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Pyridyl non-aromatic nitrogenated heterocyclic-1-carboxylate ester derivative

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(56) Related Art
US 5780484 A
US 5744485 A
US 6414149 B1
WO 2004/033422 A2
US 5780472 A
EP 477903 A2

2010202348 04 Jun 2010

ABSTRACT

[Abstract]

5 [Problem] To provide a compound usable for treatment of diseases associated with fatty acid amide hydrolase (FAAH), especially for treatment of urinary frequency and urinary incontinence, overactive bladder and/or pain.

10 [Means for Solution] We have found that a novel pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative and its pharmaceutically acceptable salt has a potent FAAH-inhibitory activity. Further, the pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of the present invention has an excellent effect for increasing an effective bladder capacity, an excellent effect for relieving urinary frequency and an excellent anti-allodynia effect, and is therefore usable
15 for treatment of urinary frequency and urinary incontinence, overactive bladder and/or pain.

2010202348 04 Jun 2010

Australian Patents Act 1990 – Regulation 3.2

**ORIGINAL COMPLETE SPECIFICATION
STANDARD PATENT**

Invention Title:

Pyridyl non-aromatic nitrogenated heterocyclic-1-carboxylate ester derivative

The following statement is a full description of this invention, including the best method of performing it known to me:-

DESCRIPTION

PYRIDYL NON-AROMATIC NITROGENATED HETEROCYCLIC-1-CARBOXYLATE ESTER DERIVATIVE

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TECHNICAL FIELD

[0001]

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The present invention relates to a pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative or its pharmaceutically acceptable salt, serving as a medicine, especially as a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain having a fatty acid amide hydrolase (hereinafter referred to as FAAH)-inhibitory activity. The present invention also relates to a screening method for an FAAH activity inhibitor serving as a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or

15 a remedy for pain; and to a pharmaceutical composition for treatment of urinary frequency and urinary incontinence, for treatment of overactive bladder and/or for treatment of pain that contains the substance obtained according to the screening method of the present invention or contains a substance which inhibits the activity of fatty acid amide hydrolase.

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BACKGROUND ART

[0002]

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Fatty acid amide hydrolase (FAAH) is known to hydrolyze endocannabinoid to inactivate it (see Non-Patent References 1 to 4). Endocannabinoid is a generic term for a biological substance that acts on a cannabinoid receptor to exhibit its physiological activity. Typical endocannabinoids are anandamide, palmitoyl ethanolamide, oleamide, 2-arachidonoyl glycerol; and they are known to be hydrolyzed by FAAH to lose their activity. Δ^9 -tetrahydrocannabinol that is considered as the active ingredient of *Cannabis* (marijuana) is known to activate a cannabinoid receptor

30 (see Non-Patent Reference 5).

In mammals, two types of cannabinoid receptor CB1 and CB2 have heretofore been known. CB1 is expressed in central and peripheral nervous systems,

and when activated, it exhibits its mental action and analgesic action. CB2 is expressed in immune systems, and when activated, it exhibits its antiinflammatory action and analgesic (and antiinflammatory) action.

On the other hand, in a cystitic rat model, a cannabinoid receptor agonist increases the bladder capacity and the urination threshold (Non-Patent Reference 6 and Non-Patent Reference 7); and the side effects of hallucination, delusion, tachycardia, orthostatic hypotension to be observed in administration of a cannabinoid receptor agonist to animals are not observed when an FAAH inhibitor is administered thereto (Non-Patent Reference 8). From these, the FAAH inhibitor is expected as a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain.

[0003]

As compounds having an FAAH-inhibitory activity, known are compounds capable of serving as analgesic, antianxiety, antiepileptic, antidepressant, antiemetic, cardiovascular agent or antiglaucomatous agent [C1-4 alkyl or polycyclic aromatic ester derivatives of aromatic ring or phenyl-substituted aliphatic hydrocarbon-carbamic acids (Patent Reference 1) and phenyl cyclohexylcarbamate (Patent Reference 2)]. Dioxane-2-alkylcarbamate derivatives, which are compounds having an FAAH-inhibitory activity, are described as a remedy for urinary incontinence, one embodiment of a large number of disorders listed therein (Patent Reference 3). However, Patent Reference 3 does not disclose experimental results to support the remedial effect for treatment of urinary frequency and urinary incontinence and/or for treatment of overactive bladder, not disclosing any suggestion for it. 4-Aminopyridyl piperidine-1-carboxylate, a type of pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylates, is described as an acetylcholine esterase inhibitor (Non-Patent Reference 9); however, the reference describes nothing about the compound to be a remedy for urinary frequency and urinary incontinence and/or a remedy for overactive bladder.

[0004]

Patent Reference 1: WO2003/065989

Patent Reference 2: WO2004/033422

Patent Reference 3: JP-A 2003-192659

2010202348 23 Jun 2011

Non-Patent Reference 1: Prostaglandins Leukotrienes and Essential Fatty Acids, (England), 2002, Vol. 66, pp. 143-160

Non-Patent Reference 2: British Journal of Pharmacology (England), 2004, Vol. 141, pp. 253-262

Non-Patent Reference 3: Nature (England), 1996, Vol. 384, pp. 83-87

Non-Patent Reference 4: Biochemical Pharmacology, (USA), 2001, Vol. 62, pp. 517-526

Non-Patent Reference 5: Current Medicinal Chemistry (USA), 1999, Vol. 6, pp. 635-664

Non-Patent Reference 6: The Journal of Neuroscience, 2002, Vol. 22, pp. 7147-7153

Non-Patent Reference 7: Pain, 1998, Vol. 76, pp. 189-199

Non-Patent Reference 8: Nature Medicine, (England), 2003, Vol. 9, pp. 76-81

Non-Patent Reference 9: Journal of Pharmaceutical Science, 1992, Vol. 81, pp. 380-385

DISCLOSURE OF THE INVENTION

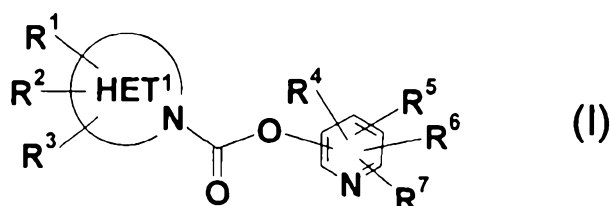
PROBLEMS TO BE SOLVED BY THE INVENTION

[0005]

The present invention seeks to provide a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain, which are free from or are relieved from cannabinoid-like side effects and a problem of addiction. The invention also seeks to provide a method for screening for an FAAH activity-inhibiting substance, or that is, a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain; and to provide a pharmaceutical composition for treatment of urinary frequency and urinary incontinence, for treatment of overactive bladder and/or for treatment of pain, which contains the substance obtained according to the screening method of the present invention or a substance capable of inhibiting the activity of a fatty acid amide hydrolase.

2010202348 23 Jun 2011

A first aspect of the invention provides a pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (I), or its pharmaceutically acceptable salt:



wherein

HET¹ represents a 5- to 7-membered non-aromatic nitrogen-containing hetero ring,
R¹, R² and R³ are the same or different, each representing

(1) H,

(2) OH,

(3) HO-CO-, lower alkyl-O-CO-, aryl-lower alkyl-O-CO-, or H₂N-CO-aryl-lower alkyl-O-CO-,

(4) cyano,

(5) lower alkyl-CO-,

(6) oxo (=O),

(7) a formula [R¹⁰¹-(O)^{m1}]^{m2}-[ALK¹ optionally substituted with OH]-(O)ⁿ¹-,

(m1 and n1 are the same or different, each indicating 0 or 1,

m2 is from 1 to 5,

ALK¹ represents lower alkylene, lower alkenylene or lower alkynylene,

R¹⁰¹ represents

(i) H,

(ii) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of:

(a) H₂N-,

(b) halo,

(c) cyano,

(d) optionally-esterified carboxyl,

(e) a group R^{1011a}R^{1012a}N-CO-,

23 Jun 2011
2010202348

- (f) HET²,
 (g) Ar^{1a} optionally substituted with halo, cyano, OH, lower alkyl-O- or lower alkyl,
 Ar^{1a} represents aryl,
 (h) lower alkyl,
 (j) OH,
 (k) lower alkyl-O- optionally substituted with Ar^{1a} or halo-Ar^{1a},
 (l) HET²-CO- optionally substituted with halo, Ar^{1a} or HETAr^{1a},
 HET² represents nitrogen-containing hetero ring,
 HETAr^{1a} represents nitrogen-containing heteroaryl,
 (s) HET²-CONR^{1011a}-,
 (t) H₂NCONH-, and
 (u) optionally-esterified carboxyl-ALK^{2a},
 ALK^{2a} represents lower alkyl or lower alkenyl,
 (iii) ALK^{2a} optionally substituted with a group R^{1011a}R^{1012a}N or Ar^{1a},
 R^{1011a} and R^{1012a} are the same or different, each representing
 (a) H,
 (b) cALK,
 cALK represents a cycloalkyl,
 (c) ALK^{2a} optionally substituted with halo, cALK, OH, lower alkyl-O- or Ar^{1a}, or
 (d) Ar^{1a}-SO₂- optionally substituted with halo,
 (iv) HET² optionally substituted with at least one substituent selected from the group consisting of
 (a) ALK^{2a} optionally substituted with Ar^{1a} or halo-Ar^{1a},
 (b) Ar^{1a},
 (c) HETAr^{1a} optionally substituted with lower alkyl,
 (d) Ar^{1a}-CO- or halo-Ar^{1a}-CO-,
 (v) cALK optionally substituted with ALK^{2a},
 or
 (vi) optionally-esterified carboxyl,

(8) a group R^{102} -ALK¹-N(R¹⁰³)-CO-,

(i) H ,

(ii) cALK,

(iii) HETAr^{1a}, or

(iv) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of

(a) HO,

(b) ALK^{2a}-O-,

(c) cALK-ALK¹-O-,

(d) cALK-Ar^{1a}-ALK¹-O-, and

(e) Ar^{1a}-ALK¹-O-,

R^{103} represents

(i) H ,

(ii) cALK,

(iii) ALK^{2a} optionally substituted with at least one substituent selected from the group consisting of

(a) HET^2 ,

(b) Ar^{1a}, and

(c) halo-Ar^{1a},

(iv) HETAr^{1a} , or

(v) Ar^{1a}-[CO]m1 optionally substituted with at least one substituent selected from the group consisting of

(a) cALK,

(b) H_2N ,

(c) a group $R^{1011a}R^{1012a}N-CO-$, or

(d) ALK^{2a}),

(9) a group $R^{104a}R^{105a}N-[CO]m1-ALK^1-$,

(R^{104a} and R^{105a} are the same or different, each representing a group R¹⁰³),

2010202348 23 Jun 2011

(10) a group R^{106} -ALK³-L¹-,

(R¹⁰⁶ represents

(i) a group R^{101} -(O)m1-,

(ii) a group $R^{104a}R^{105a}N$ -,

(iii) a group ALK^{2a}-CONH-, or

(iv) a group Ar^{1a}-CONH-,

ALK³ represents lower alkylene, lower alkenylene or cycloalkylene,

L¹ represents -C(=O)- or -SO₂-),

(11) ALK^{2a}-CONH- optionally substituted with Ar^{1a},

(12) Ar^{1a} substituted with halo,

(13) a group $[R^{107}-(O)m1]m2-Ar^2-(O)n1$ -,

(Ar² represents arylene,

R¹⁰⁷ represents

(i) H,

(ii) halo,

(iii) ALK^{2a} optionally substituted with at least one substituent selected from the group consisting of

(a) HO,

(b) cALK,

(c) HET²,

(d) Ar^{1a} optionally substituted with halo, lower alkyl, lower alkyl-O-, a group $R^{1011a}R^{1012a}N$ -[CO]p-, cyano or optionally-esterified carboxyl,

(e) optionally-esterified carboxyl,

(f) HET²-[CO]p- optionally substituted with a group $R^{1011a}R^{1012a}N$ -[CO]p-,

and

(g) a group $R^{1011a}R^{1012a}N$ -[CO]p-,

p indicates 0 or 1,

(iv) a group $R^{1011a}R^{1012a}N$ -[CO]p-, or

(v) a group $R^{1011a}R^{1012a}N$ -[CO]p-Ar^{1a},

23 Jun 2011
2010202348

in this, when m_2 is from 2 to 5, then $[R^{107}-(O)m_1]$'s may be the same or different, and further the group $[R^{107}-(O)m_1]m_2$ may be methylenedioxy to form a ring),

(14) a group $[R^{107}-(O)m_1]m_2-Ar^2-N(R^{103})-CO-$,

(in this, when m_2 is from 2 to 5, then $[R^{107}-(O)m_1]$'s may be the same or different),

(15) a group $[R^{1011a}R^{1012a}N-[CO]m_1]m_2-Ar^2-(O)n_1-$,

(in this, when m_2 is from 2 to 5, then $[R^{1011a}R^{1012a}N-[CO]m_1]$'s may be the same or different),

(16) a group $[R^{108}]m_2-Ar^2-L^2-$,

$[R^{108}]$ represents

(i) H,

(ii) halo,

(iii) HO,

(iv) cALK-O-,

(v) a group $R^{109}-ALK^1-(O)m_1-$,

(R^{109}) represents

(a) H,

(b) cALK,

(c) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of

(1') halo,

(2') cyano,

(3') NO_2 ,

(4') ALK^{2a} optionally substituted with halo,

(5') HO,

(6') $ALK^{2a}-O-$ optionally substituted with halo,

(7') optionally-esterified carboxyl, or

(8') a group $R^{104a}R^{105a}N-$,

(d) $HETAr^{1a}$, or

(e) a group $R^{104a}R^{105a}N-[CO]m_1-$,

2010202348 23 Jun 2011

(vi) a group $R^{1013}R^{1014}N-$,

R^{1013} and R^{1014} are the same or different, each representing

(i) H,

(ii) ALK^{2a} ,

(iii) $cALK-ALK^1-$, or

(iv) $Ar^{1a}-ALK^1-$ optionally substituted with at least one substituent selected from the group consisting of

(1') halo,

(2') cyano,

(3') ALK^{2a} optionally substituted with halo,

(4') $ALK^{2a}-O-$ optionally substituted with halo,

(vii) $HET^2-(O)m1-$ optionally substituted with lower alkyl,

L^2 represents $-CO-$ or $-S(O)q-$,

q indicates 0, 1 or 2,

in this, when $m2$ is from 2 to 5, then $[R^{108}]$'s may be the same or different],

(17) a group $[R^{101}]m2-Ar^2-CONH-$,

(in this, when $m2$ is from 2 to 5, then $[R^{101}]$'s may be the same or different),

(18) a group $[R^{111}]m2-HETAr^2-(O)m1-$,

(R^{111}) represents

(i) H,

(ii) halo,

(iii) oxo ($=O$), or

(iv) a group $R^{103a}-(O)n1-$,

R^{103a} represents

(i) H,

(ii) $cALK$,

(iii) ALK^{2a} optionally substituted with at least one substituent selected from the group consisting of

(a) HET^2 ,

(b) Ar^{1a} ,

(c) $cALK$ and

23 Jun 2011
2010202348

- (d) halo-Ar^{1a},
 (iv) HETAr^{1a}, or
 (v) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of (a) cALK, (b) H₂N, and (c) a group R^{1011a}R^{1012a}N-CO-,

HETAr² represents nitrogen-containing heteroarylene, in this, when m₂ is from 2 to 5, then [R¹¹¹]'s may be the same or different),

(19) a formula [R¹¹²]_{m2}-HETAr²-N(R¹⁰³)-CO-,

(R¹¹² represents

- (i) H,
 (ii) cALK,
 (iii) ALK^{2a}, or
 (iv) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of
 (a) halo,
 (b) HO,
 (c) ALK^{2a}-O-, and
 (d) Ar^{1a}-ALK¹-O-,

in this, when m₂ is from 2 to 5, then [R¹¹²]'s may be the same or different),

(20) a formula [R¹⁰⁸]_{m2}-HETAr²-L²-,

(in this, when m₂ is from 2 to 5, then [R¹⁰⁸]'s may be the same or different),

provided that, when any one group of R¹, R² and R³ is a group [R¹¹¹]_{m2}-HETAr²-(O)_{m1}- and when m₁ is 0, then the remaining groups of R¹, R² and R³ are H;

and at least one of R⁴, R⁵, R⁶ and R⁷ is selected from the following (2), (4) to (11) and

the remaining groups are the same or different selected from the following (1) to (11):

- (1) H,
 (2) halo,
 (3) optionally-esterified carboxyl,
 (4) HO,

(5) a group R¹¹³-ALK⁴-(O)_{m3}-,

(ALK⁴ represents lower alkylene, lower alkenylene, or lower alkynylene,

2010202348 23 Jun 2011

m3 indicates 0 or 1,

R^{113} represents

- (i) H,
- (ii) HO,
- (iii) lower alkyl-O- optionally substituted with optionally-esterified carboxyl,
- (iv) optionally-esterified carboxyl,
- (v) lower alkyl-CO-O-, or
- (vi) a group $R^{104b}R^{105b}N-[CO]m3-$ (R^{104b} and R^{105b} are the same or different, each representing a group R^{103}),

(6) $R^{114}R^{115}N$ (R^{114} and R^{115} are the same or different, each representing

- (i) H, or
- (ii) ALK^{2b} optionally substituted with a group $R^{104b}R^{105b}N$,
 ALK^{2b} represents lower alkyl or lower alkenyl),

(7) a group $R^{116}-(ALK^4)n2-N(R^{117})-CO-$,

(n2 indicates 0 or 1,

R^{116} represents

- (i) H,
- (ii) HO,
- (iii) lower alkyl-O-,
- (iv) optionally-esterified carboxyl,
- (v) a group $R^{104b}R^{105b}N-[CO]m3-$,
- (vi) Ar^{1b} optionally substituted with (a) OH or (b) $ALK^{2b}-O-$,

Ar^{1b} represents aryl,

(vii) HET^3 optionally substituted with a group $R^{104b}R^{105b}N-[CO]m3-$ or optionally-esterified carboxyl,

HET^3 represents nitrogen-containing hetero ring,

(viii) Ar^{1b} optionally substituted with a group $R^{104b}R^{105b}N-[CO]m3-$, or

(ix) SO_3H ,

R^{117} represents (i) H or (ii) ALK^{2b} optionally substituted with Ar^{1b}),

(8) Ar^{1b} optionally substituted with at least one substituent selected from the group consisting of optionally-esterified carboxyl and a group $R^{1011b}R^{1012b}N-[(CO)]m3-$,

23 Jun 2011
2010202348

R^{101b} and R^{1012b} are the same or different, each representing

- (i) H,
- (ii) cALK,
- (iii) ALK^{2b} optionally substituted with halo, cALK, OH, lower alkyl-O- or Ar^{1b} ,
- or
- (iv) Ar^{1b} -SO₂- optionally substituted with halo,

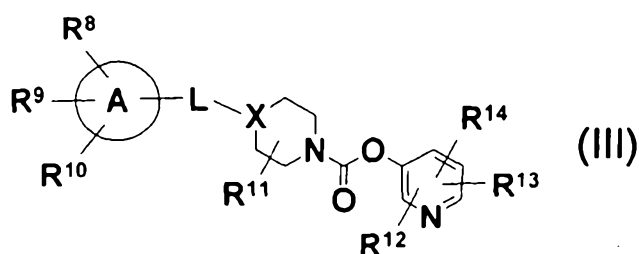
(9) HET^3 optionally substituted with optionally-esterified carboxyl,

(10) HET^3 -CO- optionally substituted with at least one substituent selected from the group consisting of ALK^{2b} and a group $R^{104b}R^{105b}N$ -[CO]_m3-, or

(11) cyano,

provided that 4-aminopyridin-3-yl piperidine-1-carboxylate, 5-ethyl-2-methoxy-6-methylpyridin-3-yl 4-(2-methoxyphenyl)piperazine-1-carboxylate, 5-ethyl-2-methoxy-6-methylpyridin-3-yl 4-(3-chlorophenyl)piperazine-1-carboxylate, 5-ethyl-2-methoxy-6-methylpyridin-3-yl 4-(3,5-dimethoxyphenyl)piperazine-1-carboxylate, and 4-[[[(dimethylamino)methyl]amino]pyridin-3-yl piperidine-1-carboxylate, 2-[(dimethylamino)methyl]pyridin-3-yl piperidine-1-carboxylate, 2-[(dimethylamino)methyl]pyridin-3-yl pyrrolidine-1-carboxylate and 2-[(dimethylamino)methyl]pyridin-3-yl morpholine-4-carboxylate are excluded.

A second aspect of the invention provides a pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (III) or its pharmaceutically acceptable salt:



wherein

ring A represents benzene ring, cyclopentane ring, cyclohexane ring, cycloheptane ring, or 5- to 7-membered nitrogen-containing hetero ring;

23 Jun 2011
2010202348

L represents single bond, lower alkylene, lower alkenylene, $-N(R^{15})-C(=O)-$,
 $-C(=O)-N(R^{15})-$, $-(\text{lower alkenylene})-C(=O)-$, $-O-$, or $-C(=O)-$,

R^{15} represents H, or lower alkyl,

X represents CH, or N,

R^8 to R^{10} are the same or different, each representing

a group selected from the following group G,

aryl optionally substituted with the same or different groups selected from the
 following group G,

nitrogen-containing heteroaryl optionally substituted with the same or different
 groups selected from the following group G,

$R^{16}-(\text{lower alkylene})-O-$,

$R^{16}-(\text{lower alkylene})-N(R^{15})-$, or

$R^{17}R^{18}N-C(=O)-$,

R^{16} represents

aryl optionally substituted with the same or different groups selected from the
 following group G,

nitrogen-containing heteroaryl optionally substituted with the same or different
 groups selected from the following group G, or

3- to 8-membered cycloalkyl,

R^{17} and R^{18} are the same or different, each representing H, lower alkyl, or 3- to 8-
 membered cycloalkyl,

(further, R^{17} and R^{18} may form, together with the N atom bonding thereto, 3- to 8-
 membered nitrogen-containing hetero ring),

the group G includes H, halo, $-CN$, $-CF_3$, lower alkyl, or $-O$ -lower alkyl,

R^{11} represents H, lower alkyl, or oxo ($=O$),

R^{12} to R^{14} are the same or different selected from the group consisting of H, lower
 alkyl, $-C(=O)-O-(\text{lower alkyl})$, $-CO_2H$ and $-CONH_2$, wherein at least one of R^{12} to R^{14}
 is lower alkyl or $-CONH_2$.

5



L¹ represents lower alkylene, lower alkenylene, -N(R¹⁵)-C(=O)-, or -O-;

10 R^{19} represents

nitrogen-containing heteroaryl optionally substituted with the same or different

$$\text{R}^{16}\text{-(lower alkylene)-O-}, \text{ or } \text{R}^{17}\text{R}^{18}\text{N-C(=O)-},$$

aryl optionally substituted with the same or different groups selected from the

nitrogen-containing heteroaryl optionally substituted with the same or different

20 3- to 8-membered cycloalkyl,

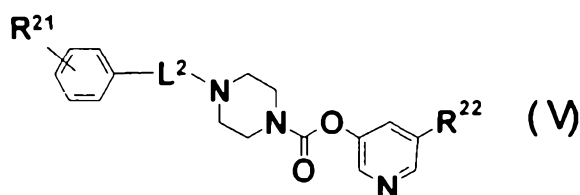
(further, R¹⁷ and R¹⁸ may form, together with the N atom bonding thereto, 5- or 6-

membered nitrogen-containing hetero ring),

the group G includes H, halo, -CN, -CF₃, lower alkyl, or -O-lower alkyl,

25 R²⁰ represents -CONH₂.

A fourth aspect of the invention provides a pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (V) or its pharmaceutically acceptable salt:



wherein

L^2 represents lower alkylene, lower alkenylene, or -(lower alkenylene)-C(=O)-,

R^{21} represents H, halo, -CN, -CF₃, lower alkyl, or -O-lower alkyl,

R^{22} represents -CONH₂.

A fifth aspect of the invention provides a pharmaceutical composition comprising the compound as defined in any one of the first, second, third or fourth aspects or its pharmaceutically acceptable salt as an active ingredient thereof.

A sixth aspect of the invention provides a use of the compound as defined in any one of the first, second, third or fourth aspects or its pharmaceutically acceptable salt for the manufacture of an FAAH inhibitor or a medicament for treatment of urinary frequency, urinary incontinence and/or overactive bladder.

A seventh aspect of the invention provides a use of the compound as defined in any one of the first, second, third or fourth aspects or its pharmaceutically acceptable salt for the manufacture of an FAAH inhibitor or a medicament for treatment of pain.

An eighth aspect of the invention provides a method for treating urinary frequency, urinary incontinence and/or overactive bladder in a subject, comprising administering to the subject a therapeutically effective amount of the compound as defined in any one of the first, second, third or fourth aspects or its pharmaceutically acceptable salt, or the pharmaceutical composition as defined in the fifth aspect.

2010202348 23 Jun 2011

5 A ninth aspect of the invention provides a method for treating pain in a subject, comprising administering to the subject a therapeutically effective amount of the compound as defined in any one of the first, second, third or fourth aspects or its pharmaceutically acceptable salt, or the pharmaceutical composition as defined in the fifth aspect.

MEANS FOR SOLVING THE PROBLEMS

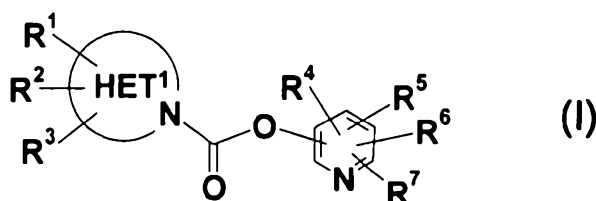
[0006]

The present inventors have assiduously studied for producing a compound having an FAAH-inhibitory activity, and as a result, have found out novel pyridyl nitrogen-containing heterocyclic-1-carboxylate derivatives.

In addition, the present inventors have found for the first time that, when a compound having an FAAH-inhibitory activity is administered to a rat suffering from urinary frequency induced by cyclophosphamide, then the effective bladder capacity of the rat increases, and have further found that the compound having an FAAH-inhibitory activity has an excellent therapeutical effect in a pain model rat, therefore providing a screening method for a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain by selecting an FAAH inhibitor, and have thus completed the present invention.

Specifically, the present invention relates to the following:

[1] A pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (I), or its pharmaceutically acceptable salt:



wherein

HET¹ represents a 5- to 7-membered non-aromatic nitrogen-containing hetero ring,

R¹, R² and R³ are the same or different, each representing

(1) H,

(2) OH,

(3) HO-CO-, lower alkyl-O-CO-, aryl-lower alkyl-O-CO-, or H₂N-CO-aryl-lower alkyl-O-CO-,

(4) cyano,

(5) lower alkyl-CO-,

(6) oxo (=O),

(7) a formula $[R^{101}-(O)m_1]m_2-[ALK^1 \text{ optionally substituted with OH}]-(O)n_1-$,

(m_1 and n_1 are the same or different, each indicating 0 or 1,

m_2 is from 1 to 5,

ALK^1 represents lower alkylene, lower alkenylene or lower alkynylene,

R^{101} represents

(i) H,

(ii) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of:

(a) H_2N- ,

(b) halo,

(c) cyano,

(d) optionally-esterified carboxyl,

(e) a group $R^{1011a}R^{1012a}N-CO-$,

(f) HET^2 ,

(g) Ar^{1a} optionally substituted with halo, cyano, OH, lower alkyl-O- or lower alkyl,

Ar^{1a} represents aryl,

(h) lower alkyl,

(j) OH,

(k) lower alkyl-O- optionally substituted with Ar^{1a} or halo- Ar^{1a} ,

(l) HET^2-CO- optionally substituted with halo, Ar^{1a} or $HETAr^{1a}$,

HET^2 represents nitrogen-containing hetero ring,

$HETAr^{1a}$ represents nitrogen-containing heteroaryl,

(s) $HET^2-CONR^{1011a}-$,

(t) $H_2NCONH-$, and

(u) optionally-esterified carboxyl- ALK^{2a} ,

ALK^{2a} represents lower alkyl or lower alkenyl,

(iii) ALK^{2a} optionally substituted with a group $R^{1011a}R^{1012a}N$ or Ar^{1a} ,

R^{1011a} and R^{1012a} are the same or different, each representing

(a) H,

(b) cALK,

cALK represents a cycloalkyl,

(c) ALK^{2a} optionally substituted with halo, cALK, OH, lower alkyl-O- or Ar^{1a} , or

(d) $\text{Ar}^{1a}\text{-SO}_2\text{-}$ optionally substituted with halo,

(iv) HET^2 optionally substituted with at least one substituent selected from the group consisting of

(a) ALK^{2a} optionally substituted with Ar^{1a} or halo- Ar^{1a} ,

(b) Ar^{1a} ,

(c) HETAr^{1a} optionally substituted with lower alkyl,

(d) $\text{Ar}^{1a}\text{-CO-}$ or halo- $\text{Ar}^{1a}\text{-CO-}$,

(v) cALK optionally substituted with ALK^{2a} ,

or

(vi) optionally-esterified carboxyl,

(in this, when m_2 is from 2 to 5, then $[\text{R}^{101}\text{-(O)}m_1]$'s may be the same or different),

(8) a group $\text{R}^{102}\text{-ALK}^1\text{-N(R}^{103})\text{-CO-}$,

(R^{102} represents

(i) H,

(ii) cALK,

(iii) HETAr^{1a} , or

(iv) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of

(a) HO,

(b) $\text{ALK}^{2a}\text{-O-}$,

(c) cALK- $\text{ALK}^1\text{-O-}$,

(d) cALK- $\text{Ar}^{1a}\text{-ALK}^1\text{-O-}$, and

(e) $\text{Ar}^{1a}\text{-ALK}^1\text{-O-}$,

R^{103} represents

(i) H,

(ii) cALK,

(iii) ALK^{2a} optionally substituted with at least one substituent selected from the group consisting of

(a) HET^2 ,

- (b) Ar^{1a} , and
 (c) halo- Ar^{1a} ,
 (iv) HETAr^{1a} , or
 (v) Ar^{1a} -[CO] m_1 optionally substituted with at least one substituent selected
 5 from the group consisting of
 (a) cALK,
 (b) H_2N ,
 (c) a group $\text{R}^{1011a}\text{R}^{1012a}\text{N-CO-}$, or
 (d) ALK^{2a} ,
 10 (9) a group $\text{R}^{104a}\text{R}^{105a}\text{N-[CO]}m_1\text{-ALK}^1\text{-}$,
 (R^{104a} and R^{105a} are the same or different, each representing a group R^{103}),
 (10) a group $\text{R}^{106}\text{-ALK}^3\text{-L}^1\text{-}$,
 (R^{106} represents
 (i) a group $\text{R}^{101}\text{-(O)}m_1\text{-}$,
 15 (ii) a group $\text{R}^{104a}\text{R}^{105a}\text{N-}$,
 (iii) a group $\text{ALK}^{2a}\text{-CONH-}$, or
 (iv) a group $\text{Ar}^{1a}\text{-CONH-}$,
 ALK^3 represents lower alkylene, lower alkenylene or cycloalkylene,
 L^1 represents -C(=O)- or $\text{-SO}_2\text{-}$,
 20 (11) $\text{ALK}^{2a}\text{-CONH-}$ optionally substituted with Ar^{1a} ,
 (12) Ar^{1a} substituted with halo,
 (13) a group $[\text{R}^{107}\text{-(O)}m_1]m_2\text{-Ar}^2\text{-(O)}n_1\text{-}$,
 (Ar^2 represents arylene,
 R^{107} represents
 25 (i) H,
 (ii) halo,
 (iii) ALK^{2a} optionally substituted with at least one substituent selected from the
 group consisting of
 (a) HO,
 30 (b) cALK,
 (c) HET^2 ,

- (d) Ar^{1a} optionally substituted with halo, lower alkyl, lower alkyl-O-, a group $\text{R}^{1011a}\text{R}^{1012a}\text{N}[\text{CO}]p$ -, cyano or optionally-esterified carboxyl,
- (e) optionally-esterified carboxyl,
- (f) $\text{HET}^2[\text{CO}]p$ - optionally substituted with a group $\text{R}^{1011a}\text{R}^{1012a}\text{N}[\text{CO}]p$ -,
- 5 and
- (g) a group $\text{R}^{1011a}\text{R}^{1012a}\text{N}[\text{CO}]p$ -,
- p indicates 0 or 1,
- (iv) a group $\text{R}^{1011a}\text{R}^{1012a}\text{N}[\text{CO}]p$ -, or
- (v) a group $\text{R}^{1011a}\text{R}^{1012a}\text{N}[\text{CO}]p\text{-Ar}^{1a}$,
- 10 in this, when m_2 is from 2 to 5, then $[\text{R}^{107}(\text{O})m_1]$'s may be the same or different, and further the group $[\text{R}^{107}(\text{O})m_1]m_2$ may be methylenedioxy to form a ring),
- (14) a group $[\text{R}^{107}(\text{O})m_1]m_2\text{-Ar}^2\text{-N}(\text{R}^{103})\text{-CO-}$,
- (in this, when m_2 is from 2 to 5, then $[\text{R}^{107}(\text{O})m_1]$'s may be the same or
- 15 different),
- (15) a group $[\text{R}^{1011a}\text{R}^{1012a}\text{N}[\text{CO}]m_1]m_2\text{-Ar}^2\text{-(O)}n_1\text{-}$,
- (in this, when m_2 is from 2 to 5, then $[\text{R}^{1011a}\text{R}^{1012a}\text{N}[\text{CO}]m_1]$'s may be the same or different),
- (16) a group $[\text{R}^{108}]m_2\text{-Ar}^2\text{-L}^2\text{-}$,
- 20 $[\text{R}^{108}]$ represents
- (i) H,
- (ii) halo,
- (iii) HO,
- (iv) cALK-O-,
- 25 (v) a group $\text{R}^{109}\text{-ALK}^1\text{-(O)}m_1\text{-}$,
- (R^{109}) represents
- (a) H,
- (b) cALK,
- (c) Ar^{1a} optionally substituted with at least one substituent selected from
- 30 the group consisting of
- (1') halo,
- (2') cyano,

- (3') NO₂,
 (4') ALK^{2a} optionally substituted with halo,
 (5') HO,
 (6') ALK^{2a}-O- optionally substituted with halo,
 (7') optionally-esterified carboxyl, or
 (8') a group R^{104a}R^{105a}N-,
 (d) HETAr^{1a}, or
 (e) a group R^{104a}R^{105a}N-[CO]m1-),
 (vi) a group R¹⁰¹³R¹⁰¹⁴N-,
 R¹⁰¹³ and R¹⁰¹⁴ are the same or different, each representing
 (i) H,
 (ii) ALK^{2a},
 (iii) cALK-ALK¹-, or
 (iv) Ar^{1a}-ALK¹- optionally substituted with at least one substituent
 selected from the group consisting of
 (1') halo,
 (2') cyano,
 (3') ALK^{2a} optionally substituted with halo,
 (4') ALK^{2a}-O- optionally substituted with halo,
 (vii) HET²-(O)m1- optionally substituted with lower alkyl,
 L² represents -CO- or -S(O)q-,
 q indicates 0, 1 or 2,
 in this, when m2 is from 2 to 5, then [R¹⁰⁸]'s may be the same or different],
 (17) a group [R¹⁰¹]m2-Ar²-CONH-,
 (in this, when m2 is from 2 to 5, then [R¹⁰¹]'s may be the same or different),
 (18) a group [R¹¹¹]m2-HETAr²-(O)m1-,
 (R¹¹¹ represents
 (i) H,
 (ii) halo,
 (iii) oxo (=O), or
 (iv) a group R^{103a}-(O)n1-,
 R^{103a} represents

- (i) H,
(ii) cALK,
(iii) ALK^{2a} optionally substituted with at least one substituent selected from the group consisting of
- 5 (a) HET^2 ,
(b) Ar^{1a} ,
(c) cALK and
(d) halo- Ar^{1a} ,
(iv) $HETAr^{1a}$, or
- 10 (v) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of (a) cALK, (b) H_2N , and (c) a group $R^{1011a}R^{1012a}N-CO-$,
CO-,

$HETAr^2$ represents nitrogen-containing heteroarylene,
in this, when m2 is from 2 to 5, then $[R^{111}]$'s may be the same or
15 different),

(19) a formula $[R^{112}]_{m2}-HETAr^2-N(R^{103})-CO-$,

(R^{112}) represents

- (i) H,
(ii) cALK,
20 (iii) ALK^{2a} , or
(iv) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of

- (a) halo,
(b) HO,
25 (c) $ALK^{2a}-O-$, and
(d) $Ar^{1a}-ALK^1-O-$,

in this, when m2 is from 2 to 5, then $[R^{112}]$'s may be the same or different,

(20) a formula $[R^{108}]_{m2}-HETAr^2-L^2-$,

(in this, when m2 is from 2 to 5, then $[R^{108}]$'s may be the same or different),

30 provided that, when any one group of R^1 , R^2 and R^3 is a group $[R^{111}]_{m2}-HETAr^2-(O)m1-$ and when m1 is 0, then the remaining groups of R^1 , R^2 and R^3 are H;
 R^4 , R^5 , R^6 and R^7 are the same or different, each representing

- (1) H,
 (2) halo,
 (3) optionally-esterified carboxyl,
 (4) HO,
 5 (5) a group R^{113} -ALK⁴-(O)m₃-,
 (ALK⁴ represents lower alkylene, lower alkenylene, or lower alkynylene,
 m₃ indicates 0 or 1,
 R¹¹³ represents
 (i) H,
 10 (ii) HO,
 (iii) lower alkyl-O- optionally substituted with optionally-esterified carboxyl,
 (iv) optionally-esterified carboxyl,
 (v) lower alkyl-CO-O-, or
 (vi) a group $R^{104b}R^{105b}N$ -[CO]m₃- (R^{104b} and R^{105b} are the same or different,
 15 each representing a group R^{103}),
 (6) $R^{114}R^{115}N$ (R^{114} and R^{115} are the same or different, each representing
 (i) H, or
 (ii) ALK^{2b} optionally substituted with a group $R^{104b}R^{105b}N$,
 ALK^{2b} represents lower alkyl or lower alkenyl),
 20 (7) a group R^{116} -(ALK⁴)n₂-N(R^{117})-CO-,
 (n₂ indicates 0 or 1,
 R¹¹⁶ represents
 (i) H,
 (ii) HO,
 25 (iii) lower alkyl-O-,
 (iv) optionally-esterified carboxyl,
 (v) a group $R^{104b}R^{105b}N$ -[CO]m₃-,
 (vi) Ar^{1b} optionally substituted with (a) OH or (b) ALK^{2b}-O-,
 Ar^{1b} represents aryl,
 30 (vii) HET³ optionally substituted with a group $R^{104b}R^{105b}N$ -[CO]m₃- or
 optionally-esterified carboxyl,
 HET³ represents nitrogen-containing hetero ring,

(viii) Ar^{1b} optionally substituted with a group $\text{R}^{104b}\text{R}^{105b}\text{N}-[\text{CO}]m3-$, or

(ix) SO_3H),

R^{117} represents i) H or ii) ALK^{2b} optionally substituted with Ar^{1b}),

(8) Ar^{1b} optionally substituted with at least one substituent selected from the group consisting of optionally-esterified carboxyl and a group $\text{R}^{1011b}\text{R}^{1012b}\text{N}-[(\text{CO})]m3-$,

R^{1011b} and R^{1012b} are the same or different, each representing

(i) H,

(ii) cALK,

(iii) ALK^{2b} optionally substituted with halo, cALK, OH, lower alkyl-O- or Ar^{1b} ,

or

(iv) $\text{Ar}^{1b}-\text{SO}_2-$ optionally substituted with halo,

(9) HET^3 optionally substituted with optionally-esterified carboxyl,

(10) $\text{HET}^3-\text{CO}-$ optionally substituted with at least one substituent selected from the group consisting of ALK^{2b} and a group $\text{R}^{104b}\text{R}^{105b}\text{N}-[\text{CO}]m3-$, or

(11) cyano,

provided that 4-aminopyridin-3-yl piperidine-1-carboxylate, 5-ethyl-2-methoxy-6-

methylpyridin-3-yl 4-(2-methoxyphenyl)piperazine-1-carboxylate, 5-ethyl-2-methoxy-

6-methylpyridin-3-yl 4-(3-chlorophenyl)piperazine-1-carboxylate, 5-ethyl-2-methoxy-

6-methylpyridin-3-yl 4-(3,5-dimethoxyphenyl)piperazine-1-carboxylate, 4-

{[(dimethylamino)methyl]amino}pyridin-3-yl piperidine-1-carboxylate, pyridin-3-yl 4-

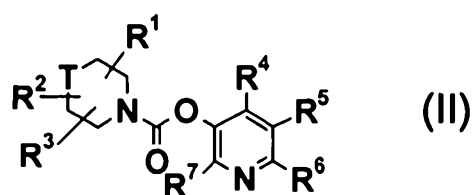
methylpiperazine-1-carboxylate and pyridin-2-yl 2-oxypyridin-1(2H)-carboxylate are

excluded.

[0007]

[2] The compound of [1], represented by a general formula (II), or its

pharmaceutically acceptable salt:



wherein R^1 to R^7 are as defined in [1],

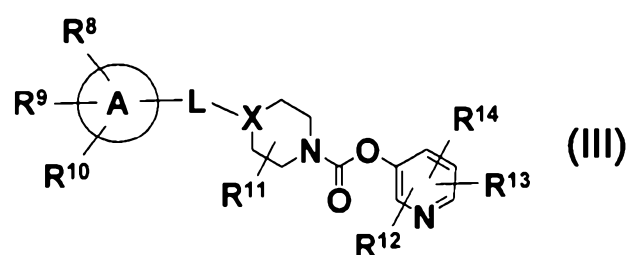
T represents CH₂, NH, NHCH₂ or O,

and wherein optionally the H in T is substituted with R¹ to R³.

[3] The compound of [2], wherein R¹ to R³ are the same or different, each representing H, a group [R¹⁰¹-(O)m₁]_{m2}-[ALK¹ optionally substituted with OH]-(O)n₁-, a group R¹⁰²-ALK¹-N(R¹⁰³)-CO-, a group R¹⁰⁶-ALK³-L¹-, a group [R¹⁰⁷-(O)m₁]_{m2}-Ar²-(O)n₁-, a group [R¹⁰⁷-(O)m₁]_{m2}-Ar²-N(R¹⁰³)-CO-, or a group [R¹⁰⁸]_{m2}-Ar²-L²-, or its pharmaceutically acceptable salt.

[0008]

[4] A pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (III) or its pharmaceutically acceptable salt:



wherein

15 ring A represents benzene ring, cyclopentane ring, cyclohexane ring, cycloheptane ring, or 5- to 7-membered nitrogen-containing hetero ring;

L represents single bond, lower alkylene, lower alkenylene, -N(R¹⁵)-C(=O)-, -C(=O)-N(R¹⁵)-, -(lower alkenylene)-C(=O)-, -O-, or -C(=O)-,

R¹⁵ represents H, or lower alkyl,

20 X represents CH, or N,

R⁸ to R¹⁰ are the same or different, each representing

a group selected from the following group G,

aryl optionally substituted with the same or different groups selected from the following group G,

25 nitrogen-containing heteroaryl optionally substituted with the same or different groups selected from the following group G,

R¹⁶-(lower alkylene)-O-,

R¹⁶-(lower alkylene)-N(R¹⁵)-, or



R^{16} represents

aryl optionally substituted with the same or different groups selected from the following group G,

5 nitrogen-containing heteroaryl optionally substituted with the same or different groups selected from the following group G, or

3- to 8-membered cycloalkyl,

R^{17} and R^{18} are the same or different, each representing H, lower alkyl, or 3- to 8-membered cycloalkyl,

10 (further, R^{17} and R^{18} may form, together with the N atom bonding thereto, 3- to 8-membered nitrogen-containing hetero ring),

the group G includes H, halo, -CN, -CF₃, lower alkyl, or -O-lower alkyl,

R^{11} represents H, lower alkyl, or oxo (=O),

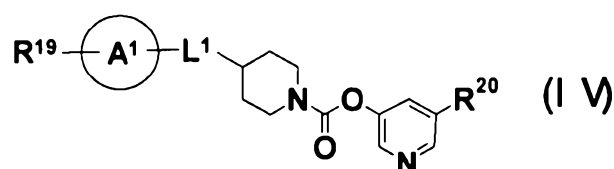
15 R^{12} to R^{14} are the same or different, each representing H, lower alkyl, -C(=O)-O-(lower alkyl), -CO₂H, or -CONH₂.

[5] The compound of [4], wherein the ring A is benzene ring, cyclohexane ring, piperidine ring, or piperazine ring, or its pharmaceutically acceptable salt.

[6] The compound of [5], wherein R^9 , R^{10} , R^{11} , R^{12} and R^{13} are H, or its pharmaceutically acceptable salt.

20 [0009]

[7] A pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (IV) or its pharmaceutically acceptable salt:



25

wherein:

ring A¹ represents benzene ring, piperidine ring or piperazine ring;

L¹ represents lower alkylene, lower alkenylene, -N(R¹⁵)-C(=O)-, or -O-;

R¹⁵ represents H, or lower alkyl,

30 R¹⁹ represents

a group selected from the following group G,
 nitrogen-containing heteroaryl optionally substituted with the same or different
 groups selected from the following group G,
 R^{16} -(lower alkylene)-O-, or $R^{17}R^{18}N-C(=O)-$,

5 R^{16} represents

aryl optionally substituted with the same or different groups selected from the
 following group G,
 nitrogen-containing heteroaryl optionally substituted with the same or different
 groups selected from the following group G, or

10 3- to 8-membered cycloalkyl,

R^{17} and R^{18} are the same or different, each representing H, or lower alkyl,
 (further, R^{17} and R^{18} may form, together with the N atom bonding thereto, 5- or 6-
 membered nitrogen-containing hetero ring),

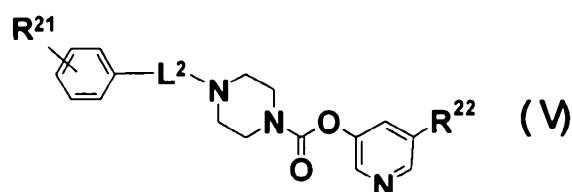
the group G includes H, halo, -CN, -CF₃, lower alkyl, or -O-lower alkyl,

15 R^{20} represents H, -C(=O)-O-(lower alkyl), -CO₂H, or -CONH₂.

[0010]

[8] A pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate
 derivative of a general formula (V) or its pharmaceutically acceptable salt:

20



wherein

L^2 represents lower alkylene, lower alkenylene, or -(lower alkenylene)-C(=O)-,

R^{21} represents H, halo, -CN, -CF₃, lower alkyl, or -O-lower alkyl,

25 R^{22} represents H, -C(=O)-O-(lower alkyl), -CO₂H or -CONH₂.

[0011]

[9] The compound of [1], selected from the following group, or its
 pharmaceutically acceptable salt:

pyridin-3-yl 4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidine-1-carboxylate,

30 5-{[(4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidin-1-yl)carbonyl]oxy}nicotinic acid,

5-({[4-(2-phenylethyl)piperidin-1-yl]carbonyl}oxy)nicotinic acid,
 5-[(4-[4-(2-cyclohexylethoxy)phenoxy]piperidin-1-yl)carbonyl]oxy)nicotinic acid,
 5-[(4-[(E)-2-phenylvinyl]piperidin-1-yl)carbonyl]oxy)nicotinic acid,
 5-[(4-[3-[1-(6-methylpyridin-2-yl)piperidin-4-yl]propyl]piperidin-1-yl)carbonyl]oxy)nicotinic acid,
 5-(aminocarbonyl)pyridin-3-yl 4-{2-[3-(aminocarbonyl)phenyl]ethyl}piperidine-1-carboxylate,
 5-(aminocarbonyl)pyridin-3-yl 4-(2-{3-[(dimethylamino)carbonyl]phenyl}ethyl)piperidine-1-carboxylate,
 5-(aminocarbonyl)pyridin-3-yl 4-{2-[3-(piperidin-1-ylcarbonyl)phenyl]ethyl}piperidine-1-carboxylate,
 5-(aminocarbonyl)pyridin-3-yl 4-{2-[3-(pyrrolidin-1-ylcarbonyl)phenyl]ethyl}piperidine-1-carboxylate,
 pyridin-3-yl 4-[(2E)-3-phenylprop-2-enoyl]piperazine-1-carboxylate,
 pyridin-3-yl 4-(anilino)carbonyl)piperidine-1-carboxylate,
 5-(aminocarbonyl)pyridin-3-yl 4-(2-phenylethyl)piperidine-1-carboxylate,
 pyridin-3-yl 4-(2-phenylethyl)piperazine-1-carboxylate,
 5-(methoxycarbonyl)pyridin-3-yl 4-(2-phenylethyl)piperazine-1-carboxylate,
 5-(aminocarbonyl)pyridin-3-yl 4-[2-(3-fluorophenyl)ethyl]piperidine-1-carboxylate,
 5-(aminocarbonyl)pyridin-3-yl 4-[2-(3-cyanophenyl)ethyl]piperidine-1-carboxylate.
 [0012]

[10] A pharmaceutical composition comprising the compound of any one of [1] to [9] or its pharmaceutically acceptable salt as an active ingredient thereof.

[11] The pharmaceutical composition of [10], which is an FAAH inhibitor.

[12] The pharmaceutical composition of [10], which is a medicament for treatment of urinary frequency, urinary incontinence and/or overactive bladder.

[13] The pharmaceutical composition of [10], which is a medicament for treatment of pain.

[14] Use of the compound of any one of [1] to [9] or its pharmaceutically acceptable salt for the manufacture of an FAAH inhibitor or a medicament for treatment of urinary frequency, urinary incontinence and/or overactive bladder.

[15] Use of the compound of any one of [1] to [9] or its pharmaceutically acceptable salt for the manufacture of an FAAH inhibitor or a medicament for treatment of pain.

5 [16] A method for treating urinary frequency, urinary incontinence and/or overactive bladder in a subject, comprising administering to the subject a therapeutically effective amount of the compound of any one of [1] to [9] or its pharmaceutically acceptable salt.

10 [17] A method for treating pain in a subject, comprising administering to the subject a therapeutically effective amount of the compound of any one of [1] to [9] or its pharmaceutically acceptable salt.

[0013]

[18] A screening method for a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain, comprising (1) a step of contacting a test substance with a polypeptide, which contains (a) an amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO:8, (b) an amino acid sequence derived from the amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO:8 through deletion, substitution and/or insertion of from 1 to 10 amino acids therein, (c) an amino acid sequence having a homology of at least 70% to the amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO:8, or (d) an amino acid sequence of the entire amino acid sequence encoded by a polynucleotide represented by SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7 or by a polynucleotide capable of hybridizing with its complementary sequence under a stringent condition, or its part not having at least the transmembrane region-containing amino terminal region thereof, and which may hydrolyze a substrate, (2) a step of analyzing the polypeptide for its activity change, and (3) a step of selecting a substance capable of inhibiting the polypeptide activity,

15

20

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(wherein the "substrate" with which FAAH or functional FAAH is contacted may be any and every endocannabinoid capable of being hydrolyzed by FAAH or functional FAAH; and concretely, it includes anandamide, palmitoylethanolamide, 2-arachidonoyl glycerol, and oleamide; and the substrate labeled with ^3H or ^{14}C , as well as a mixture of

30

the labeled substrate and the unlabeled substrate may be used - the same shall be applied hereinafter).

[0014]

[19] A screening method for a remedy for urinary frequency and urinary

5 incontinence, a remedy for overactive bladder and/or a remedy for pain, comprising (1) a step of contacting a test substance with a polypeptide, which contains (a) an amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO:8, (b) an amino acid sequence derived from the amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO:8 through deletion, 10 substitution and/or insertion of from 1 to 10 amino acids therein, (c) an amino acid sequence having a homology of at least 70% to the amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO:8, or (d) an amino acid sequence of the entire amino acid sequence encoded by a polynucleotide represented by SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7 or by a polynucleotide 15 capable of hybridizing with its complementary sequence under a stringent condition, or its part not having at least the transmembrane region-containing amino terminal region thereof, and which may hydrolyze a substrate, in the presence of a substrate of the polypeptide, (2) a step of measuring the amount of the hydrolyzed product converted from the substrate, and (3) a step of selecting a substance capable of inhibiting the 20 hydrolysis of the substrate.

[20] A screening method for a remedy for urinary frequency and urinary

incontinence, a remedy for overactive bladder and/or a remedy for pain, comprising (1) a step of contacting a test substance with a cell or a tissue expressing a polypeptide, which contains (a) an amino acid sequence represented by SEQ ID NO:2, SEQ ID 25 NO:4, SEQ ID NO:6 or SEQ ID NO:8, (b) an amino acid sequence derived from the amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO:8 through deletion, substitution and/or insertion of from 1 to 10 amino acids therein, (c) an amino acid sequence having a homology of at least 70% to the amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or 30 SEQ ID NO:8, or (d) an amino acid sequence of the entire amino acid sequence encoded by a polynucleotide represented by SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7 or by a polynucleotide capable of hybridizing with its

complementary sequence under a stringent condition, or its part not having at least the transmembrane region-containing amino terminal region thereof, and which may hydrolyze a substrate, or with a lysate or a homogenate of the cell or the tissue, in the presence of a substrate of the polypeptide, (2) a step of measuring the amount of the hydrolyzed product converted from the substrate, and (3) a step of selecting a substance capable of inhibiting the hydrolysis of the substrate.

[21] A screening method for a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain, comprising (1) a step of contacting a test substance with a fatty acid amide hydrolase, (2) a step of analyzing the enzyme for its activity change, and (3) a step of selecting a substance capable of inhibiting the activity of the enzyme.

OUTCOMES OF THE INVENTION

[0015]

The pharmacological tests of Examples 438 to Example 442 have confirmed the effectiveness of the compounds of the present invention. For example, typical compounds shown in Table 64 have an excellent FAAH-inhibitory effect; typical compounds shown in Example 441 are useful as a remedy for urinary frequency and urinary incontinence, and a remedy for overactive bladder; and typical compounds shown in Example 442 are useful as a remedy for pain. In addition, the compounds of the present invention are highly stable in aqueous solutions, and have excellent properties as medicines.

The invention described in Patent Reference 2 is useful as analgesic, antianxiety, antiepileptic, antidepressant, antiemetic, cardiovascular agent or antiglaucomatous agent; however, the present inventors have found that the present invention is useful for a remedy for urinary frequency and urinary incontinence and/or a remedy for overactive bladder, differing from Patent Reference 2. Further, the compounds of the present invention have an excellent FAAH-inhibitory effect, and are therefore useful for remedies for (1) neuropsychiatric disorders (e.g., anxiety, depression, epilepsy), (2) brain disorders, neurodegenerative disorders (e.g., head injury, cerebral ischemia, dementia), (3) immunological and inflammatory diseases, (4) vomiting, (5) eating disorders, (6) irritable bowel syndrome, ulcerative colitis, (7)

hypertension, (8) glaucoma, or (9) sleep disorders. In addition, the compounds are free from or are relieved from cannabinoid-like side effects and a problem of addiction.

Further, according to the screening method of the present invention, a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain that are free from or are relieved from cannabinoid-like side effects and a problem of addiction can be selected on the basis of inhibition of FAAH activity. The substances obtained according to the screening method and the FAAH activity-inhibitory substances may produce pharmaceutical compositions useful for treatment of urinary frequency and urinary incontinence, for treatment of overactive bladder and/or for treatment of pain.

BEST MODE FOR CARRYING OUT THE INVENTION

[0016]

The present invention is described in detail hereinunder.

The compounds of the present invention are described in detail hereinunder.

[Definitions]

Unless otherwise specifically indicated, the term "lower" in the definition of the structural formulae in this description means a linear or branched carbon chain having from 1 to 6 carbon atoms.

"Lower alkyl" includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl; preferably methyl, ethyl, propyl, butyl, tert-butyl.

"Lower alkenyl" means an aliphatic hydrocarbon group having at least one double bond, including, for example, vinyl, propenyl, allyl, isopropenyl, 1,3-butadienyl, hexenyl.

"Cycloalkyl" means a mono- to tri-cyclic aliphatic saturated hydrocarbon ring group having from 3 to 14 carbon atoms, including, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycloheptyl, bicyclooctyl, tricyclododecanyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl.

[0017]

"Aryl" means a mono- to tri-cyclic aromatic hydrocarbon ring group having from 6 to 14 carbon atoms, in which the phenyl may be condensed with cycloalkyl. For example, it includes phenyl, indenyl, naphthyl, anthryl, phenanthryl, indanyl, tetrahydronaphthyl, preferably phenyl, naphthyl.

"Heterocyclic" means a 4- to 16-membered, monocyclic, bicyclic or tricyclic, saturated or unsaturated ring having from 1 to 4 hetero atoms selected from N, S and O. The heterocyclic group may be crosslinked or spiro-structured. The unsaturated ring includes an aromatic ring (heteroaryl) and a non-aromatic ring. The monocyclic group includes azetidiny, oxetanyl, pyrrolidinyl, 1,3-dioxolanyl, pyrazolidinyl, piperazinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, pyridyl, pyrazinyl, pyrimidinyl, triazolyl, thiadiazolyl, pyridazinyl, oxadiazolyl, tetrazolyl; the bicyclic group includes indolyl, isoindolyl, 3,4-methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, benzofuranyl, benzothienyl, benzothiadiazolyl, benzothiazolyl, benzimidazolyl, indolyl, isoindolyl, quinolyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, decahydroisoquinolyl, quinoxalinyl; the tricyclic group includes carbazolyl, acridinyl, phenothiazinyl. The crosslinked heterocyclic group includes quinuclidinyl, 2,5-diazabicyclo[2.2.1]heptyl, 8-azabicyclo[3.2.1]octyl, 7-azabicyclo[2.2.1]heptyl. The spiro-structured heterocyclic group includes 1,4-dioxo-8-azaspiro[4,5]decanyl.

[0018]

"Nitrogen-containing heteroaryl" means a 4-to 10-membered, mono- or bi-cyclic aromatic nitrogen-containing heteroaryl, having from 1 to 4 nitrogen atoms of the above-mentioned heterocyclic group. It includes, for example, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzimidazolyl, benzopyrazolyl, quinolyl, isoquinolyl, quinoxalinyl, preferably imidazolyl, thiazolyl, pyridyl, benzimidazolyl, quinolyl.

"Nitrogen-containing saturated heterocyclic group" means a 3- to 10-membered, mono- or bi-cyclic nitrogen-containing heterocycloalkyl group, having from 1 to 3 nitrogen atoms of the above-mentioned heterocyclic group. It includes, for example, aziridinyl, azetidiny, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, hexahydroazepinyl, 1,4-diazepinyl, 1,4-oxazepinyl, quinuclidinyl, 2,5-diazabicyclo[2.2.1]heptyl, azabicyclooctyl (e.g., azabicyclo[3.2.1]octyl),

diazabicyclooctyl, azabicyclononyl, azabicyclodecanyl, 1,4-dioxo-8-azaspiro[4,5]decanyl, preferably pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, hexahydroazepinyl, 1,4-diazepinyl, 1,4-oxazepinyl, quinuclidinyl, 2,5-diazabicyclo[2.2.1]heptyl, azabicyclo[3.2.1]octyl.

5 "Nitrogen-containing hetero ring" means the above-mentioned nitrogen-containing heteroaryl group, the above-mentioned nitrogen-containing saturated heterocyclic group, or a condensed group of nitrogen-containing heteroaryl and nitrogen-containing heterocycloalkyl. Preferably, it is pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, hexahydroazepinyl, azabicyclo[3.2.1]octyl, 1,4-dioxo-8-azaspiro[4.5]decanyl, imidazolyl, pyridyl, quinolyl.

10 "Non-aromatic nitrogen-containing hetero ring" means a nitrogen-containing saturated heterocyclic group and an unsaturated nitrogen-containing heterocyclic group except the nitrogen-containing heteroaryl of the above-mentioned nitrogen-containing heterocyclic group. Preferably, it is a 5- to 7-membered non-aromatic nitrogen-containing heterocyclic group.

"Lower alkylene", "lower alkenylene", "cycloalkylene", "arylene" and "nitrogen-containing heteroarylene" are divalent groups derived from the above-mentioned lower alkyl, lower alkenyl, cycloalkyl, aryl and nitrogen-containing heteroaryl, by removing any one hydrogen atom from them.

20 "Esterified carboxyl" means lower alkyl-O-CO-, aryl-lower alkyl-O-CO-, or H₂N-CO-aryl-lower alkyl-O-CO-.

"Halo" means a halogen group, concretely including fluoro, chloro, bromo, iodo, preferably fluoro, chloro.

"Optionally substituted" means "unsubstituted" or "substituted with the same or different, 1 to 5 substituents".

[0019]

Depending on the type of the substituent therein, the compound (I) of the present invention may have optical isomers (optically-active isomers, diastereomers) or geometric isomers. Accordingly, the compound (I) of the present invention includes mixtures or isolated compounds of these optical isomers or geometric isomers.

30 The compound (I) of the present invention may form pharmaceutically acceptable salts such as acid-addition salts or salts with bases. For example, the salts

includes acid addition salts with an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid; or an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethanesulfonic acid, glutamic acid; as well as salts with an inorganic base such as sodium, potassium, magnesium, calcium, aluminium; or an organic base such as methylamine, ethylamine, monoethanolamine, diethanolamine, triethanolamine, cyclohexylamine, lysine, ornithine. Further, the compound (I) or its pharmaceutically acceptable salt of the present invention may form hydrates, solvates with ethanol or the like, and crystalline polymorphs.

[0020]

Further, the compound (I) of the present invention includes all compounds capable of being metabolized in living bodies to be converted into the compound (I) or its pharmaceutically acceptable salt of the present invention, that is, prodrugs. The group to form prodrugs of the compound (I) of the present invention includes those described in Prog. Med., 5:2157-2161 (1985), and those described in "PHARMACEUTICAL RESEARCH and DEVELOPMENT", VOLUME 7 Drug Design, pp. 163-198 by Hirokawa Publishing, 1990. Concretely, they are groups capable of being converted into primary amine or secondary amine, or HO-, HO-CO- or the like in the present invention through hydrolysis or solvolysis or under a physiological condition. Prodrugs of HO- are, for example, optionally-substituted lower alkyl-CO-O-, optionally-substituted aryl-CO-O-, optionally-substituted heteroaryl-CO-O-, RO-CO-optionally-substituted lower alkylene-CO-O- (R means H- or lower alkyl - the same shall be applied hereinunder), RO-CO-optionally-substituted lower alkenylene-CO-O-, RO-CO-lower alkylene-O-lower alkylene-CO-O-, RO-CO-CO-O-, ROS(=O)₂-optionally-substituted lower alkenylene-CO-O-, phthalidyl-O-, 5-methyl-1,3-dioxolen-2-on-4-yl-methyloxy.

[0021]

"Urinary frequency" as referred to in this description indicates a condition where the urination frequency has increased over a normal range. "Urinary incontinence" means a involuntary urination that is problematic in a social and sanitary life.

"Overactive bladder" as referred to in this description indicates a syndrome to be diagnosed by a subjective symptom such as urinary frequency or urgency (Neurourology and Urodynamics, USA, 2002, Vol. 21, pp. 167-178). The pathogenic cause includes, for example, neuropathy (for example, caused by neurogenic bladder, cerebral infarction), lower urinary tract obstruction (e.g., benign prostatic hypertrophy) and aging; and as the pathogenic mechanism common to these, hyperactivity of capsaicin-sensitive afferent neuron.

Overactive bladder may be treated by relieving the condition of urinary frequency, urinary incontinence and urgency. This is obvious, for example, from the fact that administration of an anticholinergic agent, oxybutynin hydrochloride (Japan Standard Product Classification Number 87259; by Aventis Pharma) to a patient suffering from overactive bladder, at a dose of from 2 to 3 mg/once and three times a day may relieve the condition of urinary frequency, urinary incontinence and urgency, and the administration is therefore effective for treatment of overactive bladder.

[0022]

The presence of the effect for treatment of urinary frequency and urinary incontinence and/or the effect for treatment of overactive bladder may be confirmed by methods known to those skilled in the art or by modified methods from them. For example, a pathologic model induced by administration of from 50 to 200 mg of cyclophosphamide (CPA) to rat, guinea pig, dog or the like is frequently used in this technical field (Ozawa et al., The Journal of Urology, Vol. 162, pp. 2211-2216, 1999; Boucher et al., The Journal of Urology, Vol. 164, pp. 203-208, 2000). This is a pathologic model that accompanies hemorrhagic cystitis, and since capsaicin-sensitive afferent neuron participates in the pathogenic mechanism of urinary frequency, it may be considered that this model may be a suitable pathologic model for various types of overactive bladder including neuropathic bladder (Carlo Alberto Maggi et al., Journal of the Autonomic Nervous System, Vol. 38, pp. 201-208, 1992). A urinary frequency condition may be confirmed by the decrease in the effective bladder capacity. To the pathologic model animal, an effective dose of a pharmaceutical composition is administered orally, intraperitoneally or intravenously, once or plural times; and when the effective bladder capacity of the animal has increased, then the effect of the

pharmaceutical composition for treatment of urinary frequency and urinary incontinence and/or for treatment of overactive bladder may be confirmed.

[0023]

"Pain" as referred to in this description is a generic term for neuropathic pain, nociceptive pain and inflammatory pain, of which "neuropathic pain" means pain caused by peripheral or central nervous system dysfunction and includes diabetic neuropathic pain, cancer pain, trigeminal neuralgia, phantom pain, postherpetic pain and thalamic pain. The essential clinical symptom of neuropathic pain includes pain as if clutched, pain as if scorched, hyperalgesia and allodynia.

Nonsteroidal antiinflammatory drugs and narcotic analgesics such as morphine that are ordinary analgesics are known to be weakly effective for neuropathic pain. In a medical site, an antiepileptic such as gabapentin, and an antiarrhythmic such as mexiletine are used for pain relief, but their analgesic potency is not sufficient.

[0024]

The presence of the effect for treatment of neuropathic pain may be confirmed by methods known to those skilled in the art or by modified methods from them. For example, using an L5/L6 spinal nerve ligated rat that is produced according to partial modification of a Kim and Chung's method (Pain, Vol. 50, pp. 355-363, 1992), the ameliorating effect of a compound for significant reduction in the response threshold to tactile stimulation (allodynia) is evaluated, and based on it, the effect of the tested compound for treatment of neuropathic pain may be confirmed.

The compound of the present invention includes those effective for urinary frequency and urinary incontinence as well as overactive bladder; those effective for pain, especially for neuropathic pain; and those effective for both the two.

[0025]

[Production Methods]

The compound and its pharmaceutically acceptable salt of the present invention can be produced by applying various known production methods, utilizing the characteristics based on its basic skeleton of the compound or the type of the substituent therein.

Depending on the type of a functional group in the compound, it may often be effective in point of its production technology to substitute the functional group with

a suitable protective group (capable of being readily converted into the functional group) in a stage of its starting material or intermediate. The functional group includes, for example, an amino group, a hydroxyl group and a carboxyl group; and their protective groups are, for example, those described in "Protective Groups in Organic Synthesis (2nd Ed)" by Greene & Wuts. These may be suitably selected and used depending on the reaction conditions.

In this method, the protective groups is removed if necessary after it has been introduced and the reaction carried out, in order to produce the desired compound.

Typical production methods for the compounds of the present invention and their intermediates are described below.

(The abbreviations given in the following description are as follows:

DMF: N,N-dimethylformamide,

DMSO: dimethylsulfoxide,

THF: tetrahydrofuran,

TFA: trifluoroacetic acid,

Tol: toluene,

EtOAc: ethyl acetate,

DCE: 1,2-dichloroethane,

TEA: triethylamine)

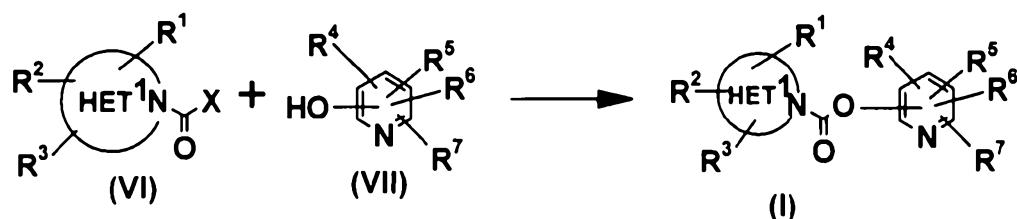
Typical production methods for the compounds of the present invention described below, to which, however, the present invention should not be limited.

In case where a similar substituent exists in a site of the compound of the present invention except that in the reaction formula in the production method for the compound, the compound that is encompassed within the scope of the present invention may be readily produced through substituent modification.

Production Method 1 (Carbamate formation):

[0026]

[Chemical Formula 6]



[0027]

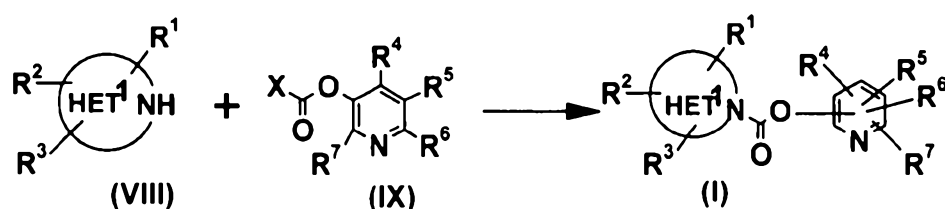
(In the formula, X represents a leaving group advantageous to the reaction, and the same shall be applied hereinunder.)

5 This reaction is for esterification of a ketone derivative of a general formula (VI) and a reaction-corresponding amount of a hydroxypyridine derivative of a general formula (VII), in a solvent inert to the reaction, with stirring with cooling or at room temperature or with heating. The leaving group X includes, for example, a halogen atom, a lower alkoxy group, a phenoxy group, an imidazolyl group. The inert solvent
10 includes, for example, DMF, dimethylacetamide, THF, dioxane, dimethoxyethane, diethoxyethane, benzene, Tol, xylene and their mixed solvents. For promoting the reaction, a base (e.g., sodium, sodium hydride, sodium methoxide, sodium ethoxide) is preferably added to the reaction mixture.

15 Production Method 2 (Carbamate formation):

[0028]

[Chemical Formula 7]



20 [0029]

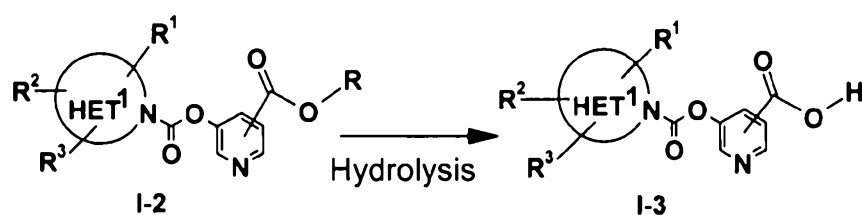
This reaction is conducted by stirring a nitrogen-containing heterocyclic compound of a general formula (VIII) and a reaction-corresponding amount of a pyridine derivative of a general formula (IX) in a solvent inert to the reaction, with cooling or at room temperature or with heating. For promoting the reaction, a base
25 (e.g., sodium, sodium hydride, sodium methoxide, sodium ethoxide, TEA, pyridine) is preferably added to the reaction mixture.

Production Method 3 (Hydrolysis):

A compound (I-3) of the present invention having a carboxyl group can be obtained through hydrolysis of the corresponding compound having an esterified carboxyl group, for example, according to deprotection described in "Protective Groups in Organic Synthesis (2nd Ed)" by Greene & Wuts.

[0030]

[Chemical Formula 8]



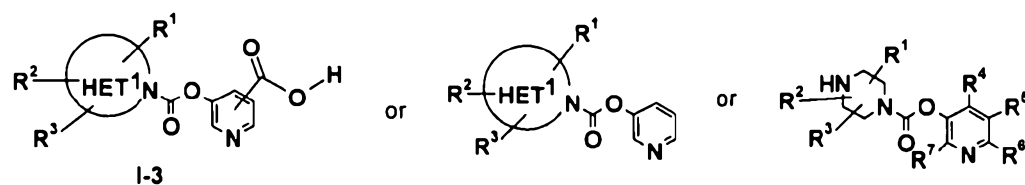
[0031]

(In the formula, the group ROCO- means an esterified carboxyl group, and the same shall be applied hereinunder.)

Production Method 4 (Amidation):

[0032]

[Chemical Formula 9]



[0033]

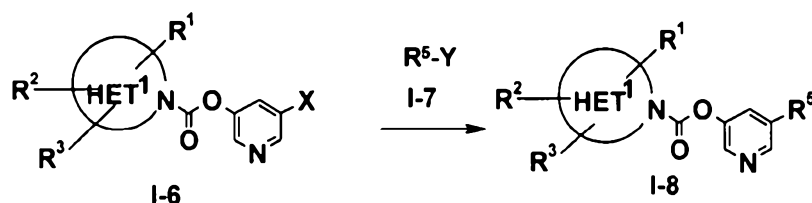
The compound (I-3) or the compound where R^1 is a carboxylic acid may react with an amine, and the compound where R^1 is an amine may react with a carboxylic acid, thereby various amide compounds can be obtained. When the nitrogen-containing heterocyclic compound is piperidine, then it may be reacted with a carboxylic acid or a sulfonic acid compound or their reactive derivative to produce various types of amide compounds. The reaction may be conducted in the presence of

a condensing agent (e.g., dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIPC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC), 1,1'-carbonylbis-1H-imidazole (CDI)) and optionally further in the presence of an additive (e.g., N-hydroxysuccinimide (HONSu) 1-hydroxybenzotriazole (HOBt),
 5 dimethylaminopyridine (DMAP)). The reactive derivative of the carboxylic acid or the sulfonic acid compound includes acid halides, acid anhydrides, active esters. The reaction may also be conducted, for example, according to the methods described in "Jikken Kagaku koza (Courses in Experimental Chemistry, 4th Ed)", Vol. 22, edited by the Chemical Society of Japan, Maruzen, 1992.

10 Production Method 5 (Coupling Reaction):

[0034]

[Chemical Formula 10]



[0035]

(In the formula, the symbols have the following meanings. X represents halogen or -O-SO₂CF₃, and Y represents -B(OH)₂, dialkylboron, dialkoxyboron or trialkyltin. X may be -B(OH)₂, dialkylboron, dialkoxyboron or trialkyltin, and Y may be halogen or
 20 -O-SO₂CF₃.)

Two aromatic rings, or that is, a combination of a compound (I-6) and a compound (I-7), are reacted preferably in the presence of a transition metal catalyst and a suitable additive, thereby producing a biaryl compound (I-8). Typical methods for it are described in "Jikken Kagaku koza (Courses in Experimental Chemistry, 4th Ed)",
 25 Vol. 25, Organic Synthesis VII, pp. 353-366, pp. 396-427, 1991 (Maruzen). The transition metal catalyst preferred for use herein includes various palladium complexes such as tetrakis(triphenylphosphine)palladium, and various nickel complexes such as dibromobis(triphenylphosphine)nickel. The additive also preferred for use herein includes triphenylphosphine, sodium carbonate, zinc; and these

may be suitably selected depending on the method to which they are applied. In general, the reaction is conducted in a solvent at room temperature or with heating. Apart from the reaction described herein, also preferably used is a reaction for biaryl structure formation, for example, a reaction of a halogenated aryl compound with an aryl-Grignard reagent in the presence of a suitable transition metal catalyst.

(Production Methods for Starting Compounds)

The starting compounds to be used for producing the compounds of the present invention may be known compounds or may be produced by optionally processing known compounds according to the above-mentioned production methods, or according to methods well known to those skilled in the art (J. March, ADVANCED ORGANIC CHEMISTRY (John WILEY & SONS (1992)) (for example, acylation, alkylation, urea formation, oxidation, reduction (preferably, COMPREHENSIVE ORGANIC SYNTHESIS 8 REDUCTION (Pergamon Press) (1991)), halogenation).

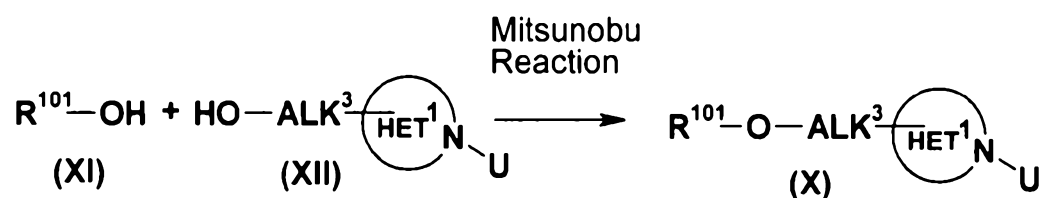
Production Method (i):

Mitsunobu Reaction:

A starting compound (X) may be produced through Mitsunobu reaction of alcohols of general formulae (XI) and (XII). This reaction is conducted by stirring the compounds (XI) and (XII) in the presence of an equivalent or excessive amount of triphenylphosphine and diethyl azodicarboxylate, in an inert solvent as in the production method 1, under cooling to heating conditions.

[0036]

[Chemical Formula 11]



[0037]

(In the formula, the symbols have the following meanings:

U represents an amino-protective group,

ALK³ represents ALK¹ optionally substituted with HO, and the same shall be applied hereinunder.)

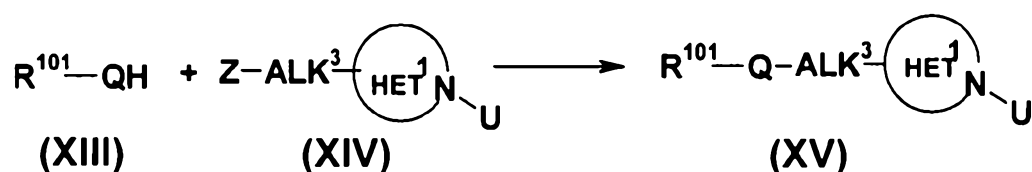
Production Method (ii):

Substitution Reaction:

This reaction is alkylation. A primary amine, a secondary amine, an alcohol, a thiol, a primary amide or a secondary amide is reacted with a reaction-
 5 corresponding amount of a compound having a leaving group, in a solvent inert to the reaction, in an equivalent ratio of the two, or in such a ratio that any one of the two is excessive, with stirring under cooling to heating conditions. As the case may be, the reaction may be conducted advantageously in the presence of a base (e.g., inorganic
 10 base such as potassium carbonate, sodium carbonate, cesium carbonate; organic base such as TEA, diisopropylethylamine; metal alkoxide such as potassium tert-butoxide, sodium tert-butoxide; sodium hydride, lithium hydride) and an additive (tetra-n-butylammonium iodide, potassium iodide, sodium iodide) for smoothly promoting the reaction. The solvent inert to the reaction includes, for example, dichloromethane,
 15 DCE, chloroform, benzene, Tol, xylene, ether, THF, dioxane, EtOAc, ethanol, methanol, 2-propanol, acetonitrile, DMF, N,N-dimethylacetamide, N-methylpyrrolidone, dimethylimidazolidinone, DMSO, acetone, methyl ethyl ketone, water, as well as their homogeneous or heterogeneous mixed solvents. The solvent may be suitably selected depending on various reaction conditions employed.

[0038]

[Chemical Formula 12]



[0039]

[In the formula, the symbols have the following meanings:

Q represents O, S or NH,

Z represents a leaving group (e.g., Cl, Br, I, or OMs).]

Accession Number NM_024132), porcine (GenBank Accession Number AB027132), rabbit, sheep, chicken, dog, cat, hamster, squirrel, bear, deer, monkey. In addition, it is not limited to a natural polypeptide, but may include artificially-produced mutants.

5 Regarding (a) a polypeptide which contains an amino acid sequence of the entire amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO:8 or a part of the amino acid sequence not having at least the transmembrane region-containing amino terminal region thereof, and which may hydrolyze anandamide, palmitoylethanolamide, oleamide, and/or 2-arachidonoyl glycerol;

10 (b) a polypeptide which contains an amino acid sequence of the entire amino acid sequence derived from the amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO:8 through deletion, substitution and/or insertion of from 1 to 10, preferably from 1 to 7, more preferably from 1 to 5 amino acids therein, or a part of the amino acid sequence not having at least the
15 transmembrane region-containing amino acid terminal region thereof, and which may hydrolyze anandamide, palmitoylethanolamide, oleamide, and/or 2-arachidonoyl glycerol;

(c) a polypeptide which contains an amino acid sequence having a homology of at least 70%, preferably at least 80%, more preferably at least 90%, most preferably
20 at least 95% to the amino acid sequence represented by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO:8, and which may hydrolyze anandamide, palmitoylethanolamide, oleamide, and/or 2-arachidonoyl glycerol;

(d) a polypeptide which contains an amino acid sequence of the entire amino acid sequence encoded by a polynucleotide represented by SEQ ID NO:1, SEQ ID
25 NO:3, SEQ ID NO:5 or SEQ ID NO:7 or by a polynucleotide capable of hybridizing with its complementary sequence under a stringent condition, or its part not having at least the transmembrane region-containing amino terminal region thereof, and which may hydrolyze anandamide, palmitoylethanolamide, oleamide, and/or 2-arachidonoyl glycerol;

30 the above (a) to (d) are generically referred to as a generic term "functional FAAH".

[0043]

The above-mentioned "transmembrane region-containing amino terminal region" as referred to in this description means an amino terminal region that includes the extracellular region at an amino terminal, and a transmembrane region buried in the cell membrane sandwiched between the extracellular region and the intracellular region. The existence and the site of the transmembrane region may be predicted from the amino acid sequence of the protein, using a protein membrane structure prediction program, TMPred, PSORT, SOSUI. Concretely, the "transmembrane region-containing amino terminal region" is, for example, the region of from the first to the 30th in SEQ ID NO:2, and the region of from the first to the 29th in SEQ ID NO:6. It is known that the polypeptide represented by the 30th to 579th amino acids in SEQ ID NO:6 excluding the region of from the 1st to the 29th in SEQ ID NO:6 also has the same enzymatic activity as that of the polypeptide from which the region is not excluded (Matthew et al., Biochemistry, Vol. 37, pp. 15177-15178, 1998).

The "homology" as referred to in this description means the values identities obtained by the use of the parameters prepared in default through search with Clustal V program (Higgins & Sharp, Gene, Vol. 73, pp. 237-244, 1998; Thompson et al., Nucleic Acid Res., Vol. 22, pp. 4673-7680, 1994). The parameters are as follows:

As pairwise alignment parameters,

K tuple 1

Gap Penalty 3

Window 5

Diagonals Saved 5.

[0044]

The above-mentioned "stringent condition" for hybridization as referred to in this description means a condition not causing any unspecific binding. Concretely, for example, the hybridization is effected in a solution comprising 50% formamide, 5 × SSC (0.75 M NaCl, 0.075 M sodium citrate, pH 7), 5 × Denhardt's solution (0.1% Ficoll 400, 0.1% polyvinylpyrrolidone, 0.1% BSA), modified salmon sperm DNA (50 g/ml), 0.1% SDS, and 10% dextran sulfate, under a temperature condition of from 37 to 42°C for about 12 to 18 hours, and then optionally after pre-washed, this is washed

with a washing solution ($0.2 \times \text{SSC}$, 0.1% SDS) under a temperature condition of from 50 to 60°C.

The above-mentioned "hydrolysis of anandamide, palmitoyl ethanolamide, oleamide and/or 2-arachidonoyl glycerol" as referred to in this description concretely means that, according to the method described in Examples 1 to 4, anandamide (N-arachidonoyl ethanolamine) is decomposed into arachidonic acid and ethanolamine; palmitoyl ethanolamide (N-palmitoyl ethanolamine) is into palmitic acid and ethanolamine; oleamide (cis-9,10-octadecenamide) is into oleic acid and ammonia, and 2-arachidonoyl glycerol is into arachidonic acid and glycerol, through hydrolysis in a buffer having a pH of from 7 to 9 at 4°C to 37°C for 30 minutes to 90 minutes.

The screening method of the present invention includes a screening method for a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain, comprising (1) a step of contacting a test substance with FAAH or functional FAAH, (2) a step of analyzing it for the activity of FAAH or functional FAAH, and (3) a step of selecting a substance that inhibits the activity of FAAH or functional FAAH.

(1) Step of contacting test substance with FAAH or functional FAAH:

For contacting a test substance with FAAH or functional FAAH, the test substance may be added to any of the following:

- a) a cell or a tissue expressing FAAH or functional FAAH,
 - b) a transformant transformed with an expression vector containing a polynucleotide that encodes FAAH or functional FAAH,
 - c) a lysate or a homogenate of a) or b),
 - d) a purified product of FAAH or functional FAAH purified from c),
- and incubated for a predetermined period of time; or
- e) a tissue homogenate or blood of a test animal to which the test substance has been administered may be used.

[0045]

a) Cell or tissue expressing FAAH or functional FAAH:

Concretely, the cell expressing FAAH or functional FAAH includes neurons, glial cells, epithelial cells, endothelial cells, lymphocytes, macrophages, platelets, mast cells, monocytes, dendritic cells, hepatocytes, renal cells, enterocytes, pancreatic cells,

uterine cells, placental cells, bladder cells, prostatic cells, keratinization cells, and muscular cells. So far as they express FAAH or functional FAAH, these cells may be derived from any species; and for example, herein employable are cells derived from mammals such as human, mouse, rat, porcine, rabbit, sheep, chicken, dog, cat, hamster, squirrel, bear, deer, monkey.

For the cells, usable are established cell lines; and cells peeled from or isolated from animal tissues may also be used. The established cell lines usable herein include human bladder epithelial cancer-derived cell line 5673 cells, human prostatic cancer-derived cell line PC-3 cells, rat basophilic leukemia cell line RBL-2H3 cells, rat neuroblastoma cell line N18TG2 cells, rat glioma cell line C6 cells, rat macrophage cell line J774 cells, rat adrenal medulla-derived pheochromocytoma cell line PC-12 cells, human monocytic cell line U937 cells, human breast cancer cell line MFC-7 cells, human breast cancer cell line EFM-19 cells, human colon cancer-derived cell line CaCo-2 cells (these cell lines are available from American Type Culture Collection (ATCC)), human epidermal keratinocyte cell line HaCaT cells, and human neuroblastoma cell line CHP100 cells. Preferred are human bladder epithelial cancer-derived cell line 5673 cells, and rat basophilic leukemia cell line RBL-2H3 cells.

The tissue expressing FAAH or functional FAAH concretely includes brain, bladder, prostate, kidney, liver, testis, muscle, vessel, pancreas, digestive tube, lung, uterus, placenta, skin, lymphocyte, platelet, macrophage, monocyte, mast cell, and prostate. Preferably used are brain, liver and monocyte. So far as they express FAAH or functional FAAH, these tissues may be derived from any species. For example, tissues derived from mammals such as human, mouse, rat, porcine, rabbit, sheep, chicken, dog, cat, hamster, squirrel, bear, deer, monkey may be used.

For determining whether or not a cell or a tissue expresses FAAH or functional FAAH, a cell or tissue extract may be used and analyzed through western blotting, using an antibody capable of detecting the intended polypeptide, or through PCR (polymerase chain reaction) using primers capable of specifically detecting a polynucleotide that encodes the intended polypeptide. In addition, a lysate or a homogenate of a cell or a tissue is reacted with a substrate such as anandamide, palmitoyl ethanolamide, oleamide, and/or 2-arachidonoyl glycerol, in a buffer having a

pH of from 7 to 9 at 4°C to 37°C for 30 minutes to 90 minutes, whereupon the system is determined whether or not the substrate is hydrolyzed for the intended determination. [0046]

b) Transformant transformed with expression vector containing polynucleotide that encodes FAAH or functional FAAH:

A polynucleotide that encodes FAAH or functional FAAH may be isolated from a cDNA library through screening by PCR or hybridization, using primers and a probe planned and synthesized on the basis of the information of known amino acid sequences and base sequences.

The fragment that contains the isolated polynucleotide is inserted into a suitable expression vector, and it may be transfected into a host cell of eukaryote or prokaryote; and in the host cell, the polypeptide encoded by the transfected polynucleotide may be thus expressed. The expression vector may be any known one suitably selected depending on the host cell, for which, in addition, also usable is a vector plasmid suitably selected depending on the host cell and having a suitable promoter and a phenotype expression-related sequence introduced thereinto. Also usable is an expression vector with a specific sequence introduced thereinto in such a manner that the polypeptide encoded by the inserted polynucleotide may be expressed as fused with glutathion-S-transferase (GST) or with a tag such as Flag or His. In case where one cell is transformed with some different types of polynucleotides at the same time, then one expression vector to be used may be so planned that it includes such different types of polynucleotides, or those polynucleotides may be separately in different expression vectors. Alternatively, a cell with a chromosomal DNA having the constitution of the type may be produced and it may be used.

The expression vector with a desired polynucleotide introduced thereinto may be given to a host cell according to a DEAE-dextran method (Luthman et al., Nucleic Acids Res., Vol. 11, pp. 1295-1308, 1983), a calcium phosphate-DNA coprecipitation method (Graham et al., Virology, Vol. 52, pp. 456-457, 1973), a method of using a commercially-available transfection reagent, Lipofectamine 2000 (by Invitrogen) or FeGENE 6 (by Roche Molecular Biochemicals), or an electroporation method (Neumann et al., EMBO J., Vol. 1, pp. 841-845, 1982) for intended transformation. In case where *E. coli* is used as the host cell, a competent

cell of *E. coli* is formed with coexistence with CaCl_2 , MgCl_2 or RbCl according to a Hanahan's method (Hanahan et al., Mol. Biol. Vol. 166, pp. 557-580, 1983), and an expression vector with the desired polynucleotide introduced thereto is given thereto for transformation of the cell.

5 [0047]

c) Lysate or homogenate of a) or b):

A cell homogenate may be prepared by washing a cell a few times with a buffer, and then homogenized using a Potter-Elvehjem homogenizer or the like thereby giving a uniform solution. A tissue homogenate may be prepared by adding a buffer cooled with ice to a tissue in an amount of from 5 to 10 volume times the weight of the tissue, homogenizing it using a Potter-Elvehjem homogenizer in ice thereby giving a uniform solution, and then further ultrasonically homogenizing it for a few seconds. The buffer may be Tris buffer (50 mM Tris-HCl (pH 8.0), 1 mM EDTA) or Hepes buffer (1 mM EDTA, 100 mM NaCl, 12.5 mM Hepes, pH 8.0). For example, the test methods of Example 438 and Example 439 are applicable to the case. A lysate of *E. coli* transformed with an expression vector that contains an FAAH or functional FAAH-encoding polynucleotide may be prepared by collecting cells of *E. coli* through centrifugation and then dissolving them in a lysis buffer (for example, 20 mM Tris-HCl (pH 8.0), 500 mM NaCl, 10% glycerol, 0.2 mM EDTA, 0.5 mM DTT, 10 mM imidazole, 1% n-octyl- β -D-glucopyranoside).

d) Purified product of FAAH or functional FAAH purified from c):

A purified product of FAAH or functional FAAH may be prepared from a) a cell or tissue expressing FAAH or functional FAAH or b) a lysate or a homogenate of a transformant transformed with an expression vector that contains an FAAH or functional FAAH-encoding polynucleotide, according to an ordinary purification method of affinity chromatography, electrochromatography, gel filtration chromatography, ion-exchange chromatography or partition chromatography.

[0048]

Concretely, the purification is as follows: A cell or tissue expressing FAAH or functional FAAH is homogenized in a solvent containing sucrose, and then subjected to centrifugation and ultra-high-speed centrifugation to obtain a microsome fraction, thereafter this is dissolved in a solvent containing Triton-X and further

centrifuged for deposit removal, and the resulting protein-lysate is processed in a high-performance protein liquid chromatography (FPLC) system (by Pharmacia) (Ueda et al., J. Biol. Chem., Vol. 270, pp. 23813-23827, 1995).

Alternatively, *E. coli* transformed so as to express a His tag-fused FAAH or functional FAAH is dissolved in a lysis buffer, then ultrasonically processed and centrifuged (e.g., at $10000 \times g$ for 20 minutes), and the resulting supernatant is mixed with a resin previously equilibrated with the lysis buffer and having a high affinity with His tag, at a low temperature for at least 12 hours. Then, the resin is washed, and the His tag-fused FAAH or functional FAAH is released from the resin to obtain its purified product.

For contacting a test substance with the above-mentioned cell or tissue, or the cell or tissue-lysate or homogenate prepared in the manner as above, or the purified FAAH or functional FAAH product, employable is a method of incubation for a predetermined period of time, with adding or not adding a test substance to them.

Concretely, a test substance is dissolved in a solution suitably selected depending on its solubility therein, such as distilled water or dimethyl sulfoxide (DMSO), and is added to the above-mentioned cell or tissue, or the cell or tissue-lysate or homogenate, or the purified FAAH or functional FAAH product to be from 0.003 nM to 10 μ M. The cell or tissue sample is incubated in a CO₂ incubator at 37°C for 30 to 60 minutes; and the others are at 4°C to 37°C for 30 to 90 minutes, thereby attaining the intended contact with the test substance.

[0049]

e) Tissue homogenate or blood of test animal administered with test substance:

When a test substance is administered to a test animal, then the test substance may be contacted with the FAAH or functional FAAH existing in the tissue or the blood of the test animal. The test animal includes, for example, mammals such as mouse, rat, dog. A test substance may be administered to the test animal as follows: A test substance is suspended or dissolved in a carrier generally used in accordance with the property of the test substance, such as physiological saline water, dimethylformamide solution or 10% methyl cellulose solution, and it may be administered to a test animal orally, subcutaneously, intraperitoneally or intravenously. After the administration, the tissue is taken out, and the tissue is homogenized

according to the method described in the above c), thereby preparing a tissue homogenate. Concretely, for example, from 1 to 3 mg/kg of a test substance is orally administered to a 9-week age rat, and its brain, liver or monocyte taken out of it after 30 minutes is homogenized to prepare the tissue homogenate. Alternatively, from 0.3 to 3 mg/kg of a test substance is intravenously administered to a 13 to 18-month age dog, and its brain, liver or monocyte taken out of it after 30 minutes is homogenized to prepare the tissue homogenate. More concretely, for example, the tissue homogenate may be prepared according to the method described in Example 440. Blood may be collected from the heart or the descending aorta of a test animal to which the test substance has been administered.

(2) Step of analyzing FAAH or functional FAAH activity change:

For analyzing the FAAH or functional FAAH activity change, employable is a method of determining the change in the enzymatic activity of FAAH or functional FAAH based on the presence or absence of contact with a test substance. The enzymatic activity of FAAH or functional FAAH may be determined by contacting FAAH or functional FAAH with a substrate for a predetermined period of time, and measuring the amount of the decomposed product of the substrate. Alternatively, it may also be determined by measuring the amount of endocannabinoid that is an endogenous substrate for FAAH contained in a tissue or blood of a test animal.

For analyzing the test substance-dependent enzymatic activity change, a substrate is contacted with FAAH or functional FAAH for a predetermined period of time in the presence or absence of a test substance, and the ratio of the amount of the decomposed product of the substrate in the presence of the test substance to the amount of the decomposed product of the substrate in the absence of the test substance is obtained for the intended analysis.

Alternatively, FAAH or functional FAAH previously contacted with a test substance, and FAAH or functional FAAH not contacted with a test substance are separately contacted with a substrate for a predetermined period of time, and the ratio of the amount of the decomposed product of the substrate by the FAAH or functional FAAH previously contacted with the test substance to the amount of the decomposed product of the substrate by the FAAH or functional FAAH not contacted with the test

substance is obtained whereby the test substance-dependent enzymatic activity change may be determined.

Further, the test substance-dependent enzymatic activity change may also be determined by measuring the amount of endocannabinoid in the tissue or blood of a test animal before and after administration of a test substance to the test animal, followed by obtaining the ratio of the endocannabinoid amount after the test substance administration to the endocannabinoid amount before the test substance administration; or by measuring the amount of endocannabinoid in the tissue or blood of a test animal administered or not administered with a test substance, followed by obtaining the ratio of the endocannabinoid amount in the tissue or blood of the test animal administered with the test substance to the endocannabinoid amount in the tissue or blood of the test animal not administered with the test substance, whereby the test substance-dependent enzymatic activity change may be determined.

[0050]

FAAH and functional FAAH may be contacted with a substrate under the condition mentioned below, in accordance with the condition of the FAAH or functional FAAH.

For contacting the FAAH or functional FAAH expressed in the cell or tissue of a) or b) in the above (1) with a substrate, there may be employed a method of adding the substrate to the cultured cell or tissue in a buffer having a pH of from 7 to 9, and reacting them in a CO₂ incubator at 37°C or room temperature preferably for 30 to 60 minutes. The reaction may be stopped by transferring the cell or tissue onto ice to rapidly cool it, whereupon an FAAH inhibitor may be contacted with it at its sufficient concentration; or by adding a 1:1 (by volume) solution of chloroform and methanol thereto. The cell or tissue is lysed or homogenized according to the method described in the above (1)c), thereby producing a lysate or a homogenate thereof.

For contacting FAAH or functional FAAH in the lysate or homogenate of a cell or tissue in c) or e) in the above (1), with a substrate, there may be employed a method of adding the substrate to the lysate or homogenate that has been diluted with a buffer having a pH of from 7 to 9 so as to have a protein concentration of preferably from 10 to 100 µg/ml, and reacting them under a temperature condition of from 4°C to 37°C. The reaction time may be suitably defined depending on the condition such as

the amount of the enzyme added, the amount of the substrate added and the reaction temperature. For example, when they are reacted at room temperature, the reaction time may be from 30 to 90 minutes.

For contacting the purified FAAH or functional FAAH in the above (1)d) with a substrate, there may be employed a method of adding the substrate to a lysate or a homogenate that has been diluted with a buffer having a pH of from 7 to 9, and reacting them under a temperature condition of from 4°C to 37°C. The reaction time may be suitably defined depending on the condition such as the amount of the enzyme added, the amount of the substrate added and the reaction temperature. For example, when they are reacted at room temperature, the reaction time may be from 30 to 90 minutes.

[0051]

For measuring the amount of the decomposed product of a substrate, the unreacted substrate and the decomposed product in the enzyme reaction solution are separated from each other, and the amount of the decomposed product may be measured. For separating the unreacted substrate from the decomposed product, the water-solubility of the decomposed product, ethanolamine may be utilized. For example, a 1:1 (by volume) solution of chloroform and methanol is added to the enzyme reaction solution in an amount of 2 times the reaction solution, followed by stirring, and then centrifuged, whereby the decomposed product containing in the upper layer, water/ethanol layer may be separated from the unreacted substrate contained in the lower layer, chloroform layer. Alternatively, the system may be mixed with a liquid scintillation cocktail agent of no water absorbability whereby the fat-soluble unreacted radioactive substrate may be taken into the cocktail agent and the decomposed product may be thereby separated from the unreacted substrate. Still alternatively, the unreacted substrate may be separated from the decomposed product through thin-layer chromatography or high-performance liquid chromatography.

In case where a ^3H - or ^{14}C -labeled substrate, or a mixture of a labeled substrate and an unlabeled substrate is used, the amount of the decomposed product or the amount of the unreacted substrate may be measured with a liquid scintillation counter, or it may be recorded as an X-ray latent image on an imaging plate and may be measured with an image plate reader.

In case where an unlabeled substrate is used, the absorbance at 205 nm of the system may be monitored through high-performance liquid chromatography, and the amount of the decomposed product or the amount of the unreacted substrate may be thereby measured (Lang et al., Anal. Biochem., Vol. 238, pp. 40-45, 1996).

5 When the amount of the unreacted substrate is measured, then amount of the unreacted substrate may be subtracted from the amount of the substrate added before the reaction, and the amount of the decomposed product may be thereby obtained. Alternatively, the amount of the decomposed product of the substrate measured in a buffer alone not containing FAAH or functional FAAH, as a control, may be subtracted
10 from the amount of the decomposed product of the substrate with FAAH or functional FAAH, whereby the net amount of the decomposed product of the substrate with FAAH or functional FAAH may be obtained.

The amount of endocannabinoid in a tissue homogenate may be measured, for example, by homogenizing a sample tissue with a 2:1:1 (by volume) solution of
15 chloroform, methanol and 50 mM Tris (pH 8.0), followed by measuring the amount of the endocannabinoid contained in the organic layer (chloroform layer) through liquid chromatography/isotope dilution mass spectrometry (Cravatt et al., Proc., Natl. Acad. Sci. USA, Vol. 98, pp. 9371-9376, 2001).

The amount of endocannabinoid in blood may be measured, for example, as
20 follows: Plasma is separated from a blood sample, and the protein in the plasma is removed through centrifugation along with the same amount of acetone (-20°C) added thereto. Acetone is evaporated by a nitrogen jet applied to the system, and a 1:2 (by volume) solution of methanol and chloroform is added to it, and the amount of endocannabinoid contained in the organic layer (chloroform layer) is measured through
25 liquid chromatography/isotope dilution mass spectrometry (Giuffraida et al., Eur. J. Pharmacol., Vol. 408, pp. 161-168, 2000).

[0052]

(3) Step of selecting substance that inhibits the activity of FAAH or functional FAAH:

A substance that inhibits the activity of FAAH or functional FAAH may be
30 selected as follows: A test substance is contacted with FAAH or functional FAAH, this is compared with a case not contacted with the test substance, and a substance that decreases the amount of the decomposed product of the substrate may be selected.

Concretely, a test substance is contacted with FAAH or functional FAAH, and this is compared with a case not contacted with a test substance. In this, the substance with which the amount of the decomposed product of the enzyme decreases preferably to 1/2 or less may be screened for a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain.

Alternatively, a test substance having a different concentration is contacted with FAAH or functional FAAH; and based on the amount of the decomposed product of the substrate not contacted with the test substance, as 100%, the relative value (%) of the decomposed product of the substrate contacted with the test substance having a different concentration is obtained; or based on the amount of the decomposed product of the substrate not contacted with the test substance, as 100%, and based on the amount of the decomposed product of the substrate in a case where a known FAAH inhibitor having a sufficient concentration is contacted with FAAH or functional FAAH for a sufficient period of time, as 0%, the relative value (%) of the amount of the decomposed product of the substrate contacted with the test substance having a different concentration is obtained. In an inhibition curve drawn on a graph in which the relative value (%) of the decomposed product of the substrate is on the vertical axis and the concentration of the test substance is on the horizontal axis, the concentration of the test substance that gives a relative value, 50%, of the decomposed product of the substrate (IC₅₀ value) is computed; and the substance of which the IC₅₀ value is preferably at most 1 μ M, more preferably at most 100 nM is screened for a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain. For example, the tests of Example 438 to Example 440 are referred to.

Still alternatively, a test substance is administered to a test animal, and the amount of endocannabinoid in the tissue or blood of the animal is compared with each other before and after the test substance administration; and the substance that increases the amount preferably to 1.5 times may be selected for a substance that inhibits the activity of FAAH or functional FAAH, or that is, the substance may be screened for a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain.

[2] Test Substance:

Not specifically defined, the test substance for use in the screening method of the present invention includes, for example, commercially-available products (including peptides), various known compound registered in Chemical File (including peptides), compound groups obtained according to combinatorial chemistry technology (Terrett et al., J. Steele. Tetrahedron, Vol. 51, pp. 8135-8173, 1995), microorganisms-derived culture supernatants, plant or sea life-derived natural components, animal tissue extracts, as well as compounds (including peptides) produced through chemical or biological modification of the compounds (including peptides) selected according to the screening method of the present invention.

[3] Pharmaceutical Composition for treatment of urinary frequency and urinary incontinence, for treatment of overactive bladder and/or for treatment of pain:

As the active ingredient of the pharmaceutical composition of the present invention, usable is a substance that inhibits the activity of FAAH or functional FAAH, in which the inhibitor substance may be selected, for example, according to the screening method of the present invention.

[0053]

The pharmaceutical composition of the present invention is not limited to a pharmaceutical composition that contains, as the active ingredient thereof, the substance obtained according to the screening method of the present invention, but may include any and every pharmaceutical composition for treatment of urinary frequency and urinary incontinence, for treatment of overactive bladder and/or for treatment of pain that contains, as the active ingredient thereof, a substance to inhibit the activity of FAAH or functional FAAH; and preferably, this is a pharmaceutical composition for treatment of urinary frequency and urinary incontinence, for treatment of overactive bladder and/or for treatment of pain.

[0054]

The effect for treatment of urinary frequency and urinary incontinence, the effect for treatment of overactive bladder and/or the effect for treatment of pain may be confirmed in the manner as above.

The composition containing, as the active ingredient thereof, a substance that inhibits the activity of FAAH or functional FAAH, for example, DNA, protein

(including antibody or antibody fragment), peptide or any other compound may be prepared as a pharmaceutical composition using pharmaceutically acceptable carrier, excipient and/or any other additive generally used in preparation of pharmaceutical compositions, depending on the type of the active ingredient therein.

5 The administration of the composition can be accompanied by, for example, oral administration via tablets, pills, capsules, granules, fine granules, powders or oral liquids; or parenteral administration via injections such as intravenous, intramuscular or intraarticular injections, suppositories, endermic preparations or intramucosal preparations. Especially for peptides that are digested in stomach, parenteral
10 administration such as intravenous injection is preferred.

 The solid composition for oral administration may comprise a mixture of at least one or more active ingredients and at least one inert diluents, for example, lactose, mannitol, glucose, microcrystalline cellulose, hydroxypropyl cellulose, starch, polyvinylpyrrolidone or magnesium aluminometasilicate. In addition to inert diluents,
15 the solid composition may contain other additives, in an ordinary manner, for example, lubricants, disintegrators, stabilizers, solubilizers or solubilaization assisting agents. The tablets and pills may be optionally coated with sugar or with gastric or enteric coat film.

 The liquid composition for oral administration includes, for example,
20 emulsions, solutions, suspensions, syrups and elixirs, and may contain ordinary inert diluents, for example, purified water or ethanol. In addition to inert diluents, the liquid composition may also contain, for example, moistening agents, suspending agents, sweeteners, aromatics or antiseptics.

[0055]

25 Injections for parenteral administration includes aseptic aqueous or non-aqueous solutions, suspensions or emulsions. The aqueous solutions or suspensions may contain, for example, distilled water for injection or physiological saline, as a diluent. The diluents for the non-aqueous solutions or suspensions includes, for example, propylene glycol, polyethylene glycol, vegetable oil (e.g., olive oil), alcohols
30 (e.g., ethanol) or Polysorbate 80. Such compositions may further contain moistening agents, emulsifiers, dispersants, stabilizers, solubilizers or solubilaization assisting agents, or antiseptics. Such compositions may be sterilized, for example, by filtration

through a bacteria retaining filter, or through addition of a germicide thereto, or through irradiation. If desired, a germ-free solid composition may be prepared, and before use, it may be dissolved in germ-free water or in any other germ-free medium for injection.

5 The dose of the composition may be suitably determined depending on the intensity of the activity of the active ingredient, or that is, the substance obtained according to the screening method of the present invention, and on the symptom, the age and the sex of the subject for its administration.

10 For example, in oral administration, the dose may be generally from about 0.1 to 100 mg/day, preferably from 0.1 to 50 mg/day to an adult (body weight of 60 kg). In parenteral administration, the injection dose may be from 0.01 to 50 mg/day, preferably from 0.01 to 10 mg/day.

EXAMPLES

15 [0056]

 The present invention is described in more detail with reference to the following Examples. The compounds of the present invention should not be limited to the compounds described in the following Examples. Production methods of starting compounds are shown in Reference Examples. Some compounds of the present invention may also be starting compounds for others; and for convenience sake, their production methods may be given herein as Reference Examples. The chemical structural formulae and the physicochemical properties of the compounds obtained in Reference Examples are shown in Tables 1 to 15. The chemical structural formulae of the compounds obtained in Examples are shown in Table 16 to Table 34; and the physicochemical properties thereof are in Tables 35 to 63. The structures of other compounds of the present invention are shown in Tables 65 to 73. These compounds may be readily produced according to the above-mentioned production methods or the methods described in the following Reference Examples and Examples, or according to methods self-obvious to those skilled in the art, or according to modifications of those methods.

30 When commercially-available kits are used, the written instructions attached thereto may be referred to.

The abbreviations given in this descriptions are as follows:

Rex: Reference Example

Ex: Example

Str: structural formula

5 DAT: physicochemical properties

^1H -NMR $\delta(\text{ppm})$, solvent: nuclear magnetic resonance spectrum

In the physicochemical data of the compounds of Examples;

DMSO: DMSO- d_6

MS m/z : mass spectral data

10 Com: compound

NC: cyano

Ph: phenyl

Me: methyl

diMe: dimethyl

15 Et: ethyl

Pr: propyl

iPr: isopropyl

Bu: butyl

tBu: tert-butyl

20 iBu: isobutyl

Pen: pentyl

Hex: hexyl

Hep: heptyl

Oct: octyl

25 cPr: cyclopropyl

cPen: cyclopentyl

cHex: cyclohexyl

cHep: cycloheptyl

cOct: cyclooctyl

30 Ac: acetyl

Cl: chloro

diCl: dichloro

	CN: cyano
	F: fluoro
	diF: difluoro
	FPh fluorophenyl
5	NPh: cyanophenyl
	diFPh: difluorophenyl
	O ₂ N: nitro
	MeO: methoxy
	diMeO: dimethoxy
10	Br: bromo
	diBr: dibromo
	BrPh: bromophenyl
	F ₃ C: trifluoromethyl
	AcO: acetoxy
15	MeOCO or COOMe: methoxycarbonyl
	tBuOCO or COOtBu: tert-butoxycarbonyl
	HO: hydroxy
	HOPh: hydroxyphenyl
	H ₂ N: amino
20	PhCONH: benzoylamino
	EtCONH: ethylcarbonylamino
	Me ₂ N: dimethylamino
	Et ₂ N: diethylamino
	BIP2: 2-biphenyl
25	BIP3: 3-biphenyl
	BIP4: 4-biphenyl
	BIP5: 5-biphenyl
	BIP6: 6-biphenyl
	Thiop2: thiophen-2-yl
30	Thiop3: thiophen-3-yl
	Thiop4: thiophen-4-yl
	Thiop5: thiophen-5-yl

	PYRR1: pyrrolidin-1-yl
	PYRR2: pyrrolidin-2-yl
	PYRR3: pyrrolidin-3-yl
	PYRR4: pyrrolidin-4-yl
5	PYRR5: pyrrolidin-5-yl
	Py2: pyridin-2-yl
	Py3: pyridin-3-yl
	Py4: pyridin-4-yl
	Py5: pyridin-5-yl
10	IM1: imidazol-1-yl
	IM2: imidazol-2-yl
	IM3: imidazol-3-yl
	IM4: imidazol-4-yl
	BenzIM1: benzimidazol-1-yl
15	BenzIM2: benzimidazol-2-yl
	BenzIM3: benzimidazol-3-yl
	BenzIM4: benzimidazol-4-yl
	BenzIM5: benzimidazol-5-yl
	BenzIM6: benzimidazol-6-yl
20	Pyrazi1: pyrazin-1-yl
	Pyrazi2: pyrazin-2-yl
	Pyrazi3: pyrazin-3-yl
	Pyrazi4: pyrazin-4-yl
	Pyrazi5: pyrazin-5-yl
25	Pyrazi6: pyrazin-6-yl
	PIPE1: piperidin-1-yl
	PIPE2: piperidin-2-yl
	PIPE3: piperidin-3-yl
	PIPE4: piperidin-4-yl
30	PIPE5: piperidin-5-yl
	PIPE6: piperidin-6-yl
	PIPERA: piperazine

	PIPERA1: piperazin-1-yl
	PIPERA2: piperazin-2-yl
	PIPERA3: piperazin-3-yl
	PIPERA4: piperazin-4-yl
5	PIPERA5: piperazin-5-yl
	Pyrazo1: pyrazol-1-yl
	Pyrazo2: pyrazol-2-yl
	Pyrazo3: pyrazol-3-yl
	Pyrazo4: pyrazol-4-yl
10	Pyrazo5: pyrazol-5-yl
	Mo: morpholine
	Mo2: morpholin-2-yl
	Mo3: morpholin-3-yl
	Mo4: morpholin-4-yl
15	Mo5: morpholin-5-yl
	Azep: hexahydroazepine
	Azep1: hexahydroazepin-1-yl
	Azep2: hexahydroazepin-2-yl
	Azep3: hexahydroazepin-3-yl
20	Azep4: hexahydroazepin-4-yl
	Thiaz2: thiazol-2-yl
	Thiaz3: thiazol-3-yl
	Thiaz4: thiazol-4-yl
	Thiaz5: thiazol-5-yl
25	QUI1: quinolin-1-yl
	QUI2: quinolin-2-yl
	QUI3: quinolin-3-yl
	QUI4: quinolin-4-yl
	QUI5: quinolin-5-yl
30	QUI6: quinolin-6-yl
	QUI7: quinolin-7-yl
	QUI8: quinolin-8-yl

ISOQUI2: isoquinolin-2-yl

ISOQUI3: isoquinolin-3-yl

ISOQUI4: isoquinolin-4-yl

ISOQUI5: isoquinolin-5-yl

5 ISOQUI6: isoquinolin-6-yl

ISOQUI7: isoquinolin-7-yl

ISOQUI8: isoquinolin-8-yl

NAPH1: naphthalen-1-yl

NAPH2: naphthalen-2-yl

10 NAPH3: naphthalen-3-yl

NAPH4: naphthalen-4-yl

NAPH5: naphthalen-5-yl

TEA: triethylamine

Sal: addition salt

15 HCl: hydrochloride

oxal: oxalate

fum: fumarate

p-tol: p-toluenesulfonate

[0057]

20 Reference Example 1:

A THF (10 ml) solution containing phenol (471 mg) and diethyl azodicarboxylate (2.83 g, 40% Tol solution) was dropwise added to a THF (15 ml) solution containing tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (1.57 g) and triphenylphosphine (1.70 g), at 0°C, followed by stirring at room temperature for 24
25 hours. Water (40 ml) was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with an aqueous 1 M sodium hydroxide solution and saturated brine in that order, and then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent; hexane:EtOAc = 4:1 (v/v)) to
30 obtain a colorless oil (1.14 g). The resulting compound was dissolved in EtOAc, a 4 M hydrogen chloride/EtOAc solution (9.6 ml) was added thereto, followed by stirring

at room temperature for 5 hours to obtain 4-(phenoxymethyl)piperidine hydrochloride (680 mg) as colorless powder.

In the same manner as in Reference Example 1, the compounds of Reference Examples 2 to 27 were obtained.

5 [0058]

Reference Example 28:

Water (10 ml), sodium carbonate (4.76 g) and tetrakis(triphenyl)phosphine palladium (866 mg) were added in that order to a dimethoxyethane (50 ml) solution containing 3-bromobenzamide (3.0 g) and (3-hydroxyphenyl)boronic acid (2.27 g),
10 followed by stirring at 60°C for 24 hours. The reaction solution was cooled, diluted with EtOAc, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: EtOAc) to obtain a pale yellow powder (2.74 g). Using the resulting compound and in the same manner
15 as in Reference Example 1, the compound of Reference Example 28 was obtained.

Reference Example 29:

A THF (80 ml) solution containing 4-(benzyloxy)phenol (8.0 g) and diethyl azodicarboxylate (26 ml, 40% Tol solution) was dropwise added to a THF (80 ml) solution containing tert-butyl 4-hydroxypiperidine-1-carboxylate (12 g) and
20 triphenylphosphine (16 g) at 0°C, followed by stirring at room temperature for 24 hours. Water (40 ml) was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with an aqueous 1 M sodium hydroxide solution and saturated brine in that order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by
25 silica gel column chromatography (eluent: hexane:EtOAc = 8:1 (v/v)) to obtain a colorless oil (12.4 g).

10% palladium-carbon (catalytic amount) was added to an ethanol (100 ml) solution containing the resulting compound (5.18 g), followed by stirring in a hydrogen gas atmosphere at room temperature under normal pressure for 16 hours. The catalyst
30 was removed by filtration, and the resulting filtrate was concentrated under reduced pressure to obtain a pale brown solid (4.0 g).

1-(Bromomethyl)-3-fluorobenzene (2.5 ml) and potassium carbonate (2.8 g) were added to an acetonitrile (100 ml) solution containing the resulting compound (4.0 g), followed by heating at 80°C for 22 hours. The solid matter was removed by filtration, the resulting filtrate was concentrated under reduced pressure, and the
5 residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 8:1 (v/v)) to obtain a colorless solid (5.15 g).

The resulting compound (5.15 g) was dissolved in EtOAc (20 ml), a 4 M hydrogen chloride/EtOAc solution (20 ml) was added thereto, followed by stirring at room temperature for 5 hours. Then, the solvent was evaporated under reduced
10 pressure. The residue was dissolved in water, neutralized with an aqueous 1 M sodium hydroxide solution, and the solid formed was dried to obtain 4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidine (3.70 g).

In the same manner as in Reference Example 29, the compounds of Reference Examples 30 to 36 were obtained.

15 [0059]

Reference Example 37:

Diethyl azodicarboxylate (11 ml, 40% Tol solution) was dropwise added to a THF (30 ml) solution containing tert-butyl 4-hydroxypiperidine-1-carboxylate (4.6 g), triphenylphosphine (6.1 g) and 6-chloro-2-pyridinol (2.0 g) at 0°C, followed by stirring
20 at room temperature for 24 hours. Water was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with an aqueous 1 M sodium hydroxide solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 10:1 (v/v)) to obtain tert-butyl 4-
25 [(6-chloro-2-pyridinyl)oxy]-1-piperidinecarboxylate (3.8 g).

(3-Fluorophenyl)methanol (220 mg) and potassium tert-butoxide (200 mg) were added to a DMF (5 ml) solution containing tert-butyl 4-[(6-chloro-2-pyridinyl)oxy]-1-piperidinecarboxylate (500 mg), followed by heating at 100°C for 30 minutes. Then, (3-fluorophenyl)methanol (220 mg) and potassium tert-butoxide (200
30 mg) were added thereto, followed by heating at 110°C for 30 minutes. Water was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with an aqueous saturated sodium hydrogencarbonate solution, and dried

over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 10:1 (v/v)) to obtain a white solid (420 mg).

The resulting compound (400 mg) was dissolved in EtOAc (5 ml), a 4 M hydrogen chloride/EtOAc solution (3 ml) was added thereto, followed by stirring overnight at room temperature. The precipitated solid was collected by filtration, washed with EtOAc, and dried under reduced pressure to obtain 2-[(3-fluorobenzyl)oxy]-6-(4-piperidinoxy)pyridine hydrochloride (310 mg).

In the same manner as in Reference Example 37, the compound of Reference Example 38 was obtained.

Reference Example 39:

Water (4 ml), sodium carbonate (610 mg) and tetrakis(triphenylphosphine) palladium (110 mg) were added in that order to a Tol (10 ml) solution containing tert-butyl 4-[(6-chloro-2-pyridinyl)oxy]-1-piperidinecarboxylate (500 mg) and [3-(aminocarbonyl)phenyl]boronic acid (320 mg), followed by heating overnight at 100°C. The reaction solution was cooled and diluted with EtOAc. The organic layer was washed with an aqueous solution of anhydrous sodium hydrogencarbonate, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:2 (v/v)) to obtain a pale yellow powder (590 mg).

The resulting compound (590 mg) was dissolved in EtOAc (5 ml), and a 4 M hydrogen chloride/EtOAc solution (5 ml) was added thereto, followed by stirring overnight at room temperature. The precipitated solid was collected by filtration, washed with EtOAc, and dried under reduced pressure to obtain 3-[6-(4-piperidinyloxy)-2-pyridinyl]benzamide hydrochloride (440 mg).

[0060]

Reference Example 40:

TEA (4.6 ml) and methanesulfonyl chloride (2.0 ml) were dropwise added to a methylene chloride (80 ml) solution containing tert-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (5.0 g) at 0°C, followed by stirring at room temperature for 3 hours. An aqueous sodium hydrogencarbonate solution and methanol were added to the reaction solution, followed by stirring at room temperature

for 30 minutes. This was extracted with chloroform, and the organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 10:1 (v/v)) to obtain a colorless solid (6.1 g).

Sodium hydride (541 mg, 60% in oil) was added to a DMF (80 ml) solution containing the resulting compound (2.0 g) and phenylpropanol (1.3 g) at 0°C, followed by heating at 100°C for 20 hours. The reaction solution was cooled, water was added thereto, followed by extraction with EtOAc. This was washed with an aqueous 1 M hydrochloric acid solution, an aqueous saturated sodium hydrogencarbonate solution and saturated brine in that order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 20:1 (v/v)) to obtain a yellow oil (1.96 g).

The resulting compound (1.96 g) was dissolved in EtOAc (5 ml), and a 4 M hydrogen chloride/EtOAc solution (10 ml) was added thereto, followed by stirring at room temperature for 2 hours. The solid formed was collected by filtration and dried to obtain 4-[2-(3-phenylpropoxy)ethyl]piperidine hydrochloride (1.55 g).

[0061]

Reference Example 41:

TEA (2.30 ml) and methanesulfonyl chloride (1.22 ml) were dropwise added to a THF (40 ml) solution containing tert-butyl 4-hydroxypiperidine-1-carboxylate (3.02 g) at 0°C, followed by stirring at room temperature for 1 hour. EtOAc (50 ml) and water (50 ml) were added to the reaction solution. The organic layer was washed with aqueous 5% citric acid solution, an aqueous saturated sodium hydrogencarbonate solution and saturated brine in that order, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain a pale orange oil. The resulting oil was dissolved in DMA (25 ml), and cesium carbonate (5.38 g) and 4-sulfanyphenol (1.89 g) were added thereto, followed by heating at 50°C for 2 hours.

The reaction solution was cooled, water was added thereto, followed by extraction with EtOAc. The organic layer was washed with an aqueous 1 M hydrochloric acid solution and saturated brine in that order, and dried over anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 4:1 (v/v)) to obtain tert-butyl 4-[(4-hydroxyphenyl)sulfanyl]piperidine-1-carboxylate (3.40 g) as colorless powder.

5 1-(Bromomethyl)-3-fluorobenzene (0.436 ml) and potassium carbonate (670 mg) were added to an acetonitrile (15 ml) solution containing tert-butyl 4-[(4-hydroxyphenyl)sulfanyl]piperidine-1-carboxylate (1.00 g), followed by heating at 80°C for 2 hours. The reaction solution was cooled, saturated brine was added thereto, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 8:1 (v/v)) to obtain tert-butyl 4-({4-[(3-fluorobenzyl)oxy]phenyl}sulfanyl)piperidine-1-carboxylate (1.50 g) as colorless powder.

10 Tert-butyl 4-({4-[(3-fluorobenzyl)oxy]phenyl}sulfanyl)piperidine-1-carboxylate (501 mg) was dissolved in EtOAc (5 ml), and a 4 M hydrogen chloride/EtOAc solution (3 ml) was added thereto, followed by stirring at room temperature for 3 hours. Then, the solvent was evaporated under reduced pressure. The residue was dissolved in water, neutralized with an aqueous 1 M sodium hydroxide solution, followed by extraction with chloroform. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to obtain 4-({4-[(3-fluorobenzyl)oxy]phenyl}sulfanyl)piperidine (328 mg).

15 In the same manner as in Reference Example 41, the compound of Reference Example 42 was obtained.

20 Reference Example 43:

25 mCPBA (1.64 g) was added to a chloroform (20 ml) solution containing tert-butyl 4-({4-[(3-fluorobenzyl)oxy]phenyl}sulfanyl)piperidine-1-carboxylate (1.50 g) obtained in the method of Reference Example 41, at 0°C, followed by stirring at room temperature for 17 hours. The solid was removed by filtration, and an aqueous 10% sodium sulfate solution was added to the filtrate, followed by extraction with chloroform. The organic layer was washed with an aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous sodium sulfate. The solvent

was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 2:1 (v/v)) to obtain a colorless powder (1.58 g). The resulting powder (1.56 g) was dissolved in EtOAc (10 ml), a 4 M hydrogen chloride/EtOAc solution (8 ml) was added thereto, followed by stirring at room temperature for 2 hours. Then, the solid was collected by filtration and washed with EtOAc to obtain 4-({4-[(3-fluorobenzyl)oxy]phenyl}sulfonyl)piperidine hydrochloride (1.13 g) as colorless powder.

In the same manner as in Reference Example 43, the compounds of Reference Examples 44 to 46 were obtained.

Reference Example 47:

A THF (5 ml) solution of tert-butyl 4-[(4-hydroxyphenyl)sulfonyl]piperidine-1-carboxylate (495 mg) obtained in the method of Reference Example 41 and diethyl azodicarboxylate (1.04 g, 40% Tol solution) were dropwise added to a THF (5 ml) solution containing cyclohexylmethanol and triphenylphosphine (629 mg), at 0°C, followed by stirring at room temperature for 24 hours. Water (40 ml) was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with an aqueous 1 M sodium hydroxide solution and saturated brine in that order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 9:1 (v/v)) to obtain tert-butyl 4-{{4-(cyclohexylmethoxy)phenyl}sulfonyl}piperidine-1-carboxylate (744 mg) as pale yellow oil.

The resulting tert-butyl 4-{{4-(cyclohexylmethoxy)phenyl}sulfonyl}piperidine-1-carboxylate (635 mg) was dissolved in EtOAc (7 ml), and a 4 M hydrogen chloride/EtOAc solution (3.6 ml) was added thereto, followed by stirring at room temperature for 6 hours. The solid was collected by filtration and washed with EtOAc to obtain 4-{{4-(cyclohexylmethoxy)phenyl}sulfonyl}piperidine hydrochloride (485 mg) as colorless powder.

In the same manner as in Reference Example 47, the compound of Reference Example 48 was obtained.

Reference Example 49:

Sodium hydride (355 mg, 60% in oil) and benzyl bromide (1.0 ml) were added to a THF (40 ml) solution containing tert-butyl 4-hydroxypiperidine-1-carboxylate (1.5 g), followed by heating at 60°C for 13 hours. The reaction solution was cooled, water was added thereto, followed by extraction with EtOAc. This was washed with an aqueous 1 M hydrochloric acid solution, an aqueous saturated sodium hydrogencarbonate solution and saturated brine in that order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 10:1 (v/v)) to obtain a colorless oil (1.91 g).

The resulting compound (1.8 g) was dissolved in EtOAc (5 ml), and a 4 M hydrogen chloride/EtOAc solution (15 ml) was added thereto, followed by stirring at room temperature for 3 hours. The reaction solution was diluted with isopropyl ether, and the solid formed was collected by filtration and dried to obtain 4-(benzyloxy)piperidine hydrochloride (1.32 g).

In the same manner as in Reference Example 49, the compounds of Reference Examples 50 to 53 were obtained.

[0063]

Reference Example 54:

Diethyl azodicarboxylate (2.6 ml, 40% Tol solution) was dropwise added to a THF (10 ml) solution containing (3-fluorophenyl)methanol (730 mg), triphenylphosphine (1.5 g) and 6-chloro-3-pyridinol (500 mg) at 0°C, followed by stirring at room temperature for 24 hours. The reaction solution was diluted with EtOAc. The organic layer was washed with an aqueous saturated sodium hydrogencarbonate solution and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 8:1 (v/v)) to obtain a white solid (810 mg).

Tert-butyl 4-hydroxypiperidine-1-carboxylate (1.0 g) and potassium tert-butoxide (570 mg) were added to a DMF (10 ml) solution containing the resulting white solid (800 mg), followed by heating at 130°C for 1 hour. Then, potassium tert-butoxide (400 mg) was added thereto, followed by further heating at 130°C for 1 hour.

The reaction solution was cooled to room temperature, diluted with EtOAc, washed with an aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent:

5 hexane:EtOAc = 7:1 (v/v)) to obtain a white solid (350 mg).

The resulting compound (345 mg) was dissolved in EtOAc (3 ml), and a 4 M hydrogen chloride/EtOAc solution (2 ml) was added thereto, followed by stirring overnight at room temperature. The solid precipitated was collected by filtration, washed with EtOAc, and dried under reduced pressure to obtain 6-[(3-fluorobenzyl)oxy]-2-(4-piperidinoxy)pyridine hydrochloride (260 mg).

10

Reference Example 55:

[1-(Tert-butoxycarbonyl)piperidin-4-yl]acetic acid (0.60 g) was dissolved in dimethylformamide (12 ml), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.89 g), 1-hydroxybenzotriazole (0.50 g) and benzylamine (0.40 g) were added thereto, followed by stirring at room temperature for 15 hours. Water was added to the reaction solution and stirred for 1 hour. Then, sodium hydrogencarbonate solution was added thereto, followed by extraction with EtOAc. The organic layer was washed with 0.5 M hydrochloric acid and saturated brine in that order. The organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:2 (v/v)) to obtain a colorless powder (0.69 g).

15

20

The resulting compound (0.69 g) was dissolved in EtOAc (10 ml), and a 4 M hydrogen chloride/EtOAc solution (2.2 ml) was added thereto, followed by stirring at room temperature for 20 hours. The reaction solution was concentrated into a dry solid to obtain N-benzyl-2-piperidin-4-ylacetamide hydrochloride (0.62 g).

25

[0064]

Reference Example 56:

Phosphoric acid (7 ml) and diphosphorus pentoxide (14 g) were heated at 150°C for 30 minutes, N-methylbenzene-1,2-diamine (1.3 g) and 4-piperidin-4-ylbutanoic acid hydrochloride (1.5 g) were added thereto, followed by heating at 120°C for 3 hours. The reaction solution was poured into water, neutralized with aqueous

30

sodium hydroxide solution, and then extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform:methanol:aqueous ammonia = 10:1:0.1 (v/v/v)) to obtain 1-methyl-2-(3-piperidin-4-ylpropyl)-1H-benzimidazole (1.61 g).

Reference Example 57 and Reference Example 58:

Potassium tert-butoxide (1.72 g) was added to a THF (30 ml) solution containing [4-(methoxycarbonyl)benzyl](triphenyl)phosphonium bromide (7.51 g) at 0°C, followed by stirring for 1 hour. A THF (20 ml) solution containing tert-butyl 4-formylpiperidine-1-carboxylate (Beilstein Registry No. 7704210, 2.96 g) was dropwise added to the reaction solution at 0°C, followed by stirring for 14 hours. Water was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 9:1 (v/v)) to obtain a yellow oil (3.77 g).

The resulting compound (3.75 g) was dissolved in methanol (20 ml) and THF (10 ml), and an aqueous 1 M sodium hydroxide solution (16.3 ml) was added thereto, followed by stirring at 50°C for 4 hours. The reaction solution was cooled, and the solvent was evaporated under reduced pressure. This was made acidic with 1 M hydrochloric acid added, and the solid precipitated was collected by filtration and washed with water to obtain a pale brown powder (2.82 g).

Ammonium chloride (2.26 g), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (3.24 g), 1-hydroxybenzotriazole (1.14 g) and TEA (5.88 ml) were added to a DMF (30 ml) solution containing the resulting compound (2.80 g), followed by stirring at room temperature for 32 hours. Water was added to the reaction solution, and the solid precipitated was collected by filtration and washed with water to obtain a pale brown powder (2.61 g).

The resulting compound (2.58 g) was dissolved in EtOAc (15 ml), and a 4 M hydrogen chloride/EtOAc solution (15 ml) was added thereto, followed by stirring at room temperature for 8 hours. The solid formed was collected by filtration, washed

with EtOAc, and dried to obtain 4-[(E)-2-piperidin-4-ylvinyl]benzamide hydrochloride (1.92 g) (Reference Example 57).

10% Palladium-carbon (catalytic amount) was added to a methanol (15 ml)/water (5 ml) solution containing 4-[(E)-2-piperidin-4-ylvinyl]benzamide hydrochloride (800 mg), followed by stirring in a hydrogen gas atmosphere at room temperature under normal pressure for 4 hours. The catalyst was removed by filtration, and the resulting filtrate was concentrated under reduced pressure. The resulting solid was recrystallized from ethanol/acetonitrile to obtain 4-(2-piperidin-4-ylethyl)benzamide hydrochloride (451 mg) (Reference Example 58).

[0065]

Reference Example 59:

Sodium triacetoxyborohydride (2.2 g) was added to a dichloromethane (30 ml) solution containing tert-butyl 4-(4-aminophenoxy)-1-piperidinecarboxylate (2.0 g, Beilstein Registry No. 9262581), cyclohexanecarbaldehyde (770 mg) and acetic acid (1.25 g), at 0°C, followed by stirring at room temperature for 2 hours. An aqueous saturated sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with an aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was recrystallized from EtOAc/hexane to obtain a pale brown crystal (2.0 g).

Sodium triacetoxyborohydride (1.1 g) was added to a dichloromethane (20 ml) solution containing the resulting crystal (970 mg), an aqueous 37% formaldehyde solution (0.94 ml) and acetic acid (0.75 g), at 0°C, followed by stirring at room temperature for 2 hours. An aqueous saturated sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with an aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting oil was dissolved in EtOAc (15 ml). A 4 M hydrogen chloride/EtOAc solution (5 ml) was added thereto, followed by stirring overnight at room temperature. The solid precipitated was collected by filtration,

washed with EtOAc, and dried under reduced pressure to obtain N-(cyclohexylmethyl)-N-methyl-4-(4-piperidinyloxy)aniline hydrochloride (820 mg).

Reference Example 60:

In an argon stream atmosphere, tris(dibenzylideneacetone)dipalladium (95 mg) was added to a Tol (10 ml) solution containing benzyl 3-iodophenyl ether (1.1 g), tert-butyl 1-piperazinecarboxylate (640 mg), sodium tert-butoxide (500 mg) and 2-biphenyl(dicyclohexyl)phosphine (70 mg), followed by heating at 80°C for 1 hour. The reaction solution was cooled, diluted with EtOAc, and the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 5:1 (v/v)) to obtain a brown solid (950 mg).

The resulting solid (940 mg) was dissolved in EtOAc (5 ml), and a 4 M hydrogen chloride/EtOAc solution (5 ml) was added thereto, followed by stirring overnight at room temperature. The solid precipitated was collected by filtration, washed with EtOAc, and dried under reduced pressure to obtain 1-[3-(benzyloxy)phenyl]piperazine dihydrochloride (840 mg).

[0066]

Reference Example 61:

Diethyl azodicarboxylate (4.8 ml, 40% Tol solution) was dropwise added to a THF (60 ml) solution containing 4-(benzyloxy)-2-chlorophenol (1.7 g, Beilstein Registry No. 6582932), triphenylphosphine (2.8 g) and tert-butyl 4-hydroxypiperidine-1-carboxylate (2.1 g) at 0°C, followed by stirring at room temperature for 24 hours. The reaction solution was diluted with EtOAc. The organic layer was washed with aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 5:1 (v/v)) to obtain a white solid (2.3 g).

The resulting compound (1.0 g) was dissolved in EtOAc (10 ml), and a 4 M hydrogen chloride/EtOAc solution (10 ml) was added thereto, followed by stirring overnight at room temperature. The solid precipitated was collected by filtration,

washed with EtOAc, and dried under reduced pressure to obtain 4-[4-(benzyloxy)-2-chlorophenoxy]piperidine hydrochloride (690 mg).

Reference Example 62:

Thionyl chloride (10 ml) was dropwise added to a DMF (5 ml) solution of sodium 4-hydroxybenzenesulfonate (1.00 g), followed by heating at 65°C for 3 hours. The reaction solution was cooled and Tol (10 ml) was added thereto. The solvent was evaporated under reduced pressure, water was added, followed by extraction with chloroform. The organic layer was washed with aqueous saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain a colorless solid (587 mg).

At 0°C, an acetonitrile (10 ml) solution of the previously-obtained compound (579 mg) was added to an acetonitrile (10 ml) solution containing 1-tert-butoxycarbonylpiperazine (672 mg) and pyridine (0.58 ml), followed by stirring at room temperature for 2 hours. The solvent was evaporated under reduced pressure, Tol (10 ml) was added thereto and azeotroped. Then, water was added, followed by extraction with EtOAc. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain a colorless solid (0.41 g).

Potassium carbonate (248 mg) was added to an acetonitrile (20 ml) solution containing the resulting compound (0.41 g) and 1-(bromomethyl)-3-fluorobenzene (340 mg), followed by heating at 80°C for 3 hours. The solid was removed through filtration, the resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 5:1 (v/v)) to obtain a colorless solid (469 mg).

The resulting compound (460 mg) was dissolved in a mixed solution of EtOAc (5 ml) and THF (5 ml), and 4 M hydrogen chloride/EtOAc solution (20 ml) was added thereto, followed by stirring at 70°C for 3 hours. Then, the solvent was evaporated under reduced pressure. The residue was dissolved in water, neutralized with an aqueous 1 M sodium hydroxide solution, and the solid formed was dried to obtain 4-{4-[(3-fluorobenzyl)oxy]benzenesulfonyl}piperazine (304 mg).

[0067]

Reference Example 63

Diethyl azodicarboxylate (3.3 ml, 40% Tol solution) was dropwise added to a THF (30 ml) solution containing 4-(benzyloxy)-3-chlorophenol (1.2 g, Beilstein
5 Registry No. 5527577), triphenylphosphine (1.9 g) and tert-butyl 4-hydroxypiperidine-1-carboxylate (1.5 g) at 0°C, followed by stirring at room temperature for 24 hours. The reaction solution was diluted with EtOAc, and the organic layer was washed with an aqueous saturated sodium hydrogencarbonate solution and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the
10 residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 5:1 (v/v)) to obtain a white solid (1.7 g).

The resulting compound (1.6 g) was dissolved in EtOAc (20 ml), and a 4 M hydrogen chloride/EtOAc solution (15 ml) was added thereto, followed by stirring overnight at room temperature. The solid precipitated was collected by filtration,
15 washed with EtOAc, and dried under reduced pressure to obtain 4-[4-(benzyloxy)-3-chlorophenoxy]piperidine hydrochloride (1.3 g).

Reference Example 64:

3-Fluorobenzenesulfonyl chloride (3.2 g) was added to a pyridine (30 ml) solution containing tert-butyl 4-(4-aminophenoxy)-1-piperidinecarboxylate (4.0 g, Beilstein
20 Registry No. 9262581) at 0°C, followed by stirring overnight at room temperature. The solvent was evaporated under reduced pressure, and diluted with chloroform. The organic layer was washed with an aqueous 10% citric acid solution, water and saturated brine in that order, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica
25 gel column chromatography (eluent: chloroform:methanol = 60:1 (v/v)) to obtain a white solid (5.3 g).

Potassium carbonate (280 mg) and methyl iodide (0.28 ml) were added to an acetonitrile (10 ml) solution containing the resulting compound (700 mg), followed by stirring at 50°C for 3 hours. The reaction solution was diluted with EtOAc, the
30 organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the

residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 3:1 (v/v)) to obtain a colorless oil (700 mg).

The resulting oil (700 mg) was dissolved in EtOAc (10 ml), and a 4 M hydrogen chloride/EtOAc solution (5 ml) was added thereto, followed by stirring overnight at room temperature. The solid precipitated was collected by filtration, washed with EtOAc, and dried under reduced pressure to obtain 3-fluoro-N-methyl-N-[4-(4-piperidinyloxy)phenyl]benzenesulfonamide hydrochloride (480 mg).

[0068]

Reference Example 65:

1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (630 mg) and 1-hydroxybenzotriazole (440 mg) were added to a DMF (10 ml) solution containing 1-[(benzyloxy)carbonyl]-4-(tert-butoxycarbonyl)-2-piperidinecarboxylic acid (1.0 g), followed by stirring at room temperature for 1 hour. Then, an aqueous concentrated ammonia (2 ml) was added thereto, followed by stirring at room temperature for 3 hours. Water was added to the reaction solution, and the solid precipitated was collected by filtration, washed with water and dried under reduced pressure to obtain a colorless solid (870 mg).

The resulting solid (860 mg) was dissolved in EtOAc (10 ml), and a 4 M hydrogen chloride/EtOAc solution (5 ml) was added thereto, followed by stirring overnight at room temperature. The precipitated solid was collected by filtration, washed with EtOAc and dried under reduced pressure to obtain benzyl 2-(aminocarbonyl)-1-piperazinecarboxylate hydrochloride (700 mg).

Reference Example 66:

Pyridine (1.62 ml) and 4-nitrophenyl chlorocarbonate (2.22 g) were added to an acetonitrile (20 ml) solution containing methyl 4-(hydroxymethyl)benzoate at 0°C, followed by stirring at room temperature for 2 hours. An aqueous 5% citric acid solution was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with an aqueous saturated hydrogencarbonate solution and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 4:1 (v/v)) to obtain a pale brown powder (2.39 g).

Tert-butyl piperazine-1-carboxylate (1.47 g) was added to an acetonitrile (30 ml) solution containing the resulting compound (2.37 g), followed by stirring at room temperature for 8 hours. The reaction solution was diluted with EtOAc and washed with an aqueous 0.5 M sodium hydroxide solution. The organic layer was washed
5 with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 2:1 (v/v)) to obtain a colorless solid (3.32 g).

[0069]

10 Methanol (0.34 ml) and an aqueous 1 M sodium hydroxide solution (8.52 ml) were added to a THF (30 ml) solution containing the resulting compound (3.30 g), followed by stirring at room temperature for 26 hours. The solvent was evaporated under reduced pressure, an aqueous 1 M hydrochloric acid solution was added to the residue, followed by extraction with chloroform. The organic layer was washed with
15 saturated brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was recrystallized from hexane/EtOAc to obtain a colorless powder (2.37 g).

Ammonium chloride (321 mg), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (767 mg), 1-hydroxybenzotriazole
20 (270 mg) and TEA (0.83 ml) were added to a DMF (10 ml) solution containing the resulting compound (729 mg), followed by stirring at room temperature for 3 hours. Water was added to the reaction solution, and the solid precipitated was collected by filtration, and washed with water to obtain a pale brown powder (722 mg).

The resulting compound (700 mg) was dissolved in EtOAc (6 ml), a 4 M
25 hydrogen chloride/EtOAc solution (4.8 ml) was added thereto, followed by stirring at room temperature for 3 hours. The solid formed was collected by filtration, washed with EtOAc, and dried to obtain 4-(aminocarbonyl)benzyl piperazine-1-carboxylate hydrochloride (541 mg).

Reference Example 67:

30 A THF (5 ml) solution containing methyl 4-hydroxybenzoate (460 mg) and diethyl azodicarboxylate (0.71 ml) was dropwise added to a THF (5 ml) solution containing cyclohexylmethanol (510 mg) and triphenylphosphine (1.18 g) at 0°C,

followed by stirring at room temperature for 24 hours. An aqueous 1 M sodium hydroxide solution (40 ml) was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 4:1 (v/v)) to obtain a colorless solid (930 mg).

An aqueous 1 M sodium hydroxide solution (4.4 ml) was added to a methanol (5 ml)/THF (3 ml) solution containing the resulting compound (920 mg), followed by stirring at 50°C for 6 hours. This was cooled to room temperature, and EtOAc (40 ml) and water (30 ml) were added thereto, followed by stirring. The organic layer was extracted with an aqueous 1 M sodium hydroxide solution. The aqueous layers were combined and made to have a pH of 1 with concentrated hydrochloric acid. Then, the aqueous layer was extracted with chloroform, and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was recrystallized from hexane/EtOAc to obtain 4-(cyclohexylmethoxy)benzoic acid (600 mg).

1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (359 mg) and 1-hydroxybenzotriazole (254 mg) were added to a DMF (10 ml) solution containing the resulting compound (370 mg) and tert-butyl 1-piperazinecarboxylate (350 mg), followed by stirring at room temperature for 12 hours. Water was added to the reaction solution, and the solid precipitated was collected by filtration, washed with water and dried under reduced pressure to obtain a colorless solid (610 mg).

The resulting compound (600 mg) was dissolved in EtOAc (6 ml), and a 4 M hydrogen chloride/EtOAc solution (4 ml) was added thereto, followed by stirring overnight at room temperature. The solid precipitated was collected by filtration, washed with EtOAc and dried under reduced pressure to obtain 1-[4-(cyclohexylmethoxy)benzoyl]piperazine hydrochloride (580 mg).

In the same manner as in Reference Example 67, the compounds of Reference Examples 68 to 72 were obtained.

[0070]

Reference Example 73:

At -70°C, a 1.59 M normal-butyllithium/THF solution (14.6 ml) was added to a 2 M dimethylamine/THF solution (11.6 ml), followed by stirring for 10 minutes.

5 This was warmed to 0°C, and 3-chloro-5-hydroxypyridine (1.00 g) was added thereto, followed by stirring overnight at room temperature. Ethanol (15 ml) was added, and the solvent was evaporated under reduced pressure. Water was added to the residue, followed by extraction with chloroform. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated
10 under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 10:1 (v/v)) to obtain 3-dimethylamino-5-hydroxypyridine (176 mg).

Reference Example 74:

Tris-dibenzylideneacetone palladium (21 mg), 2,2'-bis(diphenylphosphino)-
15 1,1'-binaphthyl (124 mg) and sodium tert-butoxide (160 mg) were added in that order to a Tol (10 ml) solution containing 3-benzyloxy-5-bromopyridine (400 mg) and morpholine (158 mg), followed by heating at 85°C for 4 hours. The solvent was evaporated under reduced pressure, and the residue was purified through silica gel column chromatography (eluent: chloroform:methanol = 20:1 (v/v)) to obtain a
20 colorless oil (372 mg).

10% Palladium-carbon (catalytic amount) was added to an ethanol (20 ml) solution containing the resulting compound (370 mg), and in a hydrogen gas atmosphere, this was stirred at room temperature and under normal pressure for 1.5 hours. The catalyst was removed by filtration, and the resulting filtrate was
25 concentrated under reduced pressure to obtain 5-hydroxy-3-morpholinylpyridine (248 mg).

In the same manner as in Reference Example 74, the compounds of Reference Examples 75 and 76 were obtained.

[0071]

30 Reference Example 77:

Sodium methoxide (393 mg) was added to a methanol (20 ml) solution containing 5-(benzenesulfonyloxy)-2-(bromomethyl)pyridine (Beilstein Registry No.

7430370, 800 mg), followed by stirring at room temperature for 4 hours. Water was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: EtOAc) to obtain 6-(methoxymethyl)pyridin-3-ol (200 mg).

Reference Example 78:

TEA (0.21 ml) and di-tert-butyl dicarbonate (463 mg) were added in that order to a THF (10 ml) solution of 3-benzyloxy-5-aminopyridine (250 mg), followed by heating at 60°C for 3 hours. The solvent was evaporated under reduced pressure, water was added thereto, followed by extraction with EtOAc. The organic layer was washed with an aqueous saturated sodium hydrogencarbonate solution and saturated brine, and then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:1 (v/v)) to obtain a colorless solid (153 mg).

10% Palladium-carbon (catalytic amount) was added to an ethanol (20 ml) solution containing the resulting compound (240 mg), and in a hydrogen gas atmosphere, this was stirred at room temperature under normal pressure for 1.5 hours. The catalyst was removed by filtration, and the resulting filtrate was concentrated under reduced pressure to obtain tert-butyl (5-hydroxypyridin-3-yl)carbamate (167 mg).

[0072]

Reference Example 79:

At 0°C, a THF (10 ml) suspension of sodium hydride (60% oil mixture, 139 mg) was added to a THF (10 ml) solution of methyl diethylphosphonoacetate (732 mg), followed by stirring for 15 minutes. Then, 5-(benzyloxy)nicotinaldehyde (495 mg) was added, followed by stirring at room temperature for 4 hours. Water was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain a colorless solid (680 mg).

10% Palladium-carbon (catalytic amount) was added to an ethanol (20 ml) solution containing the resulting compound (330 mg), and in a hydrogen gas atmosphere, this was stirred at room temperature under normal pressure for 2 hours. The catalyst was removed by filtration, and the resulting filtrate was concentrated
5 under reduced pressure to obtain methyl 3-(5-hydroxypyridin-3-yl)propanoate (150 mg).

Reference Example 80:

At -78°C, a THF (30 ml) solution of methyl 5-(benzyloxy)nicotinate (3.52 g) was added to a THF (100 ml) suspension of lithium aluminium hydride (1.49 g),
10 followed by stirring for 15 minutes and then stirring at room temperature for 2 hours. The reaction solution was cooled to 0°C, and then water (1.49 ml), an aqueous 15% sodium hydroxide solution (1.49 ml) and water (4.47 ml) were added thereto in that order. The solid was removed by filtration, and the resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column
15 chromatography (eluent: chloroform:methanol = 10:1 (v/v)) to obtain a colorless solid (1.41 g).

Tert-butyl bromoacetate (609 mg), tetrabutylammonium hydrogensulfate (35 mg) and an aqueous 50% sodium hydroxide solution (2 ml) were added in that order to a benzene (20 ml) solution containing the resulting compound (450 mg), followed by
20 stirring overnight at room temperature. This was neutralized with an aqueous 1 M hydrochloric acid, followed by extraction with EtOAc. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 6:4 (v/v)) to obtain a colorless oil (576 mg).

10% palladium-carbon (catalytic amount) was added to an ethanol (20 ml) solution containing the resulting compound (570 mg), and in a hydrogen gas atmosphere, this was stirred at room temperature under normal pressure for 1 hour. The catalyst was removed by filtration, and the resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column
25 chromatography (eluent: chloroform:methanol = 15:1 (v/v)) to obtain tert-butyl [(5-hydroxypyridin-3-yl)methoxy]acetate (400 mg).
30

[0073]

Reference Example 81:

Pentamethylbenzene (826 mg) was added to a TFA (10 ml) solution containing methyl (2E)-3-[5-(benzyloxy)pyridin-3-yl]acrylate (300 mg), followed by stirring overnight at 60°C. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 10:1 (v/v)) to obtain tert-butyl (5-hydroxypyridin-3-yl)acetate (180 mg).

Reference Example 82:

Diisopropylethylamine (2.05 ml) and methoxymethyl chloride (0.89 ml) were added in that order to a THF (60 ml) solution of methyl 3-hydroxynicotinate (1.50 g), and then stirred overnight at room temperature. The solvent was evaporated under reduced pressure, water was added thereto, followed by extraction with chloroform. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain a colorless oil (2.01 g).

At -78°C, a THF (20 ml) solution of the resulting compound (1.98 g) was added to a THF (50 ml) suspension of lithium aluminium hydride (838 mg), followed by stirring for 30 minutes and then stirring at room temperature for 2 hours. The reaction solution was cooled to 0°C, and water (0.84 ml), an aqueous 15% sodium hydroxide solution (0.84 ml) and water (2.52 ml) were added thereto in that order. The solid was removed by filtration, and the resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: EtOAc) to obtain a colorless oil (838 mg).

Acetic anhydride (1.39 ml) was added to a pyridine (10 ml) solution containing the resulting compound (828 mg), followed by stirring at room temperature for 1.5 hours. The solvent was evaporated under reduced pressure, Tol (10 ml) was added thereto and azeotroped to obtain a colorless oil (1.01 g).

4 M hydrogen chloride/dioxane solution (3.58 ml) was added to a dioxane (10 ml) solution of the resulting compound (1.01 g), followed by stirring at room temperature for 1 hour. The solvent was evaporated under reduced pressure to obtain (5-hydroxypyridin-3-yl)methyl acetate hydrochloride (973 mg).

[0074]

Reference Example 95:

Triphenylphosphine (2.8 g) was added to a Tol (50 ml) solution of 3-cyanobenzyl bromide (2.0 g), followed by stirring at 80°C for 5 hours. This was cooled to room temperature, and the precipitated solid was collected by filtration, and washed with Tol. This was dried under reduced pressure to obtain (3-cyanobenzyl)(triphenyl)phosphonium bromide (3.4 g).

Under ice cooling, sodium hydride (60% oil, 141 mg) was added to a DMF (20 ml) solution of (3-cyanobenzyl)(triphenyl)phosphonium bromide (1.6 g) and tert-butyl 4-formyl-1-piperidinecarboxylate (0.75 g), followed by stirring overnight at room temperature. The reaction liquid was diluted with EtOAc, washed with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 6:1 (v/v)) to obtain an oil. 10% Palladium-carbon (100 mg) was added to an EtOAc (30 ml) solution of the resulting oil, followed by stirring in a hydrogen stream atmosphere for 2 hours. The catalyst was removed with Celite, and the solvent was concentrated to obtain an oil. The resulting oil was dissolved in EtOAc (10 ml), and 4 M hydrogen chloride/EtOAc solution (5 ml) was added thereto, then stirred at room temperature for 6 hours, and then concentrated. The resulting solid was washed with ether and dried under reduced pressure to obtain 3-[2-(4-piperidinyl)ethyl]benzonitrile hydrochloride (506 mg).

In the same manner as in Reference Example 95, the compounds of Reference Examples 96 to 101 were obtained.

[0075]

Reference Example 102:

Triphenylphosphine (85.8 g) was added to a Tol (400 ml) solution of methyl 3-bromomethylbenzoate (50.0 g), followed by stirring at 80°C for 10 hours. After this was cooled to room temperature, the crystal precipitated was collected by filtration and washed with Tol. This was dried under reduced pressure to obtain (3-methoxycarbonylbenzyl)(triphenyl)phosphonium bromide (107.6 g).

Under ice cooling, potassium tert-butoxide (22.5 g) was added to a DMF (250 ml) solution of (3-methoxycarbonylbenzyl)(triphenyl)phosphonium bromide (84.6

g), followed by stirring at room temperature for 30 minutes. Then, a DMF (50 ml) solution of tert-butyl 4-formyl-1-piperidinecarboxylate (30.6 g) was added to it under ice cooling, and then stirred overnight at room temperature. Acetic acid (11.5 ml) was added to the reaction liquid, followed by stirring at room temperature for 1 hour. Then, this was diluted with EtOAc, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 7:1 (v/v)). The residue was dissolved in EtOAc, activated charcoal was added thereto, followed by stirring at room temperature for 2 hours. Activated charcoal was removed with Celite, and the solvent was evaporated under reduced pressure to obtain a colorless oil.

10% Palladium-carbon (4.58 g) was added to an EtOAc (400 ml) solution of the resulting oil, followed by stirring in a hydrogen stream atmosphere for 2 hours. The catalyst was removed with Celite, and the solvent was concentrated to obtain tert-butyl 4-{2-[3-(methoxycarbonyl)phenyl]ethyl}-1-piperidinecarboxylate (45.4 g).

In the same manner as in Reference Example 102, the compound of Reference Example 103 was obtained.

Reference Example 104:

Aqueous 1 M sodium hydroxide solution (196 ml) was added to a THF (200 ml)/methanol (50 ml) mixed solution of tert-butyl 4-{2-[3-(methoxycarbonyl)phenyl]ethyl}-1-piperidinecarboxylate (45.4 g), followed by stirring at 60°C for 2 hours. The organic solvent was evaporated under reduced pressure, and under ice cooling, 0.5 M hydrochloric acid (400 ml) was added to the residue. The reaction liquid was diluted with EtOAc, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated to obtain 3-{2-[1-(tert-butoxycarbonyl)-4-piperidinyl]ethyl}benzoic acid (43.5 g) was obtained.

In the same manner as in Reference Example 104, the compound of Reference Example 105 was obtained.

[0076]

Reference Example 106:

3-{2-[1-(Tert-butoxycarbonyl)-4-piperidinyl]ethyl}benzoic acid (17.8 g) was dissolved in DMF (200 ml), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide

hydrochloride (15.4 g) and 1-hydroxybenzotriazole (10.8 g) were added thereto, followed by stirring at room temperature for 2 hours. Ammonium chloride (8.57 g) and TEA (22.3 ml) were added to the reaction liquid, followed by stirring overnight at room temperature. An aqueous saturated sodium hydrogencarbonate solution was added to the reaction liquid, and the precipitated crystal was collected by filtration and dried to obtain tert-butyl 4-{2-[3-(aminocarbonyl)phenyl]ethyl}-1-piperidinecarboxylate (10.8 g).

In the same manner as in Reference Example 106, the compounds of Reference Examples 107 to 118 were obtained.

Reference Example 119:

Tert-butyl 4-[2-(4-{[(2-hydroxyethyl)amino]carbonyl}phenyl)ethyl]piperidine-1-carboxylate (280 mg), carbon tetrabromide (247 mg) and 2,6-lutidine (103 μ l) were dissolved in dichloromethane (5.6 ml), and under ice cooling, triphenylphosphine (195 mg) was added thereto, followed by stirring at room temperature for 3 hours. The solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 3:7 (v/v)) to obtain tert-butyl 4-{2-[4-(1-aziridinylcarbonyl)phenyl]ethyl}-1-piperidinecarboxylate (136 mg) as a colorless oil. [0077]

Reference Example 120:

Tert-butyl 4-{2-[3-(aminocarbonyl)phenyl]ethyl}-1-piperidinecarboxylate (13.8 g) was dissolved in EtOAc (200 ml), and 4 M hydrogen chloride/EtOAc solution (130 ml) was added thereto, followed by stirring at room temperature for 4 hours, and then concentrated. Acetonitrile was added to the resulting residue, followed by heating, and the precipitated crystal was collected by filtration, washed with EtOAc, and dried under reduced pressure to obtain 3-[2-(4-piperidinyl)ethyl]benzamide hydrochloride (11.2 g).

In the same manner as in Reference Example 120, the compounds of Reference Examples 121 to 139 were obtained.

Reference Example 140:

In an argon stream atmosphere, sodium carbonate (0.43 g) and tetrakis(triphenylphosphine)palladium (80 mg) were added to a Tol (6 ml)/water (2 ml)

solution of tert-butyl 4-[2-(3-bromophenyl)ethyl]-1-piperidinecarboxylate (0.50 g) and phenylboronic acid (0.20 g), followed by heating with stirring at 100°C for 7 hours. This was cooled to room temperature, diluted with EtOAc, and washed with aqueous saturated sodium hydrogencarbonate solution. This was dried over anhydrous magnesium sulfate, then the solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 10:1 (v/v)) to obtain tert-butyl 4-[2-(3-biphenyl)ethyl]-1-piperidinecarboxylate (0.41 g).

4 M hydrogen chloride/EtOAc (1.5 ml) was added to an EtOAc (4 ml) solution of tert-butyl 4-[2-(3-biphenyl)ethyl]-1-piperidinecarboxylate (0.41 g), followed by stirring overnight at room temperature. The precipitated crystal was collected by filtration, washed with EtOAc/hexane and dried under reduced pressure to obtain 4-[2-(3-biphenyl)ethyl]piperidine hydrochloride (0.31 g).

In the same manner as in Reference Example 140, the compounds of Reference Examples 141 and 142 were obtained.

Reference Example 143:

Under ice cooling, di-tert-butyl dicarbonate (2.6 g) was added to a dichloromethane (50 ml) solution of 4,4'-(1,3-propane-diyl)dipiperidine (5.0 g), followed by stirring overnight at room temperature. The reaction liquid was diluted with chloroform, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (eluent: chloroform:methanol:aqueous concentrated ammonia = 4:1:0.1 (v/v)) to obtain tert-butyl 4-[3-(4-piperidiny)propyl]-1-piperidinecarboxylate (2.2 g).

In an argon atmosphere, sodium tert-butoxide, (0.52 g), tris(dibenzylideneacetone)dipalladium (100 mg) and 2-(dicyclohexylphosphino)biphenyl (76 mg) were added to a Tol (22 ml) solution of 2-chloro-6-methylpyridine (0.56 g) and tert-butyl 4-[3-(4-piperidiny)propyl]-1-piperidinecarboxylate (1.1 g), followed by heating with stirring at 100°C for 1 hour. This was cooled to room temperature, diluted with EtOAc, and washed with aqueous saturated sodium hydrogencarbonate solution. This was dried over anhydrous magnesium sulfate, the solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 10:1 (v/v)) to obtain

tert-butyl 4-{3-[1-(6-methyl-2-pyridinyl)-4-piperidyl]propyl}-1-piperidinecarboxylate (1.3 g).

4 M hydrogen chloride/EtOAc (10 ml) was added to an EtOAc (25 ml) solution of tert-butyl 4-{3-[1-(6-methyl-2-pyridinyl)-4-piperidyl]propyl}-1-piperidinecarboxylate (1.3 g), followed by stirring overnight at room temperature. The reaction liquid was concentrated, then 2-propanol/diethyl ether was added thereto, followed by stirring. The precipitated solid was collected by filtration, and dried under reduced pressure to obtain 2-methyl-6-{4-[3-(4-piperidinyl)propyl]-1-piperidyl}pyridine dihydrochloride (1.1 g).

In the same manner as in Reference Example 143, the compounds of Reference Examples 144 and 145 were obtained.

[0078]

Reference Example 146:

Methanesulfonyl chloride (2.7 ml) was dropwise added to a methylene chloride (200 ml) solution of tert-butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate (8.00 g) and TEA (4.8 ml) at 0°C, followed by stirring overnight at room temperature. The reaction liquid was washed with aqueous saturated sodium hydrogencarbonate solution and saturated brine, then dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: EtOAc:hexane = 1:3 (v/v)) to obtain tert-butyl 4-{3-[(methanesulfonyl)oxy]propyl}piperidine-1-carboxylate (10.1 g).

A DMI (20 ml) suspension of tert-butyl 4-{3-[(methanesulfonyl)oxy]propyl}piperidine-1-carboxylate (1.00 g), 1-piperazin-1-yl-isoquinoline dihydrochloride (980 mg), cesium carbonate (1.02 g) and sodium iodide (467 mg) was stirred at 140°C for 1 hour. EtOAc was added to the reaction liquid, washed with water and aqueous saturated sodium hydrogencarbonate solution in that order, then dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:1 (v/v)) to obtain tert-butyl 4-[3-(4-isoquinolin-1-yl)piperazin-1-yl]propyl]piperidine-1-carboxylate (1.07 g) as a pale yellow oil.

4 M hydrogen chloride/EtOAc solution (5.0 ml) was dropwise added to an EtOAc (15 ml) solution of tert-butyl 4-[3-(4-isoquinolin-1-yl)piperazin-1-

yl)propyl]piperidine-1-carboxylate (1.44 g), followed by stirring overnight. The solvent was evaporated, the solid was washed with EtOAc and collected by filtration to obtain 1-[4-(3-piperidin-4-ylpropyl)piperazin-1-yl]isoquinoline dihydrochloride (1.32 g) as a white solid.

5 In the same manner as in Reference Example 146, the compound of Reference Example 154 was obtained.

Reference Example 147:

10 4-Nitrophenyl chloroformate (7.0 g) was added to a dichloromethane (100 ml) solution of methyl 5-hydroxynicotinate (5.3 g) and diisopropylethylamine (6.1 ml), followed by stirring at room temperature for 1 hour. The reaction liquid was washed with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the resulting solid was washed with EtOAc/hexane and dried under reduced pressure to obtain methyl 5-[(4-nitrophenoxy)carbonyl]oxy}nicotinate (8.4 g).

15 In the same manner as in Reference Example 147, the compound of Reference Example 148 was obtained.

[0079]

Reference Example 151:

20 A DMF (15 ml) solution of 3-{2-[1-(tert-butoxycarbonyl)-4-piperidinyl]ethyl]benzoic acid (1.25 g), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (863 mg) and 1-hydroxybenzotriazole (608 mg) was stirred at room temperature for 1 hour, and then a TEA (1.6 ml) solution of 2-bromoethylamine hydrobromide (2.30 g) was added thereto, followed by stirring overnight. Aqueous saturated sodium hydrogencarbonate solution was added to the
25 reaction liquid, followed by extraction with EtOAc, then washed with saturated brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated to obtain a crude product of tert-butyl 4-[2-(3-[(2-bromoethyl)amino]carbonyl}phenyl)ethyl]piperidine-1-carboxylate.

30 4 M hydrogen chloride/EtOAc solution (5 ml) was added to an EtOAc (15 ml) solution of the crude tert-butyl 4-[2-(3-[(2-bromoethyl)amino]carbonyl}phenyl)ethyl]piperidine-1-carboxylate at room temperature, followed by stirring overnight. The solvent was evaporated under

reduced pressure to obtain N-(2-bromoethyl)-3-(2-piperidin-4-ylethyl)benzamide hydrochloride (1.27 g) as a white solid.

TEA (0.90 ml) was dropwise added to an acetonitrile (30 ml) suspension of N-(2-bromoethyl)-3-(2-piperidin-4-ylethyl)benzamide hydrochloride (1.20 g) and methyl 5-[[[(4-nitrophenoxy)carbonyl]oxy]nicotinate (1.02 g), followed by stirring overnight at room temperature. The reaction solvent was evaporated under reduced pressure, then aqueous saturated sodium hydrogencarbonate solution was added thereto, extracted with EtOAc, and dried over anhydrous magnesium sulfate. This was filtered, the solvent was evaporated, and the residue was purified two times through silica gel column chromatography (basic silica with eluent: hexane:EtOAc = 1:2 (v/v), next neutral silica with eluent: chloroform:methanol = 19:1 (v/v)) to obtain methyl 5-[[[(4-[2-(3-[[[(2-bromoethyl)amino]carbonyl]phenyl)ethyl]piperidin-1-yl]carbonyl]oxy]nicotinate (762 mg) as a white powder.

A DMF (10 ml) suspension of methyl 5-[[[(4-[2-(3-[[[(2-bromoethyl)amino]carbonyl]phenyl)ethyl]piperidin-1-yl]carbonyl]oxy]nicotinate (750 mg), potassium carbonate (300 mg) and potassium iodide (361 mg) was stirred at 80°C for 1 hour. The reaction liquid was left cooled, then EtOAc was added thereto, washed with aqueous saturated sodium hydrogencarbonate solution and saturated brine in that order, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 20:1 (v/v)) to obtain methyl 5-[[[(4-[2-[3-(aziridin-1-ylcarbonyl)phenyl]ethyl]piperidin-1-yl)carbonyl]oxy]nicotinate (630 mg) as a colorless oil.

[0080]

Reference Example 152:

Under ice cooling, diphenylphosphorylazide (540 mg) was added to a Tol solution (10 ml) of 3-{2-[1-(tert-butoxycarbonyl)-4-piperidyl]ethyl]benzoic acid (600 mg) and TEA (0.3 ml), followed by stirring at room temperature for 2 hours. EtOAc was added to the reaction solution, washed with aqueous saturated sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain a colorless oil (630 mg). A Tol solution (10 ml) of the resulting oil (400 mg) was stirred at 110°C

for 1 hour. This was cooled to room temperature, and aqueous 30% ammonia solution (0.2 ml) was added thereto, followed by stirring at room temperature for 15 hours. EtOAc was added to the reaction solution, then washed with aqueous 1 N hydrochloric acid solution and saturated brine in that order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 95:5 (v/v)) to obtain tert-butyl 4-(2-{3-[(aminocarbonyl)amino]phenyl}ethyl)-1-piperidinecarboxylate (227 mg).

4 M hydrogen chloride/EtOAc (4 ml) was added to an EtOAc (9 ml) solution of tert-butyl 4-(2-{3-[(aminocarbonyl)amino]phenyl}ethyl)-1-piperidinecarboxylate (227 mg), followed by stirring at room temperature for 3 hours. The solvent was evaporated under reduced pressure to obtain 1-{3-[2-(4-piperidyl)ethyl]phenyl}urea hydrochloride (185 mg).

Methyl 5-{[(4-nitrophenoxy)carbonyl]oxy}nicotinate (228 mg) was added to an acetonitrile (5 ml) solution of 1-{3-[2-(4-piperidyl)ethyl]phenyl}urea hydrochloride (185 mg) and TEA (0.2 ml), followed by stirring overnight at room temperature. The reaction liquid was diluted with EtOAc, washed with aqueous saturated sodium hydrogencarbonate solution and saturated brine in that order, and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 10:1 (v/v)) to obtain methyl 5-([4-(2-{3-[(aminocarbonyl)amino]phenyl}ethyl)-1-piperidyl]carbonyl]oxy)nicotinate (183 mg).

In the same manner as in Reference Example 152, the compound of Reference Example 153 was obtained.

Reference Example 155:

Tert-butyl 4-ethynylpiperidine-1-carboxylate (12.5 g) and iodobenzene (12.8 g) was dissolved in THF:TEA = 1:1 (v/v) mixed solvent (125 ml), then at room temperature, copper iodide (455 mg) and palladium tetrakis(triphenyl)phosphine complex (1.38 g) were added thereto in that order, followed by stirring overnight at room temperature. The solvent was evaporated, EtOAc was added to it, and washed with aqueous 1 M hydrochloric acid solution, water and saturated brine in that order. This was dried over magnesium sulfate, and the solvent was evaporated to obtain a

light brown oil. This was purified by silica gel column chromatography (eluent: hexane:EtOAc = 19:1 (v/v)) to obtain tert-butyl 4-(phenylethynyl)piperidine-1-carboxylate (15.5 g) as a light brown oil.

4 M hydrogen chloride/EtOAc solution (70 ml) was added to tert-butyl 4-(phenylethynyl)piperidine-1-carboxylate (7.0 g), followed by stirring at room temperature for 30 minutes. The solvent was evaporated to obtain 4-(phenylethynyl)piperidine hydrochloride (5.4 g) as a white powder.

[0081]

Example 1:

3-Hydroxypyridine (400 mg), TEA (1.17 ml) and DMAP (catalytic amount) were added in that order to a THF (10 ml) solution containing piperidine-1-carbonyl chloride (745 mg), and then heated at 60°C for 5 hours. The reaction solution was cooled, then water (3 ml) was added thereto, and extracted with EtOAc. The extract was washed with water, and then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:1 (v/v)) to obtain a colorless oil. The resulting oil was dissolved in ethanol, and an ethanol solution of oxalic acid (378 mg) added thereto to obtain a colorless powder. This was recrystallized from hexane/ethanol to obtain (pyridin-3-yl) piperidine-1-carboxylate oxalate (761 mg).

Example 2:

A methylene chloride (20 ml) solution containing 3-hydroxypyridine (568 mg) and pyridine (724 μ l) was dropwise added to a methylene chloride (25 ml) solution containing triphosgene (590 mg), followed by stirring at room temperature for 1 hour. The solvent was evaporated under reduced pressure, the residue was dissolved in pyridine (30 ml), then the compound (1.2 g) obtained in Reference Example 22 was added thereto, followed by heating at 70°C for 4 hours. The reaction solution was concentrated under reduced pressure, then chloroform and aqueous sodium hydrogencarbonate solution was added thereto, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:2 (v/v)) to obtain a colorless powder. This was recrystallized from

hexane/EtOAc to obtain (pyridin-3-yl) 4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidine-1-carboxylate (861 mg).

In the same manner as in Example 2, the compounds of Examples 3 to 118, 389 to 391, 416 and 417 and Reference Examples 83 to 93 were obtained.

5 [0082]

Example 119:

A methylene chloride (20 ml) solution containing 3-hydroxypyridine (1.43 g) and pyridine (1.46 ml) was dropwise added to a methylene chloride (30 ml) solution containing triphosgene (1.48 g), followed by stirring at room temperature for 1 hour.

10 A methylene chloride (5 ml) solution containing tert-butyl 1-piperazinecarboxylate (2.0 g) and pyridine (0.97 ml) was dropwise added to the reaction solution, then pyridine (20 ml) was added thereto, followed by heating at 70°C for 4 hours. The reaction solution was concentrated under reduced pressure, diluted with EtOAc, and the organic layer was washed with aqueous saturated sodium hydrogencarbonate solution, and then
15 dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified through basic silica gel column chromatography (eluent: hexane:EtOAc = 4:1 (v/v)) to obtain a colorless solid (3.0 g).

The resulting compound (3.0 g) was dissolved in EtOAc (20 ml)/2-propanol (10 ml), then 4 M hydrogen chloride/EtOAc solution (10 ml) was added thereto,
20 followed by stirring overnight at room temperature. The reaction solution was concentrated under reduced pressure, and the resulting solid was washed with EtOAc and dried under reduced pressure to obtain 3-pyridyl 1-piperazinecarboxylate dihydrochloride (2.66 g).

1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (150 mg), 1-
25 hydroxybenzotriazole (110 mg) and diisopropylethylamine (0.23 ml) were added to a DMF (5 ml) solution containing the resulting compound (190 mg) and 4-(cyclooctylmethoxy)benzoic acid (176 mg) prepared from cyclooctylmethanol with reference to Reference Example 70, followed by stirring overnight at room temperature. The reaction solution was diluted with EtOAc, the organic layer was
30 washed with aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and

the residue was recrystallized from EtOAc/hexane to obtain 3-pyridyl 4-[4-(cyclooctylmethoxy)benzoyl]-1-piperazinecarboxylate (240 mg).

In the same manner as in Example 119, the compounds of Examples 120 to 136 were obtained.

[0083]

Example 137:

Potassium tert-butoxide (810 mg) was added to a DMF (10 ml) solution containing 6-chloronicotinonitrile (1.0 g) and 3-chlorobenzyl alcohol (1.0 g), followed by stirring overnight at room temperature. Water was added to the reaction solution, and the precipitated solid was collected by filtration, washed with water and hexane in that order, and dried under reduced pressure to obtain a brown solid (1.3 g).

An aqueous 5 M sodium hydroxide solution (10 ml) was added to an ethanol (10 ml) solution containing the resulting compound (1.3 g), followed by stirring at 100°C for 4 hours. After this was cooled to room temperature, 1 N hydrochloric acid (56 ml) was added thereto, and the precipitated solid was collected by filtration, washed with water and dried under reduced pressure to obtain a colorless solid (0.82 g).

1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (150 mg), 1-hydroxybenzotriazole (110 mg) and diisopropylethylamine (0.23 ml) were added to a DMF (5 ml) solution containing the resulting compound (176 mg) and 3-pyridyl 1-piperazinecarboxylate dihydrochloride (166 mg), followed by stirring overnight at room temperature. The reaction solution was diluted with EtOAc, the organic layer was washed with aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified through basic silica gel column chromatography (eluent: hexane:EtOAc = 1:2 (v/v)) to obtain a colorless oil (140 mg).

Oxalic acid (35 mg) was added to a 2-propanol solution containing the resulting compound (140 mg), followed by stirring for 30 minutes. The precipitated solid was collected by filtration, washed with 2-propanol/hexane, and dried under reduced pressure to obtain 3-pyridyl 4-({6-[(3-chlorobenzyl)oxy]-3-pyridyl}carbonyl)-1-piperazinecarboxylate 0.5-oxalate (120 mg).

In the same manner as in Example 137, the compound of Example 138 was obtained.

[0084]

Example 139:

5 Potassium carbonate (1.04 g) and ethyl bromoacetate (0.610 ml) were added to an acetonitrile (15 ml) solution containing 4-hydroxybenzamide (686 mg), followed by heating at 80°C for 2 hours. The reaction solution was cooled, water (45 ml) was added thereto, and the precipitated solid was collected by filtration, washed with water and dried to obtain ethyl [4-(aminocarbonyl)phenoxy]acetate (893 mg) as pale brown
10 powder.

The resulting compound (870 mg) was dissolved in THF (10 ml), and ethanol (0.274 ml) and an aqueous 1 M sodium hydroxide solution (4.68 ml) were added thereto, followed by stirring at room temperature for 4 hours. The reaction solution was concentrated under reduced pressure, acidified with an aqueous 1 M
15 hydrochloric acid solution, and the precipitated solid was collected by filtration and dried to obtain a pale brown powder [4-(aminocarbonyl)phenoxy]acetic acid (714 mg).

TEA (0.251 ml), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (259 mg), 1-hydroxybenzotriazole (122 mg) and the above-produced compound [4-(aminocarbonyl)phenoxy]acetic acid (184 mg) were added to a DMF (5
20 ml) solution containing 3-pyridyl 1-piperidinecarboxylate dihydrochloride (252 mg) obtained in the method of Example 121, followed by stirring at room temperature for 5 hours. An aqueous saturated sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced
25 pressure, the residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 95:5 (v/v)), and the resulting solid was recrystallized from EtOAc/acetonitrile to obtain pyridin-3-yl 4-{[4-(aminocarbonyl)phenoxy]acetyl}piperidine-1-carboxylate (274 mg).

In the same manner as in Example 139, the compounds of Examples 140 and
30 141 were obtained.

Example 142:

TEA (0.23 ml) and benzenesulfonyl chloride (0.075 ml) were added to a dichloromethane (5 ml) solution containing 3-pyridyl 1-piperazinecarboxylate dihydrochloride (150 mg), followed by stirring overnight at room temperature. The reaction solution was diluted with chloroform, the organic layer was washed with aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (eluent: chloroform), and the resulting solid was recrystallized from 2-propanol to obtain 3-pyridyl 4-(phenylsulfonyl)-1-piperazinecarboxylate (130 mg).

In the same manner as in Example 142, the compound of Example 143 was obtained.

[0085]

Example 144:

Benzyl chloroformate (91 mg) was added to a pyridine (3 ml) solution containing 3-pyridyl 1-piperazinecarboxylate dihydrochloride (150 mg), followed by stirring at room temperature for 12 hours. The reaction solution was concentrated under reduced pressure, diluted with EtOAc, and the organic layer was washed with aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, the residue was diluted with 2-propanol (3 ml), and toluenesulfonic acid hydrate (100 mg) was added thereto, followed by stirring. The crystal precipitated was collected by filtration and recrystallized from 2-propanol to obtain benzyl 3-pyridyl 1,4-piperazinedicarboxylate tosylate (98 mg).

In the same manner as in Example 144, the compounds of Examples 145 and 146 were obtained.

[0086]

Example 147:

10% Palladium-carbon (catalytic amount) was added to a THF (20 ml)/2-propanol (20 ml) solution containing 3-pyridyl 4-[(4-benzyloxy)benzoyl]-1-piperazinecarboxylate (1.3 g), and in a hydrogen gas atmosphere, this was stirred at room temperature under normal pressure for 12 hours. The catalyst was removed by

filtration, the filtrate was concentrated under reduced pressure, and the resulting solid was recrystallized from EtOAc/hexane to obtain 3-pyridyl 4-(4-hydroxybenzoyl)-1-piperazinecarboxylate (950 mg).

A THF (5 ml) solution containing 3-pyridyl 4-(4-hydroxybenzoyl)-1-piperazinecarboxylate (300 mg) and diethyl azodicarboxylate (0.62 ml, 40% Tol solution) was dropwise added to a THF (5 ml) solution containing 3-chlorobenzyl alcohol (200 mg) and triphenylphosphine (360 mg), at 0°C, followed by stirring at room temperature for 3 days. The reaction solution was diluted with chloroform, washed with an aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 95:5 (v/v)), and the resulting solid was recrystallized from 2-propanol to obtain 3-pyridyl 4-{4-[(3-chlorobenzoyl)oxy]benzyl}-1-piperazinecarboxylate (260 mg).

In the same manner as in Example 147, the compounds of Examples 148 to 166 were obtained.

[0087]

Example 167:

Potassium carbonate (270 mg) was added to an acetonitrile (10 ml) solution containing 3-pyridyl 4-(4-hydroxybenzoyl)-1-piperazinecarboxylate (530 mg) and methyl 3-(bromomethyl)benzoate (450 mg), followed by stirring at 80°C for 1 hour. Water was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:4 (v/v)) to obtain a colorless solid (470 mg).

The resulting solid (100 mg) was recrystallized from EtOAc to obtain 3-pyridyl 4-(4-{[3-(methoxycarbonyl)benzyl]oxy}benzoyl)-1-piperazinecarboxylate (88 mg).

Example 168:

4-Ethyl 1-pyridin-3-yl piperidine-1,4-dicarboxylate (0.732 g) was dissolved in THF (15 ml) and ethanol (8.0 ml), and under ice cooling, an aqueous 1 M sodium

hydroxide solution (3.9 ml) was dropwise added thereto. This was stirred at room temperature for 2 hours, and neutralized with 1 M hydrochloric acid (0.5 ml). The reaction liquid was concentrated under reduced pressure, methanol was added to the residue, and the precipitated salt was removed through suction filtration. The filtrate
5 was concentrated to obtain 1-[(pyridin-3-yloxy)carbonyl]piperidine-4-carboxylic acid (0.727 g) as a colorless solid.

The resulting compound (0.60 g) was dissolved in dimethylformamide (10 ml), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.93 g), 1-hydroxybenzotriazole (0.51 g) and cyclohexanemethylamine (0.43 g) were added
10 thereto, followed by stirring at room temperature for 15 hours. Water was added to the reaction solution, followed by further stirring for 1 hour. Then, sodium hydrogencarbonate solution was added thereto, followed by Extraction with EtOAc. The organic layer was washed with 0.5 M hydrochloric acid and saturated brine in that order. The organic layer was dried over anhydrous magnesium sulfate, the solvent
15 was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:4 (v/v)) to obtain a colorless powder (0.69 g). This was recrystallized from ethanol and hexane to obtain (pyridin-3-yl) 4-{[(cyclohexylmethyl)amino]carbonyl}piperidine-1-carboxylate (261 mg).

In the same manner as in Example 168, the compounds of Examples 169 to
20 192, 383 to 388 and Reference Example 94 were obtained.
[0088]

Example 193:

3-Pyridinyl chlorocarbonate (330 mg) was added to a pyridine (10 ml) solution containing 1-benzyl 2-methyl-1,2-piperazinedicarboxylate (660 mg, Beilstein
25 Registry No. 4236331), followed by stirring at 80°C for 7 hours. The reaction solution was concentrated under reduced pressure, diluted with chloroform, and the organic layer was washed with aqueous saturated sodium hydrogencarbonate solution and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified through basic silica gel column
30 chromatography (eluent: hexane:EtOAc = 1:1 (v/v)) to obtain a colorless oil (700 mg).

An aqueous 1 M sodium hydroxide solution (1.2 ml) was added to a THF (5 ml) solution containing the resulting compound (430 mg), followed by stirring at 50°C

for 3 hours. Aqueous 1 M sodium hydroxide solution (0.8 ml) was added thereto, and further heated at 50°C for 1 hours, then cooled to room temperature, and 1 N hydrochloric acid (2 ml) was added thereto. The reaction solution was extracted with EtOAc, the organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the precipitated solid was washed with EtOAc/hexane, and dried under reduced pressure to obtain 1-[(benzyloxy)carbonyl]-4-[(3-pyridyloxy)carbonyl]-2-piperadinecarboxylic acid (140 mg).

In the same manner as in Example 193, the compounds of Examples 194 and 195 were obtained.

Example 196:

Pyridin-3-yl 4-([2-(methylamino)phenyl]amino)carbonyl)piperidine-1-carboxylate (0.41 g) was dissolved in acetic acid (10 ml), followed by heating under reflux for 2 hours. The solvent was evaporated, and the residue was recrystallized from methanol and diethyl ether to obtain (pyridin-3-yl) 4-(1-methyl-1H-benzimidazol-2-yl)piperidine-1-carboxylate (307 mg).

[0089]

Example 197:

Pyridin-3-yl 4-[(tert-butoxycarbonyl)amino]piperidine-1-carboxylate (0.249 g) was dissolved in THF (5.0 ml), and under ice cooling, 4 M hydrogen chloride/EtOAc solution (2.10 ml) was added thereto, followed by stirring at room temperature for 24 hours. The reaction solution was concentrated to dryness to obtain pyridin-3-yl 4-aminopiperidine-1-carboxylate dihydrochloride (0.280 g).

The resulting compound (0.28 g) was dissolved in dimethylformamide (10 ml), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.28 g), 1-hydroxybenzotriazole (0.16 g), TEA (0.54 ml) and 6-phenylhexanoic acid (0.18 g) were added thereto, followed by stirring at room temperature for 15 hours. Water was added to the reaction solution and further stirred for 1 hour. Then, sodium hydrogencarbonate solution was added thereto, followed by extraction with EtOAc.

The organic layer was washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: EtOAc) to

obtain a colorless powder. This was recrystallized from methanol and diethyl ether to obtain (pyridin-3-yl) 4-[(6-phenylhexanoyl)amino]piperidine-1-carboxylate (108 mg).

Example 198:

10% Palladium-carbon (catalytic amount) was added to a THF (75 ml)/2-propanol (75 ml) solution containing 3-pyridyl 4-[3-(benzyloxy)phenoxy]-1-piperidinecarboxylate (4.0 g), and in a hydrogen gas atmosphere, this was stirred at room temperature under normal pressure for 24 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure, and the resulting solid was washed with EtOAc/hexane, and dried under reduced pressure to obtain 3-pyridyl 4-(3-hydroxyphenoxy)-1-piperidinecarboxylate (2.2 g).

Example 199:

10% Palladium-carbon (catalytic amount) was added to a THF (75 ml)/2-propanol (75 ml) solution containing 3-pyridyl 4-[4-(benzyloxy)phenoxy]-1-piperidinecarboxylate (3.7 g), and in a hydrogen gas atmosphere, this was stirred at room temperature under normal pressure for 24 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure, and the resulting solid was washed with EtOAc/hexane, and dried under reduced pressure to obtain 3-pyridyl 4-(4-hydroxyphenoxy)-1-piperidinecarboxylate (2.4 g).

Example 200:

Diethyl azodicarboxylate (0.35 ml, 40% Tol solution) was dropwise added to a THF (5 ml) solution containing 3-pyridyl 4-(3-hydroxyphenoxy)-1-piperidinecarboxylate (160 mg), cyclohexylmethanol (87 mg) and triphenylphosphine (200 mg), at 0°C, followed by stirring at room temperature for 24 hours. The reaction solution was diluted with chloroform, washed with aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:1 (v/v)). The resulting oil was dissolved in EtOAc (5 ml), 4 M hydrogen chloride/EtOAc solution (1 ml) was added thereto, followed by stirring at room temperature. The solvent was evaporated under reduced pressure, and the precipitated solid was washed with EtOAc/2-propanol and dried under reduced pressure to obtain 3-pyridyl 4-[3-(cyclohexylmethoxy)phenoxy]-1-piperidinecarboxylate hydrochloride (94 mg).

In the same manner as in Example 200, the compounds of Examples 201 to 205 were obtained.

[0090]

Example 206:

Diethyl azodicarboxylate (0.35 ml, 40% Tol solution) was dropwise added to a THF (5 ml) solution containing 3-pyridyl 4-(4-hydroxyphenoxy)-1-piperidinecarboxylate (160 mg), 3-chlorobenzyl alcohol (110 mg) and triphenylphosphine (200 mg) at 0°C, followed by stirring at room temperature for 24 hours. The reaction solution was diluted with chloroform, washed with aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:3 (v/v)). The resulting oil was dissolved in EtOAc (5 ml), and 4 M hydrogen chloride/EtOAc solution (1 ml) was added thereto, followed by stirring at room temperature. The solvent was evaporated under reduced pressure, and the precipitated solid was recrystallized from EtOAc/2-propanol to obtain 3-pyridyl 4-{4-[(3-chlorobenzyl)oxy]phenoxy}-1-piperidinecarboxylate hydrochloride (45 mg).

In the same manner as in Example 206, the compounds of Examples 207 to 212 were obtained.

Example 213:

10% Palladium-carbon (catalytic amount) was added to an ethanol (100 ml) solution containing methyl 5-[(4-[4-(benzyloxy)phenoxy]piperidin-1-yl)carbonyl]oxy]nicotinate, and in a hydrogen gas atmosphere, this was stirred overnight at room temperature under normal pressure. The catalyst was removed by filtration, the resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 15:1 (v/v)) to obtain a colorless oil (1.08 g).

2.2 M diethyl azodicarboxylate (1.01 ml) and triphenylphosphine (581 mg) were added to a THF (20 ml) solution containing the resulting compound (450 mg) and 3-cyclohexyl-1-propanol (315 mg), followed by heating at 50°C for 22 hours. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with saturated brine and dried over anhydrous magnesium

sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 2:1 (v/v)) to obtain methyl 5-[(4-{4-[(3-cyclohexylpropoxy)phenoxy]piperidin-1-yl}carbonyl)oxy]nicotinate (242 mg).

In the same manner as in Example 213, the compounds of Examples 214 to 216 were obtained.

Example 217:

10% Palladium-carbon (catalytic amount) was added to a THF (10 ml) solution containing 5-[(4-{4-(benzyloxy)phenoxy]piperidin-1-yl}carbonyl)oxy]nicotinic acid (200 mg), and in a hydrogen gas atmosphere, this was stirred at room temperature under normal pressure for 3 hours. The catalyst was removed by filtration, and the resulting filtrate was concentrated under reduced pressure to obtain 5-[(4-{4-(hydroxy)phenoxy]piperidin-1-yl}carbonyl)oxy]nicotinic acid (55 mg).

[0091]

Example 218:

The compound (4.0 g) of Example 29, obtained in the same method as in Example 2, was dissolved in THF (30 ml) and methanol (15 ml), and under ice cooling, an aqueous 1 M sodium hydroxide solution (12 ml) was dropwise added thereto. This was stirred at room temperature for 30 minutes, and then under ice cooling, this was neutralized with 1 M hydrochloric acid (12 ml). The colorless solid precipitated was collected by filtration to obtain 5-[(4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidin-1-yl)carbonyl]oxy]nicotinic acid (3.52 g).

In the same manner as in Example 218, the compounds of Examples 219 to 224 and Examples 226 to 243 were obtained.

Example 225:

A methylene chloride (30 ml) solution containing methyl 5-hydroxynicotinate (2.20 g) and pyridine (4 ml) was dropwise added to a methylene chloride (50 ml) solution containing triphosgene (1.56 g), followed by stirring at room temperature for 1 hour. The solvent was evaporated under reduced pressure, the residue was dissolved in pyridine (50 ml), and 4-(2-phenylethyl)piperidine hydrochloride (2.70 g) was added thereto, followed by heating overnight at 80°C.

The reaction solution was concentrated under reduced pressure, then EtOAc and an aqueous sodium hydrogencarbonate solution were added thereto. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:1 (v/v)) to obtain a colorless powder. This was recrystallized from hexane/EtOAc to obtain methyl 5-({[4-(2-phenylethyl)piperidin-1-yl]carbonyl}oxy)nicotinate (3.95 g).

Methyl 5-({[4-(2-phenylethyl)piperidin-1-yl]carbonyl}oxy)nicotinate (3.95 g) was dissolved in THF (32 ml) and methanol (16 ml), and under ice cooling, aqueous 1 M sodium hydroxide solution (16 ml) was dropwise added thereto. This was stirred at room temperature for 30 minutes, and under ice cooling, this was neutralized with 1 M hydrochloric acid (16 ml). The colorless solid precipitated was collected by filtration, and recrystallized from methanol/water to obtain 5-({[4-(2-phenylethyl)piperidin-1-yl]carbonyl}oxy)nicotinic acid (3.70 g).

Example 244:

The compound of Example 219, 5-{{[4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidin-1-yl]carbonyl}oxy}nicotinic acid (0.50 g) was dissolved in DMF (8.0 ml), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.38 g), 1-hydroxybenzotriazole (0.22 g) and glycine tert-butyl ester (0.21 g) were added thereto, followed by stirring at room temperature for 15 hours. Water was added to the reaction solution, followed by stirring for 1 hours. Then, sodium hydrogencarbonate solution was added thereto, followed by extraction with EtOAc. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:1 (v/v)) to obtain a colorless oil (0.444 g).

The resulting compound (0.444 g) was dissolved in methylene chloride (5.0 ml), and under ice cooling, TFA (1.15 ml) was added thereto. This was stirred at that temperature for 24 hours, and then the reaction liquid was concentrated to obtain a yellow solid. This was recrystallized from ethanol and diethyl ether to obtain {{[5-{{[4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidin-1-yl]carbonyl}oxy}pyridin-3-yl]carbonyl}amino}acetic acid (348 mg).

According to the amidation as in Example 244, the compounds of Examples 245 to 257 were obtained.

[0092]

Example 258:

Water (4 ml), sodium carbonate (337 mg) and tetrakis(triphenylphosphine) palladium (115 mg) were added in that order to a dimethoxyethane (12 ml) solution containing the compound (400 mg) of Example 54 and [3-(aminocarbonyl)phenyl]boronic acid (176 mg), followed by heating at 80°C for 5 hours. The reaction solution was cooled and diluted with EtOAc. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:5 (v/v)) to obtain 5-[3-(aminocarbonyl)phenyl]pyridin-3-yl-4-benzylpiperidine-1-carboxylate (205 mg).

In the same manner as in Example 258, the compounds of Examples 259, 265, 266 and 399 were obtained.

Example 260:

A 4 M hydrogen chloride/dioxane solution (1.8 ml) was added to a THF (10 ml) solution containing 5-[(tert-butoxycarbonyl)amino]pyridin-3-yl 4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidine-1-carboxylate (174 mg), followed by stirring at 60°C for 4 hours. The solvent was evaporated under reduced pressure to obtain 5-aminopiperidin-3-yl 4-{4-[(3-fluorobenzyl)oxy]phenoxy}pyridine-1-carboxylate hydrochloride (74 mg).

Example 261:

An aqueous 1 M sodium hydroxide solution (3.24 ml) was added to a THF (10 ml) solution containing 5-[4-(ethoxycarbonyl)piperidin-1-yl]pyridin-3-yl 4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidine-1-carboxylate oxalate (240 mg), followed by stirring at 60°C for 5 hours. 1 M hydrochloric acid (3.24 ml) was added to the reaction solution and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 10:1 (v/v)). The resulting oil was dissolved in ethanol/water, then oxalic acid (24 mg) was added thereto for crystallization to obtain 1-(5-{[(4-{4-[(3-

fluorobenzyl)oxy]phenoxy}piperidin-1-yl)carbonyl]oxy}pyridin-3-yl)piperidine-4-carboxylic acid oxalate (93 mg).

[0093]

Example 262:

5 TFA (1.0 ml) was added to a methylene chloride (10 ml) solution containing 5-[(2-tert-butoxy-2-oxoethoxy)methyl]pyridin-3-yl 4-{4-[(3-(3-fluorobenzyl)oxy]phenoxy}piperidin-1-carboxylate (333 mg), followed by stirring overnight at room temperature. The solvent was evaporated under reduced pressure to obtain [(5-{[(4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidin-1-yl)carbonyl]oxy}pyridin-3-yl)methoxy]acetic acid (232 mg).

Example 263:

15 An aqueous 1 M sodium hydroxide solution (7.65 ml) was added to a THF (20 ml) solution containing 5-[(acetoxymethyl)pyridin-3-yl 4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidine-1-carboxylate oxalate (1.10 g), followed by stirring at 65°C for 3 hours. The reaction liquid was neutralized with 1 M hydrochloric acid, followed by extraction with chloroform and drying over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 12:1 (v/v)) to obtain 5-(hydroxymethyl)piperidin-3-yl 4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidine-1-carboxylate (770 mg).

Example 264:

25 An aqueous 1 M sodium hydroxide solution (1.11 ml) was added to a THF (5 ml) solution containing 5-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]pyridin-3-yl 4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidine-1-carboxylate (158 mg), followed by stirring at 60°C for 3 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 10:1 (v/v)) to obtain (2E)-3-(5-{[(4-{4-[(3-fluorobenzyl)oxy]phenoxy}piperidin-1-yl)carbonyl]oxy}pyridin-3-yl)acrylic acid (88 mg).

[0094]

Example 267:

(a) Methyl 5-{[(4-nitrophenoxy)carbonyl]oxy}nicotinate (723 mg) was added to an acetonitrile (10 ml) solution of 3-[2-(4-piperidyl)ethyl]benzonitrile hydrochloride (475 mg) and TEA (0.58 ml), followed by stirring overnight at room temperature.

The reaction liquid was diluted with EtOAc, followed by washing with an aqueous saturated sodium hydrogencarbonate solution and drying over anhydrous magnesium sulfate. The solvent was evaporated, the resulting residue was subjected to basic silica gel column chromatography (eluent: hexane:EtOAc = 1:1 (v/v)) and the side-product, nitrophenol was removed. Then, this was purified by silica gel column chromatography (eluent: hexane:EtOAc = 3:2 (v/v)) to obtain methyl 5-[(4-[2-(3-cyanophenyl)ethyl]-1-piperidyl}carbonyl)oxy]nicotinate (284 mg).

(b) An aqueous 1 M sodium hydroxide solution (0.69 ml) was added to a THF (5 ml)/water (4 ml) solution of methyl 5-[(4-[2-(3-cyanophenyl)ethyl]-1-piperidyl}carbonyl)oxy]nicotinate (272 mg), followed by stirring overnight at room temperature. 1 M hydrochloric acid (0.69 ml) was added to the reaction liquid, and the crystal precipitated was collected by filtration. The crystal was washed with a hot methanol/water solution, and dried to obtain 5-[(4-[2-(3-cyanophenyl)ethyl]-1-piperidyl}carbonyl)oxy]nicotinic acid (240 mg).

In the same manner as in the step (a) in Example 267, the compounds of Reference Examples 149 to 150, and Examples 268 to 272, 392, 396, 400, 402, 413, 419, 421 and 422 were obtained.

According to the same method containing the step (b) after the step (a) as in Example 267, the compounds of Examples 273 to 317, 393 to 395, 401, 403, 405, 406, 414 and 418 were obtained.

Example 318:

1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (62 mg), 1-hydroxybenzotriazole (43 mg), ammonium chloride (43 mg) and TEA (0.038 ml) were added to a DMF (3.0 ml) solution of 5-[(4-[2-(3-cyanophenyl)ethyl]-1-piperidyl}carbonyl)oxy]nicotinic acid (102 mg), followed by stirring overnight at room temperature. An aqueous saturated sodium hydrogencarbonate solution was added to the reaction liquid, and the crystal precipitated was collected by filtration and dried.

The resulting crystal was recrystallized from EtOAc/hexane to give 5-(aminocarbonyl)-3-pyridyl 4-[2-(3-cyanophenyl)ethyl]-1-piperidinecarboxylate (81 mg).

In the same manner, the compounds of Examples 319 to 382, 397, 398, 404, 408 to 412, 415, 420 and 423 were obtained.

5 [0095]

Example 407:

Under ice cooling, potassium tert-butoxide (2.73 g) was added to a DMF (50 ml) solution of triphenyl (pyridin-4-ylmethyl)phosphonium chloride hydrochloride (4.75 g) and tert-butyl 4-formylpiperidine-1-carboxylate (1.91 g), followed by stirring overnight at room temperature. The reaction liquid was diluted with EtOAc, washed with water and saturated brine in that order, and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 1:2 (v/v)) to obtain a white solid (2.05 g).

15 The resulting solid (2.04 g) was dissolved in EtOAc (30 ml), and 10% palladium-carbon (200 mg) was added thereto, followed by stirring in the presence of hydrogen at room temperature for 3 hours. The catalyst was removed by filtration, the solvent was concentrated, and the residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate = 1:1 (v/v)) to obtain tert-butyl 4-[(E)-2-pyridin-4-ylvinyl]piperidine-1-carboxylate (1.70 g) as a white solid.

20 A 4 M hydrogen chloride/EtOAc solution (0.88 ml) and platinum oxide (100 mg) were added to an ethanol (25 ml) solution of tert-butyl 4-[(E)-2-pyridin-4-ylvinyl]piperidine-1-carboxylate (1.02 g), followed by stirring in the presence of hydrogen (3.5 atm) for 24 hours. This was purged with argon, diluted with methanol, filtered through Celite, and concentrated under reduced pressure. The solid precipitated was washed with EtOAc/hexane, and dried under reduced pressure to obtain tert-butyl 4-(2-piperidin-4-ylethyl)piperidine-1-carboxylate hydrochloride (850 mg) as a white solid.

25 2-(Dicyclohexylphosphino)biphenyl (71 mg) and (1E,4E)-1,5-diphenyl-1,4-pentadien-3-one-palladium (93 mg) were added to a toluene (10 ml) suspension of tert-butyl 4-(2-piperidin-4-ylethyl)piperidine-1-carboxylate hydrochloride (1.13 g), 2-chloro-6-methylpyridine (431 mg) and sodium tert-butoxide (487 mg), followed by

stirring at 120°C for 1 hour. The reaction liquid was left cooled, then an aqueous saturated sodium carbonate solution was added thereto, followed by extraction with EtOAc. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. Then, the solvent was evaporated and the residue was purified by silica gel column chromatography (eluent: hexane:EtOAc = 10:1 (v/v)) to obtain tert-butyl 4-{2-[1-(6-methylpyridin-2-yl)piperidin-4-yl]ethyl}piperidine-1-carboxylate (660 mg) as a red oil.

A 4 M hydrogen chloride/EtOAc solution (2 ml) was added to an EtOAc (10 ml) solution of tert-butyl 4-{2-[1-(6-methylpyridin-2-yl)piperidin-4-yl]ethyl}piperidine-1-carboxylate (650 mg), followed by stirring at room temperature for 2 days. The reaction liquid was concentrated to obtain 2-methyl-6-[4-(2-piperidin-4-ylethyl)piperidin-1-yl]pyridine dihydrochloride (644 mg) as a yellow amorphous substance.

Methyl 5-{[(4-nitrophenoxy)carbonyl]oxy}nicotinate (505 mg) was added to an acetonitrile (10 ml) solution of 2-methyl-6-[4-(2-piperidin-4-ylethyl)piperidin-1-yl]pyridine dihydrochloride (520 mg) and TEA (0.50 ml), followed by stirring at room temperature for 3 hours. The reaction liquid was diluted with EtOAc, washed with an aqueous saturated sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (eluent: chloroform:methanol = 98:2 (v/v)) to obtain methyl 5-{[(4-{2-[1-(6-methylpyridin-2-yl)piperidin-4-yl]ethyl}piperidin-1-yl)carbonyl]oxy}nicotinate (424 mg).

An aqueous 1 M sodium hydroxide solution (0.45 ml) was added to a THF (5 ml) solution of methyl 5-{[(4-{2-[1-(6-methylpyridin-2-yl)piperidin-4-yl]ethyl}piperidin-1-yl)carbonyl]oxy}nicotinate (208 mg), followed by stirring overnight at room temperature. The reaction liquid was concentrated to obtain sodium 5-{[(4-{2-[1-(6-methylpyridin-2-yl)piperidin-4-yl]ethyl}piperidin-1-yl)carbonyl]oxy}nicotinate (158 mg).

1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (103 mg), 1-hydroxybenzotriazole (90 mg) and ammonium chloride (119 mg) were added to a DMF (10 ml) solution of sodium 5-{[(4-{2-[1-(6-methylpyridin-2-yl)piperidin-4-

yl]ethyl}piperidin-1-yl)carbonyl]oxy}nicotinate (210 mg), followed by stirring overnight at room temperature.

The reaction liquid was diluted with EtOAc, washed with an aqueous saturated sodium hydrogencarbonate solution and saturated brine in that order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was recrystallized from EtOAc/hexane to obtain 5-(aminocarbonyl)pyridin-3-yl 4-{2-[1-(6-methylpyridin-2-yl)piperidin-4-yl]ethyl}piperidine-1-carboxylate (150 mg).

[0096]

10 Example 438:

Screening for FAAH activity-inhibiting substance with rat brain homogenate:

(1) Preparation of rat brain homogenate:

The head of a 10-week age SD-line male rat (Japan SLC) was cut off, and its cerebrum was taken out and weighed. Five times by volume its weight of an ice-cooled buffer (50 mM Tris-HCl (pH 7.4), 0.32 M sucrose) was added, and this was homogenized with a homogenizer in ice to give a uniform suspension. This was centrifuged ($1500 \times g$, 4°C , 15 minutes), and the supernatant was again centrifuged ($15000 \times g$, 4°C , 20 minutes) to obtain a precipitate. Further, using an ultrasonic wave generator (UR-20P, Tommy Seiko), this was ultrasonicated (power dial 4) for 5 seconds. The protein concentration of the resulting homogenate was measured according to a dye-coupling method (protein assay CBB solution, Nacalai Tesque). Using a buffer (50 mM Tris-HCl (pH 8.0), 1 mM EDTA, 0.1 mg/ml BSA, 100 mM NaCl), the rat brain suspension was diluted so that its protein concentration could be 60 $\mu\text{g/ml}$, thereby preparing an enzyme solution.

25 (2) Screening for FAAH activity-inhibiting substance:

A substrate solution was prepared, comprising 2 $\mu\text{Ci/ml}$ radiolabeled anandamide (Anandamide [ethanolamine $1\text{-}^3\text{H}$] (American Radiolabeled Chemical)), 8 μM anandamide (Funakoshi), 50 mM Tris-HCl (pH 8.0), 1 mM EDTA, 0.1 mg/ml BSA and 100 mM NaCl. Test substance solutions were prepared, dissolved in DMSO to have a concentration of from 1 nM to 100 μM . 50 μl of the substrate solution and 1 μl of the test substance solution were added to 50 μl of the enzyme solution, and left for 1 hour. As a control, DMSO was used in place of the test substance solution. To

this, added was 200 μ l of a 1:1 (by volume) solution of chloroform/methanol, followed by vortexing. This was centrifuged (15000 rpm, 2 minutes), whereby the decomposed product ethanolamine (ethanolamine 1-³H) was separated in the upper layer (water/methanol layer) and the unreacted radiolabeled anandamide (Anandamide [ethanolamine 1-³H]) was in the lower layer (chloroform layer). 30 μ l of the upper layer was transferred into a 96-well organic solvent-resistant white microplate (PicoPlate-96; Perkin Elmer), 150 μ l of Microscint-20 (Perkin Elmer) was added thereto, and this was measured with a microplate scintillation counter (TopCountTM; Beckman). As compared with the control, the substance that gave a decreased value was selected as an FAAH activity-inhibiting substance.

(3) Measurement of IC₅₀ value of FAAH activity-inhibiting substance:

A test compound was dissolved in DMSO to have a varying concentration of from 1 nM to 100 μ M to prepare test substance solutions. According to the method mentioned above, the compound was analyzed for its influence on FAAH activity. As a control, DMSO was used. A measured value of a case where a buffer (50 mM Tris-HCl (pH 8.0), 1 mM EDTA, 0.1 mg/ml BSA, 100 mM NaCl) was reacted in place of the enzyme solution was subtracted from every measured value. Based on the measured value of the control, 100%, IC₅₀ value of the test substance was obtained. For example, IC₅₀ of the compounds of Examples 2, 151, 225, 228, 273, 324, 325 and 359 was 0.14 nM, 27 nM, 0.37 nM, 0.19 nM, 0.65 nM, 0.54 nM, 2.5 nM and 1.3 nM, respectively.

The above results confirm that, when a test substance is contacted with a homogenate of a tissue that expresses FAAH or functional FAAH and when the test substance-dependent FAAH activity change is measured, then it may be screened for an FAAH activity-inhibiting substance, or that is, a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain.

[0097]

Example 439:

Screening for FAAH activity-inhibiting substance with human bladder epithelial cancer-derived cell:

(1) Screening for FAAH activity-inhibiting substance:

Human bladder epithelial cancer-derived cell line 5678 cells (HTB-9; ATCC) were seeded on a 48-well cell culture plate in an amount of 1×10^5 cell/well, using 10% fetal bovine serum (HyClone)-containing RPMI1640 medium (Invitrogen).

- 5 After incubated at 37°C for at least 12 hours, the cells were washed with 400 μ l/well of a buffer (Hank's Balanced Salt Solution, 20 mM Hepes-NaOH (pH 7.4)). A test substance dissolved in DMSO was added to a substrate solution (the above buffer containing 3 μ Ci/ml radiolabeled anandamide (Anandamide [ethanolamine 1- ^{3} H]) and 10 μ M anandamide) so as to have a concentration of from 0.003 nM to 30 nM. As a control, DMSO alone was added. 100 μ l/well of the substrate solution was added to 10 the above cells, and incubated in a CO₂ incubator at 37°C for 30 minutes. Next, the cell culture plate was transferred onto ice, and the substrate solution was removed by suction; and 75 μ l/well of a cytolytic solution (the above buffer containing 0.5% Triton X-100, and 10 μ M of FAAH-inhibitory activity-having compound, 3'-
15 carbamoylbiphenyl-3-yl cyclohexylcarbamate (URB597; Cayman chemical; Kathuria et al., Nature Med., Vol. 9, pp. 76-81, 2003)) was added thereto, followed by stirring. The resulting cell lysate in every well was individually transferred into a 1.5 ml sample tube, to which was added 150 μ l of 1:1 (by volume) chloroform/methanol solution, followed by vortexing. This was centrifuged (15000 rpm, 2 minutes), whereby the
20 decomposed product, ethanolamine (ethanolamine 1- ^{3} H) was separated in the upper layer (water/methanol layer) and the unreacted radiolabeled anandamide was in the lower layer (chloroform layer). 25 μ l of the upper layer was transferred into a 96-well organic solvent-resistant white microplate (PicoPlate-96; Perkin Elmer), 150 μ l of Microscint-20 (Perkin Elmer) was added thereto, and this was measured with a
25 microplate scintillation counter (TopCountTM; Beckman). As compared with the control, the substance that gave a decreased value was selected as an FAAH activity-inhibiting substance.

(2) Measurement of IC₅₀ value of FAAH activity-inhibiting substance:

- 30 A test compound dissolved in DMSO to have a concentration of 10 mM was dissolved in the substrate solution so as to have a varying concentration of from 0.003 nM to 30 μ M. According to the method mentioned above, the compound was analyzed for its influence on FAAH activity. As a negative control, DMSO was used.

As a positive control, URB597 was added to the substrate solution to have a concentration of 10 μ M. Based on the measured value of the positive control, 0%, and on the measured value of the negative control, 100%, IC₅₀ value of the test substance was obtained. The test results are shown in Table 64.

5 The above results confirm the excellent FAAH inhibitory activity of typical compounds of the present invention. In addition, these indicate that, when a test substance is contacted with a cell that expresses FAAH or functional FAAH and when the test substance-dependent FAAH activity change is measured, then it may be screened for an FAAH activity-inhibiting substance, or that is, a remedy for urinary
10 frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain.

[0098]

Example 440:

Screening for FAAH activity-inhibiting substance with tissue homogenate of rat
15 administered with test substance:

(1) Administration to rat, and preparation of tissue homogenate:

A test substance suspended in 0.5% methyl cellulose (MC) solution was orally administered to two 9-week age Wistar male rats (Japan SLC) at a dose of from 1 to 3 mg/kg. As a control, 0.5% MC solution was administered to other two rats.
20 After 30 minutes, the blood was collected from each rat under ether anesthesia through its aorta. With that, the head of each rat was cut off, and its cerebrum was taken out.

3 ml of the collected blood was diluted with the same amount of physiological saline water, and gently put on 3 ml of a hemocyte-separating agent (Nycoprep; AXIS-SHIELD) in a centrifugal tube. This was centrifuged (400 $\times$ g, 20
25 minutes) to collect the monocytic layer. The resulting monocytes were washed twice with physiological saline, and frozen and stored at -20°C until their use for measurement.

To the collected rat brain, added was five times by volume its weight of an ice-cooled buffer (50 mM Tris-HCl (pH 8.0), 1 mM EDTA), and this was
30 homogenized with a homogenizer in ice to give a uniform suspension. Further, using an ultrasonic wave generator (UR-20P (power dial 4), Tommy Seiko), this was ultrasonicated for 5 seconds. To the above frozen monocytes, added was 100 μ l of an

ice-cooled buffer (50 mM Tris-HCl (pH 8.0), 1 mM EDTA), and using an ultrasonic wave generator (UR-20P (power dial 4), Tommy Seiko), this was ultrasonicated for 5 seconds. The protein concentration of each of the homogenates of brain and monocytes was measured according to a dye-coupling method (protein assay CBB solution, Nacalai Tesque). Using a buffer (50 mM Tris-HCl (pH 8.0), 1 mM EDTA, 0.1 mg/ml BSA, 100 mM NaCl), the homogenates of brain and monocytes were diluted so that their protein concentration could be 80 µg/ml and 400 µg/ml thereby preparing enzyme solutions.

(2) Measurement of FAAH activity:

50 µl of the enzyme solution was reacted with 50 µl of a substrate solution (2 µCi/ml radiolabeled anandamide (Anandamide [ethanolamine 1-³H] (American Radiolabeled Chemical)), 8 µM anandamide (Funakoshi), 50 mM Tris-HCl (pH 8.0), 1 mM EDTA) added thereto, at room temperature for 1 hour. 200 µl of a 1:1 (by volume) solution of chloroform and methanol was added to it, followed by vortexing. This was centrifuged (12000 × g, 2 minutes), whereby the decomposed product ethanolamine (ethanolamine 1-³H) was separated in the upper layer (water/methanol layer) and the unreacted radiolabeled anandamide (Anandamide [ethanolamine 1-³H]) was in the lower layer (chloroform layer). 25 µl of the upper layer was transferred into a 96-well organic solvent-resistant white microplate (PicoPlate-96; Perkin Elmer), 150 µl of Microscinti-20 (Perkin Elmer) was added thereto, and this was measured with a microplate scintillation counter (TopCountTM; Beckman).

Based on the FAAH activity of the control, test substance-free, rat brain or monocyte homogenate, 100%, and on the FAAH activity of the tissue homogenate-free buffer (50 mM Tris-HCl (pH 8.0), 1 mM EDTA, 0.1 mg/ml BSA, 100 mM NaCl), 0%, the relative value (%) of the FAAH activity of the tissue homogenate of the rat administered with the test substance was obtained. The substance that decreased the relative value of FAAH activity was selected as an FAAH activity-inhibiting substance.

The above results confirm that, when a test substance is administered to a test animal and when the test substance-dependent FAAH activity change in the tissue homogenate of the animal is measured, then it may be screened for an FAAH activity-inhibiting substance, or that is, a remedy for urinary frequency and urinary incontinence, a remedy for overactive bladder and/or a remedy for pain.

[0099]

Example 441:

Effect of compound to cyclophosphamide (CPA)-induced urinary frequency in rat:

Compounds were tested for their bladder irritation-relieving effect, using
5 pathologic models. It is known that systemic administration of cyclophosphamide
(CPA) converts the compound into its metabolite, acrolein, and, as existing in urine,
this injures the bladder mucosa. In rats, CPA administration induces bladder pain or
urinary frequency accompanied by hemorrhagic cystitis, and therefore using such rats,
it is possible to evaluate the potency of drug for these symptoms. In this experiment,
10 used were 9-week age Wistar female rats (Charles River). CPA (100 mg/kg) was
intraperitoneally administered to the rats, and after 2 days, the rats were tested. A test
compound was orally administered (p.o.) to the rats; and after 15 minutes, distilled
water (30 ml/kg) was forcedly orally administered thereto. The rats were put in a
metabolic cage, and their urine was continuously measured for 1 hour. The overall
15 urine amount was divided by the overall urination frequency, and the effective bladder
capacity was thus calculated. As a result, in the group administered with the solvent,
0.5% methyl cellulose (MC), the effective bladder capacity reduced, and the rats
showed urinary frequency. In oral administration, effective dose of compounds of
Examples 2, 218 and 261 was 3 mg/kg; that of compounds of Examples 225, 228, 273,
20 313, 324, 325 and 359 was 1 mg/kg. These compounds increased the reduced
effective bladder capacity and relieved the condition of urinary frequency.

[0100]

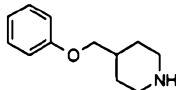
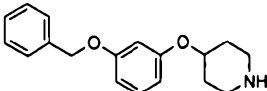
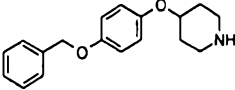
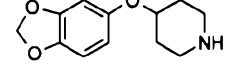
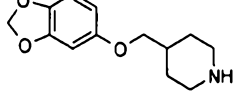
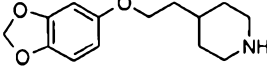
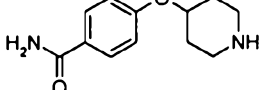
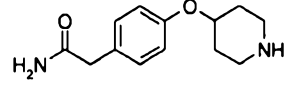
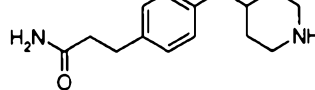
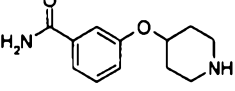
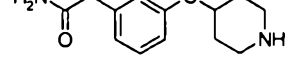
Example 442:

25 Anti-allodynia effect of compounds for L5/L6 spinal nerve-ligated rat (neuropathic
pain model):

A 5 to 6-week age male SD rat was subjected to operation of ligating its left-
side L5 and L6 spinal nerves with silk threads. For evaluating the analgesic effect of
a test substance, employed was a von Frey hair test. Briefly, the hindpaw of the
animal was picked with hair, whereupon the minimum strength of the hair for limb
30 withdrawal response was referred to as the response threshold (log gram) to the
mechanical stimulation. In the preliminary test, it was confirmed that the response
threshold of the operated paw of the animal remarkably lowered within 7 to 14 days

after the operation (under allodynia), and the anti-allodynia effect of the test compound was evaluated on any day within 7 to 14 days after the operation. On the day before the test date, the response threshold before test compound administration was measured. The test animals were so grouped that the mean value difference and
5 fluctuation in the threshold before test compound administration in the groups could be small. In the evaluation test of test compounds, the response threshold value after test compound administration was measured. The test compound was orally administered 60 minutes before the response threshold value measurement. Based on the response thresholds of operated and non-operated paws in the solvent-administered group, 0%
10 and 100%, respectively, the potency of the test compound for its anti-allodynia effect was calculated. As a result, in 10 mg/kg oral administration of the compound of Example 126, it showed an anti-allodynia potency of 74%.

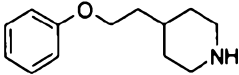
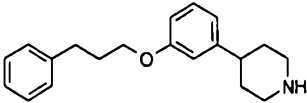
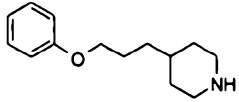
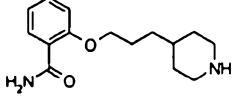
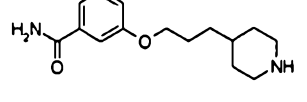
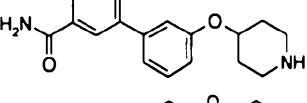
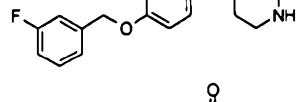
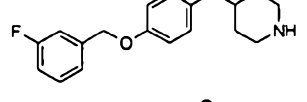
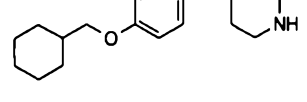
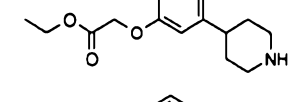
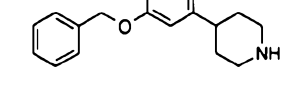
[0101] [Table 1]

Rex No.	Str	MS m/z (M+H) ⁺
1		192 : FAB
2		284 : FAB
3		284 : FAB
4		222 : ESI
5		236 : ESI
6		250 : ESI
7		221 : FAB
8		235 : FAB
9		249 : FAB
10		221 : FAB
11		235 : FAB

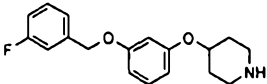
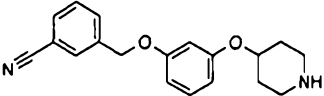
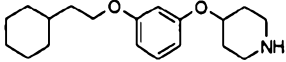
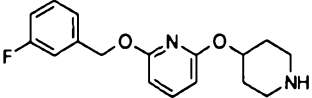
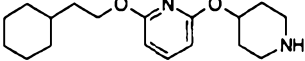
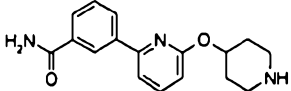
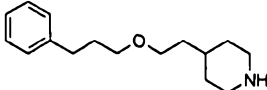
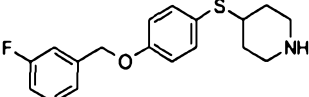
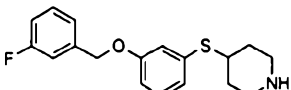
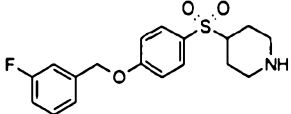
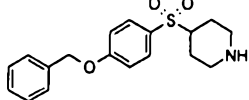
[0102] [Table 2]

Rex No.	Str	MS m/z (M+H) ⁺
12		235 : FAB
13		249 : FAB
14		221 : FAB
15		263 : FAB
16		340 : ESI
17		213 : FAB
18		213 : FAB
19		291 : FAB
20		277 : FAB
21		245 : FAB
22		192 : FAB

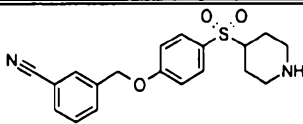
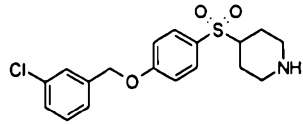
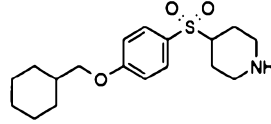
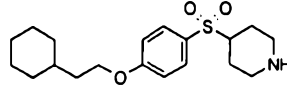
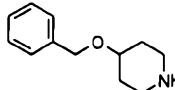
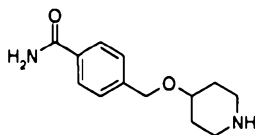
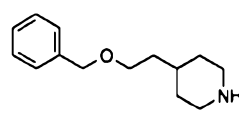
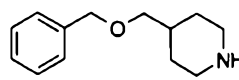
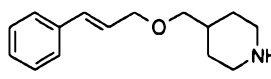
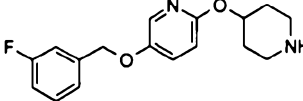
[0103] [Table 3]

Rex No.	Str	MS m/z (M+H) ⁺
23		206 : FAB
24		296 : ESI
25		220 : FAB
26		263 : FAB
27		263 : FAB
28		297 : FAB
29		302 : FAB
30		314 : FAB
31		290 : FAB
32		264 : ESI
33		268 : ESI

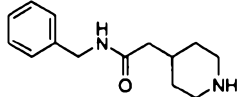
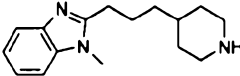
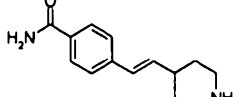
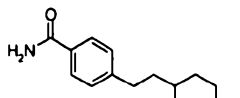
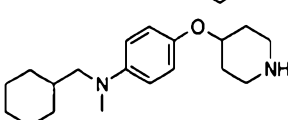
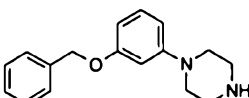
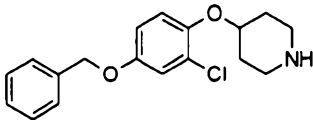
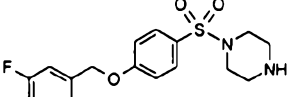
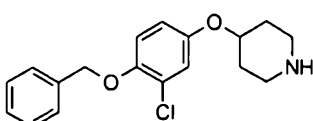
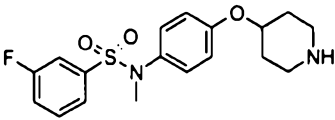
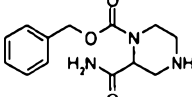
[0104] [Table 4]

Rex No.	Str	MS m/z ($M+H$) ⁺
34		302 : FAB
35		309 : FAB
36		304 : FAB
37		303 : FAB
38		305 : FAB
39		298 : FAB
40		248 : ESI
41		318 : FAB
42		318 : FAB
43		350 : FAB
44		332 : FAB

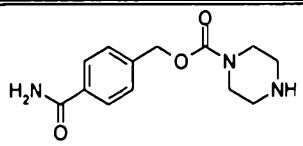
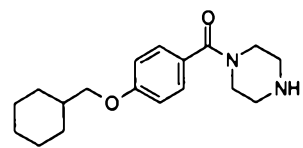
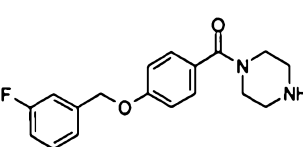
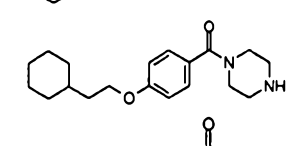
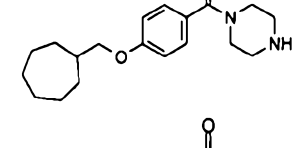
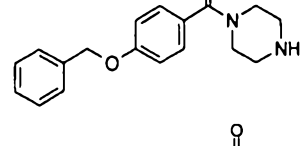
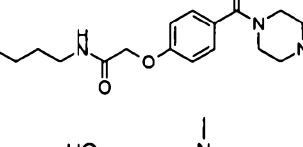
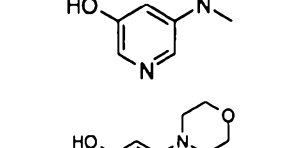
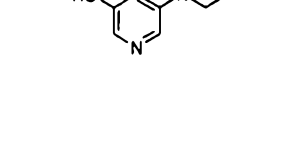
[0105] [Table 5]

Rex No.	Str	MS m/z (M+H) ⁺
45		357 : FAB
46		366 : FAB
47		338 : FAB
48		352 : FAB
49		192 : ESI
50		235 : FAB
51		220 : ESI
52		206 : ESI
53		232 : ESI
54		303 : FAB

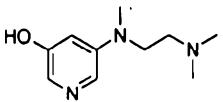
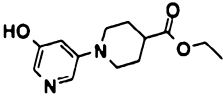
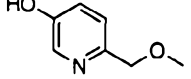
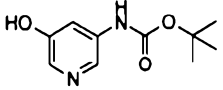
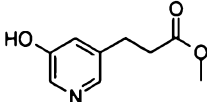
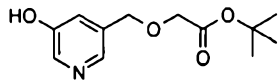
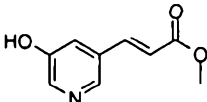
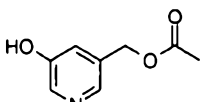
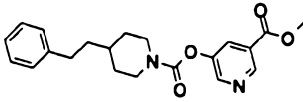
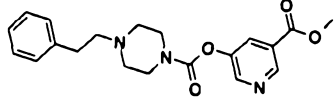
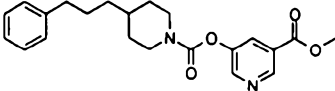
[0106] [Table 6]

Rex No.	Str	MS m/z ($M+H$) ⁺
55		233 : ESI
56		258 : ESI
57		231 : FAB
58		233 : FAB
59		303 : FAB
60		269 : FAB
61		318 : FAB
62		351 : ESI
63		318 : FAB
64		365 : FAB
65		264 : FAB

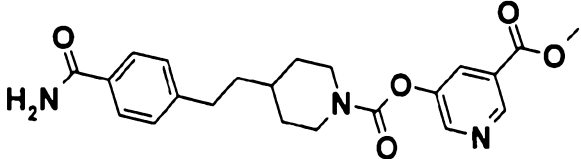
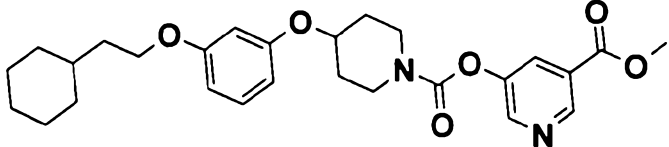
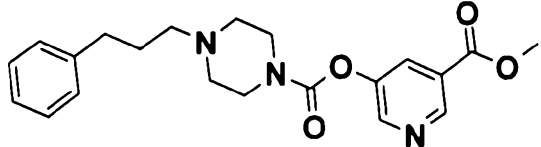
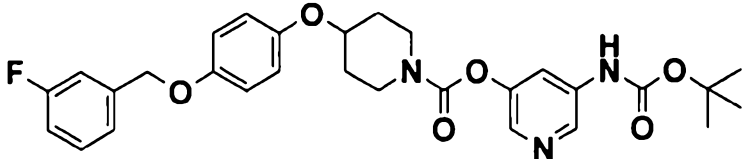
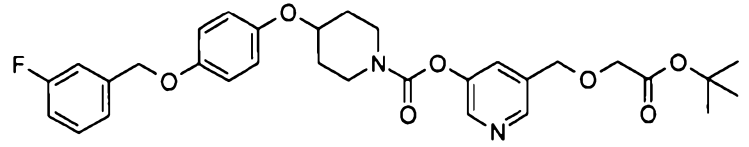
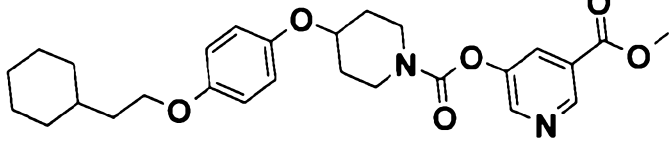
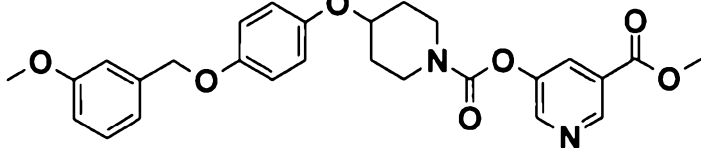
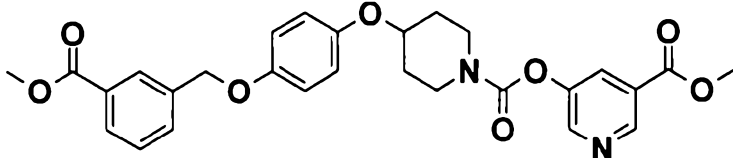
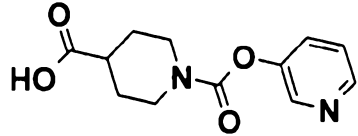
[0107] [Table 7]

Rex No.	Str	MS m/z (M+H) ⁺
66		264 : FAB
67		303 : FAB
68		315 : FAB
69		317 : FAB
70		317 : FAB
71		297 : FAB
72		320 : FAB
73		139 : ESI
74		181 : ESI

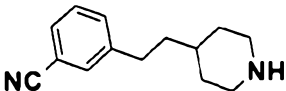
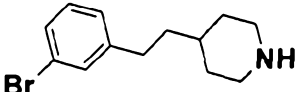
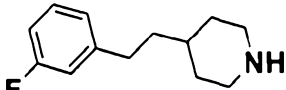
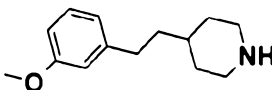
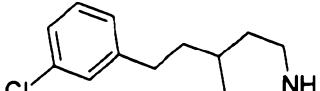
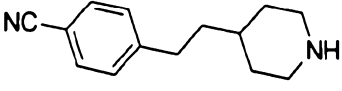
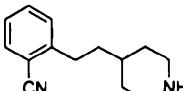
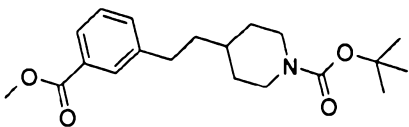
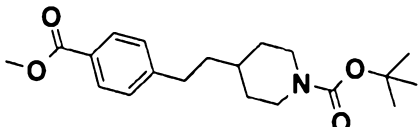
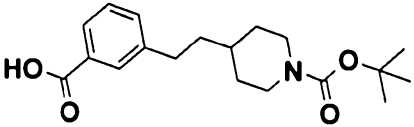
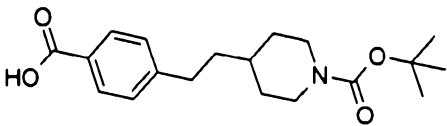
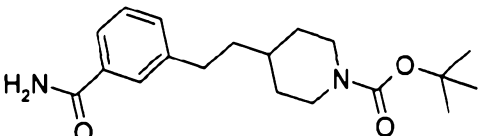
[0108] [Table 8]

Rex No.	Str	MS m/z (M+H) ⁺
75		196 : ESI
76		251 : ESI
77		140 : ESI
78		209 : ESI
79		182 : ESI
80		240 : ESI
81		180 : ESI
82		168 : ESI
83		369 : ESI
84		370 : FAB
85		383 : ESI

[0109] [Table 9]

Rex No.	Str	MS m/z ($M+H$) ⁺
86		412 : FAB
87		483 : FAB
88		384 : FAB
89		538 : ESI
90		567 : ESI
91		483 : ESI
92		493 : ESI
93		522 : ESI
94		251 : ESI

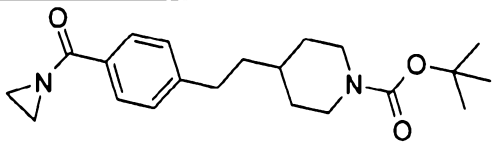
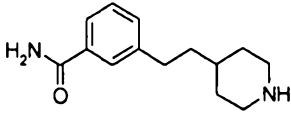
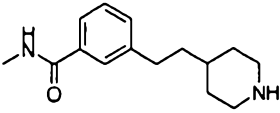
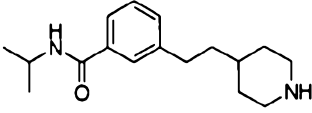
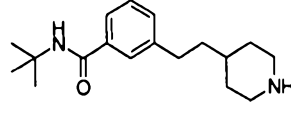
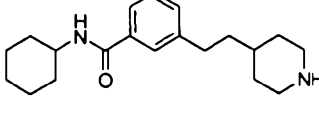
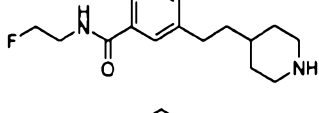
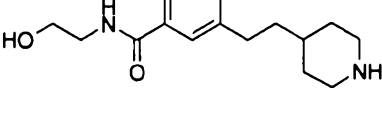
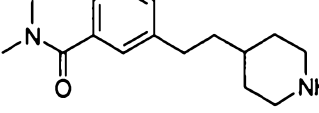
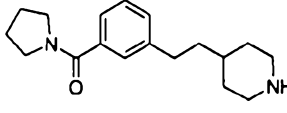
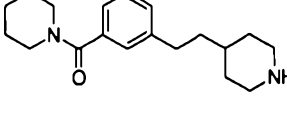
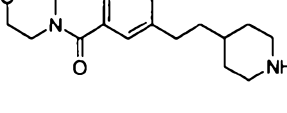
[0110] [Table 10]

Rex No.	Str	MS <i>m/z</i> (M+H) ⁺ or (M-H) ⁻ or (M) ⁺ FAB or ESI or EI
95		215(M+H) ⁺ FAB
96		268, 270(M+H) ⁺ FAB
97		208(M+H) ⁺ FAB
98		220(M+H) ⁺ FAB
99		224(M+H) ⁺ FAB
100		215(M+H) ⁺ FAB
101		215(M+H) ⁺ FAB
102		348(M+H) ⁺ FAB
103		348(M+H) ⁺ ESI
104		332(M-H) ⁻ ESI
105		332(M-H) ⁻ ESI
106		333(M+H) ⁺ ESI

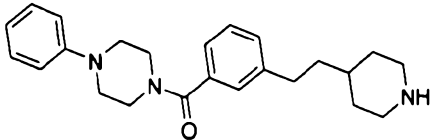
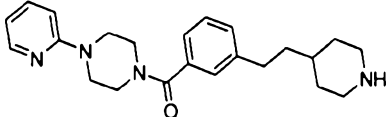
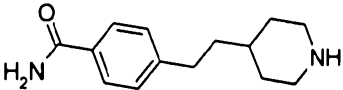
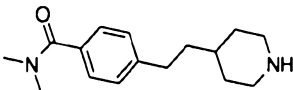
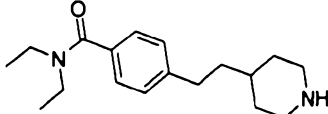
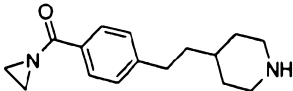
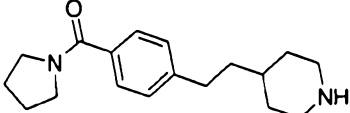
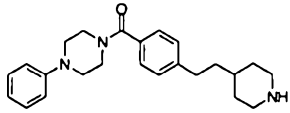
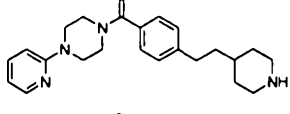
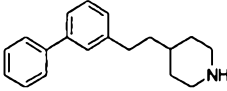
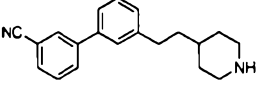
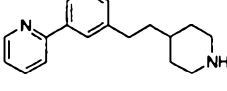
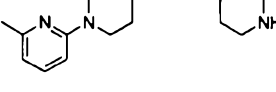
[0111] [Table 11]

Rex No.	Str	MS m/z ($M+H$) ⁺ or ($M-H$) ⁻ or (M) ⁺ FAB or ESI or EI
107		375($M+H$) ⁺ ESI
108		389($M+H$) ⁺ ESI
109		377($M-H$) ⁻ API
110		375($M-H$) ⁻ API
111		361($M+H$) ⁺ ESI
112		387($M+H$) ⁺ FAB
113		401($M+H$) ⁺ FAB
114		377($M+H$) ⁺ ESI
115		389($M+H$) ⁺ ESI
116		387($M+H$) ⁺ ESI
117		478($M+H$) ⁺ ESI
118		479($M+H$) ⁺ FAB

[0112] [Table 12]

Rex No.	Str	MS <i>m/z</i> (M+H) ⁺ or (M-H) ⁻ or (M) ⁺ FAB or ESI or EI
119		359(M+H) ⁺ ESI
120		233(M+H) ⁺ FAB
121		247(M+H) ⁺ FAB
122		275(M+H) ⁺ ESI
123		289(M+H) ⁺ ESI
124		315(M+H) ⁺ FAB
125		279(M+H) ⁺ ESI
126		277(M+H) ⁺ ESI
127		261(M+H) ⁺ FAB
128		287(M+H) ⁺ ESI
129		301(M+H) ⁺ ESI
130		303(M+H) ⁺ ESI

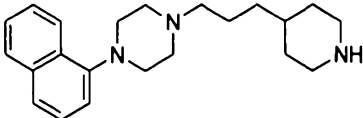
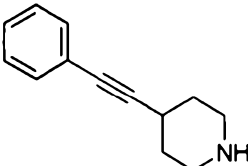
[0113] [Table 13]

Rex No.	Str	MS <i>m/z</i> (M+H) ⁺ or (M-H) ⁻ or (M) ⁺ FAB or ESI or EI
131		378(M+H) ⁺ ESI
132		379(M+H) ⁺ ESI
133		233(M+H) ⁺ ESI
134		260(M) ⁺ ESI
135		288(M+H) ⁺ ESI
136		259(M+H) ⁺ ESI
137		286(M+H) ⁺ ESI
138		378(M+H) ⁺ ESI
139		379(M+H) ⁺ ESI
140		266(M+H) ⁺ FAB
141		291(M+H) ⁺ FAB
142		267(M+H) ⁺ FAB
143		302(M+H) ⁺ FAB

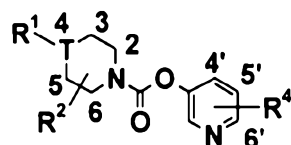
[0114] [Table 14]

Rex No.	Str	MS m/z ($M+H$) ⁺ or ($M-H$) ⁻ or (M) ⁺ FAB or ESI or EI
144		338($M+H$) ⁺ ESI
145		338($M+H$) ⁺ FAB
146		339($M+H$) ⁺ ESI
147		341 ($M+Na$) ⁺ ESI
148		261($M+H$) ⁺ ESI
149		466($M+H$) ⁺ FAB
150		480($M+H$) ⁺ ESI
151		438($M+H$) ⁺ ESI
152		427($M+H$) ⁺ ESI
153		481($M+H$) ⁺ FAB

[0115] [Table 15]

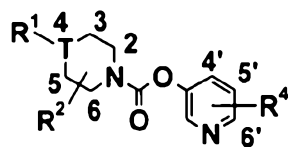
Rex No.	Str	MS m/z ($M+H$) ⁺ or ($M-H$) ⁻ or (M) ⁺ FAB or ESI or EI
154		338($M+H$) ⁺ ESI
155		186($M+H$) ⁺ ESI

[0116] [Table 16]



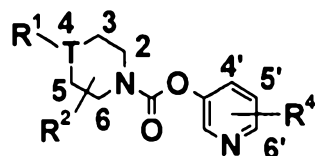
Ex No.	T	R ¹	R ²	R ⁴	Sal
001	CH	H	H	H	oxal
002	CH	4-(3-FPhCH ₂ O)PhO	H	H	free
003	CH	4-(3-FPhCH ₂ O)PhCO	H	H	free
004	N	4-(3-FPhCH ₂ O)PhCO	H	H	oxal
005	N	4-cHexCH ₂ OPhCO	H	H	free
006	N	4-cHex(CH ₂) ₂ OPhCO	H	H	free
007	N	4-cHepCH ₂ OPhCO	H	H	free
008	N	4-PhCH ₂ OPhCO	H	H	free
009	CH	4-cHexCH ₂ OPhO	H	H	free
010	CH	PhCH ₂	H	H	oxal
011	CH	3-PhCH ₂ OPhO	H	H	free
012	CH	4-PhCH ₂ OPhO	H	H	free
013	CH	4-(3-FPhCH ₂ O)PhO	H	6'-Me	HCl
014	CH	PhCO	H	H	free
015	CH	4-FPh	H	H	free
016	CH	PhCONH	H	H	free
017	N	Ph(CH ₂) ₂	H	H	free
018	CH		H	H	HCl
019	CH		H	H	free
020	CH		H	H	HCl
021	CH	PhO	H	H	HCl
023	N	Ph	H	H	free
024	CH	4-H ₂ NCOPhO	H	H	free

[0117] [Table 17]



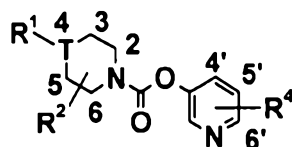
Ex No.	T	R ¹	R ²	R ⁴	Sal
025	CH	4-H ₂ NCOCH ₂ PhO	H	H	free
026	CH	4-H ₂ NCO(CH ₂) ₂ PhO	H	H	free
027	CH	3-H ₂ NCOPhO	H	H	oxal
028	CH	3-H ₂ NCOCH ₂ PhO	H	H	oxal
029	CH	4-(3-FPhCH ₂ O)PhO	H	5'-COOMe	free
030	CH	4-(3-FPhCH ₂ O)PhO	H	5'-NMe ₂	HCl
031	CH	4-cHexCH ₂ N(Me)PhO	H	H	2HCl
033	N	Ph(CH ₂) ₅	H	H	2HCl
034	N	4-PhCH ₂ OPh	H	H	free
035	CH	Ph(CH ₂) ₂	H	H	HCl
036	CH	PhCH ₂ O	H	H	HCl
037	C	Ph	4-HO	H	HCl
039	C	Ph	4-Ac	H	free
040	CH	Ph	H	H	HCl
041	CH	4-H ₂ NCOPhOCH ₂	H	H	free
042	CH	4-(3-FPhCH ₂ O)PhO	H	5'-Cl	free
043	CH	4-H ₂ NCOPhO(CH ₂) ₂	H	H	free
044	CH	4-(3-FPhCH ₂ O)PhO	H	5'-Br	free
045	CH	4-(3-FPhCH ₂ O)PhO	H	5'-Mo4	HCl
046	CH	4-H ₂ NCOPhCH ₂ O	H	H	free
047	CH	PhCH ₂ NHCO	H	H	free
048	N	3-PhCH ₂ OPh	H	H	2HCl
049	N	Ph(CH ₂) ₄	H	H	free
050	N	tBuOCO	H	H	free
051	CH	2-Cl-4-PhCH ₂ OPhO	H	H	HCl
052	CH	PhCH ₂	H	6'-Me	HCl
053	CH	PhCH ₂ O(CH ₂) ₂	H	H	HCl
054	CH	PhCH ₂	H	5'-Br	free
055	CH	PhCH ₂	H	6'-CH ₂ OMe	free
056	CH	4-(3-FPhCH ₂ O)PhO	H	5'-N(Me)(CH ₂) ₂ NMe ₂	2HCl
057	CH	2-H ₂ NCOPhO	H	H	oxal
058	N	4-(3-FPhCH ₂ O)PhSO ₂	H	H	free
059	CH	Ph ₂ (HO)C	H	H	HCl
060	CH	3-HOPh	H	H	free
061	CH	4-(3-FPhCH ₂ O)PhO	H	5'-(CH ₂) ₂ COOMe	free
062	N	Ph(CH ₂) ₂ OCO	H	H	free
063	CH	4-H ₂ NCOPh(CH ₂) ₂	H	H	free
064	CH	PhCH ₂ NHCOCH ₂	H	H	HCl

[0118] [Table 18]

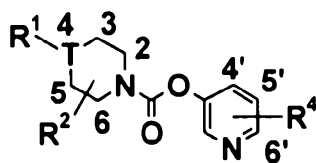


Ex No.	T	R ¹	R ²	R ⁴	Sal
066	CH	1-MeBenzIM2(CH ₂) ₃	H	H	free
067	C	Ph	4-NC	H	HCl
068	CH	2-oxoBenzIM 1	H	H	free
069	CH	4-H ₂ NCOPhO(CH ₂) ₃	H	H	free
070	CH	3-Cl-4-PhCH ₂ OPhO	H	H	oxal
071	CH	4-[3-FPhSO ₂ N(Me)]PhO	H	H	HCl
072	N	PhCH ₂ OCO	3-H ₂ NCO	H	HCl
073	CH	4-(3-FPhCH ₂ O)PhO	H	5'-(4-EtOCOPIPEI) -	oxal
074	C	PhCH ₂	4-HO	H	HCl
075	N	4-BuNHCOCH ₂ OPhCO	H	H	p-tol
076	CH	4-(3-FPhCH ₂ O)PhS	H	H	p-tol
077	CH	3-EtOCOCH ₂ OPh	H	H	oxal
078	CH	3-PhCH ₂ OPh	H	H	oxal
079	CH	4-PhCH ₂ OCOPhO(CH ₂) ₂	H	H	free
080	CH	4-(3-FPhCH ₂ O)PhSO ₂	H	H	free
081	CH	PhCH ₂ OCH ₂	H	H	oxal
082	CH	4-PhCH ₂ OPhO	H	5'-COOMe	free
083	CH	3-(3-H ₂ NCOPh)PhO	H	H	HCl
084	N	Ph(CH ₂) ₂	3-oxo	H	free
085	N	Ph(CH ₂) ₂	H	5'-Cl	free
086	N	Ph(CH ₂) ₂	H	5'-COOMe	free
087	CH	6-ClPy3O	H	H	free
088	CH	4-PhCH ₂ OPhSO ₂	H	H	free
089	CH	4-(3-NCPhCH ₂ O)PhSO ₂	H	H	free
090	CH	4-cHexCH ₂ OPhSO ₂	H	H	free
091	CH	4-cHex(CH ₂) ₂ OPhSO ₂	H	H	free
092	CH	6-ClPy2O	H	H	HCl
093	CH	6-(3-FPhCH ₂ O)Py2O	H	H	oxal
094	CH	6-(3-H ₂ NCOPh)Py2O	H	H	free
095	CH	4-(3-ClPhCH ₂ O)PhSO ₂	H	H	free
096	N	4-H ₂ NCOPhCH ₂ OCO	H	H	free
097	CH	4-(3-FPhCH ₂ O)PhO	H	5'-Me	free
098	CH	4-Me ₂ NCOPhO(CH ₂) ₃	H	H	p-tol
099	CH	4-MeNHCOPhO(CH ₂) ₃	H	H	free
100	CH	4-(3-FPhCH ₂ O)PhO	H	5'-CH ₂ OAc	oxal
101	CH	3-(3-FPhCH ₂ O)PhS	H	H	p-tol

[0119] [Table 19]

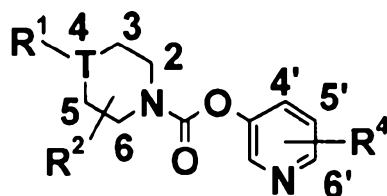


Ex No.	T	R ¹	R ²	R ⁴	Sal
102	CH	6-[cHex(CH ₂) ₂ O]Py2O	H	H	oxal
103	CH	5-(3-FPhCH ₂ O)Py2O	H	H	oxal
105	CH	3-(3-FPhCH ₂ O)PhSO ₂	H	H	free
106	CH	4-NCPHO(CH ₂) ₃	H	5'-COOMe	free
107	CH	H	3-PhOCH ₂	H	p-tol
108	CH	4-NCPHO(CH ₂) ₃	H	H	free
109	CH	HO	H	H	free
110	CH	PhOCH ₂	H	H	free
111	CH	PhO(CH ₂) ₂	H	H	p-tol
112	CH	Ph(CH ₂) ₃ O(CH ₂) ₂	H	H	oxal
113	CH	3-Ph(CH ₂) ₃ OPh	H	H	oxal
114	CH	PhO(CH ₂) ₃	H	H	free
115	CH	2-H ₂ NCOPHO(CH ₂) ₃	H	H	free
116	CH	3-H ₂ NCOPHO(CH ₂) ₃	H	H	p-tol
118	CH	4-(3-FPhCH ₂ O)PhO	H	5'-F	HCl
119	N	4-cOctCH ₂ OPhCO	H	H	free
120	N	4-[3-FPhCH ₂ N(Me)]PhCO	H	H	free
121	N	4-cHexCH ₂ N(Me)PhCO	H	H	free
122	N	3-cHexCH ₂ OPhCO	H	H	HCl
123	N	3-cHexCH ₂ N(Me)PhCO	H	H	HBr
124	N	Ph(CH ₂) ₂ CO	H	H	p-tol
125	N	PhCO	H	H	free
127	N	PhOCH ₂ CO	H	H	p-tol
128	N	PhCH ₂ CO	H	H	p-tol
129	N	PhNHCH ₂ CO	H	H	free
130	N	Ph(CH ₂) ₃ CO	H	H	p-tol
132	N	PhCONHCH ₂ CO	H	H	oxal
133	N	PhN(Me)CH ₂ CO	H	H	2oxal
134	N	4-HepOPhCO	H	H	p-tol
135	N	4-(3-NCPHCH ₂ O)PhCO	2-Me	H	HCl
136	N	4-(3-NCPHCH ₂ O)PhCO	3-Me	H	free
137	N	6-(3-ClPhCH ₂ O)Py3CO	H	H	oxal
138	N	3-(3-ClPhCH ₂ O)PhCO	H	H	HCl
139	N	4-H ₂ NCOPHOCH ₂ CO	H	H	free
140	N	2-H ₂ NCOPHOCH ₂ CO	H	H	free
141	N	3-H ₂ NCOPHOCH ₂ CO	H	H	free
142	N	PhSO ₂	H	H	free



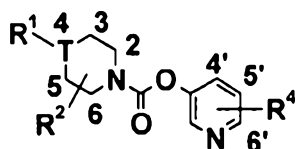
Ex No.	T	R ¹	R ²	R ⁴	Sal
143	N	PhCH ₂ SO ₂	H	H	free
144	N	PhCH ₂ O-CO	H	H	p-tol
145	N	Py3O-CO	H	H	free
146	N	PhCH ₂ NHCO	H	H	free
147	N	4-(3-ClPhCH ₂ O)PhCO	H	H	free
148	N	4-(3-MePhCH ₂ O)PhCO	H	H	oxal
149	N	4-(3-F ₃ CPhCH ₂ O)PhCO	H	H	free
150	N	4-(3-MeOPhCH ₂ O)PhCO	H	H	oxal
151	N	4-(3-NCPhCH ₂ O)PhCO	H	H	free
152	N	4-(3,5-diFPhCH ₂ O)PhCO	H	H	free
153	N	4-(3-F ₃ COPhCH ₂ O)PhCO	H	H	free
154	N	4-(3-O ₂ NPhCH ₂ O)PhCO	H	H	free
155	N	4-(4-FPhCH ₂ O)PhCO	H	H	free
156	N	4-(2-FPhCH ₂ O)PhCO	H	H	free
157	N	4-Py2CH ₂ OPhCO	H	H	free
158	N	4-(1-MeAzep3O)PhCO	H	H	free
159	N	4-(3-BrPhCH ₂ O)PhCO	H	H	free
160	N	4-[3-ClPh(CH ₂) ₂ O]PhCO	H	H	free
161	N	4-(4-NCPhCH ₂ O)PhCO	H	H	free
162	N	4-(3-IPhCH ₂ O)PhCO	H	H	free
163	N	4-(3-Me ₂ NPhCH ₂ O)PhCO	H	H	free
164	N	2-Cl-4-(3-NCPhCH ₂ O)PhCO	H	H	free
165	N	3-Cl-4-(3-NCPhCH ₂ O)PhCO	H	H	free
166	N	4-(3-NCPhCH ₂ O)-3-MeO-PhCO	H	H	HCl
167	N	4-(3-MeOCOPhCH ₂ O)PhCO	H	H	free
168	CH	cHexCH ₂ NHCO	H	H	free
169	CH	MeOCO(CH ₂) ₃	H	H	oxal
170	CH	H ₂ NCO(CH ₂) ₃	H	H	oxal
171	CH	PhCH ₂ N(Me)CO	H	H	free
172	CH	Py3CH ₂ NHCO	H	H	free
173	CH	PhNHCO	H	H	free
174	CH	Ph(CH ₂) ₂ NHCO	H	H	free
175	CH	Ph(CH ₂) ₄ NHCO	H	H	free
176	CH	4-OctPhNHCO	H	H	free
177	CH	4-H ₂ NCOPhNHCO(CH ₂) ₃	H	H	free
178	CH	3-H ₂ NCOPhNHCO(CH ₂) ₃	H	H	free
179	CH	3-H ₂ NCOCH ₂ OPh	H	H	HCl

[0121] [Table 21]



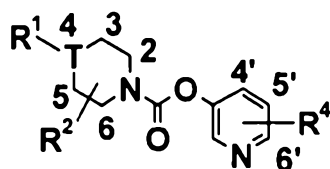
Ex No.	T	R ¹	R ²	R ⁴	Sal
180	CH	3-(4-H ₂ NCOPIPEICOCH ₂ O)Ph	H	H	HCl
181	CH	2-H ₂ NCOPhNHCO(CH ₂) ₃	H	H	fum
182	CH	4-BuPhNHCO	H	H	free
183	CH	4-BuOPhNHCO	H	H	free
184	CH	4-HexOPh(CH ₂) ₂ NHCO	H	H	free
185	CH	4-Ph(CH ₂) ₄ OPh(CH ₂) ₂ NHCO	H	H	free
186	CH	4-cPen(CH ₂) ₃ OPh(CH ₂) ₂ NHCO	H	H	free
187	CH	4-HexPhNHCO	H	H	free
188	CH	4-[4-MeOCOPh(CH ₂) ₂]PhNHCO	H	H	free
189	CH	4-HO(CH ₂) ₂ PhNHCO	H	H	free
190	CH	4-PhCH ₂ OPhNHCO	H	H	free
191	CH	2-H ₂ NCO(CH ₂) ₂ PhNHCO	H	H	free
192	CH	4-Ph-1,3-Thiaz2NHCO	H	H	free
193	N	PhCH ₂ OCO	3-COOH	H	free
194	CH	4-HOOCPhO(CH ₂) ₂	H	H	free
195	CH	3-HOOCCH ₂ OPh	H	H	free
196	CH	1-MeBenzIM2	H	H	free
197	CH	Ph(CH ₂) ₃ CONH	H	H	free
198	CH	3-HOPhO	H	H	free
199	CH	4-HOPhO	H	H	free
200	CH	3-cHexCH ₂ OPhO	H	H	HCl
201	CH	3-cHex(CH ₂) ₂ OPhO	H	H	HCl
202	CH	3-(3-FPhCH ₂ O)PhO	H	H	HCl
203	CH	3-(2-FPhCH ₂ O)PhO	H	H	HCl
204	CH	3-(4-FPhCH ₂ O)PhO	H	H	HCl
205	CH	3-(3-NCPhCH ₂ O)PhO	H	H	oxal
206	CH	4-(3-ClPhCH ₂ O)PhO	H	H	HCl
207	CH	4-cHex(CH ₂) ₂ OPhO	H	H	HCl
208	CH	4-(2-FPhCH ₂ O)PhO	H	H	HCl
209	CH	4-(4-FPhCH ₂ O)PhO	H	H	HCl
210	CH	4-(3-NCPhCH ₂ O)PhO	H	H	oxal
211	CH	4-(3-MeOCOPhCH ₂ O)PhO	H	H	free
212	CH	4-(3-H ₂ NCOPhCH ₂ O)PhO	H	H	free
213	CH	4-cHex(CH ₂) ₃ OPhO	H	5'-COOMe	free

[0122] [Table 22]



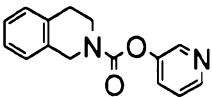
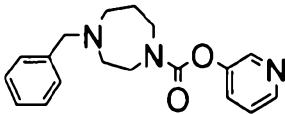
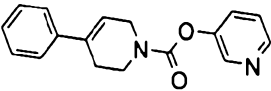
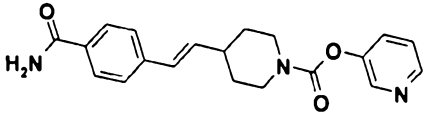
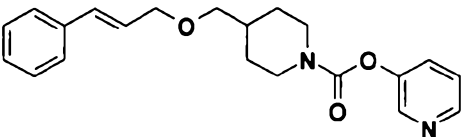
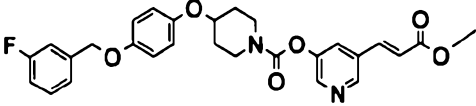
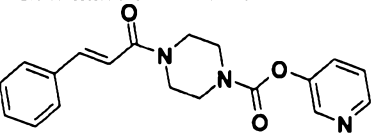
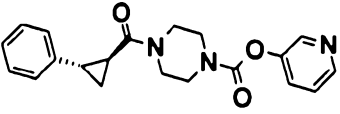
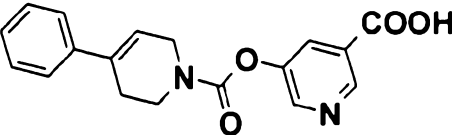
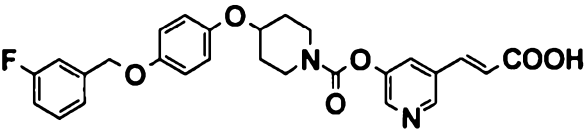
Ex No.	T	R ¹	R ²	R ⁴	Sal
214	CH	4-PIPERI(CH ₂) ₂ OPhO	H	5'-COOMe	HCl
215	CH	4-(3-NCPHCH ₂ O)PhO	H	5'-COOMe	oxal
216	CH	4-cHexCH ₂ OPhO	H	5'-COOMe	free
217	CH	4-HOPhO	H	5'-COOH	free
218	CH	4-(3-FPhCH ₂ O)PhO	H	5'-COOH	free
219	CH	PhCH ₂	H	5'-COOH	free
220	CH	Ph	H	5'-COOH	free
221	CH	4-PhCH ₂ OPhO	H	5'-COOH	free
223	CH	PhCO	H	5'-COOH	free
224	CH	PhCH ₂ O	H	5'-COOH	free
225	CH	Ph(CH ₂) ₂	H	5'-COOH	free
226	CH	4-PIPERI(CH ₂) ₂ OPhO	H	5'-COOH	free
227	CH	4-NCPHO(CH ₂) ₃	H	5'-COOH	free
228	CH	4-cHex(CH ₂) ₂ OPhO	H	5'-COOH	free
229	CH	4-cHex(CH ₂) ₃ OPhO	H	5'-COOH	free
230	CH	4-(3-NCPHCH ₂ O)PhO	H	5'-COOH	free
231	N	Ph(CH ₂) ₂	H	5'-COOH	2HCl
232	CH	PhCH ₂ OCH ₂	H	5'-COOH	free
233	CH	4-(3-MeOPHCH ₂ O)PhO	H	5'-COOH	free
234	CH	3-(3-FPhCH ₂ O)PhO	H	5'-COOH	free
235	CH	3-(3-NCPHCH ₂ O)PhO	H	5'-COOH	free
236	CH	4-(3-MeOCOPHCH ₂ O)PhO	H	5'-COOH	free
237	CH	4-cHexCH ₂ OPhO	H	5'-COOH	free
238	CH	Ph(CH ₂) ₃	H	5'-COOH	free
239	CH	PhO(CH ₂) ₃	H	5'-COOH	free
240	CH	PhO(CH ₂) ₂	H	5'-COOH	free
241	CH	4-H ₂ NCOPH(CH ₂) ₂	H	5'-COOH	free
242	CH	3-cHex(CH ₂) ₂ OPhO	H	5'-COOH	free
243	N	Ph(CH ₂) ₃	H	5'-COONa	free
244	CH	4-(3-FPhCH ₂ O)PhO	H	5'-CONHCH ₂ COOH	free
245	CH	4-(3-FPhCH ₂ O)PhO	H	5'-CONH ₂	free
246	CH	4-PhCH ₂ OPhO	H	5'-CONH ₂	free
247	CH	PhCH ₂	H	5'-CONHCH ₂ CONH ₂	HCl
248	CH	PhCH ₂	H	5'-(4-H ₂ NCOPIPERIICO) -	HCl

[0123] [Table 23]

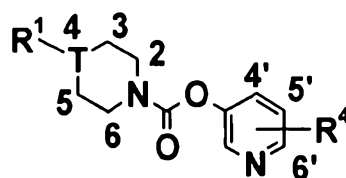


Ex No.	T	R ¹	R ²	R ⁴	Sal
249	CH	4-(3-FPhCH ₂ O)PhO	H	5'-CONHCH ₂ CONH ₂	HCl
250	CH	4-(3-FPhCH ₂ O)PhO	H	5'-Mo ₄ (CH ₂) ₂ NHCO -	oxal
251	CH	4-(3-FPhCH ₂ O)PhO	H	5'-CONH(CH ₂) ₂ OMe	oxal
252	CH	4-(3-FPhCH ₂ O)PhO	H	5'-(4-H ₂ NCOPIPE1CO) -	free
253	CH	4-(3-FPhCH ₂ O)PhO	H	5'-CONH(CH ₂) ₂ CONH ₂	HC l
254	CH	4-(3-FPhCH ₂ O)PhO	H	5'-PIPE1(CH ₂) ₂ NHCO -	2HCl
255	CH	4-(3-FPhCH ₂ O)PhO	H	5'-CONH(CH ₂) ₂ OH	HCl
256	CH	4-(3-FPhCH ₂ O)PhO	H	5'-(4-HOPh(CH ₂) ₂ NHCO) -	free
257	CH	4-(3-FPhCH ₂ O)PhO	H	5'-(4-MePIPERA1CO) -	oxal
258	CH	PhCH ₂	H	5'-(3-H ₂ NCOPh) -	free
259	CH	PhCH ₂	H	5'-Py3	free
260	CH	4-(3-FPhCH ₂ O)PhO	H	5'-NH ₂	HCl
261	CH	4-(3-FPhCH ₂ O)PhO	H	5'-(4-HOOCPIPE1) -	oxal
262	CH	4-(3-FPhCH ₂ O)PhO	H	5'-CH ₂ OCH ₂ COOH	free
263	CH	4-(3-FPhCH ₂ O)PhO	H	5'-CH ₂ OH	free

[0124] [Table 24]

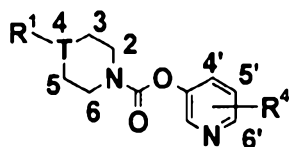
Ex No.	Str	Sal
022		free
032		2HCl
038		free
065		free
104		fum
117		free
126		p-tol
131		p-tol
222		free
264		free

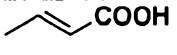
[0125] [Table 25]



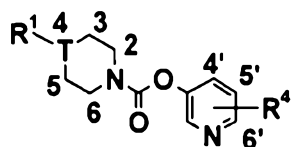
Ex No.	T	R ¹	R ⁴	Sal
265	CH	Ph(CH ₂) ₂	5'-(4-MeOCOPh) -	free
266	CH	Ph(CH ₂) ₂	5'-(3-H ₂ NCOPh)-	free
267	CH	3-NCPH(CH ₂) ₂	5'-COOH	free
268	CH		H	free
269	CH		H	free
270	CH	Ph(CH ₂) ₂	5'-Br	free
271	CH	cHex(CH ₂) ₂	H	free
272	CH	cHex(CH ₂) ₂	5'-COOMe	free
273	CH		5'-COOH	free
274	CH	3-ClPh(CH ₂) ₂	5'-COOH	free
275	CH	4-NCPH(CH ₂) ₂	5'-COOH	free
276	CH	3-MeOPH(CH ₂) ₂	5'-COOH	free
277	CH	3-FPh(CH ₂) ₂	5'-COOH	free
278	CH	2-NCPH(CH ₂) ₂	5'-COOH	free
279	CH	3-H ₂ NCOPH(CH ₂) ₂	5'-COOH	free
280	CH	3-Me ₂ NCOPH(CH ₂) ₂	5'-COOH	free
281	CH	BIP4(CH ₂) ₂	5'-COOH	Na
282	CH	4-FPh(CH ₂) ₂	5'-COOH	free
283	CH	2-ClPh(CH ₂) ₂	5'-COOH	free
284	CH	4-ClPh(CH ₂) ₂	5'-COOH	free
285	CH	4-BrPh(CH ₂) ₂	5'-COOH	free

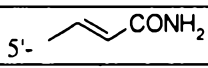
[0126] [Table 26]



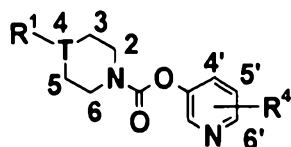
Ex No.	T	R ¹	R ⁴	Sal
286	CH	4-MeOPh(CH ₂) ₂	5'-COOH	free
287	CH	Ph(CH ₂) ₄	5'-COOH	free
288	CH	2-FPh(CH ₂) ₂	5'-COOH	free
289	CH	cHex(CH ₂) ₂	5'-COOH	free
290	CH	4-Py2Ph(CH ₂) ₂	5'-COOH	free
291	CH	Ph(CH ₂) ₂	5'- 	free
292	CH	3-BrPh(CH ₂) ₂	5'-COOH	free
293	CH	BIP3(CH ₂) ₂	5'-COOH	free
294	CH	3'-NCBIP3(CH ₂) ₂	5'-COOH	free
295	CH	Py4Ph(CH ₂) ₂	5'-COOH	free
296	CH	Py3Ph(CH ₂) ₂	5'-COOH	free
297	CH	Py2(CH ₂) ₂	5'-COOH	free
298	CH	3-Py2Ph(CH ₂) ₂	5'-COOH	Na
299	CH	4'-FBIP4(CH ₂) ₂	5'-COOH	free
300	CH	4'-MeOBIP4(CH ₂) ₂	5'-COOH	free
301	CH	4'-NCBIP4(CH ₂) ₂	5'-COOH	free
302	CH	3'-FBIP4(CH ₂) ₂	5'-COOH	free
303	CH	3'-MeOBIP4(CH ₂) ₂	5'-COOH	free
304	CH	2'-FBIP4(CH ₂) ₂	5'-COOH	free
305	CH	3-cHexNHCOPh(CH ₂) ₂	5'-COOH	Na
306	CH	3-PIPE1COPh(CH ₂) ₂	5'-COOH	Na
307	CH	3-M o4COPh(CH ₂) ₂	5'-COOH	Na
308	CH	4-PIPE1COPh(CH ₂) ₂	5'-COOH	Na
309	CH	4-M o4COPh(CH ₂) ₂	5'-COOH	Na
310	CH	3-PYRR1COPh(CH ₂) ₂	5'-COOH	Na
311	CH	3-(4-Py2PIPERA1CO)Ph(CH ₂) ₂	5'-COOH	free

[0127] [Table 27]



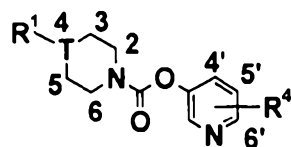
Ex No.	T	R ¹	R ⁴	Sal
312	CH	4-Et ₂ NCOPh(CH ₂) ₂	5'-COOH	free
313	CH	1-(6-MePy ₂)PIPE4(CH ₂) ₃	5'-COOH	Na
314	CH	1-ISOQUII PIPE4(CH ₂) ₃	5'-COOH	Na
315	CH	1-QUI2PIPE4(CH ₂) ₃	5'-COOH	Na
316	CH	4-ISOQUII PIPERA1(CH ₂) ₃	5'-COOH	Na
317	CH	1-NAPHI PIPE4(CH ₂) ₃	5'-COOH	Na
318	CH	3-NCPh(CH ₂) ₂	5'-CONH ₂	free
319	CH	Ph(CH ₂) ₂	5'-CONH(CH ₂) ₂ OH	oxal
320	CH	Ph(CH ₂) ₂	5'-CONH ₂	free
321	CH	3-MeOPh(CH ₂) ₂	5'-CONH ₂	free
322	CH	3-FPh(CH ₂) ₂	5'-CONH ₂	free
323	CH	2-NCPh(CH ₂) ₂	5'-CONH ₂	free
324	CH	3-H ₂ NCOPh(CH ₂) ₂	5'-CONH ₂	free
325	CH	3-Me ₂ NCOPh(CH ₂) ₂	5'-CONH ₂	free
326	CH	cHex(CH ₂) ₂	5'-CONH ₂	free
327	CH	3-ClPh(CH ₂) ₂	5'-CONH(CH ₂) ₂ OH	oxal
328	CH	3-MeOPh(CH ₂) ₂	5'-CONH(CH ₂) ₂ OH	oxal
329	CH	3-FPh(CH ₂) ₂	5'-CONH(CH ₂) ₂ OH	oxal
330	CH	3-NCPh(CH ₂) ₂	5'-CONH(CH ₂) ₂ OH	oxal
331	CH	2-NCPh(CH ₂) ₂	5'-CONH(CH ₂) ₂ OH	oxal
332	CH	Ph(CH ₂) ₂	5'-CONH(CH ₂) ₂ SO ₃ H	HCl
333	CH	Ph(CH ₂) ₂	5'-CONH(CH ₂) ₂ CONH ₂	free
334	CH	2-FPh(CH ₂) ₂	5'-CONH ₂	free
335	CH	Ph(CH ₂) ₂	5'-  CONH ₂	free
336	CH	Py4(CH ₂) ₂	5'-CONH ₂	free

[0128] [Table 28]

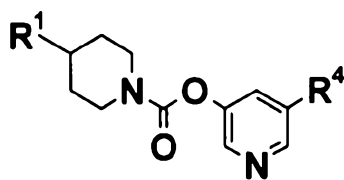


Ex No.	T	R ¹	R ⁴	Sal
337	CH	Py3(CH ₂) ₂	5'-CONH ₂	free
338	CH	4'-FBIP4(CH ₂) ₂	5'-CONH ₂	free
339	CH	4'-MeOBIP4(CH ₂) ₂	5'-CONH ₂	free
340	CH	BIP3(CH ₂) ₂	5'-CONH ₂	free
341	CH	3'-NCBIP3(CH ₂) ₂	5'-CONH ₂	free
342	CH	Ph(CH ₂) ₂	5'-CONH(CH ₂) ₃ OH	oxal
343	CH	Ph(CH ₂) ₂	5'-CONH(CH ₂) ₃ NMe ₂	oxal
344	CH	4'-NCBIP4(CH ₂) ₂	5'-CONH ₂	free
345	CH	3'-FBIP4(CH ₂) ₂	5'-CONH ₂	free
346	CH	2'-FBIP4(CH ₂) ₂	5'-CONH ₂	free
347	CH	Ph(CH ₂) ₂	5'-CONH(CH ₂) ₂ Py4	oxal
348	CH	Ph(CH ₂) ₂	5'-CONH(CH ₂) ₂ Py3	oxal
349	CH	3-Py2Ph(CH ₂) ₂	5'-CONH ₂	free
350	CH	2-Me ₂ NCOPh(CH ₂) ₂	5'-CONH ₂	free
351	CH	3-cHexNHCOPh(CH ₂) ₂	5'-CONH ₂	free
352	CH	3-MeNHCOPh(CH ₂) ₂	5'-CONH ₂	free
353	CH	4-H ₂ NCOPh(CH ₂) ₂	5'-CONH ₂	free
354	CH	4-Me ₂ NCOPh(CH ₂) ₂	5'-CONH ₂	free
355	CH	3-PIPE1COPh(CH ₂) ₂	5'-CONH ₂	free
356	CH	3-Mo4COPh(CH ₂) ₂	5'-CONH ₂	free
357	CH	4-PIPE1COPh(CH ₂) ₂	5'-CONH ₂	free
358	CH	4-Mo4COPh(CH ₂) ₂	5'-CONH ₂	free
359	CH	3-PYRR1COPh(CH ₂) ₂	5'-CONH ₂	free
360	CH	3-Et ₂ NCOPh(CH ₂) ₂	5'-CONH ₂	free
361	CH		5'-CONH ₂	free

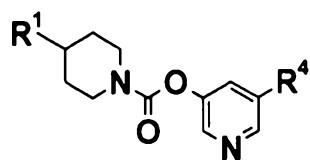
[0129] [Table 29]



Ex No.	T	R ¹	R ⁴	Sal
362	CH	4-Et ₂ NCOPh(CH ₂) ₂	5'-CONH ₂	free
363	CH	4-PYRR1COPh(CH ₂) ₂	5'-CONH ₂	free
364	CH		5'-CONH ₂	free
365	CH	3-(4-Py2PIPERA1CO) Ph(CH ₂) ₂	5'-CONH ₂	free
366	CH	3-(4-PhPIPERA1CO) Ph(CH ₂) ₂	5'-CONH ₂	free
367	CH	4-(4-Py2PIPERA1CO) Ph(CH ₂) ₂	5'-CONH ₂	free
368	CH	4-(4-PhPIPERA1CO) Ph(CH ₂) ₂	5'-CONH ₂	free
369	CH	3-FCH ₂ CH ₂ NHCOPh(CH ₂) ₂	5'-CONH ₂	HCl
370	CH	3-HO(CH ₂) ₂ NHCOPh(CH ₂) ₂	5'-CONH ₂	free
371	CH	3-tBuNHCOPh(CH ₂) ₂	5'-CONH ₂	free
372	CH	3-iPrNHCOPh(CH ₂) ₂	5'-CONH ₂	free
373	CH	4-(2,2-DIFPYRR1CO)Ph(CH ₂) ₂	5'-CONH ₂	free
374	CH	3-H ₂ NCONHPh(CH ₂) ₂	5'-CONH ₂	free
375	CH	3-PYRR1CONHPh(CH ₂) ₂	5'-CONH ₂	free
376	CH	3-(2,2-DIFPYRR1CO)Ph(CH ₂) ₂	5'-CONH ₂	free
377	CH	3-(4-NAPH1PIPERA1CO)Ph(CH ₂) ₂	5'-CONH ₂	free
378	CH	1-(6-MePy2)PIPE4(CH ₂) ₃	5'-CONH ₂	free
379	CH	1-ISOQUI1PIPE4(CH ₂) ₃	5'-CONH ₂	free
380	CH	1-QUI2PIPE4(CH ₂) ₃	5'-CONH ₂	free
381	CH	4-ISOQUI1PIPERA1(CH ₂) ₃	5'-CONH ₂	free
382	CH	1-NAPH1PIPE4(CH ₂) ₃	5'-CONH ₂	free

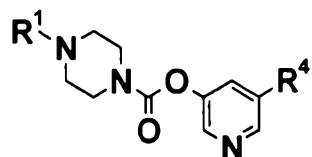


Ex No.	R^1	R^4	Sal
383	3-HepOPhNHCO	H	free
384	4-HepOPhNHCO	H	free
385	Py ₂ NHCO(CH ₂) ₃	H	2HCl
386	4-OctPhNHCO(CH ₂) ₃	H	oxal
387	Ph (CH ₂) ₄ NHCO(CH ₂) ₃	H	oxal
388	4-HexPhNHCO	CONH ₂	free
389	4-(3-FPhCH ₂ O)PhO	OAc	oxal
390	4-(3-FPhCH ₂ O)PhO	OH	free
391	4-(3-FPhCH ₂ O)PhO	CN	free
392	4-cHex(CH ₂) ₄ OPhO	H	free
393		CO ₂ H	free
394		CO ₂ H	free
395	4-cPen(CH ₂) ₂ OPhO	CO ₂ H	free
396	4-(3-FPhCH ₂ O)PhOCH ₂	H	free



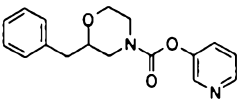
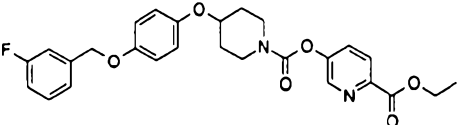
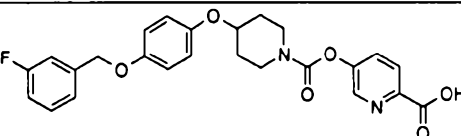
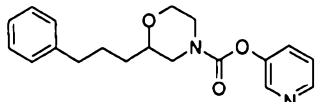
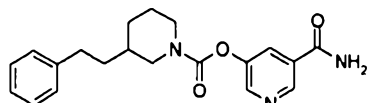
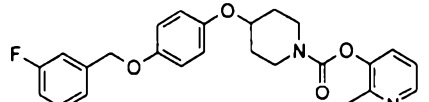
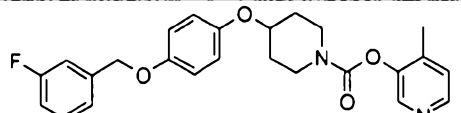
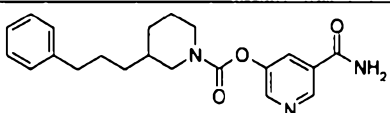
Ex No.	R ¹	R ⁴	Sal
397		CONH ₂	free
398		CONH ₂	free
399	Ph(CH ₂) ₂		free
400	4-(3-FPhCH ₂ O)PhCH ₂	H	HCl
401	4-(3-FPhCH ₂ O)PhCH ₂	CO ₂ H	free
402	Ph(CH ₂) ₂	OH	free
403		CO ₂ H	free
404		CONH ₂	free
405	4-NAPH1PIPERA1(CH ₂) ₃	CO ₂ H	Na
406	1-(6-MePy2)PIPE4(CH ₂) ₂	CO ₂ H	Na
407	1-(6-MePy2)PIPE4(CH ₂) ₂	CONH ₂	free
408	4-NAPH1PIPERA1(CH ₂) ₃	CONH ₂	free

[0132] [Table 32]

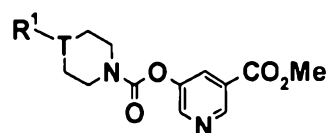


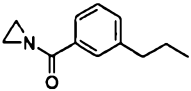
Ex No.	R ¹	R ⁴	Sal
409	Ph(CH ₂) ₃	CONH ₂	free
410	Ph	CONH ₂	free
411	Ph(CH ₂) ₅	CONH(CH ₂) ₂ OH	2HCl
412	Ph(CH ₂) ₅	CONH ₂	free
413	4-(3-FPhCH ₂ O)PhCH ₂	H	2HCl
414	BIP4(CH ₂) ₂	CO ₂ H	Na
415	BIP4(CH ₂) ₂	CONH ₂	free

[0133] [Table 33]

Ex No.	Str	Sal
416		p-tol
417		free
418		free
419		p-tol
420		oxal
421		free
422		HCl
423		free

[0134] [Table 34]



Ex No.	T	R ¹	Sal
424	CH	Ph(CH ₂) ₂	free
425	N	Ph(CH ₂) ₂	free
426	CH	Ph(CH ₂) ₃	free
427	CH	4-H ₂ NCOPh(CH ₂) ₂	free
428	CH	3-cHex(CH ₂) ₂ OPhO	free
429	N	Ph(CH ₂) ₃	free
430	CH	4-cHex(CH ₂) ₂ OPhO	free
431	CH	4-(3-MeOPhCH ₂ O)PhO	free
432	CH	4-(3-MeOCOPhO)PhO	free
433	CH	3-PYRRICOPh(CH ₂) ₂	free
434	CH	3-PIPEICOPh(CH ₂) ₂	free
435	CH		free
436	CH	3-H ₂ NCONHPh(CH ₂) ₂	free
437	CH	3-PIPEICONHPh(CH ₂) ₂	free

[0135] [Table 35]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
001	207(M+H) ⁺ FAB
002	1.59 – 1.74 (2H, br), 1.90 – 2.05 (2H, br), 3.33 – 3.45 (1H, br), 3.45 – 3.55 (1H, br), 3.65 – 3.79 (1H, br), 3.84 – 3.94 (1H, br), 4.45 – 4.55 (1H, m), 5.07 (2H, s), 6.97 (4H, s), 7.15 (1H, dt, <i>J</i> = 2.4, 8.1Hz), 7.24 – 7.30 (2H, m), 7.40 – 7.47 (2H, m), 7.64 – 7.66 (1H, m), 8.41 – 8.45 (2H, m) , DMSO : 423(M+H) ⁺ FAB
003	1.40 – 1.70 (2H, m), 1.85 (2H, d, <i>J</i> = 12.7Hz), 3.10 (1H, t, <i>J</i> = 12.7Hz) 3.25 (1H, t, <i>J</i> = 12.2Hz), 3.65 – 3.75 (1H, m), 4.06 (1H, d, <i>J</i> = 12.2Hz), 4.23 (1H, d, <i>J</i> = 12.7Hz), 5.26 (2H, s), 7.14 – 7.22 (3H, m), 7.29 – 7.34 (2H, m), 7.42 – 7.50 (2H, m), 7.64 – 7.67 (1H, m), 8.03 (2H, d, <i>J</i> = 9.3Hz), 8.44 – 8.45 (2H, m) , DMSO : 435(M+H) ⁺ FAB
004	436(M+H) ⁺ FAB
005	424(M+H) ⁺ FAB
006	438(M+H) ⁺ FAB
007	438(M+H) ⁺ FAB
008	418(M+H) ⁺ FAB
009	411(M+H) ⁺ FAB
010	1.10 – 1.30 (2H, br), 1.64 (2H, d, <i>J</i> = 12.7Hz), 1.71 – 1.82 (1H, m), 2.56 (2H, d, <i>J</i> = 7.4Hz), 2.83 (1H, t, <i>J</i> = 11.8Hz), 2.99 (1H, t, <i>J</i> = 11.8Hz), 4.00 (1H, d, <i>J</i> = 11.8Hz), 4.15 (1H, d, <i>J</i> = 11.8Hz), 7.16 – 7.23 (3H, m), 7.26 – 7.32 (2H, m), 7.44 (1H, dd, <i>J</i> = 4.4, 8.3Hz), 7.59 – 7.64 (1H, m), 8.40 (1H, d, <i>J</i> = 2.0Hz), 8.43 (1H, d, <i>J</i> = 4.4Hz) , DMSO : 297(M+H) ⁺ FAB
011	1.59 – 1.75 (2H, br), 1.90 – 2.06 (2H, br), 3.33 – 3.43 (1H, br), 3.45 – 3.55 (1H, br), 3.65 – 3.79 (1H, br), 3.83 – 3.94 (1H, br), 4.60 – 4.69 (1H, m), 5.09 (2H, s), 6.57 – 6.66 (3H, m), 7.19 (1H, t, <i>J</i> = 8.3Hz), 7.30 – 7.47 (6H, m), 7.62 – 7.66 (1H, m), 8.41 – 8.45 (2H, m) , DMSO : 405(M+H) ⁺ FAB
012	1.59 – 1.74 (2H, br), 1.90 – 2.05 (2H, br), 3.33 – 3.43 (1H, br), 3.45 – 3.55 (1H, br), 3.65 – 3.79 (1H, br), 3.84 – 3.94 (1H, br), 4.47 – 4.55 (1H, m), 5.04 (2H, s), 6.95 (4H, s), 7.30 – 7.46 (6H, m), 7.61 – 7.66 (1H, m), 8.41 – 8.45 (2H, m) , DMSO : 405(M+H) ⁺ FAB
013	1.59 – 1.76 (2H, br), 1.90 – 2.05 (2H, br), 2.69 (3H, s), 3.33 – 3.45 (1H, br), 3.45 – 3.60 (1H, br), 3.65 – 3.79 (1H, br), 3.84 – 3.94 (1H, br), 4.48 – 4.57 (1H, m), 5.07 (2H, s), 6.97 (4H, s), 7.15 (1H, dt, <i>J</i> = 2.4, 8.3Hz), 7.24 – 7.30 (2H, m), 7.40 – 7.47 (2H, m), 7.81 (1H, d, <i>J</i> = 8.7Hz), 8.19 (1H, dd, <i>J</i> = 2.5, 8.3Hz), 8.74 (1H, d, <i>J</i> = 2.4Hz) , DMSO : 437(M+H) ⁺ FAB
014	1.50 – 1.70 (2H, br), 1.89 (2H, d, <i>J</i> = 12.7Hz), 3.11 (1H, t, <i>J</i> = 11.7Hz), 3.27 (1H, t, <i>J</i> = 11.7Hz), 3.75 (1H, tt, <i>J</i> = 3.2, 11.3Hz), 4.07 (1H, d, <i>J</i> = 11.7Hz), 4.23 (1H, d, <i>J</i> = 11.7Hz), 7.45 (1H, dd, <i>J</i> = 5.4, 8.3Hz), 7.57 (2H, t, <i>J</i> = 7.8Hz), 7.63 – 7.69 (2H, m), 8.03 (2H, dd, <i>J</i> = 1.4, 8.3Hz), 8.44 (2H, dd, <i>J</i> = 1.4, 4.9Hz) , DMSO : 311(M+H) ⁺ FAB

[0136] [Table 36]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
015	1.55 – 1.75 (2H, br), 1.83 (2H, d, <i>J</i> = 12.2Hz), 2.81 (1H, tt, <i>J</i> = 3.4, 12.2Hz), 4.15 (1H, d, <i>J</i> = 12.2Hz), 4.31 (1H, d, <i>J</i> = 12.2Hz), 7.10 – 7.17 (2H, m), 7.31 – 7.37 (2H, m), 7.44 – 7.48 (1H, m), 7.63 – 7.67 (1H, m), 8.43 – 8.46 (2H, m) , DMSO : 301(M+H) ⁺ FAB
016	326(M+H) ⁺ FAB
017	2.46 – 2.62 (6H, m), 2.72 – 2.80 (2H, m), 3.40 – 3.50 (2H, br), 3.57 - 3.65 (2H, br), 7.16 – 7.32 (5H, m), 7.45 (1H, dd, <i>J</i> = 4.6, 8.3), 7.61 - 7.65 (1H, m), 8.42 – 8.45 (2H, m) , DMSO : 312(M+H) ⁺ FAB
018	1.60 – 1.75 (2H, br), 1.95 – 2.10 (2H, br), 3.33 – 3.41 (1H, br), 3.47 – 3.56 (1H, br), 3.69 – 3.78 (1H, br), 3.84 – 4.03 (1H, br), 5.96 (2H, s), 6.46 (1H, dd, <i>J</i> = 2.4, 8.7Hz), 6.73 (1H, d, <i>J</i> = 2.4Hz), 6.82 (1H, d, <i>J</i> = 8.7Hz), 7.74 – 7.78 (1H, m), 8.04 (1H, d, <i>J</i> = 8.3Hz), 8.62 (1H, d, <i>J</i> = 4.9Hz), 8.72 (1H, s) , DMSO : 343(M+H) ⁺ FAB
019	1.20 – 1.40 (2H, br), 1.79 – 1.89 (2H, br), 1.94 – 2.04 (1H, m), 2.94 (1H, t, <i>J</i> = 11.8Hz), 3.07 (1H, t, <i>J</i> = 11.8Hz), 3.80 (2H, d, <i>J</i> = 6.3Hz), 4.05 (1H, d, <i>J</i> = 11.8Hz), 4.22 (1H, d, <i>J</i> = 11.8Hz), 5.95 (2H, s), 6.37 (1H, dd, <i>J</i> = 2.5, 8.3Hz), 6.64 (1H, d, <i>J</i> = 2.5Hz), 6.80 (1H, d, <i>J</i> = 8.3Hz), 7.45 (1H, dd, <i>J</i> = 4.9, 8.3Hz), 7.630 (1H, d, <i>J</i> = 8.3Hz), 8.40 – 8.45 (2H, m) , DMSO : 357(M+H) ⁺ FAB
020	1.16 – 1.32 (2H, br), 1.64 – 1.82 (3H, m), 2.92 (1H, t, <i>J</i> = 11.7Hz), 3.06 (1H, t, <i>J</i> = 11.7Hz), 3.96 (2H, t, <i>J</i> = 6.4Hz), 4.01 (1H, d, <i>J</i> = 11.7Hz), 4.17 (1H, d, <i>J</i> = 11.7Hz), 5.95 (2H, s), 6.37 (1H, dd, <i>J</i> = 2.5, 8.3Hz), 6.63 (1H, d, <i>J</i> = 2.5Hz), 6.80 (1H, d, <i>J</i> = 8.3Hz), 7.74 – 7.80 (1H, m), 8.02 – 8.07 (1H, m), 8.61 (1H, d, <i>J</i> = 5.4Hz), 8.71 (1H, brs) , DMSO : 371(M+H) ⁺ FAB
021	1.63 – 1.80 (2H, br), 1.97 – 1.99 (2H, br), 3.35 – 3.45 (1H, br), 3.50 – 3.60 (1H, br), 3.71 – 3.79 (1H, br), 3.86 – 3.95 (1H, br), 4.63 – 4.70 (1H, m), 6.94 (1H, t, <i>J</i> = 7.3Hz), 7.01 (2H, d, <i>J</i> = 8.3Hz), 7.30 (2H, t, <i>J</i> = 7.3Hz), 7.76 (1H, dd, <i>J</i> = 4.8, 8.3Hz), 8.05 (1H, d, <i>J</i> = 8.3Hz), 8.62 (1H, d, <i>J</i> = 4.8Hz), 8.73 (1H, s) , DMSO : 299(M+H) ⁺ FAB
022	2.85 – 2.98 (2H, m), 3.68 (1H, t, <i>J</i> = 4.9Hz), 3.84 (1H, t, <i>J</i> = 5.8Hz), 4.62 (1H, s), 4.82 (1H, s), 7.20 – 7.28 (4H, m), 7.46 (1H, dd, <i>J</i> = 4.4, 8.3Hz), 7.65 – 7.69 (1H, m), 8.44 – 8.47 (2H, m) , DMSO : 255(M+H) ⁺ FAB
023	3.20 – 3.24 (4H, br), 3.55 – 3.65 (2H, br), 3.72 - 3.80 (2H, br), 6.83 (1H, t, <i>J</i> = 7.1), 7.00 (2H, d, <i>J</i> = 8.3), 7.25 (2H, t, <i>J</i> = 7.3), 7.46 (1H, dd, <i>J</i> = 4.4, 8.3), 7.63 – 7.69 (1H, m), 8.43 – 8.46 (2H, m) , DMSO : 284(M+H) ⁺ FAB
024	1.61 - 1.80 (2H, m), 1.97 - 2.12 (2H, m), 3.28 - 3.62 (2H, m), 3.68 – 3.99 (2H, m), 4.71 – 4.80 (1H, m), 7.05 (2H, d, <i>J</i> = 8.8Hz), 7.12 – 7.22 (1H, m), 7.45 (1H, dd, <i>J</i> = 4.9Hz, 8.3Hz), 7.61 – 7.68 (1H, m), 7.78 – 7.88 (3H, m), 8.41 – 8.46 (2H, m) , DMSO : 342(M+H) ⁺ FAB
025	356(M+H) ⁺ FAB
026	370(M+H) ⁺ FAB
027	342(M+H) ⁺ FAB

[0137] [Table 37]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
028	356(M+H) ⁺ FAB
029	481(M+H) ⁺ FAB
030	1.60 – 1.78 (2H, m), 1.93 – 2.06 (2H, m), 3.04 (6H, s), 3.30 – 3.93 (4H, m), 4.49 – 4.56 (1H, m), 5.07 (2H, s), 6.96 (4H, s), 7.12 – 7.18 (1H, m), 7.24 – 7.30 (2H, m), 7.40 – 7.52 (2H, m), 8.05 – 8.08 (2H, m) , DMSO : 466(M+H) ⁺ FAB
031	424(M+H) ⁺ FAB
032	2.04 – 2.20 (1H, m), 2.40 – 2.60 (1H, m), 3.10 – 4.10 (8H, m), 4.32 – 4.44 (2H, m), 7.41 – 7.50 (3H, m), 7.66 – 7.82 (2H, m), 8.05 – 8.16 (1H, m), 8.62 (1H, br), 8.80 (1H, d, <i>J</i> = 12.7Hz), 11.58 (1H, br) , DMSO : 312(M+H) ⁺ FAB
033	1.25 – 1.35 (2H, m), 1.55 – 1.66 (2H, m), 1.70 – 1.83 (2H, m), 2.60 (2H, t, <i>J</i> = 7.3Hz), 3.00 – 3.22 (4H, m), 3.40 – 3.70 (4H, m), 4.00 – 4.35 (2H, m), 7.15 – 7.33 (5H, m), 7.62 (1H, br), 7.85 (1H, br), 8.50 – 8.65 (2H, m), 10.90 – 11.40 (1H, br) , DMSO : 354(M+H) ⁺ FAB
034	3.09 (4H, br), 3.50 – 3.80 (4H, m), 5.04 (2H, s), 6.94 (4H, d, <i>J</i> = 1.7Hz), 7.30 – 7.49 (6H, m), 7.63 – 7.68 (1H, m), 8.43 – 8.46 (2H, m) , DMSO : 390(M+H) ⁺ FAB
035	1.10 – 1.32 (2H, m), 1.46 – 1.60 (3H, m), 1.80 (2H, d, <i>J</i> = 11.7Hz), 2.62 (2H, t, <i>J</i> = 7.8Hz), 2.88 (1H, t, <i>J</i> = 12.2Hz), 3.03 (1H, t, <i>J</i> = 12.2Hz), 4.17 (1H, t, <i>J</i> = 12.2Hz), 7.16 – 7.23 (3H, m), 7.27 – 7.31 (2H, m), 7.89 (1H, dd, <i>J</i> = 5.3, 8.8Hz), 8.18 – 8.22 (1H, m), 8.69 (1H, dd, <i>J</i> = 1.0, 5.3Hz), 8.82 (1H, d, <i>J</i> = 2.5Hz) , DMSO : 311(M+H) ⁺ FAB
036	1.52 – 1.68 (2H, br), 1.88 – 2.01 (2H, br), 3.22 – 3.33 (1H, br), 3.37 – 3.48 (1H, br), 3.65 – 3.75 (2H, m), 3.82 – 3.91 (1H, br), 4.56 (2H, s), 7.26 – 7.32 (1H, m), 7.36 (4H, d, <i>J</i> = 4.4Hz), 7.70 (1H, dd, <i>J</i> = 4.9, 8.3Hz), 7.95 (1H, dd, <i>J</i> = 1.0, 8.3Hz), 8.58 (1H, d, <i>J</i> = 4.9Hz), 8.66 (1H, s) , DMSO : 313(M+H) ⁺ FAB
037	1.69 (2H, d, <i>J</i> = 12.7Hz), 1.91 – 2.11 (2H, m), 3.33 (1H, t, <i>J</i> = 12.7Hz), 3.47 (1H, t, <i>J</i> = 12.7Hz), 3.93 – 4.07 (2H, m), 4.13 (1H, d, <i>J</i> = 12.7Hz), 7.23 (1H, t, <i>J</i> = 7.4Hz), 7.35 (2H, t, <i>J</i> = 7.4Hz), 7.52 – 7.55 (2H, m), 7.81 (1H, dd, <i>J</i> = 5.4, 8.3Hz), 8.10 – 8.14 (1H, m), 8.63 (1H, d, <i>J</i> = 4.9Hz), 8.77 (1H, d, <i>J</i> = 2.4Hz) , DMSO : 299(M+H) ⁺ FAB
038	2.58 (1H, br), 2.64 (1H, br), 3.67 (1H, br), 3.83 (1H, br), 4.13 (1H, s), 4.32 (1H, s), 6.21 (1H, s), 7.29 (1H, t, <i>J</i> = 7.3Hz), 7.37 (2H, t, <i>J</i> = 7.3Hz), 7.44 – 7.50 (3H, m), 7.67 (1H, d, <i>J</i> = 8.3Hz), 8.44 – 8.47 (2H, m) , DMSO : 281(M+H) ⁺ FAB
039	1.95 (3H, s), 2.00 – 2.16 (2H, br), 2.39 – 2.47 (2H, br), 3.20 – 3.30 (1H, br), 3.35 – 3.45 (1H, br), 3.63 – 3.73 (1H, br), 3.79 – 3.89 (1H, br), 7.29 – 7.34 (1H, m), 7.37 – 7.46 (5H, m), 7.60 – 7.64 (1H, m), 8.40 – 8.43 (2H, m) , DMSO : 325(M+H) ⁺ FAB

[0138] [Table 38]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
040	1.61 – 1.81 (2H, m), 1.83 (2H, d, J = 12.2Hz), 2.77 – 2.87 (1H, m), 3.05 (1H, t, J = 12.2Hz), 3.19 (1H, t, J = 12.2Hz), 4.16 (1H, d, J = 12.2Hz), 4.33 (1H, d, J = 12.2Hz), 7.19 – 7.24 (1H, m), 7.27 – 7.36 (5H, m), 7.91 (1H, dd, J = 5.3, 8.3Hz), 7.36 (1H, d, J = 8.3Hz), 8.70 (1H, d, J = 4.9Hz), 8.85 (1H, s) , DMSO : 283(M+H) ⁺ FAB
041	35(M+H) ⁺ FAB
042	1.60 – 1.76 (2H, m), 1.92 – 2.05 (2H, m), 3.30 – 3.92 (4H, m), 4.48 – 4.55 (1H, m), 5.07 (2H, s), 6.95 (4H, s), 7.12 – 7.18 (1H, m), 7.23 – 7.30 (2H, m), 7.39 – 7.48 (1H, m), 7.93 – 7.96 (1H, m), 8.44 (1H, d, J = 2.0Hz), 8.52 (1H, d, J = 2.0Hz) , DMSO : 457(M+H) ⁺ FAB
043	1.14 – 1.35 (2H, m), 1.68 – 1.84 (5H, m), 2.89 (1H, t, J = 11.7Hz), 3.05 (1H, t, J = 11.7Hz), 3.96 – 4.21 (4H, m), 6.98 (2H, d, J = 8.8Hz), 7.16 (1H, brs), 7.44 (1H, dd, J = 4.9, 8.3Hz), 7.60 – 7.65 (1H, m), 7.76 – 7.87 (3H, m), 8.40 – 8.44 (2H, m) , DMSO : 370(M+H) ⁺ FAB
044	1.60 – 1.75 (2H, m), 1.92 – 2.05 (2H, m), 3.30 – 3.92 (4H, m), 4.46 – 4.55 (1H, m), 5.07 (2H, s), 6.95 (4H, s), 7.12 – 7.18 (1H, m), 7.24 – 7.29 (2H, m), 7.40 – 7.47 (1H, m), 8.06 – 8.086 (1H, m), 8.47 (1H, d, J = 2.0Hz), 8.59 (1H, d, J = 2.0Hz) , DMSO : 501(M ⁺)FAB
045	1.60 – 1.78 (2H, m), 1.93 – 2.06 (2H, m), 3.31 – 3.57 (6H, m), 3.70 – 3.93 (6H, m), 4.49 – 4.56 (1H, m), 5.07 (2H, s), 6.96 (4H, s), 7.12 – 7.17 (1H, m), 7.24 – 7.30 (2H, m), 7.41 – 7.47 (1H, m), 7.78 (1H, s), 8.19 – 8.22 (1H, m), 8.30 – 8.33 (1H, m) , DMSO : 508(M+H) ⁺ FAB
046	1.51-1.70 (2H, m), 1.87-2.02 (2H, m), 3.20-3.31 (1H, m), 3.36-3.47 (1H, m), 3.62-3.72 (1H, m), 3.66-3.77 (1H, m), 3.80-3.93 (1H, m), 4.61 (2H, s), 7.33 (1H, br s), 7.42 (2H, d, J=8.3Hz), 7.44 (1H, dd, J=8.3, 4.4Hz), 7.63 (1H, ddd, J=8.3, 2.4, 1.5Hz), 7.86 (2H, d, J=8.3Hz), 7.94 (1H, br s), 8.42 (1H, s), 8.43 (1H, dd, J=6.3, 1.5Hz) , DMSO : 356(M+H) ⁺ FAB
047	340 (M+H) ⁺ FAB
048	390(M+H) ⁺ FAB
049	1.40 – 1.52 (2H, m), 1.55 – 1.65 (2H, m), 2.30 – 2.45 (4H, m), 2.60 (2H, t, J = 7.6Hz), 3.38 – 3.64 (4H, m), 7.12 – 7.22 (3H, m), 7.25 – 7.31 (2H, m), 7.44 (1H, dd, J = 4.8, 7.5Hz), 7.60 – 7.65 (1H, m), 8.40 – 8.45 (2H, m) , DMSO : 340(M+H) ⁺ FAB
050	308(M+H) ⁺ FAB
051	1.60 – 1.84 (2H, br), 1.92 – 2.06 (2H, br), 3.40 – 3.52 (1H, br), 3.55 – 3.75 (2H, br), 3.79 – 3.91 (1H, br), 4.59– 4.65 (1H, m), 5.08 (2H, s), 6.97 (1H, dd, J = 2.9, 9.3Hz), 7.15 (1H, d, J = 2.9Hz), 7.22 (1H, d, J = 8.8Hz), 7.31 – 7.47 (5H, m), 7.88 (1H, dd, J = 5.4, 8.8Hz), 8.20 (1H, d, J = 8.3Hz), 8.68 (1H, d, J = 5.4Hz), 8.83 (1H, d, J = 1.9Hz) , DMSO : 439(M+H) ⁺ FAB

[0139] [Table 39]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
052	311(M+H) ⁺ FAB
053	1.07 – 1.27 (2H, m), 1.53 (2H, q, J = 6.4Hz), 1.62 – 1.76 (3H, m), 2.90 (1H, t, J = 13.2Hz), 3.04 (1H, t, J = 13.2Hz), 3.50 (2H, t, J = 6.4Hz), 3.99 (1H, d, J = 13.2Hz), 4.15 (1H, d, J = 13.2Hz), 4.46 (2H, s), 7.26 – 7.39 (5H, m), 7.73 – 7.78 (1H, m), 8.03 (1H, d, J = 8.3Hz), 8.62 (1H, d, J = 4.4Hz), 8.70 (1H, s) , DMSO : 341(M+H) ⁺ FAB
054	374, 376(M+H) ⁺ FAB
055	1.10 – 1.30 (2H, m), 1.64 (2H, d, J = 13.2Hz), 1.71 – 1.83 (1H, m), 2.56 (2H, d, J = 7.4Hz), 2.83 (1H, t, J = 12.2Hz), 2.98 (1H, t, J = 12.2Hz), 3.36 (3H, s), 3.99 (1H, d, J = 12.2Hz), 4.15 (1H, d, J = 12.2Hz), 4.65 (2H, s), 7.17 – 7.22 (3H, m), 7.27 – 7.32 (2H, m), 7.43 (1H, d, J = 8.8Hz), 7.60 (1H, dd, J = 2.5, 8.8Hz), 8.33 (1H, d, J = 2.5Hz) , DMSO : 341(M+H) ⁺ FAB
056	523(M+H) ⁺ FAB
057	342(M+H) ⁺ FAB
058	471(M+H) ⁺ FAB
059	389(M+H) ⁺ FAB
060	299(M+H) ⁺ FAB
061	1.58 – 1.75 (2H, m), 1.90 – 2.04 (2H, m), 2.69 (2H, t, J = 7.8Hz), 2.89 (2H, t, J = 7.8Hz), 3.30 – 3.91 (7H, m), 4.47 – 4.55 (1H, m), 5.07 (2H, s), 6.95 (4H, s), 7.12 – 7.18 (1H, m), 7.23 – 7.30 (2H, m), 7.39 – 7.47 (1H, m), 7.51 – 7.55 (1H, m), 8.24 – 8.27 (1H, m), 8.30 – 8.34 (1H, m) , DMSO : 509(M+H) ⁺ FAB
062	356(M+H) ⁺ FAB
063	1.07-1.31 (2H, m), 1.42-1.55 (1H, m), 1.52-1.64 (2H, m), 1.72-1.86 (2H, m), 2.68 (2H, t, J=7.5Hz), 2.78-2.91 (1H, m), 2.94-3.07 (1H, m), 3.93-4.07 (1H, m), 4.09-4.23 (1H, m), 7.26 (1H, br s), 7.29 (2H, d, J=8.6Hz), 7.44 (1H, dd, J=8.6, 4.8Hz), 7.61 (1H, ddd, J=8.6, 2.7, 1.5Hz), 7.80 (2H, d, J=8.0Hz), 7.89 (1H, br s), 8.41 (1H, d, J=2.7Hz), 8.42 (1H, dd, J=4.8, 1.1Hz) , DMSO : 354(M+H) ⁺ FAB
064	354(M+H) ⁺ FAB
065	1.34-1.57 (2H, m), 1.78-1.90 (2H, m), 2.40-2.48 (1H, m), 2.92-3.08 (1H, m), 3.07-3.23 (1H, m), 3.98-4.13 (1H, m), 4.14-4.28 (1H, m), 6.44 (1H, dd, J=16.1, 5.9Hz), 6.50 (1H, d, J=16.1Hz), 7.30 (1H, br s), 7.45 (1H, dd, J=8.3, 4.4Hz), 7.48 (2H, d, J=8.3Hz), 7.63 (1H, ddd, J=8.3, 2.5, 1.5Hz), 7.83 (2H, d, J=8.3Hz), 7.92 (1H, br s), 8.43 (1H, d, J=1.9Hz), 8.43 (1H, dd, J=4.4, 1.9Hz) , DMSO : 352(M+H) ⁺ FAB
066	1.03 – 1.23 (2H, m), 1.35 – 1.43 (2H, m), 1.46 – 1.62 (1H, m), 1.72 – 1.87 (4H, m), 2.82 – 2.92 (3H, m), 3.03 (1H, t, J = 11.8Hz), 3.74 (3H, s), 4.01 (1H, d, J = 11.8Hz), 4.17 (1H, d, J = 11.8Hz), 7.11 – 7.21 (2H, m), 7.42 – 7.49 (2H, m), 7.52 – 7.56 (1H, m), 7.59 – 7.63 (1H, m), 8.40 – 8.44 (2H, m) , DMSO : 379(M+H) ⁺ ESI

[0140] [Table 40]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
067	308(M+H) ⁺ FAB
068	339(M+H) ⁺ FAB
069	1.04-1.26 (2H, m), 1.35-1.45 (2H, m), 1.48-1.61 (1H, m), 1.70-1.83 (4H, m), 2.80-2.94 (1H, m), 2.94-3.10 (1H, m), 3.96-4.06 (1H, m), 4.03 (2H, t, J=6.4Hz), 4.12-4.22 (1H, m), 6.96 (2H, d, J=8.8Hz), 7.15 (1H, br s), 7.44 (1H, dd, J=8.3, 4.9Hz), 7.61 (1H, ddd, J=8.3, 2.9, 1.5Hz), 7.81 (1H, br s), 7.83 (2H, d, J=8.8Hz), 8.41 (1H, d, J=2.4Hz), 8.42 (1H, dd, J=4.9, 1.4Hz) , DMSO : 384(M+H) ⁺ FAB
070	1.57 – 1.75 (2H, br), 1.90 – 2.06 (2H, br), 3.30 – 3.42 (1H, br), 3.45 – 3.56 (1H, br), 3.65 – 3.78 (1H, br), 3.80 – 3.95 (1H, br), 4.55– 4.61 (1H, m), 5.14 (2H, s), 6.95 (1H, dd, J = 2.9, 9.3Hz), 7.14 – 7.18 (2H, m), 7.31 – 7.48 (6H, m), 7.62 – 7.67 (1H, m), 8.42 – 8.45 (2H, m) , DMSO : 439(M+H) ⁺ FAB
071	486(M+H) ⁺ FAB
072	385(M+H) ⁺ FAB
073	578(M+H) ⁺ FAB
074	313(M+H) ⁺ FAB
075	441(M+H) ⁺ FAB
076	439(M+H) ⁺ FAB
077	1.21 (3H, t, J = 7.4Hz), 1.58 – 1.78 (2H, m), 1.83 (2H, d, J = 12.7Hz), 2.77 (1H, tt, J = 3.8, 12.2Hz), 2.98 (1H, t, J = 12.2Hz), 3.14 (1H, t, J = 12.2Hz), 4.10 – 4.21 (3H, m), 4.31 (1H, d, J = 12.2Hz), 4.76 (2H, s), 6.76 (1H, dd, J = 2.0, 7.4Hz), 6.87 (1H, t, J = 2.0Hz), 6.90 (1H, d, J = 7.4Hz), 7.23 (1H, t, J = 7.8Hz), 7.46 (1H, dd, J = 4.9, 8.3Hz), 7.64 – 7.67 (1H, m), 8.42 – 8.47 (2H, br) , DMSO : 385(M+H) ⁺ FAB
078	1.58 – 1.78 (2H, m), 1.83 (2H, d, J = 12.2Hz), 2.77 (1H, tt, J = 3.4, 12.2Hz), 2.98 (1H, t, J = 12.2Hz), 3.14 (1H, t, J = 12.2Hz), 4.15 (1H, d, J = 12.2Hz), 4.31 (1H, d, J = 12.2Hz), 5.10 (2H, s), 6.84 – 6.90 (2H, m), 6.95 (1H, t, J = 2.0Hz), 7.23 (1H, t, J = 7.8Hz), 7.31 – 7.48 (6H, m), 7.64 – 7.67 (1H, m), 8.42 – 8.47 (2H, m) , DMSO : 389(M+H) ⁺ FAB
079	461(M+H) ⁺ FAB
080	1.40-1.66 (2H, m), 1.88-2.00 (2H, m), 2.82-2.97 (1H, m), 2.97-3.14 (1H, m), 3.47-3.57 (1H, m), 4.01-4.17 (1H, m), 4.18-4.33 (1H, m), 5.26 (2H, s), 7.16-7.23 (1H, m), 7.30 (2H, d, J=9.0Hz), 7.30-7.36 (2H, m), 7.41-7.46 (1H, m), 7.45-7.51 (1H, m), 7.62 (1H, ddd, J=8.3, 2.7, 1.5Hz), 7.81 (2H, d, J=8.8Hz), 8.40 (1H, d, J=2.4Hz), 8.42 (1H, dd, J=4.7, 1.5Hz) , DMSO : 471(M+H) ⁺ FAB
081	1.10-1.34 (2H, m) 1.70-1.80 (2H, m), 1.80-1.92 (1H, m), 2.80-2.95 (1H, m), 2.95-3.10 (1H, m), 2.70-3.95 (1H, br s), 3.34 (2H, d, J=6.4Hz), 3.95-4.07 (1H, m), 4.11-4.23 (1H, m), 4.48 (2H, s), 7.25-7.38 (7H, m), 7.44 (1H, dd, J=8.3, 4.6Hz), 7.62 (1H, ddd, J=8.3, 2.6 1.2Hz) , DMSO : 327(M+H) ⁺ FAB
082	462(M ⁺)FAB
083	418(M+H) ⁺ FAB

[0141] [Table 41]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
084	326(M+H) ⁺ FAB
085	2.49 – 2.62 (6H, m), 2.73 – 2.81 (2H, m), 3.40 – 3.66 (4H, m), 7.15 – 7.32 (5H, m), 7.93 (1H, t, J = 1.9Hz), 8.44 (1H, d, J = 2.4Hz), 8.52 (1H, d, J = 2.0Hz) , DMSO : 346(M+H) ⁺ FAB
086	2.49 – 2.62 (6H, m), 2.73 – 2.81 (2H, m), 3.46 (2H, br), 3.62 (2H, br), 3.90 (3H, s), 7.15 – 7.32 (5H, m), 8.11 (1H, dd, J = 2.0, 2.7Hz), 8.70 (1H, d, J = 2.8Hz), 8.94 (1H, d, J = 1.7Hz) , DMSO : 370(M+H) ⁺ FAB
087	1.63 – 1.80 (2H, br), 1.97 – 2.11 (2H, br), 3.33 – 3.41 (1H, br), 3.43 – 3.58 (1H, br), 3.68 – 3.82 (1H, br), 3.83 – 3.96 (1H, br), 4.72– 4.80 (1H, m), 7.43 – 7.48 (2H, m), 7.59 (1H, dd, J = 3.2, 8.8Hz), 7.62 – 7.67 (1H, m), 8.19 (1H, d, J = 2.2Hz), 8.43 – 8.45 (2H, m) , DMSO : 334(M+H) ⁺ FAB
088	1.39-1.65 (2H, m), 1.88-1.98 (2H, m), 2.83-3.13 (2H, m), 3.46-3.55 (1H, m), 4.03-4.33 (2H, m), 5.23 (2H, s), 7.29 (2H, d, J=8.8Hz), 7.33-7.51 (6H, m), 7.62 (1H, ddd, J=1.5, 2.9, 8.3Hz), 7.80 (2H, d, J=8.8Hz), 8.40 (1H, d, J=2.4Hz), 8.42 (1H, dd, J=1.5, 4.9Hz) , DMSO : 453(M+H) ⁺ FAB
089	1.40-1.65 (2H, m), 1.88-1.99 (2H, m), 2.83-3.14 (2H, m), 3.47-3.57 (1H, m), 4.03-4.34 (2H, m), 5.30 (2H, s), 7.31 (2H, d, J=8.8Hz), 7.44 (1H, dd, J=4.9, 8.3Hz), 7.59-7.68 (2H, m), 7.79-7.87 (4H, m), 7.96-7.98 (1H, m), 8.40 (1H, d, J=2.4Hz), 8.42 (1H, dd, J=1.5, 4.9Hz) , DMSO : 478(M+H) ⁺ FAB
090	469(M+H) ⁺ FAB
091	473(M+H) ⁺ FAB
092	334(M+H) ⁺ FAB
093	424(M+H) ⁺ FAB
094	419(M+H) ⁺ FAB
095	487(M+H) ⁺ FAB
096	385(M+H) ⁺ FAB
097	437(M+H) ⁺ FAB
098	1.06-1.26 (2H, m), 1.37-1.44 (2H, m), 1.50-1.60 (1H, m), 1.73-1.82 (4H, m), 2.86 (1H, t, J=12.2Hz), 2.94 (6H, s), 3.05 (1H, t, J=12.2Hz), 3.97-4.04 (3H, m), 4.18 (1H, d, J=11.7Hz), 6.96 (2H, d, J=8.8Hz), 7.36 (2H, d, J=8.8Hz), 7.73 (1H, dd, J=4.8, 8.3Hz), 7.96-8.01 (1H, m), 8.59 (1H, dd, J=1.5, 4.8Hz), 8.67 (1H, d, J=2.4Hz) , DMSO : 412(M+H) ⁺ FAB
099	1.02-1.22 (2H, m), 1.36-1.44 (2H, m), 1.49-1.61 (1H, m), 1.72-1.82 (4H, m), 2.75 (3H, d, J=4.4Hz), 2.87 (1H, t, J=12.2Hz), 3.02 (1H, t, J=12.2Hz), 3.98-4.05 (3H, m), 4.17 (1H, d, J=12.2Hz), 6.97 (2H, d, J=8.8Hz), 7.43 (1H, dd, J=4.4, 8.3Hz), 7.59-7.64 (1H, m), 7.78 (2H, d, J=8.3Hz), 8.22-8.27 (1H, m), 8.38-8.43 (2H, m) , DMSO : 398(M+H) ⁺ FAB

[0142] [Table 42]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
100	1.58 – 1.74 (2H, m), 1.90 – 2.06 (2H, m), 2.50 (3H, s), 3.30 - 3.95 (4H, m), 4.48 – 4.58 (3H, m), 5.07 (2H, s), 6.95 (4H, s), 7.12 - 7.18 (1H, m), 7.24 – 7.30 (2H, m), 7.40 – 7.47 (1H, m), 7.54 – 7.57 (1H, m), 8.27 – 8.34 (1H, m), 8.34 – 8.42 (1H, m) , DMSO : 495(M+H) ⁺ FAB
101	1.40-1.64 (2H, m), 1.90-2.03 (2H, m), 3.05-3.18 (1H, m), 3.20-3.34 (1H, m), 3.51-3.62 (1H, m), 3.88-4.01 (1H, m), 4.02-4.14 (1H, m), 5.16 (2H, s), 6.90-6.95 (1H, m), 6.98-7.03 (1H, m), 7.03-7.06 (1H, m), 7.13-7.19 (1H, m), 7.25-7.32 (3H, m), 7.41-7.47 (1H, m), 7.72 (1H, dd, J=8.8, 5.4Hz), 7.99 (1H, ddd, J=8.3, 2.4, 1.0Hz), 8.56-8.61 (1H, m), 8.67 (1H, d, J=2.4Hz) , DMSO : 439(M+H) ⁺ FAB
102	426(M+H) ⁺ FAB
103	1.58 – 1.78 (2H, br), 1.97 – 2.11 (2H, br), 3.30 – 3.60 (2H, br), 3.70 – 3.79 (1H, br), 3.85 – 3.96 (1H, br), 5.11 – 5.16 (3H, m), 6.79 (1H, d, J = 8.8Hz), 7.12 – 7.20 (1H, m), 7.25 – 7.30 (2H, m), 7.40 – 7.50 (3H, m), 7.61 – 7.67 (1H, m), 7.93 (1H, d, J = 3.5Hz), 8.40 – 8.46 (2H, br) , DMSO : 424(M+H) ⁺ FAB
104	1.16-1.32 (2H, m) 1.70-1.82 (2H, m), 1.79-1.91 (1H, m), 2.82-2.99 (1H, m), 2.95-3.12 (1H, m), 3.34 (2H, d, J=6.3Hz), 3.98-4.07 (1H, m), 4.11 (2H, dd, J=5.8, 1.4Hz), 4.14-4.23 (1H, m), 6.36 (1H, ddd, J=16.1, 5.8, 5.8Hz), 6.61 (1H, d, J=16.1Hz), 6.63 (1H, s), 7.21-7.29 (1H, m), 7.30-7.38 (2H, m), 7.40-7.49 (3H, m), 7.61 (1H, ddd, J=8.3, 2.4, 1.4Hz), 8.37-8.64 (2H, m), 13.12 (1H, br s) , DMSO : 353(M+H) ⁺ FAB
105	471(M+H) ⁺ FAB
106	424(M+H) ⁺ FAB
107	313(M+H) ⁺ FAB
108	1.04-1.24 (2H, br), 1.36-1.43 (2H, m), 1.48-1.61 (1H, m), 1.72-1.82 (4H, m), 2.87 (1H, t, J=11.7Hz), 3.03 (1H, t, J=11.7Hz), 4.01 (1H, d, J=11.7Hz), 4.07 (2H, t, J=6.4Hz), 4.17 (1H, d, J=11.7Hz), 7.10 (2H, d, J=8.8Hz), 7.44 (1H, dd, J=5.4, 8.3Hz), 7.59-7.63 (1H, m), 7.76 (2H, d, J=8.8Hz), 8.40-8.44 (2H, m) , DMSO : 366(M+H) ⁺ FAB
109	223(M+H) ⁺ FAB
110	1.23-1.43 (2H, m), 1.86 (2H, d, J=12.7Hz), 1.97-2.09 (1H, m), 2.93 (1H, t, J=12.2Hz), 3.09 (1H, t, J=12.2Hz), 3.88 (2H, d, J=12.7Hz), 4.07 (1H, d, J=12.2Hz), 4.23 (1H, d, J=12.2Hz), 6.90-6.96 (3H, m), 7.26-7.31 (2H, m), 7.44 (1H, dd, J=4.4, 8.3Hz), 7.61-7.65 (1H, m), 8.41-8.44 (2H, m) , DMSO : 313(M+H) ⁺ FAB
111	1.16-1.36 (2H, m), 1.67-1.85 (5H, m), 2.93 (1H, t, J=12.2Hz), 3.08 (1H, t, J=12.2Hz), 4.00 (1H, d, J=12.2Hz), 4.03 (2H, t, J=6.3Hz), 4.17 (1H, d, J=12.2Hz), 6.90-6.96 (3H, m), 7.26-7.31 (2H, m), 7.78 (1H, dd, J=4.9, 8.3Hz), 8.03-8.08 (1H, m), 8.62 (1H, dd, J=1.0, 4.9Hz), 8.72 (1H, d, J=2.5Hz) , DMSO : 327(M+H) ⁺ FAB

[0143] [Table 43]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
112	1.05 – 1.25 (2H, m), 1.47 – 1.52 (2H, m), 1.58 – 1.68 (1H, m), 1.70 – 1.84 (4H, m), 2.62 (2H, t, J = 7.4Hz), 2.87 (2H, t, J = 12.2Hz), 3.03 (1H, t, J = 12.2Hz), 4.00 (1H, d, J = 12.2Hz), 4.15 (1H, d, J = 12.2Hz), 7.15 – 7.22 (3H, m), 7.25 – 7.30 (2H, m), 7.45 (1H, dd, J = 4.9, 8.3Hz), 7.59 – 7.64 (1H, m), 8.38 – 8.44 (2H, m) , DMSO : 369(M+H) ⁺ FAB
113	1.65 – 1.75 (2H, m), 1.83 (2H, d, J = 12.2Hz), 1.98 – 2.05 (2H, m), 2.72 – 2.80 (3H, m), 2.98 (1H, t, J = 12.2Hz), 3.14 (1H, t, J = 12.2Hz), 3.97 (2H, t, J = 6.3Hz), 4.15 (1H, d, J = 11.7Hz), 4.31 (1H, d, J = 11.7Hz), 6.75 – 6.79 (1H, m), 6.83 – 6.87 (2H, m), 7.16 – 7.32 (6H, m), 7.46 (1H, dd, J = 4.9, 8.8Hz), 7.64 – 7.68 (1H, m), 8.42 – 8.47 (2H, br) , DMSO : 417(M+H) ⁺ FAB
114	1.10-1.26 (2H, m), 1.35-1.45 (2H, m), 1.48-1.62 (1H, m), 1.70-1.82 (4H, m), 2.80-2.95 (1H, m), 2.96-3.11 (1H, m), 3.96 (2H, t, J=6.4Hz), 3.97-4.07 (1H, m), 4.10-4.24 (1H, m), 6.89-6.95 (3H, m), 7.24-7.32 (2H, m), 7.44 (1H, dd, J=8.3, 3.9Hz), 7.61 (1H, ddd, J=8.3, 2.9, 1.5Hz), 8.40 (1H, d, J=2.9Hz), 8.42 (1H, dd, J=4.4, 1.5Hz) , DMSO : 341(M+H) ⁺ FAB
115	1.06-1.26 (2H, br), 1.37-1.45 (2H, m), 1.50-1.62 (1H, m), 1.72-1.88 (4H, m), 2.88 (1H, t, J=13.2Hz), 3.03 (1H, t, J=13.2Hz), 4.01 (1H, d, J=11.7Hz), 4.13 (2H, t, J=6.3Hz), 4.18 (1H, d, J=11.7Hz), 7.02 (1H, t, J=7.8Hz), 7.14 (1H, d, J=7.8Hz), 7.42-7.49 (2H, m), 7.53-7.64 (3H, m), 7.81 (1H, dd, J=1.9, 7.8Hz), 8.40-8.44 (2H, m) , DMSO : 384(M+H) ⁺ FAB
116	1.05-1.25 (2H, br), 1.36-1.45 (2H, m), 1.52-1.64 (1H, m), 1.73-1.83 (4H, m), 2.88 (1H, t, J=12.7Hz), 3.05 (1H, t, J=12.7Hz), 3.99-4.05 (3H, m), 4.18 (1H, d, J=12.7Hz), 7.05-7.09 (1H, m), 7.34 (2H, t, J=8.3Hz), 7.41-7.46 (2H, m), 7.73 (1H, dd, J=4.9, 8.3Hz), 7.92-8.02 (2H, m), 8.57-8.60 (1H, m), 8.67 (1H, d, J=2.4Hz) , DMSO : 384(M+H) ⁺ FAB
117	1.59 – 1.74 (2H, m), 1.96 – 2.03 (2H, m), 3.27 – 3.56 (2H, m), 3.70 - 3.95 (5H, m), 4.48 – 4.58 (3H, m), 5.08 (2H, s), 6.85 (1H, d, J = 16.1Hz), 6.96 (4H, s), 7.12 - 7.18 (1H, m), 7.24 – 7.30 (2H, m), 7.40 – 7.47 (1H, m), 7.72 (1H, d, J = 16.1Hz), 8.10 (1H, dd, J = 1.5Hz, 2.4Hz), 8.46 (1H, d, J = 2.4Hz), 8.75 (1H, d, J = 1.5Hz) , DMSO : 507(M+H) ⁺ FAB
118	1.60 – 1.76 (2H, m), 1.92 – 2.05 (2H, m), 3.30 – 3.55 (2H, m), 3.66 - 3.93 (2H, m), 4.48 – 4.56 (1H, m), 5.07 (2H, s), 6.95 (4H, s), 7.12 - 7.18 (1H, m), 7.23 – 7.30 (2H, m), 7.39 – 7.47 (1H, m), 7.75 – 7.82 (1H, m), 8.35 – 8.40 (1H, m), 8.50 (1H, d, J = 2.5Hz) , DMSO : 441(M+H) ⁺ FAB
119	452(M+H) ⁺ FAB
120	449(M+H) ⁺ FAB
121	437(M+H) ⁺ FAB
122	0.96 – 1.27 (5H, m), 1.60 – 1.86 (6H, m), 3.26 – 3.82 (8H, m), 3.82 (2H, d, J = 6.3Hz), 6.92 – 7.04 (3H, m), 7.36 (1H, t, J = 8.3Hz), 7.62 – 7.69 (1H, m), 7.90 (1H, br), 8.50 – 8.66 (2H, m) , DMSO : 424(M+H) ⁺ FAB
123	437(M+H) ⁺ FAB

[0144] [Table 44]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
124	2.29 (3H, s), 2.68 (2H, t, J = 7.3Hz), 2.84 (2H, t, J = 7.3Hz), 3.37 – 3.62 (8H, m), 7.12 (2H, d, J = 7.9Hz), 7.15 – 7.22 (1H, m), 7.24 – 7.32 (4H, m), 7.49 (2H, d, J = 7.8Hz), 7.80 (1H, dd, J = 4.9, 8.3Hz), 8.05 – 8.10 (1H, m), 8.63 (1H, dd, J = 1.0, 4.9Hz), 8.73 (1H, d, J = 2.4Hz) , DMSO : 340(M+H) ⁺ FAB
125	312(M+H) ⁺ FAB
126	3.46-3.59 (2H, m), 3.61-3.77 (4H, m), 3.78-3.92 (2H, m), 7.30 (1H, d, J=15.5Hz), 7.36-7.45 (2H, m), 7.48 (1H, d, J=8.0Hz), 7.54 (1H, d, J=15.5Hz), 7.71-7.76 (1H, m), 7.80 (1H, dd, J=8.6, 4.8Hz), 8.07-8.12 (1H, m), 8.64 (1H, dd, J=5.3, 1.1Hz), 8.75 (1H, d, J=2.2Hz) , DMSO : 338(M+H)ES
127	342(M+H) ⁺ ESI
128	326(M+H) ⁺ FAB
129	341(M+H) ⁺ ESI
130	354(M+H) ⁺ FAB
131	352(M+H) ⁺ FAB
132	369(M+H) ⁺ FAB
133	355(M+H) ⁺ FAB
134	426(M+H) ⁺ FAB
135	457(M+H) ⁺ FAB
136	457(M+H) ⁺ FAB
137	453(M+H) ⁺ FAB
138	3.30 – 3.82 (8H, br), 5.08 (2H, s), 7.02 (1H, d, J = 7.8), 7.06 – 7.08 (1H, m), 7.11 – 7.14 (1H, m), 7.38 – 7.47 (4H, m), 7.53 (1H, s), 7.70 – 7.80 (1H, br), 7.95 – 8.08 (1H, br), 8.58 (2H, m) , DMSO : 452(M+H) ⁺ FAB
139	385(M+H) ⁺ ESI
140	385(M+H) ⁺ ESI
141	385(M+H) ⁺ ESI
142	348(M+H) ⁺ FAB
143	362(M+H) ⁺ FAB
144	2.29 (3H, s), 3.40 – 3.71 (8H, m), 5.12 (2H, s), 7.12 (2H, d, J = 7.8Hz), 7.30 – 7.41 (5H, m), 7.49 (2H, d, J = 8.3Hz), 7.80 (1H, dd, J = 5.4, 8.3Hz), 8.02 – 8.11 (1H, m), 8.63 (1H, d, J = 5.4Hz), 8.73 (1H, d, J = 1.9Hz) , DMSO : 342(M+H) ⁺ FAB
145	329(M+H) ⁺ FAB
146	341(M+H) ⁺ FAB
147	3.44 – 3.71 (8H, m), 5.18 (2H, s), 7.10 (2H, d, J = 8.8Hz), 7.38 – 7.50 (6H, m), 7.54 (1H, s), 7.61 – 7.67 (1H, m), 8.40 – 8.44 (2H, m) , DMSO : 452(M+H) ⁺ FAB
148	432(M+H) ⁺ FAB
149	3.40 – 3.71 (8H, m), 5.28 (2H, s), 7.12 (2H, d, J = 8.8Hz), 7.40 – 7.48 (3H, m), 7.62 – 7.68 (2H, m), 7.72 (1H, d, J = 7.8Hz), 7.79 (1H, d, J = 7.3Hz), 7.84 (1H, s), 8.42 – 8.46 (2H, m) , DMSO : 486(M+H) ⁺ FAB

[0145] [Table 45]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
150	448(M+H) ⁺ FAB
151	3.43 – 3.74 (8H, m), 5.23 (2H, s), 7.10 (2H, d, J = 8.8Hz), 7.40 – 7.48 (3H, m), 7.60 – 7.67 (2H, m), 7.79 – 7.85 (2H, m), 7.95 (1H, br), 8.42 – 8.46 (2H, m) , DMSO : 443(M+H) ⁺ FAB
152	3.43 – 3.74 (8H, m), 5.20 (2H, s), 7.09 (2H, d, J = 8.8Hz), 7.14 – 7.26 (3H, m), 7.40 – 7.49 (3H, m), 7.60 – 7.68 (1H, m), 8.42 – 8.46 (2H, m) , DMSO : 454(M+H) ⁺ FAB
153	502(M+H) ⁺ FAB
154	3.42 – 3.74 (8H, m), 5.33 (2H, s), 7.13 (2H, d, J = 8.8Hz), 7.42 – 7.49 (3H, m), 7.63 – 7.67 (1H, m), 7.72 (1H, t, J = 7.8Hz), 7.94 (1H, d, J = 8.1Hz), 8.19 – 8.23 (1H, m), 8.34 (1H, br), 8.42 – 8.46 (2H, m) , DMSO : 463(M+H) ⁺ ESI
155	3.43 – 3.74 (8H, m), 5.14 (2H, s), 7.07 (2H, d, J = 8.8Hz), 7.23 (2H, t, J = 8.8Hz), 7.40 – 7.56 (5H, m), 7.60 – 7.67 (1H, m), 8.40 – 8.46 (2H, m) , DMSO : 436(M+H) ⁺ FAB
156	436(M+H) ⁺ FAB
157	419(M+H) ⁺ FAB
158	439(M+H) ⁺ ESI
159	3.43 – 3.74 (8H, m), 5.17 (2H, s), 7.10 (2H, d, J = 8.8Hz), 7.38 (1H, t, J = 7.8Hz), 7.40 – 7.50 (4H, m), 7.55 (1H, d, J = 7.8Hz), 7.63 – 7.70 (2H, m), 8.42 – 8.47 (2H, m) , DMSO : 496, (M+H) ⁺ FAB
160	3.07 (2H, t, J = 7.0Hz), 3.43 – 3.74 (8H, m), 4.26 (2H, t, J = 6.6Hz), 7.01 (2H, d, J = 8.6Hz), 7.24 – 7.48 (7H, m), 7.62 – 7.67 (1H, m), 8.42 – 8.46 (2H, m) , DMSO : 466(M+H) ⁺ FAB
161	443(M+H) ⁺ FAB
162	544(M+H) ⁺ FAB
163	461(M+H) ⁺ FAB
164	477(M+H) ⁺ FAB
165	477(M+H) ⁺ FAB
166	473(M+H) ⁺ FAB
167	476(M+H) ⁺ FAB
168	346(M+H) ⁺ FAB
169	307(M+H) ⁺ FAB
170	1.00-1.20 (2H, m), 1.18-1.25 (2H, m), 1.35-1.50 (1H, m), 1.45-1.58 (2H, m), 1.68-1.78 (2H, m), 2.14 (2H, t, J=7.4Hz), 2.77-2.91 (1H, m), 2.92-3.09 (1H, m), 3.90-4.07 (1H, m), 4.10-4.22 (1H, m), 6.68 (1H, br s), 7.22 (1H, br s), 7.45 (1H, dd, J=8.3, 4.9Hz), 7.56-7.66 (1H, m), 8.25-8.50 (2H, m) , DMSO : 292(M+H) ⁺ FAB
171	354(M+H) ⁺ FAB
172	341(M+H) ⁺ FAB

[0146] [Table 46]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
173	1.54-1.79 (2H, m), 1.82-1.96 (2H, m), 2.62 (1H, dddd, J=11.2, 11.2, 3.4, 3.4Hz), 2.88-3.07 (1H, m), 3.04-3.23 (1H, m), 4.00-4.16 (1H, m), 4.16-4.32 (1H, m), 6.99-7.07 (1H, m), 7.25-7.34 (2H, m), 7.45 (1H, dd, J=8.3, 4.9Hz), 7.58-7.65 (2H, m), 7.65 (1H, ddd, J=8.3, 2.4, 1.4Hz), 8.41-8.46 (2H, m), 9.94 (1H, s) , DMSO : 326(M+H) ⁺ FAB
174	1.42-1.65 (2H, m), 1.65-1.79 (2H, m), 2.35 (1H, dddd, J=11.3, 11.3, 3.4, 3.4Hz), 2.72 (2H, t, J=7.3Hz), 2.83-2.99 (1H, m), 3.00-3.16 (1H, m), 3.28 (2H, t, J=7.3Hz), 3.91-4.06 (1H, m), 4.08-4.23 (1H, m), 7.16-7.23 (3H, m), 7.25-7.33 (2H, m), 7.44 (1H, dd, J=8.3, 4.9Hz), 7.62 (1H, ddd, J=8.3, 2.5, 1.0Hz), 7.90 (1H, br t, J=5.4Hz), 8.41 (1H, d, J=2.5Hz), 8.43 (1H, dd, J=4.9, 1.5Hz) , DMSO : 354(M+H) ⁺ FAB
175	1.40 (2H, tt, J=7.3, 7.3Hz), 1.56 (2H, tt, J=7.3, 7.3Hz), 1.47-1.66 (2H, m), 1.68-1.79 (2H, m), 2.30-2.40 (1H, m), 2.57 (2H, t, J=7.8Hz), 2.86-2.94 (1H, m), 3.00-3.08 (1H, m), 3.07 (2H, dt, J=6.9, 6.9Hz), 3.93-4.07 (1H, m), 4.10-4.24 (1H, m), 7.12-7.21 (3H, m), 7.23-7.31 (2H, m), 7.44 (1H, dd, J=8.3, 4.9Hz), 7.62 (1H, ddd, J=8.3, 3.0, 1.5Hz), 7.81 (1H, br t, J=5.4Hz), 8.41 (1H, d, J=2.4Hz), 8.43 (1H, dd, J=4.4, 3.0Hz) , DMSO : 382(M+H) ⁺ FAB
176	0.85 (3H, t, J=6.4Hz), 1.17-1.32 (10H, m), 1.45-1.58 (2H, m), 1.54-1.76 (2H, m), 1.80-1.93 (2H, m), 2.51 (2H, t, J=6.4Hz), 2.55-2.64 (1H, m), 2.88-3.04 (1H, m), 2.99-3.20 (1H, m), 4.00-4.14 (1H, m), 4.15-4.30 (1H, m), 7.10 (2H, d, J=8.3Hz), 7.45 (1H, dd, J=8.3, 4.4Hz), 7.50 (2H, d, J=8.3Hz), 7.64 (1H, ddd, J=8.3, 2.5, 1.5Hz), 8.40-8.46 (2H, m), 9.85 (1H, s) , DMSO : 438(M+H) ⁺ FAB
177	411(M+H) ⁺ FAB
178	411(M+H) ⁺ FAB
179	1.58 - 1.78 (2H, m), 1.85 (2H, d, J = 12.2Hz), 2.75 - 2.83 (1H, m), 3.03 (1H, t, J = 12.2Hz), 3.18 (1H, t, J = 12.2Hz), 4.15 (1H, d, J = 12.7Hz), 4.32 (1H, d, J = 12.7Hz), 4.42 (2H, s), 6.80 (1H, dd, J = 2.0, 8.3Hz), 6.88 - 6.92 (2H, m), 7.24 (1H, t, J = 8.3Hz), 7.38 (1H, br), 7.52 (1H, br), 7.77 (1H, dd, J = 5.3, 8.3Hz), 8.02 - 8.09 (1H, m), 8.62 (1H, d, J = 5.3Hz), 8.74 (1H, d, J = 2.0Hz) , DMSO : 356(M+H) ⁺ FAB
180	467(M+H) ⁺ ESI
181	411(M+H) ⁺ FAB
182	382(M+H) ⁺ FAB
183	398(M+H) ⁺ FAB
184	454(M+H) ⁺ FAB
185	502(M+H) ⁺ FAB
186	480(M+H) ⁺ FAB
187	410(M+H) ⁺ FAB
188	488(M+H) ⁺ FAB
189	370(M+H) ⁺ FAB
190	432(M+H) ⁺ FAB

[0147] [Table 47]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
191	397(M+H) ⁺ FAB
192	409(M+H) ⁺ ESI
193	386(M+H) ⁺ FAB
194	371(M+H) ⁺ FAB
195	357(M+H) ⁺ ESI
196	337(M+H) ⁺ FAB
197	1.20-1.32 (2H, m), 1.28-1.48 (2H, m), 1.47-1.62 (4H, m), 1.70-1.86 (2H, m), 2.06 (2H, t, J=7.3Hz), 2.56 (2H, t, J=7.3Hz), 2.98-3.10 (1H, m), 3.12-3.25 (1H, m), 3.73-3.86 (1H, m), 3.83-3.97 (1H, m), 3.98-4.13 (1H, m), 7.12-7.21 (3H, m), 7.22-7.30 (2H, m), 7.45 (1H, dd, J=8.3, 4.4Hz), 7.62 (1H, ddd, J=8.3, 2.5, 1.5Hz), 7.78 (1H, br d, J=7.3Hz), 8.41 (1H, d, J=2.5Hz), 8.43 (1H, dd, J=4.9, 1.5Hz) , DMSO : 396(M+H) ⁺ FAB
198	315(M+H) ⁺ FAB
199	1.57 – 1.75 (2H, br), 1.90 – 2.03 (2H, br), 3.28 – 3.40 (1H, br), 3.43 – 3.57 (1H, br), 3.64 – 3.79 (1H, br), 3.82 – 3.93 (1H, br), 4.38– 4.46 (1H, m), 6.69 (2H, brd, J = 8.8Hz), 6.83 (2H, brd, J = 8.8Hz), 7.44 (1H, dd, J = 4.9, 8.3Hz), 7.61 – 7.66 (1H, m), 8.43 (2H, d, J = 3.0Hz), 8.96 (1H, s) , DMSO : 315(M+H) ⁺ FAB
200	0.96 – 1.30 (5H, m), 1.60 – 1.83 (8H, m), 1.94 – 2.09 (2H, m), 3.33 – 3.44 (1H, br), 3.48 – 3.60 (1H, br), 3.70 – 3.80 (1H, br), 3.75 (2H, d, J = 6.3Hz), 3.85 – 3.95 (1H, br), 4.64 – 4.70 (1H, m), 6.50 – 6.60 (3H, m), 7.17 (1H, t, J = 13.7Hz), 7.87 (1H, dd, J = 5.4, 8.3Hz), 8.18 (1H, d, J = 8.8Hz), 8.68 (1H, d, J = 5.4Hz), 8.82 (1H, d, J = 1.9Hz) , DMSO : 411(M+H) ⁺ FAB
201	425(M+H) ⁺ FAB
202	1.60 – 1.76 (2H, br), 1.95 – 2.07 (2H, br), 3.33 – 3.45 (1H, br), 3.47 – 3.58 (1H, br), 3.70 – 3.80 (1H, br), 3.85 – 3.96 (1H, br), 4.63 – 4.70 (1H, m), 5.13 (2H, s), 6.59 – 6.64 (3H, m), 7.13 – 7.23 (2H, m), 7.26 – 7.31 (2H, m), 7.41 – 7.48 (1H, m), 7.78 (1H, dd, J = 5.4, 8.8Hz), 8.06 (1H, brd, J = 7.3Hz), 8.62 (1H, d, J = 4.8Hz), 8.73 (1H, d, J = 2.4Hz) , DMSO : 423(M+H) ⁺ FAB
203	1.60 – 1.80 (2H, br), 1.90 – 2.07 (2H, br), 3.33 – 3.45 (1H, br), 3.47 – 3.60 (1H, br), 3.70 – 3.81 (1H, br), 3.85 – 3.96 (1H, br), 4.63 – 4.71 (1H, m), 5.12 (2H, s), 6.60 – 6.69 (3H, m), 7.18 – 7.28 (3H, m), 7.39 – 7.47 (1H, m), 7.56 (1H, dt, J = 1.4, 7.8Hz), 7.83 – 7.89 (1H, m), 8.15 – 8.20 (1H, m), 8.68 (1H, brd, J = 5.4Hz), 8.81 (1H, br) , DMSO : 423(M+H) ⁺ FAB
204	423(M+H) ⁺ FAB
205	1.60 – 1.84 (2H, br), 1.94 – 2.06 (2H, br), 3.30 – 3.42 (1H, br), 3.45 – 3.56 (1H, br), 3.70 – 3.80 (1H, br), 3.84 – 3.96 (1H, br), 4.61– 4.69 (1H, m), 5.16 (2H, m), 6.61 (1H, d, J = 2.5Hz), 6.63 (1H, d, J = 2.5Hz), 6.66 (1H, t, J = 1.9Hz), 7.20 (1H, t, J = 7.8Hz), 7.46 (1H, dd, J = 4.9, 8.3Hz), 7.60 – 7.67 (2H, m), 7.78 – 7.83 (2H, m), 7.92 (1H, br), 8.45 (2H, m) , DMSO : 430(M+H) ⁺ FAB

[0148] [Table 48]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
206	1.59 – 1.76 (2H, br), 1.91 – 2.07 (2H, br), 3.33 – 3.42 (1H, br), 3.45 – 3.56 (1H, br), 3.69 – 3.80 (1H, br), 3.82 – 3.94 (1H, br), 4.45 – 4.55 (1H, m), 5.06 (2H, s), 6.96 (4H, s), 7.36 – 7.46 (3H, m), 7.50 (1H, br), 7.75 (1H, dd, <i>J</i> = 4.9, 8.3Hz), 8.02 (1H, d, <i>J</i> = 8.3Hz), 8.60 (1H, d, <i>J</i> = 4.9Hz), 8.70 (1H, d, <i>J</i> = 2.5Hz) , DMSO : 439(M+H) ⁺ FAB
207	0.88 – 1.01 (2H, m), 1.09 – 1.30 (3H, m), 1.40 – 1.51 (1H, m), 1.55 – 1.76 (9H, m), 1.93 – 2.05 (2H, m), 3.30 – 3.42 (1H, br), 3.46 – 3.60 (1H, br), 3.70 – 3.80 (1H, br), 3.85 – 3.95 (3H, m), 4.45 – 4.55 (1H, m), 6.84 – 6.94 (4H, m), 7.66 (1H, dd, <i>J</i> = 4.9, 8.3Hz), 7.98 (1H, d, <i>J</i> = 8.3Hz), 8.58 (1H, d, <i>J</i> = 4.8Hz), 8.66 (1H, d, <i>J</i> = 1.9Hz) , DMSO : 425(M+H) ⁺ FAB
208	1.60 – 1.80 (2H, br), 1.94 – 2.07 (2H, br), 3.31 – 3.44 (1H, br), 3.46 – 3.60 (1H, br), 3.69 – 3.82 (1H, br), 3.84 – 3.96 (1H, br), 4.50 – 4.58 (1H, m), 5.08 (2H, s), 6.97 (4H, s), 7.20 - 7.28 (2H, m), 7.39 – 7.45 (1H, m), 7.54 (1H, dt, <i>J</i> = 1.5, 7.3Hz), 7.81 (1H, dd, <i>J</i> = 5.4, 8.3Hz), 8.10 (1H, brd, <i>J</i> = 8.3Hz), 8.64 (1H, d, <i>J</i> = 5.3Hz), 8.77 (1H, s) , DMSO : 423(M+H) ⁺ FAB
209	1.60 – 1.80 (2H, br), 1.94 – 2.07 (2H, br), 3.31 – 3.44 (1H, br), 3.46 – 3.60 (1H, br), 3.69 – 3.80 (1H, br), 3.82 – 3.96 (1H, br), 4.48– 4.58 (1H, m), 5.03 (2H, s), 6.96 (4H, s), 7.18 - 7.26 (2H, m), 7.45 – 7.51 (2H, m), 7.78 – 7.89 (1H, m), 8.07 – 8.19 (1H, m), 8.67 (1H, brd, <i>J</i> = 4.9Hz), 8.80 (1H, br) , DMSO : 423(M+H) ⁺ FAB
210	1.60 – 1.75 (2H, br), 1.91 – 2.06 (2H, br), 3.30 – 3.42 (1H, br), 3.45 – 3.56 (1H, br), 3.70 – 3.80 (1H, br), 3.84 – 3.96 (1H, br), 4.49 – 4.56 (1H, m), 5.11 (2H, m), 6.96 (4H, s), 7.46 (1H, dd, <i>J</i> = 4.8, 8.6Hz), 7.61 (1H, t, <i>J</i> = 7.5Hz), 7.64 – 7.68 (1H, m), 7.76 – 7.83 (2H, m), 7.90 (1H, br), 8.43 – 8.47 (2H, m) , DMSO : 430(M+H) ⁺ FAB
211	463(M+H) ⁺ FAB
212	1.58 – 1.74 (2H, br), 1.91 – 2.05 (2H, br), 3.30 – 3.42 (1H, br), 3.45 – 3.55 (1H, br), 3.65 – 3.79 (1H, br), 3.83 – 3.94 (1H, br), 4.48– 4.55 (1H, m), 5.09 (2H, s), 6.96 (4H, s), 7.36 – 7.50 (3H, m), 7.59 (1H, d, <i>J</i> = 7.9Hz), 7.62 – 7.66 (1H, m), 7.84 (1H, d, <i>J</i> = 7.8Hz), 7.96 (1H, s), 8.00 (1H, br), 8.41 – 8.45 (2H, m) , DMSO : 448(M+H) ⁺ FAB
213	497(M+H) ⁺ FAB
214	484(M+H) ⁺ FAB
215	488(M+H) ⁺ FAB
216	0.96 – 1.08 (2H, m), 1.10 – 1.31 (3H, m), 1.60 – 1.83 (8H, m), 1.91 – 2.05 (2H, m), 3.25 - 3.57 (2H, m), 3.65 – 3.95 (7H, m), 4.46 – 4.54 (1H, m), 6.81 – 6.87 (2H, m), 6.89 – 6.95 (2H, m), 8.13 (1H, dd, <i>J</i> = 2.0Hz, 2.4Hz), 8.70 (1H, d, <i>J</i> = 2.4Hz), 8.94 (1H, d, <i>J</i> = 2.0Hz) , DMSO : 469(M+H) ⁺ FAB
217	1.58 – 1.76 (2H, m), 1.90 – 2.04 (2H, m), 2.80 – 4.00 (4H, m), 4.38 – 4.47 (1H, m), 6.70 (2H, d, <i>J</i> = 8.8Hz), 6.83 (2H, d, <i>J</i> = 8.8Hz), 8.05 – 8.10 (1H, m), 8.66 (1H, d, <i>J</i> = 2.4Hz), 8.90 – 8.94 (1H, m) , DMSO : 359(M+H) ⁺ FAB

[0149] [Table 49]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
218	1.60 – 1.78 (2H, m), 1.93 – 2.05 (2H, m), 3.35 – 3.95 (4H, m), 4.48 – 4.56 (1H, m), 5.07 (2H, s), 6.96 (4H, s), 7.12 – 7.18 (1H, m), 7.24 – 7.30 (2H, m), 7.40 – 7.47 (1H, m), 8.07 – 8.10 (1H, m), 8.67 (1H, d, J = 2.4Hz), 8.91 – 8.94 (1H, m), 13.30 – 13.75 (1H, br) , DMSO : 467(M+H) ⁺ FAB
219	341(M+H) ⁺ FAB
220	327(M+H) ⁺ ESI
221	449(M+H) ⁺ FAB
222	325(M+H) ⁺ ESI
223	353(M-H) ⁻ FAB
224	355(M-H) ⁻ FAB
225	1.12 – 1.32 (2H, m), 1.45 – 1.60 (3H, m), 1.79 (2H, d, J = 11.7Hz), 2.63 (2H, t, J = 7.5Hz), 2.87 (1H, t, J = 12.2Hz), 3.02 (1H, t, J = 12.2Hz), 4.01 (1H, d, J = 12.7Hz), 4.18 (1H, t, J = 12.7Hz), 7.15 – 7.31 (5H, m), 8.05 (1H, dd, J = 2.0, 2.4Hz), 8.65 (1H, d, J = 2.4Hz), 8.92 (1H, t, J = 2.0Hz), 13.59 (1H, br s) , DMSO : 355(M+H) ⁺ FAB
226	470(M+H) ⁺ FAB
227	410(M+H) ⁺ FAB
228	0.88 – 1.00 (2H, m), 1.08 – 1.28 (4H, m), 1.39 – 1.51 (1H, m), 1.54 – 1.77 (10H, m), 1.91 – 2.05 (2H, m), 3.20 – 3.96 (6H, m), 4.46 – 4.54 (1H, m), 6.83 – 6.88 (2H, m), 6.90 – 6.95 (2H, m), 8.08 (1H, dd, J = 2.0Hz, 2.4Hz), 8.66 (1H, d, J = 2.4Hz), 8.92 (1H, d, J = 1.5Hz) , DMSO : 469(M+H) ⁺ FAB
229	483(M+H) ⁺ FAB
230	474(M+H) ⁺ FAB
231	356(M+H) ⁺ FAB
232	371(M+H) ⁺ FAB
233	1.58 – 1.78 (2H, m), 1.91 – 2.06 (2H, m), 3.25 – 3.95 (7H, m), 4.49 – 4.56 (1H, m), 5.02 (2H, s), 6.86 – 7.03 (7H, m), 7.30 (1H, dd, J = 7.8Hz, 8.3Hz), 8.07 (1H, s), 8.64 (1H, s), 8.92 (1H, s) , DMSO : 479(M+H) ⁺ FAB
234	1.60 – 1.80 (2H, br), 1.92 – 2.10 (2H, br), 3.30 – 3.60 (2H, br), 3.70 – 3.80 (1H, br), 3.85 – 3.96 (1H, br), 4.60 – 4.70 (1H, m), 5.12 (2H, s), 6.58 – 6.68 (3H, m), 7.24 – 7.32 (4H, m), 7.42 – 7.50 (1H, m), 8.09 (1H, t, J = 2.4Hz), 8.67 (1H, d, J = 2.4Hz), 8.92 (1H, d, J = 1.9Hz), 13.50 (1H, br) , DMSO : 467(M+H) ⁺ FAB
235	1.60 – 1.80 (2H, br), 1.92 – 2.10 (2H, br), 3.30 – 3.60 (2H, br), 3.70 – 3.80 (1H, br), 3.85 – 3.96 (1H, br), 4.60 – 4.72 (1H, m), 5.16 (2H, s), 6.60 – 6.68 (3H, m), 7.21 (1H, t, J = 8.3Hz), 7.62 (1H, t, J = 8.3Hz), 7.78 – 7.84 (2H, m), 7.92 (1H, s), 8.09 (1H, dd, J = 1.4, 2.4Hz), 8.67 (1H, d, J = 3.0Hz), 8.93 (1H, d, J = 1.4Hz), 13.50 (1H, br) , DMSO : 474(M+H) ⁺ FAB

[0150] [Table 50]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
236	1.60 – 1.74 (2H, m), 1.91 – 2.06 (2H, m), 3.30 - 3.95 (7H, m), 4.47 – 4.57 (1H, m), 5.14 (2H, s), 6.96 (4H, s), 7.55 (1H, dd, J = 7.4Hz, 7.8Hz), 7.72 (1H, d, J = 7.4Hz), 7.92 (1H, d, J = 7.8Hz), 8.04 (1H, s), 8.08 (1H, dd, J = 2.0Hz, 2.4Hz), 8.67 (1H, d, J = 2.4Hz), 8.92 (1H, d, J = 2.0Hz) , DMSO : 507(M+H) ⁺ FAB
237	455(M+H) ⁺ FAB
238	369(M+H) ⁺ ESI
239	385(M+H) ⁺ ESI
240	371(M+H) ⁺ ESI
241	398(M+H) ⁺ FAB
242	0.73 – 2.10 (17H, m), 3.20 – 4.02 (6H, br), 4.60 – 4.70 (1H, m), 6.49 – 6.60 (3H, m), 7.17 (1H, t, J = 8.3Hz), 8.09 (1H, br), 8.67 (1H, d, J = 2.0Hz), 8.92 (1H, br), 13.40-13.80 (1H, br) , DMSO : 469(M+H) ⁺ FAB
243	370(M+H) ⁺ FAB
244	524(M+H) ⁺ FAB
245	1.60 – 1.77 (2H, m), 1.92 – 2.06 (2H, m), 3.35 - 3.96 (4H, m), 4.48 – 4.56 (1H, m), 5.07 (2H, s), 6.95 (4H, s), 7.12 - 7.18 (1H, m), 7.24 – 7.30 (2H, m), 7.40 – 7.47 (1H, m), 7.63 – 7.71 (1H, m), 8.07 – 8.10 (1H, m), 8.14 -8.23 (1H, m), 8.58 (1H, d, J = 2.4Hz), 8.90 (1H, d, J = 1.9Hz) , DMSO : 466(M+H) ⁺ FAB
246	1.59 – 1.78 (2H, m), 1.91 – 2.05 (2H, m), 3.25 - 3.57 (2H, m), 3.68 – 3.96 (2H, m), 4.47 – 4.56 (1H, m), 5.04 (2H, s), 6.95 (4H, s), 7.29 – 7.46 (5H, m), 7.64 – 7.70 (1H, m), 8.04 (1H, dd, J = 1.9Hz, 2.4Hz), 8.15 – 8.21 (1H, m), 8.58 (1H, d, J = 2.4Hz), 8.89 (1H, d, J = 1.9Hz) , DMSO : 448(M+H) ⁺ FAB
247	397(M+H) ⁺ FAB
248	451(M+H) ⁺ FAB
249	523(M+H) ⁺ FAB
250	579(M+H) ⁺ ESI
251	524(M+H) ⁺ FAB
252	577(M+H) ⁺ FAB
253	537(M+H) ⁺ FAB
254	577(M+H) ⁺ FAB
255	1.58 – 1.78 (2H, br), 1.93 – 2.06 (2H, br), 3.32 – 3.42 (3H, m), 3.48 – 3.58 (3H, m), 3.70 – 3.80 (1H, br), 3.85 – 3.95 (1H, br), 4.48 – 4.58 (1H, m), 4.92 (1H, br), 5.07 (2H, s), 6.95 (4H, s), 7.15 (1H, dt, J = 2.4, 8.8Hz), 7.24 – 7.30 (2H, m), 7.41 – 7.47 (1H, m), 8.14 (1H, t, J = 2.0Hz), 8.63 (1H, d, J = 2.4Hz), 8.75 (1H, t J = 5.3Hz), 8.93 (1H, d, J = 1.4Hz) , DMSO : 510(M+H) ⁺ FAB

[0151] [Table 51]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
256	586(M+H) ⁺ FAB
257	549(M+H) ⁺ FAB
258	1.13 – 1.33 (2H, br), 1.66 (2H, d, <i>J</i> = 12.7Hz), 1.73 – 1.85 (1H, m), 2.57 (2H, d, <i>J</i> = 6.8Hz), 2.86 (1H, t, <i>J</i> = 12.2Hz), 3.02 (1H, t, <i>J</i> = 12.2Hz), 4.03 (1H, d, <i>J</i> = 12.2Hz), 4.20 (1H, d, <i>J</i> = 12.2Hz), 7.18 – 7.23 (3H, m), 7.27 – 7.32 (2H, m), 7.48 (1H, s), 7.60 (1H, t, <i>J</i> = 7.8Hz), 7.93 (2H, d, <i>J</i> = 7.3Hz), 8.01 (1H, t, <i>J</i> = 2.4Hz), 8.13 (1H, s), 8.23 (1H, s), 8.44 (1H, d, <i>J</i> = 2.4Hz), 8.84 (1H, d, <i>J</i> = 2.0Hz) , DMSO : 416(M+H) ⁺ FAB
259	374(M+H) ⁺ FAB
260	1.60 – 1.75 (2H, m), 1.92 – 2.04 (2H, m), 3.30 – 3.91 (4H, m), 4.49 – 4.56 (1H, m), 5.07 (2H, s), 6.96 (4H, s), 7.12 – 7.18 (1H, m), 7.24 – 7.30 (2H, m), 7.39 – 7.47 (2H, m), 7.92 (1H, d, <i>J</i> = 2.0Hz), 8.02 (1H, d, <i>J</i> = 2.0Hz) , DMSO : 438(M+H) ⁺ FAB
261	550(M+H) ⁺ FAB
262	1.58 – 1.75 (2H, m), 1.90 – 2.05 (2H, m), 3.30 – 3.57 (2H, m), 3.67 – 3.95 (2H, m), 4.13 (2H, s), 4.48 – 4.55 (1H, m), 5.07 (2H, s), 6.95 (4H, s), 7.12 – 7.18 (1H, m), 7.24 – 7.30 (2H, m), 7.40 – 7.47 (1H, m), 7.61 – 7.64 (1H, m), 8.35 – 8.39 (1H, m), 8.40 – 8.44 (1H, m) , DMSO : 510(M ⁺)FAB
263	1.58 – 1.74 (2H, m), 1.91 – 2.04 (2H, m), 2.50 (3H, s), 3.30 – 3.95 (4H, m), 4.48 – 4.58 (3H, m), 5.07 (2H, s), 5.40 (1H, t, <i>J</i> = 5.9Hz), 6.95 (4H, s), 7.12 – 7.18 (1H, m), 7.24 – 7.30 (2H, m), 7.40 – 7.47 (1H, m), 7.53 – 7.56 (1H, m), 8.28 – 8.31 (1H, m), 8.36 – 8.39 (1H, m) , DMSO : 453(M+H) ⁺ FAB
264	1.59 – 1.74 (2H, m), 1.96 – 2.03 (2H, m), 3.27 – 3.57 (2H, m), 3.70 – 3.65 (2H, m), 4.48 – 4.58 (3H, m), 5.08 (2H, s), 6.72 (1H, d, <i>J</i> = 16.1Hz), 6.96 (4H, s), 7.12 – 7.18 (1H, m), 7.24 – 7.30 (2H, m), 7.40 – 7.47 (1H, m), 7.64 (1H, d, <i>J</i> = 16.1Hz), 8.07 (1H, dd, <i>J</i> = 2.0Hz, 2.0Hz), 8.45 (1H, d, <i>J</i> = 2.5Hz), 8.71 (1H, d, <i>J</i> = 1.4Hz), 12.40 – 12.74 (1H, br) , DMSO : 493(M+H) ⁺ FAB
265	445(M+H) ⁺ FAB
266	1.10 – 1.33 (2H, m), 1.45 – 1.61 (3H, m), 1.75 – 1.87 (2H, br), 2.64 (2H, t, <i>J</i> = 7.6Hz), 2.81 – 3.10 (2H, br), 3.92 – 4.27 (2H, br), 7.14 – 7.32 (5H, m), 7.43 – 7.52 (1H, m), 7.60 (1H, d, <i>J</i> = 8.0Hz), 7.90 – 7.98 (2H, m), 8.05 – 8.17 (2H, m), 8.21 – 8.27 (1H, m), 8.48 (1H, d, <i>J</i> = 2.4Hz), 8.87 (1H, d, <i>J</i> = 2.4Hz) , DMSO
267	380(M+H) ⁺ FAB
268	1.33 – 1.56 (2H, m), 1.77 – 1.88 (2H, m), 2.37 – 2.48 (1H, m), 2.93 – 3.04 (1H, m), 3.09 – 3.21 (1H, m), 3.98 – 4.12 (1H, m), 4.14 – 4.28 (1H, m), 6.31 (1H, dd, <i>J</i> = 16.1, 6.8Hz), 6.45 (1H, d, <i>J</i> = 16.1Hz), 7.18 – 7.24 (1H, m), 7.28 – 7.35 (2H, m), 7.38 – 7.48 (3H, m), 7.63 (1H, ddd, <i>J</i> = 8.3, 2.5, 1.5Hz), 8.41 – 8.45 (2H, m) , DMSO-d6 : 309(M+H) ⁺ FAB
269	1.33 – 1.56 (2H, m), 1.67 – 1.79 (2H, m), 2.73 – 2.88 (1H, m), 2.88 – 3.02 (1H, m), 2.88 – 3.02 (1H, m), 3.04 – 3.18 (1H, m), 3.95 – 4.07 (1H, m), 4.10 – 4.23 (1H, m), 5.54 (1H, dd, <i>J</i> = 11.8, 9.7Hz), 6.42 (1H, d, <i>J</i> = 11.8Hz), 7.23 – 7.34 (3H, m), 7.35 – 7.42 (2H, m), 7.44 (1H, dd, <i>J</i> = 8.3, 4.8Hz), 7.63 (1H, ddd, <i>J</i> = 8.3, 2.4, 1.5Hz), 8.40 – 8.45 (2H, m) , DMSO : 309(M+H) ⁺ FAB
270	1.08 – 1.30 (2H, m), 1.43 – 1.60 (3H, m), 1.73 – 1.82 (2H, br), 2.63 (2H, t, <i>J</i> = 7.8Hz), 2.77 – 3.08 (2H, br), 3.92 – 4.20 (2H, br), 7.13 – 7.32 (5H, m), 8.04 (1H, dd, <i>J</i> = 2.0, 2.4Hz), 8.45 (1H, d, <i>J</i> = 2.4Hz), 8.58 (1H, d, <i>J</i> = 2.0Hz) , DMSO : 389(M ⁺)FAB

[0152] [Table 52]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
271	0.78 – 0.94 (2H, m), 1.00 – 1.24 (10H, m), 1.37 – 1.50 (1H, m), 1.57 – 1.76 (7H, m), 2.80 – 2.92 (1H, br), 2.96 – 3.08 (1H, br), 3.93 – 4.05 (1H, br), 4.08 – 4.21 (1H, br), 7.68 (1H, dd, <i>J</i> =4.8, 7.6Hz), 7.93 – 8.00 (1H, m), 8.58 (1H, d, <i>J</i> =7.6Hz), 8.62 – 8.69 (1H, m), DMSO : 317(M+H) ⁺ FAB
272	0.79 – 0.92 (2H, m), 1.04 – 1.29 (10H, m), 1.36 – 1.49 (1H, m), 1.57 – 1.76 (7H, m), 2.80 – 2.92 (1H, br), 2.95 – 3.08 (1H, br), 3.90 (3H, s), 3.92 – 4.05 (1H, br), 4.08 – 4.21 (1H, br), 8.09 (1H, dd, <i>J</i> =2.0, 2.4Hz), 8.68 (1H, d, <i>J</i> =2.4Hz), 8.93 (1H, d, <i>J</i> =2.0Hz), DMSO : 375(M+H) ⁺ FAB
273	1.44 – 1.59 (2H, m), 1.77 – 1.88 (2H, m), 2.37 – 2.48 (1H, m), 2.93 – 3.07 (1H, m), 3.07 – 3.23 (1H, m), 3.98 – 4.14 (1H, m), 4.14 – 4.29 (1H, m), 6.31 (1H, dd, <i>J</i> = 16.1, 6.9Hz), 6.45 (1H, d, <i>J</i> = 16.1Hz), 7.17 – 7.25 (1H, m), 7.27 – 7.36 (2H, m), 7.38 – 7.44 (2H, m), 8.05 – 8.09 (1H, m), 8.67 (1H, d, <i>J</i> = 2.4Hz), 8.92 (1H, d, <i>J</i> = 1.5Hz), 13.60 (1H, br s), DMSO : 353(M+H) ⁺ FAB
274	1.10 – 1.30 (2H, m), 1.45 – 1.60 (3H, m), 1.75 – 1.85 (2H, m), 2.63 (2H, t, <i>J</i> = 8.3Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.16 – 7.34 (4H, m), 8.04 (1H, dd, <i>J</i> = 1.5, 2.0Hz), 8.64 (1H, d, <i>J</i> = 2.4Hz), 8.91 (1H, d, <i>J</i> = 1.9Hz), 13.60 (1H, s), DMSO : 389(M+H) ⁺ FAB
275	380(M+H) ⁺ FAB
276	1.10 – 1.30 (2H, m), 1.44 – 1.60 (3H, m), 1.73 – 1.82 (2H, m), 2.60 (2H, t, <i>J</i> = 7.3Hz), 2.80 – 3.10 (2H, m), 3.74 (3H, s), 3.95 – 4.24 (2H, m), 6.72 – 6.81 (3H, m), 7.19 (1H, t, <i>J</i> = 8.3Hz), 8.04 (1H, t, <i>J</i> = 1.9Hz), 8.64 (1H, d, <i>J</i> = 2.4Hz), 8.92 (1H, d, <i>J</i> = 1.5Hz), 13.60 (1H, s) DMSO : 385(M+H) ⁺ FAB
277	1.10 – 1.30 (2H, m), 1.44 – 1.60 (3H, m), 1.73 – 1.82 (2H, m), 2.60 (2H, t, <i>J</i> = 7.4Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 6.95 – 7.10 (3H, m), 7.29 – 7.36 (1H, m), 8.04 (1H, t, <i>J</i> = 2.0Hz), 8.65 (1H, d, <i>J</i> = 2.4Hz), 8.92 (1H, d, <i>J</i> = 1.9Hz), 13.60 (1H, s), DMSO : 373(M+H) ⁺ FAB
278	380(M+H) ⁺ FAB
279	396(M-H) ⁺ FAB
280	426(M+H) ⁺ FAB
281	1.10 – 1.33 (2H, m), 1.46 – 1.59 (1H, m), 1.54 – 1.66 (2H, m), 1.75 – 1.87 (2H, m), 2.68 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.79 – 2.94 (1H, m), 2.95 – 3.10 (1H, m), 3.95 – 4.09 (1H, m), 4.11 – 4.25 (1H, m), 7.29 – 7.38 (3H, m), 7.41 – 7.49 (2H, m), 7.58 (2H, d, <i>J</i> = 8.3Hz), 7.62 – 7.68 (2H, m), 7.78 – 7.81 (1H, m), 8.28 (1H, d, <i>J</i> = 2.5Hz), 8.78 (1H, d, <i>J</i> = 1.4Hz), DMSO : 431(M+H) ⁺ FAB
282	1.07 – 1.33 (2H, m), 1.42 – 1.54 (1H, m), 1.47 – 1.59 (2H, m), 1.72 – 1.83 (2H, m), 2.62 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.78 – 2.93 (1H, m), 2.93 – 3.10 (1H, m), 3.92 – 4.08 (1H, m), 4.08 – 4.24 (1H, m), 7.05 – 7.13 (2H, m), 7.20 – 7.28 (2H, m), 8.04 (1H, dd, <i>J</i> = 2.5, 2.1Hz), 8.64 (1H, d, <i>J</i> = 2.5Hz), 8.92 (1H, d, <i>J</i> = 2.1Hz), 13.62 (1H, br s), DMSO : 373(M+H) ⁺ FAB
283	1.10 – 1.35 (2H, m), 1.46 – 1.62 (3H, m), 1.74 – 1.88 (2H, m), 2.74 (2H, dd, <i>J</i> = 7.8, 7.8Hz), 2.80 – 2.96 (1H, m), 2.96 – 3.12 (1H, m), 3.94 – 4.08 (1H, m), 4.11 – 4.26 (1H, m), 7.18 – 7.32 (2H, m), 7.32 – 7.43 (2H, m), 8.05 (1H, dd, <i>J</i> = 2.1, 1.6Hz), 8.65 (1H, d, <i>J</i> = 2.1Hz), 8.91 (1H, d, <i>J</i> = 1.6Hz), 13.62 (1H, br s), DMSO : 387(M-H) ⁺ FAB
284	1.08 – 1.32 (2H, m), 1.41 – 1.55 (1H, m), 1.48 – 1.60 (2H, m), 1.71 – 1.83 (2H, m), 2.62 (2H, dd, <i>J</i> = 7.8, 7.8Hz), 2.78 – 2.93 (1H, m), 2.93 – 3.09 (1H, m), 3.94 – 4.08 (1H, m), 4.10 – 4.23 (1H, m), 7.25 (2H, d, <i>J</i> = 8.6Hz), 7.33 (2H, d, <i>J</i> = 8.0Hz), 8.04 (1H, dd, <i>J</i> = 2.2, 1.6Hz), 8.64 (1H, d, <i>J</i> = 2.2Hz), 8.91 (1H, d, <i>J</i> = 1.6Hz), 13.61 (1H, br s), DMSO : 389(M+H) ⁺ FAB
285	1.06 – 1.32 (2H, m), 1.40 – 1.54 (1H, m), 1.47 – 1.60 (2H, m), 1.70 – 1.84 (2H, m), 2.61 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.79 – 2.94 (1H, m), 2.94 – 3.09 (1H, m), 3.92 – 4.08 (1H, m), 4.08 – 4.25 (1H, m), 7.19 (2H, d, <i>J</i> = 8.4Hz), 7.46 (2H, d, <i>J</i> = 8.4Hz), 8.04 (1H, dd, <i>J</i> = 2.4, 1.2Hz), 8.64 (1H, d, <i>J</i> = 2.4Hz), 8.91 (1H, d, <i>J</i> = 1.2Hz), 13.60 (1H, br s), DMSO : 431(M-H) ⁺ FAB
286	1.08 – 1.32 (2H, m), 1.42 – 1.58 (3H, m), 1.70 – 1.84 (2H, m), 2.56 (2H, dd, <i>J</i> = 7.4, 7.4Hz), 2.78 – 2.93 (1H, m), 2.93 – 3.07 (1H, m), 3.72 (3H, s), 3.94 – 4.08 (1H, m), 4.08 – 4.23 (1H, m), 6.84 (2H, d, <i>J</i> = 8.0Hz), 7.12 (2H, d, <i>J</i> = 8.0Hz), 8.04 (1H, dd, <i>J</i> = 2.8, 1.6Hz), 8.64 (1H, d, <i>J</i> = 2.8Hz), 8.91 (1H, d, <i>J</i> = 1.6Hz), 13.60 (1H, br s), DMSO : 385(M+H) ⁺ FAB

[0153] [Table 53]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
287	1.01 – 1.74 (1H, m), 2.58 (2H, t, <i>J</i> = 7.2Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.14 – 7.31 (5H, m), 8.04 (1H, t, <i>J</i> = 2.4Hz), 8.64 (1H, d, <i>J</i> = 2.4Hz), 8.91 (1H, d, <i>J</i> = 1.6Hz), 13.60 (1H, s) , DMSO : 383(M+H) ⁺ FAB
288	1.08 – 1.34 (2H, m), 1.44 – 1.60 (3H, m), 1.73 – 1.86 (2H, m), 2.66 (2H, dd, <i>J</i> = 7.4, 7.4Hz), 2.78 – 2.95 (1H, m), 2.95 – 3.12 (1H, m), 3.93 – 4.09 (1H, m), 4.10 – 4.26 (1H, m), 7.08 – 7.18 (2H, m), 7.20 – 7.27 (1H, m), 7.27 – 7.36 (1H, m), 8.05 (1H, dd, <i>J</i> = 2.4, 1.6Hz), 8.65 (1H, d, <i>J</i> = 2.4Hz), 8.91 (1H, d, <i>J</i> = 1.6Hz), 13.60 (1H, br s) , DMSO : 373(M+H) ⁺ FAB
289	0.79 – 0.93 (2H, m), 1.00 – 1.28 (10H, m), 1.35 – 1.48 (1H, m), 1.57 – 1.76 (7H, m), 2.80 – 3.08 (2H, br), 3.96 – 4.22 (2H, br), 8.02 – 8.05 (1H, m), 8.62 – 8.66 (1H, m), 8.89 – 8.93 (1H, m), 13.53 – 13.64 (1H, br) , DMSO : 361(M+H) ⁺ FAB
290	1.13 – 1.32 (2H, m), 1.46 – 1.59 (1H, m), 1.54 – 1.62 (2H, m), 1.75 – 1.87 (2H, m), 2.69 (2H, dd, <i>J</i> = 7.8, 7.8Hz), 2.81 – 2.94 (1H, m), 2.94 – 3.10 (1H, m), 3.94 – 4.10 (1H, m), 4.10 – 4.27 (1H, m), 7.29 – 7.38 (3H, m), 7.86 (1H, ddd, <i>J</i> = 7.4, 7.4, 1.6Hz), 7.93 (1H, d, <i>J</i> = 8.0Hz), 8.01 (2H, d, <i>J</i> = 8.0Hz), 8.05 (1H, dd, <i>J</i> = 2.8, 1.6Hz), 8.62 – 8.68 (2H, m), 8.92 (1H, d, <i>J</i> = 1.6Hz), 13.60 (1H, br s) , DMSO : 432(M+H) ⁺ ESI
291	1.08 – 1.32 (2H, m), 1.44 – 1.61 (3H, m), 1.77 – 1.83 (2H, br), 2.63 (2H, t, <i>J</i> = 7.6Hz), 2.79 – 3.08 (2H, br), 3.95 – 4.23 (2H, br), 6.73 (1H, d, <i>J</i> = 16.0Hz), 7.14 – 7.22 (3H, m), 7.25 – 7.32 (2H, m), 7.64 (1H, d, <i>J</i> = 16.0Hz), 8.02 – 8.06 (1H, m), 8.40 – 8.44 (1H, m), 8.68 – 8.73 (1H, m), 12.55 – 12.63 (1H, br) , DMSO : 381(M+H) ⁺ FAB
292	1.10 – 1.32 (2H, m), 1.45 – 1.60 (3H, m), 1.75 – 1.85 (2H, m), 2.63 (2H, t, <i>J</i> = 8.4Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.20 – 7.28 (2H, m), 7.36 – 7.40 (1H, m), 7.44 (1H, br), 8.04 (1H, t, <i>J</i> = 2.0Hz), 8.64 (1H, d, <i>J</i> = 2.4Hz), 8.91 (1H, d, <i>J</i> = 1.6Hz), 13.60 (1H, s) , DMSO : 435,433(M+H) ⁺ ESI
293	1.10 – 1.32 (2H, m), 1.45 – 1.67 (3H, m), 1.75 – 1.87 (2H, m), 2.71 (2H, t, <i>J</i> = 7.6Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.22 (1H, d, <i>J</i> = 7.2Hz), 7.33 – 7.52 (6H, m), 7.64 – 7.68 (1H, m), 8.04 (1H, dd, <i>J</i> = 1.2, 2.4Hz), 8.64 (1H, d, <i>J</i> = 2.4Hz), 8.91 (1H, d, <i>J</i> = 2.0Hz), 13.60 (1H, s) , DMSO : 431(M+H) ⁺ ESI
294	1.10 – 1.32 (2H, m), 1.45 – 1.67 (3H, m), 1.75 – 1.87 (2H, m), 2.71 (2H, t, <i>J</i> = 7.6Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.29 (1H, d, <i>J</i> = 7.6Hz), 7.41 (1H, t, <i>J</i> = 8.0Hz), 7.55 (1H, d, <i>J</i> = 7.6Hz), 7.62 (1H, s), 7.67 (1H, t, <i>J</i> = 8.0Hz), 7.82 (1H, d, <i>J</i> = 8.0Hz), 8.00 – 8.08 (2H, m), 8.16 (1H, s), 8.65 (1H, br), 8.91 (1H, br), 13.60 (1H, s) , DMSO : 456(M+H) ⁺ FAB
295	1.07 – 1.34 (2H, m), 1.41 – 1.58 (1H, m), 1.50 – 1.63 (2H, m), 1.70 – 1.85 (2H, m), 2.65 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.78 – 2.94 (1H, m), 2.93 – 3.21 (1H, m), 3.92 – 4.09 (1H, m), 4.06 – 4.26 (1H, m), 7.26 (2H, d, <i>J</i> = 6.0Hz), 8.04 (1H, dd, <i>J</i> = 2.8, 2.0Hz), 8.45 (2H, br d, <i>J</i> = 4.4Hz), 8.64 (1H, d, <i>J</i> = 2.8Hz), 8.91 (1H, d, <i>J</i> = 2.0Hz) , DMSO : 356(M+H) ⁺ FAB
296	1.08 – 1.35 (2H, m), 1.43 – 1.58 (1H, m), 1.50 – 1.63 (2H, m), 1.71 – 1.86 (2H, m), 2.65 (2H, dd, <i>J</i> = 7.2, 7.2Hz), 2.77 – 2.96 (1H, m), 2.90 – 3.11 (1H, m), 3.90 – 4.08 (1H, m), 4.10 – 4.26 (1H, m), 7.31 (1H, dd, <i>J</i> = 8.0, 4.8Hz), 7.65 (1H, d, <i>J</i> = 8.0Hz), 8.04 (1H, dd, <i>J</i> = 2.4, 2.0Hz), 8.40 (1H, br d, <i>J</i> = 3.2Hz), 8.46 (1H, br s), 8.65 (1H, d, <i>J</i> = 2.4Hz), 8.91 (1H, d, <i>J</i> = 2.0Hz) , DMSO : 354(M-H) ⁺ FAB
297	1.08 – 1.35 (2H, m), 1.43 – 1.60 (1H, m), 1.60 – 1.72 (2H, m), 1.74 – 1.85 (2H, m), 2.78 (2H, dd, <i>J</i> = 7.2, 7.2Hz), 2.81 – 2.93 (1H, m), 2.94 – 3.08 (1H, m), 3.95 – 4.07 (1H, m), 4.11 – 4.24 (1H, m), 7.16 – 7.22 (1H, m), 7.27 (1H, d, <i>J</i> = 8.0Hz), 7.69 (1H, ddd, <i>J</i> = 8.0, 8.0, 2.0Hz), 8.04 (1H, dd, <i>J</i> = 2.4, 2.0Hz), 8.48 (1H, d, <i>J</i> = 4.4Hz), 8.64 (1H, d, <i>J</i> = 2.4Hz), 8.91 (1H, d, <i>J</i> = 2.0Hz) , DMSO : 354(M-H) ⁺ FAB
298	1.10 – 1.32 (2H, m), 1.45 – 1.67 (3H, m), 1.75 – 1.87 (2H, m), 2.69 – 2.75 (2H, m), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.27 – 7.46 (3H, m), 7.80 – 7.99 (5H, m), 8.30 (1H, d, <i>J</i> = 2.8Hz), 8.66 (1H, d, <i>J</i> = 4.4Hz), 8.80 (1H, d, <i>J</i> = 1.6Hz) , DMSO : 432(M+H) ⁺ FAB

[0154] [Table 54]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
299	1.10 – 1.36 (2H, m), 1.45 – 1.60 (1H, m), 1.54 – 1.66 (2H, m), 1.74 – 1.87 (2H, m), 2.67 (2H, dd, <i>J</i> = 7.2, 7.2Hz), 2.80 – 2.95 (1H, m), 2.95 – 3.10 (1H, m), 3.92 – 4.10 (1H, m), 4.10 – 4.25 (1H, m), 7.26 (2H, d, <i>J</i> = 8.8Hz), 7.30 (2H, d, <i>J</i> = 8.8Hz), 7.56 (2H, d, <i>J</i> = 8.8Hz), 7.68 (2H, dd, <i>J</i> = 8.8, 5.2Hz), 8.05 (1H, dd, <i>J</i> = 3.2, 1.6Hz), 8.65 (1H, d, <i>J</i> = 3.2Hz), 8.92 (1H, d, <i>J</i> = 1.6Hz), 13.60 (1H, br s) , DMSO : 449(M+H) ⁺ FAB
300	1.11 – 1.36 (2H, m), 1.46 – 1.59 (1H, m), 1.54 – 1.64 (2H, m), 1.74 – 1.86 (2H, m), 2.66 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.81 – 2.95 (1H, m), 2.95 – 3.10 (1H, m), 3.79 (3H, s), 3.95 – 4.07 (1H, m), 4.12 – 4.25 (1H, m), 7.01 (2H, d, <i>J</i> = 8.8Hz), 7.27 (2H, d, <i>J</i> = 8.0Hz), 7.53 (2H, d, <i>J</i> = 8.0Hz), 7.58 (2H, d, <i>J</i> = 8.8Hz), 8.05 (1H, dd, <i>J</i> = 2.8, 2.0Hz), 8.65 (1H, d, <i>J</i> = 2.8Hz), 8.92 (1H, d, <i>J</i> = 2.0Hz), 13.60 (1H, br s) , DMSO : 461(M+H) ⁺ FAB
301	1.10 – 1.36 (2H, m), 1.45 – 1.59 (1H, m), 1.55 – 1.66 (2H, m), 1.75 – 1.87 (2H, m), 2.69 (2H, dd, <i>J</i> = 7.2, 7.2Hz), 2.80 – 2.94 (1H, m), 2.96 – 3.12 (1H, m), 3.93 – 4.10 (1H, m), 4.10 – 4.27 (1H, m), 7.36 (2H, d, <i>J</i> = 8.4Hz), 7.68 (2H, d, <i>J</i> = 8.4Hz), 7.87 (2H, d, <i>J</i> = 8.8Hz), 7.91 (2H, d, <i>J</i> = 8.8Hz), 8.05 (1H, dd, <i>J</i> = 2.4, 1.6Hz), 8.65 (1H, d, <i>J</i> = 2.4Hz), 8.92 (1H, d, <i>J</i> = 1.6Hz), 13.61 (1H, br s) , DMSO : 456(M+H) ⁺ FAB
302	1.10 – 1.36 (2H, m), 1.45 – 1.58 (1H, m), 1.55 – 1.65 (2H, m), 1.71 – 1.88 (2H, m), 2.68 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.78 – 2.95 (1H, m), 2.95 – 3.12 (1H, m), 3.92 – 4.10 (1H, m), 4.10 – 4.26 (1H, m), 7.10 – 7.22 (1H, m), 7.32 (2H, d, <i>J</i> = 8.0Hz), 7.42 – 7.54 (3H, m), 7.63 (2H, d, <i>J</i> = 8.0Hz), 8.05 (1H, dd, <i>J</i> = 2.4, 2.0Hz), 8.65 (1H, d, <i>J</i> = 2.4Hz), 8.92 (1H, d, <i>J</i> = 2.0Hz), 13.61 (1H, br s) , DMSO : 449(M+H) ⁺ FAB
303	1.11 – 1.35 (2H, m), 1.46 – 1.58 (1H, m), 1.54 – 1.64 (2H, m), 1.75 – 1.86 (2H, m), 2.67 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.80 – 2.95 (1H, m), 2.95 – 3.12 (1H, m), 3.82 (3H, s), 3.94 – 4.10 (1H, m), 4.10 – 4.25 (1H, m), 6.91 (1H, ddd, <i>J</i> = 8.4, 2.4, 0.8Hz), 7.14 – 7.18 (1H, m), 7.18 – 7.23 (1H, m), 7.30 (2H, d, <i>J</i> = 8.4Hz), 7.36 (1H, dd, <i>J</i> = 8.0, 8.0Hz), 7.59 (2H, d, <i>J</i> = 8.4Hz), 8.05 (1H, dd, <i>J</i> = 2.4, 2.0Hz), 8.65 (1H, d, <i>J</i> = 2.4Hz), 8.92 (1H, d, <i>J</i> = 2.0Hz), 13.60 (1H, br s) , DMSO : 459(M-H) ⁺ ESI
304	1.10 – 1.36 (2H, m), 1.47 – 1.58 (1H, m), 1.55 – 1.66 (2H, m), 1.74 – 1.88 (2H, m), 2.87 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.82 – 2.96 (1H, m), 2.96 – 3.13 (1H, m), 3.95 – 4.10 (1H, m), 4.10 – 4.26 (1H, m), 7.24 – 7.32 (2H, m), 7.33 (2H, d, <i>J</i> = 8.4Hz), 7.36 – 7.44 (1H, m), 7.44 – 7.50 (2H, m), 7.48 – 7.55 (1H, m), 8.05 (1H, dd, <i>J</i> = 2.4, 1.6Hz), 8.65 (1H, d, <i>J</i> = 2.4Hz), 8.92 (1H, d, <i>J</i> = 1.6Hz), 13.61 (1H, br s) , DMSO : 449(M+H) ⁺ FAB
305	480(M+H) ⁺ FAB
306	488(M+Na) ⁺ ESI
307	490(M+Na) ⁺ ESI
308	1.12 – 1.29 (2H, m), 1.50 – 1.63 (9H, m), 1.78 – 1.81 (2H, br), 2.64-2.69 (2H, m), 2.86 (1H, br), 3.02 (1H, br), 3.23 – 3.38 (2H, m), 3.51 – 3.64 (2H, m), 4.01 (1H, m), 4.17 (1H, m), 7.25-7.31 (4H, m), 7.80 (1H, m), 8.28 (1H, m), 8.80 (1H, m) , DMSO : 464(M-H) ⁺ FAB
309	1.15 – 1.28 (2H, m), 1.47 – 1.60 (3H, m), 1.78 – 1.81 (2H, br), 2.65 – 2.69 (2H, br), 2.86 (1H, m), 3.02 (1H, m), 3.40 – 3.63 (8H, br), 4.01 (1H, m), 4.18 (1H, m), 7.28-7.34 (4H, m), 7.80 (1H, m), 8.28 (1H, m), 8.80 (1H, m) , DMSO : 468(M+H) ⁺ FAB
310	452(M+H) ⁺ FAB
311	544(M+H) ⁺ ESI
312	454(M+H) ⁺ ESI
313	1.10 – 1.80 (16H, m), 2.27 (3H, s), 2.65 – 2.74 (2H, m), 2.80 – 3.10 (2H, m), 3.95 – 4.32 (4H, m), 6.42 (1H, d, <i>J</i> = 7.6Hz), 6.56 (1H, d, <i>J</i> = 8.8Hz), 7.36 (1H, t, <i>J</i> = 8.0Hz), 7.80 (1H, br), 8.27 (1H, d, <i>J</i> = 3.2Hz), 8.79 (1H, br) , DMSO : 467(M+H) ⁺ FAB
314	1.07 – 1.21 (2H, m), 1.27 – 1.51 (10H, m), 1.73 – 1.77 (2H, br), 1.81-1.84 (2H, br) 2.83 – 2.89 (3H, br), 3.04 (1H, br), 3.72 – 3.76 (2H, br), 4.02 (1H, br), 4.18 (1H, br), 7.33 (1H, m), 7.58 (1H, m), 7.68 (1H, m), 7.80 (1H, m), 7.86 (1H, m), 8.04 (1H, m), 8.08 (1H, m), 8.28 (1H, m), 8.79 (1H, m) , DMSO : 503(M+H) ⁺ FAB

[0155] [Table 55]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
315	1.00 – 1.82 (16H, m), 2.77 – 3.08 (4H, m), 3.95 – 4.23 (2H, m), 4.53 (2H, d, <i>J</i> = 12.0Hz), 7.10 – 7.23 (2H, m), 7.42 – 7.58 (2H, m), 7.66 (1H, d, <i>J</i> = 7.5Hz), 7.81 (1H, s), 7.99 (1H, d, <i>J</i> = 8.5Hz), 8.29 (1H, d, <i>J</i> = 2.2Hz), 8.80 (1H, s), DMSO : 503(M+H) ⁺ FAB
316	1.08 – 1.23 (2H, m), 1.26 – 1.32 (2H, m), 1.47 – 1.57 (3H, m), 1.73 – 1.77 (2H, m), 2.37-2.41 (2H, m) 2.61 – 2.67 (4H, br), 2.87 (1H, m), 2.03 (1H, m), 3.27 – 3.33 (4H, br), 4.02 (1H, br), 4.18 (1H, br), 7.37 (1H, m), 7.59 (1H, m), 7.70 (1H, m), 7.81 (1H, m), 7.87 (1H, m), 8.06 – 8.11 (2H, m), 8.29 (1H, m), 8.80 (1H, m), DMSO : 526(M+Na) ⁺ ESI
317	1.07 – 1.21 (2H, m), 1.27 – 1.51 (10H, m), 1.73 – 1.77 (2H, br), 1.82-1.85 (2H, br) 2.67 – 2.73 (2H, br), 2.87 (1H, m), 3.02 (1H, br), 3.28 – 3.39 (2H, br), 4.02 (1H, br), 4.18 (1H, br), 7.09 (1H, m), 7.41 (1H, m), 7.46 – 7.52 (2H, m), 7.55 (1H, m), 7.82 (1H, m), 7.86 (1H, m), 8.08 (1H, m), 8.29 (1H, m), 8.80 (1H, m), DMSO : 524(M+Na) ⁺ FAB
318	1.10 – 1.30 (2H, m), 1.44 – 1.62 (3H, m), 1.75 – 1.83 (2H, m), 2.70 (2H, t, <i>J</i> = 7.3Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.47 – 7.74 (5H, m), 8.02 (1H, t, <i>J</i> = 2.5Hz), 8.17 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 2.0Hz), DMSO : 379(M+H) ⁺ FAB
319	1.10 – 1.30 (2H, m), 1.45 – 1.59 (3H, m), 1.80 (2H, d, <i>J</i> = 12.2Hz), 2.63 (2H, t, <i>J</i> = 7.4Hz), 2.88 (1H, t, <i>J</i> = 12.2Hz), 3.03 (1H, t, <i>J</i> = 12.2Hz), 3.31 – 3.38 (2H, m), 3.50 – 3.55 (2H, m), 4.02 (1H, d, <i>J</i> = 12.2Hz), 4.18 (1H, d, <i>J</i> = 12.2Hz), 7.15 – 7.31 (5H, m), 8.01 (1H, t, <i>J</i> = 2.4Hz), 8.55 (1H, s), 8.69 (1H, t, <i>J</i> = 5.6Hz), 8.88 (1H, s), DMSO : 398(M+H) ⁺ FAB
320	1.10 – 1.30 (2H, m), 1.45 – 1.60 (3H, m), 1.75 – 1.85 (2H, m), 2.63 (2H, t, <i>J</i> = 7.4Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.15 – 7.31 (5H, m), 7.67 (1H, s), 8.01 (1H, t, <i>J</i> = 1.9Hz), 8.17 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 2.0Hz), DMSO : 354(M+H) ⁺ FAB
321	1.10 – 1.30 (2H, m), 1.45 – 1.60 (3H, m), 1.75 – 1.85 (2H, m), 2.60 (2H, t, <i>J</i> = 7.3Hz), 2.80 – 3.10 (2H, m), 3.74 (3H, s), 3.95 – 4.24 (2H, m), 6.70 – 6.84 (3H, m), 7.13 -7.24 (1H, m), 7.66 (1H, s), 8.01 (1H, br), 8.18 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, br), DMSO : 384(M+H) ⁺ FAB
322	1.10 – 1.30 (2H, m), 1.44 – 1.60 (3H, m), 1.75 – 1.83 (2H, m), 2.65 (2H, t, <i>J</i> = 7.3Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 6.96 – 7.10 (3H, m), 7.29 – 7.36 (1H, m), 7.66 (1H, s), 8.01 (1H, t, <i>J</i> = 2.5Hz), 8.17 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 1.9Hz), DMSO : 372(M+H) ⁺ FAB
323	1.10 – 1.34 (2H, m), 1.50 – 1.64 (3H, m), 1.75 – 1.88 (2H, m), 2.80 – 3.10 (4H, m), 3.95 – 4.24 (2H, m), 7.41 (1H, dt, <i>J</i> = 1.0, 7.4Hz), 7.51 (1H, d, <i>J</i> = 7.8Hz), 7.62 – 7.70 (2H, m), 7.79 (1H, dd, <i>J</i> = 1.5, 7.8Hz), 8.02 (1H, t, <i>J</i> = 2.0Hz), 8.17 (1H, s), 8.56 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 2.0Hz), DMSO : 379(M+H) ⁺ FAB
324	1.10 – 1.34 (2H, m), 1.45 – 1.64 (3H, m), 1.75 – 1.88 (2H, m), 2.66 (2H, t, <i>J</i> = 7.8Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.26 – 7.40 (3H, m), 7.64 – 7.75 (3H, m), 7.92 (1H, s), 8.01(1H, br), 8.17 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 2.4Hz), DMSO : 397(M+H) ⁺ FAB
325	1.10 – 1.34 (2H, m), 1.45 – 1.64 (3H, m), 1.75 – 1.85 (2H, m), 2.66 (2H, t, <i>J</i> = 7.3Hz), 2.80 – 3.10 (8H, m), 3.95 – 4.24 (2H, m), 7.16 – 7.37 (4H, m), 7.66 (1H, s), 8.01 (1H, br), 8.17 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 1.4Hz), DMSO : 425(M+H) ⁺ FAB
326	0.79 – 0.93 (2H, m), 1.02 – 1.30 (10H, m), 1.37 – 1.49 (1H, m) 1.57 – 1.77 (7H, m), 2.81 – 2.92 (1H, br), 2.96 – 3.08 (1H, br), 3.94 – 4.05 (1H, br), 4.10 – 4.21 (1H, br), 7.63 – 7.70 (1H, br), 8.00 (1H, dd, <i>J</i> = 3.0Hz, 2.4Hz), 8.13 – 8.21 (1H, m), 8.55 (1H, d, <i>J</i> = 3.0Hz), , 8.88 (1H, d, <i>J</i> = 2.4Hz), DMSO : 360(M+H) ⁺ FAB
327	1.10 – 1.30 (2H, m), 1.45 – 1.60 (3H, m), 1.75 – 1.85 (2H, m), 2.63 (2H, t, <i>J</i> = 7.2Hz), 2.80 – 3.10 (2H, m), 3.30 – 3.38 (2H, m), 3.49 – 3.55 (2H, m), 3.95 – 4.24 (2H, m), 7.16 – 7.34 (4H, m), 8.02 (1H, t, <i>J</i> = 2.4Hz), 8.55 (1H, br), 8.69 (1H, t, <i>J</i> = 5.6Hz), 8.87 (1H, s), DMSO : 432(M+H) ⁺ FAB

[0156] [Table 56]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
328	1.10 – 1.30 (2H, m), 1.45 – 1.60 (3H, m), 1.75 – 1.85 (2H, m), 2.60 (2H, t, <i>J</i> = 7.6Hz), 2.80 – 3.10 (2H, m), 3.30 – 3.38 (2H, m), 3.49 – 3.55 (2H, m), 3.74 (3H, s), 3.95 – 4.24 (2H, m), 6.71 – 6.82 (3H, m), 7.19 (1H, t, <i>J</i> = 7.2Hz), 8.01 (1H, br), 8.55 (1H, br), 8.68 (1H, t, <i>J</i> = 6.0Hz), 8.87 (1H, br) , DMSO : 428(M+H) ⁺ FAB
329	1.10 – 1.30 (2H, m), 1.45 – 1.60 (3H, m), 1.75 – 1.85 (2H, m), 2.65 (2H, t, <i>J</i> = 8.4Hz), 2.80 – 3.10 (2H, m), 3.30 – 3.38 (2H, m), 3.49 – 3.55 (2H, m), 3.95 – 4.24 (2H, m), 7.05 – 7.10 (3H, m), 7.30 – 7.35 (1H, m), 8.00 (1H, t, <i>J</i> = 2.4Hz), 8.55 (1H, br), 8.68 (1H, t, <i>J</i> = 5.6Hz), 8.87 (1H, br) , DMSO : 416(M+H) ⁺ FAB
330	1.10 – 1.30 (2H, m), 1.45 – 1.62 (3H, m), 1.75 – 1.85 (2H, m), 2.70 (2H, t, <i>J</i> = 7.2Hz), 2.80 – 3.10 (2H, m), 3.30 – 3.38 (2H, m), 3.49 – 3.55 (2H, m), 3.95 – 4.24 (2H, m), 7.50 (1H, t, <i>J</i> = 8.0Hz), 7.56 – 7.74 (3H, m), 8.02 (1H, t, <i>J</i> = 2.0Hz), 8.55 (1H, d, <i>J</i> = 2.0Hz), 8.69 (1H, t, <i>J</i> = 6.0Hz), 8.87 (1H, br) , DMSO : 423(M+H) ⁺ FAB
331	1.10 – 1.34 (2H, m), 1.50 – 1.64 (3H, m), 1.75 – 1.89 (2H, m), 2.84 (2H, t, <i>J</i> = 8.0Hz), 2.84 – 3.11 (2H, m), 3.31 – 3.38 (2H, m), 3.49 – 3.55 (2H, m), 3.95 – 4.25 (2H, m), 7.40 (1H, dt, <i>J</i> = 0.8, 7.6Hz), 7.52 (1H, d, <i>J</i> = 7.2Hz), 7.65 (1H, dt, <i>J</i> = 1.6, 7.6Hz), 7.79 (1H, dd, <i>J</i> = 1.2, 8.0Hz), 8.04 (1H, t, <i>J</i> = 2.0Hz), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.69 (1H, t, <i>J</i> = 5.6Hz), 8.87 (1H, d, <i>J</i> = 1.6Hz) , DMSO : 423(M+H) ⁺ FAB
332	462(M+H) ⁺ FAB
333	1.10 – 1.30 (2H, m), 1.45 – 1.60 (3H, m), 1.80 (2H, d, <i>J</i> = 12.0Hz), 2.37 (2H, t, <i>J</i> = 7.2Hz), 2.63 (2H, t, <i>J</i> = 7.2Hz), 2.87 (1H, t, <i>J</i> = 12.2Hz), 3.03 (1H, t, <i>J</i> = 12.2Hz), 3.41 – 3.49 (2H, m), 4.01 (1H, d, <i>J</i> = 12.2Hz), 4.18 (1H, d, <i>J</i> = 12.2Hz), 6.83 (1H, s), 7.15 – 7.31 (5H, m), 7.36 (1H, s), 7.99 (1H, t, <i>J</i> = 2.4Hz), 8.55 (1H, d, <i>J</i> = 3.2Hz), 8.76 (1H, t, <i>J</i> = 5.6Hz), 8.85 (1H, t, <i>J</i> = 2.0Hz) , DMSO : 425(M+H) ⁺ FAB
334	1.08 – 1.32 (2H, m), 1.45 – 1.60 (3H, m), 1.74 – 1.86 (2H, m), 2.66 (2H, dd, <i>J</i> = 7.2, 7.2Hz), 2.80 – 2.95 (1H, m), 2.95 – 3.11 (1H, m), 3.95 – 4.08 (1H, m), 4.11 – 4.25 (1H, m), 7.09 – 7.17 (2H, m), 7.20 – 7.28 (1H, m), 7.28 – 7.36 (1H, m), 7.67 (1H, br s), 8.02 (1H, dd, <i>J</i> = 2.4, 2.0Hz), 8.18 (1H, br s), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 2.0Hz) , DMSO : 372(M+H) ⁺ FAB
335	1.08 – 1.32 (2H, m), 1.44 – 1.61 (3H, m), 1.77 – 1.83 (2H, br), 2.63 (2H, t, <i>J</i> = 7.6Hz), 2.79 – 3.08 (2H, br), 3.95 – 4.23 (2H, br), 6.73 (1H, d, <i>J</i> = 16.0Hz), 7.14 – 7.22 (3H, m), 7.25 – 7.32 (2H, m), 7.64 (1H, d, <i>J</i> = 16.0Hz), 8.02 – 8.06 (1H, m), 8.40 – 8.44 (1H, m), 8.68 – 8.73 (1H, m), 12.55 – 12.63 (1H, br) , DMSO : 380(M+H) ⁺ FAB
336	1.09 – 1.31 (2H, m), 1.43 – 1.56 (1H, m), 1.53 – 1.64 (2H, m), 1.71 – 1.86 (2H, m), 2.67 (2H, dd, <i>J</i> = 8.0, 8.0Hz), 2.79 – 2.96 (1H, m), 2.92 – 3.11 (1H, m), 3.93 – 4.10 (1H, m), 4.08 – 4.24 (1H, m), 7.31 (2H, d, <i>J</i> = 5.2Hz), 7.67 (1H, s), 8.01 (1H, dd, <i>J</i> = 2.4, 1.6Hz), 8.19 (1H, s), 8.49 (2H, br s), 8.56 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 1.6Hz) , DMSO : 355(M+H) ⁺ ESI
337	1.08 – 1.32 (2H, m), 1.43 – 1.57 (1H, m), 1.52 – 1.63 (2H, m), 1.72 – 1.86 (2H, m), 2.66 (2H, dd, <i>J</i> = 7.2, 7.2Hz), 2.80 – 2.95 (1H, m), 2.95 – 3.11 (1H, m), 3.93 – 4.08 (1H, m), 4.10 – 4.25 (1H, m), 7.33 (1H, dd, <i>J</i> = 7.6, 4.8Hz), 7.62 – 7.72 (2H, m), 8.01 (1H, dd, <i>J</i> = 2.4, 1.6Hz), 8.19 (1H, br s), 8.41 (1H, br s), 8.47 (1H, br s), 8.56 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 1.6Hz) , DMSO : 355(M+H) ⁺ ESI
338	1.10 – 1.33 (2H, m), 1.45 – 1.59 (1H, m), 1.54 – 1.65 (2H, m), 1.75 – 1.87 (2H, m), 2.67 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.81 – 2.95 (1H, m), 2.96 – 3.10 (1H, m), 3.92 – 4.08 (1H, m), 4.11 – 4.25 (1H, m), 7.27 (2H, t, <i>J</i> = 8.8Hz), 7.31 (2H, d, <i>J</i> = 8.4Hz), 7.56 (2H, d, <i>J</i> = 8.4Hz), 7.63 – 7.72 (3H, m), 8.02 (1H, dd, <i>J</i> = 2.4, 2.0Hz), 8.19 (1H, br s), 8.56 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 2.0Hz) , DMSO : 448(M+H) ⁺ FAB
339	1.10 – 1.33 (2H, m), 1.47 – 1.63 (1H, m), 1.53 – 1.65 (2H, m), 1.76 – 1.88 (2H, m), 2.66 (2H, dd, <i>J</i> = 7.2, 7.2Hz), 2.80 – 2.96 (1H, m), 2.96 – 3.11 (1H, m), 3.79 (3H, s), 3.96 – 4.07 (1H, m), 4.12 – 4.25 (1H, m), 7.01 (2H, d, <i>J</i> = 8.4Hz), 7.28 (2H, d, <i>J</i> = 8.4Hz), 7.53 (2H, d, <i>J</i> = 8.4Hz), 7.58 (2H, d, <i>J</i> = 8.4Hz), 7.67 (1H, br s), 8.02 (1H, dd, <i>J</i> = 2.4, 2.0Hz), 8.19 (1H, br s), 8.56 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 2.0Hz) , DMSO : 458(M+H) ⁺ FAB

[0157] [Table 57]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
340	1.10 – 1.32 (2H, m), 1.45 – 1.67 (3H, m), 1.75 – 1.87 (2H, m), 2.71 (2H, t, <i>J</i> = 8.0Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.23 (1H, d, <i>J</i> = 7.2Hz), 7.33 – 7.52 (6H, m), 7.64 – 7.71 (2H, m), 8.02 (1H, t, <i>J</i> = 2.0Hz), 8.19 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 1.6Hz), DMSO : 430(M+H) ⁺ FAB
341	1.10 – 1.32 (2H, m), 1.45 – 1.67 (3H, m), 1.75 – 1.87 (2H, m), 2.71 (2H, t, <i>J</i> = 7.6Hz), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.29 (1H, d, <i>J</i> = 7.6Hz), 7.41 (1H, t, <i>J</i> = 7.6Hz), 7.55 (1H, d, <i>J</i> = 7.2Hz), 7.60 – 7.73 (3H, m), 7.82 (1H, d, <i>J</i> = 7.2Hz), 8.00 – 8.08 (2H, m), 8.16 (1H, s), 8.20 (1H, s), 8.65 (1H, br), 8.91 (1H, br), DMSO : 455(M+H) ⁺ FAB
342	1.06 – 1.30 (2H, m), 1.43 – 1.56 (1H, m), 1.51 – 1.61 (2H, m), 1.69 (2H, q, <i>J</i> = 6.4Hz), 1.74 – 1.85 (2H, m), 2.63 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.80 – 2.94 (1H, m), 2.94 – 3.10 (2H, m), 3.33 (2H, td, <i>J</i> = 6.4, 6.4Hz), 3.47 (2H, t, <i>J</i> = 6.4Hz), 3.93 – 4.09 (1H, m), 4.09 – 4.24 (1H, m), 7.13 – 7.24 (3H, m), 7.24 – 7.31 (2H, m), 7.99 (1H, dd, <i>J</i> = 2.4, 1.6Hz), 8.54 (1H, d, <i>J</i> = 2.4Hz), 8.67 (1H, br t, <i>J</i> = 5.2Hz), 8.85 (1H, d, <i>J</i> = 1.6Hz), DMSO : 412(M+H) ⁺ FAB
343	1.08 – 1.31 (2H, m), 1.44 – 1.56 (1H, m), 1.52 – 1.61 (2H, m), 1.74 – 1.86 (2H, m), 1.82 – 1.93 (2H, m), 2.63 (2H, dd, <i>J</i> = 7.2, 7.2Hz), 2.72 (6H, s), 2.80 – 2.93 (1H, m), 2.98 – 3.09 (3H, m), 3.34 (2H, td, <i>J</i> = 6.4, 6.4Hz), 3.94 – 4.07 (1H, m), 4.10 – 4.24 (1H, m), 7.13 – 7.24 (3H, m), 7.24 – 7.32 (2H, m), 8.00 (1H, dd, <i>J</i> = 2.4, 1.6Hz), 8.57 (1H, d, <i>J</i> = 2.4Hz), 8.85 (1H, br t, <i>J</i> = 5.6Hz), 8.88 (1H, d, <i>J</i> = 1.6Hz), DMSO : 439(M+H) ⁺ FAB
344	1.09 – 1.34 (2H, m), 1.45 – 1.60 (1H, m), 1.55 – 1.66 (2H, m), 1.75 – 1.87 (2H, m), 2.70 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.80 – 2.96 (1H, m), 2.96 – 3.11 (1H, m), 3.94 – 4.09 (1H, m), 4.10 – 4.26 (1H, m), 7.37 (2H, d, <i>J</i> = 8.4Hz), 7.68 (1H, br s), 7.69 (2H, d, <i>J</i> = 8.4Hz), 7.87 (2H, d, <i>J</i> = 8.4Hz), 7.91 (2H, d, <i>J</i> = 8.4Hz), 8.02 (1H, dd, <i>J</i> = 2.4, 2.0Hz), 8.19 (1H, br s), 8.56 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 2.0Hz), DMSO : 455(M+H) ⁺ FAB
345	1.10 – 1.34 (2H, m), 1.46 – 1.60 (1H, m), 1.54 – 1.66 (2H, m), 1.75 – 1.89 (2H, m), 2.68 (2H, dd, <i>J</i> = 7.6, 7.6Hz), 2.80 – 2.96 (1H, m), 2.96 – 3.12 (1H, m), 3.95 – 4.09 (1H, m), 4.11 – 4.26 (1H, m), 7.13 – 7.21 (1H, m), 7.33 (2H, d, <i>J</i> = 8.0Hz), 7.45 – 7.52 (3H, m), 7.63 (2H, d, <i>J</i> = 8.0Hz), 7.67 (1H, br s), 8.02 (1H, dd, <i>J</i> = 2.4, 2.0Hz), 8.19 (1H, br s), 8.56 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 2.0Hz), DMSO : 448(M+H) ⁺ FAB
346	1.10 – 1.35 (2H, m), 1.48 – 1.61 (1H, m), 1.56 – 1.66 (2H, m), 1.76 – 1.90 (2H, m), 2.69 (2H, dd, <i>J</i> = 8.0, 8.0Hz), 2.81 – 2.97 (1H, m), 2.97 – 3.13 (1H, m), 3.95 – 4.10 (1H, m), 4.10 – 4.26 (1H, m), 7.25 – 7.32 (2H, m), 7.33 (2H, d, <i>J</i> = 8.0Hz), 7.36 – 7.44 (1H, m), 7.44 – 7.50 (2H, m), 7.48 – 7.56 (1H, m), 7.67 (1H, br s), 8.02 (1H, dd, <i>J</i> = 2.8, 2.0Hz), 8.19 (1H, br s), 8.56 (1H, d, <i>J</i> = 2.8Hz), 8.89 (1H, d, <i>J</i> = 2.0Hz), DMSO : 448(M+H) ⁺ FAB
347	1.08 – 1.31 (2H, m), 1.43 – 1.55 (1H, m), 1.50 – 1.61 (2H, m), 1.72 – 1.85 (2H, m), 2.63 (2H, dd, <i>J</i> = 7.8, 7.8Hz), 2.80 – 2.93 (1H, m), 2.90 (2H, t, <i>J</i> = 6.8Hz), 2.96 – 3.09 (1H, m), 3.56 (2H, td, <i>J</i> = 6.8, 6.8Hz), 3.93 – 4.08 (1H, m), 4.08 – 4.23 (1H, m), 7.14 – 7.24 (3H, m), 7.24 – 7.31 (2H, m), 7.33 (2H, d, <i>J</i> = 5.6Hz), 7.95 (1H, dd, <i>J</i> = 2.8, 1.6Hz), 8.50 (2H, br s), 8.55 (1H, d, <i>J</i> = 2.8Hz), 8.81 (1H, d, <i>J</i> = 1.6Hz), 8.81 (1H, t, <i>J</i> = 6.0Hz), DMSO : 459(M+H) ⁺ FAB
348	1.08 – 1.31 (2H, m), 1.43 – 1.57 (1H, m), 1.50 – 1.62 (2H, m), 1.73 – 1.86 (2H, m), 2.63 (2H, dd, <i>J</i> = 7.8, 7.8Hz), 2.80 – 2.93 (1H, m), 2.89 (2H, t, <i>J</i> = 6.8Hz), 2.96 – 3.09 (1H, m), 3.54 (2H, td, <i>J</i> = 6.8, 6.8Hz), 3.94 – 4.09 (1H, m), 4.09 – 4.25 (1H, m), 7.13 – 7.25 (3H, m), 7.25 – 7.32 (2H, m), 7.35 (1H, dd, <i>J</i> = 7.6, 4.8Hz), 7.71 (1H, d, <i>J</i> = 7.6Hz), 7.92 – 7.97 (1H, m), 8.44 (1H, br s), 8.49 (1H, br s), 8.52 – 8.59 (1H, m), 8.77 – 8.85 (2H, m), DMSO : 459(M+H) ⁺ FAB
349	1.10 – 1.32 (2H, m), 1.45 – 1.67 (3H, m), 1.75 – 1.87 (2H, m), 2.69 – 2.78 (2H, m), 2.80 – 3.10 (2H, m), 3.95 – 4.24 (2H, m), 7.27 – 7.46 (3H, m), 7.66 (1H, s), 7.83 – 8.03 (5H, m), 8.18 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.66 (1H, br), 8.89 (1H, d, <i>J</i> = 1.2Hz), DMSO : 431(M+H) ⁺ FAB
350	425(M+H) ⁺ FAB
351	1.05 – 1.85 (17H, m), 2.67 (2H, t, <i>J</i> = 7.6Hz), 2.80 – 3.10 (2H, m), 3.70 – 3.80 (1H, m), 3.95 – 4.24 (2H, m), 7.33 – 7.37 (2H, m), 7.62 – 7.70 (3H, m), 8.01 (1H, t, <i>J</i> = 2.0Hz), 8.13 (1H, d, <i>J</i> = 7.6Hz), 8.17 (1H, s), 8.55 (1H, d, <i>J</i> = 2.8Hz), 8.89 (1H, d, <i>J</i> = 2.0Hz), DMSO : 479(M+H) ⁺ FAB

[0158] [Table 58]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
352	411(M+H) ⁺ FAB
353	1.08 – 1.32 (2H, m), 1.43 – 1.58 (1H, m), 1.52 – 1.64 (2H, m), 1.72 – 1.87 (2H, m), 2.68 (2H, dd, <i>J</i> = 7.8, 7.8Hz), 2.78 – 2.95 (1H, m), 2.97 – 3.12 (1H, m), 3.93 – 4.09 (1H, m), 4.10 – 4.25 (1H, m), 7.26 (1H, br s), 7.29 (2H, d, <i>J</i> = 8.0Hz), 7.67 (1H, br s), 7.79 (2H, d, <i>J</i> = 8.0Hz), 7.89 (1H, br s), 8.01 (1H, dd, <i>J</i> = 2.4, 1.2Hz), 8.18 (1H, br s), 8.55 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 1.2Hz) , DMSO : 397(M+H) ⁺ FAB
354	1.08 – 1.33 (2H, m), 1.44 – 1.58 (1H, m), 1.52 – 1.64 (2H, m), 1.73 – 1.88 (2H, m), 2.67 (2H, dd, <i>J</i> = 7.8, 7.8Hz), 2.80 – 2.96 (1H, m), 2.92 (3H, s), 2.95 (3H, s), 2.96 – 3.12 (1H, m), 3.92 – 4.08 (1H, m), 4.09 – 4.25 (1H, m), 7.27 (2H, d, <i>J</i> = 7.6Hz), 7.32 (2H, d, <i>J</i> = 7.6Hz), 7.67 (1H, br s), 8.01 (1H, dd, <i>J</i> = 2.4, 1.6Hz), 8.18 (1H, br s), 8.56 (1H, d, <i>J</i> = 2.4Hz), 8.89 (1H, d, <i>J</i> = 1.6Hz) , DMSO : 425(M+H) ⁺ FAB
355	1.11 – 1.31 (2H, m), 1.40 – 1.66 (9H, m), 1.74 – 1.86 (2H, br), 2.64-2.69 (2H, m), 2.86 (1H, br), 3.02 (1H, br), 3.23 – 3.38 (2H, m), 3.51 – 3.64 (2H, m), 4.01 (1H, m), 4.17 (1H, m), 7.15-7.20 (2H, m), 7.30 – 7.37 (2H, m), 7.67 (1H, s), 8.01 (1H, m), 8.18 (1H, s), 8.55 (1H, m), 8.89 (1H, m) , DMSO : 465(M+H) ⁺ ESI
356	1.21 – 1.36 (2H, m), 1.54 – 1.59 (3H, m), 1.78 – 1.82 (2H, br), 2.64 – 2.69 (2H, br), 2.87 (1H, m), 3.03 (1H, m), 3.37 – 3.69 (8H, br), 3.99 (1H, m), 4.16 (1H, m), 7.15-7.20 (2H, m), 7.30 – 7.37 (2H, m), 7.67 (1H, s), 8.01 (1H, m), 8.18 (1H, s), 8.55 (1H, m), 8.89 (1H, m) , DMSO : 467(M+H) ⁺ ESI
357	1.15 – 1.28 (2H, m), 1.44 – 1.62 (9H, m), 1.79 – 1.83 (2H, br), 2.65-2.68 (2H, m), 2.88 (1H, br), 3.03 (1H, br), 3.24 – 3.37 (2H, br), 3.47 – 3.62 (2H, m), 4.01(1H, m), 4.18 (1H, m), 7.26-7.30 (4H, m), 7.67 (1H, s), 8.02 (1H, m), 8.18 (1H, s), 8.55 (1H, m), 8.89 (1H, m) , DMSO : 465(M+H) ⁺ FAB
358	1.13 – 1.28 (2H, m), 1.48 – 1.61 (3H, m), 1.79 – 1.82 (2H, br), 2.65 – 2.69 (2H, br), 2.88 (1H, m), 3.04 (1H, m), 3.34 – 3.65 (8H, br), 4.01 (1H, m), 4.18 (1H, m), 7.15-7.20 (2H, m), 7.28-7.34 (4H, m), 7.66 (1H, s), 8.01 (1H, m), 8.17 (1H, s), 8.55 (1H, m), 8.89 (1H, m) , DMSO : 467(M+H) ⁺ FAB
359	1.16 – 1.25 (2H, m), 1.51 – 1.61 (3H, m), 1.79 – 1.88 (6H, br), 2.65-2.69 (2H, m), 2.87 (1H, br), 3.03 (1H, br), 3.31 – 3.38 (2H, br), 3.44 – 3.47 (2H, m), 4.01 (1H, m), 4.18 (1H, m), 7.29-7.36 (4H, m), 7.68 (1H, s), 8.01 (1H, m), 8.19 (1H, s), 8.55 (1H, m), 8.89 (1H, m) , DMSO : 451(M+H) ⁺ ESI
360	1.03 – 1.31 (8H, m), 1.46 – 1.66 (3H, m), 1.78 – 1.83 (2H, br), 2.64-2.69 (2H, m), 2.87 (1H, br), 3.03 (1H, br), 3.14 – 3.24 (2H, br), 3.35 – 3.49 (2H, m), 4.03(1H, m), 4.18 (1H, m), 7.12-7.18 (2H, m), 7.27 – 7.37 (2H, m), 7.68 (1H, s), 8.02 (1H, m), 8.19 (1H, s), 8.56 (1H, m), 8.89 (1H, m) , DMSO : 453(M+H) ⁺ ESI
361	1.13 – 1.30 (2H, m), 1.48 – 1.61 (3H, m), 1.78 – 1.83 (2H, br), 2.65-2.71 (2H, m), 2.87 (1H, br), 3.03 (1H, br), 3.92 – 3.98 (2H, m), 4.00 (1H, m), 4.18 (1H, m), 4.37 – 4.43 (2H, m), 7.38-7.41 (2H, m), 7.66 – 7.70 (2H, m), 7.73 (1H, s), 8.01 (1H, m), 8.19 (1H, s), 8.56 (1H, m), 8.89 (1H, m) , DMSO : 423(M+H) ⁺ API
362	1.04-1.37 (8H, m), 1.45-1.68 (3H, m), 1.83 (2H, d, <i>J</i> = 12.8 Hz), 2.69 (2H, t, <i>J</i> = 7.3 Hz), 2.86 (1H, t, <i>J</i> = 12.1 Hz), 2.99 (1H, t, <i>J</i> = 12.1 Hz), 3.28 (2H, br), 3.53 (2H, br), 4.15-4.34 (2H, m), 7.20 (2H, d, <i>J</i> = 8.1 Hz), 7.31 (2H, d, <i>J</i> = 8.1 Hz), 8.01 (1H, s), 8.59 (1H, s), 8.89 (1H, s)CDCl ₃ : 453(M+H) ⁺ ESI
363	1.18-1.36 (2H, m), 1.44-1.68 (3H, m), 1.76-2.12 (6H, m), 2.69 (2H, t, <i>J</i> = 7.5 Hz), 2.84 (2H, t, <i>J</i> = 11.9 Hz), 2.98 (2H, t, <i>J</i> = 11.9 Hz), 4.25 (4H, br), 6.02 (1H, br), 6.73 (1H, br), 7.20 (2H, d, <i>J</i> = 7.9 Hz), 7.45 (2H, d, <i>J</i> = 7.9 Hz), 7.98 (1H, s), 8.57 (1H, s), 8.85 (1H, s)CDCl ₃ : 451(M+H) ⁺ ESI

[0159] [Table 59]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
364	1.18-1.36 (2H, m), 1.44-1.70 (3H, m), 1.77-1.92 (2H, m), 2.72 (2H, t, <i>J</i> = 7.5 Hz), 2.85 (2H, t, <i>J</i> = 11.4 Hz), 2.99 (2H, t, <i>J</i> = 11.4 Hz), 4.08 (2H, t, <i>J</i> = 9.6 Hz), 4.26 (2H, br), 4.47 (2H, t, <i>J</i> = 9.6 Hz), 7.25 (2H, d, <i>J</i> = 7.8 Hz), 7.91 (2H, d, <i>J</i> = 7.8 Hz), 7.94-7.99 (1H, m), 8.58 (1H, d, <i>J</i> = 2.4 Hz), 8.83 (1H, d, <i>J</i> = 2.4 Hz)CDCl ₃ : 423(M+H) ⁺ ESI
365	1.03 (2H, d, <i>J</i> = 6.2 Hz), 1.12 - 1.30 (2H, m), 1.48 - 1.62 (3H, m), 1.80 (2H, d, <i>J</i> = 12.8 Hz), 2.68 (2H, t, <i>J</i> = 7.4 Hz), 2.87 (1H, t, <i>J</i> = 12.8 Hz), 3.03 (1H, t, <i>J</i> = 12.8 Hz), 3.38 - 3.80 (6H, m), 4.01 (1H, d, <i>J</i> = 12.8 Hz), 4.17 (1H, d, <i>J</i> = 12.8 Hz), 6.65 - 6.68 (1H, m), 6.84 (1H, d, <i>J</i> = 8.4 Hz), 7.23 - 7.39 (4H, m), 7.53 - 7.57 (1H, m), 7.66 (1H, s), 8.00 - 8.02 (1H, m), 8.11 - 8.13 (1H, m), 8.18 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4 Hz), 8.88 (1H, d, <i>J</i> = 2.0 Hz) , DMSO : 543(M+H) ⁺ FAB
366	1.03 (2H, d, <i>J</i> = 6.2 Hz), 1.12 - 1.30 (2H, m), 1.48 - 1.62 (3H, m), 1.80 (2H, d, <i>J</i> = 12.4 Hz), 2.68 (2H, t, <i>J</i> = 7.4 Hz), 2.87 (1H, t, <i>J</i> = 12.4 Hz), 3.03 (1H, t, <i>J</i> = 12.4 Hz), 3.10 - 3.28 (3H, m), 3.40 - 3.83 (3H, m), 4.02 (1H, d, <i>J</i> = 12.4 Hz), 4.18 (1H, d, <i>J</i> = 12.4 Hz), 6.80 (1H, t, <i>J</i> = 7.6 Hz), 6.95 (2H, d, <i>J</i> = 7.6 Hz), 7.20 - 7.40 (6H, m), 7.66 (1H, s), 8.00 (1H, t, <i>J</i> = 2.4 Hz), 8.18 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4 Hz), 8.88 (1H, d, <i>J</i> = 2.0 Hz) , DMSO : 542(M+H) ⁺ FAB
367	1.12 - 1.32 (2H, m), 1.48 - 1.63 (3H, m), 1.82 (2H, d, <i>J</i> = 12.4 Hz), 2.68 (2H, t, <i>J</i> = 7.2 Hz), 2.88 (1H, t, <i>J</i> = 12.4 Hz), 3.04 (1H, t, <i>J</i> = 12.4 Hz), 3.40 - 3.75 (8H, m), 4.02 (1H, d, <i>J</i> = 12.4 Hz), 4.18 (1H, d, <i>J</i> = 12.4 Hz), 6.65 - 6.68 (1H, m), 6.84 (1H, d, <i>J</i> = 8.8 Hz), 7.31 (2H, d, <i>J</i> = 8.0 Hz), 7.36 (2H, d, <i>J</i> = 8.0 Hz), 7.53 - 7.57 (1H, m), 7.66 (1H, s), 8.01 (1H, d, <i>J</i> = 2.4 Hz), 8.11 - 8.13 (1H, m), 8.18 (1H, s), 8.55 (1H, d, <i>J</i> = 2.8 Hz), 8.89 (1H, d, <i>J</i> = 2.0 Hz) , DMSO : 543(M+H) ⁺ FAB
368	1.11 - 1.31 (2H, m), 1.48 - 1.63 (3H, m), 1.81 (2H, d, <i>J</i> = 12.2 Hz), 2.68 (2H, t, <i>J</i> = 7.2 Hz), 2.88 (1H, t, <i>J</i> = 12.8 Hz), 3.04 (1H, t, <i>J</i> = 12.8 Hz), 3.10 - 3.25 (4H, m), 3.42 - 3.81 (4H, m), 4.02 (1H, d, <i>J</i> = 12.8 Hz), 4.18 (1H, d, <i>J</i> = 12.8 Hz), 6.81 (1H, t, <i>J</i> = 7.2 Hz), 6.95 (2H, d, <i>J</i> = 8.4 Hz), 7.21 - 7.37 (6H, m), 7.66 (1H, s), 8.01 (1H, s), 8.18 (1H, s), 8.55 (1H, d, <i>J</i> = 2.4 Hz), 8.88 (1H, s) , DMSO : 542(M+H) ⁺ FAB
369	1.19-1.23 (2H, m), 1.52-1.62 (3H, m), 1.78-1.85 (2H, m), 2.70 (2H, d, <i>J</i> = 7.8Hz), 2.88 (1H, t, <i>J</i> = 11.9Hz), 3.03 (1H, t, <i>J</i> = 10.7Hz), 3.52 (2H, dd, <i>J</i> = 5.4, 5.2Hz), 3.59 (1H, dd, <i>J</i> = 5.3, 5.3Hz), 4.02 (1H, m), 4.18 (1H, m), 4.48 (1H, t, <i>J</i> = 5.2Hz), 4.60 (1H, t, <i>J</i> = 5.2Hz), 7.35-7.38 (2H, m), 7.68-7.69 (2H, m), 7.72-7.75 (1H, m), 8.02-8.07 (1H, m), 8.18-8.23 (1H, m), 8.56-8.59 (1H, m), 8.63-8.68 (1H, m), 8.89-8.91 (1H, m) , DMSO : 443(M+H) ⁺ FAB
370	1.13-1.33 (2H, m), 1.52-1.63 (3H, m), 1.75-1.85 (2H, m), 2.68 (2H, d, <i>J</i> = 7.8Hz), 2.88 (1H, t, <i>J</i> = 10.0Hz), 3.03 (1H, t, <i>J</i> = 10.0Hz), 3.30-3.35 (2H, m), 3.46-3.54 (2H, m), 4.15 (1H, d, <i>J</i> = 17.2Hz), 4.18 (1H, d, <i>J</i> = 16.0Hz), 7.33-7.39 (2H, m), 7.62-7.72 (3H, m), 8.00-8.01 (1H, m), 8.16-8.18 (1H, m), 8.35-8.29 (1H, m), 8.55 (1H, d, <i>J</i> = 3.4Hz), 8.89 (1H, d, <i>J</i> = 2.2Hz) , DMSO : 441(M+H) ⁺ ESI
371	1.21-1.35 (2H, m), 1.48 (9H, s), 1.48-1.60 (1H, m), 1.61-1.69 (2H, m), 1.79-1.87 (2H, m), 2.71 (2H, dd, <i>J</i> = 6.0,6.0 Hz), 2.86 (1H, t, <i>J</i> = 9.6 Hz), 3.00 (1H, t, <i>J</i> = 9.6 Hz), 4.18-4.33 (2H, m), 5.76 (1H, br), 5.93 (1H, s), 6.28 (1H, br), 7.27-7.35 (2H, m), 7.45-7.50 (1H, m), 7.61 (1H, s), 7.96 (1H, s), 8.58 (1H, s), 8.84 (1H, s)CDCl ₃ : 454(M+H) ⁺ ESI
372	1.27 (6H, d, <i>J</i> = 4.8 Hz), 1.61-1.69 (2H, m), 1.72-1.88 (5H, m), 2.71 (2H, t, <i>J</i> = 6.0,6.0 Hz), 2.86 (1H, t, <i>J</i> = 9.0 Hz), 3.00 (1H, t, <i>J</i> = 9.0 Hz), 4.17-4.36 (3H, m), 5.81 (1H, br), 5.95 (1H, br), 6.54 (1H, br), 7.21-7.39 (2H, m), 7.52 (1H, d, <i>J</i> = 6.0 Hz), 7.63 (1H, s), 7.97 (1H, s), 8.61 (1H, s), 8.89 (1H, s)CDCl ₃ : 439(M+H) ⁺ ESI
373	1.10 - 1.31 (2H, m), 1.47 - 1.62 (3H, m), 1.78 - 1.83 (2H, m), 2.39 - 2.51 (2H, m), 2.66 - 2.69 (2H, m), 2.82 - 2.92 (1H, br), 2.98 - 3.10 (1H, br), 3.65 - 3.73 (2H, br), 3.89 (2H, t, <i>J</i> = 13.1Hz), 3.98 - 4.22 (2H, m), 7.31 (2H, d, <i>J</i> = 8.2Hz), 7.48 (2H, d, <i>J</i> = 8.2Hz), 7.63 - 7.69 (1H, br), 8.00 - 8.02 (1H, m), 8.15 - 8.21 (1H, br), 8.55 - 8.56 (1H, m), 8.88 - 8.89 (1H, m) , DMSO : 487(M+H) ⁺ FAB

[0160] [Table 60]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS m/z
374	1.10 – 1.31 (2H, m), 1.47 – 1.59 (3H, m), 1.77 – 1.83 (2H, m), 2.56 (2H, t, $J = 7.5\text{Hz}$), 2.82 – 3.08 (2H, m), 3.99 – 4.21 (2H, m), 5.77 – 5.82 (2H, br), 6.75 (1H, d, $J = 7.5\text{Hz}$), 7.11 (1H, t, $J = 7.5\text{Hz}$), 7.17 – 7.20 (1H, m), 7.25 – 7.27 (1H, br), 7.65 – 7.70 (1H, br), 8.00 – 8.03 (1H, m), 8.15 – 8.21 (1H, br), 8.40 – 8.45 (1H, br), 8.54 – 8.56 (1H, m), 8.88 – 8.90 (1H, m), DMSO : 412(M+H) ⁺ FAB
375	1.10 – 1.30 (2H, m), 1.46 – 1.60 (3H, m), 1.76 – 1.90 (6H, m), 2.57 (2H, t, $J = 7.4\text{Hz}$), 2.82 – 3.10 (2H, m), 3.32 – 3.39 (4H, m), 3.97 – 4.23 (2H, m), 6.77 (1H, d, $J = 7.8$), 7.12 (1H, t, $J = 7.8\text{Hz}$), 7.30 – 7.38 (2H, m), 7.64 – 7.68 (1H, br), 7.99 – 8.02 (2H, m), 8.16 – 8.21 (1H, br), 8.54 – 8.56 (1H, m), 8.88 – 8.90 (1H, m), DMSO : 466(M+H) ⁺ FAB
376	1.12 – 1.30 (2H, m), 1.47 – 1.63 (3H, m), 1.77 – 1.85 (2H, m), 2.39 – 2.52 (2H, m), 2.69 (2H, t, $J = 7.8\text{Hz}$), 2.83 – 3.08 (2H, m), 3.63 – 3.75 (2H, m), 3.83 – 3.94 (2H, m), 3.97 – 4.24 (2H, m), 7.33 – 7.41 (4H, m), 7.66 – 7.70 (1H, br), 8.03 – 8.05 (1H, m), 8.18 – 8.22 (1H, br), 8.57 (1H, d, $J = 2.4\text{Hz}$), 8.90 (1H, d, $J = 1.7\text{Hz}$), DMSO : 487(M+H) ⁺ FAB
377	1.18-1.38 (2H, m), 1.48-1.71 (3H, m), 1.78-1.89 (2H, m), 2.14-2.32 (2H, m), 2.71 (2H, t, $J = 7.5\text{ Hz}$), 2.80-3.24 (6H, m), 3.57-3.83 (2H, m), 4.26 (2H, dd, $J = 7.0\text{ Hz}$), 5.80 (1H, br), 6.51 (1H, br), 7.09 (1H, d, $J = 7.5\text{ Hz}$), 7.22-7.53 (7H, m), 7.60 (1H, d, $J = 8.2\text{ Hz}$), 7.80-7.87 (1H, m), 8.05 (1H, dd, $J = 2.0, 2.0\text{ Hz}$), 8.16-8.25 (1H, m), 8.60 (1H, s), 8.96 (1H, s), DMSO : 593(M+H) ⁺ ESI
378	1.00 – 1.80 (16H, m), 2.27 (3H, s), 2.65 – 2.74 (2H, m), 2.80 – 3.10 (2H, m), 3.95 – 4.32 (4H, m), 6.42 (1H, d, $J = 7.6\text{Hz}$), 6.56 (1H, d, $J = 8.8\text{Hz}$), 7.36 (1H, t, $J = 7.6\text{Hz}$), 7.67 (1H, s), 8.00 (1H, t, $J = 2.4\text{Hz}$), 8.19 (1H, s), 8.55 (1H, d, $J = 2.4\text{Hz}$), 8.89 (1H, d, $J = 2.0\text{Hz}$), DMSO : 466(M+H) ⁺ FAB
379	1.11 – 1.21 (2H, m), 1.27 – 1.49 (10H, m), 1.74 – 1.84 (4H, br), 2.83 – 2.92 (3H, br), 3.05 (1H, br), 3.71 – 3.75 (2H, br), 4.02 (1H, br), 4.18 (1H, br), 7.34 (1H, m), 7.58 (1H, m), 7.66-7.71 (2H, m), 7.86 (1H, m), 8.00-8.03 (2H, m), 8.07 (1H, m), 8.19 (1H, s), 8.55 (1H, m), 8.89 (1H, m), DMSO : 502(M+H) ⁺ FAB
380	1.00 – 1.82 (16H, m), 2.77 – 3.10 (4H, m), 3.95 – 4.23 (2H, m), 4.53 (2H, d, $J = 12.0\text{Hz}$), 7.15 – 7.26 (2H, m), 7.45 – 7.55 (2H, m), 7.62 – 7.70 (2H, m), 7.95 – 8.05 (2H, m), 8.20 (1H, s), 8.46 (1H, d, $J = 2.8\text{Hz}$), 8.89 (1H, d, $J = 1.7\text{Hz}$), DMSO : 502(M+H) ⁺ FAB
381	1.11-1.20 (2H, m), 1.27-1.32 (2H, m), 1.47-1.61 (3H, m), 1.75-1.78 (2H, m), 2.34-2.44 (2H, m), 2.56-2.74 (4H, m), 2.88 (1H, t, $J = 12.1\text{Hz}$), 3.04 (1H, t, $J = 12.5\text{Hz}$), 3.23-3.41 (4H, m), 4.01 (1H, d, $J = 13.0\text{Hz}$), 4.18 (1H, d, $J = 12.4\text{Hz}$), 7.37 (1H, d, $J = 5.6\text{Hz}$), 7.57-7.61 (1H, m), 7.68-7.71 (2H, m), 7.87 (1H, d, $J = 8.1\text{Hz}$), 8.01 (1H, t, $J = 2.2\text{Hz}$), 8.06-8.10 (2H, m), 8.18 (1H, br), 8.55 (1H, d, $J = 2.4\text{Hz}$), 8.88 (1H, d, $J = 1.8\text{Hz}$), DMSO : 503(M+H) ⁺ FAB
382	1.15-1.19 (2H, m), 1.27-1.49 (10H, m), 1.74-1.85 (4H, m), 2.70 (2H, m), 2.89 (1H, t, $J = 12.4\text{Hz}$), 3.04 (1H, t, $J = 12.1\text{Hz}$), 3.26-3.31 (2H, m), 4.02 (1H, m), 4.18 (1H, d, $J = 12.4\text{Hz}$), 7.09 (1H, d, $J = 14.8\text{Hz}$), 7.40 (1H, t, $J = 7.8\text{Hz}$), 7.46-7.51 (2H, m), 7.55 (1H, d, $J = 8.3\text{Hz}$), 7.64-7.70 (1H, br), 7.85-7.87 (1H, m), 8.17 (1H, t, $J = 2.2\text{Hz}$), 8.07-8.09 (1H, m), 8.15-8.21 (1H, br), 8.55 (1H, d, $J = 2.8\text{Hz}$), 8.89 (1H, d, $J = 1.7\text{Hz}$), DMSO : 501(M+H) ⁺ FAB

[0161] [Table 61]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS m/z
383	0.87 (3H, t, $J = 6.4$ Hz), 1.20 – 1.46 (8H, m), 1.54 – 1.72 (2H, m), 1.70 (2H, q, $J = 6.4$ Hz), 1.81 – 1.94 (2H, m), 2.54 – 2.64 (1H, m), 2.85 – 3.05 (1H, m), 3.05 – 3.25 (1H, m), 3.91 (2H, t, $J = 6.4$ Hz), 4.00 – 4.16 (1H, m), 4.15 – 4.31 (1H, m), 6.56 – 6.63 (1H, m), 7.07 – 7.13 (1H, m), 7.17 (1H, dd, $J = 8.0, 8.0$ Hz), 7.29 – 7.36 (1H, m), 7.45 (1H, dd, $J = 7.8, 5.2$ Hz), 7.59 – 7.67 (1H, m), 8.40 – 8.46 (2H, m), 9.90 (1H, s), DMSO:440(M+H) ⁺ FAB
384	0.87 (3H, t, $J = 6.4$ Hz), 1.20 – 1.45 (8H, m), 1.55 – 1.77 (4H, m), 1.80 – 1.93 (2H, m), 2.52 – 2.62 (1H, m), 2.88 – 3.04 (1H, m), 3.04 – 3.19 (1H, m), 3.90 (2H, t, $J = 6.4$ Hz), 4.00 – 4.14 (1H, m), 4.16 – 4.30 (1H, m), 6.85 (2H, d, $J = 8.8$ Hz), 7.45 (1H, dd, $J = 8.3, 4.9$ Hz), 7.49 (2H, d, $J = 9.2$ Hz), 7.61 – 7.66 (1H, m), 8.40 – 8.45 (2H, m), 9.78 (1H, s), DMSO:440(M+H) ⁺ FAB
385	369(M+H) ⁺ FAB
386	480(M+H) ⁺ FAB
387	424(M+H) ⁺ FAB
388	0.85 (3H, t, $J = 7.2$ Hz), 1.20 – 1.32 (6H, m), 1.45 – 1.58 (2H, m), 1.56 – 1.78 (2H, m), 1.81 – 1.94 (2H, m), 2.48 – 2.54 (2H, m), 2.55 – 2.66 (1H, m), 2.90 – 3.05 (1H, m), 3.07 – 3.21 (1H, m), 4.00 – 4.15 (1H, m), 4.17 – 4.32 (1H, m), 7.10 (2H, d, $J = 8.0$ Hz), 7.50 (2H, d, $J = 8.0$ Hz), 7.68 (1H, br s), 8.04 (1H, dd, $J = 2.8, 2.0$ Hz), 8.19 (1H, br), 8.58 (1H, d, $J = 2.8$ Hz), 8.90 (1H, d, $J = 2.0$ Hz), 9.86 (1H, br), DMSO:453(M+H) ⁺ FAB
389	1.56 – 1.74 (2H, br), 1.88 – 2.04 (2H, br), 2.48 – 2.53 (3H, m), 3.25 – 3.55 (2H, br), 3.65 – 3.92 (2H, br), 4.46 – 4.55 (1H, m), 5.07 (2H, s), 6.95 (4H, s), 7.01 (1H, s), 7.15 (1H, dt, $J = 2.9, 8.8$ Hz), 7.23 – 7.30 (2H, m), 7.40 – 7.47 (1H, m), 7.70 – 8.30 (2H, br), DMSO
390	1.55 – 1.74 (2H, br), 1.88 – 2.04 (2H, br), 3.25 – 3.55 (2H, br), 3.65 – 3.92 (2H, br), 4.46 – 4.54 (1H, m), 5.07 (2H, s), 6.95 (4H, s), 7.01 (1H, s), 7.15 (1H, dt, $J = 2.9, 8.8$ Hz), 7.23 – 7.30 (2H, m), 7.40 – 7.47 (2H, m), 7.86 – 7.94 (1H, br), 7.97 – 8.05 (1H, br), 10.19 (1H, s), DMSO: 439(M+H) ⁺ FAB
391	1.58 – 1.77 (2H, br), 1.91 – 2.06 (2H, br), 3.28 – 3.41 (1H, br), 3.45 – 3.57 (1H, br), 3.65 – 3.78 (1H, br), 3.82 – 3.94 (1H, br), 4.48 – 4.57 (1H, m), 5.07 (2H, s), 6.95 (4H, s), 7.11 – 7.18 (1H, m), 7.23 – 7.30 (2H, m), 7.40 – 7.47 (1H, m), 8.29 – 8.32 (1H, m), 8.78 (1H, d, $J = 2.5$ Hz), 8.91 (1H, d, $J = 2.0$ Hz), DMSO:448(M+H) ⁺ FAB
392	0.78 – 0.93 (2H, m), 1.04 – 1.26 (6H, m), 1.35 – 1.45 (2H, m), 1.54 – 1.74 (9H, m), 1.90 – 2.04 (2H, br), 3.28 – 3.55 (2H, m), 3.66 – 3.95 (4H, m), 4.46 – 4.54 (1H, m), 6.84 (2H, d, $J = 8.8$ Hz), 6.93 (2H, d, $J = 8.8$ Hz), 7.45 (1H, dd, $J = 4.8, 8.4$ Hz), 7.60 – 7.66 (1H, m), 8.41 – 8.45 (2H, m), DMSO:453(M+H) ⁺ FAB
393	415(M+H) ⁺ FAB
394	387(M+H) ⁺ FAB
395	1.06 – 1.20 (2H, m), 1.43 – 1.82 (10H, m), 1.86 – 2.05 (3H, m), 3.24 – 3.57 (2H, br), 3.68 – 3.94 (4H, m), 4.51 – 4.55 (1H, m), 6.85 (2H, d, $J = 9.2$ Hz), 6.93 (2H, d, $J = 9.2$ Hz), 8.08 (1H, dd, $J = 1.6, 2.4$ Hz), 8.66 (1H, d, $J = 2.4$ Hz), 8.92 (1H, d, $J = 1.6$ Hz), 13.38 – 13.84 (1H, br), DMSO:455(M+H) ⁺ FAB
396	1.21 – 1.42 (2H, m), 1.78 – 1.90 (2H, br), 1.93 – 2.06 (1H, m), 2.85 – 2.99 (1H, br), 3.01 – 3.15 (1H, br), 3.81 (2H, d, $J = 8.0$ Hz), 3.99 – 4.12 (1H, br), 4.15 – 4.27 (1H, br), 5.07 (2H, s), 6.88 (2H, d, $J = 9.2$ Hz), 6.94 (2H, d, $J = 9.2$ Hz), 7.11 – 7.18 (1H, m), 7.23 – 7.29 (2H, m), 7.39 – 7.47 (2H, m), 7.62 (1H, ddd, $J = 1.2, 2.4, 8.0$ Hz), 8.40 – 8.45 (1H, m), DMSO: 437(M+H) ⁺ FAB
397	414(M+H) ⁺ FAB
398	386(M+H) ⁺ FAB
399	1.10 – 1.33 (2H, m), 1.45 – 1.61 (3H, m), 1.75 – 1.87 (2H, br), 2.64 (2H, t, $J = 7.6$ Hz), 2.80 – 3.10 (2H, br), 3.95 – 4.24 (2H, br), 7.12 – 7.32 (5H, m), 7.90 (2H, d, $J = 8.4$ Hz), 7.98 – 8.08 (3H, m), 8.43 – 8.49 (1H, m), 8.80 – 8.86 (1H, m), 12.80 – 13.30 (1H, m), DMSO: 431(M+H) ⁺ FAB

[0162] [Table 62]

Ex No.	DAT ¹ H-NMR δ (ppm), solvent : MS <i>m/z</i>
400	1.06 – 1.30 (2H, m), 1.56 – 1.80 (3H, m), 2.47 – 2.52 (2H, m), 2.76 – 2.91 (1H, br), 2.93 – 3.07 (1H, br), 3.92 – 4.05 (1H, br), 4.08 – 4.21 (1H, br), 5.10 (2H, s), 6.94 (2H, d, <i>J</i> = 8.0 Hz), 7.08 – 7.18 (3H, m), 7.24 – 7.31 (2H, m), 7.40 – 7.48 (1H, m), 7.71 (1H, dd, <i>J</i> = 4.8, 8.4Hz), 7.93 – 7.99 (1H, m), 8.58 (1H, d, <i>J</i> = 4.4 Hz), 8.62 – 8.78 (1H, m), DMSO:421(M+H) ⁺ FAB
401	1.08 – 1.31 (2H, m), 1.58 – 1.79 (3H, m), 2.47 – 2.52 (2H, m), 2.76 – 3.05 (2H, br), 3.92 – 4.22 (2H, br), 5.10 (2H, s), 6.94 (2H, d, <i>J</i> = 8.4Hz), 7.08 – 7.19 (3H, m), 7.24 – 7.31 (2H, m), 7.40 – 7.48 (1H, m), 7.98 – 8.03 (1H, m), 8.56 – 8.62 (1H, m), 8.87 – 8.93 (1H, br), DMSO:465(M+H) ⁺ FAB
402	1.07 – 1.28 (2H, br), 1.43 – 1.60 (3H, m), 1.73 – 1.82 (2H, br), 2.62 (2H, t, <i>J</i> = 7.8Hz), 2.77 – 3.05 (2H, br), 3.92 – 4.20 (2H, br), 7.00 (1H, dd, <i>J</i> = 2.0, 2.4Hz), 7.14 – 7.31 (5H, m), 8.04 (1H, dd, <i>J</i> = 2.0, 2.4Hz), 7.86 – 7.94 (1H, br), 7.97 – 8.03 (1H, br), 10.06 – 10.26 (1H, br), DMSO:327(M+H) ⁺ FAB
403	351(M+H) ⁺ FAB
404	395(M+H) ⁺ FAB
405	503(M+H) ⁺ FAB
406	453(M+H) ⁺ FAB
407	1.02 – 1.51 (6H, m), 1.68 – 1.80 (4H, m), 2.28 (3H, s), 2.66 – 2.74 (2H, m), 2.82 – 3.09 (2H, m), 3.95 – 4.31 (4H, m), 6.43 (1H, d, <i>J</i> = 7.1 Hz), 6.56 (1H, d, <i>J</i> = 8.5 Hz), 7.34 – 7.39 (1H, m), 7.65 – 7.69 (1H, br), 7.99 – 8.01 (1H, m), 8.16 – 8.19 (1H, br), 8.55 (1H, d, <i>J</i> = 2.5 Hz), 8.88 (1H, d, <i>J</i> = 1.9 Hz), DMSO:452(M+H) ⁺ FAB
408	502(M+H) ⁺ FAB
409	369(M+H) ⁺ FAB
410	327(M+H) ⁺ FAB
411	441(M+H) ⁺ ESI
412	1.25 – 1.65 (6H, m), 2.25 – 2.48 (6H, m), 2.57 (2H, t, <i>J</i> = 7.8 Hz), 3.36 – 3.64 (4H, m), 7.12 – 7.30 (5H, m), 7.68 (1H, s), 8.03 (1H, t, <i>J</i> = 2.4 Hz), 8.19 (1H, s), 8.56 (1H, d, <i>J</i> = 2.4 Hz), 8.90 (1H, d, <i>J</i> = 1.5 Hz), DMSO:397(M+H) ⁺ FAB
413	3.00 – 3.75 (6H, m), 4.01 – 4.38 (4H, m), 5.17 (2H, s), 7.10 (2H, d, <i>J</i> = 8.8Hz), 7.13 – 7.21 (1H, m), 7.27 – 7.33 (2H, m), 7.42 – 7.49 (1H, m), 7.59 (2H, d, <i>J</i> = 8.8Hz), 7.75 (1H, dd, <i>J</i> = 5.2, 7.6Hz), 7.97 – 8.02 (1H, m), 8.62 (1H, d, <i>J</i> = 4.4Hz), 8.70 (1H, d, <i>J</i> = 2.4Hz), DMSO:422(M+H) ⁺ FAB
414	432(M+H) ⁺ FAB
415	431(M+H) ⁺ FAB
416	299(M+H) ⁺ FAB
417	1.33 (3H, t, <i>J</i> = 6.8Hz), 1.60 – 1.76 (2H, br), 1.91 – 2.07 (2H, br), 3.30 – 3.43 (1H, br), 3.46 – 3.60 (1H, br), 3.67 – 3.75 (1H, br), 3.83 – 3.96 (1H, br), 4.35 (2H, q, <i>J</i> = 6.8Hz), 4.47 – 4.57 (1H, m), 5.07 (2H, s), 6.96 (4H, s), 7.11 – 7.19 (1H, m), 7.23 – 7.30 (2H, m), 7.40 – 7.47 (1H, m), 7.84 (1H, dd, <i>J</i> = 2.4, 8.8Hz), 8.12 (1H, d, <i>J</i> = 8.8Hz), 8.58 (1H, d, <i>J</i> = 2.4Hz), DMSO:495(M+H) ⁺ FAB
418	1.58 – 1.77 (2H, br), 1.90 – 2.08 (2H, br), 3.28 – 3.60 (2H, br), 3.66 – 3.98 (2H, br), 4.47 – 4.54 (1H, m), 5.07 (2H, s), 6.96 (4H, s), 7.10 – 7.19 (1H, m), 7.21 – 7.32 (2H, m), 7.38 – 7.49 (1H, m), 7.69 – 7.77 (1H, m), 8.04 (1H, d, <i>J</i> = 8.6Hz), 8.60 – 8.70 (1H, m), DMSO:467(M+H) ⁺ FAB
419	327(M+H) ⁺ FAB
420	354(M+H) ⁺ FAB
421	437(M+H) ⁺ FAB
422	437(M+H) ⁺ FAB
423	368(M+H) ⁺ FAB

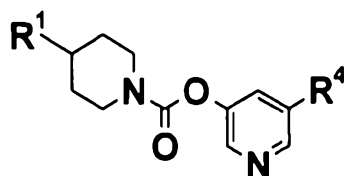
[0163] [Table 63]

Ex No.	DAT
	¹ H-NMR δ (ppm), solvent : MS m/z
424	369(M+H) ⁺ ESI
425	370(M+H) ⁺ FAB
426	383(M+H) ⁺ ESI
427	412(M+H) ⁺ FAB
428	483(M+H) ⁺ FAB
429	384(M+H) ⁺ FAB
430	483(M+H) ⁺ ESI
431	493(M+H) ⁺ ESI
432	522(M+H) ⁺ ESI
433	466(M+H) ⁺ FAB
434	480(M+H) ⁺ ESI
435	438(M+H) ⁺ ESI
436	427(M+H) ⁺ ESI
437	481(M+H) ⁺ FAB

[0164] [Table 64]

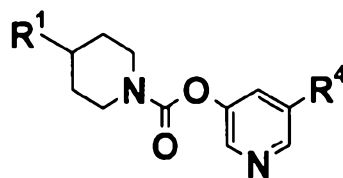
Ex No.	cell FAAH IC ₅₀ (nM)	Ex No.	cell FAAH IC ₅₀ (nM)	Ex No.	cell FAAH IC ₅₀ (nM)
002	0.11	108	0.052	293	0.24
003	0.073	113	0.056	294	0.60
009	0.67	115	0.052	300	0.43
010	0.10	116	0.078	301	0.40
013	0.27	122	0.15	302	0.17
014	0.20	124	0.35	303	0.12
015	0.033	126	0.58	304	0.24
017	0.18	138	0.078	313	0.89
018	0.35	144	0.093	315	0.51
019	0.072	147	0.28	318	0.062
021	0.23	149	0.45	319	0.24
023	0.040	151	0.17	320	0.081
030	0.19	152	0.18	321	0.040
033	0.077	154	0.17	322	0.058
034	0.046	155	0.061	323	0.085
036	0.044	159	0.23	324	0.50
037	0.69	160	0.51	325	0.54
038	0.028	173	0.69	326	0.13
039	0.30	174	0.60	327	0.12
042	0.43	175	0.37	328	0.42
043	0.21	176	0.84	329	0.39
044	0.095	179	0.060	330	0.53
046	0.41	197	0.11	333	0.43
047	0.13	199	0.58	334	0.048
049	0.10	200	0.30	335	0.075
051	0.26	206	0.17	338	0.034
053	0.063	207	0.31	339	0.12
055	0.44	208	0.13	340	0.052
061	0.35	218	0.44	341	0.078
063	0.12	225	0.89	342	0.33
065	0.41	228	0.22	344	0.13
066	0.057	261	0.54	345	0.18
069	0.095	263	0.036	346	0.27
070	0.099	266	0.31	349	0.054
077	0.071	268	0.15	351	0.13
078	0.081	269	0.081	359	0.52
080	0.044	270	0.17	362	0.42
081	0.012	272	0.48	364	0.14
088	0.37	274	0.37	371	0.21
085	0.44	281	0.082	372	0.49
098	0.26	283	0.43	373	0.49
099	0.099	284	0.36	376	0.21
100	0.035	285	0.47	378	0.20
101	0.078	287	0.031	380	0.35
103	0.092	289	0.16		
104	0.066	292	0.65		

[0165] [Table 65]



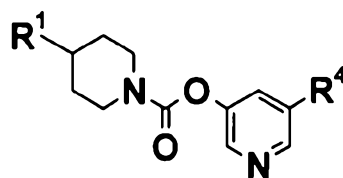
Com No	R¹	R⁴
1	HO ₂ C(CH ₂) ₃	H
2	Mo4 (CH ₂) ₂ NHCO(CH ₂) ₃	H
3	4-HexOPh (CH ₂) ₂ NHCO	CO ₂ H
4	4-OctPhNHCO	CO ₂ H
5	Ph (CH ₂) ₂ CONH	CO ₂ Me
6	Ph (CH ₂) ₂ CONH	H
7	Ph (CH ₂) ₂ CONH	CO ₂ H
8	Ph (CH ₂) ₄ NHCO	CO ₂ H
9	4-BuPhNHCO	CO ₂ H
10	4-HexPhNHCO	CO ₂ H
11	Py2(CH ₂) ₂ NHCO	H
12	Py3(CH ₂) ₂ NHCO	H
13	Ph(CH ₂) ₄ NHCO	CONH ₂
14	4-BuPhNHCO	CONH ₂
15	Ph(CH ₂) ₃ O(CH ₂) ₂	CO ₂ H
16	2-H ₂ NCOPhO(CH ₂) ₃	CO ₂ H
17	4-(3-FPhCH ₂ O)PhO	
18	Ph(CH ₂) ₂	
19	1-MeBenzlM 2 (CH ₂) ₃	CO ₂ H
20	Ph(CH ₂) ₂	CO ₂ Me
21	3-PIPE1 Ph(CH ₂) ₂	CO ₂ H
22		CO ₂ H
23	Mo4CH ₂	H
24	Mo4(CH ₂) ₂	CO ₂ Me
25	4-(3-FPhCH ₂)PIPERA1(CH ₂) ₂	CO ₂ Me
26	Mo4(CH ₂) ₃	CO ₂ Me
27	4-(3-FPhCH ₂ PIPERA1(CH ₂) ₂	H
28	Mo(CH ₂) ₃	H
29	cPen(CH ₂) ₂	H
30	cPen(CH ₂) ₂	CO ₂ Me
31	cPen(CH ₂) ₂	CO ₂ H

Com. No	R¹	R⁴
32	cPen(CH ₂) ₂	CONH ₂
33	cHexCH ₂	H
34	cHexCH ₂	CO ₂ Me
35	cHexCH ₂	CO ₂ H
36	cHexCH ₂	CONH ₂
37	cHex(CH ₂) ₃	H
38	cHex(CH ₂) ₃	CO ₂ Me
39	cHex(CH ₂) ₃	CO ₂ H
40	cHex(CH ₂) ₃	CONH ₂
41	Ph(CH ₂) ₃	H
42	Ph(CH ₂) ₃	CONH ₂
43	3-FPh(CH ₂) ₃	H
44	3-FPh(CH ₂) ₃	CO ₂ Me
45	3-FPh(CH ₂) ₃	CO ₂ H
46	3-FPh(CH ₂) ₃	CONH ₂
47	3-ClPh(CH ₂) ₃	H
48	3-ClPh(CH ₂) ₃	CO ₂ Me
49	3-ClPh(CH ₂) ₃	CO ₂ H
50	3-ClPh(CH ₂) ₃	CONH ₂
51	3-NCPH(CH ₂) ₃	H
52	3-NCPH(CH ₂) ₃	CO ₂ Me
53	3-NCPH(CH ₂) ₃	CO ₂ H
54	3-NCPH(CH ₂) ₃	CONH ₂
55	3-MeOPh(CH ₂) ₃	H
56	3-MeOPh(CH ₂) ₃	CO ₂ Me
57	3-MeOPh(CH ₂) ₃	CO ₂ H
58	3-MeOPh(CH ₂) ₃	CONH ₂
59	4-FPh(CH ₂) ₃	H
60	4-FPh(CH ₂) ₃	CO ₂ Me
61	4-FPh(CH ₂) ₃	CO ₂ H
62	4-FPh(CH ₂) ₃	CONH ₂



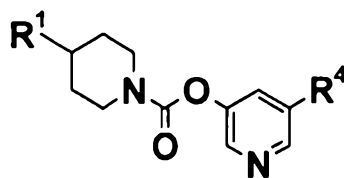
Com No	R¹	R⁴
63	4-ClPh(CH₂)₃	H
64	4-ClPh(CH₂)₃	CO₂Me
65	4-ClPh(CH₂)₃	CO₂H
66	4-ClPh(CH₂)₃	CONH₂
67	4-NCPh(CH₂)₃	H
68	4-NCPh(CH₂)₃	CO₂Me
69	4-NCPh(CH₂)₃	CO₂H
70	4-NCPh(CH₂)₃	CONH₂
71	4-MeOPh(CH₂)₃	H
72	4-MeOPh(CH₂)₃	CO₂Me
73	4-MeOPh(CH₂)₃	CO₂H
74	4-MeOPh(CH₂)₃	CONH₂
75	2-FPh(CH₂)₃	H
76	2-FPh(CH₂)₃	CO₂Me
77	2-FPh(CH₂)₃	CO₂H
78	2-FPh(CH₂)₃	CONH₂
79	2-ClPh(CH₂)₃	H
80	2-ClPh(CH₂)₃	CO₂Me
81	2-ClPh(CH₂)₃	CO₂H
82	2-ClPh(CH₂)₃	CONH₂
83	2-NCPh(CH₂)₃	H
84	2-NCPh(CH₂)₃	CO₂Me
85	2-NCPh(CH₂)₃	CO₂H
86	2-NCPh(CH₂)₃	CONH₂
87	2-MeOPh(CH₂)₃	H
88	2-MeOPh(CH₂)₃	CO₂Me
89	2-MeOPh(CH₂)₃	CO₂H
90	2-MeOPh(CH₂)₃	CONH₂
91	3,4-diFPh(CH₂)₃	H
92	3,4-diFPh(CH₂)₃	CO₂Me
93	3,4-diFPh(CH₂)₃	CO₂H
94	3,4-diFPh(CH₂)₃	CONH₂

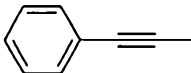
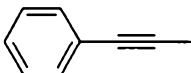
Com. No	R¹	R⁴
95	3,5-diFPh(CH₂)₃	H
96	3,5-diFPh(CH₂)₃	CO₂Me
97	3,5-diFPh(CH₂)₃	CO₂H
98	3,5-diFPh(CH₂)₃	CONH₂
99	2,5-diFPh(CH₂)₃	H
100	2,5-diFPh(CH₂)₃	CO₂Me
101	2,5-diFPh(CH₂)₃	CO₂H
102	2,5-diFPh(CH₂)₃	CONH₂
103	3-NC-5-FPh(CH₂)₃	H
104	3-NC-5-FPh(CH₂)₃	CO₂Me
105	3-NC-5-FPh(CH₂)₃	CO₂H
106	3-NC-5-FPh(CH₂)₃	CONH₂
107	3-FPh(CH₂)₂	H
108	3-ClPh(CH₂)₂	H
109	3-NCPh(CH₂)₂	H
110	3-MeOPh(CH₂)₂	H
111	3-H₂NCOPh(CH₂)₂	H
112	3-Me₂NCOPh(CH₂)₂	H
113	3-PIPECOPh(CH₂)₂	H
114	3-PYRROCOPh(CH₂)₂	H
115	3-EtNHCOPh(CH₂)₂	H
116	3-Et₂NCOPh(CH₂)₂	H
117	3-cHexNHCOPh(CH₂)₂	H
118	4-FPh(CH₂)₂	H
119	4-ClPh(CH₂)₂	H
120	4-NCPh(CH₂)₂	H
121	4-MeOPh(CH₂)₂	H
122	4-Me₂NCOPh(CH₂)₂	H
123	4-PIPECOPh(CH₂)₂	H
124	4-PYRROCOPh(CH₂)₂	H
125	4-EtNHCOPh(CH₂)₂	H
126	4-Et₂NCOPh(CH₂)₂	H

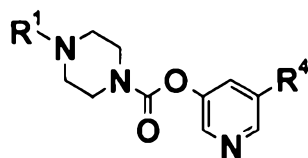


Com No	R¹	R⁴
127	4-cHexNHCOPh(CH₂)₂	H
128	2-FPh(CH₂)₂	H
129	2-ClPh(CH₂)₂	H
130	2-NCPH(CH₂)₂	H
131	2-MeOPh(CH₂)₂	H
132	3,4-diFPh(CH₂)₂	H
133	3,4-diFPh(CH₂)₂	CO₂Me
134	3,4-diFPh(CH₂)₂	CO₂H
135	3,4-diFPh(CH₂)₂	CONH₂
136	3,5-diFPh(CH₂)₂	H
137	3,5-diFPh(CH₂)₂	CO₂Me
138	3,5-diFPh(CH₂)₂	CO₂H
139	3,5-diFPh(CH₂)₂	CONH₂
140	2,5-diFPh(CH₂)₂	H
141	2,5-diFPh(CH₂)₂	CO₂Me
142	2,5-diFPh(CH₂)₂	CO₂H
143	2,5-diFPh(CH₂)₂	CONH₂
144	3-Cl-4-FPh(CH₂)₂	H
145	3-Cl-4-FPh(CH₂)₂	CO₂Me
146	3-Cl-4-FPh(CH₂)₂	CO₂H
147	3-Cl-4-FPh(CH₂)₂	CONH₂
148	3-Cl-5-FPh(CH₂)₂	H
149	3-Cl-5-FPh(CH₂)₂	CO₂Me
150	3-Cl-5-FPh(CH₂)₂	CO₂H
151	3-Cl-5-FPh(CH₂)₂	CONH₂
152	2-F-5-ClPh(CH₂)₂	H
153	2-F-5-ClPh(CH₂)₂	CO₂Me
154	2-F-5-ClPh(CH₂)₂	CO₂H
155	2-F-5-ClPh(CH₂)₂	CONH₂
156	3-MeO-4-FPh(CH₂)₂	H
157	3-MeO-4-FPh(CH₂)₂	CO₂Me
158	3-MeO-4-FPh(CH₂)₂	CO₂H
159	3-MeO-4-FPh(CH₂)₂	CONH₂

Com. No	R¹	R⁴
160	3-F-5-MeOPh(CH₂)₂	H
161	3-F-5-MeOPh(CH₂)₂	CO₂Me
162	3-F-5-MeOPh(CH₂)₂	CO₂H
163	3-F-5-MeOPh(CH₂)₂	CONH₂
164	2-F-5-MeOPh(CH₂)₂	H
165	2-F-5-MeOPh(CH₂)₂	CO₂Me
166	2-F-5-MeOPh(CH₂)₂	CO₂H
167	2-F-5-MeOPh(CH₂)₂	CONH₂
168	2,4-diFPh(CH₂)₂	H
169	2,4-diFPh(CH₂)₂	CO₂Me
170	2,4-diFPh(CH₂)₂	CO₂H
171	2,4-diFPh(CH₂)₂	CONH₂
172	2-F-4-ClPh(CH₂)₂	H
173	2-F-4-ClPh(CH₂)₂	CO₂Me
174	2-F-4-ClPh(CH₂)₂	CO₂H
175	2-F-4-ClPh(CH₂)₂	CONH₂
176	2-F-4-NCPH(CH₂)₂	H
177	2-F-4-NCPH(CH₂)₂	CO₂Me
178	2-F-4-NCPH(CH₂)₂	CO₂H
179	2-F-4-NCPH(CH₂)₂	CONH₂
180	2-F-4-MeOPh(CH₂)₂	H
181	2-F-4-MeOPh(CH₂)₂	CO₂Me
182	2-F-4-MeOPh(CH₂)₂	CO₂H
183	2-F-4-MeOPh(CH₂)₂	CONH₂
184	BIP3(CH₂)₂	H
185	3'-FBIP3(CH₂)₂	H
186	3'-NCBIP3(CH₂)₂	H
187	3'-MeOBIP3(CH₂)₂	H
188	3',4'-diFBIP3(CH₂)₂	H
189	3'-MeO-4'-FBIP3(CH₂)₂	H
190	BIP4(CH₂)₂	H
191	3'-FBIP4(CH₂)₂	H
192	3'-NCBIP4(CH₂)₂	H

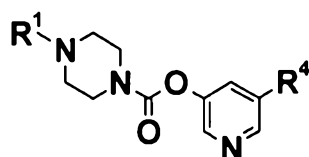


Com No	R ¹	R ⁴
193	3'-MeOBIP4(CH ₂) ₂	H
194	3',4'-diFBIP4(CH ₂) ₂	H
195	3'-MeO-4'-FBIP4(CH ₂) ₂	H
196	3-Py2Ph(CH ₂) ₂	H
197	3-MeOPhNHCO	H
198	4-MeOPhNHCO	H
199	3-MeO-4-FPhNHCO	H
200	3-F-5-MeOPhNHCO	H
201	2-F-5-MeOPhNHCO	H
202	3-F-4-MeOPhNHCO	H
203	2-F-4-MeOPhNHCO	H
204	1-(6-MePy2)PIPE4(CH ₂) ₃	H
205	1-(6-MePy2)PIPE4CH ₂	H
206	1-PhCOPIPE4(CH ₂) ₃	H
207	1-(6-MePy2)PIPERA4(CH ₂) ₂	H
208	1-(6-MePy2)PIPERA4(CH ₂) ₃	H
209	1-QUI2PIPE4(CH ₂) ₃	H
210	1-ISOQUI1PIPE4(CH ₂) ₃	H
211	1-ISOQUI1PIPERA4(CH ₂) ₃	H
212	1-NAPH1PIPE4(CH ₂) ₃	H
213		H
214		CONH ₂

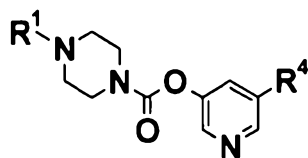


Com No	R ¹	R ⁴
215	Ph(CH ₂) ₄	CO ₂ H
216	Ph	CO ₂ H
217	Ph(CH ₂) ₃	CONH(CH ₂) ₂ OH
218	Ph(CH ₂) ₅	CO ₂ H
219	cHex(CH ₂) ₂	H
220	Ph(CH ₂) ₄	H
221	Ph(CH ₂) ₃	H
222	3-MePh(CH ₂) ₂	H
223	3-MeOPh(CH ₂) ₂	H
224	3-FPh(CH ₂) ₂	H
225	3-NCPh(CH ₂) ₂	H
226	4-MePh(CH ₂) ₂	H
227	4-MeOPh(CH ₂) ₂	H
228	4-FPh(CH ₂) ₂	H
229	4-NCPh(CH ₂) ₂	H
230	2-MePh(CH ₂) ₂	H
231	2-MeOPh(CH ₂) ₂	H
232	2-FPh(CH ₂) ₂	H
233	2-NCPh(CH ₂) ₂	H
234	3-Me-4-FPh(CH ₂) ₂	H
235	3-F-5-MePh(CH ₂) ₂	H
236	2-F-5-MePh(CH ₂) ₂	H
237	3-MeO-4-FPh(CH ₂) ₂	H
238	3-F-5-MeOPh(CH ₂) ₂	H
239	2-F-5-MeOPh(CH ₂) ₂	H
240	3,4-diFPh(CH ₂) ₂	H
241	3,5-diFPh(CH ₂) ₂	H
242	2,5-diFPh(CH ₂) ₂	H
243	3-iPrOPh(CH ₂) ₂	H
244	3-NC-4-FPh(CH ₂) ₂	H
245	4-tBucHex(CH ₂) ₂	H
246	3-H ₂ NCOPh(CH ₂) ₂	H
247	1-(6-MePy2)PIPE4(CH ₂) ₃	H
248	3-cHexCH ₂ OPhCO	CONH ₂

Com. No	R ¹	R ⁴
249	3-cHex(CH ₂) ₂ OPhCO	CONH ₂
250	3-cHepCH ₂ OPhCO	CONH ₂
251	3-PhCH ₂ OPhCO	CONH ₂
252	4-PhCH ₂ OPhCO	CONH ₂
253	3-cOctCH ₂ OPhCO	CONH ₂
254	4-cHexCH ₂ N(Me)PhCO	CONH ₂
255	4-(3-ClPhCH ₂ O)PhCO	CONH ₂
256	4-(3-F ₃ CPhCH ₂ O)PhCO	CONH ₂
257	4-(3-MeOPhCH ₂ O)PhCO	CONH ₂
258	4-(3-NCPhCH ₂ O)PhCO	CONH ₂
259	4-(3,5-diFPhCH ₂ O)PhCO	CONH ₂
260	4-cHexCH ₂ OPhCO	CONH ₂
261	PhCH ₂ OCO	CONH ₂
262	4-tBuOPhCO	CONH ₂
263	4-PhCH ₂ OPhCH ₂	CONH ₂
264	4-H ₂ NCOPhOCH ₂ CO	CONH ₂
265	Ph(CH ₂) ₂ OCO	CONH ₂
266	3-MePh(CH ₂) ₂	CONH ₂
267	3-MeOPh(CH ₂) ₂	CONH ₂
268	3-FPh(CH ₂) ₂	CONH ₂
269	3-NCPh(CH ₂) ₂	CONH ₂
270	4-MePh(CH ₂) ₂	CONH ₂
271	4-MeOPh(CH ₂) ₂	CONH ₂
272	4-FPh(CH ₂) ₂	CONH ₂
273	4-NCPh(CH ₂) ₂	CONH ₂
274	2-MePh(CH ₂) ₂	CONH ₂
275	2-MeOPh(CH ₂) ₂	CONH ₂
276	2-FPh(CH ₂) ₂	CONH ₂
277	2-NCPh(CH ₂) ₂	CONH ₂
278	3-MeO-4-FPh(CH ₂) ₂	CONH ₂
279	2-F-3-MeOPh(CH ₂) ₂	CONH ₂
280	2-F-5-MeOPh(CH ₂) ₂	CONH ₂
281	3-Me-4-FPh(CH ₂) ₂	CONH ₂
282	3-F-5-MePh(CH ₂) ₂	CONH ₂



Com No	R ¹	R ⁴	Com. No	R ¹	R ⁴
283	2-F-5-MePh(CH ₂) ₂	CONH ₂	317	3-MePh(CH ₂) ₂	CO ₂ Me
284	3,4-diFPh(CH ₂) ₂	CONH ₂	318	3-MeOPh(CH ₂) ₂	CO ₂ Me
285	3,5-diFPh(CH ₂) ₂	CONH ₂	319	3-FPh(CH ₂) ₂	CO ₂ Me
286	2,5-diFPh(CH ₂) ₂	CONH ₂	320	3-NCPh(CH ₂) ₂	CO ₂ Me
287	4-tBucHex(CH ₂) ₂	CONH ₂	321	4-MePh(CH ₂) ₂	CO ₂ Me
288	3-cHexCH ₂ OPhCO	CO ₂ Me	322	4-MeOPh(CH ₂) ₂	CO ₂ Me
289	3-cHex(CH ₂) ₂ OPhCO	CO ₂ Me	323	4-FPh(CH ₂) ₂	CO ₂ Me
290	3-cHepCH ₂ OPhCO	CO ₂ Me	324	4-NCPh(CH ₂) ₂	CO ₂ Me
291	3-PhCH ₂ OPhCO	CO ₂ Me	325	2-MePh(CH ₂) ₂	CO ₂ Me
292	4-PhCH ₂ OPhCO	CO ₂ Me	326	2-MeOPh(CH ₂) ₂	CO ₂ Me
293	3-cOctCH ₂ OPhCO	CO ₂ Me	327	2-FPh(CH ₂) ₂	CO ₂ Me
294	4-[3-FPhCH ₂ N(Me)]PhCO	CO ₂ Me	328	2-NCPh(CH ₂) ₂	CO ₂ Me
295	4-[3,4-diFPhCH ₂ N(Me)]PhCO	CO ₂ Me	329	3-Me-4-FPh(CH ₂) ₂	CO ₂ Me
296	4-[3,5-diFPhCH ₂ N(Me)]PhCO	CO ₂ Me	330	2-F-5-MePh(CH ₂) ₂	CO ₂ Me
297	4-[2,5-diFPhCH ₂ N(Me)]PhCO	CO ₂ Me	331	3-F-5-MePh(CH ₂) ₂	CO ₂ Me
298	4-cHexCH ₂ N(Me)PhCO	CO ₂ Me	332	3-MeO-4-FPh(CH ₂) ₂	CO ₂ Me
299	4-(3-ClPhCH ₂ O)PhCO	CO ₂ Me	333	2-F-5-MeOPh(CH ₂) ₂	CO ₂ Me
300	4-(3-F ₃ CPhCH ₂ O)PhCO	CO ₂ Me	334	3-F-5-MeOPh(CH ₂) ₂	CO ₂ Me
301	4-(3-MeOPhCH ₂ O)PhCO	CO ₂ Me	335	3,4-diFPh(CH ₂) ₂	CO ₂ Me
302	4-(3-MeO-4-FPhCH ₂ O)PhCO	CO ₂ Me	336	2,5-diFPh(CH ₂) ₂	CO ₂ Me
303	4-(3-F-5-MeOPhCH ₂ O)PhCO	CO ₂ Me	337	3,5-diFPh(CH ₂) ₂	CO ₂ Me
304	4-(3-NCPhCH ₂ O)PhCO	CO ₂ Me	338	4-tBucHex(CH ₂) ₂	CO ₂ Me
305	4-(3,5-diFPhCH ₂ O)PhCO	CO ₂ Me	339	3-cHexCH ₂ OPhCO	CO ₂ H
306	4-cHexCH ₂ OPhCO	CO ₂ Me	340	3-cHex(CH ₂) ₂ OPhCO	CO ₂ H
307	PhCH ₂ OCO	CO ₂ Me	341	3-cHepCH ₂ OPhCO	CO ₂ H
308	4-tBuOPhCO	CO ₂ Me	342	3-PhCH ₂ OPhCO	CO ₂ H
309	4-PhCH ₂ OPhCH ₂	CO ₂ Me	343	4-PhCH ₂ OPhCO	CO ₂ H
310	4-H ₂ NCOPhOCH ₂ CO	CO ₂ Me	344	3-cOctCH ₂ OPhCO	CO ₂ H
311	Ph(CH ₂) ₂ OCO	CO ₂ Me	345	4-(3-F ₃ CPhCH ₂ O)PhCO	CO ₂ H
312	3-Cl-4-(3-NCPhCH ₂ O)PhCO	CO ₂ Me	346	4-(3-MeOPhCH ₂ O)PhCO	CO ₂ H
313	2-Cl-4-(3-NCPhCH ₂ O)PhCO	CO ₂ Me	347	4-(3-NCPhCH ₂ O)PhCO	CO ₂ H
314	4-[3-FPhCH ₂ N(Me)]PhCO	CO ₂ H	348	4-(3,5-diFPhCH ₂ O)PhCO	CO ₂ H
315	4-cHexCH ₂ N(Me)PhCO	CO ₂ H	349	4-cHexCH ₂ OPhCO	CO ₂ H
316	4-(3-ClPhCH ₂ O)PhCO	CO ₂ H	350	PhCH ₂ OCO	CO ₂ H

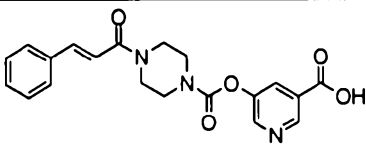
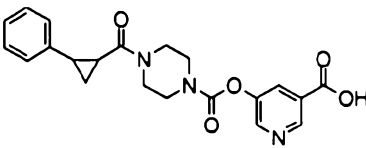
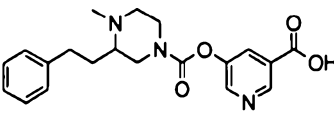
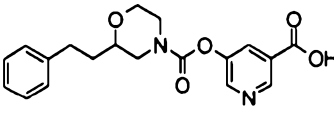
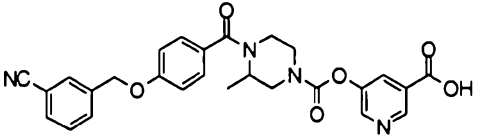
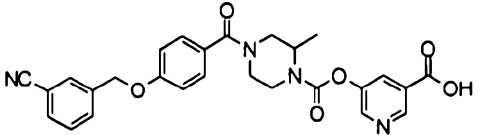
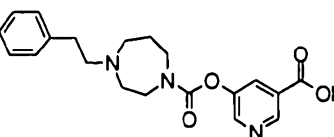


Com No	R ¹	R ⁴
351	4-tBuOPhCO	CO ₂ H
352	4-PhCH ₂ OPhCH ₂	CO ₂ H
353	4-H ₂ NCOPhOCH ₂ CO	CO ₂ H
354	Ph(CH ₂) ₂ OCO	CO ₂ H
355	3-Cl-4-(3-NCPHCH ₂ O)PhCO	CO ₂ H
356	2-Cl-4-(3-NCPHCH ₂ O)PhCO	CO ₂ H
357	3-MePh(CH ₂) ₂	CO ₂ H
358	3-MeOPh(CH ₂) ₂	CO ₂ H
359	3-FPh(CH ₂) ₂	CO ₂ H
360	3-NCPH(CH ₂) ₂	CO ₂ H
361	4-tBucHex(CH ₂) ₂	CO ₂ H
362	4-(4-FPhCH ₂ O)PhCO	CONH ₂
363	4-(4-FPhCH ₂ O)PhCO	CO ₂ Me
364	4-(4-FPhCH ₂ O)PhCO	CO ₂ H
365	4-(3,4-diFPhCH ₂ O)PhCO	CONH ₂
366	4-(3,4-diFPhCH ₂ O)PhCO	CO ₂ Me
367	4-(2,4-diFPhCH ₂ O)PhCO	CONH ₂
368	4-(2,4-diFPhCH ₂ O)PhCO	CO ₂ Me
369	Ph(CH ₂) ₂	CONH ₂
370	Ph(CH ₂) ₄	CONH ₂
371	4-[3-FPhCH ₂ N(Me)]PhCO	CONH ₂
372	4-[3,4-diFPhCH ₂ N(Me)]PhCO	CONH ₂
373	4-[3,5-diFPhCH ₂ N(Me)]PhCO	CONH ₂
374	4-[3-MeO-4-FPhCH ₂ N(Me)]PhCO	CONH ₂
375	4-[3-F-5-MeOPhCH ₂ N(Me)]PhCO	CONH ₂
376	3-Cl-4-(3-NCPHCH ₂ O)PhCO	CONH ₂
377	2-Cl-4-(3-NCPHCH ₂ O)PhCO	CONH ₂

[0172] [Table 72]

Com No	Str	Com No	Str
378		389	
379		390	
380		391	
381		392	
382		393	
383		394	
384		395	
385		396	
386		397	
387		398	
388		399	

[0173] [Table 73]

Com No	Str
400	
401	
402	
403	
404	
405	
406	

23 Jun 2011
2010202348

INDUSTRIAL APPLICABILITY

[0174]

5 The compounds of the present invention have an excellent FAAH-inhibitory activity, and are useful for treatment of FAAH-associated disorders, especially urinary frequency and urinary incontinence, overactive bladder and/or pain.

SEQUENCE LISTING FREE TEXT

[0175]

10 The inventor is shown in the numeral entry <223> of SEQ ID NO:1 in the following sequence listing.

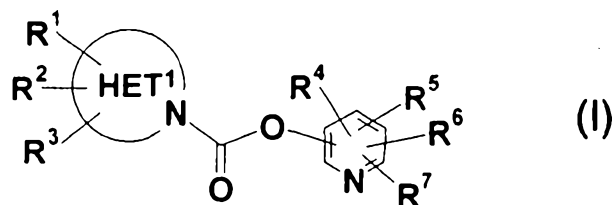
15 Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

20 The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that the prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

2010202348 23 Jun 2011

The claims defining the invention are as follows:

1. A pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (I), or its pharmaceutically acceptable salt:



wherein

HET¹ represents a 5- to 7-membered non-aromatic nitrogen-containing hetero ring,

R¹, R² and R³ are the same or different, each representing

- (1) H,
 - (2) OH,
 - (3) HO-CO-, lower alkyl-O-CO-, aryl-lower alkyl-O-CO-, or H₂N-CO-aryl-lower alkyl-O-CO-,
 - (4) cyano,
 - (5) lower alkyl-CO-,
 - (6) oxo (=O),
 - (7) a formula [R¹⁰¹-(O)m₁]_{m2}-[ALK¹ optionally substituted with OH]-(O)n₁-,
(m₁ and n₁ are the same or different, each indicating 0 or 1,
m₂ is from 1 to 5,
- ALK¹ represents lower alkylene, lower alkenylene or lower alkynylene,
R¹⁰¹ represents

- (i) H,
- (ii) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of:

- (a) H₂N-,
- (b) halo,
- (c) cyano,
- (d) optionally-esterified carboxyl,

2010202348 04 Jun 2010

(e) a group $R^{1011a}R^{1012a}N-CO-$,

(f) HET^2 ,

(g) Ar^{1a} optionally substituted with halo, cyano, OH, lower alkyl-O- or lower alkyl,

Ar^{1a} represents aryl,

(h) lower alkyl,

(j) OH,

(k) lower alkyl-O- optionally substituted with Ar^{1a} or halo- Ar^{1a} ,

(l) HET^2-CO- optionally substituted with halo, Ar^{1a} or $HETAr^{1a}$,

HET^2 represents nitrogen-containing hetero ring,

$HETAr^{1a}$ represents nitrogen-containing heteroaryl,

(s) $HET^2-CONR^{1011a}-$,

(t) $H_2NCONH-$, and

(u) optionally-esterified carboxyl- ALK^{2a} ,

ALK^{2a} represents lower alkyl or lower alkenyl,

(iii) ALK^{2a} optionally substituted with a group $R^{1011a}R^{1012a}N$ or Ar^{1a} ,

R^{1011a} and R^{1012a} are the same or different, each representing

(a) H,

(b) cALK,

cALK represents a cycloalkyl,

(c) ALK^{2a} optionally substituted with halo, cALK, OH, lower alkyl-O- or Ar^{1a} , or

(d) $Ar^{1a}-SO_2-$ optionally substituted with halo,

(iv) HET^2 optionally substituted with at least one substituent selected from the group consisting of

(a) ALK^{2a} optionally substituted with Ar^{1a} or halo- Ar^{1a} ,

(b) Ar^{1a} ,

(c) $HETAr^{1a}$ optionally substituted with lower alkyl,

(d) $Ar^{1a}-CO-$ or halo- $Ar^{1a}-CO-$,

(v) cALK optionally substituted with ALK^{2a} ,

or

(vi) optionally-esterified carboxyl,

2010202348 04 Jun 2010

in this, when m_2 is from 2 to 5, then $[R^{101}-(O)m_1]$'s may be the same or different),

(8) a group $R^{102}-ALK^1-N(R^{103})-CO-$,

(R^{102} represents

(i) H,

(ii) cALK,

(iii) $HETAr^{1a}$, or

(iv) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of

(a) HO,

(b) $ALK^{2a}-O-$,

(c) cALK- ALK^1-O- ,

(d) cALK- $Ar^{1a}-ALK^1-O-$, and

(e) $Ar^{1a}-ALK^1-O-$,

R^{103} represents

(i) H,

(ii) cALK,

(iii) ALK^{2a} optionally substituted with at least one substituent selected from the group consisting of

(a) HET^2 ,

(b) Ar^{1a} , and

(c) halo- Ar^{1a} ,

(iv) $HETAr^{1a}$, or

(v) $Ar^{1a}-[CO]m_1$ optionally substituted with at least one substituent selected from the group consisting of

(a) cALK,

(b) H_2N ,

(c) a group $R^{1011a}R^{1012a}N-CO-$, or

(d) ALK^{2a} ,

(9) a group $R^{104a}R^{105a}N-[CO]m_1-ALK^1-$,

(R^{104a} and R^{105a} are the same or different, each representing a group R^{103}),

(10) a group $R^{106}-ALK^3-L^1-$,

2010202348 04 Jun 2010

(R¹⁰⁶ represents

- (i) a group R¹⁰¹-(O)m1-,
- (ii) a group R^{104a}R^{105a}N-,
- (iii) a group ALK^{2a}-CONH-, or
- (iv) a group Ar^{1a}-CONH-,

ALK³ represents lower alkylene, lower alkenylene or cycloalkylene,

L¹ represents -C(=O)- or -SO₂-),

(11) ALK^{2a}-CONH- optionally substituted with Ar^{1a},

(12) Ar^{1a} substituted with halo,

(13) a group [R¹⁰⁷-(O)m1]m2-Ar²-(O)n1-,

(Ar² represents arylene,

R¹⁰⁷ represents

- (i) H,
- (ii) halo,
- (iii) ALK^{2a} optionally substituted with at least one substituent selected from the group consisting of

(a) HO,

(b) cALK,

(c) HET²,

(d) Ar^{1a} optionally substituted with halo, lower alkyl, lower alkyl-O-, a group R^{1011a}R^{1012a}N-[CO]p-, cyano or optionally-esterified carboxyl,

(e) optionally-esterified carboxyl,

(f) HET²-[CO]p- optionally substituted with a group R^{1011a}R^{1012a}N-[CO]p-, and

(g) a group R^{1011a}R^{1012a}N-[CO]p-,

p indicates 0 or 1,

(iv) a group R^{1011a}R^{1012a}N-[CO]p-, or

(v) a group R^{1011a}R^{1012a}N-[CO]p-Ar^{1a},

in this, when m2 is from 2 to 5, then [R¹⁰⁷-(O)m1]'s may be the same or

different, and further the group [R¹⁰⁷-(O)m1]m2 may be methylenedioxy to form a ring),

(14) a group [R¹⁰⁷-(O)m1]m2-Ar²-N(R¹⁰³)-CO-,

2010202348 04 Jun 2010

(in this, when m_2 is from 2 to 5, then $[R^{107}-(O)m_1]$'s may be the same or different),
 (15) a group $[R^{101a}R^{1012a}N-[CO]m_1]m_2-Ar^2-(O)n_1-$,

(in this, when m_2 is from 2 to 5, then $[R^{101a}R^{1012a}N-[CO]m_1]$'s may be the same or different),

5 (16) a group $[R^{108}]m_2-Ar^2-L^2-$,

$[R^{108}$ represents

(i) H,

(ii) halo,

(iii) HO,

10 (iv) cALK-O-,

(v) a group $R^{109}-ALK^1-(O)m_1-$,

$(R^{109}$ represents

(a) H,

(b) cALK,

15 (c) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of

(1') halo,

(2') cyano,

(3') NO_2 ,

20 (4') ALK^{2a} optionally substituted with halo,

(5') HO,

(6') $ALK^{2a}-O-$ optionally substituted with halo,

(7') optionally-esterified carboxyl, or

(8') a group $R^{104a}R^{105a}N-$,

25 (d) $HETAr^{1a}$, or

(e) a group $R^{104a}R^{105a}N-[CO]m_1-$,

(vi) a group $R^{1013}R^{1014}N-$,

R^{1013} and R^{1014} are the same or different, each representing

(i) H,

30 (ii) ALK^{2a} ,

(iii) cALK- ALK^1- , or

2010202348 04 Jun 2010

(iv) Ar^{1a} - ALK^1 - optionally substituted with at least one substituent selected from the group consisting of

(1') halo,

(2') cyano,

(3') ALK^{2a} optionally substituted with halo,

(4') ALK^{2a} -O- optionally substituted with halo,

(vii) HET^2 -(O) m_1 - optionally substituted with lower alkyl,

L^2 represents -CO- or -S(O) q -,

q indicates 0, 1 or 2,

in this, when m_2 is from 2 to 5, then $[\text{R}^{108}]$'s may be the same or different],

(17) a group $[\text{R}^{101}]m_2$ - Ar^2 -CONH-,

(in this, when m_2 is from 2 to 5, then $[\text{R}^{101}]$'s may be the same or different),

(18) a group $[\text{R}^{111}]m_2$ - HETAr^2 -(O) m_1 -,

(R^{111} represents

(i) H,

(ii) halo,

(iii) oxo (=O), or

(iv) a group R^{103a} -(O) n_1 -,

R^{103a} represents

(i) H,

(ii) cALK,

(iii) ALK^{2a} optionally substituted with at least one substituent selected from the group consisting of

(a) HET^2 ,

(b) Ar^{1a} ,

(c) cALK and

(d) halo- Ar^{1a} ,

(iv) HETAr^{1a} , or

(v) Ar^{1a} optionally substituted with at least one substituent selected from

the group consisting of (a) cALK, (b) H_2N , and (c) a group $\text{R}^{1011a}\text{R}^{1012a}\text{N}$ -CO-,

2010202348 04 Jun 2010

HETAr² represents nitrogen-containing heteroarylene, in this, when m₂ is from 2 to 5, then [R¹¹¹]'s may be the same or different),

(19) a formula [R¹¹²]_{m2}-HETAr²-N(R¹⁰³)-CO-,

(R¹¹² represents

(i) H,

(ii) cALK,

(iii) ALK^{2a}, or

(iv) Ar^{1a} optionally substituted with at least one substituent selected from the group consisting of

(a) halo,

(b) HO,

(c) ALK^{2a}-O-, and

(d) Ar^{1a}-ALK¹-O-,

in this, when m₂ is from 2 to 5, then [R¹¹²]'s may be the same or different),

(20) a formula [R¹⁰⁸]_{m2}-HETAr²-L²-,

(in this, when m₂ is from 2 to 5, then [R¹⁰⁸]'s may be the same or different),

provided that, when any one group of R¹, R² and R³ is a group [R¹¹¹]_{m2}-HETAr²-

(O)_{m1}- and when m₁ is 0, then the remaining groups of R¹, R² and R³ are H;

and at least one of R⁴, R⁵, R⁶ and R⁷ is selected from the following (2), (4) to (11) and

the remaining groups are the same or different selected from the following (1) to (11):

(1) H,

(2) halo,

(3) optionally-esterified carboxyl,

(4) HO,

(5) a group R¹¹³-ALK⁴-(O)_{m3}-,

(ALK⁴ represents lower alkylene, lower alkenylene, or lower alkynylene,

m₃ indicates 0 or 1,

R¹¹³ represents

(i) H,

(ii) HO,

(iii) lower alkyl-O- optionally substituted with optionally-esterified carboxyl,

(iv) optionally-esterified carboxyl,

2010202348 04 Jun 2010

- (v) lower alkyl-CO-O-, or
- (vi) a group $R^{104b}R^{105b}N-[CO]m3-$ (R^{104b} and R^{105b} are the same or different, each representing a group R^{103}),
- (6) $R^{114}R^{115}N$ (R^{114} and R^{115} are the same or different, each representing
- 5 (i) H, or
- (ii) ALK^{2b} optionally substituted with a group $R^{104b}R^{105b}N$,
 ALK^{2b} represents lower alkyl or lower alkenyl),
- (7) a group $R^{116}-(ALK^4)_n2-N(R^{117})-CO-$,
- 10 ($n2$ indicates 0 or 1,
 R^{116} represents
- (i) H,
- (ii) HO,
- (iii) lower alkyl-O-,
- (iv) optionally-esterified carboxyl,
- 15 (v) a group $R^{104b}R^{105b}N-[CO]m3-$,
- (vi) Ar^{1b} optionally substituted with (a) OH or (b) $ALK^{2b}-O-$,
 Ar^{1b} represents aryl,
- (vii) HET^3 optionally substituted with a group $R^{104b}R^{105b}N-[CO]m3-$ or
optionally-esterified carboxyl,
- 20 HET^3 represents nitrogen-containing hetero ring,
- (viii) Ar^{1b} optionally substituted with a group $R^{104b}R^{105b}N-[CO]m3-$, or
- (ix) SO_3H ,
- R^{117} represents (i) H or (ii) ALK^{2b} optionally substituted with Ar^{1b}),
- (8) Ar^{1b} optionally substituted with at least one substituent selected from the group
- 25 consisting of optionally-esterified carboxyl and a group $R^{1011b}R^{1012b}N-[(CO)]m3-$,
 R^{1011b} and R^{1012b} are the same or different, each representing
- (i) H,
- (ii) cALK,
- (iii) ALK^{2b} optionally substituted with halo, cALK, OH, lower alkyl-O- or Ar^{1b} ,
- 30 or
- (iv) $Ar^{1b}-SO_2-$ optionally substituted with halo,
- (9) HET^3 optionally substituted with optionally-esterified carboxyl,

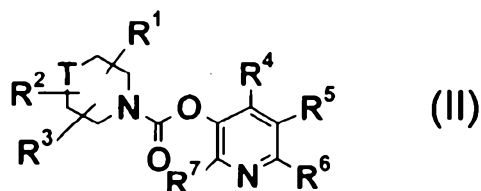
2010202348 23 Jun 2011

(10) HET³-CO- optionally substituted with at least one substituent selected from the group consisting of ALK^{2b} and a group R^{104b}R^{105b}N-[CO]m3-, or

(11) cyano,

provided that 4-aminopyridin-3-yl piperidine-1-carboxylate, 5-ethyl-2-methoxy-6-methylpyridin-3-yl 4-(2-methoxyphenyl)piperazine-1-carboxylate, 5-ethyl-2-methoxy-6-methylpyridin-3-yl 4-(3-chlorophenyl)piperazine-1-carboxylate, 5-ethyl-2-methoxy-6-methylpyridin-3-yl 4-(3,5-dimethoxyphenyl)piperazine-1-carboxylate, 4-{[(dimethylamino)methyl]amino}pyridin-3-yl piperidine-1-carboxylate, 2-[(dimethylamino)methyl]pyridin-3-yl piperidine-1-carboxylate, 2-[(dimethylamino)methyl]pyridin-3-yl pyrrolidine-1-carboxylate and 2-[(dimethylamino)methyl]pyridin-3-yl morpholine-4-carboxylate are excluded.

2. The compound according to claim 1, represented by a general formula (II), or its pharmaceutically acceptable salt:



wherein R¹ to R⁷ are as defined in claim 1,

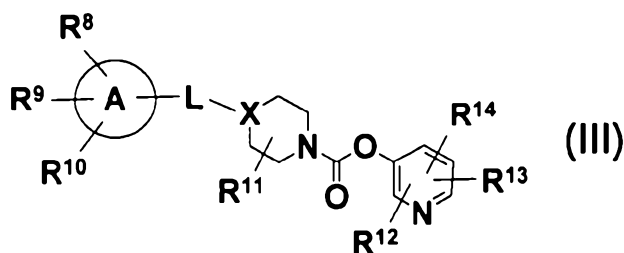
T represents CH₂, NH, NHCH₂ or O,

and wherein optionally the H in T is substituted with R¹ to R³.

3 The compound according to claim 2, wherein R¹ to R³ are the same or different, each representing H, a group [R¹⁰¹-(O)m1]m2-[ALK¹ optionally substituted with OH]-(O)n1-, a group R¹⁰²-ALK¹-N(R¹⁰³)-CO-, a group R¹⁰⁶-ALK³-L¹-, a group [R¹⁰⁷-(O)m1]m2-Ar²-(O)n1-, a group [R¹⁰⁷-(O)m1]m2-Ar²-N(R¹⁰³)-CO-, or a group [R¹⁰⁸]m2-Ar²-L²-, or its pharmaceutically acceptable salt.

4. A pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (III) or its pharmaceutically acceptable salt:

2010202348 04 Jun 2010



wherein

- 5 ring A represents benzene ring, cyclopentane ring, cyclohexane ring, cycloheptane ring, or 5- to 7-membered nitrogen-containing hetero ring;

L represents single bond, lower alkylene, lower alkenylene, $-N(R^{15})-C(=O)-$, $-C(=O)-N(R^{15})-$, $-(\text{lower alkenylene})-C(=O)-$, $-O-$, or $-C(=O)-$,

R^{15} represents H, or lower alkyl,

- 10 X represents CH, or N,

R^8 to R^{10} are the same or different, each representing

a group selected from the following group G,

aryl optionally substituted with the same or different groups selected from the following group G,

- 15 nitrogen-containing heteroaryl optionally substituted with the same or different groups selected from the following group G,

$R^{16}-(\text{lower alkylene})-O-$,

$R^{16}-(\text{lower alkylene})-N(R^{15})-$, or

$R^{17}R^{18}N-C(=O)-$,

- 20 R^{16} represents

aryl optionally substituted with the same or different groups selected from the following group G,

nitrogen-containing heteroaryl optionally substituted with the same or different groups selected from the following group G, or

- 25 3- to 8-membered cycloalkyl,

R^{17} and R^{18} are the same or different, each representing H, lower alkyl, or 3- to 8-membered cycloalkyl,

2010202348 04 Jun 2010

(further, R^{17} and R^{18} may form, together with the N atom bonding thereto, 3- to 8-membered nitrogen-containing hetero ring),

the group G includes H, halo, -CN, -CF₃, lower alkyl, or -O-lower alkyl,

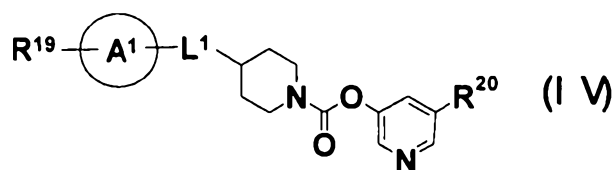
R^{11} represents H, lower alkyl, or oxo (=O),

- 5 R^{12} to R^{14} are the same or different selected from the group consisting of H, lower alkyl, -C(=O)-O-(lower alkyl), -CO₂H and -CONH₂, wherein at least one of R^{12} to R^{14} is lower alkyl or -CONH₂.

- 10 5. The compound according to claim 4, wherein the ring A is benzene ring, cyclohexane ring, piperidine ring, or piperazine ring, or its pharmaceutically acceptable salt.

- 15 6. The compound according to claim 5, wherein R^9 , R^{10} , R^{11} , R^{12} and R^{13} are H, or its pharmaceutically acceptable salt.

7. A pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (IV) or its pharmaceutically acceptable salt:



wherein

ring A¹ represents benzene ring, piperidine ring or piperazine ring;

L¹ represents lower alkylene, lower alkenylene, -N(R^{15})-C(=O)-, or -O-;

R^{15} represents H, or lower alkyl,

- 25 R^{19} represents

a group selected from the following group G,

nitrogen-containing heteroaryl optionally substituted with the same or different

groups selected from the following group G,

R^{16} -(lower alkylene)-O-, or $R^{17}R^{18}N-C(=O)-$,

- 30 R^{16} represents

2010202348 04 Jun 2010

aryl optionally substituted with the same or different groups selected from the following group G,

nitrogen-containing heteroaryl optionally substituted with the same or different groups selected from the following group G, or

5 3- to 8-membered cycloalkyl,

R^{17} and R^{18} are the same or different, each representing H, or lower alkyl,

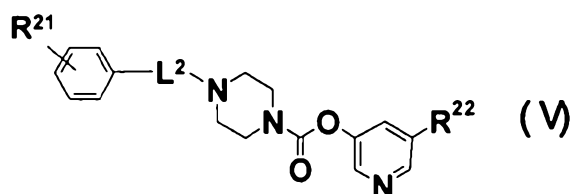
(further, R^{17} and R^{18} may form, together with the N atom bonding thereto, 5- or 6-membered nitrogen-containing hetero ring),

the group G includes H, halo, -CN, -CF₃, lower alkyl, or -O-lower alkyl,

10 R^{20} represents -CONH₂.

8. A pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (V) or its pharmaceutically acceptable salt:

15



wherein

L^2 represents lower alkylene, lower alkenylene, or -(lower alkenylene)-C(=O)-,

R^{21} represents H, halo, -CN, -CF₃, lower alkyl, or -O-lower alkyl,

20 R^{22} represents -CONH₂.

9. The compound according to claim 1, selected from the following group, or its pharmaceutically acceptable salt:

5-(aminocarbonyl)pyridin-3-yl 4-{2-[3-(aminocarbonyl)phenyl]ethyl}piperidine-1-

25 carboxylate,

5-(aminocarbonyl)pyridin-3-yl 4-(2-{3-

[(dimethylamino)carbonyl]phenyl}ethyl)piperidine-1-carboxylate,

5-(aminocarbonyl)pyridin-3-yl 4-{2-[3-(piperidin-1-ylcarbonyl)phenyl]ethyl}piperidine-1-carboxylate,

2010202348 04 Jun 2010

5-(aminocarbonyl)pyridin-3-yl 4-{2-[3-(pyrrolidin-1-
ylcarbonyl)phenyl]ethyl}piperidine-1-carboxylate,
5-(aminocarbonyl)pyridin-3-yl 4-(2-phenylethyl)piperidine-1-carboxylate,
5-(aminocarbonyl)pyridin-3-yl 4-[2-(3-fluorophenyl)ethyl]piperidine-1-carboxylate, and
5 5-(aminocarbonyl)pyridin-3-yl 4-[2-(3-cyanophenyl)ethyl]piperidine-1-carboxylate.

10. A pharmaceutical composition comprising the compound of any one
of claims 1 to 9 or its pharmaceutically acceptable salt as an active ingredient thereof.

10 11. The pharmaceutical composition according to claim 10, which is an
FAAH inhibitor.

12. The pharmaceutical composition according to claim 10, which is a
medicament for treatment of urinary frequency, urinary incontinence and/or overactive
15 bladder.

13. The pharmaceutical composition according to claim 10, which is a
medicament for treatment of pain.

20 14. Use of the compound of any one of claims 1 to 9 or its
pharmaceutically acceptable salt for the manufacture of an FAAH inhibitor or a
medicament for treatment of urinary frequency, urinary incontinence and/or overactive
bladder.

25 15. Use of the compound of any one of claims 1 to 9 or its
pharmaceutically acceptable salt for the manufacture of an FAAH inhibitor or a
medicament for treatment of pain.

30 16. A method for treating urinary frequency, urinary incontinence
and/or overactive bladder in a subject, comprising administering to the subject a
therapeutically effective amount of the compound of any one of claims 1 to 9 or its
pharmaceutically acceptable salt, or the pharmaceutical composition of claim 10.

2010202348 23 Jun 2011

17. A method for treating pain in a subject, comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1 to 9 or its pharmaceutically acceptable salt, or the pharmaceutical composition of claim 10.

18. A pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (I), or its pharmaceutically acceptable salt as defined in claim 1; a pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (III) or its pharmaceutically acceptable salt as defined in claim 4; a pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (IV) or its pharmaceutically acceptable salt as defined in claim 7; a pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative of a general formula (V) or its pharmaceutically acceptable salt as defined in claim 8; or a use of the compound as defined in claim 14 or claim 15 substantially as hereinbefore described with reference to the Examples.

SEQUENCE LISTING

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<151> 2005-02-17

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<151> 2005-10-18

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<170> PatentIn version 3.1

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<222> (36)..(1772)

<223> Inventor: Ishii, Takahiro; Sugane, Takashi; Maeda, Jun; Narazaki, Fumie; Kakefuda, Akio; Sato Kentaro; Takahashi, Tatsuhisa; Kanayama, Takatoshi; Saitoh, Chikashi; Suzuki, Jotaro; Kanai Chisato

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Trp Ala Ala Leu Pro Gly Ala Ser Gly Val Ala Leu Ala Cys Cys Phe
10 15 20

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Val Ala Ala Ala Val Ala Leu Arg Trp Ser Gly Arg Arg Thr Ala Arg
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Ser Glu Ala Leu Leu Ala Leu Pro Leu Pro Gln Leu Val Gln Lys Leu	
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His Ser Arg Glu Leu Ala Pro Glu Ala Val Leu Phe Thr Tyr Val Gly	
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aag gcc tgg gaa gtg aac aaa ggg acc aac tgt gtg acc tcc tat ctg	389
Lys Ala Trp Glu Val Asn Lys Gly Thr Asn Cys Val Thr Ser Tyr Leu	
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Ala Asp Cys Glu Thr Gln Leu Ser Gln Ala Pro Arg Gln Gly Leu Leu	
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Tyr Gly Val Pro Val Ser Leu Lys Glu Cys Phe Thr Tyr Lys Gly Gln	
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Pro Leu Gly Leu Gly Thr Asp Ile Gly Gly Ser Ile Arg Phe Pro Ser	
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 Arg Ser Ala Gly Lys Leu Trp Glu Leu Gln His Glu Ile Glu Val Tyr
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cgc aaa acc gtg att gcc cag tgg agg gcg ctg gac ctg gat gtg gtg 1445
 Arg Lys Thr Val Ile Ala Gln Trp Arg Ala Leu Asp Leu Asp Val Val
 455 460 465 470

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385 390 395 400

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Leu Ser Asn Met Lys Ser Arg Ser Ala Gly Lys Leu Trp Glu Leu Gln
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His Glu Ile Glu Val Tyr Arg Lys Thr Val Ile Ala Gln Trp Arg Ala
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Gly Val Cys Leu Ala Cys Ser Leu Leu Ser Ala Ala Val Val Leu Arg
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Trp Thr Arg Ser Gln Thr Ala Arg Gly Ala Val Thr Arg Ala Arg Gln
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acc aac tgt gtg acc tcc tat ctg act gac. tgt gag act cag ctg tcc 624
Thr Asn Cys Val Thr Ser Tyr Leu Thr Asp Cys Glu Thr Gln Leu Ser
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Gln Ala Pro Arg Gln Gly Leu Leu Tyr Gly Val Pro Val Ser Leu Lys
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Tyr Arg Ser Ser Arg Pro Leu Arg Val Gly Tyr Tyr Glu Thr Asp Asn	
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Cys Val Thr Ser Tyr Leu Thr Asp Cys Glu Thr Gln Leu Ser Gln Ala
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Lys Pro Ser Lys Ser Pro Gly Gly Ser Ser Gly Gly Glu Gly Ala Leu
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Pro Tyr Ala Leu Glu Val Leu Ser Ala Gly Gly Leu Phe Ser Asp Gly
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Leu Leu Ser Phe Leu Leu Lys Pro Leu Phe Pro Arg Leu Ala Ala Phe
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His Glu Ile Glu Met Tyr Arg Gln Ser Val Ile Ala Gln Trp Lys Ala
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Asp Leu Asp Ser Glu Ala Leu Leu Thr Leu Pro Leu Leu Gln Leu Val
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cag aag tta cag agt gga gag ctg tcc cca gag gct gtg ttc ttt act 346
Gln Lys Leu Gln Ser Gly Glu Leu Ser Pro Glu Ala Val Phe Phe Thr
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aag agc cca gga ggt tcc tca ggg ggt gag ggg gct ctc att gga tct Lys Ser Pro Gly Gly Ser Ser Gly Gly Glu Gly Ala Leu Ile Gly Ser 215 220 225	730
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Arg Ala Ser Leu Glu Thr Met Asp Lys Ala Val Gln Arg Phe Arg Leu
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Gln Leu Val Gln Lys Leu Gln Ser Gly Glu Leu Ser Pro Glu Ala Val
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Phe Phe Thr Tyr Leu Gly Lys Ala Trp Glu Val Asn Lys Gly Thr Asn
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Pro Arg Gln Gly Leu Leu Tyr Gly Val Pro Val Ser Leu Lys Glu Cys
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Phe Ser Tyr Lys Gly His Asp Ser Thr Leu Gly Leu Ser Leu Asn Glu
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04 Jun 2010
2010202348

21

Gly Met Pro Ser Glu Ser Asp Cys Val Val Val Gln Val Leu Lys Leu
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Gln Gly Ala Val Pro Phe Val His Thr Asn Val Pro Gln Ser Met Leu
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Ser Phe Asp Cys Ser Asn Pro Leu Phe Gly Gln Thr Met Asn Pro Trp
195 200 205

Lys Ser Ser Lys Ser Pro Gly Gly Ser Ser Gly Gly Glu Gly Ala Leu
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Ile Gly Ser Gly Gly Ser Pro Leu Gly Leu Gly Thr Asp Ile Gly Gly
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Ser Ile Arg Phe Pro Ser Ala Phe Cys Gly Ile Cys Gly Leu Lys Pro
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Thr Gly Asn Arg Leu Ser Lys Ser Gly Leu Lys Gly Cys Val Tyr Gly
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Gln Thr Ala Val Gln Leu Ser Leu Gly Pro Met Ala Arg Asp Val Glu
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Ser Leu Ala Leu Cys Leu Lys Ala Leu Leu Cys Glu His Leu Phe Thr
290 295 300

Leu Asp Pro Thr Val Pro Pro Leu Pro Phe Arg Glu Glu Val Tyr Arg
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Met Pro Ser Pro Ala Met Arg Arg Ala Leu Ile Glu Thr Lys Gln Arg
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Leu Glu Ala Ala Gly His Thr Leu Ile Pro Phe Leu Pro Asn Asn Ile
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Pro Tyr Ala Leu Glu Val Leu Ser Ala Gly Gly Leu Phe Ser Asp Gly
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Gly Arg Ser Phe Leu Gln Asn Phe Lys Gly Asp Phe Val Asp Pro Cys
385 390 395 400

Leu Gly Asp Leu Ile Leu Ile Leu Arg Leu Pro Ser Trp Phe Lys Arg
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Leu Leu Ser Leu Leu Leu Lys Pro Leu Phe Pro Arg Leu Ala Ala Phe
420 425 430

Leu Asn Ser Met Arg Pro Arg Ser Ala Glu Lys Leu Trp Lys Leu Gln
435 440 445

His Glu Ile Glu Met Tyr Arg Gln Ser Val Ile Ala Gln Trp Lys Ala
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Met Asn Leu Asp Val Leu Leu Thr Pro Met Leu Gly Pro Ala Leu Asp
465 470 475 480

Leu Asn Thr Pro Gly Arg Ala Thr Gly Ala Ile Ser Tyr Thr Val Leu
485 490 495

Tyr Asn Cys Leu Asp Phe Pro Ala Gly Val Val Pro Val Thr Thr Val
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Thr Ala Glu Asp Asp Ala Gln Met Glu Leu Tyr Lys Gly Tyr Phe Gly
515 520 525

Asp Ile Trp Asp Ile Ile Leu Lys Lys Ala Met Lys Asn Ser Val Gly
530 535 540

Leu Pro Val Ala Val Gln Cys Val Ala Leu Pro Trp Gln Glu Glu Leu
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Gln Arg Phe Arg Leu Gln Asn Pro Asp Leu Asp Ser Glu Met Leu Leu
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Asn Arg Gly Thr Asn Cys Val Thr Thr Tyr Leu Ala Asp Cys Glu Ala	
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Gln Leu Cys Gln Ala Pro Gly Gln Gly Leu Leu Tyr Gly Val Pro Val	
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Thr Thr Asn Pro Trp Met Ser Ser Lys Ser Pro Gly Gly Ser Ser Gly	
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Gly Glu Gly Ala Leu Ile Ala Ala Gly Gly Ser Pro Leu Gly Leu Gly	
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Thr Asp Ile Gly Gly Ser Ile Arg Phe Pro Ser Ala Phe Cys Gly Ile	
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Cys Gly Ile Lys Pro Thr Gly Asn Arg Ile Ser Lys Ser Gly Leu Lys	
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Glu Glu Val Tyr Ala Ser Ser Arg Pro Leu Arg Val Gly Tyr Tyr Glu	
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acc gac aac tac acc atg ccc acg ccg gcc atg agg cgg gcc ctg ctg	1060
Thr Asp Asn Tyr Thr Met Pro Thr Pro Ala Met Arg Arg Ala Leu Leu	
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Lys Trp Leu Lys Gly Leu Leu Ala Phe Met Leu Arg Pro Leu Leu Pro	
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Leu Trp Glu Leu Gln His Glu Ile Glu Met Tyr Arg His Ser Val Ile	
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Ser Pro Ala Leu Asp Leu Asn Ala Pro Gly Lys Ala Thr Gly Ala Val
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agc tac acg ctg ctc tac aac tgc ctg gac ttc ccc gcg ggg gtg gtg 1540
 Ser Tyr Thr Leu Leu Tyr Asn Cys Leu Asp Phe Pro Ala Gly Val Val
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cct gtc acc acg gtg act gcc gag gac gag gcc cag atg gag cat tac 1588
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aag ggc tac ttt ggg gac att tgg gac aag gtg gtg cag aag gcc atg 1636
 Lys Gly Tyr Phe Gly Asp Ile Trp Asp Lys Val Val Gln Lys Ala Met
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aag agg agc gtg ggg ctg cct gtg gcc gtg cag tgt gtg gct ctg ccc 1684
 Lys Arg Ser Val Gly Leu Pro Val Ala Val Gln Cys Val Ala Leu Pro
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 Met Ala Pro Gly Arg Gln Pro Ser
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Gln Ala Ala Leu Glu Thr Met Asp Lys Ala Ala Gln Arg Phe Arg Leu
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Gln Asn Pro Asp Leu Asp Ser Glu Met Leu Leu Ala Leu Pro Leu Pro
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Gln Leu Val Gln Lys Val Arg Ser Gly Glu Leu Ser Pro Glu Ala Val
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Leu Phe Ser Tyr Leu Gln Lys Ala Trp Glu Val Asn Arg Gly Thr Asn
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Cys Val Thr Thr Tyr Leu Ala Asp Cys Glu Ala Gln Leu Cys Gln Ala
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Pro Gly Gln Gly Leu Leu Tyr Gly Val Pro Val Ser Leu Lys Glu Cys
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Phe Ser Cys Lys Gly His Asp Ser Thr Leu Gly Leu Ser Arg Asn Gln
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Gly Thr Pro Ala Glu Cys Asp Cys Val Val Val Gln Val Leu Lys Leu
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Ser Tyr Asp Cys Ser Asn Pro Leu Phe Gly Gln Thr Thr Asn Pro Trp
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Met Ser Ser Lys Ser Pro Gly Gly Ser Ser Gly Gly Glu Gly Ala Leu
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Ile Ala Ala Gly Gly Ser Pro Leu Gly Leu Gly Thr Asp Ile Gly Gly
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Ser Ile Arg Phe Pro Ser Ala Phe Cys Gly Ile Cys Gly Ile Lys Pro
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Thr Gly Asn Arg Ile Ser Lys Ser Gly Leu Lys Gly Ser Val Tyr Gly
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Ser Leu Ala Leu Cys Leu Arg Ala Leu Leu Cys Glu Asp Met Phe Arg
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Leu Asp Pro Thr Val Pro Pro Leu Pro Phe Asn Glu Glu Val Tyr Ala
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Ser Ser Arg Pro Leu Arg Val Gly Tyr Tyr Glu Thr Asp Asn Tyr Thr
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Met Pro Thr Pro Ala Met Arg Arg Ala Leu Leu Glu Thr Lys Arg Ser
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Leu Glu Ala Ala Gly His Thr Leu Ile Pro Phe Leu Pro Ala Asn Ile
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Pro His Ala Leu Glu Ala Leu Ser Thr Gly Gly Leu Phe Ser Asp Gly
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Gly Lys Arg Leu Leu Gln Asn Phe Glu Gly Asp Tyr Val Asp Ser Cys
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Leu Gly Asp Leu Ile Ser Ile Leu Arg Leu Pro Lys Trp Leu Lys Gly
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Leu Ser Ser Leu Arg Pro Arg Ser Ala Gly Lys Leu Trp Glu Leu Gln
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His Glu Ile Glu Met Tyr Arg His Ser Val Ile Ala Gln Trp Arg Ala
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Leu Asp Leu Asp Val Val Leu Thr Pro Met Leu Ser Pro Ala Leu Asp
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Leu Asn Ala Pro Gly Lys Ala Thr Gly Ala Val Ser Tyr Thr Leu Leu
485 490 495

Tyr Asn Cys Leu Asp Phe Pro Ala Gly Val Val Pro Val Thr Thr Val
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Thr Ala Glu Asp Glu Ala Gln Met Glu His Tyr Lys Gly Tyr Phe Gly
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Asp Ile Trp Asp Lys Val Val Gln Lys Ala Met Lys Arg Ser Val Gly
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Leu Pro Val Ala Val Gln Cys Val Ala Leu Pro Trp Gln Glu Glu Leu
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2010202348 04 Jun 2010

30

Cys Leu Arg Phe Met Arg Glu Val Glu Arg Leu Met Ala Pro Gly Arg
565 570 575

Gln Pro Ser