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(54) Titre : COMPOSITIONS MEDICINALES
(54) Title: MEDICINAL COMPOSITIONS

(57) Abrégé/Abstract:
It is intended to provide medicinal compositions and the like useful in treating depression which contain a compound having an antagonism to adenosine A_{2A} receptor (for example, (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purin-2,6-dione) or a pharmacologically acceptable salt thereof together with an antidepressant (for example, a tricyclic antidepressant, a tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a selective noradrenaline reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin/noradrenaline reuptake inhibitor, a monoamine oxidase inhibitor or a serotonin 2 antagonist).

CA 2533117 A1 2005/02/03
(21) 2 533 117
(13) A1

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Abstract

The present invention provides pharmaceutical compositions, which are useful for treatment of depression and the like, and which comprises a compound having an adenosine A_{2A} receptor antagonistic activity such as (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof and an antidepressant drug (for example, a tricyclic antidepressant, a tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a selective noradrenalin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin-noradrenalin reuptake inhibitor, a monoamine oxidase inhibitor, a $5\text{-}HT_2$ antagonist or the like), and the like.

SPECIFICATION

PHARMACEUTICAL COMPOSITION

Technical Field

The present invention relates to pharmaceutical compositions which comprise a compound having an adenosine A_{2A} receptor antagonistic activity and an antidepressant drug, and the like.

Background Art

(E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof are known to show an adenosine A_{2A} receptor antagonistic activity and be useful as a therapeutic agent for depression and the like (Japanese Patent No. 2928386).

Furthermore, pharmaceutical compositions which comprise a non-xanthine derivative having an adenosine A_{2A} receptor antagonistic activity and an antidepressant drug are known (WO 03/022283).

On the other hand, a treatment of depression carried out by an administration of a tricyclic antidepressant, a tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a selective noradrenalin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin-noradrenalin reuptake inhibitor or the like, or by an administration in combination of these. However, these administrations involve medical problems of side effects such as side effects on an autonomic nervous system, cardiotoxicity, side effects on a digestive system (for example, nausea, anorexia, loose stool, diarrhea and the like), sexual dysfunctions, withdrawal syndrome, extrapyramidal disorders,

serotonin syndrome, weight loss, anxiety and impatience, syndrome of inappropriate antidiuretic hormone in the aged, urinary retention, dysuria, a rash, headache and palpitation [Pharmacia, 38, 737-742, (2001)]. Furthermore, treatment of depression is carried out by an administration of a monoamine oxidase inhibitor. However, the administration also involves medical problems of side effects such as serious hepatic function disorder and rise of blood pressure [Pharmacia, 38, 737-742 (2001)].

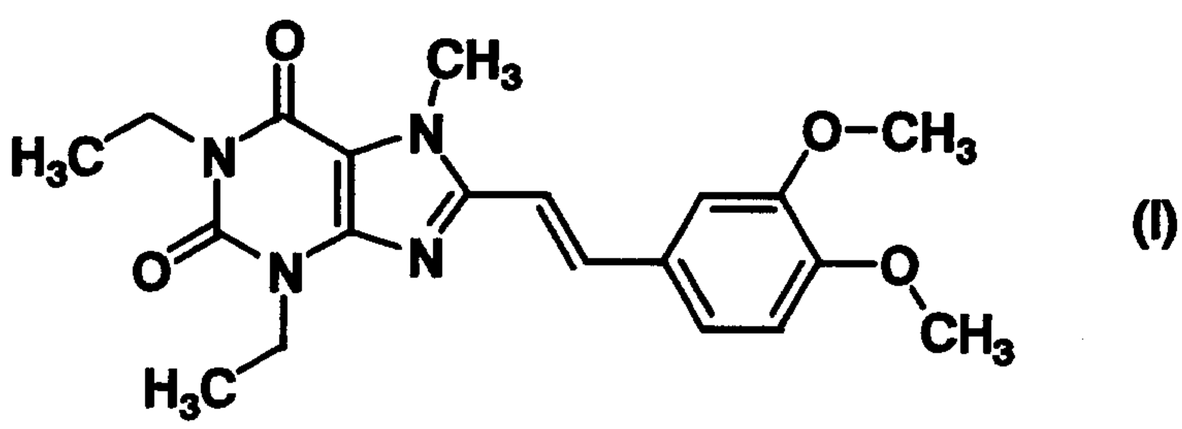
Disclosure of the Invention

An object of the present invention is to provide pharmaceutical compositions which comprise (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof and an antidepressant drug, and the like.

The invention relates to the following items (1) to (118).

(1) A pharmaceutical composition which comprises

(a) (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):

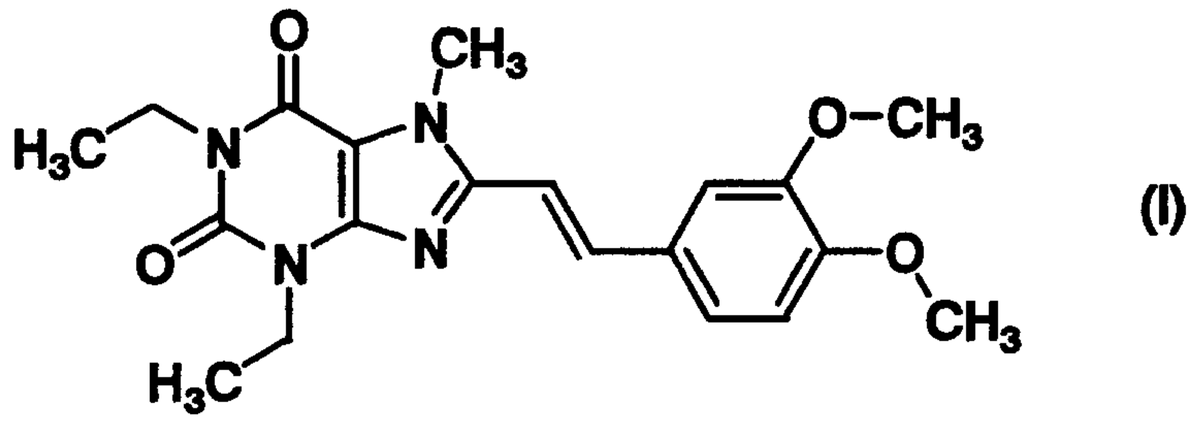


(I)

or a pharmaceutically acceptable salt thereof, and

(b) an antidepressant drug.

(2) A pharmaceutical composition which comprises (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof for administering simultaneously or separately at a time interval in combination with an antidepressant drug.

(3) The pharmaceutical composition according to the above (1) or (2), wherein the antidepressant drug is a tricyclic antidepressant, a tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a selective noradrenalin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin-noradrenalin reuptake inhibitor, a monoamine oxidase inhibitor or a serotonin 2 ($5\text{-}HT_2$) antagonist.

(4) The pharmaceutical composition according to the above (1) or (2), wherein the antidepressant drug is a tricyclic antidepressant.

(5) The pharmaceutical composition according to the above (4), wherein the tricyclic antidepressant is imipramine hydrochloride, clomipramine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, trimipramine maleate, lofepramine, lofepramine hydrochloride, dosulepin hydrochloride, protriptyline, doxepin or desipramine hydrochloride.

(6) The pharmaceutical composition according to the above (1) or (2), wherein the antidepressant drug is a tetracyclic antidepressant.

(7) The pharmaceutical composition according to the above (6), wherein the tetracyclic antidepressant is maprotiline

hydrochloride, mianserin hydrochloride or setiptiline maleate.

(8) The pharmaceutical composition according to the above (1) or (2), wherein the antidepressant drug is a selective serotonin reuptake inhibitor.

(9) The pharmaceutical composition according to the above (8), wherein the selective serotonin reuptake inhibitor is fluoxetine hydrochloride, sertraline hydrochloride, paroxetine hydrochloride, paroxetine hydrochloride hydrate, citalopram hydrobromide, fluvoxamine maleate, trazodone hydrochloride or nefazodone hydrochloride.

(10) The pharmaceutical composition according to the above (1) or (2), wherein the antidepressant drug is a selective noradrenalin reuptake inhibitor.

(11) The pharmaceutical composition according to the above (10), wherein the selective noradrenalin reuptake inhibitor is reboxetine mesylate, mirtazapine, maprotiline hydrochloride, nortriptyline hydrochloride, amoxapine, bupropion or bupropion hydrochloride.

(12) The pharmaceutical composition according to the above (1) or (2), wherein the antidepressant drug is a serotonin-noradrenalin reuptake inhibitor.

(13) The pharmaceutical composition according to the above (12), wherein the serotonin-noradrenalin reuptake inhibitor is milnacipran hydrochloride, venlafaxine hydrochloride or duloxetine hydrochloride.

(14) The pharmaceutical composition according to the above (1) or (2), wherein the antidepressant drug is a dopamine reuptake inhibitor.

(15) The pharmaceutical composition according to the above (14), wherein the dopamine reuptake inhibitor is venlafaxine

hydrochloride.

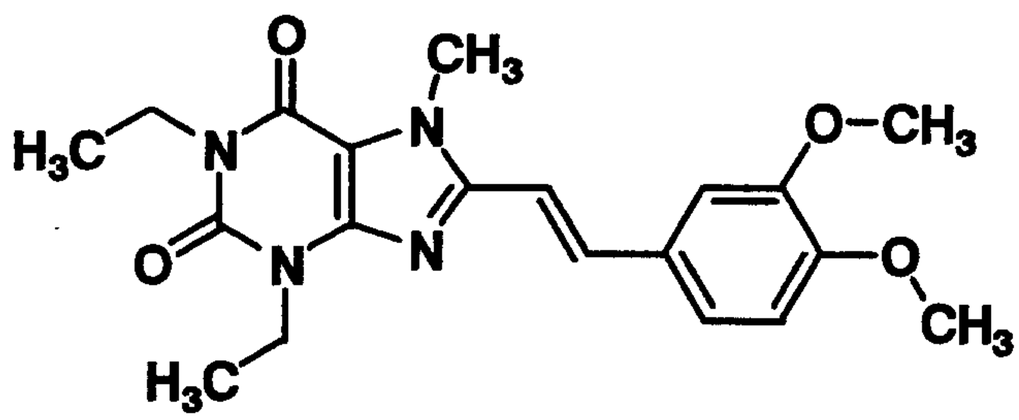
(16) The pharmaceutical composition according to the above (1) or (2), wherein the antidepressant drug is a monoamine oxidase inhibitor.

(17) The pharmaceutical composition according to the above (16), wherein the monoamine oxidase inhibitor is selegiline hydrochloride, safinamide mesylate or moclobemide.

(18) The pharmaceutical composition according to the above (1) or (2), wherein the antidepressant drug is a 5-HT_2 antagonist.

(19) The pharmaceutical composition according to the above (18), wherein the 5-HT_2 antagonist is mirtazapine, trazodone hydrochloride or nefazodone hydrochloride.

(20) A therapeutic agent for depression which comprises (a) (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof and

(b) an antidepressant drug

for administering simultaneously or separately at a time interval.

(21) The therapeutic agent for depression according to the above (20), wherein the antidepressant drug is a tricyclic antidepressant, a tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a selective noradrenalin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin-noradrenalin reuptake inhibitor, a monoamine oxidase

inhibitor or a 5-HT_2 antagonist.

(22) The therapeutic agent for depression according to the above (20), wherein the antidepressant drug is a tricyclic antidepressant.

(23) The therapeutic agent for depression according to the above (22), wherein the tricyclic antidepressant is imipramine hydrochloride, clomipramine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, trimipramine maleate, lofepramine, lofepramine hydrochloride, dosulepin hydrochloride, protriptyline, doxepin or desipramine hydrochloride.

(24) The therapeutic agent for depression according to the above (20), wherein the antidepressant drug is a tetracyclic antidepressant.

(25) The therapeutic agent for depression according to the above (24), wherein the tetracyclic antidepressant is maprotiline hydrochloride, mianserin hydrochloride or setiptiline maleate.

(26) The therapeutic agent for depression according to the above (20), wherein the antidepressant drug is a selective serotonin reuptake inhibitor.

(27) The therapeutic agent for depression according to the above (26), wherein the selective serotonin reuptake inhibitor is fluoxetine hydrochloride, sertraline hydrochloride, paroxetine hydrochloride, paroxetine hydrochloride hydrate, citalopram hydrobromide, fluvoxamine maleate, trazodone hydrochloride or nefazodone hydrochloride.

(28) The therapeutic agent for depression according to the above (20), wherein the antidepressant drug is a selective noradrenalin reuptake inhibitor.

(29) The therapeutic agent for depression according to the above (28), wherein the selective noradrenalin reuptake inhibitor is reboxetine mesylate, mirtazapine, maprotiline hydrochloride, nortriptyline hydrochloride, amoxapine, bupropion or bupropion hydrochloride.

(30) The therapeutic agent for depression according to the above (20), wherein the antidepressant drug is a serotonin-noradrenalin reuptake inhibitor.

(31) The therapeutic agent for depression according to the above (30), wherein the serotonin-noradrenalin reuptake inhibitor is milnacipran hydrochloride, venlafaxine hydrochloride or duloxetine hydrochloride.

(32) The therapeutic agent for depression according to the above (20), wherein the antidepressant drug is a dopamine reuptake inhibitor.

(33) The therapeutic agent for depression according to the above (32), wherein the dopamine reuptake inhibitor is venlafaxine hydrochloride.

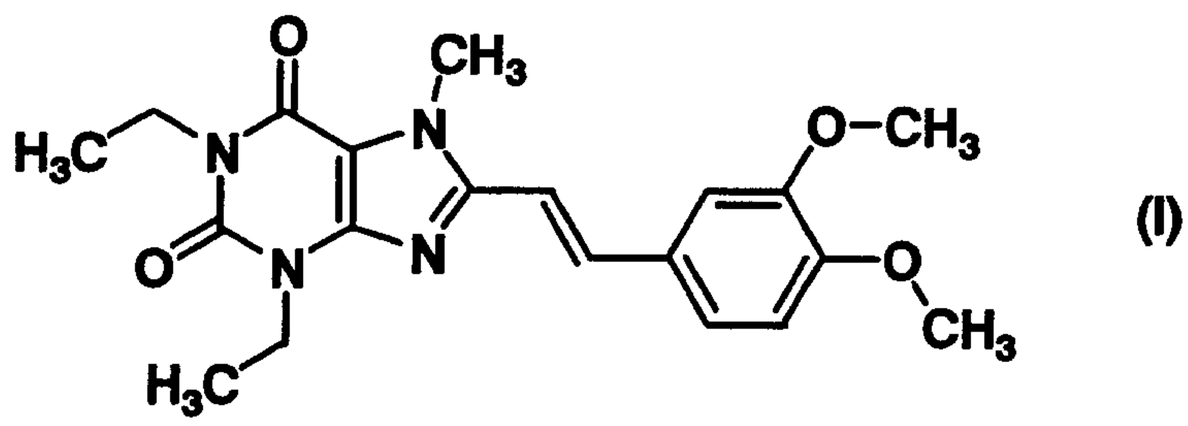
(34) The therapeutic agent for depression according to the above (20), wherein the antidepressant drug is a monoamine oxidase inhibitor.

(35) The therapeutic agent for depression according to the above (34), wherein the monoamine oxidase inhibitor is selegiline hydrochloride, safinamide mesylate or moclobemide.

(36) The therapeutic agent for depression according to the above (20), wherein the antidepressant drug is a $5\text{-}HT_2$ antagonist.

(37) The therapeutic agent for depression according to the above (36), wherein the $5\text{-}HT_2$ antagonist is mirtazapine, trazodone hydrochloride or nefazodone hydrochloride.

(38) (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof for administering simultaneously or separately at a time interval in combination with an antidepressant drug.

(39) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (38), wherein the antidepressant drug is a tricyclic antidepressant, a tetracyclic antidepressant, a selective a serotonin reuptake inhibitor, a selective noradrenalin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin-noradrenalin reuptake inhibitor, a monoamine oxidase inhibitor or a 5-HT_2 antagonist.

(40) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (38), wherein the antidepressant drug is a tricyclic antidepressant.

(41) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (40), wherein the tricyclic antidepressant is imipramine hydrochloride, clomipramine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, trimipramine maleate, lofepramine, lofepramine hydrochloride, dosulepin hydrochloride,

protriptyline, doxepin or desipramine hydrochloride.

(42) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (38), wherein the antidepressant drug is a tetracyclic antidepressant.

(43) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (42), wherein the tetracyclic antidepressant is maprotiline hydrochloride, mianserin hydrochloride or setiptiline maleate.

(44) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (38), wherein the antidepressant drug is a selective serotonin reuptake inhibitor.

(45) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (44), wherein the selective serotonin reuptake inhibitor is fluoxetine hydrochloride, sertraline hydrochloride, paroxetine hydrochloride, paroxetine hydrochloride hydrate, citalopram hydrobromide, fluvoxamine maleate, trazodone hydrochloride or nefazodone hydrochloride.

(46) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (38), wherein the antidepressant drug is a selective noradrenalin reuptake inhibitor.

(47) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (46), wherein the

selective noradrenalin reuptake inhibitor is reboxetine mesylate, mirtazapine, maprotiline hydrochloride, nortriptyline hydrochloride, amoxapine, bupropion or bupropion hydrochloride.

(48) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (38), wherein the antidepressant drug is a serotonin-noradrenalin reuptake inhibitor.

(49) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (48), wherein the serotonin-noradrenalin reuptake inhibitor is milnacipran hydrochloride, venlafaxine hydrochloride or duloxetine hydrochloride.

(50) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (38), wherein the antidepressant drug is a dopamine reuptake inhibitor.

(51) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (50), wherein the dopamine reuptake inhibitor is venlafaxine hydrochloride.

(52) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (38), wherein the antidepressant drug is a monoamine oxidase inhibitor.

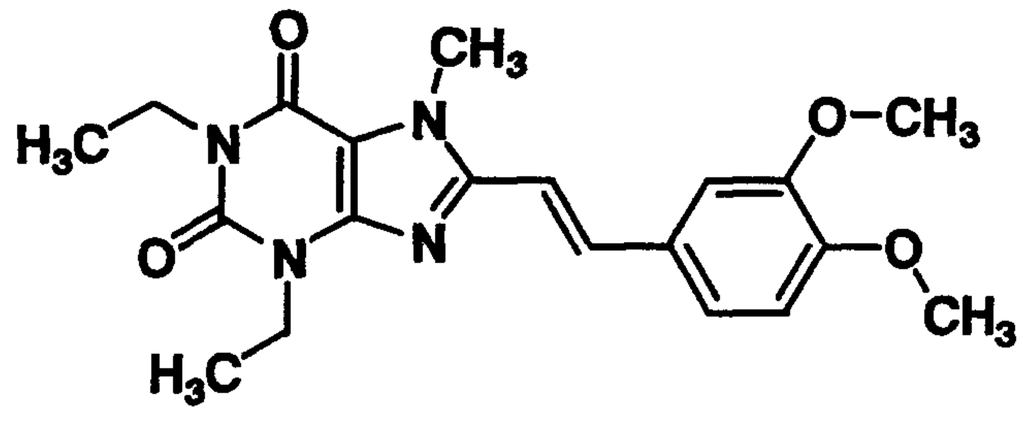
(53) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (52), wherein the monoamine oxidase inhibitor is selegiline hydrochloride,

safinamide mesylate or moclobemide.

(54) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (38), wherein the antidepressant drug is a 5-HT_2 antagonist.

(55) The (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof according to the above (54), wherein the 5-HT_2 antagonist is mirtazapine, trazodone hydrochloride or nefazodone hydrochloride.

(56) A kit which comprises (a) a first component comprising (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):

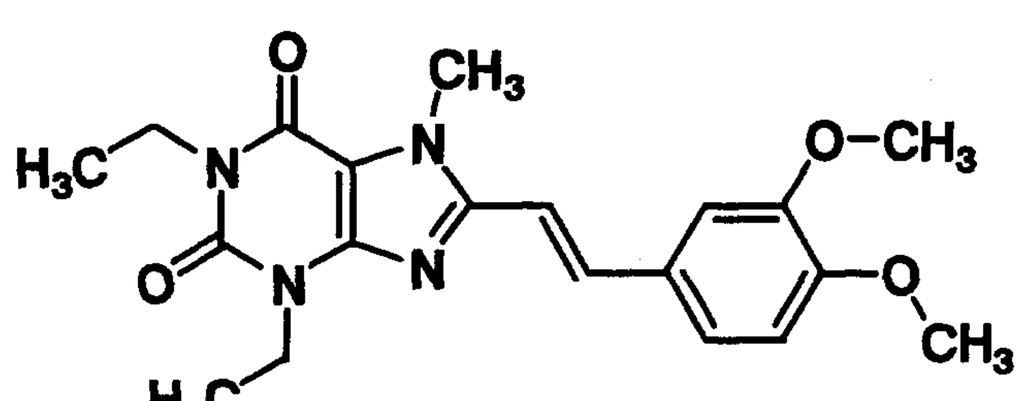


(I)

or a pharmaceutically acceptable salt thereof and

(b) a second component comprising an antidepressant drug.

(57) A kit for treatment of depression which comprises (a) a first component comprising (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof and

(b) a second component comprising an antidepressant drug.

(58) The kit according to the above (56) or (57), wherein the antidepressant drug is a tricyclic antidepressant, a tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a selective noradrenalin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin-noradrenalin reuptake inhibitor, a monoamine oxidase inhibitor or a 5-HT_2 antagonist.

(59) The kit according to the above (56) or (57), wherein the antidepressant drug is a tricyclic antidepressant.

(60) The kit according to the above (59), wherein the tricyclic antidepressant is imipramine hydrochloride, clomipramine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, trimipramine maleate, lofepramine, lofepramine hydrochloride, dosulepin hydrochloride, protriptyline, doxepin or desipramine hydrochloride.

(61) The kit according to the above (56) or (57), wherein the antidepressant drug is a tetracyclic antidepressant.

(62) The kit according to the above (61), wherein the tetracyclic antidepressant is maprotiline hydrochloride, mianserin hydrochloride or setiptiline maleate.

(63) The kit according to the above (56) or (57), wherein the antidepressant drug is a selective serotonin reuptake inhibitor.

(64) The kit according to the above (63), wherein the selective serotonin reuptake inhibitor is fluoxetine hydrochloride, sertraline hydrochloride, paroxetine hydrochloride, paroxetine hydrochloride hydrate, citalopram hydrobromide, fluvoxamine maleate, trazodone hydrochloride or nefazodone hydrochloride.

(65) The kit according to the above (56) or (57), wherein

the antidepressant drug is a selective noradrenalin reuptake inhibitor.

(66) The kit according to the above (65), wherein the selective noradrenalin reuptake inhibitor is reboxetine mesylate, mirtazapine, maprotiline hydrochloride, nortriptyline hydrochloride, amoxapine, bupropion or bupropion hydrochloride.

(67) The kit according to the above (56) or (57), wherein the antidepressant drug is a serotonin-noradrenalin reuptake inhibitor.

(68) The kit according to the above (67), wherein the serotonin-noradrenalin reuptake inhibitor is milnacipran hydrochloride, venlafaxine hydrochloride or duloxetine hydrochloride.

(69) The kit according to the above (56) or (57), wherein the antidepressant drug is a dopamine reuptake inhibitor.

(70) The kit according to the above (69), wherein the dopamine reuptake inhibitor is venlafaxine hydrochloride.

(71) The kit according to the above (56) or (57), wherein the antidepressant drug is a monoamine oxidase inhibitor.

(72) The kit according to the above (71), wherein the monoamine oxidase inhibitor is selegiline hydrochloride, safinamide mesylate or moclobemide.

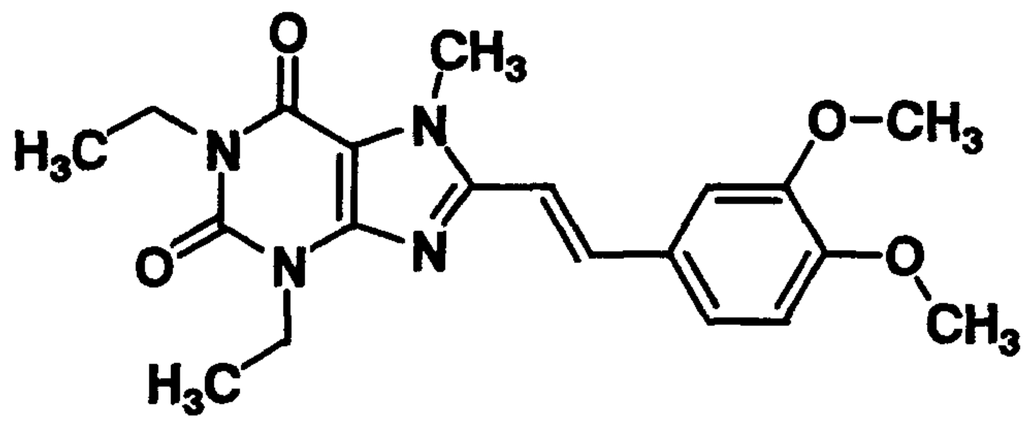
(73) The kit according to the above (56) or (57), wherein the antidepressant drug is a $5\text{-}HT_2$ antagonist.

(74) The kit according to the above (73), wherein the $5\text{-}HT_2$ antagonist is mirtazapine, trazodone hydrochloride or nefazodone hydrochloride.

(75) A method for treating depression, which comprises administering

(a) (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-

dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof and

(b) an antidepressant drug

simultaneously or separately at a time interval.

(76) The method for treating depression according to the above (75), wherein the antidepressant drug is a tricyclic antidepressant, a tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a selective noradrenalin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin-noradrenalin reuptake inhibitor, a monoamine oxidase inhibitor or a 5-HT_2 antagonist.

(77) The method for treating depression according to the above (75), wherein the antidepressant drug is a tricyclic antidepressant.

(78) The method for treating depression according to the above (77), wherein the tricyclic antidepressant is imipramine hydrochloride, clomipramine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, trimipramine maleate, lofepramine, lofepramine hydrochloride, dosulepin hydrochloride, protriptyline, doxepin or desipramine hydrochloride.

(79) The method for treating depression according to the above (75), wherein the antidepressant drug is a tetracyclic antidepressant.

(80) The method for treating depression according to the

above (79), wherein the tetracyclic antidepressant is maprotiline hydrochloride, mianserin hydrochloride or setiptiline maleate.

(81) The method for treating depression according to the above (75), wherein the antidepressant drug is a selective serotonin reuptake inhibitor.

(82) The method for treating depression according to the above (81), wherein the selective serotonin reuptake inhibitor is fluoxetine hydrochloride, sertraline hydrochloride, paroxetine hydrochloride, paroxetine hydrochloride hydrate, citalopram hydrobromide, fluvoxamine maleate, trazodone hydrochloride or nefazodone hydrochloride.

(83) The method for treating depression according to the above (75), wherein the antidepressant drug is a selective noradrenalin reuptake inhibitor.

(84) The method for treating depression according to the above (83), wherein the selective noradrenalin reuptake inhibitor is reboxetine mesylate, mirtazapine, maprotiline hydrochloride, nortriptyline hydrochloride, amoxapine, bupropion or bupropion hydrochloride.

(85) The method for treating depression according to the above (75), wherein the antidepressant drug is a serotonin-noradrenalin reuptake inhibitor.

(86) The method for treating depression according to the above (85), wherein the serotonin-noradrenalin reuptake inhibitor is milnacipran hydrochloride, venlafaxine hydrochloride or duloxetine hydrochloride.

(87) The method for treating depression according to the above (75), wherein the antidepressant drug is a dopamine reuptake inhibitor.

(88) The method for treating depression according to the

above (87), wherein the dopamine reuptake inhibitor is venlafaxine hydrochloride.

(89) The method for treating depression according to the above (75), wherein the antidepressant drug is a monoamine oxidase inhibitor.

(90) The method for treating depression according to the above (89), wherein the monoamine oxidase inhibitor is selegiline hydrochloride, safinamide mesylate or moclobemide.

(91) The method for treating depression according to the above (75), wherein the antidepressant drug is a 5-HT_2 antagonist.

(92) The method for treating depression according to the above (91), wherein the 5-HT_2 antagonist is mirtazapine, trazodone hydrochloride or nefazodone hydrochloride.

(93) A pharmaceutical composition which comprises (a) a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and (b) a monoamine oxidase inhibitor.

(94) A compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof for administering simultaneously or separately at a time interval in combination with a monoamine oxidase inhibitor.

(95) A pharmaceutical composition which comprises a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof for administering simultaneously or separately at a time interval in combination with a monoamine oxidase inhibitor.

(96) A therapeutic agent for depression which comprises (a) a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and (b) a monoamine oxidase inhibitor

for administering simultaneously or separately at a time interval.

(97) A kit which comprises

(a) a first component comprising a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and

(b) a second component comprising a monoamine oxidase inhibitor.

(98) A kit for treatment of depression which comprises

(a) a first component comprising a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and

(b) a second component comprising a monoamine oxidase inhibitor.

(99) A method for treating depression, which comprises administering

(a) a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and

(b) a monoamine oxidase inhibitor

simultaneously or separately at a time interval.

(100) Use of a combination of

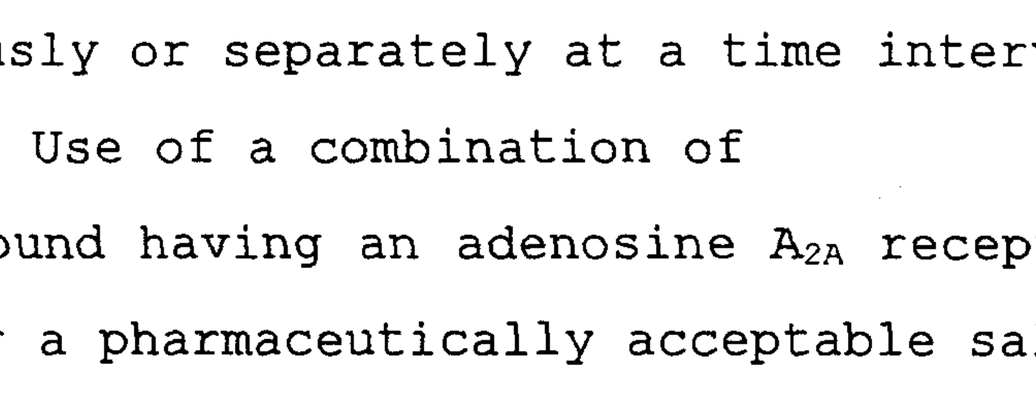
(a) a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and

(b) a monoamine oxidase inhibitor

for the manufacture of a therapeutic agent for depression.

(101) Use of a combination of

(a) (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof and

(b) an antidepressant drug

for the manufacture of a therapeutic agent for depression.

(102) The use according to the above (101), wherein the antidepressant drug is a tricyclic antidepressant, a tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a selective noradrenalin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin-noradrenalin reuptake inhibitor, a monoamine oxidase inhibitor or a 5-HT_2 antagonist.

(103) The use according to the above (101), wherein the antidepressant drug is a tricyclic antidepressant.

(104) The use according to the above (103), wherein the tricyclic antidepressant is imipramine hydrochloride, clomipramine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, trimipramine maleate, lofepramine, lofepramine hydrochloride, dosulepin hydrochloride, protriptyline, doxepin or desipramine hydrochloride.

(105) The use according to the above (101), wherein the antidepressant drug is a tetracyclic antidepressant.

(106) The use according to the above (105), wherein the tetracyclic antidepressant is maprotiline hydrochloride, mianserin hydrochloride or setiptiline maleate.

(107) The use according to the above (101), wherein the antidepressant drug is a selective serotonin reuptake inhibitor.

(108) The use according to the above (107), wherein the selective serotonin reuptake inhibitor is fluoxetine hydrochloride, sertraline hydrochloride, paroxetine hydrochloride, paroxetine hydrochloride hydrate, citalopram hydrobromide, fluvoxamine maleate, trazodone hydrochloride or nefazodone hydrochloride.

(109) The use according to the above (101), wherein the antidepressant drug is a selective noradrenalin reuptake inhibitor.

(110) The use according to the above (109), wherein the selective noradrenalin reuptake inhibitor is reboxetine mesylate, mirtazapine, maprotiline hydrochloride, nortriptyline hydrochloride, amoxapine, bupropion or bupropion hydrochloride.

(111) The use according to the above (101), wherein the antidepressant drug is a serotonin-noradrenalin reuptake inhibitor.

(112) The use according to the above (111), wherein the serotonin-noradrenalin reuptake inhibitor is milnacipran hydrochloride, venlafaxine hydrochloride or duloxetine hydrochloride.

(113) The use according to the above (101), wherein the antidepressant drug is a dopamine reuptake inhibitor.

(114) The use according to the above (112), wherein the dopamine reuptake inhibitor is venlafaxine hydrochloride.

(115) The use according to the above (101), wherein the antidepressant drug is a monoamine oxidase inhibitor.

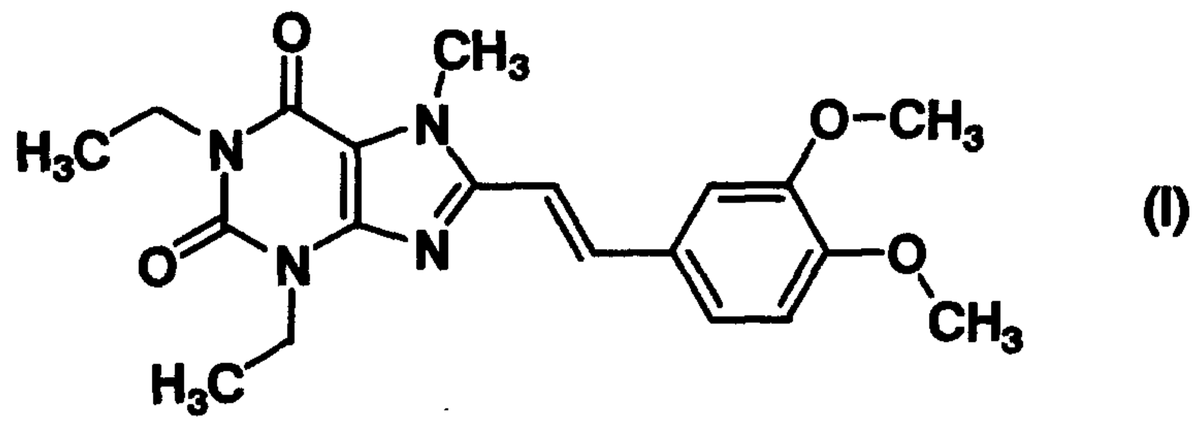
(116) The use according to the above (115), wherein the monoamine oxidase inhibitor is selegiline hydrochloride, safinamide mesylate or moclobemide.

(117) The use according to the above (101), wherein the antidepressant drug is a $5\text{-}HT_2$ antagonist.

(118) The use according to the above (117), wherein the $5\text{-}HT_2$ antagonist is mirtazapine, trazodone hydrochloride or nefazodone hydrochloride.

Hereinafter, (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-

methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

is referred to as Compound (I).

Examples of the pharmaceutically acceptable salt of Compound (I) include pharmaceutically acceptable acid addition salts. Specifically, inorganic acid addition salts such as hydrochloride, sulfate, hydrobromide, nitrate and phosphate, organic acid addition salts such as acetate, mesylate, succinate, maleate, fumarate, citrate and tartrate are included.

Although a method for production of Compound (I) is not particularly limited, Compound (I) can be obtained by any methods described in, for example, Japanese Pubilished Unexamined Patent Application No. 211856/94, EP 0590919, Japanese Published Unexamined Patent Application No. 040652/97 or the like, or modified methods thereof. The desired compound in each method of production can be isolated and purified by subjecting them to purification methods which are generally used in synthetic organic chemistry such as filtration, extraction, washing, drying, concentration, recrystallization and various types of chromatography.

When it is desired to obtain a salt of Compound (I), in instances in which Compound (I) is obtained in the form of a salt, the product may be directly purified. Alternatively, in instances in which Compound (I) is obtained in the form of a free base, the product may be dissolved or suspended in a suitable

solvent, followed by addition of an acid or the like to form a salt.

Furthermore, Compound (I) and the pharmaceutically acceptable salt thereof may exist in the form of an adduct with water or various solvents. These adducts can also be used for the pharmaceutical composition, the therapeutic agent for depression, the kit, the kit for treatment of depression or the method for treating depression of the present invention, and are included in the (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof of the present invention.

Although the compound having an adenosine A_{2A} receptor antagonistic activity is not particularly limited, as long as it is a compound having an adenosine A_{2A} receptor antagonistic activity, examples of the compound having an adenosine A_{2A} receptor antagonistic activity include compounds described in, Japanese Patent No. 2928386, WO01/92264, US5565460, US5587378, US5543415, EP1016407, WO01/17999, WO01/62233, WO01/97786, WO01/92264, WO01/13681, WO00/13682, WO01/02409, WO99/26627, WO01/40230, WO00/24742, WO98/42711, WO00/17201, WO03/022283 and the like. These compounds can be obtained by the methods of production described in the above-mentioned documents.

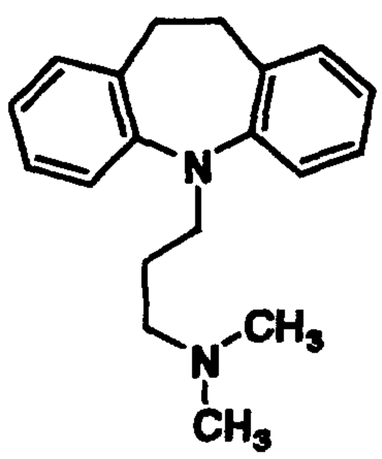
Examples of the pharmaceutically acceptable salt of the compound having an adenosine A_{2A} receptor antagonistic activity include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, amino acid addition salts and the like.

Examples of the pharmaceutically acceptable acid addition salts include an inorganic acid salt such as hydrochloride, sulfate and phosphate; and an organic acid salt such as acetate,

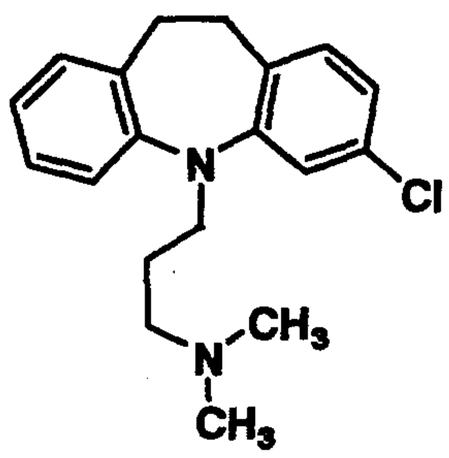
maleate, fumarate, tartrate, citrate and methanesulfonate. Examples of the pharmaceutically acceptable metal salts include an alkali metal salt such as sodium salt and potassium salt; alkaline earth metal salt such as magnesium salt and calcium salt; aluminum salt; zinc salt and the like. Examples of the pharmaceutically acceptable ammonium salts include ammonium and tetramethylammonium. Examples of the pharmaceutically acceptable organic amine addition salt include an addition salt of morpholine or piperidine. Examples of the pharmaceutically acceptable amino acid addition salts include an addition salt of lysine, glycine or phenylalanine. When it is desired to obtain a salt of the compound having an adenosine A_{2A} receptor antagonistic activity, in instances in which the compound is obtained in the form of a salt, the product may be directly purified. Alternatively, in instances in which the compound is obtained in the form of a free base, the product may be dissolved or suspended in a suitable solvent, followed by addition of an acid or a base to form a salt.

Examples of the antidepressant drug include tricyclic antidepressants, tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), selective noradrenalin reuptake inhibitors (Selective Norepinephrine Reuptake Inhibitor), serotonin-noradrenalin reuptake inhibitors (Serotonin-Norepinephrine Reuptake Inhibitor; SNRI), dopamine reuptake inhibitors, monoamine oxidase (MAO) inhibitors, 5-HT_2 antagonists and the like. These may be used alone or in combination, as long as it is not contraindicated, for the pharmaceutical composition, the therapeutic agent for depression, the kit, the kit for treatment of depression or the method for treating depression of the present invention.

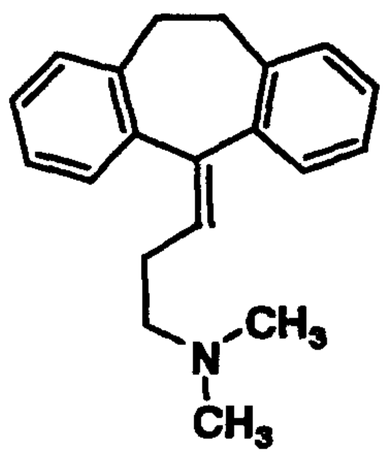
Examples of the tricyclic antidepressant include imipramine, clomipramine, amitriptyline, nortriptyline, amoxapine, trimipramine, lofepramine, dosulepin, protriptyline, doxepin, desipramine, pharmaceutically acceptable salts thereof (examples of the pharmaceutically acceptable salts include the salts illustrated as the pharmaceutically acceptable salts of the above-mentioned Compound (I)) and the like. Those may be in the form of a hydrate or the like. Among them, imipramine hydrochloride, clomipramine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, trimipramine maleate, lofepramine, lofepramine hydrochloride, dosulepin hydrochloride, protriptyline, doxepin or desipramine hydrochloride is preferred.



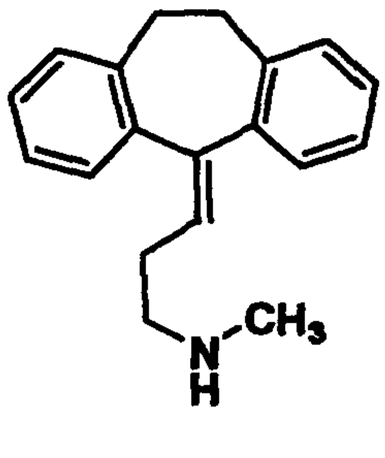
imipramine



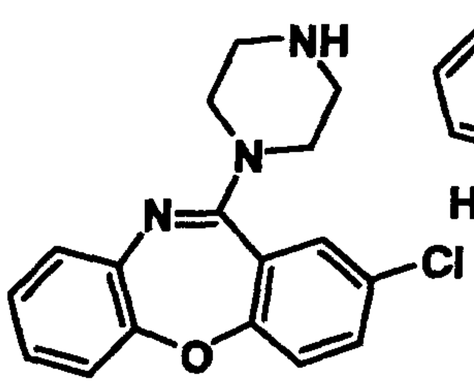
clomipramine



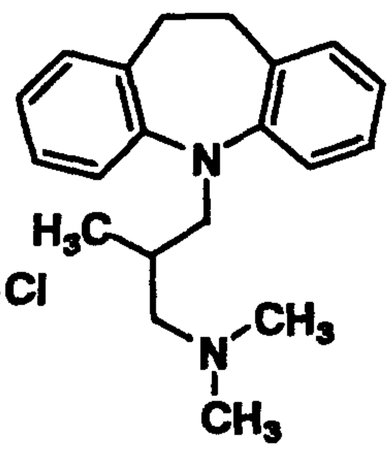
amitriptyline



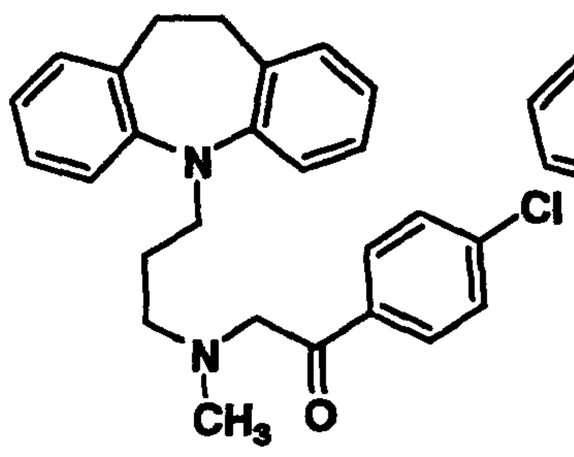
nortriptyline



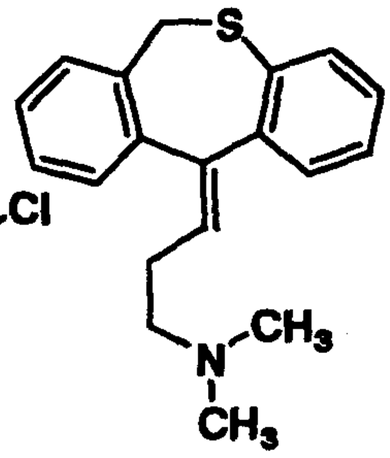
amoxapine



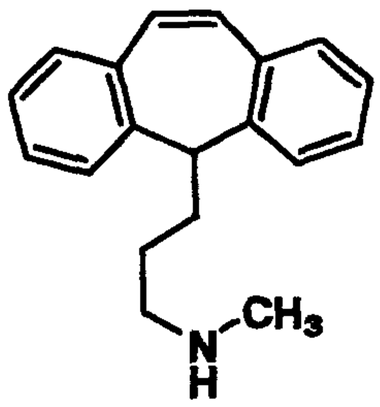
trimipramine



lofepramine

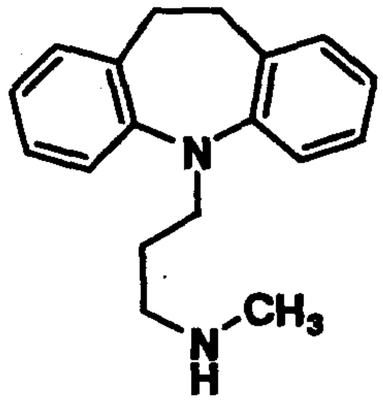


dosulepin



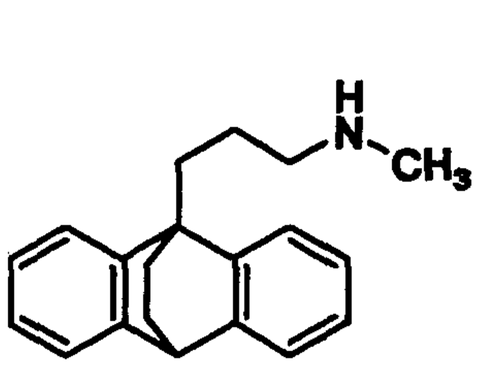
protriptyline

doxepin

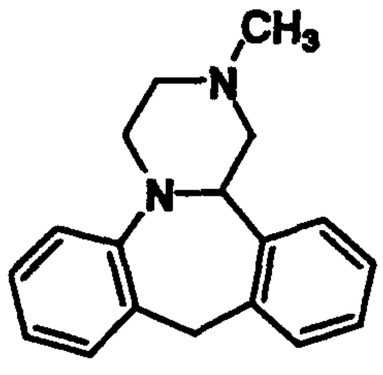


desipramine

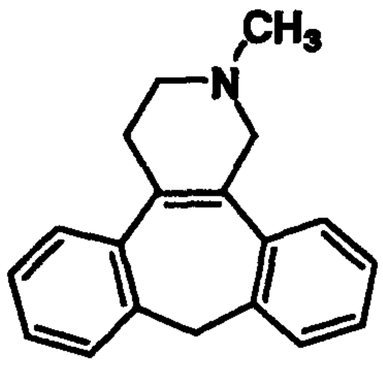
Examples of the tetracyclic antidepressant include maprotiline, mianserin, setiptiline, pharmaceutically acceptable salts thereof (examples of the pharmaceutically acceptable salt include the salts illustrated as the pharmaceutically acceptable salts of the above-mentioned Compound (I)) and the like. Those may be in the form of a hydrate or the like. Among them, maprotiline hydrochloride, mianserin hydrochloride or setiptiline maleate is preferred.



maprotiline

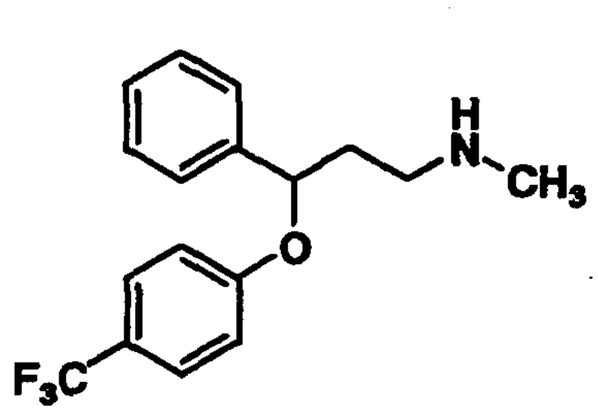


mianserin

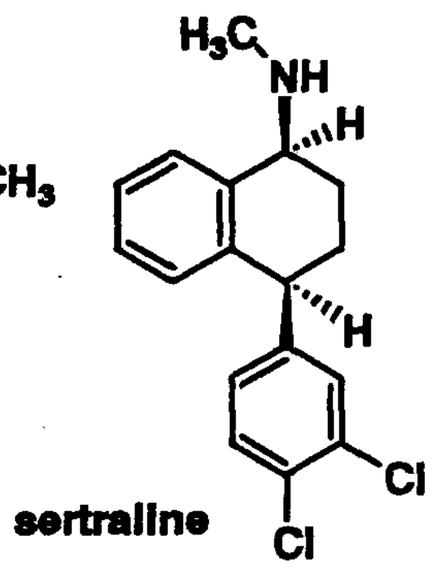


setiptiline

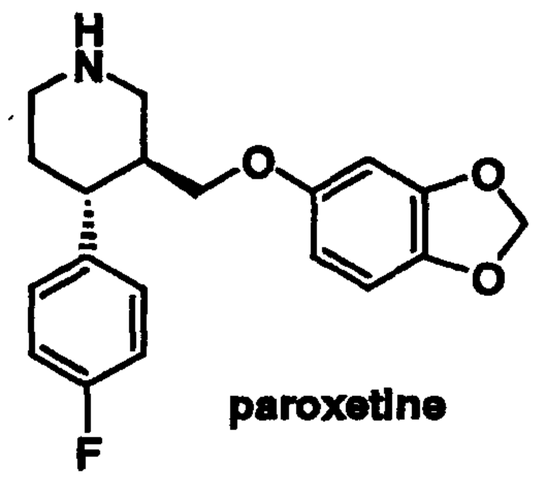
The selective serotonin reuptake inhibitor is not particularly limited, as long as it selectively inhibits reuptake of serotonin, and examples thereof include fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, trazodone, nefazodone, pharmaceutically acceptable salts thereof (examples of the pharmaceutically acceptable salt include the salts illustrated as the pharmaceutically acceptable salts of the above-mentioned Compound (I)) and the like. Those may be in the form of a hydrate or the like. Among them, fluoxetine hydrochloride, sertraline hydrochloride, paroxetine hydrochloride, paroxetine hydrochloride hydrate, citalopram hydrobromide, fluvoxamine maleate, trazodone hydrochloride or nefazodone hydrochloride is preferred.



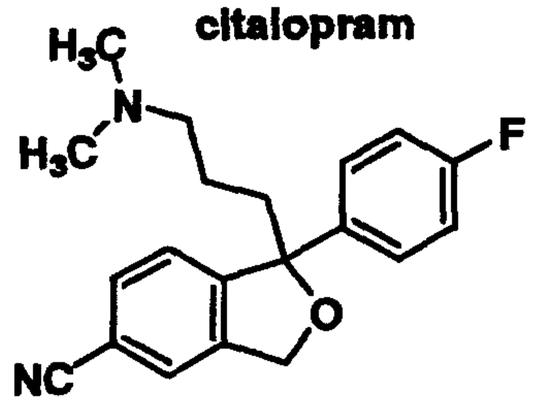
fluoxetine



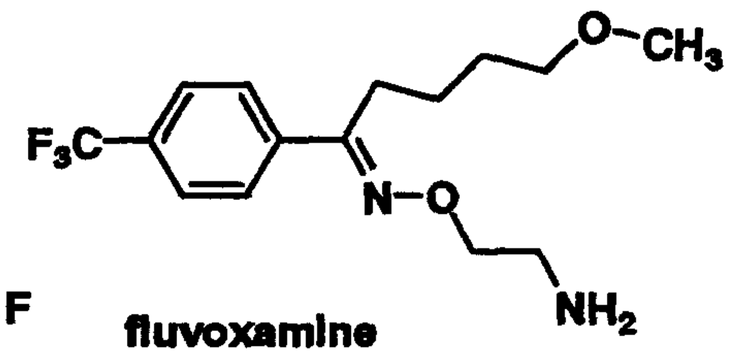
sertraline



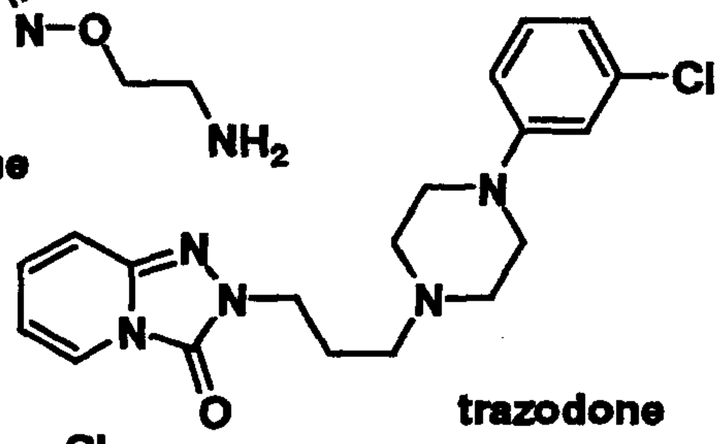
paroxetine



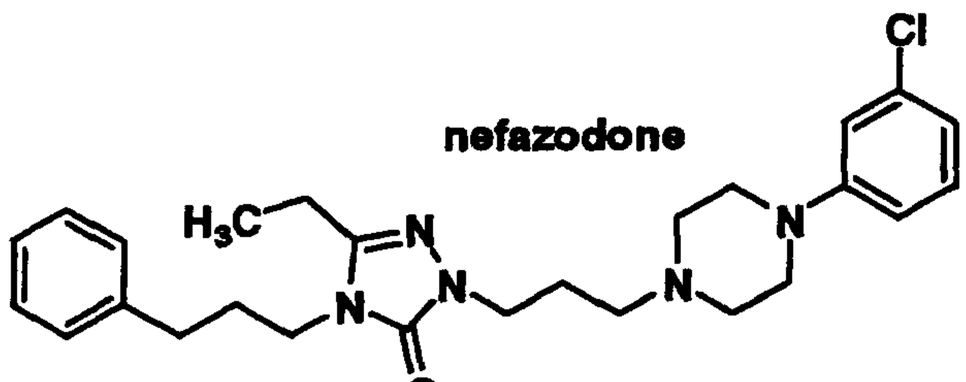
citalopram



fluvoxamine



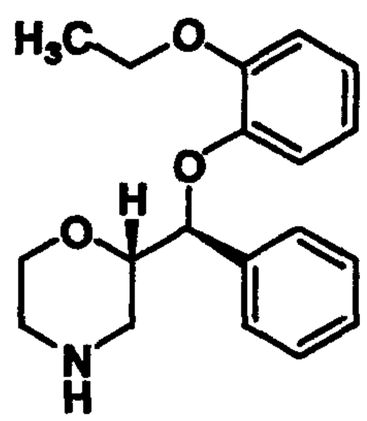
trazodone



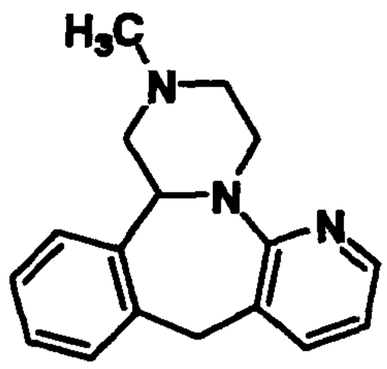
nefazodone



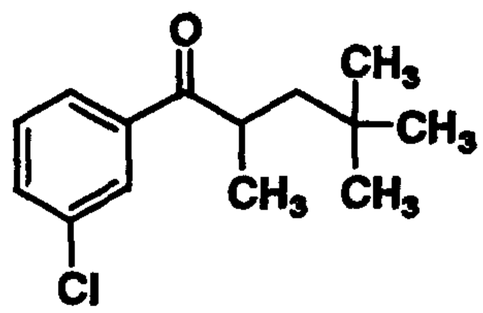
The selective noradrenalin reuptake inhibitor is not particularly limited, as long as it selectively inhibits reuptake of noradrenalin, and examples thereof include reboxetine, mirtazapine, maprotiline, nortriptyline, amoxapine, bupropion, pharmaceutically acceptable salts thereof (examples of the pharmaceutically acceptable salt include the salts illustrated as the pharmaceutically acceptable salts of the above-mentioned Compound (I)) and the like. Those may be in the form of a hydrate or the like. Among them, reboxetine mesylate, mirtazapine, maprotiline hydrochloride, nortriptyline hydrochloride, amoxapine, bupropion or bupropion hydrochloride is preferred.



reboxetine

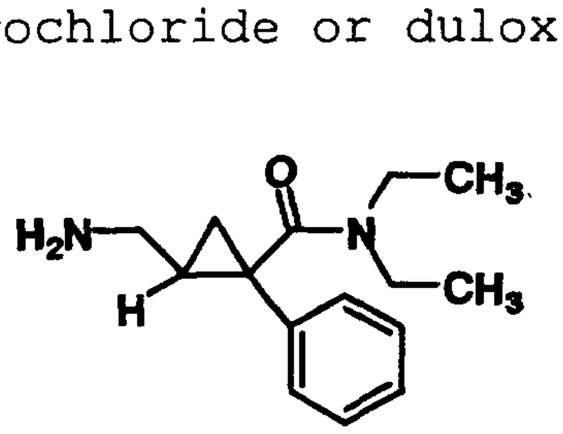


mirtazapine

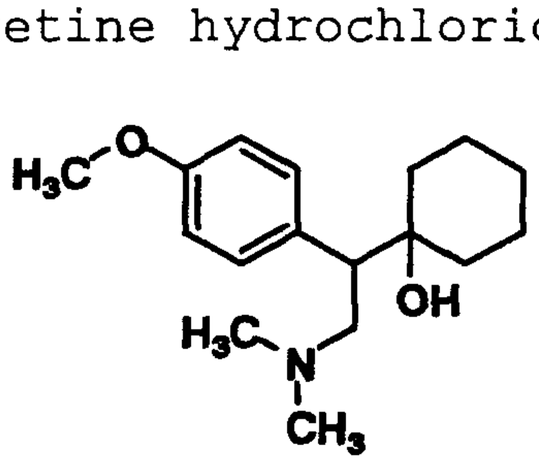


bupropion

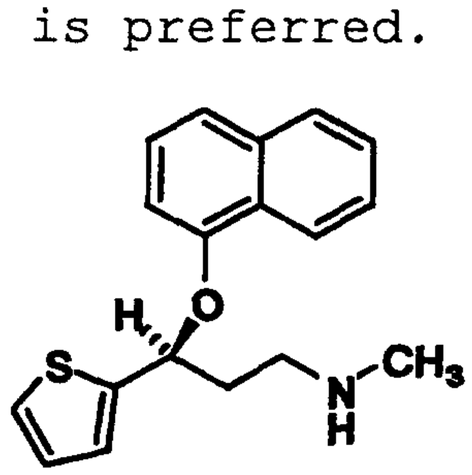
The serotonin-noradrenalin reuptake inhibitor is not particularly limited, as long as it selectively inhibits reuptake of serotonin and noradrenalin, and examples thereof include milnacipran, venlafaxine, duloxetine, pharmaceutically acceptable salts thereof (examples of the pharmaceutically acceptable salt include the salts illustrated as the pharmaceutically acceptable salts of the above-mentioned Compound (I)) and the like. Those may be in the form of a hydrate or the like. Among them, milnacipran hydrochloride, venlafaxine hydrochloride or duloxetine hydrochloride is preferred.



milnacipran



venlafaxine

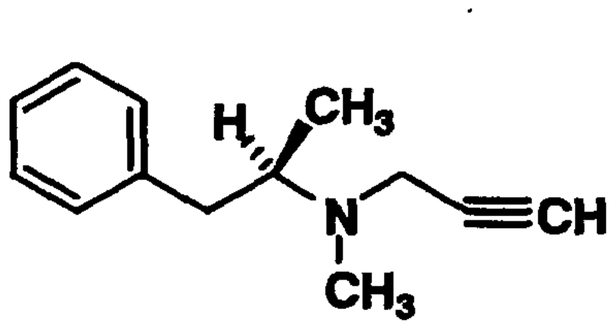


duloxetine

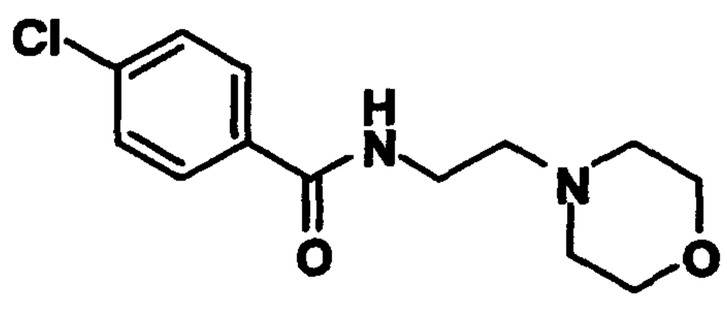
The dopamine reuptake inhibitor is not particularly limited, as long as it inhibits reuptake of dopamine, and examples thereof include venlafaxine, pharmaceutically acceptable salts thereof (examples of the pharmaceutically acceptable salt include the salts illustrated as the pharmaceutically acceptable salts of the above-mentioned Compound (I)) and the like. Those may be in the form of a hydrate or the like. Among them, venlafaxine hydrochloride is preferred.

The MAO inhibitor is not particularly limited, as long as it increases intracerebral amount of a biogenic amine (e.g.,

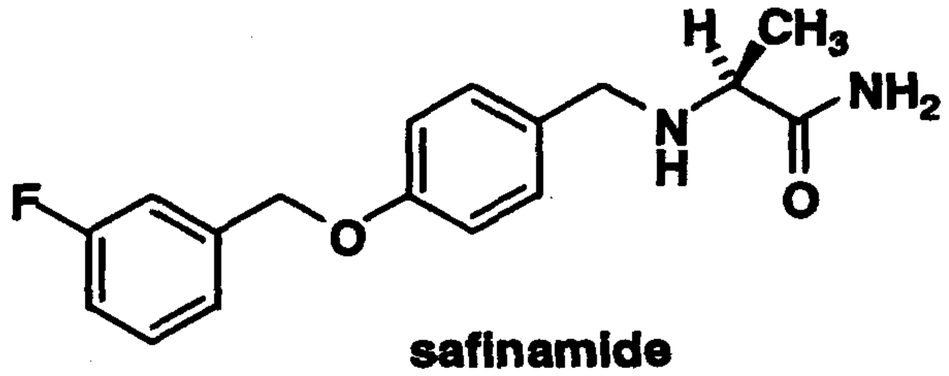
adrenaline, noradrenalin and serotonin) through inhibiting monoamine oxidase, and examples thereof include e.g., selegiline, safinamide, moclobemide, phenelzine, isocarboxazid, tranylcypromine, and pharmaceutically acceptable salts thereof (examples of the pharmaceutically acceptable salt include the salts illustrated as the pharmaceutically acceptable salts of the above-mentioned Compound (I)) and the like. Those may be in the form of a hydrate or the like. Among them, selegiline hydrochloride, safinamide mesylate or moclobemide is preferred.



selegiline



moclobemide



safinamide

Examples of the 5-HT_2 antagonist include mirtazapine, trazodone, nefazodone, and pharmaceutically acceptable salts thereof (examples of the pharmaceutically acceptable salt include the salts illustrated as the pharmaceutically acceptable salts of the above-mentioned Compound (I)) and the like. Those may be in the form of a hydrate or the like. Among them, mirtazapine, trazodone hydrochloride or nefazodone hydrochloride is preferred.

The pharmaceutical composition of the present invention can be used for treatment and/or prevention of, for example, Psychiatric disorders such as depression.

Compound (I) or a pharmaceutically acceptable salt thereof

and an antidepressant drug, which are used in the pharmaceutical composition or the therapeutic agent for depression of the present invention, or the compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and a monoamine oxidase inhibitor, which are used in the therapeutic agent for depression of the present invention, can be used or administered either as a single formulation (combined formulation) or as a combination of several formulations, as long as both of these active ingredients are formulated into formulations, respectively. Among them, combination of two or more formulations is preferred. Preferably, these formulations are used in a dosage form of, for example, a tablet, an injection or the like. In using or administrating as a combination of several formulations, these formulations may be used or administered simultaneously or separately at a time interval.

In using or administrating separately at a time interval, the time interval may be provided according to characteristics of the formulations to be combined (the onset time of the activity, peak of occurrence of the action, and the like). Although the interval, and the order of use or administration are not particularly limited, they may be used or administered, for example, at an interval of 5 minutes to 72 hours, preferably 30 minutes to 30 hours.

Compound (I) or a pharmacologically acceptable salt thereof and the antidepressant drug are combined, in which the combination ratio of the antidepressant drug is, for example, between 0.0001 to 1000wt%, preferably between 0.001 to 500wt%, and more preferably between 0.005 to 300wt% of Compound (I) or a pharmaceutically acceptable salt thereof.

The compound having an adenosine A_{2A} receptor antagonistic

activity or a pharmaceutically acceptable salt thereof and the monoamine oxidase inhibitor are combined, in which the combination ratio of the monoamine oxidase inhibitor, for example, between 0.0001 to 1000wt%, preferably between 0.001 to 500wt%, more preferably between 0.005 to 300wt%, and still more preferably between 0.01 to 200wt% of the compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof.

In administrating as a combination of several formulations, for example, a first component (a) containing Compound (I) or a pharmaceutically acceptable salt thereof and a second component (b) containing the antidepressant drug; or a first component (a) containing the compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and a second component (b) containing the monoamine oxidase inhibitor are independently formulated as described above to make a kit, and then by using this kit, each component can be administered simultaneously or separately at a time interval to the same subject, via the same route or via different routes.

Examples of the kit include those which comprise the content and two or more containers (e.g., vial, bag or the like), which are not particularly limited in material, shape and the like, as long as they do not cause denaturation of the components, which are the contents, due to external temperature or light on storage, elution of chemical ingredients from the container, and the like, and that are in a form to enable to administer the above first component and the second component, which are the contents via separate routes (e.g., tube or the like) or via the same route. Specifically, examples of the kit include the kit in the dosage form of a tablet, an injection and the like.

Furthermore, the method for treating depression of the present invention can be performed in a manner similar to that in the method of using or administering Compound (I) or the compound having an adenosine A_{2A} receptor antagonistic activity, or a pharmaceutically acceptable salt thereof, and the antidepressant drug, which are used in the pharmaceutical composition or the therapeutic agent for depression as described above. More specifically, it can be carried out by independently formulating Compound (I) or the compound having an adenosine A_{2A} receptor antagonistic activity, or a pharmaceutically acceptable salt thereof, and the antidepressant drug, as long as both of these active ingredients is formulated, respectively, and administering, for example, either as a single formulation or as a combination of several formulations, preferably as a combination of two or more formulations. In administrating as a combination of several formulations, these formulations can be administered simultaneously or separately at a time interval, and they can be also administered by using the kit as described above.

Next, therapeutic effects for depression by the combined use of Compound (I) or a pharmaceutically acceptable salt thereof and the antidepressant drug are more specifically explained by Test Examples.

Test Example 1: Forced swimming method in mice

The test was carried out with reference to the method of Porsolt et al., [Arch. Int. Pharmacodyn. Ther., 229, 327-336 (1977)], which is an animal model of depression.

Experiment was conducted using 10 ddY male mice (weighing 20 to 35 g, Nihon SLC Co., Ltd) per one group.

An acrylic transparent cylinder having a diameter of 10

cm and a height of 25 cm was filled with water having a temperature of about 24°C. Height from the bottom of the cylinder to the surface of the water was adjusted to be about 9 cm.

The mice were forced to swim individually for a period of 6 minutes, the total duration of immobility during the last 4 minutes of 6 minutes test was measured (significance test: Dunnett test).

The antidepressant drug and Compound (I) were suspended in distilled water for injection (manufactured by Otsuka Pharmaceutical Co., Ltd.) containing 0.5% MC (methyl cellulose), respectively, for use in the test. Time point of administration of the antidepressant drug was predetermined such that the peak of onset of activity by the antidepressant drug overlaps with the peak of onset of activity by Compound (I). According to the predetermined time, the suspension containing the antidepressant drug was orally administered to a group administered the antidepressant drug alone or a group administered the antidepressant drug and Compound (I) in combination (0.1 mL per 10 g of the mouse body weight). Further, the suspension containing Compound (I) was orally administered to the group administered the antidepressant drug and Compound (I) in combination, 1 hour before the test (0.1 mL per 10 g of the mouse body weight). A solution without containing a test compound [distilled water for injection (manufactured by Otsuka Pharmaceutical Co., Ltd.) containing 0.5% MC] and the suspension containing Compound (I) were orally administered to a solvent control group and to a group administered Compound (I) alone, 1 hour before the test, respectively (0.1 mL per 10 g of the mouse body weight).

Effect obtained by combining Compound (I) and the antidepressant drug was evaluated according to the following

index.

The duration of Immobility in the solvent control group was assumed to be 100%, and each rate of change (%) of the duration of immobility in the above administration group to the duration of immobility in the solvent control group was calculated, and was compared. The duration of immobility in each administration group, and the rate of change (%) of the duration of immobility are shown in Table 1.

Table 1

	Duration of immobility (sec)	
Test compound (dose: mg/kg)	Mean value ± Standard error	Rate of change of duration of immobility to solvent control group (%)
Solvent control group	196.5 ± 12.0	-
Compound (I) (0.08)	155.6 ± 13.3*	-21
Venlafaxine hydrochloride (5.00)	173.1 ± 20.7*	-12
Compound (I) (0.08) + Venlafaxine hydrochloride (5.00)	118.2 ± 17.4**	-40

*: Not Significant, **: $p < 0.01$

Test Example 2: Mouse tail suspension method

The test was carried out with reference to the method of Steru et al., [Psychopharmacol., 85, 367-370 (1985)], which is an animal model of depression.

Experiment was conducted using 10 ICR male mice (weighing 20 to 35 g, Nihon SLC Co., Ltd) per one group.

An acrylic or metallic bar was fixed horizontally such that

height of about 60 cm from the floor face is provided.

The mouse was suspended at a site of about 2 cm from the tip of the tail, from the bar for a period of 6 minutes. Duration of immobility during the last 4 minutes of 6 minutes test was measured (significance test: Student's t test). For fixing the mouse, an adhesive tape was used.

The antidepressant drug and Compound (I) were suspended in distilled water for injection (manufactured by Otsuka Pharmaceutical Co., Ltd.) containing 0.5% MC (methyl cellulose), respectively, for use in the test. Time point of administration of the antidepressant drug was predetermined such that the peak of onset of activity by the antidepressant drug overlaps with the peak of onset of activity by Compound (I). According to the predetermined time, the suspension containing the antidepressant drug was orally administered to a group administered the antidepressant drug alone or a group administered the antidepressant drug and Compound (I) in combination (0.1 mL per 10 g of the mouse body weight). Further, the suspension containing Compound (I) was orally administered to the group administered the antidepressant drug and Compound (I) in combination, 1 hour before the test (0.1 mL per 10 g of the mouse body weight). A solution without containing a test compound [distilled water for injection (manufactured by Otsuka Pharmaceutical Co., Ltd.) containing 0.5% MC] and the suspension containing Compound (I) were orally administered to a solvent control group and to a group administered Compound (I) alone, 1 hour before the test, respectively (0.1 mL per 10 g of the mouse body weight).

Effect obtained by combining Compound (I) and the antidepressant drug was evaluated according to the following index.

The duration of Immobility in the solvent control group was assumed to be 100%, and each rate of change (%) of the duration of immobility in the above administration group to the duration of immobility in the solvent control group was calculated, and was compared. The duration of immobility in each administration group, and the rate of change (%) of the duration of immobility are shown in Table 2 and Table 3.

Table 2

	Duration of immobility (sec)	
Test compound (dose: mg/kg)	Mean value ± Standard error	Rate of change of duration of immobility to solvent control group (%)
Solvent control group	81.3 ± 13.1	-
Compound (I) (0.04)	70.1 ± 19.1 *	-14
Paroxetine hydrochloride hydrate (2.50)	79.6 ± 16.6 *	-2
Compound (I) (0.04) + Paroxetine hydrochloride hydrate (2.50)	31.7 ± 9.6**	-61

*: Not Significant, **: $p < 0.01$

Table 3

	Duration of immobility (sec)	
Test compound (dose: mg/kg)	Mean value ± Standard error	Rate of change of duration of immobility to solvent control group (%)
Solvent control group	102.2 ± 9.1	-
Compound (I) (0.04)	87.9 ± 14.9 *	-26
Fluoxetine hydrochloride (10.00)	85.7 ± 18.9 *	-16
Compound (I) (0.04) + Fluoxetine hydrochloride (10.00)	40.5 ± 14.3**	-60

*: Not Significant, **: $p < 0.01$

From the results in Test Examples 1 and 2, it was found that the duration of immobility decrease drastically by administering Compound (I) and an antidepressant drug in combination, in comparison with administering an antidepressant drug or Compound (I) alone. In other words, it is believed that the use of Compound (I) or a pharmaceutically acceptable salt thereof and an antidepressant drug in combination enables more effective treatment of depression.

As described hereinabove, the pharmaceutical composition of the present invention can be used, administered or produced as a single formulation or as a combination of several formulations, as long as active ingredients, which is Compound (I) or a pharmaceutically acceptable salt thereof and an antidepressant drug, or a compound having an adenosine A_{2A} receptor antagonistic action or a pharmaceutically acceptable salt thereof and a monoamine oxidase inhibitor, are formulated into formulations,

respectively. It is desired that these pharmaceutical compositions are in a single dosage form which is suited for oral administration or parenteral administration such as injection or the like. Moreover, in using or administrating as a combination of several formulations, these formulations can be used or administrated simultaneously or separately at a time interval.

These formulations can be produced by a common method using pharmaceutically acceptable diluent, excipient, disintegrant, lubricant, binder, surfactant, water, physiological saline, vegetable oil solubilizer, isotonizing agent, preservative, anti-oxidizing agent and the like in addition to the active ingredient, respectively.

Upon preparation of a tablet, for example, an excipient such as lactose, a disintegrant such as starch, a lubricant such as magnesium stearate, a binder such as hydroxypropyl cellulose, a surfactant such as a fatty acid ester, a plasticizer such as glycerin, and the like may be used according to a common method.

Upon preparation of an injection, water, physiological saline, vegetable oil, a solvent, a solubilizer, an isotonizing agent, a preservative, an anti-oxidizing agent and the like may be used according to a common method.

When Compound (I) or a pharmaceutically acceptable salt thereof and an antidepressant drug, or a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and a monoamine oxidase inhibitor are used or administered as a combination of several formulations, respectively, with the object described above, it is preferred that Compound (I) or a pharmaceutically acceptable salt thereof and the antidepressant drug, or the compound having an adenosine A_{2A} receptor antagonistic action or a pharmaceutically acceptable

salt thereof and the monoamine oxidase inhibitor are usually administered in the following dose per day, although each dose and frequency of administration may vary depending on the dosage form, age, weight and symptoms of the patient, and the like.

When administered orally, for example, as a tablet, the Compound (I) or a pharmaceutically acceptable salt thereof and the antidepressant drug, or the compound having an adenosine A_{2A} receptor antagonistic action or a pharmaceutically acceptable salt thereof and the monoamine oxidase inhibitor are usually administered simultaneously or separately at a time interval, in an amount of 0.0001 to 50 mg/kg and 0.001 to 1000 mg/kg, preferably 0.001 to 30 mg/kg and 0.005 to 100 mg/kg, and more preferably 0.005 to 20 mg/kg and 0.01 to 50 mg/kg per day, respectively, once or in several times.

When administered parenterally, for example, as an injection, Compound (I) or a pharmaceutically acceptable salt thereof and the antidepressant drug, or the compound having an adenosine A_{2A} receptor antagonistic action or a pharmaceutically acceptable salt thereof and the monoamine oxidase inhibitor are usually administered simultaneously or separately with a time interval, in an amount of 0.0001 to 50 mg/kg and 0.0005 to 500 mg/kg, preferably 0.0005 to 20 mg/kg and 0.005 to 100 mg/kg, and more preferably 0.001 to 15 mg/kg and 0.03 to 30 mg/kg per day, respectively, once or in several times.

Furthermore, when Compound (I) or a pharmaceutically acceptable salt thereof and an antidepressant drug, or a compound having an adenosine A_{2A} receptor antagonistic action or a pharmaceutically acceptable salt thereof and a monoamine oxidase inhibitor are used or administered as a single formulation with the object described above, it is preferred that preparation is

conducted as a single formulation to give each dose as in the case of use or administration as a combination of multiple formulations described above, followed by use or administration, although each dose and frequency of administration may vary depending on the dosage form, age, weight and symptoms of the patient, and the like.

Mode of the present invention is explained below by way of Examples, however, scope of the invention is not limited by these Examples.

Best Mode for Carrying Out the Invention

Example 1: Tablet (Compound (I))

According to a conventional method, tablets having the following composition are prepared. Compound (I) in an amount of 40 g, 286.8 g of lactose and 60 g of potato starch are mixed, and thereto is added 120 g of a 10% aqueous solution of hydroxypropyl cellulose. After blending, granulating and drying this mixture according to a conventional method, whole grains are prepared to give grains for tabletting. Thereto is added 1.2 g of magnesium stearate followed by mixing. Tabletting is carried out with a tabletting machine having a pestle with a diameter of 8 mm (manufactured by KIKUSUI SEISAKUSHO LTD., type RT-15) to obtain tablets (containing 20 mg of Compound (I) per tablet).

Prescription

Compound (I)	20 mg
Lactose	143.4mg
Potato starch	30 mg
Hydroxypropyl cellulose	6 mg
Magnesium stearate	0.6mg
	200 mg

Example 2: Tablet (Imipramine hydrochloride)

According to a conventional method, tablets having the following composition are prepared. Imipramine hydrochloride in an amount of 50 g, 276.8 g of lactose and 60 g of potato starch are mixed, and thereto is added 120 g of a 10% aqueous solution of hydroxypropyl cellulose. After blending, granulating and drying this mixture according to a conventional method, whole grains are prepared to give grains for tabletting. Thereto is added 1.2 g of magnesium stearate followed by mixing. Tabletting is carried out with a tabletting machine having a pestle with a diameter of 8 mm (manufactured by KIKUSUI SEISAKUSHO LTD., type RT-15) to obtain tablets (containing 25 mg of imipramine hydrochloride per tablet).

Prescription

Imipramine hydrochloride	25 mg
Lactose	138.4mg
Potato starch	30 mg
Hydroxypropyl cellulose	6 mg
Magnesium stearate	0.6mg
	200 mg

Example 3: Tablet (Compound (I) and Selegiline hydrochloride)

According to a conventional method, tablets having the following composition are prepared. Compound (I) in an amount of 20 g, 5 g of selegiline hydrochloride, 300.8 g of lactose and 61 g of potato starch are mixed, and thereto is added 120 g of a 10% aqueous solution of hydroxypropyl cellulose. After blending, granulating and drying this mixture according to a conventional method, whole grains are prepared to give grains for tabletting. Thereto is added 1.2 g of magnesium stearate followed by mixing. Tabletting is carried out with a tabletting

machine having a pestle with a diameter of 8 mm (manufactured by KIKUSUI SEISAKUSHO LTD., type RT-15) to obtain tablets (containing 10 mg of Compound (I) and 2.5 mg of selegiline hydrochloride per tablet).

Prescription

Compound (I)	10 mg
Selegiline hydrochloride	2.5mg
Lactose	150.4mg
Potato starch	30.5mg
Hydroxypropyl cellulose	6 mg
Magnesium stearate	0.6mg
	200 mg

Example 4: Tablet (Compound (I) and Mianserin hydrochloride)

According to a conventional method, tablets having the following composition are prepared. Compound (I) in an amount of 20 g, 20 g of mianserin hydrochloride, 285.8 g of lactose and 61 g of potato starch are mixed, and thereto is added 120 g of a 10% aqueous solution of hydroxypropyl cellulose. After blending, granulating and drying this mixture according to a conventional method, whole grains are prepared to give grains for tabletting. Thereto is added 1.2 g of magnesium stearate followed by mixing. Tabletting is carried out with a tabletting machine having a pestle with a diameter of 8 mm (manufactured by KIKUSUI SEISAKUSHO LTD., type RT-15) to obtain tablets (containing 10 mg of Compound (I) and 10 mg of mianserin hydrochloride per tablet).

Prescription

Compound (I)	10 mg
Mianserin hydrochloride	10 mg
Lactose	142.9mg
Potato starch	30.5mg
Hydroxypropyl cellulose	6 mg
Magnesium stearate	0.6mg
	200 mg

Example 5: Tablet (Compound (I))

According to a conventional method, tablets having the following composition are prepared. Compound (I) in an amount of 10 g, 143.4 g of lactose and 40 g of potato starch are mixed, and thereto is added 60 g of a 10% aqueous solution of hydroxypropyl cellulose. After blending, granulating and drying this mixture according to a conventional method, whole grains are prepared to give grains for tabletting. Thereto is added 0.6 g of magnesium stearate followed by mixing. Tabletting is carried out with a tabletting machine having a pestle with a diameter of 8 mm (manufactured by KIKUSUI SEISAKUSHO LTD., type RT-15) to obtain tablets (containing 5 mg of Compound (I) per tablet).

Prescription

Compound (I)	5 mg
Lactose	71.7mg
Potato starch	20 mg
Hydroxypropyl cellulose	3 mg
Magnesium stearate	0.3mg
	100 mg

Example 6: Tablet (Fluoxetine hydrochloride)

According to a conventional method, tablets having the following composition are prepared. Fluoxetine hydrochloride

in an amount of 40 g, 286.8 g of lactose and 60 g of potato starch are mixed, and thereto is added 120 g of a 10% aqueous solution of hydroxypropyl cellulose. After blending, granulating and drying this mixture according to a conventional method, whole grains are prepared to give grains for tabletting. Thereto is added 1.2 g of magnesium stearate followed by mixing. Tabletting is carried out with a tabletting machine having a pestle with a diameter of 8 mm (manufactured by KIKUSUI SEISAKUSHO LTD., type RT-15) to obtain tablets (containing 20 mg of fluoxetine hydrochloride per tablet).

Prescription

Fluoxetine hydrochloride	20 mg
Lactose	143.4mg
Potato starch	30 mg
Hydroxypropyl cellulose	6 mg
Magnesium stearate	0.6mg
	200 mg

Example 7: Tablet (Compound (I) and Paroxetine hydrochloride hydrate)

According to a conventional method, tablets having the following composition are prepared. Compound (I) in an amount of 10 g, 40 g of paroxetine hydrochloride hydrate, 275.8 g of lactose and 61 g of potato starch are mixed, and thereto is added 120 g of a 10% aqueous solution of hydroxypropyl cellulose. After blending, granulating and drying this mixture according to a conventional method, whole grains are prepared to give grains for tabletting. Thereto is added 1.2 g of magnesium stearate followed by mixing. Tabletting is carried out with a tabletting machine having a pestle with a diameter of 8 mm (manufactured by KIKUSUI SEISAKUSHO LTD., type RT-15) to obtain tablets

(containing 5 mg of Compound (I) and 20 mg of paroxetine hydrochloride hydrate per tablet).

Prescription

Compound (I)	5 mg
Paroxetine hydrochloride hydrate	20 mg
Lactose	137.9mg
Potato starch	30.5mg
Hydroxypropyl cellulose	6 mg
Magnesium stearate	0.6mg
	200 mg

Example 8: Tablet (Venlafaxine hydrochloride)

According to a conventional method, tablets having the following composition are prepared. Venlafaxine hydrochloride in an amount of 100 g, 248.8 g of lactose and 40 g of potato starch are mixed, and thereto is added 100 g of a 10% aqueous solution of hydroxypropyl cellulose. After blending, granulating and drying this mixture according to a conventional method, whole grains are prepared to give grains for tabletting. Thereto is added 1.2 g of magnesium stearate followed by mixing. Tabletting is carried out with a tabletting machine having a pestle with a diameter of 8 mm (manufactured by KIKUSUI SEISAKUSHO LTD., type RT-15) to obtain tablets (containing 50 mg of venlafaxine hydrochloride per tablet).

Prescription

Venlafaxine hydrochloride	50 mg
Lactose	124.4mg
Potato starch	20 mg
Hydroxypropyl cellulose	5 mg
Magnesium stearate	0.6mg
	200 mg

Example 9: Tablet (Compound (I) and Milnacipran hydrochloride)

According to a conventional method, tablets having the following composition are prepared. Compound (I) in an amount of 10 g, 30 g of milnacipran hydrochloride, 285.8 g of lactose and 61 g of potato starch are mixed, and thereto is added 120 g of a 10% aqueous solution of hydroxypropyl cellulose. After blending, granulating and drying this mixture according to a conventional method, whole grains are prepared to give grains for tabletting. Thereto is added 1.2 g of magnesium stearate followed by mixing. Tabletting is carried out with a tabletting machine having a pestle with a diameter of 8 mm (manufactured by KIKUSUI SEISAKUSHO LTD., type RT-15) to obtain tablets (containing 5 mg of Compound (I) and 15 mg of milnacipran hydrochloride per tablet).

Prescription

Compound (I)	5 mg
Milnacipran hydrochloride	15 mg
Lactose	142.9mg
Potato starch	30.5mg
Hydroxypropyl cellulose	6 mg
Magnesium stearate	0.6mg
	200 mg

Example 10: Injection (Compound (I))

According to a conventional method, injections having the following composition are prepared. Compound (I) in an amount of 0.5 g is dissolved in 100 g of purified soybean oil, and thereto are added 12 g of purified yolk lecithin and 25 g of glycerin for injection. This mixture is adjusted to give 1000 mL with distilled water for injection followed by blending · emulsification according to a conventional method. Thus

resulting dispersion liquid is subjected to aseptic filtration using a 0.2 μm disposable type membrane filter. Thereafter, each 2 mL of the liquid is aseptically filled in a glass vial to obtain injections (containing 1 mg of Compound (I) per vial).

Prescription

Compound (I)	1	mg
Purified soybean oil	200	mg
Purified yolk lecithin	24	mg
Glycerin for injection	50	mg
Distilled water for injection	1.72	mL
	2.00	mL

Example 11: Injection (Bupropion)

According to a conventional method, injections having the following composition are prepared. Bupropion in an amount of 5 g is dissolved in 100 g of purified soybean oil, and thereto are added 12 g of purified yolk lecithin and 25 g of glycerin for injection. This mixture is adjusted to give 1000 mL with distilled water for injection followed by blending · emulsification according to a conventional method. Thus resulting dispersion liquid is subjected to aseptic filtration using a 0.2 μm disposable type membrane filter. Thereafter, each 2 mL of the liquid is aseptically filled in a glass vial to obtain injections (containing 10 mg of bupropion per vial).

Prescription

Bupropion	10	mg
Purified soybean oil	200	mg
Purified yolk lecithin	24	mg
Glycerin for injection	50	mg
Distilled water for injection	1.72	mL
	2.00	mL

Example 12: Injection (Compound (I) and Clomipramine hydrochloride)

According to a conventional method, injections having the following composition are prepared. Compound (I) in an amount of 1 g and 12.5 g of clomipramine hydrochloride are dissolved in 100 g of purified soybean oil, and thereto are added 12 g of purified yolk lecithin and 25 g of glycerin for injection. This mixture is adjusted to give 1000 mL with distilled water for injection followed by blending · emulsification according to a conventional method. Thus resulting dispersion liquid is subjected to aseptic filtration using a 0.2 μm disposable type membrane filter. Thereafter, each 2 mL of the liquid is aseptically filled in a glass vial to obtain injections (containing 2 mg of Compound (I) and 25 mg of clomipramine hydrochloride per vial).

Prescription

Compound (I)	2	mg
Clomipramine hydrochloride	25	mg
Purified soybean oil	200	mg
Purified yolk lecithin	24	mg
Glycerin for injection	50	mg
Distilled water for injection	1.62	mL
	2.00	mL

Example 13: Tablet (Nefazodone hydrochloride)

According to a conventional method, tablets having the following composition are prepared. Nefazodone hydrochloride in an amount of 100 g, 248.8 g of lactose and 40 g of potato starch are mixed, and thereto is added 100 g of a 10% aqueous solution of hydroxypropyl cellulose. After blending, granulating and drying this mixture according to a conventional method, whole

grains are prepared to give grains for tabletting. Thereto is added 1.2 g of magnesium stearate followed by mixing. Tabletting is carried out with a tabletting machine having a pestle with a diameter of 8 mm (manufactured by KIKUSUI SEISAKUSHO LTD., type RT-15) to obtain tablets (containing 50 mg of nefazodone hydrochloride per tablet).

Prescription

Nefazodone hydrochloride	50 mg
Lactose	124.4mg
Potato starch	20 mg
Hydroxypropyl cellulose	5 mg
Magnesium stearate	0.6mg
	200 mg

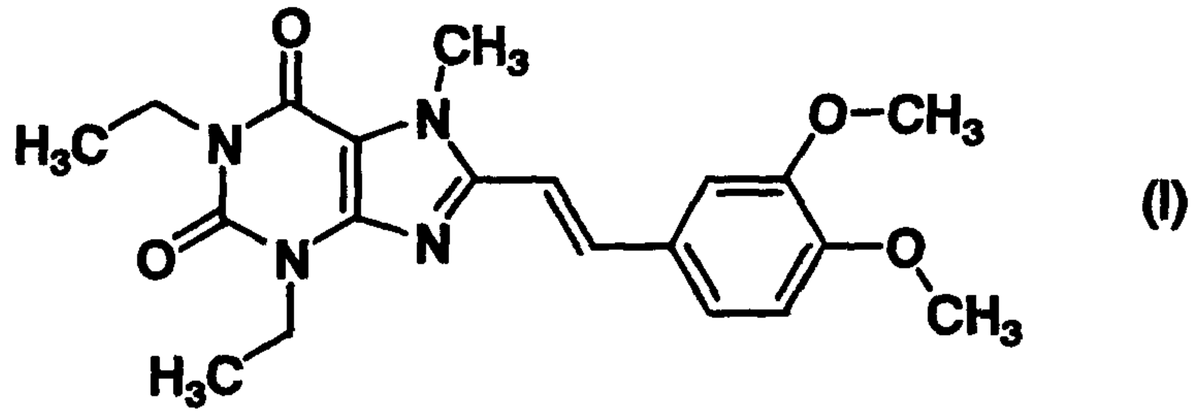
Industrial Applicability

The present invention provide pharmaceutical compositions which comprises (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione or a pharmaceutically acceptable salt thereof and an antidepressant drug, and the like.

Claims

1. A pharmaceutical composition which comprises

(a) (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):

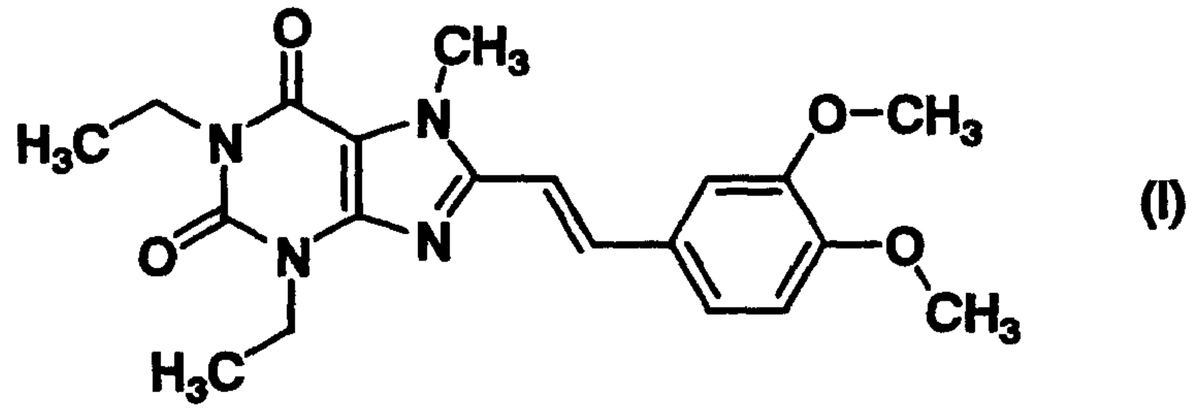


(I)

or a pharmaceutically acceptable salt thereof, and

(b) an antidepressant drug.

2. A pharmaceutical composition which comprises (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof for administering simultaneously or separately at a time interval in combination with an antidepressant drug.

3. The pharmaceutical composition according to claim 1 or 2, wherein the antidepressant drug is a tricyclic antidepressant, a tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a selective noradrenalin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin-noradrenalin reuptake inhibitor, a monoamine oxidase inhibitor or a serotonin 2 ($5\text{-}HT_2$) antagonist.

4. The pharmaceutical composition according to claim

1 or 2, wherein the antidepressant drug is a tricyclic antidepressant.

5. The pharmaceutical composition according to claim 4, wherein the tricyclic antidepressant is imipramine hydrochloride, clomipramine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, trimipramine maleate, lofepramine, lofepramine hydrochloride, dosulepin hydrochloride, protriptyline, doxepin or desipramine hydrochloride.

6. The pharmaceutical composition according to claim 1 or 2, wherein the antidepressant drug is a tetracyclic antidepressant.

7. The pharmaceutical composition according to claim 6, wherein the tetracyclic antidepressant is maprotiline hydrochloride, mianserin hydrochloride or setiptiline maleate.

8. The pharmaceutical composition according to claim 1 or 2, wherein the antidepressant drug is a selective serotonin reuptake inhibitor.

9. The pharmaceutical composition according to claim 8, wherein the selective serotonin reuptake inhibitor is fluoxetine hydrochloride, sertraline hydrochloride, paroxetine hydrochloride, paroxetine hydrochloride hydrate, citalopram hydrobromide, fluvoxamine maleate, trazodone hydrochloride or nefazodone hydrochloride.

10. The pharmaceutical composition according to claim 1 or 2, wherein the antidepressant drug is a selective noradrenalin reuptake inhibitor.

11. The pharmaceutical composition according to claim 10, wherein the selective noradrenalin reuptake inhibitor is reboxetine mesylate, mirtazapine, maprotiline hydrochloride,

nortriptyline hydrochloride, amoxapine, bupropion or bupropion hydrochloride.

12. The pharmaceutical composition according to claim 1 or 2, wherein the antidepressant drug is a serotonin-noradrenalin reuptake inhibitor.

13. The pharmaceutical composition according to claim 12, wherein the serotonin-noradrenalin reuptake inhibitor is milnacipran hydrochloride, venlafaxine hydrochloride or duloxetine hydrochloride.

14. The pharmaceutical composition according to claim 1 or 2, wherein the antidepressant drug is a dopamine reuptake inhibitor.

15. The pharmaceutical composition according to claim 14, wherein the dopamine reuptake inhibitor is venlafaxine hydrochloride.

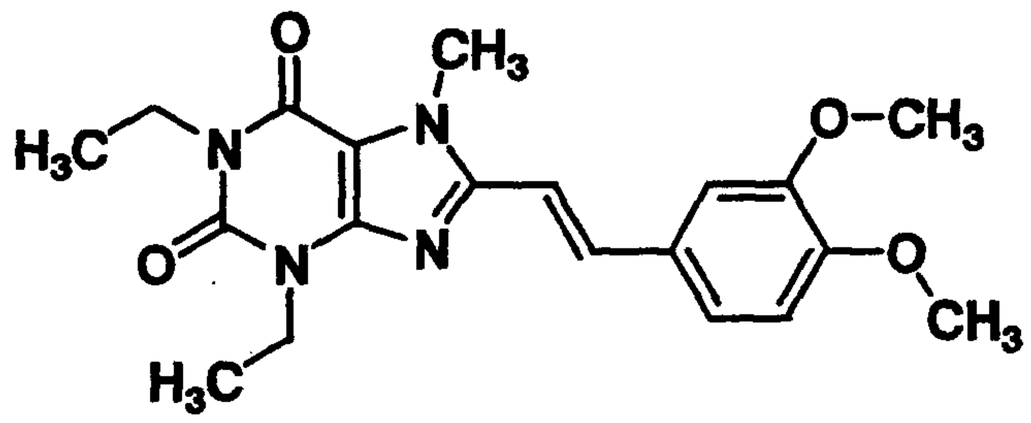
16. The pharmaceutical composition according to claim 1 or 2, wherein the antidepressant drug is a monoamine oxidase inhibitor.

17. The pharmaceutical composition according to claim 16, wherein the monoamine oxidase inhibitor is selegiline hydrochloride, safinamide mesylate or moclobemide.

18. The pharmaceutical composition according to t claim 1 or 2, wherein the antidepressant drug is a $5\text{-}HT_2$ antagonist.

19. The pharmaceutical composition according to claim 18, wherein the $5\text{-}HT_2$ antagonist is mirtazapine, trazodone hydrochloride or nefazodone hydrochloride.

20. A therapeutic agent for depression which comprises (a) (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof and

(b) an antidepressant drug

for administering simultaneously or separately at a time interval.

21. The therapeutic agent for depression according claim 20, wherein the antidepressant drug is a tricyclic antidepressant, a tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a selective noradrenalin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin-noradrenalin reuptake inhibitor, a monoamine oxidase inhibitor or a 5-HT_2 antagonist.

22. The therapeutic agent for depression according to claim 20, wherein the antidepressant drug is a tricyclic antidepressant.

23. The therapeutic agent for depression according to claim 22, wherein the tricyclic antidepressant is imipramine hydrochloride, clomipramine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, trimipramine maleate, lofepramine, lofepramine hydrochloride, dosulepin hydrochloride, protriptyline, doxepin or desipramine hydrochloride.

24. The therapeutic agent for depression according to claim 20, wherein the antidepressant drug is a tetracyclic antidepressant.

25. The therapeutic agent for depression according to claim 24, wherein the tetracyclic antidepressant is maprotiline hydrochloride, mianserin hydrochloride or setiptiline maleate.

26. The therapeutic agent for depression according to claim 20, wherein the antidepressant drug is a selective serotonin reuptake inhibitor.

27. The therapeutic agent for depression according to claim 26, wherein the selective serotonin reuptake inhibitor is fluoxetine hydrochloride, sertraline hydrochloride, paroxetine hydrochloride, paroxetine hydrochloride hydrate, citalopram hydrobromide, fluvoxamine maleate, trazodone hydrochloride or nefazodone hydrochloride.

28. The therapeutic agent for depression according to claim 20, wherein the antidepressant drug is a selective noradrenalin reuptake inhibitor.

29. The therapeutic agent for depression according to claim 28, wherein the selective noradrenalin reuptake inhibitor is reboxetine mesylate, mirtazapine, maprotiline hydrochloride, nortriptyline hydrochloride, amoxapine, bupropion or bupropion hydrochloride.

30. The therapeutic agent for depression according to claim 20, wherein the antidepressant drug is a serotonin-noradrenalin reuptake inhibitor.

31. The therapeutic agent for depression according to claim 30, wherein the serotonin-noradrenalin reuptake inhibitor is milnacipran hydrochloride, venlafaxine hydrochloride or duloxetine hydrochloride.

32. The therapeutic agent for depression according to claim 20, wherein the antidepressant drug is a dopamine reuptake inhibitor.

33. The therapeutic agent for depression according to claim 32, wherein the dopamine reuptake inhibitor is venlafaxine hydrochloride.

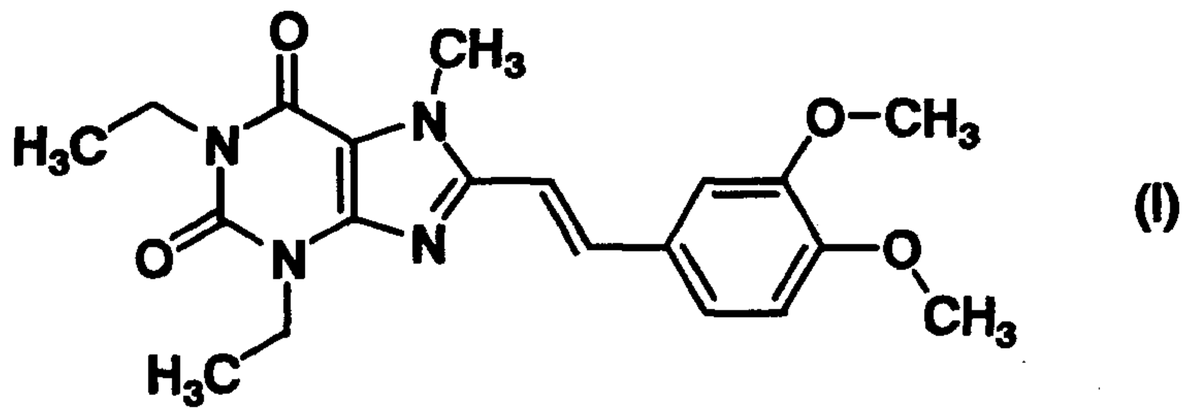
34. The therapeutic agent for depression according to claim 20, wherein the antidepressant drug is a monoamine oxidase inhibitor.

35. The therapeutic agent for depression according to claim 34, wherein the monoamine oxidase inhibitor is selegiline hydrochloride, safinamide mesylate or moclobemide.

36. The therapeutic agent for depression according to claim 20, wherein the antidepressant drug is a 5-HT_2 antagonist.

38. The therapeutic agent for depression according to claim 36, wherein the 5-HT_2 antagonist is mirtazapine, trazodone hydrochloride or nefazodone hydrochloride.

38. (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):

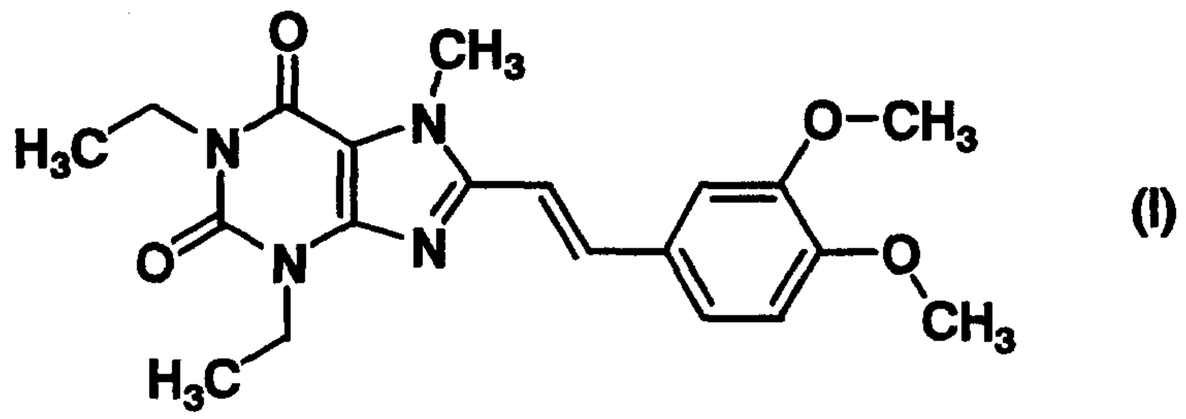


(I)

or a pharmaceutically acceptable salt thereof

for administering simultaneously or separately at a time interval in combination with an antidepressant drug.

39. A kit which comprises (a) a first component comprising (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



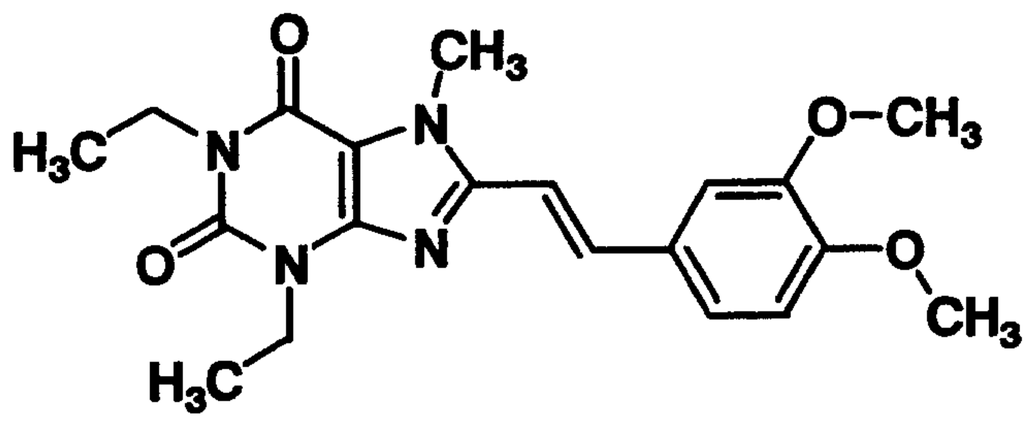
(I)

or a pharmaceutically acceptable salt thereof and

(b) a second component comprising an antidepressant drug.

40. A kit for treatment of depression which comprises

(a) a first component comprising (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



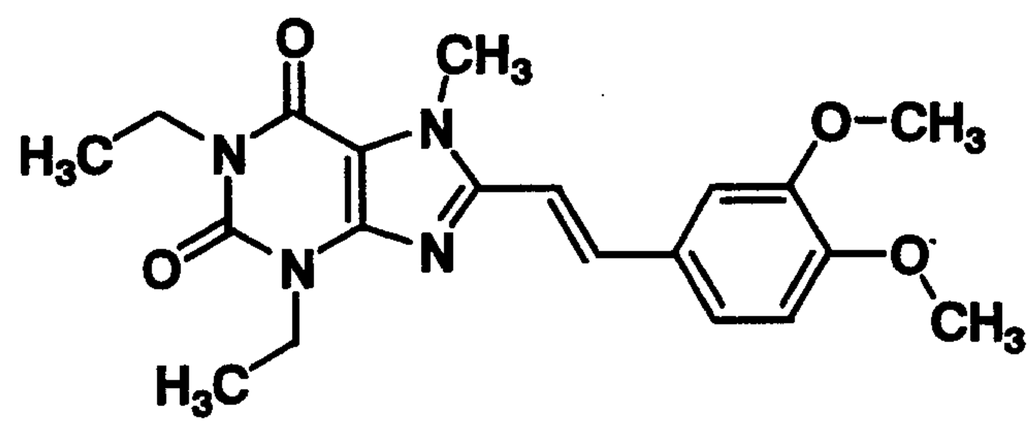
(I)

or a pharmaceutically acceptable salt thereof and

(b) a second component comprising an antidepressant drug.

41. A method for treating depression, which comprises administering

(a) (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof and

(b) an antidepressant drug

simultaneously or separately at a time interval.

42. A pharmaceutical composition which comprises

(a) a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and

(b) a monoamine oxidase inhibitor.

43. A compound having an adenosine A_{2A} receptor

antagonistic activity or a pharmaceutically acceptable salt thereof for administering simultaneously or separately at a time interval in combination with a monoamine oxidase inhibitor.

44. A pharmaceutical composition which comprises a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof for administering simultaneously or separately at a time interval in combination with a monoamine oxidase inhibitor.

45. A therapeutic agent for depression which comprises (a) a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and
(b) a monoamine oxidase inhibitor
for administering simultaneously or separately at a time interval.

46. A kit which comprises
(a) a first component comprising a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and
(b) a second component comprising a monoamine oxidase inhibitor.

47. A kit for treatment of depression which comprises (a) a first component comprising a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and
(b) a second component comprising a monoamine oxidase inhibitor.

48. A method for treating depression, which comprises administering
(a) a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and
(b) a monoamine oxidase inhibitor
simultaneously or separately at a time interval.

49. Use of a combination of

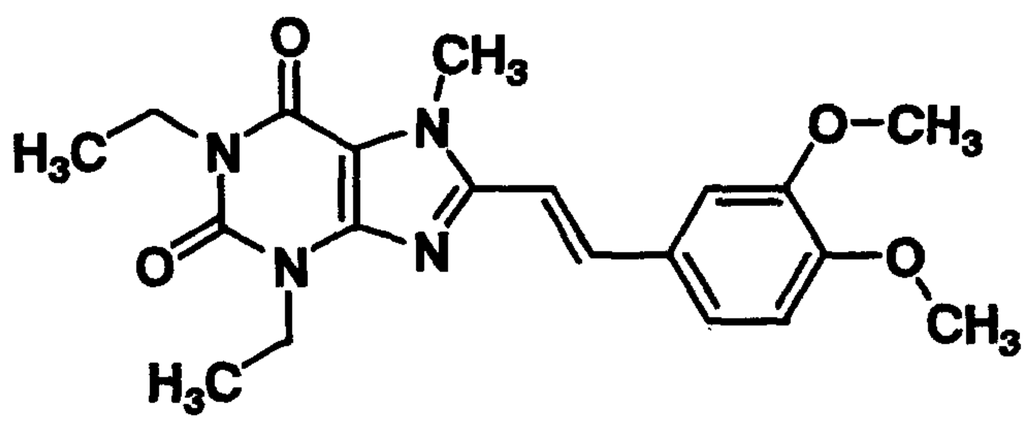
(a) a compound having an adenosine A_{2A} receptor antagonistic activity or a pharmaceutically acceptable salt thereof and

(b) a monoamine oxidase inhibitor

for the manufacture of a therapeutic agent for depression.

50. Use of a combination of

(a) (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof and

(b) an antidepressant drug

for the manufacture of a therapeutic agent for depression.