J$ = 7.4 Hz), 6.78 (1H, s), 7.22 (1H, br), 7.32-7.33 (2H, m), 7.54 (1H, d, $J$ = 7.0 Hz), 7.61 (1H, d, $J$ = 5.7 Hz), 8.61 (1H, d, $J$ = 5.7 Hz), 8.63 (1H, s).

▪ Example 325

7-({N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(2-methoxymethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

ivory powder

$^1$H NMR (DMSO-$d_6$), δppm : 0.69 (3H, s), 1.03 (3H, t, $J$ = 7.1 Hz), 1.32 (3H, s), 2.04 (3H, s), 2.71 (2H, br), 3.27 (3H, s), 3.30 (3H, br), 3.45-4.00 (6H, m), 3.85 (3H, s), 4.39-4.63 (4H, m), 6.44 (1H, br), 6.61-7.02 (2H, m), 7.05-7.95 (4H, m).

▪ Example 326

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-phenyl-N-(2-pyridin-3-ylethyl)acetamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 40 using appropriate starting materials.

white amorphous

$^1$H NMR (DMSO-$d_6$), δppm : 0.70 and 0.73 (3H, s), 0.95-1.13 (3H, m), 1.32 and 1.33 (3H, s), 2.91-3.03 (2H, m), 3.22 and 3.25 (3H, s), 3.50-3.82 (5H, m), 3.96-4.09(1H, m), 4.56-4.74 (2H, m), 7.04-7.34 (7H, m), 7.42-7.52 (1H, m), 7.78 (1H, bs), 8.19 (1H, bs), 8.65-8.77 (2H, m)

▪ Example 327

N-[2-({N'-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N'-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)phenyl]methanesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 161-163°C

▪ Example 328

7-({N-(2-Chloropyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 158.7-160.8°C

▪ Example 329

3-({N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)pyridine-2-carbonitrile

2-Chloro-3-({(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)pyridine (0.3g), zinc cyanide(120mg), tris(dibenzylideneacetone)dipalladium(24mg), 1,1'-bis(diphenylphosphino)ferrocene(14mg), and zinc powder(3.4mg) were added to DMF(3ml), and the mixture was heated at 95°C for 3 hours. The reaction liquid was cooled to room temperature. Water was added to the reaction mixture and subjected to celite filtration. Extraction with ethyl acetate was performed. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=93:7). The purified product was condensed under reduced pressure, and the residue was recrystallized from ether to give the title compound(1.35g) as a white powder.
mp: 113.5-117.5°C

▪ Example 330

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(1-methyl-1H-indol-3-yl)-N-(2-pyridin-3-ylethyl)acetamide hydrochloride

To a solution of 1-ethyl-3,3,5-trimethyl-7-[(2-pyridine 3-ylethylamino)methyl]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.5g), 1-methyl-3-indoleacetic acid(0.27g), and

1-hydroxybenzotriazole (HOBT)(0.24g) in acetonitrile (10 ml), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (WSC)(0.30g) was added and stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure. Ethyl acetate and water were added to the residue and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 1 : 3→0:1). The purified product was condensed under reduced pressure. A 1N-hydrogen chloride in ethanol solution (1.1ml) was added to a 2-propanol solution (5ml) of the residue, and the liquid was stirred at room temperature, and concentrated under reduced pressure. Ethanol and ether were added to the residue. The precipitated insoluble matter was separated, washed with ether, and dried to give the title compound(0.26g) as a pale orange white amorphous.

$^1$H NMR (DMSO-$d_6$), δppm : 0.65 and 0.69 (3H, s), 0.95-1.13 (3H, m), 1.31 and 1.32 (3H, s), 2.90-3.05 (2H, m), 3.06 and 3.14 (3H, s), 3.20-3.90 (5H, m), 3.70 and 3.73 (3H, s), 3.90-4.08 (1H, m), 4.55-4.79 (2H, m), 6.96 (1H, t, J = 7.4 Hz), 7.05-7.24 (4H, m), 7.32-7.42 (2H, m), 7.43-7.55 (1H, m), 7.63-7.79 (1H, m), 8.13 (1H, bs), 8.57 - 8.72 (2H, m)

▪ Example 331

1-Ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(1-pyridin-3-ylethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 128-132°C

▪ Example 332

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-phenyl-N-(2-pyridin-3-ylethyl)isobutyramide hydrochloride

To a solution of

1-ethyl-3,3,5-trimethyl-7-{[N-(2-pyridin-3-ylethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.5g), 2-Phenylisobutyric acid(0.24g), and diisopropylethylamine(0.23ml)in DMF(10 ml),

2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)(0.50g) was added and stirred at 40°C for 10 hours. Water was added to the reaction mixture, and stirred for 1 hour, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane: ethyl acetate = 1 : 1). The purified product was condensed under reduced pressure. A 1N-hydrogen chloride in ethanol solution was added to a 2-propanol solution (5ml) of the residue, and the liquid was stirred at room temperature, and concentrated under reduced pressure. Ethanol and ether were added to the residue. The precipitated insoluble matter was separated, washed with ether, and dried to give the title compound(0.35g) as a white amorphous.

$^1$H NMR (DMSO-$d_6$), δppm : 0.67 and 0.72 (3H, s), 0.90-1.20 (3H, m), 1.20-1.40(3H, m), 1.43 and 1.48 (6H, s), 2.30-2.50 (1H,m), 2.83-3.40 (5H, m), 3.40-4.30 (4H, m), 4.57- 4.79 (1H, m), 6.76-7.03 (1H, m), 7.03-7.56 (8H, m), 7.56-8.80 (3H, m)

▪ Example 333

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-3-phenyl-N-(2-pyridin-3-ylethyl)propionamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 40 using appropriate starting materials.

white amorphous

$^1$H NMR (DMSO-$d_6$), δppm : 0.70 and 0.72 (3H, s), 0.95-1.12 (3H, m), 1.33 (3H, s), 2.53-2.69 (2H, m), 2.69-2.86 (2H, m), 2.90-3.03 (2H, m), 3.25 and 3.28 (3H, s), 3.45-3.68 (2H, m), 3.69-3.81 (1H, m), 3.96-4.10 (1H, m), 4.53-4.69 (2H, m), 7.04-7.29 (7H, m), 7.43 and 7.45 (1H, d, J = 4.9 Hz), 7.78 - 7.86 (1H, m), 8.10 - 8.27 (1H, m), 8.57 - 8.77 (2H, m)

▪ Example 334

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-pyridin-3-ylethyl)-2-quinolin-6-ylacetamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 332 using appropriate starting materials.

white amorphous

$^1$H NMR (DMSO-$d_6$), δppm : 0.68 and 0.70 (3H, s), 1.00-1.08 (3H, m), 1.31 and 1.32 (3H, s), 3.03 (1H, t, J = 7.0 Hz), 3.10-3.18 (1H, m), 3.23 and 3.26 (3H, s), 3.40-3.90 (2H, m), 3.95 - 4.13 (4H, m), 4.60-4.88 (2H, m), 7.18-7.29 (2H, m), 7.42-7.52 (1H, m), 7.66-8.04 (4H, m), 8.07-8.21 (1H, m), 8.28-8.45 (1H, m), 8.65-8.93 (3H, m), 9.06-9.16 (1H, m)

▪ Example 335

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(2-oxo-2,3-dihydrobenzoimidazol-1-yl)-N-(2-pyridin-3-ylethyl)acetamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 332 using appropriate starting materials.

white powder

$^1$H NMR (DMSO-$d_6$), δppm : 0.71 and 0.76 (3H, s), 1.00-1.13 (3H, m), 1.33 and 1.34 (3H, s), 2.98 (1H, t, J = 7.2 Hz), 3.10-3.17 (1H, m), 3.29 and 3.33 (3H, s), 3.50-3.68 (1H, m), 3.68-3.84 (2H, m), 3.97-4.13 (1H, m), 4.55-4.72 (2H, m), 4.76-4.87 (2H, m), 6.63-7.05 (4H, m), 7.15-7.38 (2H, m) 7.41-7.60 (1H, m), 7.75-7.88 (1H, m), 8.17-8.38 (1H, m), 8.56-8.86 (2H, m), 10.84 and 10.89 (1H, s)

▪ Example 336

1-Ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]N-(pyridin-3-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 124-127°C

▪ Example 337

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(3-methyl-2-oxo-2,3-dihydrobenzoimidazol-1-yl)-N-(2-pyridin-3-ylethyl)acetamide hydrochloride

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(2-oxo-2,3-dihydrobenzoimidazol-1-yl)-N-(2-pyridin-3-ylethyl)acetamide hydrochloride(0.26g), cesium carbonate(0.43g), and methyl iodide(0.04ml) were added to DMF(5ml), and the mixture was stirred at room temperature for 1 days. Water was added to the reaction mixture, and stirred for 1 hour, followed by extraction with ethyl acetate. The organic layer was condensed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate: methanol=85:15). The purified product was condensed under reduced pressure. A 1N-hydrogen chloride in ethanol solution(0.44ml) was added to a 2-propanol solution (5ml) of the residue, and the liquid was stirred at room temperature, and concentrated under reduced pressure. Ethanol and ether were added to the residue. The precipitated insoluble matter was separated, washed with ether, and dried to give the title compound(0.20g) as a white powder.

$^1$H NMR (DMSO-$d_6$), δppm : 0.71 and 0.76 (3H, s), 1.00-1.13 (3H, m), 1.33 and 1.34 (3H, s), 2.92-3.03 (1H, m), 3.10-3.25 (1H, m), 3.30 and 3.30 (3H, s), 3.30-3.50 (3H, m), 3.50-3.81 (3H, m), 3.97-4.14 (1H, m), 4.57-4.91 (4H, m), 6.74-7.11 (3H, m), 7.11-7.40 (3H, m), 7.46 and 7.57 (1H, d, J = 8.3 Hz), 7.72-7.85 (1H, m), 8.15-8.37(1H, m), 8.63-8.86 (2H, m)

▪ Example 338

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]benzamide

The synthesis of the title compound was performed in the same manner as in Example 42 using appropriate starting materials.

white powder

$^1$H NMR (CDCl3), δppm : 0.79 (3H, bs), 1.15-1.24 (3H, m), 1.52 and 1.54

(3H, s), 2.43 (3H, d, J = 0.4 Hz), 3.33-3.42 (3H, m), 3.45-3.83 (3H, m), 3.83-5.04 (5H, m), 6.27-6.77 (2H, m), 6.80-7.14 (2H, m), 7.17-7.44 (7H, m)

▪ Example 339

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(4-methylindol-1-yl)-N-(2-pyridin-3-ylethyl)acetamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 332 using appropriate starting materials.

white powder

$^1$H NMR (DMSO-$d_6$), δppm : 0.71 and 0.77 (3H, s), 0.90-1.15 (3H, m), 1.33 and 1.35 (3H, s), 2.44 and 2.46 (3H, s), 2.89-3.13 (2H, m), 3.29 and 3.30 (3H, s), 3.58-3.65 (1H, m), 3.66-3.86 (2H, m), 3.96-4.14 (1H, m), 4.56-4.89 (2H, m), 5.10 and 5.20 (2H, s), 6.38-6.50 (1H, m), 6.77-7.03 (3H, m), 7.15-7.36 (3H, m), 7.46 and 7.57 (1H, d, J = 8.3 Hz), 7.66-7.78 (1H, m), 8.09-8.23 (1H, m), 8.60-8.79 (2H, m)

▪ Example 340

7-({N-[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methoxymethylpyridin-3-ylmethyl)amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder (Ether)

mp: 103-104°C

▪ Example 341

1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 119-122°C

▪ Example 342

1-Ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(5-methylthiazol-4-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 144-145°C

▪ Example 343

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(1-methyl-1H-indol-3-yl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]acetamide

The synthesis of the title compound was performed in the same manner as in Example 330 using appropriate starting materials.

white amorphous

$^1$1H NMR ($CDCl_3$), δppm : 0.74 and 0.78 (3H, s), 1.15-1.24 (3H, m), 1.49 and 1.51 (3H, s), 2.41 (3H, d, J = 0.6 Hz), 3.11and 3.24 (3H, s), 3.60-3.94 (9H, m), 3.94-4.26 (2H, m), 4.33-4.78 (2H, m), 6.09-6.59 (2H, m), 6.77-6.90 (1H, m), 6.90-6.98 (1H, m), 7.03-7.37 (5H, m), 7.57 (1H, d, J = 8.0 Hz), 7.66 (1H, d, J = 8.0 Hz)

▪ Example 344

7-({N-(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 138-139°C

▪ Example 345

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-pyridin-3-ylethyl)-2-quinolin-3-ylacetamide dihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 332 using appropriate starting materials.
white powder
mp: 189-194°C

• Example 346

1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carboxylic acid-N-benzyl-N-(2-pyridin-3-yl-ethyl)amide

The synthesis of the title compound was performed in the same manner as in Example 330 using appropriate starting materials.
white powder
mp: 181-182°C

• Example 347

1-Ethyl-3,3,5-trimethyl-7-({N-(5-methyloxazol-4-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 129.0-130.5°C

• Example 348

1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carboxylic acid-N-(4-methoxybenzyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amide

The synthesis of the title compound was performed in the same manner as in Example 330 using appropriate starting materials.
white powder ($Et_2O$-EtOH)
mp: 151.1-155.1°C

• Example 349

7-({N-[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(1,5-dimethyl-1H-pyrazol-3-ylmethyl)amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 113-116°C

▪ Example 350

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(2-methylbenzoimidazol-1-yl)-N-(2-pyridin-3-yl-ethyl)acetamide

The synthesis of the title compound was performed in the same manner as in Example 330 using appropriate starting materials.
white amorphous
$^1$H NMR ($CDCl_3$), δppm : 0.82 and 0.87 (3H, s), 1.15-1.30 (3H, m), 1.53 and 1.55 (3H, s), 2.41 and 2.47 (3H, s), 2.87-3.01 (2H, m), 3.33 and 3.39 (3H, s), 3.60-3.94 (3H, m), 4.05-4.26 (1H, m), 4.50-4.87 (4H, m), 6.89 (1H, t, J = 8.0 Hz), 6.98-7.60 (7H, m), 7.68 (1H, t, J = 9.1 Hz), 8.44 (1H, s), 8.52 and 8.61 (1H, d, J = 3.5 Hz)

▪ Example 351

1-Ethyl-3,3,5-trimethyl-7-({[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-(3-methylpyridin-2-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder (AcOEt-$Et_2O$)
mp: 139-143°C

▪ Example 352

1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : 0.69 (3H, s), 1.04 (3H, t, $J$ = 7.1 Hz), 1.31 (3H, s), 2.80-3.20 (2H, m), 3.29 (3H, s), 3.30 (3H, s), 3.39-3.45 (2H, m), 3.70-3.77 (1H, m), 3.92-4.04 (3H, m), 4.36 (2H, br), 4.74 (2H,

br), 6.76 (1H, d, $J$ = 6.9 Hz), 7.30-7.40 (3H, m), 7.59 (1H, br), 7.83 (2H, br), 8.07 (1H, d, $J$ = 5.2 Hz), 8.65 (2H, br).

▪ Example 353

7-({N-(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

white powder

$^1$H NMR (DMSO-$d_6$), δppm : 0.72 (3H, s), 1.08 (3H, t, $J$ = 7.1 Hz), 1.34 (3H, s), 2.24 (3H, s), 3.30-3.43 (5H, m), 3.73 (3H, s), 3.66-3.86 (3H, m), 3.97-4.06 (1H, m), 4.27 (2H, br), 4.43 (2H, br), 6.32-6.35 (1H, m), 6.85 (1H, d, $J$ = 7.4 Hz), 6.97 (1H, s), 7.54-7.57 (1H, m), 7.61-7.72 (2H, m), 7.87 (1H, br), 7.94-7.95 (1H, m).

▪ Example 354

1-Ethyl-7-({N-(6-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

white powder

$^1$H NMR (DMSO-$d_6$), δppm : 0.67 (3H, s), 1.04 (3H, t, $J$ = 7.0 Hz), 1.33 (3H, s), 2.40 (3H, s), 2.70-3.10 (2H, m), 3.27 (5H, br), 3.41 (3H, s), 3.65-4.10 (6H, m), 4.63 (2H, br), 6.51 (1H, br), 6.70 (1H, br), 7.57 (1H, d, $J$ = 7.2 Hz), 7.00-7.70 (4H, m), 8.23 (1H, br), 8.74 (1H, m).

▪ Example 355

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(2-oxo-2,3-dihydrobenzimidazol-1-yl)-N-(2-pyridin-3-ylethyl)isobutyramide

The synthesis of the title compound was performed in the same manner as in Example 332 using appropriate starting materials.

pale brown white amorphous

$^1$H NMR ($CDCl_3$), δppm : 0.74 and 0.80 (3H, s), 1.08-1.23 (3H, m), 1.50 and 1.52 (3H, s), 1.95-2.07 (6H, m), 2.15-2.35 (1H, m), 2.87 (1H, t, J = 7.5 Hz), 3.16 and 3.37 (3H, s), 3.42-3.63 (2H, m), 3.63-3.88 (1H, m), 3.95-4.18 (1H, m), 4.43-4.82 (2H, m), 6.52-6.62 (1H, m), 6.80-7.32 (7H, m), 7.48 (1H, d, J = 7.8 Hz), 7.99 and 8.10 (1H, s), 8.30 - 8.63 (2H, m)

▪ Example 356

1-Ethyl-3,3,5-trimethyl-7-({N-[1-(2-methylpyridin-3-yl)ethyl]-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder (Ether)
mp: 164-167°C

▪ Example 357

1-Ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-[1-(2-methylpyridin-3-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
ivory powder
mp: 163-164°C

▪ Example 358

7-({N-[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-[1-(2-methylpyridin-3-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 169-170°C

▪ Example 359

7-({N-(2-Ethoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-

furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimeth yl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

ivory powder

mp: 104-106°C

▪ Example 360

1-Ethyl-3,3,5-trimethyl-7-{[N-(2-pyridin-3-ylethyl)-N-(quinolin-5 -yl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

1-Ethyl-3,3,5-trimethyl-7-{[N-(2-pyridin-3-ylethyl)amino]me thyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (0.45g), 5-bromoquinoline(0.25g), tris(dibenzylideneacetone)dipalladium(5.4mg), xantphos(10mg), and cesium carbonate (0.46g) were added to toluene(9ml), and the mixture was heated at 130°C for 3 days. The reaction liquid was cooled to room temperature. Water was added to the reaction mixture, and stirred for 1 hour, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. The filtrate was condensed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate: methanol=85:15). The purified product was condensed under reduced pressure. A 1N-hydrogen chloride in ethanol solution(1ml) was added to a ethanol solution (5ml) of the residue, and the liquid was stirred at room temperature, and concentrated under reduced pressure. Ethanol and ether were added to the residue. The precipitated insoluble matter was separated, washed with ether, and dried to give the title compound(0.20g) as a yellow amorphous.

$^1$H NMR (DMSO-$d_6$), δppm : 0.55 (3H, s), 0.99 (3H, t, J = 7.0 Hz), 1.29 (3H, s), 3.03 (2H, t, J = 7.1 Hz), 3.14 (3H, s), 3.30-3.80 (3H, m), 3.90-4.03 (1H, m), 4.49 (2H, s), 7.06-7.20 (2H, m), 7.33 (1H, d, J = 8.1 Hz), 7.49 (1H, d, J = 5.4 Hz), 7.73 (1H, dd, J=4.8 Hz, 8.8 Hz), 7.78-7.90 (3H, m), 8.23 (1H, d, J = 8.1 Hz), 8.64 (1H, s), 8.69 (1H, d, J = 4.8 Hz), 8.73 (1H, d, J = 8.8 Hz), 9.07 (1H, d, J = 3.6 Hz),

▪ Example 361

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(1H-indazol-3-yl)-N-(2-pyridin-3-ylethyl)acetamide

The synthesis of the title compound was performed in the same manner as in Example 330 using appropriate starting materials.

yellow amorphous

$^1$H NMR ($CDCl_3$), δppm : 0.70 and 0.79 (3H, s), 1.08-1.23 (3H, m), 1.49 and 1.52 (3H, s), 2.77 (1H, t, J = 7.7 Hz), 2.85 (1H, t, J = 7.3 Hz), 3.06 and 3.21(3H, s), 3.52-3.82 (3H, m), 4.01-4.16 (3H, m), 4.50-4.70 (2H, m), 6.75-7.32 (5H, m), 7.32-7.50 (3H, m), 7.82-7.92 (1H, m), 8.27-8.55 (2H, m), 10.1 and 10.1 (1H, bs)

▪ Example 362

7-({N-(4-Chloropyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 114-118°C

▪ Example 363

N-[3-({N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)pyridin-2-ylmethyl]formamide

3-({N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)pyridine-2-carbonitrile(0.40g) and Raney nickel(1.2g) were suspended in formic acid(8ml), and the mixture was stirred at 60°C for 3 hours. The reaction mixture was filtered to remove insoluble matter, and the filtrate was condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=75:25→80:20). The purified product was condensed under reduced pressure. Acetone and ether were added to the residue. The precipitated insoluble matter was separated,

washed with ether, and dried to give the title compound(33mg) as a pale brown white amorphous.

$^1$H NMR ($CDCl_3$), δppm : 0.77 (3H, s), 1.16 (3H, t, J = 7.1 Hz), 1.51 (3H, s), 2.43 (3H, d, J = 0.9 Hz), 2.85 (2H, t, J = 5.8 Hz), 3.35 (3H, s), 3.58-3.84 (5H, m), 4.00-4.18 (3H, m), 4.54 (2H, d, J = 4.4 Hz), 6.41 (1H, dd, J = 0.4 Hz, 7.3 Hz), 6.47 (1H, t, J = 0.8 Hz), 6.96 (1H, d, J = 7.3 Hz), 7.06 (1H, dd, J = 4.9, 7.7 Hz), 7.12-7.20 (3H, m), 7.38 (1H, bs), 7.55 (1H, dd, J = 1.2, 7.7 Hz), 8.32 (1H, d, J = 1.2 Hz), 8.36 (1H, dd, J = 1.5, 4.9 Hz)

▪ Example 364

1-Ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]N-(quinolin-5-yl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 166-168°C

▪ Example 365

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(1-methyl-1H-indazol-3-yl)-N-(2-pyridin-3-ylethyl)propionamide

Sodium hydride (55% in oil)(52mg) was suspended in DMF(7ml), and cooled to 0°C in an ice water bath. N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(1H-indazol-3-yl)-N-(2-pyridin-3-ylethyl)acetamide(210mg) was added thereto at the same temperature, and the mixture was stirred at 0°C for 30 minutes followed at room temperature for 30 minutes. Methyl iodide(0.03ml) was added thereto, and the mixture was stirred at room temperature for 3 hours. Water was added to the reaction liquid, followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=90:10). The purified product was condensed to dryness to give the title compound(20mg) as a pale

yellow white amorphous.

$^1$H NMR ($CDCl_3$), δppm : 0.75 and 0.86 (3H, s), 1.17 and 1.21 (3H, t, J = 7.1 Hz), 1.51 (3H, s),1.54 (3H, s), 2.94 (1H, t, J = 7.7 Hz), 3.06 (1H, t, J = 7.2 Hz), 3.40 and 3.48 (3H, s), 3.44-3.54 (2H, m), 3.68 (1H, t, J = 6.7 Hz), 3.72-3.90 (1H, m), 3.95-4.22 (2H, m), 4.18 and 4.25 (3H, s), 4.70-4.84 (1H, m), 7.03-7.75 (8H, m), 8.27-8.35 (1H, m), 8.35-8.44 (1H, m), 8.51- 8.64 (1H, m)

▪ Example 366

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-pyridin-3-ylethyl)formamide

Sodium hydride (55% in oil)(52mg) was suspended in DMF(7ml), and cooled to 0°C in an ice water bath.

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(1H-indazol-3-yl)-N-(2-pyridin-3-ylethyl)acetamide(210mg) was added thereto at the same temperature, and the mixture was stirred at 0°C for 30 minutes followed at room temperature for 30 minutes. Methyl iodide(0.03ml) was added thereto, and the mixture was stirred at room temperature for 3 hours. Water was added to the reaction liquid, followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=85:15). The purified product was condensed to dryness to give the title compound(17mg) as a pale yellow white amorphous.

pale yellow white amorphous

$^1$H NMR ($CDCl_3$), δppm : 0.83 (3H, s), 1.19 and 1.20 (3H, t, J = 7.1 Hz), 1.53 (3H, bs),2.85 (2H, t, J = 7.7 Hz), 3.39 and 3.39 (3H, s), 3.44-3.54 (2H, m), 3.75-3.88 (1H, m), 4.06-4.20 (1H, m), 4.27-4.65 (2H, m), 6.98-7.10 (1H, m), 7.10-7.18 (1 H, m), 7.21-7.35 (2H, m), 7.41 and 7.53 (1H, dt, J = 7.9, 2.0 Hz), 8.05 and 8.30 (1H, s), 8.39 and 8.41 (1H, d, J = 1.8 Hz), 8.50 and 8.62 (1H, dd, J = 1.8, 4.8 Hz)

▪ Example 367

1-Ethyl-7-({N-[1-(2-methoxymethylpyridin-3-yl)ethyl]-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-tri

methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

white powder

$^1$H NMR (DMSO-$d_6$), δppm : 0.75 (3H, s), 1.04 (3H, t, $J$ = 7.1 Hz), 1.34 (3H, s), 1.41 (3H, s), 2.09 (3H, s), 2.57-2.84 (2H, m), 3.16 (2H, br), 3.35 (3H, s), 3.40 (3H, s), 3.62-3.70 (2H, m), 4.00-4.13 (1H, m), 4.18 (2H, br), 6.83 (1H, br), 7.09 (1H, br), 7.43-7.63 (3H, m), 7.83 (1H, br), 7.91-7.92 (1H, m), 8.40 (1H, br), 8.46 (1H, br).

▪ Example 368

1-Ethyl-7-({N-(2-hydroxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 187-190°C

▪ Example 369

7-({N,N-Bis-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 160-165°C

▪ Example 370

1-Ethyl-7-({N-(5-methoxymethyl-2-methyl-2H-pyrazol-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 169-170°C

▪ Example 371

1-Ethyl-7-({N-(5-methoxymethyl-2-methyl-2H-pyrazol-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 113-115°C

▪ Example 372

1-Isobutyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

ivory powder

mp: 184-186°C

▪ Example 373

1-Isobutyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 207-210°C

▪ Example 374

1-Isobutyl-3,3-dimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 180-182°C

▪ Example 375

1-Isobutyl-3,3-dimethyl-7-({N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 229-231°C

▪ Example 376

1-(2-Methoxyethyl)-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 182-185°C

▪ Example 377

1-(2-Methoxyethyl)-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 188-189°C

▪ Example 378

1-Isobutyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
ivory powder
mp: 149-151°C

▪ Example 379

1-(2-Methoxyethyl)-3,3-dimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

ivory powder

mp: 179-181°C

▪ Example 380

1-(2-Methoxyethyl)-3,3-dimethyl-7-({N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 205-206°C

▪ Example 381

1-Cyclopropylmethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

ivory powder

mp:189-191°C

▪ Example 382

1-Cyclopropylmethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 192-194°C

▪ Example 383

1-Cyclopropylmethyl-3,3-dimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 138-143°C

▪ Example 384

1-Cyclopropylmethyl-3,3-dimethyl-7-({N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 220-221°C

▪ Example 385

1-Ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 130-131°C

▪ Example 386

1-Cyclopropyl-7-({N-(2-methoxymethyl-pyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

ivory powder

mp: 213-214°C

▪ Example 387

1-Cyclopropyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 182-184°C

▪ Example 388

1-Cyclopropyl-3,3-dimethyl-7-({[2-N-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
ivory powder
mp: 172-173°C

▪ Example 389

1-Cyclopropyl-3,3-dimethyl-7-({N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 191-193°C

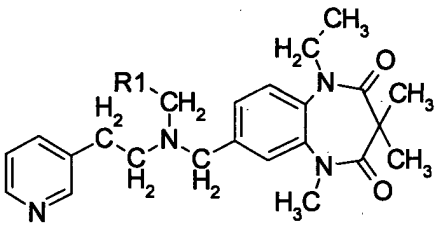
▪ Example 390

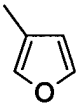
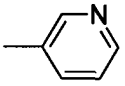
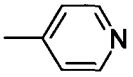
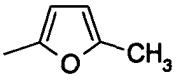
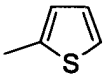
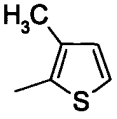
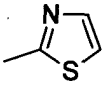
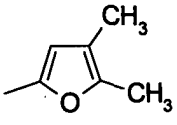
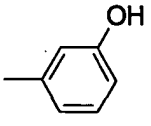
1-Ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(2-oxo-2H-quinolin-1-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

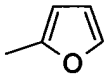
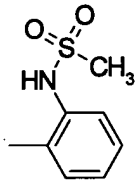
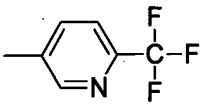
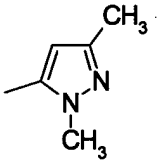
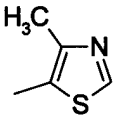
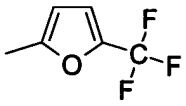
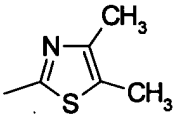
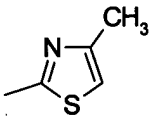
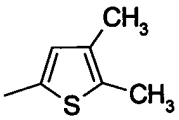
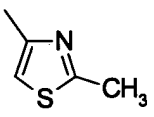
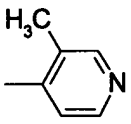
The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
white powder
mp: 149-150°C

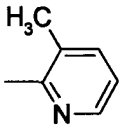
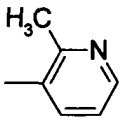
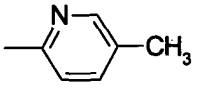
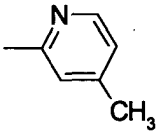
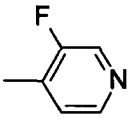
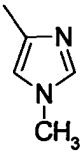
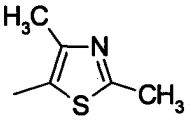
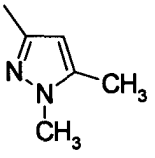
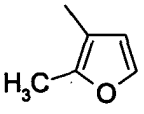
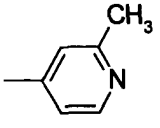
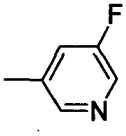
▪ Examples 391 to 582

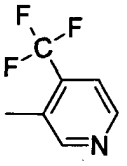
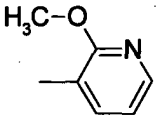
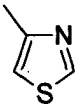
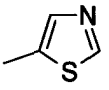
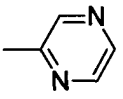
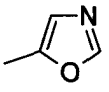
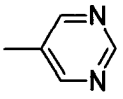
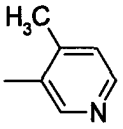
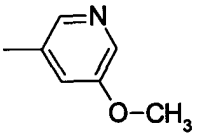
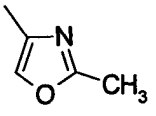
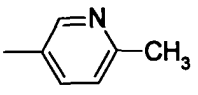
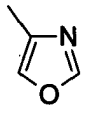
The folowing compounds were obtained in the same manner as in Examples above using appropriate starting materials.

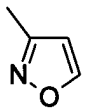
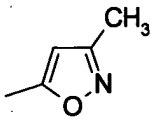
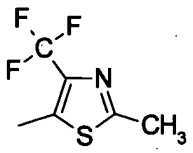
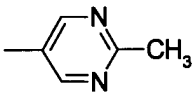
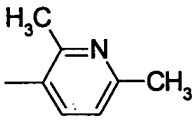


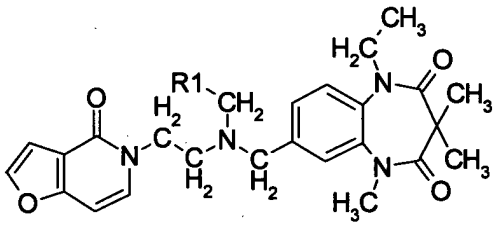
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 391 |  | 461 |
| 392 |  | 472 |
| 393 |  | 472 |
| 394 |  | 475 |
| 395 |  | 477 |
| 396 |  | 491 |
| 397 |  | 478 |
| 398 |  | 489 |
| 399 |  | 487 |

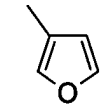
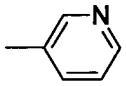
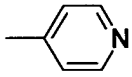
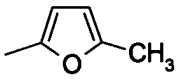
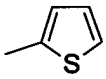
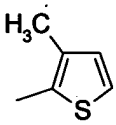
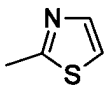
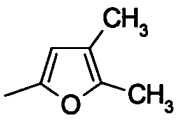
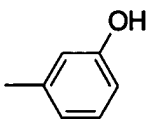
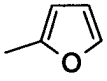
| | | |
|---|---|---|
| 400 |  | 461 |
| 401 |  | 564 |
| 402 |  | 540 |
| 403 |  | 489 |
| 404 |  | 492 |
| 405 |  | 529 |
| 406 |  | 506 |
| 407 |  | 492 |
| 408 |  | 505 |
| 409 |  | 492 |
| 410 |  | 486 |

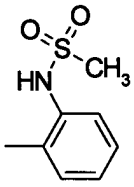
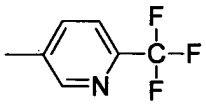
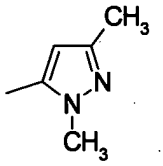
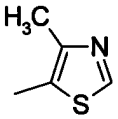
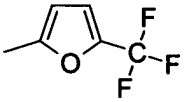
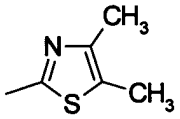
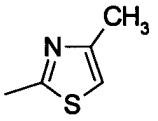
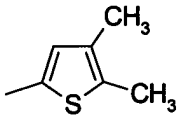
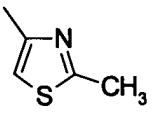
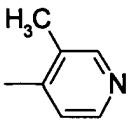
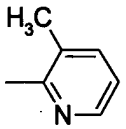
| | | |
|---|---|---|
| 411 |  | 486 |
| 412 |  | 486 |
| 413 |  | 486 |
| 414 |  | 486 |
| 415 |  | 490 |
| 416 |  | 475 |
| 417 |  | 506 |
| 418 |  | 489 |
| 419 |  | 475 |
| 420 |  | 486 |
| 421 |  | 490 |

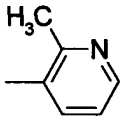
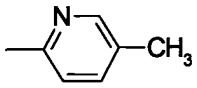
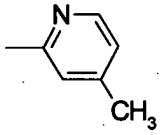
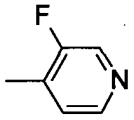
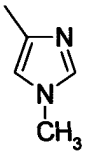
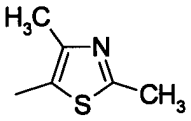
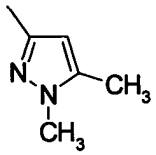
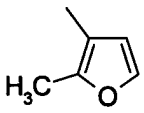
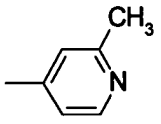
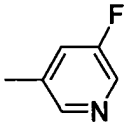
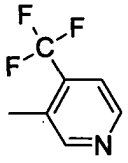
| | | |
|---|---|---|
| 422 |  | 540 |
| 423 |  | 502 |
| 424 |  | 478 |
| 425 |  | 478 |
| 426 |  | 473 |
| 427 |  | 462 |
| 428 |  | 473 |
| 429 |  | 486 |
| 430 |  | 502 |
| 431 |  | 476 |
| 432 |  | 486 |
| 433 |  | 462 |

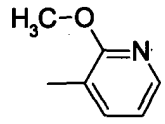
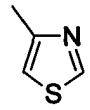
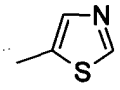
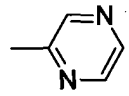
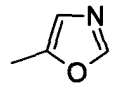
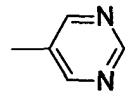
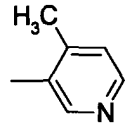
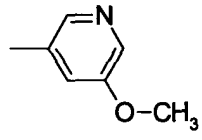
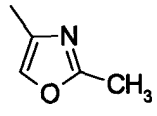
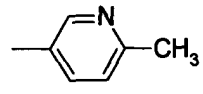
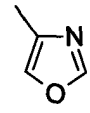
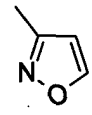
| | | |
|---|---|---|
| 434 |  | 462 |
| 435 |  | 476 |
| 436 |  | 560 |
| 437 |  | 487 |
| 438 |  | 500 |

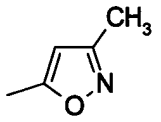
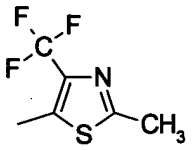
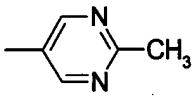
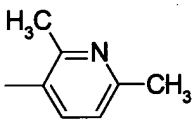


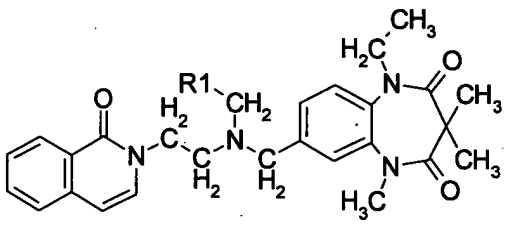
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 439 |  | 517 |
| 440 |  | 528 |
| 441 |  | 528 |
| 442 |  | 531 |
| 443 |  | 533 |
| 444 |  | 547 |
| 445 |  | 534 |
| 446 |  | 545 |
| 447 |  | 543 |
| 448 |  | 517 |

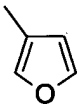
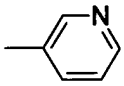
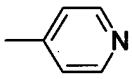
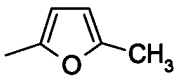
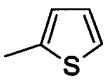
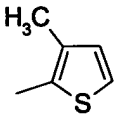
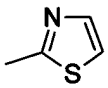
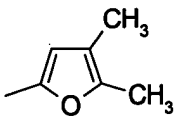
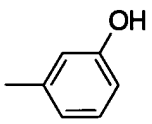
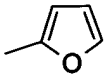
| | | |
|---|---|---|
| 449 |  | 620 |
| 450 |  | 596 |
| 451 |  | 545 |
| 452 |  | 548 |
| 453 |  | 585 |
| 454 |  | 562 |
| 455 |  | 548 |
| 456 |  | 561 |
| 457 |  | 548 |
| 458 |  | 542 |
| 459 |  | 542 |

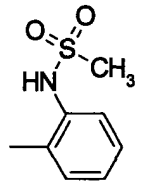
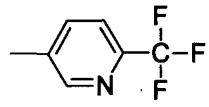
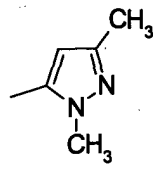
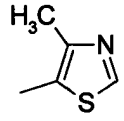
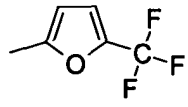
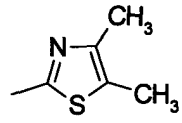
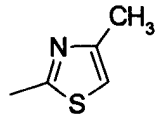
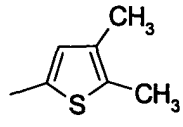
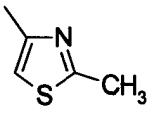
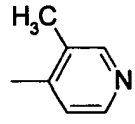
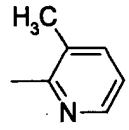
| | | |
|---|---|---|
| 460 |  | 542 |
| 461 |  | 542 |
| 462 |  | 542 |
| 463 |  | 546 |
| 464 |  | 531 |
| 465 |  | 562 |
| 466 |  | 545 |
| 467 |  | 531 |
| 468 |  | 542 |
| 469 |  | 546 |
| 470 |  | 596 |

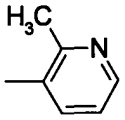
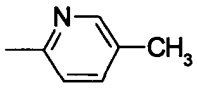
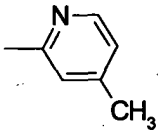
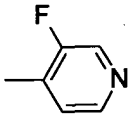
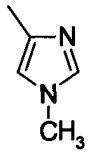
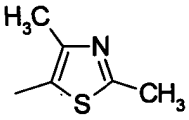
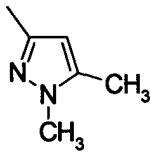
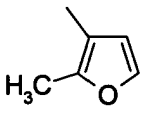
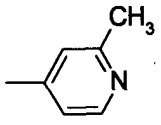
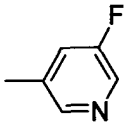
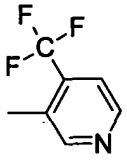
| | | |
|---|---|---|
| 471 |  | 558 |
| 472 |  | 534 |
| 473 |  | 534 |
| 474 |  | 529 |
| 475 |  | 518 |
| 476 |  | 529 |
| 477 |  | 542 |
| 478 |  | 558 |
| 479 |  | 532 |
| 480 |  | 542 |
| 481 |  | 518 |
| 482 |  | 518 |

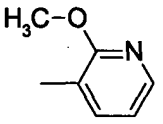
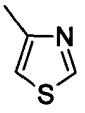
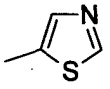
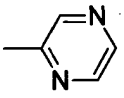
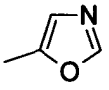
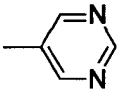
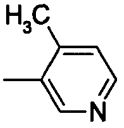
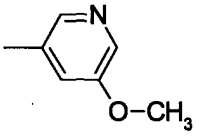
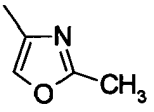
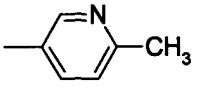
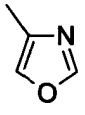
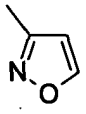
| | | |
|---|---|---|
| 483 |  | 532 |
| 484 |  | 616 |
| 485 |  | 543 |
| 486 |  | 556 |

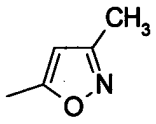
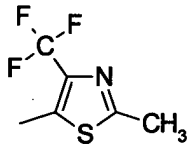
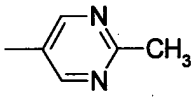
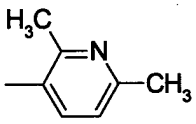


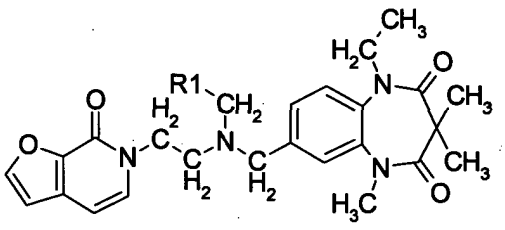
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 487 |  | 527 |
| 488 |  | 538 |
| 489 |  | 538 |
| 490 |  | 541 |
| 491 |  | 543 |
| 492 |  | 557 |
| 493 |  | 544 |
| 494 |  | 555 |
| 495 |  | 553 |
| 496 |  | 527 |

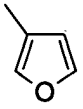
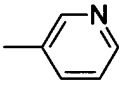
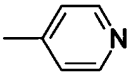
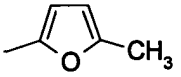
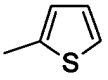
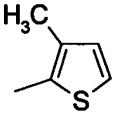
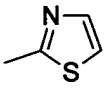
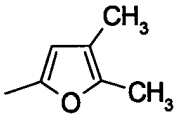
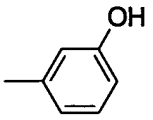
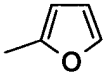
| | | |
|---|---|---|
| 497 |  | 630 |
| 498 |  | 606 |
| 499 |  | 555 |
| 500 |  | 558 |
| 501 |  | 595 |
| 502 |  | 572 |
| 503 |  | 558 |
| 504 |  | 571 |
| 505 |  | 558 |
| 506 |  | 552 |
| 507 |  | 552 |

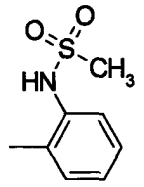
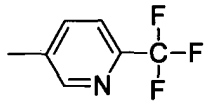
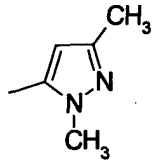
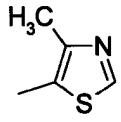
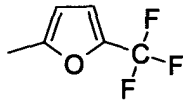
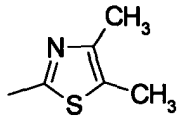
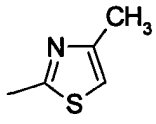
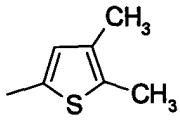
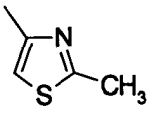
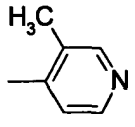
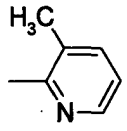
| | | |
|---|---|---|
| 508 |  | 552 |
| 509 |  | 552 |
| 510 |  | 552 |
| 511 |  | 556 |
| 512 |  | 541 |
| 513 |  | 572 |
| 514 |  | 555 |
| 515 |  | 541 |
| 516 |  | 552 |
| 517 |  | 556 |
| 518 |  | 606 |

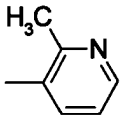
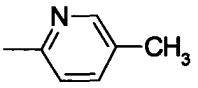
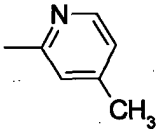
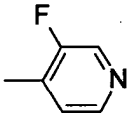
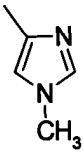
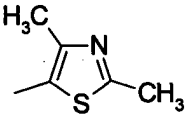
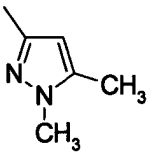
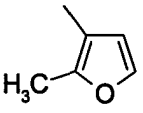
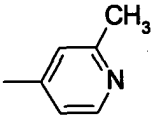
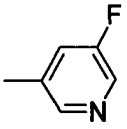
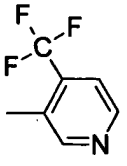
| | | |
|---|---|---|
| 519 |  | 568 |
| 520 |  | 544 |
| 521 |  | 544 |
| 522 |  | 539 |
| 523 |  | 528 |
| 524 |  | 539 |
| 525 |  | 552 |
| 526 |  | 568 |
| 527 |  | 542 |
| 528 |  | 552 |
| 529 |  | 528 |
| 530 |  | 528 |

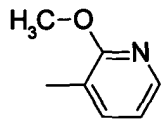
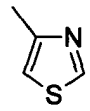
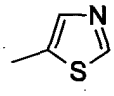
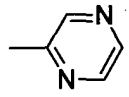
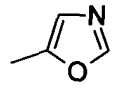
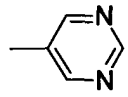
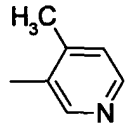
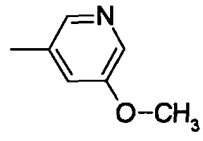
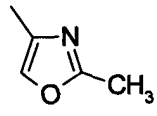
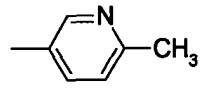
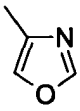
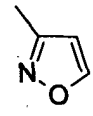
| | | |
|---|---|---|
| 531 |  | 542 |
| 532 |  | 626 |
| 533 |  | 553 |
| 534 |  | 566 |

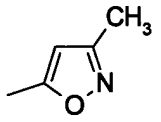
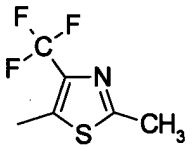
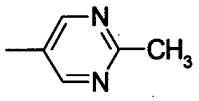
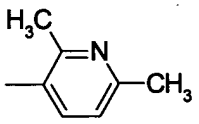


| Example No. | R1 | MS (M+1) |
|---|---|---|
| 535 |  | 517 |
| 536 |  | 528 |
| 537 |  | 528 |
| 538 |  | 531 |
| 539 |  | 533 |
| 540 |  | 547 |
| 541 |  | 534 |
| 542 |  | 545 |
| 543 |  | 543 |
| 544 |  | 517 |

| | | |
|---|---|---|
| 545 |  | 620 |
| 546 |  | 596 |
| 547 |  | 545 |
| 548 |  | 548 |
| 549 |  | 585 |
| 550 |  | 562 |
| 551 |  | 548 |
| 552 |  | 561 |
| 553 |  | 548 |
| 554 |  | 542 |
| 555 |  | 542 |

| | | |
|---|---|---|
| 556 |  | 542 |
| 557 |  | 542 |
| 558 |  | 542 |
| 559 |  | 546 |
| 560 |  | 531 |
| 561 |  | 562 |
| 562 |  | 545 |
| 563 |  | 531 |
| 564 |  | 542 |
| 565 |  | 546 |
| 566 |  | 596 |

| | | |
|---|---|---|
| 567 |  | 558 |
| 568 |  | 534 |
| 569 |  | 534 |
| 570 |  | 529 |
| 571 |  | 518 |
| 572 |  | 529 |
| 573 |  | 542 |
| 574 |  | 558 |
| 575 |  | 532 |
| 576 |  | 542 |
| 577 |  | 518 |
| 578 |  | 518 |

| | | |
|---|---|---|
| 579 |  | 532 |
| 580 |  | 616 |
| 581 |  | 543 |
| 582 |  | 556 |

▪ Example 583

1-Ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyrimidin-5-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 146.2-148.2°C

▪ Example 584

1-Ethyl-3,3,5-trimethyl-7-[4-(2-oxo-3,4-dihydro-2H-quinolin-1-yl)piperidin-1-ylmethyl]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde(0.203g) and acetic acid(0.063ml) were added to a 1,2-dichloroethane solution (5ml) of 1-(piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one (0.170g), and the mixture was stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride(0.235g) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol =100:0→90:10). The purified

product was condensed to dryness to give the title compound(0.205g) as pale yellow amorphous.

$^1$H NMR ($CDCl_3$), δppm : 0.83 (3H, s), 1.20 (3H, t, J = 7.1 Hz), 1.54 (3H, s), 1.68-1.75 (2H, m), 2.13-2.21 (2H, m), 2.55-2.60 (2H, m), 2.64-2.76 (2H, m), 2.80-2.85 (2H, m), 2.95-3.03 (2H, m), 3.44 (3H, s), 3.57(2H, s), 3.77-3.85 (1H, m), 4.10-4.19 (1H, m), 4.25-4.33 (1H, m), 7.01 (1H, dt, J = 1.9, 7.4 Hz), 7.14-7.28 (6H, m)

▪ Example 585

1-Ethyl-3,3,5-trimethyl-7-[4-(2-oxo-2H-quinolin-1-yl)-piperidin-1-ylmethyl]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.85 (3H, s), 1.21 (3H, t, J =7.0 Hz), 1.54 (3H, s), 1.70-1.77 (2H, m), 2.28-2.34 (2H, m), 2.94 (2H, br), 3.05-3.13 (2H, m), 3.46 (3H,s), 3.64 (2H,s), 3.78-3.87 (1H, m), 4.11-4.19 (1H, m), 5.33 (1H, bs), 6.67 (1H, d, J = 9.4 Hz), 7.21 (1H, t, J = 8.0 Hz), 7.27-7.32 (3H, m), 7.50-7.57 (2H, m), 7.62 (1H, d, J = 9.4 Hz), 7.78 (1H, br)

▪ Example 586

N-[1-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)piperidin-4-yl]-N-phenylbenzamide

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.81 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.55-1.63 (2H, m), 1.88-1.95 (2H, m), 2.16-2.26 (2H, m), 2.88-2.94 (2H, m), 3.38 (3H, s), 3.45-3.53 (2H, m), 3.73-3.82 (1H, m), 4.10-4.16 (1H, m), 4.70-4.82 (1H, m), 6.98-7.02 (2H, m), 7.07-7.24 (11H, m)

▪ Example 587

1-Ethyl-3,3,5-trimethyl-7-[3-(2-oxo-3,4-dihydro-2H-quinolin-1-yl)-pyrrolidin-1-ylmethyl]-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same

manner as in Example 584 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.73-0.82 (3H, m), 1.16-1.20 (3H, m), 1.51-1.53 (3H, m), 2.10-2.35 (2H, m), 2.55-3.20 (8H, m), 3.40-3.44 (3H, m), 3.61-4.16 (4H, m), 5.30-5.45 (1H, m), 6.98-7.04 (1H, m), 7.14 - 7.30 (5H, m), 7.65-7.68 (1H, m)

▪ Example 588

1-Ethyl-3,3,5-trimethyl-7-{[N-(2-methylpyridin-3-ylmethyl)-N-(2-oxo-1,2,3,4-tetrahydroquinolin-6-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.80 (3H, s), 1.18 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 2.48 (3H, s), 2.62-2.65 (2H, m), 2.94-2.98 (2H, m), 3.39 (3H, s), 3.46-3.59 (6H, m), 3.76-3.82 (1H, m), 4.09-4.13 (1H, m), 6.71 (1H, d, J = 8.0 Hz), 7.09-7.17 (4H, m), 7.21-7.24 (2H, m), 7.68 (1H, dd, J = 1.6, 7.7 Hz), 7.91 (1H, br), 8.38 (1H, dd, J = 1.7, 4.9 Hz)

▪ Example 589

1-Ethyl-3,3,5-trimethyl-7-{[N-(2-methylpyridin-3-ylmethyl)-N-(2-oxo-1,2,3,4-tetrahydroquinolin-7-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.80 (3H, s), 1.18 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 2.50 (3H, s), 2.62-2.65 (2H, m), 2.94-2.97 (2H, m), 3.39 (3H, s), 3.49-3.61 (6H, m), 3.76-3.84 (1H, m), 4.09-4.13 (1H, m), 6.74 (1H, d, J = 1.1 Hz), 6.97 (1H, dd, J = 1.4, 7.7 Hz), 7.10-7.13 (2H, m), 7.16 (1H, d, J = 1.1 Hz), 7.22-7.28 (2H, m), 7.70 (1H, dd, J = 1.6, 7.7 Hz), 8.17 (1H, br), 8.38 (1H, dd, J = 1.6, 4.9 Hz)

▪ Example 590

7-{[N-(1-Benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

1-Benzyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-carbaldehyde

(0.205g) was added to a methanol solution (10ml) of 7-(aminomethyl)-1-ethyl-3,3,5-trimethyl-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-dione (0.213g). The mixture was stirred at room temperature overnight. Sodium borohydride (0.022g) was added to the mixture, and the mixture was stirred at room temperature overnight. The liquid was then condensed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate: methanol=9:1). The purified product was condensed under reduced pressure to give the title compound(0.400g) as a white amorphous.
$^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.77-2.81 (2H, m), 2.96-3.00 (2H, m), 3.40 (3H, s), 3.73 (2H, s), 3.74-3.83 (1H, m), 3.81 (2H, s), 4.12-4.17 (1H, m), 5.17 (2H, s), 6.83 (1H, d, J = 8.3 Hz), 7.05 (1H, dd, J =1.9, 8.3 Hz), 7.16 (1H, d, J = 1.6 Hz), 7.19-7.25 (6H, m), 7.27-7.33 (2H, m)

▪ Example 591

7-{[N-(1-Benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 590 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.81 (3H, s), 1.18 (3H, t, J = 7.0 Hz), 1.53 (3H, s), 2.77-2.80 (2H, m), 2.96-3.00 (2H, m), 3.38 (3H, s), 3.67 (2H, s), 3.68 (2H, s), 3.76-3.81 (1H, m), 4.12-4.18 (1H, m), 5.20 (2H, s), 6.90-6.95 (2H, m), 7.09 (1H, dd, J = 1.8, 8.4 Hz), 7.12-7.14 (2H, m), 7.17-7.24 (4H, m), 7.25-7.30 (2H, m)

▪ Example 592

1-Cyclopropyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
ivory powder
mp: 146-148°C

▪ Example 593

1-(2-Methoxyethyl)-3,3,5-trimethyl-7-({N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

white powder

mp: 127-130°C

Example 594

1-Ethyl-3,3,5-trimethyl-7-(2-phenylpiperidin-1-ylmethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.78 and 0.81 (3H, s), 1.15-1.20 (3H, m), 1.33-1.47 (1H, m), 1.51-1.53 (3H, m), 1.55-1.84 (5H, m), 1.95-2.05 (1H, m), 2.83-2.97 (2H, m), 3.12-3.17 (1H, m), 3.38 and 3.41 (3H, s), 3.70-3.85 (2H, m), 4.07-4.18 (1H, m), 7.07-7.26 (4H, m), 7.30-7.36 (2H, m), 7.40-7.45 (2H, m)

Example 595

1-Cyclopropyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

White powder

$^1$H NMR (DMSO-$d_6$), δppm : -0.27-0.01 (1H, m), 0.43-0.46 (1H, m), 0.74 (3H, s), 0.73-0.79 (1H, m), 1.05-1.34 (1H, m), 1.34 (3H, s), 2.16 (3H, s), 2.81 (2H, br), 3.21-3.28 (1H, m), 3.28 (3H, s), 3.28 (3H, s), 3.84 (4H, br), 4.15 (2H, br), 4.55 (2H, br), 6.93 (1H, s), 7.36 (2H, br), 7.43 (2H, br), 7.77 (1H, br), 7.97 (1H, d, $J$ = 2.1 Hz), 8.38 (1H, s), 8.60 (1H, br).

Example 596

1-(2-Methoxyethyl)-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

White powder

$^1$H NMR (DMSO-$d_6$), δppm : 0.71 (3H, s), 1.35 (3H, s), 2.43 (3H, s), 2.51 (3H, s), 2.80 (2H, br), 3.12 (3H, s), 3.29 (3H, s), 3.41 (2H, t, $J$ = 5.2 Hz), 3.83 (2H, br), 3.85-3.88 (2H, m), 4.00-4.60 (4H, m), 6.46 (1H, s), 6.23 (1H, s), 7.10-7.49 (4H, m), 7.71 (1H, br), 8.28 (1H, br), 8.56 (1H, br).

Example 597

7-{N-(Benzo[1,3]dioxol-4-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]aminomethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 135.9-137.5°C

Example 598

1-Ethyl-3,3,5-trimethyl-7-{N-[3-(2-oxo-3,4-dihydro-2H-quinolin-1-ylmethyl)benzylamino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

White amorphous

$^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.77-2.83 (2H, m), 2.97-3.02 (2H, m), 3.41 (3H, s), 3.76-3.83 (5H, m), 4.10-4.18 (1H, m), 5.17 (2H, s), 6.86 (1H, d, J = 8.2 Hz), 6.97 (1H, dt, J = 1.0 and 7.4 Hz), 7.07-7.14 (2H, m), 7.17-7.29 (7H, m)

Example 599

1-Ethyl-7-({N-(1H-indol-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder
$^1$H NMR ($CDCl_3$), δppm:0.65 (3H, s), 1.08 (3H, t, J=7.1 Hz), 1.47 (3H, s), 2.48 (3H, d, J=1.0 Hz), 2.86 (2H, t, J=5.1 Hz), 3.13 (3H, s), 3.41 (2H, s), 3.61-3.72(1H, m), 3.91-4.17 (3H, m), 4.22-4.35 (1H, m ), 4.35-4.43 (1H, m), 6.24 (1H, dd, J=0.62, 7.4 Hz), 6.47 (1H, dd, J=2.0, 3.0 Hz), 6.67 (1H, d, J=0.84 Hz), 6.73-6.84 (3H, m), 6.89 (1H, d, J=1.4 Hz),6.95-7.03 (2H,m), 7.17 (1H, t, J=2.8 Hz), 7.52-7.59 (1H, m), 10.51 (1H, s).

Example 600

7-{N-(Benzo[1,3]dioxol-5-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]aminomethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder
mp: 179.7-181.8°C

Example 601

1-Ethyl-7-({N-(1H-indol-6-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White amorphous
$^1$H NMR ($CDCl_3$), δppm: 0.76 (3H, s), 1.15 (3H, t, J=7.1 Hz), 1.50 (3H, s), 2.44 (3H, d, J=1.0 Hz), 2.86 (2H, dt, J=2.4, 5.9 Hz), 3.31 (3H, s), 3.62-3.83(5H, m), 3.98-4.18 (3H, m), 6.40 (1H, dd, J=0.70, 7.3 Hz), 6.48 (1H, t, J=0.88 Hz), 6.50-6.54(1H,m), 6.95-7.11 (4H, m), 7.15 (1H, bs), 7.19 (1H, dd, J=2.5, 3.1 Hz), 7.53 (1H, d, J=8.1 Hz), 8.10 (1H, bs).

Example 602

7-({N-(1H-Benzoimidazol-5-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White amorphous

$^1$H NMR ($CDCl_3$), δppm:0.76 (3H, s), 1.16 (3H, t, J=7.0Hz), 1.51 (3H, s), 2.43 (3H, d, J=0.68 Hz), 2.80-2.92 (2H, m), 3.33 (3H, s), 3.62-3.88 (5.H, m), 3.92-4.25(3H, m), 6.40 (1H, d, J=7.4 Hz), 6.47 (1H, s), 6.82-7.25 (5H,m), 7.26-7.92 (2H, m), 8.02 (1H, s), 9.38 (1H,bs).

Example 603

1-Isobutyl-3,3-dimethyl-8-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (ethyl acetate-hexane-diisopropyl ether)

mp: 128-130°C

Example 604

1-Isobutyl-3,3-dimethyl-8-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 206-208°C

Example 605

1-Isobutyl-8-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same

manner as in Example 30 using appropriate starting materials.
Pale pink powder (ethyl acetate-hexane-diisopropyl ether)
mp: 155-159°C

Example 606

1-Ethyl-3,3,5-trimethyl-7-({N-(3-methylimidazo[1,5-a]pyridin-1-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder
mp: 104.1-109.4°C

Example 607

1-Cyclopropylmethyl-3,3-dimethyl-8-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
Ivory powder (ethyl acetate-hexane-diisopropyl ether)
mp: 153-155°C

Example 608

1-Cyclopropylmethyl-3,3-dimethyl-8-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
Ivory powder (Ether)
mp: 207-210°C

Example 609

1-Cyclopropylmethyl-8-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same

manner as in Example 30 using appropriate starting materials.
White powder (Ether)
mp: 139-141°C

Example 610

1-Isobutyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
Ivory powder (Ether)
mp: 151-152°C

Example 611

1-Ethyl-3,3,5-trimethyl-7-({N-[(1-methyl-1H-benzoimidazol-2-yl)methyl]-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder
mp: 126.9-132.6°C

Example 612

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(3-pyrazol-1-ylbenzyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White amorphous
$^1$H NMR ($CDCl_3$), δppm: 0.78 (3H, s), 1.17 (3H, t, J=7.1 Hz), 1.51 (3H, s), 2.44 (3H, d, J=1.0 Hz), 2.86 (2H, dt, J=1.8, 5.8 Hz), 3.30 (3H, s), 363-3.84 (5H, m), 3.98-4.23 (3H, m), 6.37 (1H, dd, J=0.68, 7.3 Hz), 6.49 (1H, t, J=0.88 Hz), 6.95 (1H, d, J=7.4Hz), 7.03-7.15(3H, m), 7.16-7.26 (4H, m), 7.32 (1H, d, J=7.7 Hz), 7.32-7.37 (1H, m), 7.83 (1H, t, J=1.1 Hz).

Example 613

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-pyrazol-1-yl-benzyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

Pale yellow white powder

mp: 123-130°C

Example 614

1-Ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]pyrazin-2-ylmethylamino}methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 128.7-130.7°C

Example 615

1-Ethyl-7-({N-(imidazo[1,2-a]pyridin-2-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.76 (3H, s), 1.15 (3H, t, J=7.1 Hz), 1.50 (3H, s), 2.43 (3H, d, J=0.72 Hz), 2.91 (2H, t, J=5.5 Hz), 3.32 (3H, s), 3.69-3.85 (3H, m), 3.85-3.95 (2H, m), 3.95-4.22 (3H, m), 6.43 (1H, dd, J=0.68, 7.3 Hz), 6.48 (1H, s), 6.76 (1H, dt, J=1.1, 6.8 Hz), 7.02-7.11 (2H, m), 7.12-7.23 (3H, m), 7.32 (1H, s), 7.53 (1H, q, J=3.2Hz), 7.95 (1H, td, J=1.1, 6.8 Hz).

Example 616

7-{[N-(1-Benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-ylmethyl)-N-methylamino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

7-{[N-(1-Benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-ylmethyl

)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (247mg) was dissolved in DMF(2ml), and was cooled to 0°C in ice water bath. Sodium hydride (60% in oil, 13.56mg) was added thereto at the same temperature, and the mixture was stirred at 0°C for 0.5 hours. Methyl iodide (73.5mg) was added thereto, and the mixture was stirred at room temperature for 4 hours. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried with sodium sulfate, and was condensed under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane: methanol=10:1). The purified product was condensed to dryness under reduced pressure to give the title compound(169mg) as a white amorphous.

$^1$H NMR ($CDCl_3$), δppm : 0.80 (3H, s), 1.19 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.04 (3H, s), 2.75-2.8 (2H, m), 2.95-3.00 (2H, m), 3.38 (3H, s), 3.40-3.44 (4H, m), 3.75-3.85 (1H, m), 4.07-4.19 (1H, m), 5.20 (2H, s), 6.92-6.96 (2H, m), 7.07-7.14 (3H, m), 7.17-7.31 (6H, m)

Example 617

1-Ethyl-7-({N-(2-hydroxybenzyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 166-170°C

Example 618

1-Isobutyl-8-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (ethyl acetate-hexanes)

mp: 96-100°C

Example 619

1-Cyclopropylmethyl-8-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (ethyl acetate-hexane)

mp: 95-99°C

Example 620

2-({N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)benzonitrile

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 156.7-158.6°C

Example 621

4-({N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)benzaldehyde

A 2N-hydrochloric acid (5ml) was added to an THF solution (5ml) of 7-({N-(4-diethoxymethylbenzyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione (0.52g), and the mixture was stirred at room temperature for 1 hour. 2N-Sodium hydroxide solution(5ml) was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried with sodium sulfate, and was condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate). The purified product was condensed under reduced pressure. The residue was recrystallized from ethyl acetate and ether, and dried to give the title compound(0.35g) as a white powder.

mp: 153-155 °C

Example 622

1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-oxo-2H-quinolin-1-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 152-153°C

Example 623

1-Ethyl-7-({N-(6-methoxy-2-methylpyridin-3-ylmethyl)-N-[2-(2-oxo-2H-quinolin-1-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 143-144°C

Example 624

1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-oxo-3,4-dihydro-2H-quinolin-1-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 112-114°C

Example 625

1,3,3-Trimethyl-8-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methyl-pyridin-3-ylmethyl)amino]methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

Ivory powder (Ether)

mp: 117-122°C

Example 626

1,3,3-Trimethyl-8-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (Ether)
mp: 154-157°C

Example 627

1-Ethyl-3,3-dimethyl-8-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (Ether)
mp: 108-114°C

Example 628

1-Ethyl-3,3-dimethyl-8-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (Ether)
mp: 177-179°C

Example 629

1-Ethyl-7-({N-(6-methoxy-2-methylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder
mp: 155-156°C

Example 630

1,3,3-Trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methyl-pyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (Ether)
mp: 176-178°C

Example 631

1,3,3-Trimethyl-7-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
Pale pink powder (Ether)
mp: 142-144°C

Example 632

1-Ethyl-3,3-dimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (Ether)
mp: 213-215°C

Example 633

1-Ethyl-3,3-dimethyl-7-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (Ether)
mp: 197-199°C

Example 634

1-Ethyl-3,3,5-trimethyl-7-({N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridazin-4-ylmethyl)amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 137-141°C

Example 635

1-Ethyl-3,3,5-trimethyl-7-({[N-(1-methyl-1H-indazol-3-yl)methyl]-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 96-102°C

Example 636

1-Ethyl-3,3,5-trimethyl-7-({N-(7-methyl-1H-indazol-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 111-118°C

Example 637

1-Ethyl-3,3,5-trimethyl-7-(3-{N-(2-methylpyridin-3-ylmethyl)-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}propyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δppm : 0.70 (3H, s), 1.04 (3H, t, J = 7.0 Hz), 1.32 (3H, s), 2.62-4.68 (20H, m), 6.69-8.75 (12H, m),

Example 638

1-Ethyl-3,3,5-trimethyl-7-(3-{N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}propyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 150.9-154.7°C

Example 639

1-Ethyl-3,3,5-trimethyl-7-{3-[N-(2-methylpyridin-3-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]propyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δppm : 0.72 (3H, s), 1.04 (3H, t, J = 7.0 Hz), 1.33 (3H, s), 2.09-3.79 (18H, m), 4.65 (2H, br-s), 7.22(1H, d, J = 8.0 Hz), 7.33 (1H, s), 7.43 (1H, d, J = 8.4 Hz), 7.83 (1H, t, J = 6.6 Hz), 7.93-7.97 (1H, m), 8.44 (1H, d, J = 7.5 Hz), 8.76-8.80 (3H, m), 8.90 (1H, s)

Example 640

1-Ethyl-3,3,5-trimethyl-7-(3-{N-(2-methylpyridin-3-ylmethyl)-N-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]amino}propyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 106.4-114.6°C

Example 641

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methyl-2H-pyrazol-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 128.2-130.9°C

Example 642

1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (Ether)

mp: 171-173°C

Example 643

1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (Ether)

mp: 168-170°C

Example 644

8-({N-(2-Methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,3,3-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (Ether)

mp: 179-182°C

Example 645

8-({N-(2-Methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,3,3-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (Ether)

mp: 123-134°C

Example 646

5-Cyclopropylmethyl-1-(2-methoxyethyl)-3,3-dimethyl-7-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (Ether)

mp: 159-160°C

Example 647

5-Cyclopropylmethyl-1-(2-methoxyethyl)-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (Ether)

mp: 131-135°C

Example 648

7-[2-(4-Chlorophenyl)pyrrolidin-1-ylmethyl]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.79 and 0.80 (3H, s), 1.16 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.65-1.98 (3H, m), 2.15-2.30 (2H, m), 3.05-3.17 (2H, m), 3.35-3.45 (4H, m), 3.70-3.83 (2H, m), 4.08-4.18 (1H, m), 7.06-7.23 (3H, m), 7.27-7.32 (2H, m), 7.34-7.38 (2H, m)

Example 649

7-(3-Benzylpiperidin-1-ylmethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same

manner as in Example 584 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm : 0.77 and .79 (3H, s), 0.97-2.10 (5H, m), 1.18 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.45-2.55 (2H, m), 2.80-2.90 (2H, m), 3.35 and 3.40 (3H, s), 3.41-3.60 (4H, m), 3.75-3.85 (1H, m), 4.10-4.20 (1H, m), 7.08-7.26 (8H, m)

Example 650

1-Ethyl-3,3,5-trimethyl-7-(2-phenylazetidin-1-ylmethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm : 0.70 and 0.71 (3H, s), 1.10-1.15 (3H, m), 1.50 (3H, s), 2.10-2.20 (1H, m), 2.32-2.40 (1H, m), 2.90-3.01 (1H, m), 3.26 and 3.32 (3H, s), 3.41-3.46 (1H, m), 3.58-3.78 (3H, m), 4.07-4.17 (2H, m), 7.07-7.21 (4H, m), 7.22-7.28 (2H, m), 7.33-7.38 (2H, m)

Example 651

1-Ethyl-3,3,5-trimethyl-7-(6-methyl-3',4',5',6'-tetrahydro-2'H-[2,3']bipyridinyl-1'-ylmethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm : 0.81 and 0.82 (3H, s), 1.19 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 1.54-1.83 (3H, m), 1.95-2.02 (1H, m), 2.03-2.14 (1H, m), 2.18-2.26 (1H, m), 2.51 (3H, s), 2.81-2.90 (1H, m), 2.95-3.10 (2H, m), 3.41 and 3.42 (3H, s), 3.50-3.60 (2H, m), 3.75-3.85 (1H, m), 4.08-4.17 (1H, m), 6.95-6.98 (2H, m), 7.21-7.24 (3H, m), 7.45-7.50 (1H, m)

Example 652

7-(2-Benzylpyrrolidin-1-ylmethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm : 0.83 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 1.53-1.83 (4H, m), 2.15-2.25 (1H, m), 2.53-2.63 (1H, m),

2.68-2.76 (1H, m), 2.88-3.06 (2H, m), 3.26-3.35 (1H, m), 3.42 and 3.43 (3H, s), 3.75-3.85 (1H, m), 4.03-4.20 (2H, m), 7.17-7.30 (8H, m)

Example 653

1-Ethyl-3,3,5-trimethyl-7-[(2-phenoxypyridin-3-ylamino)methyl]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.
White amorphous

$^1$H NMR ($CDCl_3$), δppm : 0.84 (3H, s), 1.20 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 3.39 (3H, s), 3.75-3.85 (1H, m), 4.09-4.19 (1H, m), 4.45 (2H, d, J = 5.8 Hz), 4.89 (1H, t, J = 5.8 Hz), 6.80 (1H, dd, J = 1.7 and 7.8 Hz), 6.85 (1H, dd, J = 4.8 and 7.8 Hz), 7.13-7.23 (3H, m), 7.24-7.34 (3H, m), 7.38-7.43 (2H, m), 7.51 (1H, dd, J = 1.7 and 4.8 Hz)

Example 654

7-[(1-Benzyl-1H-pyrazol-4-ylamino)methyl]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.
Pale brown amorphous

$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.17 (3H, t, J = 7.0 Hz), 1.51 (3H, s), 3.36 (3H, s), 3.75-3.82 (1H, m), 4.08-4.15 (1H, m), 4.17 (2H, s), 5.18 (2H, s), 6.85 (1H, d, J = 0.8 Hz), 7.15-7.20 (3H, m), 7.21-7.35 (6H, m)

Example 655

7-[(3-Benzyloxypyrazin-2-ylamino)methyl]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.
Pale yellow amorphous

$^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 3.37 (3H, s), 3.75-3.83 (1H, m), 4.07-4.15 (1H, m), 4.68 (2H, d, J = 6.1 Hz), 5.41 (2H, s), 5.46 (1H, t, J = 6.1 Hz), 7.20-7.25 (3H, m), 7.35-7.43 (4H, m), 7.44-7.47 (2H, m), 7.61 (1H, d, J = 3.2 Hz)

Example 656

1-Ethyl-3,3,5-trimethyl-7-(3-phenethylpiperidin-1-ylmethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.82 and 0.83 (3H, s), 0.90-1.00 (1H, m), 1.19 (3H, t, J = 7.1 Hz), 1.50-1.75 (6H, m), 1.53 (3H, s), 1.80-1.88 (1H, m), 1.90-2.00 (1H, m), 2.50-2.60 (2H, m), 2.71-2.84 (2H, m), 3.40 and 3.41 (3H, s), 3.45-3.52 (2H, m), 3.75-3.85 (1H, m), 4.10-4.20 (1H, m), 7.10-7.30 (8H, m)

Example 657

1-Ethyl-3,3,5-trimethyl-7-[(4-phenoxymethylthiazol-2-ylamino)methyl]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.

White amorphous

$^1$H NMR ($CDCl_3$), δppm : 0.83 (3H, s), 1.19 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 3.39 (3H, s), 3.76-3.85 (1H, m), 4.09-4.19 (1H, m), 4.53 (2H, d, J = 5.0 Hz), 5.04 (2H, s), 5.69 (1H, brs), 6.54 (1H, s), 6.95-7.00 (3H, m), 7.23-7.32 (5H, m)

Example 658

1-Ethyl-3,3,5-trimethyl-7-[2-(4-trifluoromethylphenyl)pyrrolidin-1-ylmethyl]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.79 and 0.80 (3H, s), 1.16 (3H, t, J = 7.0 Hz), 1.52 (3H, s), 1.68-2.00 (3H, m), 2.20-2.32 (2H, m), 3.10-3.23 (2H, m), 3.39 (3H, s), 3.47-3.51 (1H, m), 3.70-3.82 (2H, m), 4.09-4.16 (1H, m), 7.07-7.23 (3H, m), 7.53-7.62 (4H, m)

Example 659

7-[2-(2-Chlorophenyl)pyrrolidin-1-ylmethyl]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.79 and 0.80 (3H, s), 1.16 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.55-1.70 (1H, m), 1.75-1.95 (2H, m), 2.28-2.45 (2H, m), 3.12-3.18 (1H, m), 3.25-3.30 (1H, m), 3.39 and 3.40 (3H, s), 3.71-3.85 (2H, m), 3.92-4.00 (1H, m), 4.09-4.20 (1H, m), 7.11-7.22 (4H, m), 7.24-7.34 (2H, m), 7.73-7.78 (1H, m)

Example 660

7-[2-(3-Chlorophenyl)pyrrolidin-1-ylmethyl]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.80 (3H, s), 1.14-1.19 (3H, m), 1.52 (3H, s), 1.65-2.00 (3H, m), 2.17-2.31 (2H, m), 3.06-3.22 (2H, m), 3.35-3.44 (4H, m), 3.73-3.81 (2H, m), 4.08-4.16 (1H, m), 7.06-7.30 (6H, m), 7.43-7.47 (1H, m)

Example 661

5-Cyclopropylmethyl-1-(2-methoxyethyl)-3,3-dimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (diisopropyl ether)
mp: 127-128°C

Example 662

1-Cyclopropylmethyl-5-(2-methoxyethyl)-3,3-dimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (Ether)

mp: 131°C

Example 663

1-Cyclopropylmethyl-5-(2-methoxyethyl)-3,3-dimethyl-7-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder (Ether)

mp: 146-148°C

Example 664

1-Cyclopropylmethyl-5-(2-methoxyethyl)-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder ( ether )

mp: 128-129°C

Example 665

Acetic acid 3-({N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)pyridin-2-ylmethyl ester

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.78 (3H, s), 1.16 (3H, t, $J$ = 7.1 Hz), 1.51 (3H, s), 2.09 (3H, s), 2.43 (1H, d, $J$ = 0.96 Hz), 2.84 (2H, t, $J$ = 6.4 Hz), 3.35 (3H, s), 3.66-3.80 (5H m), 4.02-4.15 (3H, m), 5.16 (2H, s), 6.40 (1H, d, $J$ = 7.3 Hz), 6.50 (1H, br), 6.88 (1H, d, $J$ = 7.3 Hz), 7.07-7.19 (4H, m), 7.58 (1H, dd, $J$ = 7.8, 1.6 Hz), 8.46 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 666

1-Ethyl-7-({N-(2-hydroxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Potassium carbonate (2.0 g ) was added to a methanol solution (30 mL) of (3-((((1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)methyl)(2-(2-methyl-4-oxofuro[3,2-c]pyridin-5(4H)-yl)ethyl)amino)methyl)pyridin-2-yl)methyl acetate (3.0 g) and the mixture was stirred overnight at room temperature. The resulting mixture was filtered and evaporated. The residue was purified by column-chromatography (methanol : ethyl acetate = 0:100 → 1:9) to give the titled compound as ivory powder (1.95 g).
mp: 186-188°C

Example 667

5-Cyclopropyl-1-cyclopropylmethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder (ethyl acetate-hexane)
mp: 121-122°C

Example 668

1-Ethyl-3,3,5-trimethyl-7-{3-[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]propyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder
mp: 134.7-134.8°C

Example 669

3-({N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-be

nzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)pyridine-2-carbaldehyde

2-iodoxybenzoic acid (IBX, 0.235 g) was added to the dimethyl sulfoxide suspension (10 mL) of 1-ethyl-7-((N-((2-(hydroxymethyl)pyridin-3-yl)methyl)-N-(2-(2-methyl-4-oxofuro[3,2-c]pyridin-5(4H)-yl)ethyl)amino)methyl)-3,3,5-trimethyl-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-dione (0.48 g) and the mixture was stirred overnight at room temperature. Water was added to the resulting mixture and then the mixture was extracted with ethyl acetate twice. The combined organic layer was concentrated under reduced pressure, and then the residue was purified by column-chromatography (ethyl acetate : hexanes = 50:50 → 100:0). The purified product was recrystallized from ether to afford the titled compound as ivory powder (0.29 g).

mp: 147-149°C

Example 670

1-Ethyl-3,3,5-trimethyl-7-{[(1-methyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Trifluoroacetic acid (43.2mg) was added to a dichloromethane solution (5ml) of N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(1-methyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-ylmethyl)carbamic acid tert-butyl ester (208mg), and the mixture was stirred at room temperature overnight. A saturated sodium bicarbonate solution was added to the reaction mixture, followed by extraction using dichloromethane, and condensed under reduced pressure to give the title compound(148mg) as a white amorphous.

$^1$H NMR ($CDCl_3$), δppm : 0.83 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.62-2.67 (2H, m), 2.86-2.93 (2H, m), 3.37 (3H, s), 3.42 (3H, s), 3.75-3.86 (5H, m), 4.10-4.17 (1H, m), 6.97-7.02 (2H, m), 7.12-7.15 (1H, m), 7.22-7.29 (3H, m)

Example 671

1-Ethyl-3,3,5-trimethyl-7-{[(2-oxo-1-pyridin-4-ylmethyl-1,2,3,4-t

etrahydro-quinolin-7-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 670 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.80 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.75-2.81 (2H, m), 2.95-3.02 (2H, m), 3.38 (3H, s), 3.69-3.73 (4H, m), 3.75-3.83 (1H, m), 4.09-4.16 (1H, m), 5.20 (2H, s), 6.78 (1H, brs), 6.96 (1H, dd, J = 1.2 and 7.6 Hz), 7.08 (1H, dd, J = 1.9 and 8.4 Hz), 7.11-7.18 (4H, m), 7.23 (1H, d, J = 8.4 Hz), 8.50-8.53 (2H, m)

Example 672

7-({N-(3-Aminopyridin-2-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

Ivory powder

mp: 217-218°C

Example 673

7-({N-(3-Aminopyridin-2-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 188-192°C

Example 674

7-({N-(2-Diethoxymethylbenzyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

mp: 138-139°C

Example 675

2-({N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)benzaldehyde The synthesis of the title compound was performed in the same manner as in Example 621 using appropriate starting materials.

mp: 157-158°C

Example 676

1-Cyclopropylmethyl-5-(2-methoxyethyl)-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δppm : 0.00 (2H, br), 0.21-0.23 (2H, m), 0.61 (3H, s), 0.75 (1H, br), 1.26 (3H, s), 2.35 (3H, s), 2.68 (2H, br), 3.24 (3H, s), 3.12-3.80 (6H, m), 3.90-4.20 (6H, m), 4.50 (2H, s), 6.41 (1H, s), 6.55 (1H, br), 7.20 (1H, br), 7.25-7.50 (3H, m), 7.60 (1H, br), 8.20 (1H, br), 8.48 (1H, s).

Example 677

5-Cyclopropyl-1-cyclopropylmethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δppm : -0.09-0.05 (3H, m), 0.12-0.23 (2H, m), 0.35-0.46 (1H, m), 0.63-0.80 (2H, m), 0.72 (3H, s), 1.06-1.13 (1H, m), 1.33 (3H, s), 2.43 (3H, s), 2.81 (2H, br), 3.20 (1H, br), 3.34 (3H, s), 3.37-3.45 (2H, m), 3.80 (2H, br), 4.15-4.20 (3H, m), 4.67 (3H, br), 6.49 (1H, br), 6.66 (1H, br), 7.13-7.60 (4H, m), 7.77-7.80 (1H, m), 8.42 (1H, br), 8.63 (1H, br).

Example 678

7-({N-(3-Diethoxymethylbenzyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
mp: 112-114°C

Example 679

3-({N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)benzaldehyde

The synthesis of the title compound was performed in the same manner as in Example 621 using appropriate starting materials.
mp: 79-84°C

Example 680

1-Ethyl-7-({N-(2-hydroxymethylbenzyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium borohydride (47mg) were added to a methanol solution(10ml) of 2-({N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)benzaldehyde (0.59g) was stirred for 3 hours at 0°C. Water was added to the reaction mixture, followed by extraction by ethyl acetate. The organic layer was dried by anhydrous sodium sulfate, and condensed under reduced pressure. The residue was recrystallized from ethyl acetate -ether mixture to give the title compound(0.42g) as a pale brown white powder.
mp: 159-161°C

Example 681

1-Ethyl-3,3,5-trimethyl-7-{[4-(2-oxo-3,4-dihydro-2H-quinolin-1-ylmethyl)benzylamino]-methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.76-2.81 (2H, m), 2.95-3.02 (2H, m), 3.41 (3H, s), 3.74-3.83 (5H, m), 4.10-4.18 (1H, m), 5.17 (2H, s), 6.85-6.90 (1H, m), 6.96-7.00 (1H, m), 7.07-7.13 (1H, m), 7.15-7.35 (8H, m)

Example 682

5-Cyclopropylmethyl-1-(2-methoxyethyl)-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : 0.03-0.10 (2H, m), 0.25-0.29 (2H, m), 0.66 (3H, s), 0.77-0.85 (1H, m), 1.30 (3H, s), 2.38 (3H, s), 2.95-3.15 (2H, m), 3.07 (3H, s), 3.10-3.42 (4H, m), 3.30 (3H, s), 3.50-3.57 (1H, m), 3.87 (2H, br), 3.97-4.09 (1H, m), 4.33 (4H, br), 4.77 (2H, br), 6.48 (1H, s), 6.64 (1H, d, $J$ = 7.3 Hz), 7.47 (2H, br), 7.57-7.60 (1H, m), 7.79-7.82 (2H, m), 8.66-8.67 (2H, m).

Example 683

5-Cyclopropyl-1-cyclopropylmethyl-3,3-dimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : -0.09-0.03 (3H, m), 0.15-0.27 (2H, m), 0.37-0.44 (1H, m), 0.72 (3H, s), 0.65-0.76 (2H, m), 1.06-1.10 (1H, m), 1.33 (3H, s), 2.43 (3H, br), 2.49 (3H, br), 2.79 (2H, br), 3.17-3.22 (1H, m), 3.38-3.49 (1H, m), 3.77 (2H, br), 3.81 (2H, br), 4.14 (2H, br), 4.16-4.22 (1H, m), 6.45 (1H, s), 6.62 (1H, d, $J$ = 7.0 Hz), 7.26 (1H, br), 7.36 (1H, br), 7.45-7.48 (2H, m), 7.68-7.72 (1H, m), 8.29 (1H, br), 8.56 (1H, br).

Example 684

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-morpholin-4-ylmethylbenzyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Morpholine(0.06ml) and acetic acid(0.1ml) were added to a 1,2-dichloroethane solution(7ml) of 2-({N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)benzaldehyde (0.35g), and the mixture was stirred for 30 minutes at room temperature. Sodium triacetoxy borohydride(0.20g) was added, and the mixture was stirred at room temperature overnight. Water was added to the reaction liquid, followed by extraction by dichloromethane. The organic layer was dried by anhydrous sodium sulfate, and condensed under reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: hexane=3:2). The purified product was condensed under reduced pressure to give the title compound(0.30g) as a white amorphous solid.

$^1$H NMR ($CDCl_3$), d ppm : 0.78 (3H, s), 1.16 (3H, t, J=7.0 Hz), 1.51 (3H, s), 2.28-2.38(4H, m), 2.43 (3H, d, J=1.0 Hz), 2.83 (2H, t, J=6.1 Hz), 3.32 (3H, s), 3.43 (2H, s), 3.56-3.88(9H, m), 3.96-4.07 (2H, m), 4.07-4.18(1H, m), 6.40 (1H, dd, J=0.64, 7.4 Hz), 6.48 (1H, d, J=0.88 Hz), 6.89 (1H, d, J=7.3 Hz), 7.08 (2H, d, J=0.96 Hz), 7.12-7.20 (3H, m), 7.21-7.26 (1H, m), 7.37 (1H, dd, J=2.1,7.0 Hz).

Example 685

1-Ethyl-7-({N-(3-hydroxymethylbenzyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 680 using appropriate starting materials.
mp: 170-172°C

Example 686

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(3-morpholin-4-ylmethylbenzyl)amino]methyl}-1

,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

$^1$H NMR ($CDCl_3$) 0.77 (3H, s), 1.16 (3H, t, J=7.0 Hz), 1.51 (3H, s), 2.37-2.46 (4H, m), 2.43 (3H, d, J=0.96 Hz), 2.82 (2H, dt, J=2.3, 5.8 Hz), 3.31 (3H, s), 3.41 (2H, s), 3.59-3.82 (9H, m), 3.96-4.19 (3.H, m), 6.44 (1H, dd, J=0.70 7.4 Hz), 6.48 (1H, t, J=0.9Hz), 6.97-7.09 (3H,m), 7.11-7.26(5H, m).

Example 687

1-Ethyl-3,3,5-trimethyl-7-{[N-(2-oxo-1-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-quinolin-7-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 670 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.81 (3H, s), 1.18 (3H, t, J =7.1 Hz), 1.53 (3H, s), 2.75-2.81 (2H, m), 2.95-3.01 (2H, m), 3.39 (3H, s), 3.70-3.73 (4H, m), 3.74-3.84 (1H, m), 4.08-4.14 (1H, m), 5.30 (2H, s), 6.95 (1H, dd, J = 1.3 and 7.6 Hz), 7.05 (1H, brs), 7.11-7.25 (6H, m), 7.60 (1H, dt, J = 1.8 and 7.7 Hz), 8.50-8.55 (1H, m)

Example 688

1-Ethyl-3,3,5-trimethyl-7-{[N-(2-oxo-1-pyridin-3-ylmethyl-1,2,3,4-tetrahydroquinolin-7-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 670 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.81 (3H, s), 1.16 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.75-2.80 (2H, m), 2.94-2.99 (2H, m), 3.39 (3H, s), 3.70-3.73 (4H, m), 3.75-3.84 (1H, m), 4.08-4.18 (1H, m), 5.22 (2H, s), 6.91 (1H, brs), 6.96 (1H, dd, J = 1.2 and 7.6 Hz), 7.10-7.18 (3H, m), 7.20-7.24 (2H, m), 7.55 (1H, dt, J = 2.2 and 7.8 Hz), 8.47 (1H, dd, J =1.6 and 4.8 Hz), 8.56 (1H, d, J = 1.8 Hz)

Example 689

1-Ethyl-3,3,5-trimethyl-7-({N-methyl-N-[3-(2-oxo-3,4-dihydro-2H-quinolin-1-ylmethyl)benzyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 616 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.15-1.21 (3H, m), 1.53 (3H, s), 2.16 (3H, s), 2.76-2.81 (2H, m), 2.95-3.01 (2H, m), 3.40 (3H, s), 3.47-3.54 (4H, m), 3.75-3.82 (1H, m), 4.08-4.16 (1H, m), 5.18 (2H, s), 6.86 (1H, dd, J = 0.8 and 8.1 Hz), 6.95 (1H, dt, J =1.0 and 7.4 Hz), 7.04-7.12 (2H, m), 7.15-7.30 (7H, m)

Example 690

1-Ethyl-3,3,5-trimethyl-7-({N-methyl-N-[4-(2-oxo-3,4-dihydro-2H-quinolin-1-ylmethyl)-benzyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 616 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.18 (3H, s), 2.76-2.81 (2H, m), 2.95-3.01 (2H, m), 3.41 (3H, s), 3.48-3.52 (4H, m), 3.75-3.82 (1H, m), 4.08-4.17 (1H, m), 5.17 (2H, s), 6.85-6.90 (1H, m), 6.95-7.00 (1H, m), 7.06-7.13 (1H, m), 7.15-7.33 (8H, m)

Example 691

7-({N-(2-Dimethylaminomethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione trihydrochloride

To the 1,2-dichloroethan suspension (5 ml ) of 3-(((N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)methyl)-N-(2-(2-methyl-4-oxofuro[3,2-c]pyridin-5(4H)-yl)ethyl)amino)methyl)picolinaldehyde (205 mg), dimethylammonium chloride (59 mg) and triehylamine (0.10 ml) was added sodium triacetoxyborohydride (114 mg) at room temperature, and the mixture was stirred overnight. The mixture was concentrated under reduced pressure, and then the residue was purified by column-chromatography (methanol : ethyl acetate = 1:9 → 50:50). The purified product was dissolved in ethyl acetate (ca. 5 mL) and then 4 M HCl/ ethyl acetate was added to the mixture. The precipitate was

collected and dried *in vacuo* to give the titled compound as light brown powder (114 mg).

$^1$H NMR (DMSO-$d_6$), δppm : 0.70 (3H, s), 1.06 (3H, t, $J$ = 7.0 Hz), 1.34 (3H, s), 2.40 (3H, br), 2.89 (6H, s), 3.15-3.44 (2H, m), 3.34 (3H, s), 3.70-4.05 (10H, m), 6.55 (1H, s), 6.73 (1H, d, $J$= 7.4 Hz), 7.20-8.00 (5H, m), 8.26 (1H, br), 8.64 (1H, br).

Example 692

1-Ethyl-3,3,5-trimethyl-7-({N-(2-methylaminomethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

To a methanol solution (5 ml ) of 3-({N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)pyridine-2-carbaldehyde (243 mg) was added 9.8 M THF solution of methylamine (87 □l) and the mixture was stirred overnight at room temperature. $NaBH_4$ (16 mg ) was added to the mixture, and then the mixture was stirred overnight. The resulting mixture was evaporated and the residue was purified by column chromatography (methanol : ethyl acetate = 1:9 → 50:50). The purified product was dissolved in ethyl acetate (ca. 5 ml) and then 4 M HCl/ ethyl acetate was added to the mixture. The precipitate was collected and dried *in vacuo* to give the titled compound as light brown powder (18 mg).

$^1$H NMR (DMSO-$d_6$), δppm : 0.70 (3H, s), 1.06 (3H, t, $J$ = 7.0 Hz), 1.34 (3H, s), 2.40 (3H, br), 2.66 (3H, s), 3.05-3.45 (2H, m), 3.34 (3H, s), 3.70-4.05 (10H, m), 6.56 (1H, s), 6.74 (1H, d, $J$ = 7.4 Hz), 7.48 (3H, br), 7.64 (1H, d, $J$ = 6.5 Hz), 7.77 (1H, br), 8.23 (1H, br), 8.62 (1H, br), 9.32 (2H, br).

Example 693

7-({N-(2-Cyclopropylaminomethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 692 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : 0.72 (3H, s), 0.70-0.74 (2H, m), 0.98 (2H, br), 1.08 (3H, t, $J$ = 7.0 Hz), 1.35 (3H, s), 2.41 (3H, br), 2.75 (2H, br), 3.33 (3H, s), 3.60-3.90 (5H, m), 3.91-4.05 (1H, m), 4.20-4.70 (5H, m), 6.55 (1H, s), 6.73 (1H, d, $J$ = 7.3 Hz), 7.45 (3H, br), 7.59-7.61 (2H, m), 8.15 (1H, br), 8.59 (1H, br), 9.54 (2H, br).

Example 694

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-pyrrolidin-1-ylmethylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 691 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : 0.71 (3H, s), 1.06 (3H, t, $J$ = 7.0 Hz), 1.35 (3H, s), 2.00 (4H, br), 2.43 (3H, br), 2.76 (2H, br), 3.28 (7H, br), 3.75 (4H, br), 3.90-4.30 (2H, m), 4.55 (4H, br), 6.52 (1H, br), 6.70 (1H, br), 7.25 (2H, br), 7.32 (1H, br), 7.52 (2H, br), 7.69 (1H, br), 8.47 (1H, br), 10.3 (1H, br).

Example 695

1-Ethyl-7-({N-[2-(3-hydroxypyrrolidin-1-ylmethyl)pyridin-3-ylmethyl]-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 691 using appropriate starting materials.
$^1$H NMR (DMSO-$d_6$), δppm : 0.71 (3H, s), 1.07 (3H, t, $J$ = 6.9 Hz), 1.35 (3H, s), 1.95 (1H, br), 2.19 (1H, br), 2.42 (3H, br), 2.75 (2H, br), 3.10-3.60 (9H, m), 3.75 (4H, br), 3.90-4.25 (3H, m), 4.47 (2H, br), 6.52 (1H, br), 6.70 (1H, br), 7.27 (3H, br), 7.53 (2H, br), 7.69 (1H, br), 8.49 (1H, br), 10.4 (1H, br).

Example 696

1-Ethyl-3,3,5-trimethyl-7-{[2-(2-oxo-3,4-dihydro-2H-quinolin-1-yl

methyl)benzylamino]-methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.16 (3H, t, J = 7.1 Hz), 1.51 (3H, s), 2.78-2.83 (2H, m), 2.99-3.04 (2H, m), 3.32 (3H, s), 3.74-3.81 (1H, m), 3.90-3.93 (4H, m), 4.08-4.14 (1H, m), 5.30-5.34 (2H, m), 6.82 (1H, dd, J = 1.0 and 7.9 Hz), 6.91-7.03 (3H, m), 7.13-7.35 (7H, m)

Example 697

1-Ethyl-3,3,5-trimethyl-7-({N-(4-methylpyridin-3-ylmethyl)-N-[2-(2-oxo-2H-quinolin-1-yl)ethyl]amino}methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 120-121°C

Example 698

7-({N-(2,6-Dimethylpyridin-3-ylmethyl)-N-[2-(2-oxo-2H-quinolin-1-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 159-160°C

Example 699

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(7-methyl-4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 174-175°C

Example 700

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(4-methyl-7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 163-165°C

Example 701

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyrimidin-5-ylmethyl)amino]methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 166-167°C

Example 702

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(4-methyl-7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 174-177°C

Example 703

1-Ethyl-3,3,5-trimethyl-7-({N-methyl-N-[2-(2-oxo-3,4-dihydro-2H-quinolin-1-ylmethyl)benzyl]amino}methyl)-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 616 using appropriate starting materials.

White powder

mp: 125-127°C

Example 704

1-Ethyl-7-({N-(6-hydroxymethylpyridin-3-ylmethyl)-N-[2-(1-oxo-1H-isoquinolin-2-yl)-ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using 6-((tert-butyldimethylsilyloxy)methyl)nicotinaldehyde and 1-ethyl-3,3,5-trimethyl-7-((2-(1-oxoisoquinolin-2(1H)-yl)ethylamino)methyl)-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-dione, followed by deprotection of TBDMS group with tetrabutylammonium fluoride.

$^1$H NMR ($CDCl_3$), δppm : 0.75 (3H, s), 1.13 (3H, t, J = 7.1 Hz), 1.50 (3H, s), 2.85-2.88 (2H, m), 3.27 (3H, s), 3.62-3.75 (5H, m), 3.96-4.02 (1H, m), 4.13 (2H, t, J = 7.2 Hz), 4.65 (2H, s), 6.46 (1H, d, J = 7.3 Hz), 6.93 (1H, d, J = 7.3 Hz), 6.96-6.99 (2H, m), 7.05 (1H, dd, J = 1.8, 8.4 Hz), 7.13 (1H, d, J = 1.6 Hz), 7.48-7.57 (3H , m), 7.66-7.71 (1H, m), 8.33 (1H, dd, J = 0.6, 8.1 Hz), 8.41 (1H, d, J = 1.5 Hz).

Example 705

1-Ethyl-3,3,5-trimethyl-7-(3-{N-(2-methylpyridin-3-ylmethyl)-N-[2-(7-oxo-7H-thieno[2,3-c]pyridin-6-yl)ethyl]amino}propyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δppm : 0.71 (3H, s), 1.04 (3H, t, J = 7.1 Hz), 1.33 (3H, s), 1.65-2.34 (2H, m), 2.52-2.92 (6H, m), 3.25-4.82 (12H, m), 6.60-6.92 (1H, m), 7.03-7.19 (1H, m), 7.19-7.31 (1H, m), 7.31-7.41 (2H, m), 7.41-7.90 (2H, m), 8.00-8.11 (1H , m), 8.12-8.60 (2H, m).

Example 706

1-Ethyl-3,3,5-trimethyl-7-(3-{N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-thieno[3,2-c]pyridin-5-yl)ethyl]amino}propyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δppm : 0.71 (3H, s), 1.04 (3H, t, J = 7.1 Hz), 1.32 (3H, s), 1.66-2.29 (2H, m), 2.55-2.71 (2H, m), 2.71-2.92 (4H, m),

2.96-4.81 (12H, m), 6.81-7.02 (2H, m), 7.02-7.41 (4H, m), 7.41-7.69 (1H, m), 7.41-7.90 (2H, m), 8.42-8.93 (1H , m), .

Example 707

7-{[2-(2,6-Dimethylpyridin-3-yl)ethylamino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 590 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm:0.82 (3H, s), 1.18 (3H, t, $J$ = 7.1 Hz), 1.53 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 2.78-2.83 (2H, m), 2.85-2.89 (2H, m), 3.40 (3H, s), 3.74-3.84 (1H, m), 3.84 (2H, s), 4.09-4.19 (1H, m), 6.93 (1H, d, $J$ = 7.7 Hz), 7.17-7.19 (2H, m), 7.24 (1H, s), 7.32 (1H, d, $J$ = 7.7 Hz).

Example 708

7-{[N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.83 (3H, s), 1.18 (3H, t, $J$ = 7.1 Hz), 1.53 (3H, s), 2.23 (3H, s), 3.42 (3H, s), 3.75-3.83 (8H, m), 4.09-4.20 (1H, m), 5.94 (1H, s), 7.20-7.28 (3H, m).

Example 709

1-Ethyl-7-{[N-(2-methoxymethylpyridin-3-ylmethyl)amino]methyl}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.83 (3H, s), 1.18 (3H, t, $J$ = 7.1 Hz), 1.53 (3H, s), 3.41 (3H, s), 3.42 (3H, s), 3.74-3.85 (1H, s), 3.85 (2H, s), 3.91 (2H, s), 4.10-4.67 (1H, m), 4.67 (2H, s), 7.22-7.28 (4H, m), 7.72-7.74 (1H, m), 8.49-8.51 (1H, m).

Example 710

1-Ethyl-3,3,5-trimethyl-7-{[N-(3-methyl-3H-imidazol-4-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.83 (3H, s), 1.18 (3H, t, $J$ = 7.1 Hz), 1.53 (3H, s), 3.42 (3H, s), 3.69 (3H, s), 3.75-3.84 (1H, m), 3.80 (2H, s), 3.83 (2H, s), 4.11-4.18 (1H, m), 6.92 (1H, s), 7.20-7.23 (2H, m), 7.25-7.28 (1H, m), 7.42 (1H, s).

Example 711

1-Ethyl-3,3,5-trimethyl-7-[(1-pyridin-3-ylethylamino)methyl]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.81-0.82 (3H, m), 1.17 (3H, t, $J$ = 7.1 Hz), 1.42-1.44 (3H, m), 1.53 (3H, s), 3.40-3.41 (3H, m), 3.62-3.70 (2H, m), 3.73-3.83 (1H, m), 3.85-3.91 (1H, m), 4.09-4.19 (1H, m), 7.14-7.19 (2H, m), 7.22-7.31 (2H, m), 7.70-7.74 (1H, m), 8.51-8.53 (1H, m), 8.58 (1H, d, $J$ = 2.0 Hz).

Example 712

7-{[(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.82 (3H, s), 1.17 (3H, t, $J$ = 7.1 Hz), 1.53 (3H, s), 1.77 (6H, s), 2.26 (3H, s), 3.42 (3H, s), 3.74-3.85 (1H, m), 3.74 (3H, s), 3.77 (2H, s), 3.86 (2H, s), 5.96 (1H, s), 7.23-7.24 (3H, m).

Example 713

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-nitrobenzenesulfonamide

Triethylamine(0.6ml) was added to a dichloromethane solution (6ml) of 1-ethyl-3,3,5-trimethyl-7-aminomethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(1.0g). The mixture was cooled with ice. 2-Nitrobenzenesulphonyl chloride(0.80g) was added, and the mixture was stirred at room temperature overnight. A saturated sodium

bicarbonate solution was added to the reaction mixture, followed by extraction using dichloromethane.

The organic layer was washed with water and saturated saline, dried with magnecium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (hexane: ethyl acetate=1:1→1:4). The purified product was condensed under reduced pressure, and the residue was recrystallized from the ethyl acetate- hexane mixture to give the title compound(1.38g) as a white solid.

$^1$H NMR ($CDCl_3$), δppm: 0.78 (3H, s), 1.16 (3H, t, J = 7.1 Hz), 1.51 (3H, s), 3.35 (3H, s), 3.72-3.83 (1H, m), 4.06-4.17 (1H, m), 4.35 (2H, d, J = 6.4 Hz), 5.78 (1H, d, J = 6.4 Hz), 7.16-7.23 (3H, m), 7.73-7.79 (2H, m), 7.86-7.91 (1H, m), 8.12-8.15 (1H, m)

Example 714

1-Ethyl-3,3,5-trimethyl-7-{[(5-methyloxazol-4-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.83 (3H, s), 1.17 (3H, t, J=7.1 Hz), 1.53 (3H, s), 2.29 (3H, s), 3.42 (3H, s), 3.68 (2H, s), 3.72-3.86(3H, m), 4.09-4.23(1H, m), 7.20-7.30 (3H, m), 7.74 (1H, s).

Example 715

1-Ethyl-7-{[(6-methoxymethylpyridin-3-ylmethyl)amino]methyl}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.83 (3H, s), 1.18 (3H, t, *J* = 7.1 Hz), 1.53 (3H, s), 3.42 (3H, s), 3.49 (3H, s), 3.74- 3.85 (1H, m), 3.83 (2H, s), 3.85 (2H, s), 4.10-4.20 (1H, m), 4.58 (2H, s), 7.23-7.37 (3H, m), 7.40 (1H, d, *J* = 8.0 Hz), 7.71 (1H, dd, *J* = 8.0, 2.1 Hz), 8.53 (1H, d, *J* = 1.9 Hz).

Example 716

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]py

ridin-5-yl)ethyl]-N-(2-methyl-1-oxypyridin-3-ylmethyl)amino]methy l}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

To a dichloromethane solution (10 ml ) of 1-ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]py ridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5 -dihydrobenzo[b][1,4]diazepine-2,4-dione (2.0 g) was added *m*-chloroperbenzoic acid (mCPBA, 0.89 g) at 0 °C and the mixture was stirred overnight. The resulting mixture was charged on silica gel and purified by column chromatography (methanol/ethyl acetate 1:9→1:1) to give the titled compound as white amorphous (0.46 g). $^1$H NMR ($CDCl_3$), δppm: 0.79 (3H, s), 1.17 (3H, t, $J$ = 7.1 Hz), 1.52 (3H, s), 2.35 (3H, s), 2.44 (3H, d, $J$ = 1.0 Hz), 2.84 (2H, t, $J$ = 6.1 Hz), 3.35 (3H, s), 3.62 (2H, s), 3.69-3.83 (3H, m), 4.03-4.18 (3H, m), 6.41 (1H, dd, $J$ = 7.3, 0.7 Hz), 6.51 (1H, t, $J$ = 0.9 Hz), 6.85 (1H, d, $J$ = 7.3 Hz), 6.92-6.96 (1H, m), 7..09-7.11 (2H, m), 7.15-7.18 (1H, m), 7.21-7.22 (1H, m), 8.14 (1H, d, $J$ = 6.0 Hz).

Example 717

1-Ethyl-3,3,5-trimethyl-7-{[(3-methyl-pyridin-2-ylmethyl)amino]me thyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm: 0.84 (3H, s), 1.18 (3H, t, J=7.1Hz), 1.53 (3H, s), 2.28 (3H, s), 3.42 (3H, s), 3.73-3.87(1H, m), 3.91 (2H, s), 3.93 (2H, s), 4.08-4.23 (1H, m), 7.11 (1H, dd, J=4.8, 7.6 Hz), 7.22-7.34 (3H, m), 7.41-7.47 (1H, m), 8.41 (1H, dd, J=1.1, 4.8 Hz).

Example 718

1-Ethyl-3,3,5-trimethyl-7-{[1-(2-methylpyridin-3-yl)ethylamino]-m ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm: 0.82-0.83 (3H, m), 1.15-1.89 (3H, m), 1.35-1.37 (3H, m), 1.53 (3H, s), 2.52 (3H, d, $J$ = 8.0 Hz), 3.39-3.40 (3H, m), 3.66 (2H, s), 3.73-3.82 (1H, m), 4.05-4.20 (2H, m), 7.18-7.20 (3H, m), 7.23-7.24 (1H, m), 7.85 (1H, dd, $J$ = 7.8, 1.6 Hz), 8.40 (1H, d,

$J$ = 4.7 Hz).

Example 719

7-{[(2-Ethoxymethylpyridin-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.83 (3H, s), 1.17 (6H, t, $J$ = 7.0 Hz), 1.53 (3H, s), 3.42 (3H, s), 3.57 (2H, q, $J$ = 7.0 Hz), 3.74-3.83 (1H, m), 3.84 (2H, s), 3.92 (2H, s), 4.09-4.20 (1H, m), 4.71 (2H, s), 7.22-7.28 (4H, m), 7.71 (1H, dd, $J$ = 7.7, 1.6 Hz), 8.49 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 720

1-Ethyl-7-{[1-(2-methoxymethylpyridin-3-yl)ethylamino]methyl}-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 584 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: : 0.82-0.83 (3H, m), 1.16 (3H, t, $J$ = 6.9 Hz), 1.40 (3H, d, $J$ = 6.4 Hz), 1.52 (3H, s), 3.37-3.40 (6H, m), 3.60 (1H, d, $J$ = 13.6 Hz), 3.68 (1H, d, $J$ = 13.6 Hz), 3.72-3.82 (1H, m), 4.09-4.20 (1H, m), 4.23-4.30 (1H, m), 4.57-4.66 (2H, m), 7.15-7.19 (2H, m), 7.22-7.26 (1H, m), 7.27-7.32 (1H, m), 7.96-7.98 (1H, m), 8.49 (1H, dd, $J$ = 4.7, 1.7 Hz).

Example 721

1-Ethyl-3,3,5-trimethyl-7-{[2-(1-oxo-1H-isoquinolin-2-yl)ethylamino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

2-(2-Aminoethyl)-2H-isoquinolin-1-one (1.0g) was added to a methanol solution (15ml) of 1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-7-carbaldehyde (1.46g). The mixture was stirred for 0.5 hours at room temperature. Sodium borohydride (0.23g) was added to the mixture, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, followed by extraction using dichloromethane. The organic layer was washed with water and saturated saline, dried with magnesium sulfate, and

condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=9:1→8:2). The purified product was condensed under reduced pressure to give the title compound(1.92g) as a white solid.

1H NMR ($CDCl_3$), δppm : 0.78 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.51 (3H, s), 3.01-3.11(2H, m), 3.31 (3H, s), 3.71-3.81 (1H, m), 3.84 (2H, s), 4.04-4.15 (1H, m), 4.16 (2H, t, J = 6.0 Hz), 6.51 (1H, d, J = 7.3 Hz), 7.12-7.18 (4H, m), 7.48-7.56 (2H, m), 7.63-7.70 (1H, m), 8.41 (1H, d, J = 8.1 Hz)

Example 722

1-Ethyl-3,3,5-trimethyl-7-(quinolin-5-ylaminomethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.

$^1H$ NMR ($CDCl_3$), δppm : 0.86 (3H, s), 1.21 (3H, t, J=7.1 Hz), 1.54 (3H, s), 3.38 (3H, s), 3.76-3.89 (1H, m), 4.09-4.22 (1H, m), 4.56 (2H, d, J=4.4 Hz), 4.70-4.88 (1H, m), 6.62 (1H, dd, J=2.6, 6.1Hz), 7.28-7.35 (3H, m), 7.38 (1H, dd, J=4.2, 8.6 Hz), 7.50-7.58 (2H,m), 8.23 (1H, dd, J=1.4, 8.6 Hz), 8.92 (1H, dd, J=1.6, 4.2Hz).

Example 723

7-{[(4-Chloro-pyridin-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1H$ NMR ($CDCl_3$), δppm : 0.83 (3H, s), 1.18 (3H, t, J=7.1 Hz), 1.53 (3H, s), 3.42 (3H, s), 3.72-3.90 (3H, m), 3.96 (2H, s), 4.08-4.22 (1H, m), 7.22-7.27(3H, m), 7.33 (1H, d, J=5.3 Hz), 8.44 (1H, d, J=5.3Hz), 8.60 (1H, s).

Example 724

7-{[(2-Chloropyridin-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.84 (3H, s), 1.18 (3H, t, J=7.1 Hz), 1.53 (3H, s), 3.42 (3H, s), 3.74-3.86 (1H, m), 3.86 (2H, s), 3.93 (2H, s), 4.08-4.23 (1H, m), 7.21-7.31 (4H, m), 7.80 (1H, dd, J=1.9, 7.5 Hz), 8.32 (1H, dd, J=1.9, 4.8 Hz).

Example 725

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-methyl-pyridin-3-ylmethyl)carbamic acid tert-butyl ester

To a THF solution (15 ml) of 1-ethyl-3,3,5-trimethyl-7-(((2-methylpyridin-3-yl)methylamino)methyl)- 1H-benzo[b][1,4]diazepine-2,4(3H,5H)-dione (0.92 g) was added di-tert-butyl dicarbonate (0.58 g) at room temperature, the mixture was stirred overnight. The resulting mixture was concentrated and then purified by column chromatography (ethyl acetate/hexanes 1:4→1:1→7:3) to give the titled compound as colorless oil (0.88 g).

$^1$H NMR ($CDCl_3$), □.ppm: 0.82 (3H, s), 1.18 (3H, t, $J$ = 7.0 Hz), 1.49 (9H, s), 1.53 (3H, s), 2.45 (3H, s), 3.36 (3H, s), 3.75-3.84 (1H, m), 4.09-4.18 (1H, s), 4.43 (4H, br), 6.99-7.12 (3H, m), 7.23-7.25 (1H, m), 7.35-7.38 (1H, m), 8.39-8.41 (1H, m).

Example 726

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(4-methylthiazol-5-ylmethyl)carbamic acid tert-butyl ester

The synthesis of the title compound was performed in the same manner as in Example 725 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.18 (3H, t, $J$ = 7.1 Hz), 1.45-1.55 (12H, m), 2.34 (3H, s), 3.36 (3H, s), 3.76-3.84 (1H, m), 4.09-4.16 (1H, m), 4.42 (2H, s), 4.54 (2H, s), 7.00-7.09 (2H, m), 7.24-7.27 (1H, m), 8.62 (1H, s).

Example 727

N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)carbamic acid tert-butyl ester

The synthesis of the title compound was performed in the same manner as in Example 725 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.83 (3H, s), 1.19 (3H, t, $J$ = 7.1 Hz), 1.49 (9H, br), 1.54 (3H, s), 2.21 (3H, s), 3.38 (3H, s), 3.72 (3H, br), 3.75-3.85 (1H, m), 4.09-4.18 (1H, m), 4.35 (2H, br), 4.44 (2H, br), 5.88 (1H, s), 7.00-7.05 (2H, m), 7.24-7.27 (1H, m).

Example 728

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-methyl-1-oxypyridin-3-ylmethyl)carbamic acid tert-butyl ester

The synthesis of the title compound was performed in the same manner as in Example 716 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.83 (3H, s), 1.20 (3H, t, $J$ = 7.0 Hz), 1.49 (9H, s), 1.54 (3H, s), 2.45 (3H, s), 3.38 (3H, s), 3.76-3.86 (1H, m), 4.08-4.16 (1H, m), 4.43 (4H, br), 6.99-7.12 (4H, m), 7.25-7.29 (1H, m), 8.21-8.23 (1H, m).

Example 729

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-hydroxymethylpyridin-3-ylmethyl)carbamic acid tert-butyl ester

The synthesis of the title compound was performed in the same manner as in Example 666 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.81 (3H, s), 1.13 (3H, t, $J$ = 7.1 Hz), 1.49 (9H, br), 1.53 (3H, s), 3.36 (3H, s), 3.75-3.84 (1H, m), 4.07-4.18 (1H, m), 4.40 (4H, br), 4.62 (2H, s), 7.00-7.08 (2H, m), 7.24-7.27 (2H, m), 7.47-7.49 (1H, m), 8.47-8.49 (1H, m).

Example 730

1-Ethyl-3,3,5-trimethyl-7-{[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethylamino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione
1H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 3.00-3.10(2H, m), 3.34 (3H, s), 3.72-3.81 (1H, m), 3.84 (2H, s), 4.08-4.17 (1H, m), 4.21 (2H, t, J = 6.0 Hz), 6.47 (1H, d, J = 7.0 Hz), 6.67 (1H, d, J = 2.0 Hz), 7.13-7.22 (4H, m), 7.74 (1H, d, J = 2.0 Hz)

Example 731

1-Ethyl-7-{[(2-hydroxymethylpyridin-3-ylmethyl)amino]methyl}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

To a ethanol solution (20 ml ) of tert-butyl (1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)methyl((2-(hydroxymethyl)pyridin-3-yl)methyl)carbamate (0.82 g) was added 5 M HCl and the mixture was stirred at 50 °C for 7 hours. The resulting mixture was concentrated and then 5 M NaOH was added thereto. Organic materials were extracted with ethyl acetate twice and then dried over $MgSO_4$. After evaporation, the residue was purified by column chromatography (methanol/ethyl acetate 1:9→1:1) to give the titled compound as pale yellow oil (0.37 g).
$^1$H NMR ($CDCl_3$), δppm: 0.82 (3H, s), 1.18 (3H, t, $J$ = 7.0 Hz), 1.53 (3H, s), 3.42 (3H, s), 3.74-3.90 (5H, m), 4.09-4.19 (1H, m), 4.80 (2H, s), 7.20-7.29 (4H, m), 7.64-7.67 (1H, m), 8.49-8.51 (1H, m).

Example 732

1-Ethyl-7-{[(5-methoxymethyl-2-methyl-2H-pyrazol-3-ylmethyl)amino]methyl}-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.83 (3H, s), 1.18 (3, t, $J$ = 7.0 Hz), 1.53 (3H, s), 3.40 (3H, s), 3.42 (3H, s), 3.77-3.87 (5H, m), 4.11-1.18 (1H, m), 4.41 (2H, s), 6.18 (1H, s), 7.21-7.28 (3H, m).

Example 733

1-Isobutyl-3,3-dimethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.75 (3H, s), 0.77 (3H, s), 0.98 (3H, br), 1.53 (3H, br), 1.76-1.84 (1H, m), 2.56 (3H, s), 3.37-3.42 (1H, m), 3.82 (2H, s), 3.85 (2H, s), 4.34-4.40 (1H, m), 7.00-7.02 (1H, m), 7.10-7.14 (1H, m), 7.20-7.23 (1H, m), 7.24-7.27 (1H, m), 7.62 (1H, br), 7.62-7.64

(1H, m), 8.41 (1H, dd, $J$ = 4.9, 1.7 Hz).

Example 734

1-Isobutyl-7-{[(2-methoxymethylpyridin-3-ylmethyl)amino]methyl}-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.74 (3H, s), 0.76 (3H, s), 0.98 (3H, br), 1.53 (3H, br), 1.74-1.85 (1H, m), 3.39-3.42 (1H, m), 3.40 (3H, s), 3.82 (2H, s), 3.90 (2H, s), 4.34-4.39 (1H, m), 7.01-7.02 (1H, m), 7.18-7.21 (1H, m), 7.23-7.27 (2H, m), 7.68 (1H, br), 7.74 (1H, dd, $J$ = 7.7, 1.6 Hz), 8.50 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 735

1-(2-Methoxyethyl)-3,3-dimethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 1.01 (3H, br), 1.53 (3H, br), 2.56 (3H, s), 3.34 (3H, s), 3.49 (1H, br), 3.60 (1H, br), 3.81 (2H, s), 3.84 (2H, s), 3.98 (1H, br), 4.11 (1H, br), 7.00 (1H, d, $J$ = 1.8 Hz), 7.12 (1H, dd, $J$ = 7.6, 4.9 Hz), 7.22 (1H, dd, $J$ = 8.4, 1.8 Hz), 7.58 (1H, d, $J$ = 8.4 Hz), 7.64 (1H, dd, $J$ = 7.6, 1.5 Hz), 7.92 (1H, br), 8.41 (1H, dd, $J$ = 4.9, 1.5 Hz).

Example 736

1-(2-Methoxyethyl)-7-{[(2-methoxymethylpyridin-3-ylmethyl)amino]methyl}-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 1.01 (3H, br), 1.53 (3H, br), 3.34 (3H, s), 3.41 (3H, s), 3.59 (1H, br), 3.72 (1H, br), 3.81 (2H, s), 3.89 (2H, s), 3.98 (1H, br), 4.10 (1H, br), 4.67 (2H, s), 6.98-7.00 (1H, m), 7.21 (1H, dd, $J$ = 8.4, 1.9 Hz), 7.24-7.27 (1H, m), 7.57 (1H, d, $J$ = 8.4 Hz), 7.66 (1H, br), 7.73 (1H, dd, $J$ = 7.7, 1.6 Hz), 8.50 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 737

1-Cyclopropylmethyl-3,3-dimethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm: 0.18 (2H, br), 0.41 (2H, d, $J$ = 8.0 Hz), 0.96-1.07 (4H, m), 1.54 (3H, br), 3.65 (1H, br), 3.82 (2H, s), 3.85 (2H, s), 4.11 (1H, br), 7.03 (1H, d, $J$ = 1.8 Hz), 7.12 (1H, dd, $J$ = 7.6, 4.9 Hz), 7.21 (1H, dd, $J$ = 8.4, 1.8 Hz), 7.32 (1H, d, $J$ = 8.4 Hz), 7.63 (1H, dd, $J$ = 7.6, 1.6 Hz), 7.84 (1H, br), 8.41 (1H, dd. $J$ = 4.9, 1.6 Hz).

Example 738

1-Cyclopropylmethyl-7-{[(2-methoxymethylpyridin-3-ylmethyl)amino]methyl}-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm: 0.19 (2H, br), 0.40 (2H, d, $J$ = 8.1 Hz), 0.97-1.07 (4H, m), 1.54 (3H, br), 3.41 (3H, s), 3.66 (1H, br), 3.82 (2H, s), 3.90 (2H, s), 4.10 (1H, br), 4.67 (2H, s), 7.04 (1H, d, $J$ = 1.8 Hz), 7.20 (1H, dd, $J$ = 8.4, 1.8 Hz), 7.23-7.26 (1H, m), 7.32 (1H, d, $J$ = 8.4 Hz), 7.74 (1H, dd, $J$ = 7.7, 1.6 Hz), 8.07 (1H, br), 8.50 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 739

1-Cyclopropyl-3,3-dimethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm: 0.40 (2H, br), 1.00 (2H, br), 1.54 (6H, br), 2.56 (3H, s), 3.16-3.22 (1H, m), 3.82 (2H, s), 3.85 (2H, s), 6.99 (1H, br), 7.12 (1H, dd, $J$ = 7.6, 4.9 Hz), 7.23 (1H, dd, $J$ = 8.4, 1.9 Hz), 7.34 (1H, d, $J$ = 8.4 Hz), 7.64 (1H, dd, $J$ = 7.6, 1.6 Hz), 8.13 (1H, br), 8.41 (1H, dd, $J$ = 4.9, 1.6 Hz).

Example 740

1-Cyclopropyl-7-{[(2-methoxymethylpyridin-3-ylmethyl)amino]methyl}-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.40 (2H, br), 1.00 (2H, br), 1.54 (6H, br), 3.16-3.21 (1H, m), 3.41 (3H, s), 3.82 (2H, s), 3.90 (2H, s), 4.67 (2H, s), 6.96 (1H, br), 7.21 (1H, dd, $J$ = 8.4, 1.9 Hz), 7.24-7.26 (1H, m), 7.34 (1H, d, $J$ = 8.4 Hz), 7.60 (1H, br), 7.74 (1H, dd, $J$ = 7.7, 1.6 Hz), 8.50 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 741

N-[3-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)propyl]-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide

Tribuyl phosphine(1.2ml) and 1,1'-(azodicarbonyl)dipiperidine (1.17g) were added to a toluene solution(100ml) of 2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-yl)-ethyl]-benzenesulfonamide (1.39g), and 1-ethyl-7-(3-hydroxy-propyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione (0.94g). The mixture was stirred overnight. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was washed with water and saturated saline, dried with magnecium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: hexane =1:1→1:0). The purified product was condensed under reduced pressure to produce the title compound(0.54g) as a white amorphous.

$^1$H NMR ($CDCl_3$), δppm: 0.81 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.91-2.01(2H, m), 2.61 (2H, t, J = 7.7 Hz), 3.31-3.51 (2H, m), 3.40 (3H, s), 3.70 (2H, t, J = 6.7 Hz), 3.72-3.81 (1H, m), 4.09-4.17 (1H, m), 4.22 (2H, t, J = 6.7 Hz), 6.45 (1H, d, J = 7.3 Hz), 6.94 (1H, dd, J = 8.4 and 1.9 Hz), 7.02 (1H, d, J = 1.9 Hz), 7.12-7.16 (2H, m), 7.46-7.66 (6H, m), 7.90-7.94 (1H, m), 8.34 (1H, d, J = 7.5 Hz)

Example 742

1-Ethyl-3,3,5-trimethyl-7-{3-[2-(1-oxo-1H-isoquinolin-2-yl)ethylamino]propyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Lithium hydroxide(3.2g), and thioglycolic acid(2.4ml) were added to a DMF solution(27.4ml) of N-[3-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)propyl]-2-nitro-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]benzenesulfonamide (4.56g). The mixture was stirred at room temperature for 1 hour. The reaction mixture was condensed under reduced pressure. Water was added to the residue, followed by extraction using dichloromethane. The organic layer was washed with water and saturated saline, dried with magnesium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol =10:1). The purified product was condensed under reduced pressure to produce the title compound(2.24g) as a yellow oil.

1H NMR (CDCl3), δppm: 0.80 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.77-1.88(2H, m), 2.64-2.72 (4H, m), 3.04 (2H, t, J = 6.3 Hz), 3.38 (3H, s), 3.69-3.80 (1H, m), 4.08-4.17 (3H, m), 6.51 (1H, d, J = 7.3 Hz), 7.00-7.03 (2H, m), 7.11-7.17 (2H, m), 7.46-7.53 (2H, m), 7.61-7.66 (1H, m), 8.42 (1H, dd, J = 8.0 and 0.6 Hz)

Example 743

1-Cyclopropyl-7-{[(2-methoxymethylpyridin-3-ylmethyl)amino]methyl}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.12-0.19 (1H, m), 0.60-0.67 (1H, m), 0.75-0.83 (1H, m), 0.85 (3H, s), 1.24-1.28 (1H, m), 1.52 (3H, s), 3.15-3.21 (1H, m), 3.39 (3H, s), 3.40 (3H, s), 3.84 (2H, s), 3.91 (2H, s), 4.67 (2H, s), 7.19-7.20 (1H, m), 7.22-7.29 (2H, m), 7.33 (1H, d, *J* = 4.3 Hz), 7.73 (1H, dd, *J* = 7.7, 1.6 Hz), 8.50 (1H, dd, *J* = 4.8, 1.6 Hz).

Example 744

1-Isobutyl-7-{[(2-methoxymethylpyridin-3-ylmethyl)amino]methyl}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same

manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.70 (3H, d, $J$ = 6.7 Hz), 0.75 (3H, d, $J$ = 6.7 Hz), 0.81 (3H, s), 1.53 (3H, s), 1.75-1.86 (1H, m), 3.31 (1H, dd, $J$ = 13.6, 6.4 Hz), 3.85 (2H, s), 3.91 (2H, s), 4.37 (1H, dd, $J$ = 13.6, 8.6 Hz), 4.67 (2H, s), 7.23-7.26 (4H, m), 7.72 (1H, dd, $J$ = 7.7, 1.6 Hz), 8.50 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 745

1-(2-Methoxyethyl)-3,3,5-trimethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.85 (3H, s), 1.53 (3H, s), 2.56 (3H, s), 3.29 (3H, s), 3.41 (3H, s), 3.53-3.58 (1H, m), 3.69 (1H, ddd, $J$ = 10.3, 7.1, 4.4 Hz), 3.82 (2H, s), 3.87 (2H, s), 3.97 (1H, ddd, $J$ = 14.1, 5.2, 4.6 Hz), 4.07-4.15 (1H, m), 7.13 (1H, dd, $J$ = 7.6, 4.9 Hz), 7.23-7.26 (2H, m), 7.50 (1H, d, $J$ = 8.2 Hz), 7.63 (1H, dd, $J$ = 7.6, 1.6 Hz), 8.42 (1H, dd, $J$ = 4.8 , 1.6 Hz).

Example 746

1-Isobutyl-3,3-dimethyl-8-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.76 (6H, d, $J$ = 6.7 Hz), 0.98 (3H, s), 1.53 (3H, s), 1.78-1.89 (1H, m), 2.55 (3H, s), 3.41 (1H, dd, $J$ = 13.8, 6.5 Hz), 3.80 (2H, s), 3.87 (2H, s), 4.37 (1H, dd, $J$ = 13.8, 8.3 Hz), 6.97 (1H, d, $J$ = 8.1 Hz), 7.12 (1H, dd, $J$ = 7.6, 4.9 Hz), 7.19 (1H, dd, $J$ = 8.1, 1.7 Hz), 7.32 (1H, d, $J$ = 1.7 Hz), 7.62 (1H, dd, $J$ = 7.6, 1.6 Hz), 7.70 (1H, br), 8.41 (1H, dd, $J$ = 4.9, 1.6 Hz).

Example 747

1-Isobutyl-8-{[(2-methoxymethylpyridin-3-ylmethyl)amino]methyl}-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.76 (6H, d, $J$ = 6.7 Hz), 0.98 (3H, s), 1.53 (3H, s), 1.78-1.89 (1H, m), 3.39-3.46 (1H, m), 3.40 (3H, s), 3.83 (2H, s), 3.88 (2H, s), 4.33-4.42 (1H, m), 4.66 (2H, s), 6.97 (1H, d, $J$ = 8.1 Hz), 7.18 (1H, dd, $J$ = 8.1, 1.7 Hz), 7.23-7.26 (1H, m), 7.31 (1H, d, $J$ = 1.7 Hz), 7.72 (1H, dd, $J$ = 7.6, 1.6 Hz), 7.73 (1H, br), 8.41 (1H, dd, $J$ = 4.9, 1.6 Hz).

Example 748

1-Cyclopropylmethyl-3,3-dimethyl-8-{[(2-methylpyridin-3-ylmethyl) amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.18 (2H, br), 0.41 (2H, d, $J$ = 7.9 Hz), 0.95-1.08 (4H, m), 1.54 (3H, br), 2.55 (3H, s), 3.70 (1H, br), 3.80 (2H, s), 3.87 (2H, s), 4.14 (1H, br), 6.97 (1H, d, $J$ = 8.1 Hz), 7.12 (1H, dd, $J$ = 7.6, 4.9 Hz), 7.19 (1H, dd, $J$ = 8.1, 1.6 Hz), 7.39 (1H, d, $J$ = 1.6 Hz), 7.62 (1H, dd, $J$ = 7.6, 1.6 Hz), 7.74 (1H, br), 8.41 (1H, dd, $J$ = 4.9, 1.6 Hz).

Example 749

1-Cyclopropylmethyl-8-{[(2-methoxymethylpyridin-3-ylmethyl)amino] methyl}-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.18 (2H, br), 0.41 (2H, d, $J$ = 7.9 Hz), 0.95-1.08 (4H, m), 1.54 (3H, br), 3.40 (3H, s), 3.71 (1H, br), 3.84 (2H, s), 3.89 (2H, s), 4.10 (1H, br), 4.66 (2H, s), 6.97 (1H, d, $J$ = 8.1 Hz), 7.18 (1H, dd, $J$ = 8.1, 1.6 Hz), 7.23-7.26 (1H, m), 7.37 (1H, d, $J$ = 1.6 Hz), 7.72 (1H, dd, $J$ = 7.7, 1.6 Hz), 7.83 (1H, br), 8.41 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 750

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-methoxymethylpyridin-3-ylmethyl) carbamic acid tert-butyl ester

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-

benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-methyl-1-oxypyridin-3-ylmethyl)carbamic acid tert-butyl ester (188mg) was disolved in DMF(20ml), and was cooled to 0°C in ice water bath. Sodium hydride (60% in oil, 19.7mg) was added thereto at the same temperature, and the mixture was stirred at 0°C for 0.5 hours. Methyl iodide (0.028ml) was added thereto, and the mixture was stirred at 0°C for 0.5 hours. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried with sodium sulfate, and was condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=10:1). The purified product was condensed to dryness under reduced pressure to give the title compound(162mg) as a colorless oil.

$^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.48 (9H, bs), 1.53 (3H, s), 3.33 (3H, s), 3.36 (3H, s), 3.74-3.84 (1H, m), 4.08-4.18 (1H, m), 4.30-4.50 (2H, m), 4.52-4.72 (4H, m), 7.02-7.15 (2H, m), 7.20-7.25 (2H, m), 7.46-7.57 (1H, m), 8.46 (1H, dd, J = 1.5 and 4.8 Hz)

Example 751

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl)carbamic acid tert-butyl ester

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-methyl-1-oxypyridin-3-ylmethyl)carbamic acid tert-butyl ester (2.35 g) was dissolved in acetic anhydride (20 ml). The reaction mixture was stirred at 100°C for 2 h. The resulting mixture was evaporated, and dissolved in MeOH (15 ml). Potassium carbonate (6.8 g ) was added to the mixture, and the reaction mixture was stirred 2 h at room temperature. Water was added to the resulting mixture and then the mixture was extracted with ethyl acetate. The organic layer was dried with sodium sulfate, and was condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : methanol = 10:1). The purified product was condensed to dryness under reduced pressure to give the title compound(536 mg) as a pale yellow amorphous.

$^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.49

(9H, s), 1.52 (3H, s), 2.37 (3H, s), 3.37 (3H, s), 3.77-3.83 (1H, m), 4.09-4.15 (1H, m), 4.30-4.52 (4H, m), 7.00-7.08 (2H, m), 7.09-7.15 (1H, m), 7.25-7.30 (1H, m), 8.07 (1H, d, J = 2.6 Hz)

Example 752

1-Ethyl-3,3,5-trimethyl-7-[3-(2-pyridin-3-yl-ethylamino)propyl]-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 742 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.82 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 1.78-1.85 (2H, m), 2.63-2.72 (4H, m), 2.79-2.83 (2H, m), 2.86-2.92 (2H, m), 3.40 (3H, s), 3.73-3.81 (1H, m), 4.09-4.18 (1H, m), 7.01-7.06 (2H, m), 7.19-7.23 (2H, m), 7.52-7.55 (1H, m), 8.47-8.49 (2H, m)

Example 753

1-Ethyl-3,3,5-trimethyl-7-{3-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethylamino]propyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 742 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.84 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.73-1.84 (2H, m), 2.60-2.71 (4H, m), 3.03 (2H, t, J = 6.2 Hz), 3.39 (3H, s), 3.73-3.81 (1H, m), 4.09-4.18 (1H, m), 4.17 (2H, t, J = 6.2 Hz), 6.47 (1H, d, J = 7.0 Hz), 6.66 (1H, d, J = 2.0 Hz), 6.98-7.05 (2H, m), 7.14-7.20 (2H, m), 7.74 (1H, d, J = 2.0 Hz)

Example 754

Acetic acid 3-{[N-tert-butoxycarbonyl-N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)amino]methyl}pyridin-2-ylmethyl ester

The synthesis of the title compound was performed in the same manner as in Example 751 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.81 (3H, s), 1.19 (3H, t, $J$ = 7.1 Hz), 1.48 (9H, br), 1.57 (3H, s), 2.08 (3H, s), 3.36 (3H, s), 3.75-3.84 (1H, m),

4.09-4.18 (1H, m), 4.41 (2H, br), 4.57 (2H, br), 5.15 (2H, s), 7.03-7.12 (2H, m), 7.22-7.26 (2H, m), 7.47-7.50 (1H, m), 8.53 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 755

Acetic acid 3-{[(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)amino]methyl}pyridin-2-ylmethyl ester

The synthesis of the title compound was performed in the same manner as in Example 731 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm: 0.82 (3H, s), 1.17 (3H, t, $J$ = 7.1 Hz), .1.52 (3H, s), 2.11 (3H, s), 3.41 (3H, s), 3.74-3.82 (1H, m), 3.86 (2H, s), 3.90 (2H, s), 4.09-4.20 (1H, m), 5.33 (2H, s), 7.23-7.27 (4H, m), 7.72 (1H, d, $J$ = 7.7 Hz), 8.52-8.54 (1H, m).

Example 756

1-Ethyl-3,3,5-trimethyl-7-{3-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethylamino]propyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 742 using appropriate starting materials. $^1$H NMR ($CDCl_3$), δppm : 0.81 (3H, s), 1.17 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 1.76-1.83 (2H, m), 2.63-2.70 (4H, m), 3.01 (2H, t, J = 6.2 Hz), 3.39 (3H, s), 3.72-3.81 (1H, m), 4.09-4.18 (3H, m), 6.54 (1H, dd, J = 7.4 and 0.8 Hz), 6.96-7.04 (3H, m), 7.19 (1H, d, J = 8.6 Hz), 7.23 (1H, d, J = 7.4 Hz), 7.49 (1H, d, J = 2.1 Hz),

Example 757

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(6-methoxy-2-methylpyridin-3-ylmethyl)carbamic acid tert-butyl ester

N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-methyl-6-oxo-1,6-dihydropyridin-3-ylmethyl)carbamic acid tert-butyl ester (536mg) was disolved in DMF(20ml), and was cooled to 0°C in ice water bath. Sodium hydride (60% in oil, 56.1mg) was added thereto at the same temperature, and the mixture was stirred at 0°C for 0.5 hours. Methyl iodide (0.081ml)

was added thereto, and the mixture was stirred at 0°C for 0.5 hours. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried with sodium sulfate, and was condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=10:1). The purified product was condensed to dryness under reduced pressure to give the title compound(550mg) as a yellow oil.

$^1$H NMR ($CDCl_3$), δppm: 0.82 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.50 (9H, s), 1.53 (3H, s), 2.37 (3H, s), 3.36 (3H, s), 3.75-3.85 (4H, m), 4.09-4.20 (1H, m), 4.30-4.50 (4H, m), 6.85-6.98 (1H, m), 7.00-7.12 (2H, m), 7.23-7.28 (1H, m), 8.08 (1H, d, J = 2.8 Hz)

Example 758

1-Ethyl-7-{[(6-methoxy-2-methyl-pyridin-3-ylmethyl)amino]methyl}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 670 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.83 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.47 (3H, s), 3.42 (3H, s), 3.78-3.83 (3H, m), 3.85 (3H, s), 3.88 (2H, s), 4.10-4.17 (1H, m), 7.20-7.30 (4H, m), 8.10 (1H, d, J = 2.9 Hz)

Example 759

1,3,3-Trimethyl-8-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 1.08 (3H, br), 1.63 (3H, br), 2.56 (3H, s), 3.47 (3H, s), 3.81 (2H, s), 3.87 (2H, s), 6.97 (1H, d, *J* = 8.1 Hz), 7.12 (1H, dd, *J* = 7.6, 4.9 Hz), 7.19 (1H, dd, *J* = 8.1, 1.7 Hz), 7.24-7.26 (1H, m), 7.62 (1H, dd, *J* = 7.6, 1.6 Hz), 7.98 (1H, br), 8.41 (1H, dd, *J* = 4.9, 1.6 Hz).

Example 760

1-Ethyl-3,3-dimethyl-8-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 1.00 (3H, br), 1.26 (3H, t, $J$ = 7.1 Hz), 1.55 (3H, br), 2.56 (3H, s), 3.81 (2H, s), 3.87 (2H, s), 3.93 (1H, br), 4.09 (1H, br), 6.93-6.97 (1H, m), 7.12 (1H, dd, $J$ = 7.5, 4.9 Hz), 7.19 (1H, dd, $J$ = 8.2, 1.8 Hz), 7.24-7.26 (1H, m), 7.35 (1H, br), 7.63 (1H, dd, $J$ = 3.5, 1.5 Hz), 8.41 (1H, dd, $J$ = 4.8, 1.5 Hz).

Example 761

1,3,3-Trimethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 1.05 (3H, br), 1.55 (3H, br), 2.56 (3H, s), 3.46 (3H, s), 3.82 (2H, s), 3.85 (2H, s), 7.03 (1H, br), 7.12 (1H, dd, $J$ = 7.6, 4.9 Hz), 7.20-7.23 (2H, m), 7.63 (1H, dd, $J$ = 7.6, 1.6 Hz), 8.03 (1H, br), 8.41 (1H, dd, $J$ = 4.9, 1.6 Hz).

Example 762

1-Ethyl-3,3-dimethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 1.00 (3H, br), 1.22 (3H, t, $J$ = 7.1 Hz), 1.53 (3H, br), 2.56 (3H, s), 3.82 (2H, s), 3.85 (2H, s), 3.92 (1H, br), 4.12 (1H, br), 7.02 (1H, d, $J$ = 1.6 Hz), 7.12 (1H, dd, $J$ = 7.6, 4.9 Hz), 7.22 (1H, dd, $J$ = 8.4, 1.8 Hz), 7.29, (1H, d, $J$ = 8.4 Hz), 7.63 (1H, dd, $J$ = 7.6 , 1.5 Hz), 7.85 (1H, br), 8.41 (1H, dd, $J$ = 4.9, 1.5 Hz).

Example 763

1-Ethyl-7-{[(2-methoxymethylpyridin-3-ylmethyl)amino]methyl}-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 1.00 (3H, br), 1.22 (3H, t, $J$ = 7.1 Hz), 1.53

(3H, br), 3.41 (3H, s), 3.82 (2H, s), 3.90 (2H, s), 3.92 (1H, br), 4.08 (1H, br), 4.67 (2H, s), 7.01 (1H, d, $J$ = 1.5 Hz), 7.21 (1H, dd, $J$ = 8.4, 1.9 Hz), 7.23-7.29 (2H, m), 7.74 (1H, dd, $J$ = 7.7, 1.6 Hz), 7.79 (1H, br), 8.50 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 764

8-{[(2-Methoxymethyl-pyridin-3-ylmethyl)amino]methyl}-1,3,3-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 1.02 (3H, br), 1.53 (3H, br), 3.40 (3H, s), 3.47 (3H, s), 3.84 (2H, s), 3.90 (2H, s), 4.67 (2H, s), 6.97 (1H, d, $J$ = 8.2 Hz), 7.18 (1H, dd, $J$ = 8.2, 1.7 Hz), 7.23-7.26 (2H, m), 7.72 (1H, dd, $J$ = 7.7, 1.6 Hz), 7.94 (1H, br), 8.50 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 765

5-Cyclopropylmethyl-1-(2-methoxyethyl)-3,3-dimethyl-7-{[(2-methylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.12-0.22 (2H, m), 0.34-0.50 (2H, m), 0.82 (3H, s), 0.94-1.03 (1H, m), 1.53 (3H, s), 2.56 (3H, s), 3.31 (3H, s), 3.49-3.60 (2H, m), 3.70 (1H, ddd, $J$ = 10.0, 7.1, 5.5 Hz), 3.81 (2H, s), 3.87 (2H, s), 3.94 (1H, dt, $J$ = 13.9, 5.3 Hz), 4.12 (1H, dd, $J$ = 14.1, 7.4 Hz), 4.15-4.22 (1H, m), 7.12 (1H, dd, $J$ = 7.6, 4.9 Hz), 7.24-7.26 (2H, m), 7.33 (1H, br), 7.50 (1H, d, $J$ = 8.4 Hz), 7.63 (1H, dd, $J$ = 7.6, 1.6 Hz), 8.41 (1H, dd, $J$ = 4.9, 1.6 Hz).

Example 766

5-Cyclopropylmethyl-1-(2-methoxyethyl)-7-{[(2-methoxymethylpyridin-3-ylmethyl)amino]-methyl}-3,3-dimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.12-0.23 (2H, m), 0.34-0.44 (2H, m), 0.82 (3H,

s), 0.96-1.03 (1H, m), 1.53 (3H, s), 3.30 (3H, s), 3.40 (3H, s), 3.49-3.60 (2H, m), 3.69 (1H, ddd, $J$ = 10.0, 7.1, 5.5 Hz), 3.84 (2H, s), 3.89 (2H, s), 3.95 (1H, dt, $J$ = 13.9, 5.3 Hz), 4.11-4.22 (2H, m), 4.66 (2H, s), 7.23-7.26 (2H, m), 7.32 (1H, br), 7.49 (1H, d, $J$ = 8.4 Hz), 7.72 (1H, dd, $J$ = 7.6, 1.6 Hz), 8.50 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 767

1-Cyclopropylmethyl-5-(2-methoxyethyl)-3,3-dimethyl-7-{[(2-methylpyridin-3-ylmethyl)-amino]methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.11-0.22 (2H, m), 0.34-0.44 (2H, m), 0.82 (3H, s), 0.94-1.03 (1H, m), 1.52 (3H, s), 2.56 (3H, s), 3.29 (3H, s), 3.49-3.57 (2H, m), 3.71 (1H, ddd, $J$ = 10.0, 7.1, 5.5 Hz), 3.82 (2H, s), 3.87 (2H, s), 3.97 (1H, dt, $J$ = 13.9, 5.2 Hz), 4.11-4.22 (2H, m), 7.12 (1H, dd, $J$ = 7.6, 4.9 Hz), 7.23-7.27 (2H, m), 7.55 (1H, d, $J$ = 1.3 Hz), 7.64 (1H, dd, $J$ = 7.6, 1.6 Hz), 8.40 (1H, dd, $J$ = 4.9, 1.6 Hz).

Example 768

1-Cyclopropylmethyl-5-(2-methoxyethyl)-7-{[(2-methoxymethylpyridin-3-ylmethyl)amino]-methyl}-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm: 0.11-0.22 (2H, m), 0.34-0.44 (2H, m), 0.82 (3H, s), 0.94-1.04 (1H, m), 1.52 (3H, s), 3.29 (3H, s), 3.40 (3H, s), 3.48-3.57 (2H, m), 3.70 (1H, ddd, $J$ = 10.0, 7.0, 5.6 Hz), 3.85 (2H, s), 3.90 (2H, s), 3.96 (1H, dt, $J$ = 13.9, 5.3 Hz), 4.14 (1H, dd, $J$ = 14.1, 7.4 Hz), 4.18-4.25 (1H, m), 4.67 (2H, s), 7.23-7.29 (3H, m), 7.52 (1H, br), 7.75 (1H, dd, $J$ = 7.7, 1.6 Hz), 8.50 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 769

5-Cyclopropyl-1-cyclopropylmethyl-7-{[(2-methoxymethylpyridin-3-y

lmethyl)amino]methyl}-3,3-dimethyl-1,5-dihydrobenzo[b][1,4]diazep ine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 721 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm: 0.00-0.06 (1H, m), 0.07-0.13 (1H, m), 0.18-0.35 (3H, m), 0.58-0.65 (1H, m), 0.75-0.90 (2H, m), 0.84 (3H, s), 1.14-1.22 (1H, m), 1.51 (3H, s), 3.20-3.25 (1H, m), 3.36 (1H, dd, $J$ = 14.1, 6.8 Hz), 3.40 (3H, s), 3.86 (2H, s), 3.90 (2H, s), 4.30 (1H, dd, $J$ = 14.1, 7.4 Hz), 4.67 (2H, s), 7.18-7.26 (3H, m), 7.36 (1H, br), 7.73 (1H, dd, $J$ = 7.7, 1.6 Hz), 8.50 (1H, dd, $J$ = 4.8, 1.6 Hz).

Example 770

1-Ethyl-3,3,5-trimethyl-7-{2-[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c] pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]ethyl}-1, 5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 165.3-166.5°C

Example 771

7-{2-[N-[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]ethyl}-1-ethyl-3,3,5-trimethy l-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

White powder

mp: 155.1-155.8°C

Example 772

1-Ethyl-3,3,5-trimethyl-7-{2-[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c] pyridin-5-yl)ethyl]-N-(4-methylthiazol-2-ylmethyl)amino]ethyl}-1, 5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.78 (3H, s), 1.15 (3H, t, $J$ = 7.1 Hz), 1.51

(3H, s), 2.23 (3H, d, $J$ = 0.9 Hz), 2.42 (3H, d, $J$ = 0.8 Hz), 2.76 (2H, t, $J$ = 7.4 Hz), 2.84-2.92 (2H, m), 2.95-3.04 (2H, m), 3.36 (3H, s), 3.71-3.79 (1H, m), 4.01 and 4.02 (2H, s), 4.03-4.16 (3H, m), 6.77 (1H, br), 6.93 (1H, br), 6.97-7.01 (m, 3H), 7.12 (1H, d, $J$ = 9.0 Hz), 7.52 (1H, d, $J$ = 2.1 Hz).

Example 773

1-Ethyl-3,3,5-trimethyl-7-{2-[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylthiazol-2-ylmethyl)amino]ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.16 (3H, t, $J$ = 7.1 Hz), 1.51 (3H, s), 2.41 (3H, s), 2.42 (3H, s), 2.75 (2H, t, $J$ = 7.4 Hz ), 2.83-2.91 (2H, m), 2.99 (2H, t, $J$ = 6.4 Hz), 3.36 (3H, s), 3.72-3.79 (1H, m), 4.01 (2H, s), 4.07 (2H, t, $J$ = 6.4 Hz), 4.09-4.16 (1H, m), 6.43 (1H, d, $J$ = 7.3 Hz), 6.55 (1H, s), 6.77 (1H, br), 6.98-7.02 (m, 2H), 7.06 (1H, d, $J$ = 7.3 Hz), 7.13 (1H, d, $J$ = 8.7 Hz).

Example 774

1-Ethyl-3,3,5-trimethyl-7-{2-[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(3-methylpyridin-2-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.16 (3H, t, $J$ = 7.1 Hz), 1.52 (3H, s), 2.24 (3H, s), 2.41 (3H, d, $J$ = 0.9 Hz), 2.79-2.85 (2H, m), 2.88-2.93 (2H, m), 2.95 (2H, t, $J$ = 6.8 Hz ), 3.37 (3H, s), 3.71-3.79 (1H, m), 3.89 (2H, s), 3.94-3.98 (2H, m), 4.10-4.17 (1H, m), 6.34 (1H, d, $J$ = 7.4 Hz), 6.53 (1H, br), 6.89 (1H, d, $J$ = 7.4 Hz), 7.01 (1H, d, $J$ = 1.8 Hz), 7.04 (1H, dd, $J$ = 1.8, 8.3 Hz), 7.12 (1H, dd, $J$ = 4.8, 7.6 Hz), 7.16 (1H, d, $J$ = 8.30 Hz), 7.37 (1H, dd, $J$ = 1.1, 7.6 Hz), 8.39 (1H, dd, $J$ = 1.1, 4.8 Hz).

Example 775

1-Ethyl-3,3,5-trimethyl-7-{2-[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]

pyridin-5-yl)ethyl]-N-(3-methylpyridin-2-ylmethyl)amino]ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.80 (3H, s), 1.16 (3H, t, $J$ = 7.1 Hz), 1.52 (3H, s), 2.17 (3H, d, $J$ = 1.0 Hz), 2.22 (3H, s), 2.81-2.87 (2H, m), 2.89-2.97 (4H, m), 3.38 (3H, s), 3.71-3.80 (1H, m), 3.88 (2H, s), 3.93-4.00 (2H, m), 4.09-4.18 (1H, m), 6.70 (1H, br), 6.96 (1H, d, $J$ = 2.1 Hz), 7.03 (1H, d, $J$ = 1.8 Hz), 7.06 (1H, dd, $J$ = 1.8, 8.3 Hz), 7.11 (1H, dd, $J$ = 4.8, 7.6 Hz), 7.17 (1H, d, $J$ = 8.3 Hz), 7.34 (1H, dd, $J$ = 1.2, 7.6 Hz), 7.50 (1H, d, $J$ = 2.1 Hz), 8.39 (1H, dd, $J$ = 1.2, 4.8 Hz).

Example 776

7-{2-[N-[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(3-methylpyridin-2-ylmethyl)amino]ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.16 (3H, t, $J$ = 7.1 Hz), 1.52 (3H, s), 2.14 (3H, d, $J$ = 1.0 Hz), 2.23 (3H, s), 2.42 (3H, d, $J$ = 1.0 Hz), 2.80-2.86 (2H, m), 2.88-2.96 (4H, m), 3.38 (3H, s), 3.71-3.79 (1H, m), 3.88 (2H, s), 3.91-3.99 (2H, m), 4.10-4.16 (1H, m), 6.54 (1H, br), 6.63 (1H, br), 7.02 (1H, d, $J$ = 1.9 Hz), 7.05 (1H, dd, $J$ = 1.9, 8.3 Hz), 7.12 (1H, dd, $J$ = 4.8, 7.6 Hz), 7.16 (1H, d, $J$ = 8.3 Hz), 7.36 (1H, dd, $J$ = 1.1, 7.6 Hz), 8.39 (1H, dd, $J$ = 1.1, 4.8 Hz).

Example 777

N-[2-({N'-[2-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)ethyl]-N'-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)phenyl]methanesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.17 (3H, t, J=7.1 Hz), 1.52 (3H, s), 2.42 (3H, d, J=1.0Hz), 2.78-2.98 (6H, m), 3.03 (3H, s), 3.36 (3H,

s), 3.70-3.83 (1H, m), 3.88 (2H, s), 4.06-4.22 (3H, m), 6.43-6.45 (1H, m), 6.53 (1H, t, J=0.92 Hz), 6.97 (1H, d, J=1.8 Hz), 6.99-7.03 (1H, m), 7.04 (1H, d, J=7.4 Hz), 7.06-7.11 (1H, m), 7.14-7.18 (1H,m), 7.19 (1H, d, J=8.4 Hz), 7.30-7.35 (1H, m), 7.44 (1H, dd, J=0.96, 8.1 Hz), 9.88 (1H, bs).

Example 778

N-[2-({N'-[2-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)ethyl]-N'-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)phenyl]methanesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.17 (3H, t, J=7.0 Hz), 1.52 (3H, s), 2.24 (3H, s), 2.79-2.97 (6H, m), 3.01 (3H, s), 3.36 (3H, s), 3.71-3.83 (1H, m), 3.87 (2H, s), 4.06-4.20 (3H, m), 6.87 (1H, d, J=1.0 Hz), 6.94-6.99 (2H, m), 7.02 (1H, dd, J=1.9, 8.3 Hz), 7.05-7.13 (1H, m), 7.13-7.18 (1H, m), 7.19 (1H, d, J=8.3Hz), 7.29-7.36 (1H, m), 7.43 (1H, d, J=8.0 Hz), 7.53 (1H, d, J=2.1 Hz), 9.84 (1H, bs).

Example 779

N-[2-({N'-[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N'-[2-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-yl)ethyl]amino}methyl)phenyl]methanesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
$^1$H NMR ($CDCl_3$) , δppm : 0.79 (3H, s), 1.17 (3H, t, J=7.1 Hz), 1.52 (3H, s), 2.21 (3H, d, J=1.0 Hz), 2.43 (3H, d, J=1.0 Hz), 2.78-2.97 (6H, m), 3.02 (3H, s), 3.36 (3H, s), 3.72-3.85 (1H, m), 3.87 (2H, s), 4.04-4.19 (3H, m), 6.54 (1H, d, J=1.2 Hz), 6.81 (1H, d, J=1.1 Hz), 6.97 (1H, d, J=1.9 Hz), 7.01 (1H, dd, J=1.9, 8.3 Hz), 7.06-7.13 (1H, m), 7.13-7.17 (1H, m), 7.19 (1H, d, J=8.3 Hz), 7.29-7.36 (1H, m,), 7.44 (1H, dd, J=0.92, 8.1 Hz), 9.75 (1H, bs).

Example 780

7-{2-[N-[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)amino]ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder
mp: 168.5-170.5°C

Example 781

7-(2-{N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}ethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder
mp: 133.5-139.7°C

Example 782

7-(2-{N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}ethyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
White powder
mp: 171-172.9°C

Example 783

1-Ethyl-3,3,5-trimethyl-7-{2-[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylthiazol-5-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.16 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 2.39 (3H, s), 2.42 (3H, s), 2.70-2.85 (4H, m), 2.91 (2H, t, J = 6.4 Hz), 3.36 (3H, s), 3.71-3.78 (1H, m), 3.83 (2H, s), 4.03 (2H, t, J = 6.4 Hz), 4.06-4.16 (1H, m), 6.42 (1H, dd, J = 0.8 and 7.4 Hz),

6.55 (1H, t, J = 1.0 Hz), 6.95-7.02 (3H, m), 7.13 (1H, d, J = 8.8 Hz), 8.58 (1H, s)

Example 784

1-Ethyl-3,3,5-trimethyl-7-{2-[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylthiazol-5-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.16 (3H, t, J = 7.1 Hz), 1.51 (3H, s), 2.24 (3H, s), 2.39 (3H, s), 2.70-2.85 (4H, m), 2.88-2.95 (2H, m), 3.36 (3H, s), 3.70-3.80 (1H, m), 3.82 (2H, s), 4.00-4.18 (3H, m), 6.86 (1H, d, J = 1.0 Hz), 6.95-7.03 (3H, m), 7.12 (1H, d, J = 8.2 Hz), 7.52 (1H, d, 2.1 Hz), 8.59 (1H,s)

Example 785

7-{2-[N-[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylthiazol-5-ylmethyl)amino]ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δppm : 0.79 (3H, s), 1.16 (3H, t, J = 7.1 Hz), 1.51 (3H, s), 2.21 (3H, s), 2.39 (3H, s), 2.43 (3H, s), 2.70-2.85 (4H, m), 2.88-2.96 (2H, m), 3.36 (3H, s), 3.70-3.85 (3H, m), 3.96-4.18 (3H, m), 6.56 (1H, d, J = 1.1 Hz), 6.79 (1H, d, J = 1.1 Hz), 6.95-7.00 (2H, m), 7.12 (1H, d, J = 8.6 Hz), 8.60 (1H, s)

The following compounds shown in Examples 786 to 791, Examples 793 and Example 795 to 802 can be prepared by the same manner as mentioned above or a conventional manner using appropriate starting materials.

Example 786

1-Ethyl-3,3,5-trimethyl-7-{2-[N-(2-methylpyridin-3-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

Example 787

1-Ethyl-3,3,5-trimethyl-7-{2-[N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Example 788

7-{2-[N-[2-(2,7-Dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyridin-3-ylmethyl)amino]ethyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

Example 789

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-methylpyrimidin-5-ylmethyl)amino]methyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Example 790

N-[3-({N'-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N'-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]amino}methyl)pyridin-2-yl]methanesulfonamide

Example 791

N-[3-({N'-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N'-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)pyridin-2-yl]acetamide

Example 792

Acetic acid 3-({N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)pyridin-2-ylmethyl ester dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δppm : 0.69 (3H, s), 1.04 (3H, t, $J$ = 6.9 Hz), 1.34

(3H, s), 2.01-2.04 (3H, m), 2.42 (3H, s), 2.74 (2H, br), 3.26 (3H, s), 3.45-4.30 (8H, m), 5.10 (2H, br), 6.48 (1H, br), 6.64 (1H, br), 7.17 (1H, br), 7.31 (2H, br), 7.48 (2H, br), 7.79 (1H, br), 8.46 (1H, br).

Example 793

1-Ethyl-7-({N-(2-imidazol-1-ylmethylbenzyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

Example 794

1-Ethyl-7-({N-(3-imidazol-1-ylmethylbenzyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δppm : 0.77 (3H, s), 1.17 (3H, t, J=7.0 Hz), 1.51 (3H, s), 2.43 (3H, d, J=1.0 Hz), 2.79 (2H, dt, J=2.1, 5.9 Hz), 3.32 (3H, s), 3.55-3.68 (4H, m), 3.71-3.83 (1H, m), 3.99-4.17 (3H, m), 5.02 (2H, s), 6.43 (1H, dd, J=0.74, 7.3 Hz), 6.49 (1H, t, J=1.0 Hz), 6.88 (1H, t, J=1.3 Hz), 6.95 (1H, d, J=7.3 Hz), 6.98-7.07 (3H, m), 7.07-7.15 (3H, m), 7.15-7.25 (2H, m), 7.52 (1H, d, J=1.1 Hz).

Example 795

1-Ethyl-7-({N-(2-imidazol-1-ylbenzyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Example 796

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-morpholin-4-ylbenzyl)amino]methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

Example 797

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-[1,2,4]triazol-1-yl-benzyl)amino]methyl}-1

,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

Example 798

1-Ethyl-7-(N-{imidazo[1,2-a]pyridin-8-ylmethyl-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Example 799

1-Ethyl-7-(N-{imidazo[1,2-a]pyridin-6-ylmethyl-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

Example 800

1-Ethyl-3,3,5-trimethyl-7-{[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2-pyrazol-1-ylpyridin-3-ylmethyl)amino]methyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

Example 801

7-({N-(3H-Benzoimidazol-4-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-1-ethyl-3,3,5-trimethyl-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

Example 802

1-Ethyl-7-({N-(4-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Example 802-a

1-Ethyl-3,3,5-trimethyl-7-{2-[N-[2-(2,7-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)-ethyl]-N-(4-methyl-thiazol-2-ylmethyl)-amino]-ethyl}-1,5-dihydro-benzo[b][1,4]diazepine-2,4-dione

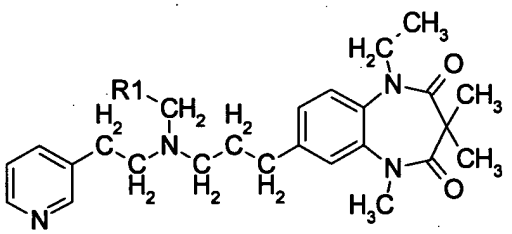
The synthesis of the title compound was performed in the same manner as in Example 30 using appropriate starting materials.

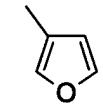
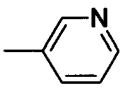
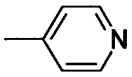
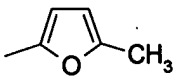
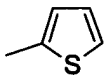
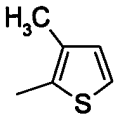
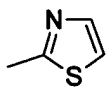
$^1$H NMR ($CDCl_3$), δppm : 0.78 (3H, s), 1.15 (3H, t, $J$ = 7.1 Hz), 1.51 (3H, s), 2.20 (3H, d, $J$ = 0.9 Hz), 2.42 (3H, d, $J$ = 0.9 Hz), 2.43 (3H, d, $J$ = 0.9 Hz), 2.76 (2H, t, $J$ = 7.4 Hz ), 2.85-2.90 (2H, m), 2.95-3.02

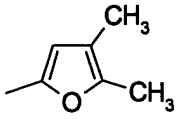
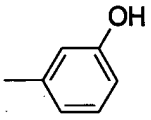
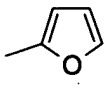
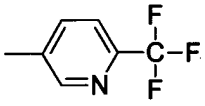
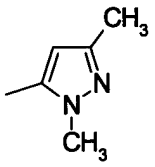
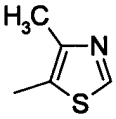
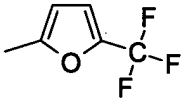
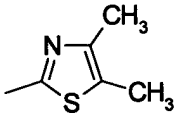
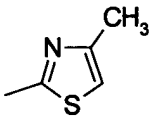
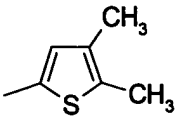
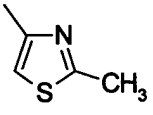
(2H, m), 3.35 (3H, s), 3.71-3.77 (1H, m), 4.01 and 4.02 (2H, s), 4.02-4.16 (3H, m), 6.57 (1H, br), 6.77 (1H, br), 6.86 (1H, br), 6.97-7.01 (m, 2H), 7.12 (1H, d, $J$ = 8.9 Hz).

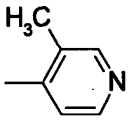
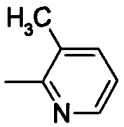
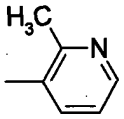
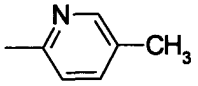
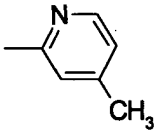
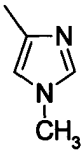
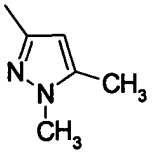
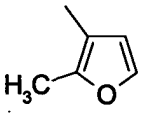
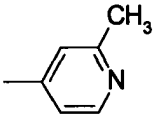
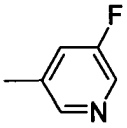
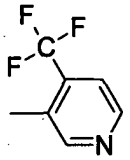
Examples 803 to 1038

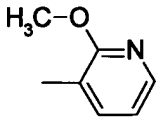
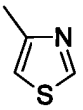
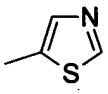
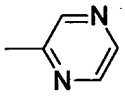
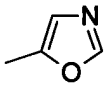
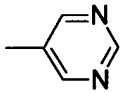
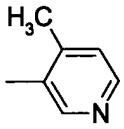
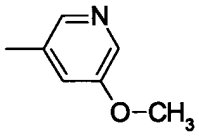
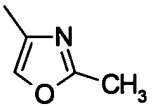
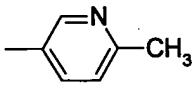
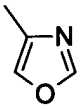
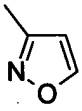
The folowing compounds were obtained in the same manner as in Examples above using appropriate starting materials.

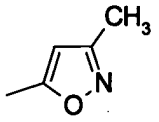
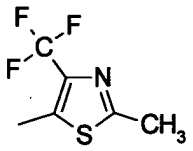
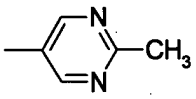
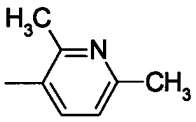


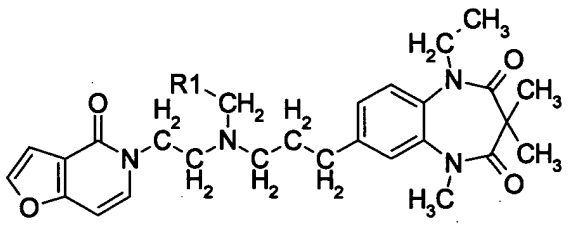
| Example No. | R1 | MS(M+1) |
|---|---|---|
| 803 |  | 489 |
| 804 |  | 500 |
| 805 |  | 500 |
| 806 |  | 503 |
| 807 |  | 505 |
| 808 |  | 519 |
| 809 |  | 506 |

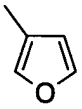
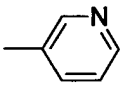
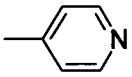
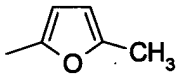
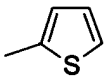
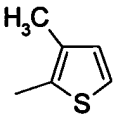
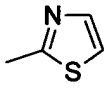
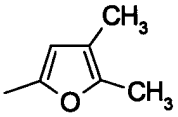
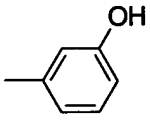
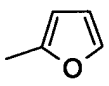
| | | |
|---|---|---|
| 810 |  | 517 |
| 811 |  | 515 |
| 812 |  | 489 |
| 813 |  | 568 |
| 814 |  | 517 |
| 815 |  | 520 |
| 816 |  | 557 |
| 817 |  | 534 |
| 818 |  | 520 |
| 819 |  | 533 |
| 820 |  | 520 |

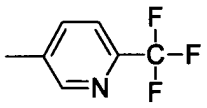
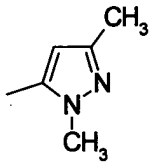
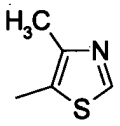
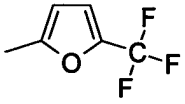
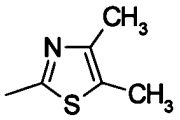
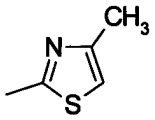
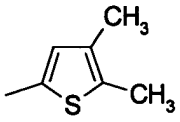
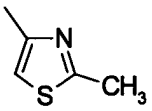
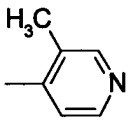
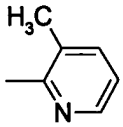
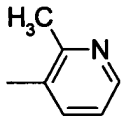
| | | |
|---|---|---|
| 821 |  | 514 |
| 822 |  | 514 |
| 823 |  | 514 |
| 824 |  | 514 |
| 825 |  | 514 |
| 826 |  | 503 |
| 827 |  | 517 |
| 828 |  | 503 |
| 829 |  | 514 |
| 830 |  | 518 |
| 831 |  | 568 |

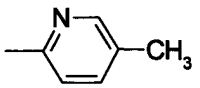
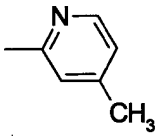
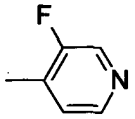
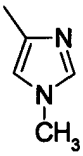
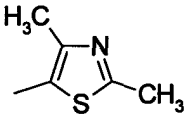
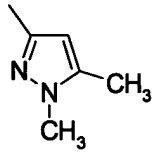
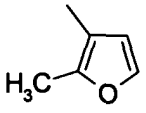
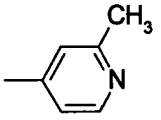
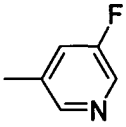
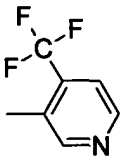
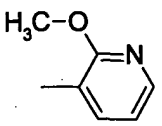
| | | |
|---|---|---|
| 832 |  | 530 |
| 833 |  | 506 |
| 834 |  | 506 |
| 835 |  | 501 |
| 836 |  | 490 |
| 837 |  | 501 |
| 838 |  | 514 |
| 839 |  | 530 |
| 840 |  | 504 |
| 841 |  | 514 |
| 842 |  | 490 |
| 843 |  | 490 |

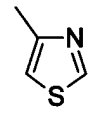
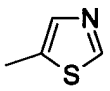
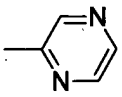
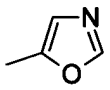
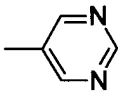
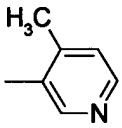
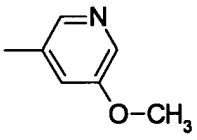
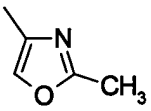
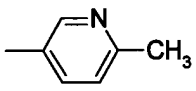
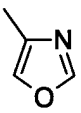
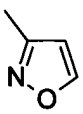
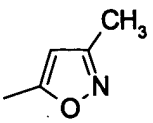
| | | |
|---|---|---|
| 844 |  | 504 |
| 845 |  | 588 |
| 846 |  | 515 |
| 847 |  | 528 |

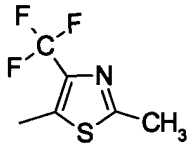
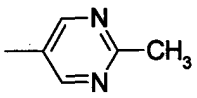
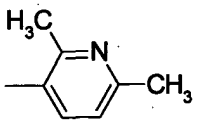


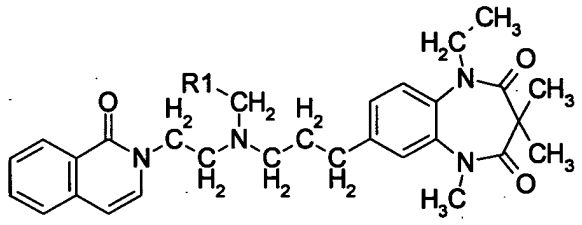
| Example No. | R1 | MS(M+1) |
|---|---|---|
| 848 |  | 545 |
| 849 |  | 556 |
| 850 |  | 556 |
| 851 |  | 559 |
| 852 |  | 561 |
| 853 |  | 575 |
| 854 |  | 562 |
| 855 |  | 573 |
| 856 |  | 571 |
| 857 |  | 545 |

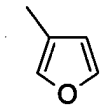
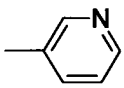
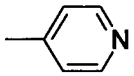
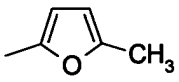
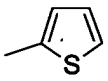
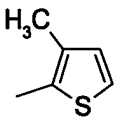
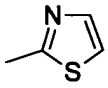
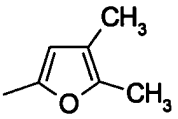
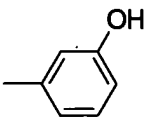
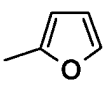
| | | |
|---|---|---|
| 858 |  | 624 |
| 859 |  | 573 |
| 860 |  | 576 |
| 861 |  | 613 |
| 862 |  | 590 |
| 863 |  | 576 |
| 864 |  | 589 |
| 865 |  | 576 |
| 866 |  | 570 |
| 867 |  | 570 |
| 868 |  | 570 |

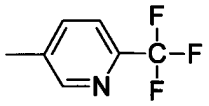
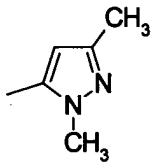
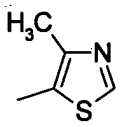
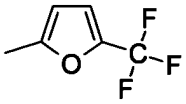
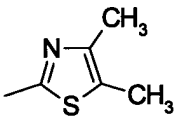
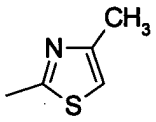
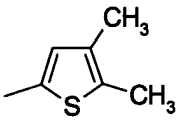
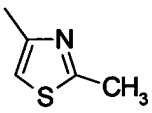
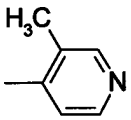
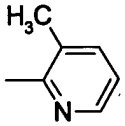
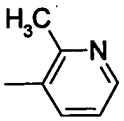
| | | |
|---|---|---|
| 869 |  | 570 |
| 870 |  | 570 |
| 871 |  | 574 |
| 872 |  | 559 |
| 873 |  | 590 |
| 874 |  | 573 |
| 875 |  | 559 |
| 876 |  | 570 |
| 877 |  | 574 |
| 878 |  | 624 |
| 879 |  | 586 |

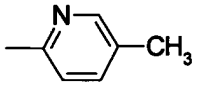
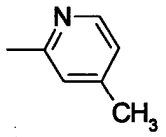
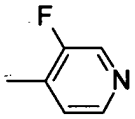
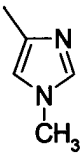
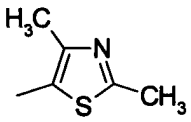
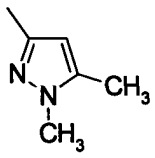
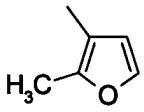
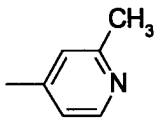
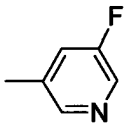
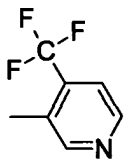
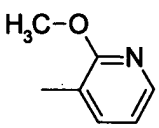
| | | |
|---|---|---|
| 880 |  | 562 |
| 881 |  | 562 |
| 882 |  | 557 |
| 883 |  | 546 |
| 884 |  | 557 |
| 885 |  | 570 |
| 886 |  | 586 |
| 887 |  | 560 |
| 888 |  | 570 |
| 889 |  | 546 |
| 890 |  | 546 |
| 891 |  | 560 |

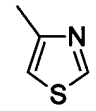
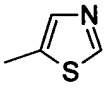
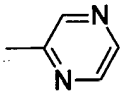
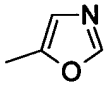
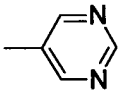
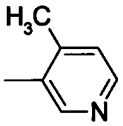
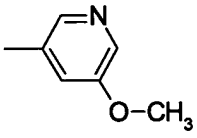
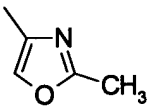
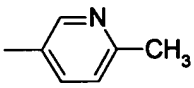
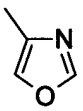
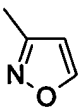
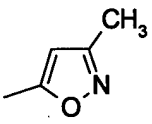
| | | |
|---|---|---|
| 892 |  | 644 |
| 893 |  | 571 |
| 894 |  | 584 |

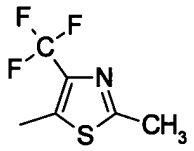
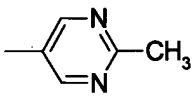
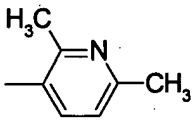


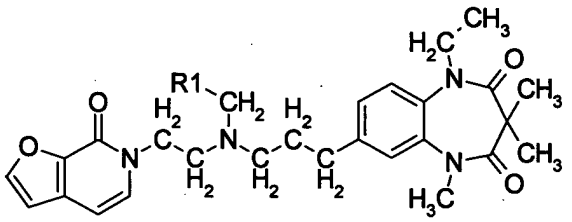
| Example No. | R1 | MS(M+1) |
|---|---|---|
| 895 |  | 555 |
| 896 |  | 566 |
| 897 |  | 566 |
| 898 |  | 569 |
| 899 |  | 571 |
| 900 |  | 585 |
| 901 |  | 572 |
| 902 |  | 583 |
| 903 |  | 581 |
| 904 |  | 555 |

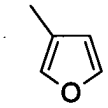
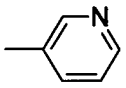
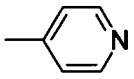
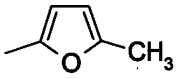
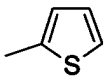
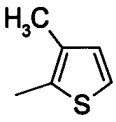
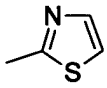
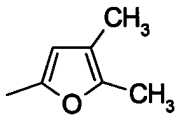
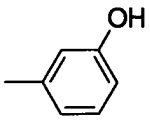
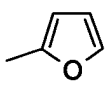
| | | |
|---|---|---|
| 905 |  | 634 |
| 906 |  | 583 |
| 907 |  | 586 |
| 908 |  | 623 |
| 909 |  | 600 |
| 910 |  | 586 |
| 911 |  | 599 |
| 912 |  | 586 |
| 913 |  | 580 |
| 914 |  | 580 |
| 915 |  | 580 |

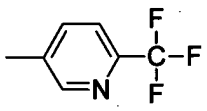
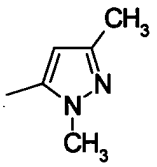
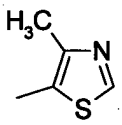
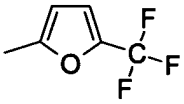
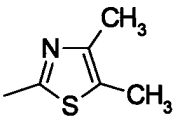
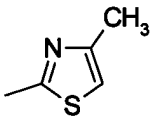
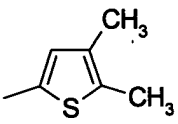
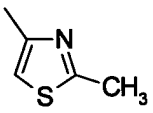
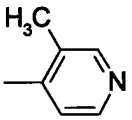
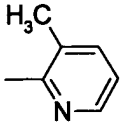
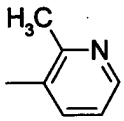
| | | |
|---|---|---|
| 916 |  | 580 |
| 917 |  | 580 |
| 918 |  | 584 |
| 919 |  | 569 |
| 920 |  | 600 |
| 921 |  | 583 |
| 922 |  | 569 |
| 923 |  | 580 |
| 924 |  | 584 |
| 925 |  | 634 |
| 926 |  | 596 |

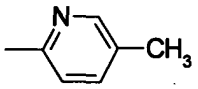
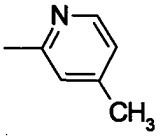
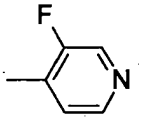
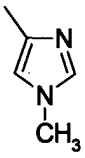
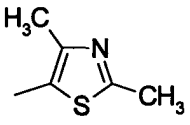
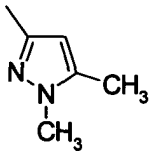
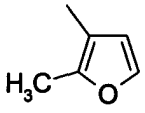
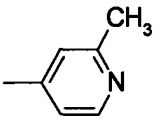
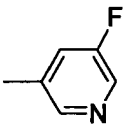
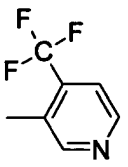
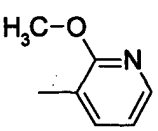
| | | |
|---|---|---|
| 927 |  | 572 |
| 928 |  | 572 |
| 929 |  | 567 |
| 930 |  | 556 |
| 931 |  | 567 |
| 932 |  | 580 |
| 933 |  | 596 |
| 934 |  | 570 |
| 935 |  | 580 |
| 936 |  | 556 |
| 937 |  | 556 |
| 938 |  | 570 |

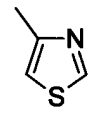
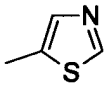
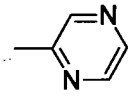
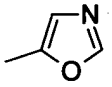
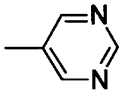
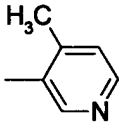
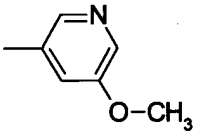
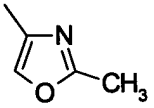
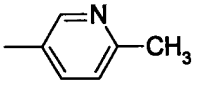
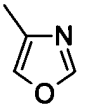
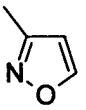
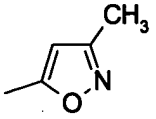
| | | |
|---|---|---|
| 939 |  | 654 |
| 940 |  | 581 |
| 941 |  | 594 |

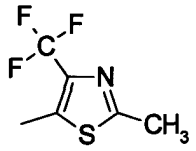
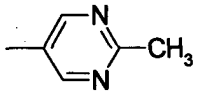
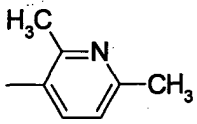


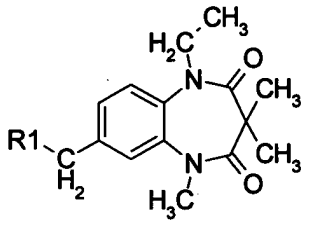
| Example No. | R1 | MS(M+1) |
|---|---|---|
| 942 |  | 545 |
| 943 |  | 556 |
| 944 |  | 556 |
| 945 |  | 559 |
| 946 |  | 561 |
| 947 |  | 575 |
| 948 |  | 562 |
| 949 |  | 573 |
| 950 |  | 571 |
| 951 |  | 545 |

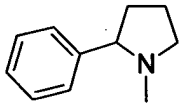
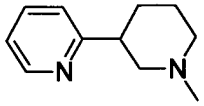
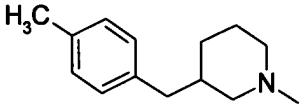
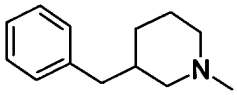
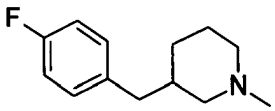
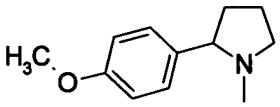
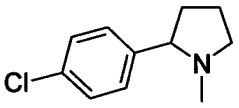
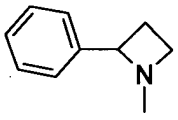
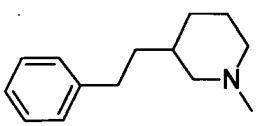
| | | |
|---|---|---|
| 952 |  | 624 |
| 953 |  | 573 |
| 954 |  | 576 |
| 955 |  | 613 |
| 956 |  | 590 |
| 957 |  | 576 |
| 958 |  | 589 |
| 959 |  | 576 |
| 960 |  | 570 |
| 961 |  | 570 |
| 962 |  | 570 |

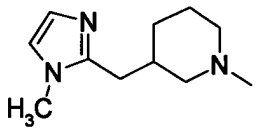
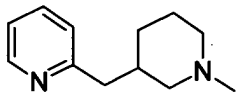
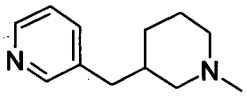
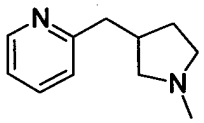
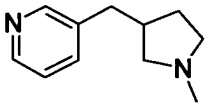
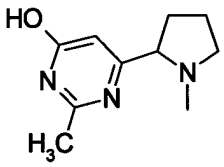
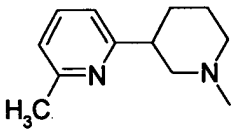
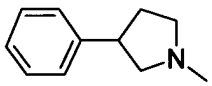
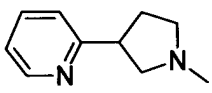
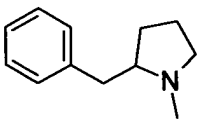
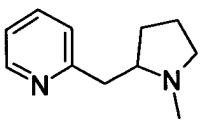
| | | |
|---|---|---|
| 963 |  | 570 |
| 964 |  | 570 |
| 965 |  | 574 |
| 966 |  | 559 |
| 967 |  | 590 |
| 968 |  | 573 |
| 969 |  | 559 |
| 970 |  | 570 |
| 971 |  | 574 |
| 972 |  | 624 |
| 973 |  | 586 |

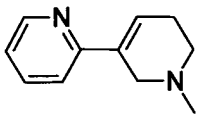
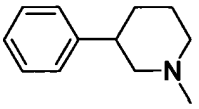
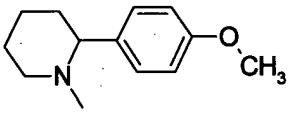
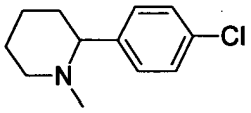
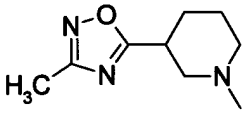
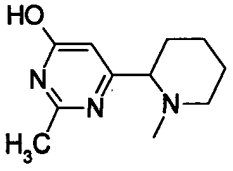
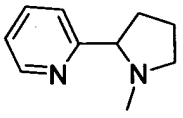
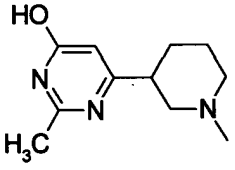
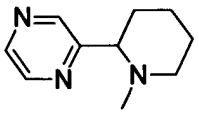
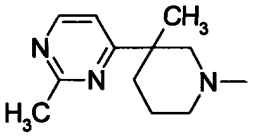
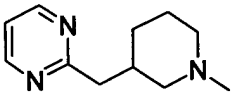
| | | |
|---|---|---|
| 974 |  | 562 |
| 975 |  | 562 |
| 976 |  | 557 |
| 977 |  | 546 |
| 978 |  | 557 |
| 979 |  | 570 |
| 980 |  | 586 |
| 981 |  | 560 |
| 982 |  | 570 |
| 983 |  | 546 |
| 984 |  | 546 |
| 985 |  | 560 |

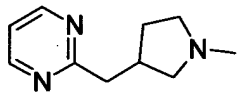
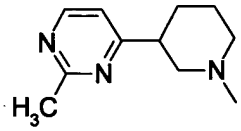
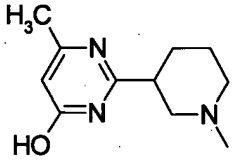
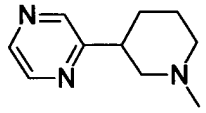
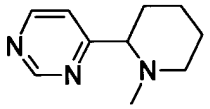
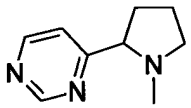
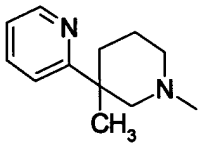
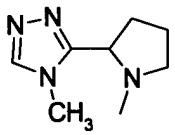
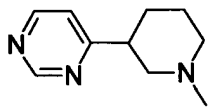
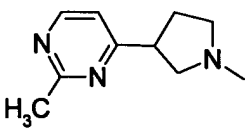
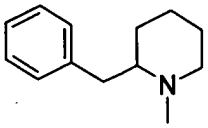
| | | |
|---|---|---|
| 986 |  | 644 |
| 987 |  | 571 |
| 988 |  | 584 |

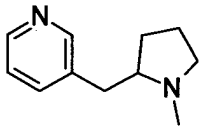
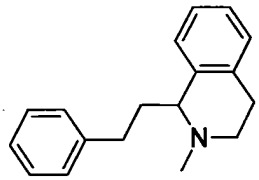
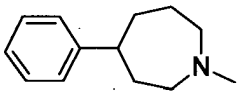
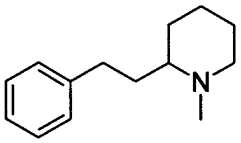
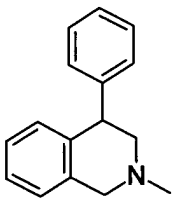
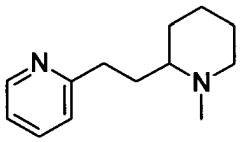
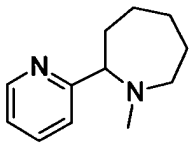
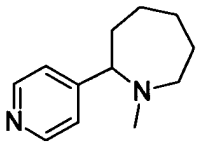


| Example No. | R1 | MS(M+1) |
|---|---|---|
| 989 |  | 406 |
| 990 |  | 421 |
| 991 |  | 448 |
| 992 |  | 434 |
| 993 |  | 452 |
| 994 |  | 436 |
| 995 |  | 440 |
| 996 |  | 392 |
| 997 |  | 448 |

| | | |
|---|---|---|
| 998 |  | 438 |
| 999 |  | 435 |
| 1000 |  | 435 |
| 1001 |  | 421 |
| 1002 |  | 421 |
| 1003 |  | 438 |
| 1004 |  | 435 |
| 1005 |  | 406 |
| 1006 |  | 407 |
| 1007 |  | 420 |
| 1008 |  | 421 |

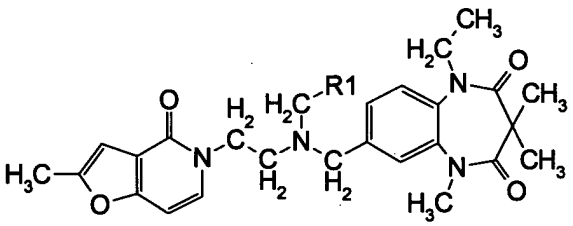
| | | |
|---|---|---|
| 1009 |  | 419 |
| 1010 |  | 420 |
| 1011 |  | 450 |
| 1012 |  | 454 |
| 1013 |  | 426 |
| 1014 |  | 452 |
| 1015 |  | 407 |
| 1016 |  | 452 |
| 1017 |  | 422 |
| 1018 |  | 450 |
| 1019 |  | 436 |

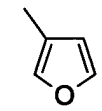
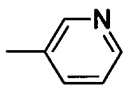
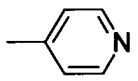
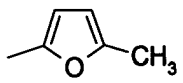
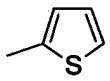
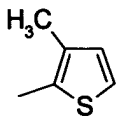
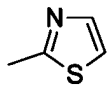
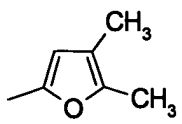
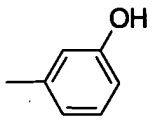
| | | |
|---|---|---|
| 1020 |  | 422 |
| 1021 |  | 436 |
| 1022 |  | 452 |
| 1023 |  | 422 |
| 1024 |  | 422 |
| 1025 |  | 408 |
| 1026 |  | 435 |
| 1027 |  | 411 |
| 1028 |  | 422 |
| 1029 |  | 422 |
| 1030 |  | 434 |

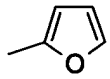
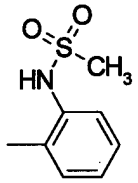
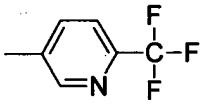
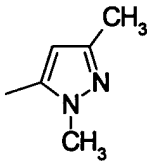
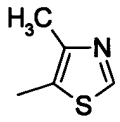
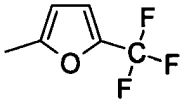
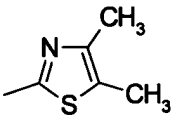
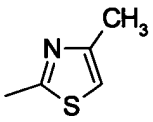
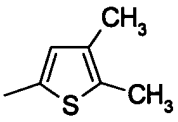
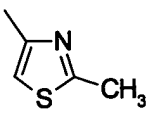
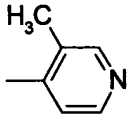
| | | |
|---|---|---|
| 1031 |  | 421 |
| 1032 |  | 496 |
| 1033 |  | 434 |
| 1034 |  | 448 |
| 1035 |  | 468 |
| 1036 |  | 449 |
| 1037 |  | 435 |
| 1038 |  | 435 |

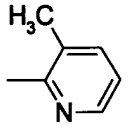
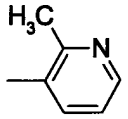
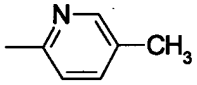
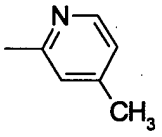
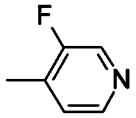
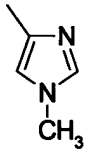
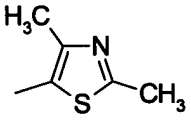
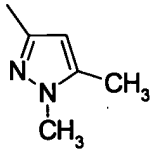
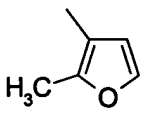
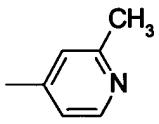
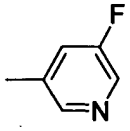
Examples 1039 to 1614

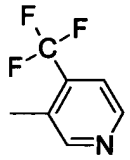
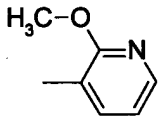
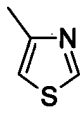
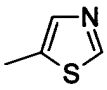
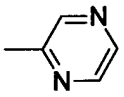
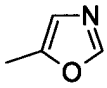
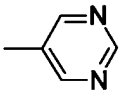
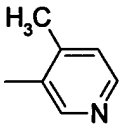
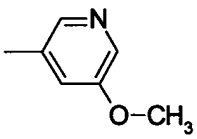
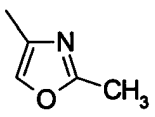
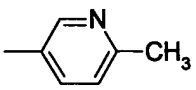
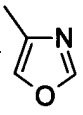
The folowing compounds can be obtained in the same manner as in Examples above using appropriate starting materials.

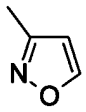
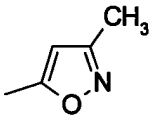
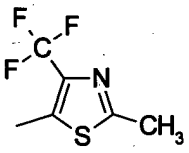
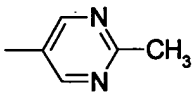
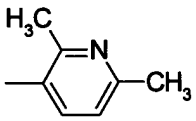


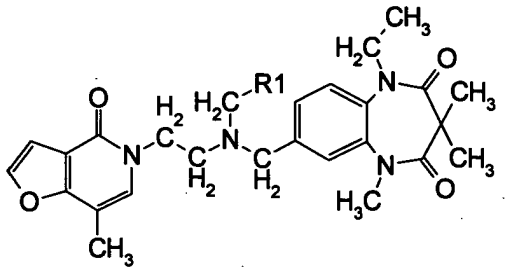
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1039 |  | |
| 1040 |  | |
| 1041 |  | |
| 1042 |  | |
| 1043 |  | |
| 1044 |  | |
| 1045 |  | |
| 1046 |  | |
| 1047 |  | |

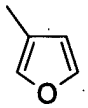
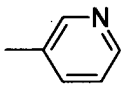
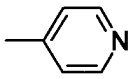
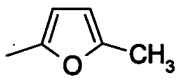
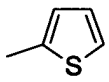
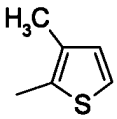
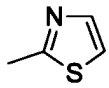
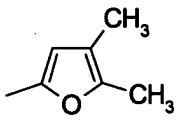
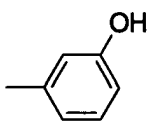
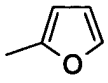
| | |
|---|---|
| 1048 |  |
| 1049 |  |
| 1050 |  |
| 1051 |  |
| 1052 |  |
| 1053 |  |
| 1054 |  |
| 1055 |  |
| 1056 |  |
| 1057 |  |
| 1058 |  |

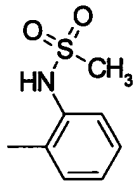
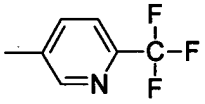
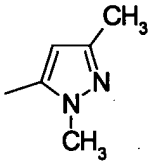
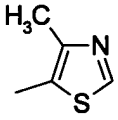
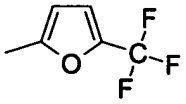
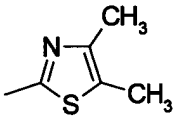
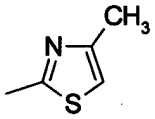
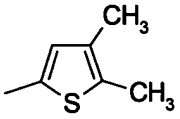
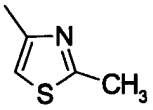
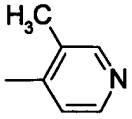
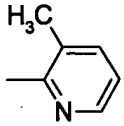
| | |
|---|---|
| 1059 |  |
| 1060 |  |
| 1061 |  |
| 1062 |  |
| 1063 |  |
| 1064 |  |
| 1065 |  |
| 1066 |  |
| 1067 |  |
| 1068 |  |
| 1069 |  |

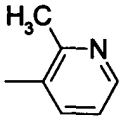
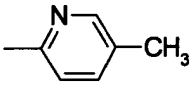
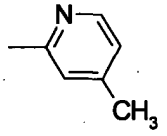
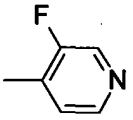
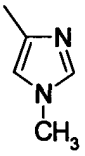
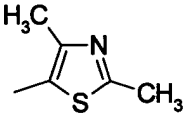
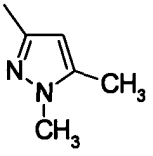
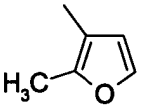
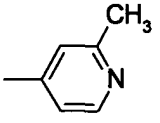
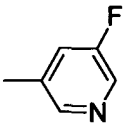
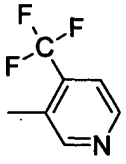
| | |
|---|---|
| 1070 |  |
| 1071 |  |
| 1072 |  |
| 1073 |  |
| 1074 |  |
| 1075 |  |
| 1076 |  |
| 1077 |  |
| 1078 |  |
| 1079 |  |
| 1080 |  |
| 1081 |  |

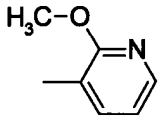
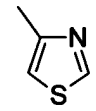
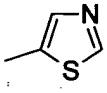
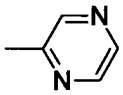
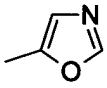
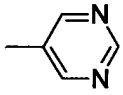
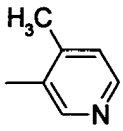
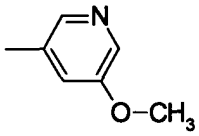
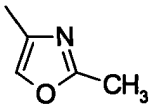
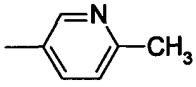
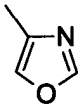
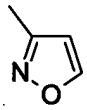
| | |
|---|---|
| 1082 |  |
| 1083 |  |
| 1084 |  |
| 1085 |  |
| 1086 |  |

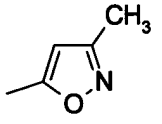
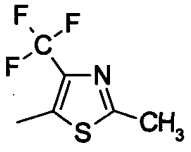
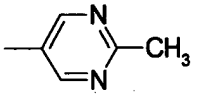
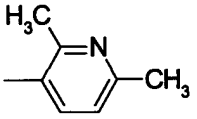


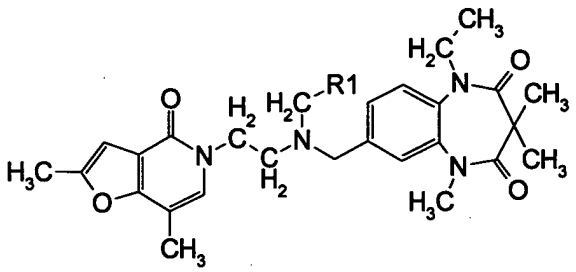
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1087 |  | |
| 1088 |  | |
| 1089 |  | |
| 1090 |  | |
| 1091 |  | |
| 1092 |  | |
| 1093 |  | |
| 1094 |  | |
| 1095 |  | |
| 1096 |  | |

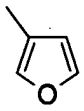
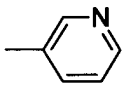
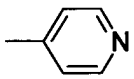
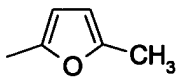
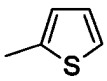
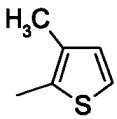
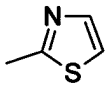
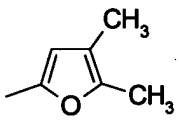
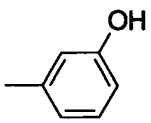
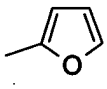
| | |
|---|---|
| 1097 |  |
| 1098 |  |
| 1099 |  |
| 1100 |  |
| 1101 |  |
| 1102 |  |
| 1103 |  |
| 1104 |  |
| 1105 |  |
| 1106 |  |
| 1107 |  |

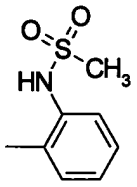
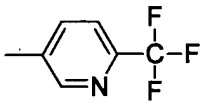
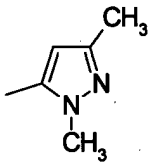
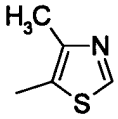
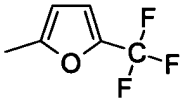
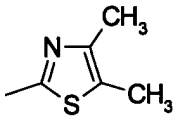
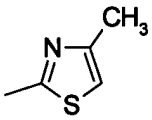
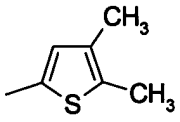
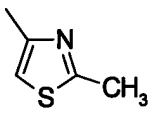
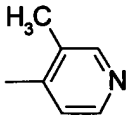
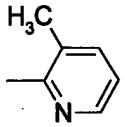
| | |
|---|---|
| 1108 |  |
| 1109 |  |
| 1110 |  |
| 1111 |  |
| 1112 |  |
| 1113 |  |
| 1114 |  |
| 1115 |  |
| 1116 |  |
| 1117 |  |
| 1118 |  |

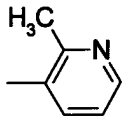
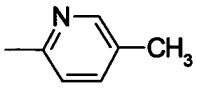
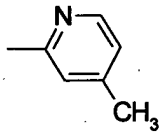
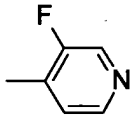
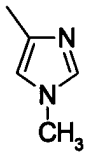
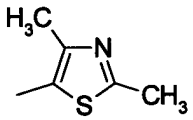
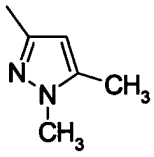
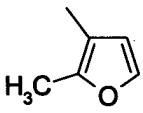
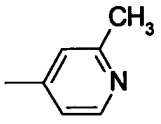
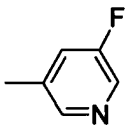
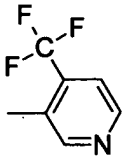
| | |
|---|---|
| 1119 |  |
| 1120 |  |
| 1121 |  |
| 1122 |  |
| 1123 |  |
| 1124 |  |
| 1125 |  |
| 1126 |  |
| 1127 |  |
| 1128 |  |
| 1129 |  |
| 1130 |  |

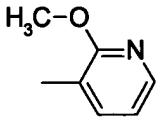
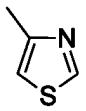
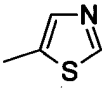
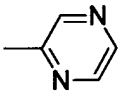
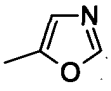
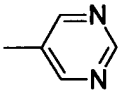
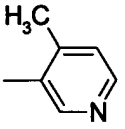
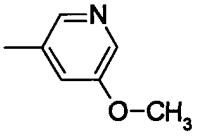
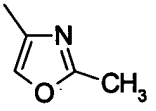
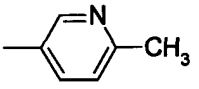
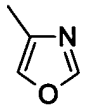
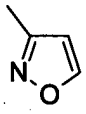
| | |
|---|---|
| 1131 |  |
| 1132 |  |
| 1133 |  |
| 1134 |  |

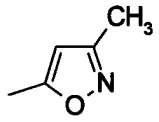
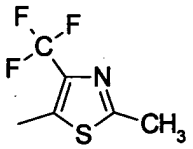
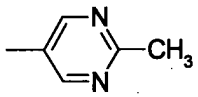
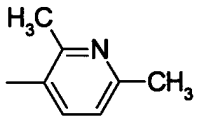


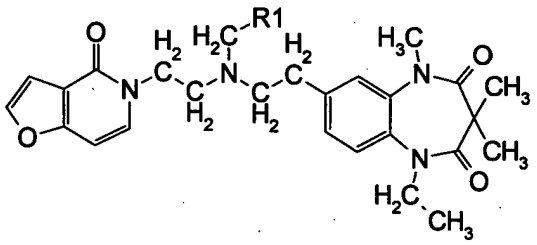
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1135 |  | |
| 1136 |  | |
| 1137 |  | |
| 1138 |  | |
| 1139 |  | |
| 1140 |  | |
| 1141 |  | |
| 1142 |  | |
| 1143 |  | |
| 1144 |  | |

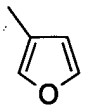
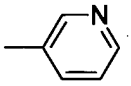
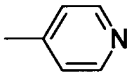
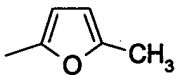
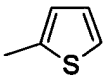
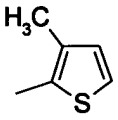
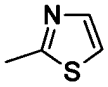
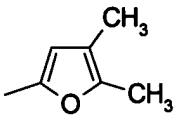
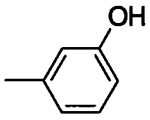
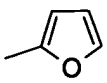
| | |
|---|---|
| 1145 |  |
| 1146 |  |
| 1147 |  |
| 1148 |  |
| 1149 |  |
| 1150 |  |
| 1151 |  |
| 1152 |  |
| 1153 |  |
| 1154 |  |
| 1155 |  |

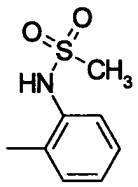
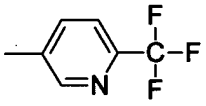
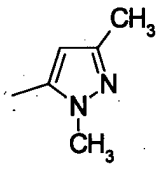
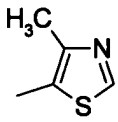
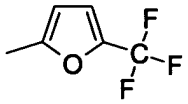
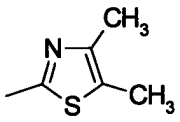
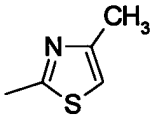
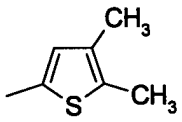
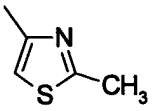
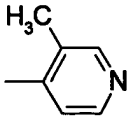
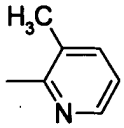
| | |
|---|---|
| 1156 |  |
| 1157 |  |
| 1158 |  |
| 1159 |  |
| 1160 |  |
| 1161 |  |
| 1162 |  |
| 1163 |  |
| 1164 |  |
| 1165 |  |
| 1166 |  |

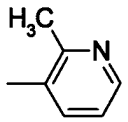
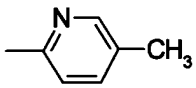
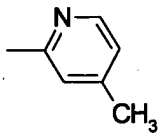
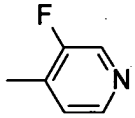
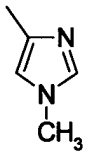
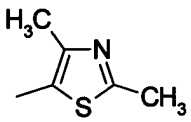
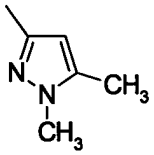
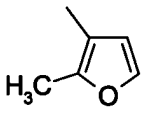
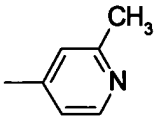
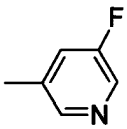
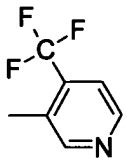
| | |
|---|---|
| 1167 |  |
| 1168 |  |
| 1169 |  |
| 1170 |  |
| 1171 |  |
| 1172 |  |
| 1173 |  |
| 1174 |  |
| 1175 |  |
| 1176 |  |
| 1177 |  |
| 1178 |  |

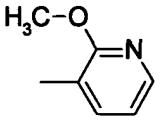
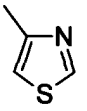
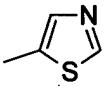
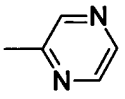
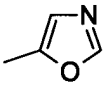
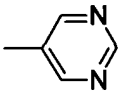
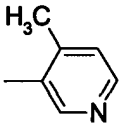
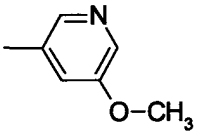
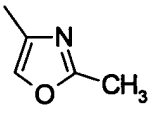
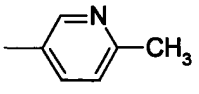
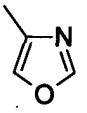
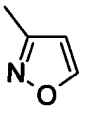
| | |
|---|---|
| 1179 |  |
| 1180 |  |
| 1181 |  |
| 1182 |  |

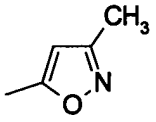
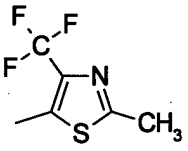
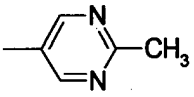
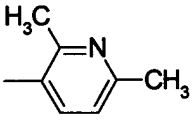


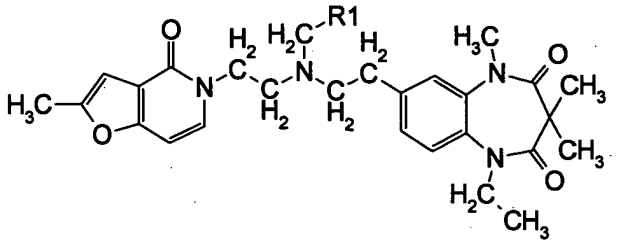
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1183 |  | |
| 1184 |  | |
| 1185 |  | |
| 1186 |  | |
| 1187 |  | |
| 1188 |  | |
| 1189 |  | |
| 1190 |  | |
| 1191 |  | |
| 1192 |  | |

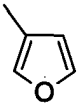
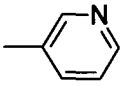
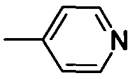
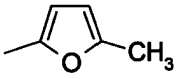
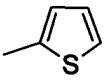
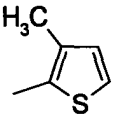
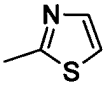
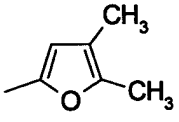
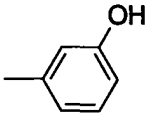
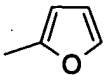
| | |
|---|---|
| 1193 |  |
| 1194 |  |
| 1195 |  |
| 1196 |  |
| 1197 |  |
| 1198 |  |
| 1199 |  |
| 1200 |  |
| 1201 |  |
| 1202 |  |
| 1203 |  |

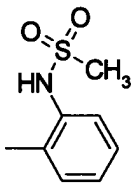
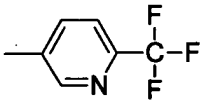
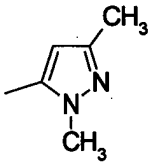
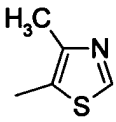
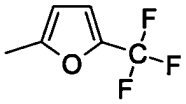
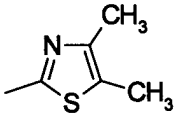
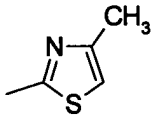
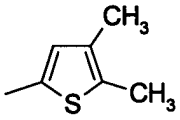
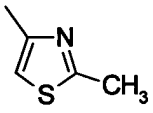
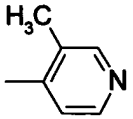
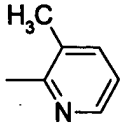
| | |
|---|---|
| 1204 |  |
| 1205 |  |
| 1206 |  |
| 1207 |  |
| 1208 |  |
| 1209 |  |
| 1210 |  |
| 1211 |  |
| 1212 |  |
| 1213 |  |
| 1214 |  |

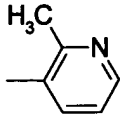
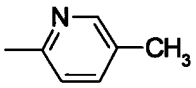
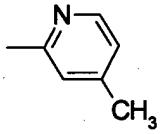
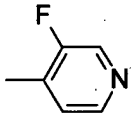
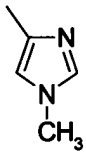
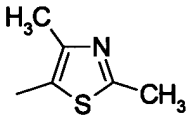
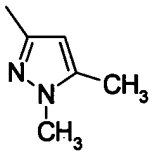
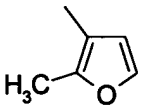
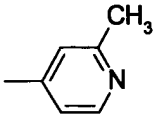
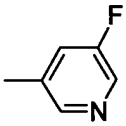
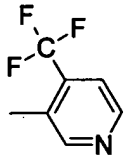
| | |
|---|---|
| 1215 |  |
| 1216 |  |
| 1217 |  |
| 1218 |  |
| 1219 |  |
| 1220 |  |
| 1221 |  |
| 1222 |  |
| 1223 |  |
| 1224 |  |
| 1225 |  |
| 1226 |  |

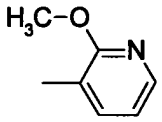
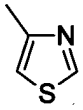
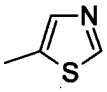
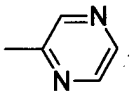
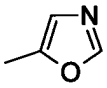
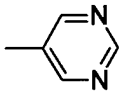
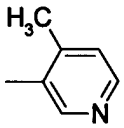
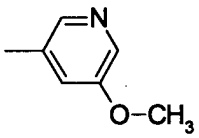
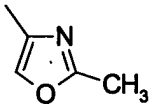
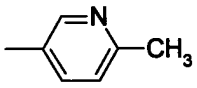
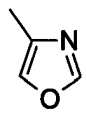
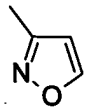
| | |
|---|---|
| 1227 |  |
| 1228 |  |
| 1229 |  |
| 1230 |  |

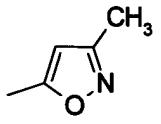
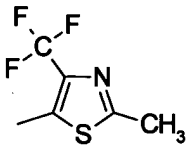
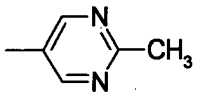
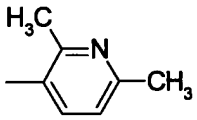


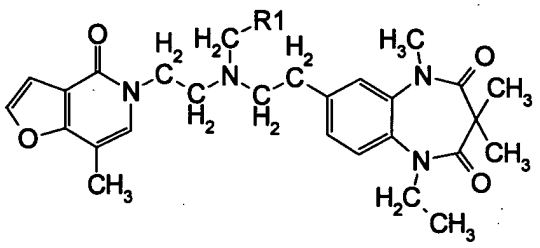
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1231 |  | |
| 1232 |  | |
| 1233 |  | |
| 1234 |  | |
| 1235 |  | |
| 1236 |  | |
| 1237 |  | |
| 1238 |  | |
| 1239 |  | |
| 1240 |  | |

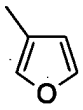
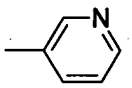
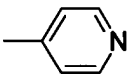
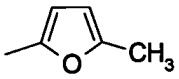
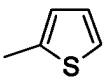
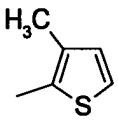
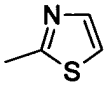
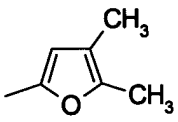
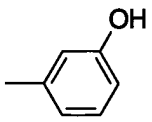
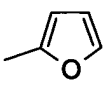
| | |
|---|---|
| 1241 |  |
| 1242 |  |
| 1243 |  |
| 1244 |  |
| 1245 |  |
| 1246 |  |
| 1247 |  |
| 1248 |  |
| 1249 |  |
| 1250 |  |
| 1251 |  |

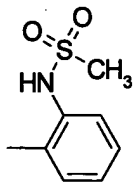
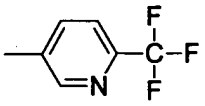
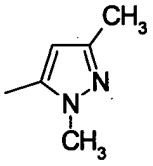
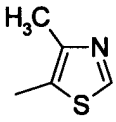
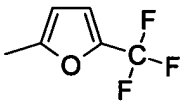
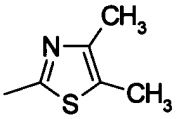
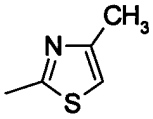
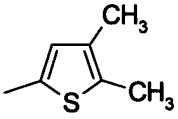
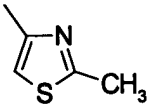
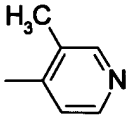
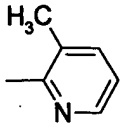
| | |
|---|---|
| 1252 |  |
| 1253 |  |
| 1254 |  |
| 1255 |  |
| 1256 |  |
| 1257 |  |
| 1258 |  |
| 1259 |  |
| 1260 |  |
| 1261 |  |
| 1262 |  |

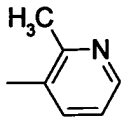
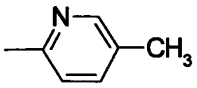
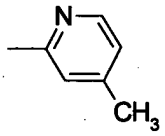
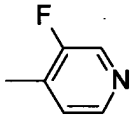
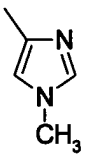
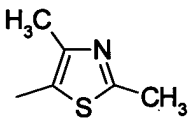
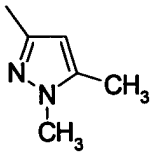
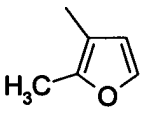
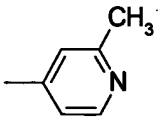
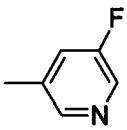
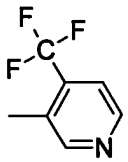
| | |
|---|---|
| 1263 |  |
| 1264 |  |
| 1265 |  |
| 1266 |  |
| 1267 |  |
| 1268 |  |
| 1269 |  |
| 1270 |  |
| 1271 |  |
| 1272 |  |
| 1273 |  |
| 1274 |  |

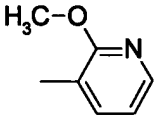
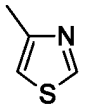
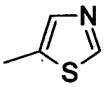
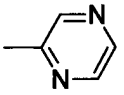
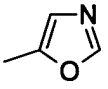
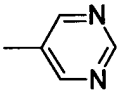
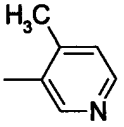
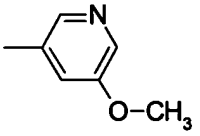
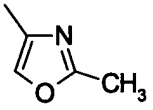
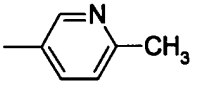
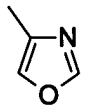
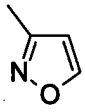
| | |
|---|---|
| 1275 |  |
| 1276 |  |
| 1277 |  |
| 1278 |  |

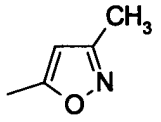
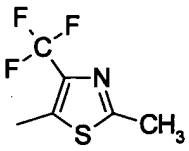
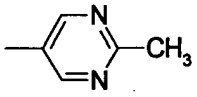
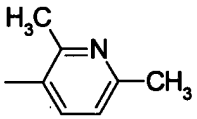


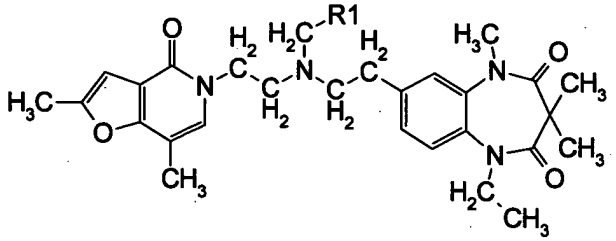
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1279 |  | |
| 1280 |  | |
| 1281 |  | |
| 1282 |  | |
| 1283 |  | |
| 1284 |  | |
| 1285 |  | |
| 1286 |  | |
| 1287 |  | |
| 1288 |  | |

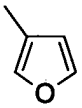
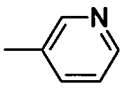
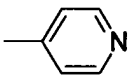
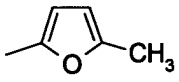
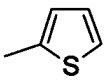
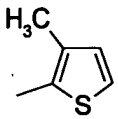
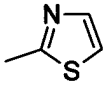
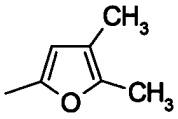
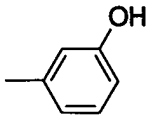
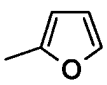
| | |
|---|---|
| 1289 |  |
| 1290 |  |
| 1291 |  |
| 1292 |  |
| 1293 |  |
| 1294 |  |
| 1295 |  |
| 1296 |  |
| 1297 |  |
| 1298 |  |
| 1299 |  |

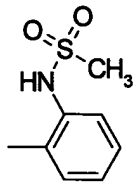
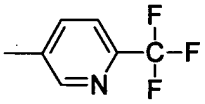
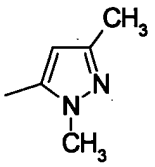
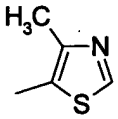
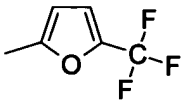
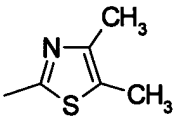
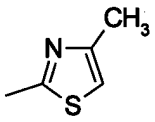
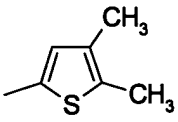
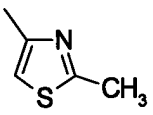
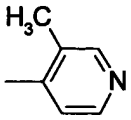
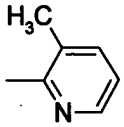
| | |
|---|---|
| 1300 |  |
| 1301 |  |
| 1302 |  |
| 1303 |  |
| 1304 |  |
| 1305 |  |
| 1306 |  |
| 1307 |  |
| 1308 |  |
| 1309 |  |
| 1310 |  |

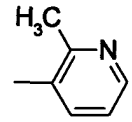
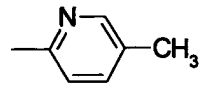
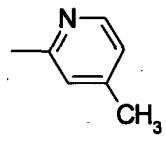
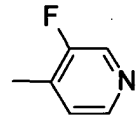
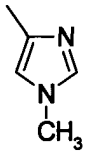
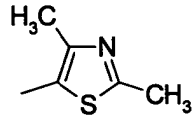
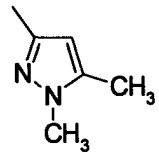
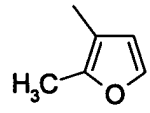
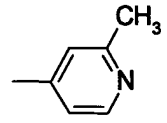
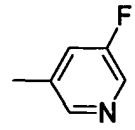
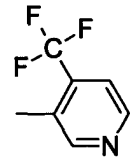
| | |
|---|---|
| 1311 |  |
| 1312 |  |
| 1313 |  |
| 1314 |  |
| 1315 |  |
| 1316 |  |
| 1317 |  |
| 1318 |  |
| 1319 |  |
| 1320 |  |
| 1321 |  |
| 1322 |  |

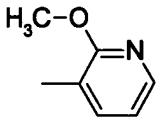
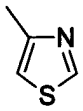
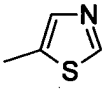
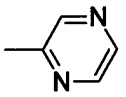
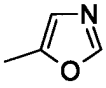
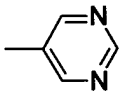
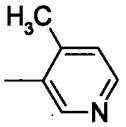
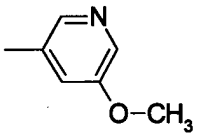
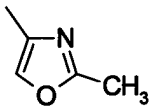
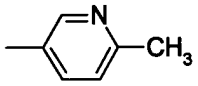
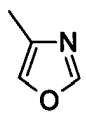
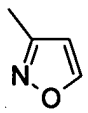
| | |
|---|---|
| 1323 |  |
| 1324 |  |
| 1325 |  |
| 1326 |  |

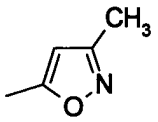
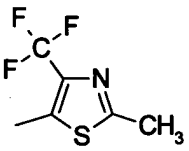
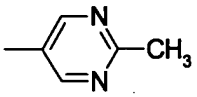
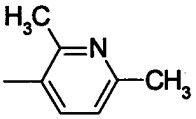


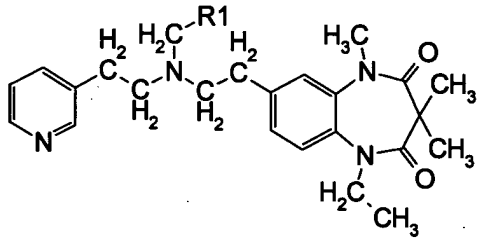
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1327 |  | |
| 1328 |  | |
| 1329 |  | |
| 1330 |  | |
| 1331 |  | |
| 1332 |  | |
| 1333 |  | |
| 1334 |  | |
| 1335 |  | |
| 1336 |  | |

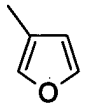
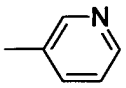
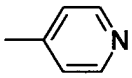
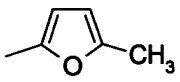
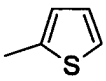
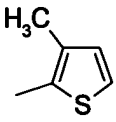
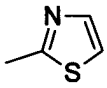
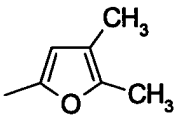
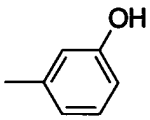
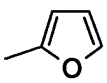
| | |
|---|---|
| 1337 |  |
| 1338 |  |
| 1339 |  |
| 1340 |  |
| 1341 |  |
| 1342 |  |
| 1343 |  |
| 1344 |  |
| 1345 |  |
| 1346 |  |
| 1347 |  |

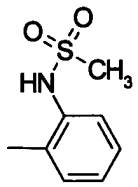
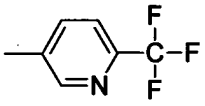
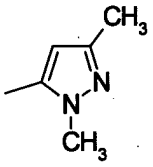
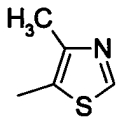
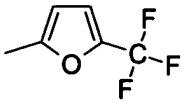
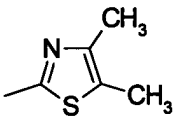
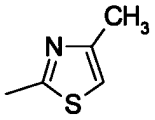
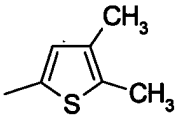
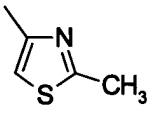
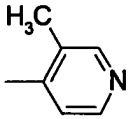
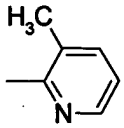
| | |
|---|---|
| 1348 |  |
| 1349 |  |
| 1350 |  |
| 1351 |  |
| 1352 |  |
| 1353 |  |
| 1354 |  |
| 1355 |  |
| 1356 |  |
| 1357 |  |
| 1358 |  |

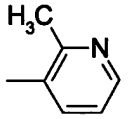
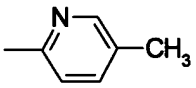
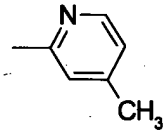
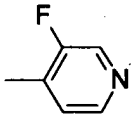
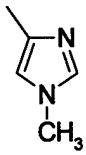
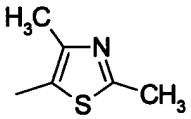
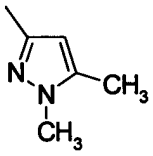
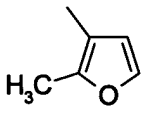
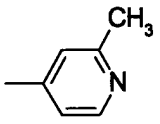
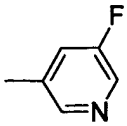
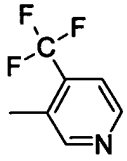
| | |
|---|---|
| 1359 |  |
| 1360 |  |
| 1361 |  |
| 1362 |  |
| 1363 |  |
| 1364 |  |
| 1365 |  |
| 1366 |  |
| 1367 |  |
| 1368 |  |
| 1369 |  |
| 1370 |  |

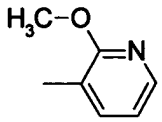
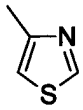
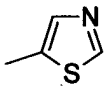
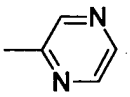
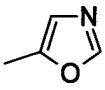
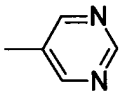
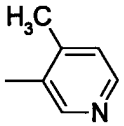
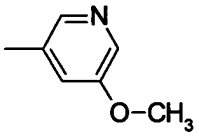
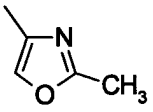
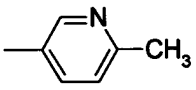
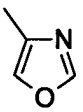
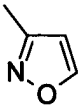
| | |
|---|---|
| 1371 |  |
| 1372 |  |
| 1373 |  |
| 1374 |  |

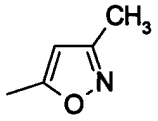
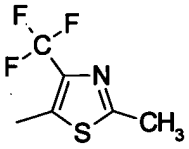
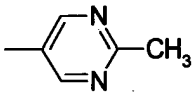
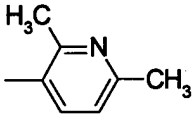


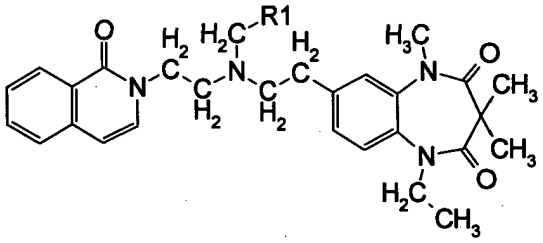
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1375 |  | |
| 1376 |  | |
| 1377 |  | |
| 1378 |  | |
| 1379 |  | |
| 1380 |  | |
| 1381 |  | |
| 1382 |  | |
| 1383 |  | |
| 1384 |  | |

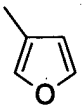
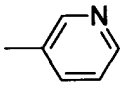
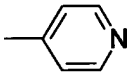
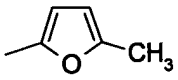
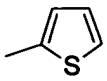
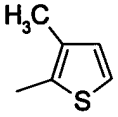
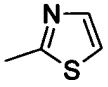
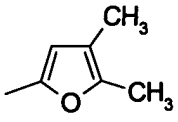
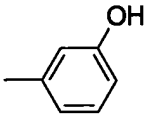
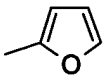
| | |
|---|---|
| 1385 |  |
| 1386 |  |
| 1387 |  |
| 1388 |  |
| 1389 |  |
| 1390 |  |
| 1391 |  |
| 1392 |  |
| 1393 |  |
| 1394 |  |
| 1395 |  |

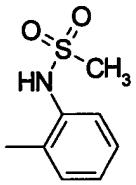
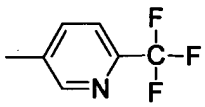
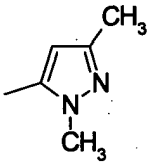
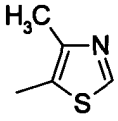
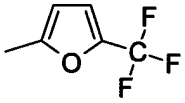
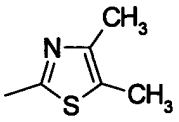
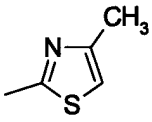
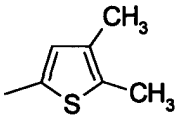
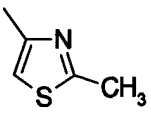
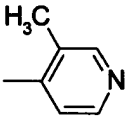
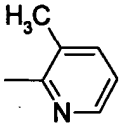
| | |
|---|---|
| 1396 |  |
| 1397 |  |
| 1398 |  |
| 1399 |  |
| 1400 |  |
| 1401 |  |
| 1402 |  |
| 1403 |  |
| 1404 |  |
| 1405 |  |
| 1406 |  |

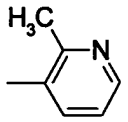
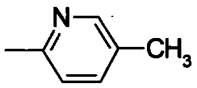
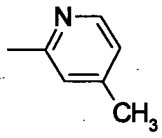
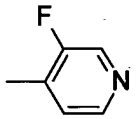
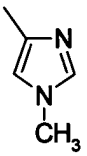
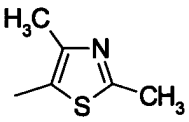
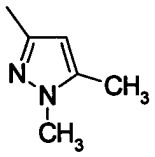
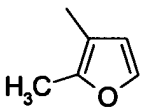
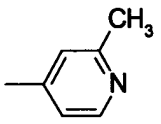
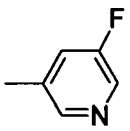
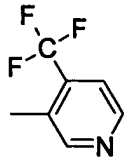
| | |
|---|---|
| 1407 |  |
| 1408 |  |
| 1409 |  |
| 1410 |  |
| 1411 |  |
| 1412 |  |
| 1413 |  |
| 1414 |  |
| 1415 |  |
| 1416 |  |
| 1417 |  |
| 1418 |  |

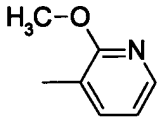
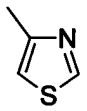
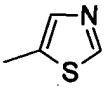
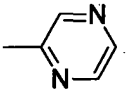
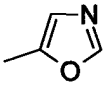
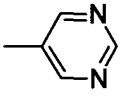
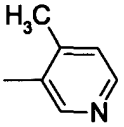
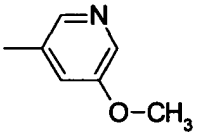
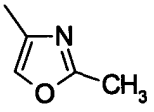
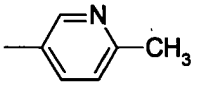
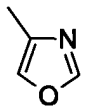
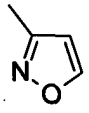
| | |
|---|---|
| 1419 |  |
| 1420 |  |
| 1421 |  |
| 1422 |  |

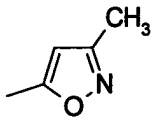
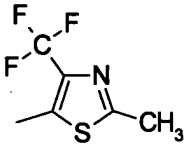
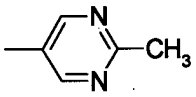
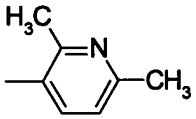


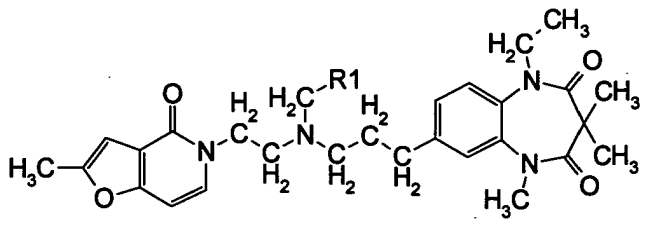
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1423 |  | |
| 1424 |  | |
| 1425 |  | |
| 1426 |  | |
| 1427 |  | |
| 1428 |  | |
| 1429 |  | |
| 1430 |  | |
| 1431 |  | |
| 1432 |  | |

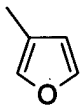
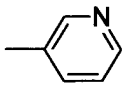
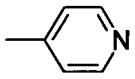
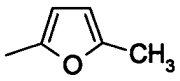
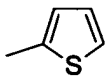
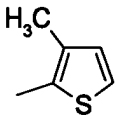
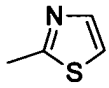
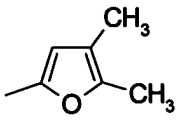
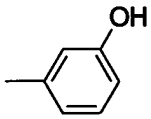
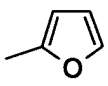
| | |
|---|---|
| 1433 |  |
| 1434 |  |
| 1435 |  |
| 1436 |  |
| 1437 |  |
| 1438 |  |
| 1439 |  |
| 1440 |  |
| 1441 |  |
| 1442 |  |
| 1443 |  |

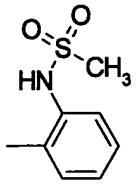
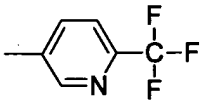
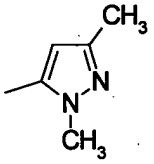
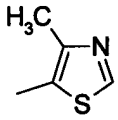
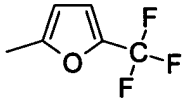
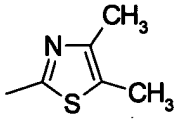
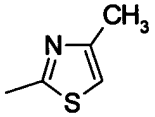
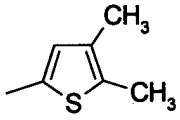
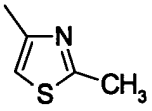
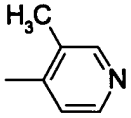
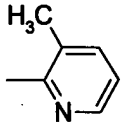
| | |
|---|---|
| 1444 |  |
| 1445 |  |
| 1446 |  |
| 1447 |  |
| 1448 |  |
| 1449 |  |
| 1450 |  |
| 1451 |  |
| 1452 |  |
| 1453 |  |
| 1454 |  |

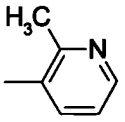
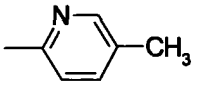
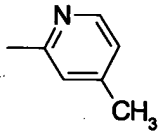
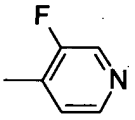
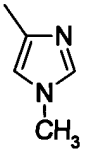
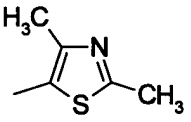
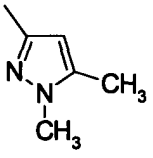
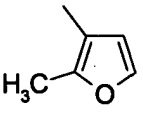
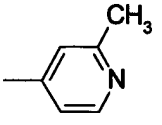
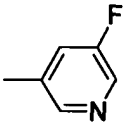
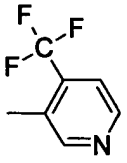
| | |
|---|---|
| 1455 |  |
| 1456 |  |
| 1457 |  |
| 1458 |  |
| 1459 |  |
| 1460 |  |
| 1461 |  |
| 1462 |  |
| 1463 |  |
| 1464 |  |
| 1465 |  |
| 1466 |  |

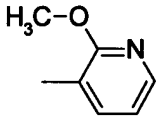
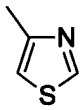
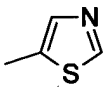
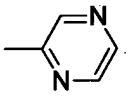
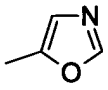
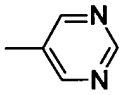
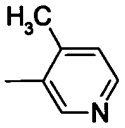
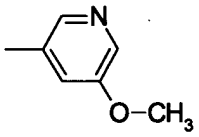
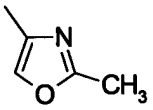
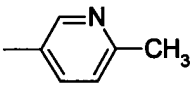
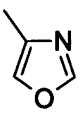
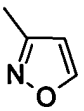
| | |
|---|---|
| 1467 |  |
| 1468 |  |
| 1469 |  |
| 1470 |  |

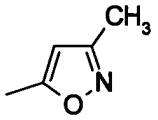
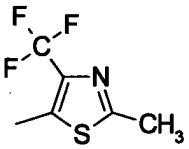
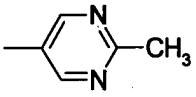
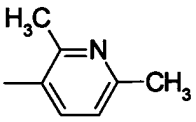


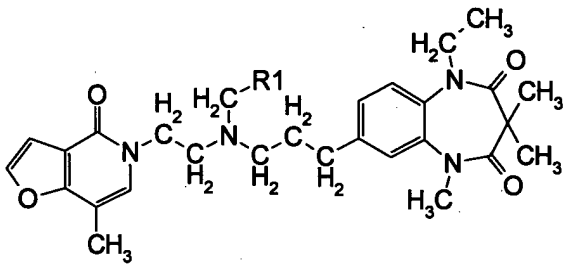
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1471 |  | |
| 1472 |  | |
| 1473 |  | |
| 1474 |  | |
| 1475 |  | |
| 1476 |  | |
| 1477 |  | |
| 1478 |  | |
| 1479 |  | |
| 1480 |  | |

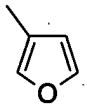
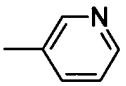
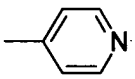
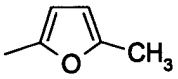
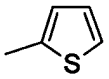
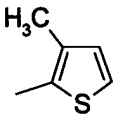
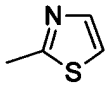
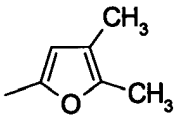
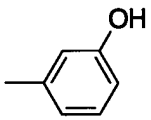
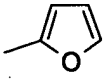
| | |
|---|---|
| 1481 |  |
| 1482 |  |
| 1483 |  |
| 1484 |  |
| 1485 |  |
| 1486 |  |
| 1487 |  |
| 1488 |  |
| 1489 |  |
| 1490 |  |
| 1491 |  |

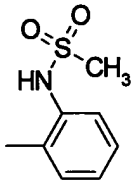
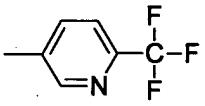
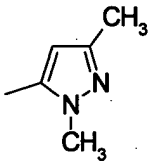
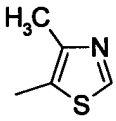
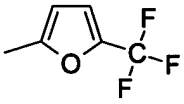
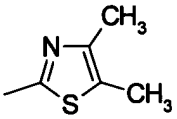
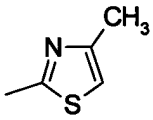
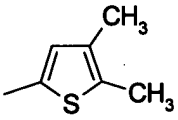
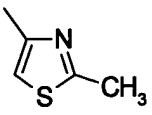
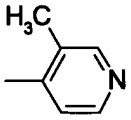
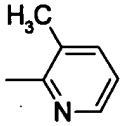
| | |
|---|---|
| 1492 |  |
| 1493 |  |
| 1494 |  |
| 1495 |  |
| 1496 |  |
| 1497 |  |
| 1498 |  |
| 1499 |  |
| 1500 |  |
| 1501 |  |
| 1502 |  |

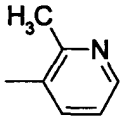
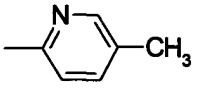
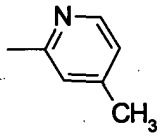
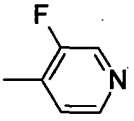
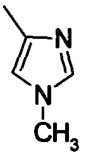
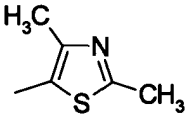
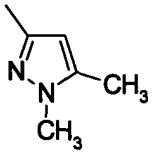
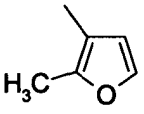
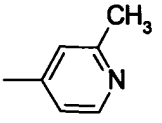
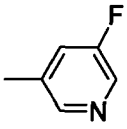
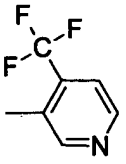
| | |
|---|---|
| 1503 |  |
| 1504 |  |
| 1505 |  |
| 1506 |  |
| 1507 |  |
| 1508 |  |
| 1509 |  |
| 1510 |  |
| 1511 |  |
| 1512 |  |
| 1513 |  |
| 1514 |  |

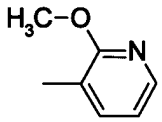
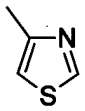
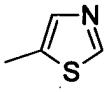
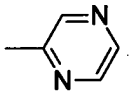
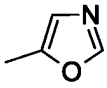
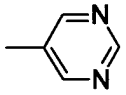
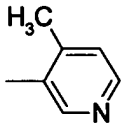
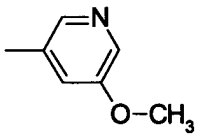
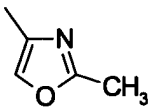
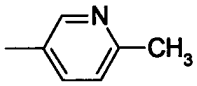
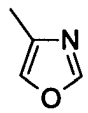
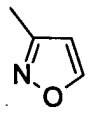
| | |
|---|---|
| 1515 |  |
| 1516 |  |
| 1517 |  |
| 1518 |  |

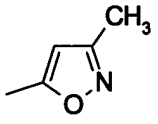
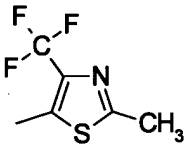
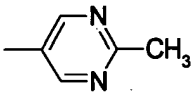
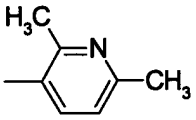


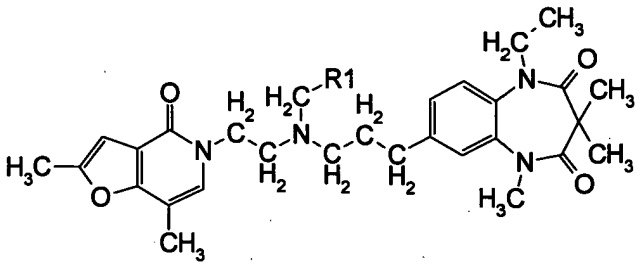
| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1519 |  | |
| 1520 |  | |
| 1521 |  | |
| 1522 |  | |
| 1523 |  | |
| 1524 |  | |
| 1525 |  | |
| 1526 |  | |
| 1527 |  | |
| 1528 |  | |

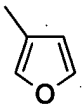
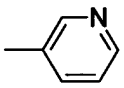
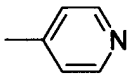
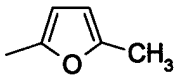
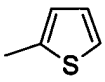
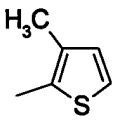
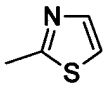
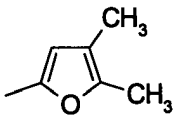
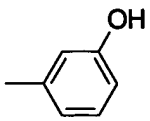
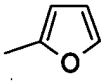
| | |
|---|---|
| 1529 |  |
| 1530 |  |
| 1531 |  |
| 1532 |  |
| 1533 |  |
| 1534 |  |
| 1535 |  |
| 1536 |  |
| 1537 |  |
| 1538 |  |
| 1539 |  |

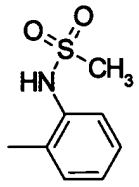
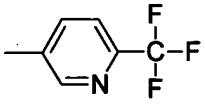
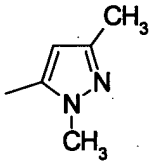
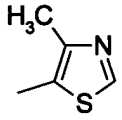
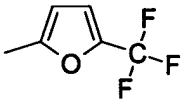
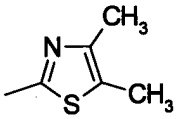
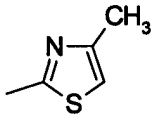
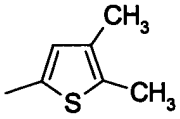
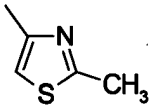
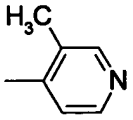
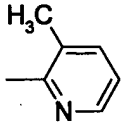
| | |
|---|---|
| 1540 |  |
| 1541 |  |
| 1542 |  |
| 1543 |  |
| 1544 |  |
| 1545 |  |
| 1546 |  |
| 1547 |  |
| 1548 |  |
| 1549 |  |
| 1550 |  |

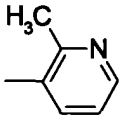
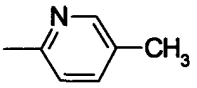
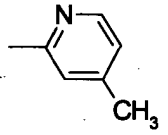
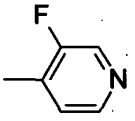
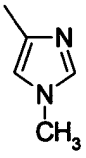
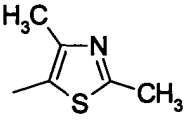
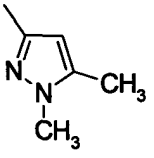
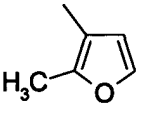
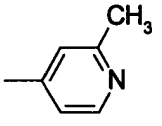
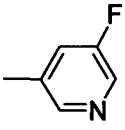
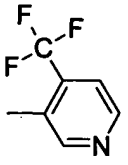
| | |
|---|---|
| 1551 |  |
| 1552 |  |
| 1553 |  |
| 1554 |  |
| 1555 |  |
| 1556 |  |
| 1557 |  |
| 1558 |  |
| 1559 |  |
| 1560 |  |
| 1561 |  |
| 1562 |  |

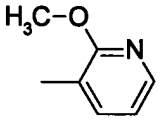
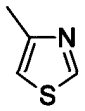
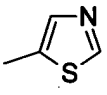
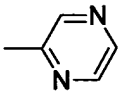
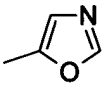
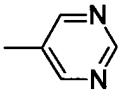
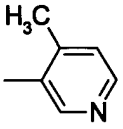
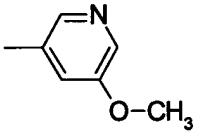
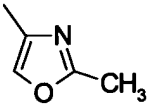
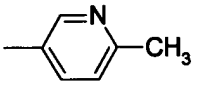
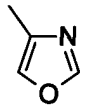
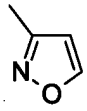
| | |
|---|---|
| 1563 |  |
| 1564 |  |
| 1565 |  |
| 1566 |  |

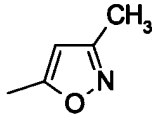
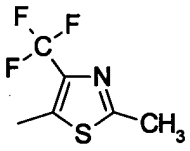
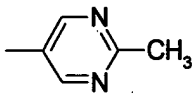
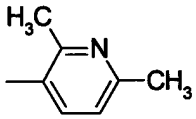


| Example No. | R1 | MS (M+1) |
|---|---|---|
| 1567 |  | |
| 1568 |  | |
| 1569 |  | |
| 1570 |  | |
| 1571 |  | |
| 1572 |  | |
| 1573 |  | |
| 1574 |  | |
| 1575 |  | |
| 1576 |  | |

| | |
|---|---|
| 1577 |  |
| 1578 |  |
| 1579 |  |
| 1580 |  |
| 1581 |  |
| 1582 |  |
| 1583 |  |
| 1584 |  |
| 1585 |  |
| 1586 |  |
| 1587 |  |

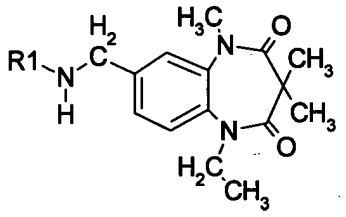
| | |
|---|---|
| 1588 |  |
| 1589 |  |
| 1590 |  |
| 1591 |  |
| 1592 |  |
| 1593 |  |
| 1594 |  |
| 1595 |  |
| 1596 |  |
| 1597 |  |
| 1598 |  |

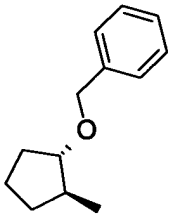
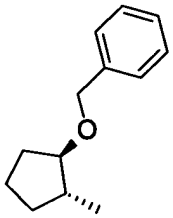
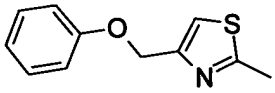
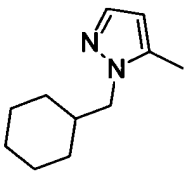
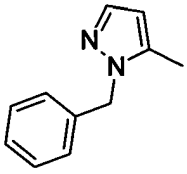
| | |
|---|---|
| 1599 |  |
| 1600 |  |
| 1601 |  |
| 1602 |  |
| 1603 |  |
| 1604 |  |
| 1605 |  |
| 1606 |  |
| 1607 |  |
| 1608 |  |
| 1609 |  |
| 1610 |  |

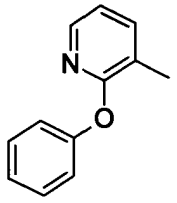
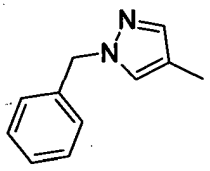
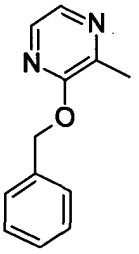
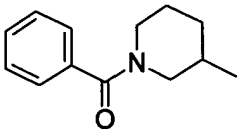
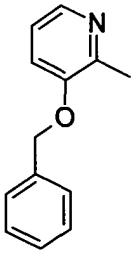
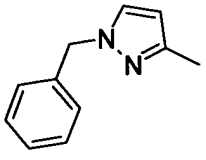
| | |
|---|---|
| 1611 |  |
| 1612 |  |
| 1613 |  |
| 1614 |  |

Examples 1615 to 1625

The folowing compounds were obtained in the same manner as in Examples above using appropriate starting materials.



| Example No. | R1 | MS(M+1) |
|---|---|---|
| 1615 |  | 450 |
| 1616 |  | 450 |
| 1617 |  | 465 |
| 1618 |  | 438 |
| 1619 |  | 432 |

| | | |
|---|---|---|
| 1620 |  | 445 |
| 1621 |  | 432 |
| 1622 |  | 460 |
| 1623 |  | 463 |
| 1624 |  | 459 |
| 1625 |  | 432 |

Pharmacological Test 1

(1) Production of human Kv1.5-expressing CHO-K1 cell lines

CHO-K1 cell lines stably expressing human Kv1.5 channels were prepared in the following manner.

Full-length human Kv1.5 cDNA was cloned from a human heart

cDNA library (produced by Stratagene). The obtained human Kv1.5 sequence corresponds to the sequence described in FASEB J. 5, 331-337 (1991).

The obtained human Kv1.5 cDNA was inserted into a plasmid encoding a CMV promoter and a G418 resistance marker to produce a Kv1.5 expression vector. The human Kv1.5 expression vector was transfected into CHO-K1 cells by the lipofectamine method. After culturing the cells in an F-12 medium (produced by Invitrogen Corp.) containing 10% FBS (produced by Invitrogen Corp.) for 3 or 4 days, the medium was replaced with a FBS-containing F-12 medium that included 1,000 μg/ml of G418 (produced by Invitrogen Corp.), and single colonies were isolated. The amount of Kv1.5 channel expression in the single colonies was quantified at the mRNA level by RT-PCR and then quantified at the protein level by western blotting. Finally, the expressed current was analyzed by patch clamp method. Cell lines expressing a current of 200 pA or more per cell were selected as channel-expressing cell lines for activity measurement by patch clamp method.

(2) Production of CHO cell line expressing human GIRK1/4

CHO cell lines stably expressing human GIRK1/4 channels were prepared in the following manner.

Full-length human GIRK1 cDNA was cloned from HuH cell- and HeLa cell-derived cDNA libraries. Full-length GIRK4 cDNA was amplified from a human heart cDNA library (produced by Clontech Laboratories, Inc.) by PCR using synthetic primers shown in Table 1, and cloned into the Eco-RI restriction enzyme site of pCR-Blunt (produced by Invitrogen Corporation) or into the HincII site of pUC118 (produced by Takara Bio, Inc.).

Table 1

| Primer | Sequence | |
|---|---|---|
| hGIRK1-S | 5'-ATGTCTGCACTCCGAAGGAAATTTG-3' | SEQ ID No.1 |
| hGIRK1-A | 5'-TTATGTGAAGCGATCAGAGTTC-3' | SEQ ID No.2 |
| hGIRK1-F2 | 5'-GCAGGGTACCCCTTCGTATTATGTCTGCACTCC-3' | SEQ ID No.3 |
| hGIRK1-A3 | 5'-GGTGTCTGCCGAGATTTGA-3' | SEQ ID No.4 |
| hGIRK1-A4 | 5'-CCGAGTGTAGGCGATCACCC-3' | SEQ ID No.5 |
| hGIRK4-S | 5'-ATGGCTGGCGATTCTAGGAATGCC-3' | SEQ ID No.6 |
| hGIRK4-A | 5'-TCTCACCGAGCCCCTGGCCTCCC-3' | SEQ ID No.7 |
| hGIRK4-S2 | 5'-AACCAGGACATGGAGATTGG-3' | SEQ ID No.8 |
| hGIRK4-A2 | 5'-GAGAACAGGAAAGCGGACAC-3' | SEQ ID No.9 |

The obtained human GIRK1 and GIRK4 cDNA sequences correspond to known sequences (NCBI database: GIRK1 (NM_002239) and GIRK4 (NM_000890) respectively). The obtained GIRK1 and GIRK4 cDNA sequences were cloned into the Eco-RI restriction enzyme site of pCR-Blunt (available from Invitrogen Corporation) or into the HincII site of pUC118 (available from Takara Bio, Inc.). A GIRK4 expression vector was constructed by insertion into the BamHI-XhoI site of pcDNA5/FRT. A GIRK1 expression vector was constructed by insertion into the KpnI-XhoI site of pcDNA3.1(+) or pCAG_neo. FLP-IN-CHO cells (produced by Invitrogen Corporation) were transfected with human GIRK1 and GIRK4 expression vectors by using Lipofectamine 2000 (produced by Invitrogen Corporation) according to the protocol enclosed with the reagent or using an electronic induction method ("Nucleofector Kit-T", produced by Amaxa). First, the cells transfected with the GIRK4 expression vector were cultured in a 10% serum-containing F12 medium (produced by Sigma) supplemented with 600 μg/ml of hygromycin in an incubator with 5% carbon dioxide at 37°C. Then the cells expressing GIRK4 were transfected with the GIRK1 expression vector and were cultured in 10% serum-containing F12 medium supplemented with 350 μg/ml of G418 and 600 μg/ml of hygromycin in an incubator with 5% carbon dioxide at 37°C to select GIRK1/4 expressing cell lines. Cell populations whose growth was observed after about 2 weeks were isolated using cloning rings, and the obtained single colonies were proliferated. RNA was extracted from single colonies, and single-stranded cDNA was synthesized by a cDNA synthesis kit (produced by Invitrogen Corporation), and the amount of expression was

quantified at the mRNA level by real-time PCR (Applied Biosystems, Ltd.). Finally, the expressed current was analyzed by patch clamp method described below. The cell lines expressing a current of 500 pA or more per cell were selected as channel-expressing cell lines for activity measurement by patch clamping method.

(3) Measurement of ion channel current by patch clamp method (human Kv1.5-expressing CHO-K1 cell line)

An experiment was carried out using a patch clamp setup at room temperature (20 to 26°C). A perfusion chamber having a diameter of 20 mm (flow rate: about 5 ml/min) was mounted on the stage of a phase-contrast inverted microscope (produced by Nikon Corporation) placed on a vibration isolated table. A poly-L-lysine (produced by Sigma)-coated coverslip (diameter: 15 mm, produced by Matsunami Glass Ind., Ltd.) on which human Kv1.5-expressing cells were cultured was placed in the perfusion chamber.

Depolarizing stimulation pulses were applied and ionic current was recorded by using a patch clamp amplifier (EPC-7 or EPC-7 PLUS, produced by HEKA) and a personal computer (manufactured by IBM Corp.) in which software for data acquisition and analysis of ion channel current (PULSE 8.77, produced by HEKA) was installed. The current was measured in the whole-cell configuration of the patch-clamp technique. The tip (resistance: 2 to 4 MΩ) of a borosilicate glass pipette (produced by Sutter Instrument Co.) was gently placed on the cell membrane by using a three-dimensional mechanical micromanipulator (produced by Shoshin EM Corporation). Weak suction resulted in giga seal formation (the pipette resistance increased to more than 1 GΩ). Subsequently, stronger suction was applied to break the cell membrane. The capacitative current derived from the cell membrane was corrected using a patch clamp amplifier. Subsequently, the series resistance (Rs) between the pipette and the interior of the cell was measured and corrected.

The composition of the extracellular solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

NaCl 140 mM,

KCl 40 mM,
$CaCl_2$ 1.8 mM,
$MgCl_2$ 1 mM,
$NaH_2PO_4$ 0.33 mM,
HEPES 5 mM
Glucose 5.5 mM (pH = 7.4)

Each test compound was prepared as a 1000-fold concentrated stock solution that was dissolved in DMSO and then diluted in the extracellular solution.

The composition of the electrode internal solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

KOH 100 mM,
KCl 40 mM,
Aspartic acid 70 mM,
$MgCl_2$ 1 mM,
MgATP 5 mM,
$K_2$ creatine phosphate 5 mM,
HEPES 5 mM
EGTA 5 mM (pH = 7.2)

(4) Measurement of ion channel current by patch clamp method (human GIRK1/4-expressing CHO-K1 cell line)

An experiment was carried out using a patch clamp setup at room temperature (20 to 26°C). A perfusion chamber having a diameter of 20 mm (flow rate: about 5 ml/min) was mounted on the stage of a phase-contrast inverted microscope (produced by Nikon Corporation) placed on a vibration isolation table. A poly-L-lysine (produced by Sigma)-coated coverslip (diameter: 15 mm, produced by Matsunami Glass Ind., Ltd.) on which human GIRK1/4-expressing cells were cultured was placed in the perfusion chamber.

Hyperpolarizing stimulation pulses were applied and ionic current was recorded using a patch clamp amplifier (EPC-7 or EPC-7 PLUS, manufactured by HEKA) and a personal computer (manufactured by IBM Corp.) in which software for data acquisition and analysis of ion channel current (PULSE 8.77, manufactured by HEKA) was installed. The

current was measured in the whole-cell configuration of the patch-clamp technique. The tip (resistance: 2 to 4 MΩ) of a borosilicate glass pipette (produced by Sutter Instrument Co.) was gently placed on the cell membrane by using a three-dimensional mechanical micromanipulator (produced by Shoshin EM Corporation). Weak suction resulted in giga seal formation (the pipette resistance increased to more than 1 GΩ). Subsequently, stronger suction was applied to break the cell membrane. The capacitative current derived from the cell membrane was corrected using a patch clamp amplifier. Subsequently, the series resistance (Rs) between the pipette and the interior of the cell was measured and corrected.

The composition of the extracellular solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

NaCl 140 mM,
KCl 4 mM,
$CaCl_2$ 1.8 mM,
$MgCl_2$ 1 mM,
$NaH_2PO_4$ 0.33 mM,
HEPES 5 mM
Glucose 5.5 mM (pH = 7.4)

Each test compound was prepared as a 1000-fold concentrated stock solution that was dissolved in DMSO and then diluted in the extracellular solution.

The composition of the electrode internal solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

KOH 100 mM,
KCl 40 mM,
Aspartic acid 70 mM,
$MgCl_2$ 1 mM,
MgATP 5 mM,
$K_2$ creatine phosphate 5 mM,
HEPES 5 mM
EGTA 5 mM (pH = 7.2)

(5) Measurement of human Kv1.5 current

While the membrane potential was holded at -80 mV, depolarizing pulses (-80 mV for 0.05 seconds →..+40 mV for 0.2 seconds →..-40 mV for 0.2 seconds →..-80 mV for 0.05 seconds) were applied at a stimulation frequency of 1 Hz to measure Kv1.5 channel current. More specifically, first, while perfusing an extracellular solution containing 0.1% DMSO and holding the membrane potential at -80 mV, depolarizing pulses were applied. The current obtained during the pulse application was recorded as a current in the absence of the test compounds. Subsequently, while perfusing an extracellular solution containing 0.1 μM of a test compound and holding the membrane potential at -80 mV, depolarizing pulses were applied. After the inhibitory effect of the test compound had been stabilized, the current was recorded. The same procedure was repeated using an extracellular solution containing 1 μM of the test compound and then using an extracellular solution containing 10 μM of the test compound. The current obtained using the solution containing the test compound at each concentration was recorded.

The data was analyzed by using the step end current recorded during the +40 mV depolarizing stimulation. The "step end current" refers to the average current flowing for a period of 195 to 199 milliseconds from the start of the +40 mV depolarizing pulse stimulation.

Using the step end current in the presence of the test compound and the step end current in the absence of the test compound, the relative current in the solution containing the test compound at each concentration was calculated according to the following formula:

Relative current =

(Step end current in the presence of the test compound) / (Step end current in the absence of the test compound)

(6) Measurement of human GIRK1/4 current

While the membrane potential was holded at -80 mV, hyperpolarizing pulses (-80 mV for 0.05 seconds →..-120 mV for 0.2 seconds →..-80 mV for 0.05 seconds) were applied at a stimulation frequency of 1 Hz to measure GIRK1/4 channel current. More

specifically, first, while perfusing an extracellular solution containing 0.1% DMSO and maintaining the membrane potential at -80 mV, hyperpolarizing pulses were applied. The current obtained during the pulse application was recorded as the current in the absence of the test compounds. Subsequently, while perfusing an extracellular solution containing 0.1 μM of a test compound and maintaining the membrane potential at -80 mV, hyperpolarizing pulses were applied. After the inhibitory effect of the test compound had been stabilized, the current was recorded. The same procedure was repeated using an extracellular solution containing 1 μM of the test compound and then using an extracellular solution containing 10 μM of the test compound. The current obtained using the solution containing the test compound at each concentration were recorded.

The data was analyzed by using the step end current recorded during the -120 mV depolarizing stimulation. The "step end current" refers to the average current flowing for a period of 195 to 199 milliseconds from the start of the -120 mV depolarizing pulse stimulation.

Using the step end current in the presence of the test compound and the step end current in the absence of the test compound, the relative current in the solution containing the test compound at each concentration was calculated according to the following formula:
Relative current =
(Step end current in the presence of the test compound) / (Step end current in the absence of the test compound)

(7) Calculation of inhibitory activity on Kv1.5 channel ionic current and GIRK1/4 channel current

The concentration for 50% inhibition of Kv1.5 channel current or GIRK1/4 channel current ($IC_{50}$ value) was calculated according to the following nonlinear regression equation:
Relative current = $1/(1+ [\text{Concentration of the compound}]/IC_{50})^{nH}$
wherein nH is the Hill coefficient.

Table 2 shows the test results.

Table 2

| Test Compound | KV1.5 $IC_{50}$ (μM) |
|---|---|
| Compound of Example 10 | 0.62 |
| Compound of Example 15 | 0.81 |
| Compound of Example 16 | 0.51 |
| Compound of Example 18 | 0.60 |
| Compound of Example 35 | 0.94 |
| Compound of Example 41 | 6.30 |
| Compound of Example 42 | 1.70 |
| Compound of Example 43 | 0.32 |
| Compound of Example 48 | 0.30 |
| Compound of Example 104 | 1.4 |
| Compound of Example 317 | 0.63 |
| Compound of Example 318 | 2.9 |
| Compound of Example 330 | 0.86 |

2. Second Invention

▪ Reference Example 1

· Synthesis of 6-hydroxy-2H-isoquinolin-1-one

A 1.0M boron tribromide/dichloromethane solution(8.5ml) was added at 0°C to a dichloromethane solution (50ml) of 6-methoxy-2H-isoquinolin-1-one(1.0g). The mixture was stirred at room temperature overnight. Water and methanol were added to the reaction mixture and extraction was carried out with a dichloromethane/methanol mixed solvent (dichloromethane:methanol = 10:1). The organic layer was dried with anhydrous sodium sulfate, followed by condensation to dryness under reduced pressure, thereby obtaining the title compound(0.4g) as a pale yellow solid.
$^1$H NMR (DMSO-$d_6$), δ ppm: 6.37 (1H, d, J = 7.1 Hz), 6.86-6.94 (2H, m), 7.03-7.08 (1H, m), 8.02 (1H, d, J = 8.7 Hz), 10.22 (1H, br), 10.90 (1H, s).

▪ Reference Example 2

· Synthesis of

6-hydroxy-1,3-dimethyl-3,4-dihydro-1H-quinazolin-2-one

The synthesis of the title compound was performed in the same manner as in Refernce Example 1 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$), δ ppm: 2.87 (3H, s), 3.13 (3H, s), 4.26 (2H, s), 6.57 (1H, d, J = 2.7 Hz), 6.65 (1H, dd, J = 2.7, 8.7 Hz), 6.73 (1H, d, J = 8.7 Hz), 9.13 (1H, s).

▪ Reference Example 3

· Synthesis of 6-hydroxy-1,3-dimethyl-1H-quinazoline-2,4-dione

The synthesis of the title compound was performed in the same manner as in Reference Example 1 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$), δ ppm: 3.29 (3H, s), 3.48 (3H, s), 7.20 (1H, dd, J=2.8, 9.0 Hz), 7.31 (1H, d, J=9.0 Hz), 7.40 (1H, d, J=2.8 Hz), 9.76 (1H, s).

▪ Reference Example 4

· Synthesis of 6-hydroxy-2-methyl-2H-isoquinolin-1-one

The synthesis of the title compound was performed in the same manner as in Reference Example 1 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$), δ ppm: 3.44 (3H, s), 6.43 (1H, d, J = 7.4 Hz), 6.86 (1H, d, J = 2.2 Hz), 6.93 (1H, dd, J = 8.7, 2.2 Hz), 7.35 (1H, d, J = 7.4 Hz), 8.04 (1H, d, J = 8.7 Hz).

▪ Reference Example 5

· Synthesis of 6-hydroxy-2-methyl-3,4-dihydro-2H-isoquinolin-1-one

The synthesis of the title compound was performed in the same manner as in Reference Example 1 using appropriate starting materials. $^1$H-NMR ($CDCl_3$), δ ppm: 2.95 (2H, t, J = 6.7 Hz), 3.13 (3H, s), 3.57 (2H, t, J = 6.7 Hz), 6.62 (1H, d, J = 2.4 Hz), 6.76 (1H, dd, J = 8.6, 2.4 Hz), 7.83 (1H, d, J = 8.6 Hz).

▪ Reference Example 6

· Synthesis of
2-methyl-1,1-dioxo-2,3-dihydro-1H-benzo[d]isothiazol-5-ol

The synthesis of the title compound was performed in the same manner as in Reference Example 1 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$), δ ppm: 2.92 (3H, s), 4.24 (2H, s), 6.75 (1H, s), 6.92 (1H, d, J = 8.5 Hz), 7.60 (1H, d, J = 8.5 Hz).

▪ Reference Example 7

· Synthesis of 3-hydroxy-7,8-dihydro-6H-5-thia-8-azabenzocyclohepten-9-one

The synthesis of the title compound was performed in the same manner as in Reference Example 1 using appropriate starting materials.

$^1$H-NMR ($CD_3OD$), δ ppm: 3.15 (2H, t, J = 6.0 Hz), 3.21-3.40 (2H, m), 6.84 (1H, dd, J = 8.4, 2.4 Hz), 6.96 (1H, d, J = 2.4 Hz), 7.46 (1H, d, J = 8.4 Hz).

▪ Reference Example 8

· Synthesis of 3-hydroxy-1-methyl-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Reference Example 1 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$), δ ppm: 3.70 (3H, s), 7.12 (1H, s), 7.17-7.28 (1H, m), 7.35-7.50 (2H, m), 7.56 (1H, d-d, J = 1.3, 7.5Hz), 9.46 (1H, br-s).

▪ Reference Example 9

· Synthesis of 7-(3-iodopropoxy)-1-methyl-1H-quinolin-2-one

7-(3-Chloropropoxy)-1- methyl-1H-quinolin-2-one(2.5g) and sodium iodide(3.0g) were added to 30ml of acetonitrile. The mixture was stirred for 18 hours while heated under reflux. After cooled to room temperature, water was added to the reaction mixture, followed by extration using dichloromethane. The organic layer was dried with sodium sulfate and was condensed under reduced pressure to give the title compound(2.4g) as a pale brown powder.

$^1$H-NMR ($CDCl_3$), δ ppm: 2.29-2.37 (2H, m), 3.41 (2H, t, J = 6.6 Hz), 3.69 (3H, s), 4.17 (2H, t, J = 5.8 Hz), 6.56 (1H, d, J = 9.4 Hz), 6.81-6.84 (2H, m), 7.45-7.58 (1H, m), 7.60 (1H, d, J = 9.4 Hz).

▪ Reference Example 10

· Synthesis of 6-(5-bromopentyloxy)-1-methyl-1H-quinolin-2-one

Sodium hydride (60% in oil, 440mg) was suspended in DMF(20ml), and was cooled to 0°C in ice water bath.

6-(5-Bromopentyloxy)-1H-quinolin-2-one(3.1g) was added thereto at the same temperature, and the mixture was stirred at 0°C for an hour. Methyl iodide(1.9ml) was added thereto, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried with sodium sulfate, and was condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=4:1→1:1). The purified product was condensed to dryness under reduced pressure to give the title compound(2.68g) as a yellow powder.

$^1$H-NMR ($CDCl_3$), δ ppm: 1.53-1.70 (2H, m), 1.81-1.97 (4H, m), 3.45 (2H, t, J = 6.7 Hz), 3.71 (3H, s), 4.00-4.04 (2H, m), 6.71 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 3.0 Hz), 7.16-7.20 (1H, m), 7.27-7.31 (1H, m), 7.59 (1H, d, J = 9.5 Hz).

▪ Reference Example 11

· Synthesis of 6-(8-bromooctyloxy)-2-methoxyquinoline

Sodium hydride (60% in oil, 40mg) was suspended in DMF(2ml), and was cooled to 0°C in ice water bath.

6-Hydroxy-2-methoxyquinoline(171mg) was added thereto at the same temperature, and the mixture was stirred at 0°C for an hour. 1,8-Dibromooctane(0.37ml) was added thereto, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was dried with sodium sulfate, and was condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=10:1). The purified product was condensed to dryness under reduced pressure to give the title compound(225mg) as a white powder.

$^1$H-NMR ($CDCl_3$), δ ppm: 1.37-1.51 (8H, m), 1.81-1.89 (4H, m), 3.41 (2H, t, J = 6.8 Hz), 4.04 (3H, s), 4.04 (2H, t, J = 6.5 Hz), 6.87 (1H, d, J = 8.8 Hz), 7.03 (1H, d, J = 2.8 Hz), 7.27 (1H, dd, J = 9.1, 2.8 Hz), 7.75 (1H, d, J = 9.1 Hz), 7.87 (1H, d J = 8.8 Hz).

▪ Reference Example 12

· Synthesis of 6-(5-bromopentyloxy)-2-methoxyquinoline

The synthesis of the title compound was performed in the same manner as in Reference Example 11 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$), δ ppm: 1.61-1.66 (2H, m), 1.821-1.96 (4H, m), 3.45 (2H, t, J = 6.7 Hz), 3.47 (3H, s), 4.00-4.04 (2H, m), 6.70 (1H, d, J = 9.5 Hz), 6.99 (1H, d, J = 2.8 Hz), 7.17 (1H, dd, J = 9.2, 2.8 Hz), 7.29 (1H, d J = 9.2 Hz), 7.59 (1H, d, J = 9.5 Hz).

▪ Reference Example 13

· Synthesis of 5-(3-iodopropoxy)-1-methyl-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Reference Example 9 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$), δ ppm: 2.30-2.44 (2H, m), 3.42 (2H, t, J = 6.7 Hz), 3.71 (3H, s), 4.19 (2H, t, J = 5.8 Hz), 6.66 (1H, d, J = 9.7 Hz), 6.70 (1H, d, J = 8.1 Hz), 6.97 (1H, d, J = 8.6 Hz), 7.48 (1H, dd, J = 8.6, 8.1 Hz), 8.11 (1H, d, J = 9.7 Hz).

▪ Reference Example 14

· Synthesis of 8-(3-iodopropoxy)-1-methyl-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Reference Example 9 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$), δ ppm: 2.32-2.40 (2H, m), 3.39 (2H, t, J = 6.6 Hz), 3.96 (3H, s), 4.15 (2H, t, J = 5.9 Hz), 6.70 (1H, d, J = 9.4 Hz), 7.08 - 7.17 (3H, m), 7.60 (1H, d, J = 9.4 Hz).

▪ Reference Example 15

· Synthesis of (2-pyridin-3-yl-ethyl)-pyridin-4-ylmethyl-amine

4-Pyridine carbaldehyde(5.36g) and 3-(2-aminoethyl) pyridine (6.5ml) were added to 100ml of methanol. The mixture was stirred at room temperature for 7 hours. The mixture was cooled to 0°C, and sodium borohydride(2.8g) was added thereto. The mixture was further stirred at 0°C for an hour. Water was added to the reaction mixture and methanol was distilled off under reduced pressure. The residue was subjected to extraction using dichloromethane. The organic layer was washed with saturated saline, dried with anhydrous sodium sulfate, and was condensed under reduced pressure. The residue was purified by basic

silica gel column chromatography (ethyl acetate: methanol =95:5→85:5). The purified product was condensed under reduced pressure to give the title compound(10.03g) as a colorless oily matter.

$^1$H-NMR ($CDCl_3$), δ ppm: 2.79-2.98 (4H, m), 3.82 (2H, s), 7.21 (2H, d, J = 5.8 Hz), 7.20-7.27 (1H, m), 7.50-7.56 (1H, m), 8.48 (1H, dd, J = 6.7, 1.6 Hz), 8.49 (1H, s), 8.51-8.57 (2H, m).

▪ Reference Example 16

· Synthesis of (2-pyridin-3-yl-ethyl)-pyridin-4-ylmethyl-[3-(tetrahydro-pyran-2-yloxy)-propyl]-amine

Sodium iodide(1.5g) was added to a DMF solution (20ml) of 2-(3-bromopropoxy)tetrahydropyran(0.85ml). The mixture was stirred at 70 °C for 7 hours. The reaction mixture was cooled to room temperature. (2-Pyridin-3-yl-ethyl)-pyridin-4-ylmethyl-amine (1.28g), and N-ethyldiisopropylamine(1.3ml) were added thereto. The mixture was stirred at room temperature overnight. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was washed with water and then saturated saline, and dried with anhydrous sodium sulfate. After condensation under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate: methanol =20:1→4:1). The purified product was condensed under reduced pressure to give the title compound(236mg) as a colorless oily matter.

$^1$H-NMR ($CDCl_3$), δ ppm: 1.40-1.90 (7H, m), 2.51-2.83 (6H, m), 3.29-3.44 (1H, m), 3.44-3.54 (2H, m), 3.54-3.70 (2H, m), 3.69-3.90 (2H, m), 4.47-4.57 (1H, m), 7.12-7.23 (3H, m), 7.37-7.48 (1H, m), 8.38-8.53 (4H, m).

▪ Reference Example 17

· Synthesis of 3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propan-1-ol

A 2N-hydrogen chloride methanol solution(1.2ml) was added to a methanol solution (4ml) of (2-pyridin-3-ylethyl)pyridin-4-ylmethyl-[3-(tetrahydropyran-2-yloxy)propyl]amine(236mg). The mixture was stirred at room temperature

overnight. A 2N-hydrogen chloride methanol solution(0.5ml) was added thereto, and the mixture was further stirred at 50°C for 3 hours. Triethylamine(0.64ml) was added to the reaction mixture, and the mixture was condensed under reduced pressure. The residue was purified by basic silica gel column chromatography (dichloromethane). The purified product was condensed under reduced pressure to give the title compound(186.3mg) as an orange oily matter.

$^1$H NMR ($CDCl_3$), δ ppm: 1.66-1.88 (2H, m), 2.59-2.77 (4H, m), 2.77-2.88 (2H, m), 3.65 (2H, s), 3.68-3.84 (3H, m), 7.11-7.25 (3H, m), 7.42 (1H, d, J=7.8 Hz), 8.42 (1H, s), 8.43-8.47 (1H, m), 8.50-8.60 (2H, m).

▪ Reference Example 18

· Synthesis of (3-chloropropyl)-(2-pyridin-3-ylethyl)pyridin-4-ylmethylamine

(2-Pyridin-3-yl-ethyl)-pyridin-4-ylmethyl-amine(210mg) and N-ethyldiisopropylamine(0.34ml) were added to a DMF solution (2ml) of 1-chloro-3-iodopropane(0.16ml). The mixture was stirred at room temperature overnight. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was washed with water and then saturated saline, and dried with anhydrous sodium sulfate. After condensation under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate: methanol =20:1→4:1). The purified product was condensed under reduced pressure to give the title compound(74mg) as a colorless oily matter.

$^1$H-NMR ($CDCl_3$), δ ppm: 1.82-1.99 (2H, m), 2.61-2.82 (6H, m), 3.52 (2H, t, J = 6.3 Hz), 3.61 (2H, s), 7.14 (2H, d, J = 5.9 Hz), 7.19 (1H, dd, J = 7.7, 4.8 Hz), 7.36-7.49 (1H, m), 8.38-8.56 (4H, m).

▪ Reference Example 19

· Synthesis of 2-nitro-N-(2-pyridin-3-ylethyl)benzenesulfonamide

2-Nitrobenzene sulfonyl chloride(11.64g) was added to a dichloromethane solution (100ml) of 3-(2-aminoethyl)pyridine(6.11g) and triethylamine(9ml) at 0°C. The mixture was stirred at room temperature for 2 hours. Water was added to the reaction mixture, followed by extraction with dichloromethane. The organic layer was

dried with anhydrous sodium sulfate, and condensed under reduced pressure. The residue was crystalized from ethyl acetate to give the title compound(5.06g) as a yellow powder.

$^1$H NMR (DMSO-$d_6$), δ ppm: 2.76 (2H, t, J = 7.1 Hz), 3.19 (2H, t, J = 7.1 Hz), 7.26 (1H, dd, J = 4.8 Hz, 7.8 Hz), 7.60 (1H, d, J = 7.8 Hz), 7.8-8.0 (4H, m), 8.19 (1H, brs), 8.3-8.4 (2H, m).

▪ Reference Example 20

· Synthesis of (2-methylbenzyl)-(2-pyridin-3-ylethyl)amine

The synthesis of the title compound was performed in the same manner as in Reference Example 15 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δ ppm: 0.95-1.95 (1H, br-s), 2.30 (3H, s), 2.77-2.88 (2H, m), 2.91-3.02 (2H, m), 3.78 (2H, s), 7.06-7.30 (5H, m), 7.53 (1H, br-d, J = 7.5Hz), 8.41-8.53 (2H, m).

▪ Reference Example 21

· Synthesis of 6-(3-chloropropoxy)-1-methyl-1H-quinolin-2-one

Potassium carbonate (0.829g) was dissolved in acetonitrile(10ml) and water(10ml), and 6-hydroxy-2-methoxyquinoline(0.875g) and 1-chloro-3-bromopropane(1.48ml) was added thereto, and the mixture was stirred while heating under reflux for 4 hours. The reaction mixture was condensed under reduced pressure. Water was added to the residue, followed by extraction using ethyl acetate. The organic layer was dried with sodium sulfate, and was condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=1:1). The purified product was condensed to dryness under reduced pressure to give the title compound(1.107g) as a white powder.

1H-NMR (CDCl3) δ ppm: 2.18-2.35 (2H, m), 3.71 (3H, s), 3.78 (2H, t, J = 6.2 Hz), 4.18 (2H, t, J = 5.9 Hz), 6.72 (1H, d, J = 9.5 Hz), 7.03 (1H, d, J = 2.8 Hz), 7.19 (1H, dd, J = 9.2, 2.8 Hz), 7.30 (1H, d, J = 9.2 Hz), 7.60 (1H, d, J = 9.5 Hz).

▪ Reference Example 22

· Synthesis of 6-(3-aminopropoxy)-1-methyl-1H-quinolin-2-one

Hydrazine hydrate (6.54 ml) was added to a ethanol solution (250 ml) of 2-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]isoindole-1,3-dione (16.28 g), and stirred while heating under reflux for 2 hours. The reaction mixture was concentrated under reduced pressure. A 1N-sodium hydroxide aqueous solution was added to the residue, and stirred for 30 minutes, and extraction with dichloromethane was performed. The organic layer was washed with water and a saturated sodium chloride aqueous solution, in this order. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound(8.04g) as a colorless oil.
1H-NMR (CDCl3) δ ppm: 1.89-2.06 (2H, m), 2.95 (2H, t, J = 6.8 Hz), 3.71 (3H, s), 4.11 (2H, t, J = 6.1 Hz), 6.72 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 2.8 Hz), 7.19 (1H, dd, J = 9.2, 2.8 Hz), 7.30 (1H, d, J = 9.2 Hz), 7.60 (1H, d, J = 9.5 Hz).

▪ Reference Example 23

· Synthesis of 6-(2-iodoethoxy)-1-methyl-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Reference Example 9 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 3.45 (2H, t, J = 6.6 Hz), 3.71 (3H, s), 4.31 (2H, t, J = 6.6 Hz), 6.73 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 2.8 Hz), 7.21 (1H, dd, J = 9.2, 2.8 Hz), 7.31 (1H, d, J = 9.2 Hz), 7.60 (1H, d, J = 9.5 Hz).

▪ Reference Example 24

· Synthesis of 6-(2-aminoethoxy)-1-methyl-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Reference Example 22 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 3.13 (2H, t, J = 5.1 Hz), 3.71 (3H, s), 4.05 (2H, t, J = 5.1 Hz), 6.72 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 2.8 Hz), 7.21 (1H, dd, J = 9.2, 2.8 Hz), 7.31 (1H, d, J = 9.2 Hz), 7.60 (1H, d, J = 9.5 Hz).

▪Reference Example 25

· Synthesis of
2-nitro-N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}benzene sulfonamide

The synthesis of the title compound was performed in the same manner as in Reference Example 19 using appropriate starting materials.

1H-NMR (CDCl3) δ ppm: 1.42-1.99 (4H, m), 2.13-2.35 (2H, m), 2.43-2.69 (4H, m), 3.21 (2H, t, J = 6.0 Hz), 3.39-3.54 (1H, m), 4.52 (2H, s), 7.28 (1H, dd, J = 7.9, 4.8 Hz), 7.63-7.70 (1H, m), 7.70-7.79 (2H, m), 7.83-7.89 (1H, m), 8.91-8.98 (1H, m), 8.53 (1H, dd, J = 4.8, 1.6 Hz), 8.56 (1H, d, J = 1.6 Hz).

▪ Reference Example 26

· Synthesis of 6-(4-aminobutoxy)-1-methyl-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Reference Example 22 using appropriate starting materials.

1H-NMR (CDCl3) δ ppm: 1.58-1.72 (2H, m), 1.81-1.98 (2H, m), 2.80 (2H, t, J = 6.9 Hz), 3.71 (3H, s), 4.03 (2H, t, J = 6.3 Hz), 6.71 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 2.8 Hz), 7.18 (1H, dd, J = 9.2, 2.8 Hz), 7.29 (1H, d, J = 9.2 Hz), 7.59 (1H, d, J = 9.5 Hz).

▪ Reference Example 27

· Synthesis of
6-(3-iodopropoxy)-1-methyl-3,4-dihydro-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Reference Example 9 using appropriate starting materials.

1H-NMR (CDCl3) δ ppm: 2.16-2.32 (2H, m), 2.56-2.70 (2H, m), 2.87 (2H, t, J = 6.7 Hz), 3.33 (3H, s), 3.31-3.45 (2H, m), 4.02 (2H, t, J = 5.8 Hz), 6.75 (1H, d, J = 2.8 Hz), 6.78 (1H, dd, J = 8.7, 2.8 Hz), 6.89 (1H, d, J = 8.7 Hz).

▪ Reference Example 28

· Synthesis of N-(3-imidazol-1-yl-propyl)-2-nitrobenzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Reference Example 19 using appropriate starting

materials.

1H-NMR (CDCl3) δ ppm: 1.71-1.95 (2H, m), 2.85 (2H, t, J = 6.8 Hz), 3.97 (2H, t, J = 6.9 Hz), 6.86 (1H, s), 7.10 (1H, s), 7.55 (1H, s), 7.83-7.92 (2H, m), 7.92-8.02 (2H, m), 8.16 (1H, s).

▪Reference Example 30

· Synthesis of N-(3-Chloropropyl)-N-(2-methylbenzyl)-N-(2-pyridin-3-ylethyl)amine

The synthesis of the title compound was performed in the same manner as in Reference Example 18 using appropriate starting materials.

1H-NMR (CDCl3) δ ppm: 1.78-1.95 (2H, m), 2.26 (3H, s), 2.60-2.79 (6H, m), 3.50 (2H, t, J = 6.5 Hz), 3.58 (2H, s), 7.08-7.24 (5H, m), 7.33-7.39 (1H, m), 8.36 (1H, d, J = 1.7 Hz), 8.41 (1H, dd, J = 4.8, 1.7 Hz).

▪ Reference Example 31

· Synthesis of 6-(3-iodopropoxy)-3,4-dihydro-2H-isoquinolin-1-one

The synthesis of the title compound was performed in the same manner as in Reference Example 9 using appropriate starting materials.

1H-NMR (CDCl3) δ ppm: 2.19-2.35 (2H, m), 2.97 (2H, t, J = 6.6 Hz), 3.37 (2H, t, J = 6.7 Hz), 3.50-3.62 (2H, m), 4.09 (2H, t, J = 5.8 Hz), 5.98 (1H, s), 6.71 (1H, d, J = 2.4 Hz), 6.86 (1H, dd, J = 8.6, 2.4 Hz), 8.01 (1H, d, J = 8.6 Hz).

▪ Reference Example 32

· Synthesis of 2-hydroxy-7,8-dihydro-6H-5-thia-8-aza-benzocyclohepten-9-one

The synthesis of the title compound was performed in the same manner as in Reference Example 1 using appropriate starting materials.

1H-NMR (CD3OD) δ ppm: 3.06 (2H, t, J = 6.0 Hz), 3.26 (2H, t, J = 6.0 Hz), 6.85 (1H, dd, J = 8.3, 2.8 Hz), 7.01 (1H, d, J = 2.8 Hz), 7.34 (1H, d, J = 8.3 Hz).

▪ Example 1

· Synthesis of

1-methyl-6-{5-[(2-methylbenzyl)-(2-pyridin-3-ylethyl)amino]pentyl oxy}-1H-quinolin-2-one dihydrochloride

Ppotassium carbonate(360mg) and (2-methylbenzyl)-(2-pyridin-3-ylethyl)amine(591mg) were added to a DMF solution (6.5ml) of 6-(5-bromopentyloxy)-1-methyl-1H-quinolin-2-one(650mg). The mixture was stirred at 60°C for 8 hours. Ice water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was washed with water and then saturated saline, dried with anhydrous sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane: ethyl acetate: methanol: aqueous ammonia =70:20:10:1). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution(1.0ml) was added to an ethyl acetate solution(20ml) of the residue, which was stirred at room temperature. The liquid was condensed to dryness under reduced pressure to give the title compound(270mg) as a pale yellow amorphus solid.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.32-1.50 (2H, m), 1.65-1.99 (4H, m), 2.47 (3H, s), 2.92-3.21 (2H, m), 3.21-3.50 (4H, m), 3.59 (3H, s), 3.88-4.09 (2H, m), 4.30-4.52 (2H, m), 6.61 (1H, d, J = 9.4Hz), 7.05-7.35 (5H, m), 7.46 (1H, d, J = 9.2Hz), 7.73 (1H, d, J = 7.2 Hz), 7.84 (1H, d, J = 9.6Hz), 7.89-8.01 (1H, m), 8.40 (1H, br-d, J = 7.8Hz), 8.79 (1H, d, J = 4.9Hz), 8.89 (1H, s).

▪ Example 2

· Synthesis of N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-2-nitro-N-(2-pyridin-3-ylethyl)benzenesulfonamide

2-Nitro-N-(2-pyridin-3-ylethyl)benzenesulfonamide(308mg), and potassium carbonate(276mg) were added to a DMF solution(5ml) of 6-(5-bromopentyloxy)-1-methyl-1H-quinolin-2-one(348mg). The mixture was stirred at room temperature for 2 hours. Ice water was poured to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was washed with water, dried with anhydrous sodium sulfate, and condensed under reduced pressure. The residue was

purified by silica gel column chromatography (ethyl acetate→ethyl acetate: methanol =10:1). The purified product was condensed to dryness under reduced pressure to give 5 the title compound(535mg) as a yellow amorphus solid.

$^1$H-NMR ($CDCl_3$) δ ppm: 1.4-1.9 (6H, m), 2.88 (2H, t, J = 7.5 Hz), 3.40 (2H, t, J = 7.5 Hz), 3.52 (2H, t, J = 7.7 Hz), 3.71 (3H, s), 3.98 (2H, t, J = 6.3 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.98 (1H, d, J = 2.8 Hz), 7.1-7.3 (2H, m), 7.29 (1H, d, J = 9.2 Hz), 7.4-7.7 (5H, m), 7.9-8.1 (1H, m), 8.40 (1H, d, J =1.8 Hz), 8.45 (1H, dd, J = 1.8 Hz, 4.8 Hz).

▪ Example 3

· Synthesis of 1-methyl-6-[5-(2-pyridin-3-ylethylamino)pentyloxy]-1H-quinolin-2-one dihydrochloride

Lithium hydroxide(102mg), and thioglycolic acid(0.141ml) were added to a DMF solution(5ml) of N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-2-nitro-N-(2-pyridin-3-ylethyl)benzenesulfonamide(535mg). The mixture was stirred at room temperature overnight. Ice water was poured to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was washed with water, dried with anhydrous sodium sulfate, and condensed under reduced pressure. A 1N-hydrogen chloride ethanol solution(1.0ml), and ethyl acetate were added to the residue. The mixture was stirred at room temperature. The precipitated insoluble matter was separated, washed with ethyl acetate, and dried to give the title compound(108mg) as a white powder.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.4-1.6 (2H, m), 1.6-1.8 (4H, m), 2.8-3.0 (2H, m), 3.2-3.4 (4H, m), 3.60 (3H, s), 4.04 (2H, t, J = 6.1 Hz), 4.0-4.8 (1H, br), 6.61 (1H, d, J = 9.5 Hz), 7.25 (1H, dd, J = 2.8 Hz, 9.2 Hz), 7.31 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.05 (1H, dd, J = 5.6 Hz, 8.1 Hz), 8.57 (1H, d, J = 8.1 Hz), 8.84 (1H, d, J = 5.6 Hz), 8.94 (1H, s), 9.36 (1H, brs).

▪ Example 4

· Synthesis of 1-methyl-6-[5-((2-methylbenzyl)-{2-[4-(pyridin-3-ylmethoxy)piperi

din-1-yl]ethyl}amino)pentyloxy]-1H-quinolin-2-one trihydrochloride

Methane sulfonyl chloride(0.59ml) was added to a dichloromethane solution(30ml) of 6-{5-[(2-hydroxyethyl)-(2-methylbenzyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one(2.83g) and N-ethyldiisopropylamine(1.81ml). The mixture was stirred at room temperature for an hour. Water was added to the reaction mixture, followed by extraction using dichloromethane. The organic layer was dried with anhydrous sodium sulfate, and condensed under reduced pressure. The residue was dissolved in acetonitrile(50ml). Sodium iodide(1.56g), 3-(piperidin-4-yloxymethyl)pyridine(1.46g) and N-ethyldiisopropylamine(3.61ml) were added thereto, and the mixture was stirred at 60°C for 3 hours. The reaction mixture was condensed under reduced pressure. Water was added to the residue, followed by extraction using dichloromethane. The organic layer was washed with water and then saturated saline, dried with anhydrous sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane: ethyl acetate: methanol: aqueous ammonia =70:20:10:1). The purified product was condensed under reduced pressure. A 1N-hydrogen chloride ethanol solution(0.41ml) was added to an isopropyl alcohol solution of the residue. The mixture was stirred at room temperature. The liquid was condensed to dryness under reduced pressure to give the title compound(2.41g) as a white amorphous solid.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.4-1.6 (2H, m), 1.7-2.3 (8H, m), 2.46 (3H, s), 3.0-3.9 (11H, m), 3.60 (3H, s), 4.02 (2H, t, J = 6.2 Hz), 4.46 (2H, s), 4.75 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.2-7.4 (5H, m), 7.47 (1H, d, J = 9.2 Hz), 7.73 (1H, d, J = 7.5 Hz), 7.86 (1H, d, J = 9.5 Hz), 8.04 (1H, dd, J = 5.7 Hz, 8.0 Hz), 8.5-8.6 (1H, br), 8.85 (1H, d, J = 5.7 Hz), 8.94 (1H, brs), 10.2-11.8 (2H, br).

▪ Example 5

· Synthesis of 6-{5-[cyclohexylmethyl-(2-pyridin-3-ylethyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one dihydrochloride

Triethylamine(0.15ml) was added to a 1,2-dichloroethane

solution (2.5ml) of 1-methyl-6-[5-(2-pyridin-3-ylethylamino)pentyloxy]-1H-quinolin-2-one dihydrochloride(219mg). The mixture was stirred at room temperature for 30 minutes. Cyclohexane carboxaldehyde(0.073ml) and sodium triacetoxyborohydrate(159mg) were added thereto, and the mixture was stirred at room temperature overnight. A saturated sodium hydrogencarbonate aqueous solution was added to the reaction mixture, followed by extraction using dichloromethane. The organic layer was dried with anhydrous sodium sulfate, and condensed under reduced pressure. The residue was purified by NH silica gel column chromatography (hexane: ethyl acetate=1:1). The purified product was condensed under reduced pressure. A 1N-hydrogen chloride ethanol solution(1.0ml) was added to an ethanol solution(20ml) of the residue, which was stirred at room temperature. The reaction mixture was condensed under reduced pressure and ethyl acetate was added to the residue. The precipitated insoluble matter was separated, washed with ethyl acetate, and dried to give the title compound(100mg) as a pale yellow powder.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 0.8-1.4 (6H, m), 1.5-2.0 (11H, m), 2.9-3.6 (8H, m), 3.59 (3H, s), 4.0-4.5 (1H, br), 4.06 (2H, t, J = 6.1 Hz), 6.61 (1H, d, J = 9.5 Hz), 7.25 (1H, dd, J = 2.8 Hz, 9.2 Hz), 7.31 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.5 Hz), 8.01 (1H, dd, J = 5.6 Hz, 8.1 Hz), 8.53 (1H, J = 8.1 Hz), 8.83 (1H, d, J = 5.6 Hz), 8.95 (1H, s), 10.4 (1H, brs).

▪ Example 6

· Synthesis of 6-{5-[(2,6-dichlorobenzyl)-(2-pyridin-3-ylethyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.3-1.6 (2H, m), 1.7-2.0 (4H, m), 3.0-3.7 (8H, m), 3.58 (3H, s), 4.02 (2H, t, J = 6.0 Hz), 4.0-5.0 (1H, br), 6.59 (1H, d, J = 9.5 Hz), 7.22 (1H, dd, J = 2.8 Hz, 9.1 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.44 (1H, d, J = 9.1 Hz), 7.4-7.7 (3H, m), 7.82 (1H, d, J = 9.5 Hz), 7.8-8.0 (1H, m), 8.38 (1H, d, J = 7.7 Hz), 8.76 (1H, d,

J = 5.3 Hz), 9.02 (1H, s), 9.9-10.2 (1H, br).

▪ Example 7

· Synthesis of

6-{5-[isobutyl-(2-pyridin-3-ylethyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

▪ Example 8

· Synthesis of

6-{5-[cyclohexyl-(2-pyridin-3-ylethyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

▪ Example 9

· Synthesis of

6-{5-[benzyl-(2-pyridin-3-ylethyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.3-1.5 (2H, m), 1.7-2.0 (4H, m), 3.0-3.2 (2H, m), 3.3-3.5 (4H, m), 3.59 (3H, s), 4.03 (2H, t, J = 6.2 Hz), 4.3-4.6 (2H, m), 4.0-4.5 (1H, br), 6.61 (1H, d, J = 9.5 Hz), 7.24 (1H, dd, J = 2.8 Hz, 9.1 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.4-7.5 (4H, m), 7.6-7.8 (2H, m), 7.83 (1H, d, J = 9.5 Hz), 7.90 (1H, dd, J = 5.3 Hz, 8.1 Hz), 8.35 (1H, d, J = 8.1 Hz), 8.78 (1H, d, J = 5.3 Hz), 8.85 (1H, s), 11.22 (1H, brs).

▪ Example 10

· Synthesis of

1-methyl-6-{5-[(2-pyridin-3-ylethyl)-o-tolylamino]pentyloxy}-1H-quinolin-2-one dihydrochloride

1-Methyl-6-[5-(2-pyridin-3-ylethylamino)pentyloxy]-1H-quinolin-2-one(183mg), 2-bromotoluene(0.072ml), palladium acetate

(II)(5.6mg), tri-tert-butylphosphine tetrafluoroborate(8mg), and sodium t-butoxide(0.19ml) were added to toluene(1ml). The mixture was heated under reflux for 8 hours under nitrogen atmosphere. After the reaction, the precipitate was removed from the reaction mixture by celite filtration. Water was added thereto, fllowed by extraction using dichloromethane. The organic layer was washed with water and then saturated saline, dried with anhydrous sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate→ethyl acetate:methanol =20:1). The purified product was condensed under reduced pressure to give the title compound(93mg) as a yellow oily matter.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.2-1.5 (2H, m), 1.6-1.9 (2H, m), 2.0-2.2 (2H, m), 2.50 (3H, s), 2.7-3.5 (6H, m), 3.59 (3H, s), 3.96 (2H, t, J = 6.3 Hz), 4.0-5.0 (2H, br), 6.59 (1H, d, J = 9.5 Hz), 7.0-7.4 (6H, m), 7.44 (1H, d, J = 9.1 Hz), 7.82 (1H, d, J = 9.5 Hz), 7.9-8.0 (1H, m), 8.3-8.4 (1H, m), 8.7-8.8 (2H, m).

▪ Example 11

· Synthesis of
1-methyl-6-{5-[(3-phenylpropyl)-(2-pyridin-3-ylethyl)amino]pentyl oxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.3-1.5 (2H, m), 1.6-1.9 (4H, m), 2.0-2.2 (2H, m), 2.63 (2H, t, J = 7.7 Hz), 3.0-3.5 (8H, m), 3.59 (3H, s), 3.8-4.2 (3H, m), 6.60 (1H, d, J = 9.5 Hz), 7.1-7.4 (7H, m), 7.46 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.97 (1H, dd, J = 5.3 Hz, 8.1 Hz), 8.48 (1H, d, J = 8.1 Hz), 8.80 (1H, d, J = 5.3 Hz), 8.92 (1H, s), 11.04 (1H, brs).

▪ Example 12

· Synthesis of
4-{[[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-(2-pyridin-3-ylethyl)amino]methyl}benzoic acid methyl ester dihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 5 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.3-1.5 (2H, m), 1.6-1.9 (4H, m), 3.0-3.2 (2H, m), 3.2-3.5 (4H, m), 3.58 (3H, s), 3.85 (3H, s), 4.00 (2H, t, J = 6.3 Hz), 4.3-4.6 (2H, m), 4.5-5.5 (1H, br), 6.59 (1H, d, J = 9.5 Hz), 7.22 (1H, dd, J = 2.8 Hz, 9.2 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.44 (1H, d, J = 9.2 Hz), 7.82 (1H, d, J = 9.5 Hz), 7.86 (2H, d, J = 8.3 Hz), 7.9-8.0 (1H, m), 7.99 (2H, d, J = 8.3 Hz), 8.42 (1H, d, J = 8.2 Hz), 8.79 (1H, d, J = 5.5 Hz), 8.88 (1H, s), 11.50 (1H, brs).

• Example 13

· Synthesis of
4-{[[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-(2-pyridin-3-ylethyl)amino]methyl}benzoic acid

A 1N-sodium hydroxide aqueous solution(0.72ml) was added to a methanol solution (2ml) of 4-{[[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-(2-pyridin-3-ylethyl)amino]methyl}benzoic acid methyl ester(153mg). The mixture was stirred at 50°C for 3 hours. The reaction mixture was condensed under reduced pressure. Water was added to the residue, and acetic acid was added for neutralization. The mixture was extracted using dichloromethane. The organic layer was dried with anhydrous sodium sulfate, and condensed under reduced pressure. Diisopropyl ether was added to the residue. The generated insoluble matter was separated by filtration and dried to give the title compound(115mg) as a white powder.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.2-1.5 (4H, m), 1.6-1.8 (2H, m), 2.3-2.6 (2H, m), 2.6-2.8 (4H, m), 3.59 (3H, s), 3.67 (2H, s), 3.96 (2H, t, J = 6.4 Hz), 6.59 (1H, d, J = 9.5 Hz), 7.1-7.3 (3H, m), 7.33 (2H, d, J = 8.2 Hz), 7.44 (1H, d, J = 9.1 Hz), 7.5-7.6 (1H, m), 7.7-7.9 (3H, m), 8.1-8.3 (2H, m), 12.5-13.0 (1H, br).

• Example 14

· Synthesis of
1-methyl-6-{5-[(2-methylbenzyl)pyridin-3-ylmethylamino]pentyloxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 5 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$) δ ppm: 1.3-1.5 (2H, m), 1.6-1.8 (2H, m), 1.8-2.0 (2H, m), 2.35 (3H, s), 3.0-3.2 (2H, m), 3.60 (3H, s), 3.9-4.1 (2H, m), 4.2-5.7 (5H, m), 6.61 (1H, d, J = 9.5 Hz), 7.1-7.4 (5H, m), 7.46 (1H, d, J = 9.2 Hz), 7.75 (1H, d, J = 7.3 Hz), 7.85 (1H, d, J = 9.5 Hz), 7.99 (1H, dd, J = 5.4 Hz, 7.9 Hz), 8.85 (1H, d, J = 7.9 Hz), 8.91 (1H, d, J = 5.4 Hz), 9.21 (1H, s), 11.64 (1H, brs).

▪ Example 15

· Synthesis of 1-methyl-6-{5-[(3-phenylpropyl)pyridin-3-ylmethylamino]pentyloxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$) δ ppm: 1.3-1.5 (2H, m), 1.6-1.9 (4H, m), 1.9-2.2 (2H, m), 2.61 (2H, t, J = 7.5 Hz), 2.9-3.2 (4H, m), 3.59 (3H, s), 4.02 (2H, t, J = 6.2 Hz), 4.0-5.0 (3H, m), 6.61 (1H, d, J = 9.5 Hz), 7.1-7.4 (7H, m), 7.46 (1H, d, J = 9.2 Hz), 7.85 (1H, d, J = 9.5 Hz), 7.9-8.1 (1H, m), 8.77 (1H, d, J = 7.9 Hz), 8.92 (1H, d, J = 5.0 Hz), 9.18 (1H, s), 11.71 (1H, brs).

▪ Example 16

· Synthesis of 6-[5-(bis{pyridin-3-ylmethyl}amino)pentyloxy]-1-methyl-1H-quinolin-2-one

Pyridine-3-carbaldehyde(0.076ml) was added to a 1,2-dichloroethane solution(3ml) of 1-methyl-6-{5-[(pyridin-3-ylmethyl)-amino]-pentyloxy}-1H-quinolin-2-one(237mg). The mixture was stirred for 30 minutes at room temperature. Sodium triacetoxyborohydride(0.23g) was added to the mixture, and the mixture was stirred at room temperature for 3 days. A saturated sodium hydrogencarbonate aqueous solution was added to the reaction mixture, followed by extraction using dichloromethane. The organic layer was dried with anhydrous sodium sulfate, and condensed under reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: hexane =1: 1). The purified

product was condensed under reduced pressure to give the title compound(247mg) as a yellow oil.

$^1$H-NMR ($CDCl_3$) δ ppm: 1.3-1.8 (6H, m), 2.47 (2H, t, J = 6.8 Hz), 3.58 (4H, s), 3.71 (3H, s), 3.95 (2H, t, J = 6.4 Hz), 6.70 (1H, d, J = 9.5 Hz), 6.98 (1H, d, J = 2.8 Hz), 7.16 (1H, dd, J = 2.8 Hz, 9.2 Hz), 7.2-7.4 (3H, m), 7.60 (1H, d, J = 9.5 Hz), 7.6-7.7 (2H, m), 8.49 (2H, dd, J= 1.6 Hz, 4.8 Hz), 8.57 (2H, d, J = 1.7 Hz).

▪ Example 17

· Synthesis of 1-methyl-6-{5-[(2-methylbenzyl)pyridin-3-ylamino]pentyloxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 16 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δ ppm: 1.5-1.7 (2H, m), 1.8-1.9 (4H, m), 2.32 (3H, s), 3.45 (2H, t, J =7.6 Hz), 3.71 (3H, s), 4.01 (2H, t, J = 6.3 Hz), 4.46 (2H, s), 6.72 (1H, d, J = 9.5 Hz), 6.8-6.9 (1H, m), 6.98 (1H, d, J = 2.8 Hz), 7.0-7.3 (6H, m), 7.29 (1H, d, J = 9.2 Hz), 7.59 (1H, d, J =9.5 Hz), 7.92 (1H, dd, J = 1.2 Hz, 4.6 Hz), 8.09 (1H, d, J = 3.0 Hz).

▪ Example 18

· Synthesis of 1-methyl-6-{5-[(3-phenylpropyl)pyridin-3-ylamino]pentyloxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 16 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δ ppm: 1.4-1.7 (4H, m), 1.8-2.1 (4H, m), 2.66 (2H, t, J = 7.7 Hz), 3.2-3.4 (4H, m), 3.70 (3H, s), 4.00 (2H, t, J = 6.3 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.8-6.9 (1H, m), 6.98 (1H, d, J = 2.8 Hz), 7.05 (1H, dd, J = 4.6 Hz, 8.6 Hz), 7.1-7.4 (7H, m), 7.58 (1H, d, J = 9.5 Hz), 7.88 (1H, dd, J = 1.2 Hz, 4.5 Hz), 8.04 (1H, d, J = 3.0 Hz).

▪ Example 19

· Synthesis of

1-methyl-6-{5-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]pentyloxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 0.80-2.02 (6H, m), 3.05-3.25 (2H, m), 3.36-3.52 (4H, m), 3.60 (3H, s), 3.97-4.10 (2H, m), 4.82 (2H, s), 6.61 (1H, d, J = 9.5 Hz), 7.25 (1H, dd, J = 9.1, 2.8 Hz), 7.32 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.1 Hz), 7.86 (1H, d, J = 9.5 Hz), 8.06 (1H, dd, J = 8.1, 5.7 Hz), 8.53 (2H, d, J = 6.3 Hz), 8.59 (1H, d, J = 8.1 Hz), 8.86 (1H, d, J = 5.7 Hz), 8.88 (1H, s), 9.04 (2H, d, J = 6.3 Hz).

▪ Example 20

· Synthesis of

1-Methyl-6-{2-[(2-pyridin-3-ylethyl)pyridin-3-ylmethylamino]ethoxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 16 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δ: 2.78-2.91 (4H, m), 3.00 (2H, t, J = 5.6 Hz), 3.69 (3H, s), 3.79 (2H, s), 4.04 (2H, t, J = 5.6 Hz), 6.70 (1H, d, J = 9.5 Hz), 6.63 (1H, d, J = 2.8 Hz), 7.15-7.30 (4H, m), 7.41-7.50 (1H, m), 7.57-7.60 (2H, m), 8.42-8.53 (4H, m).

▪ Example 21

· Synthesis of

1-methyl-6-{2-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]ethoxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δ ppm: 2.79-2.91 (4H, m), 3.01 (2H, t, J = 5.6 Hz), 3.70 (3H, s), 3.79 (2H, s), 4.05 (2H, t, J = 5.6 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.93 (1H, d, J = 2.8 Hz), 7.11-7.20 (4H, m), 7.27-7.30 (1H, m), 7.41-7.48 (1H, m), 7.58 (1H, d, J = 9.5 Hz), 8.43-8.49 (4H, m).

▪ Example 22

·Synthesis of

1-methyl-6-[3-(pyridin-4-ylmethylpyridin-3-ylmethylamino)propoxy]

-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.86-2.19 (2H, m), 3.61 (3H, s), 3.71-5.00 (8H, m), 6.62 (1H, d, J = 9.5 Hz), 7.09 (1H, dd, J = 9.2, 2.8 Hz), 7.20 (1H, d, J = 2.8 Hz), 7.44 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.80-7.94 (1H, m), 8.02-8.12 (2H, m), 8.52 (1H, d, J = 7.3 Hz), 8.73-8.83 (3H, m), 8.93 (1H, s).

▪ Example 23

· Synthesis of

1-methyl-6-[4-(pyridin-4-ylmethylpyridin-3-ylmethylamino)butoxy]-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.61-1.98 (4H, m), 2.60-3.00 (2H, m), 3.60 (3H, s), 3.23-5.11 (6H, m), 6.61 (1H, d, J = 9.5 Hz), 7.18 (1H, dd, J = 9.2, 2.9 Hz), 7.24 (1H, d, J = 2.9 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.89-8.00 (1H, m), 8.11-8.26 (2H, m), 8.64 (1H, d, J = 7.8 Hz), 8.84 (1H, d, J = 4.5 Hz), 8.88 (2H, d, J = 6.4 Hz), 9.02 (1H, s).

▪ Example 24

· Synthesis of

1-methyl-6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 16 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δ ppm: 1.88-1.96 (2H, m), 2.68-2.81 (6H, m), 3.66 (2H, s), 3.71 (3H, s), 3.93 (2H, t, J = 6.0 Hz), 6.73 (1H, d, J = 9.5 Hz), 6.92 (1H, d, J = 2.8 Hz), 7.09-7.16 (4H, m), 7.28-7.31 (1H, m), 7.39-7.46 (1H, m), 7.62 (1H, d, J = 9.5 Hz), 8.41-8.46 (4H, m).

▪ Example 25

· Synthesis of

1-Methyl-6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propo

xy}-3,4-dihydro-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 16 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δ ppm: 1.85-1.91 (2H, m), 2.60-2.88 (10H, m), 3.33 (3H, s), 3.64 (2H, s), 3.88 (2H, t, J = 6.0 Hz), 6.64-6.71 (2H, m), 6.89 (1H, d, J = 8.7 Hz), 7.13-7.19 (2H, m), 7.30-7.33 (1H, m), 7.35-7.46 (1H, m), 8.40-8.52 (3H, m), 8.53 (1H, d, J = 1.2 Hz).

▪ Example 26

· Synthesis of (2-pyridin-3-ylethyl)pyridin-4-ylmethyl-[3-(quinolin-6-yloxy)propyl]amine

The synthesis of the title compound was performed in the same manner as in Example 16 using appropriate starting materials.

$^1$H-NMR ($CDCl_3$) δ ppm: 1.93-2.02 (2H, m), 2.71-2.80 (6H, m), 3.66 (2H, s), 4.02 (2H, t, J = 6.1 Hz), 6.989 (1H, d, J = 2.8 Hz), 7.09-7.18 (3H, m), 7.28-7.39 (3H, m), 7.98-8.06 (2H, m), 8.43-8.45 (4H, m), 8.77-8.78 (1H, m).

▪ Example 27

· Synthesis of 1-methyl-5-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one trihydrochloride

(2-Pyridin-3-ylethyl)pyridin-4-ylmethylamine(128mg), and N-ethyldiisopropylamine(0.13ml) were added to a DMF solution(5ml) of 5-(3-iodopropoxy)-1-methyl-1H-quinolin-2-one(172mg). The mixture was stirred at 60°C for 3.5 hours. The reaction mixture was added to ice water, followed by extraction using ethyl acetate. The organic layer was washed with water and then saturated saline, dried with anhydrous sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol =10:1→1:1).

The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution was added to an ethyl acetate solution of the residue, which was stirred at room temperature. The generated insoluble matter was separated by filtration and dried

to give the title compound(21mg) as a white powder.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.26-2.54 (2H, m), 3.00-5.29 (10H, m), 3.60 (3H, s), 6.56 (1H, d, J = 9.7 Hz), 6.83 (1H, d, J = 8.2 Hz), 7.12 (1H, d, J = 8.6 Hz), 7.51-7.60 (1H, m), 7.92 (1H, d, J = 9.7 Hz), 8.02 (1H, dd, J = 8.0, 5.5 Hz), 8.24-8.40 (2H, m), 8.54 (1H, d, J = 8.0 Hz), 8.84 (1H, d, J = 5.5 Hz), 8.92 (2H, d, J = 5.6 Hz), 8.95 (1H, s).

▪ Example 28

· Synthesis of
1-methyl-7-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 27 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.14-2.43 (2H, m), 2.88-4.95 (10H, m), 3.59 (3H, s), 6.44 (1H, d, J = 9.4 Hz), 6.85 (1H, d, J = 8.6 Hz), 6.89 (1H, s), 7.65 (1H, d, J = 8.6 Hz), 7.83 (1H, d, J = 9.4 Hz), 7.97 (1H, dd, J = 8.0, 5.6 Hz), 8.07-8.24 (2H, m), 8.47 (1H, d, J = 8.0 Hz), 8.81 (1H, d, J = 5.6 Hz), 8.86 (2H, d, J = 5.6 Hz), 8.90 (1H, s).

▪ Example 29

· Synthesis of
1-methyl-8-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 27 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.30-2.55 (2H, m), 3.25-3.60 (6H, m), 3.77 (3H, s), 4.09-4.29 (2H, m), 4.54-5.00 (2H, m), 6.60 (1H, d, J = 9.4 Hz), 7.16-7.28 (2H, m), 7.31 (1H, dd, J = 6.8, 2.3 Hz), 7.84 (1H, d, J = 9.4 Hz), 8.04 (1H, dd, J = 8.1, 5.4 Hz), 8.32-8.46 (2H, m), 8.56 (1H, d, J = 8.1 Hz), 8.85 (1H, d, J = 5.4 Hz), 8.91-9.02 (3H, m).

▪ Example 30

· Synthesis of
6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 27 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.18-2.40 (2H, m), 3.15-3.56 (6H, m), 3.95-4.16 (2H, m), 4.59-4.87 (2H, m), 6.51 (1H, d, J = 9.5 Hz), 7.12 (1H, dd, J = 8.9, 2.7 Hz), 7.20 (1H, d, J = 2.7 Hz), 7.28 (1H, d, J = 8.9 Hz), 7.86 (1H, d, J = 9.5 Hz), 8.03 (1H, dd, J = 8.1, 5.4 Hz), 8.31-8.44 (2H, m), 8.55 (1H, d, J = 8.1 Hz), 8.84 (1H, d, J = 5.4 Hz), 8.93-9.03 (3H, m).

▪ Example 31

· Synthesis of 1-methyl-4-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one trihydrochloride

Triphenyl phosphine(102mg) and diethyl azodicarboxylate(68mg) were added to a tetrahydrofuran (THF) solution(5ml) of 4-hydroxy-1-methyl-1H-quinolin-2-one(63mg), and 3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propane-1-ol(81.4 mg). The mixture was stirred overnight. After the reaction mixture was condensed under reduced pressure, the residue was purified by silica gel column chromatography (dichloromethane: methanol =20:1→10:1). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution(0.29ml) was added to an ethyl acetate solution of the residue, which was stirred at room temperature for 30 minutes. The generated insoluble matter was separated by filtration, and dried to give the title compound(126.8mg) as a white powder.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.29-2.56 (2H, m), 3.11-3.61 (6H, m), 3.56 (3H, s), 4.11-4.30 (2H, m), 4.50-4.94 (2H, m), 6.03 (1H, s), 7.32-7.41 (1H, m), 7.52 (1H, d, J = 8.4 Hz), 7.62-7.76 (2H, m), 8.10 (1H, dd, J = 8.0, 5.3 Hz), 8.21-8.34 (2H, m), 8.53 (1H, d, J = 8.0 Hz), 8.83 (1H, d, J ≈ 5.3 Hz), 8.90 (2H, d, J = 5.7 Hz), 8.94 (1H, s).

▪ Example 32

· Synthesis of 6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-2H-isoquinolin-1-one trihydrochloride

Triphenyl phosphine(51mg) and di-tert-butyl azodicarboxylate

(45mg) were added to a tetrahydrofuran (THF) solution(1.5ml) of 6-hydroxy-2H-isoquinolin-1-one(29mg), and 3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propan-1-ol(40mg). The mixture was stirred overnight. After the reaction mixture was condensed under reduced pressure, the residue was purified by NH silica gel column chromatography (ethyl acetate: methanol =1:0→4:1). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution(0.06ml) was added to an ethyl acetate solution of the residue, which was stirred at room temperature for 30 minutes. The generated insoluble matter was separated by filtration, and was dried to produce the title compound(31.4mg) as a white powder.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.14-2.45 (2H, m), 2.91-3.78 (6H, m), 4.08-4.25 (2H, m), 4.37-4.81 (2H, m), 6.46 (1H, d, J = 7.1 Hz), 6.99 (1H, dd, J = 8.8, 2.2 Hz), 7.08 (1H, d, J = 2.2 Hz), 7.10-7.18 (1H, m), 7.92 (1H, dd, J = 8.0, 5.5 Hz), 7.99-8.14 (2H, m), 8.08 (1H, d, J = 8.8 Hz), 8.41 (1H, d, J = 8.0 Hz), 8.78 (1H, d, J = 5.5 Hz), 8.83 (2H, d, J = 5.8 Hz), 8.87 (1H, s), 10.98-11.17 (1H, m).

▪ Example 33

· Synthesis of 2-methyl-6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-2H-isoquinolin-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.09-2.41 (2H, m), 2.85-3.44 (6H, m), 3.47 (3H, s), 4.08-4.26 (2H, m), 4.26-4.66 (2H, m), 6.52 (1H, d, J = 7.3 Hz), 6.99 (1H, dd, J = 8.9, 2.3 Hz), 7.07 (1H, d, J = 2.3 Hz), 7.44 (1H, d, J = 7.3 Hz), 7.72 (1H, dd, J = 7.6, 5.3 Hz), 7.81-7.92 (2H, m), 8.11 (1H, d, J = 8.9 Hz), 8.11-8.19 (1H, m), 8.67 (1H, dd, J = 5.3, 1.2 Hz), 8.69-8.76 (3H, m).

▪ Example 34

· Synthesis of 1,3-dimethyl-6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-3,4-dihydro-1H-quinazolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.08-2.38 (2H, m), 2.88 (3H, s), 3.16 (3H, s), 3.08-3.56 (6H, m), 3.92-4.05 (2H, m), 4.32 (2H, s), 4.42-4.85 (2H, m), 6.73 (1H, br-s), 6.70-6.90 (2H, m), 7.98 (1H, d-d, J = 5.5, 8.1Hz), 8.04-8.28 (2H, m), 8.46 (1H, d, J = 8.1Hz), 8.81 (1H, d, J = 5.5Hz), 8.81-8.98 (3H, m).

▪ Example 35

· Synthesis of 6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-3,4-dihydro-2H-isoquinolin-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.13-2.40 (2H, m), 2.86 (2H, t, J = 6.5Hz), 3.10-3.57 (8H, m), 4.00-4.15 (2H, m), 4.55-4.81 (2H, m), 6.74-6.88 (2H, m), 7.66-7.80 (2H, m), 8.01 (1H, d-d, J = 5.0, 8.0Hz), 8.19-8.40 (2H, m), 8.52 (1H, d, J = 8.0Hz), 8.83 (1H, d, J = 5.0Hz), 8.85-9.00 (3H, m).

▪ Example 36

· Synthesis of 5-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-2,3-dihydro-isoindol-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.15-2.43 (2H, m), 3.00-3.58 (6H, m), 3.96-4.16 (2H, m), 4.32 (2H, s), 4.44-4.83 (2H, m), 6.96 (1H, d-d, J = 1.9, 8.3Hz), 7.07 (1H, s), 7.57 (1H, d, J = 8.3Hz), 7.92-8.05 (1H, m), 8.10-8.40 (3H, m), 8.41-8.55 (1H, m), 8.78-9.00 (4H, m).

▪ Example 37

· Synthesis of N-ethyl-4-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}benzamide trihydrochloride

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

(WSC)(95mg), and 1-hydroxy benzotriazole(HOBt)(66mg) were added to a DMF solution(4ml) of 4-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}benzoic acid(149mg), ethyl amine hydrochloride(38mg), and triethylamine (0.08ml). The mixture was stirred at room temperature overnight. The reaction mixture was added to ice water. A 1N-sodium hydroxide aqueous solution was added thereto, followed by extraction using ethyl acetate. The organic layer was washed with water and then was dried with anhydrous sodium sulfate, followed by condensation under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol =10:1→4:1). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution(0.16ml) was added to an ethyl acetate solution of the residue. The precipitated insoluble matter was separated, washed with ethyl acetate, and dried to give the title compound(80mg) as a white powder.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.11 (3H, t, J = 7.2 Hz), 2.10-2.38 (2H, m), 2.89-3.57 (8H, m), 3.95-4.20 (2H, m), 4.28-4.69 (2H, m), 6.92 (2H, d, J = 8.8 Hz), 7.75 (1H, dd, J = 7.8, 5.2 Hz), 7.82 (2H, d, J = 8.8 Hz), 7.83-7.94 (2H, m), 8.18 (1H, d, J = 7.8 Hz), 8.35 (1H, t, J = 5.4 Hz), 8.68 (1H, dd, J = 5.2, 1.3 Hz), 8.71-8.79 (3H, m).

▪ Example 38

· Synthesis of 2-methyl-6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-3,4-dihydro-2H-isoquinolin-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.10-2.40 (2H, m), 2.74-3.62 (10H, m), 2.99 (3H, s), 3.74-4.20 (2H, m), 4.39-4.82 (2H, m), 6.77 (1H, s), 6.82 (1H, d, J = 8.6 Hz), 7.79 (1H, d, J = 8.6 Hz), 7.87-8.00 (1H, m), 8.05-8.22 (2H, m), 8.46 (1H, d, J = 8.2 Hz), 8.71-8.92 (4H, m).

▪ Example 39

· Synthesis of [3-(2-methyl-1,1-dioxo-2,3-dihydrobenzo[d]isothiazol-5-yloxy)prop

yl]-(2-pyridin-3-ylethyl)pyridin-4-ylmethylamine trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.08-2.39 (2H, m), 2.79 (3H, s), 2.88-3.58 (6H, m), 4.00-4.20 (2H, m), 4.29-4.65 (2H, m), 4.35 (2H, s), 7.02-7.11 (2H, m), 7.70-7.81 (2H, m), 7.81-7.93 (2H, m), 8.18 (1H, d, J = 8.1 Hz), 8.68 (1H, dd, J = 5.2, 1.2 Hz), 8.70-8.79 (3H, m).

▪ Example 40

· Synthesis of 1-methyl-6-[3-(phenethylpyridin-4-ylmethylamino)propoxy]-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.10-2.40 (2H, m), 2.79-3.70 (6H, m), 3.60 (3H, s), 3.99-4.19 (2H, m), 4.30-4.61 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.15-7.36 (7H, m), 7.47 (1H, d, J = 9.2 Hz), 7.68-7.80 (2H, m), 7.84 (1H, d, J = 9.5 Hz), 8.67 (2H, d, J = 4.9 Hz).

▪ Example 41

· Synthesis of 1-methyl-6-{3-[(2-pyridin-2-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.12-2.31 (2H, m), 3.07-3.29 (2H, m), 3.33-3.59 (4H, m), 3.60 (3H, s), 3.95-4.19 (2H, m), 4.53 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.17 (1H, dd, J = 9.2, 2.7 Hz), 7.25 (1H, d, J = 2.7 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.58-7.67 (1H, m), 7.72 (1H, d, J = 7.9 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.04 (2H, d, J = 6.2 Hz), 8.11-8.21 (1H, m), 8.67 (1H, d, J = 4.7 Hz), 8.80 (2H, d, J = 6.2 Hz).

▪ Example 42

· Synthesis of N-methyl-N-(2-{[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.15-2.41 (2H, m), 2.95 (3H, s), 3.01-3.51(4H, m), 3.60 (3H, s), 3.70-4.24 (4H, m), 4.33-4.72 (2H, m), 6.61 (1H, d, J = 9.5 Hz), 7.18 (1H, d, J = 8.4 Hz), 7.25 (1H, s), 7.33-7.54 (6H, m), 7.82 (1H, d, J = 9.5 Hz), 7.92-8.08 (2H, m), 8.67-8.82 (2H, m).

▪ Example 43

· Synthesis of
1-ethyl-6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.19 (3H, t, J = 7.0 Hz), 2.18-2.41 (2H, m), 2.94-3.59 (6H, m), 3.96-4.18 (2H, m), 4.25 (2H, q, J = 7.0 Hz), 4.35-4.63 (2H, m), 6.61 (1H, d, J = 9.5 Hz), 7.18 (1H, dd, J = 9.3, 2.8 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.52 (1H, d, J = 9.3 Hz), 7.61-7.76 (1H, m), 7.85 (1H, d, J = 9.5 Hz), 7.85-8.00 (2H, m), 8.09-8.20 (1H, m), 8.67 (1H, dd, J = 5.3, 1.4 Hz), 8.69-8.80 (3H, m).

▪ Example 44

· Synthesis of
1-benzyl-6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.80-2.00 (2H, m), 2.52-2.82 (6H, m), 3.63 (2H, s), 3.78-3.98 (2H, m), 5.54 (2H, s), 6.82 (1H, d, J = 9.5 Hz), 6.84-6.99 (2H, m), 7.05-7.44 (10H, m), 7.67 (1H, d, J = 9.5 Hz), 8.30-8.52 (4H, m).

▪ Example 45

· Synthesis of
N-methyl-N-(2-{[3-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)benzamide dihydrochloride

Benzoyl chloride(0.14ml) was added to a dichloromethane

solution (10ml) of 6-{3-[(2-methylaminoethyl)pyridin-4-ylmethylamino]propoxy}-3,4-dihydro-2H-isoquinolin-1-one trihydrochloride(382mg), and triethylamine(0.56ml) under ice cooling. The mixture was stirred at room temperature overnight. Water was added to the reaction mixture, followed by extrcation using dichloromethane. The organic layer was dried with anhydrous sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol =10:1→4:1). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution(0.28ml) was added to an ethyl acetate solution (10ml) of the residue. The precipitated insoluble matter was separated, washed with ethyl acetate, and dried to give the title compound(242mg) as a white powder.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.04-2.36 (2H, m), 2.78-2.92 (2H, m), 2.95 (3H, s), 3.00-3.46 (6H, m), 3.64-3.94 (2H, m), 3.94-4.21 (2H, m), 4.31-4.61 (2H, m), 6.77 (1H, s), 6.81 (1H, d, J = 8.5 Hz), 7.29-7.59 (6H, m), 7.78 (1H, d, J = 8.5 Hz), 7.91-8.18 (2H, m), 8.78 (2H, d, J = 4.9 Hz).

▪ Example 46

· Synthesis of 2,3-dihydrobenzofuran-7-carboxylic acid methyl-(2-{[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)amide dihydrochloride

PS-Carbodiimide resin(1.3g) and 1-hydroxy benzotriazole (HOBt)(230mg) were added to acetonitrile and THF solution (4ml+6ml) of 1-methyl-6-{3-[(2-methylamino ethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one(304mg) and 2,3-dihydrobenzofuran-7-carboxylic acid(164mg). The mixture was stirred at room temperature overnight. After the reaction mixture was filtrated and condensed under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate: methanol =1:0→10:1). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution(0.35ml) was added to an ethyl acetate solution of the residue. The precipitated insoluble matter was separated, washed with ethyl acetate, and dried to give the title compound(324.2mg) as a white powder.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.10-2.44 (2H, m), 2.88-3.45 (6H, m), 2.91 (3H, s), 3.59 (3H, s), 3.70-4.25 (4H, m), 4.31-4.72 (4H, m), 6.58 (1H, d, J = 9.5 Hz), 6.75-6.91 (1H, m), 6.91-7.12 (1H, m), 7.12-7.32 (3H, m), 7.43 (1H, d, J = 9.0 Hz), 7.78 (1H, d, J = 9.5 Hz), 7.98-8.30 (2H, m), 8.69-8.94 (2H, m).

▪ Example 47

· Synthesis of 3-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-7,8-dihydro-6H-5-thia-8-aza-benzocyclohepten-9-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.10-2.41 (2H, m), 3.00-3.60 (10H, m), 3.99-4.19 (2H, m), 4.43-4.84 (2H, m), 6.89-7.01 (2H, m), 7.48 (1H, d, J = 8.6 Hz), 7.98 (1H, dd, J = 8.0, 5.3 Hz), 8.04-8.21 (2H, m), 8.27 (1H, t, J = 6.5 Hz), 8.46 (1H, d, J = 8.0 Hz), 8.81 (1H, d, J = 5.3 Hz), 8.81-8.98 (3H, m).

▪ Example 48

· Synthesis of 1-methyl-3-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 31 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.20-2.42 (2H, m), 3.10-3.33 (2H, m), 3.34-3.60 (4H, m), 3.67 (3H, s), 4.00-4.20 (2H, m), 4.55-4.82 (2H, m), 7.20-7.35 (2H, m), 7.40-7.53 (2H, m), 7.65 (1H, d, J = 7.7Hz), 7.93 - 8.08 (1H, m), 8.18-8.35 (2H, m), 8.53 (1H, d, J = 8.1Hz), 8.82 (1H, d, J = 5.1Hz), 8.90-9.05 (3H, m).

▪ Example 49

· Synthesis of 1-(6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-3,4-dihydro-2H-quinolin-1-yl)ethanone trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.71-1.92 (2H, m), 2.11 (3H, s), 2.01-2.39 (2H, m), 2.58-2.79 (2H, m), 3.00-3.48 (6H, m), 3.51-3.71 (2H, m), 3.89-4.10 (2H, m), 4.50 (2H, s), 6.59-6.79 (2H, m), 7.04-7.56 (1H, m), 7.78 (1H, dd, J = 7.8, 5.3 Hz), 7.94 (2H, d, J = 4.4 Hz), 8.23 (1H, d, J = 7.8 Hz), 8.63-8.82 (4H, m).

▪ Example 50

· Synthesis of 2,3-dihydrobenzofuran-7-carboxylic acid methyl-(2-{[3-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)amide dihydrochloride

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC)(144mg), and 1-hydroxy benzotriazole (HOBt)(115mg) were added to a DMF solution(5ml) of 6-{3-[(2-methylaminoethyl)pyridin-4-ylmethylamino]propoxy}-3,4-dihydro-2H-isoquinolin-1-one trihydrochloride(234mg), and 2,3-dihydrobenzofuran-7-carboxylic acid(123mg). The mixture was stirred at room temperature overnight. Water was added to the reaction mixture, followed by extraction using ethyl acetate. The organic layer was washed with water, and dried with anhydrous sodium sulfate. After condensation under reduced pressure, the residue was purified by NH silica gel column chromatography (ethyl acetate: methanol =1:0→10:1). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution(0.19ml) was added to an ethyl acetate solution of the residue. The precipitated insoluble matter was separated, washed with ethyl acetate, and dried to give the title compound(164.6mg) as a white powder.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.04-2.35 (2H, m), 2.65-3.41 (10H, m), 2.90 (3H, s), 3.69-4.66 (8H, m), 6.65-6.90 (3H, m), 6.90-7.14 (1H, m), 7.27 (1H, d, J = 5.2 Hz), 7.35-7.61 (1H, m), 7.77 (1H, d, J = 8.5 Hz), 7.86-8.19 (2H, m), 8.64-8.90 (2H, m).

▪ Example 51

· Synthesis of 1-methyl-6-(3-{[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}-propoxy)-1H-quinolin-2-one

The synthesis of the title compound was performed in the same

manner as in Example 16 using appropriate starting materials.
$^1$H-NMR ($CDCl_3$) δ ppm: 1.90-2.09 (2H, m), 2.65-2.81 (4H, m), 2.91 (2H, t, J = 6.6 Hz), 3.48 (2H, t, J = 6.6 Hz), 3.62-3.78 (4H, m), 3.70 (3H, s), 4.01 (2H, t, J = 6.1 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.88 (1H, d, J = 2.8 Hz), 7.00-7.48 (7H, m), 7.54 (1H, d, J = 9.5 Hz), 8.02-8.11 (1H, m), 8.39-8.50 (2H, m).

▪ Example 52

· Synthesis of
2-fluoro-N-methyl-N-(2-{[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]pyridin-4-ylmethylamino}ethyl)benzamide tris(phosphate)

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials.
Colorless solid (ethanol)
mp: 190-191°C

▪ Example 53

· Synthesis of
1,3-dimethyl-5-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1,3-dihydrobenzoimidazol-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.06-2.42 (2H, brs), 2.97-3.73(m, 12H), 4.04 (2H, t, J=7.0 Hz), 4.42-4.95 (2H, brs), 6.60 (1H, dd, J=2.0, 8.5 Hz), 6.78 (1H, d, J=2.0 Hz), 7.02 (1H, d, J=8.5 Hz), 8.00 (1H, dd, J=5.6, 7.9 Hz), 8.15-8.40 (2H, brs), 8.51 (1H, d, J=7.9 Hz), 8.83 (1H, d, J=5.6 Hz), 8.92 (3H, m), 12.45 (1H, Brs).

▪ Example 54

· Synthesis of
1,3-dimethyl-5-{3-[(2-pyridin-3-ylethyl)pyridin-3-ylmethylamino]propoxy}-1,3-dihydrobenzoimidazol-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.17-2.43 (2H, brs), 3.09-3.64(m, 12H),

3.95-4.18 (2H, m), 4.49-4.84 (2H, brs), 6.63 (1H, dd, J=2.2 and 8.5 Hz), 6.81 (1H, d, J=2.2 Hz), 7.03 (1H, d, J=8.5 Hz), 7.89 (1H, dd, J=7.9 and 5.6 Hz), 8.01 (1H, dd, J=7.9 and 5.6 Hz), 8.26 (1H, d, J=8.0 Hz), 8.71 (1H, d, J=8.0 Hz), 8.77-8.92 (2H, m), 8.96 (1H, s), 9.16 (1H, s), 12.18 (1H, brs).

▪ Example 55

· Synthesis of 2-[2-({3-[4-(2-oxopyrrolidin-1-yl)phenoxy]propyl}pyridin-4-ylmethylamino)ethyl]-2H-isoquinolin-1-one dihydrochloride

2-(2-{[3-(4-Bromophenoxy)propyl]pyridin-4-ylmethylamino}ethyl)-2H-isoquinolin-1-one(500mg), 2-pyrrolidone(0.228ml), potassium carbonate(415mg), copper iodide (I)(190mg), and N,N'-dimethyl ethylenediamine(0.39ml) were added to toluene(5ml). The mixture was stirred at 100°C for 12 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature. After adding aqueous ammonia, extraction was performed using ethyl acetate. The organic layer was washed with saturated saline, and dried with sodium sulfate. After the organic layer was condensed under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate: methanol =100:0→70:30). The purified product was condensed under reduced pressure. A condensed hydrochloric acid(0.3ml) was added to an ethanol solution of the residue, followed by condensation under reduced pressure. The residue was recrystallized from isopropyl alcohol/water to give the title compound(350mg) as a white powder.
mp: 210 to 214°C (dec.)

▪ Example 56

· Synthesis of N-methyl-N-[4-(3-{[2-(1-oxo-2H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}-propoxy)phenyl]acetamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 55 using appropriate starting materials.
$^1$H-NMR ($CD_3OD$) δ ppm:1.82 (3H, s), 2.35-2.54 (2H, m), 3.21 (3H, s), 3.56-3.73 (2H, m), 3.75-3.90 (2H, m), 4.16 (2H, t, J=5.7 Hz), 4.53-4.75 (2H, m), 5.05 (2H, brs), 6.71-6.92 (2H, m), 6.98 (2H, d, J=8.9 Hz),

7.20 (2H, d, J=8.9 Hz), 7.49 (1H, d, J=7.4 Hz), 7.57 (1H, d, J=8.2 Hz), 7.68 (1H, d, J=7.4 Hz), 7.76 (1H, d, J=8.2 Hz), 8.31 (1H, d, J=8.0 Hz), 8.54 (1H, d, J=6.7 Hz), 8.99 (1H, d, J=6.7 Hz).

▪ Example 57

· Synthesis of 2-[2-({3-[4-(2-oxopiperidin-1-yl)phenoxy]propyl}-pyridin-4-ylmethylamino)ethyl]-2H-isoquinolin-1-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 55 using appropriate starting materials.

$^1$H-NMR ($CD_3OD$) δ ppm:1.94 -2.11 (4H, m), 2.22-2.42 (2H, m), 2.56-2.77 (2H, m), 3.59 (2H, t, J=7.3 Hz), 3.64-3.77 (2H, m), 3.78-3.92 (2H, m), 4.08 (2H, t, J=5.5 Hz), 4.67 (2H, brs), 5.04 (2H, brs), 6.80 (1H, d, J=7.4 Hz), 6.90 (2H, d, J=8.9 Hz), 7.24 (2H, d, J=8.9 Hz), 7.51 (1H, d, J=7.4 Hz), 7.55-7.63 (1H, m), 7.68 (1H, d, J=7.5 Hz), 7.72-7.84 (1H, m), 8.32 (1H, d, J=7.8 Hz), 8.49 (2H, d, J=6.7 Hz), 8.88 (2H, d, J=6.7 Hz).

▪ Example 58

· Synthesis of 2-[2-({3-[4-(2-oxo-2H-pyridin-1-yl)phenoxy]propyl}-pyridin-4-ylmethylamino)ethyl]-2H-isoquinolin-1-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 55 using appropriate starting materials.

$^1$H-NMR ($CD_3OD$) δ ppm: 2.25-2.54 (2H, m), 3.50-3.73 (2H, m), 3.76-3.93 (2H, m), 4.16 (2H, t, J=5.6 Hz), 4.67 (2H, brs), 4.84-5.21 (2H, m), 6.79 (1H, d, J=7.4 Hz), 6.86 (1H, dt, J=1.2 and 6.8 Hz), 6.96 (1H, d, J=8.9 Hz), 7.03 (2H, d, J=8.9 Hz), 7.39 (2H, d, J=8.9 Hz), 7.52 (1H, d, 7.4 Hz), 7.57 (1H, dt, J=1.2 and 8.2 Hz), 7.67 (1H, d, J=7.4 Hz), 7.75 (1H, dt, J=1.2 and 8.2 Hz), 7.82-7.99 (2H, m), 8.32 (1H, d, J=8.1 Hz), 8.53 (1H, d, J=6.6 Hz), 8.94 (1H, d, J=6.6 Hz).

▪ Example 59

· Synthesis of 2-[2-({3-[4-(morpholine-4-carbonyl)phenoxy]propyl}-pyridin-4-ylmethylamino)ethyl]-2H-isoquinolin-1-one dihydrochloride

2-(2-{[3-(4-Bromophenoxy)propyl]pyridin-4-ylmethylamino}ethyl)-2H-isoquinolin-1-one(500mg), hexacarbonyl molybdenum(264mg), trans-di-μ-acetatobis[2-(di-o-tolylphosphino)benzyl]dipalladium (II) (Herrmann's palladacycle)(23mg), sodium carbonate(318mg), and morpholine(0.26ml) were added to THF(5ml). The mixture was heated at 170°C for 10 minutes (microwave reactor). The reaction mixture was cooled to room temperature. Water and ethyl acetate were added thereto, followed by celite filtration. The organic layer was dried with sodium sulfate, and condensed under reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: methanol =1:0→7:3). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution was added to an ethyl acetate solution of the residue. The precipitated insoluble matter was separated, washed with ethyl acetate, and dried to give the title compound(150mg) as a white powder.

$^1$H-NMR ($CD_3OD$) δ ppm: 2.17-2.41 (2H, m), 3.37-3.90 (10H, m), 3.99-4.15 2H, m), 4.50-4.64 (2H, m), 4.67-5.00 (2H, m), 6.81 (1H, d, J=7.4 Hz), 6.88 (2H, d, J=6.2 Hz), 7.38 (2H, d, J=8.5 Hz), 7.45 (1H, d, J=7.4 Hz), 7.60 (1H, t, J=8.2 Hz), 7.71 (1H, d, J=7.4 Hz), 7.79 (1H, t, J=8.2 Hz), 8.32 (1H, d, J=7.9 Hz), 8.38 (2H, brs), 8.83 (2H, brs).

▪ Example 60

· Synthesis of 1,3-dimethyl-6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinazoline-2,4-dione trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.11-2.39 (2H, m), 3.00-5.03 (16H, m), 7.25-7.37 (1H, m), 7.37-7.54 (2H, m), 7.94-8.05 (1H, m), 8.05-8.35 (2H, m), 8.49 (1H, d, J=8.2 Hz), 8.73-8.99 (4H, m), 12.24 (1H, brs).

▪ Example 61

· Synthesis of 2-[2-(pyridin-4-ylmethyl-{3-[4-(pyrrolidine-1-carbonyl)phenoxy]propyl}amino)ethyl]-2H-isoquinolin-1-one dihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 59 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$, 80°C) δ ppm: 1.75-1.89 (4H, m), 1.92-2.08 (2H, m), 2.78-2.97 (2H, m), 2.99-3.16 (2H, m), 3.35-3.58 (4H, m), 3.91-4.00 (2H, m), 4.07-4.17 (2H, m), 4.17-4.30 (2H, m), 6.57 (1H, d, J=7.3 Hz), 6.79 (2H, d, J=8.8 Hz), 7.41 (2H. d, J=8.8 Hz), 7.34-7.54 (2H, m), 7.56-7.79 (4H, m), 8.20 (1H, d, J=8.7 Hz), 8.53 (2H, d, J=6.2 Hz).

▪ Example 62

· Synthesis of

N-tert-butyl-4-(3-{[2-(1-oxo-2H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 59 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$, 80°C) δ ppm: 1.38 (9H, s), 1.92-2.08 (2H, m), 2.83-3.00 (2H, m), 3.04-3.22 (2H, m), 3.96 (2H, d, J=6.2 Hz), 4.10-4.21 (2H, m), 4.21-4.31 (2H, m), 6.59 (1H, d, J=7.3 Hz), 6.77 (2H, d, J=8.8 Hz), 7.23 (1H, brs), 7.42 (1H. d, J=7.3 Hz), 7.49 (1H, m), 7.67 (2H, t, J=7.0 Hz), 7.71 (2H, d, J=8.8 Hz), 7.81 (2H, d, J=6.3), 8.20 (1H, d, J=2.0), 8.56 (2H, d, J=6.3 Hz).

▪ Example 63

· Synthesis of

N-isobutyl-4-(3-{[2-(1-oxo-2H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 59 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$, 80°C) δ ppm: 0.90 (6H, d, J=6.5 Hz), 1.75-1.93 (1H, m), 1.93-2.14 (2H, m), 2.85-3.03 (2H, m), 3.03-3.26 (4H, m), 3.90-4.02 (2H, m), 4.15-4.35 (4H, m), 6.59 (1H, d, J=7.4 Hz), 6.80 (2H, d, J=8.8 Hz), 7.31-7.54 (2H, m), 7.61-7.74 (2H, m), 7.76 (2H. d, J=8.8 Hz), 7.86 (2H, d, J=6.3 Hz), 7.98 (1H, brs), 8.20 (1H, d, J=7.4 Hz), 8.59 (2H, d, J=6.3 Hz).

▪ Example 64

· Synthesis of

N-cyclohexyl-4-(3-{[2-(1-oxo-2H-isoquinolin-2-yl)ethyl]pyridin-4-

ylmethylamino}propoxy)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 59 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$, 80°C) δ ppm: 1.00-1.45 (4H, m), 1.53-1.66 (1H, m), 1.66-1.88 (4H, m), 1.92-2.08 (2H, m), 2.82-3.01 (2H, m), 3.04-3.22 (2H, m), 3.65-3.84 (2H, m), 3.88-4.01 (2H, m), 4.21-4.30 (4H, m), 6.58 (1H, d, J=7.3 Hz), 6.79 (2H, d, J=8.8 Hz), 7.42 (1H, d, J=7.3 Hz), 7.46-7.53(1H, m), 7.57-7.84 (7H, m), 8.20 (1H, d, J=7.3 Hz), 8.56 (2H, d, J=6.4 Hz).

▪ Example 65

1-methyl-6-(3-{[2-(1-oxo-2H-isoquinolin-2-yl)ethyl]pyridin-4-ylmethylamino}propoxy)-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

Colorless solid (isopropyl alcohol/water)

mp: 171 to 174 °C

▪ Example 66

· Synthesis of

2-[2-({3-[4-(2-oxo-oxazolidin-3-yl)phenoxy]propyl}pyridin-4-ylmethylamino)ethyl]-2H-isoquinolin-1-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 55 using appropriate starting materials.

$^1$H-NMR (DMSO-$d_6$, 80°C) δ ppm: 1.87-2.08 (2H, m), 2.79-3.00 (2H, m), 3.01-3.21 (2H, m), 3.86-3.96 (2H, m), 3.96-4.05 (2H, m), 4.11-4.33 (4H, m), 4.34-4.49 (2H, m), 6.58 (1H, d, J=7.4 Hz), 6.79 (2H, d, J=9.1 Hz), 7.39 (2H, d, J=9.1 Hz), 7.33-7.44 (1H, m), 7.44-7.55 (2H, m), 7.57-7.73 (2H, m), 7.77-7.87 (2H, m), 8.20 (1H, d, J=8.0 Hz), 8.50-8.64 (2H, m).

▪ Example 67

· Synthesis of

2-[2-({3-[3-(2-oxopyrrolidin-1-yl)phenoxy]propyl}pyridin-4-ylmethylamino)ethyl]-2H-isoquinolin-1-one dihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 55 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$, 80°C) δ ppm: 1.85-2.16 (4H, m), 2.35-2.55 (2H, m), 2.79-3.01 (2H, m), 3.01-3.21 (2H, m), 3.73-4.26 (8H, m), 6.49-6.63 (2H, m), 7.04-7.14 (1H, m), 7.14-7.28 (2H, m), 7.35-7.54 (2H, m), 7.55-7.72 (2H, m), 7.72-7.92 (2H, m), 8.19 (1H, dd, J=8.1 and 0.6 Hz), 8.47-8.66 (2H, m).

▪ Example 68

· Synthesis of
2-[2-(pyridin-4-ylmethyl-{3-[3-(pyrrolidine-1-carbonyl)phenoxy]propyl}amino)ethyl]-2H-isoquinolin-1-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 59 using appropriate starting materials.
$^1$H-NMR (DMSO-$d_6$, 80°C) δ ppm: 1.72-1.90 (4H, m), 1.94-2.14 (2H, m), 2.86-3.05 (2H, m), 3.05-3.22 (2H, m), 3.25-3.50 (4H, m), 3.70-4.36 (6H, m), 6.58 (1H, d, J=7.4 Hz), 6.78-6.95 (2H, m), 7.01 (1H, d, J=7.7 Hz), 7.28 (1H, t, J=7.9 Hz), 7.42(1H, d, J=7.4 Hz), 7.44-7.51 (1H, m), 7.55-7.74 (2H, m), 7.83 (2H, d, J=4.9 Hz), 8.20 (1H, d, J=8.1 Hz), 8.58 (2H, d, J=5.6 Hz).

▪ Example 69

· Synthesis of
5-{2-[[3-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-yloxy)propyl]-(2-methylpyridin-3-ylmethyl)amino]ethyl}-2-methyl-5H-furo[3,2-c]pyridin-4-one

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
$^1$H-NMR ($CDCl_3$) δ ppm: 1.92-1.95 (2H, m), 2.40 (3H, s), 2.48 (3H, s), 2.76 (2H, t, J = 6.9 Hz), 2.86 (2H, t, J = 6.2 Hz), 3.39 (3H, s), 3.40 (3H, s), 3.63 (2H, s), 3.90 (2H, t, J = 6.0 Hz), 4.01 (2H, t, J = 6.2 Hz), 6.31 (1H, dd, J = 7.3, 0.6 Hz), 6.49-6.51 (2H, m), 6.54 (1H, dd, J = 8.5, 2.3 Hz ), 6.83 (1H, d, J = 8.4 Hz), 6.86 (1H, dd, J = 7.7, 4.9 Hz), 6.93 (1H, d, J = 7.3 Hz), 7.42-7.44 (1H, m), 8.28-8.30 (1H, m).

▪ Example 70

· Synthesis of
2-{2-[[3-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-yloxy)propyl]-(2-methylpyridin-3-ylmethyl)amino]ethyl}-2H-isoquinolin-1-one

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
$^1$H NMR ($CDCl_3$), δ ppm: 1.92-1.96 (2H, m), 2.48 (3H, s), 2.76 (2H, t, J = 6.9 Hz), 2.88 (2H, t, J = 6.2 Hz), 3.38 (3H, s), 3.39 (3H, s), 3.63 (2H, s), 3.91 (2H, t, J = 6.0 Hz), 4.01 (2H, t, J = 6.2 Hz), 6.35 (1H, d, J = 7.3 Hz), 6.47 (1H, d, J = 2.3 Hz), 6.50 (1H, dd, J = 8.4, 2.3 Hz ), 6.72 (1H, dd, J = 7.6, 4.8 Hz), 6.81 (1H, d, J = 8.4 Hz), 6.90 (1H, d, J = 7.3 Hz), 7.41 (1H, dd, J = 7.6, 1.5 Hz), 7.44-7.49 (2H, m), 7.60-7.65 (1H, m), 8.20-8.22 (1H, m), 8.34-8.36 (1H, m).

▪ Example 71

· Synthesis of
1-methyl-6-{2-[(2-pyridin-3-ylethyl)pyridin-3-ylmethylamino]ethoxy}-1H-quinolin-2-one trihydrochloride

A 1N-hydrogen chloride ethanol solution(1.7ml) was added to an ethanol solution (10ml) of
1-Methyl-6-{2-[(2-pyridin-3-ylethyl)pyridin-3-ylmethylamino]ethoxy}-1H-quinolin-2-one(195mg), which was stirred at room temperature. The reaction mixture was condensed under reduced pressure and ethyl acetate was added to the residue. The precipitated insoluble matter was separated, washed with ethyl acetate, and dried to give the title compound(199mg) as a pale yellow powder.
$^1$H-NMR (DMSO-$d_6$), δ ppm: 3.08-5.02 (10H, m), 3.61 (3H, s), 6.64 (1H, d, J = 9.5 Hz), 7.26-7.38 (2H, m), 7.49 (1H, d, J = 9.3 Hz), 7.75-7.83 (1H, m), 7.86 (1H, d, J = 9.5 Hz), 7.92 (1H, dd, J = 8.0, 5.6 Hz), 8.41 (1H, d, J = 8.0 Hz), 8.42-8.53 (1H, m), 8.73-8.81 (2H, m), 8.87 (1H, s), 8.92-9.05 (1H, m).

▪ Example 72

· Synthesis of
1-methyl-6-{2-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]ethoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 71 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$) δ ppm: 3.02-5.62 (10H, m), 3.61 (3H, s), 6.63 (1H, d, J = 9.5 Hz), 7.21-7.34 (2H, m), 7.47 (1H, d, J = 9.1 Hz), 7.85 (1H, d, J = 9.5 Hz), 7.92-8.01 (1H, m), 8.02-8.21 (2H, m), 8.49 (1H, d, J = 8.0 Hz), 8.77 (1H, d, J = 5.3 Hz), 8.82-8.92 (3H, m).

▪ Example 73

· Synthesis of 1-methyl-6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 71 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.18-2.43 (2H, m), 3.07-3.49 (4H, m), 3.60 (3H, s), 4.05-4.18 (2H, m), 4.50-4.88 (4H, m), 6.62 (1H, d, J = 9.5 Hz), 7.19 (1H, dd, J = 9.1, 2.7 Hz), 7.27 (1H, d, J = 2.7 Hz), 7.47 (1H, d, J = 9.1 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.94-8.05 (1H, m), 8.08-8.36 (2H, m), 8.49 (1H, d, J = 7.6 Hz), 8.82 (1H, d, J = 4.9 Hz), 8.83-8.99 (3H, m).

▪ Example 74

· Synthesis of 1-methyl-6-{3-[(2-pyridin-3-ylethyl)pyridin-4-ylmethylamino]propoxy}-3,4-dihydro-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 71 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.14-2.38 (2H, m), 2.77-4.95 (14H, m), 3.22 (3H, s), 6.73-6.82 (2H, m), 6.99 (1H, d, J = 9.2 Hz), 7.99 (1H, d, J = 5.7 Hz), 8.22-8.34 (2H, m), 8.52 (1H, d, J = 8.1 Hz), 8.81-8.98 (4H, m).

▪ Example 75

· Synthesis of (2-pyridin-3-ylethyl)pyridin-4-ylmethyl-[3-(quinolin-6-yloxy)propyl]amine tetrahydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 71 using appropriate starting materials. $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.22-4.78 (12H, m), 7.51-7.61 (2H, m), 7.73-7.97 (4H, m), 8.15 (1H, d, J = 9.1 Hz), 8.20-8.33 (1H, m), 8.62-8.81 (5H, m), 8.98 (1H, d, J = 4.9 Hz).

Example 76

· Synthesis of 6-{5-[benzo[1,3]dioxol-5-ylmethyl-(2-pyridin-3-ylethyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 1.31-1.50 (2H, m), 1.68-1.93 (4H, m), 2.95-3.12 (2H, m), 3.12-3.40 (4H, m), 3.58 (3H, s), 3.91-4.38 (4H, m), 6.05 (2H, s), 6.59 (1H, d, J = 9.5 Hz), 6.96 (1H, d, J = 8.0 Hz), 7.10 (1H, dd, J = 8.0, 1.5 Hz), 7.23 (1H, dd, J = 9.1, 2.9 Hz), 7.27 (1H, d, J = 2.9 Hz), 7.30 (1H, d, J = 1.5 Hz), 7.44 (1H, d, J = 9.1 Hz), 7.78-7.87 (2H, m), 8.26 (1H, d, J = 8.0 Hz), 8.73 (1H, d, J = 5.4 Hz), 8.79 (1H, s).

Example 77

· Synthesis of 6-{5-[benzofuran-2-ylmethyl-(2-pyridin-3-ylethyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 1.40-1.59 (2H, m), 1.68-1.83 (2H, m), 1.83-2.00 (2H, m), 3.04-3.24 (2H, m), 3.24-3.50 (4H, m), 3.58 (3H, s), 3.92-4.11 (2H, m), 4.70 (2H, s), 6.59 (1H, d, J = 9.5 Hz), 7.19-7.41 (5H, m), 7.44 (1H, d, J = 9.2 Hz), 7.60 (1H, d, J = 8.4 Hz), 7.70 (1H, d, J = 7.3 Hz), 7.82 (1H, d, J = 9.5 Hz), 7.96 (1H, dd, J = 8.0, 5.2 Hz), 8.46 (1H, d, J = 8.0 Hz), 8.79 (1H, d, J = 5.2 Hz), 8.90 (1H, s).

Example 78

· Synthesis of 6-{5-[benzo[b]thiophen-3-ylmethyl-(2-pyridin-3-ylethyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.30-1.49 (2H, m), 1.60-1.98 (4H, m), 3.08-3.28 (2H, m), 3.28-3.51 (4H, m), 3.58 (3H, s), 3.90-4.08 (2H, m), 4.72 (2H, s), 6.59 (1H, d, J = 9.5 Hz), 7.20 (1H, dd, J = 9.1, 2.8 Hz), 7.26 (1H, d, J = 2.8 Hz), 7.39-7.52 (3H, m), 7.82 (1H, d, J = 9.5 Hz), 7.90 (1H, dd, J = 7.9, 5.4 Hz), 8.06 (1H, d, J = 8.7 Hz), 8.14 (1H, d, J = 7.3 Hz), 8.30-8.40 (2H, m), 8.76 (1H, d, J = 5.4 Hz), 8.85 (1H, s).

Example 79

· Synthesis of
1-methyl-6-{5-[N-(2-pyridin-3-ylethyl)-N-(pyridin-2-ylmethyl)amino]pentyloxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.39-1.55 (2H, m), 1.69-1.82 (2H, m), 1.69-2.01 (2H, m), 3.11-3.31 (2H, m), 3.39-3.57 (4H, m), 3.60 (3H, s), 3.96-4.11 (2H, m), 4.67 (2H, s), 6.61 (1H, d, J = 9.5 Hz), 7.25 (1H, dd, J = 9.2, 2.8 Hz), 7.31 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.59 (1H, dd, J = 6.8, 5.4 Hz), 7.86 (1H, d, J = 9.5 Hz), 7.94 (1H, d, J = 7.8 Hz), 8.02-8.12 (2H, m), 8.60 (1H, d, J = 8.1 Hz), 8.73 (1H, d, J = 4.7 Hz), 8.87 (1H, d, J = 5.4 Hz), 8.87 (1H, s).

Example 80

· Synthesis of
1-methyl-6-{5-[N-(2-pyridin-3-ylethyl)-N-(pyridin-3-ylmethyl)amino]pentyloxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.40-1.58 (2H, m), 1.71-1.88 (2H, m), 1.88-2.09 (2H, m), 3.08-3.32 (2H, m), 3.32-3.56 (4H, m), 3.60 (3H, s), 3.96-4.10 (2H, m), 4.79 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.26 (1H, dd, J = 9.2, 2.8 Hz), 7.33 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.87 (1H, d, J = 9.5 Hz), 8.08 (1H, dd, J = 8.1, 5.7 Hz), 8.16 (1H, dd, J = 8.1, 5.8 Hz), 8.65 (1H, d, J = 8.1 Hz), 8.87 (1H, d, J = 5.7 Hz), 9.02 (1H, d, J = 5.8 Hz), 9.04 (1H, s), 9.08 (1H, d, J = 8.1 Hz), 9.39

(1H, s).

Example 81

· Synthesis of
N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride

Triethylamine (0.35 ml) was added to a dichloromethane solution (5 ml) of 1-methyl-6-[5-(2-pyridin-3-ylethylamino)pentyloxy]-1H-quinolin-2-one (219 mg) and ice-cooled. Benzenesulfonyl chloride (0.096 ml) was added to the resulting mixture, and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with dichloromethane was performed. The organic layer was washed with water and a saturated sodium chloride aqueous solution, in this order, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate). The purified product was concentrated under reduced pressure. A 1N-hydrogen chloride ethanol solution (0.16 ml) was added to the solution of the residue in ethanol, and stirred for 30 minutes at room temperature. The precipitated insoluble matter was collected by filtration, washed with ethyl acetate, and dried to give the title compound (68 mg) as a yellow powder.
1H-NMR (DMSO-D6) δ ppm: 1.19-1.39 (2H, m), 1.39-1.55 (2H, m), 1.55-1.78 (2H, m), 2.92-3.20 (4H, m), 3.31-3.50 (2H, m), 3.58 (3H, s), 3.86-4.07 (2H, m), 6.59 (1H, d, J = 9.5 Hz), 7.21 (1H, dd, J = 9.2, 2.8 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.44 (1H, d, J = 9.2 Hz), 7.51-7.71 (3H, m), 7.71-7.89 (3H, m), 7.99 (1H, dd, J = 8.0, 5.7 Hz), 8.49 (1H, d, J = 8.0 Hz), 8.79 (1H, d, J = 5.7 Hz), 8.87 (1H, s).

Example 82

· Synthesis of
N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-2-nitro-N-(2-pyridin-3-ylethyl)benzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 2.00-2.19 (2H, m), 2.92 (2H, t, J = 7.6 Hz),

3.50-3.66 (4H, m), 3.71 (3H, s), 4.01 (2H, t, J = 5.8 Hz), 6.72 (1H, d, J = 9.5 Hz), 6.93 (1H, d, J = 2.8 Hz), 7.13 (1H, dd, J = 9.2, 2.8 Hz), 7.19 (1H, dd, J = 7.8, 5.4 Hz), 7.29 (1H, d, J = 9.2 Hz), 7.50-7.64 (5H, m), 7.96-8.02 (1H, m), 8.42 (1H, d, J = 1.7 Hz), 8.46 (1H, dd, J = 4.8, 1.7 Hz).

Example 83

· Synthesis of N-[4-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)butyl]-2-nitro-N-(2-pyridin-3-ylethyl)benzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.70-1.89 (4H, m), 2.89 (2H, t, J = 7.5 Hz), 3.40-3.60 (4H, m), 3.68 (3H, s), 4.01 (2H, t, J = 5.1 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.98 (1H, d, J = 2.8 Hz), 7.13-7.22 (2H, m), 7.29 (1H, d, J = 9.2 Hz), 7.49-7.72 (5H, m), 7.95-8.01 (1H, m), 8.40 (1H, d, J = 1.7 Hz), 8.44 (1H, dd, J = 4.9, 1.7 Hz).

Example 84

· Synthesis of 1-methyl-6-{3-[N-(2-methylbenzyl)-N-(2-pyridin-3-ylethyl)amino]propoxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.20-2.45 (2H, m), 2.48 (3H, s), 3.60 (3H, s), 3.10-4.65 (10H, m), 6.63 (1H, d, J = 9.5 Hz), 7.20 (1H, dd, J = 9.2, 2.8 Hz), 7.24-7.41 (4H, m), 7.48 (1H, d, J = 9.2 Hz), 7.73 (1H, d, J = 7.0 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.96 (1H, dd, J = 7.8, 5.5 Hz), 8.43 (1H, d, J = 7.8 Hz), 8.80 (1H, d, J = 5.5 Hz), 8.90 (1H, s).

Example 85

· Synthesis of 1-methyl-6-{4-[N-(2-methylbenzyl)-N-(2-pyridin-3-ylethyl)amino]butoxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.61-1.86 (2H, m), 1.86-2.14 (2H, m), 2.48 (3H, s), 3.10-3.33 (2H, m), 3.33-3.58 (4H, m), 3.60 (3H, s), 3.90-4.80 (4H, m), 6.61 (1H, d, J = 9.5 Hz), 7.18-7.37 (5H, m), 7.47 (1H, d, J = 9.2 Hz), 7.75 (1H, d, J = 7.4 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.05 (1H, dd, J = 8.0, 5.5 Hz), 8.56 (1H, d, J = 8.0 Hz), 8.85 (1H, d, J = 5.5 Hz), 8.98 (1H, s).

Example 86

· Synthesis of
1-methyl-6-{3-[N-(3-phenylpropyl)-N-(2-pyridin-3-ylethyl)amino]propoxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.91-2.12 (2H, m), 2.12-2.31 (2H, m), 2.59-2.78 (2H, m), 3.58 (3H, s), 3.05-4.39 (10H, m), 6.60 (1H, d, J = 9.5 Hz), 7.13-7.34 (7H, m), 7.45 (1H, d, J = 9.2 Hz), 7.82 (1H, d, J = 9.5 Hz), 7.98 (1H, dd, J = 7.9, 5.5 Hz), 8.51 (1H, d, J = 7.9 Hz), 8.80 (1H, d, J = 5.5 Hz), 8.92 (1H, s).

Example 87

· Synthesis of
1-methyl-6-{4-[N-(3-phenylpropyl)-N-(2-pyridin-3-ylethyl)amino]butoxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.71-2.15 (6H, m), 2.55-2.75 (2H, m), 3.57 (3H, s), 3.00-4.34 (10H, m), 6.59 (1H, d, J = 9.5 Hz), 7.14-7.32 (7H, m), 7.44 (1H, d, J = 9.2 Hz), 7.81 (1H, d, J = 9.5 Hz), 7.99 (1H, dd, J = 7.9, 5.5 Hz), 8.53 (1H, d, J = 7.9 Hz), 8.81 (1H, d, J = 5.5 Hz), 8.93 (1H, s).

Example 88

· Synthesis of
1-methyl-6-{5-[N-((E)-3-phenylallyl)-N-(2-pyridin-3-ylethyl)amino]pentyloxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.40-1.60 (2H, m), 1.71-2.00 (4H, m), 3.59 (3H, s), 2.97-4.20 (10H, m), 6.51 (1H, dt, J = 15.9, 7.0 Hz), 6.61 (1H, d, J = 9.5 Hz), 6.95 (1H, d, J = 15.9 Hz), 7.20-7.54 (8H, m), 7.83 (1H, d, J = 9.5 Hz), 8.00 (1H, dd, J = 8.0, 5.5 Hz), 8.53 (1H, d, J = 8.0 Hz), 8.82 (1H, d, J = 5.5 Hz), 8.96 (1H, s).

Example 89

· Synthesis of
N-methyl-4-{[N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)amino]methyl}benzamide dihydrochloride

Diethyl phosphorocyanidate (39.1 mg) was added to a DMF solution (1 ml) of
4-{[N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)amino]methyl}benzoic acid (0.10 g), methylamine hydrochloride (27 mg), and triethylamine (0.07 ml), and the mixture was stirred at room temperature overnight. Ice water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was washed with water and a saturated sodium chloride aqueous solution, in this order, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=10:1). The purified product was concentrated under reduced pressure. A 1N-hydrogen chloride ethanol solution (0.16 ml) was added to the solution of the residue in ethanol, and stirred for 30 minutes at room temperature. The precipitated insoluble matter was collected by filtration, washed with ethyl acetate, and dried to give the title compound (81.3 mg) as a white powder.
1H-NMR (CDCl3) δ ppm: 1.40-1.89 (6H, m), 2.54 (2H, t, J = 6.2 Hz), 2.71-2.76 (4H, m), 3.03 (3H, d, J = 4.9 Hz), 3.66 (2H, s), 3.73 (3H, s), 3.98 (2H, t, J = 6.4 Hz), 6.22-6.31 (1H, m), 6.74 (1H, d, J = 9.5 Hz), 7.01 (1H, d, J = 2.8 Hz), 7.16-7.20 (2H, m), 7.28-7.33 (3H, m), 7.42-7.68 (4H, m), 8.41-7.46 (2H, m).

Example 90

· Synthesis of
N-ethyl-4-{[N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)amino]methyl}benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 89 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.11 (3H, t, J = 7.2 Hz), 1.34-1.50 (2H, m), 1.70-1.96 (4H, m), 3.60 (3H, s), 3.00-4.60 (12H, m), 6.62 (1H, d, J = 9.5 Hz), 7.24 (1H, dd, J = 9.2, 2.8 Hz), 7.30 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.78 (2H, d, J = 8.2 Hz), 7.85 (1H, d, J = 9.5 Hz), 7.86-7.96 (3H, m), 8.31 (1H, d, J = 8.0 Hz), 8.55-8.64 (1H, m), 8.76 (1H, d, J = 5.2 Hz), 8.80-8.85 (1H, m).

Example 91

· Synthesis of
N,N-dimethyl-4-{[[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl](2-pyridin-3-ylethyl)amino]methyl}benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 89 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.35-1.51 (2H, m), 1.68-1.92 (4H, m), 2.89 (3H, s), 3.00 (3H, s), 3.60 (3H, s), 3.04-4.59 (10H, m), 6.62 (1H, d, J = 9.5 Hz), 7.25 (1H, dd, J = 9.2, 2.8 Hz), 7.30 (1H, d, J = 2.8 Hz), 7.43-7.52 (3H, m), 7.75 (2H, d, J = 8.1 Hz), 7.85 (1H, d, J = 9.5 Hz), 7.81-7.89 (1H, m), 8.29 (1H, d, J = 8.0 Hz), 8.75 (1H, d, J = 5.4 Hz), 8.81 (1H, s).

Example 92

· Synthesis of
1-methyl-6-{5-[N-(2-pyridin-3-ylethyl)-N-(quinolin-2-ylmethyl)amino]pentyloxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.41-1.60 (2H, m), 1.69-1.88 (2H, m), 1.88-2.06 (2H, m), 3.60 (3H, s), 3.21-4.26 (8H, m), 4.85 (2H, s), 6.61 (1H, d, J = 9.5 Hz), 7.22 (1H, dd, J = 9.2, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.45 (1H, d, J = 9.2 Hz), 7.65-7.74 (1H, m), 7.79-7.91 (3H, m), 8.02-8.13 (3H, m), 8.53 (1H, d, J = 8.5 Hz), 8.59 (1H, d, J = 8.2 Hz), 8.86 (1H,

d, J = 5.4 Hz), 9.00 (1H, s).

Example 93

· Synthesis of

1-methyl-6-{5-[N-(2-pyridin-3-ylethyl)-N-(quinolin-3-ylmethyl)amino]pentyloxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.42-1.60 (2H, m), 1.72-1.90 (2H, m), 1.90-2.10 (2H, m), 3.60 (3H, s), 3.14-4.36 (8H, m), 4.76 (2H, s), 6.61 (1H, d, J = 9.5 Hz), 7.24 (1H, dd, J = 9.2, 2.8 Hz), 7.30 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.79-7.90 (2H, m), 7.97-8.08 (2H, m), 8.17 (1H, d, J = 7.9 Hz), 8.27 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 8.1 Hz), 8.83 (1H, d, J = 5.3 Hz), 8.99 (1H, s), 9.13 (1H, s), 9.45 (1H, d, J = 1.7 Hz).

Example 94

· Synthesis of

1-methyl-6-{5-[N-(2-pyridin-3-ylethyl)-N-(quinolin-4-ylmethyl)amino]pentyloxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.33-1.52 (2H, m), 1.63-1.82 (2H, m), 1.82-2.04 (2H, m), 3.60 (3H, s), 2.99-4.26 (8H, m), 5.00-5.30 (2H, m), 6.61 (1H, d, J = 9.5 Hz), 7.22 (1H, dd, J = 9.2, 2.7 Hz), 7.28 (1H, d, J = 2.7 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.87-7.96 (1H, m), 7.96-8.12 (2H, m), 8.37 (1H, d, J = 8.5 Hz), 8.42-8.66 (3H, m), 8.83 (1H, d, J = 5.5 Hz), 8.94 (1H, s), 9.25 (1H, d, J = 5.1 Hz).

Example 95

· Synthesis of

1-methyl-6-{5-[N-(naphthalen-2-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]pentyloxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.31-1.56 (2H, m), 1.67-1.82 (2H, m), 1.82-2.05

(2H, m), 3.05-3.25 (2H, m), 3.60 (3H, s), 3.36-4.20 (6H, m), 4.49-4.75 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.22 (1H, dd, J = 9.2, 2.7 Hz), 7.28 (1H, d, J = 2.7 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.53-7.65 (2H, m), 7.81-8.08 (6H, m), 8.24 (1H, s), 8.55 (1H, d, J = 8.2 Hz), 8.83 (1H, d, J = 5.4 Hz), 8.98 (1H, s).

Example 96

· Synthesis of 1-methyl-6-{5-[N-(pyridin-2-yl)-N-(2-pyridin-3-ylethyl)amino]pentyloxy}-1H-quinolin-2-one trihydrochloride

1-methyl-6-[5-(2-pyridin-3-ylethylamino)pentyloxy]-1H-quinolin-2-one(182mg), 2-bromopyridine(0.060ml), palladium acetate (II)(11.2mg), xantphos (32mg), and sodium t-butoxide(68mg) were added to toluene(2ml). The mixture was heated at 80°C for 10 hours under nitrogen atmosphere. The reaction liquid was cooled to room temperature. Water was added to the reaction mixture, followed by extraction with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. The filtrate was condensed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate). The purified product was condensed under reduced pressure. A 1N-hydrogen chloride in ethanol solution(0.58ml) was added to a ethanol solution (5ml) of the residue, and the liquid was stirred at room temperature, and concentrated under reduced pressure. Ethanol and diethyl ether were added to the residue. The precipitated insoluble matter was separated, washed with diethyl ether, and dried to give the title compound(72mg) as a yellow powder. 1H-NMR (DMSO-D6) δ ppm: 1.42-1.91 (6H, m), 3.60 (3H, s), 3.09-4.36 (8H, m), 6.62 (1H, d, J = 9.5 Hz), 6.98 (1H, t, J = 6.6 Hz), 7.24 (1H, dd, J = 9.2, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.38 (1H, d, J = 9.1 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.85 (1H, d, J = 9.5 Hz), 7.98-8.11 (3H, m), 8.76-8.88 (2H, m), 9.16 (1H, s).

Example 97

· Synthesis of N-[4-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)butyl]-N-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.50-1.76 (4H, m), 3.00-3.15 (2H, m), 3.15-3.29 (2H, m), 3.40-3.55 (2H, m), 3.60 (3H, s), 3.91-4.01 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.23 (1H, dd, J = 9.1, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.1 Hz), 7.54-7.73 (3H, m), 7.77-7.89 (3H, m), 8.02 (1H, dd, J = 8.0, 5.6 Hz), 8.52 (1H, d, J = 8.0 Hz), 8.81 (1H, d, J = 5.6 Hz), 8.90 (1H, s).

Example 98

· Synthesis of
N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)phenylmethanesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.21-1.41 (2H, m), 1.41-1.59 (2H, m), 1.59-1.79 (2H, m), 2.91-3.18 (4H, m), 3.30-3.48 (2H, m), 3.59 (3H, s), 3.90-4.08 (2H, m), 4.44 (2H, s), 6.60 (1H, d, J = 9.5 Hz), 7.23 (1H, dd, J = 9.1, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.32-7.43 (5H, m), 7.45 (1H, d, J = 9.1 Hz), 7.83 (1H, d, J = 9.5 Hz), 8.01 (1H, dd, J = 8.0, 5.5 Hz), 8.47 (1H, d, J = 8.0 Hz), 8.81 (1H, d, J = 5.5 Hz), 8.87 (1H, s).

Example 99

· Synthesis of
2,4,6-trimethyl-N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.21-1.41 (2H, m), 1.41-1.75 (4H, m), 2.22 (3H, s), 2.37 (6H, s), 2.93-3.08 (2H, m), 3.26-3.38 (2H, m), 3.45-3.59 (2H, m), 3.60 (3H, s), 3.89-4.02 (2H, m), 6.61 (1H, d, J = 9.5 Hz), 6.87 (2H, s), 7.23 (1H, dd, J = 9.1, 2.8 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.1 Hz), 7.79-7.88 (2H, m), 8.32 (1H, d, J = 8.0 Hz), 8.71-8.79 (2H, m).

Example 100

· Synthesis of
N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)biphenyl-4-sulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.25-1.45 (2H, m), 1.45-1.63 (2H, m), 1.62-1.81 (2H, m), 3.00-3.18 (2H, m), 3.18-3.30 (2H, m), 3.41-3.57 (2H, m), 3.58 (3H, s), 3.90-4.10 (2H, m), 6.60 (1H, d, J = 9.5 Hz), 7.21 (1H, dd, J = 9.1, 2.8 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.41-7.51 (4H, m), 7.69-7.72(2H, m), 7.81 (1H, d, J = 9.5 Hz), 7.85-7.90 (4H, m), 8.00-8.05 (1H, m), 8.53 (1H, d, J = 5.5 Hz), 8.82 (1H, d, J = 5.5 Hz), 8.92 (1H, s).

Example 101

· Synthesis of
6-[3-[N,N-bis(pyridin-3-ylmethyl)amino]propoxy]-1-methyl-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.05-2.36 (2H, m), 2.84-3.19 (2H, m), 3.60 (3H, s), 3.94-4.12 (2H, m), 4.40-4.71 (4H, m), 6.62 (1H, d, J = 9.5 Hz), 7.16 (1H, dd, J = 9.2, 2.6 Hz), 7.24 (1H, d, J = 2.6 Hz), 7.45 (1H, d, J = 9.2 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.00 (2H, dd, J = 7.7, 5.4 Hz), 8.77 (2H, d, J = 7.7 Hz), 8.90 (2H, dd, J = 5.4 Hz), 9.14 (2H, s).

Example 102

· Synthesis of
N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)benzamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.21-1.44 (2H, m), 1.51-1.75 (4H, m), 2.98-3.19 (2H, m), 3.19-3.40 (2H, m), 3.59 (3H, s), 3.59-3.78 (2H, m), 3.89-4.08 (2H, m), 6.58 (1H, d, J = 9.5 Hz), 7.14-7.28 (4H, m), 7.33-7.47 (4H,

m), 7.79 (1H, d, J = 9.5 Hz), 7.87-7.99 (1H, m), 8.25-8.45 (1H, m), 8.74 (1H, d, J = 5.4 Hz), 8.69-8.85 (1H, m).

Example 103

· Synthesis of 2-methyl-N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)benzamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.21-1.49 (2H, m), 1.49-1.80 (4H, m), 2.13 (3H, s), 2.89-3.77 (6H, m), 3.58 (3H, s), 3.86-4.10 (2H, m), 6.55 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 7.4 Hz), 7.10-7.28 (5H, m), 7.35-7.43 (1H, m), 7.59-7.73 (1H, m), 7.74 (1H, d, J = 9.5 Hz), 7.89-8.23 (1H, m), 8.46-8.69 (1H, m), 8.59 (1H, d, J = 5.9 Hz).

Example 104

· Synthesis of N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)-nicotinamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.28-1.48 (2H, m), 1.52-1.79 (4H, m), 2.78-3.00 (2H, m), 3.22-3.51 (2H, m), 3.58 (3H, s), 3.51-3.67 (2H, m), 3.91-4.06 (2H, m), 6.55 (1H, d, J = 9.5 Hz), 7.15-7.28 (3H, m), 7.33-7.42 (2H, m), 7.47-7.55 (1H, m), 7.55-7.63 (1H, m), 7.74 (1H, d, J = 9.5 Hz), 8.32-8.44 (3H, m), 8.57 (1H, dd, J = 4.8, 1.7 Hz).

Example 105

· Synthesis of 1-methyl-6-{5-[N-(2-pyridin-3-ylethyl)-N-(thiophen-2-ylmethyl)amino]pentyloxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.38-1.56 (2H, m), 1.68-2.00 (4H, m), 3.00-3.19 (2H, m), 3.27-3.49 (4H, m), 3.60 (3H, s), 3.92-4.10 (2H, m), 4.67 (2H, s), 6.61 (1H, d, J = 9.5 Hz), 7.14 (1H, dd, J = 5.1, 3.5 Hz), 7.25

(1H, dd, J = 9.1, 2.8 Hz), 7.31 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.1 Hz), 7.49-7.54 (1H, m), 7.72 (1H, dd, J = 5.1, 1.1 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.02 (1H, dd, J = 8.0, 5.6 Hz), 8.50 (1H, d, J = 8.0 Hz), 8.83 (1H, d, J = 5.6 Hz), 8.93 (1H, s).

Example 106

· Synthesis of
1-methyl-6-{5-[N-(2-pyridin-3-ylethyl)-N-(thiophen-3-ylmethyl)amino]pentyloxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.35-1.55 (2H, m), 1.69-2.00 (4H, m), 2.95-3.14 (2H, m), 3.29-3.51 (4H, m), 3.60 (3H, s), 3.97-4.10 (2H, m), 4.43 (2H, s), 6.61 (1H, d, J = 9.5 Hz), 7.25 (1H, dd, J = 9.1, 2.7 Hz), 7.31 (1H, d, J = 2.7 Hz), 7.44-7.52 (2H, m), 7.63-7.69 (1H, m), 7.85 (1H, d, J = 9.5 Hz), 7.95 (1H, d, J = 1.8 Hz), 8.05 (1H, dd, J = 8.1, 5.6 Hz), 8.54 (1H, d, J = 8.1 Hz), 8.85 (1H, d, J = 5.6 Hz), 8.96 (1H, s).

Example 107

· Synthesis of
1-methyl-6-{5-[N-(pyridin-3-yl)-N-(2-pyridin-3-ylethyl)amino]pentyloxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 96 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.40-1.55 (4H, m), 1.66-1.87 (2H, m), 2.98-3.15 (2H, m), 3.32-4.10 (6H, m), 3.59 (3H, s), 6.61 (1H, d, J = 9.5 Hz), 7.22 (1H, dd, J = 9.1, 2.9 Hz), 7.28 (1H, d, J = 2.9 Hz), 7.45 (1H, d, J = 9.1 Hz), 7.77 (1H, dd, J = 9.0, 5.0 Hz), 7.83 (1H, d, J = 9.5 Hz), 7.88-8.09 (3H, m), 8.35 (1H, d, J = 2.6 Hz), 8.61 (1H, d, J = 8.1 Hz), 8.81 (1H, d, J = 5.5 Hz), 9.01 (1H, s).

Example 108

· Synthesis of
N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-3-ylmethyl)benzamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.95-2.10 (2H, m), 3.50 (2H, t, J = 7.2 Hz), 3.58 (3H, s), 3.75-4.18 (2H, m), 4.77 (2H, s), 6.57 (1H, d, J = 9.5 Hz), 7.08 (1H, dd, J = 9.1, 2.7 Hz), 7.12 (1H, d, J = 2.7 Hz), 7.35-7.45 (6H, m), 7.70-7.79 (1H, m), 7.75 (1H, d, J = 9.5 Hz), 8.18 (1H, d, J = 6.9 Hz), 8.67 (1H, d, J = 5.2 Hz), 8.71 (1H, s).

Example 109

· Synthesis of
N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.82-2.00 (2H, m), 3.02-3.15 (2H, m), 3.29-3.39 (2H, m), 3.45-3.54 (2H, m), 3.60 (3H, s), 3.97 (2H, t, J = 6.0 Hz), 6.62 (1H, d, J = 9.5 Hz), 7.19-7.27 (2H, m), 7.47 (1H, d, J = 9.1 Hz), 7.53-7.71 (3H, m), 7.77-7.83 (2H, m), 7.85 (1H, d, J = 9.5 Hz), 8.02 (1H, dd, J = 8.0, 5.5 Hz), 8.53 (1H, d, J = 8.0 Hz), 8.82 (1H, d, J = 5.5 Hz), 8.91 (1H, s).

Example 110

· Synthesis of
1-methyl-6-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-3-ylmethyl)amino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.20-2.45 (2H, m), 3.18-3.35 (2H, m), 3.35-3.53 (4H, m), 3.60 (3H, s), 4.01-4.20 (2H, m), 4.50-4.78 (2H, m), 6.63 (1H, d, J = 9.5 Hz), 7.23 (1H, dd, J = 9.1, 2.8 Hz), 7.30 (1H, d, J = 2.8 Hz), 7.48 (1H, d, J = 9.1 Hz), 7.82-7.93 (1H, m), 7.85 (1H, d, J = 9.5 Hz), 8.01 (1H, dd, J = 8.2, 5.8 Hz), 8.52 (1H, d, J = 8.2 Hz), 8.67 (1H, d, J = 7.0 Hz), 8.80-8.90 (2H, m), 8.95 (1H, s), 9.14 (1H, s).

Example 111

· Synthesis of
N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)ethanesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.15 (3H, t, J = 7.4 Hz), 1.30-1.49 (2H, m), 1.49-1.65 (2H, m), 1.65-1.82 (2H, m), 2.80-2.93 (2H, m), 3.14-3.50 (6H, m), 3.59 (3H, s), 4.02 (2H, t, J = 6.4 Hz), 6.60 (1H, d, J = 9.5 Hz), 7.23 (1H, dd, J = 9.2, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.45 (1H, d, J = 9.2 Hz), 7.39-7.48 (1H, m), 7.83 (1H, d, J = 9.5 Hz), 7.78-7.85 (1H, m), 8.48 (1H, d, J = 5.2 Hz), 8.54 (1H, s).

Example 112

· Synthesis of
N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)cyclohexylmethanesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 0.90-1.89 (17H, m), 2.75-2.95 (4H, m), 3.08-3.49 (4H, m), 3.59 (3H, s), 4.02 (2H, t, J = 6.5 Hz), 6.60 (1H, d, J = 9.5 Hz), 7.24 (1H, dd, J = 9.0, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.42 (1H, dd, J = 7.9, 4.9 Hz), 7.45 (1H, d, J = 9.0 Hz), 7.77-7.82 (1H, m), 7.83 (1H, d, J = 9.5 Hz), 8.48 (1H, dd, J = 4.9, 1.6 Hz), 8.53 (1H, d, J = 1.6 Hz).

Example 113

· Synthesis of
N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-3-ylmethyl)benzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.70-1.91 (2H, m), 3.36 (2H, t, J = 7.7 Hz), 3.60 (3H, s), 3.89 (2H, t, J = 6.0 Hz), 4.60 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.11-7.19 (2H, m), 7.44 (1H, d, J = 8.8 Hz), 7.60-7.77 (3H, m), 7.83 (1H, d, J = 9.5 Hz), 7.92 (2H, d, J = 7.2 Hz), 8.03 (1H, dd, J = 8.0, 5.6 Hz), 8.55 (1H, d, J = 8.0 Hz), 8.83 (1H, d, J = 5.6

Hz), 8.89 (1H, s).

Example 114

· Synthesis of

N-[2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)ethyl]-2-nitro-N-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 2 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 3.10-3.25 (2H, m), 3.60 (3H, s), 3.70-3.90 (4H, m), 4.11-4.28 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.10 (1H, dd, J = 9.2, 2.9 Hz), 7.23 (1H, d, J = 2.9 Hz), 7.44 (1H, d, J = 9.2 Hz), 7.74-7.91 (3H, m), 7.93-8.09 (3H, m), 8.53 (1H, d, J = 8.1 Hz), 8.79 (1H, d, J = 5.5 Hz), 8.93 (1H, s).

Example 115

· Synthesis of

N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(2-pyridin-3-ylethyl)phenylmethanesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.88-2.04 (2H, m), 3.00-3.14 (2H, m), 3.23-3.39 (2H, m), 3.39-3.51 (2H, m), 3.60 (3H, s), 3.89-4.09 (2H, m), 4.47 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.21-7.30 (2H, m), 7.33-7.44 (5H, m), 7.48 (1H, d, J = 9.0 Hz), 7.86 (1H, d, J = 9.5 Hz), 8.02 (1H, dd, J = 8.0, 5.5 Hz), 8.47 (1H, d, J = 8.0 Hz), 8.81 (1H, d, J = 5.5 Hz), 8.87 (1H, s).

Example 116

· Synthesis of

N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-3-ylmethyl)phenylmethanesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.71-1.89 (2H, m), 3.24-3.41 (2H, m), 3.59 (3H, s), 3.88 (2H, t, J = 6.0 Hz), 4.55 (2H, s), 4.67 (2H, s), 6.61 (1H, d, J = 9.5 Hz), 7.09-7.21 (2H, m), 7.34-7.51 (6H, m), 7.83 (1H,

d, J = 9.5 Hz), 7.94-8.06 (1H, m), 8.50 (1H, d, J = 7.9 Hz), 8.81 (1H, d, J = 5.1 Hz), 8.85 (1H, s).

Example 117

· Synthesis of N-[2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)ethyl]-N-(2-pyridin-3-ylethyl)phenylmethanesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 3.01-3.19 (2H, m), 3.40-3.61 (4H, m), 3.60 (3H, s), 4.00-4.15 (2H, m), 4.54 (2H, s), 6.63 (1H, d, J = 9.5 Hz), 7.26 (1H, dd, J = 9.0, 2.8 Hz), 7.30 (1H, d, J = 2.8 Hz), 7.32-7.44 (5H, m), 7.48 (1H, d, J = 9.0 Hz), 7.86 (1H, d, J = 9.5 Hz), 8.02 (1H, dd, J = 8.1, 5.6 Hz), 8.49 (1H, d, J = 8.1 Hz), 8.80 (1H, d, J = 5.6 Hz), 8.87 (1H, s).

Example 118

· Synthesis of 1-methyl-6-{2-[N-(2-methylbenzyl)-N-(2-pyridin-3-ylethyl)amino]ethoxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.48 (3H, s), 3.35-3.84 (6H, m), 3.61 (3H, s), 4.59 (4H, s), 6.64 (1H, d, J = 9.5 Hz), 7.23-7.41 (5H, m), 7.50 (1H, d, J = 9.2 Hz), 7.80 (1H, d, J = 7.4 Hz), 7.86 (1H, d, J = 9.5 Hz), 8.03 (1H, dd, J = 8.0, 5.5 Hz), 8.53 (1H, d, J = 8.0 Hz), 8.85 (1H, d, J = 5.5 Hz), 8.96 (1H, s).

Example 119

· Synthesis of 2-methyl-N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-3-ylmethyl)benzamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.80-2.06 (2H, m), 2.17 (3H, s), 3.26-3.49 (2H, m), 3.59 (3H, s), 3.78-4.00 (2H, m), 4.80-5.01 (2H, m), 6.58 (1H,

d, J = 9.5 Hz), 6.91-7.51 (7H, m), 7.77 (1H, d, J = 9.5 Hz), 7.89-8.11 (1H, m), 8.44-8.65 (1H, m), 8.73-8.90 (1H, m), 8.90-9.03 (1H, m).

Example 120

· Synthesis of 6-[2-[N,N-bis-(pyridin-3-ylmethyl)amino]ethoxy]-1-methyl-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.85-3.15 (2H, m), 3.61 (3H, s), 3.89-4.41 (6H, m), 6.62 (1H, d, J = 9.5 Hz), 7.25-7.34 (2H, m), 7.46 (1H, d, J = 8.8 Hz), 7.83 (1H, d, J = 9.5 Hz), 7.89-8.01 (2H, m), 8.50-8.60 (2H, m), 8.80 (2H, d, J = 5.2 Hz), 8.95 (2H, s).

Example 121

· Synthesis of 6-[2-[N,N-bis-(pyridin-4-ylmethyl)amino]ethoxy]-1-methyl-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.91-3.05 (2H, m), 3.60 (3H, s), 4.14 (4H, s), 4.12-4.29 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.21-7.27 (2H, m), 7.41-7.48 (1H, m), 7.80 (1H, d, J = 9.5 Hz), 8.09 (4H, d, J = 6.5 Hz), 8.84 (4H, d, J = 6.5 Hz).

Example 122

· Synthesis of 6-[3-[N,N-bis-(pyridin-4-ylmethyl)amino]propoxy]-1-methyl-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.96-2.19 (2H, m), 2.70-2.98 (2H, m), 3.60 (3H, s), 3.92-4.10 (2H, m), 4.10-4.43 (4H, m), 6.62 (1H, d, J = 9.5 Hz), 7.08 (1H, dd, J = 9.2, 2.8 Hz), 7.23 (1H, d, J = 2.8 Hz), 7.44 (1H, d, J = 9.2 Hz), 7.86 (1H, d, J = 9.5 Hz), 8.23 (4H, d, J = 6.0 Hz), 8.88 (4H, d, J = 6.0 Hz).

Example 123

· Synthesis of
N-[2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)ethyl]-N-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 3.07-3.21 (2H, m), 3.49-3.69 (4H, m), 3.60 (3H, s), 4.05-4.23 (2H, m), 6.63 (1H, d, J = 9.5 Hz), 7.17 (1H, dd, J = 9.1, 2.9 Hz), 7.25 (1H, d, J = 2.9 Hz), 7.46 (1H, d, J = 9.1 Hz), 7.53-7.72 (3H, m), 7.79-7.89 (3H, m), 8.01 (1H, dd, J = 8.1, 5.6 Hz), 8.53 (1H, d, J = 8.1 Hz), 8.79 (1H, d, J = 5.6 Hz), 8.89 (1H, s).

Example 124

· Synthesis of
2-methyl-N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.82-2,00 (2H, m), 2.12 (3H, s), 2.88-3.50 (6H, m), 3.59 (3H, s), 4.04-4.30 (2H, m), 6.59 (1H, d, J = 9.5 Hz), 6.96-7.33 (6H, m), 7.33-7.50 (1H, m), 7.69-7.97 (2H, m), 8.41-8.52 (1H, m), 8.62-8.78 (1H, m), 8.85-8.93 (1H, m).

Example 125

· Synthesis of
N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-2-nitro-N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}benzenesulfonamide

Sodium iodide (2.93 g) was added to a acetonitrile solution (20 ml) of methanesulfonic acid
2-[[3-(1-methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)propyl]-(2-nitro-benzenesulfonyl)amino]-ethyl ester (4.37 g), and stirred at 60°C for 1 hours. The reaction mixture was cooled to room temperature. 4-(pyridin-3-ylmethoxy)piperidine (1.87 g) and N-ethyl diisopropylamine (4.23 ml) were then added to the reaction mixture

and stirred at 60°C for 5 hours. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. Water was added to the residue, and extraction with dichloromethane was performed. The organic layer was washed with water, and a saturated sodium chloride aqueous solution, in this order. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=1:0→10:1). The purified product was concentrated under reduced pressure to give the title compound (3.48 g) as a yellow solid.

1H-NMR (CDCl3) δ ppm: 1.55-1.74 (2H, m), 1.82-1.99 (2H, m), 2.04-2.29 (4H, m), 2.50-2.61 (2H, m), 2.69-2.82 (2H, m), 3.35-3.52 (3H, m), 3.52-3.68 (2H, m), 3.70 (3H, s), 4.01 (2H, t, J = 5.9 Hz), 4.54 (2H, s), 6.72 (1H, d, J = 9.5 Hz), 6.93 (1H, d, J = 2.8 Hz), 7.12 (1H, dd, J = 9.2, 2.8 Hz), 7.24-7.32 (2H, m), 7.55-7.70 (5H, m), 8.04-8.13 (1H, m), 8.53 (1H, dd, J = 4.8, 1.7 Hz), 8.57 (1H, d, J = 1.7 Hz).

Example 126

· Synthesis of
1-methyl-6-{5-[N-(3-methylbenzyl)-N-(2-pyridin-3-ylethyl)amino]pentyloxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.33-1.51 (2H, m), 1.69-1.99 (4H, m), 2.32 (3H, s), 2.96-3.15 (2H, m), 3.29-3.50 (4H, m), 3.60 (3H, s), 3.95-4.10 (2H, m), 4.26-4.50 (2H, m), 6.61 (1H, d, J = 9.5 Hz), 7.21-7.38 (4H, m), 7.43-7.55 (3H, m), 7.85 (1H, d, J = 9.5 Hz), 8.01 (1H, dd, J = 8.0, 5.6 Hz), 8.48 (1H, d, J = 8.0 Hz), 8.83 (1H, d, J = 5.6 Hz), 8.93 (1H, s).

Example 127

· Synthesis of
1-methyl-6-{5-[N-(4-methylbenzyl)-N-(2-pyridin-3-ylethyl)amino]pentyloxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.35-1.54 (2H, m), 1.66-2.00 (4H, m), 2.32 (3H, s), 2.94-3.11 (2H, m), 3.28-3.51 (4H, m), 3.60 (3H, s), 4.03 (2H, t, J = 6.3 Hz), 4.24-4.50 (2H, m), 6.61 (1H, d, J = 9.5 Hz), 7.19-7.34 (4H, m), 7.46 (1H, d, J = 9.1 Hz), 7.59 (2H, d, J = 8.0 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.04 (1H, dd, J = 8.1, 5.5 Hz), 8.53 (1H, d, J = 8.1 Hz), 8.85 (1H, d, J = 5.5 Hz), 8.95 (1H, s).

Example 128

· Synthesis of

6-{5-[N-(2-methoxybenzyl)-N-(2-pyridin-3-ylethyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.33-1.51 (2H, m), 1.68-1.97 (4H, m), 2.96-3.20 (2H, m), 3.28-3.49 (2H, m), 3.59 (3H, s), 3.85 (3H, s), 3.95-4.09 (2H, m), 4.25-4.50 (2H, m), 6.61 (1H, d, J = 9.5 Hz), 6.98-7.06 (1H, m), 7.09-7.16 (1H, m), 7.24 (1H, dd, J = 9.1, 2.8 Hz), 7.30 (1H, d, J = 2.8 Hz), 7.42-7.50 (2H, m), 7.61-7.69 (1H, m), 7.84 (1H, d, J = 9.5 Hz), 7.97-8.06 (1H, m), 8.42 (1H, d, J = 8.1 Hz), 8.83 (1H, d, J = 5.3 Hz), 8.93 (1H, s).

Example 129

· Synthesis of

6-{5-[N-(2-chlorobenzyl)-N-(2-pyridin-3-ylethyl)amino]pentyloxy}-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.36-1.55 (2H, m), 1.69-2.00 (4H, m), 3.05-3.22 (2H, m), 3.34-3.64 (4H, m), 3.59 (3H, s), 4.03 (2H, t, J = 6.3 Hz), 4.46-4.72 (2H, m), 6.61 (1H, d, J = 9.5 Hz), 7.24 (1H, dd, J = 9.1, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.40-7.55 (3H, m), 7.55-7.64 (1H, m), 7.84 (1H, d, J = 9.5 Hz), 7.96-8.09 (2H, m), 8.49 (1H, d, J = 8.0 Hz), 8.83 (1H, d, J = 5.6 Hz), 8.93 (1H, s).

Example 130

· Synthesis of

1-methyl-6-{3-[N-(2-pyridin-3-ylethyl)-N-(quinolin-4-ylmethyl)amino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (CDCl3) δ ppm: 1.84-2.00 (2H, m), 2.79 (2H, t, J = 6.7 Hz), 2.84-2.96 (4H, m), 3.71 (3H, s), 3.85 (2H, t, J = 6.0 Hz), 4.10 (2H, s), 6.72 (1H, d, J = 9.5 Hz), 6.77 (1H, d, J = 2.8 Hz), 6.98 (1H, dd, J = 9.2, 2.8 Hz), 7.09-7.16 (1H, m), 7.24 (1H, d, J = 9.2 Hz), 7.33 (1H, d, J = 4.4 Hz), 7.35-7.45 (2H, m), 7.57 (1H, d, J = 9.5 Hz), 7.57-7.66 (1H, m), 8.00-8.11 (2H, m), 8.41-8.47 (2H, m), 8.74 (1H, d, J = 4.4 Hz).

Example 131

· Synthesis of

1-methyl-6-{2-[N-(2-pyridin-3-ylethyl)-N-(quinolin-4-ylmethyl)amino]ethoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (CDCl3) δ ppm: 2.72-2.86 (2H, m), 2.86-3.01 (2H, m), 3.01-3.15 (2H, m), 3.69 (3H, s), 4.00-4.14 (2H, m), 4.22 (2H, s), 6.70 (1H, d, J = 9.5 Hz), 6.89 (1H, d, J = 2.8 Hz), 7.03-7.13 (2H, m), 7.26 (1H, d, J = 9.2 Hz), 7.33-7.48 (3H, m), 7.55 (1H, d, J = 9.5 Hz), 7.64-7.72 (1H, m), 8.05-8.15 (2H, m), 8.38 (1H, dd, J = 4.7, 1.8 Hz), 8.43 (1H, d, J = 1.8 Hz), 8.79 (1H, d, J = 4.4 Hz).

Example 132

· Synthesis of

1-methyl-6-[3-N-(pyridin-3-ylmethyl)-N-(quinolin-4-ylmethyl)amino]propoxy]-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.93-2.25 (2H, m), 2.63-3.08 (2H, m), 3.62 (3H, s), 3.85-4.79 (6H, m), 6.61 (1H, d, J = 9.5 Hz), 6.99 (1H, dd, J = 9.2, 2.5 Hz), 7.07 (1H, d, J = 2.5 Hz), 7.40 (1H, d, J = 9.2 Hz), 7.79 (1H, d, J = 9.5 Hz), 7.85-8.08 (3H, m), 8.19-8.36 (1H, m), 8.33 (1H, d, J = 8.4 Hz), 8.41-8.52 (1H, m), 8.58-8.71 (1H, m), 8.83 (1H,

d, J = 5.4 Hz), 8.95-9.07 (1H, m), 9.16 (1H, d, J = 5.4 Hz).

Example 133

· Synthesis of
N-[2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)ethyl]-2-nitro-N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}benzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 2 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.52-1.79 (2H, m), 1.79-1.98 (2H, m), 2.11-2.29 (2H, m), 2.59 (2H, t, J = 6.8 Hz), 2.67-2.81 (2H, m), 3.35-3.49 (1H, m), 3.57 (2H, t, J = 6.8 Hz), 3.70 (3H, s), 3.81 (2H, t, J = 5.5 Hz), 4.21 (2H, t, J = 5.5 Hz), 4.53 (2H, s), 6.72 (1H, d, J = 9.5 Hz), 6.96 (1H, d, J = 2.8 Hz), 7.09 (1H, dd, J = 9.1, 2.8 Hz), 7.25-7.32 (2H, m), 7.58 (1H, d, J = 9.5 Hz), 7.62-7.72 (4H, m), 8.10-8.16 (1H, m), 8.53 (1H, dd, J = 4.8, 1.6 Hz), 8.57 (1H, d, J = 1.6 Hz).

Example 134

· Synthesis of
1-methyl-6-[3-[N-(2-methylbenzyl)-N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}amino]propoxy]-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.70-2.40 (6H, m), 2.45 (3H, s), 2.78-3.95 (11H, m), 3.60 (3H, s), 4.01-4.19 (2H, m), 4.38-4.60 (2H, m), 4.71 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.18 (1H, dd, J = 9.3, 2.8 Hz), 7.26 (1H, d, J = 2.8 Hz), 7.21-7.39 (3H, m), 7.47 (1H, d, J = 9.3 Hz), 7.61-7.78 (1H, m), 7.84 (1H, d, J = 9.5 Hz), 7.85-7.99 (1H, m), 8.30-8.48 (1H, m), 8.80 (1H, d, J = 4.7 Hz), 8.76-8.94 (1H, m).

Example 135

· Synthesis of
1-methyl-6-[3-[N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}-N-(pyridin-3-ylmethyl)amino]propoxy]-1H-quinolin-2-one tetrahydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.79-2.47 (6H, m), 3.01-3.98 (11H, m), 3.60 (3H, s), 3.98-4.21 (2H, m), 4.73 (2H, s), 4.78 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.24 (1H, dd, J = 9.2, 2.9 Hz), 7.32 (1H, d, J = 2.9 Hz), 7.48 (1H, d, J = 9.2 Hz), 7.87 (1H, d, J = 9.5 Hz), 8.04-8.14 (2H, m), 8.55-8.70 (1H, m), 8.87-9.04 (4H, m), 9.30 (1H, s).

Example 136

· Synthesis of
1-methyl-6-[3-[N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}-N-(pyridin-4-ylmethyl)amino]propoxy]-1H-quinolin-2-one tetrahydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.79-2.35 (6H, m), 2.90-3.95 (11H, m), 3.60 (3H, s), 3.95-4.15 (2H, m), 4.40-4.69 (2H, m), 4.76 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.19 (1H, dd, J = 9.1, 2.5 Hz), 7.28 (1H, d, J = 2.5 Hz), 7.46 (1H, d, J = 9.1 Hz), 7.86 (1H, d, J = 9.5 Hz), 7.96-8.12 (1H, m), 8.33 (2H, s), 8.60 (1H, d, J = 7.1 Hz), 8.83-9.01 (4H, m).

Example 137

· Synthesis of
1-methyl-6-[2-(N-(2-methylbenzyl)-N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}amino)ethoxy]-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.75-2.29 (4H, m), 2.46 (3H, s), 2.92-3.95 (11H, m), 3.61 (3H, s), 4.38-4.69 (4H, m), 4.75 (2H, s), 6.63 (1H, d, J = 9.5 Hz), 7.23-7.42 (5H, m), 7.50 (1H, d, J = 9.0 Hz), 7.73-7.85 (1H, m), 7.84 (1H, d, J = 9.5 Hz), 8.06 (1H, dd, J = 7.5, 5.6 Hz), 8.56 (1H, d, J = 7.5 Hz), 8.87 (1H, d, J = 5.6 Hz), 8.94 (1H, s).

Example 138

· Synthesis of

1-methyl-6-[2-(N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}-N-(pyridin-3-ylmethyl)amino)ethoxy]-1H-quinolin-2-one tetrahydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.59-1.74 (2H, m), 1.83-1.99 (2H, m), 2.09-2.25 (2H, m), 2.46-2.60 (2H, m), 2.70-2.85 (4H, m), 2.94-3.06 (2H, m), 3.39-3.50 (1H, m), 3.69 (3H, s), 3.78 (2H, s), 4.08 (2H, t, J = 5.7 Hz), 4.54 (2H, s), 6.70 (1H, d, J = 9.5 Hz), 6.96 (1H, d, J = 2.8 Hz), 7.15 (1H, dd, J = 9.2, 2.8 Hz), 7.20-7.31 (3H, m), 7.58 (1H, d, J = 9.5 Hz), 7.65-7.76 (2H, m), 8.49 (1H, dd, J = 4.8, 1.7 Hz), 8.52 (1H, dd, J = 4.8, 1.7 Hz), 8.57 (1H, d, J = 1.7 Hz), 8.60 (1H, d, J = 1.7 Hz)..

Example 139

· Synthesis of
1-methyl-6-[2-(N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}-N-(pyridin-4-ylmethyl)amino)ethoxy]-1H-quinolin-2-one tetrahydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.55-1.74 (2H, m), 1.82-1.96 (2H, m), 2.08-2.22 (2H, m), 2.45-2.57 (2H, m), 2.65-2.89 (4H, m), 2.98 (2H, t, J = 5.7 Hz), 3.35-3.49 (1H, m), 3.69 (3H, s), 3.79 (2H, s), 4.09 (2H, t, J = 5.7 Hz), 4.54 (2H, s), 6.70 (1H, d, J = 9.5 Hz), 6.95 (1H, d, J = 2.8 Hz), 7.14 (1H, dd, J = 9.2, 2.8 Hz), 7.24-7.36 (4H, m), 7.58 (1H, d, J = 9.5 Hz), 7.68 (1H, dt, J = 7.8, 1.7 Hz), 8.48-8.55 (3H, m), 8.57 (1H, d, J = 1.7 Hz).

Example 140

· Synthesis of
6-[4-(N,N-bis-(pyridin-3-ylmethyl)amino)butoxy]-1-methyl-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.60-1.80 (2H, m), 1.80-2.05 (2H, m), 2.80-3.18

(2H, m), 3.60 (3H, s), 3.69-4.71 (6H, m), 6.62 (1H, d, J = 9.5 Hz), 7.20 (1H, dd, J = 9.1, 2.8 Hz), 7.25 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.1 Hz), 7.79-7.91 (2H, m), 7.85 (1H, d, J = 9.5 Hz), 8.58 (2H, d, J = 8.0 Hz), 8.82 (2H, d, J = 4.4 Hz), 9.03 (2H, s).

Example 141

· Synthesis of
6-[4-(N,N-bis-(pyridin-4-ylmethyl)amino)butoxy]-1-methyl-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.64-1.88 (4H, m), 2.58-2.82 (2H, m), 3.60 (3H, s), 3.88-4.05 (2H, m), 4.19 (4H, s), 6.61 (1H, d, J = 9.5 Hz), 7.16 (1H, dd, J = 9.2, 2.8 Hz), 7.24 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.5 Hz), 8.19 (4H, d, J = 5.6 Hz), 8.90 (4H, d, J = 5.6 Hz).

Example 142

· Synthesis of
1-methyl-6-{4-[N-(2-methylbenzyl)-N-(pyridin-3-ylmethyl)amino]butoxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.62-1.80 (2H, m), 1.92-2.14 (2H, m), 2.33 (3H, s), 3.00-3.25 (2H, m), 3.60 (3H, s), 3.90-4.78 (6H, m), 6.62 (1H, d, J = 9.5 Hz), 7.13-7.35 (5H, m), 7.48 (1H, d, J = 9.2 Hz), 7.63-7.79 (1H, m), 7.85 (1H, d, J = 9.5 Hz), 7.79-7.92 (1H, m), 8.59-8.75 (1H, m), 8.83 (1H, s), 9.02-9.20 (1H, m).

Example 143

· Synthesis of
1-methyl-6-{4-[N-(2-methylbenzyl)-N-(pyridin-4-ylmethyl)amino]butoxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.60-1.80 (2H, m), 1.89-2.15 (2H, m), 2.36

(3H, s), 3.00-3.30 (2H, m), 3.60 (3H, s), 3.82-4.82 (6H, m), 6.62 (1H, d, J = 9.5 Hz), 7.06-7.31 (5H, m), 7.47 (1H, d, J = 9.1 Hz), 7.61-7.79 (1H, m), 7.84 (1H, d, J = 9.5 Hz), 8.11-8.40 (2H, m), 8.86 (2H, d, J = 3.5 Hz).

Example 144

· Synthesis of N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-2-nitro-N-{2-[4-(pyridin-4-ylmethoxy)piperidin-1-yl]ethyl}benzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 125 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 1.55-1.78 (2H, m), 1.78-1.95 (2H, m), 1.95-2.25 (4H, m), 2.55 (2H, t, J = 6.8 Hz), 2.65-2.81 (2H, m), 3.32-3.51 (3H, m), 3.58 (2H, t, J = 7.2 Hz), 3.71 (3H, s), 4.01 (2H, t, J = 5.8 Hz), 4.53 (2H, s), 6.72 (1H, d, J = 9.5 Hz), 6.93 (1H, d, J = 2.8 Hz), 7.12 (1H, dd, J = 9.2, 2.8 Hz), 7.23-7.30 (3H, m), 7.54-7.64 (4H, m), 8.50-8.61 (1H, m), 8.56 (2H, d, J = 6.0 Hz).

Example 145

· Synthesis of N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}benzenesulfonamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 1.51-1.74 (2H, m), 1.74-1.97 (2H, m), 2.05-2.29 (4H, m), 2.52 (2H, t, J = 6.9 Hz), 2.64-2.78 (2H, m), 3.28 (2H, t, J = 7.1 Hz), 3.36-3.50 (3H, m), 3.70 (3H, s), 4.06 (2H, t, J = 6.0 Hz), 4.53 (2H, s), 6.71 (1H, d, J = 9.5 Hz), 6.99 (1H, d, J = 2.8 Hz), 7.16 (1H, dd, J = 9.2, 2.8 Hz), 7.24-7.31 (2H, m), 7.45-7.62 (4H, m), 7.62-7.70 (1H, m), 7.81-7.88 (2H, m), 8.52 (1H, dd, J = 4.8, 1.6 Hz), 8.57 (1H, d, J = 1.6 Hz).

Example 146

· Synthesis of

N-[3-(1-Methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}phenylmethanesulfonamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.55-1.74 (2H, m), 1.85-2.08 (2H, m), 2.08-2.29 (4H, m), 2.46 (2H, t, J = 6.5 Hz), 2.69-2.83 (2H, m), 3.19 (2H, t, J = 7.3 Hz), 3.27 (2H, t, J = 6.5 Hz), 3.38-3.52 (1H, m), 3.69 (3H, s), 3.97 (2H, t, J = 6.1 Hz), 4.39 (2H, s), 4.54 (2H, s), 6.70 (1H, d, J = 9.5 Hz), 6.97 (1H, d, J = 2.8 Hz), 7.14 (1H, dd, J = 9.2, 2.8 Hz), 7.24-7.31 (2H, m), 7.34-7.46 (5H, m), 7.58 (1H, d, J = 9.5 Hz), 7.67 (1H, dt, J = 7.8, 1.8 Hz), 8.52 (1H, dd, J = 4.8, 1.7 Hz), 8.57 (1H, d, J = 1.7 Hz).

Example 147

· Synthesis of
2-methyl-N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethyl}benzamide

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.31-2.81 (10H, m), 2.21 (3H, s), 3.04-4.16 (9H, m), 3.58 (3H, s), 4.40-4.60 (2H, m), 6.57 (1H, d, J = 9.5 Hz), 6.95-7.50 (8H, m), 7.61-7.88 (2H, m), 8.47 (1H, d, J = 3.5 Hz), 8.51 (1H, s).

Example 148

· Synthesis of
N-[3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)propyl]-2-nitro-N-(2-pyridin-3-ylethyl)benzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 2 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 2.00-2.14 (2H, m), 2.55-2.68 (2H, m), 2.80-3.00 (4H, m), 3.33 (3H, s), 3.50-3.65 (4H, m), 3.94 (2H, t, J = 5.8 Hz), 6.66-6.75 (2H, m), 6.87 (1H, d, J = 8.6 Hz), 7.20 (1H, dd, J = 7.8, 4.8 Hz), 7.50-7.68 (4H, m), 7.97-8.02 (1H, m), 8.41 (1H, d, J = 1.6 Hz), 8.46 (1H, dd, J = 4.8, 1.6 Hz).

Example 149

· Synthesis of
1-methyl-6-[3-(N-(2-methylbenzyl)-N-{2-[4-(pyridin-4-ylmethoxy)piperidin-1-yl]ethyl}amino)propoxy]-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.81-2.39 (6H, m), 2.46 (3H, s), 3.01-3.51 (7H, m), 3.60 (3H, s), 3.63-3.91 (4H, m), 4.01-4.18 (2H, m), 4.30-4.52 (2H, m), 4.84 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.18 (1H, dd, J = 9.2, 2.8 Hz), 7.21-7.38 (4H, m), 7.47 (1H, d, J = 9.2 Hz), 7.73 (1H, d, J = 6.0 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.92 (2H, d, J = 5.7 Hz), 8.84 (2H, d, J = 5.7 Hz).

Example 150

· Synthesis of
1-methyl-6-[3-(N-{2-[4-(pyridin-4-ylmethoxy)piperidin-1-yl]ethyl}-N-(pyridin-3-ylmethyl)amino)propoxy]-1H-quinolin-2-one tetrahydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.95-2.33 (6H, m), 3.00-3.90 (13H, m), 3.60 (3H, s), 4.00-4.12 (2H, m), 4.87 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.21 (1H, dd, J = 9.1, 2.9 Hz), 7.28 (1H, d, J = 2.9 Hz), 7.47 (1H, d, J = 9.1 Hz), 7.79-7.89 (1H, m), 7.85 (1H, d, J = 9.5 Hz), 7.96-8.05 (2H, m), 8.56 (1H, d, J = 7.9 Hz), 8.82 (1H, d, J = 4.0 Hz), 8.89 (2H, d, J = 6.6 Hz), 9.05 (1H, s).

Example 151

· Synthesis of
1-methyl-6-[3-(N-{2-[4-(pyridin-4-ylmethoxy)piperidin-1-yl]ethyl}-N-(pyridin-4-ylmethyl)amino)propoxy]-1H-quinolin-2-one tetrahydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.82-2.30 (6H, m), 2.78-3.90 (13H, m), 3.60 (3H, s), 4.00-4.18 (2H, m), 4.87 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.17 (1H, dd, J = 9.2, 2.9 Hz), 7.27 (1H, d, J = 2.9 Hz), 7.45 (1H, d, J = 9.2 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.02 (2H, d, J = 6.4 Hz), 8.15 (2H, d, J = 5.3 Hz), 8.86 (2H, d, J = 5.3 Hz), 8.89 (2H, d, J = 6.4 Hz).

Example 152

· Synthesis of

1-methyl-6-{3-[N-(2-methylbenzyl)-N-(2-pyridin-3-ylethyl)amino]propoxy}-3,4-dihydro-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.14-2.41 (2H, m), 2.41-2.57 (2H, m), 2.70-2.85 (2H, m), 2.47 (3H, s), 3.21 (3H, s), 3.20-3.39 (2H, m), 3.39-3.62 (4H, m), 3.92-4.08 (2H, m), 4.48 (2H, s), 6.75-6.82 (2H, m), 6.99 (1H, d, J = 9.4 Hz), 7.09-7.40 (3H, m), 7.76 (1H, d, J = 7.3 Hz), 8.00 (1H, dd, J = 8.0, 5.3 Hz), 8.50 (1H, d, J = 8.0 Hz), 8.83 (1H, d, J = 5.3 Hz), 8.95 (1H, s).

Example 153

· Synthesis of

1-methyl-6-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-3-ylmethyl)amino]propoxy}-3,4-dihydro-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.19-2.40 (2H, m), 2.40-2.61 (2H, m), 2.83 (2H, t, J = 6.8 Hz), 3.22 (3H, s), 3.19-3.38 (2H, m), 3.38-3.60 (4H, m), 3.98-4.10 (2H, m), 4.67 (2H, s), 6.76-6.86 (2H, m), 7.00 (1H, d, J = 8.8 Hz), 7.92 (1H, dd, J = 8.0, 4.9 Hz), 8.02 (1H, dd, J = 8.1, 5.4 Hz), 8.54 (1H, d, J = 8.1 Hz), 8.74 (1H, d, J = 8.0 Hz), 8.83 (1H, d, J = 5.4 Hz), 8.88 (1H, d, J = 4.9 Hz), 8.96 (1H, s), 9.18 (1H, s).

Example 154

· Synthesis of

N-[3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)propyl]-N

-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 1.76-1.95 (2H, m), 2.41-2.58 (2H, m), 2.83 (2H, t, J = 7.8 Hz), 3.07 (2H, t, J = 7.2 Hz), 3.22 (3H, s), 3.32 (2H, t, J = 7.5 Hz), 3.49 (2H, t, J = 7.2 Hz), 3.87 (2H, t, J = 6.0 Hz), 6.73-6.82 (2H, m), 6.99 (1H, d, J = 8.4 Hz), 7.52-7.87 (5H, m), 7.97 (1H, dd, J = 8.1, 5.5 Hz), 8.46 (1H, d, J = 8.1 Hz), 8.79 (1H, d, J = 5.5 Hz), 8.86 (1H, s).

Example 155

· Synthesis of 3-{[N-[5-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)pentyl]-N-(2-pyridin-3-ylethyl)amino]methyl}benzoic acid methyl ester dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 1.30-1.52 (2H, m), 1.66-2.00 (4H, m), 2.98-3.19 (2H, m), 3.30-3.50 (4H, m), 3.60 (3H, s), 3.87 (3H, s), 3.95-4.11 (2H, m), 4.43-4.66 (2H, m), 6.61 (1H, d, J = 9.5 Hz), 7.24 (1H, dd, J = 9.1, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.1 Hz), 7.61 (1H, dd, J = 7.8, 7.7 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.95-8.05 (2H, m), 8.08 (1H, d, J = 7.8 Hz), 8.27 (1H, s), 8.48 (1H, d, J = 8.1 Hz), 8.83 (1H, d, J = 5.2 Hz), 8.94 (1H, s).

Example 156

· Synthesis of 3-{[N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(2-pyridin-3-ylethyl)amino]methyl}benzoic acid methyl ester dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 2.20-2.45 (2H, m), 3.28 (2H, t, J = 6.9 Hz), 3.37-3.58 (4H, m), 3.60 (3H, s), 3.87 (3H, s), 4.11 (2H, t, J = 6.0 Hz), 4.48-4.72 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.17 (1H, dd, J = 9.2, 2.8 Hz), 7.25 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.62

(1H, dd, J = 8.0, 7.7 Hz), 7.83 (1H, d, J = 9.5 Hz), 8.02 (1H, d, J = 8.0 Hz), 8.05 (1H, dd, J = 8.1, 5.5 Hz), 8.13 (1H, d, J = 7.7 Hz), 8.29 (1H, s), 8.57 (1H, d, J = 8.1 Hz), 8.86 (1H, d, J = 5.5 Hz), 8.99 (1H, s).

Example 157

· Synthesis of 6-{3-[N-(1H-imidazol-4-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]propoxy}-1-methyl-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.21-2.49 (2H, m), 3.20-3.55 (6H, m), 3.60 (3H, s), 4.15 (2H, t, J = 6.0 Hz), 4.64 (2H, s), 6.63 (1H, d, J = 9.5 Hz), 7.26 (1H, dd, J = 9.2, 2.9 Hz), 7.32 (1H, d, J = 2.9 Hz), 7.48 (1H, d, J = 9.2 Hz), 7.86 (1H, d, J = 9.5 Hz), 8.00 (1H, dd, J = 8.0, 5.3 Hz), 8.01 (1H, s), 8.56 (1H, d, J = 8.0 Hz), 8.83 (1H, d, J = 5.3 Hz), 8.99 (1H, s), 9.19 (1H, s).

Example 158

· Synthesis of 1-methyl-6-{3-[N-(3-methylbenzyl)-N-(2-pyridin-3-ylethyl)amino]propoxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.20-2.40 (2H, m), 2.32 (3H, s), 3.12-3.30 (2H, m), 3.30-3.50 (4H, m), 3.60 (3H, s), 4.11 (2H, t, J = 5.9 Hz), 4.29-4.57 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.20 (1H, dd, J = 9.2, 2.9 Hz), 7.23-7.30 (2H, m), 7.34 (1H, dd, J = 7.8, 7.6 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.49-7.56 (2H, m), 7.84 (1H, d, J = 9.5 Hz), 7.99 (1H, dd, J = 8.0, 5.5 Hz), 8.47 (1H, d, J = 8.0 Hz), 8.82 (1H, d, J = 5.5 Hz), 8.92 (1H, s).

Example 159

· Synthesis of N-(3-imidazol-1-ylpropyl)-N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-2-nitrobenzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 2 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.98-2.20 (4H, m), 3.35 (2H, t, J = 6.4 Hz), 3.52 (2H, t, J = 7.1 Hz), 3.71 (3H, s), 3.91-4.08 (4H, m), 6.73 (1H, d, J = 9.5 Hz), 6.88-6.93 (2H, m), 7.05-7.09 (1H, m), 7.10 (1H, dd, J = 9.1, 2.8 Hz), 7.24-7.31 (1H, m), 7.47 (1H, s), 7.55-7.65 (4H, m), 7.93-7.99 (1H, m).

Example 160

· Synthesis of
1-methyl-6-{3-[N-(2-methylbenzyl)-N-(2-pyridin-4-ylethyl)amino]propoxy}-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.14-2.40 (2H, m), 2.48 (3H, s), 3.14-3.40 (2H, m), 3.40-4.30 (6H, m), 3.60 (3H, s), 4.30-4.60 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.06-7.39 (5H, m), 7.47 (1H, d, J = 9.1 Hz), 7.74 (1H, d, J = 8.0 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.98 (2H, d, J = 5.6 Hz), 8.87 (2H, d, J = 5.6 Hz).

Example 161

· Synthesis of
1-methyl-6-{3-[N-(2-pyridin-4-ylethyl)-N-(pyridin-3-ylmethyl)amino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.21-2.42 (2H, m), 3.19-3.39 (2H, m), 3.39-3.60 (4H, m), 3.60 (3H, s), 4.01-4.19 (2H, m), 4.50-4.79 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.23 (1H, d, J = 9.0 Hz), 7.28 (1H, s), 7.48 (1H, d, J = 9.0 Hz), 7.85 (1H, d, J = 9.5 Hz), 7.85-7.95 (1H, m), 8.05 (2H, d, J = 5.5 Hz), 8.69 (1H, d, J = 6.7 Hz), 8.82-8.93 (3H, m), 9.15 (1H, s).

Example 162

· Synthesis of
1-methyl-6-{3-[N-(2-pyridin-4-ylethyl)-N-(pyridin-4-ylmethyl)amin

o]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.16-2.40 (2H, m), 3.13-3.40 (2H, m), 3.40-3.61 (4H, m), 3.60 (3H, s), 4.00-4.18 (2H, m), 4.58-4.88 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.19 (1H, dd, J = 9.2, 2.8 Hz), 7.26 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.05 (2H, d, J = 6.5 Hz), 8.34 (2H, d, J = 5.5 Hz), 8.89 (2H, d, J = 6.5 Hz), 8.95 (2H, d, J = 5.5 Hz).

Example 163

· Synthesis of

N-(2-methylbenzyl)-N-(2-pyridin-3-ylethyl)-N-[3-(quinolin-6-yloxy)propyl]amine trihydrochloride

Sodium iodide (113 mg) was added to to a DMF solution (5 ml) of N-(3-chloropropyl)-N-(2-methylbenzyl)-N-(2-pyridin-3-ylethyl)amine (151 mg), and stirred at 60°C for 1 hours. The reaction mixture was cooled to room temperature. Potassium carbonate (104 mg) and 6-hydroxyquinoline (87 mg) were then added to the reaction mixture and stirred at 60°C for 24 hours. The reaction mixture was added to ice water, and the extraction with ethyl acetate was performed. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=1:1→0:1). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride in ethyl acetate solution(0.014ml) was added to a ethyl acetate solution (1ml) of the residue, and the liquid was stirred at room temperature. The precipitated insoluble product was separated, washed with ether, and dried to give the title compound(7.6 mg) as a brown powder.

1H-NMR (DMSO-D6) δ ppm: 2.28-2.60 (2H, m), 2.49 (3H, s), 3.20-4.11 (6H, m), 4.27 (2H, t, J = 5.6 Hz), 4.36-4.61 (2H, m), 7.22-7.38 (3H, m), 7.63 (1H, dd, J = 9.2, 2.5 Hz), 7.68 (1H, d, J = 2.5 Hz), 7.74

(1H, d, J = 7.9 Hz), 7.87-7.96 (2H, m), 8.26 (1H, d, J = 9.2 Hz), 8.39 (1H, d, J = 7.9 Hz), 8.78 (1H, d, J = 4.3 Hz), 8.84 (1H, d, J = 8.8 Hz), 8.88 (1H, s), 9.05 (1H, d, J = 5.0 Hz).

Example 164

· Synthesis of

N-(2-methylbenzyl)-N-(2-pyridin-3-ylethyl)-N-[3-(pyridin-3-yloxy) propyl]amine trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 163 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.24-2.45 (2H, m), 2.49 (3H, s), 3.18-3.41 (2H, m), 3.41-3.68 (4H, m), 4.32 (2H, t, J = 5.8 Hz), 4.37-4.62 (2H, m), 7.20-7.38 (3H, m), 7.78 (1H, d, J = 7.4 Hz), 7.94 (1H, dd, J = 8.7, 5.4 Hz), 8.04 (1H, dd, J = 8.2, 5.7 Hz), 8.07 (1H, dd, J = 8.7, 2.3 Hz), 8.52 (1H, d, J = 5.4 Hz), 8.55 (1H, d, J = 8.2 Hz), 8.62 (1H, d, J = 2.3 Hz), 8.85 (1H, d, J = 5.5 Hz), 8.97 (1H, s).

Example 165

· Synthesis of
1-methyl-6-{3-[N-(3-methylpyridin-4-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.20-2.46 (2H, m), 2.58 (3H, s), 3.20-3.62 (6H, m), 3.61 (3H, s), 4.05-4.20 (2H, m), 4.76 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.21 (1H, dd, J = 9.2, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.86 (1H, d, J = 9.5 Hz), 8.05 (1H, dd, J = 8.0, 5.6 Hz), 8.60 (1H, d, J = 8.0 Hz), 8.51-8.67 (1H, m), 8.86 (1H, d, J = 5.6 Hz), 8.82-8.92 (2H, m), 9.00 (1H, s).

Example 166

· Synthesis of
1-methyl-6-{3-[N-(3-methylpyridin-4-ylmethyl)-N-(2-pyridin-3-ylethyl)amino]propoxy}-3,4-dihydro-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.04-2.36 (2H, m), 2.52 (3H, s), 2.83 (2H, t, J = 7.9 Hz), 3.10-3.60 (6H, m), 3.22 (3H, s), 3.64-4.85 (6H, m), 6.72-6.81 (2H, m), 6.99 (1H, d, J = 9.2 Hz), 8.00 (1H, dd, J = 8.1, 5.5 Hz), 8.51 (1H, d, J = 8.1 Hz), 8.69-8.84 (3H, m), 8.82 (1H, d, J = 5.5 Hz), 8.92 (1H, s).

Example 167

· Synthesis of

6-{3-[N-(3-imidazol-1-ylpropyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-1-methyl-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.17-2.60 (4H, m), 2.98-3.35 (4H, m), 3.60 (3H, s), 4.09 (2H, t, J = 6.4 Hz), 4.32 (2H, t, J = 7.2 Hz), 4.59 (2H, s), 6.63 (1H, d, J = 9.5 Hz), 7.19 (1H, dd, J = 9.1, 2.8 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.1 Hz), 7.71 (1H, s), 7.78-7.89 (2H, m), 8.15 (2H, d, J = 5.9 Hz), 8.86 (2H, d, J = 5.9 Hz), 9.23 (1H, s).

Example 169

· Synthesis of

N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)-N-[3-(pyridin-3-yloxy)propyl]amine tetrahydrochloride

The synthesis of the title compound was performed in the same manner as in Example 163 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.19-2.40 (2H, m), 3.06-4.10 (6H, m), 4.28 (2H, t, J = 5.8 Hz), 4.74 (2H, s), 7.89 (1H, dd, J = 8.7, 5.2 Hz), 7.96-8.06 (2H, m), 8.17 (2H, d, J = 5.4 Hz), 8.46-8.52 (2H, m), 8.60 (1H, d, J = 2.6 Hz), 8.82 (1H, d, J = 5.6 Hz), 8.88 (2H, d, J = 5.4 Hz), 8.91 (1H, s).

Example 170

· Synthesis of

6-{3-[N-(3-hydroxybenzyl)-N-(2-pyridin-3-ylethyl)amino]propoxy}-1

-methyl-1H-quinolin-2-one hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.20-2.41 (2H, m), 3.18-3.50 (6H, m), 3.60 (3H, s), 4.11 (2H, t, J = 5.9 Hz), 4.24-4.51 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 6.88 (1H, dd, J = 8.3, 1.1 Hz), 7.07-7.15 (2H, m), 7.19-7.25 (2H, m), 7.28 (1H, d, J = 2.9 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.80-7.89 (2H, m), 8.30 (1H, d, J = 8.0 Hz), 8.74 (1H, dd, J = 5.4, 1.4 Hz), 8.83 (1H, d, J = 1.4 Hz).

Example 171

· Synthesis of 6-{3-[N-(3-hydroxymethylbenzyl)-N-(2-pyridin-3-ylethyl)amino]propoxy}-1-methyl-1H-quinolin-2-one dihydrochloride

Sodium borohydride (16.5mg) was added to a THF solution (4ml) of 3-{[N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(2-pyridin-3-ylethyl)amino]methyl}benzoic acid methyl ester (192mg). Methanol (1ml) was added to the mixture and stirred for 1.5 hour while heated under reflux. The reaction liquid was cooled to room temperature. Water was added to the reaction mixture, followed by extraction with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. The filtrate was condensed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate: methanol=10:1→4:1). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride in ethyl acetate solution(0.082ml) was added to a ethyl acetate solution (1ml) of the residue, and the liquid was stirred at room temperature. The precipitated insoluble matter was separated, washed with ether, and dried to give the title compound(53.4 mg) as a white powder.

1H-NMR (DMSO-D6) δ ppm: 2.20-2.41 (2H, m), 3.14-3.47 (6H, m), 3.60 (3H, s), 4.11 (2H, t, J = 5.9 Hz), 4.30-4.60 (2H, m), 4.53 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.21 (1H, dd, J = 9.2, 2.9 Hz), 7.28 (1H, d, J = 2.9 Hz), 7.38-7.45 (2H, m), 7.47 (1H, d, J = 9.2 Hz), 7.56-7.66 (2H, m), 7.71 (1H, dd, J = 8.0, 5.2 Hz), 7.84 (1H, d, J = 9.5 Hz),

8.13 (1H, d, J = 8.0 Hz), 8.67 (1H, dd, J = 5.2, 1.5 Hz), 8.73 (1H, d, J = 1.5 Hz).

Example 172

· Synthesis of N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-2-nitro-N-(2-piperidin-1-ylethyl)benzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 125 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 1.33-1.50 (2H, m), 1.50-1.61 (4H, m), 2.08-2.19 (2H, m), 2.30-2.46 (4H, m), 2.52 (2H, t, J = 6.9 Hz), 3.50 (2H, t, J = 6.9 Hz), 3.59 (2H, t, J = 7.0 Hz), 3.70 (3H, s), 4.02 (2H, t, J = 5.9 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.94 (1H, d, J = 2.8 Hz), 7.12 (1H, dd, J = 9.2, 2.8 Hz), 7.28 (1H, d, J = 9.2 Hz), 7.55-7.66 (4H, m), 8.06-8.14 (1H, m).

Example 173

· Synthesis of N-(2-diethylaminoethyl)-N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-2-nitrobenzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 125 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 0.99 (6H, t, J = 7.1 Hz), 2.00-2.19 (2H, m), 2.53 (4H, q, J = 7.1 Hz), 2.65 (2H, t, J = 7.1 Hz), 3.44 (2H, t, J = 7.1 Hz), 3.60 (2H, t, J = 7.0 Hz), 3.69 (3H, s), 4.02 (2H, t, J = 5.9 Hz), 6.70 (1H, d, J = 9.5 Hz), 6.94 (1H, d, J = 2.8 Hz), 7.12 (1H, dd, J = 9.2, 2.8 Hz), 7.27 (1H, d, J = 9.2 Hz), 7.54-7.66 (4H, m), 8.02-8.09 (1H, m).

Example 174

· Synthesis of N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-[2-(4-methylpiperazin-1-yl)ethyl]-2-nitrobenzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 125 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 2.01-2.19 (2H, m), 2.47 (3H, s), 2.28-2.56 (8H,

m), 2.55 (2H, t, J = 6.8 Hz), 3.48 (2H, t, J = 6.8 Hz), 3.58 (2H, t, J = 7.1 Hz), 3.69 (3H, s), 4.02 (2H, t, J = 5.9 Hz), 6.69 (1H, d, J = 9.5 Hz), 6.93 (1H, d, J = 2.7 Hz), 7.11 (1H, dd, J = 9.2, 2.7 Hz), 7.27 (1H, d, J = 9.2 Hz), 7.54-7.66 (4H, m), 8.04-8.12 (1H, m).

Example 175

· Synthesis of
1-methyl-6-{3-[N-(2-piperidin-1-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.67-2.26 (8H, m), 2.71-3.60 (10H, m), 3.60 (3H, s), 3.98-4.14 (2H, m), 4.19-5.00 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.17 (1H, dd, J = 9.2, 2.8 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.13 (2H, d, J = 5.4 Hz), 8.86 (2H, d, J = 5.4 Hz).

Example 176

· Synthesis of
6-{3-[N-(2-diethylaminoethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-1-methyl-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.19 (6H, t, J = 7.2 Hz), 1.90-2.10 (2H, m), 2.58-2.82 (2H, m), 2.90-3.30 (4H, m), 3.10 (4H, q, J = 7.2 Hz), 3.60 (3H, s), 3.79-4.14 (4H, m), 6.62 (1H, d, J = 9.5 Hz), 7.16 (1H, dd, J = 9.2, 2.9 Hz), 7.26 (1H, d, J = 2.9 Hz), 7.45 (1H, d, J = 9.2 Hz), 7.67 (2H, d, J = 5.8 Hz), 7.84 (1H, d, J = 9.5 Hz), 8.62 (2H, d, J = 5.8 Hz).

Example 177

· Synthesis of
1-methyl-6-(3-{N-[2-(4-methylpiperazin-1-yl)ethyl]N-(pyridin-4-ylmethyl)amino}propoxy)-1H-quinolin-2-one tetrahydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.01-2.21 (2H, m), 2.79 (3H, s), 2.87-3.02 (2H, m), 3.11-3.42 (8H, m), 3.42-3.70 (4H, m), 3.60 (3H, s), 4.00-4.14 (2H, m), 4.31 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.17 (1H, dd, J = 9.3, 2.8 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.3 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.14 (2H, d, J = 6.3 Hz), 8.83 (2H, d, J = 6.3 Hz).

Example 178

· Synthesis of
1-methyl-5-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-3,4-dihydro-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.10-2.40 (2H, m), 2.40-2.68 (4H, m), 2.95-4.82 (10H, m), 3.23 (3H, s), 6.66-6.77 (2H, m), 7.21 (1H, dd, J = 8.3, 8.2 Hz), 7.91 (1H, dd, J = 8.0, 5.5 Hz), 7.97-8.08 (2H, m), 8.38 (1H, d, J = 8.0 Hz), 8.73-8.82 (3H, m), 8.85 (1H, s).

Example 179

· Synthesis of
1-methyl-7-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-3,4-dihydro-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 4 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.08-2.36 (2H, m), 2.78 (2H, t, J = 7.9 Hz), 2.97-4.81 (12H, m), 3.22 (3H, s), 6.50-6.58 (2H, m), 7.11 (1H, d, J = 8.9 Hz), 7.88 (1H, dd, J = 7.9, 5.4 Hz), 7.92-8.04 (2H, m), 8.35 (1H, d, J = 7.9 Hz), 8.72-8.86 (4H, m).

Example 180

· Synthesis of
N-(4-{3-[N'-(2-pyridin-3-ylethyl)-N'-(pyridin-4-ylmethyl)amino]propoxy}phenyl)acetamide trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 31 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.01 (3H, s), 2.13-2.40 (2H, m), 3.08-3.52

(6H, m), 3.90-4.10 (2H, m), 4.70 (2H, s), 6.83 (2H, d, J = 9.0 Hz), 7.49 (2H, d, J = 9.0 Hz), 8.01 (1H, dd, J = 8.1, 2.6 Hz), 8.24-8.34 (2H, m), 8.52 (1H, d, J = 8.1 Hz), 8.83 (1H, d, J = 2.6 Hz), 8.89-8.98 (3H, m).

Example 181

· Synthesis of N-[4-(1,7-naphthyridin-2-yloxy)butyl]-N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amine dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.70-2.06 (4H, m), 2.99-3.20 (2H, m), 3.20-3.43 (4H, m), 4.33-4.71 (4H, m), 7.29 (1H, d, J = 9.0 Hz), 7.64-7.72 (1H, m), 7.89 (2H, d, J = 5.8 Hz), 7.94 (1H, d, J = 5.5 Hz), 8.10 (1H, d, J = 8.0 Hz), 8.36 (1H, d, J = 9.0 Hz), 8.51 (1H, d, J = 5.5 Hz), 8.63 (1H, d, J = 5.1 Hz), 8.68 (2H, d, J = 5.8 Hz), 8.70 (1H, s), 9.16 (1H, s).

Example 182

· Synthesis of 7-{4-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]butoxy}-3,4-dihydro-1H-1,8-naphthyridin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.59-1.80 (2H, m), 1.80-2.04 (2H, m), 2.39-2.58 (2H, m), 2.78 (2H, t, J = 8.0 Hz), 2.95-3.20 (2H, m), 3.20-3.45 (4H, m), 4.16 (2H, t, J = 6.1 Hz), 4.51 (2H, s), 6.33 (1H, d, J = 8.0 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.80 (1H, dd, J = 7.9, 5.0 Hz), 7.96 (2H, d, J = 5.8 Hz), 8.24 (1H, d, J = 7.9 Hz), 8.71 (1H, d, J = 5.0 Hz), 8.75 (2H, d, J = 5.8 Hz), 8.78 (1H, s), 10.24 (1H, s).

Example 183

· Synthesis of N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzamide dihydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.21-2.42 (2H, m), 3.14-3.45 (4H, m), 3.60 (3H, s), 3.58-4.20 (4H, m), 4.58-4.75 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.18 (1H, d, J = 9.4 Hz), 7.24 (1H, s), 7.41-7.59 (4H, m), 7.82 (1H, d, J = 9.5 Hz), 7.85-7.94 (2H, m), 8.04 (2H, d, J = 5.5 Hz), 8.80 (2H, d, J = 5.5 Hz), 8.93 (1H, s).

Example 184

· Synthesis of
N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)isobutyramide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 0.98 (6H, d, J = 6.9 Hz), 1.94-2.20 (2H, m), 2.29-2.41 (1H, m), 2.59-3.09 (4H, m), 3.09-3.54 (4H, m), 3.60 (3H, s), 3.92-4.19 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.18 (1H, dd, J = 9.2, 2.8 Hz), 7.25 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.56 (2H, d, J = 4.2 Hz), 7.83 (1H, d, J = 9.5 Hz), 7.92 (1H, s), 8.57 (2H, d, J = 4.2 Hz).

Example 185

· Synthesis of
N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)nicotinamide trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.16-2.43 (2H, m), 3.20-3.51 (4H, m), 3.60 (3H, s), 3.69-3.94 (2H, m), 3.94-4.21 (2H, m), 4.76 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.18 (1H, dd, J = 9.0, 2.7 Hz), 7.25 (1H, d, J = 2.7 Hz), 7.46 (1H, d, J = 9.0 Hz), 7.77-7.89 (2H, m), 8.31 (2H, d, J = 5.5 Hz), 8.65 (1H, d, J = 8.0 Hz), 8.83-8.98 (3H, m), 9.25 (1H, s), 9.56 (1H, s).

Example 186

· Synthesis of
{N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyri

din-4-ylmethyl)carbamoyloxy}acetic acid ethyl ester

Potassium carbonate (1.66g) was added to to a DMF solution (50ml) of 1-methyl-6-{3-[(pyridin-4-ylmethyl)amino]propoxy}-1H-quinolin-2-one (1.5g). The mixture was cooled to 0°C, and ethyl bromoacetate (1.16ml) was added to the mixture and stirred at room temperature overnight. The reaction mixture was added to ice water, and extraction with ethyl acetate was performed. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=20:1→10:1). The purified product was condensed under reduced pressure. The residue was recrystallized from ether, and dried to give the title compound(0.55g) as a white powder.

1H-NMR (CDCl3) δ ppm: 1.29 (3H, t, J = 7.2 Hz), 2.00-2.19 (2H, m), 3.53 (2H, t, J = 5.9 Hz), 3.71 (3H, s), 3.95-4.11 (2H, m), 4.23 (2H, q, J = 7.2 Hz), 4.46-4.59 (2H, m), 4.63 (2H, s), 6.72 (1H, d, J = 9.5 Hz), 6.99 (1H, s), 7.10-7.35 (4H, m), 7.59 (1H, d, J = 9.5 Hz), 8.58 (2H, s).

Example 187

· Synthesis of {N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-4-ylmethyl)amino}acetic acid ethyl ester

Potassium carbonate (1.66g) and ethyl bromoacetate (1.16ml) were added to to a DMF solution (50ml) of 1-methyl-6-{3-[(pyridin-4-ylmethyl)amino]propoxy}-1H-quinolin-2-one (1.5g), and stirred at room temperature overnight. The reaction mixture was added to ice water, and extraction with ethyl acetate was performed. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=100:0→85:15). The purified product was condensed under reduced pressure to give the title compound (1.28g) as a orange oil.

1H-NMR (CDCl3) δ ppm: 1.27 (3H, t, J = 7.1 Hz), 1.89-2.04 (2H, m),

2.86 (2H, t, J = 6.8 Hz), 3.38 (2H, s), 3.71 (3H, s), 3.84 (2H, s), 4.07 (2H, t, J = 6.2 Hz), 4.17 (2H, q, J = 7.1 Hz), 6.72 (1H, d, J = 9.5 Hz), 6.96 (1H, d, J = 2.8 Hz), 7.11 (1H, dd, J = 9.2, 2.8 Hz), 7.25-7.35 (3H, m), 7.59 (1H, d, J = 9.5 Hz), 8.48 (2H, d, J = 6.0 Hz).

Example 188

· Synthesis of
2-methyl-N-(2-{N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-4-ylmethyl)amino}ethyl)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.19-2.40 (2H, m), 2.33 (3H, s), 3.07-3.45 (4H, m), 3.60 (3H, s), 3.63-3.84 (2H, m), 4.12 (2H, t, J = 5.9 Hz), 4.58 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.16-7.29 (4H, m), 7.29-7.41 (2H, m), 7.46 (1H, d, J = 9.2 Hz), 7.82 (1H, d, J = 9.5 Hz), 7.99 (2H, d, J = 6.0 Hz), 8.57 (1H, s), 8.78 (2H, d, J = 6.0 Hz).

Example 189

· Synthesis of
N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.81-1.98 (2H, m), 2.51-2.66 (4H, m), 2.98-3.10 (2H, m), 3.50 (2H, s), 3.72 (3H, s), 4.01 (2H, t, J = 5.9 Hz), 5.03 (1H, t, J = 5.4 Hz), 6.73 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 2.8 Hz), 7.10-7.18 (3H, m), 7.30 (1H, d, J = 9.2 Hz), 7.42-7.47 (2H, m), 7.48-7.55 (1H, m), 7.62 (1H, d, J = 9.5 Hz), 7.74-7.94 (2H, m), 8.47 (2H, d, J = 5.9 Hz).

Example 190

· Synthesis of
N-ethyl-2-{N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-4-ylmethyl)amino}acetamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.00 (3H, t, J = 7.2 Hz), 2.09-2.40 (2H, m), 3.00-3.17 (2H, m), 3.17-3.35 (2H, m), 3.60 (3H, s), 3.73 (2H, s), 4.10 (2H, t, J = 5.9 Hz), 4.53 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.20 (1H, dd, J = 9.2, 2.8 Hz), 7.28 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.5 Hz), 8.07 (2H, d, J = 6.2 Hz), 8.53 (1H, s), 8.85 (2H, d, J = 6.2 Hz).

Example 191

· Synthesis of

N,N-diethyl-2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}acetamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 0.97 (3H, t, J = 7.1 Hz), 1.06 (3H, t, J = 7.1 Hz), 2.17-2.35 (2H, m), 3.12-3.30 (4H, m), 3.30-3.45 (2H, m), 3.60 (3H, s), 4.11 (2H, t, J = 5.8 Hz), 4.29 (2H, s), 4.61 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.22 (1H, dd, J = 9.2, 2.8 Hz), 7.30 (1H, d, J = 2.8 Hz), 7.48 (1H, d, J = 9.2 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.06 (2H, d, J = 5.9 Hz), 8.87 (2H, d, J = 5.9 Hz).

Example 192

· Synthesis of

2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}-N-phenylacetamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.07-2.32 (2H, m), 3.12-3.40 (2H, m), 3.61 (3H, s), 3.90-4.08 (2H, m), 4.08-4.21 (2H, m), 4.60 (2H, s), 6.61 (1H, d, J = 9.5 Hz), 7.09 (1H, t, J = 7.4 Hz), 7.18 (1H, dd, J = 9.2, 2.8 Hz), 7.26 (1H, d, J = 2.8 Hz), 7.28-7.37 (2H, m), 7.44 (1H, d, J = 9.2 Hz), 7.59 (2H, d, J = 7.7 Hz), 7.82 (1H, d, J = 9.5 Hz), 8.16 (2H, d, J = 6.2 Hz), 8.88 (2H, d, J = 6.2 Hz).

Example 193

· Synthesis of

N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N

'-(pyridin-4-ylmethyl)amino}ethyl)phenylmethanesulfonamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.02-2.38 (2H, m), 2.79-3.56 (6H, m), 3.60 (3H, s), 3.96-4.16 (2H, m), 4.40-4.72 (2H, m), 4.41 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.20 (1H, dd, J = 9.1, 2.7 Hz), 7.27 (1H, d, J = 2.7 Hz), 7.31-7.41 (5H, m), 7.47 (1H, d, J = 9.1 Hz), 7.83 (1H, d, J = 9.5 Hz), 8.01 (2H, d, J = 5.8 Hz), 8.81 (2H, d, J = 5.8 Hz).

Example 194

· Synthesis of 1-methyl-6-{3-[N-(pyridin-4-ylmethyl)-N-(3-pyridin-3-ylpropyl)amino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.10-2.40 (4H, m), 2.75-2.92 (2H, m), 3.00-3.16 (2H, m), 3.16-3.31 (2H, m), 3.60 (3H, s), 4.10 (2H, t, J = 5.8 Hz), 4.50 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.19 (1H, dd, J = 9.1, 2.8 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.1 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.83-8.09 (3H, m), 8.34 (1H, d, J = 7.9 Hz), 8.64-9.02 (4H, m).

Example 195

· Synthesis of 2-methyl-6-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-2,3-dihydroisoindol-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.19-2.40 (2H, m), 3.07 (3H, s), 3.13-3.33 (2H, m), 3.33-3.53 (4H, m), 4.12 (2H, t, J = 5.8 Hz), 4.39 (2H, s), 4.66 (2H, s), 7.09 (1H, dd, J = 8.2, 2.3 Hz), 7.14 (1H, d, J = 2.3 Hz), 7.48 (1H, d, J = 8.2 Hz), 7.99 (1H, dd, J = 8.1, 5.2 Hz), 8.22 (2H, d, J = 5.0 Hz), 8.50 (1H, d, J = 8.1 Hz), 8.82 (1H, d, J = 5.2 Hz), 8.89 (2H, d, J = 5.0 Hz), 8.92 (1H, s).

Example 196

· Synthesis of
7-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-2H-isoquinolin-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.80-2.04 (2H, m), 2.63-2.86 (6H, m), 3.66 (2H, s), 4.08 (2H, t, J = 6.0 Hz), 6.54 (1H, d, J = 7.1 Hz), 7.07 (1H, d, J = 6.5 Hz), 7.15 (2H, d, J = 5.9 Hz), 7.15-7.24 (2H, m), 7.39-7.46 (1H, m), 7.49 (1H, d, J = 8.7 Hz), 7.77 (1H, d, J = 2.6 Hz), 8.39-8.45 (3H, m), 8.47 (1H, dd, J = 4.8, 1.6 Hz), 10.96 (1H, s).

Example 197

· Synthesis of
2-methyl-7-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-2H-isoquinolin-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.13-2.40 (2H, m), 3.00-3.40 (6H, m), 3.51 (3H, s), 4.13 (2H, t, J = 5.6 Hz), 4.48 (2H, s), 6.58 (1H, d, J = 7.3 Hz), 7.25 (1H, dd, J = 8.7, 2.6 Hz), 7.35 (1H, d, J = 7.3 Hz), 7.56-7.65 (2H, m), 7.75 (1H, dd, J = 7.9, 5.3 Hz), 7.90 (2H, d, J = 5.2 Hz), 8.20 (1H, d, J = 7.9 Hz), 8.68 (1H, d, J = 5.3 Hz), 8.70-8.78 (3H, m).

Example 198

· Synthesis of
3-methyl-6-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-3H-quinazolin-4-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.20-2.43 (2H, m), 3.05-3.60 (6H, m), 3.52 (3H, s), 4.10-4.30 (2H, m), 4.65 (2H, s), 7.40 (1H, dd, J = 8.9, 2.8 Hz), 7.52 (1H, d, J = 2.8 Hz), 7.67 (1H, d, J = 8.9 Hz), 7.99 (1H, dd, J = 8.0, 5.3 Hz), 8.21 (2H, d, J = 5.8 Hz), 8.43 (1H, s), 8.49 (1H, d, J = 8.0 Hz), 8.82 (1H, d, J = 5.3 Hz), 8.89 (2H, d, J = 5.8

Hz), 8.92 (1H, s).

Example 199

· Synthesis of
2-methyl-7-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-3,4-dihydro-2H-isoquinolin-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 2.16-2.39 (2H, m), 2.90 (2H, t, J = 6.6 Hz), 3.02 (3H, s), 3.10-3.46 (6H, m), 3.52 (2H, t, J = 6.6 Hz), 3.97-4.12 (2H, m), 4.59 (2H, s), 6.98 (1H, dd, J = 8.3, 2.7 Hz), 7.21 (1H, d, J = 8.3 Hz), 7.35 (1H, d, J = 2.7 Hz), 7.92 (1H, dd, J = 8.0, 5.5 Hz), 8.07 (2H, d, J = 6.1 Hz), 8.40 (1H, d, J = 8.0 Hz), 8.77 (1H, d, J = 5.5 Hz), 8.81 (2H, d, J = 6.1 Hz), 8.86 (1H, s).

Example 200

· Synthesis of
7-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-3,4-dihydro-2H-isoquinolin-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 2.18-2.41 (2H, m), 2.82 (2H, t, J = 6.6 Hz), 3.12-3.60 (8H, m), 4.00-4.18 (2H, m), 4.72 (2H, s), 7.00 (1H, dd, J = 8.4, 2.7 Hz), 7.23 (1H, d, J = 8.4 Hz), 7.34 (1H, d, J = 2.7 Hz), 7.96 (1H, s), 8.02 (1H, dd, J = 8.0, 5.7 Hz), 8.23-8.38 (2H, m), 8.53 (1H, d, J = 8.0 Hz), 8.83 (1H, d, J = 5.7 Hz), 8.89-8.99 (3H, m).

Example 201

· Synthesis of
2-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}benzoic acid ethyl ester dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 2.05-2.39 (2H, m), 2.91-3.52 (6H, m), 3.97-4.21 (2H, m), 4.17 (2H, q, J = 7.1 Hz), 4.46 (2H, s), 6.99-7.07 (1H, m), 7.11 (1H, d, J = 8.4 Hz), 7.49-7.58 (1H,

m), 7.65 (1H, dd, J = 7.7, 1.7 Hz), 7.71 (1H, dd, J = 7.5, 5.6 Hz), 7.79-7.93 (2H, m), 8.14 (1H, d, J = 7.5 Hz), 8.62-8.76 (4H, m).

Example 202

· Synthesis of 3-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}benzoic acid ethyl ester dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.32 (3H, t, J = 7.1 Hz), 2.10-2.40 (2H, m), 2.94-3.60 (6H, m), 4.00-4.18 (2H, m), 4.32 (2H, q, J = 7.1 Hz), 4.50 (2H, s), 7.11-7.24 (1H, m), 7.40 (1H, s), 7.37-7.49 (1H, m), 7.56 (1H, d, J = 7.7 Hz), 7.81 (1H, dd, J = 7.8, 5.4 Hz), 7.83-8.00 (2H, m), 8.25 (1H, d, J = 7.8 Hz), 8.64-8.84 (4H, m).

Example 203

· Synthesis of 4-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}benzoic acid ethyl ester dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.31 (3H, t, J = 7.1 Hz), 2.12-2.41 (2H, m), 3.02-3.60 (6H, m), 4.00-4.20 (2H, m), 4.28 (2H, q, J = 7.1 Hz), 4.41-4.74 (2H, m), 6.99 (2H, d, J = 8.8 Hz), 7.89 (1H, dd, J = 7.7, 5.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 7.99 (2H, d, J = 5.8 Hz), 8.36 (1H, d, J = 7.7 Hz), 8.76 (1H, d, J = 5.8 Hz), 8.79 (2H, d, J = 5.8 Hz), 8.84 (1H, s).

Example 204

· Synthesis of N-ethyl-2-{3-[N'-(2-pyridin-3-ylethyl)-N'-(pyridin-4-ylmethyl)amino]propoxy}benzamide trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.05 (3H, t, J = 7.2 Hz), 2.20-2.42 (2H, m), 3.08-3.60 (8H, m), 4.07-4.26 (2H, m), 4.52-4.82 (2H, m), 7.02 (1H,

dd, J = 7.6, 7.5 Hz), 7.09 (1H, d, J = 8.2 Hz), 7.39-7.48 (1H, m), 7.59 (1H, dd, J = 7.6, 1.7 Hz), 7.99 (1H, dd, J = 8.0, 5.2 Hz), 8.07 (1H, s), 8.22 (2H, d, J = 5.0 Hz), 8.49 (1H, d, J = 8.0 Hz), 8.82 (1H, d, J = 5.2 Hz), 8.88 (2H, d, J = 5.0 Hz), 8.92 (1H, s).

Example 205

· Synthesis of
N,N-diethyl-2-{3-[N'-(2-pyridin-3-ylethyl)-N'-(pyridin-4-ylmethyl)amino]propoxy}benzamide trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 0.91 (3H, t, J = 7.1 Hz), 1.06 (3H, t, J = 7.1 Hz), 2.01-2.41 (2H, m), 3.01 (4H, q, J = 7.1 Hz), 2.97-3.59 (6H, m), 3.94-4.19 (2H, m), 4.38-4.74 (2H, m), 6.99 (1H, dd, J = 7.4, 7.3 Hz), 7.05 (1H, d, J = 8.3 Hz), 7.12 (1H, dd, J = 7.4, 1.7 Hz), 7.31-7.40 (1H, m), 7.91 (1H, dd, J = 8.0, 5.5 Hz), 8.05 (2H, d, J = 5.9 Hz), 8.37 (1H, d, J = 8.0 Hz), 8.78 (1H, d, J = 5.5 Hz), 8.81 (2H, d, J = 5.9 Hz), 8.84 (1H, s).

Example 206

· Synthesis of
N-ethyl-3-{3-[N'-(2-pyridin-3-ylethyl)-N'-(pyridin-4-ylmethyl)amino]propoxy}benzamide trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.12 (3H, t, J = 7.2 Hz), 2.10-2.38 (2H, m), 3.00-3.41 (8H, m), 3.99-4.20 (2H, m), 4.42 (2H, s), 7.01 (1H, dd, J = 8.0, 2.3 Hz), 7.31-7.49 (3H, m), 7.58 (1H, dd, J = 7.7, 5.1 Hz), 7.79 (2H, d, J = 5.8 Hz), 7.98 (1H, d, J = 7.7 Hz), 8.51 (1H, t, J = 5.2 Hz), 8.59 (1H, dd, J = 5.1, 1.6 Hz), 8.63 (1H, d, J = 1.6 Hz), 8.69 (2H, d, J = 5.8 Hz).

Example 207

· Synthesis of
N,N-diethyl-3-{3-[N'-(2-pyridin-3-ylethyl)-N'-(pyridin-4-ylmethyl)amino]propoxy}benzamide trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 0.90-1.25 (6H, m), 2.09-2.38 (2H, m), 2.92-3.59 (10H, m), 3.98-4.16 (2H, m), 4.52 (2H, s), 6.82 (1H, d, J = 1.7 Hz), 6.89 (1H, d, J = 7.5 Hz), 6.94 (1H, dd, J = 8.2, 1.7 Hz), 7.34 (1H, dd, J = 8.2, 7.5 Hz), 7.85 (1H, dd, J = 8.0, 5.2 Hz), 7.99 (2H, d, J = 5.4 Hz), 8.31 (1H, d, J = 8.0 Hz), 8.74 (1H, dd, J = 5.2, 1.5 Hz), 8.78 (2H, d, J = 5.4 Hz), 8.82 (1H, d, J = 1.5 Hz).

Example 208

· Synthesis of N,N-diethyl-4-{3-[N'-(2-pyridin-3-ylethyl)-N'-(pyridin-4-ylmethyl)amino]propoxy}benzamide trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 1.09 (6H, t, J = 6.8 Hz), 2.12-2.40 (2H, m), 2.95-3.59 (10H, m), 3.95-4.15 (2H, m), 4.56 (2H, s), 6.92 (2H, d, J = 8.6 Hz), 7.30 (2H, d, J = 8.6 Hz), 7.91 (1H, dd, J = 8.0, 5.3 Hz), 8.06 (2H, d, J = 6.0 Hz), 8.38 (1H, d, J = 8.0 Hz), 8.77 (1H, d, J = 5.3 Hz), 8.82 (2H, d, J = 6.0 Hz), 8.86 (1H, s).

Example 209

· Synthesis of 2-methyl-8-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-3,4-dihydro-2H-isoquinolin-1-one

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 1.92-2.10 (2H, m), 2.67-3.00 (6H, m), 2.91 (2H, t, J = 6.4 Hz), 3.09 (3H, s), 3.46 (2H, t, J = 6.4 Hz), 3.69 (2H, s), 4.00 (2H, t, J = 5.9 Hz), 6.75 (1H, d, J = 7.3 Hz), 6.79 (1H, d, J = 8.5 Hz), 7.09-7.19 (3H, m), 7.31 (1H, dd, J = 8.5, 7.3 Hz), 7.44 (1H, d, J = 7.6 Hz), 8.35-8.46 (4H, m).

Example 210

· Synthesis of N,N-dimethyl-2-(4-{3-[N'-(2-pyridin-3-ylethyl)-N'-(pyridin-4-ylme

thyl)amino]propoxy}phenyl)propionamide trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 1.23 (3H, d, J = 6.8 Hz), 2.12-2.35 (2H, m), 2.80 (3H, s), 2.87 (3H, s), 3.00-3.49 (6H, m), 3.90-4.10 (3H, m), 4.56 (2H, s), 6.82 (2H, d, J = 8.6 Hz), 7.16 (2H, d, J = 8.6 Hz), 7.90 (1H, dd, J = 8.0, 5.5 Hz), 8.05 (2H, d, J = 5.5 Hz), 8.37 (1H, d, J = 8.0 Hz), 8.76 (1H, d, J = 5.5 Hz), 8.81 (2H, d, J = 5.5 Hz), 8.85 (1H, s).

Example 211

· Synthesis of 2-methyl-5-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-3,4-dihydro-2H-isoquinolin-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.06-2.40 (2H, m), 2.67 (2H, t, J = 6.7 Hz), 3.00 (3H, s), 3.06-3.42 (6H, m), 3.47 (2H, t, J = 6.7 Hz), 3.92-4.16 (2H, m), 4.16-4.78 (2H, m), 7.08 (1H, d, J = 8.0 Hz), 7.29 (1H, dd, J = 8.2, 8.0 Hz), 7.48 (1H, d, J = 8.2 Hz), 7.68 (1H, dd, J = 7.7, 5.2 Hz), 7.77-7.89 (2H, m), 8.10 (1H, d, J = 7.7 Hz), 8.65 (1H, dd, J = 5.2, 1.3 Hz), 8.66-8.75 (3H, m).

Example 212

· Synthesis of 1,4-dimethyl-6-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.14-2.41 (2H, m), 2.42 (3H, s), 2.96-3.50 (6H, m), 3.58 (3H, s), 4.01-4.22 (2H, m), 4.52 (2H, s), 6.54 (1H, s), 7.16 (1H, d, J = 2.5 Hz), 7.21 (1H, dd, J = 9.2, 2.5 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.82 (1H, dd, J = 7.9, 5.6 Hz), 7.96 (2H, d, J = 4.8 Hz), 8.29 (1H, d, J = 7.9 Hz), 8.72 (1H, d, J = 5.6 Hz), 8.76 (2H, d, J = 4.8 Hz), 8.81 (1H, s).

Example 213

· Synthesis of
1-methyl-6-{3-[N-(2-pyridin-2-ylethyl)-N-(pyridin-3-ylmethyl)amino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.22-2.40 (2H, m), 3.20-3.38 (2H, m), 3.46-3.62 (4H, m), 3.60 (3H, s), 4.11 (2H, t, J = 5.9 Hz), 4.62 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.22 (1H, dd, J = 9.1, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.1 Hz), 7.60-7.69 (1H, m), 7.74 (1H, d, J = 7.9 Hz), 7.81 (1H, dd, J = 7.9, 5.0 Hz), 7.85 (1H, d, J = 9.5 Hz), 8.14-8.23 (1H, m), 8.58 (1H, d, J = 7.9 Hz), 8.69 (1H, d, J = 5.0 Hz), 8.82 (1H, dd, J = 5.2, 1.3 Hz), 9.08 (1H, d, J = 1.3 Hz).

Example 214

· Synthesis of
N-benzyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)acetamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.99 (3H, s), 2.02-2.31 (2H, m), 2.90-3.45 (4H, m), 3.60 (3H, s), 3.50-3.89 (2H, m), 3.98-4.15 (2H, m), 4.25-4.65 (2H, m), 4.60 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.12-7.42 (7H, m), 7.46 (1H, d, J = 9.2 Hz), 7.83 (1H, d, J = 9.5 Hz), 7.87 (2H, d, J = 5.8 Hz), 8.75 (2H, d, J = 5.8 Hz).

Example 215

· Synthesis of
1-methyl-6-[3-[N-(pyridin-4-ylmethyl)-N-(quinolin-6-yl)amino]propoxy]-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.10-2.27 (2H, m), 3.60 (3H, s), 3.87 (2H, t, J = 7.4 Hz), 4.16 (2H, t, J = 5.8 Hz), 5.07 (2H, s), 6.61 (1H, d, J = 9.5 Hz), 7.24-7.32 (3H, m), 7.47 (1H, d, J = 10.1 Hz), 7.69-7.79

(4H, m), 7.81 (1H, d, J = 9.5 Hz), 8.11 (1H, d, J = 9.5 Hz), 8.61 (1H, d, J = 8.4 Hz), 8.75 (2H, d, J = 6.4 Hz), 8.82 (1H, d, J = 5.1 Hz).

Example 216

· Synthesis of 6-(3-{N-[2-(7-bromo-1-oxo-1H-isoquinolin-2-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}propoxy)-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.93-2.38 (2H, m), 2.74-3.54 (6H, m), 3.61 (3H, s), 3.79-4.15 (2H, m), 4.39 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 6.70 (1H, d, J = 7.4 Hz), 6.98-7.25 (2H, m), 7.42 (1H, d, J = 9.2 Hz), 7.60 (1H, d, J = 7.4 Hz), 7.65 (1H, d, J = 8.5 Hz), 7.80 (1H, d, J = 9.5 Hz), 7.87 (1H, dd, J = 8.5, 1.8 Hz), 8.00-8.23 (2H, m), 8.27 (1H, d, J = 1.8 Hz), 8.65-8.98 (2H, m).

Example 217

· Synthesis of N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)phenylmethanesulfonamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.82-2.02 (2H, m), 2.54 (2H, t, J = 6.7 Hz), 2.62 (2H, t, J = 6.7 Hz), 2.67 (3H, s), 2.99 (2H, t, J = 6.7 Hz), 3.58 (2H, s), 3.71 (3H, s), 4.04 (2H, t, J = 6.2 Hz), 4.22 (2H, s), 6.72 (1H, d, J = 9.5 Hz), 7.01 (1H, d, J = 2.8 Hz), 7.11 (1H, dd, J = 9.2, 2.8 Hz), 7.22 (2H, d, J = 5.9 Hz), 7.23-7.40 (6H, m), 7.61 (1H, d, J = 9.5 Hz), 8.46 (2H, d, J = 5.9 Hz).

Example 218

· Synthesis of 2,4,6,N-tetramethyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzenesulfonamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 1.82-2.01 (2H, m), 2.28 (3H, s), 2.56 (6H, s), 2.65 (3H, s), 2.61-2.79 (4H, m), 3.29 (2H, t, J = 7.2 Hz), 3.60 (2H, s), 3.71 (3H, s), 4.04 (2H, t, J = 6.1 Hz), 6.72 (1H, d, J = 9.5 Hz), 6.92 (2H, s), 6.99 (1H, d, J = 2.8 Hz), 7.11 (1H, dd, J = 9.2, 2.8 Hz), 7.19-7.35 (3H, m), 7.60 (1H, d, J = 9.5 Hz), 8.47 (2H, d, J = 5.9 Hz).

Example 219

· Synthesis of N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzenesulfonamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 1.92-2.08 (2H, m), 2.67 (3H, s), 2.61-2.80 (4H, m), 3.12 (2H, t, J = 6.5 Hz), 3.66 (2H, s), 3.71 (3H, s), 4.11 (2H, t, J = 6.2 Hz), 6.72 (1H, d, J = 9.5 Hz), 7.04 (1H, d, J = 2.8 Hz), 7.14 (1H, dd, J = 9.2, 2.8 Hz), 7.24-7.35 (3H, m), 7.43-7.61 (3H, m), 7.63 (1H, d, J = 9.5 Hz), 7.74 (2H, d, J = 6.0 Hz), 8.48 (2H, d, J = 6.0 Hz).

Example 220

· Synthesis of 4-methoxy-N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzenesulfonamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 1.85-2.08 (2H, m), 2.64 (3H, s), 2.60-2.79 (4H, m), 3.09 (2H, t, J = 6.6 Hz), 3.66 (2H, s), 3.71 (3H, s), 3.85 (3H, s), 4.11 (2H, t, J = 6.2 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.94 (2H, d, J = 8.9 Hz), 7.04 (1H, d, J = 2.8 Hz), 7.13 (1H, dd, J = 9.1, 2.8 Hz), 7.20-7.32 (3H, m), 7.56-7.73 (3H, m), 8.47 (2H, d, J = 6.0 Hz).

Example 221

· Synthesis of
2-nitro-N-[3-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 2 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.96-2.20 (2H, m), 2.82-3.04 (4H, m), 3.47-3.69 (6H, m), 3.99 (2H, t, J = 5.8 Hz), 5.97 (1H, s), 6.62 (1H, d, J = 2.4 Hz), 6.74 (1H, dd, J = 8.6, 2.4 Hz), 7.20 (1H, dd, J = 7.8, 4.8 Hz), 7.49-7.64 (4H, m), 7.94-8.01 (2H, m), 8.42 (1H, d, J = 1.7 Hz), 8.46 (1H, dd, J = 7.8, 1.7 Hz).

Example 222

· Synthesis of
6-{3-[N-(2-methylbenzyl)-N-(2-pyridin-3-ylethyl)amino]propoxy}-3,4-dihydro-2H-isoquinolin-1-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.15-2.42 (2H, m), 2.51 (3H, s), 2.86 (2H, t, J = 6.5 Hz), 3.19-3.65 (8H, m), 4.11 (2H, t, J = 6.0 Hz), 4.33-4.62 (2H, m), 6.78-6.91 (2H, m), 7.22-7.40 (3H, m), 7.70-7.82 (3H, m), 8.04 (1H, dd, J = 8.0, 5.3 Hz), 8.54 (1H, d, J = 8.1 Hz), 8.85 (1H, d, J = 5.3 Hz), 8.97 (1H, s).

Example 223

· Synthesis of
6-{3-[N-(2-pyridin-3-ylethyl)-N-(quinolin-4-ylmethyl)amino]propoxy}-3,4-dihydro-2H-isoquinolin-1-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.10-2.45 (2H, m), 2.84 (2H, t, J = 6.4 Hz), 3.10-3.73 (8H, m), 3.95-4.10 (2H, m), 4.91-5.41 (2H, m), 6.70 (1H, s), 6.74 (1H, d, J = 8.4 Hz), 7.64-7.80 (2H, m), 7.86-7.98 (1H, m), 7.98-8.12 (2H, m), 8.38 (1H, d, J = 8.4 Hz), 8.43-8.69 (2H, m), 8.53 (1H, d, J = 8.2 Hz), 8.82 (1H, d, J = 5.2 Hz), 8.94 (1H, s), 9.23 (1H, d, J = 1.7 Hz).

Example 224

· Synthesis of
2-methyl-N-[3-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.82-2.24 (2H, m), 2.08 (3H, s), 2.85 (2H, t, J = 6.1 Hz), 2.90-3.51 (6H, m), 3.36 (2H, t, J = 6.6 Hz), 3.51-4.04 (2H, m), 6.46-7.30 (7H, m), 7.60-8.08 (2H, s), 8.35-9.00 (2H, m).

Example 225

· Synthesis of
N-[3-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)propyl]-N-(2-pyridin-3-ylethyl)benzenesulfonamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 81 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.89-2.09 (2H, m), 2.80-3.04 (4H, m), 3.24-3.45 (4H, m), 3.45-3.60 (2H, m), 3.98 (2H, t, J = 5.9 Hz), 5.92 (1H, s), 6.66 (1H, d, J = 2.4 Hz), 6.82 (1H, dd, J = 8.6, 2.4 Hz), 7.12-7.39 (1H, m), 7.43-7.63 (4H, m), 7.74-7.89 (2H, m), 8.00 (1H, d, J = 8.6 Hz), 8.40 (1H, d, J = 1.7 Hz), 8.46 (1H, dd, J = 7.8, 1.7 Hz).

Example 226

· Synthesis of
4-methoxy-N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.10-2.46 (2H, m), 2.99 (3H, s), 3.08-3.49 (4H, m), 3.60 (3H, s), 3.78 (3H, s), 3.74-3.98 (2H, m), 3.98-4.20 (2H, m), 4.62 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 6.96 (2H, d, J = 8.9 Hz), 7.18 (1H, dd, J = 8.9, 2.6 Hz), 7.25 (1H, d, J = 2.6 Hz), 7.31-7.54 (3H, m), 7.82 (1H, d, J = 9.5 Hz), 8.14 (2H, d, J = 5.7 Hz), 8.85 (2H, d, J = 5.7 Hz).

Example 227

· Synthesis of
thiophene-3-carboxylic acid
methyl-(2-{N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-4-ylmethyl)amino}ethyl)amide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.11-2.38 (2H, m), 3.05 (3H, s), 3.02-3.47 (4H, m), 3.60 (3H, s), 3.47-4.21 (4H, m), 4.56 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.17 (1H, dd, J = 9.1, 2.6 Hz), 7.25 (1H, d, J = 2.6 Hz), 7.20-7.36 (1H, m), 7.46 (1H, d, J = 9.1 Hz), 7.60 (1H, dd, J = 4.9, 2.9 Hz), 7.82 (1H, d, J = 9.5 Hz), 7.80-7.96 (1H, m), 8.03 (2H, d, J = 5.2 Hz), 8.80 (2H, d, J = 5.2 Hz).

Example 228

· Synthesis of
N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)isobutyramide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 0.99 (6H, d, J = 6.7 Hz), 2.11-2.41 (2H, m), 2.75-2.89 (1H, m), 3.05 (3H, s), 3.05-3.41 (4H, m), 3.60 (3H, s), 3.68-3.84 (2H, m), 4.00-4.21 (2H, m), 4.63 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.20 (1H, dd, J = 9.1, 2.6 Hz), 7.27 (1H, d, J = 2.6 Hz), 7.47 (1H, d, J = 9.1 Hz), 7.83 (1H, d, J = 9.5 Hz), 8.19 (2H, d, J = 5.4 Hz), 8.90 (2H, d, J = 5.4 Hz).

Example 229

· Synthesis of
2-methoxy-N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.12-2.40 (2H, m), 2.79 (3H, s), 2.71-3.02 (2H, m), 3.10-3.33 (2H, m), 3.59 (3H, s), 3.76 (3H, s), 3.81-4.25 (4H, m), 4.55 (2H, s), 6.58 (1H, d, J = 9.5 Hz), 6.90-7.27 (5H, m), 7.27-7.50 (2H, m), 7.78 (1H, d, J = 9.5 Hz), 8.12 (2H, d, J = 5.0 Hz), 8.81 (2H, d, J = 5.0 Hz).

Example 230

· Synthesis of
2-fluoro-N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.13-2.41 (2H, m), 2.88 (3H, s), 2.76-3.10 (2H, m), 3.10-3.48 (2H, m), 3.59 (3H, s), 3.80-4.05 (2H, m), 4.05-4.21 (2H, m), 4.62 (2H, s), 6.59 (1H, d, J = 9.5 Hz), 7.08-7.58 (7H, m), 7.79 (1H, d, J = 9.5 Hz), 8.25 (2H, s), 8.86 (2H, s).

Example 231

· Synthesis of
3,N-dimethyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.31 (3H, s), 2.21-2.45 (2H, m), 2.95 (3H, s), 3.12-3.49 (4H, m), 3.60 (3H, s), 3.79-4.21 (4H, m), 4.65 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.11-7.40 (6H, m), 7.46 (1H, d, J = 9.2 Hz), 7.82 (1H, d, J = 9.5 Hz), 8.18 (2H, s), 8.86 (2H, s).

Example 232

· Synthesis of
benzo[1,3]dioxole-5-carboxylic acid
N-methyl-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)amide hydrochloride

The synthesis of the title compound was performed in the same

manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.19-2.46 (2H, m), 2.97 (3H, s), 3.05-3.49 (4H, m), 3.60 (3H, s), 3.71-3.94 (2H, m), 3.94-4.20 (2H, m), 4.66 (2H, s), 6.06 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 6.87-7.12 (3H, m), 7.19 (1H, dd, J = 9.1, 2.7 Hz), 7.25 (1H, d, J = 2.7 Hz), 7.46 (1H, d, J = 9.1 Hz), 7.82 (1H, d, J = 9.5 Hz), 8.21 (2H, d, J = 5.6 Hz), 8.89 (2H, d, J = 5.6 Hz).

Example 233

· Synthesis of
2-(3-methoxyphenyl)-N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)acetamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.09-2.31 (2H, m), 2.78-3.30 (4H, m), 3.03 (3H, s), 3.59 (3H, s), 3.68 (2H, s), 3.72 (3H, s), 3.53-3.89 (2H, m), 3.96-4.19 (2H, m), 4.44 (2H, s), 6.58 (1H, d, J = 9.5 Hz), 6.70-6.90 (3H, m), 7.10-7.29 (3H, m), 7.43 (1H, d, J = 9.0 Hz), 7.78 (1H, d, J = 9.5 Hz), 8.00 (2H, d, J = 5.3 Hz), 8.76 (2H, d, J = 5.3 Hz).

Example 234

· Synthesis of
4,5-dimethylfuran-2-carboxylic acid
N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)amide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.91 (3H, s), 2.23 (3H, s), 2.13-2.42 (2H, m), 3.04-3.46 (4H, m), 3.17 (3H, s), 3.60 (3H, s), 3.81-4.21 (4H, m), 4.68 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 6.89 (1H, s), 7.18 (1H, dd, J = 9.1, 2.8 Hz), 7.25 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.1 Hz), 7.83 (1H, d, J = 9.5 Hz), 8.26 (2H, d, J = 5.1 Hz), 8.92 (2H, d, J = 5.1 Hz).

Example 235

· Synthesis of
2-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-7,8-dihydro-6H-5-thia-8-aza-benzocyclohepten-9-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.10-2.40 (2H, m), 2.93-3.57 (10H, m), 3.95-4.15 (2H, m), 4.61 (2H, s), 6.97 (1H, dd, J = 8.4, 2.7 Hz), 7.03 (1H, d, J = 2.7 Hz), 7.40 (1H, d, J = 8.4 Hz), 7.96 (1H, dd, J = 8.1, 5.4 Hz), 8.11 (2H, s), 8.36 (1H, t, J = 6.7 Hz), 8.44 (1H, d, J = 8.1 Hz), 8.80 (1H, d, J = 5.4 Hz), 8.81-8.96 (3H, m).

Example 236

· Synthesis of
1-ethyl-6-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-3,4-dihydro-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 32 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.10 (3H, t, J = 7.0 Hz), 2.08-2.30 (2H, m), 2.40-2.54 (2H, m), 2.80 (2H, t, J = 7.9 Hz), 3.00-3.45 (6H, m), 3.87 (2H, q, J = 7.0 Hz), 3.94-4.11 (2H, m), 4.49 (2H, s), 6.69-6.80 (2H, m), 7.03 (1H, d, J = 9.0 Hz), 7.79 (1H, dd, J = 8.0, 5.4 Hz), 7.93 (2H, d, J = 4.9 Hz), 8.24 (1H, d, J = 8.0 Hz), 8.70 (1H, d, J = 5.4 Hz), 8.70-8.82 (3H, m).

Example 237

· Synthesis of
1-methyl-6-{2-[N-((E)-3-pyridin-4-ylallyl)-N-(pyridin-3-ylmethyl)amino]ethoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 3.00 (2H, t, J = 5.6 Hz), 3.43 (2H, d, J = 2.1 Hz), 3.70 (3H, s), 3.81 (2H, s), 4.13 (2H, t, J = 5.6 Hz), 6.46-6.55 (1H, m), 6.53 (1H, d, J = 2.1 Hz), 6.72 (1H, d, J = 9.5 Hz), 6.96 (1H, d, J = 2.8 Hz), 7.10-7.35 (5H, m), 7.57 (1H, d, J = 9.5 Hz), 7.73 (1H, d, J = 5.3 Hz), 8.42-8.58 (3H, m), 8.63 (1H, s).

Example 238

· Synthesis of
1-methyl-6-{2-[N-(pyridin-3-ylmethyl)-N-(3-pyridin-3-ylpropyl)amino]ethoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.07-2.31 (2H, m), 2.70-2.95 (2H, m), 3.03-3.25 (2H, m), 3.40-3.69 (2H, m), 3.61 (3H, s), 4.37-4.68 (4H, m), 6.64 (1H, d, J = 9.5 Hz), 7.20-7.42 (2H, m), 7.51 (1H, d, J = 9.2 Hz), 7.58-7.72 (1H, m), 7.78-7.99 (2H, m), 8.30-8.50 (2H, m), 8.68-8.80 (2H, m), 8.85 (1H, s), 8.98 (1H, s).

Example 239

· Synthesis of
1-methyl-6-{2-[N-(pyridin-4-ylmethyl)-N-(3-pyridin-3-ylpropyl)amino]ethoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.01-2.31 (2H, m), 2.69-2.90 (2H, m), 2.90-3.22 (2H, m), 3.22-3.55 (2H, m), 3.61 (3H, s), 4.30-4.66 (4H, m), 6.63 (1H, d, J = 9.5 Hz), 7.26 (1H, dd, J = 9.2, 2.7 Hz), 7.33 (1H, d, J = 2.7 Hz), 7.50 (1H, d, J = 9.2 Hz), 7.76-7.92 (2H, m), 7.98 (2H, d, J = 6.1 Hz), 8.33 (1H, d, J = 7.9 Hz), 8.72 (1H, d, J = 6.5 Hz), 8.73-8.88 (3H, m).

Example 240

· Synthesis of
1-methyl-6-{2-[N-((E)-3-pyridin-3-ylallyl)-N-(pyridin-3-ylmethyl)amino]ethoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 3.47-3.68 (2H, m), 3.60 (3H, s), 3.94-4.12 (2H, m), 4.46-4.70 (2H, m), 4.70 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 6.87-7.08 (2H, m), 7.29-7.54 (3H, m), 7.78-7.94 (3H, m), 8.49 (1H, d, J = 8.0 Hz), 8.66 (1H, d, J = 8.0 Hz), 8.75 (1H, d, J = 5.4 Hz),

8.82 (1H, d, J = 5.4 Hz), 9.01 (1H, s), 9.12 (1H, s).

Example 241

· Synthesis of

1-methyl-6-{2-[N-((E)-3-pyridin-3-ylallyl)-N-(pyridin-4-ylmethyl)amino]ethoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 3.21-3.48 (2H, m), 3.59 (3H, s), 3.70-3.98 (2H, m), 4.28-4.59 (4H, m), 6.62 (1H, d, J = 9.5 Hz), 6.68-6.94 (2H, m), 7.18-7.38 (2H, m), 7.46 (1H, d, J = 9.0 Hz), 7.57-7.71 (1H, m), 7.82 (1H, d, J = 9.5 Hz), 8.02 (2H, d, J = 5.1 Hz), 8.23 (1H, d, J = 7.1 Hz), 8.62 (1H, d, J = 5.1 Hz), 8.66-8.91 (3H, m).

Example 242

· Synthesis of

N-methyl-3-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}-N-phenylpropionamide

Sodium ethoxide (34mg) and 3-chloro-N-methyl-N-phenylpropionamide (148mg) were added to to a ethanol solution (5ml) of 1-methyl-6-{3-[(pyridin-4-ylmethyl)amino]propoxy}-1H-quinolin-2-one (161mg), and stirred at 60°C for 8.5 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=10:0→4:1). The purified product was condensed under reduced pressure to give the title compound (5.6mg) as a colorless oil.

1H-NMR (CDCl3) δ ppm: 1.80-1.98 (2H, m), 2.26 (2H, t, J = 7.3 Hz), 2.53 (2H, t, J = 6.5 Hz), 2.81 (2H, t, J = 7.3 Hz), 3.24 (3H, s), 3.44 (2H, s), 3.72 (3H, s), 3.98 (2H, t, J = 6.0 Hz), 6.73 (1H, d, J = 9.5 Hz), 6.93 (1H, d, J = 2.7 Hz), 7.00-7.19 (5H, m), 7.24-7.41 (4H, m), 7.60 (1H, d, J = 9.5 Hz), 8.42 (2H, d, J = 5.4 Hz).

Example 243

· Synthesis of

3-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(

pyridin-4-ylmethyl)amino}-N-o-tolylpropionamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.30 (3H, s), 2.20-2.40 (2H, m), 2.91-3.18 (2H, m), 3.18-3.37 (2H, m), 3.37-3.55 (2H, m), 3.60 (3H, s), 3.93-4.20 (2H, m), 4.66 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.00-7.31 (5H, m), 7.36 (1H, d, J = 7.3 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.82 (1H, d, J = 9.5 Hz), 8.20 (2H, d, J = 5.2 Hz), 8.90 (2H, d, J = 5.2 Hz), 9.72 (1H, s).

Example 244

· Synthesis of

N-methyl-3-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}-N-o-tolylpropionamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.18 (3H, s), 2.08-2.42 (2H, m), 2.95-3.19 (2H, m), 3.06 (3H, s), 3.19-3.49 (4H, m), 3.60 (3H, s), 3.93-4.13 (2H, m), 4.48 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.15 (1H, dd, J = 9.2, 2.8 Hz), 7.19-7.41 (5H, m), 7.48 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.5 Hz), 7.97 (2H, d, J = 6.0 Hz), 8.80 (2H, d, J = 6.0 Hz).

Example 245

· Synthesis of

furan-3-carboxylic acid methyl-(2-{N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-4-ylmethyl)amino}ethyl)amide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.13-2.41 (2H, m), 2.98-3.48 (4H, m), 3.15 (3H, s), 3.60 (3H, s), 3.78-3.98 (2H, m), 3.98-4.20 (2H, m), 4.65 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 6.74 (1H, s), 7.18 (1H, dd, J = 9.1, 2.6 Hz), 7.26 (1H, d, J = 2.6 Hz), 7.46 (1H, d, J = 9.1 Hz), 7.75 (1H, s), 7.83 (1H, d, J = 9.5 Hz), 8.15 (1H, s), 8.20 (2H, d, J = 5.2 Hz), 8.89 (2H, d, J = 5.2 Hz).

Example 246

· Synthesis of
N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)-2-thiophen-2-ylacetamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.12-2.49 (2H, m), 3.08 (3H, s), 3.12-3.41 (4H, m), 3.60 (3H, s), 3.65-3.88 (2H, m), 3.97 (2H, s), 4.00-4.16 (2H, m), 4.44-4.93 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 6.87-7.02 (2H, m), 7.19 (1H, dd, J = 9.2, 2.7 Hz), 7.26 (1H, d, J = 2.7 Hz), 7.37 (1H, dd, J = 5.0, 1.3 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.83 (1H, d, J = 9.5 Hz), 8.24 (2H, d, J = 5.4 Hz), 8.91 (2H, d, J = 5.4 Hz).

Example 247

· Synthesis of
cyclohexanecarboxylic acid
N-methyl-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)amide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.03-1.45 (6H, m), 1.45-1.80 (4H, m), 2.17-2.41 (2H, m), 2.41-2.65 (1H, m), 3.05 (3H, s), 3.08-3.40 (4H, m), 3.60 (3H, s), 3.66-3.82 (2H, m), 4.00-4.20 (2H, m), 4.68 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 7.20 (1H, dd, J = 9.2, 2.8 Hz), 7.27 (1H, d, J = 2.8 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.5 Hz), 8.26 (2H, d, J = 5.5 Hz), 8.94 (2H, d, J = 5.5 Hz).

Example 248

· Synthesis of
3-methoxy-N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.20-2.48 (2H, m), 2.95 (3H, s), 3.13-3.51 (4H, m), 3.60 (3H, s), 3.77 (3H, s), 3.82-4.01 (2H, m), 4.01-4.22 (2H, m), 4.76 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 6.82-7.09 (3H, m), 7.09-7.40 (3H, m), 7.46 (1H, d, J = 9.2 Hz), 7.83 (1H, d, J = 9.5 Hz), 8.32 (2H, s), 8.94 (2H, s).

Example 249

· Synthesis of
5-methylisoxazole-3-carboxylic acid
N-methyl-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-4-ylmethyl)amino}ethyl)amide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.85-2.09 (2H, m), 2.66 (3H, s), 2.59-2.82 (4H, m), 2.98-3.30 (2H, m), 3.20 (3H, s), 3.64 (2H, s), 3.71 (3H, s), 3.98-4.15 (2H, m), 6.25 (1H, s), 6.71 (1H, d, J = 9.5 Hz), 6.99 (1H, d, J = 7.4 Hz), 7.03-7.16 (1H, m), 7.16-7.35 (3H, m), 7.62 (1H, d, J = 9.5 Hz), 8.36-8.51 (2H, m).

Example 250

· Synthesis of
benzo[b]thiophene-3-carboxylic acid
N-methyl-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)amide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.15-2.41 (2H, m), 3.03 (3H, s), 3.11-3.51 (4H, m), 3.59 (3H, s), 3.75-4.88 (6H, m), 6.61 (1H, d, J = 9.5 Hz), 7.09-7.35 (2H, m), 7.35-7.54 (3H, m), 7.67-7.87 (2H, m), 7.87-8.32 (4H, m), 8.88 (2H, s).

Example 251

· Synthesis of
2,4-dimethoxy-N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 2.08-2.32 (2H, m), 2.68-3.00 (2H, m), 2.84 (3H, s), 3.00-3.34 (2H, m), 3.59 (3H, s), 3.75 (3H, s), 3.77 (3H, s), 3.65-4.58 (6H, m), 6.45-6.62 (3H, m), 6.98-7.22 (3H, m), 7.41 (1H, d, J = 9.0 Hz), 7.78 (1H, d, J = 9.5 Hz), 7.94 (2H, s), 8.71 (2H, s).

Example 252

· Synthesis of 2,3-dimethoxy-N-methyl-N-(2-{N'-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N'-(pyridin-4-ylmethyl)amino}ethyl)benzamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 46 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 2.16-2.40 (2H, m), 2.80 (3H, s), 2.80-3.11 (2H, m), 3.11-3.40 (2H, m), 3.59 (3H, s), 3.70 (3H, s), 3.82 (3H, s), 3.85-4.05 (2H, m), 4.05-4.21 (2H, m), 4.59 (2H, s), 6.58 (1H, d, J = 9.5 Hz), 6.64-6.87 (2H, m), 7.00-7.29 (3H, m), 7.43 (1H, d, J = 9.0 Hz), 7.78 (1H, d, J = 9.5 Hz), 8.20 (2H, s), 8.82 (2H, s).

Example 253

· Synthesis of 6-{3-[N-(1-benzoylpiperidin-4-yl)-N-(pyridin-4-ylmethyl)amino]propoxy}-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials. 1H-NMR (DMSO-D6) δ ppm: 1.78-2.02 (2H, m), 2.02-2.42 (4H, m), 2.63-3.50 (5H, m), 3.59 (3H, s), 3.50-4.90 (6H, m), 6.62 (1H, d, J = 9.5 Hz), 7.17 (1H, dd, J = 9.0, 2.6 Hz), 7.22 (1H, d, J = 2.6 Hz), 7.35-7.56 (6H, m), 7.82 (1H, d, J = 9.5 Hz), 8.27 (2H, s), 8.89 (2H, s).

Example 254

· Synthesis of 6-(3-{N-[1-(2,3-dihydrobenzofuran-7-carbonyl)piperidin-4-yl]-N-(pyridin-4-ylmethyl)amino}propoxy)-1-methyl-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 50 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.68-1.93 (2H, m), 2.03-2.41 (4H, m), 2.60-3.36 (5H, m), 3.59 (3H, s), 3.62-4.79 (6H, m), 4.04 (2H, t, J = 7.1 Hz), 4.56 (2H, t, J = 8.6 Hz), 6.62 (1H, d, J = 9.5 Hz), 6.89 (1H, dd, J = 7.2, 7.1 Hz), 7.09 (1H, d, J = 7.2 Hz), 7.16 (1H, dd, J = 9.2, 2.7 Hz), 7.22 (1H, d, J = 2.7 Hz), 7.31 (1H, d, J = 7.1 Hz), 7.45 (1H, d, J = 9.2 Hz), 7.82 (1H, d, J = 9.5 Hz), 8.28 (2H, s), 8.89 (2H, s).

Example 255

· Synthesis of
1-methyl-6-{3-[N-(1-phenylpiperidin-4-yl)-N-(pyridin-4-ylmethyl)amino]propoxy}-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 96 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.91-2.43 (6H, m), 2.63-4.31 (9H, m), 3.60 (3H, s), 4.31-4.83 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 6.79-7.39 (7H, m), 7.45 (1H, d, J = 9.2 Hz), 7.83 (1H, d, J = 9.5 Hz), 8.09 (2H, d, J = 5.0 Hz), 8.79 (2H, d, J = 5.0 Hz).

Example 256

· Synthesis of
1-Methyl-6-(3-{N-[2-(N'-methyl-N'-phenylamino)ethyl]-N-(pyridin-4-ylmethyl)amino}propoxy)-1H-quinolin-2-one trihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 96 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 2.12-2.33 (2H, m), 2.90 (3H, s), 3.07-3.34 (4H, m), 3.60 (3H, s), 3.34-4.00 (2H, m), 4.00-4.16 (2H, m), 4.57 (2H, s), 6.62 (1H, d, J = 9.5 Hz), 6.68 (1H, t, J = 7.3 Hz), 6.79 (2H, d, J = 7.3 Hz), 7.11-7.23 (3H, m), 7.24 (1H, d, J = 2.8 Hz), 7.46 (1H, d, J = 9.0 Hz), 7.83 (1H, d, J = 9.5 Hz), 8.04 (2H, d, J = 4.9 Hz), 8.81 (2H, d, J = 4.9 Hz).

Example 257

· Synthesis of
6-{3-[N-(1-methoxyisoquinolin-4-yl)-N-(pyridin-4-ylmethyl)amino]p

ropoxy}-1-methyl-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.

1H-NMR (CDCl3) δ ppm: 1.92-2.17 (2H, m), 3.34 (2H, t, J = 6.9 Hz), 3.70 (3H, s), 3.99 (2H, t, J = 5.9 Hz), 4.09 (3H, s), 4.26 (2H, s), 6.70 (1H, d, J = 9.5 Hz), 6.85 (1H, d, J = 2.8 Hz), 7.04 (1H, dd, J = 9.1, 2.8 Hz), 7.19-7.35 (3H, m), 7.52 (1H, d, J = 9.5 Hz), 7.51-7.62 (1H, m), 7.62-7.74 (1H, m), 7.80 (1H, s), 8.18 (1H, d, J = 8.2 Hz), 8.26 (1H, d, J = 7.6 Hz), 8.48 (2H, d, J = 5.9 Hz).

Example 258

· Synthesis of 1-methyl-6-{3-[N-(1-oxo-1,2-dihydroisoquinolin-4-yl)-N-(pyridin-4-ylmethyl)amino]propoxy}-1H-quinolin-2-one

6-{3-[N-(1-Methoxyisoquinolin-4-yl)-N-(pyridin-4-ylmethyl)amino]propoxy}-1-methyl-1H-quinolin-2-one (55mg) was added to a 1N-hydrogen chloride in ethanol solution(5ml), and stirred at 75°C for 2 hours. The reaction mixture was cooled to room temperature. 1N-Sodium hydroxide aqueous solution(5ml) was added to the reaction mixture, followed by extraction with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. The filtrate was condensed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate: methanol=10:0→4:1). The purified product was condensed under reduced pressure to give the title compound(20.6mg) as a colorless oil.

1H-NMR (CDCl3) δ ppm: 1.92-2.14 (2H, m), 3.22 (2H, t, J = 6.8 Hz), 3.70 (3H, s), 4.02 (2H, t, J = 5.9 Hz), 4.16 (2H, s), 6.71 (1H, d, J = 9.5 Hz), 6.89 (1H, d, J = 2.8 Hz), 7.01 (1H, s), 7.09 (1H, dd, J = 9.1, 2.8 Hz), 7.20-7.33 (3H, m), 7.54 (1H, d, J = 9.5 Hz), 7.52-7.67 (1H, m), 7.67-7.80 (1H, m), 8.08 (1H, d, J = 8.2 Hz), 8.46 (1H, d, J = 7.2 Hz), 8.51 (2H, d, J = 5.9 Hz).

Example 259

· Synthesis of 1-Methyl-6-(3-{N-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}propoxy)-1H-quinolin-2-one dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 5 using appropriate starting materials.
1H-NMR (DMSO-D6) δ ppm: 1.79-2.09 (2H, m), 2.60-4.15 (8H, m), 3.61 (3H, s), 4.76 (2H, s), 6.58 (1H, d, J = 7.0 Hz), 6.63 (1H, d, J = 9.5 Hz), 6.90 (1H, d, J = 1.8 Hz), 6.99-7.19 (2H, m), 7.44 (1H, d, J = 9.1 Hz), 7.51 (1H, d, J = 7.0 Hz), 7.68 (2H, d, J = 4.6 Hz), 7.83 (1H, d, J = 9.5 Hz), 8.13 (1H, d, J = 1.8 Hz), 8.53 (2H, d, J = 4.6 Hz).

Example 260

· Synthesis of
1-methyl-6-[3-(2-pyridin-3-ylethylamino)propoxy]-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.90-2.06 (2H, m), 2.76-3.00 (6H, m), 3.72 (3H, s), 4.08 (2H, t, J = 6.1 Hz), 6.73 (1H, d, J = 9.5 Hz), 6.99 (1H, d, J = 2.8 Hz), 7.15 (1H, dd, J = 9.2, 2.8 Hz), 7.21 (1H, ddd, J = 7.7, 4.8, 0.6 Hz), 7.29 (1H, d, J = 9.2 Hz), 7.51-7.57 (1H, m), 7.60 (1H, d, J = 9.5 Hz), 8.47 (1H, dd, J = 4.8, 1.7 Hz), 8.51 (1H, d, J = 1.7 Hz).

Example 261

· Synthesis of
1-methyl-6-[4-(2-pyridin-3-ylethylamino)butoxy]-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.58-1.76 (2H, m), 1.76-1.92 (2H, m), 2.71 (2H, t, J = 7.2 Hz), 2.78-3.00 (4H, m), 3.70 (3H, s), 4.00 (2H, t, J = 6.2 Hz), 6.70 (1H, d, J = 9.5 Hz), 6.98 (1H, d, J = 2.8 Hz), 7.15 (1H, dd, J = 9.2, 2.8 Hz), 7.22 (1H, dd, J = 7.7, 4.8 Hz), 7.28 (1H, d, J = 9.2 Hz), 7.49-7.56 (1H, m), 7.59 (1H, d, J = 9.5 Hz), 8.46 (1H, dd, J = 4.8, 1.8 Hz), 8.48 (1H, d, J = 1.8 Hz).

Example 262

· Synthesis of
1-methyl-6-{3-[(pyridin-3-ylmethyl)amino]propoxy}-1H-quinolin-2-o

ne

3N-Hydrochloric acid(5ml) was added to a ethanol solution(5ml) of N-[3-(1-Methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-3-ylmethyl)benzamide(250.1mg), and stirred for 60 hours while heated under reflux. The reaction mixture was cooled to room temperature. Water was added thereto, washed with ethyl acetate. A saturated sodium hydrogencarbonate aqueous solution was added to the aqueous layer, followed by extraction using dichloromethane. The organic layer was dried with anhydrous sodium sulfate, and condensed under reduced pressure to give the title compound(168mg) as a colorless oil.

1H-NMR (CDCl3) δ ppm: 1.93-2.10 (2H, m), 2.86 (2H, t, J = 6.8 Hz), 3.71 (3H, s), 3.84 (2H, s), 4.11 (2H, t, J = 6.2 Hz), 6.71 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 2.8 Hz), 7.16 (1H, dd, J = 9.2, 2.8 Hz), 7.22-7.33 (2H, m), 7.59 (1H, d, J = 9.5 Hz), 7.65-7.72 (1H, m), 8.50 (1H, dd, J = 4.8, 1.7 Hz), 8.58 (1H, d, J = 1.7 Hz).

Example 263

· Synthesis of 1-methyl-6-[2-(2-pyridin-3-ylethylamino)ethoxy]-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.

1H-NMR (CDCl3) δ ppm: 2.76-2.90 (2H, m), 2.90-3.04 (2H, m), 3.07 (2H, t, J = 5.2 Hz), 3.71 (3H, s), 4.12 (2H, t, J = 5.2 Hz), 6.72 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 2.8 Hz), 7.16 (1H, dd, J = 9.2, 2.8 Hz), 7.23 (1H, dd, J = 7.7, 4.8 Hz), 7.30 (1H, d, J = 9.2 Hz), 7.52-7.59 (1H, m), 7.59 (1H, d, J = 9.5 Hz), 8.48 (1H, dd, J = 4.8, 1.7 Hz), 8.51 (1H, d, J = 1.7 Hz).

Example 264

· Synthesis of 1-methyl-6-{2-[N-(pyridin-3-ylmethyl)amino]ethoxy}-1H-quinolin-2-one

3-Pyridine carbaldehyde(0.99ml) and 6-(2-Aminoethoxy)-1-methyl-1H-quinolin-2-one(2.18g) were added to

methanol (50ml). The mixture was stirred at room temperature for 7 hours. The mixture was cooled to 0°C, and sodium borohydride (0.757g) was added thereto. The mixture was further stirred at room temperature overnight. Water was added to the reaction mixture and methanol was distilled off under reduced pressure. The residue was subjected to extraction using dichloromethane. The organic layer was washed with saturated saline, dried with anhydrous sodium sulfate, and was condensed under reduced pressure. The residue was purified by basic silica gel column chromatography (ethyl acetate). The purified product was condensed under reduced pressure to give the title compound (3.063g) as a yellow oil.

1H-NMR (CDCl3) δ ppm: 3.06 (2H, t, J = 5.0 Hz), 3.71 (3H, s), 3.91 (2H, s), 4.14 (2H, t, J = 5.0 Hz), 6.72 (1H, d, J = 9.5 Hz), 7.01 (1H, d, J = 2.8 Hz), 7.19 (1H, dd, J = 9.2, 2.8 Hz), 7.24-7.33 (2H, m), 7.59 (1H, d, J = 9.5 Hz), 7.68-7.75 (1H, m), 8.52 (1H, dd, J = 4.8, 1.7 Hz), 8.61 (1H, d, J = 1.7 Hz).

Example 265

· Synthesis of methanesulfonic acid 2-[N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(2-nitro-benzenesulfonyl)amino]ethyl ester

Methane sulfonyl chloride (1.14ml) was added to a dichloromethane solution (50ml) of N-(2-hydroxy-thyl)-N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-2-nitro-benzenesulfonamide (4.52g) and triethylamine (2.73ml). The mixture was stirred at room temperature overnight. 1N-Sodium hydroxide aqueous solution was added to the reaction mixture, followed by extraction using dichloromethane. The organic layer was washed with saturated saline, and dried with sodium sulfate. After the organic layer was condensed under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate). The purified product was condensed under reduced pressure to give the title compound (4.37g) as a yellow solid.

1H-NMR (CDCl3) δ ppm: 2.00-2.21 (2H, m), 3.03 (3H, s), 3.63 (2H, t, J = 7.6 Hz), 3.71 (3H, s), 3.75 (2H, t, J = 5.5 Hz), 4.01 (2H, t, J

= 6.0 Hz), 4.40 (2H, t, J = 5.5 Hz), 6.72 (1H, d, J = 9.5 Hz), 6.92 (1H, d, J = 2.8 Hz), 7.11 (1H, dd, J = 9.2, 2.8 Hz), 7.28 (1H, d, J = 9.2 Hz), 7.56-7.67 (4H, m), 8.02-8.08 (1H, m).

Example 266

· Synthesis of 1-methyl-6-(3-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethylamino}propoxy)-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 1.54-2.24 (8H, m), 2.49 (2H, t, J = 6.1 Hz), 2.66-2.90 (6H, m), 3.33-3.50 (1H, m), 3.70 (3H, s), 4.00-4.18 (2H, m), 4.54 (2H, s), 6.71 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 2.8 Hz), 7.19 (1H, dd, J = 9.2, 2.8 Hz), 7.23-7.32 (2H, m), 7.59 (1H, d, J = 9.5 Hz), 7.63-7.71 (1H, m), 8.53 (1H, dd, J = 4.7, 1.5 Hz), 8.57 (1H, d, J = 1.5 Hz).

Example 267

· Synthesis of 1-methyl-6-(2-{2-[4-(pyridin-3-ylmethoxy)piperidin-1-yl]ethylamino}ethoxy)-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials. 1H-NMR (CDCl3) δ ppm: 1.58-1.85 (2H, m), 1.85-2.02 (2H, m), 2.10-2.25 (2H, m), 2.51 (2H, t, J = 6.1 Hz), 2.70-2.85 (4H, m), 3.05 (2H, t, J = 5.5 Hz), 3.36-3.50 (1H, m), 3.71 (3H, s), 4.13 (2H, t, J = 5.5 Hz), 4.56 (2H, s), 6.72 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 2.8 Hz), 7.20 (1H, dd, J = 9.2, 2.8 Hz), 7.25-7.33 (2H, m), 7.60 (1H, d, J = 9.5 Hz), 7.65-7.72 (1H, m), 8.53 (1H, dd, J = 4.8, 1.6 Hz), 8.58 (1H, d, J = 1.6 Hz).

Example 268

· Synthesis of 1-methyl-6-{4-[(pyridin-4-ylmethyl)amino]butoxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same

manner as in Example 264 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.62-1.80 (2H, m), 1.80-2.00 (2H, m), 2.72 (2H, t, J = 7.0 Hz), 3.71 (3H, s), 3.83 (2H, s), 4.03 (2H, t, J = 6.2 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.98 (1H, d, J = 2.8 Hz), 7.16 (1H, dd, J = 9.2, 2.8 Hz), 7.22-7.32 (3H, m), 7.59 (1H, d, J = 9.5 Hz), 8.54 (2H, d, J = 5.9 Hz).

Example 269

· Synthesis of
1-methyl-6-{4-[(pyridin-3-ylmethyl)amino]butoxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 264 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.60-1.80 (2H, m), 1.80-1.98 (2H, m), 2.72 (2H, t, J = 7.0 Hz), 3.71 (3H, s), 3.83 (2H, s), 4.02 (2H, t, J = 6.2 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.98 (1H, d, J = 2.8 Hz), 7.16 (1H, dd, J = 9.2, 2.8 Hz), 7.22-7.33 (2H, m), 7.59 (1H, d, J = 9.5 Hz), 7.63-7.71 (1H, m), 8.51 (1H, dd, J = 4.7, 1.5 Hz), 8.57 (1H, d, J = 1.5 Hz).

Example 270

· Synthesis of
1-methyl-6-(3-{2-[4-(pyridin-4-ylmethoxy)piperidin-1-yl]ethylamino}propoxy)-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.54-2.24 (8H, m), 2.49 (2H, t, J = 6.0 Hz), 2.62-2.90 (6H, m), 3.30-3.49 (1H, m), 3.70 (3H, s), 4.10 (2H, t, J = 6.2 Hz), 4.54 (2H, s), 6.71 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 2.7 Hz), 7.19 (1H, dd, J = 9.2, 2.7 Hz), 7.20-7.32 (3H, m), 7.59 (1H, d, J = 9.5 Hz), 8.56 (2H, d, J = 5.9 Hz).

Example 272

· Synthesis of
1-methyl-6-[3-(2-pyridin-3-ylethylamino)propoxy]-3,4-dihydro-1H-quinolin-2-one

The synthesis of the title compound was performed in the same

manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.82-2.02 (2H, m), 2.55-2.68 (2H, m), 2.78-2.99 (8H, m), 3.33 (3H, s), 3.99 (2H, t, J = 6.1 Hz), 6.70 (1H, d, J = 2.7 Hz), 6.74 (1H, dd, J = 8.6, 2.7 Hz), 6.88 (1H, d, J = 8.6 Hz), 7.21 (1H, dd, J = 7.8, 4.8 Hz), 7.50-7.57 (1H, m), 8.46 (1H, dd, J = 4.8, 1.8 Hz), 8.49 (1H, d, J = 1.8 Hz).

Example 273

· Synthesis of
1-methyl-6-[3-(2-pyridin-4-ylethylamino)propoxy]-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.92-2.08 (2H, m), 2.77-2.90 (4H, m), 2.90-3.01 (2H, m), 3.71 (3H, s), 4.07 (2H, t, J = 6.1 Hz), 6.72 (1H, d, J = 9.5 Hz), 6.96 (1H, d, J = 2.8 Hz), 7.09-7.19 (3H, m), 7.29 (1H, d, J = 9.3 Hz), 7.59 (1H, d, J = 9.5 Hz), 8.50 (2H, d, J = 6.0 Hz).

Example 274

· Synthesis of
6-[3-(3-imidazol-1-yl-propylamino)propoxy]-1-methyl-1H-quinolin-2-one

3-(1-Methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propionaldehyde (127.5mg) prepared from 6-hydroxy-1-methylquinolin-2(1H)-one and N-(3-aminopropyl)imidazole (82.9mg) were added to methanol (10ml). The mixture was stirred at room temperature for 7 hours. The mixture was cooled to 0°C, and sodium borohydride(31.4mg) was added thereto. The mixture was further stirred at room temperature overnight. Water was added to the reaction mixture and methanol was distilled off under reduced pressure. The residue was subjected to extraction using dichloromethane. The organic layer was washed with saturated saline, dried with anhydrous sodium sulfate, and was condensed under reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: methanol=10:0→4:1). The purified product was condensed under reduced pressure to give the title compound(21mg) as a yellow oil.

1H-NMR (CDCl3) δ ppm: 1.81-2.02 (4H, m), 2.49-2.58 (2H, m), 2.80 (2H, t, J = 6.9 Hz), 3.70 (3H, s), 3.93-4.15 (4H, m), 6.71 (1H, d, J = 9.5 Hz), 6.91 (1H, s), 7.01 (1H, d, J = 2.8 Hz), 7.05 (1H, s), 7.18 (1H, dd, J = 9.2, 2.8 Hz), 7.29 (1H, d, J = 9.2 Hz), 7.47 (1H, s), 7.60 (1H, d, J = 9.5 Hz).

Example 275

· Synthesis of 1-methyl-6-[3-(2-piperidin-1-ylethylamino)propoxy]-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.32-1.49 (2H, m), 1.49-1.63 (4H, m), 1.94-2.08 (2H, m), 2.28-2.41 (4H, m), 2.45 (2H, t, J = 6.2 Hz), 2.73 (2H, t, J = 6.2 Hz), 2.83 (2H, t, J = 6.9 Hz), 3.70 (3H, s), 4.10 (2H, t, J = 6.2 Hz), 6.70 (1H, d, J = 9.5 Hz), 7.01 (1H, d, J = 2.8 Hz), 7.18 (1H, dd, J = 9.2, 2.8 Hz), 7.28 (1H, d, J = 9.2 Hz), 7.59 (1H, d, J = 9.5 Hz).

Example 276

· Synthesis of 6-[3-(2-diethylaminoethylamino)propoxy]-1-methyl-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.00 (6H, t, J = 7.1 Hz), 1.90-2.08 (2H, m), 2.41-2.60 (6H, m), 2.69 (2H, t, J = 5.7 Hz), 2.83 (2H, t, J = 6.9 Hz), 3.71 (3H, s), 4.10 (2H, t, J = 6.3 Hz), 6.71 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 2.8 Hz), 7.19 (1H, dd, J = 9.2, 2.8 Hz), 7.29 (1H, d, J = 9.2 Hz), 7.59 (1H, d, J = 9.5 Hz).

Example 277

· Synthesis of 1-methyl-6-{3-[2-(4-methylpiperazin-1-yl)ethylamino]propoxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same

manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.91-2.08 (2H, m), 2.26 (3H, s), 2.31-2.63 (10H, m), 2.73 (2H, t, J = 6.1 Hz), 2.83 (2H, t, J = 6.8 Hz), 3.70 (3H, s), 4.10 (2H, t, J = 6.2 Hz), 6.71 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 2.6 Hz), 7.19 (1H, dd, J = 9.2, 2.6 Hz), 7.29 (1H, d, J = 9.2 Hz), 7.59 (1H, d, J = 9.5 Hz).

Example 278

· Synthesis of
N-{2-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propylamino]ethyl}benzamide

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.92-2.10 (2H, m), 2.82-3.00 (4H, m), 3.49-3.61 (2H, m), 3.68 (3H, s), 4.11 (2H, t, J = 6.1 Hz), 6.70 (1H, d, J = 9.5 Hz), 6.81 (1H, s), 6.97 (1H, d, J = 2.8 Hz), 7.14 (1H, dd, J = 9.2, 2.8 Hz), 7.23 (1H, d, J = 9.2 Hz), 7.31-7.39 (2H, m), 7.41-7.48 (1H, m), 7.54 (1H, d, J = 9.5 Hz), 7.70-7.77 (2H, m).

Example 279

· Synthesis of
N-{2-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propylamino]ethyl}isobutyramide

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.13 (6H, d, J = 6.9 Hz), 1.90-2.08 (2H, m), 2.25-2.41 (1H, m), 2.75-2.90 (4H, m), 3.30-3.42 (2H, m), 3.70 (3H, s), 4.09 (2H, t, J = 6.1 Hz), 6.09 (1H, s), 6.71 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 2.8 Hz), 7.17 (1H, dd, J = 9.2, 2.8 Hz), 7.29 (1H, d, J = 9.2 Hz), 7.59 (1H, d, J = 9.5 Hz).

Example 280

· Synthesis of
N-{2-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propylamino]ethyl}nicotinamide

The synthesis of the title compound was performed in the same

manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.90-2.10 (2H, m), 2.80-3.00 (4H, m), 3.49-3.62 (2H, m), 3.68 (3H, s), 4.11 (2H, t, J = 6.2 Hz), 6.69 (1H, d, J = 9.5 Hz), 6.96 (1H, d, J = 2.7 Hz), 7.02 (1H, s), 7.14 (1H, dd, J = 9.1, 2.7 Hz), 7.24 (1H, d, J = 9.1 Hz), 7.31 (1H, dd, J = 7.9, 4.8 Hz), 7.56 (1H, d, J = 9.5 Hz), 8.03-8.11 (1H, m), 8.67 (1H, dd, J = 4.8, 1.9 Hz), 8.95 (1H, d, J = 1.9 Hz).

Example 281

· Synthesis of
N-{2-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propylamino]ethyl}benzenesulfonamide

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.80-1.99 (2H, m), 2.65-2.81 (4H, m), 2.99-3.12 (2H, m), 3.70 (3H, s), 4.05 (2H, t, J = 6.1 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.99 (1H, d, J = 2.7 Hz), 7.16 (1H, dd, J = 9.1, 2.7 Hz), 7.28 (1H, d, J = 9.1 Hz), 7.45-7.63 (4H, m), 7.82-7.90 (2H, m).

Example 282

· Synthesis of
{N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-4-ylmethyl)amino}acetic acid

A 1N-sodium hydroxide aqueous solution(3ml) was added to a methanol solution (15ml) of
{N-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]-N-(pyridin-4-ylmethyl)amino}acetic acid ethyl ester (614mg). The mixture was stirred at room temperature overnight. 1N-Hydrochloric acid(3ml) was added to the reaction mixture and condensed under reduced pressure. Metanol was added to the residue, and the generated insoluble matter was separated by filtration. The filtrate was condensed under reduced pressure to give the title compound(468mg) as a white amorphous solid.
1H-NMR (DMSO-D6) δ ppm: 1.75-1.94 (2H, m), 2.73 (2H, t, J = 6.8 Hz), 3.03 (2H, s), 3.59 (3H, s), 3.82 (2H, s), 4.04 (2H, t, J = 6.4 Hz), 6.59 (1H, d, J = 9.5 Hz), 7.17 (1H, dd, J = 9.1, 2.9 Hz), 7.23 (1H, d, J = 2.9 Hz), 7.32 (2H, d, J = 5.9 Hz), 7.44 (1H, d, J = 9.1 Hz),

7.83 (1H, d, J = 9.5 Hz), 8.40 (2H, d, J = 5.9 Hz).

Example 283

· Synthesis of
1-methyl-6-{3-[(pyridin-4-ylmethyl)amino]propoxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 264 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.86-2.10 (2H, m), 2.70-2.92 (2H, m), 3.71 (3H, s), 3.85 (2H, s), 4.12 (2H, t, J = 6.0 Hz), 6.72 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 2.8 Hz), 7.08-7.38 (4H, m), 7.59 (1H, d, J = 9.5 Hz), 8.53 (2H, d, J = 5.9 Hz).

Example 284

· Synthesis of
6-{3-[(2-aminoethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}-1-methyl-1H-quinolin-2-one

A 4N-hydrogen chloride ethyl acetate solution(0.22ml) was added to an ethyl acetate solution (3ml) of (2-{[3-(1-Methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)-propyl]-pyridin-4-ylmethyl-amino}-ethyl)-carbamic acid tert-butyl ester (137mg), and the mixture was stirred at room temperature overnight. 5N-Ammoia methanol solution(1ml) was added to the reaction mixture, and the generated insoluble matter was separated by filtration. The filtrate was condensed under reduced pressure to give the title compound(85.7mg) as an colorless oil.
1H-NMR (CDCl3) δ ppm: 1.88-2.08 (2H, m), 2.57 (2H, t, J = 6.0 Hz), 2.67 (2H, t, J = 6.9 Hz), 2.80 (2H, t, J = 6.0 Hz), 3.62 (2H, s), 3.71 (3H, s), 4.05 (2H, t, J = 6.0 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.95 (1H, d, J = 2.8 Hz), 7.10 (1H, dd, J = 9.2, 2.8 Hz), 7.22-7.32 (3H, m), 7.59 (1H, d, J = 9.5 Hz), 8.49 (2H, d, J = 6.0 Hz).

Example 285

· Synthesis of
2-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}benzoic acid

A 1N-sodium hydroxide aqueous solution(1.8ml) was added to a methanol solution (3ml) of 2-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}benzoic acid ethyl ester(372mg). The mixture was stirred at room temperature overnight. 6N-Hydrochloric acid(0.3ml) was added to the reaction mixture and condensed under reduced pressure. Metanol was added to the residue, and the generated insoluble matter was separated by filtration. The filtrate was condensed under reduced pressure to give the title compound(458mg) as a colorless oil.

1H-NMR (DMSO-D6) δ ppm: 2.12-2.38 (2H, m), 3.09-3.48 (6H, m), 4.01-4.19 (2H, m), 4.46 (2H, s), 6.92-7.08 (1H, m), 7.10 (1H, d, J = 6.9 Hz), 7.41-7.56 (1H, m), 7.64-7.77 (2H, m), 7.85 (2H, s), 8.13 (1H, d, J = 7.6 Hz), 8.65 (1H, dd, J = 5.2, 1.2 Hz), 8.68-8.80 (3H, m).

Example 286

· Synthesis of 3-{3-[N-(2-pyridin-3-yl-ethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}benzoic acid

The synthesis of the title compound was performed in the same manner as in Example 285 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.10-2.41 (2H, m), 3.02-3.59 (6H, m), 3.98-4.22 (2H, m), 4.43-4.72 (2H, m), 7.19 (1H, d, J = 8.3 Hz), 7.31-7.46 (2H, m), 7.54 (1H, d, J = 7.7 Hz), 7.63-7.77 (1H, m), 7.83 (2H, s), 8.04-8.20 (1H, m), 8.65 (1H, d, J = 5.3 Hz), 8.66-8.79 (3H, m).

Example 287

· Synthesis of 4-{3-[N-(2-pyridin-3-ylethyl)-N-(pyridin-4-ylmethyl)amino]propoxy}benzoic acid

The synthesis of the title compound was performed in the same manner as in Example 285 using appropriate starting materials.

1H-NMR (DMSO-D6) δ ppm: 2.16-2.38 (2H, m), 3.00-3.99 (6H, m), 3.99-4.16 (2H, m), 4.35-4.69 (2H, m), 6.96 (2H, d, J = 8.8 Hz), 7.62-7.80 (1H, m), 7.80-7.99 (4H, m), 8.19 (1H, d, J = 6.7 Hz), 8.60-8.80 (4H, m).

Example 288

· Synthesis of
1-methyl-6-[3-(2-pyridin-2-ylethylamino)propoxy]-1H-quinolin-2-on
e

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.91-2.12 (2H, m), 2.86 (2H, t, J = 6.8 Hz), 2.92-3.14 (4H, m), 3.71 (3H, s), 4.07 (2H, t, J = 6.2 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.99 (1H, d, J = 2.8 Hz), 7.07-7.25 (3H, m), 7.28 (1H, d, J = 9.5 Hz), 7.51-7.68 (2H, m), 8.51 (1H, dd, J = 4.8, 0.8 Hz).

Example 289

· Synthesis of
1-methyl-6-[3-(quinolin-6-ylamino)propoxy]-1H-quinolin-2-one

6-Aminoquinoline(360mg) was added to the methanol solution(10ml) of 6-(3-iodopropoxy)-1-methyl-1H-quinolin-2-one(172mg) and stirred at 60°C for 17 hours. The reaction mixture was added to ice water, and extraction with dichloromethane was performed. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: methanol=10:0→4:1). The purified product was condensed under reduced pressure to give the title compound(86.4 mg) as a yellow amorphous solid.
1H-NMR (CDCl3) δ ppm: 2.13-2.29 (2H, m), 3.50 (2H, t, J = 6.6 Hz), 3.70 (3H, s), 4.18 (2H, t, J = 5.8 Hz), 6.67-6.77 (2H, m), 7.01 (1H, d, J = 2.7 Hz), 7.11 (1H, dd, J = 9.1, 2.7 Hz), 7.18-7.27 (2H, m), 7.29 (1H, d, J = 9.1 Hz), 7.56 (1H, d, J = 9.5 Hz), 7.86 (1H, s), 7.89 (1H, s), 8.61 (1H, dd, J = 4.2, 1.6 Hz).

Example 290

· Synthesis of
N-benzyl-N-{2-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yloxy)prop
ylamino]ethyl}acetamide

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.87-2.06 (2H, m), 2.12 (3H, s), 2.70-2.90 (4H,

m), 3.51 (2H, t, J = 6.5 Hz), 3.71 (3H, s), 3.98-4.15 (2H, m), 4.58 (2H, s), 6.71 (1H, d, J = 9.5 Hz), 6.98-7.03 (1H, m), 7.13-7.21 (2H, m), 7.21-7.40 (5H, m), 7.59 (1H, d, J = 9.5 Hz).

Example 291

· Synthesis of 6-{3-[2-(7-bromo-1-oxo-1H-isoquinolin-2-yl)ethylamino]propoxy}-1-methyl-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.88-2.05 (2H, m), 2.87 (2H, t, J = 6.6 Hz), 3.06 (2H, t, J = 6.1 Hz), 3.70 (3H, s), 4.04 (2H, t, J = 6.1 Hz), 4.12 (2H, t, J = 6.1 Hz), 6.37 (1H, d, J = 7.3 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.93 (1H, d, J = 2.8 Hz), 7.09 (1H, dd, J = 9.2, 2.8 Hz), 7.12 (1H, d, J = 7.3 Hz), 7.23 (1H, d, J = 9.2 Hz), 7.32 (1H, d, J = 8.5 Hz), 7.55 (1H, d, J = 9.5 Hz), 7.67 (1H, dd, J = 8.5, 2.1 Hz), 8.52 (1H, d, J = 2.1 Hz).

Example 292

· Synthesis of 1-Methyl-6-{3-[(2-methylamino-ethyl)-pyridin-4-ylmethyl-amino]-propoxy}-1H-quinolin-2-one trihydrochloride

A 4N-hydrogen chloride ethyl acetate solution(4.2ml) was added to an ethyl acetate solution (30ml) of methyl-(2-{[3-(1-methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)-propyl]-pyridin-4-ylmethyl-amino}-ethyl)-carbamic acid tert-butyl ester (1.0g), and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was condensed under reduced pressure to give the title compound(1.0g) as a white powder.
1H-NMR (DMSO-D6) δ ppm: 1.95-2.22 (2H, m), 2.52 (3H, s), 2.56 (2H, t, J = 5.4 Hz), 2.77-3.40 (4H, m), 3.61 (3H, s), 3.99-4.16 (2H, m), 4.16-5.10 (2H, m), 6.62 (1H, d, J = 9.5 Hz), 7.16 (1H, dd, J = 9.2, 2.8 Hz), 7.28 (1H, d, J = 2.8 Hz), 7.45 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.5 Hz), 8.17 (2H, d, J = 5.0 Hz), 8.83 (2H, d, J = 5.0 Hz).

Example 293

· Synthesis of
1-Methyl-6-{3-[(2-methylamino-ethyl)-pyridin-4-ylmethyl-amino]-propoxy}-1H-quinolin-2-one

A 4N-hydrogen chloride ethyl acetate solution(48ml) was added to an ethyl acetate solution (300ml) of methyl-(2-{[3-(1-methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)-propyl]-pyridin-4-ylmethyl-amino}-ethyl)-carbamic acid tert-butyl ester (11.5g), and the mixture was stirred at room temperature overnight. The reaction mixture was condensed under reduced pressure. PL-HCO3(40g) was added to the methanol solution of the residue and followed by celite filtration. The filtrate was condensed under reduced pressure to give the title compound(9.96g) as a brown oil.
1H-NMR (CDCl3) δ ppm: 1.88-2.07 (2H, m), 2.43 (3H, s), 2.68 (2H, t, J = 6.9 Hz), 2.70-2.88 (4H, m), 3.64 (2H, s), 3.70 (3H, s), 4.04 (2H, t, J = 5.9 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.97 (1H, d, J = 2.8 Hz), 7.10 (1H, dd, J = 9.1, 2.8 Hz), 7.20-7.36 (3H, m), 7.59 (1H, d, J = 9.5 Hz), 8.49 (2H, d, J = 6.0 Hz).

Example 294

· Synthesis of
6-[3-(2-Pyridin-3-yl-ethylamino)-propoxy]-3,4-dihydro-2H-isoquinolin-1-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.84-2.02 (2H, m), 2.74-2.87 (4H, m), 2.87-3.02 (4H, m), 3.48-3.61 (2H, m), 4.06 (2H, t, J = 6.1 Hz), 5.88 (1H, s), 6.66 (1H, d, J = 2.4 Hz), 6.81 (1H, dd, J = 8.6, 2.4 Hz), 7.20 (1H, dd, J = 7.7, 4.8 Hz), 7.47-7.60 (1H, m), 8.00 (1H, d, J = 8.6 Hz), 8.46 (1H, dd, J = 4.8, 1.8 Hz), 8.49 (1H, d, J = 1.8 Hz).

Example 295

· Synthesis of
1-Methyl-6-{2-[(pyridin-4-ylmethyl)-amino]-ethoxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 264 using appropriate starting materials.

1H-NMR (CDCl3) δ ppm: 3.05 (2H, t, J = 5.2 Hz), 3.71 (3H, s), 3.92 (2H, s), 4.15 (2H, t, J = 5.2 Hz), 6.72 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 2.8 Hz), 7.19 (1H, dd, J = 9.2, 2.8 Hz), 7.23-7.46 (3H, m), 7.59 (1H, d, J = 9.5 Hz), 8.56 (2H, d, J = 6.0 Hz).

Example 296

· Synthesis of 3-[3-(1-Methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)-propylamino]-N-o-tolyl-propionamide

Sodium ethoxide(34mg) was added to an ethanol solution (5ml) of 6-(3-amino-propoxy)-1-methyl-1H-quinolin-2-one (116mg) and 3-chloro-N-o-tolyl-propionamide(148mg). The mixture was stirred at 60°C for 5 hours. The reaction mixture was condensed under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane: methanol=20:1→10:1). The purified product was condensed under reduced pressure to give the title compound(115 mg) as a white powder.

1H-NMR (CDCl3) δ ppm: 2.15-2.36 (2H, m), 2.26 (3H, s), 2.99-3.56 (6H, m), 3.63 (3H, s), 4.11 (2H, t, J = 5.6 Hz), 6.66 (1H, d, J = 9.5 Hz), 6.92-7.29 (6H, m), 7.47 (1H, d, J = 9.5 Hz), 7.59 (1H, d, J = 6.9 Hz), 9.25 (1H, s).

Example 297

· Synthesis of N-Methyl-3-[3-(1-methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)-propylamino]-N-o-tolyl-propionamide

6-(3-Amino-propoxy)-1-methyl-1H-quinolin-2-one(194mg) was added to an ethanol solution (5ml) of N-methyl-N-o-tolyl-acrylamide(146mg). The mixture was stirred at room temperature overnight. The reaction mixture was condensed under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane: methanol=20:1→10:1). The purified product was condensed under reduced pressure to give the title compound(172.6 mg) as a colorless oil.

1H-NMR (CDCl3) δ ppm: 2.06-2.25 (2H, m), 2.24 (3H, s), 2.25-2.50 (2H, m), 2.86-3.03 (4H, m), 3.20 (3H, s), 3.70 (3H, s), 4.12 (2H, t, J =

6.0 Hz), 6.71 (1H, d, J = 9.5 Hz), 7.07 (1H, d, J = 2.3 Hz), 7.13 (1H, dd, J = 8.3, 2.3 Hz), 7.19-7.38 (5H, m), 7.60 (1H, d, J = 9.5 Hz).

Example 298

· Synthesis of 1-Methyl-6-[3-(piperidin-4-yl-pyridin-4-ylmethyl-amino)-propoxy]-1H-quinolin-2-one

Trifluoroacetic acid (30ml) was added to a dichloromethane solution (10ml) of 4-{[3-(1-methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)-propyl]-pyridin-4-ylmethyl-amino}-piperidine-1-carboxylic acid tert-butyl ester (1.08g), and the mixture was stirred at room temperature overnight. The reaction mixture was condensed under reduced pressure. PL-HCO3(40g) was added to the dichloromethane solution of the residue and followed by celite filtration. The filtrate was condensed under reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate: methanol=4:1). The purified product was condensed under reduced pressure to give the title compound(758mg) as an orange oil.

1H-NMR (CDCl3) δ ppm: 1.45-1.65 (2H, m), 1.70-1.99 (4H, m), 2.50-2.69 (3H, m), 2.74 (2H, t, J = 6.7 Hz), 3.11-3.25 (2H, m), 3.68 (2H, s), 3.71 (3H, s), 4.00 (2H, t, J = 6.0 Hz), 6.72 (1H, d, J = 9.5 Hz), 6.93 (1H, d, J = 2.8 Hz), 7.10 (1H, dd, J = 9.2, 2.8 Hz), 7.23-7.35 (3H, m), 7.60 (1H, d, J = 9.5 Hz), 8.47 (2H, d, J = 6.0 Hz).

Example 299

· Synthesis of 6-[3-(1-Methoxy-isoquinolin-4-ylamino)-propoxy]-1-methyl-1H-quinolin-2-one

6-(3-Amino-propoxy)-1-methyl-1H-quinolin-2-one(232mg), 4-bromo-1-methoxy-isoquinoline(286mg), palladium acetate (II)(22mg), xantphos (558mg), and sodium t-butoxide(192mg) were added to dioxane(10ml). The mixture was heated at 80°C for overnight under argon atmosphere. The reaction liquid was cooled to room temperature. Water was added to the reaction mixture, and followed by celite filtration. The filtrate was extracted with dichloromethane. The

organic layer was dried over anhydrous sodium sulfate. The filtrate was condensed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate: hexane =2: 1→1:0). The purified product was condensed under reduced pressure to give the title compound(99mg) as a brown amorphous solid.
1H-NMR (CDCl3) δ ppm: 2.20-2.37 (2H, m), 3.48 (2H, t, J = 6.5 Hz), 3.68 (3H, s), 4.06 (3H, s), 4.22 (2H, t, J = 5.9 Hz), 6.69 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 2.7 Hz), 7.13-7.31 (2H, m), 7.39 (1H, s), 7.51-7.62 (2H, m), 7.62-7.73 (1H, m), 7.79 (1H, d, J = 8.3 Hz), 8.25 (1H, dd, J = 8.3, 0.5 Hz).

Example 300

· Synthesis of
1-Methyl-6-{3-[2-(7-oxo-7H-furo[2,3-c]pyridin-6-yl)-ethylamino]-propoxy}-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.87-2.03 (2H, m), 2.86 (2H, t, J = 6.7 Hz), 3.06 (2H, t, J = 6.2 Hz), 3.70 (3H, s), 4.06 (2H, t, J = 6.1 Hz), 4.18 (2H, t, J = 6.2 Hz), 6.39 (1H, d, J = 7.0 Hz), 6.61 (1H, d, J = 2.1 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.97 (1H, d, J = 2.8 Hz), 7.08-7.19 (2H, m), 7.21-7.32 (1H, m), 7.59 (1H, d, J = 9.5 Hz), 7.71 (1H, d, J = 2.1 Hz).

Example 301

· Synthesis of
1-Methyl-6-[5-(2-pyridin-3-yl-ethylamino)-pentyloxy]-1H-quinolin-2-one

The synthesis of the title compound was performed in the same manner as in Example 3 using appropriate starting materials.
1H-NMR (CDCl3) δ ppm: 1.44-1.72 (4H, m), 1.72-1.90 (2H, m), 2.67 (2H, t, J = 6.9 Hz), 2.74-2.97 (4H, m), 3.71 (3H, s), 4.00 (2H, t, J = 6.4 Hz), 6.71 (1H, d, J = 9.5 Hz), 6.99 (1H, d, J = 2.8 Hz), 7.17 (1H, dd, J = 9.2, 2.8 Hz), 7.22 (1H, dd, J = 7.8, 4.8 Hz), 7.29 (1H, d, J = 9.2 Hz), 7.50-7.56 (1H, m), 7.59 (1H, d, J = 9.5 Hz), 8.47 (1H, dd, J = 4.8, 1.8 Hz), 8.49 (1H, d, J = 1.8 Hz).

Example 302

N-(2-Methyl-benzyl)-4-(1-methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)-N-{2-[4-(pyridin-3-ylmethoxy)-piperidin-1-yl]-ethyl}-butyramide dihydrochloride

To a DMF solution (3 ml) of 4-(1-Methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)-butyric acid (100 mg) were sequentially added (2-methyl-benzyl)-{2-[4-(pyridin-3-ylmethoxy)-piperidin-1-yl]-ethyl}-amine (143 mg), triethylamine (47mg), diethylphosphorocyanidate (DEPC, 84 mg) while ice-cooling, followed by stirring at room temperature overnight. Water was added to the reaction mixture and then subjected to extraction using ethyl acetate. The thus-obtained organic layer was washed with an aqueous saturated sodium chloride solution twice, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified using silica gel column chromatography (dichloromethane :ethyl acetate :methanol : 28% ammonia solution= 70 : 20 : 10 : 1). The purified product was concentrated under reduced pressure. A 4N-hydrogen chloride in ethyl acetate solution was added to a ethyl acetate solution of the residue. The mixture was condensed under reduced pressure to give the title compound (165 mg) as a pale yellow amorphous solid.

1H-NMR (DMSO-d6) δ ppm: 1.79-2.60 (8H, m), 2.24, 2.28 (total 3H, each-s), 2.68-4.28 (11H, m), 3.58 (3H, s), 4.45-4.76 (4H, m), 6.59, 6.60 (total 1H, each-d, J = 9.5Hz), 6.82-7.50 (7H, m), 7.75-7.88 (1H, m), 7.88-8.00 (1H, m), 8.35-8.50 (1H, m), 8.72-8.95 (2H, m).

Example 303

N-(2-Methyl-benzyl)-4-(1-methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)-N-(2-pyridin-3-yl-ethyl)-butyramide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 302 using appropriate starting materials.

1H-NMR (DMSO-d6) δ ppm: 1.80-2.08 (2H, m), 2.23, 2.27 (total 3H, each-s), 2.29-2.63 (2H, m), 2.96-3.14 (2H, m), 3.59 (3H, s), 3.48-3.70 (2H, m), 3.93, 4.04 (total 2H, each-t, J = 6.3Hz), 4.57, 4.61 (total 2H,

each-s), 6.60, 6.61 (total 1H, each-d, J = 9.5Hz), 6.85-7.33 (6H, m), 7.38-7.50 (1H, m), 7.78-7.89 (1H, m), 7.89-8.00 (1H, m), 8.82-8.47 (1H, m), 8.70-8.80 (1H, m), 8.80-8.92 (1H, m).

Example 304

1-[5-(1-Methyl-2-oxo-1,2-dihydro-quinolin-6-yloxy)-pentyl]-3-phenyl-1-(2-pyridin-3-yl-ethyl)-urea hydrochloride

N-Ethyldiisopropylamine (0.192ml) was added to a dichloromethane solution(5ml) of 1-methyl-6-[5-(2-pyridin-3-ylethylamino)pentyloxy]-1H-quinolin-2-one dihydrochloride (219mg). The mixture was stirred at room temperature for 5 minutes. The reaction mixture was condensed under reduced pressure. Phenylisocyanate(0.065ml) and toluene(2ml) were added to the residue. The mixture was stirred at 100°C for 1 hour. The reaction mixture was purified by NH silica gel column chromatography (ethyl acetate: hexane =1:1→1:0). The purified product was concentrated under reduced pressure. A 1N-hydrogen chloride ethanol solution was added to the solution of the residue in ethanol, and stirred for 30 minutes at room temperature. The precipitated insoluble matter was collected by filtration, washed with ethyl acetate, and dried to give the title compound (147mg) as a pale yellow flakes.

1H-NMR (DMSO-d6) δ ppm: 1.38-1.83 (6H, m), 3.04 (2H, t, J = 7.0 Hz), 3.36 (2H, t, J = 7.1 Hz), 3.59 (3H, s), 3.65 (2H, t, J = 7.1 Hz), 4.03 (2H, t, J = 6.4 Hz), 6.60 (1H, d, J = 9.5 Hz), 6.93 (1H, t, J = 7.3 Hz), 7.18-7.28 (4H, m), 7.38-7.45 (3H, m), 7.81 (1H, d, J = 9.5 Hz), 7.89-7.94 (1H, m), 8.26 (1H, s), 8.42 (1H, d, J = 8.1 Hz), 8.73 (1H, d, J = 5.5 Hz), 8.86 (1H, s)

Example 305

2-Methyl-N-[3-(1-methyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yloxy)-propyl]-N-(2-pyridin-3-yl-ethyl)-benzamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.

1H-NMR (DMSO-D6, 100°C) δ ppm: 1.81-2.08 (2H, m), 2.14 (3H, s), 2.40-2.60 (2H, m), 2.70-2.84 (2H, m), 2.85-3.03 (2H, m), 3.21 (3H,

s), 3.38-3.73 (4H, m), 3.78-4.00 (2H, m), 6.56-6.82 (2H, m), 6.85-7.04 (2H, m), 7.08-7.31 (3H, m), 7.32-7.48 (1H, m), 7.54-7.84 (1H, m), 8.28-8.60 (2H, m).

Example 306

4-Methyl-N-[3-(1-methyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yloxy)-propyl]-N-(2-pyridin-3-yl-ethyl)-benzamide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.

1H-NMR (DMSO-D6, 100°C) δ ppm : 1.86-2.02 (2H, m), 2.32 (3H, s), 2.40-2.60 (2H, m), 2.73-2.88 (2H, m), 2.89-3.02 (2H, m), 3.21 (3H, s), 3.40-3.52 (2H, m), 3.56-3.69 (2H, m), 3.87-3.96 (2H, m), 6.70 (1H, s), 6.62-6.78 (1H, m), 6.93 (1H, d, J=9.0 Hz), 7.10 (2H, d, J=8.0 Hz), 7.17 (2H, d, J=8.0 Hz), 7.41-7.58 (1H, m), 7.73-7.93 (1H, m), 8.38-8.58 (2H, m).

Example 307

N-[3-(1-Methyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yloxy)-propyl]-N-(2-pyridin-3-yl-ethyl)-isobutyramide hydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.

1H-NMR (DMSO-D6, 100°C) δ ppm: 0.94 (6H, d, J=6.6 Hz), 1.86-2.00 (2H, m), 2.43-2.53 (2H, m), 2.65-2.89 (3H, m), 2.89-3.02 (2H, m), 3.21 (3H, s), 3.34-3.50 (2H, m), 3.52-3.66 (2H, m), 3.90-4.04 (2H, m), 6.70-6.84 (2H, m), 6.89-7.01 (1H, m), 7.56-7.70 (1H, m), 7.98-8.12 (1H, m), 8.50-8.67 (2H, m).

Example 308

N-[3-(1-Methyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yloxy)-propyl]-N-(2-pyridin-3-yl-ethyl)-isonicotinamide dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 45 using appropriate starting materials.

1H-NMR (DMSO-D6, 100°C) δ ppm: 1.90-2.05 (2H, m), 2.49-2.53 (2H, m), 2.74-2.88 (2H, m), 2.91-3.12 (2H, m), 3.21 (3H, s), 3.32-3.54 (2H, m), 3.54-3.75 (2H, m), 3.81-4.02 (2H, m), 6.60-6.81 (2H, m), 6.94 (1H, d, J=8.7 Hz), 7.23 (2H, d, J=5.1 Hz), 7.43-7.68 (1H, m), 7.76-8.09

(1H, m), 8.42-8.70 (4H, m).

Examples 310 to 986

The folowing compounds were obtained in the same manner as in Examples above using appropriate starting materials.

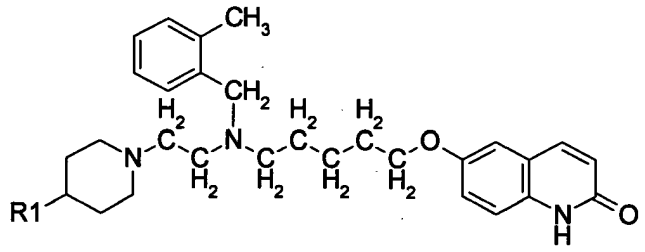


Table A

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 310 | $-OCH_3$ | 492 |
| 311 | $-O(CH_2)_2C_6H_5$ | 582 |
| 312 | $-N(CH_3)(CH_2)_2N(CH_3)C_6H_5$ | 624 |
| 313 | $-OCH(C_6H_5)_2$ | 644 |
| 314 | $-N(CH_3)(CH_2)_2C_6H_5$ | 595 |
| 315 | $-N(CH_3)(CH_2)_2N(C_2H_5)_2$ | 590 |
| 316 | $-OC_6H_5$ | 554 |
| 317 | $-C_6H_5$ | 538 |
| 318 | $-CH_2CONHC_2H_5$ | 547 |

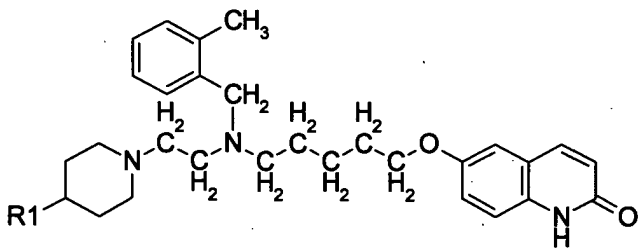
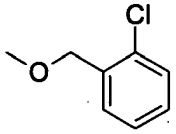
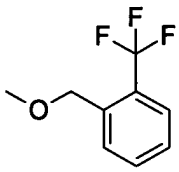
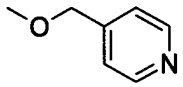
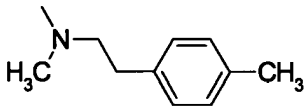
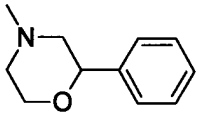
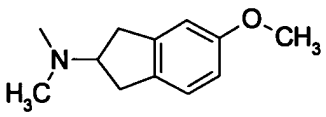
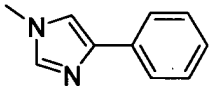
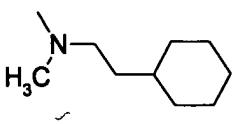
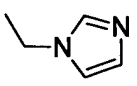
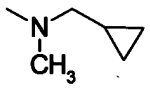
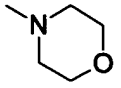
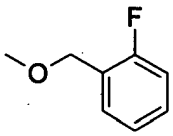
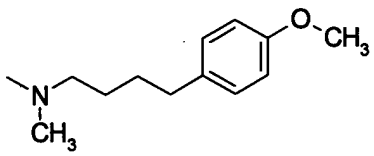
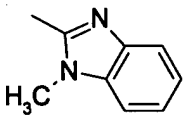
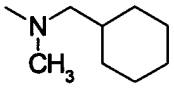
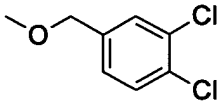
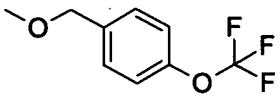
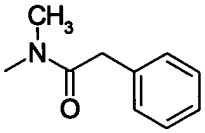
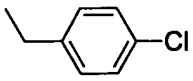
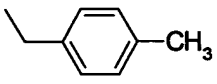
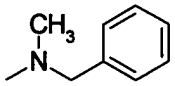
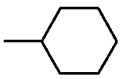
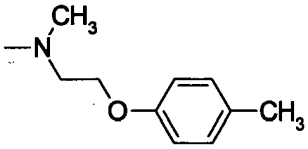
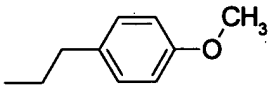
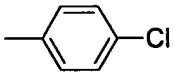
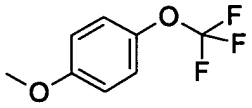
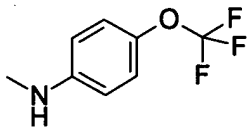
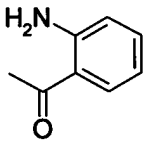
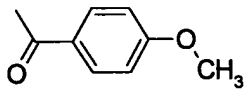
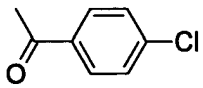
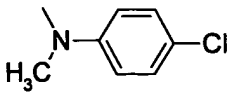
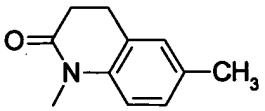
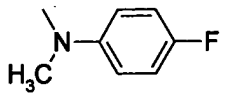


Table B

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 319 |  | 602 |
| 320 |  | 636 |
| 321 |  | 569 |
| 322 |  | 609 |
| 323 |  | 623 |
| 324 |  | 637 |
| 325 |  | 604 |
| 326 |  | 601 |
| 327 |  | 542 |

| | | |
|---|---|---|
| 328 |  | 545 |
| 329 |  | 547 |
| 330 |  | 586 |
| 331 |  | 653 |
| 332 |  | 592 |
| 333 |  | 587 |
| 334 |  | 636 |
| 335 |  | 652 |
| 336 |  | 609 |
| 337 |  | 586 |
| 338 |  | 566 |

| | | |
|---|---|---|
| 339 |  | 581 |
| 340 |  | 544 |
| 341 |  | 625 |
| 342 |  | 596 |
| 343 |  | 572 |
| 344 |  | 638 |
| 345 |  | 637 |
| 346 |  | 581 |
| 347 |  | 596 |
| 348 |  | 600 |
| 349 |  | 601 |
| 350 |  | 621 |

| | | |
|---|---|---|
| 351 |  | 585 |

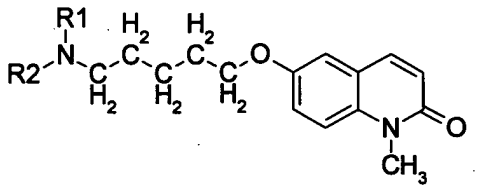


Table C

| Example No. | R1 | R2 | MS(M+1) |
|---|---|---|---|
| 352 | $-(CH_2)_3CH_3$ | $-(CH_2)_3CH_3$ | 373 |
| 353 | $-CH_2C_6H_5$ | $-(CH_2)_3N(CH_3)_2$ | 436 |
| 354 | $-CH_3$ | $-(CH_2)_3N(CH_3)CH_2C_6H_5$ | 436 |
| 355 | -H | $-(CH_2)_3N(CH_3)_2$ | 346 |
| 356 | $-CH_3$ | $-CH_3$ | 289 |

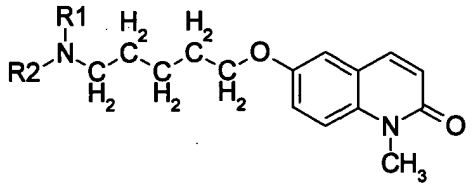
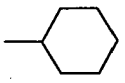
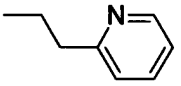
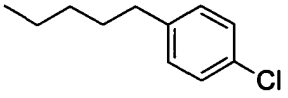
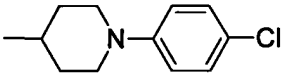
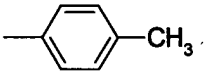
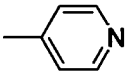
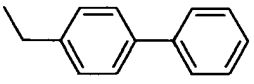
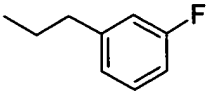
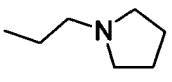
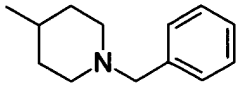
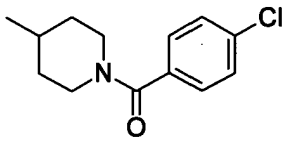
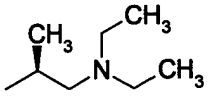


Table D

| Example No. | R1 | R2 | MS(M+1) |
|---|---|---|---|
| 357 | -$CH_3$ |  | 357 |
| 358 | -$CH_3$ |  | 380 |
| 359 | -$C_2H_5$ |  | 455 |
| 360 | -$CH_3$ |  | 468 |
| 361 | -$CH_3$ | | 399 |
| 362 | -H |  | 351 |
| 363 | -H |  | 338 |
| 364 | -$C_2H_5$ |  | 455 |
| 365 | -H |  | 383 |
| 366 | -H |  | 358 |

| | | | |
|---|---|---|---|
| 367 | -$CH_3$ |  | 448 |
| 368 | -$CH_3$ |  | 496 |
| 369 | -H |  | 374 |

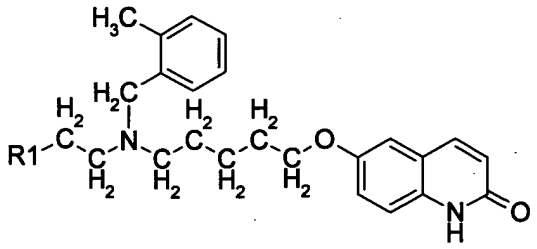
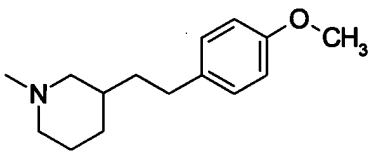
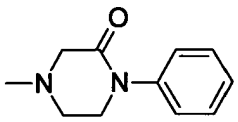
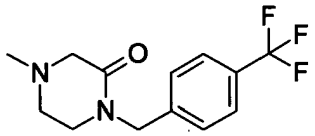
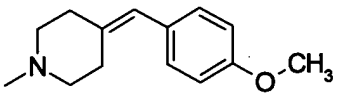
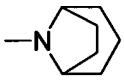
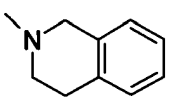
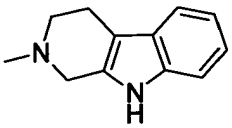
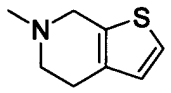
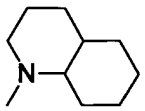
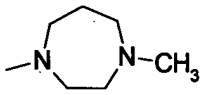
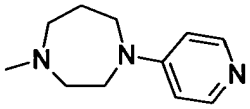
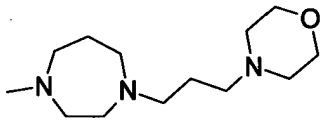
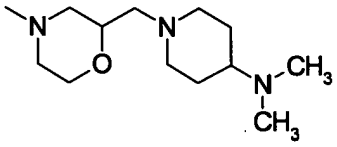
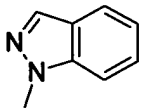
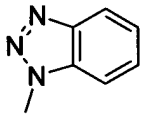
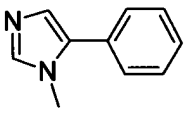
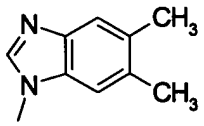
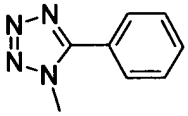
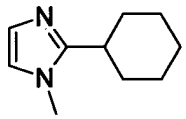
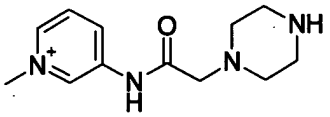
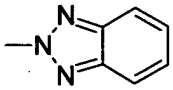
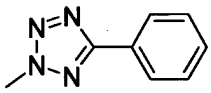
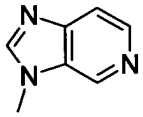


Table E

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 370 |  | 596 |
| 371 |  | 553 |
| 372 |  | 635 |
| 373 |  | 580 |
| 374 |  | 488 |
| 375 | | 530 |
| 376 |  | 510 |
| 377 |  | 549 |

| | | |
|---|---|---|
| 378 |  | 516 |
| 379 |  | 516 |
| 380 |  | 491 |
| 381 |  | 554 |
| 382 |  | 604 |
| 383 |  | 604 |
| 384 |  | 495 |
| 385 |  | 496 |
| 386 |  | 521 |
| 387 |  | 523 |
| 388 |  | 523 |

| | | |
|---|---|---|
| 389 |  | 527 |
| 390 |  | 597 |
| 391 |  | 496 |
| 392 |  | 523 |
| 393 |  | 496 |

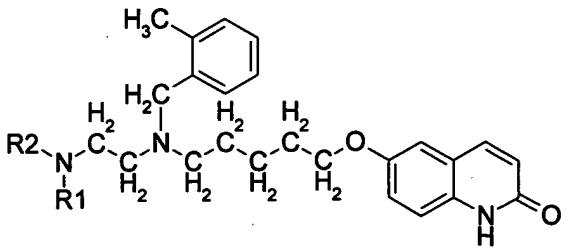


Table F

| Example No. | R1 | R2 | MS(M+1) |
|---|---|---|---|
| 394 | $-(CH_2)_2CH_3$ | $-(CH_2)_3C_6H_5$ | 554 |
| 395 | $-(CH_2)_2N(CH_3)_2$ | $-CH_2C_6H_5$ | 555 |
| 396 | -H | $-CH_2C(CH_3)_3$ | 464 |
| 397 | $-CH_3$ | $-(CH_2)_2N(C_2H_5)_2$ | 507 |
| 398 | -H | $-(CH_2)_2SCH_3$ | 468 |

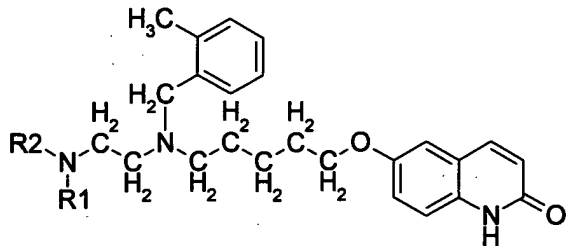
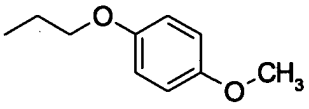
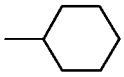
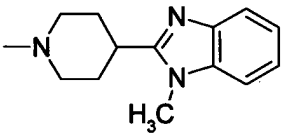
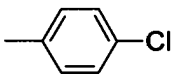
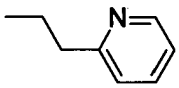
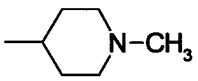
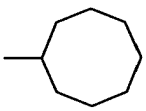
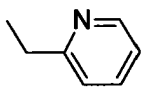
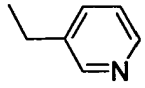
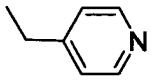
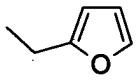
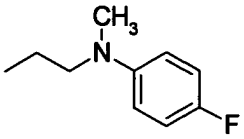
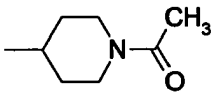
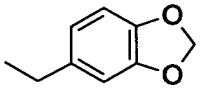
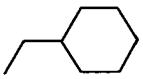
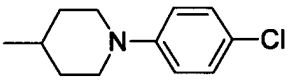
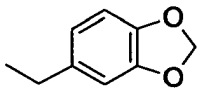
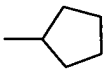
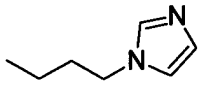
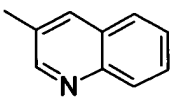
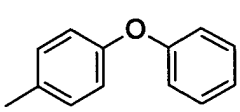
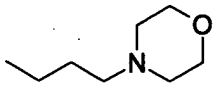
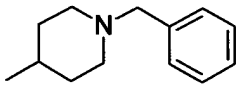
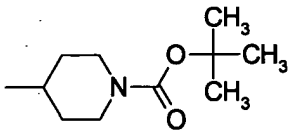
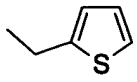
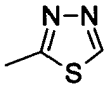
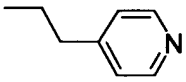
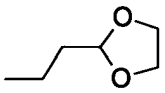
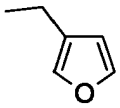
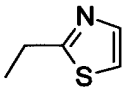
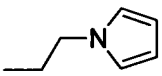


Table G

| Example No. | R1 | R2 | MS(M+1) |
|---|---|---|---|
| 399 | $-C_2H_5$ |  | 572 |
| 400 | $-CH_3$ |  | 490 |
| 401 | -H |  | 607 |
| 402 | $-CH_3$ |  | 518 |
| 403 | $-CH_3$ |  | 513 |
| 404 | $-CH_3$ |  | 505 |
| 405 | -H |  | 504 |
| 406 | -H |  | 485 |
| 407 | -H |  | 485 |

| | | | |
|---|---|---|---|
| 408 | -H |  | 485 |
| 409 | -H |  | 474 |
| 410 | $-CH_3$ |  | 559 |
| 411 | $-CH_3$ |  | 533 |
| 412 | $-C_2H_5$ |  | 556 |
| 413 | $-C_2H_5$ |  | 518 |
| 414 | $-CH_3$ |  | 601 |
| 415 | -H |  | 528 |
| 416 | -H |  | 462 |
| 417 | -H |  | 502 |
| 418 | -H |  | 521 |
| 419 | -H |  | 562 |

| | | | |
|---|---|---|---|
| 420 | -H |  | 521 |
| 421 | $-CH_2C_6H_5$ |  | 657 |
| 422 | $-CH_3$ |  | 591 |
| 423 | -H |  | 490 |
| 424 | -H |  | 478 |
| 425 | -H |  | 499 |
| 426 | -H |  | 494 |
| 427 | -H |  | 474 |
| 428 | -H |  | 491 |
| 429 | -H |  | 487 |

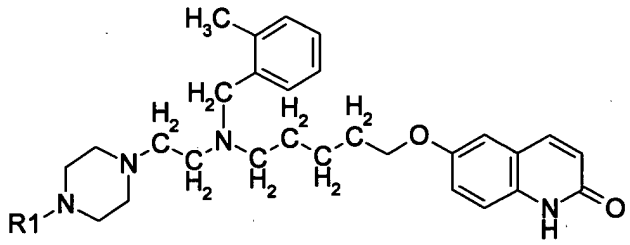


Table H

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 432 | $-(CH_2)_3CH_3$ | 519 |
| 433 | $-(CH_2)_2N(CH_3)_2$ | 534 |
| 434 | $-(CH_2)_3OCH_3$ | 535 |
| 435 | $-(CH_2)_5CH_3$ | 547 |
| 436 | $-CO_2C(CH_3)_3$ | 563 |

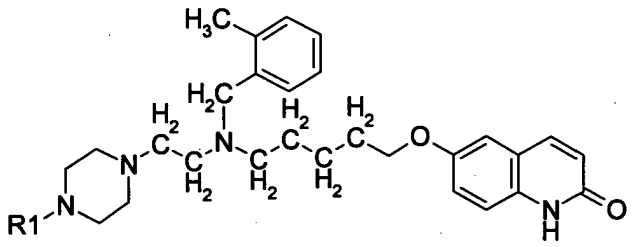
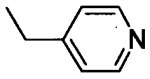
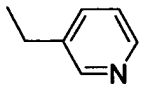
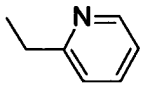
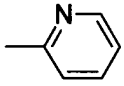
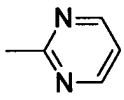
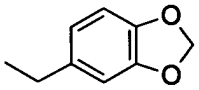
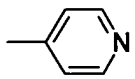
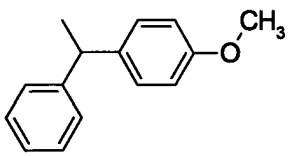
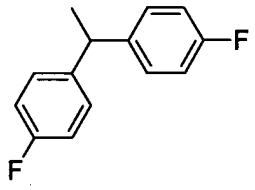
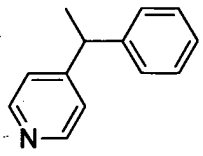
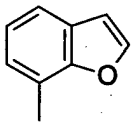
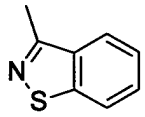
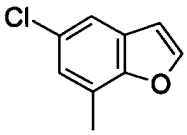
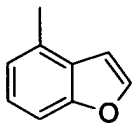
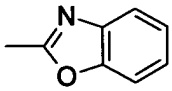
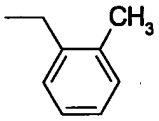
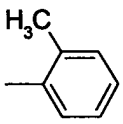
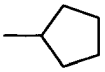
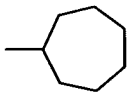
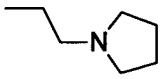
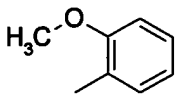
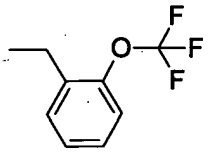
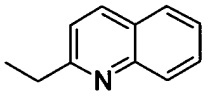
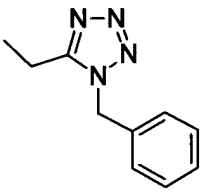
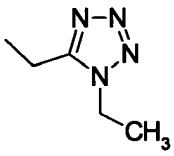
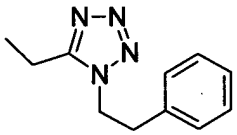
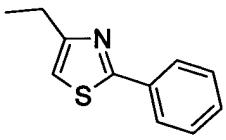
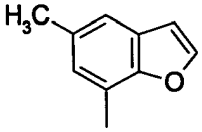
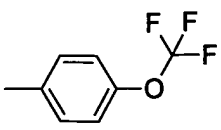
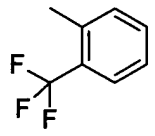
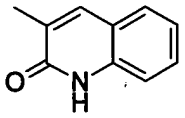
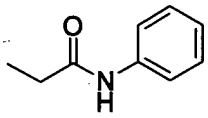
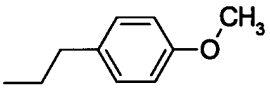
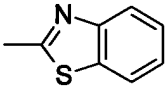
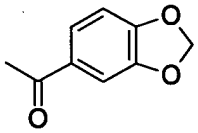
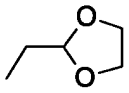
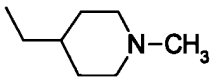
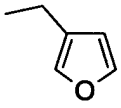
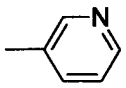
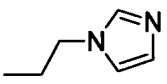
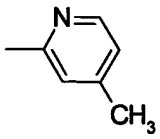


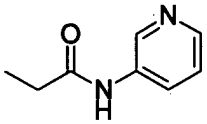
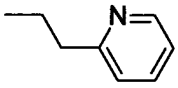
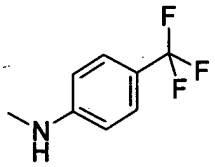
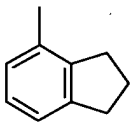
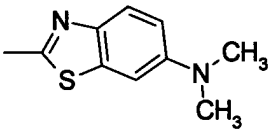
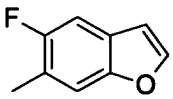
Table I

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 437 |  | 554 |
| 438 |  | 554 |
| 439 |  | 554 |
| 440 |  | 540 |
| 441 |  | 541 |
| 442 |  | 597 |
| 443 |  | 540 |
| 444 |  | 659 |

| | | |
|---|---|---|
| 445 |  | 665 |
| 446 |  | 630 |
| 447 |  | 579 |
| 448 |  | 596 |
| 449 |  | 613 |
| 450 |  | 579 |
| 451 |  | 580 |
| 452 |  | 567 |
| 453 |  | 553 |
| 454 |  | 531 |
| 455 |  | 559 |

| | | |
|---|---|---|
| 456 |  | 560 |
| 457 |  | 569 |
| 458 |  | 637 |
| 459 |  | 604 |
| 460 |  | 635 |
| 461 |  | 573 |
| 462 |  | 649 |
| 463 |  | 636 |
| 464 |  | 593 |
| 465 |  | 623 |

| | | |
|---|---|---|
| 466 |  | 607 |
| 467 |  | 606 |
| 468 |  | 596 |
| 469 |  | 597 |
| 470 |  | 596 |
| 471 |  | 611 |
| 472 |  | 549 |
| 473 |  | 574 |
| 474 |  | 543 |
| 475 |  | 540 |
| 476 |  | 557 |
| 477 |  | 554 |

| | | |
|---|---|---|
| 478 |  | 597 |
| 479 |  | 568 |
| 480 |  | 622 |
| 481 |  | 579 |
| 482 |  | 639 |
| 483 |  | 597 |

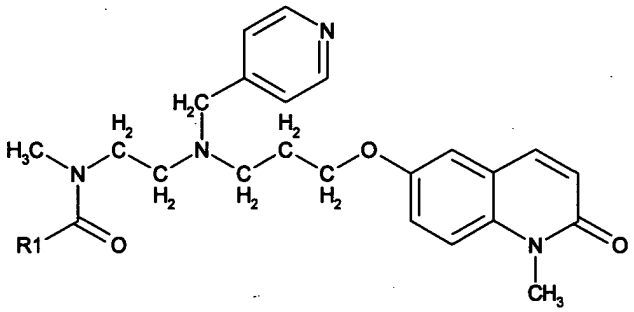


Table J

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 484 | $-CH_2OC_6H_5$ | 515 |
| 485 | $-(CH_2)_2C_6H_5$ | 513 |
| 486 | $-CH=CHC_6H_5$ | 511 |
| 487 | $-(CH_2)_2OC_6H_5$ | 529 |
| 488 | $-(CH_2)_3C_6H_5$ | 527 |
| 489 | $-CH(CH_3)_2$ | 451 |
| 490 | $-(CH_2)_2N(COCH_3)C_6H_5$ | 570 |

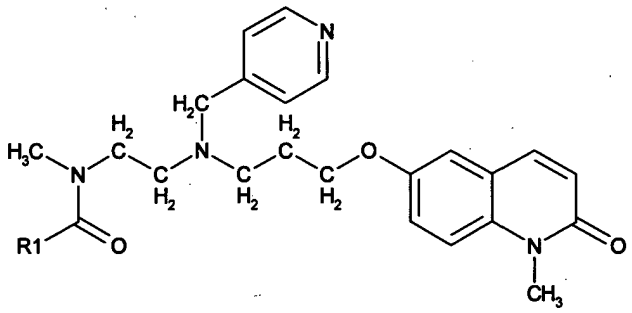
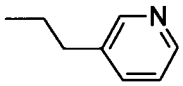
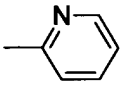
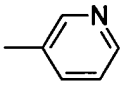
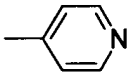
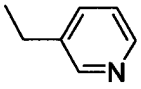
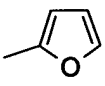
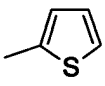
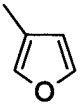
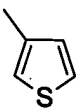
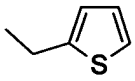
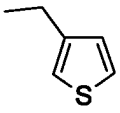
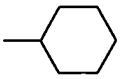
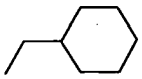
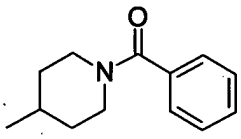
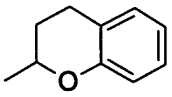
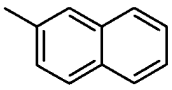
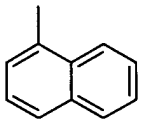
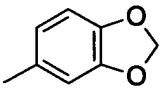
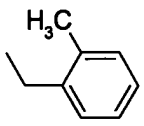
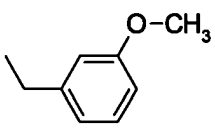
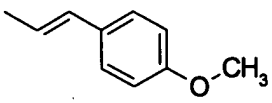
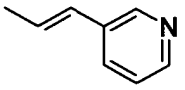
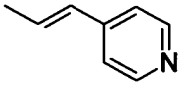
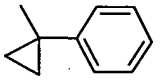
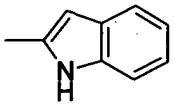
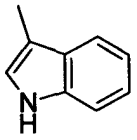
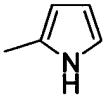
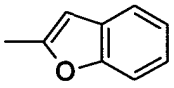
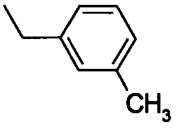
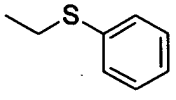
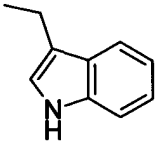
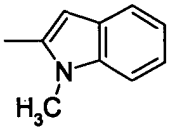
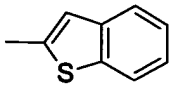
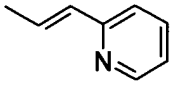
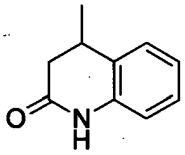
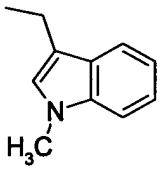
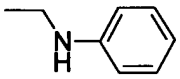
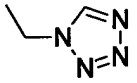
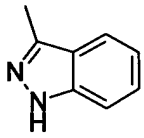
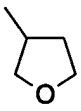
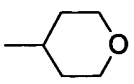
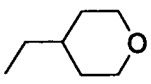
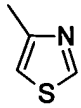


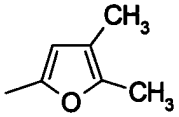
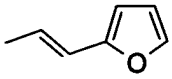
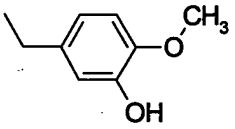
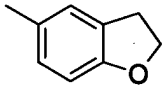
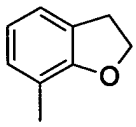
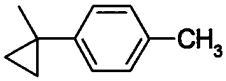
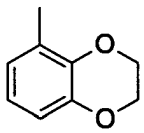
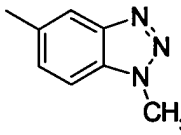
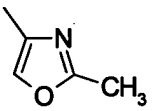
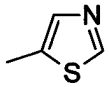
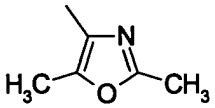
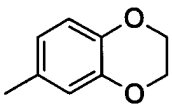
Table K

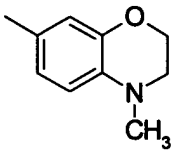
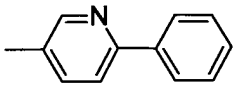
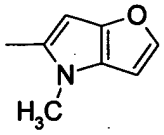
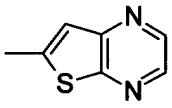
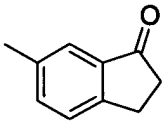
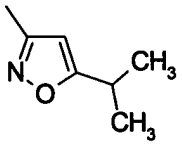
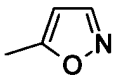
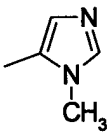
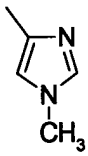
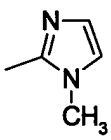
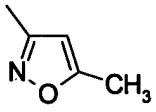
| Example No. | R1 | MS(M+1) |
|---|---|---|
| 491 |  | 514 |
| 492 |  | 486 |
| 493 |  | 486 |
| 494 |  | 486 |
| 495 |  | 500 |
| 496 |  | 475 |
| 497 |  | 491 |
| 498 |  | 475 |
| 499 |  | 491 |

| | | |
|---|---|---|
| 500 |  | 505 |
| 501 |  | 505 |
| 502 |  | 491 |
| 503 |  | 505 |
| 504 |  | 596 |
| 505 |  | 541 |
| 506 |  | 535 |
| 507 |  | 535 |
| 508 |  | 529 |
| 509 |  | 513 |
| 510 |  | 529 |
| 511 |  | 541 |

| | | |
|---|---|---|
| 512 |  | 512 |
| 513 |  | 512 |
| 514 |  | 525 |
| 515 |  | 524 |
| 516 |  | 524 |
| 517 |  | 474 |
| 518 |  | 525 |
| 519 |  | 513 |
| 520 |  | 531 |
| 521 |  | 538 |
| 522 |  | 538 |

| | | |
|---|---|---|
| 523 |  | 541 |
| 524 |  | 512 |
| 525 |  | 554 |
| 526 |  | 552 |
| 527 |  | 514 |
| 528 |  | 491 |
| 529 |  | 525 |
| 530 |  | 479 |
| 531 |  | 493 |
| 532 |  | 507 |
| 533 |  | 492 |

| | | |
|---|---|---|
| 534 |  | 503 |
| 535 |  | 501 |
| 536 |  | 545 |
| 537 |  | 527 |
| 538 |  | 527 |
| 539 |  | 539 |
| 540 |  | 543 |
| 541 |  | 540 |
| 542 |  | 490 |
| 543 |  | 492 |
| 544 |  | 504 |
| 545 |  | 543 |

| | | |
|---|---|---|
| 546 |  | 556 |
| 547 |  | 562 |
| 548 |  | 528 |
| 549 |  | 543 |
| 550 |  | 539 |
| 551 |  | 518 |
| 552 |  | 476 |
| 553 |  | 489 |
| 554 |  | 489 |
| 555 |  | 489 |
| 556 |  | 490 |

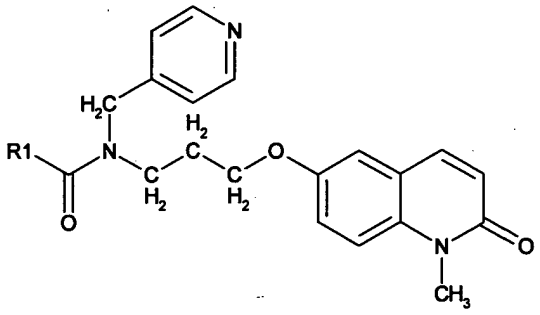
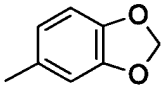
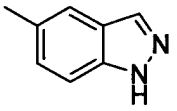
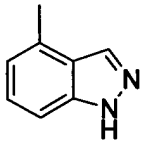
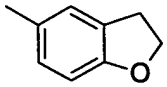
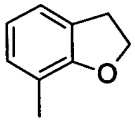
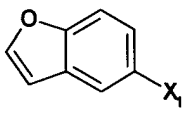
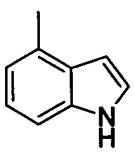
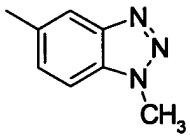
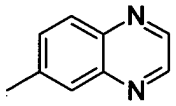
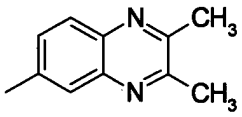
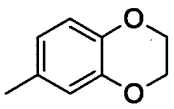
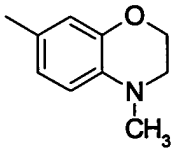
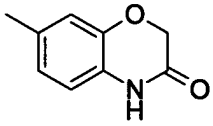
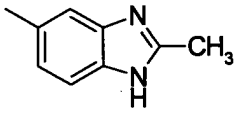
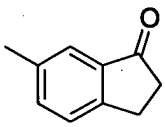
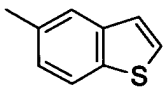
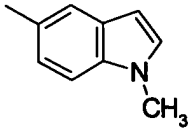


Table L

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 557 |  | 472 |
| 558 |  | 468 |
| 559 |  | 468 |
| 560 |  | 470 |
| 561 |  | 470 |
| 562 |  | 468 |
| 563 |  | 467 |

| | | |
|---|---|---|
| 564 |  | 483 |
| 565 |  | 480 |
| 566 |  | 508 |
| 567 |  | 486 |
| 568 |  | 499 |
| 569 |  | 499 |
| 570 |  | 482 |
| 571 |  | 482 |
| 572 |  | 484 |
| 573 |  | 481 |

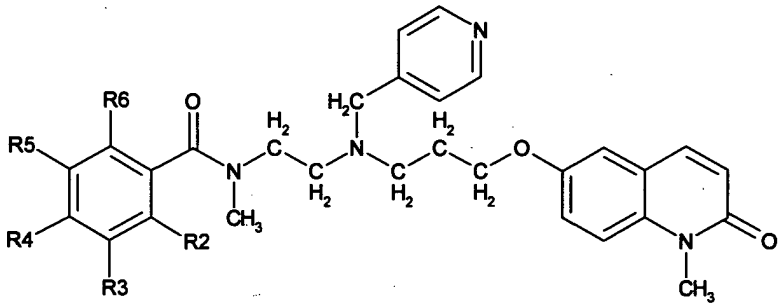
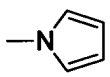
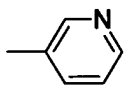


Table M

| Example No. | R2 | R3 | R4 | R5 | R6 | MS(M+1) |
|---|---|---|---|---|---|---|
| 574 | -H | -H | $-OCH_3$ | -H | -H | 515 |
| 575 | -H | -H | $-NHCOCH_3$ | -H | -H | 542 |
| 576 | -H | -H | -H | $-NHCOCH_3$ | -H | 542 |
| 577 | -H | -H | $-CF_3$ | -H | -H | 553 |
| 578 | -H | -H | -H | -H | $-OCH_3$ | 515 |
| 579 | -H | -H | -H | -H | $-CH_3$ | 499 |
| 580 | -H | -H | -H | -H | -F | 503 |
| 581 | -H | -H | -H | -H | $-N(CH_3)_2$ | 528 |
| 582 | -H | -H | -H | $-OCH_3$ | -H | 515 |
| 583 | -H | -H | -H | $-CH_3$ | -H | 499 |
| 584 | -H | -H | $-COCH_3$ | -H | -H | 527 |
| 585 | -H | -H | $-C_6H_5$ | -H | -H | 561 |
| 586 | -H | -H | $-SO_2NH_2$ | -H | -H | 564 |
| 587 | -H | -H |  | -H | -H | 550 |
| 588 | -H | -H |  | -H | -H | 562 |

5

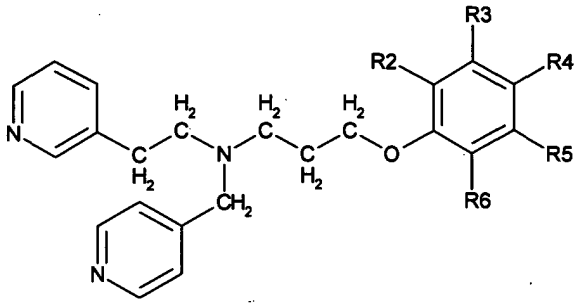
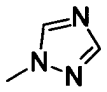
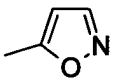
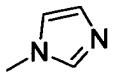
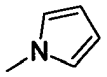
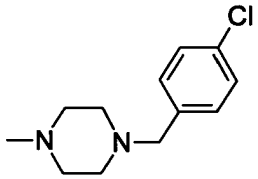



Table N

| Example No. | R2 | R3 | R4 | R5 | R6 | MS(M+1) |
|---|---|---|---|---|---|---|
| 589 | -H | -H | -H | -H | $-OCH_3$ | 378 |
| 590 | -H | -H | -H | $-OCH_3$ | -H | 378 |
| 591 | -H | -H | $-OCH_3$ | -H | -H | 378 |
| 592 | -H | -H | -H | -H | -H | 348 |
| 593 | -H | -H | -H | -H | -CN | 373 |
| 594 | -H | -H | -H | -CN | -H | 373 |
| 595 | -H | -H | -CN | -H | -H | 373 |
| 596 | -H | -H | -H | -H | $-CF_3$ | 416 |
| 597 | -H | -H | -H | $-CF_3$ | -H | 416 |
| 598 | -H | -H | $-CF_3$ | -H | -H | 416 |
| 599 | -H | -H | -H | -H | $-OCF_3$ | 432 |
| 600 | -H | -H | -H | $-OCF_3$ | -H | 432 |
| 601 | -H | -H | $-OCF_3$ | -H | -H | 432 |
| 602 | -H | -H | -H | $-C_6H_5$ | -H | 424 |
| 603 | -H | -H | -H | $-N(C_2H_5)_2$ | -H | 419 |
| 604 | -H | -H | $-(CH_2)_2COCH_3$ | -H | -H | 418 |
| 605 | -H | -H | $-COC_2H_5$ | -H | -H | 404 |
| 606 | -H | -OH | $-COCH_3$ | -H | -H | 406 |
| 607 | -H | -H | $-SCH_3$ | -H | -H | 394 |
| 608 | -H | -H | $-C_6H_5$ | -H | -H | 424 |
| 609 | -H | -H | -H | -H | $-C_6H_5$ | 424 |
| 610 | -H | -H | -H | $-OC_6H_5$ | -H | 440 |
| 611 | -H | -H | $-COCH_3$ | -H | -H | 390 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 612 | -H | -H |  | -H | -H | 415 |
| 613 | -H | -H | -H | -H |  | 415 |
| 614 | -H | -H |  | -H | -H | 414 |
| 615 | -H | -H |  | -H | -H | 413 |
| 616 | -H | -H |  | -H | -H | 556 |

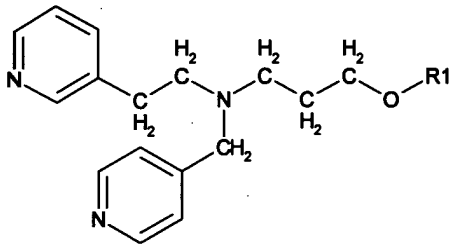
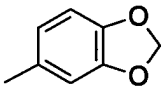
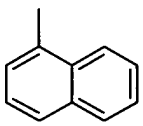
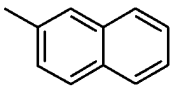
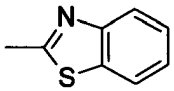
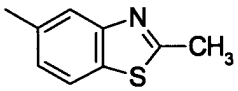
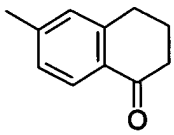
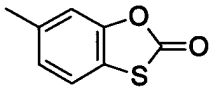
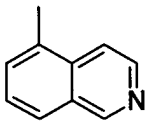
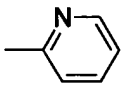
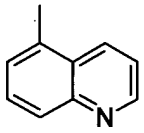
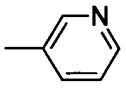
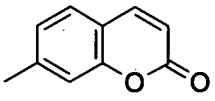
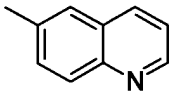
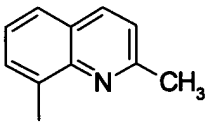
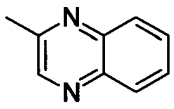
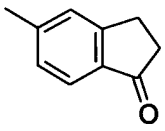
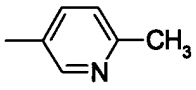
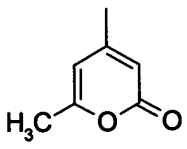
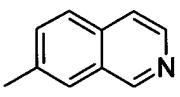
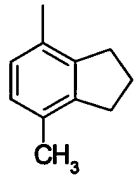
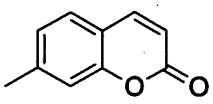
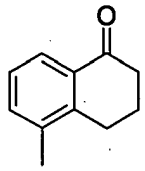
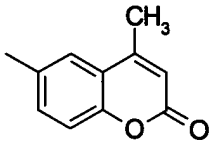
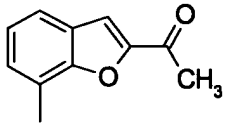
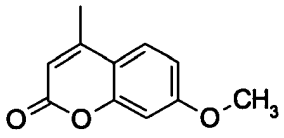
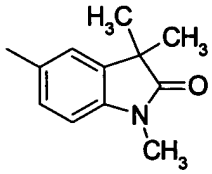
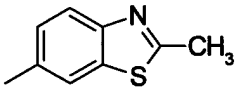
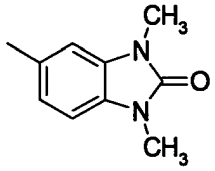
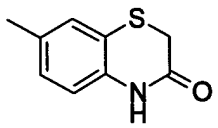
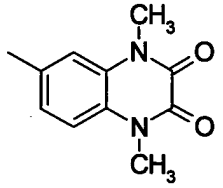
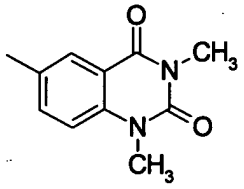
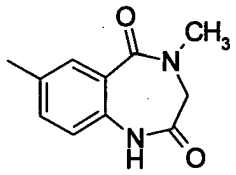
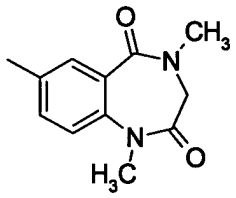
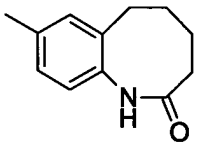
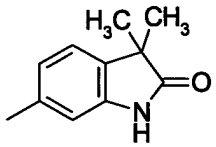
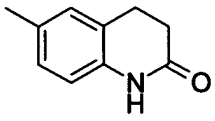
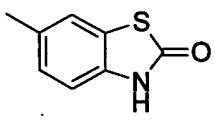
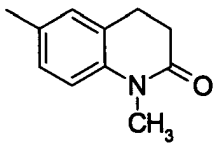


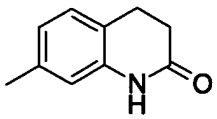
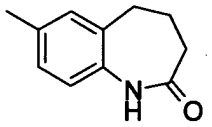
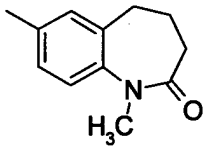
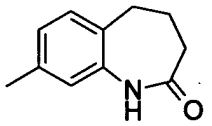
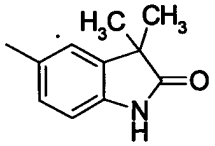
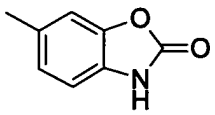
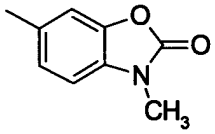
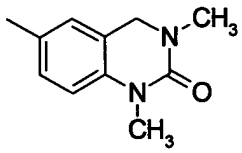
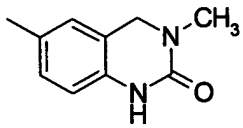
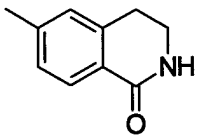
Table O

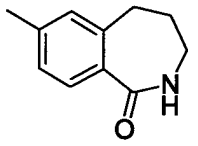
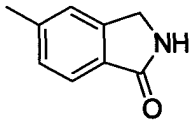
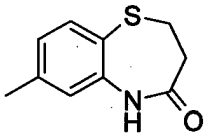
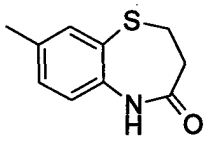
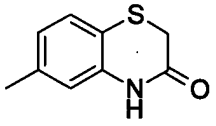
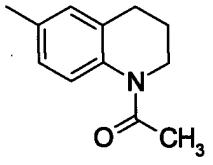
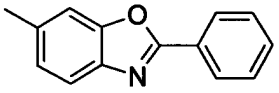
| Example No. | R1 | MS(M+1) |
|---|---|---|
| 617 |  | 392 |
| 618 |  | 398 |
| 619 |  | 398 |
| 620 |  | 405 |
| 621 |  | 419 |
| 622 |  | 416 |
| 623 |  | 422 |
| 624 |  | 399 |

| | | |
|---|---|---|
| 625 |  | 349 |
| 626 |  | 399 |
| 627 |  | 349 |
| 628 |  | 416 |
| 629 |  | 399 |
| 630 |  | 413 |
| 631 |  | 400 |
| 632 |  | 402 |
| 633 |  | 363 |
| 634 |  | 380 |
| 635 |  | 399 |

| | | |
|---|---|---|
| 636 |  | 402 |
| 637 |  | 416 |
| 638 |  | 416 |
| 639 |  | 430 |
| 640 |  | 430 |
| 641 |  | 446 |
| 642 |  | 445 |
| 643 |  | 419 |
| 644 |  | 432 |
| 645 |  | 435 |

| | | |
|---|---|---|
| 646 |  | 460 |
| 647 |  | 460 |
| 648 |  | 460 |
| 649 |  | 474 |
| 650 |  | 445 |
| 651 |  | 431 |
| 652 |  | 417 |
| 653 |  | 421 |
| 654 |  | 431 |

| | | |
|---|---|---|
| 655 |  | 417 |
| 656 |  | 431 |
| 657 |  | 445 |
| 658 |  | 431 |
| 659 |  | 431 |
| 660 |  | 405 |
| 661 |  | 419 |
| 662 |  | 446 |
| 663 |  | 432 |
| 664 |  | 417 |

| | | |
|---|---|---|
| 665 |  | 431 |
| 666 |  | 403 |
| 667 |  | 449 |
| 668 |  | 449 |
| 669 |  | 435 |
| 670 |  | 445 |
| 671 |  | 465 |

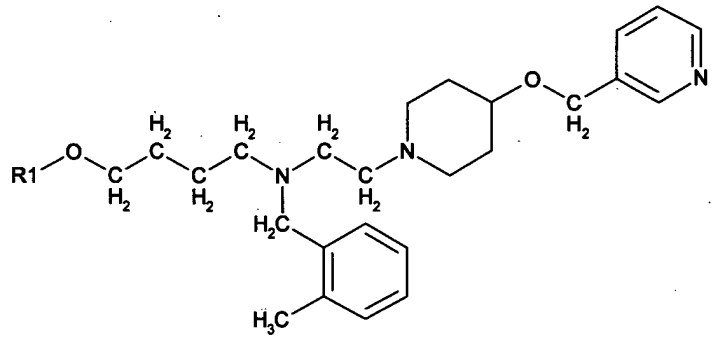
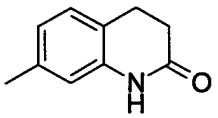
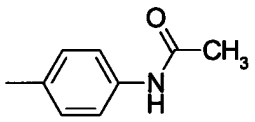
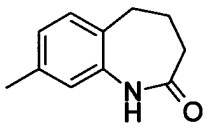
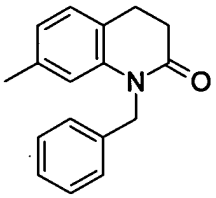
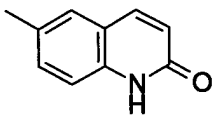
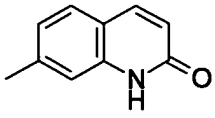
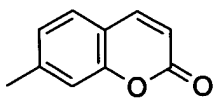
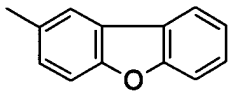
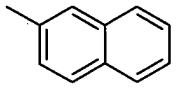
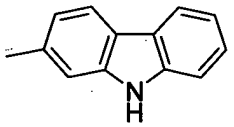
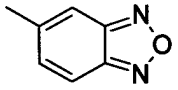
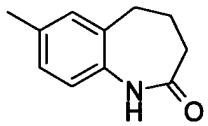
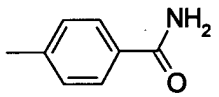
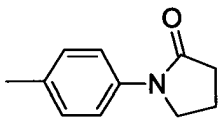
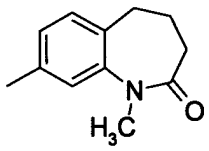
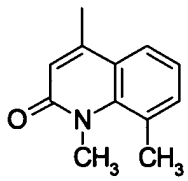
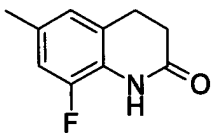
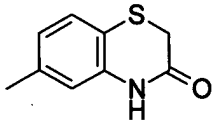
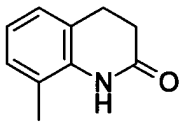
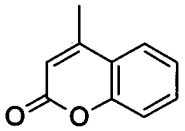
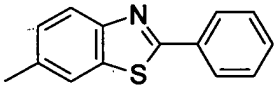
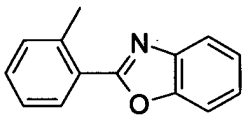


Table P

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 672 |  | 557 |
| 673 |  | 545 |
| 674 |  | 571 |
| 675 |  | 647 |
| 676 |  | 555 |
| 677 |  | 555 |
| 678 |  | 556 |

| | | |
|---|---|---|
| 679 |  | 578 |
| 680 |  | 538 |
| 681 |  | 577 |
| 682 |  | 530 |
| 683 |  | 571 |
| 684 |  | 531 |
| 685 |  | 571 |
| 686 |  | 585 |
| 687 |  | 583 |
| 688 |  | 575 |
| 689 |  | 575 |

| | | |
|---|---|---|
| 690 |  | 557 |
| 691 |  | 556 |
| 692 |  | 621 |
| 693 |  | 605 |

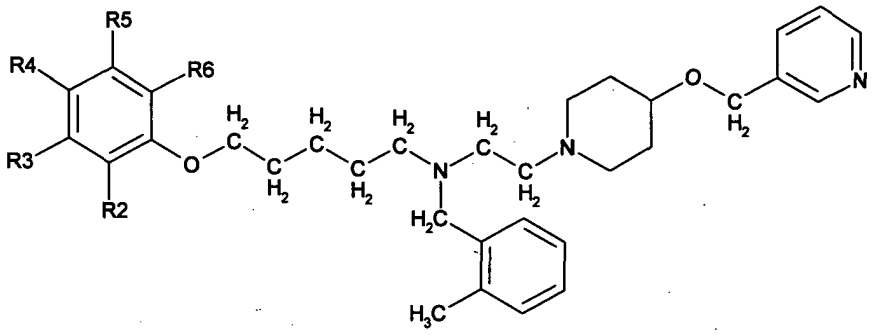
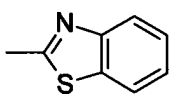
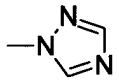
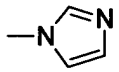
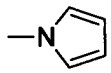
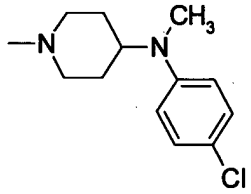
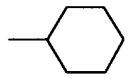
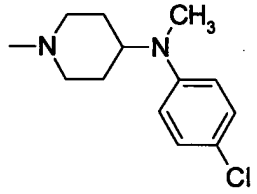
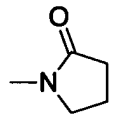


Table Q

| Example No. | R2 | R3 | R4 | R5 | R6 | MS(M+1) |
|---|---|---|---|---|---|---|
| 694 | -H | -H | $-OCH_3$ | -H | -H | 532 |
| 695 | -H | $-OCH_3$ | $-OCH_3$ | -H | -H | 562 |
| 696 | -Cl | -H | -H | -H | -H | 536 |
| 697 | -H | -Cl | -H | -H | -H | 536 |
| 698 | -H | -H | -Cl | -H | -H | 536 |
| 699 | -H | -Cl | -Cl | -H | -H | 570 |
| 700 | -H | -H | $-CH_3$ | -H | -H | 516 |
| 701 | -H | $-CH_3$ | $-CH_3$ | -H | -H | 530 |
| 702 | -H | -H | $-CO_2C_2H_5$ | -H | -H | 574 |
| 703 | -H | -H | -CN | -H | -H | 527 |
| 704 | -H | -H | $-CF_3$ | -H | -H | 570 |
| 705 | -H | -H | $-OCF_3$ | -H | -H | 586 |
| 706 | -H | -H | $-(CH_2)_2CH_3$ | -H | -H | 544 |
| 707 | -H | -F | -Cl | -H | -H | 554 |
| 708 | $-OCH_3$ | -H | $-CH_2CH=CH_2$ | -H | -H | 572 |
| 709 | -H | $-N(C_2H_5)_2$ | -H | -H | -H | 573 |
| 710 | -H | -H | $-CH(CH_3)_2$ | -H | -H | 544 |
| 711 | -H | -H | $-(CH_2)_2COCH_3$ | -H | -H | 572 |
| 712 | -H | $-NHC_6H_5$ | -H | -H | -H | 593 |
| 713 | -H | -H | $-SCH_3$ | -H | -H | 548 |
| 714 |  | -H | -H | -H | -H | 635 |
| 715 | -H | -H | $-C_6H_5$ | -H | -H | 578 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 716 | -H | -H | $-OCH_2C_6H_5$ | -H | -H | 608 |
| 717 | -H | -H | $-CH_2C_6H_5$ | -H | -H | 592 |
| 718 | -H | -H | $-O(CH_2)_7CH_3$ | -H | -H | 630 |
| 719 | -H | $-OC_6H_5$ | -H | -H | -H | 594 |
| 720 | -H | -H | $-(CH_2)_5CH_3$ | -H | -H | 586 |
| 721 | -H | -H | $-NO_2$ | -H | -H | 547 |
| 722 | -H | -H | $-COCH_3$ | -H | -H | 544 |
| 723 | -H | -H | -H | -H | -H | 502 |
| 724 | -H | -H | $-NHCOCH_3$ | -H | -H | 559 |
| 725 | -H | -H |  | -H | -H | 569 |
| 726 | -H | -H |  | -H | -H | 568 |
| 727 | -H | -H |  | -H | -H | 567 |
| 728 | -H | -H |  | -H | -H | 724 |
| 729 | -H | -H |  | -H | -H | 584 |
| 730 | -H | -H |  | -H | -H | 724 |
| 731 | -H | -H |  | -H | -H | 585 |

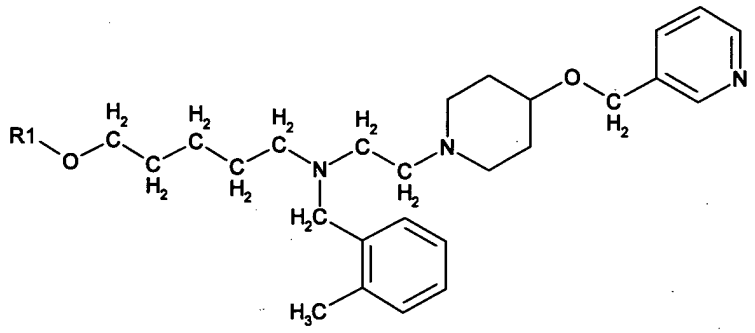
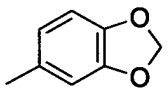
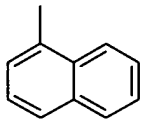
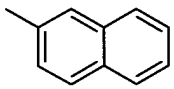
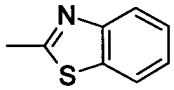
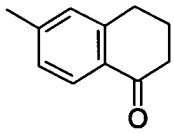
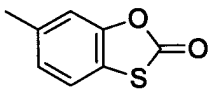
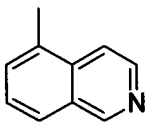
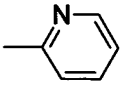
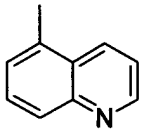
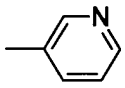
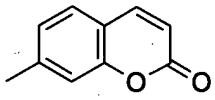
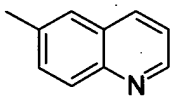
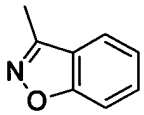
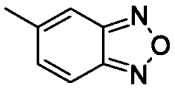
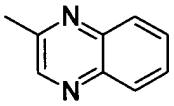
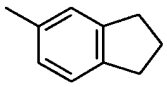
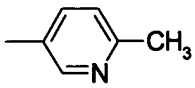
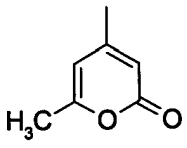
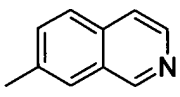
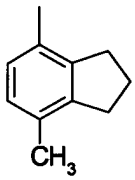
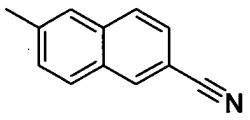
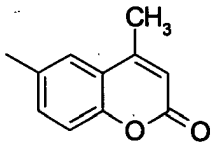
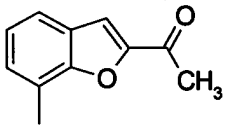
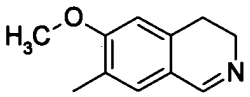
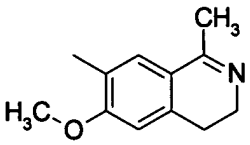
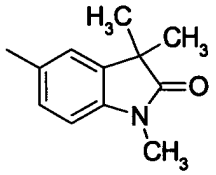
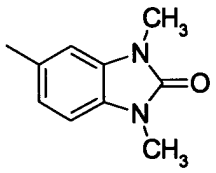
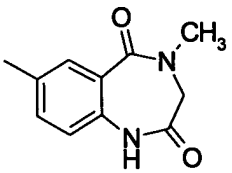
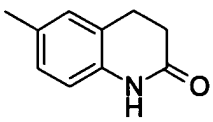
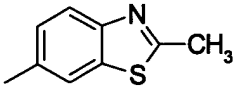
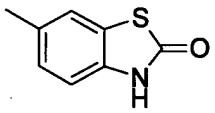
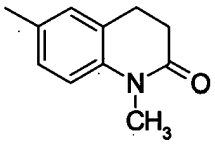
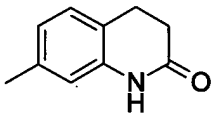
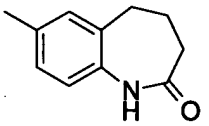
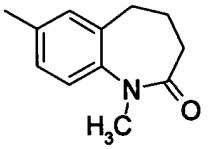
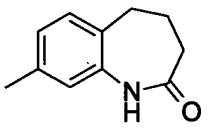
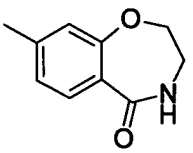
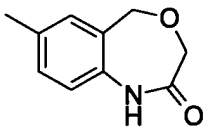
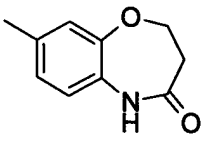


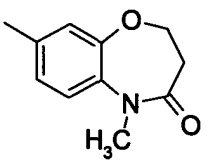
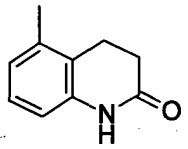
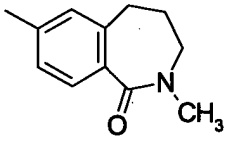
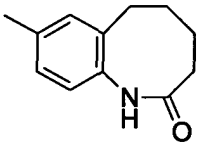
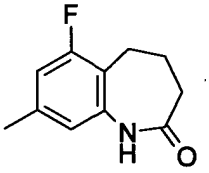
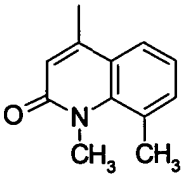
Table R

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 732 |  | 546 |
| 733 |  | 552 |
| 734 |  | 552 |
| 735 |  | 559 |
| 736 |  | 570 |
| 737 |  | 576 |
| 738 |  | 553 |
| 739 |  | 503 |

| | | |
|---|---|---|
| 740 |  | 553 |
| 741 |  | 503 |
| 742 |  | 570 |
| 743 |  | 553 |
| 744 |  | 543 |
| 745 |  | 544 |
| 746 |  | 554 |
| 747 |  | 542 |
| 748 |  | 517 |
| 749 |  | 534 |
| 750 |  | 553 |

| | | |
|---|---|---|
| 751 |  | 556 |
| 752 |  | 577 |
| 753 |  | 584 |
| 754 |  | 584 |
| 755 |  | 585 |
| 756 |  | 599 |
| 757 |  | 599 |
| 758 |  | 586 |
| 759 |  | 614 |
| 760 |  | 571 |

| | | |
|---|---|---|
| 761 |  | 573 |
| 762 |  | 575 |
| 763 |  | 585 |
| 764 |  | 571 |
| 765 |  | 585 |
| 766 |  | 599 |
| 767 |  | 585 |
| 768 |  | 587 |
| 769 |  | 587 |
| 770 |  | 587 |

| | | |
|---|---|---|
| 771 |  | 601 |
| 772 |  | 571 |
| 773 |  | 599 |
| 774 |  | 599 |
| 775 |  | 603 |
| 776 |  | 597 |

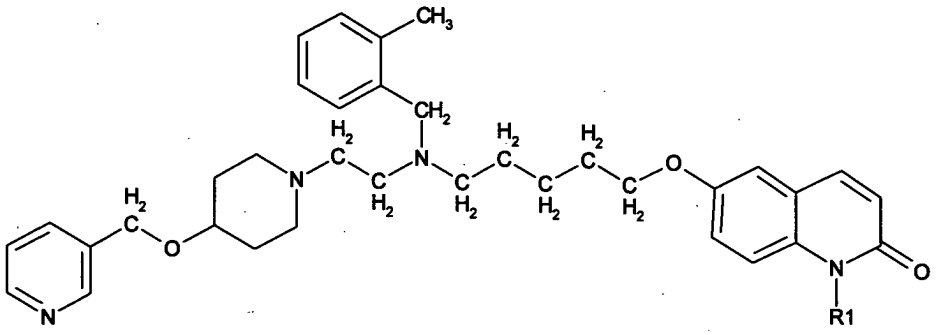


Table S

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 777 | $-CH_2C_6H_5$ | 659 |
| 778 | $-CH_2CH=CH_2$ | 609 |
| 779 | $-CH_2CH=CHC_6H_5$ | 685 |
| 780 | $-(CH_2)_3C_6H_5$ | 687 |
| 781 | $-CH_2COC_6H_5$ | 687 |
| 782 | $-CH_3$ | 583 |
| 783 | $-C_2H_5$ | 597 |
| 784 | $-(CH_2)_2CH_3$ | 611 |
| 785 | $-CH_2CH(CH_3)_2$ | 625 |
| 786 | $-(CH_2)_2N(CH_3)_2$ | 640 |
| 787 | $-(CH_2)_3CH_2CH=CH_2$ | 651 |
| 788 | $-(CH_2)_3OH$ | 627 |

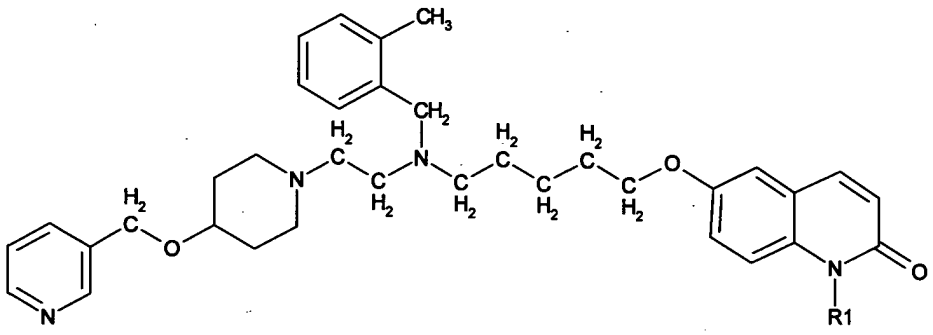
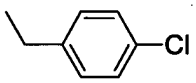
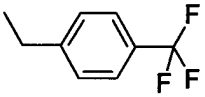
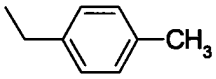
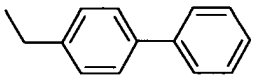
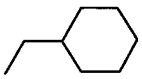
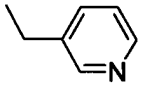
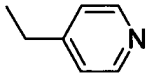
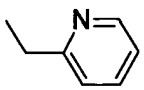
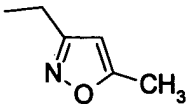


Table T

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 789 |  | 693 |
| 790 |  | 727 |
| 791 |  | 673 |
| 792 |  | 735 |
| 793 |  | 665 |
| 794 |  | 660 |
| 795 |  | 660 |
| 796 |  | 660 |
| 797 |  | 664 |

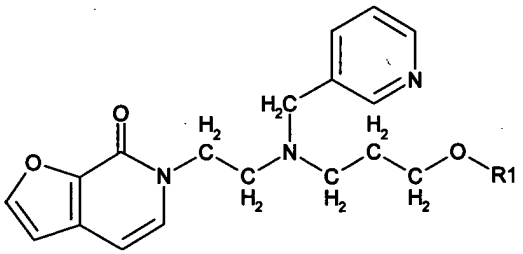
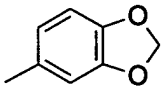
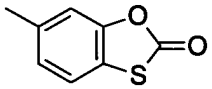
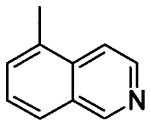
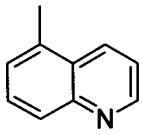
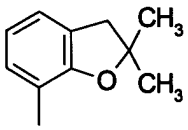
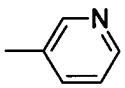
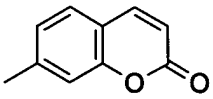
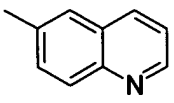
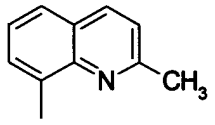
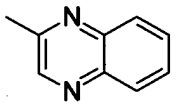
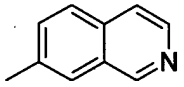
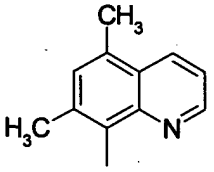
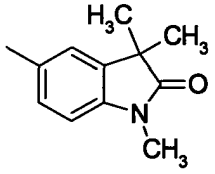
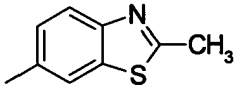
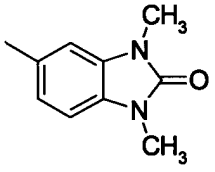
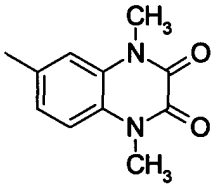
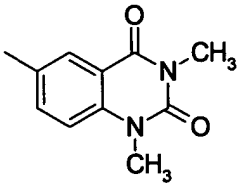
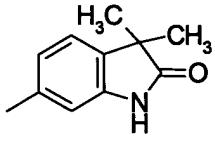
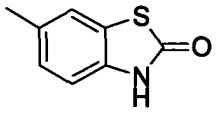
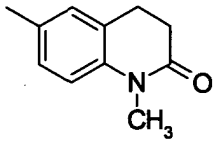
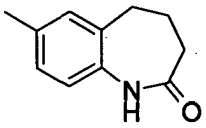
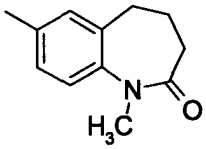
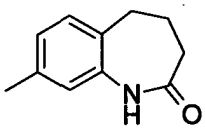
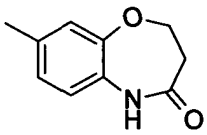
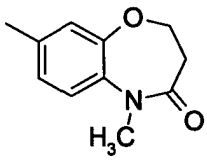
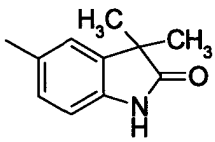
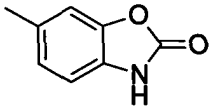
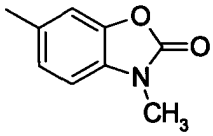
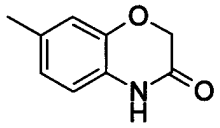
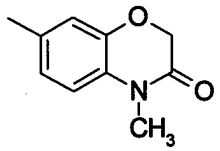
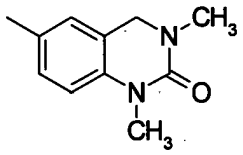
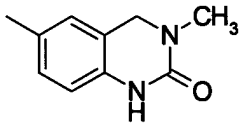
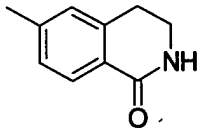
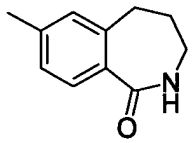
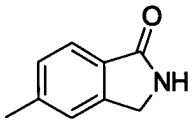
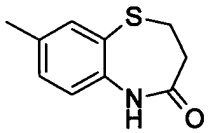
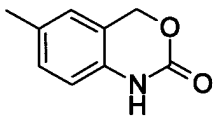
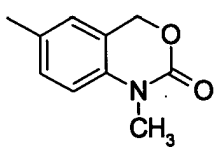


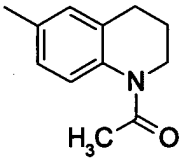
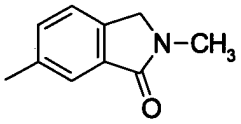
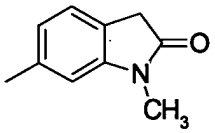
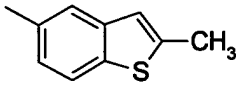
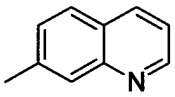
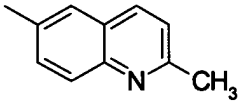
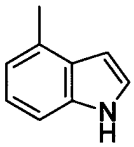
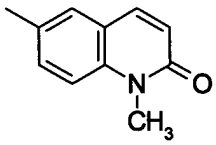
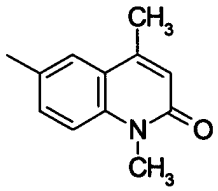
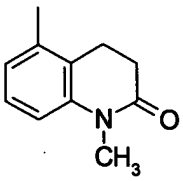
Table U

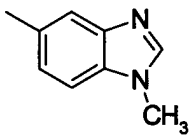
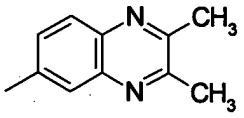
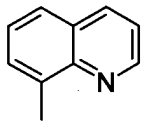
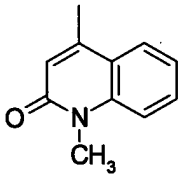
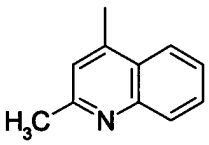
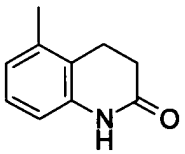
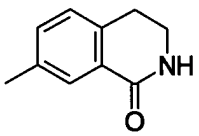
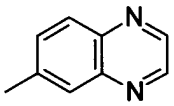
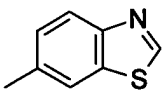
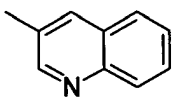
| Example No. | R1 | MS(M+1) |
|---|---|---|
| 798 |  | 448 |
| 799 |  | 478 |
| 800 |  | 455 |
| 801 |  | 455 |
| 802 |  | 474 |
| 803 |  | 405 |
| 804 |  | 472 |
| 805 |  | 455 |

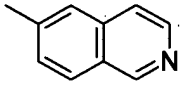
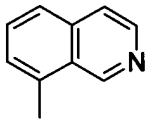
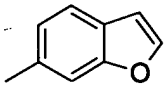
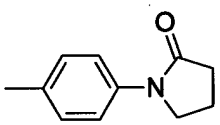
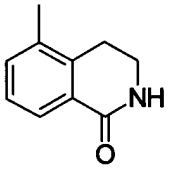
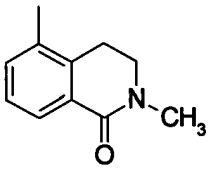
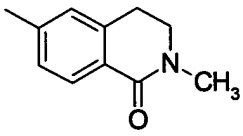
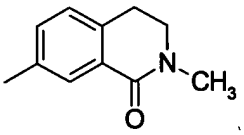
| | | |
|---|---|---|
| 806 |  | 469 |
| 807 |  | 456 |
| 808 |  | 455 |
| 809 |  | 483 |
| 810 |  | 501 |
| 811 |  | 475 |
| 812 |  | 488 |
| 813 |  | 516 |
| 814 |  | 516 |
| 815 |  | 487 |

| | | |
|---|---|---|
| 816 |  | 477 |
| 817 |  | 487 |
| 818 |  | 487 |
| 819 |  | 501 |
| 820 |  | 487 |
| 821 |  | 489 |
| 822 |  | 503 |
| 823 |  | 487 |
| 824 |  | 461 |
| 825 |  | 475 |

| | | |
|---|---|---|
| 826 |  | 475 |
| 827 |  | 489 |
| 828 |  | 502 |
| 829 |  | 488 |
| 830 |  | 473 |
| 831 |  | 487 |
| 832 |  | 459 |
| 833 |  | 505 |
| 834 |  | 475 |
| 835 |  | 489 |

| | | |
|---|---|---|
| 836 |  | 501 |
| 837 |  | 473 |
| 838 |  | 473 |
| 839 |  | 474 |
| 840 |  | 455 |
| 841 |  | 469 |
| 842 |  | 443 |
| 843 |  | 485 |
| 844 |  | 499 |
| 845 |  | 487 |

| | | |
|---|---|---|
| 846 |  | 458 |
| 847 |  | 484 |
| 848 |  | 455 |
| 849 |  | 485 |
| 850 |  | 469 |
| 851 |  | 473 |
| 852 |  | 473 |
| 853 |  | 456 |
| 854 |  | 461 |
| 855 |  | 455 |

| | | |
|---|---|---|
| 856 |  | 455 |
| 857 |  | 455 |
| 858 |  | 444 |
| 859 |  | 487 |
| 860 |  | 473 |
| 861 |  | 487 |
| 862 |  | 487 |
| 863 |  | 487 |

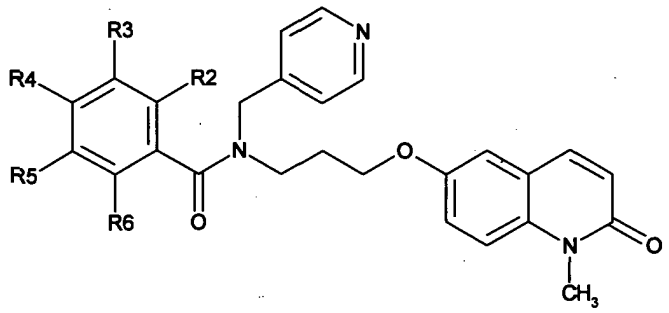
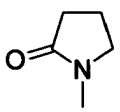
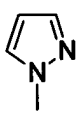
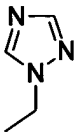
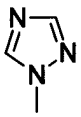


Table V

| Example No. | R2 | R3 | R4 | R5 | R6 | MS(M+1) |
|---|---|---|---|---|---|---|
| 864 | -H | -H | -H | -H | -H | 428 |
| 865 | -H | -H | $-OCH_3$ | -H | -H | 458 |
| 866 | -H | $-N(CH_3)_2$ | -H | -H | -H | 471 |
| 867 | -H | -H | $-N(CH_3)_2$ | -H | -H | 471 |
| 868 | -H | -H | -CN | -H | -H | 453 |
| 869 | $-COCH_3$ | -H | -H | -H | -H | 470 |
| 870 | -H | -H | $-COCH_3$ | -H | -H | 470 |
| 871 | $-OC_6H_5$ | -H | -H | -H | -H | 520 |
| 872 | -H | -H | $-OC_6H_5$ | -H | -H | 520 |
| 873 | -CN | -H | -H | -H | -H | 453 |
| 874 | -H | -H | $-C_6H_5$ | -H | -H | 504 |
| 875 | -H | -H | $-SO_2CH_3$ | -H | -H | 506 |
| 876 | -H | -H | $-N(C_2H_5)_2$ | -H | -H | 499 |
| 877 | -H | $-C_6H_5$ | -H | -H | -H | 504 |
| 878 | -H | -H |  | -H | -H | 511 |
| 879 | -H | -H | | -H | -H | 493 |
| 880 | -H | -H |  | -H | -H | 494 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 881 | -H |  | -H | -H | -H | 509 |
| 882 | -H |  | -H | -H | -H | 495 |

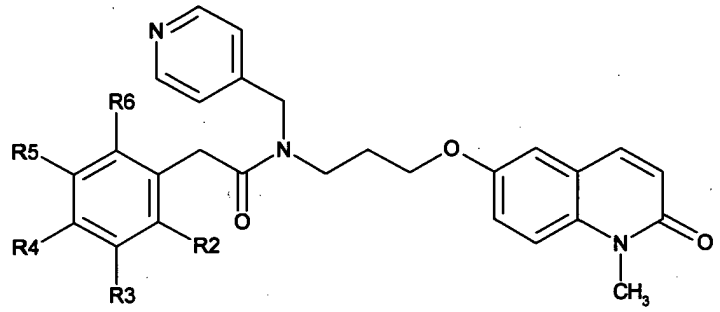


Table W

| Example No. | R2 | R3 | R4 | R5 | R6 | MS(M+1) |
|---|---|---|---|---|---|---|
| 883 | -H | -H | $-CH_3$ | -H | -H | 456 |
| 884 | -H | -H | -F | -H | -H | 460 |
| 885 | -H | -H | $-OCH_3$ | -H | -H | 472 |
| 886 | -H | -H | -H | -H | $-CH_3$ | 456 |
| 887 | -H | -H | -H | $-OCH_3$ | -H | 472 |
| 888 | -H | -H | -H | -H | $-OCH_3$ | 472 |
| 889 | -H | -H | $-OCH_3$ | -OH | -H | 488 |

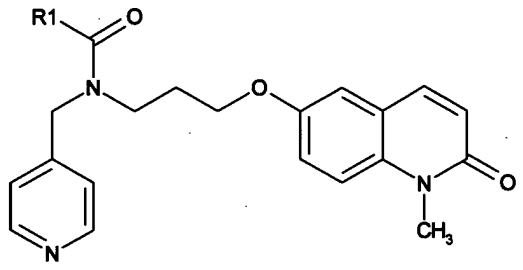


Table X

| Example No. | R1 | MS(M+1) |
|---|---|---|
| 890 | $-CH_2OC_6H_5$ | 458 |
| 891 | $-(CH_2)_2C_6H_5$ | 456 |
| 892 | $-CH=CHC_6H_5$ | 454 |
| 893 | $-(CH_2)_2OC_6H_5$ | 472 |
| 894 | $-(CH_2)_3C_6H_5$ | 470 |
| 895 | $-(CH_2)_4C_6H_5$ | 484 |
| 896 | $-CH_2SC_6H_5$ | 474 |
| 897 | $-(CH_2)_2COC_6H_5$ | 484 |

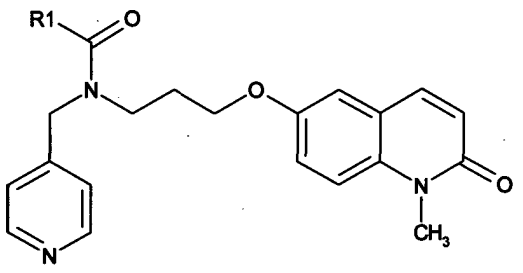
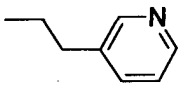
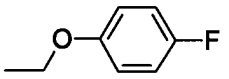
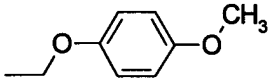
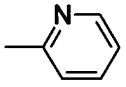
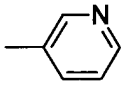
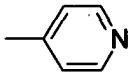
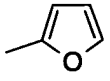
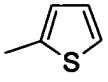
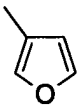
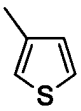
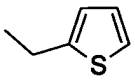
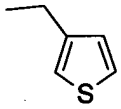
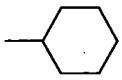
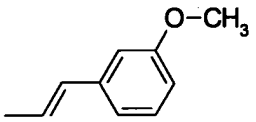
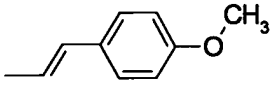
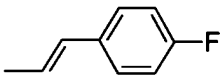
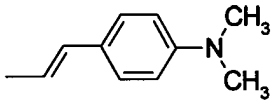
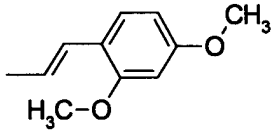
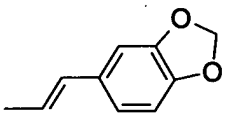
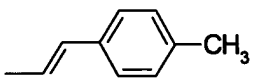
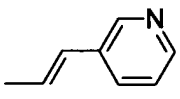
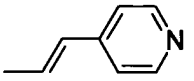
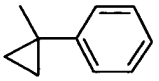
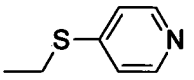
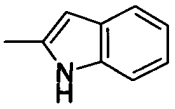
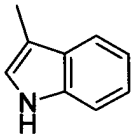
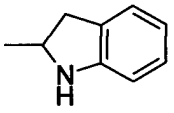
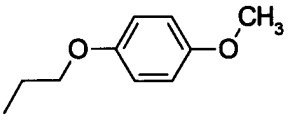
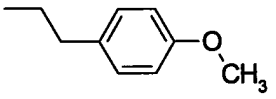
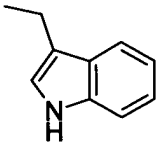
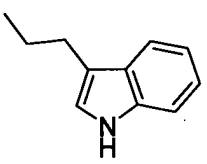
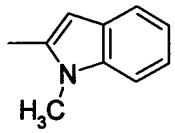
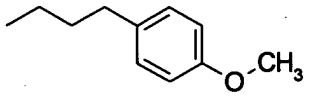
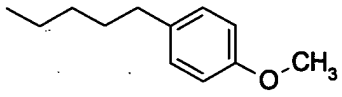
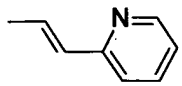
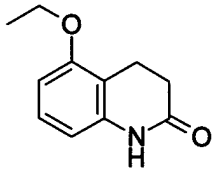
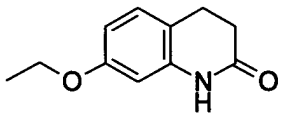
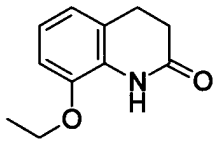
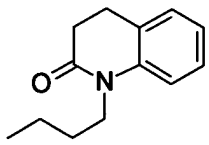
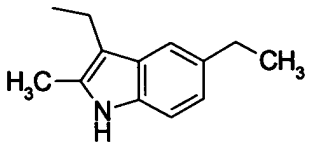
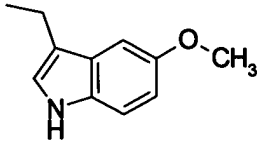


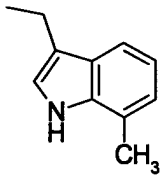
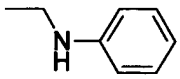
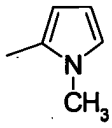
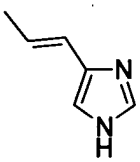
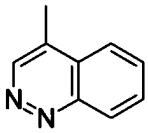
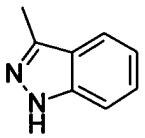
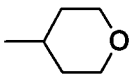
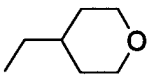
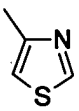
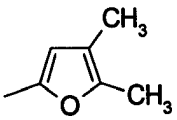
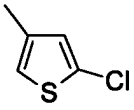
Table Y

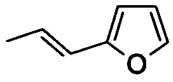
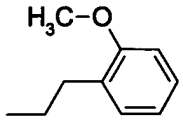
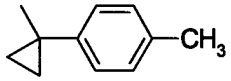
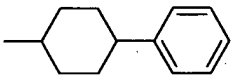
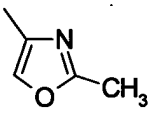
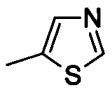
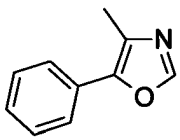
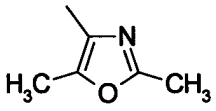
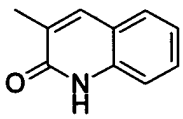
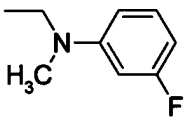
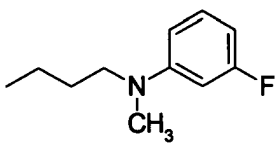
| Example No. | R1 | MS(M+1) |
|---|---|---|
| 898 |  | 457 |
| 899 |  | 476 |
| 900 |  | 488 |
| 901 |  | 429 |
| 902 |  | 429 |
| 903 |  | 429 |
| 904 |  | 418 |
| 905 |  | 434 |
| 906 |  | 418 |

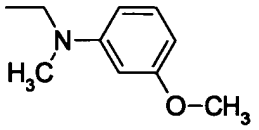
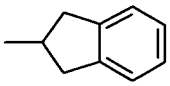
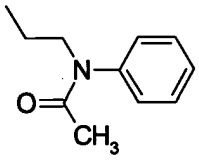
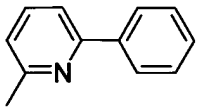
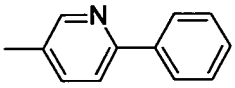
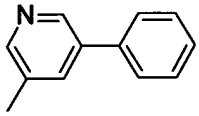
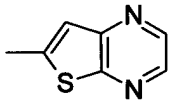
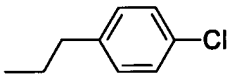
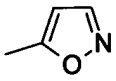
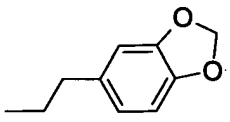
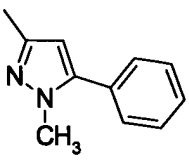
| | | |
|---|---|---|
| 907 |  | 434 |
| 908 |  | 448 |
| 909 |  | 448 |
| 910 |  | 434 |
| 911 |  | 484 |
| 912 |  | 484 |
| 913 |  | 472 |
| 914 |  | 497 |
| 915 |  | 514 |
| 916 |  | 498 |
| 917 |  | 468 |
| 918 |  | 455 |

| | | |
|---|---|---|
| 919 |  | 455 |
| 920 |  | 468 |
| 921 |  | 475 |
| 922 |  | 467 |
| 923 |  | 467 |
| 924 |  | 469 |
| 925 |  | 502 |
| 926 |  | 486 |
| 927 |  | 481 |
| 928 |  | 495 |

| | | |
|---|---|---|
| 929 |  | 481 |
| 930 |  | 500 |
| 931 |  | 514 |
| 932 |  | 455 |
| 933 |  | 527 |
| 934 |  | 527 |
| 935 |  | 527 |
| 936 |  | 539 |
| 937 |  | 523 |
| 938 |  | 511 |

| | | |
|---|---|---|
| 939 |  | 495 |
| 940 |  | 457 |
| 941 |  | 431 |
| 942 |  | 444 |
| 943 |  | 480 |
| 944 |  | 468 |
| 945 |  | 436 |
| 946 |  | 450 |
| 947 |  | 435 |
| 948 |  | 446 |
| 949 |  | 468 |

| | | |
|---|---|---|
| 950 |  | 444 |
| 951 |  | 486 |
| 952 |  | 482 |
| 953 |  | 510 |
| 954 |  | 433 |
| 955 |  | 435 |
| 956 |  | 495 |
| 957 |  | 447 |
| 958 |  | 495 |
| 959 |  | 489 |
| 960 |  | 517 |

| | | |
|---|---|---|
| 961 |  | 501 |
| 962 |  | 468 |
| 963 |  | 513 |
| 964 |  | 505 |
| 965 |  | 505 |
| 966 |  | 505 |
| 967 |  | 486 |
| 968 |  | 490 |
| 969 |  | 419 |
| 970 |  | 500 |
| 971 |  | 508 |

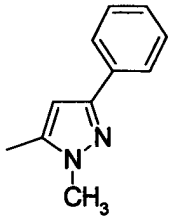
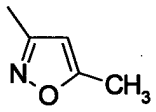
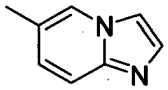
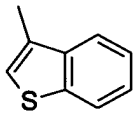
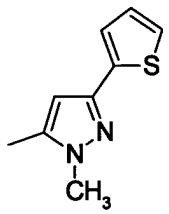
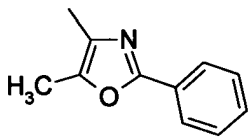
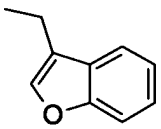
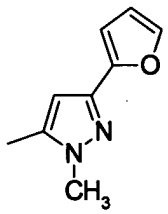
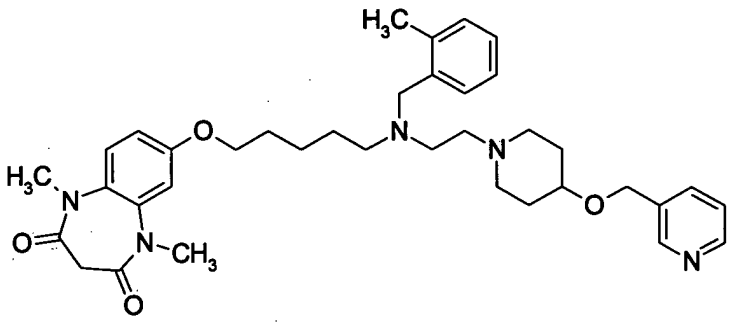
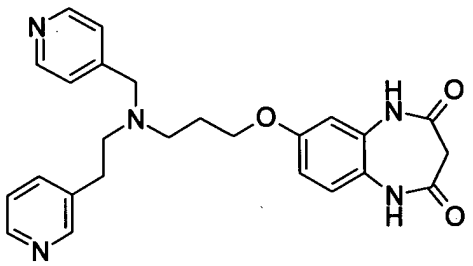
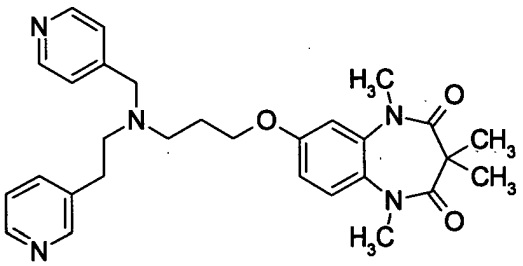
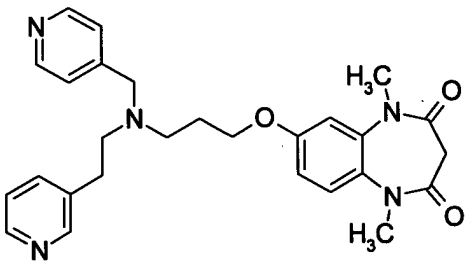
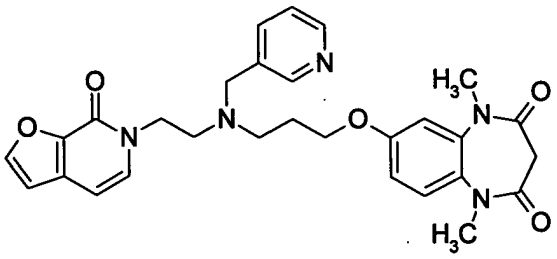
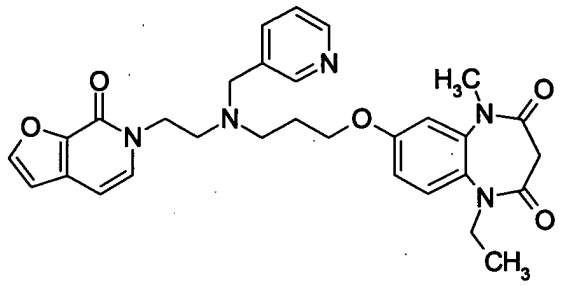
| | | |
|---|---|---|
| 972 |  | 508 |
| 973 |  | 433 |
| 974 |  | 468 |
| 975 |  | 484 |
| 976 |  | 514 |
| 977 |  | 509 |
| 978 |  | 482 |
| 979 |  | 498 |

Table Z

| Example No. | structure | MS(M+1) |
|---|---|---|
| 981 |  | 628 |
| 982 |  | 446 |
| 983 |  | 502 |
| 984 |  | 474 |
| 985 |  | 530 |

| | | |
|---|---|---|
| 986 |  | 544 |

Pharmacological Test 1

(1) Production of human Kv1.5-expressing CHO-K1 cell lines

CHO-K1 cell lines stably expressing human Kv1.5 channels were prepared in the following manner.

Full-length human Kv1.5 cDNA was cloned from a human heart cDNA library (produced by Stratagene). The obtained human Kv1.5 sequence corresponds to the sequence described in FASEB J. 5, 331-337 (1991).

The obtained human Kv1.5 cDNA was inserted into a plasmid encoding a CMV promoter and a G418 resistance marker to produce a Kv1.5 expression vector. The human Kv1.5 expression vector was transfected into CHO-K1 cells by the lipofectamine method. After culturing the cells in an F-12 medium (produced by Invitrogen Corp.) containing 10% FBS (produced by Invitrogen Corp.) for 3 or 4 days, the medium was replaced with a FBS-containing F-12 medium that included 1,000 μg/ml of G418 (produced by Invitrogen Corp.), and single colonies were isolated. The amount of Kv1.5 channel expression in the single colonies was quantified at the mRNA level by RT-PCR and then quantified at the protein level by western blotting. Finally, the expressed current was analyzed by patch clamp method. Cell lines expressing a current of 200 pA or more per cell were selected as channel-expressing cell lines for activity measurement by patch clamp method.

(2) Production of CHO cell line expressing human GIRK1/4

CHO cell lines stably expressing human GIRK1/4 channels were prepared in the following manner.

Full-length human GIRK1 cDNA was cloned from HuH cell- and HeLa cell-derived cDNA libraries. Full-length GIRK4 cDNA was

amplified from a human heart cDNA library (produced by Clontech Laboratories, Inc.) by PCR using synthetic primers shown in Table 1, and cloned into the Eco-RI restriction enzyme site of pCR-Blunt (produced by Invitrogen Corporation) or into the HincII site of pUC118 (produced by Takara Bio, Inc.).

Table 1

| Primer | Sequence | |
|---|---|---|
| hGIRK1-S | 5'-ATGTCTGCACTCCGAAGGAAATTTG-3' | SEQ ID No.1 |
| hGIRK1-A | 5'-TTATGTGAAGCGATCAGAGTTC-3' | SEQ ID No.2 |
| hGIRK1-F2 | 5'-GCAGGGTACCCCTTCGTATTATGTCTGCACTCC-3' | SEQ ID No.3 |
| hGIRK1-A3 | 5'-GGTGTCTGCCGAGATTTGA-3' | SEQ ID No.4 |
| hGIRK1-A4 | 5'-CCGAGTGTAGGCGATCACCC-3' | SEQ ID No.5 |
| hGIRK4-S | 5'-ATGGCTGGCGATTCTAGGAATGCC-3' | SEQ ID No.6 |
| hGIRK4-A | 5'-TCTCACCGAGCCCCTGGCCTCCC-3' | SEQ ID No.7 |
| hGIRK4-S2 | 5'-AACCAGGACATGGAGATTGG-3' | SEQ ID No.8 |
| hGIRK4-A2 | 5'-GAGAACAGGAAAGCGGACAC-3' | SEQ ID No.9 |

The obtained human GIRK1 and GIRK4 cDNA sequences correspond to known sequences (NCBI database: GIRK1 (NM_002239) and GIRK4 (NM_000890) respectively). The obtained GIRK1 and GIRK4 cDNA sequences were cloned into the Eco-RI restriction enzyme site of pCR-Blunt (available from Invitrogen Corporation) or into the HincII site of pUC118 (available from Takara Bio, Inc.). A GIRK4 expression vector was constructed by insertion into the BamHI-XhoI site of pcDNA5/FRT. A GIRK1 expression vector was constructed by insertion into the KpnI-XhoI site of pcDNA3.1(+) or pCAG_neo. FLP-IN-CHO cells (produced by Invitrogen Corporation) were transfected with human GIRK1 and GIRK4 expression vectors by using Lipofectamine 2000 (produced by Invitrogen Corporation) according to the protocol enclosed with the reagent or using an electronic induction method ("Nucleofector Kit-T", produced by Amaxa). First, the cells transfected with the GIRK4 expression vector were cultured in a 10% serum-containing F12 medium (produced by Sigma) supplemented with 600 μg/ml of hygromycin in an incubator with 5% carbon dioxide at 37°C. Then the cells expressing GIRK4 were transfected with the GIRK1 expression vector and were cultured in 10% serum-containing F12 medium supplemented with 350 μg/ml of G418 and 600 μg/ml of hygromycin in an incubator with

5% carbon dioxide at 37°C to select GIRK1/4 expressing cell lines. Cell populations whose growth was observed after about 2 weeks were isolated using cloning rings, and the obtained single colonies were proliferated. RNA was extracted from single colonies, and single-stranded cDNA was synthesized by a cDNA synthesis kit (produced by Invitrogen Corporation), and the amount of expression was quantified at the mRNA level by real-time PCR (Applied Biosystems, Ltd.). Finally, the expressed current was analyzed by patch clamp method described below. The cell lines expressing a current of 500 pA or more per cell were selected as channel-expressing cell lines for activity measurement by patch clamping method.

(3) Measurement of ion channel current by patch clamp method (human Kv1.5-expressing CHO-K1 cell line)

An experiment was carried out using a patch clamp setup at room temperature (20 to 26°C). A perfusion chamber having a diameter of 20 mm (flow rate: about 5 ml/min) was mounted on the stage of a phase-contrast inverted microscope (produced by Nikon Corporation) placed on a vibration isolated table. A poly-L-lysine (produced by Sigma)-coated coverslip (diameter: 15 mm, produced by Matsunami Glass Ind., Ltd.) on which human Kv1.5-expressing cells were cultured was placed in the perfusion chamber.

Depolarizing stimulation pulses were applied and ionic current was recorded by using a patch clamp amplifier (EPC-7 or EPC-7 PLUS, produced by HEKA) and a personal computer (manufactured by IBM Corp.) in which software for data acquisition and analysis of ion channel current (PULSE 8.77, produced by HEKA) was installed. The current was measured in the whole-cell configuration of the patch-clamp technique. The tip (resistance: 2 to 4 MΩ) of a borosilicate glass pipette (produced by Sutter Instrument Co.) was gently placed on the cell membrane by using a three-dimensional mechanical micromanipulator (produced by Shoshin EM Corporation). Weak suction resulted in giga seal formation (the pipette resistance increased to more than 1 GΩ). Subsequently, stronger suction was applied to break the cell membrane. The capacitative current derived from the cell membrane was corrected using a patch clamp amplifier.

Subsequently, the series resistance (Rs) between the pipette and the interior of the cell was measured and corrected.

The composition of the extracellular solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

| | |
|---|---|
| NaCl | 140 mM, |
| KCl | 40 mM, |
| $CaCl_2$ | 1.8 mM, |
| $MgCl_2$ | 1 mM, |
| $NaH_2PO_4$ | 0.33 mM, |
| HEPES | 5 mM |
| Glucose | 5.5 mM (pH = 7.4) |

Each test compound was prepared as a 1000-fold concentrated stock solution that was dissolved in DMSO and then diluted in the extracellular solution.

The composition of the electrode internal solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

| | |
|---|---|
| KOH | 100 mM, |
| KCl | 40 mM, |
| Aspartic acid | 70 mM, |
| $MgCl_2$ | 1 mM, |
| MgATP | 5 mM, |
| $K_2$ creatine phosphate | 5 mM, |
| HEPES | 5 mM |
| EGTA | 5 mM (pH = 7.2) |

(4) Measurement of ion channel current by patch clamp method (human GIRK1/4-expressing CHO-K1 cell line)

An experiment was carried out using a patch clamp setup at room temperature (20 to 26°C). A perfusion chamber having a diameter of 20 mm (flow rate: about 5 ml/min) was mounted on the stage of a phase-contrast inverted microscope (produced by Nikon Corporation) placed on a vibration isolation table. A poly-L-lysine (produced by Sigma)-coated coverslip (diameter: 15 mm, produced by Matsunami Glass Ind., Ltd.) on which human GIRK1/4-expressing cells were cultured was

placed in the perfusion chamber.

Hyperpolarizing stimulation pulses were applied and ionic current was recorded using a patch clamp amplifier (EPC-7 or EPC-7 PLUS, manufactured by HEKA) and a personal computer (manufactured by IBM Corp.) in which software for data acquisition and analysis of ion channel current (PULSE 8.77, manufactured by HEKA) was installed. The current was measured in the whole-cell configuration of the patch-clamp technique. The tip (resistance: 2 to 4 MΩ) of a borosilicate glass pipette (produced by Sutter Instrument Co.) was gently placed on the cell membrane by using a three-dimensional mechanical micromanipulator (produced by Shoshin EM Corporation). Weak suction resulted in giga seal formation (the pipette resistance increased to more than 1 GΩ). Subsequently, stronger suction was applied to break the cell membrane. The capacitative current derived from the cell membrane was corrected using a patch clamp amplifier. Subsequently, the series resistance (Rs) between the pipette and the interior of the cell was measured and corrected.

The composition of the extracellular solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

NaCl 140 mM,
KCl 4 mM,
$CaCl_2$ 1.8 mM,
$MgCl_2$ 1 mM,
$NaH_2PO_4$ 0.33 mM,
HEPES 5 mM
Glucose 5.5 mM (pH = 7.4)

Each test compound was prepared as a 1000-fold concentrated stock solution that was dissolved in DMSO and then diluted in the extracellular solution.

The composition of the electrode internal solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

KOH 100 mM,
KCl 40 mM,
Aspartic acid 70 mM,

| | |
|---|---|
| $MgCl_2$ | 1 mM, |
| MgATP | 5 mM, |
| $K_2$ creatine phosphate | 5 mM, |
| HEPES | 5 mM |
| EGTA | 5 mM (pH = 7.2) |

(5) Measurement of human Kv1.5 current

While the membrane potential was holded at -80 mV, depolarizing pulses (-80 mV for 0.05 seconds →..+40 mV for 0.2 seconds →..-40 mV for 0.2 seconds →..-80 mV for 0.05 seconds) were applied at a stimulation frequency of 1 Hz to measure Kv1.5 channel current. More specifically, first, while perfusing an extracellular solution containing 0.1% DMSO and holding the membrane potential at -80 mV, depolarizing pulses were applied. The current obtained during the pulse application was recorded as a current in the absence of the test compounds. Subsequently, while perfusing an extracellular solution containing 0.1 μM of a test compound and holding the membrane potential at -80 mV, depolarizing pulses were applied. After the inhibitory effect of the test compound had been stabilized, the current was recorded. The same procedure was repeated using an extracellular solution containing 1 μM of the test compound and then using an extracellular solution containing 10 μM of the test compound. The current obtained using the solution containing the test compound at each concentration was recorded.

The data was analyzed by using the step end current recorded during the +40 mV depolarizing stimulation. The "step end current" refers to the average current flowing for a period of 195 to 199 milliseconds from the start of the +40 mV depolarizing pulse stimulation.

Using the step end current in the presence of the test compound and the step end current in the absence of the test compound, the relative current in the solution containing the test compound at each concentration was calculated according to the following formula:
Relative current =
(Step end current in the presence of the test compound) / (Step end current in the absence of the test compound)

(6) Measurement of human GIRK1/4 current

While the membrane potential was holded at -80 mV, hyperpolarizing pulses (-80 mV for 0.05 seconds →..-120 mV for 0.2 seconds →..-80 mV for 0.05 seconds) were applied at a stimulation frequency of 1 Hz to measure GIRK1/4 channel current. More specifically, first, while perfusing an extracellular solution containing 0.1% DMSO and maintaining the membrane potential at -80 mV, hyperpolarizing pulses were applied. The current obtained during the pulse application was recorded as the current in the absence of the test compounds. Subsequently, while perfusing an extracellular solution containing 0.1 μM of a test compound and maintaining the membrane potential at -80 mV, hyperpolarizing pulses were applied. After the inhibitory effect of the test compound had been stabilized, the current was recorded. The same procedure was repeated using an extracellular solution containing 1 μM of the test compound and then using an extracellular solution containing 10 μM of the test compound. The current obtained using the solution containing the test compound at each concentration were recorded.

The data was analyzed by using the step end current recorded during the -120 mV depolarizing stimulation. The "step end current" refers to the average current flowing for a period of 195 to 199 milliseconds from the start of the -120 mV depolarizing pulse stimulation.

Using the step end current in the presence of the test compound and the step end current in the absence of the test compound, the relative current in the solution containing the test compound at each concentration was calculated according to the following formula:
Relative current =
(Step end current in the presence of the test compound) / (Step end current in the absence of the test compound)

(7) Calculation of inhibitory activity on Kv1.5 channel ionic current and GIRK1/4 channel current

The concentration for 50% inhibition of Kv1.5 channel current or GIRK1/4 channel current ($IC_{50}$ value) was calculated

according to the following nonlinear regression equation:

[0423]

Relative current = $1/(1+ [\text{Concentration of the compound}]/IC_{50})^{nH}$

wherein nH is the Hill coefficient.

[0424]

Table 2 shows the test results.

[0425]

Table 2

| Test Compound | KV1.5 $IC_{50}$ (μM) |
|---|---|
| Compound of Example 14 | 0.23 |
| Compound of Example 18 | 0.39 |
| Compound of Example 24 | 0.32 |
| Compound of Example 26 | 0.30 |
| Compound of Example 34 | 0.33 |
| Compound of Example 38 | 0.38 |
| Compound of Example 40 | 0.86 |
| Compound of Example 42 | 0.77 |
| Compound of Example 46 | 0.42 |
| Compound of Example 62 | 0.12 |

3. Third Invention

▪ Reference Example 1

· Synthesis of ethyl N-(5-methoxy-2-nitrophenyl)-N-methyl malonamate

Sodium hydride (60% in oil, 96 mg) was suspended in 10 ml of dimethylformamide (DMF). N-Methyl-5-methoxy-2-nitroaniline (364 mg) was added thereto at 0°C, and stirring was conducted at room temperature for 30 minutes. Ethyl malonyl chloride (0.38 ml) was added at 0°C to the stirred mixture, and the reaction mixture was stirred at room temperature overnight. Water was added thereto, and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=2:1→1:2). The purified product was

concentrated under reduced pressure to give the title compound(554mg) as a yellow oil.

$^1$H-NMR ($CDCl_3$) δppm:

1.24 (3H, t, J = 7.1 Hz), 3.15 - 3.17 (2H, m), 3.25 (3H, s), 3.92 (3H, s), 4.13 (2H, q, J = 7.1 Hz), 6.93 (1H, d, J = 2.8 Hz), 7.02 (1H, dd, J = 2.8 and 9.2 Hz), 8.15 (1H, d, J = 9.2 Hz).

▪ Reference Example 2

· Synthesis of ethyl N-(2-amino-5-methoxyphenyl)-N-methyl malonamate

Palladium on carbon (10%, 0.5 g) was added to an ethanol solution (150 ml) of ethyl N-(5-methoxy-2-nitrophenyl)-N-methyl malonamate (3.0 g), and catalytic reduction was conducted at room temperature and normal pressure. The reaction mixture was filtered through Celite to remove the catalyst. The filtrate was concentrated under reduced pressure to give the title compound(2.68g) as a yellow oil.

$^1$H-NMR ($CDCl_3$) δppm:

1.22 (3H, t, J = 7.1 Hz), 3.19 - 3.27 (5H, m), 3.52-3.68 (2H, br), 3.74 (3H, s), 4.11 (2H, q, J = 7.1 Hz), 6.62 (1H, d, J = 2.7 Hz), 6.73 (1H, d, J = 8.7 Hz), 6.79 (1H, dd, J = 2.7 and 8.7 Hz).

▪ Reference Example 3

·Synthesis of 8-methoxy-1-methyl-1,5-dihydrobenzo[b][1,4] diazepine-2,4-dione

Sodium ethoxide (204 mg) was added to an ethanol solution (15 ml) of ethyl N-(2-amino-5-methoxyphenyl)-N-methyl malonamate (266 mg), and stirred at 65°C for 2.5 hours. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=1:0→10:1). The purified product was concentrated to dryness under reduced pressure to give the title compound(176.3mg) as a white powder.

$^1$H-NMR ($CDCl_3$) δppm:

3.36 (2H, s), 3.43 (3H, s), 3.84 (3H, s), 6.79-6.83 (1H, m), 7.06-7.09 (1H, m), 8.72 (1H, br-s).

▪ Reference Example 4

· Synthesis of 1-ethyl-7-methoxy-5-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium hydride (60% in oil, 44 mg) was suspended in dimethylformamide (DMF) (8 ml), and cooled in an ice water bath to 0°C.

8-Methoxy-1-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (220 mg) was added to the suspension at the same temperature, and stirred at 0°C for 1 hour. Ethyl iodide (187 mg) was added to the mixture and stirred at room temperature overnight. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=4:1→1:1). The purified product was concentrated to dryness under reduced pressure to give the title compound(190.2mg) as a yellow solid.

$^1$H-NMR ($CDCl_3$) δppm:

1.11 (3H, t, J = 7.1 Hz), 3.31 - 3.32 (2H, m), 3.40 (3H, s), 3.59-3.68 (1H, m), 3.85 (3H, s), 4.18-4.30 (1H, m), 6.78 (1H, d, J = 2.8 Hz), 6.84 (1H, dd, J = 9.0 and 2.8 Hz), 7.26 (1H, d, J = 9.0 Hz).

▪ Reference Example 5

·Synthesis of 1-ethyl-7-methoxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Sodium hydride (60% in oil, 76 mg) was suspended in DMF (8 ml). 1-Ethyl-7-methoxy-5-methyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (190 mg) was added thereto at 0°C, and stirring was conducted at the same temperature for 1 hour. Methyl iodide (0.19 ml) was added to the mixture, and stirred at room temperature for 3 days. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate). The purified product was concentrated to dryness under reduced pressure to give the title compound(169mg) as a yellow powder.

$^1$H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 3.40 (3H, s), 3.65-3.76 (1H, m), 3.85 (3H, s), 4.12-4.24 (1H, m), 6.73 (1H, d, J = 2.8 Hz), 6.83 (1H, dd, J = 9.0 and 2.8 Hz), 7.22 (1H, d, J = 9.0 Hz).

▪ Reference Example 6

·Synthesis of 1-ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

A 1.0 M boron tribromide/dichloromethane solution (1.22 ml) was added to a dichloromethane solution (3 ml) of 1-ethyl-7-methoxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (169 mg) at 0°C, and stirred at room temperature overnight. Water and methanol were added to the reaction mixture and extraction with the mixture solvent (dichloromethane:methanol=10:1) was performed. The organic layer was dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure to give the title compound(156.4mg) as a white powder.

$^1$H-NMR ($CDCl_3$) δppm:

0.90 (3H, s), 1.16 (3H, t, J = 7.0 Hz), 1.55 (3H, s), 3.41 (3H, s), 3.66-3.78 (1H, m), 4.12-4.23 (1H, m), 6.79 (1H, d, J = 2.7 Hz), 6.84 (1H, dd, J = 8.8 and 2.7 Hz), 6.88 (1H, d, J = 2.7 Hz), 7.18 (1H, d, J = 8.8 Hz).

▪ Reference Example 7

·Synthesis of 7-(3-chloropropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

1-Ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (1.85 g) and potassium carbonate(1.2 g) were added to 50% water-containing acetonitrile (40 ml), and dissolved by heating to 70°C. 1-Bromo-3-chloropropane (2.1 ml) was added thereto, and heating was conducted under reflux for 6 hours. The reaction mixture was cooled to room temperature. Water was added, and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (n-hexane:ethyl acetate=2:1→1:1). The purified product was concentrated to dryness under reduced pressure to give the title compound (2.18g) as a colorless oil.

$^1$H-NMR ($CDCl_3$) δppm:

0.86 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.21-2.38 (2H, m), 3.40 (3H, s), 3.63-3.89 (4H, m), 4.10-4.26 (2H, m), 6.74 (1H, d, J = 2.8 Hz), 6.83 (1H, dd, J = 2.8 and 9.0 Hz), 7.21 (1H, d, J = 9.0 Hz).

▪ Reference Example 8

·Synthesis of 1-ethyl-7-(3-iodopropoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

7-(3-Chloropropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (2.18 g) and sodium iodide (4.8 g) were added to acetone (50 ml), and heated under reflux for 8.5 hours. The reaction mixture was cooled to room temperature, water was added, and extraction with ethyl acetate was performed. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=1:1). The purified product was concentrated under reduced pressure to give the title compound (2.76g) as a colorless oil.

$^1$H-NMR ($CDCl_3$) δppm:

0.87 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.26 - 2.34 (2H, m), 3.39 (2H, t, J = 6.6 Hz), 3.65-3.76 (1H, m), 3.41 (3H, s), 4.07 (2H, t, J = 5.8 Hz), 4.12-4.24 (1H, m), 6.74 (1H, d, J = 2.8 Hz), 6.83 (1H, dd, J = 9.0 and 2.8 Hz), 7.22 (1H, d, J = 9.0 Hz).

▪ Reference Example 9

· Synthesis of 3-iodoquinolin-4-ol

Potassium carbonate (5.2g) was added to a DMF solution (50ml) of 4-hydroxy quinoline (5.0g) and the mixture was stirred. Iodine (9.6g) was added to the mixture, followed by stirring at room temperature for 3 hours. A saturated sodium hydrogencarbonate aqueous solution

(73ml) of 25% sodium sulfite, and water(50ml) were added to the reaction mixture. The mixture was stirred and the precipitated insoluble matter was separated. The filtrate was washed with water and dried to give the title compound (9.0g) as a white powder.
mp: 288 to 294°C (dec.)

▪ Reference Example 10

· Synthesis of 3-bromoquinolin-4-ol

N-Bromosuccinimide(1.3g) was added to a DMF solution (15ml) of 4-hydroxy quinoline(1.0g) and the mixture was stirred at room temperature for 15 hours. A sodium hydrogencarbonate aqueous solution of 25% sodium sulfite was added to the mixture. The mixture was stirred and the precipitated insoluble matter was separated. The filtrate was dissolved in a mixture of ethyl acetate and methanol, and an insoluble matter was removed by filtration. The filtrate was condensed under reduced pressure, and the residue was washed with ethyl acetate and dried to give the title compound(1.1g) as a white powder.
mp: 286 to 287°C

▪ Reference Example 11

· Synthesis of 3-bromo-1H-quinolin-2-one

Hydrogen peroxide solution(5.9ml) was added to a THF solution (16ml) of methyltrioxorhenium (VII)(24mg). The mixture was stirred for 10 minutes at room temperature. 3-Bromoquinoline(4.0g) was added thereto, and the mixture was stirred at room temperature for four days. Ethyl acetate(20ml) was added to the reaction mixture. 20% Sodium sulfite aqueous solution(30ml) was added slowly to the mixture under ice cooling. The mixture was stirred at room temperature. The organic layer was condensed to a half volume under reduced pressure. Ethyl acetate(20ml) and 15% potassium carbonate aqueous solution(19ml) were added thereto, and the organic layer was extracted. 15% Potassium carbonate aqueous solution(19ml) of p-toluenesulfonyl chloride(4g) were added thereto. The mixture was stirred for 10 minutes at room temperature. The generated insoluble matter was separated, washed with ethyl acetate, water, and then with ether, and dried to give the title compound(3.2g) as a white powder.

mp: 263 to 265°C

▪ Reference Example 12

· Synthesis of 1-(pyridin-3-yl)-2,3-dihydrobenzoimidazol-2-one

N,N'-Carbonyldiimidazole(0.57g) was added to a DMF solution (5ml) of N-pyridine-3-ylbenzene-1,2-diamine(0.5g). The mixture was stirred at room temperature for 1.5 hours. Water was added to the reaction mixture and the precipitated insoluble matter was separated, washed with water, and dried to give the title compound(0.5g) as a pale whitish purple powder.

mp: 232 to 233°C (dec.).

▪ Reference Example 13

Synthesis of

5-(2,2-dihydroxyethyl)-2-methyl-5H-furo[3,2-c]pyridin-4-one

Sodium hydride (60% in oil, 0.32g) was suspended in DMF(10ml), and was cooled to 0°C in an ice water bath.

2-Methyl-5H-furo[3,2-c]pyridin-4-one (0.57g) was added thereto at the same temperature, and the mixture was stirred at 0°C for an hour. Bromoacetaldehyde dimethylacetal(2.3ml) was added thereto, and the mixture was stirred at 80°C for 5 hours. Water was added to the reaction liquid, followed by extraction by ethyl acetate. The organic layer was dried over sodium sulfate, and condensed under reduced pressure. A 3N-hydrochrolic acid(2ml) was added to an acetone solution (10ml) of the residue, and the liquid was stirred at 70°C for 10 hours. Water was added to the reaction liquid and stirred at room temperature. The precipitated insoluble matter was separated, washed with water, and dried to give the title compound(0.56g) as a white solid.

$^1$H-NMR (DMSO-$D_6$), δppm : 2.36 (s, 3H), 3.86 (d, J = 5.4 Hz, 2H), 4.94-4.98 (m, 1H), 6.04 (d, J = 6.4 Hz, 2H), 6.52 (s, 1H), 6.59 (d, J = 7.4 Hz, 1H), 7.41 (d, J = 7.4 H, 1H).

▪ Reference Example 14

Synthesis of

5-(1H-benzoimidazol-2-ylmethyl)-2-methyl-5H-furo[3,2-c]pyridin-4-one

5-(2,2-Dihydroxyethyl)-2-methyl-5H-furo[3,2-c]pyridine-4-on e (2.1g) and o-phenylenediamine(1.1g) were suspended in ethanol(20ml). Sodium hydrogensulfite(5.2g) was added, and the mixture was heated and stirred overnight under reflux. The reaction mixture was cooled to room temperature. Water was added thereto and the precipitated insoluble matter was separated, washed with water, and dried to give the title compound(2.25g).

$^1$H NMR ($CDCl_3$), δ ppm : 2.36 (3H, s), 5.44 (2H, s), 6.55 (1H, s), 6.73 (1H, d, J = 7.4 Hz), 7.05-7.15 (2H, m), 7.43 (1H, d, J = 7.0 Hz), 7.50 (1H, d, J = 8.3 Hz), 7.70 (1H, d, J = 7.4 Hz).

▪ Reference Example 15

· Synthesis of 3-(pyridin-3-yl)-1H-quinolin-4-one

2N Hydrochloric acid(10ml) was added to a DMF solution(5ml) of 4-chloro-(3-pyridin-3-yl)quinoline(0.51g), and the mixture was stirred at 80°C for 1 hour. After the reaction mixture was cooled to room temperature, 2N sodium hydroxide aqueous solution(10ml) was added dropwise under ice cooling. The mixture was stirred. The precipitated insoluble matter was separated, washed with water and ether, and dried to give the title compound(0.35g) as a pale whitish purple powder.

mp: 240 to 242°C (dec.)

▪ Reference Example 16

· Synthesis of 5-[{1-(3-chloropropyl)-1H-benzoimidazol-2-yl}methyl]-2-methyl-5H-furo[3,2-c]pyridin-4-one

5-(1H-Benzimidazol-2-ylmethyl)-2-methyl-5H-furo[3,2-c]pyrid ine-4-one(0.75g), 1-bromo-3-chloropropane(1.3ml), and potassium carbonate(0.95g) were added to 50% hydrous acetonitrile(16ml). The mixture was heated overnight under reflux. The reaction mixture was cooled to room temperature. Water was added thereto, followed by extraction by ethyl acetate. The organic layer was dried over sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=1:1→0:1). The purified product was condensed to dryness under

reduced pressure to give the title compound(0.18g) as a colorless oily matter.

$^1$H NMR ($CDCl_3$), δ ppm: 2.02-2.09 (2H, m), 2.41 (3H, s), 3.54 (2H, t, J = 6.1 Hz), 4.55-4.61 (2H, m), 5.56 (2H, s), 6.51-6.53 (2H, m), 7.24-7.32 (2H, m), 7.40-7.46 (1H, m), 7.54 (1H, d, J = 5.9 Hz), 7.73-7.79 (1H, m).

▪ Reference Example 17

· Synthesis of

5-(3-chloropropyl)-2-methyl-5H-furo[3,2-c]pyridin-4-one

Methane sulfonyl chloride(0.24ml) was added to a dichloromethane solution(10ml) of 5-(3-hydroxypropyl)-2-methyl-5H-furo[3,2-c]pyridine-4-one (0.28g) and triethylamine(0.45ml). The mixture was stirred at room temperature for two days. The reaction liquid was condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: hexane =1:4→1:1). The purified product was condensed to dryness under reduced pressure to give the title compound(0.16g) as a white amorphous solid.

$^1$H NMR ($CDCl_3$), δ ppm : 2.25-2.41 (2H, m), 2.41 (3H, s), 3.56 (2H, t, J = 6.1 Hz), 4.18 (2H, t, 6.6 Hz), 6.48 (1H, d, J = 7.4 Hz), 6.55 (1H, s), 7.17 (1H, d, J = 7.4 Hz).

▪ Reference Example 18

· Synthesis of

7-(2-chloroethoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

1-Ethyl-7-hydroxy-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(1.2g) and potassium carbonate(0.95g) were added to 50% hydrous acetonitrile(24ml). The mixture was heated to 70°C to be dissolved. 1-Bromo-2-chloroethane(1.9ml) was added, and the mixture was heated under reflux for 7 hours. The reaction mixture was cooled to room temperature. Water was added thereto, followed by extraction by ethyl acetate. The organic layer was dried by sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=2:1→1:1). The purified product was condensed to dryness under

reduced pressure to give the title compound(1.4g) as a colorless oily matter.

$^1$H NMR ($CDCl_3$), δ ppm : 0.86 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 3.40 (3H, s), 3.64-3.77 (1H, m), 3.85 (2H, t, J = 5.7 Hz), 4.03-4.15 (1H, m), 4.26 (2H, t, J = 5.7 Hz), 6.77 (1H, d, J = 2.8 Hz), 6.83 (1H, dd, J = 9.0, 2.8 Hz), 7.23 (1H, d, J = 9.0 Hz).

▪ Reference Example 19

· Synthesis of

7-[3-(3-aminopyridin-4-ylamino)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

10% Palladium on carbon(0.7g) was added to a methanol solution (30ml) of

1-ethyl-3,3,5-trimethyl-7-[3-(3-nitropyridin-4-ylamino)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(1.8g). The mixture was subjected to catalytic reduction at room temperature under normal pressure. The reaction mixture was subjected to celite filtration to remove the catalyst. The filtrate was condensed under reduced pressure to give the title compound(1.4g) as an orange amorphous solid.

$^1$H NMR ($CDCl_3$), δ ppm : 0.86 (3H, s), 1.14 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.12-2.24 (2H, m), 3.40 (3H, m), 3.40-3.52 (2H, m), 3.63-3.74 (1H, m), 4.03-4.14 (3H, m), 6.51 (1H, d, J = 5.4 Hz), 6.75-6.76 (1H, m), 6.84 (1H, dd, J = 9.0, 2.8 Hz), 7.22 (1H, d, J = 9.0 Hz), 7.93 (1H, s), 7.98 (1H, d, J = 5.4 Hz).

▪ Example 1

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-[3-(2-phenylpiperidin-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

Potassium carbonate(0.54g), sodium iodide(0.21g), and 2-phenyl piperidine(0.23g) were added to a DMF solution(15ml) of 7-(3-chloropropoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.44g). The mixture was stirred at 70°C for 5 hours. The reaction mixture was cooled to room temperature. Water was added thereto, followed by extraction by ethyl acetate. The organic layer was washed with water and then with saturated saline,

and dried with anhydrous magnesium sulfate. After condensation under reduced pressure, the residue was purified by silica gel column chromatography (hexane: ethyl acetate=2:1→1:1). The purified product was condensed under reduced pressure. A 4N-Hydrogen chloride ethyl acetate solution(0.2ml) was added to an ethyl acetate solution (10ml) of the residue, which was stirred at room temperature. The liquid was condensed to dryness under reduced pressure to give the title compound(0.18g) as a white amorphous solid.

$^1$H NMR ($CDCl_3$), δ ppm: 0.82(3H, s), 1.12 (3H, t, J = 7.0 Hz), 1.51 (3H, s), 1.89-3.22(11H, m), 3.36(3H, s), 3.62-3.97 (5H, m), 4.09-4.18 (1H, m), 6.53-6.54 (1H, m), 6.62-6.67 (1H, m), 7.16 (1H, d, J = 9.0 Hz), 7.36-7.47 (3H, m), 7.61-7.90 (2H, m), 12.40 (1H, brs).

▪ Example 2

· Synthesis of
7-[3-((R)-2,4-dibenzylpiperazin-1-yl)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

The synthesis of the title compound was performed in the same manner as in Example 1 using appropriate starting materials.

$^1$H NMR (DMSO-$d_6$), δ ppm: 0.75(3H, s), 1.01 (3H, t, J = 6.8 Hz), 1.33 (3H, s), 2.15-2.40(2H, m), 2.83-3.90 (13H, m), 3.97-4.61 (7H, m), 6.96-7.01 (2H, m), 7.28-7.44 (9H, m), 7.59 (2H, br).

▪ Example 3

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-{3-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-ylmethyl)benzimidazol-1-yl]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

5-(1H-Benzimidazol-2-ylmethyl)-2-methyl-5H-furo[3,2-c]pyridine-4-one(0.28g) and potassium carbonate(0.9g) were added to a DMF solution(2ml) of
1-ethyl-7-(3-iodopropoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione (0.43g). The mixture was stirred at 60°C overnight. After the reaction liquid was condensed under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate: methanol =20:1→4:1). The purified product was

condensed to dryness under reduced pressure to give the title compound(0.43g) as a white amorphous solid.

$^1$H NMR ($CDCl_3$), δ ppm : 0.85 (3H, s), 1.15 (3H, t, J = 7.1 Hz), 1.53 (3H, s), 2.12-2.23 (2H, m), 2.40 (3H, s), 3.38 (3H, s), 3.61-3.72 (1H, m), 3.95 (2H, t, J = 5.7 Hz), 4.05-4.15 (1H, m), 4.65 (2H, t, J = 6.5 Hz), 5.53 (2H, s), 6.49-6.55 (2H, m), 6.70-6.71 (1H, m), 6.74-6.80 (1H, m), 7.19 (1H, d, J = 9.0 Hz), 7.24-7.27 (2H, m), 7.33-7.38 (1H, m), 7.54 (1H, d, J = 7.5 Hz), 7.75-7.79 (1H, m).

▪ Example 4

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{2-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-ylmethyl)benzimidazol-1-yl]ethoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Potassium carbonate(0.58g), sodium iodide(0.21g), and 5-(1H-benzimidazol-2-ylmethyl)-2-methyl-5H-furo[3,2-c]pyridine-4-one(0.39g) were added to a DMF solution(30ml) of 7-(2-chloroethoxy)-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.47g). The mixture was stirred at 65°C overnight. The mixture was further stirred at 100°C overnight. After the reaction mixture was condensed under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate: methanol =95:5→85:15). The purified product was condensed to dryness under reduced pressure to give the title compound(0.44g) as a white amorphous solid.

$^1$H NMR ($CDCl_3$), δ ppm: 0.77 (3H, s), 1.09 (3H, t, J = 7.1 Hz), 1.49 (3H, s), 2.40 (3H, s), 3.26 (3H, s), 3.61-3.74 (1H, m), 4.05-4.18 (1H, m), 4.24 (2H, t, J = 5.0 Hz), 4.93 (2H, t, J = 5.0 Hz), 5.55-5.66 (2H, m), 6.44-6.45 (1H, m), 6.51-6.54 (2H, m), 6.57-6.64 (1H, m), 7.00 (1H, d, J = 9.0 Hz), 7.25-7.36 (2H, m), 7.58-7.62 (1H, m), 7.63 (1H, d, 7.6 Hz), 7.77-7.80 (1H, m).

▪ Example 5

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-[3-(2-phenyl-benzoimidazol-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

2-Phenyl-1H-benzimidazole(0.2g) and potassium carbonate(0.29g) were added to a DMF solution(5ml) of 1-ethyl-7-(3-iodopropoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.49g). The mixture was stirred at 60°C for 7 hours. The reaction mixture was poured to ice water(50ml), and the generated insoluble matter was separated. The insoluble matter was dissolved in ethyl acetate. The liquid was dried over sodium sulfate and condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=1:3). The purified product was condensed under reduced pressure. A 1N-hydrogen chloride ethanol solution(1.0ml) was added to an isopropyl alcohol solution of the residue. The mixture was condensed under reduced pressure. Ether was added to the residue. The generated insoluble matter was separated by filtration and dried to give the title compound(0.32g) as a white powder.
mp: 132 to 134°C

- Example 6
- Synthesis of 7-[3-(4-chloro-2-oxo-3-phenyl-2H-quinolin-1-yl)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

4-Chloro-3-phenyl-1H-quinoline-2-one(0.3g) was suspended in DMF(6ml). Sodium hydride (60% in oil)(51mg) was added, and the mixture was stirred for 15 minutes at room temperature. 1-Ethyl-7-(3-iodopropoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.55g) was added thereto and the mixture was stirred at room temperature for 7 days. The reaction mixture was poured to ice water(50ml), and the generated insoluble matter was separated. The insoluble matter was dissolved in ethyl acetate. The liquid was dried over sodium sulfate and condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=1:1→1:3). The purified product was condensed under reduced pressure, and the residue was recrystallized from ether, thereby obtaining the title compound(0.28g) as a white powder.
mp: 122 to 128°C

▪ Example 7

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-{3-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-ylmethyl)imidazo[4,5-c]pyridin-1-yl]propoxy}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride

A DMF solution(4ml) of 5-(2,2-dihydroxyethyl)-2-methyl-5H-furo[3,2-c]pyridine-4-one(0.20g), 7-[3-(3-aminopyridin-4-ylamino)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.37g), and sodium hydrogensulfite(0.47g) were heated at 180°C for 10 minutes (microwave reactor). After the reaction liquid was condensed under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate: methanol =95:5→60:40). The purified product was condensed under reduced pressure. A 4N-hydrogen chloride ethyl acetate solution was added to an ethyl acetate solution of the residue, which was stirred at room temperature. The generated insoluble matter was separated by filtration, and dried to give the title compound(0.47g) as a white amorphous solid.

$^1$H NMR (DMSO-$d_6$), δ ppm : 0.70 (3H, s), 0.95 (3H, t, J = 7.1 Hz), 1.30 (3H, s), 2.31-2.41 (2H, m), 2.40 (3H, s), 3.29 (3H, s), 3.60-3.70 (1H, m), 3.98-4.09 (1H, m), 4.16 (2H, t, J = 6.0 Hz), 4.79 (2H, t, J = 6.6 Hz), 5.67 (2H, s), 6.54 (1H, s), 6.80-6.85 (3H, m), 7.33 (1H, d, J = 6.5 Hz), 7.76 (1H, d, J = 7.5 Hz), 8.33 (1H, d, J = 6.5 Hz), 8.60 (1H, d, J = 6.5 Hz), 9.36 (1H, s).

▪ Example 8

· Synthesis of 7-[3-(3-bromo-2-oxo-2H-quinolin-1-yl)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

Under ice cooling, sodium hydride (60% in oil、0.2g) was added to a DMF solution(10ml) of 3-bromo-1H-quinoline-2-one(1.0g). The mixture was stirred at the same temperature for 15 minutes. Lithium bromide(0.76g) was added to the mixture, and the liquid was stirred at the same temperature for another 15 minutes, and then at room temperature for an hour. The reaction mixture was cooled to 0°C, and

1-ethyl-7-(3-iodopropoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(2.1g) was added thereto. The mixture was stirred at room temperature for 2 hours, and at 50°C for 8 hours. The reaction mixture was poured to ice water, and the generated insoluble matter was separated. The insoluble matter was dissolved in a mixed solvent of ethyl acetate and dichloromethane. The liquid was dried with sodium sulfate and condensed under reduced pressure. Ethyl acetate was added to the residue. The generated insoluble matter was separated and dried to give the title compound(1.2g) as a white powder.
mp: 168 to 169°C

▪ Example 9

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-[3-(2-oxo-2H-quinolin-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 8 using appropriate starting materials.
White powder
mp: 134 to 135°C

▪ Example 10

· Synthesis of
1-ethyl-7-[3-(3-iodo-4-oxo-4H-quinolin-1-yl)propoxy]-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 8 using appropriate starting materials.
White powder
mp: 97 to 106°C

▪ Example 11

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-[3-(4-oxo-3-(pyridin-3-yl)-4H-quinolin-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 8 using appropriate starting materials.
White powder

mp: 199 to 201°C

▪ Example 12

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-[3-(4-oxo-4H-quinolin-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 8 using appropriate starting materials.

White powder

mp: 174 to 177°C

▪ Example 13

· Synthesis of

7-[3-(3-bromo-4-oxo-4H-quinolin-1-yl)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 8 using appropriate starting materials.

White powder

mp: 180 to 183°C

▪ Example 14

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-[3-(2-oxo-3-phenyl-2,3-dihydrobenzimidazol-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 6 using appropriate starting materials.

$^1$H NMR ($CDCl_3$), δ ppm: 0.84(3H, s), 1.14 (3H, t, J = 7.1Hz), 1.52 (3H, s), 2.27-2.41 (2H, m), 3.36(3H, s), 3.6-3.78 (1H, m), 4.09(2H, t, J = 5.9 Hz), 4.11-4.26 (1H, m), 4.20(2H, t, J = 6.6 Hz), 6.68 (1H, d, J = 2.8 Hz), 6.80 (1H, dd, J = 2.8, 9.0 Hz), 6.99-7.14 (4H, m), 7.19 (1H, d, J = 9.0 Hz), 7.33-7.47 (1H, m), 7.47-7.58 (4H, m).

▪ Example 15

· Synthesis of

1-ethyl-7-[3-(3-hydroxy-2-oxo-3-phenyl-2,3-dihydroindol-1-yl)propoxy]-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 6 using appropriate starting materials.
White powder
mp: 153 to 156°C

▪ Example 16

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-[3-(2-oxo-3-(pyridin-3-yl)-2,3-dihydrobenzimidazol-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride

1-(Pyridin-3-yl)-1,3-dihydrobenzimidazole-2-one(0.2g) was suspended in DMF(6ml). Sodium hydride (55% in oil, 48mg) was added under ice cooling, and the mixture was stirred at room temperature for 30 minutes. 1-Ethyl-7-(3-iodopropoxy)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.45g) was added to the mixture. The mixture was stirred at room temperature for 3 hours. The reaction mixture was poured to ice water(100ml), followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate). The purified product was condensed under reduced pressure. A 0.5N-hydrogen chloride ethanol solution(1.9ml) was added to an isopropyl alcohol solution of the residue. The mixture was condensed under reduced pressure. Ether was added to the residue. The generated insoluble matter was separated by filtration and dried to give the title compound(0.38g) as a white powder.
White powder
mp: 119 to 125°C

▪ Example 17

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-[3-(2'-oxospiro[[1,3]dioxolane-2,3'-indoline]-1'-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 6 using appropriate starting materials.

White powder

mp: 143 to 147°C

▪ Example 18

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-[3-(2-phenylindol-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 6 using appropriate starting materials.

White powder

mp: 140 to 142°C

▪ Example 19

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-[3-(2-oxo-3-phenyl-2H-quinolin-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

7-[3-(3-Bromo-2-oxo-2H-quinolin-1-yl)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.5g), phenylboronic acid(0.12g), tetrakis (triphenyl phosphine) palladium (0) (0.11g), and potassium carbonate(0.39g) were added to dioxane(5ml). The mixture was heated under reflux for 2 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature. Water was added thereto, followed by extraction by ethyl acetate. The organic layer was dried over sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: hexane =1:1→3:1). The purified product was condensed to dryness under reduced pressure, thereby obtaining the title compound(0.34g) as a white amorphous solid.

$^1$H NMR ($CDCl_3$), δ ppm: 0.84(3H, s), 1.14 (3H, t, J = 7.1Hz), 1.52 (3H, s), 2.27-2.42(2H, m), 3.37(3H, s), 3.62-3.80 (1H, m), 4.05-4.28 (3H, m), 4.62(2H, t, J = 7.2 Hz), 6.72 (1H, d, J = 2.7 Hz), 6.83 (1H, dd, J = 2.7, 9.0 Hz), 7.19 (1H, d, J = 9.0 Hz), 7.20-7.30 (1H, m), 7.32-7.58 (5H, m), 7.60-7.67 (1H, m), 7.67-7.74 (2H, m), 7.84(1H, s).

▪ Example 20

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-[3-(4-oxo-3-phenyl-4H-quinolin-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 19 using appropriate starting materials.

White powder

mp: 150 to 152°C

▪ Example 21

Synthesis of

1-ethyl-7-{3-[3-(6-methoxypyridin-3-yl)-4-oxo-4H-quinolin-1-yl]propoxy}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 19 using appropriate starting materials.

White powder

mp: 159 to 161°C

▪ Example 22

Synthesis of

1-ethyl-7-{3-[3-(6-methoxypyridin-3-yl)-4-oxo-4H-quinoline-1-yl]propoxy}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione mesylate

Methanesulfonic acid(0.024ml) was added to an ethyl acetate / isopropyl alcohol solution(1:1, 8ml) of 1-ethyl-7-{3-[3-(6-methoxypyridin-3-yl)-4-oxo-4H-quinoline-1-yl]propoxy}-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.2g) at 0 °C, which was stirred at the same temperature for 2 hours. The precipitated insoluble matter was separated, washed with isopropyl alcohol, and dried to give the title compound(0.19g) as a white powder.

White powder

mp: 188 to 189°C

▪ Example 23

· Synthesis of

1-ethyl-3,3,5-trimethyl-7-[3-(2-oxo-3-phenyl-3,4-dihydro-2H-quinolin-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

10% Palladium on carbon(20mg) was added to an ethanol/ethyl acetate solution (1:1, 4ml) of 7-[3-(4-chloro-2-oxo-3-phenyl-2H-quinoline-1-yl)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.19g). The mixture was subjected to catalytic reduction at 50°C under normal pressure for 6 hours. The reaction mixture was subjected to celite filtration to remove the catalyst. The filtrate was condensed under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=1:1). The purified product was condensed under reduced pressure, and the residue was recrystallized from ether/hexane, thereby obtaining the title compound(0.1g) as a white powder.

mp: 100 to 105°C

▪ Example 24

· Synthesis of 7-[3-(2,3-dioxo-2,3-dihydroindol-1-yl)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

The synthesis of the title compound was performed in the same manner as in Example 6 using appropriate starting materials.

Orange powder

mp: 162 to 163°C

▪ Example 25

· Synthesis of 1-ethyl-3,3,5-trimethyl-7-[3-(2-oxo-2,3-dihydroindol-1-yl)propoxy]-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione

7-[3-(2,3-Dioxo-2,3-dihydroindol-1-yl)propoxy]-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione(0.3g) was suspended in hydrazine hydrate(3ml), and the liquid was stirred for two hours while heated under reflux. The reaction mixture was cooled to room temperature. Water was added thereto, followed by extraction by ethyl acetate. The organic layer was dried by anhydrous sodium sulfate, and condensed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: hexane =85:15). The purified product was condensed under reduced pressure,

and the residue was recrystallized from ether/hexane, thereby obtaining the title compound(0.18g) as a pale brownish white powder.
mp: 146 to 149°C

▪ Example 26

Synthesis of
1-ethyl-3,3,5-trimethyl-7-(3-((3-(1-oxoisoquinolin-2(2H)-yl)propyl)(pyridin-4-ylmethyl)amino)propoxy)-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-dione

The synthesis of the title compound was performed in the same manner as in Example 6 using appropriate starting materials.
$^1$H-NMR ($CDCl_3$) δppm: 0.84 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.51 (s, 3H), 1.90-2.00 (m, 4H), 2.58 (t, J = 6.8 Hz, 2H), 2.68 (t, J = 6.8 Hz, 2H), 3.38 (s, 3H), 3.61 (s, 2H), 3.62-3.72 (m, 1H), 3.95-4.00 (m, 4H), 4.08-4.22 (m, 1H), 6.44 (d, J = 7.3 Hz, 1H), 6.68 (d, J = 2.7 Hz, 1H), 6.75 (dd, J = 9.0 and 2.7 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 7.17 (d, J = 9.0 Hz, 1H), 7.25-7.27 (m, 2H), 7.45-7.52 (m, 2H), 7.60-7.70 (m, 1H), 8.40 (d, J = 7.9 Hz, 1H), 8.48 (d, J = 1.5 Hz, 2H).

▪ Example 27

· Synthesis of
1-ethyl-3,3,5-trimethyl-7-(3-((3-(1-oxoisoquinolin-2(2H)-yl)propyl)(pyridin-4-ylmethyl)amino)propoxy)-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-dione dihydrochloride

A 4N-hydrogen chloride in ethyl acetate solution(0.3ml) was added to an ethyl acetate solution (3ml) of
1-ethyl-3,3,5-trimethyl-7-(3-((3-(1-oxoisoquinolin-2(2H)-yl)propyl)(pyridin-4-ylmethyl)amino)propoxy)-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-dione (159mg), and the mixture was stirred at room temperature for two hours. The reaction mixture was condensed under reduced pressure to give the title compound(178mg) as a amorphous solid.
$^1$H-NMR (DMSO-$d_6$) δppm: 0.74 (s, 3H), 1.00 (t, J = 7.0 Hz, 3H), 1.32 (s, 3H), 2.25 (br, 4H), 3.01-3.31 (m, 4H), 3.31 (s, 3H), 3.61-3.70 (m, 1H), 4.00-4.12 (m, 5H), 4.61 (br, 2H), 6.65 (d, J = 7.4 Hz, 1H), 6.86-6.91 (m, 2H), 7.39 (d, J = 8.9 Hz, 1H), 7.47-7.53 (m, 2H), 7.65-7.74

(m, 2H), 8.08 (br, 2H), 8.21 (d, J = 8.0 Hz, 1H), 8.80 (br, 2H).

Pharmacological Test 1

(1) Production of human Kv1.5-expressing CHO-K1 cell lines

CHO-K1 cell lines stably expressing human Kv1.5 channels were prepared in the following manner.

Full-length human Kv1.5 cDNA was cloned from a human heart cDNA library (produced by Stratagene). The obtained human Kv1.5 sequence corresponds to the sequence described in FASEB J. 5, 331-337 (1991).

The obtained human Kv1.5 cDNA was inserted into a plasmid encoding a CMV promoter and a G418 resistance marker to produce a Kv1.5 expression vector. The human Kv1.5 expression vector was transfected into CHO-K1 cells by the lipofectamine method. After culturing the cells in an F-12 medium (produced by Invitrogen Corp.) containing 10% FBS (produced by Invitrogen Corp.) for 3 or 4 days, the medium was replaced with a FBS-containing F-12 medium that included 1,000 μg/ml of G418 (produced by Invitrogen Corp.), and single colonies were isolated. The amount of Kv1.5 channel expression in the single colonies was quantified at the mRNA level by RT-PCR and then quantified at the protein level by western blotting. Finally, the expressed current was analyzed by patch clamp method. Cell lines expressing a current of 200 pA or more per cell were selected as channel-expressing cell lines for activity measurement by patch clamp method.

(2) Production of CHO cell line expressing human GIRK1/4

CHO cell lines stably expressing human GIRK1/4 channels were prepared in the following manner.

Full-length human GIRK1 cDNA was cloned from HuH cell- and HeLa cell-derived cDNA libraries. Full-length GIRK4 cDNA was amplified from a human heart cDNA library (produced by Clontech Laboratories, Inc.) by PCR using synthetic primers shown in Table 1, and cloned into the Eco-RI restriction enzyme site of pCR-Blunt (produced by Invitrogen Corporation) or into the HincII site of pUC118 (produced by Takara Bio, Inc.).

Table 1

| Primer | Sequence | |
|---|---|---|
| hGIRK1-S | 5'-ATGTCTGCACTCCGAAGGAAATTTG-3' | SEQ ID No.1 |
| hGIRK1-A | 5'-TTATGTGAAGCGATCAGAGTTC-3' | SEQ ID No.2 |
| hGIRK1-F2 | 5'-GCAGGGTACCCCTTCGTATTATGTCTGCACTCC-3' | SEQ ID No.3 |
| hGIRK1-A3 | 5'-GGTGTCTGCCGAGATTTGA-3' | SEQ ID No.4 |
| hGIRK1-A4 | 5'-CCGAGTGTAGGCGATCACCC-3' | SEQ ID No.5 |
| hGIRK4-S | 5'-ATGGCTGGCGATTCTAGGAATGCC-3' | SEQ ID No.6 |
| hGIRK4-A | 5'-TCTCACCGAGCCCCTGGCCTCCC-3' | SEQ ID No.7 |
| hGIRK4-S2 | 5'-AACCAGGACATGGAGATTGG-3' | SEQ ID No.8 |
| hGIRK4-A2 | 5'-GAGAACAGGAAAGCGGACAC-3' | SEQ ID No.9 |

The obtained human GIRK1 and GIRK4 cDNA sequences correspond to known sequences (NCBI database: GIRK1 (NM_002239) and GIRK4 (NM_000890) respectively). The obtained GIRK1 and GIRK4 cDNA sequences were cloned into the Eco-RI restriction enzyme site of pCR-Blunt (available from Invitrogen Corporation) or into the HincII site of pUC118 (available from Takara Bio, Inc.). A GIRK4 expression vector was constructed by insertion into the BamHI-XhoI site of pcDNA5/FRT. A GIRK1 expression vector was constructed by insertion into the KpnI-XhoI site of pcDNA3.1(+) or pCAG_neo. FLP-IN-CHO cells (produced by Invitrogen Corporation) were transfected with human GIRK1 and GIRK4 expression vectors by using Lipofectamine 2000 (produced by Invitrogen Corporation) according to the protocol enclosed with the reagent or using an electronic induction method ("Nucleofector Kit-T", produced by Amaxa). First, the cells transfected with the GIRK4 expression vector were cultured in a 10% serum-containing F12 medium (produced by Sigma) supplemented with 600 μg/ml of hygromycin in an incubator with 5% carbon dioxide at 37°C. Then the cells expressing GIRK4 were transfected with the GIRK1 expression vector and were cultured in 10% serum-containing F12 medium supplemented with 350 μg/ml of G418 and 600 μg/ml of hygromycin in an incubator with 5% carbon dioxide at 37°C to select GIRK1/4 expressing cell lines. Cell populations whose growth was observed after about 2 weeks were isolated using cloning rings, and the obtained single colonies were proliferated. RNA was extracted from single colonies, and single-stranded cDNA was synthesized by a cDNA synthesis kit (produced

by Invitrogen Corporation), and the amount of expression was quantified at the mRNA level by real-time PCR (Applied Biosystems, Ltd.). Finally, the expressed current was analyzed by patch clamp method described below. The cell lines expressing a current of 500 pA or more per cell were selected as channel-expressing cell lines for activity measurement by patch clamping method.

(3) Measurement of ion channel current by patch clamp method (human Kv1.5-expressing CHO-K1 cell line)

An experiment was carried out using a patch clamp setup at room temperature (20 to 26°C). A perfusion chamber having a diameter of 20 mm (flow rate: about 5 ml/min) was mounted on the stage of a phase-contrast inverted microscope (produced by Nikon Corporation) placed on a vibration isolated table. A poly-L-lysine (produced by Sigma)-coated coverslip (diameter: 15 mm, produced by Matsunami Glass Ind., Ltd.) on which human Kv1.5-expressing cells were cultured was placed in the perfusion chamber.

Depolarizing stimulation pulses were applied and ionic current was recorded by using a patch clamp amplifier (EPC-7 or EPC-7 PLUS, produced by HEKA) and a personal computer (manufactured by IBM Corp.) in which software for data acquisition and analysis of ion channel current (PULSE 8.77, produced by HEKA) was installed. The current was measured in the whole-cell configuration of the patch-clamp technique. The tip (resistance: 2 to 4 MΩ) of a borosilicate glass pipette (produced by Sutter Instrument Co.) was gently placed on the cell membrane by using a three-dimensional mechanical micromanipulator (produced by Shoshin EM Corporation). Weak suction resulted in giga seal formation (the pipette resistance increased to more than 1 GΩ). Subsequently, stronger suction was applied to break the cell membrane. The capacitative current derived from the cell membrane was corrected using a patch clamp amplifier. Subsequently, the series resistance (Rs) between the pipette and the interior of the cell was measured and corrected.

The composition of the extracellular solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

| | |
|---|---|
| NaCl | 140 mM, |
| KCl | 40 mM, |
| $CaCl_2$ | 1.8 mM, |
| $MgCl_2$ | 1 mM, |
| $NaH_2PO_4$ | 0.33 mM, |
| HEPES | 5 mM |
| Glucose | 5.5 mM (pH = 7.4) |

Each test compound was prepared as a 1000-fold concentrated stock solution that was dissolved in DMSO and then diluted in the extracellular solution.

The composition of the electrode internal solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

| | |
|---|---|
| KOH | 100 mM, |
| KCl | 40 mM, |
| Aspartic acid | 70 mM, |
| $MgCl_2$ | 1 mM, |
| MgATP | 5 mM, |
| $K_2$ creatine phosphate | 5 mM, |
| HEPES | 5 mM |
| EGTA | 5 mM (pH = 7.2) |

(4) Measurement of ion channel current by patch clamp method (human GIRK1/4-expressing CHO-K1 cell line)

An experiment was carried out using a patch clamp setup at room temperature (20 to 26°C). A perfusion chamber having a diameter of 20 mm (flow rate: about 5 ml/min) was mounted on the stage of a phase-contrast inverted microscope (produced by Nikon Corporation) placed on a vibration isolation table. A poly-L-lysine (produced by Sigma)-coated coverslip (diameter: 15 mm, produced by Matsunami Glass Ind., Ltd.) on which human GIRK1/4-expressing cells were cultured was placed in the perfusion chamber.

Hyperpolarizing stimulation pulses were applied and ionic current was recorded using a patch clamp amplifier (EPC-7 or EPC-7 PLUS, manufactured by HEKA) and a personal computer (manufactured by IBM Corp.) in which software for data acquisition and analysis of ion

channel current (PULSE 8.77, manufactured by HEKA) was installed. The current was measured in the whole-cell configuration of the patch-clamp technique. The tip (resistance: 2 to 4 MΩ) of a borosilicate glass pipette (produced by Sutter Instrument Co.) was gently placed on the cell membrane by using a three-dimensional mechanical micromanipulator (produced by Shoshin EM Corporation). Weak suction resulted in giga seal formation (the pipette resistance increased to more than 1 GΩ). Subsequently, stronger suction was applied to break the cell membrane. The capacitative current derived from the cell membrane was corrected using a patch clamp amplifier. Subsequently, the series resistance (Rs) between the pipette and the interior of the cell was measured and corrected.

The composition of the extracellular solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

| | |
|---|---|
| NaCl | 140 mM, |
| KCl | 4 mM, |
| $CaCl_2$ | 1.8 mM, |
| $MgCl_2$ | 1 mM, |
| $NaH_2PO_4$ | 0.33 mM, |
| HEPES | 5 mM |
| Glucose | 5.5 mM (pH = 7.4) |

Each test compound was prepared as a 1000-fold concentrated stock solution that was dissolved in DMSO and then diluted in the extracellular solution.

The composition of the electrode internal solution used is shown below. Unless otherwise specified, these components were obtained from Wako Pure Chemical Industries, Ltd.

| | |
|---|---|
| KOH | 100 mM, |
| KCl | 40 mM, |
| Aspartic acid | 70 mM, |
| $MgCl_2$ | 1 mM, |
| MgATP | 5 mM, |
| $K_2$ creatine phosphate | 5 mM, |
| HEPES | 5 mM |
| EGTA | 5 mM (pH = 7.2) |

(5) Measurement of human Kv1.5 current

While the membrane potential was holded at -80 mV, depolarizing pulses (-80 mV for 0.05 seconds →..+40 mV for 0.2 seconds →..-40 mV for 0.2 seconds →..-80 mV for 0.05 seconds) were applied at a stimulation frequency of 1 Hz to measure Kv1.5 channel current. More specifically, first, while perfusing an extracellular solution containing 0.1% DMSO and holding the membrane potential at -80 mV, depolarizing pulses were applied. The current obtained during the pulse application was recorded as a current in the absence of the test compounds. Subsequently, while perfusing an extracellular solution containing 0.1 μM of a test compound and holding the membrane potential at -80 mV, depolarizing pulses were applied. After the inhibitory effect of the test compound had been stabilized, the current was recorded. The same procedure was repeated using an extracellular solution containing 1 μM of the test compound and then using an extracellular solution containing 10 μM of the test compound. The current obtained using the solution containing the test compound at each concentration was recorded.

The data was analyzed by using the step end current recorded during the +40 mV depolarizing stimulation. The "step end current" refers to the average current flowing for a period of 195 to 199 milliseconds from the start of the +40 mV depolarizing pulse stimulation.

Using the step end current in the presence of the test compound and the step end current in the absence of the test compound, the relative current in the solution containing the test compound at each concentration was calculated according to the following formula:
Relative current =
(Step end current in the presence of the test compound) / (Step end current in the absence of the test compound)

(6) Measurement of human GIRK1/4 current

While the membrane potential was holded at -80 mV, hyperpolarizing pulses (-80 mV for 0.05 seconds →..-120 mV for 0.2 seconds →..-80 mV for 0.05 seconds) were applied at a stimulation

frequency of 1 Hz to measure GIRK1/4 channel current. More specifically, first, while perfusing an extracellular solution containing 0.1% DMSO and maintaining the membrane potential at -80 mV, hyperpolarizing pulses were applied. The current obtained during the pulse application was recorded as the current in the absence of the test compounds. Subsequently, while perfusing an extracellular solution containing 0.1 μM of a test compound and maintaining the membrane potential at -80 mV, hyperpolarizing pulses were applied. After the inhibitory effect of the test compound had been stabilized, the current was recorded. The same procedure was repeated using an extracellular solution containing 1 μM of the test compound and then using an extracellular solution containing 10 μM of the test compound. The current obtained using the solution containing the test compound at each concentration were recorded.

The data was analyzed by using the step end current recorded during the -120 mV depolarizing stimulation. The "step end current" refers to the average current flowing for a period of 195 to 199 milliseconds from the start of the -120 mV depolarizing pulse stimulation.

Using the step end current in the presence of the test compound and the step end current in the absence of the test compound, the relative current in the solution containing the test compound at each concentration was calculated according to the following formula:
Relative current =
(Step end current in the presence of the test compound) / (Step end current in the absence of the test compound)

(7) Calculation of inhibitory activity on Kv1.5 channel ionic current and GIRK1/4 channel current

The concentration for 50% inhibition of Kv1.5 channel current or GIRK1/4 channel current ($IC_{50}$ value) was calculated according to the following nonlinear regression equation:
Relative current = $1/(1+ [\text{Concentration of the compound}]/IC_{50})^{nH}$
wherein nH is the Hill coefficient.

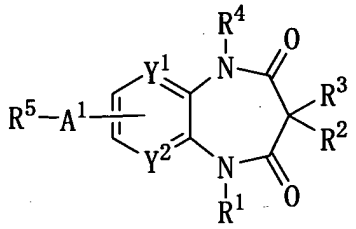
Table 2 shows the test results.

Table 2

| Test Compound | KV1.5 $IC_{50}$ (μM) |
|---|---|
| Compound of Example 2 | 1.10 |
| Compound of Example 5 | 0.87 |
| Compound of Example 6 | 0.60 |
| Compound of Example 14 | 0.40 |
| Compound of Example 20 | 0.34 |
| Compound of Example 21 | 0.84 |
| Compound of Example 22 | 1.50 |

CLAIMS

[Claim 1] A diazepine compound represented by General Formula (1)



(1)

or a salt thereof,

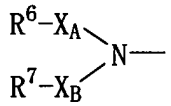
wherein $R^1$, $R^2$, $R^3$, and $R^4$ are each independently hydrogen, lower alkyl, cyclo lower alkyl or lower alkoxy lower alkyl;

$R^2$ and $R^3$ may be linked to form lower alkylene;

$A^1$ is lower alkylene optionally substituted with one or more substituents selected from the group consisting of hydroxyl and oxo;

$Y^1$ and $Y^2$ are each independently -N= or -CH=;

$R^5$ is group represented by



wherein $R^6$ and $R^7$ are each independently hydrogen or an organic group;

$R^6$ and $R^7$ may be linked to form a ring together with the neighboring group $-X_A-N-X_B-$;

$X_A$ and $X_B$ are each independently a bond, alkylene, alkenylene, -CO-, $-SO_2-$, or -CONH-, wherein each of the alkylene and alkenylene chains can optionally contain one or more substituents selected from the group consisting of -S-, -C(=S)-, $-SO_2-$, -CO-, -O-, -NH-, -CONH- and $-SO_2NH-$, and the hydrogen atom (H) bonded to the nitrogen atom (N) in $X_A$ and $X_B$ is optionally substituted with a substituent selected from the group consisting of lower alkyl, phenyl lower alkyl and phenyl.

[Claim 2] A diazepine compound or a salt thereof according to claim 1, wherein $R^6$ and $R^7$ are each independently hydrogen, lower alkyl, cyclo lower alkyl, aryl or heterocyclic group, each of which is optionally substituted, and $X_A$ and $X_B$ are each independently a bond, lower alkylene, lower alkenylene, -CO-, $-SO_2-$, -lower alkylene-$SO_2-$, -lower alkylene-CO-, -lower alkenylene-CO-, -lower alkylene-CO-N(lower alkyl)-lower alkylene-, -N(lower alkyl)-lower alkylene-, -CO-N(lower

alkyl)-lower alkylene-, -O-lower alkylene-, -N(phenyl lower alkyl)-lower alkylene-, -CO-lower alkylene-CO-, -CO-NH-lower alkylene-, -lower alkylene-N(lower alkyl)-lower alkylene-, -lower alkylene-N(lower alkyl)-lower alkylene-O-, -lower alkylene-NH-lower alkylene-, -lower alkylene-$SO_2$-NH-lower alkylene-, -N(lower alkyl)-CO-lower alkylene-, -N(lower alkyl)-lower alkylene-CO-, -N(lower alkyl)-lower alkylene-N(lower alkyl)-lower alkylene-, -N(phenyl)-lower alkylene-CO-, -N(phenyl)-lower alkylene-CO-, -NH-CO-, -NH-CO-lower alkylene-, -NH-lower alkylene-, -O-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -O-lower alkylene-CO-, -NH-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -S-lower alkylene-CO-N(lower alkyl)-lower alkylene-, -$SO_2$-N(lower alkyl)-lower alkylene-, -$SO_2$-NH-lower alkylene-, -lower alkenylene-CO-N(lower alkyl)-lower alkylene-, lower alkylene-N(phenyl lower alkyl)-lower alkylene-, -N(phenyl lower alkyl)-lower alkylene-, -N(phenyl)-lower alkylene-CO-N(lower alkyl)-lower alkylene-, or -CO-lower alkylene-O-CO-lower alkylene-O-.

[Claim 3] A diazepine compound or a salt thereof according to claim 2, wherein $R^6$ and $R^7$ are each independently hydrogen, lower alkyl, cyclo lower alkyl, aryl or saturated or unsaturated monocyclic or polycyclic heterocyclic groups containing at least one hetero atom selected from the group consisting of oxygen, sulfur and nitrogen, each of which is optionally substituted.

[Claim 4] A diazepine compound or a salt thereof according to claim 3, wherein $R^6$ and $R^7$ are each independently hydrogen, lower alkyl, cyclo lower alkyl, phenyl, naphthyl, piperidyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, triazolyl, imidazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazo[2,1-b]thiazolyl, thieno[2,3-b]pyrazinyl, 2,3-dihydroimidazo[2,1-b]thiazolyl, benzothiazolyl, indolyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, benzothienyl, benzimidazolyl, 2,3-dihydrobenzimidazolyl, 2,3-dihydrobenzo[b]furyl, benzofuryl,

indazolyl, furo[2,3-c]pyridyl, 6,7-dihydrofuro[2,3-c]pyridyl, furo[3,2-c]pyridyl, 4,5-dihydrofuro[3,2-c]pyridyl, furo[2,3-b]pyridyl, 6,7-dihydrofuro[2,3-b]pyridyl, thieno[2,3-c]pyridyl, 6,7-dihydrothieno[2,3-c]pyridyl, thieno[3,2-c]pyridyl, 4,5-dihydrothieno[3,2-c]pyridyl, thieno[2,3-b]pyridyl, 6,7-dihydrothieno[2,3-b]pyridyl, benzo[1,3]dioxolyl, benzisoxazolyl, pyrazolo[2,3-a]pyridyl, indolizinyl, 2,3-dihydroindolyl, isoquinolyl, 1,2-dihydroisoquinolyl, 1,2,3,4-tetrahydro-1H-isoquinolyl, carbostyril, 3,4-dihydrocarbostyril, quinolyl, 1,4-dihydroquinolyl, 1,2-dihydroquinolyl, 3,4-dihydroquinolyl, 1,2,3,4-tetrahydroquinolyl, pyrido[3,4-d]imidazolyl, pyrido[2,3-d]imidazolyl, chromanyl, 5,6,7,8-tetrahydroisoquinolyl, 3,4-dihydro-1H-isoquinolyl, 3,4-dihydroisoquinolyl, naphthyridinyl, 1,4-benzodioxanyl, cinnolinyl, quinoxalinyl, 2,3-dihydrobenz-1,4-oxazinyl, azetidinyl, 1,2,4-oxadiazolyl and azepanyl, each of which is optionally substituted.

[Claim 5] A diazepine compound or a salt thereof according to claim 4, wherein $R^6$ and $R^7$ are each independently selected from the group consisting of the following substituents (1) to (54):

(1) hydrogen;

(2) lower alkyl;

(3) cyclo lower alkyl optionally substituted with one or more phenyl lower alkoxys;

(4) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4-1) to (4-27):

(4-1) cyano;

(4-2) hydroxyl;

(4-3) halogen;

(4-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, lower alkoxy, imidazolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl and morpholinyl;

(4-5) lower alkoxy optionally substituted with one or more substituents selected from the group consisting of amino and lower

alkyl amino;

(4-6) pyridyl;

(4-7) thienyl;

(4-8) piperazinyl optionally substituted with one or more lower alkyls;

(4-9) phenyl;

(4-10) pyrazolyl optionally substituted with one or more lower alkyls;

(4-11) pyrimidinyl optionally substituted with one or more lower alkyls;

(4-12) piperidyl optionally substituted with one or more lower alkyls;

(4-13) furyl;

(4-14) carboxy;

(4-15) lower alkoxycarbonyl;

(4-16) amino optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl and lower alkylsulfonyl;

(4-17) lower alkylthio;

(4-18) triazolyl;

(4-19) imidazolyl;

(4-20) pyrrolidinyl optionally substituted with one or more oxos;

(4-21) lower alkylsulfonyl;

(4-22) lower alkylenedioxy optionally substituted with one or more halogens;

(4-23) nitro;

(4-24) oxazolyl;

(4-25) thiazolyl optionally substituted with one or more lower alkyls;

(4-26) lower alkanoyl; and

(4-27) morpholinyl;

(5) naphthyl;

(6) furyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen, carboxy, sulfo, pyridyloxy, lower alkoxycarbonyl and phenyl;

(7) thienyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylenedioxy, carboxy, halogen, pyridyl, lower alkoxy, lower alkoxycarbonyl, oxazolyl and furyl;

(8) imidazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl and halogen;

(9) pyrazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen or lower alkoxy; cyclo lower alkyl; halogen; phenyl optionally substituted with lower alkoxy; furyl and thienyl;

(10) oxazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl;

(11) isoxazolyl optionally substituted with one or more substituents selected from the group consisting of phenyl, lower alkyl, thienyl and furyl;

(12) thiazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl optionally substituted with halogen or lower alkoxy; phenyl; phenoxy and lower alkanoylamino;

(13) pyrrolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and lower alkoxycarbonyl;

(14) triazolyl optionally substituted with one or more lower alkyls;

(15) pyridyl optionally substituted with one or more substituents selected from the group consisting of the following (15-1) to (15-14):

(15-1) halogen;

(15-2) cyano;

(15-3) amino optionally substituted with one or more substituents selected from the group consisting of lower alkanoyl and lower alkylsulfonyl;

(15-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkoxy, lower alkanoyloxy, cyclo lower alkyl amino, lower alkyl amino, lower alkanoyl amino, hydroxyl and pyrrolidinyl optionally substituted with one or more hydroxyls;

(15-5) oxo;

(15-6) hydroxyl;

(15-7) lower alkoxy optionally substituted with one or more phenyls;

(15-8) pyrrolidinyl;

(15-9) lower alkanoyl;

(15-10) morpholinyl;

(15-11) phenoxy;

(15-12) pyrazolyl;

(15-13) thienyl; and

(15-14) N-oxide

(16) pyrimidinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and phenyl;

(17) pyridazinyl;

(18) pyrazinyl optionally substituted with one or more phenyl lower alkoxys;

(19) imidazo[2,1-b]thiazolyl optionally substituted with one or more halogens;

(20) thieno[2,3-b]pyrazinyl;

(21) 2,3-dihydroimidazo[2,1-b]thiazolyl optionally substituted with one or more phenyls;

(22) benzothiazolyl optionally substituted with one or more lower alkyls;

(23) indolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkanoyl and halogen;

(24) imidazo[1,2-a]pyridyl or imidazo[1,5-a]pyridyl, each of which is optionally substituted with one or more lower alkyls;

(25) benzothienyl optionally substituted with one or more lower alkyls;

(26) benzimidazolyl optionally substituted with one or more lower alkyls;

(27) 2,3-dihydrobenzo[b]furyl;

(28) benzofuryl optionally substituted with one or more halogens;

(29) indazolyl optionally substituted with one or more lower alkyls;

(30) furo[2,3-c]pyridyl or 6,7-dihydrofuro[2,3-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl optionally substituted

with lower alkoxy;

(31) furo[3,2-c]pyridyl or 4,5-dihydrofuro[3,2-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl optionally substituted with halogen or lower alkoxy, halogen, furyl, pyridyl and phenyl optionally substituted with one or more substituents selected from the group consisting of amino and lower alkoxy;

(32) thieno[2,3-c]pyridyl or 6,7-dihydrothieno[2,3-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo group and lower alkyl;

(33) thieno[3,2-c]pyridyl or 4,5-dihydrothieno[3,2-c]pyridyl, each of which is optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(34) thieno[2,3-b]pyridyl;

(35) benzo[1,3]dioxolyl optionally substituted with one or more halogens;

(36) benzisoxazolyl;

(37) pyrazolo[2,3-a]pyridyl;

(38) indolizinyl;

(39) 2,3-dihydroindolyl optionally substituted with one or more substituents selected from the group consisting of oxo, lower alkyl and lower alkanoyl;

(40) isoquinolyl or 1,2-dihydroisoquinolyl, each of which is optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halogen and oxo;

(41) 1,2,3,4-tetrahydroisoquinolyl optionally substituted with one or more oxos;

(42) quinolyl optionally substituted with one or more substituents selected from the group consisting of amino optionally substituted with one or two lower alkyls, lower alkoxy, lower alkyl and oxo

(43) 1,2,3,4-tetrahydroquinolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl, pyridyl lower alkyl, aralkyl, lower alkoxy and oxo;

(44) 1,2-dihydroquinolyl optionally substituted with one or more substituents selected from the group consisting of amino optionally substituted with one or two lower alkyls, lower alkoxy, lower alkyl

and oxo;

(45) chromanyl optionally substituted with one or more lower alkyls;

(46) 5,6,7,8-tetrahydroisoquinolyl optionally substituted with one or more oxos;

(47) 3,4-dihydroisoquinolyl optionally substituted with one or more oxos;

(48) naphthyridinyl;

(49) 1,4-benzodioxanyl;

(50) cinnolinyl;

(51) quinoxalinyl;

(52) 2,3-dihydrobenz-1,4-oxazinyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo;

(53) 2,3-dihydro-1H-benzo[d]imidazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo; and

(54) piperidyl optionally substituted with one or more aryl carbonyls.

[Claim 6] A diazepine compound or a salt thereof according to claim 5, wherein $R^6$ and $R^7$ are each independently (1), (4a), (6a), (7a), (8a), (9a), (10a), (11a), (12a), (15a), (16a), (17), (18), (23a), (24a), (24b), (26), (29), (30a), (30b), (31a), (31b), (32a), (32b), (33a), (33b), (35), (40a), (40b), (42a), (43a), (44a), and (53):

(1) hydrogen;

(4a) phenyl optionally substituted with one or more substituents selected from the group consisting of the following (4-1), (4-2), (4-4), (4a-5), (4-10), (4a-16), (4-18), (4-19), (4-23), (4-26), and (4-27):

(4-1) cyano;

(4-2) hydroxyl;

(4-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogens, hydroxyl, 2-oxo-1,2,3,4-tetrahydroquinolyl, lower alkoxy, imidazolyl, and morpholinyl;

(4a-5) lower alkoxy;

(4-10) pyrazolyl optionally substituted with one or more lower alkyls;

(4a-16) amino optionally substituted with one or more lower alkylsulfonyls;

(4-18) triazolyl;

(4-19) imidazolyl;

(4-23) nitro;

(4-26) lower alkanoyl; and

(4-27) morpholinyl;

(6a) furyl optionally substituted with one or more lower alkyls optionally substituted with halogen;

(7a) thienyl optionally substituted with one or more lower alkyls;

(8a) imidazolyl optionally substituted with one or more lower alkyls;

(9a) pyrazolyl optionally substituted with one or more lower alkyls optionally substituted with lower alkoxy;

(10a) oxazolyl optionally substituted with one or more lower alkyls;

(11a) isoxazolyl optionally substituted with one or more lower alkyls;

(12a) thiazolyl optionally substituted with one or more lower alkyls optionally substituted with halogen;

(15a) pyridyl optionally substituted with one or more substituents selected from the group consisting of the following (15-1) to (15-5), (15a-7), (15-9), (15-11), (15-12) and (15-14):

(15-1) halogen;

(15-2) cyano;

(15-3) amino optionally substituted with one or more substituents selected from the group consisting of lower alkanoyl and lower alkylsulfonyl;

(15-4) lower alkyl optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkoxy, lower alkanoyloxy, cyclo lower alkyl amino, lower alkyl amino, lower alkanoyl amino, hydroxyl and pyrrolidinyl optionally substituted with one or more hydroxyls;

(15-5) oxo;

(15a-7) lower alkoxy;

(15-9) lower alkanoyl;

(15-11) phenoxy;

(15-12) pyrazolyl; and

(15-14) N-oxide

(16a) pyrimidinyl optionally substituted with one or more lower alkyls;

(17) pyridazinyl

(18) pyrazinyl optionally substituted with one or more phenyl lower alkoxys;

(23a) indolyl optionally substituted with one or more lower alkyls;

(24a) imidazo[1,2-a]pyridyl;

(24b) imidazo[1,5-a]pyridyl optionally substituted with one or more lower alkyls;

(26) benzimidazolyl optionally substituted with one or more lower alkyls;

(29) indazolyl optionally substituted with one or more lower alkyls;

(30a) furo[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(30b) 6,7-dihydrofuro[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(31a) furo[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(31b) 4,5-dihydrofuro[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl optionally substituted with halogen or lower alkoxy;

(32a) thieno[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(32b) 6,7-dihydrothieno[2,3-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo group and lower alkyl;

(33a) thieno[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(33b) 4,5-dihydrothieno[3,2-c]pyridyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(35a) benzo[1,3]dioxolyl;

(40a) isoquinolyl optionally substituted with one or more oxos;

(40b) 1,2-dihydroisoquinolyl optionally substituted with one or more substituents selected from the group consisting of oxo and lower alkyl;

(42a) quinolyl optionally substituted with one or more oxos;
(43a) 1,2,3,4-tetrahydroquinolyl optionally substituted with one or more substituents selected from the group consisting of aralkyl (e.g., phenyl lower alkyl, etc.), pyridyl lower alkyl and oxo;
(44) 1,2-dihydroquinolyl optionally substituted with one or more oxos; and
(53) 2,3-dihydrobenzo[d]imidazolyl optionally substituted with one or more substituents selected from the group consisting of lower alkyl and oxo.

[Claim 7] A diazepine compound or a salt thereof according to claim 6, wherein $R^6$ and $R^7$ are each independently phenyl, pyridyl, pyrazolyl, indolyl, 4,5-dihydrofuro[3,2-c]pyridyl, and 1,2-dihydroisoquinolyl, each of which is optionally substituted with one or two substituents selected from the group consisting of oxo, lower alkyl, lower alkoxy lower alkyl, and lower alkylsulfonylamino.

[Claim 8] A diazepine compound or a salt thereof according to claim 7, which is selected from the group consisting of the following compounds:
1-ethyl-3,3,5-trimethyl-7-(3-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}propyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(2-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}ethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-(2-{N-(2-methylpyridin-3-ylmethyl)-N-[2-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}ethyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-{2-[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]ethyl}-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[

b][1,4]diazepin-7-ylmethyl)-4-methyl-N-(2-pyridin-3-ylethyl)benza
mide,
N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[
b][1,4]diazepin-7-ylmethyl)-N-(2-pyridin-3-ylethyl)benzenesulfona
mide,
7-{[N-benzyl-N-(2-pyridin-3-ylethyl)amino]methyl}-1-ethyl-3,3,5-t
rimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
N-(2-{[(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-b
enzo[b][1,4]diazepin-7-ylmethyl)(2-pyridin-3-ylethyl)amino]methyl
}phenyl)methanesulfonamide,
7-{[N-[2-(2,7-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-
(2,5-dimethyl-2H-pyrazol-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-t
rimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-
4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimet
hyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-
4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimet
hyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[
b][1,4]diazepin-7-ylmethyl)-2-(1-methyl-1H-indol-3-yl)-N-(2-pyrid
in-3-ylethyl)acetamide.

[Claim 9] A diazepine compound according to claim 8, which is selected from the group consisting of the following compounds:
1-ethyl-3,3,5-trimethyl-7-(3-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]
pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}propyl)-1,5-dihyd
robenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-(2-{N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]
pyridin-5-yl)ethyl]-N-(pyridin-4-ylmethyl)amino}ethyl)-1,5-dihydr
obenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-(2-{N-(2-methylpyridin-3-ylmethyl)-N-[2
-(4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}ethyl)-1,5-dihydro
benzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-{2-[N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]
pyridin-5-yl)ethyl]-N-(4-methylpyridin-3-ylmethyl)amino]ethyl}-1,

5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
1-ethyl-3,3,5-trimethyl-7-({N-(2-methylpyridin-3-ylmethyl)-N-[2-(1-oxo-1H-isoquinolin-2-yl)ethyl]amino}methyl)-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione dihydrochloride,
N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-4-methyl-N-(2-pyridin-3-ylethyl)benzamide hydrochloride,
N-(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-N-(2-pyridin-3-ylethyl)benzenesulfonamide,
7-{[N-benzyl-N-(2-pyridin-3-ylethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione hydrochloride,
N-(2-{[(1-ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)(2-pyridin-3-ylethyl)amino]methyl}phenyl)methanesulfonamide dihydrochloride,
7-{[N-[2-(2,7-dimethyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]-N-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)amino]methyl}-1-ethyl-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(2-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione,
1-Ethyl-7-({N-(2-methoxymethylpyridin-3-ylmethyl)-N-[2-(7-methyl-4-oxo-4H-furo[3,2-c]pyridin-5-yl)ethyl]amino}methyl)-3,3,5-trimethyl-1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione, and
N-(1-Ethyl-3,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-7-ylmethyl)-2-(1-methyl-1H-indol-3-yl)-N-(2-pyridin-3-ylethyl)acetamide hydrochloride.

[Claim 10] A diazepine compound or a salt thereof according to claim 1, wherein $Y^1$ and $Y^2$ are each -CH=.

[Claim 11] A pharmaceutical composition comprising a diazepine compound or a salt thereof according to claim 1, and a pharmacologically acceptable carrier.

[Claim 12] A pharmaceutical composition according to claim 11 for preventing and/or treating arrhythmia.

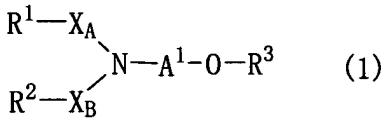
[Claim 13] A diazepine compound or a salt thereof according to claim 1 for use in the pharmaceutical composition.

[Claim 14] Use of a diazepine compound or a salt thereof according to claim 1 as a pharmaceutical composition.

[Claim 15] Use of a diazepine compound or a salt thereof according to claim 1 for the production of a pharmaceutical composition.

[Claim 16] A method of preventing and/or treating arrhythmia, comprising administering to a patient a diazepine compound or a salt thereof according to claim 1.

[Claim 17] An amino compound represented by General Formula (1):



(1)

or a salt thereof,

wherein $R^1$ and $R^2$ are each independently hydrogen or organic group;

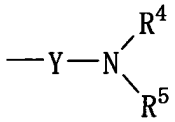
$X_A$ and $X_B$ are each independently a bond, alkylene, alkenylene, -CO-, $-SO_2-$, or -CONH-, wherein each of the alkylene and alkenylene chains can optionally contain one or more substituents selected from the group consisting of -S-, -C(=S)-, $-SO_2-$, -CO-, -O-, -NH-, -CONH- and $-SO_2NH-$, and the hydrogen atom (H) bonded to the nitrogen atom (N) in $X_A$ and $X_B$ is optionally substituted with a substituent selected from the group consisting of lower alkyl, phenyl lower alkyl and phenyl;

$A^1$ is lower alkylene optionally substituted with one or more substituents selected from the group consisting of hydroxyl and oxo;

$R^3$ is (i) a heterocyclic group which is optionally substituted with one or more substituents, or

(ii) an aryl group substituted with one or more substituents selected from the group consisting of oxo, lower alkyl, carboxyl, halo-lower alkyl, lower alkanoyl lower alkyl, phenyl lower alkyl, cyclo lower

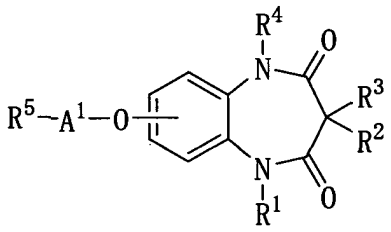
alkyl, lower alkoxy, halo lower alkoxy, phenyl lower alkoxy, phenoxy, cyano, hydroxyl, halogen, nitro, lower alkyl thio, lower alkanoyl, lower alkoxy carbonyl, lower alkenyl, phenyl, triazolyl, isoxazolyl, imidazolyl, pyrrolyl, benzo[d]oxazolyl, benzo[d]thiazolyl and the group represented by General Formula (2):



(2)

wherein Y is a bond, lower alkylene, or -CO-; $R^4$ and $R^5$ are each independently hydrogen, lower alkyl, cyclo lower alkyl, phenyl, or lower alkanoyl; or $R^4$ and $R^5$ may be linked to form a ring together with the neighboring nitrogen, and the ring may optionally have one or more substituents.

[Claim 18] A benzodiazepine compound represented by General Formula (1):



(1)

or a salt thereof,

wherein $R^1$, $R^2$, $R^3$, and $R^4$ are each independently hydrogen or lower alkyl; $R^2$ and $R^3$ may be linked to form lower alkylene;

$A^1$ is lower alkylene optionally substituted with one or more hydroxyls; and $R^5$ is an aryl or heterocyclic group, each of which is optionally substituted.